Therapeutic targeting of the IL-17 signaling pathways displays significant outcomes in Phase 2 clinical trials


**Summary**

Brodalumab (AMG 827) is a human, anti–interleukin-17 (IL17) receptor antagonist monoclonal antibody. The manuscript by Papp et al., depicts the results from a 198 patient phase 2 clinical trial to investigate brodalumab as a potential therapy for the treatment of moderate-to-severe plaque psoriasis. A subset of helper T cells, Th17, has been increasingly implicated in the inflammation that manifests in plaque psoriasis. Brodalumab binds with high affinity to the human interleukin-17 receptor thus blocking the action of IL17A as well as IL17E and F. This placebo controlled trial assessed doses of 70, 140, and 210 mg brodalumab administered at weeks 0, 1, 2, 4, 6, 8 and 10. In addition, a dose of 280 mg was administered at weeks 0, 4 and 8. At the week 12 primary endpoint, 33% (70mg), 77% (140mg), & 82% (210mg) and 67% (280mg with 3 doses) achieved PASI 75, respectively. This was statistically significant for all doses versus the placebo. Moreover, 18% (70mg), 72% (140mg), 75% (210mg) and 57% (280mg with 3 doses) of patients achieved PASI 90. This trial also reported PASI-100 rates of 10% (70mg), 38% (140mg), 62% (210mg) and 29% (280mg with 3 doses) respectively.

Cont. Page 3,
Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s co-editors Dr. Marieke Seyger, MD, PhD of Radboud University (Nijmegen, the Netherlands) and Dr. Brian Kirby, MD of St. Vincent’s University Hospital (Dublin, Ireland), I am honored to introduce the December 2012 issue of IPC’s *Psoriasis Review*.

In this issue, IPC presents the semi-annual top-five clinical and research articles from the first half of 2012. To qualify, manuscripts had to be published either in print or electronically (epub) between January 1 to June 30, 2012. IPC councilors both selected candidate articles and then voted on those that they deemed were most impactful to the literature. This issue’s selection includes a pair of articles from the New England Journal discussing therapies that target the IL-17 cytokine pathway (brodalumab and ixekizumab) and exemplify the prominent role that our field of psoriasis research now occupies in the broader scientific community. In support of this concept, IPC’s councilors also selected a pair of manuscripts published in the American Journal of Human Genetics which identify a series of truly pathogenic rare variants (CARD14) in psoriasis thus contributing to our knowledge of the genetic basis of psoriasis. Our final selection offers evidence for an infectious component to psoriasis initiation and/or exacerbation related to throat-residing hemolytic streptococci in a model of molecular mimicry. We hope you enjoy our summaries of these important contributions to the literature.

Also in this issue, we include a series of articles by IPC’s future psoriasis leaders:

1. Catriona Ryan reviews IPC’s Pre-Conference Event that was held at the 3rd World Psoriasis and Psoriatic Arthritis Conference 2012 in Stockholm, Sweden.
2. The Firas Report, written by Firas Al Niaimi, focuses on the 21st European Academy of Dermatology and Venereology Congress that was held from September 27 – 29, 2012, in Prague, Czech Republic.
3. Ivie Manalo and Benjamin Stoff deliver an appraisal of selected novel psoriasis therapies in development.

Throughout 2012, IPC has continued an aggressive agenda designed to make a great impact on psoriasis care. IPC has held “Meet the Experts” programs in Huntington Beach (CA), Prague (Czech Republic), Durban (S. Africa) and Buenos Aires (Argentina). In addition, IPC hosted a symposium at the 3rd World Congress of Psoriasis and Psoriatic Arthritis in Stockholm, Sweden as well as a Mechanisms of Disease workshop at the 42nd Annual ESDR meeting in Venice, Italy.

In November 2012, IPC hosted its 3rd Annual “Think Tank” in Amsterdam, the Netherlands. The Think Tank is designed to bring the councilors together toward building an impactful agenda of psoriasis research and treatment programs. This year’s eclectic agenda included a focus on stratifying psoriasis, cardiovascular co-morbidities, unmet needs in the management and education of psoriasis, and healthcare guidelines all culminating in IPC’s First Annual Lecture delivered by Professor Enno Christophers. I am proud to say that it was truly a productive event that highlighted several areas of focus for IPC in the coming years.

In 2012, IPC welcomed seventeen new councilors from ten different countries into its community. These new councilors are listed in the News section at the end of this *Psoriasis Review*. 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’s *Psoriasis Review*, or to learn more about IPC, please visit www.psoriasiscouncil.org.

Sincerely,

Professor Peter van de Kerkhof, MD, PhD
President, International Psoriasis Council

On a more personal note, it is with great sadness that I would like to acknowledge the passing of former IPC CEO and Executive Director, Karen Baxter Rodman, this past October. Karen served as an enthusiastic and dedicated leader of our organization from 2008 – 2012. During her tenure, IPC’s resources have grown significantly, our programming has more than doubled and IPC has become an internationally known organization advancing psoriasis research, treatment and education. As a colleague, a leader and a friend, she will be greatly missed.
The results in patients who experienced the higher doses indicate a dose response effect relative to the 70 mg group. The data indicate a higher rate of adverse events in the brodalumab groups and note two cases of grade 3 (0.5-1 x 109/L) asymptomatic neutropenia. The mechanism for neutropenia with brodalumab administration remains unknown. The most commonly reported adverse events in the combined brodalumab groups were nasopharyngitis (6%) and injection-site erythema (6%). It was noted that the trial was not sufficiently large to make valid assessments on the risk of infection or cardiovascular events relative to placebo.

COMMENTARY The results validate the pivotal role played by IL-17, and inferentially Th-17 T cells, in the pathogenesis of psoriasis. Most poignant is the cumulative probability curve (or population curve) which displays the response of an entire cohort. The vast majority of patients experience profound suppression of their psoriasis. Brodalumab displayed a high level of efficacy in patients with moderate-to-severe plaque psoriasis, and worked with a rapid onset of action. Further evaluation in phase 3 trials is warranted.


Summary

The results of a 142 patient, phase 2 clinical trial, to evaluate ixekizumab (humanized anti-interleukin-17 monoclonal antibody) for psoriasis treatment are presented. The study was initiated based upon the putative pathogenic role for Type 17 helper T cells in psoriasis. The experimental hypothesis is that inhibition of interleukin-17A (IL-17A) will ameliorate the inflammation leading to psoriasis. The trial consisted of a placebo and four dose groups of ixekizumab (10, 25, 75 & 150 mg) administered at 0, 2, 4, 8, 12, and 16 weeks. At the primary endpoint of 12 weeks, the 25, 75 and 150 mg dose groups yielded statistically significant percent of patients who achieved PASI75. There were not statistical differences for the 10 mg group. Moreover, the percentage of patients with a PASI 90 was 150 mg (71.4%), 75 mg (58.6%), and 25 mg (50.0%). PASI 100 was achieved in the 150-mg group (39.3%) and the 75-mg group (37.9%). The results were reported to be observable as early as week 1 and were sustained through the 20 week trial. Significant
improvements were also reported in nail and scalp psoriasis for the 75 and 150 mg dose groups. Joint pain was relieved to a statistical degree in those that received 150 mg ixekizumab. No serious adverse events or major cardiovascular events were observed. There were no obvious dose-related adverse events, including infections.

**COMMENTARY** The outcomes of this phase 2 clinical study indicated that the targeting of IL17A may present a new therapeutic strategy for psoriasis. Ixekizumab displayed high efficacy, a rapid onset of action, and a sustained effectiveness through the trials. Consequently, Ixekizumab, in targeting IL17, represents a downstream refinement of the IL23 pathway. This was a good, clean, well designed study with convincing results. Aside from efficacy, perhaps the most important aspect was ixekizumab’s impressive safety: there were no SAEs in this trial with only a few, mild constitutional symptoms experienced by study subjects. No MACE events were reported in this trial. The confirmation of this pattern in phase III trials will be important to support ixekizumab as a viable new option in the therapeutic armory for Dermatologists.

A CARD-carrying candidate for the genetic basis of psoriasis susceptibility


**Summary**

Jordan et al., contributed back-to-back manuscripts to the American Journal of Human Genetics that delivers important information related to the genetic basis of psoriasis and its functional consequence. The initial work identifies mutations in caspase recruitment domain family, member 14 (CARD14) contained within human chromosomal region 17q25, being responsible for the elusive PSOR2 locus. The authors identified mutations in CARD14 in two large families from Europe and Taiwan. The authors then identified a sporadic (de-novo) CARD14 mutation in a child with severe generalized pustular psoriasis.

CARD14 encodes a 1,004 amino acid protein that is expressed in keratinocytes and immune cells. The familial mutations and the sporadic mutation were unique gain-of-function mutations. These led to enhanced up-regulation of NF-kB, a transcription factor already known to play an important role in inflammation and apoptosis, and which is known to be over-expressed in psoriatic skin. This group also showed that the gain-of-function psoriasis mutations activated expression of psoriasis-associated genes in keratinocytes, including chemokines CCL20 and IL8. This is hypothesized to lead to the inflammatory recruitment seen in psoriatic skin, and ultimately to the vicious cycle associated with the disease. CARD14 was found to be localized to the basal and suprabasal layers of healthy skin epidermis but was reduced in the basal layer and diffusely upregulated in the suprabasal layers of the epidermis of psoriatic skin.

