Review paper

Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases

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Abstract

Psoriasis is a chronic skin disease caused by the excessive secretion of inflammatory cytokines. Available therapeutic options include biologic drugs such as tumor necrosis factor alpha inhibitors and interleukin 12/23 (IL-12/23) inhibitors. The recent discovery of IL-17, which contributes to development of psoriasis, opened new possibilities for further treatment modalities. Currently, one anti-IL17 biological agent is approved for the treatment – a fully human monoclonal antibody that targets IL-17A (secukinumab). Further clinical trials, including a humanized IgG4 specific for IL-17 (ixekizumab) and a fully human antibody that targets the IL-17 receptor A (brodalumab).

Key words: alopecia areata, fynomer, lichen planus, pemphigoid, pemphigus.

Introduction

Psoriasis is a chronic inflammatory skin disease affecting about 2% of the Western population [1, 2]. It presents as erythematous scaly plaques with induration. Psoriasis can affect the patient's quality of life and self-esteem [3, 4]. Topical treatment includes application of coal tar, dithranol, retinoids, corticosteroids and vitamin D_3 analogues. Systemic treatment includes phototherapy, methotrexate, cyclosporine, retinoids and biological agents. Despite many options, many patients do not respond to therapy or report side effects. Thus, new drugs are still being searched for.

Interleukin-17 and pathogenesis of psoriasis

T helper cells have been classically divided into Th1 and Th2. In 2005, a new class of T helper cells (Th17) was discovered [5]. It was demonstrated that Th17 cells play a role in the protection from both extracellular and intracellular agents [6]. Transforming growth factor (TGF)-β and interleukin (IL)-6 stimulate the differentiation of naïve CD4+ T cells into Th17. This induces the expression of IL-17A [7]. IL-17A is a pro-inflammatory cytokine. It belongs to the IL-17 family, which consists of IL-17A-F [8]. IL-17A plays a role in neutrophil recruitment, host defense and immuno-inflammatory pathology [7]. It is secreted mainly by Th17, but also by Treg cells, NK cells, mast cells and neutrophils [9]. IL-17A and IL-17F bind to the same receptor, however the influence of IL-17A on gene regulation is 10–30 times stronger. The function of IL-17B, IL-17C and IL-17D is poorly defined. IL-17E limits Th17 development and promotes Th2 cytokines [10]. IL-17 plays a role in numerous immune-mediated disorders, such as rheumatoid arthritis, Crohn's disease, multiple sclerosis and autoimmune encephalomyelitis [11–13]. The role of IL-17A in atherosclerosis is under discussion. Studies showed both its proatherogenic and protective influence [14].

It is believed that an unknown antigen triggers NK cells, plasmacytoid dendritic cells and macrophages to secrete tumor necrosis factor (TNF)-α, IL-1β, interferon (IFN)-α and IL-6 in genetically susceptible patients. Local myeloid dendritic cells, activated during this process, produce IL-12 and IL-23 [15]. IL-23 plays a role in the maintenance of Th17 response. IL-12, on the other hand, upregulates the proliferation of Th1 cells. IL-17A upregulates the keratinocyte chemokine CCL20, and recruits CCR6+ cells (mDCs and Th17). Moreover, it induces the expression of neutrophil chemoattractant chemokines and antimicrobial peptides [7, 11, 16]. IL-17A sustains chronic inflammations [17].

Interleukin-17 inhibitors

As a result of the success of biological treatment targeting the IL-23/Th17 pathway, investigators still search

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for new therapeutic options. Three agents that block IL-17 are investigated at the moment. Secukinumab, brodalumab and ixekizumab have successfully completed phase II clinical trial and are currently at phase III [11]. The results are very promising.

Secukinumab (AIN457)

Secukinumab is a fully human anti-IL-17A monoclonal antibody. Secukinumab showed efficacy in the treatment of moderate-to-severe plaque psoriasis in a randomized double-blind placebo-controlled phase II regimen finding study. In the study, the patients were randomized to a placebo group, a single drug administration group, an early group (at weeks 0, 1, 2, 4) or a monthly group (at weeks 0, 4, 8). At week 12, the early and monthly induction regimens resulted in higher PASI75 response rates vs. placebo (54.5% and 42.0% vs. 1.5%; $p < 0.001$ for both). After 12 weeks, patients who achieved Psoriasis Area Severity Index (PASI)75 were re-randomized to a secukinumab fixed interval regimen (150 mg at weeks 12 or 24) or a treatment-at-start-of-relapse maintenance regimen. Between weeks 20 and 28, PASI75 or PASI90 were more frequently achieved in the fixed interval group than with the fixed interval regimen (85% and 58% vs. 67% and 21%, respectively) [18].

