6th EADV Spring Symposium

Quality of life: an important consideration in psoriasis

The 6th European Academy of Dermatology and Venereology (EADV) Spring Symposium was held April 23-26, 2009, in Bucharest, Romania, with a focus on skin and quality of life (QOL). Multiple dermatologic diseases can have a lasting impact on QOL. In some individuals, skin diseases may affect long-term life decisions, including the choice of a partner, the choice of type of work, and the choice of whether or not to have a family. Specific age groups, such as adolescents, may have unique QOL issues that need special considerations.

Dr. Francesca Sampogna, Istituto Dermopatico dell’Immacolata, Rome, Italy, stressed the importance of comparing QOL across different skin conditions, including those with no physical symptoms, where the burden may be underestimated. Using the survey instrument Skindex, which measures symptoms, emotions and functioning, the impact of arthropathic psoriasis was greater than psoriasis, which was greater than vitiligo, which was greater than nevi (arthropathic psoriasis > psoriasis > vitiligo > nevi). In another study where nearly 1,000 psoriasis patients completed the dermatology life quality index (DLQI), the areas of greatest impact included problems with friends or partners, challenges with work or study, feeling embarrassed, and symptoms of itch, soreness or pain.

Measuring QOL

Professor Andrew Finlay, Cardiff University School of Medicine, Cardiff, U.K., suggested that measuring QOL may improve patient care, enhance clinical research, inform health services research or audits, and provide insight into the psychological aspects of dermatology. Multiple QOL instruments are currently available, including general instruments (SF-36, Euroquol), dermatology specific instruments (DLQI, Skindex, VQ-Dermato), and disease-specific instruments [psoriasis disability index (PDI), PsoriQOL]. In psoriasis, Professor Finlay recommends using the rule of tens, or body surface area (BSA) greater than 10%, or psoriasis area severity index (PASI) greater than 10, or DLQI greater than 10 (>10% BSA, or >10 PASI, or DLQI >10). The rule of tens has been recently incorporated into the British Association of Dermatology (BAD) guidelines for use of biological intervention in psoriasis in 2009.

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Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s co-editors, Esteban Dauden, M.D., Ph.D., Hospital Universitario de la Princesa, Madrid, Spain, and Gerald Krueger, M.D., University of Utah School of Medicine, Salt Lake City, USA, I am pleased to present the May 2009 edition of our clinical newsletter, IPC Psoriasis Review.

Published several times per year, IPC Psoriasis Review appraises the most recent clinical and research publications and provides commentary on those that we believe make the greatest contribution to our understanding of the disease and its treatment. In this issue, we include meeting reviews from the 6th European Academy of Dermatology and Venereology (EADV) Spring Symposium, Skin and Quality of Life, and the 69th Annual Meeting of the Society of Investigative Dermatology (SID). In addition, we introduce a new online clinical trials handbook, "What You Need to Know to Conduct a Clinical Trial and How to Avoid Common Pitfalls."

It is with great pleasure that we welcome our new members to IPC. Members serve in an advisory capacity and lend their global expertise on psoriasis research, treatment and education to support all IPC programs, events and initiatives. IPC honors specific members with the title of “councilor” to acknowledge their special contributions to the field of dermatology with regard to psoriasis.

New IPC Councilors include:
- Hervé Bachelez, M.D., Ph.D., Hôpital Saint-Louis, Paris, France
- Ian Bruce, MB, BCh, BAO, M.D., FRCP, University of Manchester, Manchester, U.K.
- Errol Prens, M.D., Ph.D., University Medical Center Rotterdam, Rotterdam, The Netherlands

New IPC General Members include:
- Edgardo Chouela, M.D., Ph.D., Hospital General de Agudos Cosme Argerich, Buenos Aires, Argentina
- Lars Iversen, M.D., DMSc, Aarhus University Hospital, Aarhus, Denmark
- Ricardo Romiti, M.D., Ph.D., University of São Paulo, São Paulo, Brazil

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.