In the second manuscript, the authors performed a population-based study of CARD14 mutations. The comprehensive analysis spanned seven psoriasis cohorts (>6,000 cases and >4,000 controls). They identified additional CARD14 rare variants, some of which are likely to be pathogenic because they impacted NF-kB activity. Some mutations in CARD14 were found to be neutral alterations or common polymorphisms. Thus, some additional rare CARD14 variants predispose to psoriasis. Collectively, a meta-analysis of common variants revealed an association between psoriasis and an arginine to tryptophan amino acid substitution in CARD14 that increases risk of psoriasis in the general population.
COMMENTARY Attributing a genetic basis to disease susceptibility is challenging since there are many potentially neutral polymorphisms that have minimal impact on function. In this work, the authors have identified a series of truly pathogenic rare variants in psoriasis, thus contributing to the understanding of the genetic foundation of the condition. They determined that these mutations cause disease by enhancing the activation of a protein (NF-kB) that regulates many genes involved in inflammation and proliferation. These mutations lead to psoriasis by either increasing activation of NF-kB, or by leading to its sustained activation. Mechanistically, a triggering event (that might include epidermal injury or infection) in individuals harboring certain CARD14 alterations initiates an inflammatory cascade orchestrated by keratinocytes. The result is the prototypical cycle of epidermal inflammation and regeneration which constitutes the hallmark of psoriasis. Thus, collectively these studies contribute to our understanding of the genetic basis of psoriasis and in so doing contributes a plausible hypothesis for disease pathogenesis.

Clinical support for infectious molecular mimicry as a pathogenic mechanism for the initiation and propagation of psoriasis


Summary

Based upon the anecdotal association of streptococcal throat infections with exacerbation of psoriasis and the identification of T cells specific for streptococcal M proteins and skin keratins, Thorleifsdottir et al. conducted the first controlled, prospective study to assess the impact of tonsillectomy on psoriasis. Thirteen out of twenty-nine patients with chronic psoriasis exhibited a sustained improvement after tonsillectomy experiencing disease improvement in the range of 30 to 90%. To measure the frequency of putatively pathogenic T cells, peripheral blood mononuclear cells were isolated and cultured with a series of overlapping peptides derived from the highly homologous human cytokeratin 17 or streptococcal M6 proteins. The results indicated that tonsillectomy was associated with a striking reduction in the frequency of circulating specific T cells that recognized cytokeratin or streptococcal M protein. No effect was seen in control psoriasis patients who did not undergo tonsillectomy. Moreover, it remains to be investigated whether patients who have not noticed worsening in association with sore throat also improve after tonsillectomy.

Nevertheless, effector T cells residing in the tonsils that recognize keratin determinants in the skin and migrate to the epidermis apparently coordinate the psoriasis phenotype.

COMMENTARY These results implicate infectious agents as a potential cause and/or contributor to the psoriasis condition. Prior studies have demonstrated that chronic plaque psoriasis can be exacerbated after streptococcal throat infections specifically of β-hemolytic streptococci (A, C, and G) that express M protein on their surface. The study presented herein represents the first controlled, prospective study to assess the clinical and immunologic impact of tonsillectomy on chronic psoriasis. Furthermore, the authors demonstrate data that primed M protein-specific T cells contribute to a pathogenic role in psoriasis, since the numbers decrease with reduced disease severity. Collectively, the results open up new avenues for potential therapy development that might revolve around Ag-specific immunotherapy; examples of which are curative in animal models of other autoimmune conditions.
CONTINUING THE DIALOGUE: THE FUTURE OF PSORIASIS

Review of the IPC Pre-Conference Event at the 3rd World Psoriasis and Psoriatic Arthritis Conference 2012 in Stockholm, Sweden

Caitriona Ryan, MB BAO BCh
Department of Dermatology, Baylor University Medical Center, Dallas, Texas, USA
Baylor Institute of Immunology Research, Dallas, Texas, USA

An IPC Pre-Conference Event was held at the recent World Psoriasis and Psoriatic Arthritis Conference in Stockholm, Sweden, under the chairmanship of Peter van de Kerkhof on June 27, 2012. This was the third World Psoriasis and Psoriatic Arthritis Conference, which is held every three years by the International Federation of Psoriasis Associations (IFPA) in association with world-leading dermatologists and rheumatologists. The objective of the conference is to integrate dermatologists and rheumatologists in further understanding both scientific and clinical aspects of the disease spectrum. The theme of the 3rd conference was “Psoriasis – a global health challenge,” and was presided over by Alan Menter, former president of the IPC. This conference had a greater focus on the patient's perspective of psoriasis, particularly the psychosocial impact of psoriasis on disease-related quality of life.

The IPC pre-conference event was comprised of two symposiums; a patient-driven symposium entitled “The Dialogue between Patients and Dermatologists” and a scientific, research-driven symposium entitled “Continuing the Dialogue: The Future of Psoriasis.”

The Dialogue between Patients and Dermatologists

The first symposium entitled “The Dialogue between Patients and Dermatologists,” was attended by dermatologists and representatives from patient associations. The objective of this symposium was to involve patients in decision-making and to obtain feedback with regard to treatment goals and initiatives to address the psychosocial implications of the disease. The panel for this symposium consisted of three dermatologists and three patient representatives.

1. Treatment goals in the management of psoriasis
Professor Ulrich Mrowietz, IPC Councilor, Germany

In the first session, Dr. Mrowietz addressed the importance of determining treatment goals for the effective management of psoriasis. Large discrepancies can exist between the individual treatment expectations of a patient and what a dermatologist aspires to achieve with regard to disease control. Similarly, there can be great variation in treatment expectations between individual patients with similar disease severity, depending on its impact on their quality of life. The definition of clear treatment goals prior to initiation of treatment can help to provide realistic treatment expectations and enhance the patient-dermatologist relationship in the long-term management of psoriasis, which, in the majority, is a chronic, life-long disease. Treatment goals can be difficult to define and must be individualized to the patient based on clinical disease severity, the associated impairment of quality of life and patient co-morbidities. Dermatologists and psychologists can co-operate to optimize the global treatment of psoriasis and its associated psychosocial burden, but feedback from patients is essential to ensure that patients are satisfied with management of all aspects of their disease and that we fully understand their needs. The identification of treatment goals is also important to ensure that measures are taken to improve treatment outcomes when these goals are not met. Communication is essential with regard to expectations and limitations of a given treatment and poor education can result in the failure of treatment goals. It is important to explain to a patient when optimal treatment response is likely to occur and what further options are available if treatment goals are not achieved.
CONTINUING THE DIALOGUE: THE FUTURE OF PSORIASIS

Many patients develop psoriasis before the age of 18, which can lead to considerable psychosocial impact for the vast majority of their life. A recent article was presented which showed that symptom severity is directly related to skin discomfort and the stigmatization experience and inversely related to skin-related quality of life. Another recent study of 936 patients by an Italian group showed that even patients with moderate disease as determined by Physician’s Global Assessment (PGA) had statistically significant increases in shame, worry, annoyance, anger and personal interactions.

There have been huge advances in treatment options for psoriasis in the past decade. Twenty-five years ago, systemic treatment options for moderate-to-severe psoriasis were limited to etretinate, methotrexate, PUVA, and even systemic steroids in some cases. A generation later has shown the advent of a range of new biologic agents in addition to these conventional treatment options, including TNF-alpha inhibitors and ustekinumab, an IL-12/23 inhibitor. Fumaric acid esters are also available in Europe. With increasing knowledge of the immunopathogenesis of psoriasis, a multitude of new targeted therapies are currently in the pipeline, including anti-IL-23p19 antibodies, anti-IL-17A antibodies, anti-IL-17-receptor antagonists, anti-IL-22 antibodies, dimethylfumarate, janus kinase inhibitors (tofacitinib) and phosphodiesterase-4 inhibitors (apremilast). With limited treatment options in the past and the risk of toxicities with chronic use of some of these agents, the same level of disease control was not always possible. A PASI-75 response has traditionally been considered an acceptable efficacy cut off to determine a satisfactory response to treatment. With the imminent arrival of these newer and more efficacious treatments and a growing armamentarium of treatment options, should treatment goals be changed?

We now know that psoriasis is associated with chronic systemic inflammation, resulting in increased cardiovascular morbidity and mortality. This begs the question as to whether efficacious cutaneous and joint treatment would also reduce systemic inflammation and associated cardiovascular morbidity. A cardio-protective effect has been shown within rheumatoid arthritis patients treated with TNF-alpha inhibitors and methotrexate in the CORRONA-registry (2001-2006). Further studies are needed to determine if this is the case in psoriasis patients.

Prof. Mrowietz next discussed a consensus meeting of psoriasis experts from 19 European countries to identify treatment goals for moderate-to-severe psoriasis. Several treatment goals were identified by the group to supplement current guidelines and promote the use of goal-oriented therapy. Firstly, plaque psoriasis was re-categorized into two categories only: mild disease and moderate-to-severe disease. Mild disease was defined as body surface area (BSA), PASI and DLQI all equal to or less than 10. This grade of psoriasis can usually be controlled by topical therapy. Moderate-to-severe psoriasis was defined as BSA, PASI or DLQI greater than 10. In the majority of cases, these patients warrant systemic treatment. The group described an “upgrade system,” where certain clinical presentations could “upgrade” a mild form of the disease to “moderate-to-severe,” supporting the use of systemic or biologic therapy. These clinical scenarios included the involvement of visible areas such as the face, large parts of the scalp, the genitalia, non-pustular palmo-plantar involvement, finger-nail onycholysis or onychodystrophy, the presence of intense, disabling pruritus, or the presence of single recalcitrant plaques.

The consensus group also agreed that the time-point for assessing whether treatment goals had been achieved varied depending on the agent in question. The induction phase, or point when optimal treatment effect is expected, is generally defined as the treatment period until week 16 for agents such as infliximab, adalimumab and ustekinumab. The group agreed that the “induction phase” could be extended until week 24 depending on the agent in question. Methotrexate, for example has been shown to reach maximum efficacy at approximately week 20 and other agents can similarly take longer to achieve maximal response, including etanercept, especially when it is used
in a low dose schedule, and acitretin. Everything beyond the “induction phase” was defined as the “maintenance phase,” during which time dermatologists need to ensure durability of treatment response and to monitor patients for adverse effects and cumulative toxicities.

