

IPC PSORIASIS REVIEW

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CME OVERVIEW

The *IPC Psoriasis Review* is a continuing medical education activity for U.S. dermatologists. The goal of this publication is to provide practicing dermatologists with the International Psoriasis Council's perspective on the most clinically relevant psoriasis publications of the past six to twelve months. Readers may use the newly acquired information in this activity to enhance their own professional development in a way that will ultimately improve patient outcomes. The information presented in this activity is not meant to serve as a guideline for patient management. Primary references and full prescribing information should be consulted.

EDUCATIONAL OBJECTIVES

Upon completion of the activity, the participants should be able to:

- Identify which psoriasis publications from the past 12 months have been the most significant toward the advancement of psoriasis research, diagnosis, and treatment.
- Explain the impact of each publication on existing knowledge and understanding of psoriasis.
- Describe how clinical and research discoveries may impact clinical practice.

CME CREDIT

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 the A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, and the International Psoriasis Council. The A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, is accredited by the ACCME to provide continuing medical education for physicians.

The A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, designates this educational activity for a maximum of 0.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

CO-EDITORS

Jean-Paul Ortonne is Professor of Dermatology and Chairman of the Department of Dermatology of the University of Nice-Sophia Antipolis.

John R. Sullivan is the Deputy Medical Director, Department of Dermatology of the Liverpool Hospital in Sydney, Australia.

DISCLOSURE

Professor Ortonne receives consulting fees from Wyeth, Schering-Plough, Centocor, Galderma and Abbott for speaking and consulting board membership.

Dr. Sullivan receives honoraria from Biogen Idec for speaking.

Conflicts of interest were resolved through a board review process and a CME review of the content.

The reviews in the CME activity include discussion of investigational and/or unlabeled uses of the following drugs: Alefacept and Efalizumab. Please refer to the full prescribing information for each drug discussed in this newsletter for FDA-approved dosing, indications and warnings.

CME INSTRUCTIONS

To receive CME credit, read the publication, complete the Self-Assessment Quiz (achieving 80% correct) and submit with complete Registration-Evaluation Form to CME provider.

Release Date:	September 7, 2005
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Estimated time to complete this activity:	30 Minutes
Medium:	Printed material

TNF- α is crucial for the development of psoriasis

Many psoriasis mouse models using SCID mice have been described. These models necessitate the injection of exogenous cells or factors to induce a psoriatic phenotype in a human asymptomatic pre-psoriasis skin graft. However, they do not allow the analysis of early mechanisms leading to the psoriatic phenotype. Indeed, SCID mice lack T and B-cells but show mature NK cells with the potential to reject xenogeneic tissue.

A newly developed "spontaneous psoriasis" mouse model (AGR 129 mouse) does, in fact, show immature NK cells with severely impaired cytotoxic activity due to a deficiency in IFN receptors. In addition, this mouse lacks T and B-cells and thus accepts xenogeneic tissue with no evidence of rejection. The psoriatic phenotype developed spontaneously upon transplantation of symptomless pre-psoriatic skin onto these mice with no exogenous cells or factors required to initiate the psoriasis lesions. Histology demonstrates that epidermal keratinocytes, dendritic cells, endothelial cells and immune cells in the grafts all became activated to create fully fledged psoriasis.

Blocking T-cell functions, by injecting a monoclonal anti-human CD3 antibody after transplantation of non-involved psoriatic skin, inhibited development of the psoriasis phenotype. The same effect resulted from the administration of a neutralizing anti-human IL-2 monoclonal antibody, demonstrating the crucial role of proliferating T-cells in the induction of the lesions. These observations strongly suggest that proliferation of local resident T-cells in the graft is an essential element of psoriasis lesion formation.

In the graft, TNF- α was predominantly localized to antigen presenting cells. Application of a neutralizing anti-human TNF- α monoclonal antibody, or TNF receptor fusion protein, led to a significant decrease of T-cells in the graft and to the inhibition of the psoriasis phenotype development.

Comment:

These data demonstrate that development of psoriasis lesions is mediated by TNF- α and indicate that proliferation of resident T-cells is dependent on local TNF- α production. These findings underline the importance of resident immune cells in psoriasis and will have implications for new therapeutic strategies for psoriasis. The availability of this novel mouse model of spontaneous psoriasis will aid in the understanding of the early molecular event leading to the psoriasis phenotype and be very useful in evaluating the potential therapeutic efficacy of new anti-psoriasis agents prior to clinical development.

Boyman O, Hefti HP, Conrad C, Nickoloff BJ, Suter M, Nestle FO. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T-cells and tumor necrosis factor- α . J Exp Med. 2004;199:731-6.

A Key Role of the Corneodesmosin Gene (CDSN) in the Pathogenesis of Psoriasis?

Evidence has accumulated over the past five years demonstrating that PSORS1 on chromosome 6p21 is the major susceptibility locus responsible for the development of psoriasis. PSORS1 contains several potential candidate genes for psoriasis susceptibility, most notably corneodesmosin (CDSN). CDSN genes encode corneodesmosin, a protein specifically expressed in terminally differentiated epidermal keratinocytes. Several CDSN risk alleles bearing single nucleotide polymorphism (SNP) have been identified.

