Focus on Asia-Pacific

As a truly global organization, the International Psoriasis Council (IPC) routinely interacts with healthcare professionals dedicated to the management of psoriasis in different regions of the world. In this and upcoming issues of the IPC Psoriasis Review we deliver a focus on selected regions throughout the world with a view to sharing insights, appreciation and learning. At a 2009 Psoriasis Symposium held in Dallas, Texas, IPC hosted representatives from several countries in the Asia-Pacific region, allowing for the international psoriasis community to discuss the similarities and differences in the management of psoriasis in the varied regions.

Figure 1 - University of Philippines-PGH Psoriasis Club celebrating the World Psoriasis Day. Dr. Claire Habito (1st from right, 3rd-year resident), Dr. Lorna Frez (2nd from right, adviser), and Dr. Eillen Visconde (1st from left, 1st-year resident)

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**Get Involved**

**Call for Articles**

The IPC Psoriasis Review is interested in hearing about the management of psoriasis, its treatment, epidemiology or research, in your institution, country or region.

Please review the published articles from the last two issues of IPC Psoriasis Review (available at www.psoriasiscouncil.org) and consider developing your own contribution which we will look forward to.

In preparing your article, please be as specific as possible and use references where applicable.

Send completed article to paul.tebbey@psoriasiscouncil.org for consideration.

**Pediatric Psoriasis Epidemiology Study**

The IPC is currently recruiting additional non-U.S. based sites to participate in this study.

We are looking to enroll patients with psoriatic plaques for more than 6 months, atopic dermatitis patients or controls, age 5-17, without other systemic diseases.

Study sites are required to receive approval from IRB or University Ethics Committee and enroll a minimum of 30 patients with mild, moderate or severe psoriasis. Financial support for study costs is available.

For more information, contact christy.langan@psoriasiscouncil.org.

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A LETTER FROM THE PRESIDENT

Dear Colleagues,

On behalf of the International Psoriasis Council (IPC) and this issue’s editor Professor Lars Iversen, I am delighted to introduce the May 2010 edition of our IPC Psoriasis Review.

Published three 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 a review of the latest scientific advances in psoriasis as presented at the 70th Annual Meeting of the Society of Investigative Dermatology (SID) held in Atlanta (May 3rd – 5th, 2010). In addition, we embrace the global psoriasis community by introducing the clinical practices utilized in the management of psoriasis in the Asia-Pacific region with reports from Australia, Japan and the Philippines. This regional specific focus represents a continuation of the series that highlights the unique approaches and challenges to managing psoriasis in populations around the world.

It is with great pleasure that we welcome two new IPC board members; Alexa Boer Kimball, Director of the Clinical Unit for Research Trials in Skin, Harvard Medical School, Vice-Chair of the Department of Dermatology at Massachusetts General Hospital and Associate Professor at Harvard Medical School; and Hervé Bachelez, Professor at the Department of Dermatology of the Saint-Louis University Hospital in Paris, France. The addition of new board members represents a much needed expansion of IPC that is necessary to continue and enhance our ambitious agenda to profoundly impact the understanding, treatment, and management of psoriasis around the world.

To that end, in 2010, IPC continues to enact psoriasis-focused programs in different regions that will advance psoriasis education, research, and treatment. Such programs have comprised large educational symposia with participants from across the globe; high-level round-table discussions with key opinion leaders that typically have resulted in peer-reviewed publications; and a pilot program to reach out to the future leaders in psoriasis. This year, for the first time, we are planning a Think Tank “Toward Transforming Psoriasis” which will sequester the best psoriasis minds to identify and develop the key needs for psoriasis research, treatment and education that we hope will set the agenda for future interest and investment. Beyond this, IPC continues to provide opportunities for professional collaboration through its website and through additional international, national, and regional programming. In addition, through its global forum at www.psoriasiscouncil.org, IPC continues to expand its reach by adding to its global database and enhancing the services delivered to those medical professional involved in the management of psoriasis around the world.

We hope this newsletter is informative and that the knowledge, experience and insights of our faculty are valuable to you in furthering your understanding and treatment of this complex disorder. We thank all of you who have contributed as well as our sponsors, without whom none of this would be achieved. We wish you all a healthy and happy remainder of 2010.

