Psoriasis top research and clinical papers for January to June 2011

ARTICLES REVIEWED IN THIS ISSUE


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The Firas Report: Clinical & Scientific Advances from the 20th Congress of the Academy of Dermatology and Venereology, Lisbon, Portugal

2012 Calendar of Events

January 15
IPC Meet the Experts, Maui, Hawaii
Winter Clinical Dermatology Conference - Hawaii®

February 22
IPC Meet the Experts, Manila, Philippines
20th Regional Conference of Dermatology - Asian-Australasian

March 16 – 20
IPC Exhibit, San Diego, California
American Academy of Dermatology 70th Annual AAD Meeting

June 29
IPC Psoriasis Symposia, Stockholm, Sweden
3rd World Psoriasis & Psoriatic Arthritis Conference

August 24
IPC Meet the Experts, Huntington Beach, California
64th Annual Meeting of the Pacific Dermatologic Association

September
IPC Meet the Experts, Prague, Czech Republic
21st Congress of the European Academy of Dermatology and Venereology
Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s co-editors Professor Yves Poulin of Hospital Hotel-Dieu de Quebec, Quebec, Canada and Professor Esteban Dauden of Hospital Universitario del la Princesa, Madrid, Spain, I am honored to introduce the December 2011 issue of the IPC Psoriasis Review.

In this CME accredited issue, we include an opportunity to earn CME credit for the review of the 20th Congress of the European Academy of Dermatology and Venereology held in Lisbon, Portugal October 20 – 24, 2011.

Also in this issue, IPC presents the top five clinical and research articles from the first half of 2011. To qualify manuscripts had to be published either in print or electronically in the time frame from January 1st to June 30th, 2011. As always the list includes an eclectic collection of informative and provocative reading. The selections included one manuscript which identified a novel IL-1 cytokine family signaling system that is active in psoriasis and correlates with therapeutic effect. Three of the articles focused on the IL-17 cytokine; its role as a key inflammatory pathogenic circuit; that Foxp3p regulatory T-cells differentiate into IL-17-producing cells in the skin; and that both mast cells and neutrophils can also express IL-17 in the formation of specialized structures called extracellular traps which may play a fundamental role in psoriasis pathogenesis.

Finally, a prestigious article from the Journal of the American Medical Association that was authored by several IPC Councilors, was selected. The authors performed a meta-analysis to investigate an association between biologic therapies for chronic plaque psoriasis and cardiovascular events. In so doing, these authors highlighted some of the deficiencies in data that can result from the traditional clinical trials required to support registration of new entities.

Earlier this year IPC Councilors responded to two surveys. The first was one related to the publication by the European Medicines Agency (EMA) of draft guidance on biosimilars. As a consequence of that survey IPC was invited to a closed workshop held at the EMA offices in London, England on October 24th, 2011. A review of that workshop is contained within this issue of IPC Psoriasis Review and it highlights the important impact that the IPC Councilors can have on evolving regulatory policy.

Additionally, IPC performed a survey to define the key research needs in psoriasis. This survey highlighted several areas of focus that included the completion of the genetic map of psoriasis; the need to better comprehend the mechanism of psoriasis pathogenesis; and the need to better define the association of psoriasis with various comorbidities and undesirable health outcomes. The survey results were published in Psoriasis Forum (A Strategic Approach to Setting the Research Agenda in Psoriasis. Psoriasis Forum; Summer 2011 Vol. 17, No. 2) and will serve as the framework for how IPC will hope to influence future research in the disease; as well as its funding. To that end, IPC recently held a workshop in association with the 12th meeting of the International Congress on Human Genetics in Montreal, Canada. With the objective to establish a forum to foster and develop international collaboration towards completing the genetic map of psoriatic disease, IPC invited several of the world’s leading geneticists to contribute knowledge and perspective to the progress of completing the genetic map. The workshop was chaired by Goncalo Abecasis from University of Michigan, Ann Arbor, USA and Richard Trembath from King’s College, London, England. The subject matter consisted of the psoriasis genetic architecture, post-genome wide association scans and the transition to mechanisms of gene function. Indeed, specific action plans were developed that IPC now hopes to support to continue this important initiative. IPC expects a summary of the workshop to be published soon in a peer-reviewed journal.

Finally, it is with great pleasure that we welcome three new Councilors into the IPC community, Dr. Andy Blauvelt of Oregon Medical Research Center, Dr. Joel Gelfand of University of Pennsylvania and Professor Charles Lynde of University of Toronto. We are delighted to continue to expand the involvement of psoriasis key opinion leaders from around the world.

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

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

Sincerely,

Professor Peter van de Kerkhof, M.D.
President, International Psoriasis Council
PRESENTING SUMMARIES AND COMMENTARY

1) Cytokine synergy at the keratinocyte may explain the psoriasis gene signature.

To better elucidate the mechanisms by which cytokines regulate psoriasis inflammation, Chiricozzi and colleagues investigated the combined effects of TNF-α and IL-17 on the keratinocyte (KC) gene profile. The analyses proceeded via the collection of RNA from primary keratinocytes that had been cultured with IL-17 or TNF-α alone, or in combination. Gene responses were quantified by gene array analysis, followed by reverse transcriptase-PCR confirmation for significant genes. The results identified 160 genes that were synergistically up-regulated by IL-17 and TNF-α, genes that largely explain the psoriasis gene signature. Examples of the most highly induced genes included the cytokines, IL-8 and IL-19, the chemokine, CCL-20 and the immune response genes, DEFB4 (Defensin, beta 4), (CFB) Complement factor B and the S100 calcium-binding proteins (S100A7 & S100A7A). These genes express proteins in the keratinocyte whose functions contribute to the skin alterations seen in psoriasis. Thus, KCs may be key drivers of pathogenic inflammation in psoriasis through the integration of responses to TNF-α and IL-17. The concept is supported by the observation that a much larger set of significant disease-signature genes in the psoriasis transcriptome can be traced to TNF-α/IL-17 synergism.


COMMENTARY

Comprehension of psoriasis pathogenesis continues to be dissected. Research is now advancing beyond the study of the impact of single growth modulators to that of multiple co-regulating factors. This study supports the notion that different cytokines can act in concert to drive broad gene expression and the resultant symptoms of psoriasis. Furthermore, selected therapeutic strategies (e.g., anti-TNF or anti-IL-17) are validated and potential new ones highlighted as a consequence of the results. Future work might help in better defining the broader interactive roles of TNF-α/IL-17 responses both in psoriasis as well as other immune-mediated diseases.
A novel IL-1 family signaling system that is active in psoriasis inflammation.

