Mutual Antagonism of T Cells Causing Psoriasis and Atopic Eczema


Summary

The simultaneous occurrence of psoriasis driven by type 1 helper T (Th1) cells and type 17 helper T (Th17) cells and atopic eczema dominated by type 2 helper T (Th2) cells is both rare and theoretically intriguing. Thus the question of whether these conditions are epithelial or immunologic disorders since both involve complex interactions of hereditary factors and environmental influences. Herein, Eyerich et al., describe three patients with co-occurring psoriasis and atopic eczema with an antagonistic course and distinct T-cell infiltrates in lesions from psoriasis and atopic eczema. Punch biopsies from Psoriasis and Atopic Eczema lesions were obtained simultaneously from the same patient exhibiting a dual-disease course. T-cell lines were established from each lesion in vitro and activated with PMA and ionomycin. Psoriasis lesion originating T cells preferentially secreted the Th1 and Th17 cytokines (interferon-γ and interleukin-17), whereas T cells from atopic eczema lesions secreted greater amounts of interleukin-4. Interleukin-22 was secreted similarly...
A Letter from the President

Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s co-editors Professor Amnon D. Cohen of Clalit Health Services (Tel Aviv, Israel) and Professor Charles Lynde of University of Toronto (Ontario, Canada), I am honored to introduce the June 2012 issue of IPC’s Psoriasis Review.

In this CME accredited issue, we include an opportunity to earn CME credit for the review of the 70th Annual Meeting of the American Academy of Dermatology which was held in San Diego, CA from March 16th – 20th, 2012.

IPC also presents the top-five clinical and research articles from the latter half of 2011. To qualify manuscripts had to be published either in print or electronically (epub) in the time frame from July 1 to Dec 31, 2011. IPC councilors both selected candidate articles and then voted on those that they deemed were most impactful to the literature. This issue’s collection includes a focus on the rare, but life threatening, form of psoriasis, Generalized Pustular Psoriasis. Two articles mapped genetic loci to the IL-36RN gene in individuals possessing the recessive trait for Generalized Pustular Psoriasis; the articles propose mechanisms for disease pathogenesis that might illuminate new treatment modalities. Another manuscript investigates the mutual coexistence of the diagnostically opposed conditions of Chronic Plaque Psoriasis and Atopic dermatitis in the same patients at the same time! The data generated support the notion that the two conditions are independently regulated at the level of both IL-23p19 and IL-12p35 transcription. The briakinumab article presents the results of a unique comparative clinical study that included methotrexate thus providing insight into the safety and efficacy of both agents simultaneously.

In 2012, IPC continues an aggressive agenda designed to make a great impact on psoriasis care. We have translated insights gained from a recent workshop that was held in association with the 12th International Congress on Human Genetics (Montreal, Canada) into a formal research proposal designed to exome map the human genome of psoriasis patients to identify novel loci that underpin disease. Several renowned geneticists have agreed to participate in the study once the appropriate funding has been secured.

We are pleased to continue offering education programs to physicians around the world. This year IPC’s Meet the Experts programs will be held in Huntington Beach, California, Prague, Czech Republic, Durban, S. Africa and Buenos Aires, Argentina. In addition, we are hosting a symposium at the 3rd World Congress of Psoriasis and Psoriatic Arthritis in Stockholm, Sweden.

Finally, it is with great pleasure that we welcome seventeen new councilors from ten countries into the IPC community. See the IPC News section at the end of the publication for the complete list. IPC is delighted to continue to expand the involvement of psoriasis key opinion leaders around the globe into its community.

We hope this newsletter is informative and that the knowledge, experience and insights of our faculty are valuable to you in treating your psoriasis patients.

For additional copies of IPC Psoriasis Review, or to learn more about IPC, please visit www.pсорiasiscouncil.org.

Sincerely,

Professor Peter van de Kerkhof, M.D.
President, International Psoriasis Council
by both T cell types. A patch test challenge of the patient with a major house-dust mite allergen resulted in clinical and histological signs of eczema driven by antigen-specific Th2 T cells that secreted IL-4. In addition to differences in cellular infiltrates atopic eczema lesions and psoriasis lesions were also distinguished according to skin colonization with microorganisms and filaggrin expression. The results of light-microscope examination of representative lesion-infiltrate samples stained with hematoxylin and eosin illustrated that all atopic eczema lesions, but not psoriasis lesions, were colonized with Staphylococcus aureus, as determined by smear-test culture. Furthermore, filaggrin expression, measured immunohistochemically was higher in psoriasis lesions than in atopic eczema lesions reflecting the known inhibition of filaggrin expression by Th2 cytokines. These findings support a causative role for T cells triggered by independent but specific antigens in the pathogenesis of psoriasis and atopic eczema.

COMMENTARY In view of their clinical phenotype, one would expect these diametrically opposed conditions to be mutually exclusive. However, this study did identify 3 patients who experienced periods with simultaneous active lesions of both diseases, although the clinical course of psoriasis and atopic eczema was noted to rarely overlap. The data generated support the notion that the two conditions are independently regulated with differing immune phenotypes. Thus, parallel occurrence of antagonistic inflammatory skin reactions may require distinct antigen triggers driven by distinct antigen-specific T-cell subsets. For atopic eczema, such specificity seems to correlate with Staphylococcus aureus, whereas any antigen that correlates with psoriasis has yet to be defined.

2. Fumarates Improve Psoriasis and Multiple Sclerosis By Inducing Type II Dendritic Cells


Summary

The mechanism of action of small molecule fumaric acid esters has been elucidated in this paper by Ghoreschi et al. The results demonstrate that fumarates act via repression of IL-12 and IL-23 expression, two cytokines known to be involved in the pathogenesis of inflammatory diseases such as psoriasis and multiple sclerosis (MS). Intracellular cytokine analysis was performed on stimulated CD4 T cells isolated from patients with psoriasis and treated with either fumarates or placebo. The results demonstrated that a high proportion of CD4 T and Dendritic (DC) cells in patients treated with fumarates exhibited a type 2 phenotype as measured by the presence of IL-4 or IL-10, respectively. Similarly, in mice, fumarates also generated type II DCs that induce IL-4–producing Th2 cells resulting in protection from experimental autoimmune encephalomyelitis (EAE), an animal model for MS. Using a colorimetric assay to determine the presence of glutathione (GSH), the cell’s most important scavenger of reactive oxygen species, therapeutic fumarate concentrations depleted intracellular GSH by 50% in DC’s from either mice or human. The molecular consequences of the fumarate-induced GSH depletion were mapped by quantitative real-time PCR (RT-PCR) of LPS-activated DCs; revealing an increase in the expression of the heat shock protein, HO-1, which suppressed IL-23p19 without affecting IL-12p35. The authors proposed that the N-terminal fragment of HO-1 translocates into
the nucleus and interacts with AP-1 and NF-κB sites on the IL-23p19 promoter. To support this hypothesis the authors determined that macrophages transfected with an IL-23p19 luciferase promoter construct reduced luciferase expression in response to fumarate treatment. Fumarates were also observed to reduce IL-12p70 expression via a distinct mechanism involving impaired STAT1 phosphorylation and inactivation. That fumarates could protect from autoimmune disease was tested in the EAE model. After stimulation, the resultant phenotype of the CD4+ T cells was Th1 and Th17 dominant which resulted in a severe EAE condition when the T cells were adoptively transferred into wild type (normal) mice. When primed with fumarates prior to stimulation, the result was expansion of type II DCs leading to a Th2 type phenotype that failed to confer EAE.

