Future Integrative Medicine **2025** vol. 4(2) | 128–134
DOI: 10.14218/FIM.2024.00057

Review Article

A Review of CD4+ T Cell-mediated Immune Drift and Mechanisms in the Treatment of Immune Inflammatory Skin Diseases with Biological Agents

Fangyuan Miao[1], Chen Luo[2], Jinfeng Chen[2], Changjie Shang[2], Zechao Zhang[2], Liuyun Yang[2] and Min Zhu[2*]

[1]*Guangxi University of Chinese Medicine, Nanning, Guangxi, China;* [2]*Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning, Guangxi, China*

Received: December 05, 2024 | **Revised:** April 22, 2025 | **Accepted:** May 08, 2025 | **Published online:** May 30, 2025

Abstract

Immunoinflammatory skin diseases are characterized by an imbalance in immune homeostasis, and their chronic inflammatory processes involve a complex regulatory network of CD4+ T cell differentiation. With the widespread use of biologics (e.g., interleukin-17/interleukin-23 inhibitors) in psoriasis, atopic dermatitis, and other diseases, the adverse effects triggered by the phenomenon of CD4+ T cell-mediated immune drift have attracted significant attention, with the skin being the primary target as an immune organ. In this paper, we provide a review of the clinical features of the skin and the mechanisms of immune drift caused by different types of biologics, as well as the therapeutic modalities.

Introduction

The immune system plays a variety of important roles in a healthy body, including immune defense, immune surveillance, immune self-stabilization, and immune memory. These functions work together to maintain the health and stability of the body, enabling it to resist attacks from various pathogens and maintain the balance of the internal environment. As a core component of the immune system, lymphocytes play a crucial role in maintaining human health, fending off pathogen invasion, and fighting tumors. T-lymphocytes are a group of cells capable of regulating the immune function of the body, and the CD4+ T-cell subpopulation is an important component of T-lymphocytes, playing a crucial role in the immune system. CD4+ T cell subsets are capable of producing a variety of cytokines that regulate the body's immune response to various antigens. Depending on the cytokines they secrete, CD4+ T cells can be categorized into subpopulations such as Th1, Th2, Th17, follicular helper T cells (Th cells), and regulatory T cells (Treg cells).

Immunoinflammatory diseases are a group of chronic diseases with a high degree of heterogeneity, resulting from an inflammatory cascade response triggered by immune-mediated inflammation leading to multiple tissue and organ involvement.[1] The pathogenesis of these diseases is complex and involves multiple components of the immune system, with inflammation being a central feature throughout the pathogenesis and clinical manifestations of many diseases.

The pathogenesis of CD4+ T-lymphocyte-associated immune-inflammatory skin diseases centers on imbalances in immune subpopulations and abnormalities in inflammatory pathways. For example, in psoriasis, which is mainly driven by a Th17/Treg imbalance, activation of the interleukin (IL)-23/STAT3 axis leads to keratinocyte overproliferation. In atopic dermatitis, which is dominated by a Th2-type response, IL-4/IL-13 disrupts the skin barrier and activates Th17/Th22 for synergistic inflammation. These diseases reflect the aberrant differentiation of CD4+ T-cell subpopulations and the disturbances in cytokine networks (IL-17/IL-23/IL-4, etc.),[2] which provide key intervention targets for targeted biologics and immunomodulatory therapies.

Biologics have dramatically improved the treatment of a wide range of immune-inflammatory skin diseases by precisely modulating the immune response. Common biologics include tumor necrosis factor-α (TNF-α) inhibitors, IL-17 inhibitors, Th-12/23 inhibitors, and IL-4/13 inhibitors. These biologics are biologically prepared drugs that can specifically recognize and neutralize target molecules, intervene in relevant signaling pathways by binding to their receptors, or indirectly block immune differentiation and subsequent inflammatory cascades mediated by relevant cytokines, thereby providing better therapeutic effects for patients.

Keywords: Adverse reactions; Biological agents; Immune drift; Skin; CD4+ T cells; IL-17 inhibitors; IL-12/23 inhibitors; IL-4/13 inhibitors; PD-1/PD-L1 inhibitors; TNF-α inhibitors.

