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Emerging Treatments for Psoriasis: What Do Interleukin-17 Antagonists Promise?

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Abstract

Background: IL-17 antagonists are a new class of biologic agents consisting of antibodies against IL-17A and its receptor. Three biologic agents belong to this novel category: Secukinumab, ixekizumab and brodalumab. These new agents are highly effective for treatment of moderate to severe psoriasis leading to complete or almost complete clearance of psoriatic lesions in a substantial proportion of patients. Results reported on the safety of IL-17 antagonists are also promising.

Introduction

Psoriasis is a chronic inflammatory skin disease affecting approximately 2% of western population [1]. Recently there has been substantial research concerning the pathogenesis of the disease pointing to the role of various inflammatory cytokines [2]. T helper17 cells (Th17) are thought to play a critical role in the development of psoriasis. This subset of cells is abundantly found in psoriatic lesions and they are the primary source of IL-17. The levels of the IL-17A and IL-17F were shown to correlate with disease activity [3].

IL-17 Antagonists

IL-17 antagonists are a new class of biologic agents consisting of antibodies against IL-17A and its receptor. Three biologic agents belong to this novel category: Secukinumab, ixekizumab and brodalumab.

Secukinumab is a fully human monoclonal antibody to the IL-17A ligand [2]. Secukinumab was approved by the FDA for the treatment of moderate-to-severe plaque psoriasis in 2015. One year later, FDA also approved the use of secukinumab for the treatment of patients with ankylosing spondylitis and psoriatic arthritis [4]. Standard dosing regimen is 300 mg once weekly at weeks 0, 1, 2, 3, 4 followed by 300 mg every 4 weeks applied subcutaneously. In some patients 150 mg per dose may be used, however with less efficacy [5].

Ixekizumab is a humanized IgG4 monoclonal antibody targeting IL-17A [5]. The FDA approved the use of ixekizumab for the treatment of moderate-to-severe plaque psoriasis in March 2016. Ixekizumab is applied subcutaneously with a dosing regimen of once 160 mg, followed by 80 mg at weeks 2, 4, 6, 8, 10, 12, and then 80 mg every 4 weeks [6].

Brodalumab is a IgG2 human monoclonal antibody that antagonizes the alpha subunit of the IL-17 receptor (IL-17RA). It binds IL-17RA with high affinity and thus inhibits the action of IL-17A, IL-17F and IL-17E [**5**]. Brodalumab was FDA approved in February 2017 for the treatment of moderate-to-severe plaque psoriasis. Dosing regimen is 210 mg at weeks 0, 1 and 2, followed by 210 mg once every 2 weeks subcutaneously [**7, 8**].

Efficacy

Biologic agents targeting IL-17 are highly effective for treatment of moderate to severe psoriasis leading to complete or almost complete clearance of psoriatic lesions in a substantial proportion of patients. The fact that IL-17 antagonists have a more significant effect compared to TNF inhibitors and ustekinumab, led to the idea that the standard treatment responses should be evaluated using PASI 90 instead of PASI 75 [**9,10**].

Secukinumab

Two randomized, double blind, placebo-controlled phase III trials revealed the high eff icacy of secukinumab. At 12th week of treatment, PASI 75 responses were achieved by 81,6% and by 4,5% of patients in secukinumab and placebo groups respectively. PASI 75 response rates observed at 12th week were higher with secukinumab than that with etanercept and placebo, with percentages of 77,1%, 44% and 4,9% respectively. Similarly, at the end of 52nd week, proportion of PASI 75, PASI 90 and PASI 100 responders was significantly greater with secukinumab as compared with etanercept[**11**]. Another study found secukinumab to be superior to ustekinumab in reduction of PASI scores. Improvement in PASI of 90% was observed in 79% and in 57% of patients under secukinumab and ustekinumab treatments respectively at 16th week of treatment [**12**].

Anti-drug antibodies were detected in less than 0.5% of patients during 52-week treatment period with secukinumab. Thus, it is considered safe to reinitiate secukinumab treatment as needed. It was shown that 69% of patients relapsing after treatment cess ation regained PASI 75 response rates wit h 300 mg secukinumab treatment applied every 4 weeks [**13**]. Another study found that more than 90% of patients regained PASI 75 responses with retreatment regimen dosing at weeks 0, 1, 2, 3, 4 followed by 300 mg every 4 weeks [**14**].

Ixekizumab

Three randomized, placebo-controlled, double-blind clinical trials have proved the efficacy and response maintenance for 60 weeks in a majority of ixekizumab-treated patients [**15,16**].UNCOVER-2 and UNCOVER-3 phase III studies aimed to compare the efficacy of ixekizumab administered every 2 weeks (IXE Q2W), ixekizumab administered every 4 w eeks (IXE Q4W), etanercept 50 mg twice weekly and placebo. At 12th week of treatment, both doses of ixekizumab have been shown to have significantly superior efficacy compared to placebo and etanercept. Proportion of patients who achieved PASI 90 treated with IXE Q2W, IXE Q4W, etanercept and placebo was 70.7%, 59.7%, 18.7% and 0.6% respectively in UNCOVER-2 trial and 68.1%, 65.3%, 25.7% and 3.1% respectively in UNCOVER-3 trial. After a 12-week induction period, patients treated with IXE Q2W and IXE Q4W received IXE Q4W maintenance therapy until 60th week. In UNCOVER 3 trial, at 60th week PASI 75 responses were achieved in 83% and 80% of patients and PASI 90 responses were achieved in 73% and 52% of patients in IXE Q2W and IXE Q4W groups respectively.