In two phase III, double blind, 52-week trials, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis), the efficacy of secukinumab was investigated in patients with moderate-to-severe plaque psoriasis. The ERASURE study included 738 patients, and the FIXTURE one – 1306 patients. Both groups received either placebo or secukinumab subcutaneously once a week for 5 weeks, then once a month. Patients in the FIXTURE study were also given etanercept of 50 mg twice a week for 12 weeks, then once a week.

In the ERASURE study, PASI75 at week 12 was achieved by 81.6% and 71.6% of patients administered with 300 mg and 150 mg of secukinumab, respectively and 4.5% of placebo patients. In the FIXTURE study, 77.1% of patients administered with 300 mg of secukinumab, 67% of those administered with 150 mg of secukinumab, 44% of etanercept patients and only 4.9% of placebo patients achieved PASI75 at week 12. In the ERASURE study, the percentage of patients who got a response of 0 or 1 in the modified Investigator's Global Assessment at week 12 was 65.3%, 51.2%, and 2.4% among patients who received secukinumab of 300 mg, 150 mg and placebo, respectively; in the FIXTURE study the rates were 62.5% with 300 mg of secukinumab, 51.1% with 150 mg of secukinumab, 27.2% with etanercept, and 2.8% with placebo ($p < 0.001$ for each secukinumab dose vs. comparators). Adverse effects in the ERASURE study were more common in the secukinumab group than in the placebo group and mostly included nasopharyngitis, headache and upper respiratory tract infections. In the FIXTURE study, the incidence of adverse effects was similar among secukinumab and etanercept patients. The most common side effects were nasopharyngitis, headache and diarrhea [19].

A 24-week, randomized, double blind, placebo-controlled, phase II proof-of-concept trial included 42 patients with moderate-to-severe psoriatic arthritis who met CASPAR criteria. Twenty-eight patients were administered with two intravenous secukinumab doses of 10 mg/kg every 3 weeks and 14 patients were administered with placebo. The primary endpoint was ACR20 responses at week 6. The results were 39% in secukinumab vs. 23% in placebo patients. The respective results for weeks 12 and 24 were 39% vs. 15% and 43% vs. 18%. Two patients from the secukinumab group dropped out of the study due to withdrawal of consent and 1 due to the unsatisfactory therapeutic effect. In the placebo group, 3 patients dropped out of the study due to the withdrawal of consent and 1 had an unsatisfactory effect. The most common adverse effects included nasopharyngitis, headache, nausea, dizziness, fatigue and diarrhea [20].

Self-administration of secukinumab via sc route was safe and more effective than placebo. At week 12, PASI75 was achieved by 75.9%, 69.5%, and 0% of patients who were administered with secukinumab of 300 mg, 150 mg and placebo, respectively [21].

The evaluation of the safety, tolerability and efficacy of secukinumab is being carried out in an ongoing clinical trial FUTURE 1. The study includes patients with active psoriatic arthritis who did not tolerate or were irresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs and/or TNF-α inhibitor therapy. It evaluates patients treated with 75 mg or 150 mg of secukinumab vs. placebo who achieved ACR20. The study is expected to be completed in November 2014 (Clinicaltrials.gov identifier NCT01392326).

Another ongoing study is a study on safety, tolerability, and efficacy of secukinumab in subjects with moderate-to-severe nail psoriasis (TRANSFIGURE) (ClinicalTrials.gov identifier NCT01807520).

In phase III randomized, double-blind, placebo-controlled multicenter study, secukinumab is being evaluated in patients with moderate-to-severe palmoplantar psoriasis. The results will be available in November 2015 (ClinicalTrials.gov identifier NCT01806597).

Brodalumab (AMG 827)

Brodalumab is a human, anti-IL17RA monoclonal antibody. It blocks the activity of IL17RA, 17A/F and 17E.

