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Review Article

Research Progress of IL-17A Inhibitor in the Treatment of Psoriasis Induced or Secondary Skin Diseases

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Abstract

Psoriasis is a chronic inflammatory skin disease caused by multiple factors. With the widespread use of biological agents, the therapeutic effect of psoriasis is gradually recognized, among which interleukin-17A (IL-17A) inhibitor has remarkable efficacy, which has aroused great attention in the academic world. However, some cases abroad have shown that IL-17A inhibitors may induce or secondary to other skin diseases in the treatment of psoriasis. In this review, we will review the case reports of other skin diseases induced or secondary to IL-17A inhibitors in the treatment of psoriasis in recent years, in order to provide a reference for clinicians in the use of this drug.

Keywords: Interleukin-17A; Psoriasis; Induced; Secondary; The research progress

Introduction

Psoriasis is an immune-related inflammatory skin disease mediated by T cells. Epidemiological data analysis of more than 20 countries and regions around the world shows that the prevalence of psoriasis in adults is about 0.51%-11.43%, and the prevalence of psoriasis in children is about 0-1.37% [1]. The pathogenesis of psoriasis is multifactorial and difficult to be cured at present. With the advent of biotherapy, the treatment of psoriasis has undergone a revolution, including tumor necrosis factor -α (TNF-α), IL-17, IL-12, IL-23 inhibitors are widely used in the treatment of psoriasis. Il-17 pathway has been proved to be a key axis in the pathogenesis of psoriasis. It inhibits keratinocytes differentiation and promotes their proliferation by down-regulating human islet derived protein 3A, thus stimulating keratinocytes to produce antimicrobial peptides and attract more inflammatory cell infiltration, thereby aggravating the inflammatory response [2]. Currently, interleukin-17 inhibitors commonly used mainly target IL-17A and act on the IL-17 pathway, including whole human antibody Secukinumab that specifically inhibits IL-17A and Ixekizumab that selectively binds cytokines and inhibits their interaction with IL-17 receptors [3]. Il-17A inhibitor has a significant effect on improving psoriasis lesions [4], but it has been reported in several cases that its application in the treatment of psoriasis can easily induce the variation of the original lesions and further develop into other skin diseases. In this paper, we will review the recent cases of IL-17A inhibitor induced other skin diseases in the treatment of psoriasis.

Dermatitis and Eczema Skin Diseases

The pathogenesis of atopic dermatitis is very complex, and strong genetic susceptibility, epidermal dysfunction, abnormal skin microbiome, immune disorders and neuroimmune system are all crucial in the occurrence and development of atopic dermatitis [5]. Brambilla et al. [6] reported a case of psoriasis with acute symmetrical eczema at the anterior elbow and popliteal fold accompanied by intense itching after treatment with Secukinumab, Skin biopsy was in line with the diagnosis of atopic dermatitis, the author analyzed that the Th1 and Th17 pathways are the main inflammatory factors produced by psoriasis, while Th2 is the dominant inflammatory factor in atopic dermatitis. When patients use Secukinumab, the imbalance of Th1 and Th2 pathways will lead to the occurrence of atopic dermatitis. It also provides new ideas for us to better understand the pathogenesis of psoriasis and atopic dermatitis.

Psoriasis and eczema are caused by opposite immune and genetic mechanisms, but Picciani BLS et al. [7] systematically reviewed all cases of eczema in patients with psoriasis treated with biologic agents. A total of 92 patients in 24 studies were found to have outbreaks of eczema after treatment with six biologic agents: the anti-tumor necrosis factor -α drug (adalimumab, Etanercept, or infliximab), the anti-IL-17 drug (Secukinumab or Ixekizumab), or the anti-IL-12/23P40 drug (Ustekinumab). Secukinumab is the most common cause of such outbreaks. Miyagawa et al. [8] also pointed out that a patient with psoriasis was diagnosed with numismatic eczema after receiving Secukinumab treatment, but his condition improved after changing the treatment with guselkumab. Although there is no specific mechanism study on this kind of paradoxical reaction at present, timely replacement of biological agents will be a reliable choice in the face of such clinical situation.