Prof. Mrowietz stressed that it is essential that if treatment goals are not met by pre-determined time-points, action must be taken, either by increasing the dose, reducing dose intervals, using combination therapy with a topical agent or another systemic treatment, or finally, by changing the drug if these strategies fail. A treatment algorithm was proposed to help guide treatment goals which includes the patient’s subjective judgement of treatment response in the decision making process. If a patient’s DLQI suggests poor quality of life, this should be addressed and treatment modified to achieve treatment goals. In general, the group consensus was that if a PASI-75 response was achieved, treatment should be continued. If PASI-50 response was not achieved by the end of the drug-specific induction period, an alternative treatment plan should be instituted. If objective treatment response lay between a PASI-50 and PASI-75 response, but DLQI was less than 10, treatment could be continued. If DLQI was 10 or more, however, reflecting a poor disease-related quality of life, an alternative treatment regimen should also be sought.

Prof. Mrowietz concluded that the definition of treatment goals and co-operation between dermatologists and patients are of utmost importance in the optimization of psoriasis management.

2. The possibilities which the internet offers for consultations for psoriasis
Dr. Chris Bundy, Manchester, UK

The second session of the patient-focused symposium, led by Dr. Chris Bundy from Manchester, related to the development of e-health. Patients’ views of this novel technology and its current role in the management of psoriasis were discussed. There is significant evidence that stress and heightened levels of anxiety may trigger psoriasis flares. Psoriasis is well recognized to cause a significant reduction in health-related quality of life measures comparable to other chronic diseases such as cancer, arthritis, diabetes and depression. Social embarrassment, stigmatization and feelings of rejection are common and the condition has been shown to have a negative impact on social and personal decisions, including career choices, levels of employment and personal relationships. The impact psoriasis has on a patient's everyday psychological, emotional and social functioning is considerable, and the psychological impact of the disease can have more of a bearing on a patient’s life than the physical symptoms. It is associated with substantial psychological morbidity with high rates of anxiety, depression and increased suicidal ideation. Psoriasis patients have also been shown to have high levels of alexithymia, which is an inability to recognize or discuss their feelings or emotional states.

Unfortunately, there is a lack of trained personnel to manage psychosocial issues in the outpatient clinic and, equally, there is limited dermatology-specific knowledge in mainstream mental health services. Moreover, referral to mental health services in itself can carry stigma for the patient. Several mechanisms such as relaxation techniques and cognitive based therapy have been effective in reducing the distress associated with psoriasis but have shown limited efficacy in managing symptoms. A mindfulness meditation based intervention, however, has shown efficacy in both symptom management and distress, with increased treatment success when phototherapy and PUVA is used in combination with mindfulness based meditation compared with phototherapy alone.

The internet can act as a medium to deliver psychological support to psoriasis patients. E-Health is now a complementary health management tool used in many disciplines. It has many advantages, allowing patients great flexibility with regard to the timing of their appointments and pace of their involvement, a lack of travel time or costs...
and decreased time and resources for the consultation. With regard to psychological interventions, it may have the added benefit of allowing a patient to overcome social anxiety and social avoidance. Significant limitations do exist, however, as some patients do not have constant access to the internet, and others may find the interaction impersonal.

Cognitive-behavioural therapy is a systematic intervention to identify and change unhelpful core beliefs and modify situation specific automatic thoughts. CBT computer and web-based delivery platforms have been used for a variety of psychological disorders, and the structured nature of this methodology lends itself well to computer-based programmes. Dr. Bundy discussed a study examining a tailored CBT web-based programme for patients with mild-to-moderate psoriasis. The main objectives of the study were to examine if this web-based programme would be effective in reducing psychological morbidity while improving psoriasis and to determine how well patients engaged with on-line CBT. It was a community-based, control-led study of 135 patients with physician diagnosed mild-to-moderate chronic plaque psoriasis, comparing immediate (n=67) and delayed (n=68) on-line CBT treatment. Patients had six modules of tailored CBT addressing self management, modification of beliefs and changing behaviour. These encompassed general information about psoriasis, stress and tension (self management); modules to manage low mood and thinking styles (belief modification); and modules to enhance coping and management of self-esteem (behaviour modification). Of those enrolled in the study, five withdrew and there was one death in the experimental arm and five did not complete follow up measures in the control arm.

Following CBT, the Hospital Anxiety and Depression Scale (HADS) anxiety scores decreased (p<0.01) but HADS depression scores did not (p=0.92). Although self-reported psoriasis improved in both groups, the experimental arm did not show a superior response compared with the control arm using either the Self Administered Psoriasis Area and Severity Index (SAPASI; p=0.67) or the DLQI (p=0.92). Larger studies are needed to determine this conclusively.

Continuing the Dialogue: The Future of Psoriasis

The second symposium was an invite-only event entitled “Continuing the Dialogue: The Future of Psoriasis,” which was attended by IPC councillors and board members and dermatologists who had previously attended one of IPC’s 1.5 day psoriasis symposiums. The purpose of this symposium was to have interactive dialogue regarding IPC’s current and planned activities, particularly with regard to IPC-driven genetic and systemic disease programs.

1. Overview of IPC activities
Professor Peter van de Kerkhof, IPC President, the Netherlands

The first session was presented by Professor Peter van de Kerkhof, current President of the IPC, who discussed the mission, history, current and proposed future activities of the IPC.

The IPC was founded in 2004 as a dermatologist led, international, non-profit organization dedicated to innovation across the full spectrum of psoriasis through research, education and treatment. It is governed by a board of 10 directors and guided by 59 councilors (with an added 17 councilors in 2012), who are considered key-opinion leaders in the field of psoriasis and represent 20 countries world-wide. IPC councilors are selected by the IPC Board of Directors based on their level of expertise in psoriasis. Prospective councilors are nominated and seconded by either an IPC Board Member
or IPC councilor, both of whom should be from different countries. Councilors participate in IPC projects, advise the IPC and act as ambassadors for the IPC. The organization is run on an operating budget of $1 million. Objectives of the organization include increasing access to timely and relevant information across the dermatology community, enhancing the ability of dermatologists to treat to the standard of care, creating a collaborative forum for professionals to share best practices, building a comprehensive understanding of psoriasis through research and education, documentation of consensus meetings, prioritization of targeted research projects, identification of important gaps in research and definition of standards for high quality research and treatment practices. Most importantly, the IPC aims to provide supporting programs to help dermatologists meet and exceed standards that the organization has set.

The IPC also liaises with other dermatological societies relevant to psoriasis such as the International League of Dermatological Societies (ILDS), the European Dermatology Forum (EDF), the European Academy of Dermatology and Venereology (EADV), the European Society of Dermatological Research and the Society of Investigative Dermatology; regulatory authorities and public health agencies, particularly the FDA and EMA; psoriasis patient organizations such as the International Federation of Psoriasis Associations (IFPA), Europso and the National Psoriasis Foundation (NPF); and corporations with an interest in psoriasis. Information or resources generated by the IPC are available for physicians who currently manage or are interested in managing psoriasis, physician assistants, nurse practitioners, nurses, scientists and skin biologists, patients, and all those who seek unbiased, authoritative information on psoriasis.

One of the primary objectives of the organization is research and education. Symposia are held in a wide variety of countries worldwide to ensure that psoriasis management is advanced globally. The IPC symposium is a 1.5 day, intensive training symposium on psoriasis and its treatments, led by world-renowned experts, and designed to provide dermatologists with the most up-to-date information regarding the understanding of the disease and treatment modalities. This year venues will include the Philippines, California, Venice, Prague, Johannesburg and Buenos Aires. One of the most valuable educational tools provided by the IPC is their “Meet the Experts” program, which addresses the management of difficult and complex cases. The IPC publishes a newsletter biannually (June and December), in which it presents the five most recent key articles to advance psoriasis knowledge. This publication is translated into Spanish and Portuguese, emailed and mailed to IPC members, distributed at various congresses and to psoriasis and dermatology groups.

A new IPC Website has also just been launched. The goals of the new site are to improve navigation and access to educational psoriasis resources, such as a psoriasis image library, webcasts, videos and previous issues of the IPC’s Psoriasis Review. The web-site will also serve as an interface to allow promotion and registration for psoriasis events by other organizations and to allow access to meeting materials. In the next phases of this venture, an on-line community will be created to allow IPC councilors to interact with each other.

The IPC systemic therapy working group is led by Prof. Jonathan Barker, Prof. Christopher Griffiths, Dr. Alan Menter and Dr. Bruce Strober. The objectives of this group are to highlight psoriasis as a systemic disease with far reaching health consequences, to define appropriate use for traditional and novel systemic therapies, and to improve clinical research by promoting a better clinical understanding of the disease and developing improved mechanisms for research. In 2012 a multitude of programs were conducted. An EMA biosimilars workshop, described in the last IPC publication, was held in October 2011. A pediatric database under the chairmanship of Dr. Amy Paller, has also been sponsored by the IPC to examine the impact of pediatric psoriasis on childhood body mass index and co-morbid risk factors, and to assess how this relates to disease severity. A topical therapy working group is led by Prof. Peter van de Kerkhof, Prof. Knud Kragballe, Dr. Mark...
Lebwohl and Dr. Alan Menter. The primary objective of this group is to investigate new innovations and to develop treatment recommendations for topical therapies. This includes recommendations for the long-term treatment of scalp psoriasis and investigation of new mechanisms for topical administration. Other current projects include “The Standardization of Clinical Trials Project” under the chairmanship of Dr. Alexa Kimball, “The Psoriasis Susceptibility-genetics Project” under Prof. Jonathan Barker and “The Mechanisms of Disease Project” under Prof. Hervé Bachelez. Outcomes and future objectives of the IPC-driven genetics workshop held in Montreal in October 2011 which are reviewed in the next session were also discussed. Further projects planned for 2013 include the “Clinical outcomes, Co-morbidities and Therapeutics Project” under the chairmanship of Dr. Alexa Kimball.