The IL-1 family of cytokines contains 11 cytokines including IL-1α, IL-1RA and IL-18. Several novel members were recently identified but their roles remain to be elucidated. In this report, Johnston et al., investigate the role of these novel members of the IL-1 cytokine family in skin inflammation. To do so, they acquired biopsies of healthy control, uninvolved, and lesional psoriasis skin and assessed the expression of IL-1F5, -1F6, -1F8, -1F9, and their receptors by real-time quantitative RT-PCR (qRT-PCR). Expression levels were confirmed by immunohistochemical evaluation. The results indicated increase expression of IL-1F5, -1F6, -1F8, and -1F9 by 2 to 3 orders of magnitude in psoriasis plaques versus uninvolved psoriasis skin. Moreover, treatment of psoriasis with the anti-TNF blocker, etanercept led to significantly decreased IL-1F5, -1F6, -1F8, and -1F9 mRNAs, concomitant with clinical improvement. IL-1α and TNF-α were both found to induce the expression of IL-1F5, -1F6, -1F8, and -1F9 transcripts in normal human keratinocytes. This observation illustrates a potential cytokine network that contributes to psoriasis inflammation. Microarray analysis revealed that these novel cytokines, IL-1F5, -1F6, -1F8, and -1F9 were also able to induce the expression of various antimicrobial peptides (e.g., β-defensins) and matrix metalloproteinases by reconstituted human epidermis.


COMMENTARY

As evidenced by this paper as well as the previous one by Chiricozzi et al., the inflammatory network that leads to psoriasis is driven by the coordinated action of a number of cytokines and growth factors including TNF-α, IL-17 and novel members of the IL-1 family (IL-1F5(IL36Ra), -IL-1F6 (IL36alpha), -IL-1F8 (IL36beta) –and IL-1F9 (IL36gamma)). Both papers implicated TNF-α and IL-17 in the induction of IL-1F9 and human β-defensins. Collectively, the data suggest important roles for these novel cytokines in inflammatory skin diseases and identify these peptides as possible targets in therapeutic strategies for psoriasis.
3) Mast cells and neutrophils, not T-cells, are the major sources of IL-17 in psoriasis.

While much focus recently has been on the proposed role of Th17 T-cells that secrete IL-17 and thereby propagate the inflammatory state leading to psoriasis, in this report Lin and colleagues identify mast cells and neutrophils as major sources of IL-17 in human skin. Dual-color immunofluorescence staining of cells from punch biopsies of involved and non-involved psoriatic skin illustrated the co-localization of IL-17 with T-cells (CD3), mast cells (tryptase & chymase) and neutrophils (myeloperoxidase). Interestingly, IL-17(+) mast cells and neutrophils were found at higher densities than IL-17(+) T-cells in psoriasis lesions whereas there was no difference in the numbers of IL-17-labeled T-cells. Mast cells and neutrophils were found to release IL-17 in the process of forming specialized structures called extracellular traps (ETs). The functional relevance of extracellular traps was confirmed by confocal microscopy to plot the co-existence of IL-17 with either neutrophil or mast cell morphological structures. Combinations of IL-23 and IL-1β were found to induce mast cell ET formation and degranulation of human mast cells. Thus, increased numbers of mast cells and neutrophils in psoriasis lesions contribute to the release of the pathogenic cytokine IL-17 through the formation of ETs and that IL-23 and IL-1β provide a novel mechanistic stimulus for this phenomenon.


COMMENTARY

Although T-cells have been central to the study of IL-17 biology, it is increasingly appreciated that diverse types of innate immune cells are involved in the complex network that is psoriasis pathogenesis. Mast cells and neutrophils may be central to the pathogenesis of psoriasis. The data in this manuscript depict a fundamental interaction between innate and adaptive immunity mediated at the IL-23-IL-17 axis. The authors performed some quite stunning tricolor staining and confocal microscopy to plot the co-existence of IL-17 specifically with neutrophil or mast cell morphological structures. These observations support a model in which mast cells and neutrophils play significant roles in the pathophysiology of psoriasis and potentially other auto-inflammatory diseases driven by the IL-23-IL-17 axis. In a typical host response to infection, there is an important role for mast cells and neutrophils to clear the infectious agent. As the invading pathogens are cleared, the inflammatory cycle is disrupted returning the host to normal cytokine equilibrium. In psoriasis, IL-23 signaling may be dysregulated, resulting in the sustained release of IL-17 and other mediators from mast cells, neutrophils, as well as T-cells. A better understanding of the cellular contributors to psoriasis may help define new therapeutic strategies for psoriasis as well as related inflammatory conditions.
4) Family ties between Foxp3+ regulatory T-cells and T helper-17 (Th17) effector cells in the psoriasis lesion.

This paper by Bovenschen et al., delivers data that connects prior independent observations related to the chronic inflammatory state of psoriasis. The current paradigm proposes an association with IL-23, and IL-17 secreting T helper-17 (Th17) effector cells. Previous observations illustrated impaired CD4+CD25(high) regulatory T-cell (Treg) function in psoriasis, and hypotheses that such regulatory cells are inhibitory to autoimmune inflammation. In this report, it is revealed that Tregs of severe psoriasis patients easily differentiate into a Th17-associated phenotype, in the presence of IL-23. Thus, differentiated IL-17 producing Tregs might have a role in stimulating the chronic inflammatory process.

Luminex cytokine assays demonstrated that ex vivo-stimulated CD4+CD25hi Treg from patients with severe psoriasis increased IL-17A production. Flow cytometry was used to determine that the IL-17 production was occurring within the CD4+CD25hi cells, thus demonstrating that these Tregs have an enhanced propensity to differentiate into IL-17A-producing cells on ex vivo stimulation. Furthermore, it was found that the enhanced Treg differentiation was linked to unexpectedly high retinoic acid orphan receptor (RORγt) levels and loss of Foxp3. IL-23, the pro-inflammatory cytokine, further reduced Foxp3 expression while leaving the high RORγt levels unaffected. Additionally, by using immunohistochemistry techniques that triple stained cells, the presence of intermediate IL-17A+/Foxp3+/CD4+ triple-positive cells in skin lesions of patients with severe psoriasis was demonstrated.


COMMENTARY

These observations connect two phenomena related to the induction of Th17 T-cells and the suppression of CD25 Tregs that have been previously extensively reported in the literature. Consequently, those phenomena are now interconnected by virtue of demonstrating the clinical relevance of Treg differentiation in the perpetuation of the chronic inflammatory state that leads to psoriasis. In so doing, potential novel pathways for immunotherapy that targets Treg differentiation have been highlighted.
5) On the trail of rare events that may influence the treatment paradigm for biologic therapies.