Pigmented Skin Disease

Vitiligo is a relatively common decolorization disorder, mostly secondary to the loss of melanocytes. The specific pathogenesis is still unclear, but it is generally believed that there is an autoimmune condition [9]. Marasca et al. [10] reported a male psoriasis patient with partial facial vitiligo plaques after treatment with Ixekizumab. After ruling out family history and hypopigmentation in post inflammatory psoriasis, the authors suggest that vitiligo may be a rare adverse reaction to anti-IL-17 therapy. For similar situations, Giordano et al. [11] put forward different ideas. They reported the female patients with psoriasis by the Secukinumab to treatment, especially new and pigmentation of vitiligo lesions, the author analysis the vitiligo may be a contradiction skin reaction of biological agents, under the complex mechanism, may involve a variety of proinflammatory

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cytokines and anti-inflammatory pathway, is responsible for the destruction of melanocyte and the onset of vitiligo, it is related to the biological treatment. Zhang San quan et al. [12] reported that a patient with chronic psoriasis vulgaris developed small dark brown spots from needle tip to rice grain size in the cured psoriasis lesion area after treatment with Secukinumab. The authors speculate that the treatment of psoriasis with biologic agents (e.g., Secukinumab) may trigger episodes of pigmented nevus, in which a network of pro-inflammatory cytokines in the psoriatic skin may be involved in melanocyte growth and melanin production.

Diseases of Skin Appendages

The main theory of the pathogenesis of alopecia areata is that, starting from autoimmunity, different immune cell lines are caused by disorders caused by excessive pressure and other factors [13]. At present, some scholars believe that IL-17A inhibitors are likely to be used in the treatment of alopecia areata [14], but patients with psoriasis show completely different manifestations after the use of IL-17A inhibitors. Mashima et al. [15] and Sacchelli et al. [16] found that patients with psoriasis experienced abnormal hair growth events after treatment with Secukinumab. However, Yalici Armagan B et al. [17] and Eldirany SA et al. [18] found that patients with psoriasis showed abnormal hair loss after treatment with IL-17A inhibitor. According to this contradictory reaction, some scholars speculated that hypertrichosis and common hair regeneration after alopecia areata are two different pathways, but more detailed explanations are scarce, and further experimental studies are still needed.

Studies have shown that the IL-17 pathway plays a key role in the pathogenesis of suppurative sweat adenitis, and anti-IL-17 antibodies will become an effective treatment for suppurative sweat adenitis in the future [19,20]. However, French scholar Faivre C et al. [21] found that in 25 similar patients, contradictory hidradenitis suppurativa was completely relieved after the treatment was stopped or another biological agent was used, and recurrence occurred in all cases after the same biological agent was used again. Although Navarro-Trivino et al. [22] suggested that the possible explanation was the increased concentrations of TNF-alpha, IL-26, IL-29, and IFN-γ produced by T cells, as well as the increased concentrations of IL-12 and IL-23 produced by dendritic cells, and the amplification of ICAM-1 and TGF-B signals. Excessive proliferation of keratinocytes is triggered, leading to hidradenitis suppurativa lesions, but Secukinumab is likely to be a paradoxical trigger for hidradenitis suppurativa [21].

Connective Tissue Disease

Lupus erythematosus is an autoimmune disease involving multiple organs, and biological agents have been used to treat systemic lupus erythematosus by reducing the number of B cells and thus reducing the formation of autoantibodies [23]. Some researchers have shown that anti-TNF-α, proton pump inhibitors, anti-tumor drugs, especially checkpoint inhibitors, can induce lupus-like syndrome in the skin [24]. Chatzimichail et al. [25] reported a case of cutaneous discoid lupus erythematosus in a male patient who was treated with Secukinumab for chronic plaque psoriasis. The authors analyze this phenomenon in terms of infection and inflammatory response. On the one hand, inhibition of IL-17 caused changes in antimicrobial peptides and microbiota as well as skin and mucosal immunity, thus increasing the incidence of infection. On the other hand, inflammatory factors originally produced by IL-17A could lead to the manifestation of lupus erythematosus after stimulating B cells. However, the use of IL-17A inhibitors produced an paradoxical reaction, which made the original therapeutic effect disappear, but induced lupus erythematosus. As a matter of fact, the above two ideas are the authors' speculations on this pathological change, and further experimental studies are needed to clarify the mechanism.

