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Infliximab

İnfliksimab

İlgen Ertam Sağduyu

Ege University Faculty of Medicine, Department of Dermatology and Venereology, İzmir, Turkey

Abstract

Infliximab is a TNF-α inhibitor in the form of a chimeric monoclonal antibody. It received FDA approval in 2006 for the treatment of adult patients with severe chronic plaque psoriasis who developed side effects with conventional therapies or in whom these therapies were contraindicated or did not produce any response. Infliximab is administered via intravenous infusion, and infusion reactions are one of its common side effects. It is not suitable for intermittent treatment due to the high risk of infusion reaction, risk of developing antibodies, and loss of efficacy. Infliximab has the advantage of showing rapid clinical response in the treatment of unstable psoriasis and generalized pustular psoriasis.
Keywords: Infliximab, TNF-α, psoriasis

Öz

İnfliksimab, TNF-α inhibitörü olan şimerik bir monoklonal antikordur. Konvansiyonel tedavilerle yan etki gelişmiş, kontrendikasyon bulunan veya yanıtsız şiddetli kronik plak psoriasisi olan erişkin hastaların tedavisinde 2006 yılında FDA onayı almıştır. İnfliksimab intravenöz infüzyon yoluyla uygulanmaktadır ve infüzyon reaksiyonları sık görülen bir yan etkisidir. Artmış infüzyon reaksiyon riski, antikor gelişim riski ve etkinlik kaybı nedeniyle aralıklı tedavi için uygun değildir. İnfliksimab, stabil olmayan psoriasis ve generalize püstüler psoriasis tedavisinde hızlı klinik yanıt avantajına sahiptir.
Anahtar Kelimeler: İnfliksimab, TNF-α, psoriasis

General Information

Infliximab is a chimeric (human-mouse) monoclonal antibody which is a tumour necrosis factor-α (TNF-α) inhibitor. It shows high affinity and specificity to TNF-α. With this mechanism, it is used for the treatment of psoriasis and other inflammatory diseases involving an increase in TNF-α. Besides blocking soluble TNF-α, infliximab also binds to transmembrane TNF-α to produce complement fixation and antibody-mediated cytolysis. It forms stable complexes with TNF-α, which explains its fast action. It was approved by the American Food and Drug Administration (FDA) in 2006. Other than for the treatment of adult psoriasis, it is also used for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, adult and child Crohn's disease, and ulcerative colitis. It is indicated for the treatment of adult patients with severe chronic plaque psoriasis in whom conventional therapies involved side effects, were contraindicated or did not produce any response[1-3].

Mechanism of action

Infliximab is a chimeric tumour necrosis factor-alpha inhibitor in the form of immunoglobulin G1 (IgG1) monoclonal antibody containing mouse and human regions (25% from mouse). It binds to both soluble and transmembrane TNF-α molecules. Infliximab can bind to both the monomeric and trimeric forms of TNF[4,5]. It prevents vascular changes and endothelial cell adhesion molecule growth that are seen in psoriasis; it also prevents secretion of proinflammatory

Address for Correspondence/Yazışma Adresi: İlgen Ertam Sağduyu MD, Ege University Faculty of Medicine, Department of Dermatology and Venereology, İzmir, Turkey **E-mail:** ilgenertam@gmail.com **Received/Geliş Tarihi:** 07.02.2022 **Accepted/Kabul Tarihi:** 11.02.2022
ORCID: orcid.org/0000-0003-2341-3935

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cytokines from T-cells and inhibits keratinocyte proliferation. It binds to transmembrane TNF-α with a high selectivity, causing apoptosis, complement lysis, and antibody-related cellular cytotoxicity[1]. Its half-life is approximately 7-10 days[3].

