DOI: 10.4274/turkderm.galenos.2022.64715
Turkderm-Turk Arch Dermatol Venereol 2022;56(Suppl 1):67-9

Tofacitinib

Tofasitinib

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Abstract

Tofacitinib is an oral inhibitor of janus kinases, which is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis in adults; its efficacy in the treatment of psoriasis has also been demonstrated in clinical studies. A 10 mg daily dose has been observed to achieve a PASI75 response in 40-64% of the patients with moderate to severe psoriasis at week 12 or 16. It provides advantage in the treatment of psoriasis due to oral use, lower cost compared to other biologics, and absence of organ toxicity.
Keywords: Psoriasis, tofacitinib, JAK inhibitor

Öz

Yetişkinlerde romatoid artrit, psoriatik artrit ve ülseratif kolit tedavisi için onaylı oral janus kinaz inhibitörü olan tofasitinibin psoriasis tedavisinde de etkinliği klinik çalışmalarda gösterilmiştir. Günlük 10 mg dozda orta ve şiddetli psoriasisde 12 veya 16 haftalarda hastaların %40-64'ünde PAŞİ75 yanıtına ulaşıldığı gözlenmiştir. Oral kullanılması, diğer biyolojiklere göre düşük maliyeti ve organ toksisitesinin olmaması ile psoriasis tedavisinde avantaj sağlamaktadır.
Anahtar Kelimeler: Psoriasis, tofasitinib, JAK inhibitörü

General information

Tofacitinib is an oral inhibitor of janus kinases (JAK), which is approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis in adults. Although not approved for the treatment of psoriasis, its effectiveness in psoriasis and psoriatic arthritis has been demonstrated in clinical studies[1,2].

Mechanism of action

As a potent inhibitor of JAK1 and JAK3, tofacitinib also shows partial activity against JAK2 and tyrosine kinase (Tyk2)[3,4]. It affects many factors playing a role in the pathogenesis of psoriasis by way of a direct effect on the inhibition of JAK signalling and keratinocyte dysregulation, decreasing inflammatory infiltration and IL23/Th17 axe normalization[5].
While reducing secretion of proinflammatory mediators through JAK1, it also suppresses proliferation and activation of helper and cytotoxic T-cells through JAK3[6,7].
Tofacitinib in its low doses modulates the immune system through JAK1 and JAK3 and in its high doses affects haematopoiesis by suppressing JAK2-mediated erythropoietin signalling[8].

Dosage and treatment scheme

It has been used in daily oral doses of 2x5 mg and 2x10 mg in studies. Its 2x5 mg dose is approved for rheumatoid arthritis. Although it has no approved dose for the treatment

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E-mail: senturk.nilgun@gmail.com **Received/Geliş Tarihi:** 07.02.2022 **Accepted/Kabul Tarihi:** 11.02.2022
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Cite this article as: Şentürk N. Tofacitinib. Turkderm-Turk Arch Dermatol Venereol 2022;56(Suppl 1):67-9

of psoriasis, 10 mg dose of tofacitinib has been found more effective than its 5 mg dose[1,2]. A single daily dose of 5 mg is recommended in those with mild to moderate hepatic and renal dysfunction[9].

Efficacy

Randomized, controlled studies on the efficacy of tofacitinib in psoriasis (7 RCSs with 3743 patients) have shown that it improved the physician global assessment (PGA) scores, and PASI75, PASI90 responses. The effect is more prominent with a 10 mg dose[9-13].

When compared to placebo, it was seen to achieve PASI75 response in 40-64% of the patients with moderate to severe psoriasis at week 12 or 16. When used in daily 10 mg doses (not 5 mg), it showed an effect similar to that of etanercept[13]. Clinical response improved from week 16 to 28 and most of the patients maintained the responses they achieved at week 52[2].