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

Sincerely,

Alan Menter, M.D., President
International Psoriasis Council
Psoriasis is relatively common in the Philippines. In a five year (2004-2008) review of cases seen at our University of the Philippines-Philippine General Hospital (UP-PGH) Dermatology clinic, the prevalence is about 2.4 percent. On the average, 10 new cases of psoriasis are seen at the clinic each day. It has consistently ranked among the top 20 dermatologic cases seen every year. About 70 percent of them are mild (BSA < 5 percent) and 30 percent are either moderate or severe (BSA > 5-10 percent). In some cases, severity is induced by a secondary allergic contact dermatitis due to an applied concoction by “faith or quack” healers or as a rebound from oral corticosteroids taken by the patients themselves thinking they are having an allergic rash or given to them by the general practitioners.

In the Philippines, dermatologists see most of the psoriatic patients. Some would seek consultations with the general practitioners for financial reasons or because of non-availability of a specialist. However, referral to a dermatologist is usually done in refractory (not responding well to topical steroids) or severe cases. Skin biopsy is usually obtained for diagnosis and or when systemic therapy is contemplated.

Treatment of psoriasis in the Philippines is always a challenge to both the dermatologists and the general practitioners. Topical corticosteroid and emollients are the mainstay of therapy for all cases. Many patients remain in this form of therapy for several years. Topical tar used as shampoos and soaps are favorite add-ons. Clobetasol shampoo, calcineurin inhibitors and vitamin D analogues are other topical preparations commonly used. Systemic therapy is usually added when dealing with moderate to severe conditions. Dermatologists seldom use oral corticosteroid. Among the most commonly used drugs in their order of preference are:

1. Methotrexate (MTX) 15mg in three (3) divided doses at 12-hour intervals given weekly. Liver function test is determined before the start of therapy and every 1-2 months thereafter. Liver biopsy is usually not done in our country. Treatment is usually stopped if a significant rise of the liver enzyme. A cumulative dose of 1.5 gram methotrexate is the upper total limit due to the fear of liver toxicity. MTX is commonly started when psoriatic arthritis develops. The patients usually consult a rheumatologist when their joints are involved.

2. Acitretin is administered when MTX cannot be given or as a rotational alternative. However, this drug is regulated and requires a special prescription available only to dermatologists. This limits its use to a certain extent even to specialists. Fear of teratogenic side-effects is another consideration. The drug is therefore only given to patients without child-bearing potential. The use of contraception is not approved in our predominantly Catholic population.

3. The use of Cyclosporine (CyA) is quite expensive in our country although a lot of dermatologists are reluctant to its use because of the potent immunosuppression and the risk of side effects on the kidney.

4. Phototherapy is available only in some dermatology centers and a few private clinics. PUVA is seldom used nowadays. Narrowband UVB is given three times a week for 16-20 sessions ($10-50 per session). Most patients find it tedious and costly.

5. Biologics are a very expensive medication especially because only a few patients have medical insurance. The government insurance covers only a small amount depending on the monthly salaries and contributions. Also, both private and public health insurances pay only for in-patient medications and services. Thus, most patients who are put on this therapy finish only the first few doses or are given a reduced amount, usually half the recommended dose.

In our country, the Philippine Dermatological Society (together with its 11 training institutions) regularly celebrates the World Psoriasis Day with a fun walk, public information activities, and health foray (Figure 1 on
Dermatologists in major cities, like Baguio, Bicol, Pangasinan, Cebu, Cagayan de Oro, and Davao, organize radio and television education campaigns especially emphasizing on lay awareness that psoriasis is not contagious. Last year, the highlight was the “Hug Me” campaign, where we invited celebrities including the Health Secretary, movie actors, and actresses who were photographed holding or hugging patients. At our UP-PGH Dermatology clinic, our psoriatic patients have a support group that is very active and strong. At present there are more than fifty members. They elect their set of officers and meet every 1st and 3rd Monday of the month. Livelihood projects such as candle-making, flower arrangements are taught to augment income for some patients. Lectures about their disease, psycho-social development, and self-empowerment are regular topics of discussion. Some speakers are dermatologists, psychologists, and even testimonies of co-patients. Those in the managerial positions hire their co-patients when qualified. Some do household jobs for co-patients or doctors for a fee. Everyone is able to wear clothes showing as much skin as possible without fear of humiliation.