As corneodesmosin is upregulated in involved psoriatic skin, the authors hypothesize that CDSN risk alleles may contribute to the CDSN gene over-expression by altering the rate of mRNA decay. Using transfection-based RNA stability assays, they demonstrate that one of the two CDSN risk haplotypes did, in fact, show altered RNA stability. Site directed mutagenesis revealed that a single synonymous SNP

(CDSN* 971 T) accounts for the observed increase in RNA stability. In addition, the sequence immediately upstream of SNP 971 closely matches the consensus for the mRNA stability/instability motifs that overlap the binding sites for cytoplasmic RNA binding proteins. UV cross-linking analysis indicated that the CDSN* 971 T affects the rate of RNA decay by decreasing the affinity for a 39 kDa cytoplasmic RNA-binding protein. Finally, they demonstrate that CDSN* 971 T is significantly associated with psoriasis in a wide range of ethnic groups.

Comment:

This publication provides the first evidence for a functional impact of a psoriasis-associated CDSN allele. The results strongly suggest a key role of CDSN in the molecular pathogenesis of psoriasis and may be helpful in clarifying the respective involvement of the different candidate genes contained in the major psoriasis susceptibility locus PSORS1. These preliminary results should be followed with further investigations to exclude the possibility that regulatory SNPs other than CDSN* 971 T may also contribute to corneodesmosin upregulation in psoriatic skin.

Capon F, Allen MH, Ameen M et al. A synonymous SNP of the corneodesmosin gene leads to increased mRNA stability and demonstrates association with psoriasis across diverse ethnic groups. Hum Mol Genet. 2004;13:2361-8.

PSORS9 May Be An Interesting Locus for Psoriasis Susceptibility

In this paper, a meta-analysis of six previous linkage scans for psoriasis susceptibility loci was performed with evidence to suggest the potential importance of the human genome region on chromosome 4q28-q31. Five of these studies were conducted on families of Northern European origin and the sixth in families from the Chinese population. This region was given the name PSORS9 but was not considered as a major locus for psoriasis predisposition. Particularly compelling candidate genes present among the 300 genes lying within the 4q28-q35 interval include the interferon regulatory factor 2 gene (IRF2), in the negative regulation of IFN γ signalling, as well as the interleukin-15 gene. Indeed, IL-15 triggers inflammatory cell recruitment

angiogenesis and production of inflammatory cytokines as IFN γ and TNF- α , essential elements in the pathogenesis of psoriasis. Toll-like receptor genes 2 and 3 (TLR2 and TLR3), and vascular endothelial growth factor C (VEGF C), should also be included in this list of candidate genes.

Interestingly, several groups had already found evidence of linkage on chromosome 4q, either slightly more proximal or closer to the end of this chromosome arm, this raising the question whether 4q28-q31 harbors a single or several psoriasis susceptibility locus genes.

Comment:

This study draws attention to an important psoriasis susceptibility locus at chromosome 4q28-q31 in two separate population groups (North Europe and Asia). Further association studies across this interval are now warranted to identify potential causative gene(s) and associated variant(s). This study also illustrates the power of meta-analysis to identify linkage peaks that are borderline in one scan, but consistently observed in others.

P.S. As expected the strongest evidence for linkage was obtained with markers from the MHC region (chromosome 6p21 PSORS1 gene).

Bowcock AM. Psoriasis genetics: the way forward. J Invest Dermatol. 2004;122,6,XV-XVII. Sagoo GS, Tazi-Ahnini R, Barker JWN et al. Meta-analysis of genome-wide studies of psoriasis susceptibility reveals linkage to chromosome 6p21 and 4q28-q31 in Caucasian and Chinese Hans population. J Invest Dermatol. 2004;122:1401-5.

Genotype-Phenotype Correlation Study of Psoriasis

Late onset psoriasis (LOP), also termed type II psoriasis, is rarely familial, shows onset at or after 40 y, with a peak age of onset between 57 y and 60 y, and typically demonstrates an increased frequency of HLA-CW2 and HLA-B27. This study assesses the role of PSORS1, the major susceptibility locus for psoriasis vulgaris in the genetic susceptibility of LOP. 145 psoriasis patients were categorized as having LOP if the disease initially presented after the age of 40 y. All patients had a diagnosis of chronic plaque psoriasis, confirmed by a qualified dermatologist. Evidence of only a weak association for HLA-CW*6, CDSN*5,

HCR*WC and HCR SNP + 325T was observed in the late-onset group taken as a whole. However, patients with age of onset for psoriasis of 50 y or above provided no evidence of linkage with any of the following PSORS1 alleles: HLA (human leukocyte antigen) CW*6, CDSN* (corneodesmosin) 5, HCR* (a-helical coiled-coil rod) WC and HCR SNP + 325.

