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Ustekinumab

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Abstract

Ustekinumab is an antagonistic human monoclonal immunoglobulin G1 antibody that targets p40, a common subunit of interleukin-12 (IL-12) and IL-23. In clinical trials, 66-81% of the patients using ustekinumab achieved a PASI75 response. Its long drug survival time has been found remarkable in real-world experiences. Other advantages of ustekinumab include ease of use in obese patients as its dose can be adjusted according to body weight and its administration every 12 weeks in the maintenance period.
Keywords: Anti-IL-12/23, p40, ustekinumab

Öz

Ustekinumab interlökin-12 (IL-12) ve IL-23'ün ortak alt birimi p40'ı hedef alan immünoglobulin G1 yapısında bir monoklonal antikordur. Klinik araştırmalarda PAŞİ75 yanıtı sağlanan hasta oranları %66 ile 81 arasında değişmektedir. Gerçek yaşam çalışmalarında ise uzun ilaç sağkalım süresi ile öne çıkmaktadır. Vücut ağırlığına göre doz seçimi yapıldığı için obez hastalarda kullanım kolaylığı ve idame döneminde 12 haftada bir uygulanması ustekinumabın diğer avantajlarıdır.
Anahtar Kelimeler: Anti-IL-12/23, p40, ustekinumab

General information

Ustekinumab shows its action in the treatment of psoriasis by targeting p40 subunit of IL-12 and IL-23 and thereby blocking IL-12 and IL-23. In this way, it differs from molecules that target TNF-α such as etanercept, adalumimab, infliximab and certolizumab, and from those that target IL-17 such as secukinumab and ixekizumab. Its mechanism of action partially resembles those of the more recent agents that block IL-23 by targeting its p19 unit, which are not yet available in our country[1,2].

Ustekinumab;

- It can be used in patients with moderate to severe plaque psoriasis who do not respond to, have a contraindication for, or cannot tolerate conventional systemic therapies (FDA, EMA 2009, Turkey 2013).
- Ustekinumab started to be used also in the treatment of psoriatic arthritis (FDA, EMA, Turkey 2013) and there are data showing that it is successful.
- It is also authorized in Turkey for the indication of Crohn's disease (FDA 2016).

Mechanism of action

The pathogenesis of psoriasis involves overactivity of cytokines such as IL-12 and IL-23 and these induce T-cell response. IL-12 and IL-23 are heterodimers involving a common p40 subunit that is covalently attached to a p35 or p19 subunit.

IL-12 is a heterodimeric protein containing disulfide-linked, glycated p35 and p40 subunits. It is secreted from dendritic antigen-presenting cells as a result of an inflammation or infection. IL-12 activates T-cell responses including

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differentiation of natural killer (NK) and CD4 + T-cells into a CD4 + Th1 phenotype. IL-23 is a heterodimeric protein containing p40 subunit, which is linked to p19 subunit with a disulfide bond. IL-23 shows its action by activating IL-6 and TGF-b to induce production of Th17 cells together with TNF-α. The p40 subunits of both IL-12 and IL-23 bind to IL-12 receptor-β1 (IL-12Rβ1). IL-12p35 and IL- 23p19 subunits bind to IL-12Rβ2 and IL-23R, respectively. In this way, IL-12 and IL-23 control different immunological pathways despite some structural similarities between them. By stimulating differentiation of CD4 + T-cell into a CD4 + Th1 phenotype, IL-12 promotes secretion of IFN-γ, TNF-α and IL-2. Conversely, IL-23, in combination with IL-21 and TGF-β, causes CD4 + Th17 cell differentiation, leading to secretion of other cytokines such as L-17, IL-22, TNF-α and IL-1β. Ustekinumab is a human recombinant G1 (lgG1) monoclonal antibody that inhibits p40 protein. It shows its action through this p40 inhibition, which blocks IL-12 and IL-23[3,4].

Dosage and treatment scheme

- For patients with a body weight below 100 kg, an initial dose of 45 mg, and 4 weeks later, a second dose of 45 mg will be administered subcutaneously, which will be followed by 45 mg doses once in every 12 weeks.
- For patients with a body weight over 100 kg, an initial dose of 90 mg, and 4 weeks later, a second dose of 90 mg will be administered subcutaneously, which will be followed by 90 mg doses once in every 12 weeks. A dose of 45 mg has been shown to be effective also in patients with a body weight over 100 kg, but 90 mg is more effective in this frequency and duration of administration.
- The half-life of ustekinumab is 15-32 days and maintenance doses given in intervals of 12 weeks are sufficient to preserve the effectiveness.
- In patients giving no response to the treatment by week 28, discontinuation of the therapy should be considered (as per SUT, a PASI75 response should have been achieved at week 28 to continue with the drug).