C. Ryan and colleagues performed a meta-analysis to evaluate a possible association between biologic therapies and major cardiovascular adverse events (MACE). The authors utilized published reports on randomized controlled trials (RCTs) of anti-IL-12/23 (ustekinumab and briakinumab) agents and anti-tumor necrosis factor α (TNF-α) agents (adalimumab, etanercept, and infliximab) from the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Ovid MEDLINE. Additionally, the authors collected results of registered nonpublished completed studies through abstract publications, poster presentations and direct requests for information from study sponsors. The dataset included a total of 22 RCTs comprising 10,183 patients. MACE events included a composite end point of myocardial infarction, cerebrovascular accident, or cardiovascular death during the placebo-controlled phase of treatment. The combined dataset identified 10 of 3,179 patients that received anti-IL-12/23 therapies to also experience a MACE compared to zero events in 1,474 patients receiving placebo. Statistical analysis (Mantel-Haenszel fixed-effects method) showed a risk-difference of 0.012 events/person/year with a p value of 0.12. However, in the anti-TNF-α trials, only 1 of 3,858 patients receiving anti-TNF-α agents experienced a MACE compared with 1 of 1,812 patients receiving placebo (risk difference = -0.0005 events/person/year; p = 0.94). The authors conclude that compared with placebo, there was no significant difference in the rate of MACEs observed in patients receiving anti-IL-12/IL-23 antibodies or anti-TNF-α treatments.

IPC PARTICIPATES IN EMA BIOSIMILAR MONOCLONAL ANTIBODIES WORKSHOP

On Monday 24th October 2011, the European Medicines Agency (EMA), held a closed workshop to evaluate the mechanisms for entry of monoclonal antibody biosimilars into the global marketplace. IPC was invited as a consequence of the response that we collectively delivered to EMA on their draft guidance, which was published in Nov 2010. IPC was represented by Drs. Catherine Smith (St. John’s Institute of Dermatology, London, UK) and Paul Tebbey (IPC’s Director of Scientific and Medical Affairs). Herein, we provide our personal viewpoint of the proceedings and outcomes of the workshop. IPC was stimulated to respond to the draft guidance based upon the following rationale:

- Differences exist between small molecules and large therapeutic agents, such as monoclonal antibodies, with regard to their inherent molecular structure and their process of manufacture
- Recognition of key differences between original biopharmaceutical agents (i.e., the name brand) and the biosimilar (i.e., the generic) is necessary to support optimal therapy management and patient care
- Dermatologists are accustomed to the use of a wide range of generic topical and systemic agents
- Current global regulatory status of biosimilar approval pathways is evolving and there is opportunity to impact the dialogue related to the introduction of biosimilars into the dermatology setting for the treatment of psoriasis

Accordingly, in March to May of 2011, IPC distributed a survey to its councilors that addressed the draft guideline on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010). The collective results represented the viewpoint of 10 councilors who completed the survey (4 from EU, 3 from US, 2 from Latin America & 1 from Canada). The results of the survey were collated and submitted to the EMA in June 2011. Excerpts from the survey are displayed throughout this article. It is clear that IPC’s efforts impacted both the agenda and dialogue on the topic as illustrated below.

**IPC Councilor Survey Q1: How do you define the promise of Biosimilars for the treatment of a chronic lifelong disease with a high prevalence, such as psoriasis?**

**IPC Councilor Comments:**

- More competition leading to lower prices. However, equal efficacy and safety data should be provided by biosimilars.
- To reduce costs for the management of these diseases and still provide the high efficacy seen under biologics.
- The main objective of biosimilars should be promoting the accessibility of patients to such therapies through the substantial reduction of the total economic cost of treatment.
- The complexity of the molecules and the need for more stringent definitions of equivalence impacts the promise of biosimilars.
EMA Workshop Participants: The workshop was chaired by Dr. Christian Schneider of EMA. Attendees at the workshop included US FDA and Health Canada as well as the pharmaceutical industry represented by both the innovator and biosimilar groups. The innovator companies were represented through the European Biopharmaceutical Enterprises (EBE) organization (which includes member companies such as Pfizer, Novartis, Johnson & Johnson, Merck, Astra-Zeneca). In contrast the Biosimilar companies were represented by member companies of the European Generic Medicines Association (EGA) an organization supported by companies such as Teva, Hospira, Ranbaxy & Sandoz.

Workshop Overview: There was a predictable tension between the innovators (EBE) group related to maintaining the uniqueness of any individual agent and the potential risks of biosimilars versus the biosimilars EGA camp who aimed to push through a shortened clinical development programme based upon following an approach to demonstrate physicochemical and biological similarity. The EGA also brought up the notion that there are already significant changes in innovator products (e.g., Enbrel glycosylation changes over time) that are not subject to any regulatory approval. Finally, it is worth noting that there was minimal discussion on the real cost/benefit of the biosimilars in the primarily regulatory focused agenda. Below we have summarized some of the key points of the workshop under categories under which interesting discussions were held, not necessarily reflective of the workshop agenda.

Regulatory Approach to Biosimilar Approval: The EMA approach to Biosimilars was stated to be scientifically tailored to establish biosimilarity and not an abbreviated program to determine benefit to risk. Thus, to constitute regulatory approval, a risk-based approach will be mandated that incorporates in vitro pharmacodynamic analysis with clinical pharmacokinetic measurements. This of course depends on the presence of specific risk factors (e.g., different expression system to innovator agent = higher risk). This direction is supported by previous statements from CHMP that pharmacodynamic analysis might constitute the mainstay of biosimilar approval. Moreover, there seemed to be an accepted premise that biosimilar candidates can be fully characterized in terms of structure and function in the absence of robust clinical analysis.

Scope of Clinical Studies: Clinical studies would need to be parallel group design versus the innovator agent and would take into consideration antigen levels (e.g., for agents targeting tumors). There was not explicit agreement on whether a biosimilar studied in one indication would receive an indication for all of the conditions approved for the innovator agent. On one hand it was proposed that relevant pharmacodynamic data may be considered as sufficient to support approval in all indications in the absence of a clinical trial in each indication. Although, there was broad acknowledgment that in any scenario, biosimilar approval in one indication is likely to lead to use in all relevant conditions. Although, the innovator companies suggested that there was a need to ascertain the benefit:risk profile with sufficient human clinical data in each indication and this may not be evident in simple PD/PK studies. In terms of trial design, it was suggested that the same clinical endpoints should be used to as those of the original innovator where ever possible; although it was accepted that for expedience, for cancer drugs - surrogate endpoints such as complete remission (rather than disease free survival) can be used. Additionally, there was discussion about doing the trials in 'the most sensitive population' – i.e., with minimal variation in age/sex/disease homogeneity in order to demonstrate bioequivalence with a view to minimizing the numbers needs in trials.
**Special Report**

IPC Councilor Survey Q2: What minimal data will you look for in order to support prescribing a biosimilar therapy?