Sincerely,

Alan Menter, M.D., President
International Psoriasis Council
Using QOL measures in the clinic

Dr. Sam Salek, Welsh School of Pharmacy, Cardiff, U.K., provided examples for assessing the frequency of QOL in the clinic. In one study of 238 consults, 39% had no mention, 52% had one to two mentions, and 8% had three or more mentions of QOL. When examining 100 patients with inflammatory skin disease, QOL was discussed 74% of the time, 30% initiated by patients and 44% initiated by clinicians. In another study of 242 consults, DLQI influenced clinical decision making in 27 patients with a mean DLQI of 11. Although this is a small number of patients, QOL was severely affected in these patients. Professor Finlay recommends asking the routine question, “How much is your life being affected by your skin disease this week?” For critical decisions, he suggests the use of the DLQI or the rule of tens.

The greater patient

The concept of quality of life was originally thought to be exclusive to the patient, but recent reports indicate that skin diseases also impact family members and caregivers. Thus, it is not just the patient, but also “the greater patient” who may be affected. Dr. Mohammad Basra, Cardiff University School of Medicine, Cardiff, U.K., discussed the following ways in which family members can be impacted: 98% reported emotional distress, 54% were impacted by the burden of care, 48% reported negative impact on their social life, 42% reported an increase in housework, and 30% reported financial difficulty. Family quality of life can be measured with the family dermatology life quality index (FDLQI), a dermatology-specific measure, or psoriasis family index (PFI), a psoriasis-specific measure. QOL of family members is correlated with QOL in patients and is important in assessing the overall burden of skin disease.

References
1 Sampogna F. Comparison of QOL across different skin conditions. 6th EADV Spring Symposium.
2 Finlay A. Placing quality of life in dermatology care. 6th EADV Spring Symposium.
3 Salek S. Practical reality of using quality of life measures in routine clinics. 6th EADV Spring Symposium.
4 Basra MK. Does family quality of life correlate with the quality of life of dermatological patients? 6th EADV Spring Symposium.

COMMENTARY

Chronic skin diseases can impact patient quality of life as well as QOL of partners or family members. Measuring QOL is an important assessment in clinical decision-making, and discussing QOL is likely to enhance the quality of consultations. It may be appropriate to ask patients a simple question, such as “How much is your life being affected by your skin disease this week?”

Biologics: advantages and pitfalls

(Editor’s note: Professor Christopher Griffiths, University of Manchester, U.K., provided insight on efficacy and safety of biologics, and described how these agents have changed the landscape of psoriasis therapy during a plenary lecture at the EADV. The following is an excerpt from this lecture.)

Nine years ago, rotational therapy was required to temper the safety issues of the current systemic treatments. With the advent of the cytokine-blocking agents, specifically, the anti-tumor necrosis factor-alpha (anti-TNF-α) agents and the anti-p40 agents, rotational therapy is not frequently required and, in some patients, there is the ability to maintain remission. As a therapeutic class, there are varying levels of efficacy. With some biologics, the majority of patients respond. With others, such as the T-cell agents, only 25-30% of patients respond. For the non-responders, there is the need to switch from one biologic to another, and this occurs more frequently in psoriasis than in rheumatoid arthritis (RA). The phenotype of psoriasis may influence response, which may necessitate psoriasis classification by molecular phenotype.

Psoriasis co-morbidities continue to be an area of increased focus, and individuals with severe psoriasis are at greater risk of cardiovascular disease (CVD), myocardial infarction and even death. To better monitor these potential
Biologics have provided important advances in the treatment of psoriasis over the past decade. There is a great need for registries to study the safety of biologics over longer-term use in the psoriasis population.

