TREATMENT STRATEGIES
DERMATOLOGY

Volume 2 Issue 2

- Acne
- Bullous Diseases
- Lasers
- Paediatric Dermatology
- Psoriasis
- Skin and Venereal Oncology

Articles include:

A New Treatment for Severe Burn and Post-traumatic Scars: A Preliminary Report

Diagnosis and Treatment of Pemphigus Vulgaris

Immunocryosurgery for Basal Cell Carcinoma: An Audit for Combination, Minimally Invasive Approaches

Influence of Lipid Profile on Serum Levels of NT-proBNP, IL-23 and Resistin in Male Psoriatic Patients

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TREATMENT STRATEGIES
Dermatology

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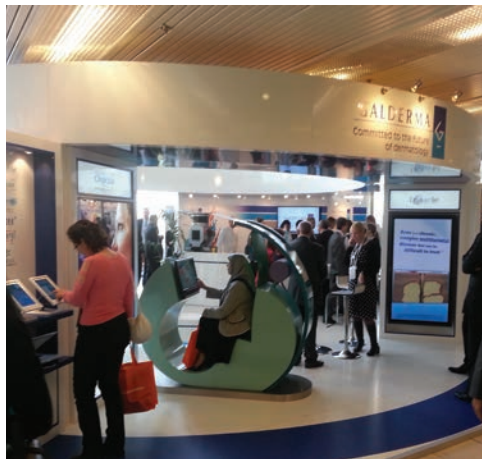

Welcome...

I am delighted to welcome you to the latest edition of *Treatment Strategies – Dermatology*. This issue will address key topical areas in dermatologic medicine and features an exciting collection of articles from leading dermatology specialists. After the success of the previous edition, we once again hope to provide you with a comprehensive review of the latest updates and advances from the field of dermatology.

We have included balanced and comprehensive articles written by the leading specialists and professors that address the most important issues and developments in the field. Key topical areas include acne, bullous diseases, lasers, paediatric dermatology, psoriasis and skin and venereal oncology.

In addition, there will also be a review of the European Academy of Dermatology and Venereology (EADV) 2012 Congress, which this year took place in Prague. This review includes the latest updates from the industry featuring all the highlights and exhibitors from the conference. The congress featured a plethora of sessions, with highlights including symposia, plenary lectures, workshops and meet the expert sessions, which offered the opportunity to become involved in debates and interact with other professionals. The European Academy of Dermatology and Vereology is a non-profit organisation which aims to advance excellence in clinical care, research, education and training within the field of dermatology and venereology. The Congress is an excellent forum within which the newest breakthroughs, treatments and products within the field of dermatology can be shared.

We hope that this information will be useful for the readers and will act as a forum in which to present the constantly evolving and developing findings from the dermatology field. We hope to provide the highest standards for the series. It would be most helpful if you would provide us with your feedback. By working with your opinions, we will ensure that the *Treatment Strategies Series* is one of the most useful publications in healthcare.

We are looking forward to meeting you next year in Amsterdam for the 2013 EADV Congress.

Nigel Lloyd, Editorial Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

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EDITORIAL ADVISORY PANEL

Foreword

Enzo Berardesca
San Gallicano Dermatological Institute, Rome

Welcome to the latest issue of *Treatment Strategies – Dermatology*. We hope that this edition continues the resounding success of the last, and fulfils its aim of bringing healthcare professionals the latest updates and developments within the field of dermatology.

Dermatologic treatment has never been so innovative and exciting as today. Indeed, in this particular area of medicine where until few years ago the main role of treatment was played by topical products and quite often galenic presciption, in these years we have seen an important development lead by antipsoriatic drugs (biologics) providing targeted and highly effective therapeutic solutions for psoriasis and psoriatic arthritis. In this area many new molecules are in the pipeline offering interesting new perspectives in these patients troubled by this chronic disease. The goal shall be early treatment to prevent chronic disease as well as comorbidities. At the same time, we have now developed systemic drugs and new protocols for immunotherapy in some skin cancers including melanoma and metastatising basal cell carcinoma which provide new hopes in these difficult cases where surgery doesn't provide answers. New topical immunomodulators can also be a very promising area to treat skin disease and prevent skin cancers. Atopic dermatitis, localised immunomediated skin diseases, actinic keratosis, basal cell carcinoma can all now more easily be prevented and treated; skin cancer in general can particularly be treated without surgery: apart from topical creams, advances in photodynamic therapy (both in terms of devices and photosensitising molecules) and laser treatment open new breakthroughs in the management of skin problems in elderly subjects. The increase worldwide in the aged population boosts the demand for innovation in this area including new pharmacological treatments but also new cosmetic procedures and formulations to address skin aging and skin care. New insights into the skin physiology and the deeper mechanisms of skin regulation and function allows the development of a new generation of more active dermatocosmetics optimising skin care regimens and contributing to preventing skin disease by regulating barrier homeostasis and the pro-inflammatory cascade occurring at different levels from the upper stratum corneum to the deeper dermis.

I think really that never like today dermatologists had so many powerful options (and many more in the near future!) to treat, control and prevent skin disease and aesthetic disorders, making our commitment to patients' health more and more successful and dedicated to the improvement of their quality of life.

We hope that you enjoy the latest edition of *Treatment Strategies – Dermatology* and the papers that have been included. Dermatology is one of the most dynamic areas of medicine, in which new discoveries and developments are constantly being made. We hope that the publication gives an in-depth overview of some of the most important and interesting topics within the field today.

Enzo Berardesca is Director of Clinical Dermatology at the San Gallicano Dermatological Institute, Rome, Italy. Dr. Berardesca, obtained his training at the University of Pavia and received the M.D. degree in 1979. He served as resident and dermatologist the Department of Dermatology, IRCCS Policlinico S. Matteo, Pavia from 1982 to 1987, as assistant research the Department of Dermatology, University of California School of Medicine in San Francisco, USA in 1987. From 1988 to 2001 he has been at the Department of Dermatology of the University of Pavia, head of the Dermatoallergology Unit and of the Skin Bioengineering Lab. Dr. Berardesca has been Chairman of the International Society for Bioengineering and the Skin from 1990 to 1996. He has organised several international meetings on skin bioengineering and irritant contact dermatitis in Europe. He is member of the editorial board of *Skin Pharmacology*, *Skin Research and Technology*, *The American Journal of Clinical Dermatology* and the *Journal of Cutaneous and Ocular Toxicology*. He is member of the Society for Investigative Dermatology, the European Society for Dermatological Research, the Italian Group for Research on Contact Dermatitis (GIRDCA), and vice-chairman of the European Group For standardisation of Efficacy Measurements of Cosmetics (EEMCO group). His current major research interests are irritant dermatitis, barrier function and noninvasive techniques to investigate skin physiology with particular regard to skin color and racial differences in skin function, sensitive skin and efficacy evaluation of topical products. He is author of 11 books and more than 400 papers and book chapters. *Clinical Trials: Biologics in psoriasis*, *topical immunomodulators in atopic dermatitis*, *desloratidine in chronic urticaria*, *cyclosposrine in chronic urticaria*, *teicoplanine in acne*, *limecicline in acne*.

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21st EADV Congress Review

27 - 30 September 2012 - Prague

21st European Academy of Dermatology and Venereology (EADV) Congress — Review

INSIDE...

Hannah Corby, *Treatment Strategies*, takes a look over a number of key sessions, as well as spotlighting several stands and products being demonstrated at the exhibition. We then follow with papers and reviews which give a brief insight from a number of sessions highlighting findings that will have direct repercussions on clinical practise that are still very much being discussed.

The European Academy of Dermatology and Venereology (EADV) is a non-profit organisation, which aims to advance excellence in clinical care, research, education and training within the field of dermatology and venereology. It also acts as an advocate and educator of patients, particularly those with cutaneous or venereal diseases.

The 21st EADV Congress is an excellent forum within which the newest breakthroughs, treatments and products within the field of dermatology can be shared. This years congress showcased 1653 abstracts and was attended by over 8300 participants.

The theme of this year's congress was 'Skin is Vital', a theme which emphasised the central importance of skin in our health and well-being.

Introduction *continues on page 10*

The 21st EADV Congress was held in the picturesque ciy of Prague.

continued from page 9

The congress offered a wide range of different sessions in which attendees were encouraged to share their knowledge and debate the most important issues within dermatology. Sessions included workshops, which covered topics such as melanoma campaigns, teledermatology and pigmentary disorders, and courses on topics including basic dermatological surgery and hair and scalp diseases. Meet the Expert sessions and forums offered the opportunity to become involved in debates and interact with other professionals. Plenary lectures were also an important staple in the programme, covering areas such as new therapeutic developments in oncology and cancer and inflammation.

The congress also featured a variety of symposiums throughout the five-day event. Psoriasis was one of the main focuses in these sessions, with several covering different research and treatment options within this area. Highlights included Pfizer's symposium entitled 'Considerations for the Optimal Management of Patients with Plaque Psoriasis', which discussed the emerging area of immunogenicity of biological therapies and focussed upon identifying similarities and differences between various biologic treatment options. Additionally, this session looked at the long-term efficacy and safety data of biologic therapies and addressed the wider implications of plaque psoriasis on patients. Pfizer hosted an additional symposium entitled 'The Puzzle of Psoriasis: Searching for the Missing Pieces', which reviewed the underlying mechanisms of psoriasis, as well as the most recent developments in the field. Celgene also sponsored a symposium entitled 'Navigating the Course of Psoriatic Disease', which reviewed the results of a large international survey of patient's attitudes regarding psoriasis, psoriasis arthritis and its treatment. It also summarised the present state of knowledge regarding the pathogenesis of psoriasis and psoriatic arthritis, and reviewed current and upcoming pharmacological therapies for the management of both psorasis and psoriatic arthiritis.

Atopic dermatitis was also a much discussed topic. Astellas' symposium, 'Personalised Medicine: a Vision for the Future Treatment of Atopic Dermatitis?' explored the possibility of a patient-focussed approach to the treatment of atopic dermatitis and discussed the long-term treatment options. A further symposium, 'How to Manage Prurits in Children with Atopic Dermatitis in Daily Practise – Alleviating the Itch-scratch Cycle' focussed upon how to deal with the psychosocial aspects of the itch-scratch cycle, as well as long-term treatment options.

Other notable symposiums include Almirall's symposium entitled 'Improving Patient Outcomes in Actinic Keratosis: Insights and What Matters to Patients', which explored the application of technical advances in improving diagnosis and management in actinic keratosis, as well as how to engage a patient in their treatment and field and lesion-directed treatment approaches, and Galderma's symposium 'No More Red - Erythema of Rosacea: Clinical Challenges and Management Options' which covered the latest research on the subject of rosacea including the underlying pathophysiology and treatment options.

This year, the congress was held in Prague. Prague is the capital and the largest city of the Czech Republic. It is also the historic capital of Bohemia Proper. Situated in the northwest of the country on the Vltava river, it is home to over 1.3 million people. The city's name is derived from an old Slavic root, praga, meaning ford, which refers to the city's origin at a crossing point in the Vltana river.

Prague has been a political, cultural and economic centre of Europe, with fluctuating fortunes. Founded during Romanesque, Prague flourished in the Gothic and

Renassiance eras, and was also the seat of two holy Roman emperors. Prague was also an important city to the Habsburg monarchy and the Aystri-Hungarian empire. It also played a major role in the Protestatnt Reformation, the Thirty Years War, World War I and II and the post-war communist era.

The city is a popular tourist destination, and receives more than 4.1 million visitors annually. In 2011, Prague was the 6th most visited European country. The city houses more than 10 major museums including the National Museum and The Museum of the Capital City of Prague , as well as numerous theatres, galleries, cinemas and historical exhibits. The city hosts music and film festivals, including the Prague Spring International Music Festival and the One World Film Festival. Many films have been made at Barrandov Studios and at Prague Studios, and Hollywood films such as Mission Impossible and Alien vs. Predator were set in Prague. Other cultural attractions include the Prague castle, Charles Bridge, the Jewish Quarter and the Lennon Wall. Since 1992, the extensive historic centre of Prague has been included in the UNESCO list of world heritage sites.

Prague is also an important centre of research, which seats 39 out of 54 institutes of the Czech Academy of Sciences, including the largest ones, the Institute of Physics, the Institute of Microbiology and the Institute of Organic Chemistry and Biochemistry. It is also a seat of 10 public research institutes, four business incubators and large hospitals performing research and development activities such as the Institute for Clinical and Experimental Medicine in Prague or the Motol University Hospital. This backdrop made it the perfect location to host the 21st EADV congress.

The congress was held in the Prague Congress Centre, which is one of the leading congress centres in Europe. Its size means that it can hold up to 9300 participants in more than 50 halls, reception rooms and conference rooms, and it has state of the art technical equipement and acoustics. It also boasts a panoramic view of Prague from the congress foyer and its neighbouring halls.

Following on from the last edition, we have once again commissioned a number of authors to discuss the various sessions that took place across the four-days, spotlighted findings and research that were presented, as well as bringing you a round-up of the stands found within the lively exhibition hall.

New App 'SKIN PEACE' Advises How to Use Topical Corticosteroid for Eczema Correctly

Bayer HealthCare Dermatology launched a free app for patients with eczema conditions, such as atopic dermatitis (AD) at the occasion of the 21st Congress of the European Academy of Dermatology and Venerology (EADV) in Prague, Czech Republic.

By entering the patient's age, gender and the affected body part, the app calculates the right amount of topical treatment per application. To make it easier for patients and their caregivers, the app uses a common unit of measurement: the FingerTipUnit (FTU) in the SKIN PEACE dosage finder. The app is free to download and available from the App Store (iTunes Store and Market Place) for use on different technical devices such as smart phones or tablets.

An FTU is the amount of topical product that should be dispensed from fingertip to the first joint of the finger. Since this amount varies largely between adults and children and significantly between infants, toddlers, and children as well, the SKIN PEACE dosage finder app calculates the correct selection of the amount for each group. The proper application of topical corticosteroid is a key factor to a rapid healing and therapeutic success in atopic dermatitis, and so this new app will prove very useful for patients and healthcare professionals.

Syneron Announces Global Launch of Gentle Pro-U Series at the EADV

New Gentle Pro-U Series Allows Customers to Upgrade Systems to Dual Wavelength Configurations for Enhanced Performance and Additional Clinical Indications

Syneron Medical Ltd., the leading global aesthetic device company, have announced the global launch of the Gentle Pro-U series of upgradeable aesthetic laser systems at the 21st European Academy of Dermatology and Venereology (EADV) Congress, which took place from September 27-30, 2012 in Prague, Czech Republic.

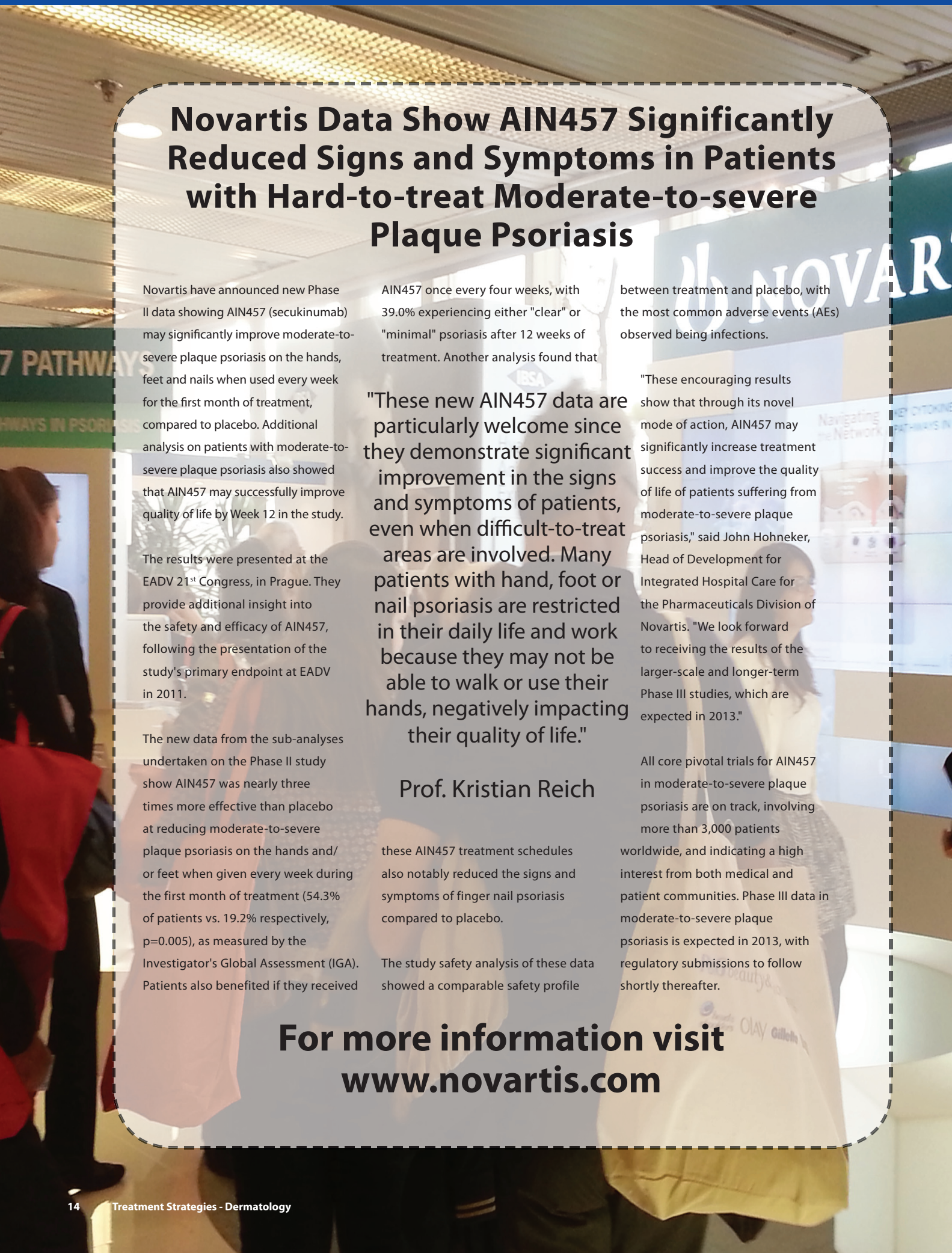
The Pro-U family of products includes the GentleLase Pro-U long pulse alexandrite laser for hair removal and the treatment of pigmented and vascular lesions, and the GentleYag Pro-U long pulse laser for hair removal and the treatment of spider veins and telangiectasia. The new Pro-U series builds on the strong brand history of the Gentle family of aesthetic laser systems with the ability to upgrade either system from single to dual wavelength, providing an even more diverse range of treatment capabilities.

Louis P. Scafuri, Chief Executive Officer of Syneron, commented, "The new Pro-U series provides our customers with best-in-class technology with the added flexibility to upgrade the system as their practice grows. This allows our customers to upgrade their GentleLase or GentleYag Pro-U system, at a time of their choice, into a dual wavelength system that essentially has the same treatment capabilities as our popular GentleMax Pro system, which has been one of our best selling systems since its launch earlier this year."

Syneron will also feature the recently launched elos Plus™ system at the EADV Congress. elos Plus™ is a next generation multi-platform system featuring Syneron's proprietary elos technology. It is customizable or upgradable utilising a full range of up to ten in-demand aesthetic applicators, which also includes the Company's globally successful Sublative™ and Sublime™ applications. It has an intuitive fifteen-inch touch screen that offers unparalleled ease-of-use through simple but powerful guided treatment modes for all applications. The system is also equipped with the most popular features from recent Syneron models such as the proprietary Active Dermal Monitoring™, Intelligent Feedback System™ (IFS) and Sublative iD™, making elos Plus™ an ideal choice for any aesthetic practice.

Mr. Scafuri added, "Similar to the new Pro-U series, the elos Plus™ system allows our customers to scale their initial investment in a platform system that provides multiple treatment capabilities and that can be upgraded in the future to further enhance its utility. Both platforms were developed to meet the diverse and evolving needs of customers and underscore Syneron's customer-centric approach to new product development."

For more information visit www.syneron-candela.com



Novartis Data Show AIN457 Significantly Reduced Signs and Symptoms in Patients with Hard-to-treat Moderate-to-severe Plaque Psoriasis

Novartis have announced new Phase II data showing AIN457 (secukinumab) may significantly improve moderate-to-severe plaque psoriasis on the hands, feet and nails when used every week for the first month of treatment, compared to placebo. Additional analysis on patients with moderate-to-severe plaque psoriasis also showed that AIN457 may successfully improve quality of life by Week 12 in the study.

The results were presented at the EADV 21st Congress, in Prague. They provide additional insight into the safety and efficacy of AIN457, following the presentation of the study's primary endpoint at EADV in 2011.

The new data from the sub-analyses undertaken on the Phase II study show AIN457 was nearly three times more effective than placebo at reducing moderate-to-severe plaque psoriasis on the hands and/or feet when given every week during the first month of treatment (54.3% of patients vs. 19.2% respectively, p=0.005), as measured by the Investigator's Global Assessment (IGA). Patients also benefited if they received AIN457 once every four weeks, with 39.0% experiencing either "clear" or "minimal" psoriasis after 12 weeks of treatment. Another analysis found that these AIN457 treatment schedules also notably reduced the signs and symptoms of finger nail psoriasis compared to placebo.

"These new AIN457 data are particularly welcome since they demonstrate significant improvement in the signs and symptoms of patients, even when difficult-to-treat areas are involved. Many patients with hand, foot or nail psoriasis are restricted in their daily life and work because they may not be able to walk or use their hands, negatively impacting their quality of life."

Prof. Kristian Reich

The study safety analysis of these data showed a comparable safety profile between treatment and placebo, with the most common adverse events (AEs) observed being infections.

"These encouraging results show that through its novel mode of action, AIN457 may significantly increase treatment success and improve the quality of life of patients suffering from moderate-to-severe plaque psoriasis," said John Hohneker, Head of Development for Integrated Hospital Care for the Pharmaceuticals Division of Novartis. "We look forward to receiving the results of the larger-scale and longer-term Phase III studies, which are expected in 2013."

All core pivotal trials for AIN457 in moderate-to-severe plaque psoriasis are on track, involving more than 3,000 patients worldwide, and indicating a high interest from both medical and patient communities. Phase III data in moderate-to-severe plaque psoriasis is expected in 2013, with regulatory submissions to follow shortly thereafter.

For more information visit www.novartis.com

Dermapen for Advanced Skin Needling

Equipmed has taken Dermapen international, leading the way at the Prague EADV Congress 2012 in September. It was a fantastic success and a great event to attend. Thank you to everybody who visited us over there. Prof. Tony Chu also presented his renowned Dermapen study at the Congress.

Dermapen advanced skin needling delivers better results for patients with its unique vertical needling action. The multi-speed piercing action of Dermapen is more effective than needling rollers. It improves the effectiveness of product absorption, and rejuvenates collagen and elastin. Dermapen is just as effective as ablative laser treatments, such as Fraxel, IPL, laser resurfacing and chemical peels. It can also easily treat difficult-to-treat areas, such as the top of the lip and around the eyes.

For more information visit www.equipmed.com

Oral Tasocitinib Demonstrates Statistically Significant Response by 12 Weeks in Phase 2 Study of People With Moderate to Severe Plaque Psoriasis

Pfizer Inc. today announced that data from a Phase 2 efficacy and safety study of tasocitinib (proposed INN name for CP-690,550), the company's investigational oral JAK inhibitor, met its primary endpoint of a statistically significant greater proportion of patients achieving at least a 75 percent reduction from baseline in PASI (Psoriasis Area and Severity Index) at week 12 in individuals with chronic moderate to severe plaque psoriasis.

At week 12, PASI 75 responses for tasocitinib 2, 5 and 15 mg twice daily groups were 25.0%, 40.8% and 66.7% respectively, versus placebo, 2.0% (all doses, $p<0.001$). As early as week 4, treatment with 5 and 15 mg twice daily of tasocitinib significantly improved patient reported health-related quality of life outcomes. These results were presented in two posters at the annual meeting of the European Academy of Dermatology and Venereology (EADV).

The double-blind, placebo-controlled, dose-ranging Phase 2 study was conducted in 197 adult patients with moderate to severe plaque psoriasis. Study participants were randomised to receive 2, 5 or 15 mg tasocitinib or placebo twice daily. In the study, the most frequently reported treatment-emergent adverse events were upper respiratory tract infection and headache.

Three patients experienced a total of five serious adverse events during the study. Dose dependent decreases in mean neutrophil counts and hemoglobin values and increases in mean LDL, HDL and total cholesterol levels were observed.

Dermaroller Honoured as the Only Micro-Needling Company Attending the 2012 EADV Congress in Prague

Thanks to its impeccable reputation and its third party verification of quality control with micro-needling techniques, Dermaroller ® was the ONLY micro-needling company to exhibit at the "world's most respected and largest skin show" , at the 21st Annual EADV (European Academy of Dermatology and Venereology) Congress, September 27-30. The event was held in Prague, the capital of the Czech Republic, with the theme: "Skin is Vital."

"We're proud to say that Dermaroller is continuing to grow, despite the presence of 'knock-offs' in the market-place," says Phillip Terrazas, Director of Sales & Marketing for Dermaroller US. He believes that the amazing results patients regularly experience with Dermaroller medical micro-needling devices, whether in acne scar treatment or anti-aging skin procedures such as reduction of wrinkles and skin tightening, are the reason Dermaroller has been selected as the only micro-needling treatment provider invited to attend this year's EADV Congress.