Comment:

From the design of the study, it is possible that both early onset-psoriasis (type 1 psoriasis) and LOP patients were included for evaluation. Indeed, the age ranges for late-(LOP) and early onset psoriasis potentially represent two overlapping normal distribution regions (from 40 y to 50 y). Overall, this study does demonstrate that PSORS1 is not a risk factor for LOP and suggests diminished association with PSORS1 alleles with increasing age of onset of psoriasis initial presentations.

Allen MH, Ameen H, Veal C, Evans J, Ramrakha-Jones VS, Marsland AM, Burden AD, Griffiths CEM, Tembath RC, Barker JNWN. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J Invest Dermatol*. 2005;124:103-6.

What Changes Are Seen In Psoriatic Skin During Alefacept Treatment?

This study helps address some speculation on the mechanism of action (MOA) of alefacept the first biologic agent approved for the treatment of psoriasis. The authors detail preliminary results that raise clinically important questions which, if answered, could assist in the optimal, individualized administration of alefacept.

This study reports changes in the cells (immunohistochemistry, particularly of lesional lymphocytes, and dendritic cells) and markers of inflammatory cytokines (mRNA gene expression) associated with the immunopathogenesis of psoriasis and other diseases also characterized by a type I T-cell weighted immune response. These were prospectively quantified in lesional skin taken from twenty-two psoriatics before, during, and after treatment with a standard 12-week course of alefacept. Alefacept response was based on histologic clearance of psoriasis at week 13 (12/22). Although this is not a standard clinical

A Letter from the President

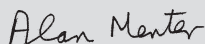
Dear Readers,

On behalf of IPC and co-editors Professor Jean-Paul Ortonne and Dr. John Sullivan, I am pleased to present the first issue of the International Psoriasis Council's semi-annual psoriasis literature research review, The IPC Psoriasis Review. Since its inception in 2004, IPC has worked hard to create programs, events, and materials that have provided a collaborative forum for psoriasis professionals to share knowledge, experiences, and insights with one another in pursuit of optimal treatment for psoriasis patients. In addition to The IPC Psoriasis Review, IPC has launched a series of "hot topics" round table conversations to build consensus among international psoriasis experts on cutting edge issues, as well as a series of educational symposia to inform the dermatology community about the latest in psoriasis clinical research and treatment. For the remainder of 2005, in 2006 and beyond, we will continue to expand our efforts to foster collaboration among psoriasis researchers, thought leaders, and medical professionals. Our plans include international projects on psoriasis outcome measurements, the impact of obesity on psoriasis patients, guidelines for the safety and monitoring of systemic therapies for psoriasis, and a scholarly review of topical therapies in psoriasis.

In The IPC Psoriasis Review, we have collected what we believe to be a cross section of eleven important psoriasis research publications from the past year, and we have provided comments on each article and its value to clinical practice. As specialty dermatologists dedicated to advancing psoriasis education, research, and treatment, we are hopeful that you, as a practicing physician, will find this publication helpful as you evaluate and treat psoriasis patients in your hospitals, clinics, and individual practices throughout the world. If you are interested in future issues or in other IPC programs and events, please take a moment to fill out and fax back the evaluation form. In addition to registering you for additional information, these forms will help us to optimize future issues of The IPC Psoriasis Review.

I hope you find this publication valuable.

Sincerely,



Alan Menter
IPC President

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measure of response, this group went on to have a 74% average reduction in their PASI when reassessed at week 23, consistent with good clinicopathological correlation.

Alefacept is a lymphocyte function-associated antigen (LFA)-3 immunoglobulin fusion protein. Analysis of biopsies in this study demonstrated that alefacept was found primarily bound to lymphocytes in psoriatic

lesions. No significant binding to dendritic or other cell types was observed. Overall, alefacept therapy was associated with a significant reduction in lesional lymphocyte numbers and a proportionally greater fall in epidermal CD8+ cells. These researchers reported that the degree of this reduction in lesional T-cell numbers more closely correlated with ultimate therapeutic outcome

than changes in circulating lymphocytes and/or memory CD4+ T-cell levels. A greater decrease in dermal and epidermal dendritic cells was also observed in responders who similarly showed a greater reduction in gene expression of several type I T-cell disease-associated cytokines, including Interferon gamma, IL-23 and iNOS.

Comment:

This research supports the specific targeting of T-cells by alefacept in skin affected by psoriasis. Differences from baseline measures were generally noted to be proportionally greater in those who ultimately responded, suggesting possibly greater similarities than differences between the groups. A progressive fall in both total and particularly epidermal T-cell numbers was observed in all treated psoriatics. This reduction in skin lymphocytes was more marked in responders with depletion of lesional lymphocytes by alefacept more likely to be associated with remission. All these observations support a central immunopathogenic role for T-cells in psoriasis. Clinically meaningful benefits with alefacept may be delayed weeks into therapy and vary in their degree and duration. This research raises the possibility that a simple validated measure able to predict and/or quantify early skin T-cell changes could be of great potential clinical assistance in optimizing our use of alefacept, as current measures of circulating CD4 cells do not appear to parallel clinical responses in a significant proportion of patients. It will also be of interest to assess whether these changes are central to our understanding of why a small percentage of alefacept-treated patients obtain long clinical remissions.