With these new agents, appropriate safety data must be collected. It is possible that arthritis may not predict what occurs in psoriasis, as psoriasis patients may have higher rates of skin cancer and hepatotoxicity, compared to the RA population. Efalizumab has become a cautionary tale. There have been at least three cases of progressive multifocal leukoencephalopathy (PML) in patients treated with efalizumab for greater than three years, resulting in efalizumab being withdrawn from the market in 2009. PML is a rare, opportunistic infection that is usually fatal and occurs in those with suppressed immune systems, including as many as 5% of those with AIDS. It is imperative that safety data are collected over the long-term for these agents. Any psoriasis patient started on a biologic should be entered into a registry to study the safety profiles of these agents.

References
Griffiths C. Advantages and pitfalls on biologics in psoriasis. 6th EADV Spring Symposium.
The 69th Annual Meeting of the Society of Investigative Dermatology (SID) was held May 6-9, 2009, in Montreal, Canada. Following are meeting highlights in the areas of genetics, co-morbidities, immunology and therapeutics.

Genetics
Dr. James T. Elder, University of Michigan, Ann Arbor, USA, presented the Eugene Farber lecture and discussed the relationship between psoriasis (PsO) genetics and biology.1 In the Collaborative Association Study of Psoriasis (CASP), 450,000 single nucleotide polymorphisms (SNPs) were examined, with 18 hits identified and seven signals replicated at the level of genome-wide significance. Relevant genes included HLA-Cw6, interleukin (IL) IL12B, IL23R, IL23A, tumor necrosis factor-a-induced protein 3 (TNFAIP3), TNFAIP3 interacting protein 1 (TNIP1), and IL4/IL13, and their possible biological significance to PsO pathogenesis was presented. HLA-C presents peptides to CD8+ T cells that selectively infiltrate the epidermis. IL12B, IL23R and IL23A are integral to cytokines IL-12 and IL-23, with IL23B encoding the shared p40 subunit, IL23R encoding the IL-23 receptor, and IL23A encoding the p19 subunit of IL-23. IL4/IL13 are involved in the regulation of the Th1/Th2 balance, while TNFAIP3 and TNIP1 interact to inhibit NFκB activation. TNFAIP3 has been implicated in other autoimmune diseases, including lupus, diabetes, rheumatoid arthritis and celiac disease. There is an increased focus in understanding the genetics of psoriatic arthritis (PsA), with considerable overlap in the genetic signals discovered to date, including signals within the major histocompatibility complex (MHC), IL12B, IL13 and TNFAIP3, but the alleles may be distinct. A genome-wide association study of PsA is needed to identify PsA-specific loci and provide insight into other inflammatory diseases.

In the Utah Psoriasis Initiative (UPI) cohort, IL13 polymorphism was associated with PsO and protects from PsA.2 The minor alleles of IL13 SNPs were protective for risk of PsA when compared to patients with PsO only and controls. Smoking had a borderline association with increased time to developing PsA after developing PsO. Genes and environment may interact to influence development of PsA, and it will be important to elucidate biological pathways of IL-13 and tobacco use. In another study of the UPI, obesity in early adulthood increased the risk of developing PsA.3 Body mass index (BMI) was higher in those with PsA compared to PsO alone, and BMI at age 18 was predictive of developing PsA. Prevention and treatment of obesity may decrease the risk of PsA, particularly in patients with lower age of onset of PsO.

Co-morbidities
Co-morbidities, particularly cardiovascular disease (CVD), continue to be an area of intense research interest in PsO. A study using the General Practice Research Database (GPRD), examined 3,000 severe psoriasis patients compared to 14,000 controls.4 Patients with severe PsO had a significantly increased risk of mortality. After controlling for traditional cardiovascular risk factors including stroke, transient ischemic attack, diabetes, hypertension, hyperlipidemia, age, gender, BMI and smoking, PsO patients had an increased risk of cardiovascular death, and the risk was greatest for patients under 40. Another study examined risk and cause of death in a cohort of 1,376 patients who received PUVA treatment and were followed from 1976-2004.5 There were 617 deaths compared to 542 expected; and while deaths from CVD and cancer were as expected, there were more deaths due to liver disease than expected. In this cohort, only those patients with severe PsO and exceptional body surface area (BSA) had an increased risk of death compared to the general population, and the risk was greatest for causes of death other than CVD. It is possible that PUVA treatment, a strong inhibitor of inflammation, may alter the natural history of inflammation and cardiovascular risk in this population.