**IPC Councilor Comments:**
- Pharmacokinetic, efficacy and safety data from animal models
- Pharmacokinetic comparisons in small human trials (10 - 20 patients)
- Effectiveness (non-statistical), Safety and Pharmacokinetic information in relatively small human trials (40-50 patients)
- Efficacy (statistically supported), Safety and Pharmacokinetic information in larger human trials (>200 patients)
- 100% of respondents selected answer d) Efficacy (statistically supported), Safety and Pharmacokinetic information in larger human trials (>200 patients).

Selected comments from IPC Councilors:
- As can be seen in the epoietin experience, one needs to FULLY characterize each compound produced as a "biologic."
- Best would be a RCT head-to-head with the parent compound.
- The equivalence margins are far too small to yield anything more than slightly biosimilar

IPC Councilor Survey Q3: Should a biosimilar agent receive total class labeling for all indications based upon one study in a single indication? For example, should clinical studies for a TNF-inhibiting biosimilar performed in rheumatoid arthritis be also sufficient for an indication for psoriasis. (Yes / no) Why or why not?

**IPC Councilors Poll:** 70% of respondents answered “No”; 30% of respondents answered “Yes”

**IPC Councilor Comments:**
- We see differences between biologics with similar modes of action between indications. Thus, some variability may be expected, which might affect the rationale to use a biosimilar in different indications
- Biosimilars should have to be proven effective for every indication, just as innovator biologics. The size and complexity of this sampling may be different (and cheaper to perform) but they would have to be proven effective and safe in humans for individual indications.
- Higher doses are often required in psoriasis. Monotherapy is the rule in psoriasis, while combination therapy is standard in rheumatoid arthritis. In this context it should also be noted that methotrexate changes the pharmacokinetics of some TNF-inhibitors.
- Different diseases need different clinical and pharmacologic studies.
- There are differences in the pk-pd models for the innovative products. The margin of biosimilarity is far too coarse to derive reliable estimates of response across indications.
**Equivalence vs. Non-inferiority Trial Design:** Non-inferiority was accepted to be less restrictive a design than that for equivalence. But it was acknowledged that for a biosimilar, dissimilarity in either direction (positive or negative) is not acceptable. Thus, an equivalence trial with 2 confidence margins appears to be the logical requirement, since superior efficacy (as would be permitted in non-inferiority trials) may infer physiologic differences and thus not biosimilarity.

However, it was acknowledged that in certain conditions (e.g., oncology), with justification, non-inferiority might be acceptable due to the nature of the endpoints. Additionally, equivalence trials were acknowledged to be larger, but there is not anticipated to be a huge difference — maybe 20% more patients versus non-inferiority, in trials ranging in size from 50 – 200 patients on average.

**Biosimilar Product/Class Specific Guidance:** The need for specific scientific guidance based upon specific products, product classes and targeted disease was controversial. On the one hand, additional guidance on how to address targets and types of molecule was deemed necessary to improve transparency and benefit development e.g., TNF blockers contain many class members consisting of chimeric, humanized and human proteins. They also have different indications specific to each product. The guidelines are sufficiently directive on some aspects e.g., in vitro pharmacodynamic studies and clinical efficacy. Thus the proposed recommendation is for general guidance only, with specific guidance to be provided later and on a case by case basis. Indication specific guidance would not be feasible since there are too many product classes and indications to be able to address them in a meaningful way. Indeed, given that the state of knowledge of biosimilars is in its infancy, there is insufficient data available to provide such guidelines.

**Immunogenicity:** An interesting debate ensued on this topic. mAbs were proposed as being part of a high immunogenicity risk class wherein assay requirements are standard and sampling frequency would vary relative to risk of the specific product. The direct comparison of innovator and biosimilar agent in this dimension was proposed but it was acknowledged that this would be a very high bar, to power trials to compare an immunogenicity endpoint. An alternative view suggested that biosimilars should be treated like a process change for the innovator. In short, the EMA view was to monitor immunogenicity, not power for it, in the human trials. If differences were observed, the mandate might be for additional information and follow-up, possibly in controlled studies.
IPC Councilor Survey Q4: What is the best way to monitor patients on biosimilars with a view to collecting data to support biosimilar use and to minimize any risks or uncertainties?

IPC Councilor Comments:
- Mandatory 5-year safety follow-up.
- Registries should be required to include biosimilars and all treatments for psoriasis.
- Post marketing vigilance. Implement national vigilance programs, possibly centralized by Dermatology Societies such as the international Psoriasis Council.

Pharmacovigilance: Good vigilance practice requires that additional monitoring may be required for any medicine, including biosimilars. General issues discussed included; traceability and naming; substitution; labeling; off-label use and post-marketing requirements. The final guideline may require “recording brand names to reinforce traceability” – but the EMA regulatory viewpoint was that the language does not need to be stronger than this. In support, it was acknowledged that in standard EU pharmacovigilance plans, an AE needs to be clearly specified by Brand; Company and Batch Number. EMA further indicated an expectation that biosimilars should and will participate in already existing registries (disease or drug) that allow collection and comparison of rare events and that this would be incorporated into the finalized version of the guidelines.

IPC Councilor Survey Q5: What aspects of biosimilars need to be different from the original innovator agent to support identification of the specific therapy; please prioritize (1 = most important, 4 = least important)

a) Brand / Proprietary name
b) Generic / Non-proprietary name
c) Packaging (Colors)
d) Classification

IPC Councilors Poll: 60% of respondents answered a) Brand / Proprietary name and b) generic / non-proprietary name as the most important mechanisms to distinguish biosimilar agents
**Special Report**

**Naming Convention for Biosimilars:** Discussion focused on the non-proprietary, generic or International Nonproprietary Name (INN) name for the compounds. Surprisingly the influence of regulatory bodies over the naming conventions for specific biosimilars was deemed to be fairly limited. Regulatory bodies can determine if they accept a new INN name for a biosimilar or otherwise can propose naming conventions. Addition of a Greek letter to the end of the INN, e.g., alpha, beta etc will be considered as this has worked in previous cases of biosimilar proteins (e.g., filgrastims). Robin Thorpe, a WHO INN committee member indicated that companies can apply for a new INN in which case they will likely get it, even for a biosimilar. It is up to regulatory bodies to determine if they accept this. It was acknowledged that the INN naming convention related to mAb biosimilars is not clearly resolved yet. Regardless of a new INN name, traceability will be enforced by mandated pharmacovigilance plans for biosimilars.