A recent study investigating the efficacy of retreatment with ixekizumab after an interrupted therapy showed that patients experienced relapse in approximately 20 weeks after the cessation of treatment. Furthermore, most importantly, the study showed that with a retreatment with ixekizumab applied every 4 weeks most of the patients regained baseline responses. There was no di fference in the incidence of anti-drug antibodies between patients under continous therapy and patients under interrupted therapy [**17**]. Moreover, the efficacy of ixekizumab did not differ among biologic naive patients and those with previous exposure to biologics, in contrast to etanercept treatment which showed lower efficacy in the latter group [**18**].

Brodalumab

First phase III trial of brodalumab demonstrated that 83%, 70% and 42% of patients achieved PASI 75, PASI 90 and PASI 100 responses respectively [**19**]. AMAGINE-2 and

AMAGINE-3 trials compared efficacy of brodalumab (every 2 weeks 210 or 140 mg) with ustekinumab and placebo. In AMAGINE-2 study, 49% of patients in 140 mg group, 70% of patients in 210 mg group, 47% of patients in ustekinumab group and 3% of patients in placebo group have achieved PASI 90 at 12th week with very similar results to that of AMAGINE-3 study. PASI 100 response rates obtained with 210 mg brodalumab treatment were also significantly superior to ustekinumab [**20**]. Another study showed that clinical responses were maintained during 120-week treatment period with brodalumab. PASI 75, PASI 90 and PASI 100 responses were reported in 95%, 85%, 63% of patients, respectively, at 12th week, and in 86%, 70%, 51% of patients, respectively, at 120th week of treatment [**21**].

Speed of onset of action

IL-17 antagonists have a markedly rapid onset of action in improving clinical signs and symptoms. Significant improvements of PASI from baseline were observed in patients receiving IL-17 antagonists only after 1 to 4 weeks of treatment [**22**].

Secukinumab

A study showed that 31% and 37% of patients treated with secukinumab 300 mg and 150 mg attained PASI 75 responses at only 4th week of treatment [**23**]. Clinical response rate assessed as 50% reduction in PASI score was more rapid with secukinumab (3 weeks) as compared with etanercept (7 weeks) [**11**]. Clinical response rate with secukinumab was also found to be superior to ustekinumab. At 4th week, proportions of patients achieving PASI 90 and PASI 100 responses were significantly elevated with secukinumab compared with ustekinumab [**12**].

Ixekizumab

PASI 75 response was achieved in nearly half of the patients at the 4th week of treatment with ixekizumab [16]. Assessment of health-related quality of life and pruritus using specific scales [Dermatology Life Quality Index (DLQI) and Itch Numeric Rating Scale (itch NRS)] indicated that ixekizumab treatment acted rapidly to relieve itch and improve life quality compared to etanercept and placebo. Median time to achieve minimally clinically important differences in DLQI and itch NRS was 2.1 weeks under ixekizumab treatment [**24**].

Brodalumab

Brodalumab treatment was associated with superior responses than placebo beginning from second week of treatment [**25**]. Median time to attain PASI 75 response was almost 2 times shorter with brodalumab 210 mg compared with ustekinumab [**20**].

Adverse effects

Regarding safety of IL-17 antagonists, infections and cardiovascular diseases are the main concerns among the adverse effects of the use of IL-17 antagonists [**22**].

Meta-analysis results indicate that IL-17 antagonists are associated with a higher risk of infection than placebo. However, incidence of serious infections did not differ between IL-17 antagonists and placebo. The most co mmonly reported infection events were nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, pharyngitis, sinusitis or rhinitis [**22**].

As IL-17A has various roles in host defence including expression of antimicrobial peptides, maturation and survival of neutrophils; patients receiving IL-17 antagonists should be followed-up closely for candida infections and neutropenia [**7, 22**]. Candidial infections were more commonly seen in secukinumab-treated patients than in etanercept-treated patients [**11,12**]. Similarly, oral and genital candidiasis were more prevalent in patients treated with ixekizumab compared with etanercept and placebo. Brodalumab was also associated with a higher incidence of candidial infections than ustekinumab. Reported candidial infections were all mild and moderate in severity and none of them were systemic [**20**]. Regarding neutropenia, IL-17 antagonist-related neutropenia was reported to be a transient and reversible event, not associated with any serious infection [**15, 16, 20**]. As for tuberculosis, according to both clinical (phase III) and in vitro studies secukinumab was not associated with an increase in M.tuberculosis infections. There were no cases of tuberculosis at the end of 1 year secukinumab treatment. Moreover, active t uberculosis did not develop under secukinumab therapy in cases with a history of lung tuberculosis or cases with latent tuberculosis

[**26**].

In a meta-analysis including nine randomized controlled studies it was reported that IL-17 antagonists showed no significant di fferences from placebo in the proportion of patients with cardiovascular disease. Larger scale clinical studies are required to investigate the possible protective roles of IL-17 antagonists against cardiovascular diseases [**22**].

During maintenance phase of brodalumab treatment two patients died from suicide raising suspicion of a causal relationship between brodalumab and suicide. In the safety investigations, it was reported that suicides were coincidential events and brodalumab treatment was not related with an increased risk of suicide [**27**]. However, this observation led to insertion of a "black box warning" [**7**].

IL-17 antagonists are associated with a flare in inflammatory bowel diseases. Use of IL-17 antagonists should be avoided in psoriasis patients having inflammatory bowel disease [**28**].

IL-17 antagonists showed no significant differences from placebo in the proportion of patients with malignancy. Further information about the safety of IL-17 inhibitors will be obtained in the following years with phase IV studies [**29**].

Conclusion

In the management of psoriasis, despite existing biologic agents targeting TNF-alfa and IL-12/23, there is continuing search for new and more effective biologic agents. IL-17 antagonists are a new class of biologic treatment with promising clinical outcomes.

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