The challenge of being able to give an effective, safe, systemically acting, sustainable, and cheap drug for our patients with psoriasis continues to be a dream for us. The increased understanding of the immune pathogenesis of psoriasis has led to the advent of T-cell modulating agents and TNF-Alpha antagonists. It may be the most exciting form of therapy in developed countries, but unfortunately, these drugs are unreachable to most of our patients here in the Philippines.

References
2. Interview on the commonly used systemic medications for psoriasis to ten practicing dermatologists.
3. University of the Philippine-Philippine General Hospital Psoriasis Club.

Figure 2 - University of Philippines-PGH Psoriasis Club celebrating World Psoriasis Day. Dr. Claire Habito (1st from right, 3rd-year resident), Dr. Lorna Frez (2nd from right, adviser), and Dr. Eillen Visconde, 1st from left, 1st-year resident)
Australia is the world’s sixth largest country in terms of total area and the world’s smallest continent. The population is 22 million, with approximately 60 percent concentrated in and around the mainland State capitals of Melbourne, Sydney, Brisbane, Perth and Adelaide. We are lucky in Australia, in that citizens and permanent residents of the country have access to the public health system, known as Medicare. Through the Pharmaceutical Benefits Scheme (PBS), Medicare at least partially funds the treatment of most medications for psoriasis in Australia, in patients who meet qualification criteria. For topical therapies, most patients will have an out of pocket cost, but the bulk of the expense for these drugs is paid for by the government. Coal tar containing preparations, topical steroids (except clobetasol propionate), calcipitriol, dithranol and pimecrolimus are all available through the PBS. Tazarotene, tacrolimus, and clobetasol are all available in Australia, but must be paid for in total by the patient. The main challenge in using topical therapies to treat psoriasis in Australia, is, that in order to obtain appropriate quantities of medication for patients, the dermatologist must make a phone call to the PBS with each prescription to get approval and funding to give the patient enough quantities of medication. Without such a phone call, patients can only access, for example, 15g of mometasone furoate, or betamethasone dipropionate with one repeat on the PBS. This is obviously not enough to most patients! So, in Australia, a Dermatologist will make multiple phone calls daily to the PBS to ensure that their patients have adequate treatment available. This is very time consuming during a busy day of consulting, but a necessary evil.

All of the main systemic agents that we may use to treat moderate-severe psoriasis are available on the PBS in Australia. Methotrexate, cyclosporin and acitretin have all been available in Australia for many years and are used fairly widely. Phototherapy is also covered by Medicare, so that most patients who attend for this treatment do not pay any out of pocket cost for their treatment. One of the main issues that we have in Australia is the very high rate of non-melanoma skin cancer and melanoma. We live in a sun-drenched country under a thin ozone layer and Australia and New Zealand have the highest melanoma incidence rates in the world. The high incidence rates are attributed to the high proportions of the population in both countries who are of Anglo-Celtic descent, and who are inevitably exposed to high levels of solar radiation from earliest childhood. While melanoma is comparatively infrequent globally, it is an important contributor to the burden of cancer in Australia and New Zealand. Together, Australia and New Zealand contributed 6.4 percent of the cases and 3.2 percent of the deaths to the estimated global totals of 160,000 newly diagnosed melanomas and 41,000 deaths from melanoma in the year 2002. Because cancer registries do not routinely report skin cancers apart from melanoma, exact incidence rates are not known. The best available Australia-wide data have come from four national surveys in 1985, 1990, 1995, and 2002. These surveys across random households show that the incidence rates of skin cancer in Australia are the highest in the world. In 2002, it was estimated that 256,000 people were treated for basal cell carcinoma (BCC), and 118,000 for squamous cell carcinoma (SCC), and age-standardized incidence rates were estimated to be 884 per 100,000 for BCC, and 387 per 100,000 for SCC. This high rate of non-melanoma skin cancer and melanoma is something that the Australian dermatologist must consider every day in treating patients with moderate-severe psoriasis, as methotrexate, cyclosporine, phototherapy, and potentially biologics may contribute to the development or
recurrence of these tumors. On occasions, we will use acitretin to diminish the risk of further SCCs in biologics patients who have developed several of these tumors after long periods of treatment with phototherapy and systemic treatments for psoriasis, who then go on to develop SCCs while on e.g. TNF-α inhibitors. However, acitretin in this instance cannot be subsidized by the PBS (see below). Certainly, we use phototherapy in appropriate patients in Australia, but its use can frequently be limited by past history on skin malignancy as well as geographic constraints. Because Australia is such a vast country, and there are very few phototherapy facilities outside the main centers, many patients live too far away to access phototherapy as a treatment.