**COMMENTARY** Comprehending the mechanism of therapies will logically lead to an enhanced capacity to customize treatment options for patients. Explaining the mode of action of fumarates to the IL-23p19 and IL-12p35 genes also provides potentially important insights that might lead to the design of better therapies for selected inflammatory and autoimmune diseases. For example, prior clinical trials of an anti-IL-12p40 mAb resulted in the amelioration of psoriasis but had no impact on MS suggesting that the inhibition of IL-12p40 is not sufficiently therapeutic versus the dual action of fumarates which act at the level of IL-23p19 and IL-12p35 transcription. Alternatively, the results may indicate that macromolecular therapies such as mAbs may not be useful tools to target all organs of the body especially those that are privileged in terms of access, such as the brain. The results presented highlight the important role for GSH (and other reactive oxygen scavengers) in regulating immune phenotype. That is, the inhibition of Th1/Th17 immune polarization to a Th2 phenotype at the level of the DC which involves two distinct mechanisms involving HO-1 and STAT-1.

3. Interleukin-36-Receptor Antagonist Deficiency and Generalized Pustular Psoriasis


**Summary**

In this study, Marrakchi and colleagues have performed genetic mapping of nine families found to contain autosomal recessive generalized pustular psoriasis. Their findings implicate aberrant interleukin-36Ra structure and function in the unregulated secretion of inflammatory cytokines that lead to the condition. The methodology utilized whole-genome scans using an Affymetrix GeneChip to analyze DNA that was extracted from patients’ blood leukocytes. Polymerase-chain reaction assays with fluorescent-labeled primers were used to amplify microsatellite DNA markers from the chromosomal region of interest, 2q12-q13, in order to make detailed assessments at the gene level. Nine genes encoding members of the interleukin-1 family were found to reside at this chromosomal locus, and their exons and exon–intron boundaries were sequenced. As a result, a homozygous variant in IL36RN was identified that was predicted to result in the substitution of a proline for leucine at amino acid position 27 (L27P) of the interleukin-36Ra protein. This mutation was found to be common in all affected individuals within the population studied. No mutations were observed in the other eight genes within the region. Genes which encoded proteins also involved in the inflammation response. The missense mutation in IL36RN encodes an interleukin-36-receptor antagonist (interleukin-36Ra) which has anti-inflammatory cytokine activity. The proline substitution (an amino acid known to disrupt α-helix protein structure) was hypothesized...
to affect both the stability of interleukin-36Ra and its interaction with its receptor, interleukin-1 receptor-like 2 (interleukin-1 receptor-related protein 2). Biochemical analyses of transfected human cell lines demonstrated that the L27P variant was poorly expressed, as measured by western blot, relative to the wild-type gene. Moreover, the expressed mutated protein was less potent than the nonvariant interleukin-36Ra in inhibiting a cytokine-induced response in an interleukin-8 luciferase reporter assay, leading to enhanced production of inflammatory cytokines (interleukin-8 in particular) by keratinocytes from patients. In confirmatory observations, the results of plasma cytokine measurements with the use of multiplex ELISA in six of the affected persons at the time of an acute flare showed substantially higher levels of interleukin-8 versus levels in unaffected individuals.

**COMMENTARY** Generalized pustular psoriasis is a life-threatening, multisystemic inflammatory disease involving repeated flare-ups of sudden onset, which are characterized by a diffuse, erythematous, pustular rash combined with high-grade fever, general malaise, and extracutaneous organ involvement. Attesting to the life-threatening nature of this condition, 5 deaths subsequent to septicemia were reported among the 9 families. Generalized pustular psoriasis is included within the spectrum of psoriasis because it is often observed in conjunction with psoriasis vulgaris and because it involves the recruitment of T cells and neutrophils. The homozygous mutation in IL36RN, the gene encoding interleukin-36Ra (also known as interleukin-1F5), is an antagonist of three cytokines belonging to the interleukin-1 family; interleukin-36α, interleukin-36β, and interleukin-36γ (also known as interleukin-1F6, interleukin-1F8, and interleukin-1F9, respectively). These cytokines activate several proinflammatory signaling pathways, such as the nuclear factor-κB and mitogen-activated protein kinase pathways. The crucial role of innate immune pathways in tissue inflammation and protective immunity is evidenced by the study reported herein as well as other genetically inherited defects involving interleukin-1 previously reported in the literature. That generalized pustular psoriasis may have common pathophysiological mechanisms to other forms of psoriasis is evidenced by the observation that patients initially present with various subtypes of psoriasis and that approximately 30% of patients with generalized pustular psoriasis also present with the lesions of psoriasis vulgaris. Thus, dysregulation of the interleukin-36–interleukin-36Ra signaling pathway may confer a predisposition to all common forms of psoriasis.

4. Mutations in IL-36RN/IL-1f5 are Associated with the Severe Episodic Inflammatory Skin Disease Known as Generalized Pustular Psoriasis


**Summary**

In this study which, like the prior article, is focused on the pathogenesis of generalized pustular psoriasis (GPP), Onoufriadis et al., deliver evidence that GPP has much different etiology than psoriasis vulgaris. Consequently, the authors highlight novel treatment strategies based upon targeting the IL-1 signaling pathway. The analysis was performed upon five unrelated individuals who met the following criteria; (1) recurrent, severe GPP requiring hospital admission; (2) absence of associated PV; and (3) absence of the HLA-Cw*0602 allele, the major genetic determinant of PV, at the HLA-C locus. DNA was extracted from blood, and whole-exome capture was performed by in-solution hybridization followed by massively parallel sequencing. This process involves separation of DNA
coding regions from non-coding regions in the genome using RNA-probes to bind to the cognate sequences in the genome. The resultant coding regions (exons) are then amplified by PCR prior to sequencing and analysis relative to the reference human genome to define mutations. Mutations occurring at a higher frequency than those in the general population were identified as candidate pathogenic mutations. The only gene harboring low frequency variants compatible with the expected recessive inheritance was mapped to the IL36RN gene (IL1F5). Moreover, this mutation was revealed in three of the five subjects. In two of the individuals, the mutation was a missense amino acid substitution of a serine for a leucine at position 113 of the IL36RN protein. A second mutation occurred at position 48 consisting of an arginine to tryptophan mutation. The functional impact of the Ser113Leu mutation was evaluated in a cytokine release assay using peripheral blood mononuclear cells. The results demonstrated a relative increase in pro-inflammatory cytokines (IL-1a, IL-6, IL-8, and TNF) revealing reduced capacity for the IL-36RN to antagonize IL36A-induced NF-kB signaling, thus resulting in GPP.

