ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 1, 60 SECTIO D 2003

Chair and Department of Dermatology, Medical University of Lublin
Department of Clinical Immunology, Medical University of Lublin

ALDONA PIETRZAK, GRAŻYNA CHODOROWSKA,
IWONA JAZIENICKA, AGNIESZKA JUNAK- BOJARSKA,
JACEK ROLIŃSKI

New development in the treatment of psoriasis – infliximab

Psoriasis is a typical hyperproliferative epidermal disease of undefined aethiopathogenesis. One of the most likely hypotheses is that it is related to intrinsic keratinocyte abnormalities of an immunological nature (21). Psoriasis is recognized as an autoimmune disease in which immunocyte-derived cytokines are thought to drive the development of the altered keratinocyte phenotype (15, 4). An explosion of knowledge concerning immunological events in psoriasis and the clinical efficacy of immunologically directed therapies, such as cyclosporin, support this concept (6). Although the role of tumor necrosis factor alpha (TNF-alpha) in psoriasis is not completely understood, it may underline many of the key steps that lead to the induction and maintenance of the disease (18, 11). More recently, biotechnology, using genetic engineering techniques, has created a real possibility for efficacious and safe psoriasis therapy. Recombinant proteins, the outcome of recent biotechnology initiatives, function as agents that comprise biological therapy (19).

Cytokines are mostly glicoproteids with a wide range of molecule mass, from several to 100–200 kD; they are elements of a very extensive system regulating the function of many systems, including the haematoiesis system, immune system, nervous system, connective and structural system. Their characteristic feature is the function of transporting information between the cells at relatively small distances (5).

TNF-α is a pleiotropic cytokine produced by many cell types: monocytes/macrophages, T lymphocytes, NK cells, keratinocytes, Langerhans' cells, mast cells, neutrophils and fibroblasts (3). In the skin, TNF-alpha is a prominent cytokine that seems to be important in allergic and irritant contact dermatitis and inflammatory skin conditions and particular in states that are characterized by lymphocyte infiltration, like among the others psoriasis, atopic skin inflammation, Lyell's toxic epidermonecrolysis (3, 8). TNF-α is able to induce adhesion molecules ICAM-1, ELAM-1 and VCAM-1 in the skin and promote leukocyte infiltration and maturation of Langerhans cells in psoriatic skin lesions, resulting in an increased capacity to activate T cells (18) and induce ICAM-1 expression on keratinocytes (3). TNF-α synthesized by dendritic dermal cells is able to increase the expression IL-8 and tumor growth factor α in adjacent keratinocytes. This indicates that TNF-α affects pathogenesis by activating T lymphocytes, enhancing the infiltration of T lymphocytes into the epidermis, and augmenting the proliferation of keratinocytes in psoriatic plaques (18).

A lot of reports indicate the central role of TNF-α in the cytokine network. Nickloloff considers this cytokine as the crucial factor responsible for the development of psoriasis lesions. TNF-can influence directly or indirectly the principal pathological phenomena in psoriatic skin

through inducing inflammatory cells migration from skin vessels, activation of antigen presenting cells and influence the growth and differentiation of cells playing a role in skin inflammation process. TNF-induced cytokine production (3). TNF-α, a proinflammatory cytokine may play a role in the maintenance of psoriatic plaques because of its elevated biologic activity in lesional skin compared with uninvolved skin (18). Although normal skin only exhibits TNF-α immunoreactivity in eccrine sweat gland epithelium, in psoriatic skin lesions TNF-α can be localized through the epidermis as well as within dermal dendrocytes (18). It was shown that elevated TNF-α activity was observed in psoriatic skin lesions and psoriatic synovium (10). It follows that blockade of TNF-α should diminish inflammation and normalize keratinocyte proliferation in psoriasis (18). A few reports have already suggested that etanercept and infliximab may offer a therapeutic effect in patients with psoriasis (8).