The pathogenesis of scleroderma is mainly related to the activation of the immune system and tissue fibrosis [26]. Elias et al. [27] reported that a female patient with psoriatic arthritis experienced skin tightening at the distal elbow and knee, increased limb edema, and finger sclerosis after treatment with Secukinumab, which was consistent with the characteristic manifestations of scleroderma. After analysis, the authors concluded that Secukinumab may cause immune disorders, and the anti-fibrosis properties of IL-17 may lead to the production of type I collagen in fibroblasts and the expression of α -smooth muscle actin triggered by TGF, which may be associated with the occurrence of scleroderma to some extent.

Fungal Dermatosis

IL-17 has been shown to be particularly important in maintaining antifungal immunity against opportunistic fungal pathogens (such as Candida albicans) and symbiotic organisms (such as malassezia) [28], and the use of interleukin-17A inhibitors will undoubtedly lead to a decrease in the body's antifungal ability. Alam et al. [29] reported that a patient with a long history of psoriasis developed scaly spots and plaques in his chest, abdomen, back and buttock after Ixekizumab treatment. Fungal hyphae and spores were found after potassium hydrate drawing test, and he was diagnosed as tinea versicolor. Dziedzic et al. [30] reported that a female patient with psoriasis developed burning sensation and pain in oral mucosa after treatment with Secukinumab, and histopathological examination of biopsy showed incomplete keratosis, acanthosis, pseudohypha and candida filaments. Based on clinical and laboratory evaluation, oral candidiasis was clearly diagnosed. Miyagawa F et al. [31] confirmed in 2021 that the treatment of IL-17 inhibitors was associated with an increased risk of candidiasis, especially oropharyngeal and esophageal candidiasis, through data analysis of who database, EU Medicines Agency safety reports, population-based drug prescription registrations and cohort of patients with psoriasis.

Conclusion

Based on the above case reports, IL-17A inhibitors in the treatment of patients with psoriasis may induce other skin lesions, but the use of the same drug may cause contradictory reactions, which is not under human control. These unexpected reactions due to IL-17A blockade have increased our understanding of the role of IL-17A in other skin diseases and contributed to a better understanding of the inflammatory pathogenesis of various skin diseases and their corresponding therapeutic mechanisms. IL-17A amplifies inflammatory responses in psoriatic lesions by mediating the stimulation of macrophages, fibroblasts and endothelial cells, and also down-regulates filaggrin expression [32]. It is true that inhibitors developed for IL-17A can effectively relieve erythema, induration and flaking caused by inflammatory reaction in the treatment of psoriasis,

but the specific mechanism of inducing or secondary skin diseases and drug paradoxical reactions in the treatment still needs further research. This is most likely due to new autoinflammation caused by disruption of the patient's fragile cytokine network. Therefore, in clinical use, comprehensive medical history and physical examination should be carried out, as well as appropriate laboratory evaluation, so as to avoid inducing new skin diseases or corresponding skin lesions. When patients have skin diseases caused by the use of IL-17A inhibitors, they should change the biological agents in time and closely observe the changes of skin lesions in patients to avoid misdiagnosis of the disease. As the frequency and breadth of the use of IL-17A inhibitors gradually deepen, the related cases will gradually increase. Clinicians should be fully aware of the correlation between IL-17A inhibitors and new skin diseases when treating patients with IL-17A inhibitors, and try to avoid this situation.

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