The IPC scientific committee was established in May 2010. This committee, chaired by Prof. Jonathan Barker, is comprised of Prof. Wolfram Sterry, Dr. Alexa Kimball and Dr. Paul Tebbey, medical director of the IPC. As international experts, members of the IPC are uniquely positioned to identify research gaps and to formulate viewpoints on key topics. The mandate of this working group is to build a comprehensive understanding of psoriasis, to document consensus opinions from working groups, and to prioritize targeted research projects with a view to enhancing disease prevention and therapeutic strategies. The key research priorities identified by the working group include the creation of a complete “genetic map” of psoriasis susceptibility genes to define phenotype-genotype relationships; to develop robust, long-term, prospective population epidemiology studies in order to determine the true prevalence and natural history of psoriasis; to examine the effect of early, aggressive intervention on the natural history of psoriasis; to perform genetic and epidemiologic studies of psoriasis phenotypic variants; to examine the effect of environmental factors on the triggering and exacerbation of psoriasis; and to perform genetic and epidemiologic studies of psoriasis in all ethnic groups.

Another key objective of the scientific committee is the elucidation of mechanisms of disease. This includes the identification of psoriasis antigens or auto-antigens; identification and validation of biomarkers of disease severity, treatment response and treatment toxicity; definition of the roles of key inflammatory cell subsets in psoriasis; delineation of the molecular pathways and functional biology of psoriasis; mechanistic determination of the relationship between the pathogenesis of cutaneous psoriasis and psoriatic arthritis; definition of key mediators and downstream pathways in psoriasis pathogenesis; elucidation of molecular pathways in other psoriasis phenotypes; and the definition of alterations in the epidermal barrier in psoriatic skin.

The other main focus of the scientific committee is the area of healthcare economics, therapeutics and co-morbidities. This encompasses many areas, including determination of the cumulative cost of psoriasis to the patient, to the health care system and to society in general; development of better clinical outcome measures to measure the global burden of disease with regard to clinical severity, symptoms, quality of life and quality of care; implementation of objectives and describe outcomes of patient registries; and determination of the efficacy, safety of numerous new therapeutics in clinical use and development; and the proposal of suggested regimens of combination therapy. Another key issue is affordability, access to and reimbursement of psoriasis treatments across the world, especially in poorer countries, to optimize psoriasis management globally.

2. IPC’s new genetics initiative

Professor Hervé Bachelez, IPC Board Member, France

In the next session, Prof. Bachelez discussed IPC’s new genetics initiative to positively impact education, research and treatment though advances in the genetics of psoriasis. The objective of this initiative was to foster and develop international collaboration towards completing the genetic map of psoriatic disease. A genetic forum was held in Montreal in October 2011 in
advancing knowledge | enhancing care

CONTINUING THE DIALOGUE: THE FUTURE OF PSORIASIS

association with the International Congress of Human Genetics, chaired by Goncalo Abecasis (Ann Arbor) and Richard Trembath (London). A proposal was developed to allow implementation of a comprehensive consortium project. Outcomes were published in the British Journal of Dermatology and the JAAD under the authorship of IPC councilors from various parts of the world, thus attesting to the globalization of this topic.

Previously, high powered GWAS (Genome-wide Association Scan) have lead to the identification of over 20 psoriasis susceptibility regions, including the HLA-C locus (accounting for > 50% of disease heritability), loci related to Th17 cell activation (IL23R, IL12B, IL23A and TRAF3IP2), type I interferon induction (IFIH1, RNF114 and TYK2), NF-kB signaling (REL, NFKBIA, TNFAIP3 and TNIP1) and skin barrier function (the LCE3 gene cluster on chromosome 1q21). The Psoriasis Immunochip Consortium was a multi-center project in the US and EU, developed to validate loci tentatively associated with psoriasis and to identify additional susceptibility regions. The immunochip platform incorporated 200,000 single nucleotide polymorphisms (SNPs), and a total of 10,000 cases and 24,000 controls were analyzed. This resulted in the identification of 17 novel & independent SNPs with highly significant associations that mapped to a variety of genomic regions. Fine mapping of several of the association signals to identify single genes is now planned. The PsA Genetics in Europe (PAGE) Consortium showed significant association signals at several psoriasis susceptibility loci, with multiple association signals for the MHC region and IL-12B. Susceptibility markers for PsA were shown to be independent from psoriasis, with no particular genetic determinant unique to PsA.

The genetics forum also discussed the potential for human knockout models, with the identification of individuals harboring rare susceptibility alleles allowing further insights into disease processes through the analysis of gene function e.g. loss-of-function mutations in generalized pustular psoriasis. Next-generation sequencing technologies should lead to the establishment of extended collaborative networks, tasked with the recruitment of specific patient resources and the development of methods for the interrogation of whole-genome sequence data. The IPC’s current genetic proposal towards “Completing the Genetic Map of Psoriasis” aims to identify rare protein altering variants in 10,000 psoriasis cases and 10,000 controls. It will use the Illumina exome chip (Illumina, CA) to increase coverage of genes and regions implicated in psoriasis susceptibility and to examine genotype exome variation in between 10,000 psoriasis cases and 10,000 controls. It will systematically evaluate the contribution of rare coding variants to disease susceptibility, within previously indentified loci, and evaluate the contribution of rare and common coding variants to disease susceptibility across the genome to identify new susceptibility loci. This will utilize new cost-effective genotyping technologies to systematically evaluate the contribution of rare protein coding variations. Sequence data for over 12,000 individuals will be leveraged to design arrays to enable the analysis of the majority of the variation. It is anticipated that the project will identify genes where one or more rare coding variants of clear functional impact are associated with psoriasis thus providing clear insights into disease mechanisms and susceptibility.

Data sharing and publication will occur in accordance with international policies and guidelines promoting open science (US National Institutes of Health, the UK MRC/Wellcome Trust and the Canadian NRC). This is designed to encourage collaboration, data sharing and the dissemination of new knowledge quickly in order to foster scientific progress, meet humanitarian goals, and to maximize the impact of the research. It also allows principal investigators to publish primary manuscripts and to immediately deposit the information into the public domain in the form of an open-access website.
3. Psoriasis and Systemic Disease

Dr. James Krueger, IPC Councilor, United States

The final session was presented by Dr. James Krueger, a world renowned dermato-immunologist. Dr. Krueger discussed the association between psoriasis and systemic inflammation and what is known about the immunologic basis of this relationship.

From emerging clinical research it has become clear that psoriasis is associated with a number of co-morbid conditions, the most common of which appears to be obesity, followed by psoriatic arthritis. Other significant associations include diabetes mellitus, cardiovascular disease and increased mortality. Dr. Krueger suggested that there are two major potential pathways that may explain this association – one would be the view that both sets of problems are associated with complex genetic susceptibility and that there may be co-inheritance of genes associated with psoriasis and genes associated with obesity, diabetes and premature atherosclerosis. Examination of published susceptibility genes for these disorders, however, shows very little overlap. Alternatively, the association may be physiological, and that in some way the presence of psoriasis may alter the function of other tissues and cell subsets outside the skin. The “march of psoriasis” is often described. One theoretical model suggests that psoriasis primarily drives metabolic dysregulation, which in turn drives dyslipidemia and the increase in cardiovascular risk. Dr. Krueger and his research group have proposed an alternative hypothesis – this model suggests that inflammation in the skin can independently affect the function of other cells and organs in the body and may not be caused by metabolic dysfunction but by a direct immunological effect of psoriasis. Dr. Krueger described a comprehensive review article in the Journal of Investigative Dermatology which described potential molecular pathways at play in the complex relationship between psoriasis and cardiovascular co-morbidities. Possible mechanistic links were described between skin inflammation and both obesity and cardiovascular disease.

Adipocytes and macrophages are the main cell types in adipose tissue. Inflammatory macrophages infiltrating adipose tissue in obese patients create an inflammatory microenvironment and stimulate the production of inflammatory mediators from adipocytes to maintain a chronic inflammatory state in obesity. Adipokines are proteins which are produced by adipose tissue. When there is inflammation in adipose tissue, adipokines may be released into the circulation which in turn may have effects on other tissues. Adipokines play an important role in the pathogenesis of insulin resistance and the metabolic syndrome, acting through the monocyte/macrophage system to produce pro-inflammatory cytokines such as TNF-α, which attenuates signalling through insulin receptors to produce a state of hyperinsulinemia. Adipokines can also have effects on vascular endothelium and increase the expression of adhesion molecules on endothelial cell walls.

In patients with severe psoriasis, there are increased levels of TNF-α in the systemic circulation. This suggests that TNF-α from cutaneous psoriasis lesions may leak into the bloodstream. Alternatively, the increased macrophage infiltrate observed in cutaneous lesions is seen to extend into the deep dermis, unlike the more superficial lymphocytic infiltrate, and may potentially extend further into adipose tissue of the subcutis. Currently, Dr. Krueger and his group at Rockefeller Institute are engaged in a project to define the role of psoriasis in systemic inflammation. As part of this, PET-CT is being used to image metabolic and inflammatory activity in psoriatic plaques in patients with severe psoriasis and to evaluate the effect of systemic treatment on this inflammation. A one-year study is currently underway of patients with moderate-to-severe psoriasis commenced on treatment with etanercept. Patients are being evaluated with skin and fat biopsies at baseline and several time-points, cardiovascular function studies, PET-CT of psoriasis lesions at baseline and one year and serum is being collected for analysis of serum cytokines and adipokines.
CONTINUING THE DIALOGUE: THE FUTURE OF PSORIASIS

Another concept being explored is the association between psoriasis and cardiovascular inflammation. The complex immunopathogenesis of increased cardiovascular risk in psoriasis patients remains to be fully elucidated. One hypothesis is that the systemic release of skin-derived cytokines and inflammatory mediators from psoriasis lesions and up-regulation of cell adhesion molecules in peripheral leukocytes which have been exposed to inflamed skin may result in compartmental shifts in inflammatory cells between the skin, the peripheral blood and atheromatous plaques of the coronary vasculature. The pro-inflammatory cytokine profile of psoriasis lesions is remarkably similar to that of atherosclerotic lesions, and a similar inflammatory cell infiltrate of T cells, macrophages and monocytes, with extravasation of leukocytes through the endothelium being demonstrated in both conditions.14 Transcriptional profiling of lesional skin by Dr. Krueger and his group has identified over-expression of several gene transcripts in the skin of psoriasis patients which may have mechanistic links to the observed increase in cardiovascular inflammation. This data has yet to be published.