More recently, immune-mediated diseases, for instance psoriasis, Crohn disease and rheumatoid arthritis, have been treated with biological agents designed to inhibit immune responses that are central to their pathological condition. As a consequence of successful biologic therapy for immune-mediated diseases, psoriasis has become a primary target for biologic therapy in dermatology (19).

The immunopathological features of psoriasis provide the basis for a conceptual model that incorporates the mechanism of action and target for rationally designed biologic therapy. There are 4 strategies within this model that clarify the mechanism of action for the various biological agents. These strategies include: 1) reduction of the pathogenic T cells, 2) inhibition of T – cell activation, 3) immune deviation, 4) and blocking the activity of inflammatory cytokines. Some biologic agents may have multiple mechanism of action (19). Infliximab belongs to this group.

Infliximab is an immunoglobulin monoclonal antibody – antagonist of TNF- alfa that binds and inactivates TNF-alpha and has been successfully used in the management of this cytokine mediated diseases (15). Infiximab is an anti TNF-α antibody to be administered intravenously at 4–8 week intervals (1). Infliximab is a mouse-human chimeric monoclonal antibody that neutralizes the biologic activity of tumor necrosis factor α (TNF-α) by binding to the soluble and transmembrane forms of TNF-α and inhibiting the binding of TNF-α with its receptors (18). Infliximab is an anti-tumor necrosis factor alpha monoclonal antibody IgG effective in the treatment and maintenance of remission of active refractory Crohn disease and associated draining enterocutaneous fistulae (20). Binding assays using (125)I-labeled TNF showed that infliximab binds to both monomer and trimer forms of soluble TNF (sTNF). Infliximab formed stable complexes with sTNF, Infliximab also formed more stable complexes with the transmembrane form of TNF expressed on transfected cells. Infliximab was significantly more effective in inhibited transmembrane TNF-mediated activation of human endothelial cells than others (17).

Oh et al. (14) for the very first time used successful anti-tumor necrosis factor alpha therapy in psoriasis in 2000. They treated a 57-year-old woman for refractory inflammatory bowel disease with a humanized anti-tumor necrosis factor alpha monoclonal antibody (Infliximab). The patient also had a 15-year history of Crohn's disease and a 20-year history of moderate to severe psoriasis. She received a single infusion of Infliximab (5 mg/kg). Two weeks after the infusion her psoriasis dramatically improved in appearance. Kirby et al. (7) reported successful treatment of severe, recalcitrant psoriasis when infliximab (a monoclonal antibody to TNF-alpha) was used in combination with methotrexate. Mang et al. (10) treated a 41-year-old-male patient with a 23-year history of severe psoriasis, erytrodermic form and psoriatic arthritis with infliximab which was given intravenously as a single infusion as a dose of 3mg/kg body weight which has to be repeteated every 3–4 weeks. After 10 infusions complete remission was observed.

Schopf et al. (18) conducted eight patients with severe psoriasis. The patients received infliximab, 5 mg/kg, intravenously at weeks 0, 2, and 6. The PASI score was used to monitor disease activity at weeks 0, 2, 4, 6, 8, 10, and 14. Week 10 was the end point of the treatment

phase; week 14 was the follow-up end point. Pruritus was assessed on a scale of 0 to 3. Histological sections were prepared from biopsy specimens of uninvolved skin and of psoriatic lesions at weeks 0, 1, and 10 to measure epidermal thickness with the use of a microscopic micrometer grid. The authors generally observed the improvement of the lesion on the skin, based on the PASI score, pruritus, histological features estimated by epidermal thickeness. No adverse effects other than fatigue during infusion on some occasions were reported. Although psoriasis tends to recur beyond 2 months of the infusions, this open study provides evidence that infliximab is an effective treatment (2002).