**Commentary**

Collectively, the two manuscripts (Onoufriadis et al., and Marrakchi et al.) implicate IL36RN as a key component in the pathogenesis of GPP. The studies are mutually validating in this regard but also deliver novel observations. The hereditary component in the Marrakchi study reveals potential epigenetic factors (including environmental influences) as defined by the interfamilial variation in the age at disease onset. In the Onoufriadis study, the data indicate that mutations in IL36RN underlie a distinct form of pustular disease that is separate from other forms of psoriasis. The genetic defects identified in each study resulted in missense mutations in the IL36RN gene, a key component of the innate immune system. Not all missense mutations lead to appreciable protein changes. However, these homozygous recessive changes were observed to result in enhanced pro-inflammatory cytokine patterns consistent with disease pathology. This suggests that the mutations occur in structurally and functionally important regions of the IL36RN protein thus impeding / modulating its function. IL36RN belongs to the IL-1 cytokine family, which comprises a group of evolutionary ancient cytokines with potent and critical roles in innate immunity; a system of cells, receptors, and mediators that provides a rapid and nonspecific response to pathogens. Thus, the results also highlight IL-1 signaling as a potential target for therapeutic intervention. On this note it was mentioned that anakinra, a recombinant IL-1 receptor antagonist (IL-1RA), has been reported to be effective in two individuals with GPP providing evidence for the clinical benefit of treatments that target the IL-1 pathway.

5. A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis


**Summary**

This manuscript by Reich et al. reports on a comparative study between briakinumab and methotrexate in patients with psoriasis. Briakinumab is a monoclonal antibody against the p40 molecule shared by interleukin-12 (IL-12) and interleukin-23 (IL-23), which is known to be over expressed in psoriatic skin lesions. The trial involved 317 patients and was 52 weeks in length. Briakinumab was administered subcutaneously at a starting dose of 200mg per patient for weeks 0 and 4 week and then with 100mg per dose every 4 weeks thereafter. Methotrexate was administered orally, with folate, on an ascending dose schedule that increased from 5mg to 25mg (5mg initially; 10mg at week 1; 15mg per week from week 2 through week 9; 20mg per week at week 10 and to 25mg per week at
week 16 in patients who did not meet the criterion of at least a 75\% improvement in the PASI score or of a score on the physician’s global assessment of 0 or 1). Responses were assessed at weeks 24 and 52, and briakinumab displayed statistically significant differences at each time point (P<0.001 for all comparisons). At week 24, 81.8\% of briakinumab patients achieved PASI 75 versus 39.9\% in the methotrexate group. At week 52, 66.2\% achieved PASI 75 with briakinumab versus only 23.9\% for methotrexate. Serious adverse events occurred in 9.1\% of the patients exposed to briakinumab (12.9 events per 100 patient-years) and in 6.1\% in the methotrexate group (10.6 events per 100 patient-years). Serious infections occurred in 2.6\% of briakinumab patients (4.1 events per 100 patient-years) and in 1.8\% in the methotrexate group (2.7 events per 100 patient-years). Thus, briakinumab showed higher efficacy than methotrexate in patients with moderate-to-severe psoriasis. Serious infections and cancers occurred more frequently with briakinumab, but the differences were not significant.

**COMMENTARY**

The performance of comparative studies against the accepted standard of care remains uncommon, despite the guidance of regulatory and health organizations around the world. This especially relates to novel therapies in development that have yet to gain any marketing authorization. Thus, the approach of briakinumab has to be commended; and the results are certainly insightful for both briakinumab and methotrexate, itself which has not been comprehensively studied in well-controlled clinical trials. Briakinumab targets the shared p40 subunit of IL-12 and IL-23; cytokines the type 1 helper T-cell (Th1) phenotype, leading to production of interferon-\(\gamma\), while IL-23 stimulates type 17 helper T-cell (Th17) activity and the secretion of IL-17 and IL-22. IL-23 and IL-17 have been linked to psoriasis in various genetic studies as reviewed in previous issues of Psoriasis Review. Methotrexate remains the most commonly used systemic therapy for psoriasis worldwide and as such is the leading candidate for the most appropriate comparator for any new therapy. Such studies do need to focus on both the efficacy and safety dimensions of the therapies. In the case of briakinumab, the efficacy results are significant at both weeks 24 and 52. That efficacy is not fully sustained for either therapy from week 24 to week 52 implies a temporal tolerance that on the part of briakinumab might be explained by an increased immunogenic response, although no antibody assay data are presented in the manuscript. The most notable differences in the adverse event profile observed in the study were the rate of cancers which occurred in 1.9\% (2.0 events per 100 patient-years) patients receiving briakinumab versus 0\% in the methotrexate group. The cancers consisted of breast cancer in one patient, breast neoplasm [intraductal carcinoma] in one, and prostate cancer in one, at 276, 184, and 205 days, respectively, after the commencement of therapy. In contrast to prior reports with IL-12p40 targeting agents there were no major cardiovascular events such as myocardial infarction, stroke, or death from cardiovascular causes. While the difference in cancers was not statistical it certainly would be justified to follow up in long-term studies of anti-p40 agents. IL-12 has been shown to stimulate in vitro antitumor activity of lymphocytes from patients with cancer and in vivo antitumor activity in many murine tumor models. However, further investigation is required to elucidate the precise mechanisms involved in the antitumor activity of interleukin 12. It should be emphasized that although the study showed convincing evidence about the efficacy of briakinumab, the study does not provide data about long term safety of the drug in large populations. Dermatologists should be aware that new agents for the treatment of psoriasis, such as briakinumab need to be well studied in clinical trials and subsequently surveyed. We will be able to conclude that briakinumab or other new drugs are safe for patients with psoriasis only in such a manner. In the case of briakinumab, it has been withdrawn by its sponsor from further clinical trial development because of MACE events.
CONTINUING MEDICAL EDUCATION

This section of the IPC Psoriasis Review has been specifically written to offer you the opportunity to receive a maximum of 1.0 AMA PRA category 1 credit through Purdue University. At the end of the section you will find a series of questions and instructions on submitting the answer to receive your CME credit.

Release Date: September 12, 2012
Expiration Date: September 12, 2013

70th Annual Meeting of the American Academy of Dermatology, San Diego, CA

Authors

Dr. Firas Al Niaimi
Specialist Registrar
Salford Royal NHS Foundation Trust
Manchester, England

Professor Arnon Cohen
Clalit Health Services
Tel Aviv, Israel

Professor Charles, Lynde
University of Toronto
Ontario, Canada

Learning Objectives

Upon completion of this activity, participants will be able to:
• Review and analyze the benefit to risk differences between approved psoriasis therapeutic agents and incorporate these into clinical practice.
• Discuss the relative mechanisms of action of approved therapies and those in clinical development.
• Apply new knowledge and learning to practice techniques to more effectively and optimally manage the patient.

Speaker-Specific Disclosure Statement

Dr. Firas Al-Niaimi
Dr. Firas Al-Niaimi has not served as an investigator, speaker or consultant for any pharmaceutical companies.

Professor Arnon Cohen
Professor Cohen has received honorarium from ETWAL, MSD, Lucid and Janssen..

Professor Charles Lynde
Professor Lynde has received grants/research support from Abbott, Amgen, Janssen, Leo and Celgene.
He has served on an advisory boards for Abbott, Amgen and Janssen. He has served as a consultant/speaker for Abbott, Amgen, Janssen and Leo.

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Accredited by: Purdue University Program
Sponsored by: International Psoriasis Council
This material was supported by an educational grant from Amgen.
The Firas Report: Scientific Highlights from the 70th Annual Meeting of the American Academy of Dermatology, San Diego, California

The author: Firas Al-Niaimi graduated from The University of Amsterdam and completed his dermatology residency in Manchester, United Kingdom. He has in excess of 50 publications and has worked in the internationally-renowned psoriasis centre under the supervision of professor Christopher Griffiths. He is currently a fellow at St. John’s Institute of dermatology in London.