**Next Steps:** Final Guidelines are to be completed by year end and published in 1Q12.

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**IPC Councilor Survey Q6: What other thoughts do you have related to Biosimilars? (e.g. related to therapeutic rationale for their use; or maintaining the physician-patient continuum of care?)**

**IPC Councilor Comments:**

- We need to decrease the cost of biologics and allow access to these wonderful medications for a greater number of patients.
- My major concern is essentially related to the commitment to regulating biosimilars to ensure good efficacy, tolerance and safety.
- Pricing is a concern. Unless prices really do decrease significantly, why do we need biosimilars?
- It might turn out that a proposed biosimilar in clinical assessment shows superior efficacy compared to the original. This may be due to different pharmacokinetic properties. Would this mean that the biosimilar become a second generation biological?
- Key is really to show immunological similarity!
- Biosimilars have to show the same characteristics of originals in all aspects of the issue, with better accessibility and lower prices.
- Manufacturing stringency has to be maintained and regulated given the delicate manufacturing processes.
CONTINUING MEDICAL EDUCATION SECTION

This section of the *IPC Psoriasis Review* has been specifically written to offer you the opportunity to receive a maximum of 1.0 AMA PRA category1 credit through Purdue University. At the end of the section, you will find a series of questions and instructions on submitting the answer to receive your CME credit.

Clinical and Scientific Advances from the 20th Congress of the Academy of Dermatology and Venereology, Lisbon Portugal

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Authors

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

Professor Esteban Dauden, MD, PhD  
Hospital Universitario de la Princesa  
Madrid, Spain

Professor Yves Poulin, MD, FRCPC, FAAD  
Hospital Hotel-Dieu de Quebec  
Quebec, Canada

Speaker-Specific Disclosure Statement

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

Professor Esteban Dauden, MD, PhD
Professor Esteban Dauden has received grants and research support from Abbott, Janssen, Pfizer and MSD. He has served as a consultant/speaker bureau for Abbott, Janssen-Cilag, Pfizer, MSD, Leo Pharma and Novartis. He has also served on advisory boards for Abbott, Janssen-Cilag, Pfizer, MSD, Amgen, Centocor, Leo Pharma and Celgene.

Professor Yves Poulin, MD, FRCPC, FAAD
Professor Poulin has received grants/research support from Abbott, Amgen, Centocor, Janssen, Leo Pharma, Merck and Pfizer. He has served on an advisory boards from Abbott, Amgen and Janssen and has received honorarium from Abbott, Amgen, Janssen and Leo Pharma. He also received an unrestricted educational grant from Abbott.

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 psoriasis patient

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 (ACCME) through the joint sponsorship of Purdue University College of Pharmacy, the International Psoriasis Council and Focus Medical Communications. Purdue University College of Pharmacy, an equal access/equal opportunity institution, is accredited by the ACCME to provide continuing medical education for physicians.
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This material was supported by an educational grant from Abbott, Amgen and Janssen Biotech, Inc.
European consensus on definition of treatment goals:

Expert dermatologists in the field of psoriasis from 19 European countries reached a consensus to fill the void on treatment goals for moderate to severe psoriasis (Mrowietz U, Arch Dermatol Res. 2011;303:1-10). Severity of plaque psoriasis was graded into mild and moderate-to-severe disease. Mild disease was defined as body surface area (BSA), PASI and DLQI each equal to or less than 10. Mild plaque psoriasis can usually be controlled by topical therapy. In refractory cases, the addition of phototherapy should be considered. Moderate-to-severe psoriasis was defined as (BSA > 10 or PASI > 10) and DLQI > 10. It is recommended to treat these cases with systemic treatments, including phototherapy. Importantly, certain clinical situations can “upgrade” a mild form of the disease to “moderate-to-severe” which may necessitate the use of systemic or biologic therapy in this particular group. These clinical situations include: involvement of visible areas such as the face, major involvement of large parts of the scalp, involvement of the genital area, non-pustular palmo-plantar involvement, finger-nail onycholysis or onychodystrophy, presence of intense disabling pruritus, and presence of single recalcitrant plaques.

Treatment strategies were also defined in this consensus report. Systemic therapy was defined in two phases: induction followed by a maintenance phase. The induction phase was defined as the treatment period until 16 weeks; however this can be extended to 24 weeks in the case of some drugs (methotrexate, acitretin and etanercept for example). The maintenance phase was defined as the treatment period following the induction phase. For definition of treatment goals, the changes in both the PASI and DLQI from baseline until time of evaluation were used. Following induction and during maintenance therapy, treatment can be continued if reduction in PASI is equal to or greater than 75%. The treatment regimen should however be modified if improvement of PASI was less than 50%. In a situation where the therapeutic response improved by 50% or more but less than 75% of PASI, therapy should only be modified if the DLQI is greater than 5 and continued if the DLQI is equal to or less than 5. Treatment modification may include: increase of the dose, reduction in the dose interval, the addition of a topical or systemic agent, and substitution of the existing therapy. It is anticipated and hoped that this consensus programme defines treatment goals and its implementation will lead to improvement in patient care and mitigation of the problem of undertreatment.


Future therapies:

Dr. Papp from Canada presented data from phase II trial of the human monoclonal antibody (AMG827) that selectively targets IL17RA (receptor) and inhibits the signalling of cytokines IL-17A, IL-17A/F, IL-17F and IL-25. Different doses administered subcutaneously at Week 0, 1, 2, 4, 6, 8 and 10 were compared against placebo (70 mg, 140 mg, 210 mg and 280 mg). In a 22-week open label analysis PASI 75 at Week 12 was reached by 33%, 77%, 83% and 67% respectively and PASI 90 was 18%, 72%, 75% and 57% respectively. There was some loss of response at week 22 (12 weeks post-treatment); however the overall results support the role of IL17A in the pathogenesis of psoriasis.

In a different phase I trial for the same drug (AMG827) using a single intravenous infusion at three different doses of 140 mg, 350 mg and 700 mg versus placebo no serious adverse events were reported and improvements in PASI were higher in the higher dose arm group. Subsequent histological analysis from the previously involved areas showed reduction in epidermal thickness in addition to reduced expression of the proliferation marker Ki67 on immunohistochemical analysis.
Dr. Papp also presented data from three phase II studies using the monoclonal antibody that targets IL17A (AIN457-Secukinumab). Secukinumab was administered subcutaneously at Week 0, 4 and 8, using different dosages: 25, 75 or 150 mg. The primary end-point at week 12 was the PASI 75. There was a clear dose-dependent response with PASI 75 achieved by 57% of patients on the dose of 75 mg and 81% at the higher dose of 150 mg. No serious adverse events were reported.

