

Psoriatic arthritis

TNF α therapy in psoriatic arthritis and psoriasis

P Mease

How and why does it work?

Specific inhibition of the cytokine tumour necrosis factor α (TNF α) has yielded dramatic improvements in the symptoms, signs, and quality of life of patients with chronic inflammatory diseases of Th1 phenotype such as rheumatoid arthritis (RA),¹⁻⁹ psoriatic arthritis (PsA),¹⁰⁻¹⁴ ankylosing spondylitis,¹⁵⁻¹⁷ psoriasis,¹⁸⁻²¹ and Crohn's disease.^{22, 23} The ability of anti-TNF α therapy to inhibit disease progression in RA^{5, 6, 24} and PsA^{14, 25} as evidenced by retardation of joint destruction by χ ray analysis, has also been documented. Although these clinical results have been clearly demonstrated, our understanding of disease pathophysiology and demonstration of the specific cellular and immunohistochemical effects of new treatments continue to evolve. This review focuses on what has been recently learnt about the mechanism of treatment in PsA and psoriasis.

Psoriasis, occurring in approximately 1-3% of the population,^{26, 27} is a disease characterised by unsightly erythematous and indurated lesions, often with extensive silvery scale, which may cause significant impairment of quality of life and emotional wellbeing.^{28, 29} Although the exact prevalence of PsA is not as precisely known, studies suggest that at least 7%³⁰ and probably closer to 31%,^{31, 32} or higher,^{26, 33, 34} of all patients with psoriasis may demonstrate this unique inflammatory arthropathy. It is probably underdiagnosed given that its various subtypes (oligoarticular, polyarticular, distal interphalangeal or axial predominant, and arthritis mutilans), originally described by Moll and Wright,³⁵ may be confused with other conditions such as osteoarthritis, RA, other spondyloarthropathies, gout, and chronic tendonitis. A new classification scheme in development, through a patient database project known as CASPAR, led by Philip Helliwell, is expected to yield more sensitive and specific criteria for PsA and its subsets using clinical, laboratory, and radiological parameters. Although a diagnosis of psoriasis usually precedes that of PsA, often by many years, in 15-20% of cases the arthritic component will appear

first.³⁶ As in RA, patients with PsA may have significant morbidity, disability, and early mortality.³⁶⁻³⁸

CELLULAR AND IMMUNOHISTOCHEMICAL STATE OF PsA AND PSORIASIS

What do we know at a cellular and immunohistochemical level of the joints and skin of patients with PsA and psoriasis? As in RA, the synovial membrane in PsA demonstrates increased cellular infiltrates, which may either be diffuse or show focal perivascular accumulation of lymphocytes, together with plasma cells and mast cells. Fibrosis of varying degree may be present. The cellular depth of the synovial lining layer in PsA is much less than that in RA, as is the number of macrophages/monocytes in this layer, but the overall number of T and B lymphocytes, including the proportion of CD4 and CD8 cells in the lining and sublining layers, is similar.^{39, 40} A striking feature of the PsA synovium is its increased vascularity, characterised by tortuous, bushy vessels, as compared with the straighter vessels seen in RA.^{39, 41}

The class II antigen HLA-DR is expressed on the majority of cells in the PsA infiltrate. The adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are richly expressed in both PsA and RA synovium, whereas endothelial leucocyte adhesion molecule-1 (ELAM-1) is scarcely expressed in PsA, though it is in RA.³⁹ It is speculated that the relative absence of ELAM-1 accounts for the paucity of macrophage/monocyte cells in the PsA synovial lining layer.³⁹

The proinflammatory lymphokine profile suggests a Th1 driven process with raised interleukin (IL)2 and interferon γ , and an absence of IL4 and IL5.⁴² Ritchlin's group showed an increase of TNF α , IL1 β , and IL10 in PsA synovial tissue.⁴² Synovial tissue was removed from patients with PsA, RA, and osteoarthritis (OA) at the time of joint replacement, synovectomy, or arthroscopy, and showed the highest level of these cytokines in PsA tissue, followed

by RA, and the lowest in OA. At the National Institute of Health and Glasgow, synovial biopsy specimens from a larger number of patients showed increases in TNF α , IL1 α , IL1 β , IL15, IL10, and the transcription factor NF- κ B in PsA and RA relative to OA, but less overall TNF α , IL1 β , and IL15 expression in PsA, probably reflecting lower macrophage numbers. IL10, an anti-inflammatory cytokine was expressed in similar quantity in PsA and RA. Subtle differences were noted in expression between the lining and sublining layers, reflecting differences in cellular constituency of these layers. NF- κ B expression was similar in PsA and RA lining layers but lower in the PsA sublining layer. This group speculated that there might be subtly different mechanisms of T cell activation, with a proportionally larger role for macrophages/IL15 in RA and T cells/IL2 in PsA, perhaps accounting for some of the difference in disease manifestations. A study of synovial fluid samples from patients with PsA found increases in TNF α , IL1 β , IL6, and IL8 intermediate between the higher levels in RA and the lower levels in OA.⁴³