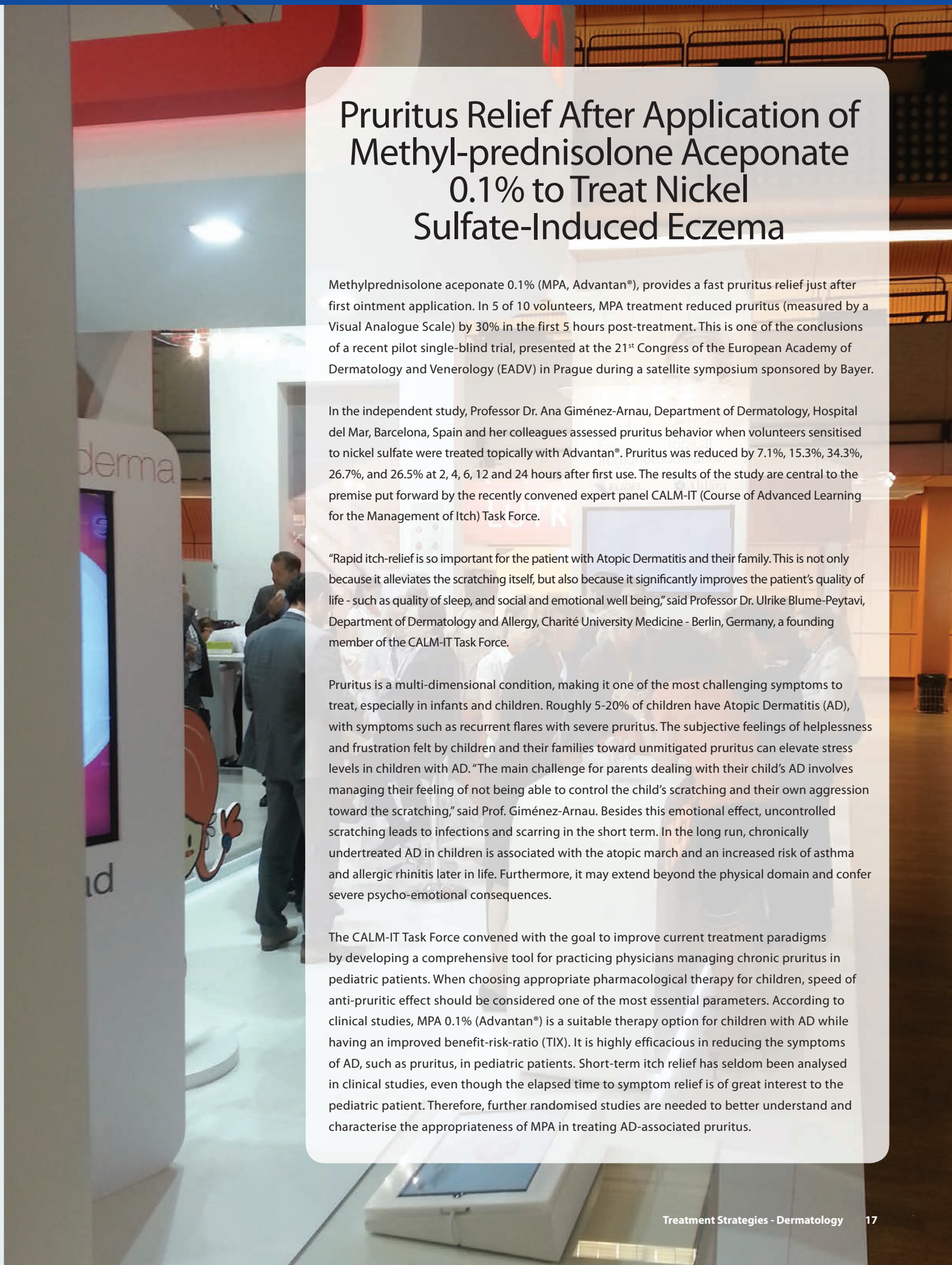
Less than 15 years ago, Horst Liebl began researching, engineering, and perfecting the micro-needling concept –resulting in the development of the Original Dermaroller. Since the founding of the company in 2000, Dermaroller has been the subject of numerous studies worldwide. It is now considered not only the original pioneer in this field, but also the leader in micro-needling technology. Dermaroller is also proud to acknowledge that they are the only micro needle company that is both CE (Conformité Européenne) and TGA (Therapeutics Goods Administration-Australia) Class 2 Medial Device listing in the world. No other micro-needle company has established their quality with any of these governmental bodies.

Micro-needling involves the use of ultra-fine, sterile, surgical-strength micro-needles. In a procedure called Collagen Induction Therapy (CIT), the Medical Dermaroller uses these needles to cause new collagen, elastin and tissue matrix to be deposited in the deep skin layers, new capillaries to be formed, and new skin cells to be created.

Based in Germany, Dermaroller ® has been in the United States since 2003, with an active trademark since 2008. The U.S. branch of the company, Dermaroller US, sells medical Dermaroller micro-needling rollers to qualified medical professionals who have completed our training program. It also has a staff that supports, educates, and promotes the legal, proper, and most efficient and ethical way to use and apply skin micro-needling devices. (While medical Dermarollers are designed for sterile single-use and are only sold to qualified medical professionals, Dermaroller US does distribute a home use version micro-needling roller to the public that is reusable).

Cynergy, LLC is the exclusive U.S. distributor of Dermaroller ®.

For more information visit www.dermarollerus.com



Pruritus Relief After Application of Methyl-prednisolone Aceponate 0.1% to Treat Nickel Sulfate-Induced Eczema

Methylprednisolone aceponate 0.1% (MPA, Advantan®), provides a fast pruritus relief just after first ointment application. In 5 of 10 volunteers, MPA treatment reduced pruritus (measured by a Visual Analogue Scale) by 30% in the first 5 hours post-treatment. This is one of the conclusions of a recent pilot single-blind trial, presented at the 21st Congress of the European Academy of Dermatology and Venerology (EADV) in Prague during a satellite symposium sponsored by Bayer.

In the independent study, Professor Dr. Ana Giménez-Arnau, Department of Dermatology, Hospital del Mar, Barcelona, Spain and her colleagues assessed pruritus behavior when volunteers sensitised to nickel sulfate were treated topically with Advantan®. Pruritus was reduced by 7.1%, 15.3%, 34.3%, 26.7%, and 26.5% at 2, 4, 6, 12 and 24 hours after first use. The results of the study are central to the premise put forward by the recently convened expert panel CALM-IT (Course of Advanced Learning for the Management of Itch) Task Force.

"Rapid itch-relief is so important for the patient with Atopic Dermatitis and their family. This is not only because it alleviates the scratching itself, but also because it significantly improves the patient's quality of life - such as quality of sleep, and social and emotional well being," said Professor Dr. Ulrike Blume-Peytavi, Department of Dermatology and Allergy, Charité University Medicine - Berlin, Germany, a founding member of the CALM-IT Task Force.

Pruritus is a multi-dimensional condition, making it one of the most challenging symptoms to treat, especially in infants and children. Roughly 5-20% of children have Atopic Dermatitis (AD), with symptoms such as recurrent flares with severe pruritus. The subjective feelings of helplessness and frustration felt by children and their families toward unmitigated pruritus can elevate stress levels in children with AD. "The main challenge for parents dealing with their child's AD involves managing their feeling of not being able to control the child's scratching and their own aggression toward the scratching," said Prof. Giménez-Arnau. Besides this emotional effect, uncontrolled scratching leads to infections and scarring in the short term. In the long run, chronically undertreated AD in children is associated with the atopic march and an increased risk of asthma and allergic rhinitis later in life. Furthermore, it may extend beyond the physical domain and confer severe psycho-emotional consequences.

The CALM-IT Task Force convened with the goal to improve current treatment paradigms by developing a comprehensive tool for practicing physicians managing chronic pruritus in pediatric patients. When choosing appropriate pharmacological therapy for children, speed of anti-pruritic effect should be considered one of the most essential parameters. According to clinical studies, MPA 0.1% (Advantan®) is a suitable therapy option for children with AD while having an improved benefit-risk-ratio (TIX). It is highly efficacious in reducing the symptoms of AD, such as pruritus, in pediatric patients. Short-term itch relief has seldom been analysed in clinical studies, even though the elapsed time to symptom relief is of great interest to the pediatric patient. Therefore, further randomised studies are needed to better understand and characterise the appropriateness of MPA in treating AD-associated pruritus.

Syneron Honours Company Founder and IPL Inventor Shimon Eckhouse at Gala Dinner at the 2012 EADV Congress

Syneron Medical Ltd., the leading global aesthetic device company, honoured Dr. Shimon Eckhouse, its founder and the inventor of IPL (Intense Pulsed Light), at a gala dinner held during the EADV (European Academy of Dermatology and Venerology) congress in Prague.

The event, which was attended by over 100 key opinion leaders and industry professionals, celebrated the 20th anniversary of the invention of IPL, a technology that revolutionised and paved the way for the expansion of the aesthetic device market in a multi-billion dollar category. IPL, which is derived from selective photothermolysis, utilises a wide range of light wavelengths to treat a variety of skin conditions and aesthetic procedures, including spider veins, birthmarks, port-wine stains, acne scars, fine lines and wrinkles, and permanent hair reduction.

Medical professionals, industry experts and long-time friends attended the event to honour Dr. Eckhouse and his invention. Dr. Moshe Lapidoth, M.D., M.P.H, Dermatologist, Head of the Laser Unit, Dermatology Dep., Rabin Medical Center, Israel and President of the European Society of Laser in Dermatology (ESLD) shared the story of how IPL started: Dr. Eckhouse developed the IPL technology out of a small room filled with machine parts in tools, creating a technology that in a few years would revolutionise the non-invasive aesthetic industry.

Dr. Christine Dierickx, Medical Director of the Laser and Skin Clinic in Boom, Belgium, described her initial doubts on the IPL technology when it was first introduced in the United States 20 years ago, and how her view has changed given the numerous applications that the non-invasive IPL technology offers to meet the needs of both doctors and their patients. Michael Moretti, CEO of Medical Insight, Inc., editor and publisher of THE Aesthetic Guide® and long-time friend, praised Dr. Eckhouse for his courage and ability to overcome the hurdles he faced during his career to become the successful inventor and entrepreneur in the field of medical devices and medical technology that he is today.

Louis Scafuri, Chief Executive Officer of Syneron, provided guests with insights on Dr. Eckhouse, describing him as a man who always looks towards the positive aspects in life and never gives up. He spoke of his devotion to family and summed up his comments saying that Dr. Eckhouse's positive outlook and attitude represents a great resource and inspiration for managing Syneron's high growth trajectory in the highly competitive aesthetic device industry.

STELARA® Improves QoL in Patients with Plaque Psoriasis

New Five Year Data Presented at EADV 2012

A series of data presentations released at the 21st European Academy of Dermatology and Venereology (EADV) congress, in Prague, Czech Republic, demonstrate that STELARA® (ustekinumab) is effective, generally well-tolerated and improves quality of life in patients with moderate-to-severe plaque psoriasis.

Specifically, results from the 52-week TRANSIT study showed that ustekinumab is effective and generally well-tolerated in patients inadequately responsive to methotrexate,[1] and that ustekinumab substantially improved quality of life outcomes in these patients transitioned from methotrexate regardless of transition strategy.[2] Additionally, results from the PHOENIX 2 study demonstrated that high levels of clinical responses were achieved and maintained with up to five years of ustekinumab treatment.[3]

Ustekinumab targets interleukin-12 (IL-12) and interleukin-23 (IL-23), naturally occurring proteins that are important in regulating immune responses and are thought to be associated with immune-mediated inflammatory diseases such as plaque psoriasis.

Professor Jörg Prinz, University of Munich, Germany, said "The findings from these studies are promising and support a favourable benefit-to-risk profile for ustekinumab with up to five years of treatment. Importantly results demonstrated in clinical trials are consistent with the real-world experience to date. These findings further advance our understanding of biologics, not just in terms of efficacy, safety and tolerability, but also health-related quality of life."

Psoriasis is a chronic, immune-mediated inflammatory disease, which is highly visible on the patient but incurable. It is often very painful and associated with multiple physical and psychological burdens such as depression.[4] There is now a recognised need for improved standards of care for each and every person living with psoriasis in the UK and Europe today, and to address this need the European Expert Working Group for Healthcare in Psoriasis recently launched a Europe-wide framework[5] (White Paper) to improve standards of care for patients, especially in terms of access to the right targeted treatment appropriate for their disease severity.

1. Paul C *et al*. Long-term safety and efficacy of ustekinumab in patients with psoriasis inadequately responding to methotrexate: Week 52 TRANSIT results. Presented at the 21st European Association of Dermatology & Venereology (EADV) congress; 2012 September 27–30; Prague, Czech Republic. Oral session FC02.
2. Reich K *et al*. Long-term improvement in patient-reported outcomes after transition from methotrexate to ustekinumab in moderate to severe psoriasis: TRANSIT Week 52 results. Poster presented at the 21st European Association of Dermatology & Venereology (EADV) congress; 2012 September 27–30; Prague, Czech Republic. Poster P955.
3. Langley R *et al*. Long term efficacy and safety of ustekinumab in patients with moderate to severe psoriasis through 5 years of follow-up: results from the PHOENIX 2 long-term extension. Poster presented at the 21st European Association of Dermatology & Venereology (EADV) congress; 2012 September 27–30; Prague, Czech Republic. Poster P976.
4. National Psoriasis Foundation. Related Health concerns: Psoriasis comorbidities. Available at: http://www.psoriasis.org/about-psoriasis/related-conditions. Last accessed September 2012.
5. Augustin M et al. A framework for improving the quality of care for people with psoriasis. JEADV 2012; 26 (Supplement 4):1–16.

Agfa HealthCare Launches SKINTELL Non-invasive High-definition Optical Coherence Tomography Solution

High resolution technology provides 3D imaging of the epidermal and dermal skin layers in three different viewing modes

Agfa HealthCare has announced the launch of its SKINTELL high-definition optical coherence tomography (HD-OCT) solution at the 21st Congress of the European Academy of Dermatology and Venereology (EADV) in Prague. This non-invasive imaging technology allows the examination of the epidermal morphology and superficial dermis, potentially avoiding a biopsy.

Speed and Comfort for Patient and Doctor

SKINTELL HD-OCT non-invasively visualises skin layers up to 1mm in depth, with no discomfort for the patient. It offers three viewing modes: slice, 3D and the unique en face, which gives a parallel perspective to the skin, in real time.

The 3 µm high-resolution solution, which can be adapted to all skin types, provides views in all three dimensions of the epidermal layers and the dermal-epidermal junction down to the upper part of collagen tissue. A 3D image takes one second.

Complements and Adds to Dermatological Examinations

"SKINTELL is a truly new solution for dermatologists, dermato-oncologists, plastic surgeons and the cosmetic industry, and it is backed by several Agfa HealthCare patents," comments Dirk Debusscher, Vice President Imaging at Agfa HealthCare. "It complements current dermatological examinations, combining the advantages of several types of exams, but with a speed and comfort that will be appreciated by doctor and patient alike. For example, it provides a subcutaneous view not possible with dermatoscopy, a deeper view than confocal microscopy, and 3D zoom for regions of interest."

Fits in to Daily Practice and with Advanced Technologies

Dr. Marc Boone uses SKINTELL HD-OCT at his dermatology practice near Brussels, Belgium. "My patients appreciate the speed and real-time analysis of the image. It creates confidence in the doctor," he comments. Dr. Boone uses all advanced imaging technologies, such as digital microscopy, high-frequency ultrasound and confocal scanning microscopy.

Dr. Tanja Maier uses SKINTELL HD-OCT at the Ludwig-Maximilians-Universität in Munich, Germany. She comments: "SKINTELL offers the possibility of immediate imaging of epithelial skin cancer and has potential in the non-invasive monitoring of skin tumors under topical treatment. It facilitates and accelerates the process of evaluation in daily practice."

Prof. Dr. Johannes Wohlrab performed a successful pre-clinical trial at the Martin-Luther-Universität Halle-Wittenberg, Halle, Germany. He states: "We have validated the HD-OCT solution SKINTELL in comparison with high frequency ultrasound (50 MHz) and presented the potential of a non-invasive depiction of the epidermal structures in particular. In my opinion, the clinical use of SKINTELL can enhance the non-invasive diagnostics of intra-epidermal processes considerably."

For more information visit www.agfahealthcare.com

Lumenis Launches Four New Modes of the AcuPulse™ CO2 Laser at the European Academy of Dermatology and Venereology (EADV)

Lumenis Ltd., the world's largest medical laser company which develops, manufactures and distributes a broad range of medical lasers and sophisticated energy delivery equipment for surgical, aesthetic and ophthalmic applications, announces the launch of its upgraded AcuPulse™ CO2 Laser, with four new modes of treatment. AcuPulse with SuperPulse technology now offers physicians a total of ten different modes, allowing for unmatched versatility for treating 34 aesthetic indications.

Lumenis showcased the versatile and affordable AcuPulse™ laser at the 21st European Academy of Dermatology and Venereology (EADV), held in Prague, Czech Republic on September 27-30, 2012.

The four new treatment modes which have been added to the AcuPulse™ include:

- **Combo™** – Combo mode maximises time and efficiency by safely treating both superficial and deep targets in a single scan. This can be used for facial lines, wrinkles or sun damage, and in the same scan, deep irregular lesions.
- **StretchTouch™** – StretchTouch treats skin furrows and other textual irregularities on larger body areas using SuperPulse technology.
- **FineTouch™** – FineTouch can be used for precise ablation and coagulation of irregular pigmented lesions at various depths.
- **ToeTouch™** – ToeTouch offers a solution to podiatry ailments using continuous wave ablation. Now physicians can treat toenail fungus, plantar warts, ingrown toenails and more.

> "Lumenis recognises the importance of being able to offer physicians a rich range of treatment options while economising on capital costs. Built on Lumenis' 40 year experience with CO2 technology, AcuPulse™ continues the tradition of providing gold standard CO2 devices to physicians."
>
> Rami Sharon, President of Lumenis EMEA.

"Lumenis recognises the importance of being able to offer physicians a rich range of treatment options while economising on capital costs," says Rami Sharon, President of Lumenis EMEA. "Built on Lumenis' 40 year experience with CO2 technology, AcuPulse™ continues the tradition of providing gold standard CO2 devices to physicians."

"I have found that FineTouch mode on AcuPulse™ has the precision that I need to treat fine pigmented lesions. I have also found that FineTouch has the capability to ablate layers evenly into deep nevus cells with visual contact," says Dr. Nariaki Miyata, Director of Miyata Plastic Surgery and Dermatology Clinic in Japan. "The FineTouch mode is very easy to control and easy to operate with minimum damage to normal tissue that is unrivalled by any other products."

Treatments performed with the AcuPulse™ can be done using the SurgiTouch™ or AcuScan120™ high precision scanners. The AcuScan120™ incorporates precision optics with real-time monitoring algorithms for treating fractionally both superficially and deep. The SurgiTouch™ scanner enjoys a reputation of quality and precision based on extensive clinical experience.

Stiefel Signs Worldwide Acquisition and License Agreement for Toctino®

Stiefel, a GSK company, today announced that it has entered into a worldwide agreement to acquire Toctino (alitretinoin) from Basilea Pharmaceutica Ltd. (Basilea). Toctino is a once-daily oral retinoid and the only prescription medicine specifically approved for the treatment of severe chronic hand eczema unresponsive to potent topical steroids in adults. It is commercially available in 14 countries, approved in an additional 15 countries, and is in a Phase 3 trial in the US. In 2011, worldwide sales of Toctino were £22m.

Under the terms of the agreement, Stiefel will acquire all Toctino patent rights, trademarks and product registrations owned by Basilea and will license certain clinical information and product know-how from Basilea. Stiefel will be responsible for the product's further development, manufacture and commercialisation worldwide. Basilea will receive an initial payment of £146m in cash from Stiefel and is eligible to receive further payments of up to £50m upon FDA approval of the product in the US and double-digit success payments on US net sales, beginning three years after launch of the product in the US. The transaction is subject to competition approval in Germany.

Simon Jose, President, Stiefel said: "Toctino is an important and growing product that complements the Stiefel portfolio and offers a proven therapy for patients with a significant unmet medical need. This acquisition gives us an immediate opportunity to develop and expand the availability of this new and innovative product of value and reinforces Stiefel and GSK's commitment to dermatology."

Hand eczema is a common recurring dermatological condition and leading cause of sick leave and disability. It is estimated to affect up to 10 percent of the general population. Approximately 5 - 7 percent of patients with hand eczema are estimated to suffer from severe chronic hand eczema and 2 - 4 percent of patients are unresponsive to topical treatment. Severe chronic hand eczema is usually characterised by a combination of signs and symptoms of thick scaly skin that gives rise to red patches, itching, and painful cracks and blisters.

24th EADV Congress

02 — 06 October 2013
Istanbul, Turkey

The European Academy of Dermatology and Vereology (EADV) is a non-profit organisation, which aims to advance excellence in clinical care, research, education and training within the field of dermatology and venereology. It also acts as an advocate and educator of patients, particularly those with cutaneous or venereal diseases. The theme of the 2013 congress will be 'Dermatovenereology in a Changing World', and the programme will cover many fields of dermatology and the most recent developments, with contributions from leading experts in the field.

For more information please visit www.eadv.org

Breaking the Acne Code – Learn What Patients are not Telling You and What to do About it

Introduction

The satellite symposium entitled, "Breaking the Acne Code – Learn What Patients are not Telling You and What to do About it" was held during the 21st Congress of the European Academy of Dermatology and Venereology on Friday 28th September 2012 in Prague, Czech Republic.

Background

Physical and Emotional Impact of Acne

Acne has a physical impact and emotional consequences. Furthermore, many acne sufferers are more self-concious and embarrassed about their appearance and have less self-confidence. Previous studies in acne patients have shown higher rates of depression, anxiety, anger and frustration.

Acne Scarring – Permanent Impact

Acne scarring is a long-term sequelae of acne and can have an enduring adverse impact on patients. Studies have shown that at least 50% of all acne patients develop scars,[1] even in mild and moderate acne. Once it has been established, acne scarring is very challenging to treat. Studies suggest that early effective therapy for acne may reduce the development of acne scars.[1, 2]

Breaking the Acne Code – Learn What Patients are not Telling You and What to do About it
Galderma Sponsored Satellite Symposium at the European Academy of Dermatology and Venereology (EADV) Congress, Prague, Czech Republic, 28th September 2012

Improving the Connection Between Patients and Physicians
Brigitte Dréno, Professor of Dermatology Department of Dermatology University of Nantes, France

Understanding the Patient
Jerry Tan, Adjunct Professor, Western University, London, Ontario, Canada

Improving the Connection Between Patients and Physicians
Invited Guest: Cassandra, USA

Practical Solutions from a Dermatologists' Perspective
Alison Layton, Consultant Dermatologist, Harrogate and District NHS Foundation Trust, Harrogate, UK

Patients use various coping strategies to deal with acne and scarring, predominantly covering up with clothes, hair or make-up. In adolescents, this behaviour can be a trigger for parents to present to a physician.

Acne Affects Social Lives

As a consequence of the impact of acne, many patients express that this has an effect on their social behaviour, including how their mood affects the way they present themselves to the world, withdrawal from social activities, concerns about forming relationships and fear or experiences of being bullied.

Acne Highs and Lows

Acne patients experience emotional highs and lows. Emotional highs include: when acne is relatively quiescent; after (initially) seeing a physician or getting referred to a dermatologist; when starting a new treatment; and when treatments (begin to) work. Lows include: when acne is flaring or gets worse and seriously impacts the patient's life; when meeting new people or having to attend social events; just before finally seeing a physician; when needing to keep seeing physicians; and when treatments do not work, especially prescription treatments.

Improving the Connection Between Patients and Physicians

Brigitte Dréno
(Nantes, France)

Knowing the Acne Patient

The key to meeting the expectations of the acne patient is to know him or her better and to try to understand his or her fears and/or feelings, as what the acne physician sees does not always match the acne a teenage patient sees. This is demonstrated by a French study in which, between November and December 1996, an epidemiological survey of acne in secondary schools was performed.[3] In total, 913 adolescents between 11 and 18 years were questioned and examined.[3] Although 52% said they had acne, medical examination showed that, in fact, 72% had acne.[3] A similar discrepancy has been found in other studies,[4] demonstrating that there is a gap

between the dermatologist's clinical definition of acne and the young patient's own perception of the disorder.

To understand the acne patient, it is important to observe young people in their natural environment, without any medical context. For example, in a study published in 2007, a questionnaire focusing on perceptions of acne was completed by 1,566 subjects calling a youth helpline.[5] It showed that 51% of respondents with acne did not seek medical help. Further, acne has as big a psychological impact as some far more severe diseases and many respondents with no history of acne said they were very worried that they would develop this skin disorder.[5] This underlines the major psychological impact of acne and shows that young people need to be informed so that acne can be treated.[5]

What do Acne Patients Think About Acne?

In a further study, in which 852 adolescents aged 12 to 25 years were surveyed about their knowledge of acne and its treatment in a non-medical context, it was considered a normal phenomenon caused by puberty by many patients and many thought it disappeared spontaneously. Also, many thought that gender, excess weight, eating dairy products and physical activity did not influence acne, and that frequent washing could improve acne.[6] The majority (80.8%) did not believe acne to be a disease, but rather a normal phase of adolescence, yet 69.3% agreed it should be treated.[6] There was also a preference for topical over systemic treatment.[6] Many (38.6%) of the respondents with acne had not consulted a physician.[6]

Knowing the Acne Patient – Crucial Messages

Patients do not always feel the need to be treated. The results of the 2007 study revealed that one-third of young people reporting severe acne did not consult a physician.[5] Reasons cited for not consulting a physician were that the patient did not see the need (35%), fear (12%), neglect (17%), patient did not know who to consult (10%), cost (6%) and that the patient did not ask parents (20%).[5]

The physician is not the only resource for acne patients and the likelihood of seeking treatment increases with greater severity of acne. In response to the question, "Have you ever been treated (for acne), either currently or previously?", globally, only 41% said they had followed a medical prescription, but of those patients with severe acne, 59% had followed a medical prescription.[5] Thirty-seven per cent of respondents with mild acne received no medical treatment, compared to 15% of respondents with severe acne.[5] The perceived severity of acne also correlated with the feelings it provoked, it was found, with "angry", "anxious" and ashamed" being the words most frequently associated with acne.[5]

Acne Affects the Daily Lives of Patients

Acne also has an effect on the daily lives of patients, with more severe acne having more of an effect on daily activities, relationships with friends, boyfriends and girlfriends, and leisure activities. But even mild acne can impact patients' daily lives.[5] Furthermore, teenagers without acne were found to have a negative opinion of those with acne and 53% of teenagers without acne said they were very uncomfortable with the idea of having acne.[5] Sixty-nine per cent also perceived that acne interferes with activities with friends.[5]

Understanding What is Good Adherence for an Acne Patient

Understanding adherence is also important in deciding how best to meet the expectations of patients.[7] A worldwide survey by the Global Alliance published in 2010 found that, of 3,339 patients, 1,675 (50.2%) had poor adherence.[8] The survey also found that poor knowledge about treatment was associated with risk of poor adherence. Solutions to this could include patient education, which is probably one of the best methods to increase the success of acne treatment.[8]

Knowing how Society Considers Acne Patients

Knowing how society considers acne patients is also integral to ensuring that the expectations of patients are met. Two separate online surveys were conducted with the American Acne and Rosacea Society, in which 1,002 teenagers aged between 13 and 17 years and 1,006 adults over the age of 18 were asked about their impressions of images of teenagers with clear skin and images that were digitally enhanced to simulate acne.[9] Each respondent reacted to three randomly selected pictures, with the only condition being that it was a combination of either one clear and two acne pictures, or two clear and one acne pictures.[9] With respect to impressions of photo images, the first thing teenagers and adults noticed about a person with acne was their skin (65% and 75%, respectively). Teenagers with acne were perceived most often by other teenagers and adults (teenaged responder %, adult responder %) as being shy (39%, 43%), nerdy (31%, 21%), stressed (24%, 20%), lonely (23%, 22%), boring (15%, 6%), unkempt (13%, 7%), unhealthy (12%, 8%), introverted (9%, 23%) and rebellious (7%, 5%).[9] Most teenagers with acne (64%) felt embarrassed by it and thought that getting acne was the most difficult aspect of puberty (55%).[9] Teenagers with acne reported lower self-confidence or shyness (71%), difficulty finding dates (43%), problems making friends (24%), challenges with school (21%) and trouble getting a job (7%). Ritvo *et al.* concluded from these results that acne has a negative effect on the way people are perceived by others.[9]

How Acne Patients are Seen by Others

The results of these studies show that people judge others by their physical appearance. Teenagers with acne are also perceived differently to those without. They are seen as being more shy, less confident, less intelligent and popular, lonely, less fun, less socially active and less prepared for the future. It is clear from this evidence that acne is a chronic disease that can have physical, emotional and psychological implications.

