DRUG REVIEW

Etarnacept

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Introduction

With new advances in the world of chronic inflammatory diseases, newer biological agents are promising. Steroids have been described as the best anti inflammatory drugs but their long term use has significant side effects (1). There is always a need for the agent which provides long term remission and fewer side effects. Evidence is now accumulating that anti tumor necrosis factor (TNF) therapy is highly effective in various inflammatory diseases which are refractory to commonly used drugs. In this group etanercept is one of the newer biologic agents available and is being used in the treatment of number of conditions. In this article we have attempted to review the profile of this drug and its role as immunosuppressant.

Mechanism of Action (1,2)

Tumor necrosis factor (TNF) á, a pro inflammatory cytokine has been implicated as the main culprit in pathogenesis of various inflammatory diseases like rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel diseases and psoriasis. In most of the inflammatory conditions, activated T cells in the synovial tissue of the joints produces interferon and other proinflammatory cytokines that in turn stimulate macrophages and fibroblasts. Activated macrophages and fibroblasts release a variety of cytokines, interleukins and TNF á in stem of cytokine system. TNF á exerts its effect with the help of two receptors; type I receptor (P 55) and type II receptor (P 75). Etanercept is a recombinant soluble P75 tumor necrosis factor receptor protein. It is a dimer of covalently bound receptors of the type II TNF receptors linked to Fc portion of human IgG1. It binds specifically to tumor necrosis factor á and prevents its binding to the receptor. Etanercept competitively inhibits the interaction of TNF with cell receptor and prevents TNF mediated cellular response and moderates the activity of other proinflammatory cytokines, rendering the TNF biologically inactive. It effectively reduces erosive damage to the joint, decreases the disability and improves the quality of life in patients of rheumatoid arthritis and ankylosing spondylitis. Tumor necrosis factor inhibitors were first licensed for use in 1998.

Pharmacokinetics

The standard dose of etanercept in adults is 25 mg subcutaneous twice-weekly (2). Recommended dosage for pediatric patients with age ranging from 4 – 17 years with juvenile rheumatoid arthritis is 0.4 mg/kg (maximum up to 25 mg) given twice weekly. Etanercept is slowly absorbed from the site of injection after subcutaneous administration. Peak concentration is 1460 ± 720 ngm/ml achieved at a mean time of 51 ± 14 hours. Elimination of etanercept in healthy subjects has mean half life of 68 ± 19 hours. Volume of distribution is 12 ± 6 lit. It is well absorbed and its bioavailability after single subcutaneous dose is approximately 58%. Its mean elimination half life is 102 ± 30 hours. Pharmacokinetic parameters have not been shown to vary with age or gender. There is no literature available till date regarding the effects of renal or hepatic impairment on etanercept disposition.

Indications

***Rheumatoid Arthritis*:** In patients with rheumatoid arthritis, etanercept has been shown to have improvement in number of swollen joints, number of tender joints, disease activity score, erythrocyte sedimentation rate, C-reactive protein, and global health status(3). In addition to this, TNF blockers in rheumatoid arthritis have shown increased bone formation and decreased bone resorption (4). So far this drug has been used in patients with progressive and erosive rheumatoid arthritis who had

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inadequate response to conventionally used DMARDs (disease-modifying antirheumatic drugs) but not as a first line drug.It is effective as monotherapy (5) as well as with other DMARDs like methotrexate in patients with established rheumatoid arthritis. On the basis of data available so far it seems that patients who have suboptimal response to methotrexate at adequate doses (20 – 25mg/ week) are the best candidates for this biologic therapy (5).

One major trial done by Bathon *et al* (5) compared the results in 632 patients with early rheumatoid arthritis with either twice-weekly subcutaneous etanercept (10 or 25 mg) or weekly oral methotrexate (mean, 19 mg per week) for 12 months. The study showed that patients who received the 25-mg dose of etanercept had a more rapid rate of improvement, more efficacy and less bone erosion. If compared to oral methotrexate, etanercept acts more rapidly to reduce symptoms and slows joint damage in patients with early rheumatoid arthritis. In addition to reducing signs of rheumatoid arthritis, inhibition of TNF may prevent or slow down the progressive joint destruction.

***Ankylosing spondylitis*:** Till date no therapy with disease controlling antirheumatic drug is available for spondyloarthropathies especially ankylosing spondylitis. Inman conducted a retrospective study to determine the effect of etanercept in early onset ankylosing spondylitis. After 24 weeks of treatment, 66% of patients receiving etanercept responded, versus 18% of patients receiving placebo (6)

A double blind randomized trial conducted by P Geher et al has confirmed that etanercept significantly reduces the symptoms and disease activity and this effect is sustained during the therapy (7). In patients of ankylosing spondylitis with BASDAI score more than 4 after maximam dose of 2 diffrent NSAIDs for one month etanercept is recommended. This agent is also useful in undifferentiated spondyloarthropathies (8).

Jennifer *et al* (9) conducted a randomized double blind, placebo controlled trial in 40 patients of ankylosing spondylitis. After 4 months 80% of patients on etanercept therapy showed treatment response as compared to 30% in placebo group. Etanercept group showed improvement in various measures of disease activity including morning stiffness, spinal pain, functioning, quality of life, chest expansion, erythrocyte sedimentation rate, and C-reactive protein. Response to etanercept was rapid and did not diminish with time in this study.

