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Etanercept

Etanersept

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Abstract

Etanercept is a recombinant human receptor fusion protein that suppresses, as a contestant, the interaction of TNF-α with cell surface receptors. It received FDA approval in 1999 to be used in children older than 2 years for the treatment of juvenile idiopathic arthritis. In September 2004, it received approval for the treatment of patients with moderate to severe psoriasis who do not respond to conventional systemic treatments or for whom these therapies are contraindicated or intolerable.
Keywords: Etanercept, TNF-α, psoriasis

Öz

Etanersept, TNF-α'nın hücre yüzey reseptörleri ile etkileşimini yarışmacı olarak baskılayan rekombinant insan reseptör füzyon proteinidir. Juvenil idiyopatik artritte iki yaş üstü için 1999 yılında FDA onayı almıştır. Eylül 2004'te ise sistemik konvansiyonel tedavilere yanıt vermeyen, bu tedavilerin kontrendike olduğu veya tolere edilemediği orta-şiddetli psoriasis hastalarının tedavisi için onay almıştır ve aralıklı tedavide de etkindir.
Anahtar Kelimeler: Etanersept, TNF-α, psoriasis

Introduction

Etanercept is a recombinant human receptor fusion protein that suppresses, as a contestant, the interaction of TNF-α with cell surface receptors. It prevents TNF-α mediated cellular response and regulates the activities of other proinflammatory cytokines that are affected by TNF-α[1].

Etanercept shows its action by binding and neutralizing TNF-α, which is an important cytokine in many inflammatory diseases such as arthritis, Crohn's disease and psoriasis. It is used in the treatment of patients with moderate to severe psoriasis who do not respond to conventional systemic therapies, or for whom these therapies are contraindicated or intolerable. It received approval for the treatment of psoriasis in September 2004[2].

Mechanism of action

Etanercept is the human dimeric fusion protein of the Fc IgG1 receptor and the extracellular area of the TNF-α receptor. It suppresses as a contestant the interaction of TNF-α in circulation with cell surface receptors[3]. It is slowly absorbed from the injection site with an absolute bioavailability of 60%; it reaches its maximum concentration in 51 hours and has a 68-hour half-life. It diffuses through all tissues and becomes stable before week 12. If used in a dose of 50 mg twice weekly instead of 25 mg twice weekly, its serum concentration becomes twice as much at the end of week 12. Before re-entering the circulation or being eliminated in bile or urine, it is most probably metabolized through a proteolytic process[4].

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The dimeric nature of etanercept allows the protein to bind to two, either free or receptor-bound, TNF-α molecules[2].

Dosage/treatment scheme

- Induction dose (weeks 0-12): 2x25 mg or 2x50 mg weekly.
- Maintenance dose (weeks 13-24): If PASI75 has been achieved at week 12, 2x25 mg/week, 50 mg/week.
- If PASI75 has not been achieved but there is a PASI50 response as a minimum, 2x50 mg/week.

Etanercept has also been found effective in intermittent treatment. In a study efficacy was found higher in patients who had a good response at week 12 but still used it continuously for 24 weeks compared to those who, after the response, received treatment only at weeks 16 and 20 when they needed it[5].

The cumulative dose is lower in intermittent treatment. A low-dose intermittent therapy is more economical than a low-dose continuous therapy or a high-dose intermittent therapy[6].

Efficacy

In their meta-analysis on efficacy, Lucka et al.[7] reviewed 33 articles involving a total of 6575 patients who actively received treatment in 27 studies. At the end of 24-week treatment, infliximab and ustekinumab (90 mg every 12 hours) were found most efficacious, and adalimumab was found to have a similar efficacy to etanercept in different doses (etanercept 50 mg/week, etanercept 25 mg twice weekly, etanercept 50 mg twice weekly, etanercept 50 mg twice weekly until week 12 and then 25 mg twice weekly). After week 24, there was a drop in the efficacy of infliximab, adalimumab and etanercept.

PASI75 response with etanercept ranged between 25-75.3% depending on the dose; 50 mg twice weekly showed 59% efficacy and 25 mg twice weekly a 44-57% efficacy[7].

According to the results of a meta-analysis made by Puig et al.[8], the PASI75 response rates at the end of 24 weeks were 78% for infliximab, 77% for ustekinumab 90 mg, 70% for ustekinumab 45 mg, 60% for adalimumab, 50% for etanercept 100 mg/week for 12 weeks and 50 mg/week thereafter, 45% for etanercept 50 mg/week.

The meta-analysis showed that the most effective agent for a PASI75 response at the end of 24 weeks was ustekinumab, which was followed by infliximab, adalimumab and enanercept[9].

The studies have reported different anti-etanercept antibody levels; 3 studies found between 1.1 and 1.6%, reporting that it was not correlated with response to treatment. Another study found 18.3% when a 50 mg dose was used twice weekly and noted that antibodies were non-neutralizing and unrelated to the efficacy and side effect status[10].

Follow-up

Patients should be assessed in terms of infection during every examination. If the intended efficacy as shown by PASI and/or DLQI has not been achieved at the end of a 12-week therapy, etanercept should be discontinued[2,11]. See the introduction and general information sections for the laboratory examinations required to be done before and during an etanercept therapy.

Side effects/safety

Etanercept is a safe biological agent when used in line with the guidelines. The risk of kidney and liver failure is rarely seen in an etanercept therapy.