Russell *et al.* reported that IL-17R blockade with brodalumab normalizes the psoriasis transcriptome. Keratinocyte expressed genes, e.g. KRT6A, IL1F6, chemokine CXCL6, antimicrobial peptide gene S100A7A normalize

faster than T cell genes. Ki67 cell counts returned to normal after 2 weeks, but the inflammatory leukocyte infiltrate decreased after 6 weeks [22].

In a placebo-controlled phase I study, 25 patients with moderate-to-severe psoriasis received either a single dose of brodalumab: 140 mg *s.c.* (n = 4), 350 mg *s.c.* (n = 8), 700 mg *i.v.* (n = 8), or placebo (n = 5). All the patients who received brodalumab 700 mg *i.v.* achieved PASI50 by day 29, 7 of them had PASI75 by Day 43 and 3 patients achieved PASI90 by day 43. In the 350 mg brodalumab sc group, 6 patients achieved PASI50 and 3 patients PASI75. Only 2 patients in the 140 mg brodalumab group achieved PASI50, and none in the placebo group. The 350 mg *s.c.* and 700 mg *i.v.* brodalumab groups also showed a reduction in epidermal thickening and keratin 16 levels and a significant improvement in mRNA levels of IL-17 modulated keratinocyte-derived factors, e.g. DEFB4, cathelicidin, KRT 16, CCL18, CCL20. Moreover, cytokines not directly regulated by IL-17R, (IL-22, IL-23) were reduced. The levels of IL-17A, IL-17C and IL-17F were similar to those in healthy individuals. The safety of brodalumab was similar to placebo [23].

In phase II, randomized, double-blind, placebo-controlled, dose-ranging study in moderate-to-severe plaque psoriasis, brodalumab proved to be effective. One hundred and ninety-eight patients received either placebo or the following doses of brodalumab: 70 mg, 140 mg, 210 mg on day 1 and at weeks 1, 2, 4, 6, 8 and 10. The last group received 280 mg of brodalumab on day 1 and at weeks 4 and 8. At week 12 the improvement in PASI was 85.9%, 86.3%, 76%, 45% in 140 mg, 210 mg, 280 mg, 70 mg brodalumab groups, respectively, versus 16% in the placebo group. At week 12 PASI75 and PASI90 were observed in 77% and 72%, respectively, in patients of 140 mg brodalumab group and 82% and 75%, respectively, in patients of 210 mg brodalumab group in comparison with 0% in the placebo group. The most common adverse events in brodalumab groups were nasopharyngitis, upper respiratory tract infection and injection-site erythema. There were 2 cases of grade 3 neutropenia which resolved with the discontinuation of the drug [24].

In phase II randomized double-blind placebo-controlled study 168 patients with psoriatic arthritis were randomized to brodalumab 140 mg, brodalumab 280 mg or a placebo group. The drug was administered on day 1 and at weeks 1, 2, 4, 6, 8 and 10. After 12 weeks, the patients who did not discontinue the study, were offered open label brodalumab 280 mg every 2 weeks. At week 12, 37%, 39% and 18% of patients met American College of Rheumatology response criteria (ACR20) in brodalumab 140 mg, brodalumab 280 mg and placebo groups, respectively. Moreover, patients from both brodalumab groups had a higher ACR50 response in comparison with placebo (14% vs. 4%). At week 24, ACR20 was achieved in 51% and 64% of patients in brodalumab 140 mg and 280 mg groups, respectively, and 44% of patients who switched from placebo to open label brodalumab group. Adverse events occurred in 62%, 71% and 65% in brodalumab 140 mg, 280 mg and placebo groups, respectively. The most common adverse effects were the infections of the upper respiratory tract, fatigue, diarrhea and headache. Serious adverse events, which occurred in four patients, included abdominal pain, cholecystitis and cellulitis on the knee and the upper chest [25].