Psoriasis: Treatment with etanercept is being widely adopted for moderate to severe psoriasis due to favorable safety and efficacy profiles (10). Long term efficacy has been proved after 48 weeks of continuous therapy.A placebo controlled double blind phase III study was conducted in 672 patients. Patients were randomized 1:1:1:1 to receive placebo, etanercept 25 mg once weekly, 25 mg twice weekly, & 50 mg twice weekly. Analysis showed thatpatients who received 25 or 50 mg twice weekly, showed 32 & 47% improvement at 12 weeks & 41 and 54% at 24 weeks respectively (11).

Other Uses : Etanercept can induce a high response rate in patients with steroid refractory acute as well as chronic graft vs. host disease (12). Recently etanercept has also been used in treatment of patients with Alzheimer's disease with encouraging results (13). It might be effective in familial Mediterranean fever in combination with thalidomide in colchicin resistant cases (14). It has also been successfully used in patients of mucous membrane pemphigoid, though it has been used in very limited number of patients (15). Etanercept 25mg SC twice daily has been shown to produce a noticeable decrease in all pathological and laboratory findings of severe gouty arthritis and refractory chronic tophaceous gout (16).

Precautions

Prior to initiation of the treatment with etanercept, possibility of latent tuberculosis should be excluded and if the patient is at risk, anti tubercular treatment prophylaxis should be considered as reactivation of latent ***Mycobacterium tuberculosis*** has been reported (17).

However, more cases of TB have been reported with infliximab than with etanercept or adalimunab. Differences between infliximab and etanercept have also emerged with respect to their utility.Infliximab is efficacious in granulomatous inflammatory diseases such as luminal and fistulising Crohn's disease, and sarcoidosis whereas etarnacept is ineffective in these conditions. Possibly, infliximab has a capacity to disrupt established granulomas thereby causing reactivation of TB. Since TNF-alpha is initially expressed on the surface TNF

blockers and cells such as memory T cells, activated lymphocytes and monocytes before being cleaved off by the TNF-alpha converting enzyme, a wide range of cells including T cells may be susceptible. Infliximab and adalimumab (but not etanercept) fix the complement and can lyse cells that express TNF-alpha on their surface. Indeed, preliminary reports confirm this in vivo, with a decrease in the absolute number of peripheral blood CD4+ T cells which express interferon and TNF- alpha in patients on infliximab and a reciprocal increase in those on etanercept.Infliximab has longer half-life (210 hours) and attains higher serum levels immediately after dose administration.It produces a continuous blockade of TNF-alpha in irreversible manner in contrast to etanercept.Etanercept tends to form relatively unstable complexes, allowing dissociation of TNF-alpha. Differential inhibition of TNF-alpha signalling is also responsible for this difference in reactivation of TB. Infliximab inhibits both TNF-alpha receptor p55 and p75 mediated events. Etanercept, on the other hand, leaves TNF-alpha receptor p55 mediated signalling partially intact(18).

Serious infections have been reported with the use of etanercept. Therefore any co existing serious illness should be ruled out before starting etanercept (19). Any patient developing new infection while on etanercept should be monitored closely.Previous malignancy (within 5 years) should be ruled out (10).

Etanercept should also be avoided in chronic infections like hepatitis B and hepatits C. Live vaccination is contraindicated in patients who are receiving etanercept. Combination of TNF inhibitors with new biological agents such as anakinra (interleukin 1 receptor antagonist) and abatacept is not recommended as it has been shown to increase the risk of serious infections. Rarely pancytopenia and aplastic anemia have been reported with etanercept therapy.Etanercept should be used with caution in patients with congestive heart failure although there is no conclusive data available as of now. Caution is recommended in use of etanercept with past history of demyelinating disease (19).

Pregnancy & Lactation

Patient should be advised not to conceive while on etanercept.Safety of etanercept has not been established in pregnancy and lactation. Therefore it should be used during pregnancy & Lactation (20).

Adverse Reactions

Although etanercept is very effective therapy, greatest concern is about the undesired and potential severe side-effects. The adverse effects of etanercept are as follows:Injection site reactions, Increased risk of serious infections (21),Opportunistic infections have been reported as the commonest adverse effects (22) ,Exacerbation of previously quiescent multiple sclerosis(23) ,Aplastic anemia, Interstitial lung disease.Lupus like syndrome, Hepatotoxicity, Reactivation of prior tuberculosis, Optic neuritis (rare), An increased risk of lymphoma has also been reported. Therefore it should be used cautiously in patients with history of malignancy (24).

Advantages

Higher incidence of granulomatous infections like tuberculosis and histoplasmosis has been reported with use of infliximab and adalimumab as compared to etanercept (24,25) Several trials have shown increased risk of malignancy with use of infliximab and adalimumab but not with etanercept.

Discontinuation of Treatment

Treatment should be stopped if there is drug related toxicity or the efficacy is not seen with in 3 – 6 months of treatment. If one TNF inhibitor is stopped because of drug related toxicity or lack of efficacy, another one can be tried. Temporary withdrawal of treatmentis also required in severe infections or in the event of pregnancy. Some authors recommend temporary withdrawal of the treatment during surgery to avoid infections (24,25).

Limitations

Unavailability of data on long term efficacy and safety.Lack of statistical comparison of this drug with new drugs.High cost, especially for people in developing country like India. 24 weeks therapy costs approximately Rs 4.32 lacs Increased risk of infection as well as aplastic anemia (24,25)

Conclusion

Etanercept appears a promising newer biologic agent but long term follow up of patients will be required for more frequent usage of this drug.

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