The 70th annual meeting of the American Academy of Dermatology was a major successful international event attracting thousands of dermatologists from around the globe. Once again, psoriasis was an important topic that featured highly with eminent international speakers presenting their experiences in the field of psoriasis in addition to presenting the latest important published data in all aspects of the disease. The Firas report highlights these issues in a concise manner with various sections on each topic.

Co-morbidities:
The relationship between psoriasis and obesity is well-known. New observations and data were presented on the improvement of psoriasis following gastric bypass surgery (Hossler, et al. J Am Acad Dermatol. 2011). Although the observation was on a very small number of patients, weight loss may be considered as an adjunctive therapy for obese patients with psoriasis. A review of the literature relating to obesity and psoriasis and the relationship of weight loss on the disease was recently done and published by L. Puig from Spain (J Eur Acad Dermatol Venereol. 2011). The study showed increased association of psoriasis with obesity which significantly contributes to the increased cardiovascular risk in these patients. Furthermore, the study showed that optimal responses with fixed dose biological agents are less frequent in patients with increasing weight, particularly in those above 100 kg.

The risk for cardiovascular disease among patients with moderate-to-severe psoriasis is well-established and is a matter of ongoing observation. A cohort study in the General Practice Research Database in the United States showed that severe psoriasis was a risk factor for major adverse cardiovascular events (hazard ratio 1.53) after adjusting for other variables (Mehta, et al. Am J Med. 2011). After fully adjusted analysis, the study showed severe psoriasis conferred an additional 6.2% absolute risk of 10-year major adverse cardiac events. The effects of anti-TNF therapy on the cardiovascular risk is an important topic and a recent study from the Consortium of Rheumatology Researchers of North America rheumatoid arthritis registry involving 10,156 patients showed that the use of anti-TNF therapy was associated with an overall reduction of cardiovascular events in patients with rheumatoid arthritis (Greenberg, et al. Ann Rheum Dis. 2011). This, and other published studies, constitutes growing evidence for the protective role these drugs have on the cardiovascular system. This is possibly related to an overall reduction in the inflammatory markers that lead to atherosclerosis.

An interesting study among 206 patients with psoriasis undergoing cardiac catheterization showed that patients with moderate-to-severe psoriasis have an independently higher risk for myocardial infarction compared to patients with mild psoriasis (P4984).

An evaluation of the association between biological therapies and the risk for cardiovascular events was presented in a recently conducted meta-analysis of all randomized controlled trials of anti-IL-12/23 and anti-TNF therapy agents (Ryan, et al. JAMA 2011). The analysis
CONTINUING MEDICAL EDUCATION

included 22 randomized controlled trials comprising a total of 10,183 patients. Ten patients of the 3179 receiving anti-IL-12/23 therapies experienced major adverse cardiovascular events (this included the patients in the briakinumab trial) with only one patient of 3858 receiving anti-TNF therapies experienced a major cardiovascular event. Overall the authors concluded that compared with placebo; there was no significant difference in the rate of major adverse cardiovascular events observed in patients receiving anti-IL-12/23 blockers or anti-TNF therapies. But further long-term studies would be required to define an association.

Adding to the multitude of co-morbidities in patients with psoriasis is a possible new association with obstructive sleep apnea. Data from a small study showed the incidence of obstructive sleep apnea to be 54% in patients with psoriasis (Karaca, et al. Sleep Breath. 2012). A different Taiwanese study looked at the risk of developing psoriasis in patients suffering from obstructive sleep apnea and found that after adjusting for all variables, the hazard ratio for developing psoriasis in their 3-year follow-up was 2.3, suggesting that obstructive sleep apnea is associated with an increased risk for subsequent psoriasis (Yang, et al. Sleep Med 2012).

Phototherapy:
An interesting finding regarding the role of UVB phototherapy in the suppression of interferon and Th17 pathways was highlighted. In a recent study, down-regulation of Th17 signaling pathway was observed during narrowband UVB phototherapy in psoriatic epidermis (Racz, et al. J Invest Dermatol. 2011). Strong inhibition of the Th17 pathway by UVB was confirmed in an ex vivo organ culture system by demonstrating reduced signal transducer and activator of transcription 3 (STAT3) phosphorylation and β-defensin-2 production. These results were further substantiated by demonstrating that narrowband UVB inhibited the Th17-dependent psoriasis-like dermatitis in mice. A different study involving a small number of patients showed that concomitant treatment of narrowband UVB with ustekinumab resulted in acceleration in clearance of psoriatic lesions (Wolf, et al. Br J Dermatol. 2012).

Biologics:
A brief synopsis on the newly-designed and published Canadian guidelines for the management of plaque psoriasis was presented (Papp, et al. J Cutan Med Surg. 2011). An updated version of the guidelines was recently published following a review by the National Psoriasis Foundation Medical Board and includes sections on children, pregnant patients, nursing mothers, the elderly, patients with hepatitis B or C virus infections, human immunodeficiency virus-infected patients, and patients with malignant neoplasms. Further sections include elective surgery and vaccinations before and during anti-TNF therapy (Hsu, et al. Arch Dermatol. 2012).

Dr. Alan Menter from Dallas gave an excellent presentation on psoriasis and its management, including a section on biological therapy. Vast personal experience in the management of difficult cases was shared and backed with current trends and experiences from various international centres. The issue of the efficacy of biological therapies in obese patients was discussed and Dr. Menter gave an account of experiences of the need for higher doses – and frequency in some cases – in the management of obese patients with psoriasis. Infliximab for example has been used at a dose of 8 mg/kg for 6 weeks in a selected group of patients. Similarly, adalimumab was used at a dose of 40 mg weekly as maintenance in some patients and etanercept twice weekly instead of the once weekly dose.

The issue of infections and vaccinations with biological therapies gained considerable attention. Infliximab can cross the placenta and care should be taken with live vaccines in infants born to female patients who received infliximab therapy during pregnancy. A recent FDA drug safety communication included both listeria and legionella as potential infections to be aware of with the use of anti-TNF therapy.

Etanercept: Dr. Gottlieb presented data on the efficacy of adding methotrexate to etanercept compared to
etanercept as monotherapy (P5381). Results from the randomized controlled trials showed that at week 24, PASI 75 was achieved by 77.3% in the combination arm compared to 60.3% in the etanercept only arm. Patients enrolled in the trial received etanercept at a dose of 50 mg twice weekly for 12 weeks followed by 50 mg once weekly for an additional 12 weeks.

**Adalimumab:** Data were presented on the efficacy and safety of retreatment with adalimumab and disease recurrence following withdrawal from therapy (Papp, et al. Br J Dermatol. 2011 and P4792). The data showed that adalimumab-treated patients who discontinued therapy and subsequently relapsed had a good likelihood of regaining clinical efficacy following adalimumab re-initiation. The use of adalimumab for the treatment of moderate-to-severe plaque psoriasis affecting the hands and feet was presented (Leonardi, et al. Arch Dermatol. 2011 and P4790/P5061). A multi-centre study in the United States and Canada involving 72 patients were randomized to receive either placebo or adalimumab at a starting dose of 80 mg, followed by 40 mg every other week starting at week one. The Physician’s Global Assessment of hands and/or feet (hfPGA) score was used. At week 16, 31% and 4% of patients randomized to adalimumab and placebo, respectively, achieved a hands-feet PGA (hfPGA) score of clear or almost clear. At week 28, 80% of the hfPGA clear or almost clear response was maintained from week 16. Adverse events in both groups were generally mild to moderate.