References


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

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Scientific Highlights from the 21st EADV Congress and So Long To Scale

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

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Professor Kirby has received grants/research support from Abbott Ltd, Pfizer and Janssen. He has served as a consultant/speaker bureau member for Pfizer, Abbott, and Janssen and as an advisory board member for Pfizer and Janssen. In addition, he has received honorarium from Abbott, Pfizer and Janssen.

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Physician Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Annenberg Center for Health Sciences at Eisenhower and the International Psoriasis Council. The Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.
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Target Audience
This activity has been designed to meet the educational needs of dermatologists, physician assistants and nurse practitioners involved in the care of patients with psoriasis.

Goal Statement
The primary goal of this enduring material is to provide information on how to integrate the latest data on the treatment of psoriasis into clinical practice to optimize long-term outcomes for patients with psoriasis.

Credit Designation
Annenberg Center for Health Sciences designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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The Firas Report:  
Scientific Highlights from the 21st Annual EADV Congress from Prague, Czech Republic

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

The 21st annual meeting of the European Academy of Dermatology and Venereology was held in the beautiful and historic city of Prague, Czech Republic. Psoriasis was featured throughout the agenda with eminent international speakers presenting their experiences and perspectives across the field of psoriasis. The Firas Report summarizes the major topics and latest developments.

Biological Therapies

Immunogenicity of Biologic Therapies:
Immunogenicity to biologic therapies represented a topic that received much attention throughout the conference. Notably, the humoral immune response against adalimumab was found to be highly restricted and limited to the idiotype of the therapeutic antibody. The specificity toward the region that binds to the TNF-alpha antigen represents one explanation for the neutralizing efficacy of such immunogenic antibodies (van Schouwenburg PA, Ann Rheum Dis, 2012). In one study, antibody formation against adalimumab was measured for a period of up to 24 weeks of adalimumab treatment in 29 patients. Antibodies to adalimumab were found in 45% of the patients and a direct correlation was found between low adalimumab trough concentrations and antibody titre. Thus, reduced efficacy to the adalimumab therapy may be explained because the formation of neutralizing antibodies would inhibit the beneficial capacity of the adalimumab therapy by signaling its degradation and removal via phagocytosis (Lecluse LL, Arch Derm, 2010). Data from clinical observations show that antibody formation against TNF-alpha therapies tends to achieve a maximum concentration during the first year of drug exposure (Ducoureau E, Arthritis Res Ther, 2011). Thus, management of patients through this critical period with consistent antibody monitoring might support enhanced outcomes in the long-term.

Safety of Biologic Therapies:
Biologic therapies have been marketed for almost fifteen years and the associate long-term safety data continues to accumulate. Multiple presentations throughout the congress support the safety of the currently marketed biologics. Overall, they appear to be safe and associated with only low rates of complications when used in appropriate patients. A recent review on the safety of biologics in patients with psoriasis or psoriatic arthritis showed a slight increase in the incidence of infection and lymphoma among patients treated with the anti-TNF alpha monoclonal antibodies infliximab and adalimumab, compared with etanercept (Girolomoni G, Immunopharmacol Immunotoxicol, 2012). Whether these effects are entirely due to the use of TNF-alpha biologic therapies or are a result of a patient population that has also been exposed to other immune suppressive systemic agents remains to be elucidated.

However, the use of biologics in patients with psoriasis has also demonstrated beneficial effects beyond the clearance of the disease. In a large study involving 8845 patients, the association between TNF-alpha inhibitor therapy and myocardial infarction risk was studied. After adjusting for myocardial infarction risk factors, the TNF-alpha inhibitor cohort of patients had a significantly lower risk...
of myocardial infarction compared with the cohort of patients receiving topical therapy. Compared to the cohort of patients receiving systemic therapy, there was a lower rate of myocardial infarction albeit non-statistical. The data suggest a benefit to the overall reduction of systemic inflammation and myocardial infarction risk with the use of anti-TNF alpha therapies in patients with moderate-to-severe psoriasis (Wu JJ, Arch Dermatol, 2012).

Psoriatic Arthritis:
An important component of the psoriasis condition, psoriatic arthritis received much attention given the importance of the role of the dermatologist in identifying and treating patients with psoriatic arthritis. New recommendations for the treatment of psoriatic arthritis with topical or systemic therapies were published by the European League Against Rheumatism (EULAR) which, for the first time, acknowledged the importance of dermatological intervention in the condition (Gossec L, Ann Rheum Dis, 2012).

Data from a double-blind, placebo-controlled, phase-II trial for abatacept were presented (Mease P, Arthritis Rheum, 2011). The drug is currently used in rheumatoid and juvenile arthritis and is a selective T cell co-stimulation modulator. A total of 170 patients with psoriatic arthritis who had previously taken disease-modifying anti-rheumatic drugs, including anti-tumor necrosis factor (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 every 28 days thereafter. The primary end point was the American College of Rheumatology 20% criteria for improvement (ACR20 response) at week 24. 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, abatacept 3 mg/kg, 10 mg/kg, and 30/10 mg/kg groups, respectively. Compared with placebo, improvements were significantly higher for the abatacept 10 and 30/10 mg/kg groups, but not for the 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. No information was presented on the effectiveness of abatacept on the skin component of psoriasis.

Erythrodermic and Generalized Pustular Psoriasis:
Data on management techniques was presented for these two more severe and relatively rare variants of psoriasis. The first trial of erythrodermic psoriasis with biologics was with etanercept. Since then, various biologics have been used to treat this form of psoriasis. Results of a multi-centre national retrospective study on the use of biologics in erythrodermic psoriasis in France were presented. A total of 28 patients, representing 42 flares of erythrodermic psoriasis were reviewed. The patients were treated with adalimumab, infliximab, etanercept, ustekinumab, or efalizumab. The results showed an improvement of around 50% with those treated with adalimumab and infliximab, and a rate of 40% with those treated with etanercept. Overall, biologics showed good short-term efficacy; however treatment changes due to lack of long-term efficacy or side-effects were frequently observed. One year on from the first drug administration, only one-third of the patients continued to receive the same drug. The most significant safety concern consisted of severe infections (Viguier M, Br J Dermatol, 2012).

For the treatment of generalized pustular psoriasis, results were presented (In press). A total of 16 patients were treated (infliximab 10, adalimumab 3, and etanercept 3). Three quarters of the patients responded to the treatment. The mean time to pustule clearance was 6.5 days, with the fastest results observed in the infliximab group (a mean of two days). The use of anti-TNF therapy also demonstrated efficacy in prevention of subsequent flares of generalized pustular psoriasis with around 80% of patients not experiencing a flare in the subsequent eleven months of follow-up. These data show the efficacy of anti-TNF therapy in generalized pustular psoriasis.
Ustekinumab:
The IL12/23 biologic ustekinumab was featured prominently at the meeting. Data of its use both within and beyond psoriasis were presented. This included pityriasis rubra pilaris, sarcoidosis, hidradenitis suppurativa, and pyoderma gangrenosum. Some reports focused on combination therapy with ustekinumab across a variety of conditions. The addition of methotrexate to ustekinumab did not appear to deliver additional benefit. While there is no robust data on combined cyclosporine and ustekinumab therapy, anecdotal reports seem to indicate an added beneficial effect. Overall, no data on the long-term safety of combination therapy with ustekinumab is yet available.

The 5-year safety data of ustekinumab was presented. The data were obtained from extension of PHOENIX 1, PHOENIX 2, and ACCEPT trials (P965). The analysis included 3117 patients (8998 patient years); with 1482 (47.5%) patients treated continuously for at least four years or more (including 838 [26.9%] for at least 5 years). The rates of overall adverse events and infections consistently decreased over time from years one to five. Concomitantly, the rates of serious adverse events and adverse events leading to discontinuation were stable over time. The cumulative rate of serious infections per 100 patient years for ustekinumab 45mg and ustekinumab 90mg groups were 0.98 (0.69, 1.35) and 1.19 (0.91, 1.52), respectively. The cumulative rates of non-melanoma skin cancer per 100 patient years for ustekinumab 45mg and ustekinumab 90mg groups were 0.64 (0.41, 0.95) and 0.44 (0.28, 0.66), respectively. Investigator-reported major adverse cardiovascular events (MACE) rates per 100 patient years for ustekinumab 45mg and ustekinumab 90mg groups were 0.45 (0.26, 0.72) and 0.31 (0.17, 0.50), respectively. No cases of tuberculosis, or serious hypersensitivity reactions were reported. Rates of serious infections, malignancies, and MACE were stable over time and were consistent with rates previously described as well as with observations in the general psoriasis population. The data concludes that with continuous exposure for up to five years and approximately 9000 patient-years exposure, the long-term safety profile of ustekinumab remained stable over time and consistent with that previously reported after four years of follow-up.

IL17 in Psoriasis Pathogenesis:
The role of IL17 in psoriasis was presented. This cytokine is produced by TH17 cells (under the influence of IL23 produced by the activated dendritic cells) and is involved in neutrophil migration, angiogenesis, keratinocyte proliferation, bone erosion, and cartilage damage. It is now understood that psoriasis is a disease with high levels of circulating TH17-producing cells (Auriemma M, J Invest Dermatol, 2012). Controlling IL17 can therefore lead to control of the aforementioned mechanisms and this has been demonstrated in novel therapies that target this cytokine. Further evidence of the involvement of IL17 in psoriasis comes from the use of cyclosporine, a drug that has shown to down-regulate the levels of IL17A (Lowes MA, J Invest Dermatol, 2008). Recent therapeutic advances have focused on targeting the receptors of IL17, as well as IL17A and IL17F. Thus far, studies in mice have shown IL17A to play a more central role in auto-immunity compared to IL17F. IL17A also binds with a much higher affinity to IL17RA than IL17F.