In a double-blind, placebo-controlled study involving 100 patients who were randomized in a 3:3:3:1 ratio to one of three intravenous induction dose regimens of secukinumab [3mg/kg given at day 1 only (n=30); 10mg/kg at day 1 only (n=30); 10mg/kg at days 1, 15 and 29 (n=30)] or to placebo (n=10); PASI 75 response rates were 40%, 75% and 83% versus 10% in the placebo group at week 12. The rate of adverse events was higher in the secukinumab arm compared to placebo. Other future therapies include sotrastaurine, apremilast, tofacitinib, IL 22 blocker and IL 23 blocker (p19 blocker).

**Biological therapy data:**

Dr. Kimball presented pooled data from three studies looking at the value of the induction dosing with or without initiation dose for adalimumab. The Odds ratio for the induction group with dose initiation (loading dose) was almost 2 to achieve PASI 75 at week 12. The cost per PASI 75 responder was also more effective in this group.

Dr. Armstrong presented data looking at the week 12 benefit/risk profile of adalimumab compared to etanercept stratified by weight (less or more than 100 kg). The results were from the REVEAL and CHAMPION trials for adalimumab versus placebo and etanercept versus placebo M10-114 and M10-315 trials. In both weight classes the adalimumab-treated patients had significantly greater Odds ratio of achieving PASI 75 or 90 than the etanercept-treated patients. The Odds ratio for PASI 75 in the group under 100 kg body weight was 2.47 compared to an Odds ratio of 2.79 in the group over 100 kg. Furthermore, no significant differences in drug-related adverse events rates were observed in the adalimumab treated group compared to etanercept.

Dr. L. Puig presented data analyzed from the PRISTINE study in the use of etanercept looking at the effect of biomarkers across three groups; non-diabetics, pre-diabetics, and diabetic patients. The most significant reduction was found in the C-reactive protein levels at week 12 across all three groups. No marked differences were found in the biomarkers adiponectin, apolipoproteins, fasting glucose and insulin levels. In the diabetic group Etanercept did not appear to have a clinically meaningful impact on the cardiometabolic biomarkers.

Dr. Gordon presented data from the REVEAL trial for adalimumab in the non-responder group (PASI less than 50) and partial responders (PASI 50-75) at the primary end-point of 16 weeks. Those two groups completed an open-label extension for 52 weeks in which some patients did eventually get good response suggesting some benefit in continuing therapy in the partial responders group if treatment is continued as shown in the data when compared between week 12 and 52. Data was also presented on the long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over three years (Gordon K, *J Am Acad Dermatol*. 2011, July-Epub ahead of print). The data were extracted from an open-label extension study for patients from the REVEAL trial. The data showed that adalimumab maintained efficacy over more than three years of continuous therapy in patients with sustained initial PASI 75 responses and no increased rates of adverse events were noted in comparison to data from the REVEAL trial.

In a study by Warren RB et al. (*BR J Dermatol* 2010;163:859-862), published data on the experience of adalimumab in psoriasis showed that nearly two-thirds of treated patients reached PASI 75 after 16 weeks of treatment. More importantly, 68% of patients who had previously received another anti-TNF alpha biologic met the national criteria set by NICE for continuation of treatment at 16 weeks.
Interesting data on the use of ustekinumab in both the anti-TNF agent-naive versus anti-TNF agent-exposed patients showed that PASI 75 was achieved in 80% of the ustekinumab-treated patients after a median time of 112 days (Clemmensen A, J Eur Acad Dermatol Venereol. 2011;25(9):1037-40). There was no difference in efficacy in anti-TNF agent-naive compared with anti-TNF agent-unresponsive patients. The data show that lack of response to previous anti-TNF therapy does not impair clinical response to ustekinumab.

Data from week 12 results of the TRANSIT study looking at the efficacy of transitional therapy from systemic treatment to biologics were presented (PO1121). In this trial, 489 patients on methotrexate were randomized 1:1 into two arms: initiation of ustekinumab with either immediate cessation of methotrexate (arm 1) or four weeks overlap with methotrexate (arm 2). By week 12, baseline PASI scores fell from 17.44 and 16.93 in arms 1 and 2 respectively, to 4.42 and 4.22. No cases of malignancy, MACE or tuberculosis occurred. The results show that ustekinumab is effective in patients inadequately responsive to methotrexate with no difference in either transition strategy.

**When to stop biologics:**

Professor Griffiths gave a presentation on the use of biologics and the development of measurement tools for severity of the disease as well as the identification of patients who respond to therapy based upon PASI and DLQI reduction. There are however no biomarkers available to measure or predict the severity or possible flare-up of psoriasis.

Biologic therapy should be discontinued in the following: failure to reach adequate response, failure to maintain response, serious adverse events, pregnancy, elective surgery, and vaccination.

In the case of vaccinations, the current recommendations are that no live vaccines should be given whilst on biologic therapy including a period of less than two weeks prior to therapy or less than six months following discontinuation.

In the case of elective surgery the evidence is lacking in psoriasis, however therapy should be discontinued in the case of major surgery. The timeframe of discontinuation of the biologic therapy to undergoing major surgery should be that of at least four half-life times of the drug. This would be two weeks for etanercept, eight weeks for adalimumab, six weeks for infliximab and 12 weeks for ustekinumab.

Current practice and the recommendation is to avoid the use of biologic therapy in pregnancy and to avoid breast feeding in patients who are using biologic therapy although studies have shown that infliximab is not excreted in breast milk.

Switching between biologics in psoriasis is more frequent than in rheumatoid arthritis. Long-term remission with few cycles of alefacept has been observed. Ustekinumab can be restarted following discontinuation and around 80% regain PASI 75 response in a multi-centered evaluation of the response to retreatment among initial responders following withdrawal from therapy in the PHOENIX1 and ACCEPT trials (PO1152).

In a study based on data from the Danish nationwide database DERMBIO covering patients with psoriasis treated with a biologic agent, the overall efficacy of anti-TNF therapy diminishes with time as envisaged by the progressive loss of patient adherence to treatment. The major reasons for treatment discontinuation were loss of efficacy, followed by adverse events (Gniadecki R, Br J Dermatol. 2011;164:1091-1096).

**Pregnancy and psoriasis:**

The topic of pregnancy and psoriasis featured on several occasions at the meeting with various data presented from different groups. The possible complications and effects of psoriasis to the pregnant woman is a matter of intense investigation.
Dr. L. Puig from Spain presented the most recent published literature on the topic of pregnancy and psoriasis. In a study by Lima XT et al. (J Invest Dermatol. 2011 Sept 15-epub ahead of print) evaluating the outcomes of 162 pregnancies in 122 women with psoriasis, there was a 1.89-fold increase in odds of poor outcome composite (preterm birth and/or low birth weight) in patients with moderate to severe psoriasis. There was however no association found with caesarean delivery, eclampsia, and spontaneous abortion. Similar findings were found in a study from Taiwan by Yang YW et al. (J Am Acad Dermatol. 2011;64:71-77) looking at 1,463 mothers with psoriasis. Their findings showed that moderate to severe psoriasis – and not mild psoriasis – is associated with an increased risk of low birth weight.