**Infliximab:** The efficacy and safety of infliximab compared to etanercept was presented (Gottlieb, et al. J Am Acad Dermatol. 2011). In patients who had an inadequate response to etanercept who were switched to infliximab (n=215) a substantial proportion of patients (61.3%) achieved a PGA score of clear (0) or minimal (1). The study did not show any unexpected side-effects or safety concerns with the use of infliximab. Data was also presented on the phenomenon of severe infusion reactions with infliximab (Steenholdt, et al. Aliment Pharmacol Ther. 2011). In 315 patients being treated with infliximab at a Danish University hospital, eight percent experienced acute severe infusion reactions. This was strongly associated with the development of anti-infliximab IgG antibodies, but not with IgE antibodies. Despite this, the absence of anti-infliximab IgG antibodies in patients who were previously treated with infliximab did not rule out the occurrence of infusion reactions. The risk was particularly high at the second infusion. A prospective cohort study involving 415 patients with a total of 2165 infliximab infusions showed that concurrent use of immunosuppressive therapy was associated with a lower infusion reaction rate whereas corticosteroid premedication had no impact on the infusion reaction rates (Lee, et al. Aliment Pharmacol Ther. 2011). The study also showed that in patients with no past history of significant infliximab infusion reactions, a one-hour infusion is safe and is not associated with any increased risk of reactions compared to a two-hour infusion rate.

**Ustekinumab:** Results of a large retrospective multi-centered cohort study across the United Kingdom and Ireland involving 129 patients treated with ustekinumab showed that treatment was well-tolerated and efficacious with only few observed adverse events (Laws, et al. Br J Dermatol. 2012). A PASI 75 response was seen in 29.4% (n=5/17) of individuals weighing 90-100kg and treated with the standard 45mg ustekinumab dose compared with PASI 75 of 70.3%, 71.4%, 75.0% and 55.6% for weight groups <80, 80-90, 100-110 and >110kg, respectively. Safety data with up to four years of follow-up showed that the rates of non-melanoma skin cancers and infections remained stable and the risk does not appear to be cumulative (P4777 and P4931). An update on the cardiovascular safety of ustekinumab from pooled phase-II/III trials with up to four years of follow-up showed that the rates for major adverse cardiovascular events remain low and are consistent with, or lower than expected, in other populations (P4932). Analyses with five years of safety data will be presented at the forthcoming European Academy of Dermatology and Venereology meeting this year.
**Safety:** The risk of hospitalization for infection in patients with autoimmune diseases receiving anti-TNF therapies was presented (Grijalva, et al. JAMA 2011). In a large cohort that included 10,484 rheumatoid arthritis patients, 2323 inflammatory bowel disease patients, and 3215 psoriasis patients, the data showed that initiation of anti-TNF therapy was not associated with an increased risk of hospitalizations for infections compared with treatment with non-biologic therapies. A systematic review and meta-analysis of registries observational studies looking into the risk of malignancies with anti-TNF therapies was presented (Mariette, et al. Ann Rheum Dis 2011). The results from this review showed that treatment with anti-TNF therapy is associated with an overall increased risk of cutaneous malignancies, including melanoma. The increased risk for non-melanoma skin cancer was 1.45 (95% CI 0.7 to 1.76). The pooled estimate for melanoma from two studies was 1.79 (95% CI 0.92 to 2.67). A different study looking at the incidence of and risk factors for non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis showed that patients with anti-TNF therapy may have an increased risk for developing non-melanoma skin cancers compared to those on disease-modifying anti-rheumatic drugs (Amari, et al. Rheumatology (Oxford) 2011). The authors recommended regular screening for dysplastic and cancerous lesions for patients on anti-TNF therapy.

Recent updated data from the British Society for Rheumatology Biologics Register involving a total of 11,798 patients with rheumatoid arthritis treated with anti-TNF therapy compared to 3598 non-biologic disease-modifying anti-rheumatic drugs-treated patients showed an increased risk, albeit small, for serious infections in the anti-TNF therapy group - particularly in the first six months of treatment (Galloway, et al. Rheumatology (Oxford) 2011). The adjusted hazard ratio for serious infections in the anti-TNF cohort was 1.2 (95% CI 1.1 to 1.5). Interestingly, the risk did not differ significantly between the three anti-TNF biologics (adalimumab, etanercept, and infliximab).

Results from a 3-year prospective national French registry (RATIO) describing the spectrum of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy showed that the risk is higher with the use of monoclonal anti-TNF therapy compared to soluble TNF receptor therapy (Salmon-Ceron, et al. Ann Rheum Dis. 2011). Importantly, concomitant use of a systemic steroid greater than 10 mg a day was independently associated with opportunistic infections.

The issue of elective surgery during anti-TNF therapy has often attracted a lot of attention and this was discussed at the academy. Recent data from an Italian centre involving 114 patients being treated with anti-TNF therapy for inflammatory bowel disease who underwent abdominal surgery was presented (Rizzo, et al., Int J Colorectal Dis. 2011). The study showed that the overall post-surgery infection rate was 15%. This was significantly higher in patients who are on concomitant high-dose systemic corticosteroids (50% versus 11%). No increased rates of post-operative complications were observed. The current weight of evidence suggests that concomitant use of anti-TNF therapy with systemic corticosteroids is associated with a higher rate of infections overall and as such; these patients should be monitored closely.

Data on the outcome of 130 pregnancies during anti-TNF therapies pregnancy were presented from the British Society of Rheumatology Biologics Register (Verstappen, et al. Ann Rheum Dis. 2011). Eighty-eight live births in a total of 130 pregnancies were reported in patients who received anti-TNF therapy before or during pregnancy. The rate of spontaneous abortion was highest among patients exposed to anti-TNF at the time of conception (with methotrexate/leflunomide 33% and without methotrexate/leflunomide 24%). This compared with 17% spontaneous abortions in those with prior exposure to anti-TNF therapies and 10% spontaneous abortions in the control group. Ten terminations were performed. Although other recent data showed an overall favorable profile for anti-TNF therapies in pregnancy, no firm conclusions can be drawn on the safety of these drugs in pregnancy.
CONTINUING MEDICAL EDUCATION

pregnancy and the general advice and consensus is that these drugs should be avoided at the time of conception.

Genetics:
The link between genetics and psoriasis was eloquently explained by Dr. W. Liao. The concept of psoriasis being a complex disease with gene(s)-environment interaction in susceptible individuals was explained. The link with genetics was known due to the increased individual risk for psoriasis in the presence of psoriasis in the parent(s). So far more than 20 susceptibility genes have been linked to psoriasis through traditional linkage analysis studies, association studies, and the more recent use of genome wide association studies. The importance of copy number variants in the pathogenesis of psoriasis was highlighted through gene mutations which are inherent in epidermal barrier function (LCE and β-defensin). The current cluster of genes responsible in psoriasis are known to affect specific pathways involved in inflammation, angiogenesis and epidermal differentiation such as the NFκB and IL23 pathways. Very recent findings has found a novel gene – CARD14 – in the pathogenesis of psoriasis (Jordan, et al. Am J Hum Genet. 2012). This gene is believed to correspond to the previously identified PSORS2 locus.