Another difference in cytokine expression between PsA and RA is an increased expression of vascular endothelial growth factor (VEGF) and Ang 2 in PsA synovium, as compared with RA, which may be associated with noted differences in PsA and RA synovial vascularity.⁴⁴ Again this may partially account for differences in disease manifestations. As we move slightly away from the synovium to the enthesis, which in PsA and other spondyloarthropathies is a key site of inflammation, recent data suggest similar pathological features.⁴⁵

OSTEOCLAST ACTIVATION

Although our focus has been on increased synovial cellularity and cytokine expression in PsA, there have also been interesting observations about osteoclast activation and the unique bone erosions seen in this disease. Ritchlin has shown that patients with PsA, particularly those with current bone erosions, have markedly increased levels of circulating osteoclast precursor cells, form osteoclasts in vitro without exogenous receptor activation of NF- κ B ligand (RANKL), have higher levels of TNF α than controls, and richly express RANKL, while the natural antagonist of RANKL, osteoprotegerin is restricted to the endothelium.⁴⁶

"Osteoclast precursor cells may be stimulated by RANKL and TNF α to become mature osteoclasts and erode bone"

The suggested model is that osteoclast precursor cells arise from TNF α activated peripheral blood mononuclear cells and migrate to inflamed synovium at the bone pannus junction as well as subchondral bone. There they are stimulated by unopposed RANKL and TNF α to become mature osteoclasts which erode bone.³⁷

SKIN LESIONS OF PSORIASIS

Our understanding about the pathogenesis of the skin lesions of psoriasis is based on a large body of research that cannot be fully reviewed here but has been recently reviewed.⁴⁷ Over the years, there has been a shift in consensus about the key effector mechanisms. The previous model was one of keratinocyte hyperproliferation related to abnormal epidermal differentiation. The current model is that epidermal hyperplasia is related to activation of various immunologically reactive cells, cytokines and chemokines, analogous to the orchestration seen in inflammatory joint disease, which is mediated by CD8+ and CD4+ T lymphocytes that accumulate in lesional skin.⁴⁷ Dendritic antigen presenting cells, termed Langerhans' cells, if from the epidermis, and dermal dendritic cells, if from the dermis, become "armed" with antigen—for example, after macromolecule ingestion in the skin. Cell surface expressed antigen, bound to major histocompatibility complex class I or II molecules, together with cell-surface "counter-receptors" such as CD80 (B7-1), CD 86 (B7-2), leucocyte function associated antigen-3 (LFA-3), ICAM-1, and CD40 are presented to naïve T cells which have also migrated from skin to lymph node. These are then converted to activated memory T cells expressing cutaneous-lymphocyte associated antigen, which allows the cell to home back to the skin under adhesion molecule direction. Here, clonal proliferation of autoreactive T cells occurs, stimulated by resident dendritic cells and cytokines such as TNF α . The consequent proliferation of immunologically activated cells, including keratinocytes, and their prolonged life and delayed clearance are the constitutive elements of psoriatic plaque.⁴⁶

ACTION OF TNF α

TNF α is increased in the joint tissue and lesional skin of patients with PsA and psoriasis.^{40 42 43 48 49} It is produced by a number of cells, including macrophages, monocytes, keratinocytes, Langerhans' cells, dermal dendritic cells, mast cells, and activated T cells.⁵⁰⁻⁵² It induces the expression of adhesion molecules on the surface of endothelial, keratinocyte, and dendritic cells, promoting leucocyte

migration.⁵³ By interaction with T cell surface receptors, TNF α triggers intracellular signalling through NF- κ B and thereby activates T cells and increases production of a variety of proinflammatory cytokines such as IL1, IL6, and IL8, which in turn contribute to the inflammatory cascade. TNF α mediates key processes involved in inflammatory joint destruction: cartilage destruction through metalloproteinase and other effector molecule induction, bone resorption through activation of osteoclasts, and inhibition of bone formation and synthesis of proteoglycan.^{46 54-57}

In the skin, increased TNF α leads to increased IL1, and thereby keratin 6, resulting in activated, hyperproliferative keratinocytes, as does TNF α stimulated IL6 increase.⁵² An increase in IL8 induced by TNF α leads to T cell and neutrophil activation, chemotaxis, and keratinocyte hyperproliferation. TNF α leads to decreased keratinocyte apoptosis and cell cycling, thus contributing to a hyperproliferative epidermis.