A study in the USA by Bandoli G et al. (Br J Dermatol. 2010;163:334-339) showed that pregnant women with psoriasis were more likely to be overweight/obese prior to pregnancy, to smoke, to have a diagnosis of depression, and were less likely to have been taking preconceptional vitamin supplements. This study highlights the increased presence of comorbidities in pregnant women with psoriasis.

Cohen-Barak E et al. (J Eur Acad Dermatol. 2011;25:1041-1047) found that pregnant women with severe psoriasis have an increased risk for spontaneous abortions and premature rupture of the membranes. Their study also showed a high prevalence of co-morbidities in this group.

An interesting finding by El-Saie LT et al. (Lasers Med Sci. 2011;26:481-85 and PO1063) in pregnant women with psoriasis who are undergoing treatment with narrowband UVB phototherapy is reduced levels of serum folic acid in the pregnant women and the increased risk of neural tube defects in the newborn babies. The authors hypothesize that UVB therapy may induce folate photodegradation leading to low levels of folic acid in pregnancy.

Researchers from Taiwan studied the safety of topical steroids in pregnant women and found that there does appear to be an association of very potent topical corticosteroids with low birth weight (Chi CC, J Am Acad Dermatol. 2010;62:694-705). Furthermore, the same group found no association of maternal exposure to topical corticosteroids with orofacial clefting, preterm delivery, and fetal death (Chi CC, J Invest Dermatol. 2011;131:884-891).

An interesting finding by a group in France (Beghin D, J Rheumatol. 2011;38:628-632) reporting on the outcome of 42 pregnancies involving 40 men treated with methotrexate at the time of conception showed no congenital malformations at birth. The authors concluded that paternal exposure to methotrexate at the time of conception does not seem to raise any major concern for offspring.

Available data from registry studies and case reports analyzed by a group in Toronto in Canada (Djokanovic N, Reprod Toxicol. 2011;32:93-97) showed that infants born with detectable levels of infliximab do not seem to have an increased risk of infections in their first year of life and have normal responses to non-live vaccines. A review by Puig et al. (Dermatology. 2010;220(1):71-6) showed that the current available data do not show an adverse outcome of pregnancy in women exposed to biologic therapy at the time of conception.

Psoriasis and skin cancer:

The relationship between skin cancer and psoriasis (largely related to therapy) was highlighted and presented by Professor Van de Kerkhof. The risk of skin cancer following therapy with photochemotherapy (PUVA) appears to be persistent following discontinuation of therapy. The carcinogenic potential of PUVA therapy appears to be permanent. This is in contrast to the risk for developing skin cancer due to cyclosporine, of which the risk appears to be related to the immunosuppression during the cyclosporine use.

Treatment of psoriasis patients with skin cancer was also discussed. Recommended therapies include topical treatments and the use of systemic retinoids. Both methotrexate and fumaric acid esters can be used but should preferably be considered as second-line agents after the use of systemic retinoids. Therapies which are contra-indicated – or should be largely avoided – in the setting of skin cancer include PUVA, cyclosporine and biological therapies to a degree. The addition of acitretin to biologic therapy in high-risk patients was highlighted.
**Methotrexate in psoriasis:**

Dr. Warren from Manchester presented a synopsis of issues related to the use of methotrexate in psoriasis. Contraindications to methotrexate therapy include nephro- or hepatotoxicity, pregnancy, pulmonary fibrosis, active duodenal or gastric ulceration, immune deficiency, and active tuberculosis. The importance of blood monitoring following the initial test dose was explained as in rare cases unexpected dose-independent idiosyncratic bone marrow suppression may occur. Unlike azathioprine – an immunsuppressive drug used in some inflammatory disorders – there is no biochemical predictive marker to identify “at risk” patients of this adverse reaction.

The importance of drug interactions with methotrexate was presented. Non-steroidal anti-inflammatory drugs need to be used cautiously with methotrexate due to the increased risk of toxicity. Experience with the biochemical assay of procollagen III peptide shows that in patients with persistent normal levels of this biochemical marker, the presence of hepatic fibrosis due to methotrexate is very low. Finally, the nausea that can accompany the use of methotrexate may be alleviated by the use of ondansetron two hours prior to taking methotrexate and 12 hours afterwards.

**Co-morbidities and psoriasis:**

The presence of co-morbidities in psoriasis patients and the concept of psoriasis as a systemic disease featured highly in this congress which reflects the increasing evidence of its importance and consequences this poses to the patients. It is now well-known that severe psoriasis is associated with an increased risk for developing the metabolic syndrome (PO1065). A study from Italy (PO1068) showed a positive correlation between PASI and body mass index which was statistically significant between overweight and normal weight patients.

Professor Boehncke from Germany presented the concept of the “psoriatic march” in which systemic inflammation causes insulin resistance, which in turn triggers endothelial cell dysfunction, leading to atherosclerosis and eventually myocardial infarction or stroke (Boehncke WH, *Exp Dermatol*. 2011;20:303-307). Professor Boehncke also presented data from his group showing the profile of elevated biomarkers of inflammation in severe psoriasis patients. C-reactive protein and selectin- were ameliorated in patients with severe psoriasis who responded to continuous systemic therapy (Boehncke S, *J Eur Acad Dermatol Venereol*. 2011;25:1187-1193). The impact on the patients' metabolic state was found to be better if the psoriatic inflammation was controlled for longer. In another study conducted by the same group (Boehncke S, *Arch Dermatol Res*. 2011;303:381-88) other biomarkers of cardiovascular disease such as resistin and vascular endothelial growth factor decreased with systemic therapy. In addition, assessment of endothelial function assessed by venous occlusion plethysmography revealed an improvement of endothelial vasodilator function after 24 weeks of treatment. The results showed the effect of systemic inflammation on endothelial dysfunction and the beneficial effect of control of the systemic inflammation with systemic therapy. In a study in Austria involving 49 patients (PO1083) the investigators showed that patients without systemic therapy have significantly higher levels of insulin resistance irrespective of the severity of the disease. The speakers highlighted the importance of psoriasis being recognized as an independent cardiovascular risk factor and that psoriasis patients need to be assessed for their cardiovascular risk.