Chamian F et al. Alefacept reduces infiltrating T-cells, activated dendritic cells, and inflammatory genes in psoriasis vulgaris. PNAS 2005 Feb; 102:2075-80

An In Vitro Model of Psoriasis

Research in psoriasis has been hindered by the absence of relevant models of the disease. Several psoriasis models are available, but an organotypic culture system that accurately models the disease has not yet been characterized. This recent report describes a unique in vitro model of psoriasis using keratinocytes and

fibroblasts derived from both involved and uninvolved areas of psoriasis.

Fibroblasts from involved or uninvolved skin were initially embedded in collagen gels. Thereafter, psoriasis keratinocytes from involved or uninvolved skin were seeded onto the surface of the gels. The resulting psoriasis in vitro models (PM) were compared to a normal skin in vitro model (NM) constructed from normal keratinocytes and fibroblasts from non-psoriatic individuals.

Crucial differences were noted between the PM and NM when pro-inflammatory gene expression and keratinocyte proliferation were investigated. A significant increase in keratinocyte proliferation in the PM compared to the NM was observed. Tumor necrosis factor alpha, interferon gamma and interleukin-8 were expressed at high levels in the PM, but were only minimally expressed in the NM. Further, the chemokine receptor CXCR2 was strongly expressed in the suprabasal keratinocytes, with a concentrated band of expression in the terminally differentiating granular layer in PM, regardless of whether the cells were derived from the involved or uninvolved skin. In contrast, CXCR2 was not detectable in the NM.

Comment:

Psoriatic skin reconstructed in vitro partially displays the psoriatic phenotype. This includes an abnormal differentiated phenotype typical of a hyperproliferative epidermis and expression of pro-inflammatory cytokines and chemokine receptor and their ligands. These observations suggest that the keratinocytes and fibroblasts of psoriatic individuals possess an inherent predisposition to develop the disease phenotype even in the absence of T-cells. This psoriatic in vitro model could be a useful tool to investigate the relative role of different cell types in the induction of the psoriatic phenotype (keratinocytes versus lymphocytes), and potentially also be a valuable tool in anti-psoriasis drug discovery.

Barker CL, McHale MT, Gillies AK et al. The development and characterization of an in vitro model of psoriasis. J Invest Dermatol. 2004;123:892-901.

Upregulation of Stat3 In Keratinocytes and Psoriasis

A great deal of recent research has focused on the immunopathogenesis of psoriasis. These researchers report a keratinocyte abnormality that may prove important in the pathogenesis of psoriasis and could also provide insight into the pathogenic mechanisms behind the Koebner phenomenon. They report that activated Stat3 is abnormally expressed by keratinocytes in patients with psoriasis.

Stat3 (signal transducer and activator of transcription 3) activation of keratinocytes is essential for skin wound healing. These researchers have shown that Stat3 is also activated in keratinocytes of human psoriatic lesions and in some psoriatic patients is also found in the adjacent uninvolved epidermis. This study also describes a novel transgenic mouse model which constitutively expresses active Stat3 in keratinocytes that developed skin lesions either spontaneously or in response to wounding that closely resemble human psoriasis. Development of psoriasis-like lesions in these mice was also shown to be dependent on the presence of activated T lymphocytes.

Comment:

The importance of both activated Stat3 expression by keratinocytes and activated T lymphocytes in the skin of this mouse model is in keeping with psoriasis being due to deregulation of the immune system and/or a primary abnormality in epidermal keratinocytes.

The expression of Stat3 protein and the expression of Stat3-regulated genes in keratinocytes following skin injury, be it scratching or minor repetitive trauma such as resting on one's elbows (Koebner phenomenon), appears possibly key to the formation of psoriatic plaques. Thus, therapies directed both against Stat3 activation, together with the specific effects of this protein, could prove beneficial in psoriasis. It would be of interest to evaluate the effects of our current systemic therapies, both traditional agents and biologic therapies, in this mouse model, as well as in Stat3 expression in human patients.

Sano S et al. *Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. Nat Med* 2005 Jan;11:43-9

Psoriasis Continues To Improve For 24 Weeks With Efalizumab

The biologic efalizumab targets leukocyte function-associated antigen (LFA)1 and is thought to interfere with pathogenic T-cells in psoriasis at several levels, including their activation (in lymph nodes) and trafficking to skin (along with their reactivation and activation in the skin). This report suggests that continued therapy with efalizumab from 12 to 24 weeks leads to further improvement in efficacy in moderate to severe plaque psoriasis.

The authors compared patient outcomes after an additional 12-week open-label extended treatment with efalizumab that immediately followed a randomized, double-blind, parallel-group, initial 12 week trial of efalizumab 1mg/kg or placebo.