In two phase-3 studies (AMAGINE 2 and AMAGINE 3) brodalumab at doses of 140 mg *s.c.* and 210 mg *s.c.* was compared with ustekinumab and placebo in patients with moderate-to-severe plaque psoriasis. At week 12 patients who received brodalumab were re-randomized to receive brodalumab of 210 mg every 2 weeks or 140 mg every 2, 4 or 8 weeks. Patients in ustekinumab continued with ustekinumab and patients in the placebo group received brodalumab of 210 mg every 2 weeks. At week 12, PASI75 was achieved in 86% and 67% patients in the brodalumab group 210 mg and 140 mg (AMAGINE-2), respectively, and 85% and 69% in AMAGINE-3. PASI75 was achieved by 70% and 69% of patients in the ustekinumab group, AMAGINE-2 and AMAGINE-3, respectively. PASI100 was achieved by 44% (AMAGINE-2) and 37% (AMAGINE-3) of patients in brodalumab 210 mg group and 22% (AMAGINE-2) and 19% (AMAGINE-3) in the ustekinumab group. At week 52 the best results were seen in patients who received 210 mg of brodalumab every 2 weeks. In AMAGINE-2, 63% of patients score 0 or 1 in sPGA and 61% in AMAGINE-3. The adverse effects were more frequent in the brodalumab group than in the ustekinumab group. The most common adverse effect included nasopharyngitis, arthralgia, headache and upper respiratory tract infections and *Candida* infections. There were reported cases of death among patients in the brodalumab group – due to stroke, cardiac arrest, carcinoma of pancreas, cardiomyopathy and hematophagic histiocytosis syndrome. Two deaths were due to suicides [26].

In another phase-III randomized, double-blind, placebo-controlled study, the safety and efficacy of brodalumab in comparison with placebo at week 16 are being evaluated in patients with psoriatic arthritis. The results of the study are expected to be available in April 2018 (ClinicalTrials.gov Identifier NCT02024646).

In 2015, Amgen ended the participation in the project related to brodalumab because of two deaths due to suicide. The project is continued by AstraZeneca.

Ixekizumab (LY2439821)

Ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17 [27].

In a 20-week randomized double-blind placebo-controlled phase I study, ixekizumab was evaluated in 40 individuals with chronic moderate-to-severe plaque psoriasis. Patients received 5 mg, 15 mg, 50 mg or 150 mg of ixekizumab sc or placebo at weeks 0, 2 and 4. Punch biopsies were performed at weeks 0, 2 and 6. At week 2

there were a reduction in keratinocyte proliferation, epidermal hyperplasia, dermal infiltration of T cells and dendritic cells and keratinocyte expression of innate defense peptides. The reduction was dependent on the dosage. At week 6 the skin was normal [28].

In phase II, double-blind, placebo-controlled trial, 142 patients with moderate-to-severe plaque psoriasis were randomized to receive 10, 25, 75, 150 mg of ixekizumab *s.c.* or placebo at weeks 0, 2, 4, 8, 12 and 16. At week 12, 76.7%, 82.8% and 82.1% of patients achieved PASI75 in groups: 25 mg, 75 mg, 150 mg of ixekizumab, respectively, versus 7.7% ($p < 0.001$) in the placebo group. More patients treated with a high dosage of ixekizumab at week 12 achieved PASI90 (150 mg – 71.4%, 75 mg – 58.6%, 25 mg – 50%, placebo – 0%) and PASI100 (150 mg – 39.3%, 75 mg – 37.9%). The side effects included nasopharyngitis, upper respiratory tract infections, injection site reactions and headache. Two patients receiving ixekizumab had grade 2 neutropenia according to the Common Terminology Criteria for Adverse Events. Four patients dropped out of the study because of adverse effects: hypertriglyceridemia, peripheral edema, hypersensitivity, and urticaria [29].

A post-hoc analysis conducted by Zhu *et al.* proved that with an early clinical improvement in PASI we can predict the PASI response when treating psoriasis patients with ixekizumab. According to the study, achieving PASI40 at weeks 4 or 6 was associated with high negative predictive values (80% and 95%, respectively) and positive predictive values (89% and 84%, respectively). Achieving PASI50 showed more accuracy – negative predictive values (NPVs) of 71% and 89% and positive predictive values (PPVs) of 94% and 89%, respectively. Patients who do not achieve PASI40 at weeks 4–6 are unlikely to respond ixekizumab therapy. Since biological treatment is very costly, these findings may be very helpful to predict therapy results and further investigation needs to be conducted [30].