Understanding the Patient

Jerry Tan

(Ontario, Canada)

The Patient-physician Encounter: A Meeting of Two Experts

The meeting of doctor and patient at a consultation is a meeting of two complementary but disparate perspectives. In this meeting of experts, doctors are considered experts in disease and management while patients are experts in their illness experience, and in their preferences for treatment, health states, and outcomes.[10] Informed shared decision making reflects this convergence of patient experience and values with the clinical expertise of physicians around the central ethic of patient autonomy.[11]

In most skin disorders where impact of disease is not measurable in easily objectified metrics such as loss of work time, days of hospitalisation or mortality – the adverse impact of skin disease on patient QoL is of paramount importance. Knowledge of this impact is only available by inquiry and patient disclosure.

Divergent Perspectives

However, research has demonstrated that, in consultations, doctors and patients can have divergent perspectives, and that doctors infrequently inquire about dimensions of illness beyond measurement of disease severity. Studies on the conduct of clinical consultations have documented deficiencies including physician dominated interactions, absence of physician encouragement for patients to express their views, active inhibition or evasion of patient questions by doctors, infrequent probing of patient understanding and knowledge, and absence of tailored advice based on individual patient circumstances. In particular, physicians presume knowledge of patient preferences – therefore, they do not inquire, or think such knowledge unimportant.[10, 12]

Whereas dermatologists judge clinical severity of acne by lesion type, lession counts, extent of acne and scarring; the patient who experiences acne may perceive symptoms, emotional dysfunction, and issues with socialisation and self-perception. My coauthors and I found that, in the almost 900 acne subjects surveyed, those most severely affected clinically were males, tended to be younger (teen years) and had shorter durations of acne. In contrast, those most severely impacted as measured by psychosocial dimensions (emotions, self-perception, socialisation and symptoms) were females, tended to be beyond teen years, and had longer durations of acne.[13] Thus, those who were most severely affected by clinical assessment were not those most impacted in terms of quality of life. This disparity underscores the importance of inquiry for psychosocial impact as it cannot be inferred from clinical measures of acne severity grading.

Harmonising Perspectives – Informed Exchange Between Patient and Doctor

Harmonising these divergent perspectives involves both process and content. There is an inferred power imbalance in medical consultations – where doctors are considered as experts in disease and its management and patients are those seeking their medical intervention. Accordingly, patients may feel that their perspectives and experiences may be less important in contrast to the technical expertise of doctors. Informed exchange, however, requires both parties to recognise the importance of each other as experts – and potentially uninformed of their counterpart's perspectives. Given the implied power disparity, it is the physician who can establish the tone of the encounter to recognise the importance of this information exchange: encouraging patient input about impact of acne, their specific values (what is important to them) and preference to adequately inform their doctors. Engaging patients by welcoming their account of experiences with empathy, offering hope, extending a commitment to care and achievement of mutually established outcomes can help to establish the therapeutic partnership.

Illness Impact – Quality of Life Instruments

There are six acne-specific quality of life (QoL) questionnaires available, with lengths ranging from four to 48 items. These instruments include the Assessment of the Psychological and Social Effects of Acne (APSEA), the Acne Disability Index (ADI), the Cardiff Acne Disability Index (CADI), the Acne Quality of Life Scale (AQOL), the Acne Quality of Life (Acne-QoL) and the four-item index of Acne-QoL (Acne-Q4).

Are Quality of Life Scales Reliable?

QoL scales may be more reliable than dermatologist-determined acne severity. A study to determine the reliability of acne lesion counting and global severity assessments when performed by trained dermatologists found that dermatologists tended to be reliable in acne lesion counting but less so in global assessments.[14] Eleven dermatologists were divided into two groups that evaluated the same six acne subjects twice on the same day. A training session was provided either after (group A) or before (group B) the first patient evaluation sessions. The reliability of raters in lesion counting and global severity assessment was determined by calculation of intraclass correlation coefficients (ICCs). Where ICC of 1 represent perfect reliability, intrarater ICC's raging from 0.37 to 0.99 for non-inflammatory lesions, 0.26 to 0.97 for inflammatory lesions and 0.56 to 0.83 for global assessments (group A); and 0.84 to 0.98, 0.61 to 0.95, and 0.43 to 0.91 (group B). Interrater ICCs for groups A and B after the first evaluation session were 0.17 versus 0.68 for non-inflammatory counts, 0.84 versus 0.72 for inflammatory counts, and 0.71 versus 0.65 for global assessments, respectively. Corresponding values after session 2 were 0.79 and 0.77 for non-inflammatory, 0.81 and 0.90 for inflammatory, and 0.61 and 0.77 for global assessments. In contrast, the reliability of patients in QoL measures is routinely high: the ADI (Acne Disability Index) was found to have a reliability estimate of 0.96, the CADI (Cardiff Acne Disability Index) 0.98, the AQOL (Acne Quality of Life) 0.98, Acne-QoL 0.84, and the Acne Q4 index 0.97.

In summary, as a measure of acne severity – patient reporting of impact is more reliable than dermatologist determination of acne severity grade.

Are Quality of Life Scales Practical?

While full QoL scales with multiple items may impede the workflow of a busy clinic, there are two acne QoL instruments that comprise only a few items. For example, the CADI has five items regarding acne, based on whether the patient has been aggressive, frustrated or embarrassed; whether the disease has interfered with daily social life, social events or relationships with members of the opposite sex; whether the patient has avoided public changing facilities or wearing swimming costumes because of acne; how the patient would describe his or her feelings about the appearance of their skin over the last month; and how bad he or she thinks the acne is now.[15] Even more brief, the Acne-Q4 has four items, referencing facial acne over the past week: feeling upset about acne; dissatisfied with his or her appearance because of acne; concern about meeting new people due to acne; and concern about scarring from acne. These were selected as they represented items of greatest patient-perceived importance.[16]

Risk of Scarring Increases with Delay in Acne Treatment

The likelihood of scarring increases with delay in acne treatment. In a study of 185 acne patients, Layton *et al*. reported that the degree of facial scarring was correlated with the length of time until adequate treatment of acne, with longer delays leading to a higher prevalence of scarring.[2] Their results indicated that facial scarring affects both sexes equally and occurs to some degree in 95% of cases. A time delay of up to three years between acne onset and adequate treatment related to the ultimate degree of scarring. This emphasises the need for earlier adequate therapy in an attempt to minimise the subsequent scarring.

A larger study performed almost a decade later confirmed those results.[1] In a cohort of almost 1,000 acne patients, the likelihood of acne scarring increased with longer duration of disease. In that study, a six-category global severity scale (SCAR-S) was developed for assessment of acne scarring. Of these patients, with primarily mild to moderate acne, the prevalence of acne scars was 87%. Overall, 55% had acne scars that were clinical relevant (mild or greater severity) at the face, 14% at the chest and 24% at the back.

These data collectively emphasise the goal of early treatment and education of patients.[1, 2]

Acne Scars Can Develop Rapidly

New data show that acne scars can develop rapidly. In 2010, Kang *et al*. conducted a study utilising digital photography and computerised superimposition of images to evaluate the presence of acne lesions and scars on specific skin sites over time in patients with mild to moderate acne.[17] In that study, acne scars were observed to arise within just 12 weeks, a finding that dispels the conventional thinking that acne scars are slow to develop.[17] In addition, scars arose from all types of acne lesions and even normal-appearing skin (implying involvement of the microcomedo).[17] This finding was quite surprising, since there is a perception that scars arise from only inflammatory lesions. However, it should be noted that the 1994 study by Layton also found that scars could arise from a variety of acne lesions, including relatively mild and superficial inflammatory lesions.[17]

Practical Measures of Acne Severity and Impact

The validated tools presented here are pertinent to clinical practice as they are time efficient, and practical and straightforward to apply. The Comprehensive Acne Severity Scale is simple to learn and includes the most relevant areas affected by acne. Specifically, it uses a six-category global severity scale (clear/almost clear/mild/moderate/severe/very severe) applied to each of the face, chest and back.[1] Acne-Q4 and CADI are brief QoL indices focused on the relevant domains of illness impact in acne.

Improving the Connection Between Patients and Physicians – Talking with Cassandra

Cassandra is a model and online personality in the US. She has connected with acne sufferers through many media outlets to talk about her experiences with acne and share skincare tips. Cassandra's acne developed early, in elementary school, and was alone among her fellow students in suffering with the disease. Starting on her face, her acne became progressively worse through middle and high school until it covered her chest and her back.

The main issue Cassandra faced was psychological, as she found as she not only felt bad about the way she looked, but she also faced being stared at and commented on in her daily life. Cassandra describes how feeling that people did not perceive her in the way they used to made her feel self-conscious. She describes feeling traumatised at developing acne in elementary school and she began trying to treat it by using topical creams available over the counter. She then sought professional help and, by the time she had reached middle school, she had seen 12 different dermatologists. She describes feeling that she was always getting "run-of-the-mill" treatment from them and not really being taken care of as an individual, just being handed a prescription for medication and told that "it would work". But unfortunately, at that point, nothing had worked.

Cassandra dealt with the issues her acne caused by switching to private study, which isolated her from other peers and students. However, studying at home gave her the opportunity to research and understand her skin better from a non-professional perspective. It was at this point that she started blogging and sharing tips and tricks to covering the acne with make-up, and experimenting with cutting out certain foods such as dairy to see what worked, and sharing her findings with her followers.

Regarding her experiences with seeing dermatologists, as a patient Cassandra felt that, although the professionals she saw were

experienced and knowledgeable, when a treatment did not work for her, she felt disheartened and hopeless. This sense of hopelessness contributed to the overall emotional and psychological impact the acne had on Cassandra, as well as being commented on or treated differently by others, whether she was wearing make-up or not.

Given the choice, Cassandra says she wishes that her doctors had taken more time to understand her personal track record: what had worked for her and what had not and which treatments she felt comfortable with. Cassandra perceives that are some common concerns among her online followers, in that acne sufferers often do not feel they are being taken care of by their doctors and that the doctor does not have a connection with him or her, in regard to their feelings and their preferences for treatment.

Providing support and connecting with the acne patient is therefore clearly an important aspect of treating him or her, however, in clinical practice, there is a high demand for acne care and low supply in terms of time and resources available. One option to tackle this may be the use of nurse counselors, as nurses have a wealth of caring expertise and can help the patient to open up and to feel more comfortable, asking the patient direct questions to get to the specific issues the patient is facing. This would then enable the doctor to have a better understanding of the patient's concerns and experiences.

Outside of medical care for acne, non-medical care includes covering of the acne with make-up as a way to cope with the psychological discomfort of acne which persists during the three months or so that most acne medications take to work. Although this is an effective way for the patient to cope with the acne during the recovery period, patients should be educated about make-up, for example, using non-comedogenic make-up and ensuring make-up is thoroughly removed at night. This could be an important part of the role of the nurse practitioner, who could explain this directly to the patient.

Practical Solutions from a Dermatologist's Perspective

Alison Layton
(Nantes, France)

Improving the Patient Experience

Time at consultation with opportunity for discussion is crucial to improving the patient experience. Clinicians should be good educators and counsellors about the different kinds of acne treatments, they should also be approachable – warm, empathic, non-judgemental and non-dogmatic – motivational and positive about the outcome and belief in therapy.

Nurse-led clinics have also been shown to result in a positive outcome.[18] In a study by Courtenay *et al*., semistructured interviews were undertaken with a consecutive sample of 42 patients with acne, psoriasis or eczema who attended the clinics of seven dermatology specialist nurse prescribers. The responses in the interviews showed that patients believed that nurse prescribing improved access to, and efficiency of, dermatology services. Also, the nurses' specialist knowledge, interactive and caring consultation style, and continuity of care improved the patients' confidence in the nurse and treatment concordance.[18]

Make Time for Education – Involve Staff

Patients indicate that they have little knowledge of acne and treatment (n=1,149).[19] When asked the question "How much do you know about acne?", five per cent (n=54) responded that they knew nothing and 40% (n=458) knew "a little". In response to the question, "How much do you know about anti-acne treatments, 9% (n=99) said they knew nothing, while 45% (n=522) knew "a little".[19]

Innovative Ways to Improve Education

Innovative ways to improve education include dispelling myths in terms of what patients believe is causing their acne or may be making their acne worse; using written information, using visual aids, demonstrating practically how to use treatment and using photography to identify lesions and assess progress. Photometric grading scales in clinics can also be used, as can algorithms to tailor treatment to disease severity. Graphics to explain the pathogenesis and actions of anti-acne treatments and IT (websites) are also useful tools.

Use Photos to Set Expectations

Photographs taken at each consultation can help reinforce improvement to treatments. In clinical trials more sophisticated digital imaging has been used. A randomised, vehicle-controlled, multicentre, double-blind study by Gold *et al*.[20] which evaluated the efficacy and safety of a fixed-dose combination gel with systemic antibiotic in the treatment of severe acne, used a digital ultraviolet fluorescence photography. The study demonstrated a rapid reduction in Propionibacterium acnes particularly within the first four weeks using this novel technique.[20]

Acne Treatment Algorithm

Acne treatment algorithms have been developed to demonstrate best practice and to take advantage of newer products.[21] Sharing this information with patients can help to engage them in successful management.

Set Expectations by Explaining Therapeutic Time Ladder

Providing patients with realistic expectations about treatment response is important.

The therapeutic time ladder, as described by Cunliffe *et al*,[22] shows expected improvement rates in moderate to severe acne with daily long-term antibiotic therapy (median 78% after six months). Adopting regimes that work more rapidly is more acceptable to patients. Clinical trials using fixed combination therapy alongside

antibiotics have demonstrated more rapid efficacy.

Gold *et al*.[20] reported that using a fixed-dose combination gel with an oral antibiotic in the treatment of severe acne vulgaris resulted in efficacy as early as week 2 compared with the vehicle arm.

Simplify Routines Even With Moderate-to-Severe Acne

It is important to simplify treatment routines for patients, as this will make it easier for the patient in their everyday lives. Fixed combination products are not only efficacious, but may also improve adherence. The results of a 2009 study by Gollnick *et al*. in which 1,670 subjects were randomised in a double-blind controlled trial to receive a fixed-dose combination, individual constituents as monotherapy or vehicle for 12 weeks revealed that the fixed dose combination was significantly more effective than corresponding monotherapies, with significant differences in percentage lesion count change observed as early as one week.[23]

Patient Associations and Groups

Public and patient involvement is important in education and patient experience groups, patient user groups and information technology/ social media all have a role to play, as do websites such as: http://www.acneacademy.org/.

Improving the Patient Experience

Improving the patient experience is about identifying the impact of acne, addressing psychosocial issues, assessing QoL – which can be easily achieved by using a simple QoL scale such as the Acne-Q4 in daily practice – and recognising psychosocial impact. Also important to consider are the economic implications (always evaluating the efficacy ratio), and ensuring treatments are affordable, for example, giving patients three or four different treatments may not be viable in terms of the patient's economic status. Provision of cosmetic advice and camouflage also has a significant impact on patient experience.

Areas in which improvement can be made in acne clinics include access to psychological support, better access to IT and informatics, changes in the perception of acne, more research and more patient user groups, improving the interface between patient experience and clinical research.

The perspective of the doctor and the patient can be different and the patient-doctor relationship is crucial to ensure that patients receive the optimal treatment. In conclusion, improving the patient experience means putting them at the heart of their care.

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Improving Patient Outcomes in Actinic Keratosis: Insights and What Matters to Patients

Introduction

The satellite symposium titled, "Improving Patient Outcomes in Actinic Keratosis: Insights and What Matters to Patients" was held during the 21st Congress of the European Academy of Dermatology and Venereology on Friday 28th September 2012 in Prague, Czech Republic. The meeting was chaired by Professor Jan Simon from the Department of Dermatology, Venereology and Allergology, Philipp-Rosenthal-Straße, Leipzig, Germany.

Background

Actinic keratoses (AKs) are the initial epidermal lesions in a disease continuum that arises in UV damaged skin and may progress to invasive squamous cell carcinoma (SCC). Unfortunately, it is not possible to predict which lesions will progress into an invasive form. Therefore, early detection and effective treatment of all AK lesions is critical. Interest in novel diagnostic techniques and effective treatment options has risen over the last few years. This satellite symposium highlighted some of the most recent advances in AK (in relation to technology and treatment options), while considering the patient's perspective of their disease.

Improving Patient Outcomes in Actinic Keratosis: Insights and What Matters to Patients
Almirall Sponsored Satellite Symposium at the European Academy of Dermatology and Venereology (EADV) Congress, Prague, Czech Republic, 28th September 2012

Chair: Jan Simon, Department of Dermatology, Venereology and Allergology, Philipp-Rosenthal-Straße, Leipzig, Germany

Welcome by the Chair
Jan Simon, Department of Dermatology, Venereology and Allergology, Philipp-Rosenthal-Straße, Leipzig, Germany

Applying Technical Advances to Improve Diagnosis and Management of Actinic Keratosis
Giovanni Pellacani, University of Modena and Reggio Emilia, Italy

Engaging the Patient to Optimise their Treatment of Actinic Keratosis
Uwe Gieler, Head of Department of Dermatology and Clinic for Psychosomatic Medicine, Justus-Liebig-Universität Gießen, Germany

Field-directed Treatment
Jean-Jacques Grob, Department of Dermatology and Skin Cancers, Aix Marseille University, Hôpital Timone, France.

Approaching Single Hyperkeratotic Actinic Keratosis with a Topical Treatment
Jan Simon, Department of Dermatology, Venereology and Allergology, Philipp-Rosenthal-Straße, Leipzig, Germany

Applying Technical Advances to Improve Diagnosis and Management of Actinic Keratosis

Giovanni Pellacani,
(University of Modena and Reggio Emilia, Italy)

Actinic Keratoses are proliferations of transformed, neoplastic keratinocytes that are confined to the epidermis. They may develop into intra epidermal carcinoma (IEC) and finally invasive SCC. A progression model describes the dermatological features of AK lesion development as grades I, II or III in the continuum of the disease.[1]

Accurate clinical diagnosis of AKs is difficult and often suboptimal, even for experienced clinicians. Dermatoscopy and *in vivo* reflectance confocal microscopy (RCM) are imaging techniques that are currently used in clinical practice and research for the diagnosis and management of AKs. Dermatoscopy allows viewing of features that are not visible with the naked eye. The key diagnostic features of AKs detectable by dermatoscopy include the presence of tiny surface scales indicating hyperkeratosis, identification of the red pseudonetwork (also called the strawberry pattern) that is representative of the pattern of progression of AKs and prominent hair follicles possibly with a yellow central keratin plaque and surrounded by a white halo. The white halo, or white starburst pattern, may indicate more rapid evolution of AKs. Small red dotted vessels that are a marker of Bowen's disease are also visible using dermatoscopy.[1, 2]

Reflective Confocal Microscopy is a new noninvasive imaging technique that enables visualisation of cells and structures in living skin in real time with resolution close to that of histological analysis. RCM generates images of dark and bright structures in the skin, and represents them as thin sections of horizontal tissue *in vivo*. When viewing the skin using RCM, the keratinocytes in normal skin have a regular honeycombed pattern. However, in AKs there is disruption of the stratum corneum and the keratinocytes

have an irregular honeycombed pattern. The features of AK detectable by RCM also include parakeratosis, architectural disarray and keratinocyte pleomorphism and esocytosis.[3, 4] The features of SSC that are detectable by RCM include the presence of an atypical honeycomb or a disarranged pattern of the spinous granular layer, round nucleated cells at the spinous granular layer and round blood vessels traversing through the dermal papilla.[5]

Reflective Confocal Microscopy is a useful tool for the grading of AK lesions.[6] The grade I AK histopathological features visible using RCM include the presence of keratin, scale, esocytosis and irregularly shaped keratinocytes with hyporeflective nuclei. Grade II features include irregularly shaped keratinocytes with hyporeflective nuclei and increased cell pleomorphism. Grade III features include marked keratinocyte pleomorphism and the presence of picnotic nuclei.

In summary, dermatoscopy offers the possibility of accurate diagnosis of AK. It allows the characterisation of some morphological aspects of AK that enable subtype classification and may be correlated with biological behaviour. RCM removes the need for biopsy and is a promising tool for clinical diagnosis and monitoring of treatment at a cellular level. It enables the grading of AKs and allows the identification of lesions at higher risk to progress into an SCC. A combination of dermatoscopy and RCM imaging techniques enables the optimal diagnosis and management of AK.

Engaging the Patient to Optimise their Treatment of Actinic Keratosis

Uwe Gieler

(Justus-Liebig-Universität Gießen, Germany)

The social life scores obtained from the Freiburg Life Quality Assessment (FLQA), a quality of life (QOL) questionnaire for patients with skin disease, suggest that skin cancer patients have a higher QOL than most other skin disease patients. However, this may not reflect the true picture, as the questionnaire is not specifically tailored to address patients with skin cancer. Clinical experience with these patients suggests that they do in fact suffer significant impairment to their QOL.[7, 8]

Actinic Keratosis is considered a chronic condition and requires long term management. Clinicians should be alert to the potential impact of the disease and its treatments on the emotional health of their patients. Some patients may appear to be coping well, but still suffer anxieties that may impede the successful management of their condition. Additive therapy (laser treatment, surgery, topical treatment) affects approximately 20% of patients with skin cancer, with patients having difficulties adjusting to their condition and its treatment, as well as experiencing significant levels of psychological distress.[9] The sympathetic and neuroendocrine responses to stress can lead to alterations in inflammation, tumour growth, progression and metastasis, each of which can impact on the outcomes of cancer treatment.[10] Approximately 1/3 of patients with chronic somatic conditions have slight to severe psychological adjustment problems, and related generic or disease-specific, cognitive-behavioural risk factors. These risk factors are, in turn, predictive for worse long term physical and psychological functioning.[11]

The anxiety level an AK patient is likely to experience does not remain stable over the course of the disease. On diagnosis of AK, there is a sharp rise in the level of anxiety that lowers after surgery, when an improvement is seen. However, anxiety rises again each time a change occurs. Recognition that patients may be suffering stress and the provision of timely support is known to improve adherence to treatment.[12]

The signs of psychological stress in patients that doctors should particularly note include: anxieties about life perspectives, restlessness, chronic fatigue, high exhaustion, depressive mood, suicidal ideation, social avoidance behaviour and sleeping disorders. Research suggests that the suppressive effect of chronic stress on cellular immunity may be partly negated if support of sufficient length and intensity is made available to patients.[13]

A stepwise care approach of screening and then tailoring treatment can be used to manage chronic conditions such as AK. Screening patients with a standardised questionnaire assessment enables those at risk, who could benefit from individualised psychosomatic treatments, to be identified at an early stage.[11]

Dermatological treatment may be considered to have two arms. The first is where the focus is on the understanding of necessary treatment options, establishment of evidence based treatment and ensuring compliance. The second focuses on good communication, the satisfaction of the doctor/patient partnership and increasing the patient's QOL.

The challenge of engaging patients to optimise their treatment with AK may best be undertaken by keeping them involved in treatment decisions at every stage. This includes checking that patients understand and agree with their treatment, asking them about their anxieties and fears about cancer and explaining carefully the need for treatment. Patients should be encouraged to repeat what they have been told to ensure they understand clearly, and to talk about problems and long term follow up. Clearly the establishment of a high quality relationship between the doctor and patient is a key factor for in the long term management of AK.

In summary, clinicians require excellent communication skills with an ability to actively listen and show empathy with their patients. A shared decision making approach between clinicians and patients should facilitate the optimum management of AK.

Field-directed Treatment

Jean-Jacques Grob

(Hôpital Timone, France)

The concept of what AKs are and how they should be treated has

evolved over time. AKs were once thought of as a dysaesthetic problem of the ageing skin that should possibly be left untreated. Then they were considered to be low risk precursors for SCC with 65% of SCC arising from pre-existing AK lesions.[14] Although only a few AK lesions transform into SCC, it is still not known which AKs are high risk precursors of SCC (annual risk of SCC ranging from 0.15% to 80%) or when they are likely to transform. Deciding which AKs to treat and which lesion directed treatment (Cryotherapy; laser therapy; curettage, 5-flurouracil (FU); diclofenac/ hyaluronic acid (HA), imiquimod and lesion directed photodynamic therapy [PDT]) has been a challenging problem in the management of AKs.

Actinic Keratoses are now considered as early *in situ* SCC and should be treated. They are believed to be the visible and transient manifestation of a widely spread invisible keratinocytic epithelial disease. This has led to the concept of subclinical AKs and a cancerisation field, and posed new questions about the rationale for treatment. Field directed approaches are primarily used to clear multiple AKs and subclinical lesions and offer an additional strategy to lesion directed treatment.

The evidence for the field cancerisation of AKs may be seen from extra-cutaneous models of field cancerisation (oesophagus, bladder), clinical evidence ('moving' AKs and PDT revealing invisible AKs) and the molecular evidence of field cancerisation in normal sun exposed skin. This includes P53 expression, mitochondrial DNA mutations and infrequent increased signalling (RAS, bcl2). The risk of SCC may increase more in patients with many AKs. Also AKs and SCC have arisen in patients with melanoma treated with B-RAF inhibitors.

An argument in favour of field directed treatment is the advantage of treating more than just the visible part of the disease, as in lesion directed treatment. This is especially relevant with an increasingly aging population who are more at risk of field cancerisation. Although, it is important to remember that the individual risk of metastatic SCC remains low.[15]

The five treatments with different modes of action approved for AKs and currently proposed for a field directed approach in the EU[16] are shown in Table 1. These treatments have yet to be validated for a field directed approach.

A candidate treatment under consideration for a field directed approach for AKs needs to fulfil predetermined evidence based criteria. These include preconditions, conditions and demonstrations of effectiveness.

The preconditions require that the mechanism of action of the candidate treatment should be compatible with an effect on the early step of field cancerisation, there should be an immediate efficacy documented on the visible expression of field cancerisation (a reduction in the number of visible AK lesions), the treatment should be applicable to a large area and finally it should have a tolerance profile compatible with long term use.

The conditions should provide evidence that the treatment's action is not limited only to visible AKs and that the activity is not only short term.

The effectiveness of the proposed treatment should have been demonstrated in a randomised controlled trail (RCT) with relevant outcomes in the very long term (>5-10 years).