Adhesion molecule expression induced by TNF α leads to increased skin cellular infiltrate, as it does in the inflamed joint. TNF α induced VEGF production stimulates angiogenesis in the skin and joints.⁵² As is apparent, the skin and joints display closely parallel pathological processes.

TNF α INHIBITION

It stands to reason that TNF α inhibition will lead to decreased signs of inflammation in both joints and skin as well as decreased tissue destruction.

Etanercept

Two controlled studies in PsA employing a standard dose of the soluble anti-TNF α receptor protein, etanercept, both with and without concomitant methotrexate, showed significant improvements in the American College of Rheumatology and Psoriatic Arthritis Response Criteria scores, skin lesions as measured by the Psoriasis Area and Severity Index (PASI), target lesion, and static global scores, and functional indices as measured by the Health Assessment Questionnaire, Short Form-36,⁵⁸ and Dermatology Life Quality Index.¹²⁻¹⁴ Furthermore, for the first time in PsA, inhibition of progression of joint damage, as shown by retardation of α ray change, was demonstrated.¹⁴

Infliximab

Open and controlled studies with a chimeric monoclonal antibody directed against TNF α , infliximab, showed similar effects in the joints and in functional indices, and in the skin a faster effect was achieved.^{12 13}

Other anti-TNF α agents

PsA studies are currently underway with a fully human anti-TNF α monoclonal antibody, adalimumab. A phase II trial with a p55 anti-TNF receptor, onercept, has also shown promising results in PsA. In parallel, studies in psoriasis alone have shown that anti-TNF α therapy has significant ability to clear or at least improve the skin and nail lesions.

"Etanercept, infliximab, and adalimumab cause rapid changes in skin and nail lesions"

Usually, studies which have focused on the skin recruit patients with a more severe degree of skin involvement—for example, affecting more than 10% of the body surface area. Rapid and significant changes in skin and nail lesions have been shown with etanercept,^{18 19} infliximab,²⁰ and, recently, adalimumab.²¹

CORRELATION OF CELLULAR AND IMMUNOHISTOCHEMICAL CHANGES WITH CLINICAL IMPROVEMENT

What is the cellular and immunohistochemical correlate of these clinical improvements when anti-TNF α therapy is introduced? In this issue of the *Annals* Goedkoop *et al* report on these effects in 12 patients with PsA and psoriasis, 6 treated with infliximab (3 mg/kg) and 6 with placebo. Skin and synovial biopsy samples were obtained at baseline and 48 hours.⁵⁹ Response in the skin and joints mirrored each other. There was a significant decrease in epidermal and synovial sublining T cell infiltrate noted *not* to be due to apoptosis, as shown by TUNEL assay and caspase-3 staining. Thus, the decrease might have been due to decreased cell trafficking, owing to a lower TNF α induced expression of adhesion molecules and chemokines. Indeed, this group observed marked reduction of ICAM-1 in synovium and skin, and E-selectin in skin after infliximab therapy.⁶⁰ Also noted was a reduction in the number of macrophages in the synovial sublining layer. These observations underline the central role of the T cell and TNF α in the inflammatory lesions of both joints and skin. These results are similar to those seen in RA.⁶¹

In a Belgian cohort of 20 patients enrolled in three studies of infliximab in spondyloarthropathy and who had synovial biopsies, 8 patients had PsA. Compared with baseline, week 12 biopsies showed a significant reduction of the lining layer thickness, vascularity, endothelial expression of aVb3, VCAM-1, sublining expression of ICAM-1 and E-selectin. Significantly fewer macrophages, CD4+ and CD8+ T cells, and

neutrophils were found. There was no change in CD20+ B cells or plasma cells. There were no significant differences between patients with ankylosing spondylitis (n = 10) and those with PsA.⁶² Ritchlin's group has shown that osteoclast precursors are significantly reduced with etanercept therapy.⁴⁶ A recent study has demonstrated reduction in VEGF and another angiogenic growth factor, Ang 2, VEGF receptors, and neovessel area, as well as inflammatory infiltrate in PsA synovium after three infliximab infusions.⁶³

"TNF α therapy reduces cellular infiltration of multiple cell types in the skin and synovium"

There have been a number of observations on the effects of anti-TNF α therapy on cellular and cytokine profiles in the skin. In the lesional skin of 12 patients with PsA and psoriasis, Veale's group has recently demonstrated significant reduction in inflammatory cell infiltrate and the angiogenic growth factors, VEGF and Ang 2, in lesional skin biopsy samples after three infusions of infliximab.⁶⁴ This correlated with significant skin and joint clinical improvement.