Infliximab, adalimumab, etanercept and ustekinumab (from March 1, 2010) are all subsidized by the Pharmaceutical Benefits Scheme for the treatment of severe psoriasis in patients who meet eligibility criteria. Unfortunately, these criteria do not contain any quality of life measures (in comparison with e.g. the United Kingdom). To qualify for one of the above biologic agents for the treatment of psoriasis in Australia, individuals must meet the following criteria:

1. Must be at least 18 years of age
2. Chronic plaque psoriasis subtype (i.e. not pustular disease)
3. They must receive the biologic as monotherapy (but may receive concomitant methotrexate)
4. At least six months from the time of diagnosis of severe body plaque psoriasis with a baseline PASI of at least 15, or
5. Severe plaque psoriasis of the palm, sole or face for at least six months
6. Patients must also have failed to achieve an adequate response or have severe toxicities, or be contraindicated to at least three out of four of the following therapies for a minimum of six weeks at the following minimum dosing regimes:
   a) Phototherapy (PUVA or narrow-band UVB) three times weekly
   b) Methotrexate 10mg weekly
   c) Cyclosporin 2mg/kg/day
   d) Acitretin 0.4mg/kg/day

Overall, in Australia we are blessed with access to many very effective treatments with which to benefit our patients with moderate to severe psoriasis. However, the cost involved and the strict nature of the criteria to obtain biologic agents via the PBS in Australia means that many who would certainly benefit from their use, must jump through metaphorical “hoops” over long periods of time before they qualify for treatment with these agents.

References

A Focus on Asia-Pacific

Japan - The Epidemiology and Current Treatment of Psoriasis

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The incidence of psoriasis in Japan is relatively low. The estimated prevalence rate is around 0.05～0.1 percent, which is much lower than Korea or China, even though the genetic background is similar in these countries ethnologically. The total number of patients is estimated at approximately 50,000 -100,000, and the severe type of psoriasis is almost 1/10 of these patients.

Two biologics, adalimumab and infliximab, are to be approved early in 2010. Ustekinumab is preparing for the submission. Under these circumstances mentioned above, I think three or four biologics may be enough for the treatment of severe psoriasis in Japan.

Currently, we mainly prescribe cyclosporine for severe psoriasis patients. Curiously and unfortunately, methotrexate, which is standard medication for psoriasis worldwide, is not approved in Japan. So, we have little experience with methotrexate for psoriasis except for a few cases of off-label use. Regarding retinoids, we can use etretinate whereas acitretin or topical retinoids are not available. Phototherapy is also frequently adopted for the treatment of moderate to severe psoriasis. We used to apply PUVA therapy, but recently narrowband UVB therapy has become more common. For topical therapy, we have three kinds of high concentrated vitamin D3 analogues, maxacalcitol, calcipotriol and tacalcitol. Maxacalcitol is most commonly used because it is less irritative.

Many Japanese dermatologists have huge expectations for the new biologics as life changing medicines which will improve the quality of life of patients with severe psoriasis. However, we have to be careful about side effects such as infections, among which tuberculosis should be especially considered because it is still fairly common in Japan.
Society of Investigative Dermatology

Annual Meeting Highlights

The 70th Annual Meeting of the Society of Investigative Dermatology was held May 5-8, 2010, in Atlanta, Georgia. The following are selected meeting highlights relevant to new developments in psoriasis research.

Professor James G. Krueger from Rockefeller University, New York, delivered the Eugene M. Farber lecture on the topic of “Psoriasis: The Path of Translational Medicine.” Professor Krueger explained that the evolution in the understanding of psoriasis pathogenesis began with a logical focus on the keratinocyte and the up-regulation of genes such as KRT16 and S100A12 as the first molecular signature of disease. By the mid 1990’s, interferon-γ secreting type 1 T-cells were implicated in disease pathogenesis as a consequence of the effectiveness of developmental therapies that targeted IL-2. The continued clinical assessment of a series of T-cell-modulating research strategies that targeted IL-11, IL-4 and IL-10, led to a focus on the IL-12 cytokine which was found to be up-regulated in psoriatic lesions. Together with positive results from therapeutic strategies on CTLA4-Ig and alefacept, both of which impact T-cell signaling, appropriate emphasis was then placed upon the T-cell as being central to the disease state.

