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Ixekizumab

İksekizumab

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Abstract

Ixekizumab is a human immunoglobulin G4 monoclonal antibody targeting interleukin-17A. Clinical trials have reported that 82-84% of the patients using ixekizumab achieved a PASI90 response at week 12 and 85% at week 60. It has been found effective in chronic plaque psoriasis as well as genital, hairy skin, nail, and generalized pustular psoriasis in adults. It has been approved by the FDA for use in moderate psoriasis in patients aged between 6 and 18 years.
Keywords: Anti-IL-17, ixekizumab, psoriasis

Öz

İksekizumab interlökin-17A'ya yönelik immünoglobulin G4 tipinde insan kaynaklı bir monoklonal antikordur. Klinik araştırmalarda PAŞİ90 yanıtı elde edilen hasta oranı 12. haftada %82-84 arası, 60. haftada ise %85 olarak bildirilmiştir. Erişkinlerde kronik plak tip psoriasisin yanında genital, saçlı deri, tırnak ve generalize püstüler tip psoriasiste de etkili bulunmuştur. Altı-18 yaş arası hastalarda da orta şiddetli psoriasiste kullanımı için FDA onayı bulunmaktadır.
Anahtar Kelimeler: Anti-IL-17, iksekizumab, psoriasis

General information

Ixekizumab is indicated for the treatment of moderate to severe psoriasis that do not respond to conventional systemic therapies or for which such therapies are contraindicated. Ixekizumab is a human IgG4 monoclonal antibody that neutralizes proinflammatory cytokine IL-17A which plays a role in various inflammatory diseases. It was approved by FDA on 22 March 2016 for moderate to severe psoriasis and psoriatic arthritis that require systemic treatment or phototherapy. It also received approval on 30 March 2020 to treat moderate to severe paediatric psoriasis for ages 6-18. It is also used in ankylosing spondylitis and non-radiographic axial spondylarthritis[1,2].

Mechanism of action

Ixekizumab is a human IgG4 monoclonal antibody that was developed to act against IL-17A. It shows its action by blocking IL-17A from binding to IL-17A receptor, thereby neutralizing IL17A activity. The half-life of ixekizumab is 13 days. The histopathological action of ixekizumab starts at week 2 of its administration and becomes apparent at week 6, which leads to a noticeable decrease in IL-17-regulated proteins in epidermal keratinocytes, cathelicitin, b-defensin 2, S100A7 and S100A8. After administration of a single 160 mg dose, it reaches its maximum concentration at day 4. The bioavailability of ixekizumab is between 60 and 81% following a subcutaneous injection[3].

Dozage/treatment scheme

Ixekizumab is administered via subcutaneous route. After the initial dose of 160 mg, it is administered in 80 mg doses at weeks 2th, 4th, 6th, 8th, 10th and 12th. Its maintenance dose is 80 mg every 4 weeks. Resistant patients may require 80 mg

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every other week. The paediatric dose is 80 mg monthly after the initial dose of 160 mg for weights >50 kg, 40 mg monthly after the initial dose of 80 mg for weights 25-50 kg, and 20 mg monthly after the initial dose of 40 mg for weights <25 kg[1,2].

Efficacy

Many studies have been published about the efficacy and safety of ixekizumab. The most appropriate time to evaluate the efficacy is week 12 in uninterrupted treatment. In the case of loss of efficacy, the dose may be increased or it can be combined with topical agents, methotrexate or ultraviolet therapies. A small amount of anti-neutralizing antibody can develop when ixekizumab is used[2].

In a review assessing safety data in a period of 5 years, and the randomized, double-blind Phase 3 studies named UNCOVER-1 and UNCOVER-2, the most common side effects with the use of ixekizumab in the approved dose for a period of 60 weeks were reported to be mild and moderate nasopharyngitis and upper respiratory tract infection. Mild and moderate Candida infection in particular was seen more frequently[4]. While the PASI75, 90 and 100 values for ixekizumab at week 60 were 94.7%, 85% and 62.1%, respectively, these values in the 5th-year (week 264) turned out to be 90.3%, 71.3% and 46.3%.

Similar results were reported for PGA and DLQI[5]. In UNCOVER-3, another randomized, controlled Phase 3 study, ixekizumab was found superior to placebo and etanercept after a 12-week induction phase in the treatment of moderate to severe psoriasis. The patients received ixekizumab in an 80 mg dose every 4 weeks. At week 12, 84.2% of the patients using ixekizumab achieved PASI75, whereas only 53.4% of those using etanercept and 7.3% of those using placebo could achieve PASI75. The percentage of patients who achieved PASI90 were 65.3% for ixekizumab, 25.7% for etanercept, and 3.1% for placebo. While 35% of the patients using ixekizumab achieved PASI100, only 7.3% of those using etanercept and 0% of those using placebo could achieve this result[6]. As a continuation of these studies, a safety and efficacy profile of ixekizumab for a period of more than 4 years (204 weeks) was also published. Of the patients, 48.3% remained in PASI100, 66.4% in PASI90 and 82.8% in PASI75. The majority of patients (88.6%) had mild and moderate (70.7%) side effects[7,8]. In a randomized, double-blind trial (IXORA-R), ixekizumab was compared one-to-one with guselkumab, an IL-23 inhibitor, in moderate to severe psoriasis and ixekizumab was reported to be more effective in rapid control of psoriasis symptoms[9].