O'Quinn and Ryan (15) observed two patients with recalcitrant psoriasis unresponsive to multiple skin-directed and systemic therapies. They were treated with a single infusion of infliximab. The treatments resulted in rapid and complete clearing of psoriatic erythroderma and resolution of symptoms of arthritis in one case and complete clearing of widespread psoriatic plaques and improvement of symptoms of arthritis and inflammatory bowel disease in the other. The single treatments with infliximab were well tolerated with no immediate or long-term adverse effects noted. A single infusion of infliximab at 5 to 10 mg/kg resulted in the rapid and complete clearing of recalcitrant psoriatic plaques and erythroderma with a disease-free interval of 3 to 4 months in those 2 patients and improved the symptoms of psoriatic arthritis (2002).

Ogilvie et al. (13) conducted six patients with progressive joint disease and psoriatic skin lesions unresponsive to methotrexate therapy they were treated with anti-TNF-alpha antibody. The Psoriasis Area and Severity Index was determined before and 10 weeks after initiation of therapy. Improvement of psoriatic skin lesions was observed in all patients. In addition, a marked improvement of the joint disease was noted. Therapy with anti-TNF-alpha antibody may be an effective treatment regimen for both psoriatic arthritis and psoriatic skin lesions (2001).

Chaudhari et al.(2) treated 33 patients with moderate to severe plaque psoriasis . They were dived into 3 groups, randomly assigned intravenous placebo (n=11), infliximab 5 mg/kg (n=11), or infliximab 10 mg/kg (n=11) at weeks 0, 2, and 6. Patients in the infliximab were better responders compared with the placebo group. The mean time to response was 4 weeks for patients in both infliximab groups. There were no serious adverse events, and infliximab was well tolerated. In this controlled test, patients receiving the anti-TNF-alpha agent infliximab as monotherapy experienced a high degree of clinical benefit and rapid time to response in the treatment of moderate to severe plaque psoriasis compared with patients who received placebo (2001).

Infliximab has been associated with a number of adverse events. Infusion reactions are reported in 19% of patients in clinical tests and consist of fever or chills or, more rarely, chest pain, hypotension, hypertension, or dyspnea. Pruritus and urticaria have been also reported. Neutralizing antibodies are formed, and patients can developed a serum sickness reaction days after administration of infliximab (9). Finally, it is possible that drugs targeting TNF-alpha may have yet-unrecognized serious side effects. Because TNF-alpha seems to be a central cytokine in UVR-induced apoptosis, the chronic use of TNF-alpha-altering drugs might increase the risk for skin cancers. Tumor necrosis factor-alpha also plays some role in cutaneous wound healing; the effect these drugs might have on this process is also unknown at this time (8). Infections are common in infliximab-treated patients, probably because many of the patients receive other immunosuppressive therapies such as systemic corticosteroids or methotrexate. In controlled clinical tests, however, there does not appear to be an increased risk of serious infection in infliximab-treated patients (9).

Despite concerns about immunosuppression and infusion reactions, infliximab will undoubtedly play a role in the treatment of our patients with most severe psoriasis. This medication is reliable, resulting in marked improvement in 82% to 91% of patients. The treatment is fast, with patients beginning to respond in 2 weeks, and remissions are long-lasting, with many patients clear of psoriasis for more than 6 months after their last infusion. Infliximab is compatible with methotrexate, and is not associated with nephrotoxicity or hepatotoxicity.

Morover, severe infusion reactions that have been reported occur in fewer than 1% of patients and can be avoided by appropriate pretreatment and monitoring at the time of infusions (9).

Multiple infusions of infliximab show promising results in patients with rheumatoid arthritis. Tan et al. (20) describe 2 patients with Crohn disease and pyoderma gangrenosum and 1 patient with Crohn disease and psoriasis who were treated with infliximab for recalcitrant Crohn fistulae, with concurrent improvement in their skin diseases. These cases suggest that infliximab, a promising therapeutic agent for refractory Crohn disease and fistulae, may also be effective in the treatment of pyoderma gangrenosum and psoriasis associated with Crohn disease (2001).