***Correspondence to:** Min Zhu, Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Nanning, Guangxi 530000, China. ORCID: https://orcid.org/0000-0001-5900-5330. Tel: +86-0771-2188120, E-mail: chao616317728@foxmail.com

How to cite this article: Miao F, Luo C, Chen J, Shang C, Zhang Z, Yang L, *et al*. A Review of CD4+ T Cell-mediated Immune Drift and Mechanisms in the Treatment of Immune Inflammatory Skin Diseases with Biological Agents. *Future Integr Med* 2025;4(2):128–134. doi: 10.14218/FIM.2024.00057.

However, many studies have reported adverse skin reactions during treatment with biologics, such as psoriasis-like lesions, eczema-like lesions, and pemphigus herpetiformis. These are mostly associated with CD4$^+$ T-lymphocyte-mediated immune drift due to the use of biologics. Adverse skin reactions exacerbate patient suffering, increase treatment costs, and place tremendous pressure on social healthcare resources and economic productivity. With the increasing popularity and application of biologics, the incidence of such adverse reactions has correspondingly risen.[3,4] If not managed and regulated, these reactions may lead to a public health crisis, reduced treatment adherence, and a decrease in disease control as patients refuse to use biologics due to concerns about dermal toxicity. This may even delay the approval and marketing of novel biologics.

The aim of this study was to elucidate the mechanisms by which biologics-induced shifts in CD4$^+$ T-cell subsets lead to specific cutaneous adverse reactions. We aimed to provide a review of cutaneous adverse reactions caused by immune drift due to the use of biologics in the treatment of immune-mediated inflammatory diseases through a literature search. Mechanisms are analyzed with the aim of advancing precision medicine, identifying patient-specific immune subpopulation imbalance patterns, and developing individualized intervention protocols. We attempt to provide a theoretical basis for the optimization of cytokine network targeting in the future and the reduction of compensatory immune drift triggered by single-pathway inhibition. By revealing the double-edged sword effect of biologics, we hope to promote the innovation of precision medicine and dynamic monitoring systems to provide better treatment for patients.

Biological agents that induce immune drift and their possible mechanisms

Immune drift is closely related to the mechanism of action of biologics, which may directly and/or indirectly affect the key factors of CD4$^+$ T-cell differentiation by modulating the production of cytokines, leading to an imbalance between Th1/Th17 and Th2.[5] Changes in cytokine levels may result in the appearance of a skin reaction or a shift in the type of disease in the skin. For example, TNF-α inhibitors may inhibit the production of Th1 cytokines, leading to a relative increase in Th2 cytokines, which can alter the direction of CD4$^+$ T-cell differentiation, ultimately resulting in immune drift and the development of skin disorders such as eczema and atopic dermatitis, which are characterized by predominantly Th2-type inflammation. The term "immune drift" has not been officially defined, and related concepts include Th cell polarization and phenotypic switching. Th cell polarization is a key process in the regulation of the immune response, where specific cytokines promote the differentiation of Th0 into various Th cell subpopulations.[6] Phenotypic switching is the process by which cells switch between multiple cellular morphologies.[7] The skin has been reported numerous times as a target organ for immune drift, with eczema-like skin lesions and psoriasis-like skin lesions being the most common skin manifestations. Immune drift occurs not only in the treatment of dermatologic diseases but may also occur in the treatment of other classes of immune-mediated inflammatory diseases using such biologics. The following is a review of such biologics and their possible mechanisms.

TNF-α inhibitors

TNF-α is a pro-inflammatory cytokine involved in various physiological processes, including inflammation, cell proliferation, differentiation, and apoptosis.[6] It has been implicated in the pathogenesis of chronic inflammatory diseases (e.g., inflammatory bowel disease, Crohn's disease, and ulcerative colitis), as well as rheumatic and dermatologic disorders (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis). The mechanism of action of TNF-α inhibitors is to block the biological effects of TNF-α by binding to TNF-α and/or its receptor, activating the complement system, and killing or destroying TNF-α-secreting cells.[8,9] Currently, etanercept, infliximab, and adalimumab are commonly used in clinical practice.