Data on a novel anti-interleukin-17 monoclonal antibody that targets IL17A (ixekizumab) were presented. 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 milligrams or placebo (Leonardi CL, 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 in the ixekizumab dose groups; 150 mg (82.1%), 75 mg (82.8%), and 25 mg (76.7%) versus placebo (7.7%, P<0.001 for each comparison). Similarly, a 100% reduction in the PASI score was achieved in significantly more patients in the 150 mg (39.3%) and 75 mg (37.9%) groups than in placebo (0%). Significant differences occurred at as early as 1 week and were sustained through 20 weeks.
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The results of a phase 2 trial evaluating the developmental novel therapy, brodalumab, were also presented (Papp KA, Br J Dermatol, 2012). Brodalumab is a fully human monoclonal antibody that targets IL-17RA. The trial involved 198 patients and was randomized to receive either placebo or brodalumab at doses of 70, 140, or 210 mg at day 1 and weeks 1, 2, 4, 6, 8, and 10 or a separate group that received 280 mg monthly. The primary endpoint 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% (70 mg), 85.9% (140 mg), 86.3% (210 mg), 76.0% (280 mg) versus 16.0% for 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%).

A third novel therapy targeting IL-17A, secukinumab, also reported promising results in the treatment of moderate-to-severe chronic plaque psoriasis. Secukinumab is a fully human IL-17A-neutralizing antibody therapy given as subcutaneous injection. In a placebo-controlled phase-II study involving 404 patients who were randomized to receive either placebo or one of three secukinumab regimens: “single” (at week 0), “early” (at weeks 1, 2, 4) and “monthly” (at weeks 0, 4, 8). The primary endpoint was PASI75 at week 12. After 12 weeks (induction period), PASI75 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 PASI75 responses compared to placebo (55% and 42% versus 2%). The PASI90 responses were significantly greater in the “early” and “monthly” arms versus placebo (32% and 17% versus 2%). After a further 12 weeks of treatment in the maintenance period, 71% of the subjects in the fixed-interval regimen were PASI75 responders. The results suggest that secukinumab may be useful in the treatment of plaque psoriasis.

**Novel Oral Therapies**

Data on future novel therapies with small molecules were presented. These involved molecules which act by targeting intracellular signal transduction pathways. Tofacitinib is a novel, orally administered Janus Kinase (JAK) inhibitor that demonstrated data in the effective management of psoriasis. In a 12-week, phase II trial involving 197 patients, PASI75 responses were observed in a dose-dependent fashion with the highest dose (15 mg) being most effective (Papp KA, Br J Dermatol, 2012).

Apremilast is an oral phosphodiesterase-4 inhibitor. The trial was a multi-centred, phase-II, randomized, placebo-controlled trial involving 89 patients on 10 mg 2x daily, 87 patients on 20 mg 2x daily, and 88 patients on 30 mg daily; 88 patients were assigned to placebo. At week 16, PASI75 was achieved by five patients in placebo, ten patients in the 10 mg, 25 patients in the 20 mg, and 36 patients in the 30 mg groups. The differences from placebo were significant for both the 20 and 30 mg groups. Most adverse events were mild or moderate with no apparent effect on haematological or biochemical parameters.

**Traditional Systemic Therapies**

**Methotrexate:**

A worldwide survey on the use of methotrexate in psoriasis was presented. The survey took place between April and August of 2012 and included 481 dermatologists from all continents. On the question of whether methotrexate is considered as a systemic therapy in the treatment of psoriasis, more than 80% of the participants responded with yes. With regard to the starting weekly dose there was clear continental variation. The majority of dermatologists in North America use 2.5 mg as a starting dose, whereas those from South America start with a dose ranging between 7.5 – 10 mg. Interestingly, a quarter of...
the respondents worldwide start with a dose of 12.5 – 15 mg. Worldwide, by week 4, most dermatologists converge to a dose of 12.5 – 15 mg. Male dermatologists displayed tendency to start with higher doses and increase the dose at more rapid intervals.

On the question of long-term maintenance dose, the results appeared to be largely similar to the dose at week four. The findings showed that dermatologists in Asia were more likely to use lower doses as maintenance, this included maintenance doses of less than 10 mg. In terms of the maximum dose used, the majority of the participants responded that they would not use doses higher than 25 mg. Worldwide, around 20% of the participating dermatologists would not use doses higher than 15 mg.

On the question of route of administration, the majority appear to use the oral route. In Africa, however, use of the intramuscular route was preferred in approximately a quarter of the cases. The use of subcutaneous methotrexate appears to be mainly in the European continent, albeit in a small percentage.

On the timing of assessing for efficacy, the responses ranged between week eight and twelve. In Europe and North America, the trend was that week twelve was used as an optimal assessment time for efficacy versus eight weeks in Africa and a subgroup of Asia respondents. Successful therapy was seen by the majority as a PASI75 reduction. However, in Asia the majority would regard PASI50 reduction as treatment success.

With regards to the clinical and laboratory work-up prior to the use of methotrexate, almost all dermatologists surveyed sought a hematology and liver function profile. This was followed by electrolyte testing and hepatitis serology. In terms of long-term monitoring for potential liver pathology, the majority of the dermatologists worldwide still rely on biochemical liver function testing. The use of liver biopsies is still a widely used practice according to the results of the survey. The use of pro-collagen and fibroscan testing seem to be high among European dermatologists. In contrast, still around a third of the North American dermatologists perform serial liver biopsies to detect methotrexate-induced hepatic changes.
An Oral PED-4 Inhibitor, apremilast

CC-10004 apremilast is an orally-administered, targeted PDE-4 (phosphodiesterase-4) inhibitor. PDE-4 is one of the chief enzymes responsible for degrading cAMP. This promotes a pro-inflammatory milieu in cells such as epithelial cells and T cells. Apremilast’s mechanism of inhibiting PDE-4 increases the intracellular concentration of cAMP preferentially decreasing the production of pro-inflammatory cytokines (e.g. TNF-alpha, and IL-23) usually elevated in psoriatic tissue. Apremilast also simultaneously promotes the expression of anti-inflammatory mediators (e.g. IL-10) (Schafer P).

Several characteristics of apremilast contribute to its relatively favorable adverse effect profile compared to cilomilast and other PDE-4 inhibiting compounds. For example, apremilast does not exhibit the same selectivity as cilomilast for the PDE-4D subfamily, which is associated with emesis in mice. This likely explains the improved gastrointestinal tolerance of apremilast in clinical trials as compared to other PDE-4 inhibitors. (Schafer P, Parton A, et al.; Robichaud A).

A double-blind, placebo-controlled Phase 2 clinical study demonstrated statistically significant improvement in the number of patients achieving PASI-75 and PASI-50 for the apremilast arm (where subjects were treated with 20 mg apremilast BID) - with 24.4% of apremilast arm subjects achieving at least a 75% improvement from their baseline PASI after 12 weeks (versus 10.3% in the placebo arm), and 57% of apremilast arm subjects achieving at least a 50% improvement from their baseline PASI (versus 23% in the placebo arm) (Papp K, Zeldis JB, et al.). A phase 2b double-blind, placebo-controlled, dose-finding study in subjects with moderate-to-severe psoriasis showed that 11.2%, 28.7%, and 40.9% of subjects treated with 10, 20, and 30 mg apremilast BID, respectively, achieved PASI-75 or better compared to 5.7% in the placebo arm (Papp K, Hu A, Day RM). Adverse events in psoriasis and psoriatic arthritis subjects included nausea, upper respiratory tract infection, nasopharyngitis, diarrhea, and headache. None of these events led to dose reduction or treatment withdrawal.

Apremilast is now in Phase 3 clinical trials with the initiation of six multi-center international clinical trials for psoriasis and psoriatic arthritis, as well as Phase 2 clinical trials for rheumatoid arthritis and ankylosing spondylitis (Celgene Corporation; Schafer P). With its success in demonstrating clinical efficacy and tolerability as well as meeting safety endpoints with relatively few significant side effects, drugs like apremilast may supplement, and perhaps ultimately replace, some of the systemic agents.

AN-2728, A Topical Phosphodiesterase-4 Inhibitor

AN-2728, a novel topical anti-inflammatory compound has demonstrated safety and efficacy in 7 (three Phase 1b and four Phase 2) clinical trials for psoriasis. By inhibiting phosphodiesterase-4, AN-2728 suppresses the release of...
CONTINUING MEDICAL EDUCATION

cytokines such as TNF-alpha, IL-12, and IL-23, key drivers of inflammation in psoriasis and targets of corresponding systemic agents (Nazarian R). AN-2728 appears to lack well-known adverse effects of other topical therapies on the market for psoriasis, such as atrophy with long-term use of potent topical steroids and skin irritation with vitamin D derivatives and retinoids. In all 12 completed Phase 1 and 2 clinical trials for psoriasis and atopic dermatitis, AN-2728 has been generally well tolerated with no observed serious adverse events (Anacor Pharmaceuticals, Inc).

In June 2011, results were reported of the second and final Phase 2b trial involving AN-2728, in which 145 adult patients with mild-to-moderate plaque-type psoriasis underwent treatment to determine safety and efficacy of various treatment regimens. Of the 4 regimens tested, AN-2728 2% ointment twice daily provided the greatest therapeutic benefit, with 54.1% of the treatment group achieving improvement in Overall Target Plaque Severity Score (OTPSS) from baseline (OTPSS measures plaque severity on a 9-point static scale: 0=no evidence of disease, 8=very severe) compared to 2.7% in the vehicle group. AN-2728 also appears safe and well tolerated in adult patients with mild-to-moderate plaque-type psoriasis, with reports of only mild adverse effects in the treatment group including pruritus, contact dermatitis and the common cold. The majority of these events were considered unrelated or unlikely to be treatment-related (Zane LT).