However, in parallel, it was also noticed that therapeutic strategies targeting TNFα were having a significant impact on psoriasis. This shifted focus to the innate part of the immune system since TNFα was classically understood to stimulate neutrophil activation and tissue destruction through cytokines such as IL-1β and IL-8. Such results confused the understanding of the pathogenic mechanisms that lead to psoriasis. However, genomic analysis would highlight the path forward. With improving genetic techniques, over 4,000 genes were noticed to be expressed differently in psoriatic lesional skin versus non-lesional skin. These genes included the cellular signaling molecules such as S100A12 and S100A7 but also included the gene for nitric oxide synthase, an enzyme that catalyzes the production of nitric oxide, an important cellular signaling molecule, having a vital role in many biological processes. Using antibodies to stain for iNOS and TNFα in psoriatic skin, it was noticed that the cells predominantly stained had dendritic-cell (DC) like qualities (Figures 3 and 4). Acknowledgement that the role of DCs to act as messengers between the innate and adaptive immune systems thus facilitated a convergent understanding of the previously disparate observations. Thus, there was now an explanation for the effects observed from the T-cell-targeted therapeutics and those that targeted TNFα and CD11a, the alpha 4 integrin that is involved in establishing the immune synapse.
The DCs accumulating in the skin of psoriasis were a specific type, named TIP-DCs, and they are now implicated as a major player in the onset of psoriasis. Up-regulation of IL-12p40 in the TIP DCs of psoriatic skin leads to the secretion of the cytokine, IL-23, which itself activates a subset of T-cells known as Th17 cells that secret IL-17. The subsequent observation that keratinocytes display receptors for IL-17 seemingly completes the circle of the pathogenic cycle in psoriasis. In support, therapies that target the IL-23 signaling pathway have demonstrated a remarkable clinical impact on psoriasis.

Nevertheless, the picture of psoriasis pathogenesis remains incomplete. For example, much still needs to be understood regarding the perpetuation of psoriasis and its antigenic triggers. To this end, focus has recently shifted toward understanding the TNFα interaction with IL-23 and to explaining the potent effects of TNF-targeting agents in the clinic. The working hypothesis is that TNFα synergizes with IL-17 at the keratinocyte level. Over 160 genes have been identified as being up-regulated as a consequence of such synergy and invariably these genes tend to correlate with those over-expressed in the molecular signature of psoriasis, termed the “psoriasis transcriptome.” Two of those genes are CCL19 and CCR7. Mature DCs express both CCL19 and CCR7 whereas T-cells tend to express only CCR7. It is theorized that to propagate psoriasis, CCL19 expression by DCs leads to chemoattraction of CCR7+ T-cells toward creating self-sustaining lymphoid tissue in the psoriasis lesions.

While much has been defined on the road of translational medicine over the past two decades, further discoveries are needed. The goal remains to develop even more selective agents to target the root cause of the disease as well as to clarify the subtle genetic patterns that are associated with the condition. In a follow up presentation later in the meeting, Professor Krueger delivered some recent results relating to the gene expression patterns in Psoriasis. The data derived from the ACCEPT comparator trial (abstract #298) that involved etanercept and ustekinumab, therapies targeted at TNFα and IL-12p40, respectively. Despite the clinical evidence that both of these therapies are remarkably effective in reversing the symptoms of psoriasis, there are approximately 500 genes that are modulated by the psoriatic state but which remain immune to change using these potent therapies. Examples of genes not affected by these treatments include DEFB4, S100A7, CCL18 and SERPINB3. Additionally, the cell surface co-receptors CD3δ and CD8 as well as the gene encoding Fatty Acid Desaturase (FADS2) remained within 80 percent of pre-treatment levels, and thus essentially refractory to treatment. It is theorized that these genes may represent a molecular remnant of the psoriasis signature indicating a potential for disease relapse. Strategies that target these genes may help in defining a permanent modification of the natural history of the disease.

