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Adalimumab

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Abstract

Adalimumab, an entirely human monoclonal antibody, specifically blocks the cell-surface receptor relationship of tumor necrosis factor-alpha (TNF-α) with p55 and p75 TNF-α, thereby suppressing the biological activity of TNF-α. It received FDA approval in 2008 for the treatment of moderate to severe psoriasis that does not respond to conventional treatments or for which these treatments are contraindicated or intolerable. Adalimumab is also indicated for the treatment of moderate to severe chronic plaque psoriasis in children aged 4 and over. Administered via subcutaneous injections, adalimumab is also suitable for intermittent use under certain conditions.
Keywords: Adalimumab, TNF-α, psoriasis

Öz

Tamamı insan monoklonal antikoru olan adalimumab, spesifik olarak tümör nekroz faktörü-alfa (TNF-α) ile p55 ve p75 TNF-α hücre-yüzey reseptör ilişkisini bloke ederek, TNF-α'nın biyolojik aktivitesini baskılar. Konvansiyonel tedavilere yanıt vermeyen, bu tedavilerin kontrendike olduğu veya tolere edilemediği orta-şiddetli psoriasis tedavisinde 2008'de FDA onayı almıştır. Adalimumab, 4 yaş ve üzeri çocuklarda da orta ve şiddetli kronik plak tip psoriasis tedavisinde endikedir. Subkütan enjeksiyonlar şeklinde uygulanan adalimumab, belli koşullarda aralıklı kullanıma da uygun bir ajandır.
Anahtar Kelimeler: Adalimumab, TNF-α, psoriasis

Introduction

Adalimumab is used for the treatment of moderate to severe plaque psoriasis in adults and the treatment of chronic plaque psoriasis in children and adolescents aged 4-17 years who do not give sufficient response to, or are not eligible for, systemic therapies (cyclosporine, methotrexate or PUVA). Adalimumab received in 2008 an FDA approval for the treatment of adult plaque psoriasis and an EMA approval for the treatment of paediatric severe chronic plaque psoriasis[1].

Mechanism of action

Being entirely a human monoclonal antibody, adalimumab specifically blocks the cell-surface-receptor relationship of tumour necrosis factor-α (TNF-α) with p55 and p75 TNF-α, thereby suppressing the biological activity of TNF-α. Adalimumab also induces apoptosis of all TNF-expressing mononuclear cells[2]. It has been shown during treatment that the number of regulator T (Treg) lymphocytes increases in peripheral blood but the number of memory B lymphocytes does not change, and the reason was linked to the fact that adalimumab did not block lymphotoxins (TNF-beta)[3]. Pharmacokinetic and pharmacodynamic studies have demonstrated that the average half-life is 11.8 days after a dose of 0.5 mg/kg[4].

Dosage/treatment scheme

Adalimumab is administered as subcutaneous injections. When treating psoriasis, an induction dose of 80 mg is given

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first, and a week later, another dose of 40 mg; and then, the therapy continues with 40 mg subcutaneous adalimumab given regularly every 2 weeks. A fixed dose is used in overweight and obese patients[4,5].

Efficacy

In a 52-week, multicenter, randomised and placebo-controlled Phase III study (REVEAL) conducted by Menter et al.[6], the short- and long-term clinical efficacy, safety and tolerability of adalimumab was investigated. The study randomised 1212 patients with psoriasis and the rate of achieving PASI75 turned out to be 71% in the adalimumab group and 7% in the placebo group at week 16. The same study included 840 patients who completed the 52 weeks and continued with the adalimumab therapy in the long-term efficacy and safety study. At the end of this 3-year study, the rates of achieving PASI75, 90 and 100 were 83%, 59% and 33% respectively at week 100, and 76%, 50% and 31% at week 160[7]. Adalimumab is also successfully used in psoriatic arthritis. In a study made with 51 patients with active psoriatic arthritis resistant to other therapies, subcutaneous adalimumab 40 mg was administered every other week for 12 weeks, and when compared with the placebo group at the end of 12 weeks, arthritis symptoms, quality of life and psoriasis lesions improved significantly in the patient group taking adalimumab[8]. In another study made by Gladman et al.[9], adalimumab was used for 48 weeks and found safe and effective in the long-term; at the end of the treatment, ACR20 was found 56%, ACR50 44% and ACR70 30%, and PASI75 58%, PASI90 46% and PASI100 33%. In the BELIVE study conducted by Thaci et al.[10] with 730 patients, 366 patients used adalimumab in combination with topical calcipotriol and betamethasone and 364 patients adalimumab alone, and the time it took them to achieve PASI75 response was evaluated.

While the rate of achieving PASI75 response at weeks 2 and 4 was considerably higher in the group receiving the combination therapy compared to the group using adalimumab alone, it was found similar in both groups at week 16[10]. Adalimumab is also suitable for intermittent use under certain conditions. 460 patients who had joined the REVEAL study and achieved PASI75 response were randomised at week 33 to continue with an extended open-label protocol.

Of these patients, 233 continued without a break to take adalimumab under the same protocol, The 227 patients who used placebo were included in the treatment again when their response fell below PASI50. This study, which was conducted by Papp et al.[11] to investigate the efficacy and safety of intermittent versus continuous long-term treatment, reported that long-term drug therapy had similar efficacy and safety to that of a 33-week therapy. When compared with the group using long-term treatment, the group that restarted the therapy after having a 19-week break was observed to have a very similar efficacy. Particularly the response obtained in the intermittent treatment where new treatment cycles were started before dropping to a PASI50 response was far better[11]. According to the ADEPT study, the efficacy of adalimumab in patients with psoriatic arthritis lasts 2 years and its joint damage inhibiting effect as shown in radiological imaging continues for a period of 144 weeks[12]. Studies on the efficacy of adalimumab in palmoplantar and nail psoriasis recommend it as a monotherapy due to its rapid and profound effect in these conditions[13-15]. When the effect is inadequate or has a declining trend at the beginning or during an adalimumab therapy, a transition to a 40 mg SC weekly dose may be considered; this has been shown to be more successful in controlling the disease[16]. If the desired effect could not be attained with a 40 mg weekly dose within 4 months, then switching to another agent should be considered.

