ANNALES
UNIVERSITATIS MARIE CURIE-SKŁODOWSKA
LUBLIN-POLONIA
VOL. LVIII, N 1, 41 SECTIO D 2003

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Etanercept in psoriasis treatment

The T cell-driven immunopathogenesis of psoriasis has been well recognized since cyclosporine first revolutionized the treatment of psoriasis 20 years ago. It appeared that epidermal hyperproliferation is preceded by invasion of mononuclear cells, in particular the activated forms of T cells. Moreover monocytes/macrophages, polynuclear lymphocytes, mast cells, eozynophils, Langerhans cells are also involved in the formation of inflammatory skin infiltration (4).

Physiotherapy, non-steroidal anti-inflammatory agents, corticosteroids, and disease modifying antirheumatic agents, such as methotrexate, are the most commonly used treatments for psoriatic arthritis (PsA)–11. The methods of general treatment that have been used till now are not only unsatisfactory for many patients, both with psoriasis and psoriatic arthritis, but also cause various side-effects and require permanent monitoring of some biochemical parameters.

Lately, new therapeutical strategies have been investigated, especially so-called biological approaches, based on psoriasis pathogenesis. They include: targeting pathogenic T cells, inducing immune deviation, inhibiting T-cell activation and production of inflammatory cytokines (4,11). Thus, a need for more specific systemic therapy targeting the T lymphocyte appears (3). Without exception, these new systemic agents appear to be remarkably free of systemic organ toxicities (liver, renal, bone-marrow, etc.), with adverse effects being limited to mild flu-like symptoms with only slight increase in the number of infections (e.g., herpes simplex) in comparison with placebo. Not all the agents under evaluation give clinical responses equal to methotrexate or cyclosporine (75% or greater clearing in 75% of cases) (3,9). Although the cellular events underlying the pathogenesis of psoriasis and psoriatic arthritis have not yet been fully elucidated, it is believed that cytokines are important mediators in psoriasis pathophysiology (14).

TNF-α with its ability to affect keratinocyte function, proliferation and differentiation plays crucial role in psoriatic inflammation, as was reported in our previous paper (14). Apart from acting as antineoplastic factor, TNF-α is also a markedly proinflamatory agent. Such a prominent role of TNF-α has been established especially in rheumatoid and psoriatic arthritis (3,4,5,7-15,17). Human TNF-α binding type I and type II receptors (p55 and p75) that are present on the cell surface, induce a reaction cascade that causes its biological effects (6).

One of therapeutic approaches for psoriasis is treatment with inhibitors of proinflamatory cytokines, especially TNF-α, such as monoclonal antibodies or fusion proteins including etanercept and infliximab. These two agents, TNF-α antagonist infliximab and etanercept, have been approved for treatment of rheumatoid arthritis (16) and more recently have been shown to

delay joint damage (3,9). Infliximab (chimeric monoclonal antibody) was presented in our previous article (14). Etanercept (p75TNF-R/ Fc fusion protein) is a monoclonal antibody connected with the domain of human IgG1 which binds to the soluble recombinant TNF-α receptor (2). This agent, being administered subcutaneously twice a week, is the first TNF-α inhibitor approved for use in PsA managing both the joint and cutaneous manifestations of psoriasis (15). Currently, there are many of these 'biologic' drugs in various stages of development and clinical trials, either by the subcutaneous, intramuscular or intravenous route.

Apart from the symptomatic relief that patients achieve, one of the most important advantages of etanercept therapy is the prevention of joint destruction on radiography. Etanercept has been proven to be superior to methotrexate in its ability to prevent radiographic progression of rheumatoid arthritis (13). In the published clinical trials for psoriatic arthritis, psoriasis severity scores, including PASI score, have improved by nearly 50% (1,13). More recent studies have shown a comparable improvement in PASI score in 3 months and additional improvement in 6 months of treatment (10).

Many scientific reports focus on side-effects of TNF-α treatment. During TNF-α infusion and in consecutive 6-8 hours many undesirable reactions were observed in patients: shivering, fever (maximum 39 C), lowering of blood pressure (minimum 80.50 mmHg) nausea, vomiting, muscles pain, headache and fatigue. In laboratory investigations, leukocytosis, granulocytosis, lymphocytopenia, trombocytopenia, and after a few weeks anemia were detected. In the first 24 hours after TNF-α administration the transient increase of transaminases, creatinine, urea was detected. The observed changes of hematological and biochemical parameters were normalized within a few days (6).