Van den Bosch et al. (22) conducted a monocentre, open-label pilot study of 21 patients with different subtypes of spondyloarthropathy. Eight of them were suffering form psoriasis arthritis. They used loading dose regimen of three intravenous infusions with infliximab in all patients. Treatment resistant patients with an active disease (fulfilling inclusion criteria) received three infusions of 5 mg/kg infliximab (at weeks 0, 2, and 6). Standard clinical assessments were performed at baseline, and on days 3, 7, and 14, and from then on every two weeks. In patients who fulfilled the criteria for ankylosing spondylitis, axial assessment was performed at baseline and on days 14, 42, and 84. In all global assessments (visual analogue scale of patient global assessment, patient pain assessment, doctor global assessment), erythrocyte sedimentation rate, and C reactive protein, a highly significant decrease could be seen already at day 3 (compared with baseline), which was maintained up to day 84. In patients with peripheral disease (n=18), tender and swollen joint count significantly decreased. In patients with axial disease (n=11), functional and disease activity indices significantly improved. The treatment was well tolerated in all patients; no significant adverse events were seen. There was a fast and significant improvement of axial and peripheral articular manifestations, without major adverse experiences (22). Newland et al.(12) reported a case of rapid response and clinical benefit using infliximab in severe pustular psoriasis of von Zumbusch (2002).

TNF< alpha > blockade, in addition to reducing joint inflammation and leukocyte infiltration, also results in decreased formation of new blood vessels in the synovium. Many endothelial growth factors have been demonstrated in RA, but vascular endothelial growth factor (VEGF) is the most endothelial specific mitogen characterized to date. Expression of VEGF is upregulated in many angiogenesis-dependent diseases, including RA. The central role of angiogenesis in RA suggests that suppression of pannus growth could be a beneficial element of anti-arthritic therapy. Paleolog et al. reported that VEGF blockade, using a human form of the soluble VEGF receptor Flt-1, reduced disease severity, and synergised with anti-TNF< alpha > antibody. These results suggest that in diseases such as RA, anti-inflammatory treatments such as anti-TNF< alpha > might synergise with anti-angiogenic approaches, including VEGF inhibitors, leading to long term benefit. This may be the case not only for RA, but also in other pathologies associated with inflammation and angiogenesis, for example inflammatory bowel disorders, psoriasis and atherosclerosis (16). Modulating TNF-alpha activity in the skin may provide therapeutic benefits for a variety of skin conditions (8).

Patients suffering from psoriasis with a great hope await the safe, "new generation" drugs that would reduce the necessity either to apply daily local medicaments of unpleasant smell, colour, and inconvenient in use, or to receive general treatment also involving different limitations and complications.