Follow-up

Achieving PASI75 response by week 16 of an adalimumab therapy is the main indicator of efficacy. Patients giving insufficient response may benefit from increasing the dosing frequency to 40 mg weekly after week 16. In patients who achieve satisfactory response with a 40 mg weekly dose, the therapy should be continued with a 40 mg biweekly dose again. The treatment will be continued in this way as long as the efficacy prevails and no adverse effect develops. Patient follow-up should be carried out as outlined in Table 1.

Table 1. Before and during an adalimumab therapy

	Pre-treatment	Every 3 months	Every year
CBC	x	x	x
ALT/AST	x	x	x
FBS/urea/creatinin	x	x	x
Complete urinalysis	x	x	x
HBs	x		x
Anti-HBs	x		x
Anti-HBc total	x		x
Anti-HCV	x		x
Anti-HIV	x		x
Quantiferon	x		x
Chest X-ray	x		x

Adverse effects/safety

The most common side effect seen during the treatment is the injection site reaction. In clinical studies conducted with adults and children, injection site reactions (erythema and/or itching, haemorrhage, pain or swelling) have been observed in 12.9% of the patients treated with adalimumab and 7.2% of those who received placebo or an active control. Injection site reactions have not usually necessitated the discontinuation of the drug[17]. Other common adverse reactions include upper respiratory tract infections, nasopharyngitis, sinusitis, headache, musculoskeletal pain and morbilliform skin rashes. Urticaria, elevated transaminases, pustular dermatitis, itching, angioedema, thrombocytopenia, and leukopenia are seen rarely. Worsening congestive heart failure, increased risk of malignancy and tuberculosis reactivation have been reported very rarely[8]. In their study, Gordon et al.[18] did not see a significant difference between the groups taking adalimumab and placebo in terms of infection and reported tuberculosis in only one patient. Menter et al.[6] reported in the REVEAL study made with 1212 patients that 2% of the patients using adalimumab had mild and moderate side effects. Another study published by Gordon et al.[7] in 2012 reported that no peculiar safety issue occurred in those patients in the REVEAL study who continued with the treatment using adalimumab for 3 years without a break. Side effects occurring during

treatment are mostly seen in older patients and have more serious outcomes[19]. Despite its pregnancy category being B, use of it during pregnancy and lactation is not recommended[1]. In the presence of psoriasis and hepatitis B or C together, adalimumab must definitely be used according to the suggestions of gastroenterology and under close monitoring[20,21]. Discontinuation of adalimumab, whose half-life is 2 weeks, is not considered necessary during minor surgeries[22].

Contraindications

Adalimumab is contraindicated for patients who are oversensitive to it or its excipients and who have severe infections such as active tuberculosis or sepsis, opportunistic infections, any malignancy, moderate to severe heart failure (NYHA [New York Heart Association] class III/IV) or a demyelinating disease[17,23].

Drug interactions

As it increases serious infection risk, adalimumab should not be used in combination with other anti-TNFs, anakinra, or abatacept[17].

Combinations

It is argued that when adalimumab is used in combination with low-dose (7.5-15 mg/week) methotrexate, its effectiveness increases. Its combinations with topical corticosteroids, systemic acitretin and narrow-band UVB are also recommended to increase the effectiveness of adalimumab[17-19,23].

Paediatric use

Adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in children aged 4 and over[1]. For children, a subcutaneous dose of 0.8 mg/kg (maximum 40 mg) twice with 1 week interval and then continuing with the same dose every other week is recommended. In an efficacy study comparing it with methotrexate, which is used frequently in children, 58% of the children using adalimumab achieved a PASI75 response at week 16 while only 32% of those using methotrexate could achieve the same result[24]. Adverse effects were found similar in both groups.

Use during COVID-19 pandemic

Using adalimumab during the pandemic is said to not increase the risk of viral infections and continuation of the therapy without a break is recommended keeping the benefit-harm ratio in mind. In 62 observational studies published in the first 5 months of the pandemic, 319,000 patients who used immunosuppressive therapy and had an autoimmune disease were analysed and the prevalence of COVID-19 was found to be 0.011. When the therapies used were assessed against increased infection risk, hospitalization and death risk, only systemic steroid use was shown to increase the risk of COVID-19 infection and to play a role in increasing its prevalence. While combinations with biological and conventional DMARDs contributed to an increase in COVID-19 severity, biological DMARD monotherapy, and particularly the anti-TNF monotherapy, was linked to decreased risk of severe disease[25].

EVIDENCE-BASED TREATMENT SUGGESTIONS

- It is indicated for the treatment of moderate to severe chronic plaque psoriasis in adults and children aged 4 and over. It is recommended as a monotherapy in the treatment of both groups.
- It is highly effective in patients with psoriatic arthritis and has been shown to have a joint damage preventing effect as revealed radiologically, with this effect continuing for years.
- It is also effective in palmoplantar and nail psoriasis and is recommended as a monotherapy.
- Doses of 40 mg/week are more successful in controlling the disease when need arises. This is used when the desired efficacy could not be obtained or the response declines, and if the desired effect could not be achieved in a period of 4 months, then a transition to another agent will be made.
- There is no new safety alert as per various records and world experiences data.
- In the presence of psoriasis and hepatitis B or C together, it can be used according to the suggestions of gastroenterology and under close monitoring.

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