Efficacy

The efficacy of ustekinumab has been shown in double-blind, placebo-controlled studies as well as in one-to-one comparison studies with other treatment methods. Ustekinumab has also been seen to be effective in real world experiences. It was found more effective than placebo and etanercept in the PHOENIX-1, PHOENIX-2, ACCEPT and PEARL studies. In these studies, the PASI75 values for a 45 mg dose were found to be 67.1%, 66.7%, 67.1%, and 67.0%, respectively. In Phase 1, Phase 2 (4 weekly administration), PHOENIX-1, PHOENIX-2 and ACCEPT studies using 90 mg doses, the PASI75 results were 76.0%, 81.0%, 66.4%, 75.7% and 73.8%, respectively. In these studies the PASI75 values for placebo ranged between 2 and 5% and the PASI75 value for etanercept turned out to be 55.8% in the ACCEPT study. Its efficacy in psoriatic arthritis was shown in the PSUMMIT and PSUMMIT24 studies[5-8].

The data best demonstrating the efficacy and favourableness of ustekinumab in the treatment of psoriasis come from real world experiences that show medication adherence times. The data from PSOLAR (Psoriasis Longitudinal Assessment and Registry) on approximately 3,500 patients who started biological therapies (1,115 patients their first biological agent, 1,436 patients their second and 922 patients their third) showed that ustekinumab had the longest medication adherence in all patients who started taking their first, second and third biological agents. Similarly, in the DermBio study with 3,495 patients [adalimumab (n=1,332), etanercept (n=579), infliximab (n=333), ustekinumab (n=1,055), secukinumab (n=196)], BADBIR study (3,523 patients between 2,997 and 2,014), and ORBIT study, in all real world experiences retrospective studies in Canada, Germany and Hungary, the molecule that achieved longest medication adherence was again ustekinumab. The factor that effected medication adherence most was found to be the efficacy of the drug. Other factors included secondary inefficacy, side effects, ease of using, and frequency of use[9-12].

Follow-up

As in other biological agents, to find possible risk factors associated with an ustekinumab therapy, detailed anamnesis, physical examination and laboratory tests will be required.

What needs to be done before treatment:			
	Pre-treatment	Week 4	Every 12 weeks
Whole blood count	x	x	x
Liver transaminases	x	x	x
Hepatitis viral serology	x		
HIV antibody	x		
Pregnancy test	x		
PA chest X-ray	x		
PPD test	x		

It is important for safety reasons to repeat these tests except for the pregnancy test also during the treatment at certain intervals.

Side effects/safety

Safety data for ustekinumab have been revealed in both phase studies and real world experiences. Looking at the studies of real world experiences, we see that side effects in the PSOLAR study and cardiovascular events were more common in the group that did not take biologics. Serious infections were found less frequent in the group treated with ustekinumab than in the Inflixumab group.

Malignancies were also fewer in the group treated with ustekinumab[3,4]. In phase studies of PHOENIX-1 and PHOENIX-2, the number of common and serious adverse drug reactions in ustekinumab was similar to that of the placebo groups. Most common adverse drug reactions: Infections in general: 21.5% and 31.4%, respectively (placebo: 20% and 26.7%), Nasopharyngitis: 6.8% and 10.2% (placebo: 7.1% and 8.6%), Upper respiratory tract infections: 2.9% and 7.1% (placebo: 3.4% and 6.3%), headache: 4.6% and 5.5% (placebo: 2.4% and 4.1%) arthralgia: 2.4% and 3.4% (placebo: 2.7% and 2.9%) Incidence of serious adverse events 0.8% and 2.0%, respectively (placebo group: 0.8% and 2.0%). In the PHOENIX-1 study, there were two infections agreed to be serious adverse drug reactions (erysipelas and herpes zoster), and in the PHOENIX-2 study, a serious infection (erysipelas) occurred only in one patient who was treated with ustekinumab. The

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number of severe infections remained low also in the other studies (<1%). In both studies, 15 malignancies including 11 skin cancers were detected. The number of malignancies was also small similar to that found in placebo patients[7,8].

