Novel Treatments for Atopic Dermatitis

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Atopic Dermatitis is a chronic, inflammatory skin disease characterized by strong pruritus that less commonly affects adults. This condition is associated with a poorer quality of life in comparison with the general population and causes sleep disturbances and coexisting comorbidities. Recently, new agents have been developed to treat this condition.

atopic dermatitis (AD) interleukin-4 (IL-4) interleukin-13 (IL-13) interleukin-22 (IL-22) interleukin-31 (IL-31) JAK-STAT inhibitors JAK inhibitors

1. New Medications in Atopic Dermatitis

Atopic Dermatitis （AD） is thought to be the hallmark of Th-2 microenvironment diseases. Th-2 profile cytokines, such as IL-4, IL-5 and IL-13, play a significant role in the pathogenesis of the disease by switching the immunoglobulin class to IgE and stimulating afferent neurons via IL-4Rα, thereby promoting pruritus [1]. Therefore, drugs blocking these pathways should be clinically effective in reducing the symptoms of this eczematous disease, as they act against the inflammation [2].

One of them is dupilumab—a fully human monoclonal antibody that blocks IL-4Rα, a shared receptor unit for IL-4 and IL-13, actively participating in the decrease of Th-2 mediated immunological response [3]. It is already used in America, Europe, and in several other countries on children, adolescents, and adults. The analysis of four phase-three trials has revealed that patients treated with this monoclonal antibody achieve a significantly higher percentage reduction from the baseline in the most important AD management scales—Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM) versus control [4]. Notably, these superior effects have been achieved in monotherapy without topical corticosteroids, regardless of previous use of systemic non-steroidal immunosuppressants, e.g., methotrexate or cyclosporine [4].

Other drugs targeting the IL-13 are lebrikizumab and tralokinumab. IL-13 binds and neutralizes the activity of the mentioned cytokine with high affinity [5]. In phase IIb of several randomized clinical trials, it showed promising results [6][7]. Even though adverse effects of this drug were reported in the significant group of patients, they were mostly mild to moderate [6][7]. Phase III clinical trials on patients who suffer from moderate to severe AD are currently ongoing [8][9][10][11][12][13][14]. Another promising emerging drug is tralokinumab—a fully human, monoclonal anti-IL-13 IgG4 antibody that binds to two subunits of IL-13R (IL-13Rα1 and IL-13Rα2), thus neutralizing the

cytokine from the interaction [3][15]. Recently, three phase III clinical trials (ECZTRA1, ECZTRA2, and ECZTRA3) were completed for this drug [16][17]. Tralokinumab, in combination with topical corticosteroids, is not only effective in reducing the pruritus and improving sleep quality, but it is also well tolerated for up to 52 weeks of treatment, which brings a promising perspective we mentioned earlier [16]. Moreover, this medicament is safe and well tolerated in combination with topical corticosteroids [17]. Interestingly, a long-term extension trial for patients who were participants in the previous studies is currently ongoing and the estimated completion date is in 2024 [18].

IL-22 and IL-31 are also the targets of new drugs, which have been or currently still are under investigation in phases IIa and III of clinical trials [19][20][21]. Fezakinumab, an anti-IL-22 antibody, has been shown in the IIa randomized, double-blind clinical trial on adults with moderate to severe AD to be well tolerated and to have sustainable improvements after the last dose [19]. Despite the small sample size and common adverse effects, which were upper respiratory tract infections, improvements in SCOring AD (SCORAD) were significant in patients with severe disease [3][19]. Thus, this drug is thought to be suitable for patients with severe AD, but no further clinical trials are currently ongoing [3]. Another interesting medication, especially for managing the pruritus in patients with AD is nemolizumab, a human monoclonal IL-31 receptor α (IL-31Rα) antagonist [3][21][22]. This drug targets small-diameter neurons and it is thought that the relieving effect of nemolizumab is due to action on cutaneous sensory neurons [3][22]. In the phase III trial, the patients who could not achieve proper control of pruritus by solely using topical treatment were recruited and enrolled [20]. Not only were the primary end points of the study achieved with a significant decrease in pruritus measured in the VAS scale, but also a series of secondary endpoints including EASI, DLQI or Insomnia Severity Index were met [20]. Other phase III trials are currently ongoing [23].

Various systemic and topical JAK inhibitors are about to be widely used in the treatment of AD [24]. The data on the double blind control trials evaluating the efficacy of these drugs in the treatment of AD are promising [25][26]. Baricitinib, abrocitinib, and upadacitinib belong to the group of oral drugs, while ruxolitinib is known as a topical agent considered in the therapy of AD [25].

Baricitinib is known as the first-generation JAK1/2 selective inhibitor [25][27][28]. The efficacy of the drug in monotherapy and combined with topical corticosteroids has been evaluated and the dose of 4 mg appears to significantly improve symptoms [29][30][31]. In the pooled safety analysis of baricitinib in adults, which contained previously mentioned studies, there were four major cardiovascular-adverse events and one death, however, no malignancies were reported [32].

Abrocitinib is an oral selective JAK1 inhibitor that achieved satisfying results in the phase III trial, proving that it is effective and well tolerated in monotherapy [29][33]. Patients from these studies have been enrolled in the extended trial (NCT03422822) and in the 48th week of this trial, it has been shown, that between 24 and 36 weeks, the proportion of patients meeting primary endpoints increased and was stable thereafter [25]. Comparing abrocitinib, dupilumab, and the placebo in clinical trial, both drugs significantly more reduced AD symptoms; however, a 200 mg dose of abrocitinib was superior to dupilumab in limiting itchiness [34].

The next oral selective JAK1 inhibitor is upadacitinib [25]. It safe and efficient in the monotherapy of moderate to severe AD in three phase III trials [35][36]. Moreover, in comparison with dupilumab it was superior, showing significantly higher proportion of patients who achieved the primary and secondary endpoints of the study [37]. Extension of the mentioned trials and also new ones with pediatric patients are ongoing [38][39].

Ruxolitinib (JAK1/2 inhibitor) and delgocitinib (pan-JAK inhibitor) have proved to be effective topical drugs in AD [25][26]. In the two phase III trials, ruxolitinib has shown anti-inflammatory and anti-pruritic effects superior to the vehicle cream [40]. Adverse effects were infrequent and clinically insignificant [40]. Clinical trials with atopic children are underway [41]. Delgocitinib also seems to be satisfactory, since in the phase III trial it was effective and well tolerated in Japanese patients for up to 28 weeks [42]. Currently, two phase III trials on moderate to severe chronic hand eczema are ongoing [43][44].

Also we have shown the considerations on the possible effects mentioned drugs may have on the development of primary cutaneous lymphomas in patients with AD.[45] Future epidemiologic data will show us if the influence of these new agents is significant. Until then, during admission of biologics and small molecule inhibitors the attention should be raised.

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