Gottlieb studied lesional skin biopsy samples taken at weeks 0, 2, and 10 of 33 patients with psoriasis treated with infliximab, 5 or 10 mg/kg compared with placebo.⁶⁵ As early as week 2, and increasingly at week 10, there was significant decrease in epidermal thickness, CD3+ T cells, ICAM-1, and K16 keratin. K16 keratin expression is associated with hyperplastic epidermis and is absent in normal epidermis. Conversion of K16+ to K16- represents normalisation of epidermal differentiation. There was a good correlation of these changes with clinical measures of psoriasis improvement.

Analogous results have been demonstrated in a phase II placebo controlled study of etanercept in psoriasis. Of 112 patients enrolled, 31 underwent lesional skin biopsies and were assessed for epidermal Ki67 and keratin 16 expression as well as epidermal thickness. Eleven patients were evaluated for CD3 count and keratinocyte ICAM-1 expression. There was significant reduction in epidermal thickness, Ki67 and CD3 cells, keratinocyte ICAM-1, and keratin 16 expression, all correlated with clinical improvement of psoriasis.⁶⁶

KEY MESSAGES AND FURTHER QUESTIONS

What are some key take home messages in all this? Clearly there are parallel paths of immunological pathological mechanisms going on in the epidermis

and synovial lining layer, dermis and sublining layer involving antigen presenting cells (macrophages, Langerhans' cells) and T lymphocytes, both CD4+ and CD8+. Although in established synovial and skin inflammation, CD4+ cells are as abundant as CD8+ cells, in early psoriatic skin lesions, CD8+ cells predominate, an interesting distinction from RA and a possible explanation for the sometimes explosive behaviour of psoriasis, and possibly PsA, when CD4+ cells are depleted with HIV infection.⁶⁷

Similar parallels of cytokine expression such as TNF α , IL1, IL6, VEGF, Ang 2, and adhesion molecules promote the cellularity and neoangiogenesis seen, with subtly differing cytokine profiles from those in RA, possibly accounting for differences in histological morphology and disease expression. For example, greater expression of VEGF in PsA may contribute to the tortuous, highly proliferative capillaries seen in synovium and skin, or lower expression of ELAM-1, resulting in fewer macrophages in PsA. Why this difference? If osteoprotegerin precursor cells are increased and RANK ligand highly expressed and uniquely located in PsA, leading to striking erosive changes, why not more periarticular or generalised osteopenia than is seen in RA? Note as well the absence of a key autoreactive T cell of the skin, the cutaneous lymphocyte associated antigen+ T cell, in the synovium. Although it now appears that TNF α inhibition benefits most patients with PsA, as in RA, we cannot yet determine a priori which patients will not adequately respond or why, and we cannot rationally predict a preferable target. As other approaches to specific immunological targeting are shown to be beneficial in psoriasis and/or PsA—for example, "costimulatory blockade" of targets such as LFA-3 or ICAM-1, or other cytokines such as IL1, IL6, or IL15, we will need to try to predict individualised optimal targets.

TNF α therapy clearly has a pleiotropic effect on a variety of key cells and effector molecules. Its central role is to reduce cellular infiltrate of multiple cell types in the skin and synovium, apparently not by apoptosis, but presumably through effects such as decreased adhesion molecule attraction of cells to sites of inflammation. With TNF α inhibition, there is a domino effect of decreased expression of other proinflammatory cytokines and decreased recruitment of activated cells, with consequent down regulation of inflammation both in joints and skin. Because of its central role, inhibition of TNF α has yielded impressive clinical and quality of life improvement in most patients treated and represents a significant advance in

disease management. Demonstration of the specific cellular and immunohistochemical changes that occur with such treatment allows us to understand this effect, deepen our understanding about disease mechanisms, and perhaps point to additional approaches to treatment in the future.

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