Dosage/treatment scheme

Infliximab is administered through intravenous infusion. It is stored in powder form in 100 mg bottles. The bottles should be kept at a temperature between 2 and 8 degrees. The dose for administration is 5 mg/kg. It is well tolerated up to 20 mg/kg in patients. It is administered in 250-millilitre 0.9% physiological saline solution. The infusion time should not be less than 2 hours. It should be given immediately after preparing the solution or within 3 hours at the most[1-3]. During the infusion and within an hour after its completion, the patients should be monitored under conditions that would allow emergency intervention in the hospital for any infusion reaction[5]. After administering the induction dose at weeks 0, 2 and 6, a maintenance dose will be given every 8 weeks. Setting the dose based on kilograms makes it convenient for obese patients[5].

If the clinical efficacy declines during the treatment, a dose interval of 4 weeks may be used. A dose interval longer than 8 weeks may lead to loss of efficacy due to the risk of infusion reaction and antibody generation[1,2].

Since there is increased risk of infusion reaction and lower efficacy in intermittent therapy compared to continuous therapy, intermittent treatment with infliximab is not recommended[6,7].

Efficacy

Randomized controlled studies have shown that infleximab is effective in the treatment of moderate to severe plaque psoriasis[8-10].

Reich et al.[9] found that in the group of patients who used infliximab 5 mg/kg, the rate of achieving PASI75 was 80% at week 10 (3% in the placebo group), 82% at week 24 (4% in the placebo group) and 61% at week 50. In the study comparing it with methotrexate, infliximab was found more effective in moderate to severe plaque psoriasis (at week 16, PASI75 was 78% in the infliximab group and 42% in the methotrexate group)[11]. Studies have shown that treatment with infliximab led to an improvement in the dermatology life quality index of patients with psoriasis[12,13].

Besides moderate to severe plaque psoriasis, it was also shown to be effective in the treatment of palmoplantar psoriasis[14], nail psoriasis[15], psoriatic arthritis[16], pustular psoriasis[17], scalp involvement[18], and erythrodermic psoriasis[19].

Transitions between therapies are possible in the presence of loss of efficacy or side effects. The period in between will vary depending on the reason for transition, the substitute drug and the previously used drug. If a drug needs to be replaced due to side effects, it is recommended to wait until the parameters related to the side effects get better or the condition of the patient improves. There are expert views stating that if a drug needs to be replaced due to inefficacy, it would be necessary to wait as long as 3-4 times the half-life of the previously used drug[2]. A transition to any other biologic can be made 2-4 weeks after the last dose of infliximab[20].

Follow-up

Laboratory examinations that need to be done before and during an infliximab therapy are the same as those of other anti-TNF agents. Patients should be assessed in terms of infection at every visit. If efficacy continues and no side effects occur after a 12-week therapy, the treatment may be continued. The tests to be conducted before starting an infliximab therapy include a whole blood and peripheral smear, blood biochemistry, complete urinalysis, pregnancy test, tuberculin skin test or Quantiferon test, hepatitis B, hepatitis C and HIV serology, and chest X-ray. During follow-up, a peripheral smear, blood biochemistry and complete urinalysis should be performed every 3 months, a hepatitis B and C serology and chest X-ray every year, and a quantiferon or tuberculin skin test whenever necessary. These tests may be performed more frequently depending on the patient's condition and the physician's opinion (Table 1)[2,5,21].

Table 1. Tests to be conducted before and during an infliximab therapy

	Pre-treatment	Every 3 months	Every year
Whole blood count, peripheral smear	+	+	+
SGOT, SGPT, GGT	+	+	+
Complete urinalysis	+	+	+
HBV serology	+		+
HCV serology	+		+
HIV serology	+		+
Pregnancy test	+		
PPD, Quantiferon test	+		+
Chest X-ray	+		+
*Tests may be performed more frequently under physician control			

Side effects/safety

Infusion reactions, a common side effect of infliximab, are seen in approximately 3-22% of patients and are divided into 2 as acute (within the first 24 hours) and latent (in 1-14 days) depending on the time at which they occur. Infusion reactions generally occur after the 2nd or 3rd infusion. Infusion reactions, which are induced by the antibodies generated against infliximab, are usually mild. The risk of neutralizing antibody generation is approximately 10-30%. Prolonged infusion intervals (>8 weeks) increase the risk of antibody generation. When an immunosuppressive drug such as methotrexate is used together with infliximab, the risk of antibody generation and thus occurrence of an infusion reaction is mitigated[1,5,22].