PASI-75 response was reported to increase from 26.6% at 12 weeks to 43.8% at 24 weeks, with a corresponding improvement in PASI-50 from 58.5% to 66.6%. There was also an improvement in the static Physician's Global Assessment rating of minimal or clear from 25.7% to 35.9%. No additional safety concerns were noted in the second 12 weeks of therapy.

Comment:

Initial response rates seen with efalizumab at 12 weeks were shown to continue to improve over an additional 12 weeks when assessed using standard physician assessed severity measures. Overall patient-reported outcomes did not statistically significantly improve further between week 12 and 24. This physician/patient discrepancy reflects some of the limitations of current scoring systems used to quantifying psoriasis severity and emphasizes that the choice of measures used to assess outcomes of therapy should not rely solely on single measures such as the 12-week PASI-50 and/or 75 response.

Reassuringly, no safety concerns were raised during this 13-24 week continuation phase.

Of interest is the confirmation of the slower onset of action of efalizumab as compared to the anti-TNF agents (etanercept, adalimumab, and infliximab). Taken together with the slow onset of action of alefacept, it appears that the anti-TNF agents in their individual maximum dosing schedules are more of value in obtaining an initial rapid response, whereas the two "T-cell agents" continue to show improving efficacy with continued therapy. Studying these important differences will be of value in optimizing our expanded clinical arsenal of systemic psoriasis therapies, possibly paving the way for optimal long-term safe control of this lifelong distressing disease.

Menter A et al. Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. Arch Dermatol 2005 Jan; 141:31-8

Immunopathogenesis of Psoriasis - From Bench Top To Clinic

This is a thoughtful and insightful review of the immunopathogenesis of psoriasis. The authors present their working hypothesis highlighting how it incorporates knowledge gained from basic research into the immunopathogenic mechanisms of psoriasis. They use their hypothesis to help explain the mechanisms of action (MOA) of our current targeted therapies, in addition to pointing out potential targets for new therapies. The following is a brief summary of their working model and supporting research data.

Psoriasis is a chronic relapsing, remitting skin disease. Thus, psoriasis plaques can revert back to symptomless, apparently healthy skin, either spontaneously or following treatment. There are numerous molecular differences in psoriatic skin when compared to the skin of those without psoriasis. In non-psoriasis skin, normal trafficking of leukocytes (LCs and T cells) occurs between the skin and lymph nodes and is important in helping fight off infections and surveying the skin for damaged cells, including precancerous and cancerous lesions. Targeted psoriasis treatments should ideally not interfere with this normal skin immune surveillance function.

Co-editors' Credentials and Affiliations

Jean-Paul Ortonne, is Professor of Dermatology and Chairman of the Department of Dermatology of the University of Nice-Sophia Antipolis. He is scientific Director of the Clinical Pharmacology Center Applied to Dermatology.

Professor Ortonne's major medical interests are in the areas of Melanin pigmentary disorders, mostly vitiligo and pigmentary genodermatoses, dermo-epidermal junction and clinical pharmacology in dermatology. He is a founding member of the French Society for Dermatological Research and is presently a member of the Board of Directors of the Société Française de Dermatologie et de Vénérologie. Professor Ortonne has also served as the President of European Academy of Dermatology and Venereology and Secretary General of the 2002 World Congress of Dermatology in Paris. He is member of the International Committee of Dermatology.

John R. Sullivan, is the Deputy Medical Director Department of Dermatology of the Liverpool Hospital in Sydney, Australia. He is also Lecturer of Dermatology at the University of New South Wales and the Dermatology representative to the Australian Council for Health Care Standards. Specialty interests include clinics and research in the areas of inflammatory skin diseases, hand and occupational dermatoses, drug safety, and basic skin physiology.

Psoriasis can flare following a known or unknown trigger or stimulus. Such a trigger leads to what the authors describe as the development of an acute psoriatic lesion in which the immunological synapse between activated dendritic cells (DCs) and T-cells is a critical key interaction. While no consistent antigenic stimulus, however, has been identified for this immune synapse, the authors speculate that a danger signal in the skin following a trigger of either intrinsic and/or extrinsic origin may also be able to activate or enhance this interaction. Danger signals triggering psoriasis for example could result directly or indirectly by skin trauma or injury, or skin stress,

damage or changes due to infections and/or medications. They speculate that the danger signal leads to the release of preformed or rapidly produced skin cytokines such as IL-1 and TNF- α and occurrence of disease by way of the immune synapse.

This immunological synapse activates immune cells leading to release and production of a range of cytokines, chemokines, and growth factors. These changes cascade and lead to the development of the clinical lesions of psoriasis characterized by keratinocyte hyperproliferation and altered differentiation, the trafficking of a variety of immune cells to the affected area including intraepidermal CD8+ T-cells, dermal memory CD4+ T-cells, and increased angiogenesis. Innate immune cells are also found in lesions and include NK type T-cells and epidermal neutrophils.