Higher doses need to be used in patients with severe disease and in those who are not biologically naive[14]. Continuous treatment with tofacitinib is more effective than intermittent treatment. When the treatment is resumed in patients who had a break, 60% of them obtained their previous response and 40% had a loss of efficacy. The tofacitinib therapy was also found effective in nail involvements and regions resistant to treatment[12]. It also improves quality of life scores and itching symptoms[2]. Tofacitinib should not be combined wth immunosuppressive agents (azathioprine, cyclosporine and other biological agents. It may be combined with methotrexate when necessary[9].

Follow-up

Due to increased risk of infection, patients who will use tofacitinib should be screened for tuberculosis, hepatitis and HIV infections before the treatment. A zoster vaccine may be administered before the treatment. A whole blood count and lipid panel should be performed before starting the treatment and these values should be checked after 4-8 weeks and at 3-month intervals thereafter (Table 1)[9].

Side effects/safety

Although tofacitinib is well tolerated in short and long-term use, studies have reported some side effects including nasopharyngitis, upper respiratory tract infections, headache, urinary tract infections and diarrhoea. Its side effects are more compared to placebo and this risk increases when 10 mg is used[1]. Patients using tofacitinib have an increased risk of herpes zoster compared to placebo; the risk is dose-dependent but no visceral involvements have been observed. The risk further increases with old age and high doses, and in Asians and patients who are not biologically naive; thus, they should be monitored more closely. Even in the absence of marked changes in laboratory parameters, monitoring of haemoglobin, absolute neutrophil count, and total cholesterol, HDL, LDL, liver enzyme and creatinin levels is recommended. It may increase the risk of thromboembolism; organ toxicity has not been observed[2].

Contraindications

Due to bone marrow suppression risk, it should not be used in patients with a low lymphocyte count (<500/mm^3), neutrophil count (<1000/mm^3) and haemoglobin value (<9 g/dL), in those with a serious hepatic dysfunction, and in the presence of infection[9].

Drug interactions

Tofacitinib is metabolised in the liver by CYP3A4 and at a lower degree by CYP2C19. When taken in combination with CYP3A4 inhibitors (e.g. ketoconazole) or CYP2C19 inhibitors (e.g. Fluconazole), it causes the blood level to increase and when taken with drugs inducing the CYP3A4 enzyme (e.g. rifampin), it causes the blood level to drop[15].

Table 1. Pre-treatment and follow-up tests to be performed in patients using tofacitinib

	Pre-treatment	Follow-up
Whole blood count	+	- After 4-8 weeks - Every 3 months thereafter - Suspend or end treatment if lymphocyte count is <500/mm^3 - Suspend or end treatment if leukocyte count is <500/mm^3 - Suspend or end treatment if haemoglobin dropped by more than 2 g/dL or is <8 g/dL
Liver enzymes	+	After 4-8 weeks Every 3 months thereafter Use 5 mg in the presence of moderate to severe dysfunction
Kidney functions	+	After 4-8 weeks Every 3 months thereafter Use 5 mg in the presence of moderate to severe dysfunction
Beta HCG	+	At baseline and whenever necessary
Hepatitis B	+	
Hepatitis C	+	
HIV	+	
PPD/quantiferon test	+	Once a year
Chest X-ray	+	Once a year

Special cases

Pregnancy

It can be used in pregnancy if its potential benefit outweighs its risks[9].

Vaccination

Live vaccines should be avoided in patients using tofacitinib[9].

SUGGESTIONS

- Oral tofacitinib is effective in the treatment of moderate to severe psoriasis and is well tolerated.
- It provides advantages in the treatment of psoriasis due to oral use, lower cost compared to other biologics, and absence of organ toxicity[16].
- Although the efficacy of tofacitinib has been assessed mostly in moderate to severe psoriasis, it may also be a good option in mild psoriasis and in difficult-to-treat areas such as the face and genital region[17].
- Presence of comorbidities such as psoriatic arthritis[18], cardiovascular risk[19] and depressive symptoms[20] may also be a reason for choosing tofacitinib.

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