In another study, markers of CVD were examined in 77 PsO patients and 39 controls.6 In PsO patients, there was an increased incidence of smoking, systolic blood pressure and waist to hip ratio compared to controls. There were also increases in levels of inflammatory markers including myeloperoxidase, resistin, high sensitivity C-reactive protein (hsCRP), and s100 A8/A9, as well as CACS score (coronary artery calcification screening) and number of carotid plaques. Pro-inflammatory markers were positively correlated with each other and were negatively correlated with cardioprotective markers. Increased systemic inflammation may contribute to increased risk of CVD in patients with PsO.

Immunology
Researchers continue to study T-cell subsets and cytokine profiles to understand their significance in PsO. T cells differentiate into three major subsets, Th1, Th2 and Th17 (Figure 1, page 6). Th1 and Th17 subsets have been implicated in PsO pathogenesis (Figure 2, page 6). One study examined the cytokine profile of cells of the PsO plaque.7 There were increased numbers of CD4+ and CD8+ T cells expressing IL-17, IFN-γ or IL-22. Most T cells that produced IL-17, IFN-γ or IL-22, also produced IL-13 with increased time to developing PsA after developing PsO. Genes and environment may interact to influence development of PsA, and it will be important to elucidate biological pathways of IL-13 and tobacco use. In another study of the UPI, obesity in early adulthood increased the risk of developing PsA.3 Body mass index (BMI) was higher in those with PsA compared to PsO alone, and BMI at age 18 was predictive of developing PsA. Prevention and treatment of obesity may decrease the risk of PsA, particularly in patients with lower age of onset of PsO.

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TNF-α. The independent expression of IL-17 and IL-22 suggests that these cytokines, while induced by immune stimuli (IL-23), may have distinct roles in pathogenesis. Another study examined cytokine profiles in patients with atopic dermatitis (AD) or PsO. While levels of IFN-γ were increased in both AD and PsO, IL-13 and IL-22 were increased in AD, while IL-17 was increased in PsO. There were also distinct profiles of T-cell populations in these two diseases. Unique IL-22 CD4+ CD8+ subsets were abundant in AD lesions, and IL-22+CD8+ T cells correlated with disease severity. The functional specificity of T cells may drive distinct features of epidermal pathology and inflammatory skin diseases.

The roles of cytokines and other molecules are being studied in PsO. IL-1 cytokine family members IL-1B, IL-1RA, IL-1F5, IL-1F8 and IL-1F9 are increased in PsO lesions, while IL-1F7 is decreased. Some family members are induced by TNF-α, while others are induced by IL-17A and augmented by IL-22. IL-1F7 is decreased after exposure to IL-1a, IL-17 and IL-22. The interaction and roles of these family members remain to be elucidated. IL-17C is a pro-inflammatory cytokine elevated in PsO lesions. IL-17C is induced by IL-1a, IL-17 and IL-22, and IL-17C induces DEF84, which encodes human β-defensin, an antimicrobial peptide. The role of LL-37, an antimicrobial peptide and the predominant form of cathelicidin in PsO, continues to be examined. LL-37 induced Toll-like receptor 9 (TLR9) expression and IL-23 expression in keratinocytes, suggesting a role for this molecule in PsO pathogenesis. Understanding the molecular profile of PsO lesions will improve our understanding of PsO immunology.