It has been shown that the incidence of eczema-like lesions in patients receiving TNF-α inhibitors for the treatment of non-dermatologic conditions ranges from 2–20%.[10] The incidence of eczema-like lesions due to TNF-α inhibitors is lower in patients with psoriasis (about 1–6%).[11] In a statistical review of adverse reactions in the treatment of psoriasis with TNF-α inhibitors, eczema was observed in nearly 90 patients.[11] A 64-year-old female patient with psoriasis reportedly developed eczema-like changes on her hands during treatment with adalimumab.[12] In addition to dermatologic disorders, adverse skin reactions due to immune drift have been observed in the use of these biologics in the treatment of other types of immune-mediated inflammatory diseases. Cleynen *et al*.[13] conducted a retrospective cohort study and found that 23.5% of patients with inflammatory bowel disease developed eczema after initiating TNF-α inhibitors. An eczema-like reaction occurred in 36.2% of 175 IBD patients treated with TNF-α inhibitors.[14] A 14-year-old girl diagnosed with Crohn's disease developed skin lesions on both upper extremities and neck after two months of treatment with adalimumab, which was clinically diagnosed as atopic dermatitis.[12]

When using TNF-α inhibitors to treat psoriasis with predominantly Th1-type inflammation, blocking the Th1 pathway may lead to an immune imbalance and the emergence of eczema and atopic dermatitis with predominantly Th2-type inflammation. This is due to the weakening of the inhibition of Th2 cells by Th1 cells, leading to the activation and gradual predominance of Th2 cells. This shifts the immune balance toward Th2, increasing the activity of the Th2 pathway associated with eczema, atopic dermatitis, and other diseases.[15] In contrast, eczema-like lesions have been observed in the treatment of other autoimmune diseases, such as inflammatory bowel disease, with TNF-α inhibitors. Relevant tests performed on patients with eczema-like lesions revealed upregulation of the Th2-associated cytokines IL-13 and IL-5.[16] This suggests that immune drift can also occur as a result of inhibiting the expression of the Th1 pathway, the main TNF-α secreting pathway, when using TNF-α inhibitors to treat other diseases, thereby allowing increased activation of Th2 cells.

IL-17 inhibitors

IL-17A belongs to the IL-17 family, which plays an important role in the inflammatory response in autoimmune diseases such as psoriasis, inflammatory bowel disease, and systemic lupus erythematosus. IL-17A inhibitors bind IL-17A highly selectively, block its interaction with the receptor, inhibit its downstream pathway, and target and rapidly alleviate inflammatory responses.[17,18] Currently, there are two drugs commonly used in the market to target IL-17A: stavudine and ezekizumab. Eczema-like, atopic dermatitis-like lesions, as well as herpetic pemphigoid, have been documented in patients using these biologics both domestically and internationally.

In the treatment of psoriasis patients with anti-IL-17A drugs, about 2.2–12.1% of patients experienced eczema-like skin le-

sion flare-ups. Pathology showed that these lesions were consistent with the features of eczema or atopic dermatitis.[19,20] A case of extensive pustular psoriasis combined with asthma has been reported, with associated eczematous manifestations after treatment with IL-17A inhibitors.[21] Mi *et al*.[22] reported two patients who developed eczema due to the use of secukinumab, with recurrent erythema, papules, and oozing at different sites, which severely affected the patients' quality of life. Another report by He *et al*.[23] described the development of foot and back eczema after 24 weeks of using scuccizumab for the treatment of nail psoriasis. Biclizumab is indicated for adult patients with moderate to severe plaque psoriasis, and a 62-year-old female patient with psoriasis developed eczema-like dermatitis after two months of treatment with biclizumab.[4] An eczematous reaction was found in 7.0% of patients with moderate-to-severe psoriasis treated with biclizumab in a 52-week prospective study.[24]

There are several mechanisms by which IL-17 inhibitors trigger immune drift. The first of these may be suppression of the Th1/Th17 phenotype, shifting the immune balance toward the Th2 phenotype, which can lead to the development of eczema or atopic dermatitis. This idea is supported by the successful use of the IL-4/13 inhibitor dupilumab to clear eczema-like lesions induced by ixekizumab.[25] Moreover, a history of previous atopic dermatitis, eosinophilia, and elevated serum immunoglobulin E (IgE) may be risk factors for the development of eczematoid reactions.[11] In addition, the high expression of IL-22 found in such patients who develop eczematous conditions suggests that IL-17 inhibitor-induced eczema may be secondary to the blockade of IL-17A activity by stauroschizumab and ezekizumab, resulting in an imbalance of the Th2/Th22 response.[26] On the other hand, inhibition of IL-17 impairs skin barrier function, and reduced production of antimicrobial peptides by keratinocytes leads to colonization by Staphylococcus aureus,[27] which plays an important role in eczema and in Th2-type inflammatory responses such as atopic dermatitis.[28]