Diclofenic/HA is a candidate treatment for field directed treatment in AKs. Its use in AKs is well documented in 18 studies that include two RCTs versus a placebo and three open label comparative studies (two studies versus imiquimod and one versus 5-FU).[17]

Diclofenac/HA meets most of the criteria for field directed treatment in AK. It has a mechanism of action compatible with an effect on the early step of field cancerisation,[18, 19] and is an inhibitor of

Topical and physical treatments	Mode of action
Diclofenac in hyaluronic acid gel	Inhibition of COX-2 and angiogensis Induction of apoptosis
5% 5-FU ointment	Topical chemotherapeutic antimetabolite that destroys clinical foci via interference with DNA and RNA by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid
Imiquimod	Binds to toll-like receptor-7 and -8 inducing interferon-α Generation of a non-specific immune response and induction of apoptosis
PDT	Acts through the selective destruction of atypical keratinocytes (depth of penetration 3-4 mm) through light activation of a photosensitiser in the presence of oxygen
Chemical Peels	Topical applied wounding agents creates smooth, rejuvenated skin by an organised repair process and exfoliation

Table 1. Treatments approved for AK and currently proposed for field directed approach[16]

cyclooxygenase-2 (COX-2), which mediates prostaglandin E_2 synthesis in AK and SCC. A recent study suggests its role in the activation of the mitochondrial apoptosis pathways is at the level of Bcl-2 proteins.[20]

Indirect evidence of immediate efficacy documented on the visible expression of field cancerisation is provided by a number of studies in which efficacy was measured after 90 days of therapy and at 30 days follow up. These studies demonstrated that diclofenac/HA had immediate efficacy.[21-27] In addition, when using diclofenac/HA, clearance of AK lesions increased over time, even after treatment was stopped.[23] Organ transplant recipients (OTR) with immunosuppression have a 50-250 fold higher risk of developing AK and invasive SCC. A RCT study found that, at 4 weeks post treatment, OTRs receiving the active treatment of diclofenac/HA had a 53% reduction in lesion count from baseline vs. a 17% increase for the placebo group. This suggested that diclofenac/HA is an efficient and well tolerated treatment for multiple AKs in OTR.[28]

The applicability of Diclofenac/HA to a large area is well documented. It has been used in clinical practice for treatment of single and / or multiple AK in different anatomical locations with diverse[24, 29-31] and extensive surface areas (50-80 cm^2).[29, 31]

Diclofenac/HA is usually well tolerated by patients without needing to interrupt treatment.[24, 29-32] even in the immunosuppressed population.[28] Any local skin reactions that occurred were characterised mainly by erythema, pruritus and dryness.[21, 22]

Evidence that the treatment activity is not limited to visible AKs has been provided by an assessment of the "cumulative lesion number score", which includes target as well as new lesions in a designated area. Improvements in this score with diclofenac/HA have been seen up to 3 months.[23] This evidence is supported by two additional studies in which no new AK lesions were identified through the course of the study (n=28) after 24 months,[30] and no reoccurrence in 45% of those who responded to treatment.[24]

There is some evidence that the activity of diclofenic/HA is not only a short term effect, with demonstrated longer term clearance over 1 year.[30] In addition, in the OTR model (50-250 fold higher risk for developing AK and invasive SCC), 63% of patients not receiving diclofenac/HA developed AK (stages II and III), 5% developed Bowen's disease, and 15% and 21% developed invasive SCC and basal cell carcinoma, respectively.[33] Of those receiving treatment 4/9 of those who completely responded to treatment had no reoccurrence.[28]

RCTs for any field directed strategy for currently available treatments or those in development using new SCC development as the primary outcome with >5 years of follow up are yet to be published

In summary, field directed treatment may be the right approach for UV induced keratinocytic epidermal disease. A number of strategies are candidates for treatment. Diclofenac/HA fulfills the majority of criteria required of an appropriate drug candidate for a field directed approach to treatment. However, very long term follow up data with new SCC developing as a primary outcome is still lacking for any drug.

Approaching Single Hyperkeratotic Actinic Keratosis with a Topical Treatment

Jan Simon

(Philipp-Rosenthal-Straße, Leipzig, Germany)

The combination of low dose 5-FU (0.5%) and salicylic acid (10%) in a cutaneous solution (5-FU/SA) is a new treatment option for AK now available in Germany, Switzerland and the UK (the licence is pending in the Czech Republic).

5-FU/SA is indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic AKs in immunocompetent adult patients (clinical grades I and II according to Olsen). It is applied once daily with an easy brush.[34]

The product profile specifies that 100 g of solution also contains the excipients dimethyl sulphoxide, ethanol, ethyl acetate, pyroxyline, poly (butyl methacrylate, methyl methacrylate). The pharmaceutical formulation is a film forming lacquer.[34]

The proof of concept pilot study demonstrated that low dose 5-FU/SA used as a topical treatment of AK was well tolerated and efficient.[35]

Evidence supporting the licence is from a randomised, double blind, Phase III study that compared 5-FU/SA with the cutaneous solution vehicle and with diclofenac 3% gel in patients with AK.[36] This study included 470 adult patients randomised in a 2:1:2 ratio to treatment with 5-FU/SA once daily, diclofenac/HA gel twice daily or vehicle (solution) once daily. Treatment was continued until complete clearance of lesions or for a maximum of 12 weeks.

The results showed that in the low dose 5-FU/SA, diclofenac/HA and vehicle groups, respectively, there was complete histological clearance in 72·0%, 59·1% and 44·8% of patients, and clinical healing of target lesions (mean per patient, 20 week follow up) in 76%, 57% and 36% of patients.

When using low dose 5-FU/SA, there was 72% complete histological clearance, 76% reduction of target lesions and a 91% reduction of the lesion area. 92% of the investigators rated the clinical efficacy as very good / good. At the post treatment visit 93.2% of patients also rated clinical improvement as very good or good. There was sustained clinical clearance of 92% at 6 months and 86% at 12 months. With regards to the safety and tolerability of 5-FU/SA no systemic 5-FU levels were measured. 92% of patients had reactions at the

application site that were considered to be mild (24%), moderate (41%), or severe (28%). At week 20, 70% of investigators rated treatment as either very good or good. Overall there was good tolerability and high patient satisfaction with 94.7% of patients reporting they would recommend treatment with 5-FU/SA. It was easy to apply and there was a high compliance rate of 85%.

Preliminary results from an exploratory, open, prospective, two armed Phase III study designed to investigate 5-FU/SA versus cryotherapy for the treatment of AK are available.

Subjects were randomised to receive either 5-FU/SA applied once daily, 7 days a week for 6 weeks (a dose reduction to 3 days per week was possible if a patient experienced adverse events) or cryotherapy performed on Day 1 (a second cryotherapy could be performed at 3 weeks if considered necessary by the investigator). Final follow up will be at 6 months. The interim analysis of histological clearance of AKs at 98 days suggests 5-FU/SA may be superior to cryotherapy (62% and 42% of patients, respectively).

Evidence from two case studies also illustrates the effectiveness of low dose 5-FU/SA for lesion directed treatment for AKs in clinical practice.

In conclusion, AKs have been classified as early in situ SCCs and should be treated. Topical low dose 5-FU/SA has demonstrated sustained clinical efficacy when compared to diclofenac/HA and has an acceptable level of tolerability and good patient satisfaction.

Disclaimers

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Potential for Missing Pregnancies in Patients on Isotretinoin

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Background

Acne vulgaris (hereafter referred to as acne) is a common, chronic inflammatory dermatosis of the pilosebaceous units, predominantly affecting the face. Acne usually starts in adolescence, with approximately 20% of sufferers seeking medical help,[1] and typically resolves by the mid-20s.[2] Factors underlying resolution are not fully understood and clinically significant acne may persist in up to 20% of patients; this shows a strong family history.[3]

Isotretinoin

Isotretinoin (13-*cis*-retinoic acid) is a synthetic derivative of vitamin A and has been available since early 1980s. It was initially indicated for the treatment of severe and scarring acne, although it is now increasingly used in moderately severe, treatment resistant, acne.[4] Isotretinoin is the only acne therapy that targets all four factors involved in the pathophysiology of acne; seborrhea, comedogenesis, colonisation of the pilosebaceous ducts with bacteria and inflammation.[5] Although isotretinoin's precise mechanism of action remains unresolved, this might include apoptosis of sebaceous gland cells.[6] As isotretinoin therapy can lead to sustained remission in the majority of patients, it is both an effective treatment and a cost-efficient option.

However, isotretinoin also has potential serious side effects[7] including hepatotoxicity, hyperlipidaemia, myalgia, benign intracranial hypertension, thrombocytopaenia and neutropenia. Fortunately, these are rare events and the majority of patients only have mild to moderate mucosal dryness, facial erythema and occasional skin rash. There are reports of isotretinoin causing depression and inflammatory bowel disease, although the exact relationship is not clear. Interestingly in 2009, Roche, the original creator and distributor of isotretinoin (under the trade name Accutane®) discontinued manufacture and distribution of Accutane® in the U.S.A.

One of isotretinoin's most serious side effects is its teratogenicity; isotretinoin exposure during embryogenesis carries a 30% risk of birth defects[8] and, apart from thalidomide, retinoids like isotretinoin are the strongest teratogens in humans known today.[9] Birth defects associated with isotretinoin include craniofacial, central nervous system cardiovascular and thymic abnormalities.[10] Furthermore, the risk of spontaneous abortion is approximately 20%;[11] and, even where there are no gross congenital malformations detected, up to 60% of infants have mental retardation or impaired neuropsychological function.[10] It is unknown how isotretinoin causes these abnormalities, although it might relate to altered DNA transcription, as is the case with other retinoids. It is recognised that there is no safe dose of isotretinoin during pregnancy; birth defects are associated with even only one day of isotretinoin treatment.[12]

Isotretinoin Prescribing and Monitoring Guidelines

To minimise inappropriate exposure of patients to isotretinoin, and its potential side effects, in many countries including the U.K., isotretinoin is only prescribed under the supervision of a consultant dermatologist. In addition, to help prescribing clinicians monitor and minimise side effects, the British Association of Dermatologists (B.A.D.) released guidelines on the prescribing and monitoring of patients on isotretinoin.[7] As well as general recommendations, including monitoring of patients' full blood count, serum liver function test and lipid levels; and documentation of skin dryness, joint or muscle pain headaches and mood, the B.A.D. make specific recommendations for pregnancy prevention during isotretinoin treatment. This advice is in conjunction with the U.K. Medicines and Healthcare Products Regulatory Agency's (MHRA) Pregnancy Prevention Programme (PPP). This advice includes:

1) Documentation of current and predicted sexual activity.
2) Menstrual history.
3) Patients should be educated about isotretinoin's teratogenic effects and receive written information about this.
4) Contraception education, along with written information, with advice to use two effective forms of contraception.
5) Female patients should sign a form acknowledging the aim of pregnancy prevention.
6) Documented, medically supervised pregnancy tests (from blood or urine samples); specifically this should be done prior to commencing isotretinoin, at 28-day intervals during treatment and, in particular, at 5 weeks after completion of treatment.
7) Female patients who are exempt or who decline to participate in the

PPP, must still receive written information on contraception and the teratogenic risk of isotretinoin and sign a form confirming they have received this information. In addition, prescribers may ask these patients to provide written documentation regarding exclusion/exemption from the normal PPP (the B.A.D. provide a specific form covering this).

Many countries have a similar PPP and guidelines to the U.K. For example, iPLEDGE is a compulsory register of all patients (male and female) prescribed isotretinoin in the U.S.A. aimed at eliminating fetal exposure to isotretinoin.[13] In Europe, the European Medicines Agency released guidelines regarding safe use of isotretinoin in 2003, and required each member state to implement these guidelines along with a supporting PPP.[14]

Despite these guidelines and the PPP, pregnancies during isotretinoin exposure continue to be reported. One study in France revealed that there were 147 pregnancies in patients exposed to isotretinoin over 4 years; 65% occurred during isotretinoin treatment and, of note, a further 23% of these pregnancies occurred within one month after completion of isotretinoin.[15] In the U.K., as of January 2010, 105 pregnancies had been reported to the MHRA.[7]

Audit of Isotretinoin Pregnancy Prevention Programme

In order to investigate compliance to B.A.D. guidelines, we undertook a retrospective audit of isotretinoin use in a district general hospital with a particular focus on pregnancy prevention testing. A total of 40 patients, who had completed isotretinoin in the past year, were randomly selected from the department of dermatology, and the patient's clinical and electronic records were reviewed by a single investigator to assess compliance with guidelines. Adherence to the PPP was a particular focus. In addition, in cases where the patient was asked to visit their General Practitioner (GP) for pregnancy testing 5 weeks after completion of isotretinoin, the relevant GP practice was contacted to verify whether patients had done this or not.

Of the 40 patients, 28 (70%) were female of childbearing potential (mean age 25.2 years, range 14-46 years). Of these, 4 (14%) opted out of the PPP. The remaining 24 (86%) were included in the PPP, of which 23 (96%) had definitely signed the "acknowledgement of PPP information" and had a pregnancy test prior to starting isotretinoin. In the one patient, isotretinoin was initiated in another hospital before being transferred to our department for continuation of treatment, and unfortunately we did not have access to that hospital's records to verify the pre-treatment negative pregnancy test. All 24 patients in the PPP had pregnancy tests at each monthly follow up. 16 (67%) of the 24 patients were reminded at the final consultation to have a pregnancy test at 5 weeks after completing the course of isotretinoin and were instructed where to have this done. Only 7 of the 24 patients (29%) had their post-treatment pregnancy test; 4 were asked to return to the dermatology department for testing, of which 3 did. However, of the 12 who were asked to attend their GP practice, only 4 (33%) did. There were no recorded positive pregnancy tests at any point in the patients that were tested.

National Surveys

A U.K.-wide survey by the B.A.D. in 2012 showed findings, relating to 663 patients, which were broadly consistent with our department's audit results. The national audit showed that in female patients of child-bearing potential; 91% signed the "acknowledgement of PPP information" form, 94% had pregnancy tests before and at monthly intervals during treatment. Only 51% of these patients had a pregnancy test 5 weeks after completion of isotretinoin.[16] This national audit also reported 17 pregnancies, over the previous year, during isotretinoin treatment or occurring within 5 weeks of completing treatment. A variety of reasons for these pregnancies were given including contraception being stopped or changed by the patient, contraceptive pill failure relating to antibiotic use, patient incorrectly informing the clinician that they were not sexually active and one patient holding back isotretinoin for later use without informing the clinician.

Clinicians' practices can vary greatly across different countries. For example, in contrast to the relatively high compliance to guidelines in the U.K., a study in Saudi Arabia, where similar guidelines exist, showed that 71% of dermatologists in Saudi Arabia performed a pregnancy test prior to initiating isotretinoin treatment but only 22% requested a monthly pregnancy test during treatment; there was no data presented for the 5 week post-treatment pregnancy test.[17] The authors also found that written information on isotretinoin's teratogenic effects was provided in only 44% of cases. Of the 792 females of childbearing potential prescribed isotretinoin, 7 were found to become pregnant during treatment.

A recent systematic review of 17 publications looking at compliance to the PPP in different countries across Europe, found that only 6-26% of patients prescribed isotretinoin were in complete accordance with the PPP.[18] There was a reported pregnancy incidence of 0.2-1.0 per 1000 women of child bearing age prescribed isotretinoin. Up to 87% of these pregnancies were terminated.

Medico-legal Aspects

Personal communication with a medical defence union indicated that pregnancy prevention should be the joint responsibility of the clinician and patient. The clinician must advise the patient to avoid pregnancy during and up to 5 weeks post-isotretinoin use. They should provide written information on the drug, its teratogenic nature and advice on contraception to a patient. Documentation of this provision is important. It is the patient's responsibility to ensure they read this information and attend for monthly pregnancy tests to confirm that they are not pregnant. However, the defence union advise that "*it is important that it is made clear to the patient how they should ensure that the final post-treatment test is performed. For example, should they reattend the clinic 5 weeks after treatment is completed, or should they arrange this through their GP?*" If a clinician documents this advice, it is unlikely that a patient

would be able to successfully claim that they were not informed of isotretinoin's risks and of the need to attend for post-treatment pregnancy testing. In our department, we now routinely ask patients to return for a consultation 5 weeks after treatment has been completed. At this visit, we review the patient's skin, advise on any particular treatments that might be useful now or in the future if needed and agree on a plan of action for their GP in this regard. The final pregnancy test is undertaken as part of that consultation.

Conclusions

Oral isotretinoin is one of the most effective therapies in the treatment of acne, but carries the risk of serious side effects including teratogenicity. In general, prescribers in the UK take necessary steps to ensure that patients understand this risk and also exclude pregnancy before and during isotretinoin treatment. However, approximately half of patients do not have a medically supervised documented pregnancy test post-completion of treatment. Given that almost 1 in 4 pregnancies in patients receiving isotretinoin occur within 1 month post-treatment[15] and the knowledge that there is no safe dose of isotretinoin during pregnancy, it is imperative that dermatologists confirm the patient's pregnancy status post-treatment. In many cases, patients are instructed to attend their GP practice to have this done; however our data suggests patients cannot be relied upon to attend their GP surgery to have this done. Clinicians should place a high priority on patient safety. Given that a significant proportion of patients do not appear to have post-treatment pregnancy testing, it might be useful for dermatologists within their individual departments to agree on local protocols to ensure such testing is better implemented.

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Diagnosis and Treatment of Pemphigus Vulgaris

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Introduction

Pemphigus is a group of acquired autoimmune blistering diseases in which immunoglobulin G (IgG)[1] antibodies target various keratinocyte antigens that, when targeted, cause acantholysis and result in intraepidermal blister formation. The two main subclasses of pemphigus are pemphigus vulgaris (PV) and pemphigus foliaceous (PF). Pemphigus vulgaris is the most common type of pemphigus and accounts for approximately 70% of cases.[2]

Pemphigus, if left untreated, is almost invariably fatal. Prior to the advent of corticosteroids in the early 1950s, the mortality rate of PV was 60-90%[3] within a year, 75% on average.[4] While corticosteroids have resulted in a dramatic improvement in prognosis, the disease is still associated with a mortality rate of approximately 5-8%, despite the use of various adjuvants.[5, 6] Today, mortality is usually the result of the side effects of the high doses of steroids and other immunosuppressive drugs used to treat the disease.[7]

The treatment of pemphigus has been the subject of much debate. While there are many therapies available, few have been assessed in randomised clinical trials, and no consensus among experts regarding treatment has been achieved.[2] A detailed discussion of the proper approach to diagnosing pemphigus vulgaris as well as the traditional and novel treatment options are presented here.

The incidence of pemphigus ranges from 0.76 to 5 new cases per million per year, with much higher incidence in those of Mediterranean or Jewish ancestry.[8] The prevalence of pemphigus vulgaris in men and women is approximately equal, with a disease onset most commonly between 40-60 years.[9]

Pathophysiology

Autoantibodies of the immunoglobulin G4 (IgG4) subclass to desmoglein 3 (dsg3) are the major pathogenic antigen for PV, but 50-60% of patients have additional antibodies to desmoglein 1 (Dsg1), the pathogenic antigen in PF.[10, 11] The underlying antibody profile is a major determinant of the clinical phenotype of pemphigus,[12, 13] with antibodies to dsg3 alone and involvement limited to the oral mucosa associated with a better prognosis.[2]

Desmogleins are components of the desmosome, and are intercellular adhesion molecules essential to the structural stability of the epidermis. When these desmosomal proteins are targeted by autoantibodies, a set of poorly understood pathways leads to acantholysis of the epidermis and blister formation. Various models have been proposed to clarify these complex intercellular processes, with emphasis on the role of apoptotic signaling in the pathogenesis of PV.[14-17] Besides desmogleins, patients develop antibodies against additional desmosomal (i.e. desmocollins, plakins) and nondesmosomal proteins (nicotinic acetylcholine receptor, pemphaxin, thyroperoxidase and other annexins), which may also play a role in the pathogensis.[1,14]

Clinical Findings

In approximately 50% of the cases, PV begins with multiple, painful, superficial ulcerations involving the tongue or buccal, labial or palatal surfaces of the mouth.[18] In over half the cases of pemphigus vulgaris, the lesions will involve the skin, with accentuation over the scalp, face, and upper torso. The skin lesions usually begin as small, flaccid blisters arising from normal-appearing skin. These blisters easily rupture, evolving into sharply demarcated erosions with a collarette of loose epidermis.

While the mouth and skin are the most clinically obvious sites of involvement, any surface with stratified squamous epithelium can be affected including the throat, esophagus, conjunctivae, nasal mucosa, vagina, vulva, penis and anus.[8] Upper respiratory tract involvement is large, with one study identifying 49% of patients presenting with symptoms of laryngeal, nasal or both sites involved.[19]

The severity of PV can vary widely, with potentially more severe disease in those with dsg1 antibodies.[11] Although the course of the disease may follow different patterns between individuals, 75% of patients enter a durable remission (defined as an average of 4 years) within 10 years.[6] Two clinical factors that have been identified as predictive of the disease course include initial severity and extent of disease and early

response to treatment.[6]

Diagnosis

The diagnosis of PV requires a combination of clinical features, histopathology, tissue-fixed antibodies identified by direct immunofluorescence studies (DIF) and circulating antibodies measured by indirect immunofluorescence (IIF), enzyme linked immunosorbant assays (ELISA) or immunoblots. The histological findings of suprabasal acantholysis with resultant intraepidermal blister formation are highly suggestive of pemphigus, but should be confirmed by identification of tissue-fixed and circulating antibodies. A lace-like pattern of fluorescence within the epidermis is seen by both direct and indirect immunofluorescence studies, and is diagnostic of pemphigus. Approximately 90% of patients with clinical and histological findings consistent with pemphigus will demonstrate tissue-fixed immunoglobulin G (IgG) autoantibodies by DIF of perilesional skin,[8] with or without deposition of complement component 3 (C3). Circulating antibodies are present in approximately 80% of patients with active disease, as quantified by IIF, ELISA or less commonly immunoblot assays, with titers shown to correlate with disease activity. ELISA for antibodies against dsg1 and dsg3 offers many advantages over IIF including reproducible and standardised results with less operator variability and a less labour-intensive technique. Furthermore, ELISA is more specific and somewhat more sensitive than indirect immunofluorescence.[8]

Treatment Background

The ultimate goal of therapy is to induce partial remission on the fewest number and lowest doses of medications, or complete remission with subsequent withdrawal of all medications when possible. Even more challenging is developing a treatment regimen in a manner that minimises side effects. Over 80% of patients with PV will eventually enter a partial remission in which they can be maintained on minimal doses (<15 mg/day) of prednisone without active lesions.[5] Complete remission, where patients can remain disease-free and off all medications, can be achieved in 50% of patients in 5 years and 75% in 10 years.[6]

Systemic steroids remain the cornerstone of treatment for pemphigus because they are the most effective and rapidly acting treatment. Thus, corticosteroids are often the first medication used and are initiated at high doses. Unfortunately, the high doses and prolonged courses of systemic steroids required to control disease activity are accompanied with serious dose-dependent side effects. Therefore, adjuvant therapies have been introduced into the armamentarium of therapies to replace or reduce the need for steroids. These adjuvant therapies include immunosuppresants, biologics, anti-inflammatory medications and therapies that modulate levels of serum immunoglobulins (plasmapheresis, immunoadsorption, and extracorporeal photopheresis).

Systemic Corticosteroids

Despite their adverse side effect profile, systemic corticosteroids remain the mainstay of treatment for pemphigus. While the efficacy of corticosteroids is clearly highlighted by the dramatic decline in mortality, from 90% to approximately 10% with the advent of systemic steroids, the optimal dosing regimen is less clear and largely empirical. One randomised control trial (RCT) found no difference between low (45-60 mg/day; 1 mg/kg/d) verses high-dose (100-150 mg/day; 2.0-2.5 mg/kg/d) prednisone. Although the low number of participants made the study underpowered (n = 22), all patients achieved remission with no significant difference regarding duration of remissions and relapse rates at 5 years.[20]

Pulsed corticosteroid therapy has been studied with the goal of achieving faster disease control, reducing the duration and cumulative dose of steroids and limiting the side effects associated with systemic steroids. One small case series of 15 patients with PV found high-dose intravenous pulse glucocorticoid therapy was associated with higher rates of remission, a reduced duration of prednisone therapy and longer time in remission compared to conventional oral prednisone treatment.[21] Continuous verse pulsed corticosteroid regimens have also been evaluated with 2 RCTs that showed disparate results. In one study, the pulsed group showed shorter healing time and lower side effects[22] while the other showed no difference between pulsed and continuous steroid therapy in conjunction with azathioprine.[23] All of the studies evaluating the efficacy of pulsed steroid therapy, however, have been limited by a small participant size and were, therefore, underpowered to detect a clinically relevant outcome. Thus, no difference in these studies does not translate to no difference in real practice, particularly in the setting of severe, recalcitrant and progressive cases of PV.

Overall, the data indicates that corticosteroids are the quickest and most effective treatment for PV and are first line. A tailored dosing regimen of CS according to disease severity has been advocated,[24] and the guidelines for management of PV by the British Association of Dermatologists has recommended patients with mild disease receive an initial prednisolone dosage of 40-60 mg/d and more severe cases 60-100 mg/d. If there is no response within one week, the dose should be increased in 50-100% increments until disease control is attained, defined by no new lesions and healing of existing ones. Furthermore, if doses exceed 100 mg/d then pulsed intravenous dosing should be considered. A 25% dose reduction may be performed biweekly with slower decreases when doses below 20 mg/d are reached.[25] Our practice is to taper the dosage of corticosteroids biweekly with an alternating day regimen (for example tapering from 40 mg daily to 40 mg every other day, alternating with 30 mg for 2 weeks then 40 mg alternating with 20 mg for 2 weeks and so on). This goal of this dosing regimen is to decrease steroid toxicity while minimising the risk of disease flare.

Short and long-term toxicities of corticosteroids include hyperglycemia, diabetes mellitus, weight gain, hypertension, hypokalemia, hypertriglyceridemia, osteoporosis, osteonecrosis, peptic ulcer disease, esophageal reflux, psychiatric and neurologic disorders, ophthalmologic disease and infection (including tuberculosis reactivation).[26] Therefore, it is critical to minimise the dosage of systemic steroids with tapering as soon as possible and to use adjuvant agents when indicated.

Traditional Adjuvants

Azathioprine

Azathioprine is an immunosuppressive agent whose effective use in pemphigus is supported by multiple case series.[27] The efficacy of azathioprine as a steroid-sparing agent has been demonstrated in few RCTs comparing azathioprine to mycophenolate mofetil,[28, 29] cyclophosphamide[29] and glucocorticoids alone,[29] but no significant difference concerning disease remission between treatments were shown.[29] In another trial, azathioprine was less effective but faster than mycophenolate in achieving disease remission.[28] These studies suggest that azathioprine is most effective as an adjuvant, steroid-sparing agent.