CT-327: Not Just Another JAK
Another novel topical therapy under development is CT-327, a tyrosine-kinase blocker for patients with psoriasis vulgaris and atopic dermatitis. CT-327 has completed one Phase 2a clinical trial for the treatment of psoriasis vulgaris and is currently recruiting for a Phase 2b trial. Results from the completed Phase 2a study showed that CT-327 0.1% cream applied twice daily produced good responses for endpoints such as PGA (Physician Global Assessment). The PGA analysis showed that the percent of patients who had “controlled disease” increase from 8% at the outset of the study to 33% at the conclusion of the 8-week treatment period (vs 6% at the start to 7% at the end for placebo). The number of “severe or very severe” patients was also reduced by 50% over the treatment period. CT-327 is also well tolerated with no reported application site (Creabilis SA).

CT-327’s mechanism of action differs from the other topical JAK inhibitors by working at the level of the keratinocyte and preventing hyperproliferation through inhibition of Tyrosine Kinase A specifically associated with nerve growth factor receptor. Nerve growth factor (NGF) is synthesized and released by human keratinocytes and serves as a neurotrophic molecule, stimulating the growth of nerve fibers and synthesis of neuropeptides. NGF is involved in neurogenic inflammation in several dermatoses including psoriasis and its levels have been reported to be increased in psoriatic skin (Pincelli; Wickramasinghe, Traversa and Roblin; Creabilis, SA). CT-327 was also developed using Creabilis’ proprietary Low Systemic Exposure (LSE) technology, which conjugates molecules to low molecular weight polyoxyethylene, optimizing the molecules for high local concentrations but low systemic exposure. This optimized topical route was confirmed in the Phase 2a trial, in which pharmacokinetic analysis showed no detectable plasma CT-327. The dose finding Phase 2b trial, which began earlier this year, will study the efficacy and safety of a new CT-327 ointment formulation (0.05%, 0.1%, 0.5%) administered for up to 8 weeks with results expected by the end of 2012 (Creabilis SA).

Tofacitinib (CP-690550), an oral JAK kinase Inhibitor
CP-690550 (tofacitinib) is a novel oral treatment for psoriasis. Many of the adverse effects of traditional systemic therapies for psoriasis are due to non-selective immunosuppression. CP-690550 has a more targeted
approach by selectively inhibiting JAK3 kinase. Compared to other members of the JAK family (JAK1, JAK2, tyrosine kinase 2), JAK3 kinase is generally expressed only by hematopoietic cells (particularly T cells and NK-cells) and associates specifically with the gamma chain shared by tissue receptors for IL-2, -4, -7, -9, -15, and -21. Genetic absence or mutation of JAK3 displays a Severe Combined Immunodeficiency (SCID) phenotype, thus demonstrating a central role of JAK3 in immunity (West; Vincenti F). Although the precise mechanism is unknown, potently inhibiting JAK3 kinase with CP-690550 is thought to suppress the intracellular signal transduction from the gamma chain receptors for cytokines IL-2, -4, -7, -9, -15, and -21, thereby uncoupling early T cell receptor mediated signaling from downstream pro-inflammatory events (Borie DC). Thus, CP-690550 achieves targeted T cell suppression while minimizing global immunosuppression (Boy MG).

Currently, only one Phase 2 clinical trial assessing the use of tofacitinib for psoriasis has been completed, involving 197 adults with moderate-to-severe plaque type psoriasis. Results demonstrated a greater proportion of patients achieving PASI 75 at week 12 for all doses compared to placebo. Specifically, tofacitinib 2, 5, and 15 mg twice daily achieved a PASI 75 of 25%, 40.8%, and 66.7%, respectively, compared to only 2% for placebo. The most frequently reported treatment-related adverse events were upper respiratory tract infection and headache: 3 patients reported a total of 5 serious adverse events. Mild dose-dependent decreases in mean neutrophil count and hemoglobin level, and increases in mean LDL-C, HDL-C, and total cholesterol were also observed (Tofacitinib; Pfizer, Inc). At least 6 Phase 3 clinical trials evaluating oral tofacitinib for moderate-to-severe chronic plaque psoriasis are underway. Four of the trials are estimated to be completed by early-mid 2013, including a trial evaluating efficacy, treatment withdrawal, and retreatment in 660 psoriasis patients. The other two Phase 3 studies are evaluating the long-term safety of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis and/or psoriatic arthritis.

Oral Therapies in the Pipeline… with Potential Cardiovascular Benefit: VBL-201

VB-201, an oxidized phospholipid analog, was developed from the lecinoxoid molecular class of oral anti-inflammatory agents. VB-201’s mechanism of action, which differs from the JAK3 inhibition seen with tofacitinib, includes inhibition of dendritic cell and macrophage production of IL-12/23p40, a subunit common to IL-12 and IL-23 and strongly implicated in the pathogenesis of psoriasis as demonstrated by the success of the injectable agent ustekinumab (Elliot M; Business Wire; Kurjeza M).

VBL Therapeutics has successfully completed four Phase 1 clinical trials in which safety and tolerability were similar to placebo with no treatment-related serious adverse events. The company has also recently completed a Phase 2 trial in which patients received the agent once daily for 12 weeks. The study evaluated treatment of patients with moderate-to-severe psoriasis and atherosclerosis, demonstrating VB-201’s simultaneous anti-inflammatory effect on both inflammatory disorders. As atherosclerotic cardiovascular disease has been recognized as a major cause of morbidity and mortality in psoriasis patients, this novel therapy may provide treatment for both (Horn). Statistically significant improvements in Physician Global Assessment and Patient Global Assessment of psoriasis were achieved (p=0.019), and a statistically significant dose response in PASI was shown across all five VB-201 groups (p=0.04). The company reported positive results for atherosclerosis from its Phase 2 safety and efficacy trial in patients with moderate-to-severe plaque psoriasis at the American Academy of Dermatology 70th Annual Meeting. VB-201 80 mg daily produced a statistically significant, dose-responsive mean reduction of 12.7% in inflammation associated with vascular endothelial lesions over the 12-week dosing period, as evaluated by PET-CT scans. Yael Cohen, MD, vice president, clinical development at VBL has announced that an additional trial with higher dosage and longer duration is underway (VBL Therapeutics; Business Wire).
How Targeting IL-17 May Be Different From Targeting IL-23

Studies have demonstrated that local administration of IL-23, a key cytokine that induces naïve T cells to differentiate into Th17 cells, produces an inflammatory milieu similar to that of psoriasis lesions. Further, the p40 subunit of IL-23 has proven an effective target for psoriasis therapeutics. According to a recent editorial in the New England Journal of Medicine, however, targeting the product of Th17 cells, IL-17, may be even more precise in psoriasis than targeting IL-23 (Waisman). That is, IL-23 appears to be involved in regulating a wide variety of inflammatory processes, from angiogenesis to neutrophil chemotaxis to tumorigenesis (Langowski, Zhang and Wu). Thus, new agents targeting IL-17 may reduce undesired effects on essential immune processes.

Secukinumab (AIN457), An injectable IL-17 blocker

Novartis is developing secukinumab (AIN457), an injectable Interleukin-17A blocker for treatment of psoriasis, as well as other inflammatory diseases including psoriatic arthritis, rheumatoid arthritis, and uveitis. Secukinumab is a fully-human monoclonal antibody to Interleukin 17A, a key pro-inflammatory cytokine in the pathogenesis of psoriasis and psoriatic arthritis (Kurjeza M).

Novartis has completed five Phase 2 clinical trials involving use of secukinumab for the treatment of moderate-to-severe psoriasis, with seven more trials ongoing. In October 2011, the results of three completed Phase 2 trials were announced at the annual European Academy of Dermatology and Venereology Congress. The three clinical trials demonstrated that secukinumab was more effective than placebo in achieving 50% and 75% improvement in PASI at 12 weeks (Sivamani RK; Hueber W). In the three studies, the percentage of patients with at least 75% improvement in PASI at week 12 was 81% for those administered AIN457 150 mg subcutaneously (versus 9% in placebo), 83% for patients injected AIN457 intravenously in the same index (versus 10% in placebo), and 55% for patients receiving AIN457 150 mg subcutaneously in the first month only (versus 2% in placebo). The rates of adverse events in the treatment arm for all three studies were similar to placebo (60% for secukinumab group, 61% for placebo group), with the most common adverse effects being infections and headache (Novartis International AG; Papp KA; Rich PA; Papp; Waisman).

In another small clinical trial, the efficacy and safety of secukinumab infusions were investigated in patients with select inflammatory disorders, including those affecting skin and other organs. Secukinumab infusion resulted in 63% mean improvement in PASI from baseline versus only 9% with placebo. Secukinumab also induced improvement in symptoms in those with rheumatoid arthritis and uveitis. Again, all observed infections were not deemed serious and the rates of adverse effects in the AIN457 arm were similar to the placebo group (Hueber W). Novartis has already commenced Phase 3 studies involving patients with moderate-to-severe plaque psoriasis. Three Phase 2/3 trials are also being undertaken to investigate the short-term and long-term safety and efficacy of secukinumab in treating psoriatic arthritis.
CONTINUING MEDICAL EDUCATION

References


CONTINUING MEDICAL EDUCATION


Scientific Highlights from the 21st EADV Congress and So Long to Scale

Annenberg Center for Health Sciences respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

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(Signature is required for recognition by ACCME, ACPE, ANCC, and most state licensing boards)
1. Clinical observations indicate that antibody formation against TNF-alpha therapies tends to achieve a maximum concentration during which period of drug exposure?
   a. Induction phase
   b. First dose
   c. First year
   d. Maintenance phase

2. For the treatment of generalized pustular psoriasis; which agents have displayed effectiveness in small clinical studies [please check all that apply]?
   a. Adalimumab
   b. Infliximab
   c. Ustekinumab
   d. Etanercept

3. Which of the following biologics does NOT act via the direct targeting of the IL-17 pathway?
   a. Brodalumab
   b. Ixekizumab
   c. Secukinumab
   d. Tofacitinib

4. Which mechanism of action involves inhibition of Nerve Growth Factor’s effects on Tyrosine Kinase A?
   a. CT-327, a topical therapy
   b. AN-2728, a topical therapy
   c. Apremilast, an oral therapy
   d. VBL-201, an oral therapy