Full activation of T-cells and DCs and trafficking of new immune cells to lesional skin produces what they designate as a "storm" of mediators (cytokines, chemokines and growth factors). This "storm of mediators" is able to maintain the classical plaques of psoriasis in a chronic state seen. Cytokine analysis of plaques shows a predominantly Th1 profile similar to rheumatoid arthritis and Crohn's disease, including IFN- γ , TNF- α and IL-12. Other cytokines elevated in psoriatic plaques include IL-1, IL-6, IL-8, IL-15, IL-17, IL-18, IL-10 and IL-23. Growth factors include TNF- α , IGF-1, KGF, VEGF, NGF and amphiregulin. Elevated growth factor and nitric oxide levels are speculated to enhance angiogenesis. In animal models TNF- α has been important in driving the proliferation of T-cells in psoriatic plaques and is similarly likely to be important in man, where they are then subsequently activated by their synaptic interaction with Antigen Presentation Cells (APCs).

This immunological synapse is emphasized as being key to the activation of pathogenic T-cells and the development of psoriatic lesions. This synapse involves the binding of LFA-1 on the surface of T-cells to ICAM-1 on APCs such as dermal dendritic cells and keratinocytes. Selective targeting or blocking of this T-cell-APC synapse by the anti-LFA-1 antibody efalizumab, is credited for its clinical benefits in psoriasis.

Other adhesion and costimulatory molecules are also important in this T-cell signalling process and T-cell activation. An example is the costimulatory pairing of CD2 and LFA-3, which is targeted by the LFA-3 Ig fusion protein (alefacept), highlighting the therapeutic benefits of interfering with this interaction and subsequent T-cell response.

How do inherited factors support such a model? Mutations or polymorphisms affecting or altering regulation of genes coding for molecules involved in T-cell signalling pathways are being studied in a number of autoimmune diseases including psoriasis, rheumatoid arthritis and lupus and include a variety of animal models. Researchers have now mapped at least six different psoriasis susceptibility loci, designated PSORS1-PSORS6, several of which are also linked to other inflammatory diseases including asthma, eczema and rheumatoid arthritis.

These genetic polymorphisms are speculated to alter signals generated by this pathway, such as transcription factors and changes in gene expression. Altered T-cell signalling due to such mechanisms could adversely affect a variety of T-cell (antigen) specific responses such as central tolerance leading to emergence of autoreactive T-cell or dysregulated and/or inappropriate T-cell activation leading to autoimmune disease.

PSORS1 is the major genetic determinant linked to psoriasis and accounts for 30-50% of genetic susceptibility. PSORS1 closely links to HLA-Cw*0602 and corneodesmosin genes. These code for keratinocyte adhesion proteins which are also important in keratinocyte differentiation. The authors highlight recent research, however, that speculates that this genetic determinant might be linked to causing disequilibrium in the expression of another gene or block of genes that have been shown to be expressed in lesional NK cells and a subset of lesional T-cells.

This working hypothesis helps provide a good framework to build on or alter as new research provides further insights into the pathogenesis of psoriasis. This model can also be used to help understand where and how our current targeted biologics are likely to acting in reducing or

interfering with the immunopathogenesis of psoriasis. The immune synapse between T-cells and APC's is central to this hypothesis. The authors speculate that future therapeutic strategies for psoriasis could include novel agents targeting inter alia, T-cell trafficking, T-cell activation, cytokine inhibitors other than those targeting TNF- α and/or the enhancement of regulatory suppressive T-cell subsets to counter balance the pathogenic T-cell subsets. This review is extremely timely and likely to be of value to clinicians and researchers alike with an interest in this fascinating disease.

Nickoloff BJ et al. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. J Clin Invest. 2004 Jun;113(12):1664-75

Guidelines for TNF- α Use In Psoriatic Arthritis

The need for guidelines in utilizing the new anti-TNF- α agents for psoriasis is essential. Psoriatic arthritis, as discussed by the guideline committee, was "once considered a benign condition and is now recognized as a potentially destructive, erosive arthropathy." The pivotal role of TNF- α in the synovium has produced a number of new TNF- α blocking agents, some of which are already approved for psoriatic joint disease, having formerly been approved for rheumatoid arthritis. Thus, etanercept and infliximab are licensed for psoriatic arthritis in the U.S., with etanercept approved in the U.K. in 2003 for psoriatic joint disease. In this Working Party paper, a rigorous literature review was compiled from comprehensive electronic databases and a "level of evidence" was provided utilizing an important grading, i.e. Grade A, Grade B, Grade C. A treatment algorithm for psoriatic arthritis was published, based on the form of psoriatic arthritis, e.g. peripheral psoriatic arthritis with or without axial disease, and secondly, the axial form of psoriatic arthritis without peripheral psoriatic arthritis. The importance of an initial trial of NSAIDs, with or without corticosteroids as a first step, was stressed and/or the use of disease modifying antirheumatic drugs, DMARDs, such as sulfasalazine and methotrexate in the presence of persisting synovitis or joint damage. These DMARDs should be used either as monotherapy or in combination with

leflunomide or even possibly cyclosporine or low-dose systemic steroids.