Novel findings in linking generalized pustular psoriasis to interleukin-36 receptor antagonist deficiency were presented. Direct sequencing and homozygosity mapping in nine Tunisian multiplex families with autosomal recessive generalized pustular psoriasis showed a homozygous mis-sense mutation in IL-36RN, encoding an IL-36 receptor antagonist that acts as an anti-inflammatory cytokine (Marrakchi, et al. N Engl J Med 2011). A different study identified a similar mutation in patients with generalized pustular psoriasis and postulate that loss of function of IL-36RN acts as the genetic basis of the disease and highlight the potential for IL-1 signaling as a potential target for therapeutic intervention (Onoufriadis A, et al. Am J Hum Genet. 2011). Dr. Liao concluded that personalized medicine, a concept presented also by Dr. A. Menter, will dictate future therapies in psoriasis as well as medicine overall. Individual pharmacogenomic markers for drug metabolism may revolutionize the way psoriasis patients are managed.

Systemic therapies:

**Methotrexate:** The efficacy of methotrexate compared to infliximab in patients with moderate-to-severe chronic plaque psoriasis was presented. Results were from an open-label, active-controlled, randomized trial (RESTORE1) comparing the efficacy and safety of infliximab versus methotrexate (Barker, et al. Br J Dermatol. 2011). Methotrexate-naïve patients (n = 868) were randomized 3:1 to receive infliximab at a dose of 5 mg/kg at weeks 0, 2, 6, 14 and 22 or methotrexate at a dose of 15 mg a week with a dose increase to 20 mg weekly at week 6 if the PASI response was less than 25%. PASI 75 was achieved by a significantly greater proportion of infliximab-treated patients (508/653, 78%) than methotrexate-treated patients (90/215, 42%). Overall adverse events were comparable between the two groups; however the incidence of serious and severe adverse events was slightly higher in the infliximab-treated group. Infliximab was also efficacious in methotrexate-failed patients who switched to infliximab during the study. Methotrexate is widely used in the treatment of chronic plaque psoriasis and is still considered the gold standard first-line systemic therapy for the disease. A recent pharmacoeconomic analysis of severe psoriasis therapy showed methotrexate to be the lowest cost per patient achieving PASI 75, making methotrexate a very cost-effective treatment in psoriasis (Staidle, et al. Expert Opin Pharmacother. 2011).

**Acitretin:** The risk of fractures with vitamin A analogues was presented (Vestergaard, et al. Arch Dermatol. 2010). Results from a case-control study of a national registry including a total of 124,655 patients with fractures and 373,962 age- and sex-matched controls showed that there was no trend in risk of any fracture during treatment with vitamin A analogues. Subdividing the results into patients using acitretin did not alter the results; hence the authors concluded that the use of acitretin is not associated with an increased risk for fractures.
Future therapies:

A novel anti-interleukin-17 monoclonal antibody (ixekizumab) recently underwent a clinical trial. In a phase-II, double-blind, placebo-controlled trial, a total of 142 patients with moderate-to-severe chronic plaque psoriasis were randomized to subcutaneous injections of ixekizumab at doses of 10, 25, 75, or 150 mg or placebo (Leonardi, et al. N Engl J Med 2012). At 12 weeks, the percentage of patients with a reduction in the PASI score by at least 75% was significantly greater with ixekizumab (except with the lowest, 10-mg dose)--150 mg (82.1%), 75 mg (82.8%), and 25 mg (76.7%)--than with placebo (7.7%). Similarly, a 100% reduction in the PASI score was achieved in significantly more patients in the 150-mg group (39.3%) and the 75-mg group (37.9%) than in the placebo group (0%). Significant differences occurred at as early as 1 week and were sustained through 20 weeks.

Results of a phase-II randomized, placebo-controlled trial using PEGylated certolizumab were presented (Reich, et al. Br J Dermatol. 2012). Certolizumab Pegol is a PEGylated anti-TNF agent. In the study, 176 patients with moderate to severe psoriasis received placebo or certolizumab 400 mg at week 0 followed by placebo or certolizumab (200 or 400 mg) every other week until week 10. PASI 75 was achieved by 44/59 (74.6%), 48/58 (82.8%) and 4/59 (6.8%) patients in the certolizumab 200, 400 mg and placebo groups, respectively. A PGA score of clear-almost clear was achieved by 52·5%, 72·4% and 1·7%, respectively. These data show that certolizumab significantly improves psoriasis at week 12 of therapy.

The efficacy of the novel therapy brodalumab (AMG 827) was presented (Papp, et al. Br J Dermatol. 2012 and P5414). Brodalumab is a humanized monoclonal antibody that blocks IL-17R. The trial involved 198 patients who were randomized to receive brodalumab (70 mg, 140 mg, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or 280 mg monthly) or placebo. The primary end point was the percentage improvement from baseline in the PASI score at week 12. Results at week 12 showed that the mean percentage improvements in the PASI score were 45% among patients receiving 70 mg of brodalumab, 85.9% among those receiving 140 mg, 86.3% among those receiving 210 mg, 76.0% among those receiving 280 mg, and 16.0% among those receiving placebo. Two cases of grade 3 neutropenia were reported in the 210-mg brodalumab group. The most commonly reported adverse events in the combined brodalumab groups were nasopharyngitis (8%), upper respiratory tract infection (8%), and injection-site erythema (6%).

Apremilast, a novel small molecule that specifically targets the PDE4, thereby increasing cellular cAMP, which modulates inflammatory mediators has shown promising results in the treatment of nail psoriasis. Results from a phase-IIb study in 352 subjects with nail psoriasis showed improvement in the NAPSI score at week 16 (P5559). Patients receiving the higher dose (50 milligrams) showed a better response. Apremilast has shown to be very effective in the treatment of plaque psoriasis and data of its efficacy were presented in previous meetings (Gottlieb, et al. Curr Med Res Opin. 2008).

Future novel therapies for psoriatic arthritis gained an interest too at the academy. Data from a double-blind, placebo-controlled, phase-II trial for abatacept were presented (Mease, et al. Arthritis Rheum 2011). The drug is currently used in rheumatoid and juvenile arthritis and is a selective T-cell costimulation modulator. A total of 170 patients with psoriatic arthritis who had previously taken disease-modifying anti-rheumatic drugs, including anti-TNF agents, were randomized to receive placebo or abatacept at doses of 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 initial doses of 30 mg/kg, followed by 10 mg/kg) on days 1, 15, and 29 and then once every 28 days thereafter. The primary end point was the American College of Rheumatology 20% criteria for improvement (ACR20 response) on day 169. Other key end points were magnetic resonance imaging (MRI) scores for joint erosion, osteitis, and synovitis. The results showed that the proportion of patients achieving an ACR20 response were 19%, 33%, 48%, and 42% in the placebo, the abatacept 3 mg/kg, the abatacept 10 mg/kg, and the abatacept 30/10 mg/kg groups, respectively.
Compared with placebo, improvements were significantly higher for the abatacept 10 mg/kg and 30/10 mg/kg groups, but not for 3 mg/kg group. The safety profiles were similar among the treatment arms. The results show that the currently used dose of 10 mg/kg (in rheumatoid arthritis) may be an effective treatment option for psoriatic arthritis.

