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Brodalumab

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Abstract

Brodalumab is a human monoclonal antibody that inhibits interleukin-17 (IL-17) pathway by binding to IL-17 receptor. In clinical trials, a PASI75 response has been achieved in 82-84% of the patients at week 12. It was shown to be effective also in generalized pustular and erythrodermic psoriasis. As with other IL-17 inhibitors, brodalumab should be used with caution in patients with inflammatory bowel disease.
Keywords: Anti-IL-17RA, brodalumab, psoriasis

Öz

Brodalumab interlökin-17 (IL-17) reseptörüne bağlanarak IL-17 yolağını inhibe eden insan kaynaklı bir monoklonal antikordur. Klinik araştırmalarda, 12. haftada hastaların %82 ila 84'ünde PAŞİ75 yanıtı elde edilmiştir. Generalize püstüler ve eritrodermik psoriasiste de etkili olduğu gösterilmiştir. Diğer IL-17 inhibitörlerinde olduğu gibi inflamatuar barsak hastalığı olanlarda dikkatli kullanılmalıdır.
Anahtar Kelimeler: Anti-IL-17RA, brodalumab, psoriasis

General information

Brodalumab is a human anti-interleukin-17 (IL-17) receptor monoclonal antibody that shows its action by binding to IL-17 receptor to prevent IL-17 activation. Brodalumab received FDA and EMA approvals for the treatment of moderate to severe psoriasis in 2017[1].

Mechanism of action

Brodalumab is the only IL-17 inhibitor that can, by binding to human IL-17RA with high affinity, neutralize the activities of IL-17A, IL-17F, IL-25, IL-17C and heterodimeric IL-17-A-F simultaneously[2].

It is reported that its bioavailability is 57.6% and it reaches two fold higher serum concentrations in patients below 75 kg than in heavier patients. However, no dose adjustment for body weight is recommended. Age, gender and race have no effect on the pharmacokinetic characteristics of brodalumab. Its estimated half-life is 10.9 days. The maximum plasma concentration of brodalumab is reached 3 to 4 days after a single subcutaneous dose of 210 mg and its stable concentration after 10 to 12 weeks. Brodalumab is eliminated via intracellular catabolism in the same way as endogenous IgG. Its elimination does not differ in the presence of liver and kidney failures[3-5].

Dosage and treatment scheme

In moderate to severe psoriasis, an induction dose of 210 mg s.c. is administered at weeks 0, 1 and 2, followed by 210 mg maintenance doses given every 2 weeks.

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Efficacy

In Phase 3 clinical studies AMAGINE-1, AMAGINE-2 and AMAGINE-3, the PASI75 responses after a 12-week treatment ranged between 83% and 86% and PASI100 responses between 37% and 44%. It was compared with placebo only in AMAGINE-1, with both placebo and ustekinumab in AMAGINE-2 and AMAGINE-3 and was found superior to placebo in all parameters and superior to ustekinumab in PASI100 response[6,7].

The multicenter, randomized, double-blind, placebo controlled, parallel-group Phase 2 study of brodalumab made with Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis found the improvements in both PASI scores and ACR values markedly superior to those of placebo. An analysis of other Phase 2 and 3 studies with respect to psoriasis symptoms and quality of life indexes also found brodalumab markedly effective and superior to placebo. Its effectiveness in psoriatic arthritis was also found superior to placebo[8].

An open-label, multicenter, long-term Phase 3 study was conducted with Japanese patients with rare and severe psoriasis (pustular and erythrodermic psoriasis). It was shown to be effective in patients with generalized pustular and erythrodermic psoriasis. Its anti-drug antibody level was found to be 2.2%, but this did not have a neutralizing effect.

Follow-up

The pre-treatment tests recommended for brodalumab are not any different from those for other biological agents. Although there are data indicating that IL-17 inhibitors are safer in terms of TBC risk, this did not lead to any modifications in the currently required tests or follow-up tests and measures.

Side effects/safety

The most frequently reported side effect is nasopharyngitis. None of the serious side effects occurred in five patients was found associated with the treatment. It has also been shown to be effective in hairy skin psoriasis. It was shown to be favourable in efficacy-cost analyses, noting that it was one of the top molecules that had the capability of achieving a PASI90 response[9,10].

Most common side effects as seen in Phase 3 studies AMAGINE-1, AMAGINE-2 and AMAGINE-3 were similar to those of other IL-17 inhibitors, which include nasopharyngitis, upper respiratory tract infections, headache and arthralgia. Temporary mild neutropenia was seen more than it was seen in the placebo group. Candida infections were also seen more than they were seen with ustekinumab and placebo. No serious infections were reported that relate to these studies[6,7].

Contraindications

- Active infections (sepsis, abscess, opportunistic infections),
- Active tuberculosis,
- Oversensitivity to the drug or other substances in it,
- Presence of malignancy,
- Immunosuppressive therapies,
- Live vaccines,
- Active Crohn's disease.

One of the most caution-requiring issue with IL-17 inhibitors is the inflammatory bowel disease. IL-17 inhibitors are usually not recommended for those who have an inflammatory bowel disease. IL-17A is considered as a protective cytokine for the integrity of intestinal epithelium. Blocking IL-17A is believed to trigger or facilitate the impairment of this integrity. IL-17F, on the other hand, has an inflammation-increasing effect on intestinal mucosa. The effects of IL-17A and IL-17F on intestinal mucosa are complex and still unclear in some aspects[8].

Drug interactions

If it is used concurrently with midazolam, the serum concentration of midazolam may change. It may have effects on cytochrome p 3A4 and 3A5.

Special cases

Use in pregnancy, lactation and children

There is no data on its use during pregnancy and lactation, and thus should be avoided. It should not be used in children under the age of 18.

Another important issue specific to brodalumab is the concern about the risk of suicide and depression among the patients treated with brodalumab in the past. In one of the 4 suicide attempts occurred during an open-label extension to AMAGINE-1 and 2, it was later agreed that it occurred as a result of taking unintentional heroin overdose. Considering that the prevalence of depression is relatively high among patients with psoriasis and patients with a history of depression, drug and alcohol abuse or suicidal ideation were not excluded from the studies, it is difficult to say if such suicides were associated with the above-mentioned tendencies or with the medication. It was reported that there were underlying psychiatric disorders in all of the 4 patients and none of the suicides occurred during active treatment with brodalumab. Although the half-life of brodalumab is approximately 10.9 days, the suicides occurred 58, 27 and 19 days after the last brodalumab dose of each subject. As a result, the FDA report stated "Brodalumab does not increase the risk of depression or suicide more than any other medication used in the treatment of psoriasis"[8].

SUGGESTIONS

- In conclusion, brodalumab seems to be a molecule that has an efficacy, tolerability and safety profile comparable with other biological agents.
- It is recommended to take caution when using it in patients prone to inflammatory bowel disease, Candida infection, neutropenia although seen rarely, and suicide although already agreed to be disassociated.
- Brodalumab is not yet available in our country and has not been approved for use.

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