Selective blockade of IL-17A leads to IL-17C overexpression. IL-17C has been shown to be associated with Th2-driven skin inflammation, such as eczema and atopic dermatitis.[29] Chang *et al*.[30] reported a case in which, during the treatment of severe psoriasis with sterculizumab, erythema, blisters, and maculopapular blisters appeared on the patient's trunk and extremities after three injections, with markedly aggravated itching. The diagnosis was bullous pemphigoid. Cui *et al*.[31] also reported the diagnosis of bullous pemphigoid after the second injection of secukinumab, 4 months after the diagnosis of psoriasis, which resulted in the appearance of numerous erythematous plaques and blisters on the skin. Bullous pemphigoid is an autoimmune skin disease, predominantly a Th2 response with infiltration of eosinophils and neutrophils. It has been suggested that during the application of skuticosumab, the balance between the Th17/Th2 response was altered, potentially shifting from Th17 dominance to Th2 dominance, thereby triggering the development of bullous pemphigoid.

Th-12/23 inhibitors

Ustekinumab is the world's first monoclonal antibody with dual-targeted antagonism against IL-12/23, which inhibits the common p40 subunit of IL-12/23, blocking Th1 and Th17 differentiation and subsequent inflammatory responses mediated by IL-12 and IL-23. There are few reports of immune drift during treatment with ustekinumab. A male patient with a 19-year history of psoriasis developed numerous symptoms of itching and chronic eczema during treatment with ustekinumab. He was diagnosed with atopic dermatitis with elevated IgE, and the symptoms of atopic dermatitis resolved rapidly after discontinuation of treatment.[32] Another 39-year-old Japanese female psoriasis patient with a history of atopic dermatitis and elevated blood IgE was treated with ustekinumab, which resulted in significant relief of psoriasis symptoms but worsening of atopic dermatitis symptoms.[32] Guselkumab is a monoclonal antibody against IL-23 that selectively binds to IL-23 and inhibits its activity, thereby blocking the IL -23-dependent signaling pathway and reducing the inflammatory response. It has been indicated for adult patients with moderate to severe plaque psoriasis, with eczema also being a common adverse effect.[33]

The possible mechanism by which Th-12/23 inhibitors cause immune drift is that they block Th1 and Th17 differentiation mediated by IL-12 and IL-23 by inhibiting the p40 subunit, which may lead to dysfunction of IL-17. IL-17 has a protective role in skin barrier function, and its inhibition can result in Th2 dominance. In addition, the inhibition of the Th1 pathway by blocking IL-12 may cause an immune imbalance favoring the Th2 pathway, ultimately leading to immune drift. It has also been suggested that ursinumab acts as a TNF-α inhibitor, which may contribution to immune drift.[34] Furthermore, elevated serum IgE levels, resulting from overreaction of Th2 cells, may mediate involvement in diseases such as eczema and atopic dermatitis. Therefore, treatment with ursinumab may exacerbate eczema or atopic dermatitis in patients with a history of Th2-type inflammatory diseases or high serum IgE levels, making them potentially inappropriate candidates for ursinumab treatment.[32]

IL-4/13 inhibitors

Dupliyuzumab is a fully human monoclonal antibody that specifically binds to the α-chain subunit shared by the IL-4 and IL-13 receptors, thereby inhibiting IL-4 and IL-13 signaling. It has not only shown good therapeutic efficacy but also excellent tolerability after being marketed.[35] As early as 2018, a case of atopic dermatitis was reported in which the lesions continued to worsen and involved most of the skin after treatment with dupliyuzumab, which was diagnosed as suggestive of erythrodermic psoriasis.[36] Psoriasis was also reported in 43 patients with atopic dermatitis using dupliyuzumab, with varying extents of skin lesions.[37] Subsequently, Paumier reported that a male patient with atopic dermatitis since childhood, who was treated with duprizumab for eight weeks, developed new scattered red scaly papules on the trunk. Histopathological examination of the lesions showed keratosis imperfecta, hyperkeratosis, hypertrophy of the stratum spinosum, and capillary dilatation of the upper part of the dermis, which, in combination with the clinical presentation, suggested that the new lesions were plaque-type psoriasis.[38] Additionally, a 66-year-old woman diagnosed with atopic dermatitis, who began treatment with dupilumab (300 mg every two weeks), was diagnosed with plaque psoriasis after two years of treatment, with the development of widespread, well-demarcated erythematous plaques.[39] A 51-year-old man diagnosed with atopic dermatitis, treated with dupliyuzumab for three years, developed diffuse erythematous squamous plaques mainly confined to the buttocks and lower extremities, including hand involvement, and was diagnosed with psoriasis after a pathological biopsy.[4]