As in all anti-TNF agents, the risk of infection increases with the use of infliximab. The most common infectious disease is the upper respiratory tract infection. But what is more important is the increased risk of opportunistic infection and particularly tuberculosis reactivation in endemic regions. The risk of tuberculosis is higher in anti-TNF agents in the form of monoclonal antibody such as infliximab and adalimumab compared to etanercept which has a receptor-type structure. Patients should be monitored with chest X-ray, tuberculin skin test and/or interferon gamma test before the treatment and in regular intervals,

and those carrying the risk of latent tuberculosis should be given prophylactic isoniazide for 9 months[1,2,5,22]. A study reviewing the risk of infection from the records of PSOLAR has reported that adalimumab and infliximab in particular had a higher serious infection risk than methotrexate and non-biological agents[23].

As it worsens a current heart failure, infliximab should not be used in NYHA class 3 and 4 heart failures. It also increases risk of demyelinating disease. Other reported side effects include impaired liver function test results, development of antinuclear antibody (ANA) and lupus-like syndrome, and haematologic disorders such as leukopenia, neutropenia, thrombocytopenia and life-threatening pancytopenia. Unless necessitated by clinical symptoms, an assessment of untinuclear antibody is not required in patients using infliximab[1]. Use of infliximab may increase the risk of lymphoma and skin cancer[1,22].

Contraindications

It should not be used in the presence of class 3-4 heart failure, active tuberculosis or another serious infection, allergic reaction to the drug, malignancies (except treated non-melanoma skin cancer and malignancies that had been treated 5 years ago), demyelinating diseases, multiple sclerosis, live vaccines, and autoimmune diseases[5]. The therapy may begin after the active infection is brought under control.

Drug interactions

It should not be used together with anakinra and abatacept[5]. It can be combined with topical steroids, topical calcipotriol, methotrexate and acitretin[2].

Special cases

Inactive vaccines are allowed during an infliximab therapy. Live vaccines can be administered after waiting 4-5 times the half-life of the drug following its discontinuation.

Infliximab is known to have an immunosuppressive effect and an increased risk of infection. Despite the hypothesis that anti-TNF agents can treat the COVID-19-associated cytokine storm, infliximab should be discontinued in patients whose COVID-19 test is positive or who are symptomatic[24].

An outline of information on infliximab is given in Table 2.

Table 2. An outline of information on infliximab

Administration	Intravenous infusion
Mechanism of action	Chimeric anti-TNF
Induction therapy	A 5 mg/kg dose at weeks 0, 2 and 6
Maintenance treatment	A 5 mg/kg dose at 8-week intervals
Significant side effects	Infusion reactions, opportunistic infections and tuberculosis reactivation
Infusion reactions	To prevent these, the time between doses should not be exceeded, it may be combined with methotrexate if needed. Infusion should be given in a period of at least 2 hours.
Main contraindications	Serious active infection, active tuberculosis Class 3-4 heart failure Known hypersensitivity reactions to the drug Demyelinating disease Presence of malignancy
Drug interaction	Anakinra or abatacept
Pregnancy category	B

SUGGESTIONS

- One of the systemic treatment options for the treatment of patients with moderate to severe psoriasis.
- Infliximab has the advantage of rapid clinical response (8-10 weeks) in the treatment of unstable psoriasis and generalized pustular psoriasis.
- The dose for administration is 5 mg/kg. Administered through intravenous infusion. Infusion intervals are 8 weeks.
- Irregular and long infusion intervals increase the risk of neutralizing antibody development.
- Caution should be taken for the risk of infusion reactions.
- It can be combined with low-dose methotrexate to diminish neutralizing antibody generation.
- Infliximab may be combined with topical agents, acitretin, methotrexate and apremilast that are used in the treatment of psoriasis.
- Continuous treatment is recommended in patients who achieved PASI75 and PASI90 and had no side effects.
- Although its is safe during pregnancy and lactation, transplacental transmission is more in the last trimester. After birth, the infant should be considered immunosuppressed.

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