The Guidelines continued with the important message that, should there be active joint disease, defined as more than three tender or swollen joints on two separate occasions one month apart (with dactylitis counting as one joint), then the next step would be the initiation of anti-TNF- α therapy. In addition, active skin disease per se may require these therapies with or without concomitant psoriatic joint disease.

The algorithm continues with a review of the response at 12 weeks, using PsARC as the denominator. This is defined as improvement in two factors, with at least one being the joint score with no worsening in any of the following other four factors, e.g. Physician's Global Assessment, Patient Global Assessment, Tender and Swollen Joint Scores, as well as response in the PASI. At 12 weeks, should one initial anti-TNF- α agent fail to show adequate response, a secondary anti-TNF- α agent could be tried.

In the paper, the concerns relating to prescribing TNF- α agents in adults with rheumatoid arthritis, as previously laid down by the British Society for Rheumatology, was maintained in the Guidelines for psoriatic arthritis, i.e. patients with congestive cardiac failure or cardiovascular disease should be carefully screened. In addition, for this, patients should be screened at baseline for tuberculosis, infections, and demyelination, and screening should be continued at intervals throughout the course of anti-TNF- α therapy. Withdrawal of therapy, again utilizing anti-TNF- α guidelines for rheumatology arthritis in the event of the following adverse events should be considered:

- Malignancy
- Severe drug-related toxicity
- Pregnancy (temporary withdrawal)
- Severe intercurrent infection (temporary withdrawal)
- Temporary withdrawal for surgical procedures
- Inefficacy: failure to respond over a 3 month period

The following guidelines for blood test monitoring were recommended. This should include a full blood count, urea and electrolytes and liver functions at baseline, at 3 months and 6 months, and thereafter at 6 month intervals. Should lupus-like

symptoms develop, blood tests for ANA and DNA binding would be considered with the drug discontinued in the presence of active lupus-like syndrome.

Quality of Life (QOL) issues pertaining to psoriasis and psoriatic arthritis was also addressed and, hence, the need for utilizing well known QOL parameters such as Health Assessment Questionnaire (HAQ), as well as Short Form (SF)-36. Finally, the issue of radiological outcome utilizing anti-TNF- α agents was discussed. It is well known that anti-TNF- α agents have the ability to prevent radiographic progression in psoriatic arthritis. However, the Working Group felt that this needed further validation and should be "reserved for further clinical trials."

Comment:

The understanding of psoriatic arthritis as a specific entity by dermatologists has gained tremendous momentum since the introduction of anti-TNF- α therapy for psoriatic joint disease. As the majority of patients with psoriasis will be under the care of a dermatologist prior to their development of joint disease, it is obviously incumbent upon all dermatologists to be aware of this potential. Currently it is considered that up to 1/3 of patients with psoriasis may develop psoriatic joint disease, which may be erosive and deforming in approximately half of the patients and progressive from the first year of diagnosis. With an approximate interval of 5-10 years before the onset of joint disease, it is likely that with increasing awareness amongst the dermatology community, the potential to limit joint destruction, utilizing current anti-TNF- α agents as monotherapy or in combination (e.g. MTX), will prove highly effective. Thus, the importance of guidelines for anti-TNF- α therapy by a major group of British rheumatologists, with Chris Griffiths (Manchester) as the dermatology representative, is highly important for all clinicians with an interest in psoriasis.

The most important point arising from these guidelines is the decision to initiate anti-TNF- α therapy, either by the dermatologist alone or in concert with his/her consultant rheumatologist. Anti-TNF- α therapies are highly effective for both skin and joint disease, but have obvious potential side effects, with important

differences between the three agents, adalimumab, etanercept, and infliximab, in addition to the overall class effect relating to this group, e.g. infections, demyelination, lymphoma, etc. What actual percentage of patients do develop progressive radiological joint progression? Papers have been published on small numbers of patients, but until larger numbers of patients are followed prospectively, the exact place for anti-TNF- α therapy, as monotherapy or in combination with DMARDs, remain to be finalized. Cost aspects are obviously of primary concern worldwide, with low dose steroids, sulfasalazine, leflunomide, and methotrexate obviously being significantly cheaper than the anti-TNF- α therapies.

In conclusion, these are well done and carefully worded guidelines using a rigorous methodology, including literature review and level of evidence. As the literature and clinical understanding of the use of anti-TNF- α therapy evolves and more evidence becomes available, guidelines such as this will inevitably need updating. The role of clinical registries, both in psoriasis and psoriatic joint disease, is highly important and will be discussed by the International Psoriasis Council at an upcoming meeting on November 30, prior to the Gene to Clinic meeting in London, December 1-3, 2005.

Guideline for anti-TNF- α therapy in psoriatic arthritis. S Kyle, D Chandler, CEM Griffiths, P Helliwell, J Lewis, I McInnes, S Oliver, D Symmons and N McHugh, on behalf of the British Society for Rheumatology Standards Guidelines Audit Working Group (SGAWG). Rheumatology 2005. 44(3):390-397.