The efficacy and safety of ixekizumab were investigated in a 52-week open-label study in patients with chronic plaque psoriasis. Patients received 10 mg, 25 mg, 75 mg or 150 mg of ixekizumab at weeks 0, 2, 4, 8, 12 and 16 or placebo. At week 20, patients who did not achieve PASI75 were switched to open label extensions (OLE) and received 120 mg *s.c.* of ixekizumab every 4 weeks. Patients who achieved PASI75 entered a treatment-free period between weeks 20 and 32, then entered the open label extension after meeting the criteria. Those who completed the randomized double-blind clinical trial entered the open label extension. Fifty-eight percent of them achieved PASI75 at week 20 and entered a treatment-free period at weeks 20–32. Thirty-five percent lost PASI75 within this period and entered the OLE. Patients who did not respond to ixekizumab at week 20 entered the OLE. At week 52, 77% of those who entered the OLE achieved PASI75, 68% achieved PASI90 and 48% – PASI100. Among patients who had PASI75 at week 20, 95% still had PASI75 at week 52. In patients who achieved PASI90 or PASI100 at week 20, the respective PASI rates were 94% and 82%. The initial dosage of ixekizumab was not important for the results at week 52 and the improvement was similar in each group. Serious adverse effects observed in 10 patients included rectal cancer, hidradenitis suppurativa, depression, suicide attempt, atherosclerosis, congestive heart failure, urinary tract obstruction, cellulitis, pyelonephritis, acute coronary syndrome, nephrolithiasis, wrist fracture and laceration of the arm. No cases of neutropenia higher than grade 2 were reported [31].

There is an ongoing multicenter, randomized, double-blind, active (with adalimumab) and placebo-controlled study which investigates the efficacy and safety of ixekizumab in patients with psoriatic arthritis (ClinicalTrials.gov identifier NCT01695239).

The results of phase III study comparing the efficacy and safety of ixekizumab to etanercept and placebo in patients with moderate-to-severe plaque psoriasis will be known in December 2018 (ClinicalTrials.gov Identifier NCT01597245).

Novel drug candidates targeting IL-17

Several agents which target the IL-17–TH17 pathway are currently under investigation [31, 32]. The ongoing studies focus on the efficacy of anti-IL-17 antibodies (bimekizumab, ALX-0761, CJM112, CNTO 6785, LY3074828, and SCH-900117). A novel approach is the application of anti-IL-17 nanoantibodies (e.g. MSB0010841) in treatment of psoriasis. Dual anti IL-17/TNF-α inhibitors (e.g. ABT-122, COVA322) are currently in early phases of clinical trials. Fynomers are small binding proteins engineered to target molecules with the same affinity and specificity as antibodies. Genetic fusion of fynomers to antibodies allows the production of a bi-specific, fully human anti-TNF and anti-IL-17A antibody (FynomAb® COVA322) [33].

Agents targeting IL-17 beyond psoriasis

Several pre-clinical data indicate that IL-17 inhibitors may be effective in multiple muco-cutaneous disorders beyond psoriasis. The possible targets for IL-17 inhibitors include oral lichen planus [34], alopecia areata [35], pyoderma gangrenosum [36], palmo-plantar pustulosis [36], systemic lupus erythematosus [37], systemic sclerosis [37], mixed connective tissue disease [37], pemphigus vulgaris [38], pemphigoid [38, 39], dermatitis herpetiformis [39], atopic dermatitis [40] and chronic periodontitis [41].

Conclusions

Psoriasis is a chronic inflammatory disease. Despite many options of treatment, psoriasis is still a challenge

for doctors and a burden for patients. The recent discovery of IL-17, which contributes to development of psoriasis, opened new possibilities for further treatment modalities. In January 2015, secukinumab was approved for the treatment of adults with moderate-to-severe plaque psoriasis. Two anti-IL-7 inhibitors, brodalumab and ixekizumab, are currently in phase III clinical trials (as of February 2015). A novel approach is the development of bi-specific antibodies, which target both IL-17 and TNF-α. The preliminary results show significant efficacy and a high safety profile of biological drugs in clinical trials. However, more studies must be conducted for further elucidation of the long-term treatment using this group of agents.

Conflict of interest

The authors declare no conflict of interest.

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