A 5-year prospective follow-up study investigating the safety of biologics on 173 subjects, the majority of whom were in the etanercept group, found that the incidences of malignancies excluding skin malignancies, serious infections and serious cardiovascular side effects were similar to those in the general population. A total of 1530 side effects in 169 subjects were reported. Two of the four deaths were due to cardiac arrest at months 12 and 15 of the etanercept therapy. One of these subjects had a history of hypertension and stroke, and the other chronic obstructive pulmonary disease. Myocardial infarction was found in one patient during autopsy 4 days after the etanercept therapy. Squamous-cell carcinoma was seen in the first year of the etanercept therapy of a patient who had a history of long-term UVB/PUVA therapy. Invasive ductal carcinoma was reported in a 66-year-old female patient and colon-originated metastatic cancer in a 76-year-old male patient who both were receiving etanercept. A patient who had been diagnosed with breast cancer 8 years before her etanercept therapy received the drug for 3 months and another patient who had been diagnosed with urinary bladder cancer took etanercept for 2.7 years and neither of them had any recurrence. Latent tbc was detected in a patient during the therapy; the drug was stopped and isoniazid was started. Perimesencephalic bleeding developed in a patient after a 10-month etanercept therapy. Pre-existing hidradenitis suppurativa aggravated in two patients.

Three births occurred while taking etanercept. Father was using the drug in two cases and mother in one. In the female patient, the therapy was discontinued at gestational week 4. Ductus arteriosus was detected in the baby of one of the male patients and the child had a complete recovery.

Bilateral uveitis found at year 3.8 of the therapy in a patient was not linked to the drug. As a result of these, it was agreed that etanercept was a low-risk agent in terms of drug-associated side effects[12]. Histoplasmosis was not observed in any of the 17696 patients (1283 with psoriasis) who were assessed in 38 etanercept clinical studies and 4 cohort studies. Cutaneous cryptococcus was reported in a 14-year-old patient who was using etanercept due to psoriasis. Based on the studies, it can be said that deep fungal infections are not seen in patients with psoriasis who are taking etanercept[13].

Paediatric use

Etanercept received FDA approval in 1999 to be used in children older than 2 years for the treatment of juvenile idiopathic arthritis.

The efficacy and safety of etanercept was investigated in 211 children and adolescents (age: 4-17) with moderate to severe psoriasis during or after a topical therapy, phototherapy or conventional systemic therapy. The endpoint was PASI75 at the end of week 12. Etanercept was found markedly superior to placebo (PASI75, 57% and 11%). In the later period, the rate of PASI75 was 65% at the end of week 36 in the children who first received placebo and then switched to etanercept and 68% in those who received etanercept from the beginning. The rate of PASI75 at the end of week 48 turned out to be 80%[14].

Absolute contraindications

Active infections, active TB, immunosuppressive therapies, malignancies (except treated non-melanoma skin cancers and malignancies that had been treated 5 years ago), demyelinating diseases, congestive heart failure [New York Heart Association (NYHA) classes 3 and 4] cause hypersensitivity to the drug.

Relative contraindications

These include over 200 sessions of psoralen ultraviolet A (PUVA) therapy, over 350 sessions of ultraviolet B (UVB) and particularly patients who used cyclosporine thereafter, HIV positive or AIDS patients, hepatitis B or C positive patients, congestive heart failure (NYHA class 1 and 2), recurrent infections, live vaccines, and infections.

Drug interaction

There is the risk of neutropenia and serious infections when taken with anakinra, increased immunosuppression when taken with immunosuppressive drugs, and skin cancer when used with PUVA[2].

Combination therapies

Its combination with methotrexate may increase the efficacy[15]. Its combination with acitretin has been found more effective than acitretin alone, without additional toxicity[16]. Its use with cyclosporine is not recommended. In a study where etanercept and NB-UVB were used in combination, the combination therapy was found more effective than etanercept alone, but increased risk of skin cancer should be taken into consideration[17]. Its use with PUVA is not recommended although there is no evidence-based study on their use in combination.

Transition

In combination therapies, a conventional agent should be added to a biological agent in its lowest dose (e.g. methotrexate 5-10 mg/week). Prolonging treatment intervals for etanercept may be necessary. Any transition between biologics due to inefficacy should be made in the standard induction dose in the next scheduled treatment time without waiting for the washout period. If it is being made due to safety concerns, the transition should wait until the safety parameters return to normal. In the case of primary or secondary non-response, the dose of etanercept should be increased from 50 mg/week to 2x50 mg/week. When switching from etanercept to another biological agent, adalimumab, infliximab and ustekinumab may be given in their induction dose a week after the last dose of etanercept[18].

EVIDENCE-BASED TREATMENT SUGGESTIONS

- It is used for the treatment of moderate to severe psoriasis and psoriatic arthritis in patients not responding to other systemic treatments including cyclosporine, methotrexate and PUVA, or for whom these therapies are contraindicated or intolerable.
- Induction dose (weeks 0-12): 2x25 mg or 2x50 mg weekly.
- Maintenance dose (weeks 13-24): If PASI75 has been achieved at week 12, 2x25 mg/week, 50 mg/week.
- If PASI75 has not been achieved but there is a PASI50 response as a minimum, 2x50 mg/week.
- Efficacy assessment at week 12; if efficacious, treatment to continue as long as viable.
- Etanercept has also been found effective in intermittent treatment.
- A combination with low-dose (7.5 mg/week) methotrexate may be considered to improve efficacy during treatment.
- When switching to another biological agent, the next intended therapy may be started in its standard induction dose without waiting for the washout period.

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