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International Psoriasis Council
5310 Harvest Hill Road
Suite 260
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Imbalance In Immune Regulation In Psoriatics

Major reviews on the immunopathogenesis of psoriasis have highlighted the importance of ongoing activation of effector pathogenic CD4+ T-cells in the development and ongoing inflammatory changes seen in psoriasis. Recent reports of new T-cell subsets with regulatory functions have led to their quantitative and qualitative assessment in several autoimmune human diseases.

These researchers looked for changes in the number and function of a subset of regulatory T-cells, namely regulatory T (Treg)⁴ cells, similar to those previously found to be impaired in their regulatory functions in multiple sclerosis (MS) along with several other diseases with an autoimmune basis.

These researchers quantified and isolated these cells for study from the blood and lesional skin of psoriatics and compared their number and function to healthy volun-

teers. This included analysis and comparison of other cell surface markers and intracellular antigen expression known to characterize these cells normally. The proliferative response of these Treg cells following T-cell dependent direct activation was also quantified and compared along with their previously described inhibitory functions.

As in MS, the researchers characterized a similarly defective subgroup of regulatory immune cells, suppressor effector CD4+ CD25^{high} T-cells in the blood, and skin lesions of people with psoriasis. Although blood levels of these cells along with their surface antigen expression were similar to controls, these researchers characterized psoriatic skin and blood Treg cells as less able to suppress the proliferation of T effector cells such as those immunopathogenic in psoriasis. They also showed that they had impaired activation and proliferation following direct T-cell stimuli compared to controls.

Comment:

The identification and characterization of dysfunctional Treg cells in several different autoimmune diseases, including psoriasis, suggests that their normal function may be important in preventing autoimmune disease. The presence of dysfunctional regulatory T-cells in those with psoriasis could also help explain why effector T-cells which are considered immunopathogenically important in psoriasis are able to escape normal controls, thus leading to ongoing tissue inflammation and damage and the clinical manifestation of psoriasis. These findings suggest that treatments aimed at replicating or restoring the suppressive T regulatory functions of dysfunctional Treg cells in psoriatic lesions could restore immune balance, leading to the clearance of psoriatic plaques and/or prevention of flares.

Sugiyama H et al. Dysfunctional blood and target tissue CD4+ CD25^{high} regulatory T-cells in psoriasis: Mechanism underlying unrestrained pathogenic effector T-cell proliferation. J Immunol 2005, 174; 164-73

SELF ASSESSMENT QUIZ

To obtain CME credit, read this publication and then complete the Self-Assessment Quiz below and the Registration/Evaluation Form on the other side of this page. Mark only one answer as correct. Participants must answer a minimum of 80% of the test questions correct, attest to their time spent, indicate that they are a licensed U.S. physician, and execute the form to receive a CME certificate. Please allow 3–4 weeks for certification of completion or other notification. There is no fee for this activity.

1. Which of the following statements on the role of T-cells and TNF- α in the immunopathogenesis of psoriasis is true?

- a.** TNF- α in skin grafts in a spontaneous psoriasis mouse model is localized specifically to keratinocytes.
- b.** The proliferation of resident T-cells in psoriasis is predominantly dependent on local TNF- α production.
- c.** The administration of an anti tumor IL-2 monoclonal antibody in the mouse model did not change the psoriasis phenotype.
- d.** The concentration of TNF- α in affected psoriasis skin is dependent on the number of activated T-cells in the skin.

2. Which of the following statements on PSORS1 as an important psoriasis susceptibility gene is not true?

- a.** Location on chromosome 17.
- b.** Has only one definitive candidate gene, corneodesmosin (CDSN).
- c.** Is the most significant psoriasis susceptibility gene.
- d.** Is of significance only in a single defined ethnic group.

3. Which of the following statements on alefacept therapy is true?

- a.** Alefacept is a lymphocyte function-associated antigen (LFA)-3 immunoglobulin fusion protein.
- b.** There was no correlation between histologic clearance of psoriasis and good PASI response.
- c.** Alefacept specifically targets TNF- α in the skin.
- d.** Alefacept therapy reduces circulating CD4 counts but has no effect on CD8 counts.

4. Which of the following statements on efalizumab is correct?

- a.** Efalizumab has a single Mode of Action, i.e. inactivation (apoptosis) of activated T-cells in the epidermis.
- b.** Efalizumab therapy produces optimal PASI reduction at 12 weeks of therapy.
- c.** The PASI 50 response at week 24 was identical to that at week 12.
- d.** There were no new safety signals noted regarding side effects at week 24.

5. In discussing the key role of the immunological synapse between dendritic cells (antigen presenting cells) and T-cells, which of the following is true?

- a.** The majority of antigens for psoriasis have been identified.
- b.** Once the immunological synapse has been activated, a “storm” of mediators are released, including cytokines, chemokines, and growth factors.
- c.** Analysis of the cytokine makeup in psoriatic skin reveals predominantly a Th2 profile.
- d.** Interferon gamma and IL23, but not nitric oxide, are among the substances produced once the immunological synapse is activated and are important for increased angiogenesis.

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