REFERENCES

1. Błaszczyk M., Jabłońska S.: Nowoczesne leczenie twardziny. Przegl. Dermatol., 89, 223, 2002.
2. Chaudhari U. et al.: Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. Lancet, 357, 1842, 2001.
3. Chodorowska G.: Badania zachowania się wybranych cytokin prozapalnych i białek ostrej fazy w łuszczycy. Praca habilitacyjna AM Lublin, 1999.
4. Gottlieb A.B. et al.: Psoriasis as a model for T-cell-mediated-disease. Arch. Dermatol., 138, 591, 2002.
5. Jędrzejczak W.W., Podolak-Dawidziak M.: Cytokiny. Zastosowanie kliniczne. Volumed, Wrocław 1997.
6. Kirby B., Griffiths C.E.M.: Novel immune-based therapies for psoriasis. Br. J. Dermatol., 146, 546, 2002.
7. Kirby B. et al.: Successful treatment of severe recalcitrant psoriasis with combination infliximab and methotrexate. Clin.Exp.Dermatol., 26, 27, 2001.
8. LaDuca J.R., Gaspari A.A.: Targeting tumor necrosis factor alpha. New drugs used to modulate inflammatory diseases. Dermatol.Clin., 19, 617, 2001.
9. Lebwohl M.: New developments in the treatment of psoriasis.Editorial. Arch. Dermatol., 138, 686, 2002.
10. Mang R. et al.: Response of severe psoriasis to infliximab. Dermatology, 204,156, 2002.
11. Mease P.J.: Cytokine blockers in psoriatic arthritis. Ann. Rheum. Dis., 60 (SUPPL. 3), 37, 2001.
12. Newland M.R. et al.: Rapid response to infliximab in severe pustular psoriasis, von Zumbusch type. Int. J.Dermatol., 41, 449, 2002.
13. Ogilvie A.L. et al.: Treatment of psoriatic arthritis with antitumour necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. Br. J. Dermatol., 144, 587, 2001.
14. Oh C.J. et al.: Treatment with anti-tumor necrosis factor alpha (TNF-alpha) monoclonal antibody dramatically decreases the clinical activity of psoriasis lesions. Am. Acad. Dermatol., 42, 829, 2000.
15. O' Quinn R.P., Miller J.L.: The effectiveness of Tumor Necrosis Factor antibody (Infliximab) in treating recalcitrant psoriasis. Arch. Dermatol., 138, 644, 2002.
16. Paleolog E.: Anti-TNF< alpha > in the treatment of inflammatory diseases Cent. Eur.J. Immunol., 26, 140, 2001.
17. Scallon B. et al.: Binding and functional comparisons of two types of tumor necrosis factor antagonists. J. Pharmacol. Exper. Ther., 301, 418, 2002.
18. Schopf R.E. et al.: Treatment of psoriasis with the chimeric monoclonal antibody against tumor necrosis factor, infliximab. J. Am. Acad. Dermatol., 46, 886, 2002.
19. Singri P. et al.: Biologic Therapy for Psoriasis. The new theraupetic frontier. Arch. Dermatol., 138, 675, 2002.
20. Tan M.H. et al.: Improvement of Pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. Arch. Dermatol., 137, 930, 2001.
21. Vaccaro M. et al.: Cutaneous Biology. Changes in the distribution of laminin 1 chain in psoriatic skin: immunohistochemical study using confocal laser scanning microscopy Br. J. Dermatol., 146, 392, 2002.
22. Van den Bosch F. et al.: Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann. Rheum. Dis., 59, 428, 2000.

SUMMARY

TNF-α may have an impact on principal pathological phenomena in psoriatic skin through inducing inflammatory cells migration from blood vessels. It follows that blockade of TNF-α should diminish inflammation and normalize keratinocyte proliferation in psoriasis. Infliximab is a mouse-human chimeric monoclonal antibody that neutralizes the biologic activity of tumor necrosis factor α (TNF-α) by binding to the soluble and transmembrane forms of this cytokine and inhibiting its binding to the receptors. We present literature data concerning both application of infliximab in patients with psoriasis and its side effects.

Nowe osiągnięcia w leczeniu łuszczycy - Infliximab

TNF-α może wpływać na zasadnicze zjawiska patologiczne w skórze łuszczycowej poprzez promowanie rekrutacji komórek zapalnych z naczyń do skóry, wpływ na komórki prezentujące antygen oraz wpływ na rozwój i różnicowanie komórek uczestniczących w procesie zapalnym w skórze. Wynika z tego, że zablokowanie TNF-α powinno prowadzić do zmniejszenia reakcji zapalnej oraz normalizacji proliferacji keratynocytów w łuszczycy. Infliximab jest mysio-ludzkim chimerycznym przeciwciałem monoklonalnym, które neutralizuje biologiczną aktywność czynnika martwicy nowotworu α (TNF-α) przez wiązanie rozpuszczalnych i błonowych form TNF-α oraz blokowanie jego wiązania z receptorami. Prezentowany jest przegląd piśmiennictwa dotyczący leczenia za pomocą infliximabu chorych na łuszczycę i jego działań ubocznych.