In a Danish nationwide cohort study involving 2,793 patients with severe psoriasis (Ahlehoff O, *Eur Heart J*. 2011;August 25-Epub ahead of print), the relative risk for atrial fibrillation (following adjustments for other variables) was 2.98 in patients aged less than 50 years and 1.29 in patients aged over the age of 50.
Safety of Biological Therapies:

This important aspect of psoriasis therapy, in particular with the increasing use of biologics, was presented by several speakers. The concern of major adverse cardiovascular events (MACE) occurring with the use of biological therapy was discussed. Ryan C et al. published data from a comprehensive meta-analysis of the MACE events with the use of biologics (JAMA 2011;306:864-871) from 22 randomized controlled trials comprising a total of 10,183 patients. Results showed that compared with placebo, there was no significant difference in the rate of MACE observed in patients receiving anti-IL12/IL23 antibodies or anti-TNF treatments. The results highlight the need for persistent and enhanced vigilance to monitor rare events that might be associated with biological therapies. Therefore, with increased exploration and data availability, a follow-up meta-analysis of this phenomenon may be warranted.

A study from The Netherlands (van Lumig P, J Eur Acad Dermatol Venereol. 2011;March 24-Epub ahead of print) involving a cohort of 173 psoriasis patients on biological therapy were prospectively followed up for five years with a total number of patient-years of 409. Only one serious adverse event was certainly linked to biological therapy. The results of the study showed that with the exception of a slight increase in the risk of non-melanoma skin cancer, the incidence of malignancies, serious infections and MACE was comparable with the population incidence rate.

Data from registries from rheumatology centers with large numbers of patients receiving biological therapy showed an overall small risk of serious infections, the highest risk being within the first six months of biological therapy. Data were presented from the British Society for Rheumatology Biologics Register (Dixon WG, Ann Rheum Dis. 2010;69:522-528) comparing the tuberculosis rates in 10,712 rheumatoid arthritis patients treated with anti-TNF therapy (etanercept, adalimumab and infliximab) and 3,232 patients treated with traditional disease-modifying anti-rheumatic drugs. A total of 40 cases of tuberculosis were reported, all in the anti-TNF cohort that consisted of adalimumab, infliximab and etanercept patients.

The overall follow-up period to determine the risk of malignancy in patients on biologic therapy is relatively short in number of years to determine the exact risk as yet. The argument that the risk for developing malignancy secondary to the immunosuppressive effect of the biological therapy was challenged by a counter argument that the overall risk for malignancy may be somewhat decreased with control of the “systemic inflammation”. It is therefore essential that patients treated with biological therapies enter registries for which these long-term data can be gathered and analyzed in the future.

Ustekinumab 4-year safety data:

The safety of biological therapies has always been a subject which has gained great attention and importance both in clinical trials and in daily clinical practice. The 4-year safety data of the IL12/23 mAb, ustekinumab, were presented by professor Griffiths. A total of 208 weeks safety data involving 3,117 patients and 6,791 patients — years of treatment are now available for ustekinumab. The overall rates of non-melanoma skin cancer are in the ratio of 3:1 for basal cell carcinoma to squamous cell carcinoma (PO1158). This ratio is favorable relative to the rates observed in patients on cyclosporine; an observation to support the notion that ustekinumab does not lead to profound immunosuppression. As for the overall infection rate, no patterns of infections have emerged and the majority of serious infections were caused by common pathogens. The overall rates of infections remained stable with up to 4 years of follow-up and did not appear to increase with cumulative exposure (PO1151).

Overall, from the 4-year safety data their does not appear to be a trend toward increased rates of malignancy overall including non-melanoma skin cancer. The data show that to date there is no statistical increase in cumulative risk for MACE in patients using ustekinumab in both doses. The rates of myocardial infarction and strokes were less than expected versus the US population as a whole based on the Framingham Heart Study as well as a UK psoriasis population in the General Practice Research Database (PO1153). Overall, to date, ustekinumab appears to have an acceptable risk/benefit ratio supporting its use.
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Posttest

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Please select the one best answer by circling the appropriate letter.

1. Secukinumab is a monoclonal antibody that directly targets which cytokine?
   a. IL12
   b. IL23
   c. IL17A
   d. IL6

2. According to the new European consensus document, treatment of psoriasis with biological therapy following an adequate induction period can be continued without modification if:
   a. Reduction in PASI is less than 75%
   b. Reduction in PASI is equal to or greater than 75%
   c. Reduction of DLQI by 2 points
   d. PASI improvement of 60% with a DLQI greater than 10

3. The CHAMPION trial involved which biologic agent?
   a. Etanercept
   b. Infliximab
   c. Ustekinumab
   d. Adalimumab

4. In the PRISTINE study, which of the following biomarkers was reduced to a statistically significant value following control of psoriasis with etanercept?
   a. Adiponectin
   b. Insulin
   c. C-reactive protein
   d. Glucose

5. Some studies have shown that severe psoriasis in pregnant women may lead to:
   a. Increased risk of high birth weight
   b. Increased risk of low birth weight
   c. Orofacial clefting of the newborn
   d. Increased risk of cardiac defects in the newborn

6. Which of the following agents can be used as a chemopreventive in psoriasis patients who are at risk of non-melanoma skin cancer?
   a. Cyclosporine
   b. Methotrexate
   c. PUVA therapy
   d. Acitretin

7. According to the current data available from registries of patients on biologic therapy, the highest risk of infections during treatment is:
   a. After 3 years of continuous therapy
   b. The risk is equal throughout treatment
   c. Following discontinuation of treatment
   d. Within the first 6 months of treatment

8. Which of the following biological therapies had their 4-year safety data presented at the EADV meeting in Lisbon?
   a. Etanercept
   b. Adalimumab
   c. Ustekinumab
   d. Infliximab

9. Which of the following does not require discontinuation of biological therapy?
   a. Localized hypersensitivity reaction
   b. Pregnancy
   c. Vaccination with live vaccines
   d. Major elective surgery

10. Which study looked at the efficacy of transitional therapy with or without a "wash out" period with methotrexate followed by ustekinumab?
    a. REVEAL
    b. CHAMPION
    c. TRANSIT
    d. PRESTA

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December 2011  23
# Evaluation

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

Please answer the following questions by circling the appropriate rating:

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

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

### Overall Effectiveness of the Activity
- Was timely and will influence how I practice: 5 4 3 2 1
- Will assist me in improving patient care: 5 4 3 2 1
- Fulfilled my educational needs: 5 4 3 2 1
- Avoided commercial bias or influence: 5 4 3 2 1

### Impact of the Activity

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

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- How committed are you to making these changes? (Very committed) 5 4 3 2 1 (Not at all committed)

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

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

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### 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:

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25 Highland Park Village, Ste 100-370 • Dallas, TX, USA 75205 • 972-861-0503 • www.psoriasiscouncil.org