Azathioprine is metabolised by thiopurine S-methyltransferase (TPMT). As TPMT levels are genetically determined, patients should undergo monitoring for TPMT before initiation of azathioprine. Approximately 10% of the population may have high levels of TPMT levels and these patients are at risk of under treatment.[25] The side effect profile of azathioprine includes leukopenia, gastrointestinal disturbances, hepatotoxicity, pancreatitis, increased risk of infection, and immunosuppression induced malignancies.[27, 30-32]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a relatively new agent in the treatment of PV. The initial evidence of the benefit of MMF for treatment of pemphigus stems from several case series reporting the efficacy of MMF in inducing remission and facilitating the reduction of prednisone dosing.[33-36]

Despite the strong results from these case series, one prospective controlled trial including 40 patients with pemphigus compared methylprednisolone (2mg/kg/d) plus adjuvant azathioprine (2 mg/kg/d) to meythlyprednisolone plus mycophenolate mofetil (2 g/d) and showed no significant differences in cumulative steroid dose, efficacy and adverse events.[28] However, MMF appeared to be more effective at inducing disease remission.[28] Another RCT showed similar response rates when comparing adjuvant MMF vs. placebo in combination with prednisone, with faster and more durable responses in the MMF treated group.[37] A third RCT compared methylprednisolone vs. methylprednisolone plus mycophenolate mofetil (3g/d) in the treatment of newly diagnosed pemphigus patients and found no difference in rate of response, total dose of prednisone required to control disease, and time and length of disease remission between the two groups.[38] Despite the conflicting findings of this most recent RCT, the majority of the data supports the use of MMF as an adjuvant in the treatment of pemphigus.

Due to its selective inhibitory action of mainly T and B-lymphocytes, MMF is believed to have a favourable safety profile compared with other less selective adjuvant immunosuppressants like azathioprine.[27] Mycophenolate mofetil is usually well tolerated. Adverse effects include gastrointestinal discomfort, genitourinary symptoms, opportunistic infections, anemia, leukopenia, neutropenia and thrombocytopenia. No consensus or guideline for dosing or laboratory monitoring of MMF in dermatological conditions have been set, however, MMF is typically prescribed as 2-3g/d in two divided doses with lower doses in those with renal impairment. It is our practice to start at lower doses of MMF (500 mg once to twice daily) and increase to a maximum dose of 3g/day as indicated by clinical response and patient tolerability.

MMF has been shown to have benefits in the treatment of pemphigus, however, cost has been the biggest limiting factor in its use compared to other immunosuppressive agents. While azathioprine is a less expensive option with faster response rates, we observe that patients are more tolerant to MMF and therefore, use MMF as our first line adjuvant in combination with corticosteroids.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that selectively suppresses the function of lymphocytes, with particular activity against B- cells, and as a result reduces antibody production. For this reason it has been used to treat pemphigus vulgaris. In a systematic review of 2 RCTs including comparisons of cyclophosphamide against glucocorticoids, azathioprine, cyclosporine and mycophenolate, cyclophosphamide had a greater steroid-sparing effect compared with mycophenolate but lesser than that of azathioprine.[2, 29, 39] No difference in disease control was noted between cyclophosphamide and the other treatment groups.[29, 39]

Pulsed cyclophosphamide regimens have also been investigated and have been suggested to be less toxic when delivered in IV pulses,[40, 41] however this treatment regimen has failed to show any benefit in RCTs.[42, 43] Two recent non-comparative studies assessing the efficacy of pulsed intravenous glucocorticoid-cyclophosphamide in pemphigus showed a steroid-sparing effect with significant clinical responses, however the side effects in both studies were severe including sepsis, premature ovarian failure and death (in 7 patients, 2 of which were likely a consequence of treatment).[44, 45]

Overall, current studies show no significant difference in clinical outcomes, disease control or relapse rates when comparing cyclophosphamide with other more conventional immunosuppressive agents (Frew *et al.* 2011). Furthermore, the risks of cyclophosphamide

are well-documented and severe including, but not limited to, bone marrow suppression, hepatotoxicity, haemorrhagic cystitis, increased risk of cancer (i.e. lymphoma and transitional cell carcinoma of bladder), infections, amenorrhea and azoospermia.[27, 31, 32, 45] Thus cyclophosphamide should be considered in patients who have disease refractory to combinations of corticosteroids and azathioprine or mycophenolate mofetil, who have significant side effects with other therapies, or have rapidly progressive and severe disease.[32]

Other Immunosuppressants

Methotrexate

Methotrexate (MTX) was used for the treatment of PV, at doses up to 150 mg weekly, which led to severe toxic effects[46] and consequently MTX lost favour for the ensuing 25 years. More recently, methotrexate was reintroduced into the treatment regimen using lower doses of 10-50 mg orally once weekly. A meta-analysis on the use of methotrexate in the treatment of pemphigus demonstrated that 83% of 116 patients treated with doses of 10-50 mg/week in combination with corticosteroids, showed clinical improvement.[47] While no RCT investigating MTX for the treatment of PV has been conducted, currently available data suggest it may have a steroid sparing effect. Thus, methotrexate may be considered a cost-effective adjuvant for the treatment of PV.

The most common adverse effects of MTX include nausea, anorexia, vomiting, diarrhea, fatigue and malaise. Myelosuppression occurs in 2-11% and is potentially fatal.[48] Folic acid supplementation can help prevent this side effect. Liver fibrosis and cirrhosis can develop with long-term use and patients with obesity, diabetes mellitus and excessive alcohol consumption are considered at higher risk.[48] MTX is contraindicated in pregnancy, in patients with renal impairment, hepatitis and cirrhosis.

Anti-inflammatory Therapies

Dapsone

Dapsone is an anti-inflammatory agent used in many dermatologic diseases including pemphigus. A meta-analysis summarised findings from 55 patients found that 32 patients with pemphigus vulgaris and 14 patients with pemphigus foliaceous responded to adjuvant dapsone.[49] These studies showed a trend toward effectiveness of dapsone but were underpowered. One series showed a significant steroid sparing effect when dapsone was added to the regimen of prednisolone with or without adjuvant therapy,[50] however the results were not reproducible in a RCT using the same protocol.[51]

Haemolysis is the most common adverse reaction observed with dapsone and is reversible upon dose reduction or cessation. Other rare side effects of dapsone include agranulocytosis and peripheral neuropathy.

Sulfasalazine and Pentoxifylline

Tumour necrosis factor-alpha (TNF-alpha) has been suggested to play a role in the mechanism of acantholysis in pemphigus vulgaris.[52] Thus, sulfasalazine and pentoxifylline, with their known anti-TNF effects,[53-57] have been investigated as possible adjuvant. A RCT of 64 patients with pemphigus were treated with prednisone and cyclophosphamide with 42 of these patients receiving sulfasalazine (500 mg three times daily) and pentoxifylline (400 mg three times daily) while 22 patients received placebo.[58] The results showed that the use of sulfasalazine and pentoxifylline as adjuvants for PV induced a faster and more significant decrease in the serum levels of TNF-alpha associated with more rapid clinical improvement compared to the placebo group and normal healthy controls.[58] Side effects of sulfasalazine include bone marrow suppression and gastrointestinal irritation.

Other TNF-alpha antagonists including etanercept[59, 60] and infliximab[57, 61] have shown success in treatment of PV in few small case studies. However, their high cost and safety profile may make their use as adjuvant treatment for PV less desirable. Thus, pentoxifylline and sulfasalazine may be an effective, cost-efficient, treatment for PV without the unwanted side effects and immunosuppression of other medications. It is our experience that pentoxyfilline and sulfasalazine are useful in young patients, with limited disease, in which the lifetime risk of immunosuppression related malignancies is higher.

Rituximab

Rituximab is a monoclonal humanised antibody to the B-cell specific cell-surface antigen CD20 that was originally developed for treatment in B-cell non-Hodgkin's lymphoma. Rituximab has been used for multiple autoimmune disorders. It was first used in the treatment of paraneoplastic pemphigus in 2001[62, 63] and in 2002 it was first reported in the treatment of pemphigus vulgaris.[64]

A recent review described the efficacy of rituximab in 153 PV patients derived from case reports and series as well as small prospective studies. Sixty-six percent of the 153 pemphigus vulgaris patients treated with rituximab achieved a complete remission (defined as a cessation of disease progression and subsequent healing of all lesions), 23% achieved a partial remission (defined as clinical improvement but with persisted disease following rituximab therapy) and 5 % were non-responders.[65] More than a third of these complete remission patients who responded to rituximab achieved a sustained remission off systemic medications. The majority of the patients in this study were on concomitant therapies including prednisone with or without an immunosuppressive agent and/or immunoadsorption. This review highlighted that those on concomitant immunosuppressive agents had similar efficacy and increased rates of infection compared to those treated with adjuvant prednisone only. A major limitation in the available data is that the majority of patients (118 patients) came from small case series with variable dosing regimens and too short of a follow-up period to draw meaningful conclusions (mean follow-up 14.2 months).[65]

Although the number of adverse events reported is low in comparison to

other pemphigus treatments and usually infusion related, serious adverse effects have been reported, most notably infection in 7-10% of those treated.[65, 66] At least two fatalities have been reported in PV patients treated with rituximab, both deaths related to infections.[65] Deep venous thrombosis, pulmonary emboli, long-term hypogammaglobulinemia and neutropenia are other serious complications.

Overall, rituximab seems to be an efficacious and steroid-sparing drug for pemphigus, but given the severity of potential adverse events this treatment should be reserved for those patients in whom conventional therapy has failed.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) was first introduced into the armamentarium of treatment modalities for PV in 1989, when it was used as monotherapy. Until 2009, only small reports analysing the effectiveness of IVIG were available. A review of these cases has identified over 100 treatment-resistant PV patients treated with IVIG, with the majority of the patients sustaining a good response with a decline in skin lesions and serum antibody levels as early as one week after initiation of IVIG.[67] In 2009, the first randomised, multicenter, double-blind trial of IVIG for PV was published,[68] confirming high-dose IVIG group was more effective at lowering disease severity scores and autoantibodies levels compared to those in the placebo group. Only a few small reports have disputed the efficacy of IVIG demonstrated by these studies.[69, 70]

The safety profile of IVIG is an advantage when compared with other treatments. It is not immunosuppressive and side effects such as headaches, which are the most common,[27, 71-73] and can be avoided with pre-administration with non-steroidal anti-inflammatory agents and antihistamines.[73] Before administration, a complete blood count, complete metabolic panel, rheumatoid factor, serum cryoglobulin and immunoglobulin (Ig) levels, to exclude complete IgA deficiency should be performed.

Plasmapheresis, Immunoadsorption and Extracorporeal Photopheresis

The rationale behind therapies that modulate serum levels of immunoglobulins for the treatment of PV is based on the observation that autoantibodies are pathogenic in PV1, and that the levels of these autoantibodies correlate with the disease severity.[8, 74] While many small trials and case series have demonstrated the potential of obtaining partial and complete remission of PV with plasmapheresis,[75-80] results from a prospective controlled therapeutic trial of 34 patients with pemphigus revealed that plasmapheresis in combination with low-dose corticosteroids was ineffective and associated with severe adverse events.[81]

There have been approximately 50 cases of PV treated with immunoabsorbation (IA) (a procedure that is similar to plasmapheresis but with less side effects) with complete remission (healing of all lesions with no further therapy required) and clinical remission (healing of lesions but further treatment required) achieved in 10% and 54% of the cases respectively.[82-93] These studies showed a rapid decline of autoantibodies with healing of lesions within a few weeks.[93] However, because these small studies used different protocols and no prospective controlled study has been completed yet, assessing the real value of IA in pemphigus is difficult.

The exact mechanism of extracorporeal photopheresis (ECP) is unknown but in approximately 25 patients with PV, ECP was an effective treatment, with all but 2 patients achieving a complete or partial remission.[26, 94] Given the limited data and the lack of RCTs, however, there remains insufficient evidence to support the use of ECP in patients with pemphigus.

Conclusion

The goal of therapy in pemphigus is to induce and maintain remission with the fewest drugs and minimal side effects. Treatment should be dictated by the degree of involvement and the rate of disease progression. Corticosteroids in combination with a corticosteroid-sparing immunosuppressive adjuvant remain the first-line therapy for pemphigus. Azathioprine and mycophenolate mofetil are among the most frequently used steroid-sparing agents. If patients fail to respond to this traditional therapy, newer immunomodulators including rituximab, IVIG, immunoadsorption may be considered. For mild cases and young patients where immunosuppression is unwanted and unnecessary to control disease activity, selecting anti-inflammatory medications as adjuvants to corticosteroids may be warranted. Despite the advances in therapies for pemphigus vulgaris, more prospective studies and RCTs are needed to fine-tune the recommendations for treatment of pemphigus. Nonetheless, each case should be individualised, taking disease severity, co-morbidities, age, as well as cost into account.

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A New Treatment for Severe Burn and Post-traumatic Scars: A Preliminary Report

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Introduction

Burns are considered amongst the most devastating of injuries and are the fourth most common type of trauma worldwide, following traffic accidents, falls, and interpersonal violence.[1] Fortunately, survival and mortality rates have improved substantially as a direct result of medical advancements. As a consequence of this increased survival rate, the number of people with burn scars has increased during recent years. Scars can have significantly negative physical and psychological impact. In addition to serving as visible reminders of the burn injury and compromising self-esteem and self-image, burn scars produce considerable functional morbidity, including contractures, hypertrophic changes, and keloid formation. The stigmata of burn scars are plainly visible, but the injury to the patient is usually more than skin deep. Burn and traumatic scars are usually thick, wide and contracted scars that reduce the function of an anatomical region or that create a body deformity. There are 2 main problems with the scars: Appearance and Function. These problems can co-exist to different severities. Large unsightly scars may not have any functional compromise and small barely noticeable scars in anatomically important areas may impair function considerably. The idea of using a laser to modify the burns scar is to try to improve both appearance and function.

Traditional Approach

Plastic Surgeons and Dermatologists utilise many techniques to try to improve these scars, but sometimes there are situations where these kind of procedures have limited efficacy. Depending on the patient's symptoms and functional deficits, treatment of burn scars involves a number of modalities[2-3] that may include massage and moisturising agents, silicone sheeting or creams, pressure garments, topical and intralesional steroids. Surgical incision or excision of a burn scar may be necessary, and defects can be reconstructed with biologic skin substitutes, split-thickness and full-thickness skin grafts, tissue rearrangement (multiple Z o W plasty), tissue-expanded or pedicled flaps, and even free tissue transfer. Despite these techniques, restoring form and function after a burn injury remains challenging.

Lasers Treatment of Scars

It is at this point, where the usual techniques may be less useful, that lasers therapy may be used to reduce disfigurement and improve appearance and functionality of scarred tissue that results from severe burns and trauma. Either in combination with reconstructive surgery or as mono-therapy, lasers can be now considered as part of the medical and surgical treatment offering. They can help patients by increasing function of contracted scars and reducing the extent of disfigurement.

Pulse Dye Laser

Immature burn and post-traumatic scars can be improved by some Pulse Dye Laser (PDL) treatments. Developed several decades ago, the vascular-specific, flashlamp-pumped 585 and 595 nm PDLs became the standard of care for treating different vascular malformations. This laser selectively targets haemoglobin and coagulates microvasculature in the papillary and reticular dermis. Hypertrophic burn scars are characterised by excessive inflammation, overabundant collagen production, abnormal extracellular matrix remodelling, and inhibition of fibroblast apoptosis, all of which result from or are related to pathologic neovascularisation. The PDL causes photothermolysis that induces coagulation of capillaries. When applied to burn scars, the PDL reduces the hypervascular response.

Over the past 10 years, the efficacy of PDL therapy for the treatment of sub-acute burns and hypertrophic burn scars has been established unequivocally by many investigators. Donelan, Parrett, and Sheridan[4] from the Shriners Burns Hospital in Boston, for example, presented their experience with 57 patients. This group noted that PDL improves burn scar texture, pliability, erythema, pruritus, and pain while reducing scar volume. Extremely recently Yang[5] demonstrated that pulsed dye laser treatment of keloids significantly down-regulates the expression of CTGF (connective tissue growth factor) in most cases. Increased CTGF growth factor activity has been considered to play an important role in the pathogenesis of keloids. Therefore a down regulation of its expression may partially explain the mechanism of action of PDL in the treatment of keloids. A study by Kuo *et al.*[6] showed that 86% of keloid patients had 50% remission after 1–11 PDL treatments. Moreover, a study by Manuskiatti *et al.*[7] demonstrated that the texture of scar improved after PDL treatment in 12 of 19 patients (including keloids and hypertrophic scars). In most of these patients,

keloid volume was shown to be reduced after treatment.

Ultrapulsed Fractional CO2 Laser: the SCAAR FX Treatment

Sharing from the experience of Dr. Jill Waibel from Miami (Miami University),[8-9] Dr. Nathan Uebelhoer and Dr. Peter Shumaker[10-12] from San Diego (Naval Medical Center – US Navy) , Dr. Chad Hivnor from San Antonio (Lackland Air Force Base - US Air Force) and Dr. David Ozog[13-14] from Detroit (Michigan - Henry Ford Hospital), 3 years ago we started to use a fractional ultrapulse ablative CO2 laser to treat mature severe burn and post-traumatic scars. How and why this treatment should deliver such good results remained unclear, but more and more data was now appearing, histologically and immunohistochemically, that suggested multiple changes inside the scarred tissue after this kind of treatment. As laser operators, we had our initial doubts. The questions were:

1) Why should a laser traditionally used to tighten elastotic skin, now be used in contracted scarred skin to lengthen it? In other words:
2) Why "burn" a burn?

The answers are still not completely known today but there is now some research that can try to explain the mechanisms. This whole concept represents a real paradigm shift. Whether it is elastotic, sun-damaged, or hypertrophic scarred skin, fractional ultrapulsed CO2 injury will steer it towards a more normal pattern.

The laser device creates thousands of very deep holes inside the scar (with the new SCAAR FX software the depth of penetration is now up to 4 mm – Figure 1).

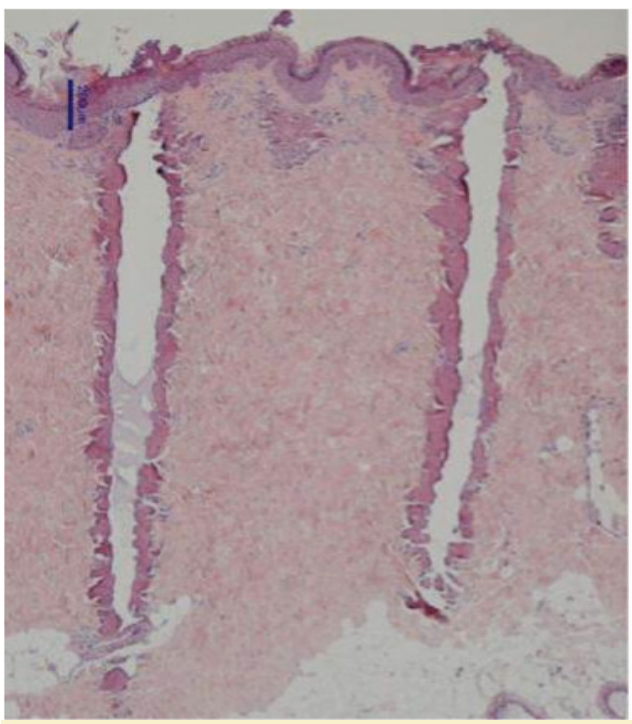

Figure 1. The histology that shows the 4 mm penetration of the new SCAAR FX treatment.

Thousands of very deep holes create an interruption of the mechanical forces that characterise a contracted scar. Patients have an immediate relaxation of the scar but this is not the key to the secret of this treatment. If we create thousands of holes with a needle inside a scar we will obtain an immediate relaxation of it but all these holes will be replaced by scarred tissue and the long term result will be minimal if not worse. The secret is the heat generated by the device. Around each small, deep hole there is a controlled heat damage of the scarred tissue.

This controlled heat damage promotes a cascade of biochemical events that can be summarised as follow:

1) an up-regulation of Heat Shock Proteins production (HSP 72, HSP73, HSP 47).[15-18]
2) Both types I and III procollagen mRNA levels were dramatically down-regulated immediately after the treatment.[13]
3) The ratio of types I/III procollagen mRNA was not different immediately after the treatment (2 days later).[13]
4) But the ratio of types I/III procollagen mRNA decreases 6 months after the treatment.[14]
5) The expression of MMP-1 was significantly up-regulated immediately after the treatment.[13]
6) TGF-b2, -b3, and bFGF levels were significantly down-regulated immediately after the treatment but TGF-b3 increase again 2 weeks after the treatment.[13, 17]
7) Expression of miR-18a and miR-19a were dramatically up-regulated after the treatment.[13]
8) A shift toward a normal dermal architecture (less thick collagen bundles parallel to surface and more finer Fibrillar appearance; vessels are not only parallel to surface but also perpendicular).[14]

What this data suggests is that following ultrapulsed CO2 fractional

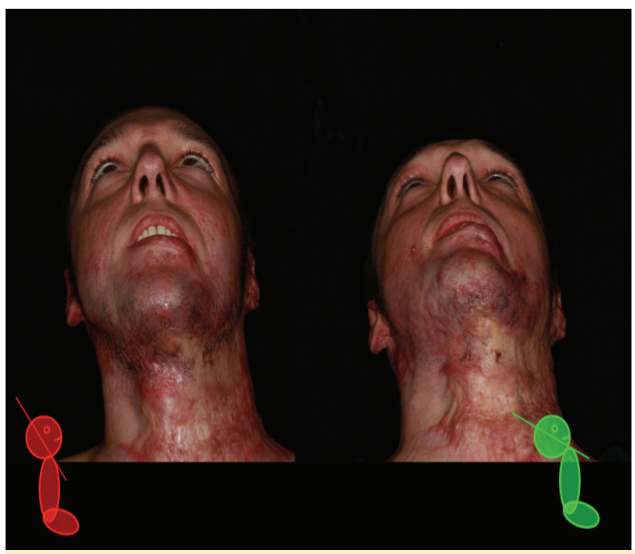

Figure 2. A patient with a severe burn scar of the face and neck before and after the treatment. With the treatment he gained 17° degrees in the extension of his head.

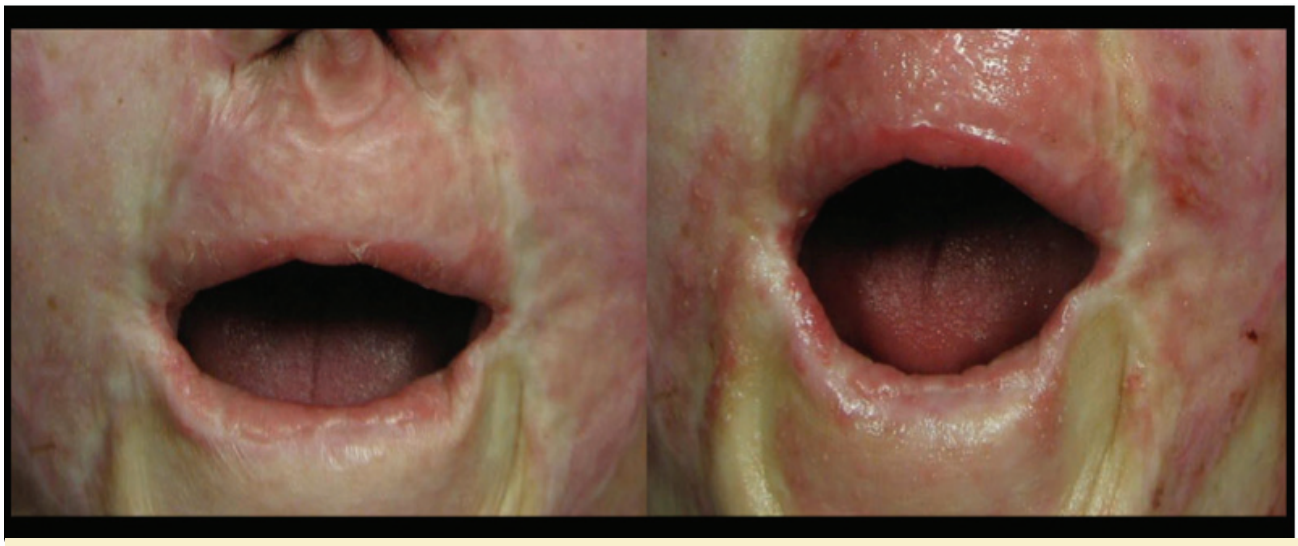

Figure 3. A patient with a severe burn scar of the face. After the treatment she has increased range of movement in opening her mouth.

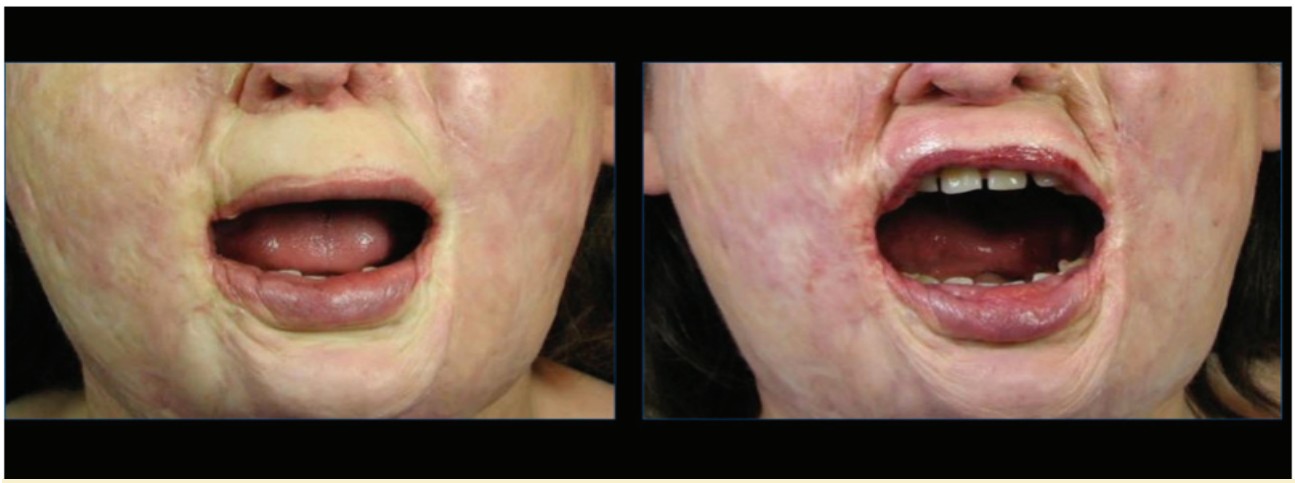

Figure 4. A patient similar to that in Figure.3. Note the extension of the mouth aperture after the treatment

treatment, there is an initial suppression of collagen production, followed by a remodelling phase. The vertical cylinders created in the scar tissue will be replaced by tissue that has a more normal collagen architecture, more normal vascular array and a more normal collagen type I type III ratio. Thus, the treatment can be considered to be guiding the skin to a more normal healing pattern.