The most common side effects reported were upper respiratory tract infections, nasofaryngitis, headache and arthralgia. As other immunosuppressing agents, ustekinumab is also thought to increase the risk of infection. Studies have reported no active tuberculosis, latent tuberculosis reactivation, other microbacterial infections, or *Salmonella* infection in patients treated with ustekinumab. At the end of 100 weeks, 30 different types of malignancies were seen in 28 of the patients participating in the PHOENIX-2 study, two of which were solid tumours and 28 skin tumours. It is suspected to increase malignancy in rat models. This is thought to occur due to ustekinumab's inhibition of anti-tumour activity of IL-12, but the incidence of malignancies and serious cardiovascular events was found close to that expected in healthy individuals. An analysis of the data from a total of 2,266 patients showed no lymphopenia or cumulative toxic effect. Based on the data obtained from studies and pharmacovigilance records, there is no evidence that ustekinumab increases the risk of cardiovascular events (MACE). The prevalence of MACE in long-term studies is similar to that seen in the long-term studies of TNF antagonists like adalimumab[8-15].

Pharmacokinetics

* Pharmacokinetic data is not available in patients with kidney or liver dysfunction. Since ustekinumab is not metabolised through cytochrome p450 enzyme, drug interactions are not expected.

Immunogenicity

* Less than 8% (5.2%) of the patients treated with ustekinumab developed antibodies against ustekinumab, but these generally had a low titre. Neutralizing antibodies were seen in most of the patients who developed antibodies against ustekinumab, but antibody positivity does not hinder clinical response.

Contraindications

Absolute contraindications

- Active infections (sepsis, abscess, opportunistic infections),
- Active tuberculosis,
- Oversensitivity to the drug or other substances in it,
- Malignancy (excluding treated nonmelanoma skin cancers and malignancies that were treated 10 years ago),
- Immunosuppressive therapies.

Relative contraindications

- Patients who had more than 200 sessions of PUVA therapy and especially those who also used cyclosporine thereafter,
- HIV positive or AIDS patients,
- Hepatitis B or C positive patients,
- Comorbid systemic erythematous lupus,
- Recurrent infections,
- Live vaccines.

Drug interactions

Use of ustekinumab in combination with other biologics is not recommended. It has no known interaction with a conventional drug.

Combination therapies

No controlled studies on combination therapies are available. Combinations with local anti-psoriatic agents are possible. There are no efficacy and safety data on its use with other immunosuppressors including biological agents or with phototherapy[16-18].

Special cases

Use in pregnancy and paediatrics

- There is no sufficient data on the use of ustekinumab in pregnant women. It is not known whether or not ustekinumab mixes with mother milk in humans. Reproductive women are recommended to use reliable contraceptives during treatment with ustekinumab and until 15 weeks thereafter.
- There is no data on the paediatric (ages 0-11) use of ustekinumab. Ustekinumab received approval from EMEA to be used in adolescent patient group (ages 12-17) in 2015.

Vaccination

- As in other biological agents, live bacterial or viral vaccines should be avoided during treatment with ustekinumab.
- The therapy should be suspended for at least 15 weeks before the vaccination and be restarted 2 weeks after the vaccination.
- Inactivated vaccines can be used concurrently with ustekinumab[19-21].

Measures and alerts

- If an anaphylactic shock or another allergic reaction occurs, the ustekinumab therapy should be discontinued immediately and appropriate treatment initiated.
- Severe allergic reactions may develop in patients sensitive to the latex rubber in the needle covers of prefilled syringes.
- No general difference has been observed between patients aged 65 and over and young patients.
- There are no studies specific to patients with hepatic or renal dysfunction.
- Women with childbearing potential should use effective birth control pills during the therapy and until 15 weeks after the therapy.
- Since it is not certain if ustekinumab passes into the mother's milk or not, babies should not be breastfed during the therapy and until 15 weeks after the therapy.
- Its pregnancy category is B.

SUGGESTIONS

• The infrequent use of ustekinumab (every 12 weeks) is favourable to patients. An additional advantage is the need for infrequent administration of injections during the pandemic and their subcutaneous route of administration.