A novel therapy targeting IL-17A, a cytokine which is increased in patients with psoriasis, is showing very promising results in the treatment of moderate-to-severe chronic plaque psoriasis (P5463 and P5393). Secukinumab is a fully human IL-17A-neutralizing antibody therapy given as subcutaneous injections. In a placebo-controlled phase-II study involving 404 patients who were randomized to receive either placebo, or one of the three secukinumab regimens: “single” (at week 0), “early” (at weeks 1, 2, 4) and “monthly” (at weeks 0, 4, 8). The primary endpoint was PASI 75 at week 12. After the first 12 weeks (induction period), PASI 75 responders were further randomized to one of the two maintenance regimens: the fixed time interval regimen (n=65 patients received secukinumab 150 mg at weeks 12 and 24) or the treatment at start-of-relapse regimen (n=67 patients received secukinumab 150 mg at visits at which a start of relapse was observed). At week 12, “early” and “monthly” induction regimens achieved statistically higher PASI 75 responses compared to placebo (55% and 42% versus 2%). The PASI 90 responses were significantly greater in the “early” and “monthly” arms versus placebo (32% and 17% versus 2%) at week 12. After 12 weeks of treatment in maintenance, 71% of the subjects in the fixed-interval regimen were PASI 75 responders. The results suggest that secukinumab may be useful in the treatment of plaque psoriasis.
CONTINUING MEDICAL EDUCATION

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70th Annual Meeting of the American Academy of Dermatology,
San Diego, California

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1. Which interleukin has recently found to be linked to generalized pustular psoriasis?
   a. IL-12
   b. IL-23
   c. IL-36
   d. IL-5

2. The RESTORE1 trial compared the efficacy of methotrexate with which of the following biologics?
   a. Infliximab
   b. Ustekinumab
   c. Adalimumab
   d. Etanercept

3. The FDA safety communication regarding anti-TNF therapies recently included additional possible infections. Which of the following infections was recently included?
   a. Tuberculosis
   b. Pneumocystis jaroveci
   c. Listeria
   d. Haemophilus influenza

4. Care should be taken with administration of live vaccines in infants with which of the following biologics, since it is known to cross the placenta?
   a. Adalimumab
   b. Infliximab
   c. Etanercept
   d. Ustekinumab

5. In this report, which novel therapy in development displayed data exhibiting an impact on nail psoriasis?
   a. Secukinumab
   b. Brodalumab
   c. Ixekizumab
   d. Apremilast

6. Risk of fracture should be considered with which of the following systemic therapies?
   a. Methotrexate
   b. Acitretin
   c. Ciclosporin
   d. Fumaric acid esters

7. Which biological therapy was demonstrated in clinical trials to be effective in the treatment of hand and foot psoriasis?
   a. Adalimumab
   b. Ustekinumab
   c. Etanercept
   d. Infliximab

8. Which of the following novel therapies is a pegylated anti-TNF therapy?
   a. Secukinumab
   b. Apremilast
   c. Certolizumab
   d. Brodalumab

9. Brodalumab is a humanized monoclonal antibody that blocks:
   a. IL17A
   b. IL17R
   c. IL6
   d. PDE4

10. Which of the following systemic therapies in psoriasis was found to be the most cost-effective in achieving PASI75 in a recent pharmacoeconomic analysis?
    a. Acitretin
    b. Methotrexate
    c. Ciclosporin
    d. Etanercept
70th Annual Meeting of the American Academy of Dermatology, San Diego, California

You must complete this evaluation form to receive acknowledgement of participation for this activity.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding  4 = Good  3 = Satisfactory  2 = Fair  1 = Poor

Extent to Which Program Activities Met the Identified Objectives

- Review and analyze the benefit to risk differences between approved psoriasis therapeutic agents and incorporate these into clinical practice .........................5 4 3 2 1
- Discuss the relative mechanisms of action of approved therapies and those in clinical development ................................................................ 5 4 3 2 1
- Apply new knowledge and learning to practice techniques to more effectively and optimally manage the patient .............................................5 4 3 2 1

Overall Effectiveness of the Activity

- Was timely and will influence how I practice ........................................................................................................................................................5 4 3 2 1
- Will assist me in improving patient care ....................................................................................................................................................... 5 4 3 2 1
- Fulfilled my educational needs .............................................................................................................................................................................5 4 3 2 1
- Avoided commercial bias or influence .................................................................................................................................................................5 4 3 2 1

Impact of the Activity

- The Information presented: (check all that apply)
  □ Reinforced my current practice/treatment habits
  □ Will improve my practice/patient outcomes
  □ Provided new ideas or information I expect to use
  □ Enhanced my current knowledge base

If yes, please describe any change(s) you plan to make in your practice as a result of this conference:

_________________________________________________________________________________________________________________________________________

_________________________________________________________________________________________________________________________________________

How committed are you to making these changes?

(Very committed)  5  4  3  2  1  (Not at all committed)

Future Activities

- Do you feel future activities on this subject matter are necessary and/or important to your practice?  □ Yes  □ No

Please list any other topics that would be of interest to you for future educational activities:

_________________________________________________________________________________________________________________________________________

Follow-up

As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

□ Yes, I would be interested in participating in a follow-up survey
□ No, I'm not interested in participating in a follow-up survey

Additional comments about this activity:

_________________________________________________________________________________________________________________________________________

_________________________________________________________________________________________________________________________________________
Recent papers published

**Long-Term Management of Scalp Psoriasis: Perspectives from the International Psoriasis Council.** (2012)
Knud Kragballe, MD, Alan Menter, MD, PhD, Mark Lebwohl, MD, Paul W. Tebbey, PhD and Peter C.M. van de Kerkhof, MD, PhD for the International Psoriasis Council. J. Dermatological Treatment. Posted online on March 28, 2012.

**Abstract:**
The scalp is a well-known predilection site for psoriasis. Epidemiological data on the various manifestations of scalp psoriasis as well as on its therapeutic management are sparse. The understanding of the natural course of scalp psoriasis is relevant for its therapeutic management. In over 25% of patients, scalp psoriasis is the first signal of the psoriatic condition. Nevertheless, few of the therapies currently used for the treatment of scalp psoriasis have been evaluated for efficacy in the setting of well-designed, well-controlled clinical studies. The lack of comparative data impedes the interpretation of the results from studies of scalp psoriasis. Long-term studies of the efficacy and safety of scalp treatments are lacking. Moreover, clinical studies generally do not incorporate quality of life impact or mechanisms to enhance adherence thus hindering the optimal management of the patient over the long-term. Consequently, this report will evaluate the available data and the associated factors to be considered in the development of a treatment paradigm for the long-term management of the scalp psoriasis patient.