From a clinical point of view each patient has to be treated more than once, adjusting the settings on the improvements observed after each session of treatment and each session must be customised to the specific features of the scar(s). Treatments are usually performed under topical anesthesia but if required, intravenous sedation may be administered. Following the procedure, the majority of patients report no discomfort after 20 minutes and usually resume normal pre-procedure activity within a few days. There may be some moderate swelling and serous exudate during the early recovery phase. Antibiotics and antiviral medication are routinely prescribed as prophylaxis against infection. Patients are encouraged to follow intensive physiotherapy, occupational therapy and/or massage where

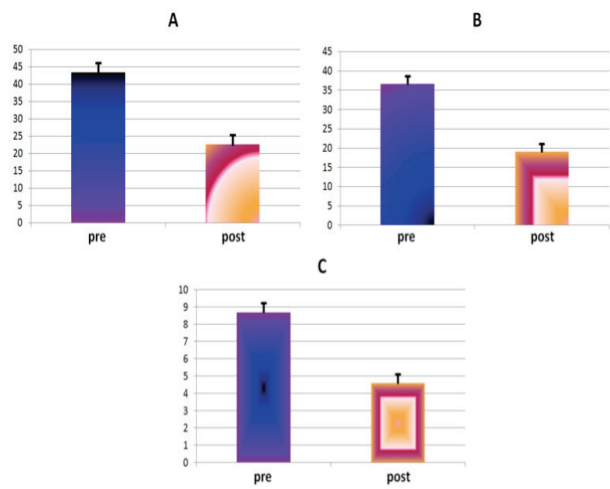

Table 1. Pre and post treatment scores for; A. the Patient portion of the POSAS Scale, B. the Observer portion of the POSAS Scale and C. the Vancouver Scar Scale

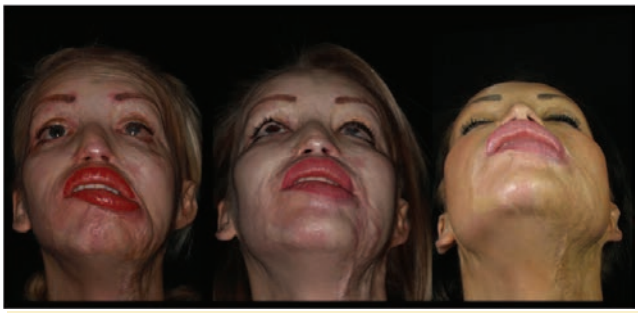

Figure 5. A patient with a severe acid burn on her face. 2 years after the treatment, there is noticeable improvement in neck extension and the retraction of the left oral commissure is dramatically decreased.

possible to maximise the outcomes.

24 patients with mature burn scars from various causes were recruited to complete a series of 3 treatments with the fractional CO2 laser. Patients ranged from 9 to 47 years of age, with an average age of 29 (Table 1). The causes of the burns included hot water (n° 7), acid (n° 2), grease (n° 2), and fire (n° 13). It is very difficult to objectively evaluate improvement and therefore the authors decide to use two evaluating scales.

1) The Vancouver Scar Scale, the most widely used assessment scale which measures vascularity, pigmentation, pliability, and height.
2) The POSAS (Patient and Observer Scar Assessment scale),[18] which asks more concrete questions regarding scar conditions such as pruritus, pain, and stiffness. The Patients completed the Patient portion of this scale while the treating physicians completed the Observer portion of the Observer Scar Assessment Scale.

What it is surprising is that every treated patient reported an improvement of their physical and psychological situation. The appearance of mature burn scars markedly improved after a series of three treatments with fractional CO2 laser (Table 1).
Subjects had statistically significant improvement in scar quality after treatment as measured by both patient and observer validated scar scales.

Discussion and Conclusion

The exact mechanism by which fractional CO2 laser treatment

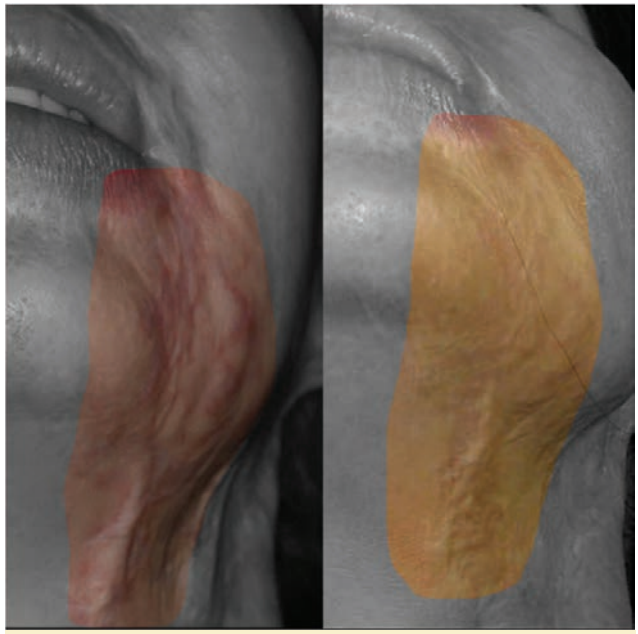

Figure 6. A close-up picture of the patient in Figure 5. Note the improvement and the textural changes of the scar.

improves the appearance of mature hypertrophic burn and post traumatic scars is presently unknown, but our results indicated that fractional CO2 laser treatment induced mature hypertrophic burn scar regression. Further studies are needed to determine how fractional CO2 laser treatment induces the biochemical pathways that suppress hypertrophic scar formation. Nonetheless, our results, the immunohistochemical demonstrations, the clinical demonstrations and the positive reports from numerous patients allow us to consider this laser treatment of severe burn and post-traumatic scars as part of an entire medical and surgical armamentarium that can obtain very good results on this devastating condition. Further studies are needed to determine the parameters that may lead to improved outcomes on burn scars patients.

Another aspect of this therapy is the potential to deliver drugs through the scar.[19] On the horizon, there are two therapies that show some promise: stem cell therapy and application/injection of growth factors.[20-21]

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Management of Infantile Haemangioma

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Introduction

Infantile haemangioma (IH) are benign vascular tumours found in approximately 4-10% of Caucasian infants.[1,2] Females, premature infants, infants with a low birth weight (<1500 gram), and twins are at a higher risk of IH development. Most IH (>60%) are found in the head and neck region.[3] IH can be categorised in nodular IH, which are localised, and segmental IH, which are more plaque-like.[4]

Normally IH are absent at birth and develop in the weeks and months thereafter. In some cases there is a precursor lesion present at birth, such as a small red macule, telangiectasia, or blue macule.[1,5] During the proliferation phase there is disproportionate growth for an average of 3-9 months.[5] Most growth is seen in the first two months.[6] After the growth phase there is usually a stable period, before the regression phase starts. Most IH do not improve significantly after the age of 3.5 years.[7] IH can resolve without sequelae however, in 69% of all IH wrinkled atrophic skin, telangiectasias, pigmentation, scars or fibro-fatty tissue are left behind.[1,8]

Diagnostic Evaluation: Associated Structural Anomalies

IH, especially segmental IH, can be associated with underlying congenital anomalies and have a much higher risk for the development of complications.[9] Two syndromes are now identified: PHACES syndrome and LUMBAR syndrome (also known as SACRAL/PELVIS syndrome). The exact etiology of these syndromes is yet unknown, but an anomaly in the field of morphological development related to the defect of one or more regulatory genes is suspected.[10]

PHACE(S) syndrome: PHACE is an acronym that was introduced in 1996 by Frieden *et al.*[11] to describe the association of posterior fossa malformations, haemangiomas, arterial anomalies, cardiac anomalies, and eye abnormalities. In case of sternal clefting or supraumbilical raphe, this acronym is expanded to PHACES syndrome. About 70% of the children with PHACE syndrome present with a single extracutaneous anomaly.[12] The exact frequency of PHACES syndrome is unknown. In a prospective multicenter cohort study of 1096 children with IH, 20% of the 200 segmental facial IH met the criteria for PHACE syndrome, and 88% of these cases were girls.[13] PHACE syndrome is therefore not a rare clinical entity.[14]

LUMBAR syndrome: Different terms have been suggested for describing segmental IH in the lumbar and perineal region and their associated anomalies: PELVIS syndrome (Perineal haemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag),[15-18] SACRAL syndrome (Spinal Dysraphism, Anogenital, Cutaneous, Renal and Urologic Anomalies, Associated with an Angioma of Lumbosacral Localisation),[19] and LUMBAR syndrome (Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformaties, Anorectal malformations and Arterial anomalies, and Renal anomalies).[20,21] Since different terms are used in the literature there is little data about incidence and prevalence of the associated anomalies in lumbosacral and perineal IH. And, in contrast to PHACES syndrome, there is no consensus about the diagnostic criteria for LUMBAR syndrome.

Segmental IH in the face and on the lower body need further diagnostic evaluation to rule out other structural anomalies.

In the presence of four or more cutaneous IH, the clinician should be aware that haemangiomas could be located extracutaneously. These lesions are mostly located in the liver, and ultrasonography is advised when four or more cutaenous IH are encountered. In case of hepatic haemangiomatosis, additional laboratory testing to look for thrombocytopenia and hypothyroidism should be performed.[22]
IH on the eyelid may occlude the visual axis or compress the eyeball and the cornea. This can lead to permanent impairment of the visual function due to strabismus, astigmatism or amblyopia.[23] Therefore, infants with periocular IH should have eye examinations and sometimes an ultrasound or Magnetic Resonance Imaging (MRI) to explore the intra-orbital extension.[10]

Indications for Treatment: Risks and Complications

Since most IH have an uncomplicated course and go in regression spontaneously most do not need treatment (wait and see policy). However, occasionally they may cause life-threatening risk, functional impairment, cosmetic risk or local complications, like ulceration or bleeding. In those cases treatment may be indicated.

Ulceration is the most common complication of IH and is found in approximately 23% of the patients.[9] Ulceration is more commonly seen in IH in the face and genital area and frequently occurs in the first 3 months after birth.[24] Ulceration can be very painful and so therefore, proper wound care and adequate pain relief is needed. In the case of secondary infection, treatment with antibiotics may be necessary. Ulceration will leave a scar after healing which can be disfiguring. Ulceration can also be complicated by bleeding and may occasionally lead to severe anaemia in need of transfusion.[10] IH in the beard region, subglottic IH, extensive IH or hepatic haemangiomatosis can cause a life-threatening by risk of airway obstruction and heart failure respectively.[22, 25-27] IH located in the face can be responsible for functional impairment, especially IH on the eyelid, lips, nose and ear. Extensive bleeding may occasionally complicate IH, especially in IH in the gastrointestinal tract.[28] Finally, IH can lead to cosmetic impairment, especially in the case of IH in the centre of the face; IH with a large subcutaneous component can lead to anatomical deformities and IH with extensive teleangiectasia can lead to necrosis.[10]

Since most IH growth is completed by 2 months of age, IH which is at risk of complications needs close observation during the first weeks of life.[6] And, if necessary, treatment should be started as soon as possible.

In deciding whether to start treatment it is important to take all characteristics of the patient and his/her IH into account. Treatment of individual IH is determined by the size of the IH, its morphology (localised/segmental) and its location, as well as the presence or risk of complications, likeliness of scarring or (permanent) disfigurement, the age of the infant, and the growth rate or involution rate.[5, 29]

Léauté-Labrèze *et al*.[10] suggested treating IH in case of life-threatening risk (airway obstruction, cardiac distress, bleeding etc.), functional risk (orbital, ear, nasal, and perineal IH), painful ulcerated IH, and cosmetic risk (segmental facial IH, IH of the nose, lips or eyelids, breast IH in girls).

Treatment of IH

A range of medical and surgical treatment options for IH is described in the literature.

From 1930 to 1950 x-irradiation therapy was widely used as an effective treatment of IH. In the sixties, systematic corticosteroids were found to be an effective treatment for IH and for a long time this has been the first choice treatment. However, besides varying efficacy, numerous serious side effects can complicate the treatment of IH with systemic corticosteroids.[30]

In 1989 the pulsed dye laser (PDL) became commercially available, and is used in the treatment of IH.[31] Interferon-α was first described as a novel therapy for IH in 1991 but is associated with severe neurotoxicity.[31, 32] Other treatment options described are cytostatics, like vincristine and cyclophosphamide. Surgical debulking or complete resection are used in the treatment of IH as well.[22]

Propranolol

Propranolol is a lipophilic, non-selective beta blocker released in 1964. Since then, the agent has been widely used in paediatric cardiology. In 2008, the efficacy of propranolol, a non-selective beta blocker, on IH was accidently discovered.[33] In two children propranolol treatment was started because of cardiac complications due to the treatment with systemic corticosteroids. The IH stopped growing and early and rapid involution was observed.[33] Since then many others reported equally favourable effects of propranolol treatment in IH even after the proliferation phase and in ulcerated IH. Propranolol is now seen as the first choice treatment for IH.

The working mechanism of propranolol in the treatment of IH is not completely understood but it is thought to originate from vasoconstriction of capillaries. This causes discoloration and softening of the tumour, as well as decreased expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), leading to a decrease of proliferating endothelial cells.[34, 35] Furthermore, propranolol induces apoptosis of capillary endothelial cells by blocking IH Glut-1 receptors and inhibits the expression of angiogenic and extracellular matrix degrading proteinase (MMP-9) and human brain microvascular endothelial cells (HBMEC), which may result in an anti-angiogenic effect.[36, 37] These mechanisms involve the beta-2 receptor blockade pathway.[34, 37] Itinteang *et al*.[38] recently suggested that propranolol may act via blockage of beta-1 receptors in the kidneys, leading to suppression of the renin-angiotensin-aldosterone system (RAAS system) by reduction of renin activity and thereby decreasing the conversion of angiotensinogen to angiotensin I, and finally to angiotensin II. This, together with a reduction of the VEGF concentration, causes inhibition of proliferating CD34+/VEGFR-2+ endothelial progenitor cells in the capillaries of proliferating IH.[38]

There may be currently unknown mechanisms through which beta blockers mediate their effect on IH.

Due to beta-2 receptor blockage, propranolol can be associated with side effects. The most common side effects of the treatment with propranolol are hypotension, hypoglycaemia, bronchial hyperreactivity, cold extremities, restless sleep, hyperkaliemia and diarrhea.[39-44] Symptomatic hypoglycaemia can be a serious complication and patients using propranolol may be especially vulnerable to hypoglycaemia during periods of prolonged fasting. Therefore propranolol should be given during feeding and caution should be taken in young children, in case of a low birth weight, illness, reduced food intake and in combination with oral corticosteroids.[36, 43] Other side effects are less life-threatening and usually transient, but may lead to discontinuation of the treatment.

Protocols for initiation of therapy, dosing, monitoring, and the duration of treatment vary widely and there are no research data available on the preferred age to start treatment, the optimal dosage, the duration of treatment, and the criteria for stopping treatment. In our opinion treatment with beta blockers should be started as early as possible, preferably during the proliferation phase. An early start of the treatment can prevent complications. However it has also been demonstrated that propranolol could be effective in children older than one year.[43] In our experience propranolol treatment can be started in the outpatient clinic in all children aged >1 month. Before starting propranolol a careful cardiac (family) history should be taken and an electrocardiogram (ECG) should be performed to detect any pre-existent cardiac conduction disturbances. We recommend a starting dosage of 1.0 mg/kg/day in two or three times daily doses. The dosage can be gradually increased to 2.0-3.0 mg/kg/day (adjusted dosage in patients at risk for side effects). During treatment propranolol dosage can be adjusted for weight.[43] During this treatment all patients should be evaluated frequently (e.g. in the beginning every 2-3 weeks, later on monthly) to judge the efficacy and monitor possible side effects (measurement of blood pressure and heart rate). The duration of the treatment with propranolol will depend on the type of IH, the indication for treatment, and the time of starting the treatment. To prevent rebound growth after stopping the treatment propranolol should be continued during the proliferation phase (approximately until the age of 9-18 months). Of course the individual approach can differ strongly between patients, and so patients should be treated on a case-by-case basis.

Randomised controlled trials should prove the efficacy, safety and treatment regimen of propranolol.

Topical Timolol

Topical timolol has been described by different authors as effective in the treatment of small superficial IH and even ulcerated IH.[45, 46] Timolol is a non selective beta blocker and has been used by ophthalmologists for the treatment of glaucoma since 1978. In most IH studies a timolol 0.5% gel forming solution is used for topical application and positive results have been described. However, timolol is a very potent beta blocker and systemic absorption has been suggested.[47] Therefore systemic side effects may occur and monitoring heart rate is recommended.[47]

Other Treatment Options

Since the first publication of the effective treatment of IH with propranolol few other beta blockers are described as effective in IH. The use of a hydrophilic, selective beta-1 blocker could prevent the side effects attributable to the beta-2 activity and lipophilicity of propranolol. We have shown a good clinical response to atenolol treatment, a hydrophilic, selective beta-1 blocker, in two cases of IH.[48] Since then we have treated up to 75 patients with atenolol with good results and few side effects, especially no hypoglycaemia and bronchial hyperreactivity (submitted data). The working mechanism of beta blockers acting via the renin-angiotension-aldosterone (RAAS) system may explain the effect of atenolol in the treatment of IH.[38] This also suggests that other drugs blocking the RAAS system, like ACE inhibitors, may be effective in the treatment of IH. Recently captopril has been described as effective in the treatment of IH.[49]

Furthermore rapamycin, a calcineurin inhibitor, has been suggested as a treatment option for IH.[50] Rapamycin is used in the treatment of kaposiform hemangioendothelioma and has anti-vasculogenic activity.[51] The efficacy in the treatment of IH has yet to be proven.

Finally, topical propranolol 1% ointment has shown efficacy in the treatment of superficial IH.[52]

Future studies

There are still several uncertainties in the treatment of IH with beta blockers. Clinicians are getting more experience with the treatment of IH with beta blockers and indications are changing. Previously, only life-threatening IH were treated with systemic corticosteroids but nowadays it is also initiated in cosmetically disturbing IH propranolol. It is unknown whether the long-term outcome of the treatment for cosmetic indications is favourable above the natural course.

Future studies should provide clarity about the best treatment regimen. Maybe it is better to first start with topical treatment and, if not sufficient, to switch to an oral beta blocker. However, it is not so easy to determine when the treatment is insufficient, and starting with topical treatment in cases where systemic treatment is a better option may delay results.

Lastly, no data are available on the possible side effects of long term treatment of healthy children with beta blockers. Therefore further clinical studies about the treatment of IH with beta blockers are necessary.

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Influence of Lipid Profile on Serum Levels of NT-proBNP, IL-23 and Resistin in Male Psoriatic Patients

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Introduction

Psoriasis is a systemic inflammatory disease, which is estimated to affect 120-180 milion people worldwide, and its incidence is increasing.[1] Despite extensive research, the pathogenesis of psoriasis is not entirely understood.[2] Th1 immune response dominates in psoriasis, but dendritic cells, Langerhans cells, Th17, Th22 and regulatory T lymphocytes also play an important role in regulating the immune response in psoriasis.[3-5] It seems that keratinocyte hyperproliferation and impaired diffentiation observed in psoriatic plaques is due to overexpression of many cytokines and their receptors.[6] Therefore, novel cytokine and antycytokine medications have been introduced.[7] However, the immunological disturbances are not limited to skin lesions and may exert systemic effects. Multiple psoriasis comorbidities have been recognised including atherosclerosis, obesity, hypertension, coronary artery disease and type 2 diabetes.[8] Additionally, concomitant metabolic disturbances, such as lipid abnormalities and hyperuricemia have been reported.[9, 10] Psoriatic patients are also at an increased risk of cardiovascular events.[11, 12] A connection between psoriasis and the metabolic syndrome has also been suggested, and this is believed to be the link between psoriasis and cardiovascular and diabetic complications.[13] The above mentioned comorbidities may negatively influence the quality of life and significantly decrease life expectancy in psoriatic patients.[14] That is why any new information concerning complex interactions between psoriasis, metabolic syndrome and cardiovascular disease (CVD) may be crucial for identifying high risk patients and introducing proper management and prophylaxis. In this study we have decided to investigate the levels of IL-23 (interleukin 23), resistin and NT-proBNP (N-terminal prohormone of brain natriuretic peptide) in serum of normolipidemic and hyperlipidemic psoriatic patients to determine if lipid disturbances can modify serum profile of these parameters.

Fat tissue cells (adipocytes) secrete bioactive adipokines (hormones, cytokines and growth factors) that modulate the inflammatory and immune responses and regulate lipid and glucose metabolism.[15, 16] The role of many adipokines in the pathogenesis of psoriasis, CVD and metabolic syndrome has been suggested.[17] Resistin, a 108 amino acid polypeptide, is mainly synthesised by fat tissue macrophages and monocytes,[18] but also in placenta, pancreas, bone marrow, joint tissue and peripheral blood,[17] Resistin increases insulin resistance,[19] but also influences the inflammatory response by stimulating the release of TNF-α and IL-12.[20] Moreover, elevated resistin levels were found in psoriatic patients and in type 2 diabetes patients during myocardial infarction.[17]

IL-23 is produced by dendritic cells and other antigen presenting cells,[21] and is a key cytokine in peripheral tissue inflammatory response.[22] IL-23 stimulates type 1 T cell immune response and increases the synthesis of IL17, IL-22 and TNF-α by Th 17 cells.[21] The role of IL-23 in autoimmune diseases has been suggested, as it promotes immunogenic presentation by antigen presenting cells.[23] Significantly increased IL-23 levels have been reported in psoriatic patients,[24] but also in obese patients.[25] Interestingly monoclonal antibodies against IL-12/IL-23 result in significant decrease of IL-17[26] and regression of psoriatic lesions.[27] Considering the suggested role of IL-17 in the pathogenesis of atherosclerotic plaques, inhibition of IL-17 synthesis may be beneficial in preventing atherosclerosis.[26]

NT-proBNP is 76 amino acid N-terminal fragment of brain natriuretic peptide that is used for screening and diagnosis of congestive heart failure.[28] A positive correlation was found between the level of NT-proBNP in blood serum of psoriatic patients and heart disease.[29]

Lipid disturbances appear to be an important part in the pathogenesis of psoriasis. Most studies point to an increase in total cholesterol, LDL cholesterol and triglycerides and decrease in HDL cholesterol.[30] These abnormalities are typical for the metabolic syndrome and can contribute to the cardiovascular comorbidities of psoriasis. Additionally, many cytokines, such as TNF-α, IL-1, IL-6, IL-8, Il-17 and IFN-γ can intensify proatheromatous abnormalities, such as dyslipidemia, insulin resistance, endothelial dysfunction, oxidative stress and clotting system activation.[30] Therefore, psoriasis is considered as an immunometabolic disease. Influence of lipid disturbances on IL-23, NT-proBNP and resistin serum levels may have a significant impact on the course of psoriasis and its complications.

	HC (n=20)	HP (n=20)	P Value
NT-proBNP (pg/ml)	20,45 (19,5 – 28,6)	96,15 (63 – 209)	<0,001
IL-23 (pg/ml)	35,45 (31,26 – 45,48)	41,19 (35,43 – 53,81)	0,04
Resistin (ng/ml)	4,32 (3,04 – 5,25)	5,81 (3,78 – 7,17)	0,051

Table 1. Serum concentrations (pg/ml) of NT-proBNP, IL-23 and resistin in hyperlipidemic psoriatic patients and hyperlipidemic controls. Results are presented as median concentrations (interquartile range). HC – hyperlipidemic controls, HP – hyperlipidemic psoriatics.

	NC (n=15)	NP (n=25)	P Value
NT-proBNP (pg/ml)	32,00 (19,00 – 45,8)	43,75 (25,10 – 104,00)	0,046
IL-23 (pg/ml)	23,38 (21,24 – 37,98)	30,23 (25,08 – 40,19)	0,22
Resistin (ng/ml)	4,25 (3,26 – 5,61)	4,89 (3,76 – 6,38)	0,44

Table 2. Serum concentrations of NT-proBNP, IL-23 and resistin in normolipidemic psoriatic patients and normolipidemic controls. Results are presented as median concentrations (interquartile range). NC – normorlipidemic controls, NP – normolipidemic psoriatics.

Material and Methods

The study protocol was accepted by the ethics committee of the Medical University of Lublin. All participants signed an informed consent to participate in the study. Study participants had Polish nationality, were inhabitants of Lublin and Lublin area and were of European ethnic origin. The studied group consisted of 45 previously untreated male psoriatic patients, 20 of whom were hyperlipidemic (HP) and 25 normolipidemic (NP). Mean psoriasis area severity index (PASI) score in the HP group was 25,24 ± 4,16 SD (standard deviation). In the NP group mean PASI score was 23,98 ± 4,14 SD. The control group consisted of 20 hyperlipidemic (HC) and 15 normolipidemic (NC) healthy volunteers without psoriasis. The control group was matched by BMI and age to the psoriatic group. Subjects with concomitant diseases potentially disturbing lipid metabolism (cardiovascular diseases, hypertension, diabetes mellitus, thyroid gland disorders, nephritic syndrome, chronic kidney failure and obstructive liver disease) and a recent history of infections were not included in the study.

Serum levels of total cholesterol <200 mg%, LDL-cholesterol <120 mg% and total triglycerides <200 mg% were considered as normolipidemic.

Blood samples were drawn in fasting condition between 8:00 am and 10.00 am into clot tubes in volumes of 7 ml, prior to the antipsoriatic treatment. Serum was separated from the collected blood samples by centrifugation for 10 min at 2000 rpm, aliquoted and stored frozen at -20°C until analysis.

The concentration of NT proBNP in blood serum was estimated with the use of IMMULITE® 2000NT-proBNP (Diagnostic Products Corporation, USA) chemiluminescence kit. Resistin and IL-23 serum concentrations were evaluated by enzyme immunoassays: Human IL-23 enzyme-linked immunosorbent assay (ELISA) (Diaclon, France) and Human Resistin ELISA (BioVendor, Czech Republic). Triglycerides, total cholesterol and LDL-cholesterol serum levels were estimated using Triglycérides Enzymatique PAP 150 (bioMérieux, France), Cholesterol RTU (bioMérieux, France) and LDL Cholesterol Direct (bioMérieux, France) enzymatic kits, respectively.

The statistical analysis was performed using Statistica (Statsoft, Poland) software. Results were presented as median concentrations (interquartile range) in pg/ml or ng/ml. Differences between the groups were evaluated with the Mann-Whitney test. $P < 0,05$ was considered as statistically significant.

Results

In the HP group, median concentrations of NT-proBNP and IL-23 were significantly increased in comparison to the HC group (96,15 vs 20,45 pg/ml and 41,19 vs 35,45 pg/ml, respectively) (Table 1). The difference in median concentration of resistin between HP and HC groups was not statistically significant (5,81 vs 4,32 ng/ml), however with the p value of 0,051, a trend towards significance can be postulated (Table 1). In the NP group, the median concentration of NT-proBNP was significantly increased in comparison to the NC group (43,75 vs 32,00 pg/ml) (Table 2). Median concentrations of IL-23 and resistin were not significantly different between the NP and NC groups (30,23 vs 23,38 pg/ml and 4,89 vs 4,25 ng/ml, respectively) (Table 2).