**New Therapeutics in Development for Psoriasis**

New entities with novel mechanisms of action are in clinical development for mild to moderate psoriasis. Dr. Callis-Duffin presented the results (abstract #261) for INCB018424 in a 200 patient phase 2b trial. INCB018424 is a selective janus kinase 1 and 2 (JAK1/2) inhibitor that targets the signaling events in Th1 and Th17 cells. In so doing, the agent is able to potently inhibit cytokine-induced JAK signaling and function in both lymphocytes and keratinocytes. In the clinical trial, the topical application of INCB018424 cream resulted in significant improvement in the psoriatic lesions of treated patients at day 28. Overall, the total lesional scores decreased two-fold versus vehicle with the effects seen as early as two weeks post initial treatment and extending through the 12-week study. Immuno-histochemical staining and microarray gene analysis data confirmed the improvement in skin histology and the reduction in the molecular signature that characterizes psoriasis.

Another novel therapeutic, AMG827, is in development for moderate to severe psoriasis. AMG827 (abstract #273) is an anti-IL-17 receptor antagonist that blocks the IL-17 receptor leading to a rapid reversal of gene
expression and histopathology abnormalities in the skin of psoriasis patients. The therapy was studied in a trial involving 10 patients (two placebo) who were treated IV with 700 mg. Effects were seen as early as day 14 and by day 42, 7 out of 8 treated patients had reached PASI 75. Histologically, AMG827 led to improvements in skin thickness, K16 mRNA levels, Ki67 cell counts and reductions in T-cell and DC-cell surface markers (CD3, CD11a, CD-LAMP). Microarray analysis revealed an impact of the therapy on the molecular signature of psoriasis with the majority of genes reducing their expression level at week 2 and 6 post treatment. Interestingly, approximately 500 genes remained refractory to treatment in this analysis, similar to that observed in the ACCEPT clinical trial, described above.

Toward identifying potential new therapeutic agents, Dr. T. Labuda and colleagues have developed an animal model of psoriasis that is based upon multiple injections of the cytokine IL-23. The injections were given every 2nd day for 10 days intradermally into the right ear of the mice. Indeed, the data show that the injections resulted in a sustainable psoriasis like phenotype that was manifest in all of the measures expected for the disease state; increased ear thickness, Ki-67+ cells as well as expression of the genes that make up the molecular signature of psoriasis (STAT3, IL-22, IL-17, IL-6 and IL-8). Systemic administration of cyclosporine A or dexamethazone significantly reduced the IL-23-induced skin inflammation whereas methylcellulose, used as a control, had no impact.

And finally, just when you thought it was safe to venture back into the cytokine milieu, up pops yet another candidate new therapeutic agents, Dr. T. Labuda and colleagues have developed an animal model of psoriasis that is based upon multiple injections of the cytokine IL-23. The injections were given every 2nd day for 10 days intradermally into the right ear of the mice. Indeed, the data show that the injections resulted in a sustainable psoriasis like phenotype that was manifest in all of the measures expected for the disease state; increased ear thickness, Ki-67+ cells as well as expression of the genes that make up the molecular signature of psoriasis (STAT3, IL-22, IL-17, IL-6 and IL-8). Systemic administration of cyclosporine A or dexamethazone significantly reduced the IL-23-induced skin inflammation whereas methylcellulose, used as a control, had no impact.

Psoriasis is increasingly associated with a variety of co-morbidities, and now, in a paper presented by Dr. Abuabara and colleagues (abstract #378), the cause-specific mortality of patients with severe psoriasis has been measured. The authors performed an analysis of the UK’s General Practice Research Database that contains over nine million patient records. The results indicated that indeed severe psoriasis is associated with an increased risk of mortality from a variety of causes, most notably, cardiovascular disease, infection and malignancies. While the authors point out that additional studies are necessary to determine the degree to which the psoriasis disease state impacts such mortality others are already attempting to define the underlying mechanisms in animal models of disease. In trying to comprehend the molecular mechanisms for the promotion of atherosclerosis in psoriasis patients, Dr. Tom McCormick (abstract #701) described the spontaneous development of atherosclerotic plaques in the, KC-Tie2 murine model of psoriasis. Approximately 40 percent of these mice developed aortic atherosclerotic plaques by 12 months of age. The presence of atherosclerotic plaques was preceded by changes in the pro-inflammatory milieu that included increases in IL-17, IL-12, TNFα as well as increases in C-reactive protein (CRP). The research also noticed an increase in CD11b+Ly6Chi monocytes in the peripheral blood, bone marrow and spleen; of interest because previous reports linking these cell types to the initiation of the atherosclerotic plaque. The work contributes to the knowledge regarding the propagation of the psoriasis state since the Tie2 phenotype is restricted to keratinocytes in the transgenic model. Thus, cardiovascular related co-morbidities related to psoriasis may be driven by skin inflammation.
**Effector Cells in the Psoriatic Plaque**