5. Which of the following therapies has demonstrated anti-inflammatory effects in both psoriasis and atherosclerosis?
   a. AN-2728
   b. Secukinumab
   c. Tofacitinib
   d. VBL-201

6. How does apremilast differ from cilolimast?
   a. Apremilast demonstrates more gastrointestinal adverse effects than cilolimast
   b. Apremilast is more selective for the PDE-4D subfamily than cilolimast
   c. Apremilast is less selective for the PDE-4D subfamily than cilolimast
   d. Apremilast has a less favorable adverse effect profile than cilolimast

7. Which of the following trials did not involve the biologic ustekinumab?
   a. REVEAL
   b. PHOENIX I
   c. CADMUS
   d. ACCEPT

8. Tofacitinib (CP-690550) is an oral therapy that selectively targets which of the following?
   a. Tyrosine Kinase
   b. Janus Kinase 3
   c. Phosphodiesterase-4
   d. Interleukin 17
Scientific Highlights from the 21st EADV Congress and So Long to Scale

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

Please answer the following questions by circling the appropriate rating:

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

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 .......................................................................................................................... 1 2 3 4 5
- Discuss the relative mechanisms of action of approved therapies and these in clinical development ......................................................................................................................... 1 2 3 4 5
- Apply new knowledge and learning to practice techniques to more effectively and optimally manage the patient ........................................................................................................... 1 2 3 4 5

Overall Effectiveness of the Activity

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

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

- Will the information presented cause you to make any changes in your practice? □ Yes □ No

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

________________________________________________________________________________________
Education and Outreach

Meet the Experts programs

Huntington Beach, California

The 64th Annual Meeting of the Pacific Dermatological Association was held on August 24th, 2012 where IPC presented its Meet the Experts: Case Based Learning Discussion. Drs. Alan Menter, MD, Texas; Andrew Blauvelt, MD, Oregon; Kevin Cooper, MD, Ohio; and Amy Paller, MD, Illinois were in attendance. Each presented a challenging psoriasis case for discussion amongst one another and invited the participation of the audience. Topics included erythrodermic psoriasis, cardiovascular effects of biologics, obesity and psoriasis and pediatric psoriasis. This interactive forum was recorded, and can be viewed for CME as a webcast found on our website.

Prague, Czech Republic

On September 29th, 2012, IPC held its Meet the Experts: Case Based Learning Discussion at the 21st Annual Meeting of the European Association of Dermatology & Venereology in Prague, Czech Republic. Our panel of presenters included Christopher Griffiths, MD, UK; Hervé Bachelez, MD, France; Paul Carle, MD, PhD, France; and Lluis Puig, MD, PhD, Spain. A variety of cases were presented to the audience of over 200 physicians which included impetigo herpetiformis, liver tests abnormalities in plaque psoriasis and optimizing efficiency of systemic agents in psoriasis.

Durban, South Africa

October 24th, 2012 was another exciting opportunity for IPC to share its Meet the Experts: Case Based Learning Program with physicians from all over the world by participating in the 3rd Continental Congress of Dermatology in Durban, South Africa. Presenters included IPC President, Peter van de Kerkhof, MD, PhD, the Netherlands; Alan Menter, MD, Texas; Gail Todd, MD, South Africa; and Aleksandr Litus, MD, PhD, Ukraine. Topics presented for discussion included biologics and classical systems, obese psoriatic patients, pediatric psoriasis and systemic agents in children. With over 400 physicians in attendance, this was one of our most popular programs to date.

Buenos Aires, Argentina

In November, IPC took the opportunity to share its Meet the Experts program at the 1st Solapso Congress on Psoriasis held in Buenos Aires, Argentina. The faculty panel was comprised of Alan Menter, MD, Texas; Craig Leonardi, MD, Missouri; Claudia de la Cruz, MD, Chile; and Edgardo Chouela, MD, Argentina. Each presented topics for discussion which included the obese psoriasis patient, psoriasis and myelitis, psoriatic erythroderma, and infliximab and interstitial pneumonitis.

New Councilors appointed

At IPC’s recent Think Tank, the IPC Board of Directors appointed 7 new Councilors. IPC Councilors play an important role in the work of IPC. Councilors serve in an advisory capacity and lend their global expertise on psoriasis research, treatment, and education to support all IPC programs, events, and initiatives. They provide expert opinion on current psoriasis therapeutic and research-related issues, participate in roundtable conferences, contribute manuscripts to top tier journals and present at important congresses around the world. New Councilors include:

Michel Gilliet - Switzerland
Diamant Thaçi - Germany
Robert Bissonnette - Canada
Robert Strohal - Austria
Menno Alexander de Rie - Netherlands
Peter Foley - Australia
Vermén Verallo-Rowell - Philippines
IPC NEWS

Research

IPC has recently published the following papers:


Abstract:

OBJECTIVE To investigate the relationship of excess and central adiposity with pediatric psoriasis severity. DESIGN, SETTING, AND PARTICIPANTS Multicenter, cross-sectional study of 409 psoriatic children. Psoriasis was classified as mild (worst Physician’s Global Assessment score ≤ 3 with body surface area ≤ 10%) or severe (worst Physician’s Global Assessment score ≥ 3 with body surface area ≥ 10%). Children were enrolled from 9 countries between June 19, 2009, and December 2, 2011. MAIN OUTCOME MEASURES Excess adiposity (body mass index percentile) and central adiposity (waist circumference percentile and waist to height ratio). RESULTS Excess adiposity (body mass index ≥ 85th percentile) occurred in 37.9% of psoriatic children (n = 155) vs 20.5% of controls (n = 42) but did not differ significantly by severity. The odds ratio (95% CI) of obesity (body mass index ≥ 95th percentile) overall in psoriatic children vs controls was 4.29 (1.96-9.39) and was higher with severe (4.92; 2.20-10.99) than with mild (3.60; 1.56-8.30) psoriasis, particularly in the United States (7.60; 2.47-23.34, and 4.72; 1.43-15.56, respectively). Waist circumference above the 90th percentile occurred in 9.3% of the control (n = 19), 14.0% of the mild psoriasis (n = 27), and 21.2% of the of severe psoriasis (n = 43) participants internationally; this incidence was highest in the United States (7.60; 2.47-23.34, and 4.72; 1.43-15.56, respectively). Waist to height ratio was significantly higher in psoriatic (0.48) vs control (0.46) children but was unaffected by psoriasis severity. Children with severe psoriasis at its worst, but mild at enrollment, showed no significant difference in excess or central adiposity from children whose psoriasis remained severe. CONCLUSIONS Globally, children with psoriasis have excess adiposity and increased central adiposity regardless of psoriasis severity. The increased metabolic risks associated with excess and central adiposity warrant early monitoring and lifestyle modification. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00879944.


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.
IPC NEWS

Genetics Project
IPC has initiated a project designed to clarify the genetic architecture of psoriasis with the specific goal being to help design targeted therapies, the development of markers to monitor disease progression and drug responsiveness ultimately with a view to helping the vast numbers of patients afflicted with this condition. The project was derived from a workshop and summary report in the June issue of the *British Journal of Dermatology* that highlighted IPC's efforts to establish collaboration among leading geneticists and dermatologists to advance the understanding of the genetic basis of psoriasis. “*The quest for psoriasis susceptibility genes in the postgenome-wide association studies era: charting the road ahead.*” Dr. Francesca Capon, Division of Genetics and Molecular Medicine, King’s College, London, UK and Professor Jonathan Barker of St. Johns Institute of Dermatology, King’s College, London, UK (*Br J Dermatol*, 2012 Jun;166(6):1173-5). The summary publication outlined the remarkable progress achieved through the implementation of genome-wide association studies that have highlighted the key pathogenic pathways leading to psoriasis. IPC now plans to use this knowledge by completing a joint scientific, laboratory and patient-related study to better define the genetic architecture of psoriasis. Involved in the program are investigators from the genetic research laboratories of Professors Goncalo Abecasis (University of Michigan, USA); Richard Trembath (King’s College, London, UK); J.T. Elder (University of Michigan, USA); Andre Reis (University of Erlangen-Nuremburg, Germany); Andre Franke (Christian-Albrechts University, Kiel, Germany); and Anne Bowcock (Washington University, St Louis, USA). The collaboration is expected to lay the groundwork for innovative approaches to novel treatment strategies as well as to define the therapeutic response to treatments in specific psoriasis patients by building a bridge between the genotype and phenotype of the disease.

Mechanisms of Disease
In September 2012, IPC held a “Mechanisms of Disease” workshop at the 42nd Annual ESDR meeting in Venice, Italy. The objective was to assemble world-leading dermatologists and immunologists to evaluate the current status of science that underpins the mechanisms that lead to the inflammatory state of psoriasis. By deriving new insights and learning from the current body of information the hope is that new research avenues will be illuminated that will lead to novel therapeutic agents. The purpose of each of the presentations was to drive discussion between the participant experts. Co-chaired by Hervé Bachelez (Paris, France) and Frank Nestle (London, UK) the agenda included topics on the contribution of the IL-1 family in psoriatic inflammation (Hervé Bachelez), the IL-23/TH17 axis in psoriasis (Frank Nestle), transcriptomic approaches for the understanding of psoriasis (Michele Lowes, New York, USA) and signaling pathways involved in the dysregulation of the epidermal homeostasis and its cross-talk with the immune system in psoriasis (Antonio Costanzo, Roma, Italy). A summary publication is currently in development.
ACKNOWLEDGMENTS

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EDITOR DISCLOSURES

Marieke Seyger, MD, PhD

Professor Seyger has received grants/research support from Pfizer and Leo Pharma and has served on advisory boards and as a consultant/speakers bureau member for Pfizer.

Brian Kirby, MD

Professor Kirby has received grants/research support from Abbott Ltd, Pfizer and Janssen. He has served as a consultant/speaker bureau member for Pfizer, Abbott, and Janssen and as an advisory board member for Pfizer and Janssen. In addition, he has received honorarium from Abbott, Pfizer and Janssen.