**Therapeutics**

Researchers continue to be interested in the effects of various therapies on specific subsets of immune cells. In a Phase III trial (ACCEPt) comparing ustekinumab and etanercept treatment regimens, tissue biopsies and blood samples were taken. Only ustekinumab data were presented. At 12 weeks, the epidermis was thinner and resident T cells were decreased to levels found in normal skin. Inflammatory dendritic cells, TIP-DC, and mature activated dendritic cells (DC) were decreased, while resident DCs, including Langerhans cells, were unaffected. There was also a decrease in gene expression of iNOS, P40, p19, INF-γ, IL-17, IL-22, IL-20, LCN2, CCL20, DEF84 and MX1, many of which are part of the Th17 inflammatory pathway. The reduction of immune cells in skin appeared to be linked to the resolution of inflammation, suggesting the cutaneous immune system remains intact. When examining the effect of ustekinumab on circulating lymphocytes, there was no reduction in number of cells or change in mean percentage of CD4 or CD8 cells. There was minimal change in regulatory T cells and no apparent effects on NKT cells. Ustekinumab did not impact the ability of T cells to be activated or produce cytokines in response to stimulation, suggesting there is no effect on functional activation of T cells. In another study utilizing samples from the ACCEPt trial, peripheral blood mononucleocytes (PBMCs) were isolated. There were no consistent serum protein changes associated with treatment response within or across treatment groups. At 12 weeks, the median number of circulating lymphocytes remained unchanged, and there was no significant effect on percentage of PBMC subsets or ex vivo stimulation of PBMCs, suggesting a minimal impact of ustekinumab or etanercept on the systemic immune system. These studies need to be repeated over longer time periods to better understand the effects of treatment on the immune system.

Cytokine profiles after treatment were also examined in response to TNF-inhibitors and IL-4 therapy. In patients treated with etanercept, IL-20 related cytokines including IL-19, IL-20, IL-22, IL-24 and STAT-3 were decreased. In another study, the antimicrobial peptide LL-37 and β-defensins, HBD2 and HBD3, were decreased in skin biopsies after etanercept treatment. Treatment with...
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FACULTY DISCLOSURES
Professor Dauden has served as a consultant, investigator, speaker or advisory board member for Abbott, Astellas, Biogen, Galderma, GlaxoSmithKline, Janssen-Cilag, Leo Pharma, Merck Serono, Novartis, Schering-Plough, Wyeth Pharmaceuticals, and 3M.

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This activity has been planned and implemented in accordance with IPC's program planning policy.

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infliximab decreased CCR6+ and CCR6+TNFα cells.\textsuperscript{16}
Another study examined the effects of IL-4 treatment.\textsuperscript{17}
DCs were the primary target of IL-4 therapy, inducing a stable DC phenotype incapable of IL-23 production but able to secrete IL-12. IL-4 treatment suppressed Th17 cells but not Th1 cells, suggesting IL-4 could attenuate the inflammatory autoimmune response while preserving control against intracellular bacteria and viruses.

Improvement in PsO after tonsillectomy was first reported in the 1960s. Recently, the impact of tonsillectomy on 15 psoriasis patients who underwent tonsillectomy was examined compared to 14 controls who did not.\textsuperscript{18} After two months, those in the tonsillectomy group reported a 39% reduction in PASI while the controls remained unchanged. This remained consistent for 12 months. A majority of those who underwent tonsillectomy also reported improvement in QOL. There was a decrease in IFN-γ producing cross-reactive CD8+ T cells and IL-17 producing cross-reactive CD8+ T-cells in the tonsillectomy group compared to the controls, through 12 months. Tonsillectomy has a temporary beneficial effect on psoriasis, consistent with the idea that tonsils are significant breeding stations for cross-reactive T cells that contribute to chronic psoriasis. Additional studies are needed.

COMMENTARY
The SID Annual Meeting produced robust data on the immunobiology of psoriasis. Researchers continue to focus on cytokines and immune cells driving psoriasis development, as well as the effects of treatment on inflammatory and resident immune cells. Co-morbidities, such as obesity and cardiovascular disease, continue to be important aspects of psoriasis. Counseling psoriasis patients to lead healthy lifestyles and reduce modifiable risk factors for cardiovascular disease is appropriate.

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The International Psoriasis Council is a global nonprofit organization dedicated to advancing psoriasis research and treatment by providing a forum for education, collaboration and innovation among physicians, researchers and other professionals interested in psoriasis.