Lebwohl (10) described the characteristics of this drug. Etanercept is administered subcutaneously by patients at home. It results in dramatic and rapid improvement in psoriatic arthritis and has been used safely in patients previously treated with metothrexate. Unlike infliximab, etanercept is fully humanized, resulting in substantially less immunogenicity. Nonneutralizing antibodies, anticardiolipin antibodies, and anti-double-stranded DNA antibodies commonly occur, but systemic lupus erythematosus is rare, and in the few reported cases, the major organ involvement has not occurred (10). Because of the mycobacterial infections reported in patients treated with infliximab, the safety of etanercept intake was carefully considered, but routine skin testing for tuberculosis or chest radiography was not performed. There have been rare reports of exacerbation of demyelinating disorders such as multiple sclerosis, or allergic reactions and aplastic anemia (10). Considering the large numbers of patients who have been treated with this medication, it is not clear if the association is real or simply coincidental. Injection site reactions are common adverse effects reported with etanercept therapy (10).

Zeltser et al. (17) studied injection site reactions (ISRs) associated with etanercept therapy. Patients with rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory seronegative arthritis, psoriatic arthritis, psoriasis, or inflammatory bowel disease were investigated. Skin biopsy specimens were taken from selected patients experiencing ISRs. 20% of 103 patients receiving etanercept reported ISRs, all within the first 2 months of beginning the therapy. The reactions occurred 1 to 2 days after the last injection and resolved within a few days. Moreover, eventual waning of reactions was observed, with none proving to be dose limiting. Histological examination of all biopsy specimens taken from ISR areas showed inflammatory infiltrates composed of predominantly lymphoid cells and some eosinophils, in a perivascular cuffing pattern, without evidence of leukocytoclastic vasculitis (17). The infiltrating lymphoid cells were predominantly activated mature cytotoxic T lymphocytes, with a small number of CD4 (+) cells. A biopsy specimen from a recall ISR showed strong HLA-DR expression by epidermal keratinocytes. Injection site reactions associated with etanercept therapy are common, and may be an example of a T-lymphocyte-mediated delayed-type hypersensitivity reaction, with waning over time due to eventual induction of tolerance (17).

Most authors reported a good tolerance of Etanercept (1, 5, 7, 11, 12, 15). Kamarashev et al. (7) reported a case of a 50-year-old male patient with a 15-year history of psoriasis including mutilating psoriatic arthritis, in whom the withdrawal of cyclosporin A induced a generalized pustular exacerbation and aggravation of the joint condition. Two weekly injections of 25 mg of etanercept led to a rapid improvement of his psoriatic arthritis, as well as regression of the pustular eruption, while residual erythema was still present. The clinical response was reflected by an increase in circulating interleukin IL 10 and a decrease in IL-6 and IL-8 serum levels during treatment. Kamarashev et al. (7) concluded that etanercept may be a safe and effective therapy not only in severe psoriatic arthritis, but also in cases of pustular rebound after withdrawal of immunosuppressive agents .

Ruderman (15) described clinical effectiveness of etanercept in patients cases with psoriatic arthritis. The drug was shown to be well tolerated, even for long-term use, and potentially superior to disease-modifying antirheumatic agents.

Scallon et al. (16) using (125) I-labeled TNF showed that etanercept binding is restricted to the trimer form of soluble TNF (sTNF). Etanercept formed relatively unstable complexes with sTNF, resulting in release of dissociated TNF. KYM-1D4 cell killing assays and human umbilical vein endothelial cell activation assays demonstrated that TNF that had dissociated from etanercept was bioactive (16). Etanercept formed complexes with the transmembrane form of TNF expressed on transfected cells but weaker than complexes formed with infliximab (16). Although both infliximab and etanercept inhibited transmembrane TNF-α mediated activation of human endothelial cells, infliximab was significantly more effective (16). The differences between infliximab and etanercept in their TNF binding characteristics may help explain their differential efficacy in Crohn disease and psoriasis clinical trials (16).