Toward defining the cellular content of the psoriatic plaque, Dr. A.T. Bruce and colleagues (abstract #717) isolated cells directly from the psoriatic lesion. Typically, cells are isolated and then expanded in cell culture prior to analysis. In this case, collagenase digestion was applied to the psoriatic plaques prior to staining of the resultant single cell suspensions for intra and cell surface proteins by flow cytometry. The results revealed that psoriatic skin is enriched in IL-17 and IL-22 producing CD4 and CD8 T-cells. However, those T-cells that expressed IL-17 then did not concomitantly tend to express IL-22 revealing a distinct phenotypic identity of the different cell types. Defining the exact make-up of the effector cells in the psoriatic plaque will contribute to better mechanistic understanding and thus to more selective therapeutics. Dr. I. Campbell presented data (abstract #691) which contributes to the elucidation of the chemokine requirements for epidermal T-cell trafficking. It has been reported that CD4 T-cells express the chemokine receptors, CCR4, CCR6 and CCR10 on their cell surfaces but the relative function of each receptor is less well understood. Using a unique model system involving the MHCII-peptide tetramer to stain antigen-specific CD4 T-cells in transgenic knock-out mice, it was determined that CCR4 deficiency caused a 20-fold reduction in Ag-specific CD4 T-cells at the lesional skin. In contrast, neither CCR6 nor CCR10 knock-out mice displayed a similar impact. Thus, while CCR4 is apparently responsible for the accumulation of CD4 T-cells in the psoriatic skin, the role of other chemokine receptors is less clear.

On the potential source for autoreactive T-cells that lead to psoriasis, Dr. M. Lichtman and colleagues (abstract #61) have identified that cutaneous regulatory T-cells can produce IL-17. IL-17 producing Th17 cells have been implicated in a variety of autoimmune conditions, including psoriasis. A subset of skin residing FoxP3+ T regulatory cells were identified as being able to express IL-17 even without additional stimulation (2.4 percent). However, expansion of the skin T-cell population with IL-2 and IL-15 resulted in an expansion of those FoxP3+ T-cells producing IL-17 to 8.4 percent. Additionally, those FoxP3+ T-cells that produced IL-17 were also found to express TNFα. Thus, T regulatory cells possess the capacity to be converted into potentially autoreactive IL-17-producing Th17 cells which may contribute to the inflammatory state leading to psoriasis. These cells were determined to be polyclonal since they had various Vβ T-cell receptor components. Moreover, they expressed CCR4 but not CCR7, and thereby potentially align with the report described above by Dr. Campbell (abstract # 691).

Collectively, the body of innovative science presented at the congress signals that we are on a path to a better understanding of the disease-causing mechanisms that underpin psoriasis and, as a consequence, more effective and selective therapeutic agents for the entire population of afflicted patients.
ACKNOWLEDGMENTS

IPC gratefully acknowledges our co-editor Professor Lars Iversen, Department of Dermatology, Aarhus University Hospital, Denmark, for his contribution to the May 2010 IPC Psoriasis Review.

FACULTY DISCLOSURES

Professor Iversen: Speaker for MSD, Pfizer, Abbott and LEO Pharma. Consulting or serving on expert/advisory boards with Pfizer, Abbott and MSD; and receiving research and educational grant from Pfizer and MSD.

CORPORATE SUPPORT

IPC gratefully acknowledges Amgen, Abbott and Medicis for their generous support of our organization and the specific grants that they provided for the IPC Psoriasis Review. This publication has been developed in accordance with IPC’s program planning policy. Our sponsors have no control over the content or the articles selected for review.

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