Discussion

The concept of psoriasis is changing from the traditional inflammatory skin disorder of unknown etiology into a systemic inflammatory disorder.[31, 32] A possible connection between psoriasis and atherosclerotic coronary artery disease was proposed by Reed *et al.* in 1961.[33] In 1973 it was first suggested that psoriasis should be considered as a condition, which has high association with occlusive vascular type diseases.[34] In the last decade, numerous papers suggesting a connection between psoriasis and cardiovascular diseases as well as metabolic syndrome were published.[35] Increased levels of acute-phase proteins, C Reactive Protein (CRP) and fibrinogen, that are observed in the course of psoriasis, are also risk and prognostic factors of cardiovascular diseases.[35] Many epidemiological studies indicate that there is a connection between long-term risk of cardiovascular diseases and psoriasis. The mechanism of these interactions remains unclear, but probably includes

various conventional and nonconventional cardiovascular risk factors.[31]

Furthermore, the risk of various cardiovascular diseases, such as atherosclerosis, congestive heart failure, arterial hypertension, ischaemic heart disease, myocardial infarction and stroke, is presumably increased in psoriatics.[36] It has been reported that changes in renin-angiotensin system activity and higher concentration of endothelin observed in patients with psoriasis may lead to development of cardiovascular diseases.[37] According to Ena *et al*. hypertension, cardiovascular disorders and diabetes mellitus are more likely to develop in psoriatic patients.[38] Many biomarkers of psoriatic inflammation are discussed in the literature. Some of them can also be correlated with CVD.[39] It seemed worthy to estimate the serum level of NT-proBNP, which can be elevated both in CVD and the psoriatic process.[29]

Acute coronary syndrome is associated with increased erythrocyte sedimentation rate, as well as increased levels of some blood chemokines and cytokines including IL-6, IL-8, IL-10, IL-18, TNF-α and monocyte chemoattractant protein–1.[40] These disorders are similar to those observed in psoriasis. It is known that chronic inflammatory disorders (rheumatoid arthritis, periodontitis, systemic lupus erythematosus, and some types of infections) may enhance acute coronary events.[40] Antigen presenting cells, macrophages and dendritic cells, release IL-23, which belongs to IL-12 cytokine family, consisting of two heterodimer subunits: p40 and p19. Il-23/Th17 axis is thought to play a major role in the pathogenesis of psoriasis.[41] There are numerous studies showing that dendritic cells and T cells take part in the pathogenesis of psoriasis. Some reports describe the expression of p40 and p19 subunits in epidermal cells, suggesting that keratinocytes have the ability to produce IL-23. According to Piskin *et al.* expression of the p40 subunits was twofold higher in psoriatic lesions in comparison to healthy skin.[42]

It is known that mediators of inflammation, like TNF-α, stimulate subcutaneous fat cells, adipocytes, to produce proinflammatory cytokines as well as CRP in chronic inflammation milieu, which is observed in psoriasis. Recent studies indicate the possibility of a complex interaction between adipocytes, psoriatic inflammatory process and other coexisting inflammatory diseases. A decrease in adiponectin expression with a simultaneous increase of leptin and resistin expression was observed in psoriasis.[32]

Resistin is a secretory factor, associated with inflammation and leading to insulin resistance.[32] This adipokine plays a crucial role in connecting obesity and diabetes mellitus. Interestingly, resistin can be used as a prognostic factor in arteriosclerosis and in estimating the severity of myocardial infarctions. Resistin stimulates growth and migration of endothelial cells and increases expression of vascular endothelial growth factor receptor 1 and 2 (VEGFR-1 and 2) and metalloproteinases 1 and 2, thus causing angiogenesis *in vitro* and enhancing the psoriatic process.[43]

Our results of serum IL-23 levels confirm the results obtained by Coimbra *et al*., who also determined the plasma concentration of this cytokine in patients with psoriasis.[44] The authors reported significantly increased plasma concentrations of IL-23 in psoriatics in comparison to controls (70,5 vs 50,1 pg/ml). We found a significantly higher concentration of IL-23 in the hiperlipidemic psoriatic group, but not in the normolipidemic psoriatic group in comparison to respective controls.

Similarly, NT-proBNP concentrations were significantly higher in hiperlipidemic psoriatic patients. It is worth noticing that the differences in NT-proBNP concentrations between psoriatic groups and respective controls were much more profound in the hiperlipidemic group. According to the literature, NT-proBNP can be used as cardiovascular disorders biomarker in both hyperlipidemic and normolipidemic patients with psoriasis.[45]

In our study no differences were found in the serum concentrations of resistin. However, in the hiperlipidemic psoriatic group the difference was nearly significant. A statistically insignificant increase of serum resistin concentration in psoriatics was also reported by Ozdemir.[46] Other groups have reported statistically significant increases of resistin levels in psoriatics.[44, 47, 48]

It has been recently proposed that the number of circulating endothelial progenitor cells, which contribute to neovascularisation and play an important role in repair of endothelial injury, may be reduced in psoriasis resulting in endothelial dysfunction and increased CVD risk.[49]

Our results show that lipid disturbances may enhance the changes of NT-proBNP, IL-23 and resistin serum levels in psoriatic patients. Lipid profile of psoriatic patients should be taken into consideration to prevent study bias.

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Immunocryosurgery for Basal Cell Carcinoma: An Audit for Combination, Minimally Invasive Approaches

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A paradigm change is currently going on in the treatment of non-melanoma skin cancer, and in particular basal cell carcinoma (BCC), with an emerging shift mainly from 'traditional' surgical approaches to newer minimally invasive procedures and biologically targeted pharmacological interventions. Important steps in the understanding of the pathobiology of this cancer as well as increasing patients' numbers impose this change. Nowadays BCC is the most frequent cancer in humans, and additionally a malignancy with rapidly increasing incidence, in particular among Caucasians worldwide. In Canada, for example, the lifetime risk to get BCC is 11.0% in women and 12.3% in men,[1] while in Australia it is predicted to affect yearly up to 2,614 /100,000 males older than 60 years of age.[2] Moreover, from a therapeutic point of view, a major challenge is that half of these patients will develop a second or multiple tumours, with most of them located on the face.[2]

Currently, gold standard in the therapy of 'difficult-to-treat' BCC is the micrographic (Mohs') surgery with optimised 5-year recurrence rates of 0.8–1.7%,[3] however this is an approach that, besides being labour intensive and requiring trained personnel,[4] shares all the core limitations of the surgical approaches to BCC treatment. Metastases of this tumour are extremely rare and thus do not constitute an assessable problem in BCC therapy as a whole. Nevertheless, surgical modalities would be challenged in the treatment of local recurrences and multiple lesions, especially in anatomical regions that are relatively difficult to reconstruct[5] (compare Figure 1A). All of these challenges explain the increasing interest in exploring minimally invasive procedures for the treatment of the majority of BCC cases, ideally in the office-based / outpatient settings.

Although novel pharmacological modalities for the treatment of both confined primary and advanced BCC are on the pipeline,[6-8] combination approaches of existing/established modalities have not yet been thoroughly evaluated. Such an efficacious pathophysiologically designed combination modality for BCC is the application of cryosurgery (liquid N_2, open spray, 2 freeze-thaw cycles of 15sec effective ice-ball duration each) during continued daily 5% imiquimod cream.[9, 10] This treatment protocol, that we have termed "immunocryosurgery", as cryosurgery is carried out during and not before immune modulation with topical imiquimod ("cryoimmunotherapy" or "adjuvant imiquimod"), is under continued evaluation in the Dermatology Department of the University of Ioannina since its introduction in 2004.[11, 12]

After having established the effectiveness and optimised the combination scheme of this approach in a series of founding preliminary studies and larger cohorts,[9-13] we currently look over the outcomes of the systematic application of this modality to more than 250 non-melanoma skin cancer tumours in >150 patients (Figure 1), including large not-amenable to surgery BCC, patients with multiple tumours, extensive Bowen's diseases or actinic keratoses and a few cases of locally advanced squamous cell carcinoma, the later with mainly palliative intention. The results of a recently completed prospective clinical trial (www.clinicaltrials.gov;NCT01212562) showed that the initial clearance rate of a single 'standard' 5-week immunocryosurgery course in primary, non-superficial BCC with clinical diameter <2cm is 116/119 (97.5%) tumours in 79 patients.[13] During follow-up, relapses occurred in three additional BCC sites and accordingly, the relapse-free rate after a single immunocryosurgery treatment cycle was 95±2% (Kaplan-Meier method). Retreatment of the initially non-responded (N=3) and of the relapsed tumours (N=3) with additional immunocryosurgery cycles resulted in an overall treatment efficacy of 99% (least follow-up period 18 months, mean 29 months). Moreover, in a comparative trial we had already confirmed the significance of the timing of cryosurgery for the outcome of the treatment with the combination of cryosurgery and imiquimod.[10] We showed that in accordance with our theoretical prediction (see below) cryosurgery during -and not before- imiquimod treatment optimises the effectiveness of this approach.[10]

However, the high efficacy of this method and the decisive impact of the timing of the combination denotes at an least additive interaction of the two separate modalities in immunocryosurgery. Figure 2 displays a modified isobologram plot of the efficacy of the combination of cryosurgery and imiquimod to treat non-superficial, primary BCC and the anticipated isoeffect region of the efficacy of immunocryosurgery (95±2% relapse free rate[13]) ±95% confidence intervals. It is obvious from the knowledge of the corresponding effectiveness of each of the

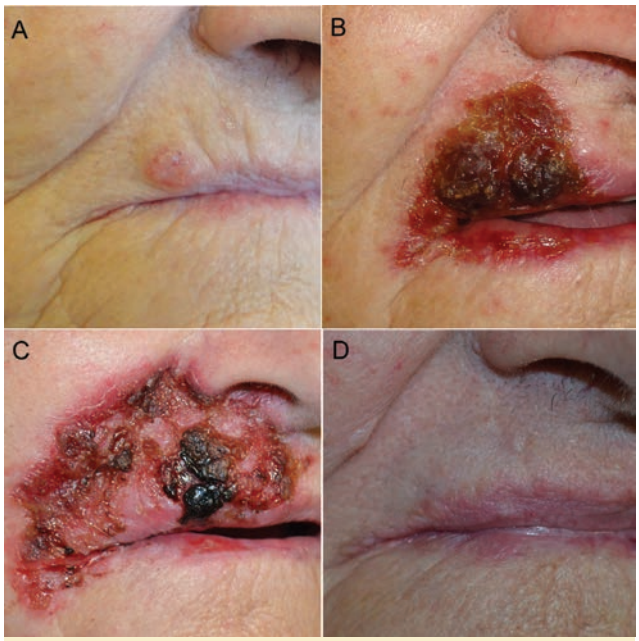

Figure 1. Treatment of a nodular BCC with immunocryosurgery in a 74 year old female patient. Panel A: At baseline the tumour had a maximum diameter of 9mm and infiltrated the upper lip. Panel B: Day of cryosurgery session (day 14 of immunocryosurgery cycle). The patient had been applying imiquimod daily for 14 days at bedtime and an area corresponding to the tumour was treated with 2 cycles of cryosurgery (liquid N_2, open spray, 15 sec each). Panel C: The patient at the end of treatment (day 35). The local inflammatory reaction is potentiated by cryosurgery and the continued uninterupted daily application of imiquimod. Panel D: The tumour site at 12 months follow-up appointment, with sustained complete tumour remission and an excellent cosmetic outcome.

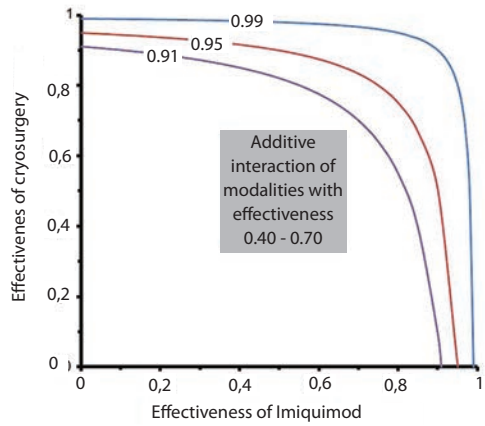

Figure 2. Isobole display of the treatment of primary, non-superficial basal cell carcinoma with immunocryosurgery: evidence for supra-additive (synergistic) interaction of topical imiquimod and mild cryosurgery. The lines represent iso-effect curves of the efficacy rate of immunocryosurgery (95%) and its 95% confidence intervals (91-99%).[13] Note that an anticipated additive interaction of the two modalities is predicted to be distinctly inferior to that achieved by immunocryosurgery, since none of the two modalities alone is expected to effect clearance rates well-above 70%, which is required for an additive efficacy >91%.

separate modalities that immunocryosurgery is significantly more efficient than that predicted for a simply additive interaction. Actually, for nodular BCC, as currently recruited, corresponding effectiveness rates of monomodal imiquimod do not exceed 50%, maximal 70% in different studies (compare:[14, 15]) which means that efficiency levels like that presently achieved with immunocryosurgery are only expected for the case of cryosurgery effectiveness of at least 70% in a monomodal setting. However, according to established experience this is a quite unreliable assumption, particularly for the rather mild cryosurgery session of two cycles of 15 sec freezing time each, as presently practiced. Hence, our analysis strongly favours a supra-additive (synergistic) interaction mode of the two modalities within the current immunocryosurgery combination design.

The above evidence for the synergistic potential of cryosurgery and imiquimod prompts the question on the biological background of this synergy in immunocryosurgery. The mechanism by which immunocryosurgery effects tumour destruction seems to be quite complex, and may result from mutual potentiation of the effects of the two modalities on tumour cell survival through direct cell killing actions and indirectly through tumour vascular bed alterations and targeted immunomodulation.[12, 16] Both cryosurgery and imiquimod are multifaceted modalities with respect to their tissue and cell effects,[17, 18] a fact that underlies the biological basis for their effective therapeutic combination. According to our working model, pretreatment with imiquimod creates a pro-apoptotic environment within and around the tumour[17] that may intensify the immediate destruction of tumour cells during the 'physical' phase of the subsequent cryosurgery. This might be particularly important for the more peripheral parts of the treated lesion, where freezing temperatures lower than -40 °C - which is considered prerequisite to directly kill tumour cells by cryosurgery - are not effectively achieved in many instances in the clinical practise.[18] Furthermore, there might be enhanced destruction of the vascular tumour bed during immunocryosurgery initially through imiquimod-induced increased killing of apoptosis-predisposed endothelia and subsequently through further inhibition of tumour neovascularisation due to the continuous application of imiquimod.[19, 20] Lastly, and probably more importantly, immunocryosurgery seems to fulfill the prerequisites to induce an effective antitumour immune response at tissue level (Figure 3).

Thus, in the case of BCC it is known that tumours grow within a Th2 cytokine-dominated microenvironment of actively suppressed and/or by-passed antitumour host response.[21] This aberration can be partially restored by topical imiquimod,[17] probably through the attraction and *in loco* activation of immature plasmacytoid dendritic cells (pDCs). This latter step is regarded essential for the commencement of the antineoplastic immune response cascade:[22] Naive pDCs are attracted into the tumour by imiquimod treatment,[20, 23] however this does not suffice for complete tumour clearance in many cases. At this point the role of cryosurgery seems to be crucial. During cryosurgery, large amounts of 'functionally intact' tumour antigens are liberated into the pro-inflammatory milieu of the imiquimod-pretreated tumour tissue. Within the imiquimod-conditioned environment the newly recruited dendritic cells are loaded with tumour-specific antigens, mature and

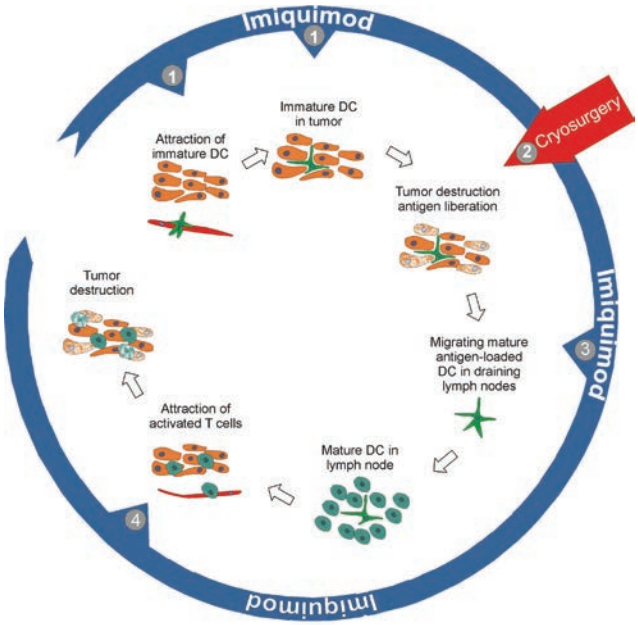

Figure 3. Model of the induction of an effective antitumour immune response (adapted according to[22]) through the immunomodulatory effects of immunocryosurgery (cryosurgery during continued imiquimod application). (1) Treatment with imiquimod effects attraction and accumulation of naïve – immature plasmacytoid dendritic cells (pDCs) into the tumour tissue.[20, 23] (2) Subsequent subcurative cryosurgery liberates huge amounts of tumour antigens in situ through partial tumour ablation that may load the preconditioned pDCs, thus breaking inherent tumour immune tolerance[24, 30] with (3) activation and initial maturation of pDCs in loco[23] that migrate to draining lymph nodes and induce antitumour immunity. (4) Pro-inflammatory signals that result from continued imiquimod application after cryosurgery potentiate the effector phase of antitumour immunity, ultimately participating to tumour erradication.[20, 23, 24]

ultimately prime a cell-mediated immune cascade that may break tumour immune tolerance,[24] in a process that simulates the conditions that are presumed to lead to the development of a so-called "*in situ* dendritic cell vaccine".[25, 26]

The significance of the need for continuous uninterrupted imiquimod availability for the effectiveness of immunocryosurgery is supported by experimental data[27] and is also documented by the observation of increased failure rates of the BCC treatment in patients with poor protocol adherence, who skipped imiquimod application the last 2 days before cryosurgery (unpublished data). Continuous imiquimod application establishes an inflammatory cytokine environment in the tumour basin that is conducive of effective tumour cell death during subsequent cryosurgery. For example, in a prostate cancer model in mice tumour pre-conditioning with TNFa resulted in enhanced efficacy of all anti-tumour aspects of the ensuing cryosurgery that lasted up to 3 days after treatment.[27] Furthermore, local application of imiquimod on the skin has recently been shown to modify the absolute and relative numbers of immune-effector cells either in the circulation of healthy volunteers[28] or in distant organs, like the lungs in an experimental model of *Klebsiella pneumoniae* infection in mice.[29] Likewise, in preliminary experiments we have observed significant alterations in the levels of lymphocytes and dendritic cells that express the skin homing profile (CLA positive) in the circulation of patients during immunocryosurgery for BCC.[13]

In conclusion, the therapeutic effectiveness of immunocryosurgery with cryosurgery during and not before the daily 5 weeks imiquimod application can be satisfactorily explained by available experimental and clinical data, although important details have still to be determined. Furthermore, and in the advent of targeted pharmacological interventions for the treatment of BCC, our results demonstrate the significant potential of effective treatment combinations that could at least partially replace surgery as a first-line treatment approach for BCC.

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An Overview of Random Flap Repair on the Nose after Mohs Surgery

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Introduction

Skin cancer of the nose is frequent. The nose is a difficult area to reconstruct as it is a tridimensional structure with two free margins, which has a potential risk of retraction and consequent asymmetry. The nose is situated in the middle of the face and is important for self recognition and identification. Therefore the reconstruction of the nose after Mohs surgery for epidermal skin cancer has to be performed with extreme prudence, as distortion of the nose is strongly disfiguring and might lead to psychological problems of the patient. As reconstruction with flaps is mostly effectuated from the closest donor site, the defect size should be better defined in relation to the donor site, which in our situation is mostly the nose itself.

Anatomic Subunits of the Nose

Anatomic subunits are regions which vary in skin texture, shade and brightness. The borders of two anatomic subunits enable scars to be hidden.[1] Anatomic subunits are also responsible for our eye defining a nose as such, and this is particularly important for the convexity of the tip and the alar and the concavity of the alar sulcus.[1,2] Any reconstruction of the nose should respect the principles of maintaining and restoring the form and symmetry of the nose.

Anatomy of the Nose

There are three different regions which are important in the anatomy of the nose; the upper half of the back of the nose, which is underlied by the nasal bone, the distal half and nasal tip, which is mostly formed by the underlying cartilage and the ala, which is only in the distal and his very proximal part reinforced by a cartilage. Most of the ala is a fatty fibrous tissue, well vascularised and rather stiff.

Vascular Anatomy of the Nose

The vascular anatomy is only secondarily important for the survival of the flaps as we are mostly speaking about random flaps. For the preparation of flaps, a basic knowledge of the vascularisation is essential to avoid accidental bleeding. We differentiate an external vascular network arising from the carotis externa artery, which communicates with the carotis interna artery via the dorsal nasal and ophtalmic artery. The carotis externa system includes the columella branch of the superior labial artery at the base of the nose, the lateral nasal artery in the nasal groove following the crease and giving a branch on the side of the ala which is called naso-alar marginal artery. On the lateral side of the nose is the angular artery which is joining the dorsal nasal artery. The dorsal nasal artery takes its origin between angular and ophthalmic artery and turns caudal on the back of the nose.[3]

Surgical Techniques

One Time Procedures

Second Intention Healing

Second intention healing (SIH) is an important technique to know. Zitelli has published an article which highlights defect depth and surfaceform, which define the outcomes of SIH. In general, any concave surface (alar sulcus, canthus) is an excellent localisation for SIH.[2] The side wall of the nose might be a good localisation for medium deep defects, however on the back of the nose and the tip I would only use this technique for superficial defects (Figure 1). Generally one has to allow the formation of granulation tissue to fill up the defect by using hydrocolloid bandages. If the defect is deep and close to the nostril, one has to observe the patient to avoid retraction and lifting of the ala. One technique to avoid retraction is to control the tension forces by directing sutures which are placed perpendicular to the potentially expected retraction, as we published in 1997.[4]

Full Thickness Skin Grafts

Full thickness skin grafts (FTSG) have, from my point of view, a limited place in reconstructions on the nose. The disadvantages of FTSG are well known. Beside tissue, texture and colour mismatch there is a lengthy healing process before you have a perfect result which, nowadays, even for the elderly but very active generation is a problem. On the other hand, the technique is easy to perform and has low risks. The donorsite for FTSG is general the pre- and postauricular region as well the clavicular region. There are three situations where I would use a full thickness skin graft. 1. A superficial defect of more than one third of the nose. 2. A superficial defect which takes a whole anatomic subunit (in general the nasal ala or lateral side wall, back of the nose), on the nasal ala it might be useful to use a composite graft of the ear

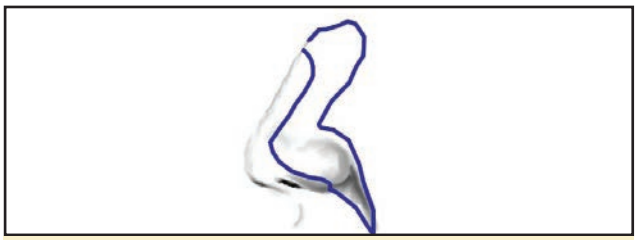

Figure 1. The blue zone delimitates the region where SIH gives good to excellent results even with deep defect.

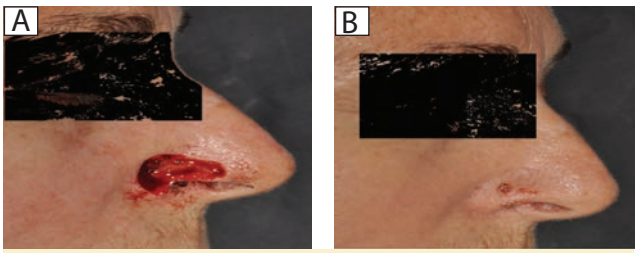

Figure 2A. Deep defect of the ala **2B.** Reconstruction with a composite graft of the ear.

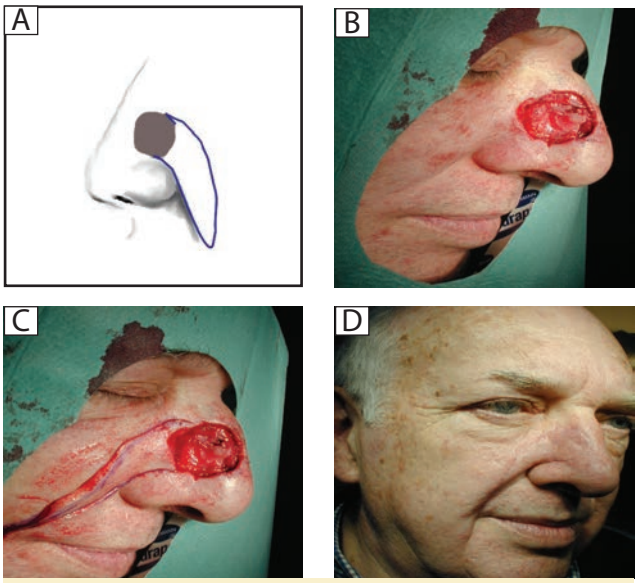

Figure 3A. Design of an island pedicle flap from the melalabial fold. **3B.** Extended defect on the sidewall of the nose **3C.** Reconstruction by an island pedicle flap **3D.** Result after one year.

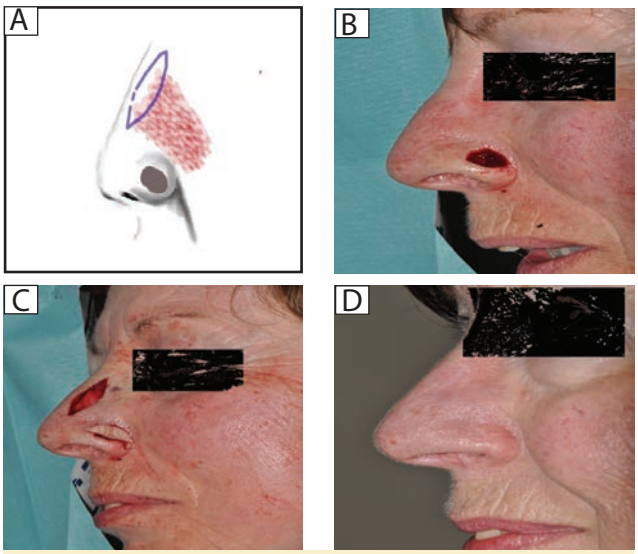

Figure 4A. Design of a myocutaneous island pedicle flap pediculated on the *m. transversus nasalis*. **4B.** Deep defect on the ala **4C.** Flap moved into the defect without tension **4D.** Result after one year.

with underlying cartilage to recreate the convex surface (Figure 2A, 2B).[3] In a deep defect of the nasal sulcus. In this situation I would use a FTSG which was thinned out and sutured down into the alar groove to avoid pinkushening and unpleasant buckling of the latter.

Flaps

Advancement Flaps

From the whole panoplia of advancement flaps I mostly use only the pedicle island advancement flap and the musculocutaneous island advancement flap. The pedicle island flap is used in two situations 1.) A large deep defect on lateral nasal side wall (Figure 3A, B, C, D) 2.) A defect of the canthal area. The disadvantage of these two flaps are their geometric shape and tendency for trapdoor deformity. Trapdoor deformity can mostly be treated by injecting corticosteroids into the flap by the 4th week. Wide undermining has, in my experience, shown only a limited effect on trapdoor deformation. In some cases dermabrasion might be necessary to camouflage the geometric shape. I stongly recommend to prepare the flap as published in 2004 and 2012.