**Biopharmaceuticals and Biosimilars in Psoriasis: What the Dermatologist Needs to Know.** (2012)

**Abstract:**
The entry of biosimilar forms of biopharmaceutical therapies for the treatment of psoriasis and other immune-mediated disorders has provoked considerable interest. Although dermatologists are accustomed to the use of a wide range of generic topical agents, recognition of key differences between original agent (ie, the name brand) and the generic or biosimilar agent is necessary to support optimal therapy management and patient care. In this review we have summarized the current state of the art related to the impending introduction of biosimilars into dermatology. Biosimilars represent important interventions that are less expensive and hence offer the potential to deliver benefit to large numbers of patients who may not currently be able to access these therapies. But the development of biosimilars is not equivalent to that of small molecule generic therapies because of differences in molecular structure and processes of manufacture. The planned regulatory guidelines and path to approval may not encompass all of these potentially important differences and this may have clinical relevance to the prescriber and patient. Consequently, we have identified a series of key issues that should be considered to support the full potential of biosimilars for the treatment of psoriasis; ie, that of increased access to appropriate therapy for the psoriasis population worldwide.
IPC NEWS

New IPC Members

IPC Board of Directors is pleased to announce the appointment of 17 new Councilors. The new Councilors will add to the breadth and knowledge that makes IPC the leading organization working to increase knowledge and enhance care of patients with psoriasis.

The new Councilors include:

Professor Matthias Augustin, Germany
Dr. Marc Bourcier, Canada
Dr. Elke MGJ de Jong, the Netherlands
Professor Giampiero Girolomoni, Italy
Dr. Wayne Gulliver, Canada
Dr. Brian Kirby, Ireland
Dr. Luigi Naldi, Italy
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Professor Kristian Reich, Germany
Professor Nick Reynolds, United Kingdom
Dr. Robert Sabat, Germany
Dr. Marieke B. Seyger, the Netherlands
Dr. Colin Theng, Singapore
Professor Claus Zachariae, Denmark

International Psoriasis Council Convenes Collaborative Efforts Toward Completing Genetic Map of Psoriasis

IPC convened a workshop in November 2011 in Montreal, Canada to advance the understanding of the genetic basis of psoriasis. The workshop included groups from the genetic research laboratories of Professors Goncalo Abecasis (University of Michigan, USA); Richard Trembath (King’s College, London, UK); Professors J.T. Elder (University of Michigan, USA); Andre Reis (University of Erlangen-Nuremberg, Germany); Andre Franke (Christian-Albrechts University, Kiel, Germany); Anne Bowcock (Washington University, St Louis, USA). Also in attendance were dermatologists, Herve Bachelez (Hospital Saint-Louis, Paris, France), Wolfram Sterry, (Charité University, Berlin, Germany); Alexa Kimball, (Massachusetts General Hospital, Boston, USA) and Craig Leonardi (St Louis University, USA).

The collaboration is expected to lay the groundwork for innovative approaches to novel treatment strategies as well as to defining the therapeutic response to treatments in specific psoriasis patients by building a bridge between the genotype and phenotype of the disease. Professor Jonathan Barker of St. John’s Institute of Dermatology, King’s College, London, UK, and an IPC board member, is facilitating the initiative. “There have been huge advances in the understanding of the inherited basis of psoriasis. But we are only about 50% complete in clarifying the genetic effect. To complete the genetic map, we need all of the leading groups around the world to join forces.”

A manuscript of the workshop will has been accepted for publication in the British Journal of Dermatology. In addition, IPC will launch a major fundraising effort this year to raise $1.1 million to fund the purchase of the chips needed to complete the genetic map.
IPC NEWS

IPC’s Meet the Experts | Hawaii

IPC held its Meet the Experts: Case-based learning program at the 65th Annual Hawaii Clinical Dermatology Meeting in Maui, Hawaii, January 15, 2012. Faculty included IPC Councilors Craig Leonardi, MD, St. Louis; Alice Gottlieb, MD, PhD, Boston; Mark Lebwohl, MD, New York; and David Pariser, M.D., Norfolk. The panel presented challenging psoriasis cases on psoriatic arthritis, pregnancy and pediatrics. More than 150 physicians attended this interactive program and had an opportunity to ask questions of the panel and to discuss challenging issues they have faced in treating psoriasis patients.

New IPC Website Launched

IPC has launched its new website to allow for easier access to its resources including the psoriasis image library, educational web casts and the IPC Psoriasis Review. In addition, the new website will allow for IPC to better promote its Councilors by adding new features including a listing of the Councilor’s most recent publications on psoriasis.
IPC NEWS

IPC’s Inaugural Councilor Conflab

In December of 2011, IPC was pleased to hold its inaugural meeting for its councilors, contiguous with the “6th International Congress: Psoriasis, From Gene to Clinic” in London, UK. Attended by 25 IPC councilors, the forum was an opportunity to discuss the latest medical advances in psoriasis as well as define IPC’s strategy and focus for the foreseeable future. The topics of discussion ranged from genetics to the IL-1 family of cytokines to the ICD11 code for psoriasis. In his discussion of the IL-1 family, Prof. Herve Bachelez (Saint-Louis University Hospital, Paris, France) described the identification of conserved mutations in the IL-36RN (IL-1F5) gene that account for generalized pustular psoriasis. IL-36RN encodes an antagonist to IL-36 stimulation of other inflammatory mediators including IL-8. While no mutations were observed in the IL-36RN gene of psoriasis vulgaris, Prof. Bachelez indicated that the IL36/IL36R pathway is one of the innate immune circuits contributing to the inflammatory cascade leading to pathogenesis. Dr. Alexa Boer Kimball (Massachusetts General Hospital, Boston, US), indicated that with pharmacogenomics, we are at a watershed moment in time and potentially on the verge of profound breakthroughs in medical science. The increasing incorporation of genomics into clinical trials will help predict those patients who will respond to a therapy or have adverse effects. Dr Kimball illustrated a variety of case studies to indicate how targeted therapies might be optimized using pharmacogenomics. Dr. Robert Chalmers (Salford Royal Hospital, Manchester, UK) on behalf of Prof. Michael Weichenthal (Universitäts-Hautklinik, Kiel, Germany) delivered a status update on progress toward developing the ICD11 classification for psoriasis. IPC councilors had submitted comments on an earlier rendition of the classification in May 2011. Areas of dialogue spanned the topics of disease severity, phenotype and co-morbidities.
ACKNOWLEDGEMENTS AND SUPPORT

IPC PSORIASIS REVIEW

Co-Editors
Professor Arnon D. Cohen, Tel Aviv, Israel
Professor Charles Lynde, Ontario, Canada

Writers
Paul Tebbey, Ph.D., M.B.A.
Firas Al-Niaimi, MSc, MRCP.

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International Psoriasis Council
1034 S. Brentwood Blvd., Suite 600
St. Louis, MO USA 63117
Tel 972.861.0503
Fax 214.242.3391
www.psoriasiscouncil.org

ACKNOWLEDGMENTS

IPC gratefully acknowledges Co-editors Professor Charles Lynde of Ontario, Canada and Professor Arnon Cohen of Tel Aviv, Israel for their contributions to the 2012 June issue of IPC Psoriasis Review.

FACULTY DISCLOSURES

Professor Lynde has received grants/research support from Abbott, Amgen, Janssen, Leo and Celgene. He has served on an advisory boards for Abbott, Amgen and Janssen. He has served as a consultant/speaker for Abbott, Amgen, Janssen and Leo.

Professor Cohen has received honorarium from ETWAL, MSD, Lucid and Janssen.

Dr. Firas Al-Niaimi has not been compensated as a speaker or consultant for any pharmaceutical companies.