Mease et al. (12) examined the effects of etanercept in patients with psoriatic arthritis. Etanercept treatment was well tolerated and resulted in significant improvement in the signs and symptoms of PsA and in psoriatic skin lesions. Infliximab has also been shown to be effective in patients with PsA (12). Such studies confirm the importance of proinflammatory cytokines in PsA and create new options for treatment of this disease (11, 13, 14) .

Iyer et al. (5) conducted an uncontrolled trial. Etanercept was added to the treatment regimen in six patients with severe recalcitrant psoriasis (including three with psoriatic arthritis) partially resistant to other ongoing systemic agents. In each case, the disease activity showed marked improvement on addition of etanercept therapy. No added toxicity was connected with etanercept (5).

Mease et al. (12) assessed the efficacy and safety of etanercept (25 mg twice-weekly subcutaneous injections) during a 12-week study in 60 patients with psoriasis and psoriatic arthritis. 26% of etanercept-treated patients achieved a 75% improvement in the PASI, compared with none of the placebo-treated patients. The mean PASI improvement was 46% in etanercept-treated patients versus 9% in placebo groups. Etanercept was well tolerated during 12 weeks of treatment (12).

The primary pathologic sites of psoriatic spondyloarthropathy are the entheses (the sites of bony insertion of ligaments and tendons); the axial skeleton, including the sacroiliac joints; the limb joints. Spondyloarthropathies occur in genetically predisposed persons and are triggered by environmental factors, but the cellular and molecular mechanisms of inflammation are not yet fully understood. HLA-B27 molecule is involved in enhancing genetic susceptibility, but the underlying molecular basis is still unknown; additional genes include the putative susceptibility genes for Crohn disease, ulcerative colitis, and psoriasis (8,13). The efficiacy of the spondylorthropaties treatment with etanercept was described by Khan et al. (8) .

Etanercept may also play an important role in modulating the inflammatory activity and progression of human immunodeficiency virus (HIV)-associated psoriasis and psoriatic arthritis (1). Aboulafia et al. (1) reported the case of a 45-year-old homosexual man with a CD4 cell count of less than 0.05 x 10(9)/L and an HIV viral load of 4200 copies/mL (while receiving highly active antiretroviral therapy), who developed extensive psoriatic plaques, 4.5-kg weight

loss, onychodystrophy, and psoriatic arthropathy with severe periarticular bone demineralization. The arthritis progressed despite the use of several disease-modifying medications, including corticosteroids, hydroxychloroquine, and minocycline. Because of uncontrolled, progressive, and disabling arthritis resulting in profound disability, he was treated with etanercept. Within 3 weeks, his psoriasis improved dramatically and his joint inflammation was stabilized. For the next 4 months, immunologic and viral parameters remained stable, but his clinical course was complicated by frequent polymicrobial infections. Etanercept was thus withdrawn despite continued improvements in his psoriasis, psoriatic arthritis and functional status. While both cutaneous and joint manifestations of psoriasis improved dramatically, the experience with this patient dictates that caution and careful follow-up must be exercised when prescribing etanercept in the setting of HIV infection (1).

Etanercept appears to be a promising immunomodulatory agent that can be used in combination therapy for the treatment of psoriasis, and a prospective controlled trials may be warranted.

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SUMMARY

More recently, lots of new drugs regulating the several steps of immune reaction have been introduced for psoriasis treatment. These include TNF-α inhibitors. One of such inhibitors is Etanercept – a monoclonal antibody connected with human IgG1 binding the soluble form of TNF-α receptor. We present the literature data concerning the attempts of Etanercept treatment and local and general complications of its use.

Etanercept w leczeniu łuszczycy

Ostatnie lata przynoszą wiele odkryć leków stosowanych w leczeniu łuszczycy i łuszczycowego zapalenia stawów, opartych na blokowaniu poszczególnych etapów reakcji immunologicznych. Należą do nich inhibitory TNF-alfa. Jednym z nich jest Etanercept – przeciwciało monoklonalne połączone z ludzką IgG1, które wiąże się z rozpuszczalnym receptorem TNF-alfa. Opisano dotychczasowe próby leczenia tym preparatem, powikłania miejscowe i ogólne, podane w literaturze.