The musculocutaneous pedicle island flap is used for deep defects of the ala (Fig 4A, B, C, D). The aim is to harvest the flap on the border between the anatomic subunits between lateral sidewall and back of the nose. This lancet formed skin is pedicled on the transversal nasal muscle and tunneled under the skin bridge between the donor site and the defect, and then brought into the defect on the ala. Care has to be taken so that the patient does not present a nasal septal deviation to the reconstructed side in order to avoid walve formation of the nostril.[5]

Rotation Flaps

Rotation flaps are extremely important for nasal defect reconstruction. This flaps can be used for nearly all anatomic subunits. The most well known is the so called hatched flap for defects on the tip and back of the nose (Figure 5A, C, D). The donor site for a rotation flap is the whole surrounding of the flap, which also means the distal part of the defect opposite the flap. This point is essential, and in some cases one has to be careful not to shorten the distance nose tip - glabella crease. Therefore one has to be attentive to avoid lifting of the nose tip mostly in young patients and/or creation of a "greek nose" with loss of the nasoglabellar crease. This side effect can mostly be avoided in harvesting the flap very laterally and by "thinking large", that means a flap which is at least four times the defect diameter.

Another rotation flap is the sail flap published by Santhoul, (publication unfortunately not avaliable) (Figure 5B). This is one of my favoured flaps for small defects on the distal lateral side wall of the nose. This flap hides the scarline perfectly between the anatomic subunits of the nose side wall. If the defect is too distal (nose tip), this flap will create unilateral lifting of the nose tip.

For small defects on the slightly lateral nose tip I like to use a rotation flap from the caudal tip of the nose. (Figure 6A, B, C) This flap is nearly invisible

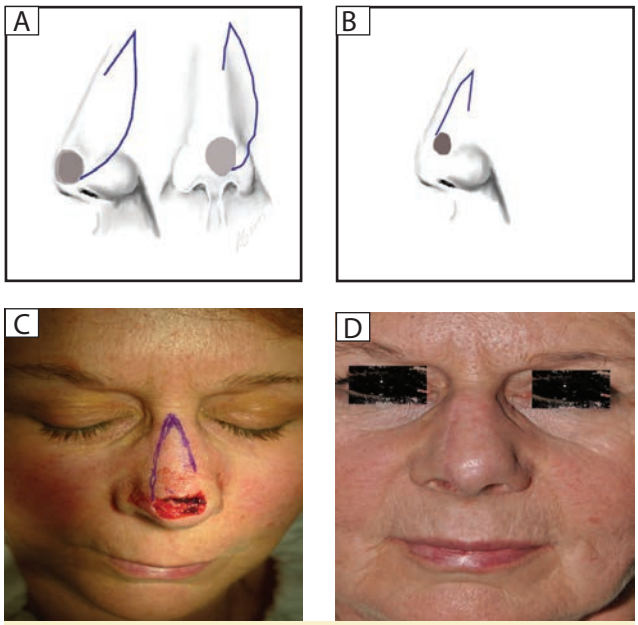

Figure 5A. Design of hatched flap for a defect on the tip of the nose. **5B.** Design of a so called sail flap for a small defect on the lateral sidewall of the nose **5C.** Reconstruction planned with a hatched flap **5D.** Result after 4 weeks, the oedema will seize after three months.

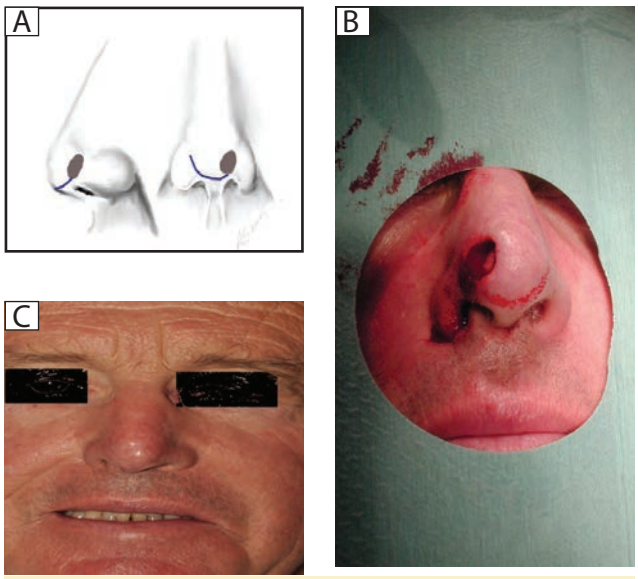

Figure 6A. Design of a rotation flap for a defect on the tip of the nose. **6B.** Tracing of the flap **6C.** Result after one year, note how the scar is hidden in the shadow of the tip of the nose.

as the scarline is on the caudal surface of the nose tip, hidden by the shade of the nose tip. In this flap it is important that the incision line is driven wide on the opposite side of the defect on the other ala to avoid asymmetry of the nostrils. This flap can easily be used in young patients with good elasticity of the skin.[6]

Transposition Flaps

Transposition flaps as a one time procedure are widely used in nasal repair. Contrary to literature I never use a simple transposition flap from the nasolabial fold to cover defects on the proximal ala as a one time procedure. This flap always washes out the nasal sulcus which is difficult to correct in a second time. The transposition flap shows various applications in nasal repair on the back of the nose, on the tip and on the distal ala of the nose in small defects less than one 5th of the nose size. (Figure 7A) There is an overlap between the usefulness of a transposition or bilobed flap, generally if you doubt on the fiesability of a local transposition flap you should process to a bilobed flap on the lateral tip and ala of the nose, mostly for defects of more than one 4th of the nose length. (Figure 7B)

The Bilobed and Trilobed Flap

The bilobed flap produces a combination of rotation and transposition movement. Dependent on the design, the angle of each transposition is varying between 45 – 60° as this was already mentioned by Zitelli for the bilobed flap and others.[3] The sum of the angles define the total rotation at the pivot point, which ranges from 90 to 120 degrees. The design of the flap varies depending on the laxity and thickness of the skin and defects size. The defect should always be evaluated in relation to the nose length, and therefore the bilobed flap is convenient for defects which take not more than one 4th of the nose length and corresponds mostly to 15 mm diameter, as is often mentioned in literature.[7]

The design of the flap for alar defects is shown in Figure 7B, C, D and is generally pediculated medially. This has several reasons; on one hand we respect the borders of the anatomic subunits and we can horizontalise the traction on the closure of the tertiary defect. However, we also try to respect the sulcus of the nasal alar for harvesting of the lobes and try to avoid to cross the nasal sulcus so not to fill out this important landmark for defects on the ala.

Generally we choose the first lobe with a smaller diameter than the defect, but as the tip of the nose is convex and/or the first lobe has to be rotated on itself, one has to be careful not to underestimate the radius or length of the first lobe. The second lobe is designed with a smaller diameter in function of laxity and disponibility in the donor site. When defects are on the tip of the nose as shown in Figure 7E and F, we then base the bilobed flap laterally.

The surrounding skin has to be undermined widely. The first suture is between the first and second lobe (A) and the angle of the defect (B). This gives us the first impression as to whether the flap will move in correctly. In patients with redundand skin (e.g. rhinophyma, status after cryotherapy, scartissue) we prefer to use a trilobed flap as rotation of each lobe is less than 45°.[8]

The Birhombic Flap

The birhombic flap produces a combination of transposition and rotation movement. When the defect is more oval or rectangular and the biggest diameter is in the axis of the ala, the design of the bilobed flap has to be adapted to a birhombic flap. I call it birhombic flap as the design of the first lobe of the flap corresponds to a rhombic flap and the pivot point is not really in the axis of the defect

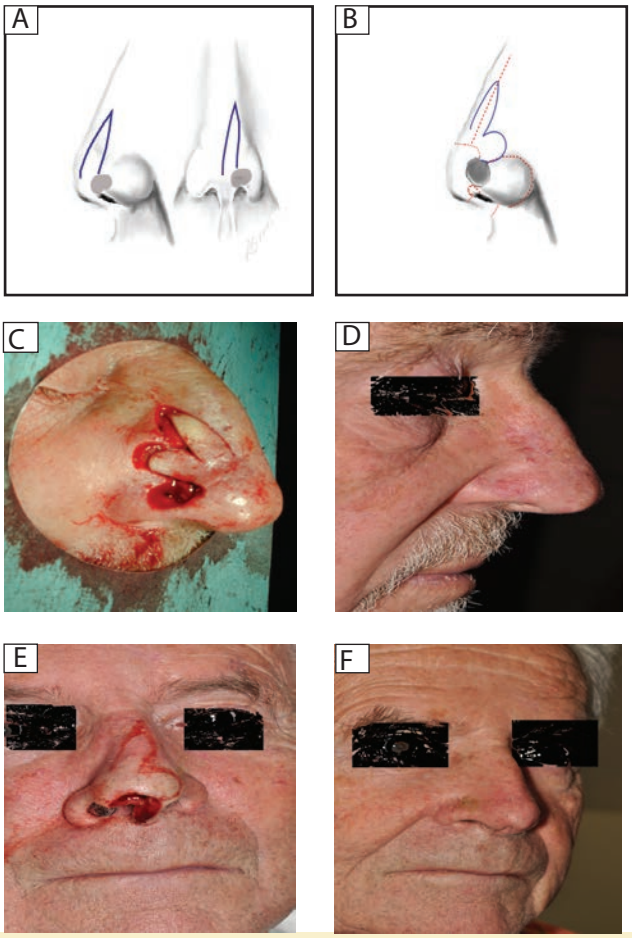

Figure 7A. Design of a transposition flap for a defect on the lateral tip of he nose **7B.** Design of a bilobed flap for a similar defect as 7A but larger. **7C.** Defect on the middle of the ala, design of a medially based bilobed flap, scar lines hidden between anatomic subunits **7D.** Result after one year. **7E**. A laterally based bilobed flap for a defect on the tip of the nose **7F.** Result after one year.

but more cranial as explained in our paper in the *British Journal of Dermatology*.[9] When the defect is partially on the lateral tip or is more on the distal part of the alar, the flap can be pediculated laterally or medially. The more the defect is located on the lateral ala the more the flap is pediculated medially.

The pivot point is in contrast to a classic transposition flap, and is not in the

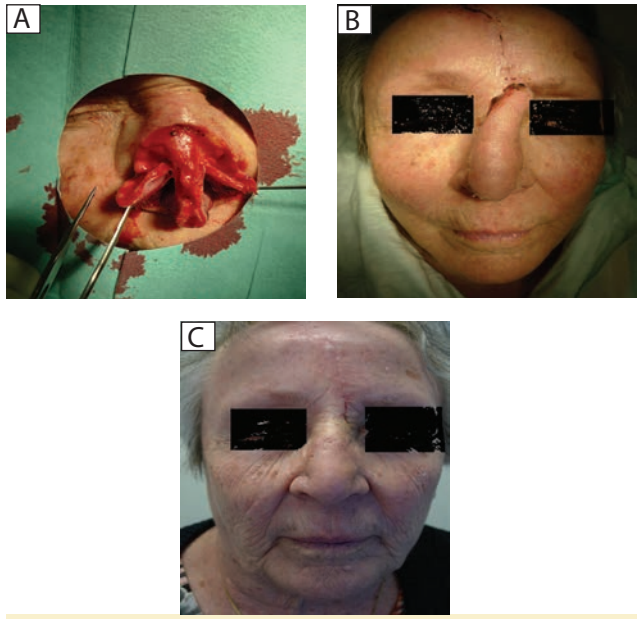

Figure 8A. A through and through defect of the tip of the nose. **8B.** Design of a paramedin forehead flap. **8C.** Result after one year.

length axis of the defect but is in the prolongation of the lateral border of a virtual rectangular defect slightly medial or lateral. In contrary to the classic bilobed flap the lobe needs not to be rotated on itself, therefore the length of this lobe corresponds to the length of the defect.

Two Times Procedures

Pedicled Flaps From the Melolabial Crease

For big defects which are deep sometimes the donor site of the nose is insufficient for local flap repair, and therefore one has to switch to another site, which in this situation is either the front or the cheek.

From the cheek you can often harvest skin to reconstruct the whole or partial ala. I prefer the turned transposition flap to all other techniques for through and through alar defects as we published in the J Dermatol Surg.[10]

For complete ala repair or extended deep defects on the back of the nose a paramedian or median forehead flap is most often necessary. (Figure 8A, B, C).[1, 11]

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Upcoming Congresses and Meetings

6th World Meeting of Interdisciplinary Melanoma Skin Cancer Centers & 8th European Association of Dermato-Oncology (EADO) Congress

14 – 17 November 2012

Barcelona, Spain

The 6th World Meeting of Interdisciplinary Melanoma Skin Cancer Centers & 8th Association of Dermato-Oncology (EADO) Congress welcomes delegates to Barcelona. This year, the conference's main focus will be on melanoma, cutaneous lymphoma and epithelial skin cancers. The plenary sessions, featuring speakers who are recognised experts in melanoma and skin cancer treatment and research, will act as the backdrop for the meeting, and will highlight problem areas and opportunities in melanoma today. This will be followed by a series of Breakout sessions, which are designed to focus attention and lead to new collaborative approaches in key areas, such as strategies for melanoma follow-up examinations and messages for skin cancer prevention. Other topic areas addressed at the conference include early detection and new diagnostic tools, different aspects of epidemiology and prevention and melanoma surgery and immunotherapy.

The 8th Joint BAD/RCP Medical Dermatology Conference

10 January 2013

London, United Kingdom

For the 8th Medical Dermatology Conference, The British Association of Dermatologists, along with the Association of British Neurologists and the British Society for Medical Dermatology have put together an exciting programme, which will focus upon Dermatology and Neurological Aspects of Medical Dermatology. Leaders in the field will present the latest research and findings, and there will be much to interest both dermatologists and other healthcare professionals.

2nd Dermatology Update

28 - 31 January 2013

Val d'Isere, French Alps

The 2nd Dermatology Update is part of the Doctorsupdates annual multidisciplinary conference, which is billed as 'a real festival of medicine.' Meetings will be held in the morning and evening, with the opportunity to enjoy the ambiance of Val d'Isere, one of the finest alpine skiing resorts in the world. Topics planned for this year's conference include Adjuvant therapy in malignant melanoma, Management of VIN – Advances in Medical Therapy and Tuberculosis in the Era of Biological Therapy.

11th Anti-Aging Medicine World Congress & Medispa 2013

04 - 06 April 2013

Monte-Carlo, Monaco

The 11th Anti-Aging Medicine World Congress will be held in Monte-Carlo under the High Patronage of S.A.S. Le Prince Albert II de Monaco. An outstanding programme has been prepared in line with a strong commitment to innovation, expertise, and excellence, allowing attendees to share a wealth of experience as well as teaching-skills. The Scientific Committee of the AMWC have designed a large and mature programme with international faculty members from over 95 countries invited to contribute to the improvement of everyday practice. In addition, following the development of the Preventive and Anti-Aging medicine, the AMWC 2013 will propose numerous advanced academic and clinical sessions with lectures presented by prominent experts in the field, as well as from research centres and universities.

7th World Congress for Hair Research

04 - 06 May 2013

Edinburgh, United Kingdom

This triennial congress is the joint meeting of hair research societies worldwide, and is attended by specialist physicians, dermatologists, surgeons and scientists from academia and industry. Scientific sessions will include contributions from new and established thought leaders in the specialty, and will cover topics such as psychology and hair disorders, androgenetic alopecia, hormonal regulation of the hair and hair follicle development. Additionally, up and coming scientists and clinicians are encouraged to share their latest research findings, as the exchange of ideas will have a major impact upon future research strategies and clinical care.

International Investigative Dermatology Conference

08 - 11 May 2013,

Edinburgh, United Kingdom

The International Investigative Dermatology conference is jointly organised by the Euopean Society for Dermatological Research (ESDR), the Japanese Society for Investigative Dermatology (JSID) and the Society for Investigative Dermatology (SID), and have created an exciting meeting where both quality scientific and social meetings are encouraged. Internationally renowned leaders in the field will present the latest scientific research in a variety of areas

within dermatology. A strong effort is made by all three societies to provide travel grants to gifted young scientists to facilitate their participation in the meeting.

European Wound Management Association (EWMA) 2013

15 - 17 May 2013

Copenhagen, Denmark

The theme of the EWMA 2013 Conference is Organisation and Cooperation in Copenhagen, and is organised in collaboration with the Danish Wound Healing Society (DSFS). The EWMA conference gathers colleagues from all over the world who will meet and benefit from high level scientific presentations, network with fellow delegates and speakers, exchange views and experiences and evaluate clinical practice. The scientific programme will be a mixture of key sessions, workshops, free papers sessions and satellite symposia.

24th Annual European Association of Plastic Surgeons (EURAPS) Meeting

23 - 25 May 2013

Antalya, Turkey

EURAPS mission is to promote the excellence of Plastic Surgery in Europe, as well as stimulating research and coordinating various forms of teaching. The EURAPS Annual Meeting offers an excellent opportunity for attendees to update their knowledge and gain new insights into the field of plastic surgery. The meeting provides the best occasion for fruitful scientific cooperation and highlights a variety of different aspects within plastic surgery.

10th EADV Spring Symposium

23 - 26 May 3013

Cracow, Poland

The theme of the 10th EADV Spring Symposium is 'The Burden of Skin Diseases', a multidimensional concept which places emphasis not only on diseased skin, but also the impact which this has upon the patient's wellbeing and family. Furthermore, it incorporates the financial and social consequences which may occur. Topics including lasers, dermoscopy, inflammatory diseases and dermatologic surgery will be covered within plenary lectures, symposia and workshops.

4th Congress of the Psoriasis International Network

04 - 07 July 2013

Paris, France

The 4th Congress of the Psoriasis International Network has been organised by the Foundation René Tourraine, and aims to enhance the knowledge of attendees as well as the level of understanding and care for psoriasis patients. Leading experts in the field will explore a range of topics such as psoriasis and global health, new drugs, psoriatic arthritis and phototherapy through a combination of plenary lectures, satellite symposia, workshops and courses.

93rd Annual Meeting of British Association of Dermatologists

09 - 11 July 2013

Liverpool, United Kingdom

The British Association of Dermatologists (BAD) will be holding their Annual Meeting in Liverpool in July 2013. The British Association of Dermatologists is the leading professional organisation for Consultant, Trainee and Staff and Associate Specialist Dermatologists in the UK and Eire. The BAD works with many other organisations to achieve its aims of supporting patients and improving standards. In addition to the Annual Meeting this is achieved through Patient Support Groups, Special Interest Groups, International Dermatology Groups and the Medical Royal Colleges.

23rd Annual Meeting of the British Dermatological Nursing Group

09 - 11 July 2013

Liverpool, United Kingdom

The British Dermatological Nursing Group Annual Meeting will take place across the same dates and in the same location as the 93rd Annual Meeting of British Association of Dermatologists. The BDNG was established in 1989 to offer an independent speciality group of nurses and healthcare professionals with an interest in dermatology. At the conference, attendees will focus on a wide variety of topics to enhance their dermatology skills and promote professional development.

22nd European Academy of Dermatology and Venereology (EADV) Congress 2013

03 - 06 September 2013

Istanbul, Turkey

The European Academy of Dermatology and Venereology (EADV) Congress 2013 will provide attendees with a rich and diverse scientific programme. There will be sessions of different formats that will cover all fields of dermatology and venereology. The subjects will be treated with different approaches and from different perspectives to give a wider range of information on the different topics. The congress will also feature plenary lectures, symposia, workshops, focus sessions, test yourself sessions, controversy sessions, masters of dermatology, free communications sessions and what's new sessions. The EADV is a non-profit association whose mission is to advance excellence in clinical care, research, education and training in the field of dermatology and venereology and to act as the advocate and educator of patients particularly those with cutaneous or venereal diseases. The 2013 Congress welcomes attendees to Istanbul to discover the latest developments in the field of dermatology and venereology.

12th World Congress of Pediatric Dermatology

25 - 27 September 2013

Madrid, Spain

The World Congress of Pediatric Dermatology takes place once every four years, and is an excellent meeting where all physicians interested in paediatric dermatology can meet leading experts in the field. The meeting will showcase the most recent acquisitions and emerging advances in paediatric dermatology research over a variety of different sessions. The congress is hosted in association with the International Society of Psediatric Dermatology, which promotes and develops advanced education, research and care for the diagnosis and treatment for skin diseases in children.

TREATMENT STRATEGIES

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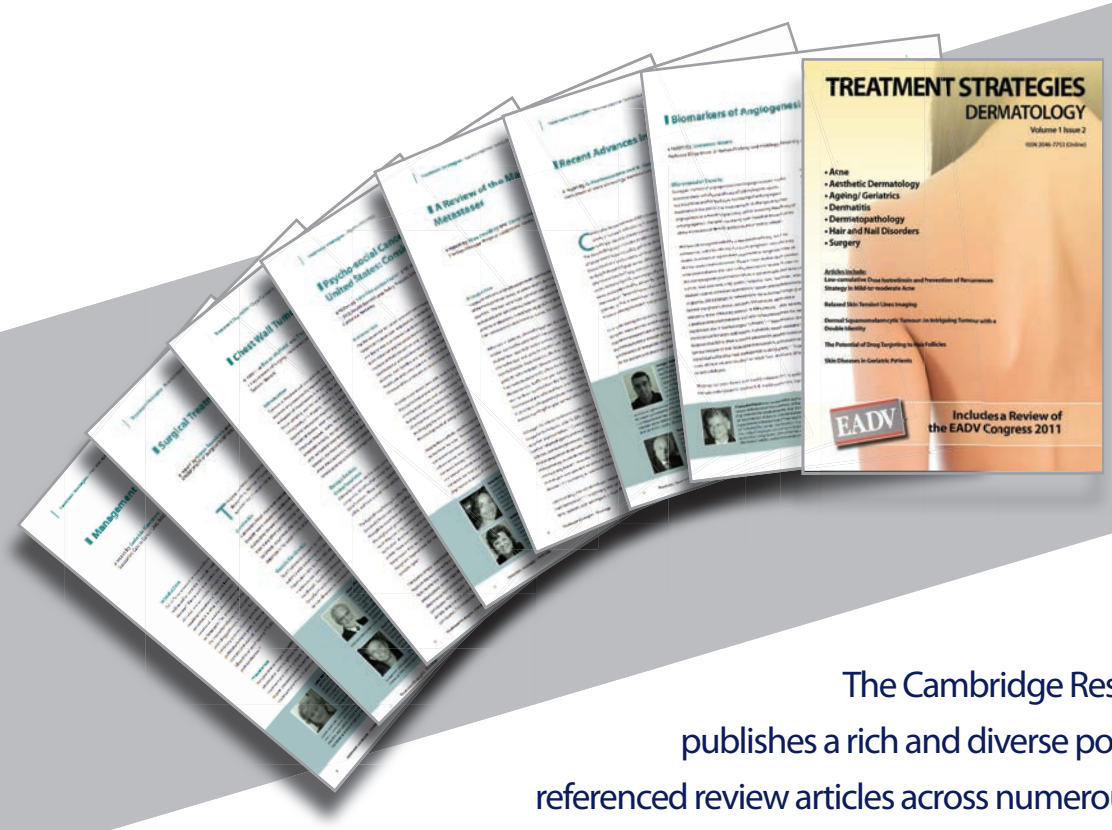

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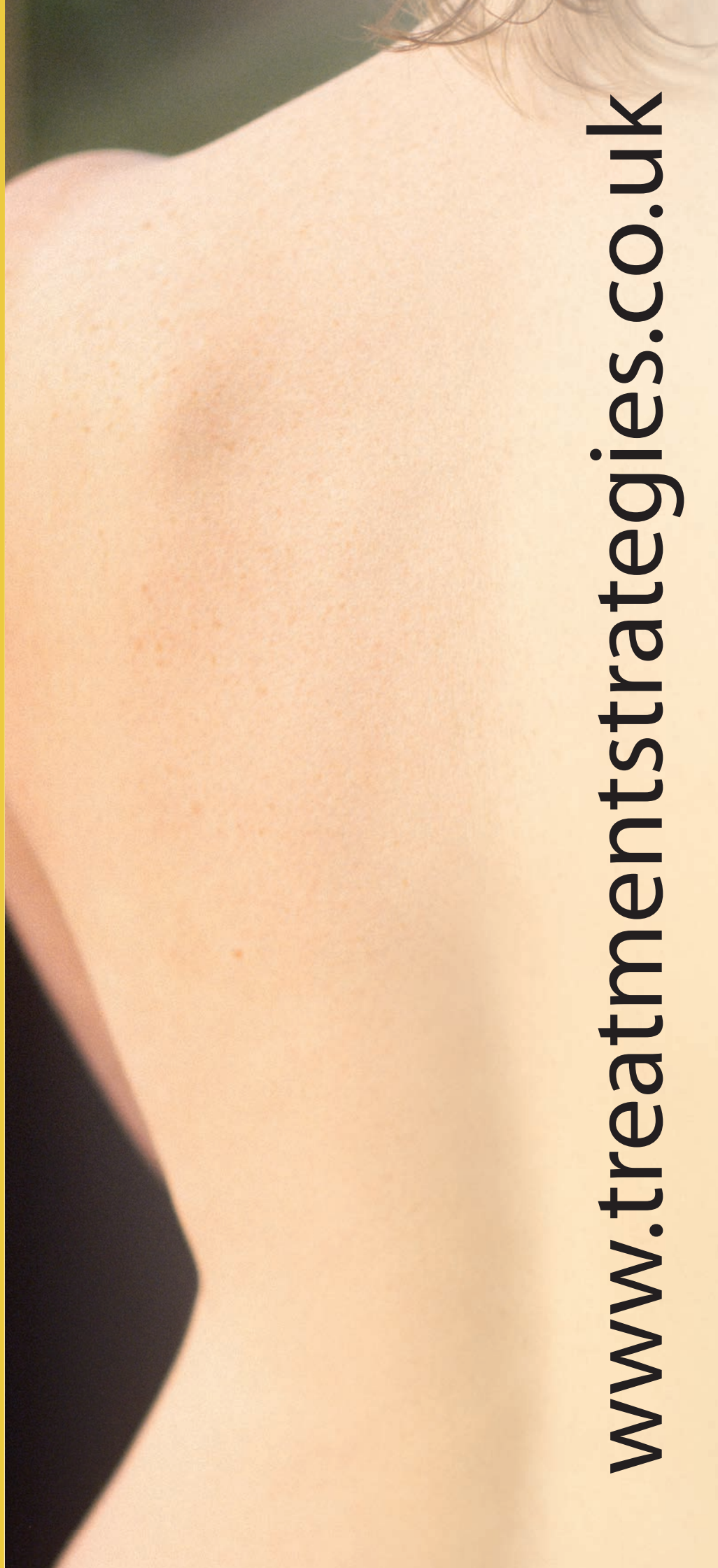

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