• Its high medication adherence rate shows that it is an effective and convenient option for long-term maintenance treatment.

• It is easier to use it in obese patients as the dose can be adjusted according to body weight.

• It is effective in both rapid disease control and intermittent treatment.

• Its efficacy has been shown also in special area involvements.

• Being able to use it in comorbidities as a first choice in demyelinating diseases, lupus erythematosus and heart failure, and as a second choice in inflammatory bowel disease as well as its being effective in psoriatic arthritis are the other advantages.

• Its efficacy should be evaluated at week 16[21-23].

References

1. Kimball AB, Papp KA, Wasfi Y, et al.: Long term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. J Eur Acad Dermatol Venereol 2013;27:1535-45.
2. Nast A, Boehncke WH, Mrowietz U, et al.: S3-Guidelines on the treatment of psoriasis vulgaris (English version) Update. J Dtsch Dermatol Ges 2012;10(Suppl2):1-95.
3. Croxtall JD: Ustekinumab: a review of its use in the management of moderate to severe plaque psoriasis. Drugs 2011;71:1731-53.
4. Luo J, Wu SJ, Lacy ER, et al.: Structural basis for the dual recognition of IL-12 and IL-23 by ustekinumab. J Mol Biol 2010;402:797-812.
5. Smith CH, Anstey AV, Barker JN, et al.: British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. Br J Dermatol 2009;161:987-1019.
6. Langley R, et al.: Poster presented at the EADV. Prague, Czech Republic 2012;P976.
7. Nast A, Gisondi P, Ormerod AD, et al.: European S3-Guidelines on the systemic treatment of psoriasis vulgaris - Update 2015 - Short version-EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015;29:2277-94.
8. Leonardi CL, Kimball AB, Papp KA, et al.: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.
9. Papp KA, Langley RG, Lebwohl M, et al.: Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebocontrolled trial (PHOENIX 2). Lancet 2008;371:1675-84.
10. Griffiths CE, Strober BE, van de Kerkhof P, et al.: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 2010;362:118-28.
11. Kimball AB, Gordon KB, Fakharzadeh S, et al.: Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis: results from the PHOENIX 1 trial through up to 3 years. Br J Dermatol 2012;166:861-72.
12. Clemmensen A, Spon M, Skov L, Zachariae C, Gniadecki R: Responses to ustekinumab in the anti-TNF agent-naïve vs. anti-TNF agent-exposed patients with psoriasis vulgaris. J Eur Acad Dermatol Venereol 2011;25:1037-40.
13. Takahashi N, Noda S, Taniguchi T, Adachi M: Efficacy comparison of ustekinumab between anti-tumor necrosis factor- drug-naïve and anti-tumor necrosis factor- drug-resistant Japanese psoriasis cases. Int J Dermatol 2015;54:1194-8.
14. Landells I, Marano C, Hsu MC, et al.: Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. J Am Acad Dermatol 2015;73:594-603.
15. Warren RB, Smith CH, Yiu ZZ, et al.: Differential drug survival of biologic therapies for the treatment of psoriasis: a prospective observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol 2015;135:2632-40.
16. Gniadecki R, Bang B, Bryld LE, Iversen L, Lasthein S, Skov L: Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. Br J Dermatol 2015;172:244-52.
17. No authors listed: Abstracts of the Third International Congress on Psoriasis. July 1-4, 2010. Paris, France. J Eur Acad Dermatol Venerol 2010;24(Suppl4):1-83.
18. Hugh J, Van Voorhees AS, Nijhawan RI, et al.: From the Medical Board of the National Psoriasis Foundation: the risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol 2014;70:168-77.
19. Papp K, Gottlieb AB, Naldi L, et al.: Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). J Drugs Dermatol 2015;14:706-14.
20. Meng Y, Dongmei L, Yanbin P, et al.: Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis. Clin Exp Dermatol 2014;39:696-707.
21. Molina-Leyva A, Husein-Elahmed H, Naranjo-Sintes R, Ruiz-Carrascosa JC: Safety and effectiveness of ustekinumab for treatment of moderate to severe psoriasis: a prospective study in a clinical setting. J Drugs Dermatol 2014;13:971-4.
22. Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE: Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol 2018;178:509-19.
23. Menter A, Papp KA, Gooderham M, et al.: Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) J Eur Acad Dermatol Venereol 2016;30:1148-58.