A randomized, controlled Phase 3 study compared ixekizumab to ustekinumab and found that the rates of achieving PASI90 at week 12 were 82.8% for ixekizumab and 42.2% for ustekinumab (IXORA-S)[10].

Ixekizumab was also found effective in paediatric psoriasis and received approval from FDA. In IXORA-PEDS, a randomized, double-blind, placebo controlled Phase 3 study, ixekizumab was compared to placebo in a 12-week period and then the patients were divided into ixekizumab, placebo and etanercept arms. Ixekizumab was observed to cause improvements in skin symptoms and itching at week 1 and this effect continued through week 48[11].

Ixekizumab was found effective in genital[12,13], hairy skin, nail[14], palmoplantar[15], erythrodermic, inverse and generalized pustular psoriasis[16].

When switching to another biological agent due to loss of efficacy, some authors recommend waiting for 3-4 times the half-life while others suggest switching at the earliest time convenient for the patient[17,18].

Follow-up

Before starting the drug, a whole blood count, complete urinalysis, liver function tests, chest x-ray, PPD and quantiferon tests for latent tuberculosis screening, serologic tests for hepatitis B and C (HBsAg, anti-HBsAg, anti-HBc, anti-HCV), and a pregnancy test should be conducted. The frequency of follow-up in patients using ixekizumab should be scheduled based on the duration of treatment, response and tolerance to the drug. Follow-up visits should include anamnesis, physical examination (non-melanoma skin cancer screening...), assessment of infection foci, questioning for the risk of developing inflammatory bowel disease, and an annual chest X-ray. Patients at risk of tuberculosis should be administered annual PPD, Quantiferon tests (Table 1)[17,18].

Table 1. Tests to be conducted before and during an ixekizumab 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

Ixekizumab is generally tolerated well. No unpredicted side effects have been reported in the data related to its long-term use. Its most common side effects include injection site reaction (20%), upper respiratory tract infection, nasopharyngitis, mucocutaneous Candida infection, tinea, and conjunctivitis[17]. Injection site reactions can range from mild itching to macular erythema and annular erythematous plaques. Infection risk increases when used in combination with methotrexate. Inflammatory bowel disease[19], hepatotoxicity, and neutropenia are among less common side effects seen in patients using ixekizumab[17,20].

Contraindications

Any allergic reaction to ixekizumab or the carrier is an absolute contraindication. A history of inflammatory bowel disease or presence of active disease is defined as a relative contraindication[17-19].

Drug interactions

Interleukin 17 may block cytochrome P450 enzymes. Therefore, expression of cytochrome P450 enzymes may come to a normal level during the use of ixekizumab. Care should be taken especially when using drugs with a narrow therapeutic index (A dose adjustment may be needed for warfarin and cyclosporine)[1].

Special cases

There are no studies on the use of ixekizumab in pregnant women. In animal trials, no negative effect on the development of fetus has been shown even at high doses, but there was an increase in neonatal deaths. It has been found to pass into the mother's milk in experimental animals. No data is available to see whether or not it passes into the milk in humans during lactation[17].

Live vaccines should be avoided when using ixekizumab. Inactive vaccines may be used. Although there seems to be no increased risk for herpes zoster, since it is a relatively new agent, vaccination for herpes zoster should be decided for each patient individually[21].

Ixekizumab can be prescribed or continued during the pandemic, but it should be discontinued in patients who are positive for COVID-19 infection and in symptomatic patients[22].

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

Table 2. An outline of information on ixekizumab

Administration	Subcutaneous
Mechanism of action	Anti-IL-17A
Induction therapy	After the initial dose of 160 mg, 80 mg doses at weeks 2, 4, 6, 8, 10 and 12.
Maintenance treatment	80 mg every 4 weeks
Significant side effects	Injection site reaction, nasopharyngitis, Candidiasis
Main contraindications	Allergic reaction to the drug, severe infection, inflammatory bowel disease
Drug interaction	Dose adjustment may be needed for drugs that are metabolised with cytochrome P450 (Warfarin, cyclosporine), the patient should be monitored.
Pregnancy category	B

SUGGESTIONS

- One of the systemic treatment options for the treatment of patients with moderate to severe psoriasis.
- It is effective in hairy skin and nail psoriasis, erythrodermic, pustular and arthropathic psoriasis.
- Recommended initial dose for adults is a 160 mg subcutaneous injection. After this, an 80 mg dose is to be administered at weeks 2th, 4th, 6th, 8th, 10th and 12th. Recommended maintenance dose is 80 mg every 4 weeks.
- Evaluation of efficacy at week 12 is recommended. Continuous treatment is recommended also in patients who achieved PASI75 and PASI90 responses.
- In paediatric psoriasis, ixekizumab is used for ages 6-18.
- The paediatric dose is 80 mg monthly after the initial dose of 160 mg for weights >50 kg, 40 mg monthly after the initial dose of 80 mg for weights 25-50 kg, and 20 mg monthly after the initial dose of 40 mg for weights <25 kg.

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