In addition to the induction or exacerbation of psoriasis in the treatment of atopic dermatitis, duplizumab has also been reported to induce psoriasis in the treatment of asthma.[40] In another case, after 48 weeks of treatment for atopic dermatitis with dupliyuzumab, the patient developed bilateral shoulder pain, elevated CRP and ESR, morning stiffness, and limited hip motion, which was clinically considered to be rheumatic polymyalgia rheumatica. The im-

Table 1. Biological agents and their corresponding immune drift phenomena

Class of drugs	Target point	Typical lesions	Reference
TNF-α inhibitors	TNF-α	Eczema-like lesions	11–14
IL-17 inhibitor	IL-17A	Eczema-like lesions; atopic dermatitis; herpetic pemphigoid	19,21–24,29,31
Th-12/23 inhibitor	p40 subunit	Eczema-like lesions; atopic dermatitis	32,33
IL-4/13 inhibitor	IL-4Rα	Psoriasiform lesions; polymyalgia rheumatica	36–39,41
PD-1/PD-L1 inhibitors	PD-1 and PD-L1 molecules	Psoriasiform lesions	43–45

IL, interleukin; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; TNF-α, tumor necrosis factor-α.

mune mechanism of polymyalgia rheumatica pathogenesis is related to the proliferation of T helper cells polarized toward Th17, and it is considered that the immune drift triggered by the use of biological agents leads to the emergence of a Th17 phenotype.[41] A 17-year-old patient with atopic dermatitis was diagnosed with ulcerative colitis after developing intermittent abdominal pain and diarrhea following treatment with duplizumab.[42] The onset of ulcerative colitis is associated with Th1 cell hyperfunction and the secretion of large amounts of pro-inflammatory cytokines.

Dupliyuzumab acts as an antibody to IL-4 and IL-13 and may block the Th2 response while amplifying the Th1/Th17 pathway by targeting the IL-4/IL-13 signaling pathway. Under specific immune states, dulpolyumab may promote a shift in the immune response, causing a shift from a Th2 to a Th1/Th17 phenotype, ultimately leading to immune drift and the development of psoriatic lesions.

Programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors

Biological agents are the most common cause of immune drift. In addition to tumor PD-1 immunomarker inhibitors, they can also cause adverse skin reactions due to the occurrence of immune drift.

The development of psoriasis after treatment with immune checkpoint inhibitors, such as anti-PD-1/PD-L1, in tumor patients is one of the most common cutaneous side effects and has a high prevalence.[43] Anti-PD-1/PD-L1 therapy enhances anti-tumor immune responses by blocking the immune checkpoint pathway, but it may also trigger immune drift.[44] The mechanism of action of anti-PD-1/PD-L1 therapy activates T cells, releasing interferon-γ to disrupt epidermal homeostasis, and may inhibit Th2 cell differentiation. The release of IL-12 by a subpopulation of dendritic cells within the tumor leads to psoriasis or psoriasiform skin lesions.[45] Additionally, tumor-associated macrophages with high PD-L1 expression tend to be M2-type polarized and secrete IL-10 and TGF-β to inhibit anti-tumor immunity. After PD-1 blockade, the increase in M1-type macrophages may release excessive inflammatory factors (e.g., TNF-α), which indirectly promote Th17 expansion, leading to immune drift and skin lesions.[46]

Summary and novel treatments

Immunoinflammatory dermatoses include psoriasis, atopic dermatitis, herpetic pemphigoid, lichen planus, systemic lupus erythematosus, and pharmacologic dermatitis (e.g., immune checkpoint inhibitor-associated dermatitis), among others. Imbalances in the ratio or abnormal functioning of Th1, Th2, Th17, and Treg cells are the core drivers of immunoinflammatory dermatoses. Key cytokines such as IL-17, IL-23, IL-4, and others amplify the inflammatory response by activating keratinocytes, fibroblasts, or B cells.[47] Normal body CD4$^+$ T lymphocytes differentiate into Th1, Th2, Th17, Treg, and other subpopulations, exerting synergistic or antagonistic effects to regulate the immune response. Each subpopulation maintains a dynamic balance through cytokine cross-regulation (e.g., interferon-γ inhibiting Th2, IL-4 antagonizing Th1) and forms a synergistic network with dendritic cells, B cells, macrophages, etc. An imbalance in these CD4$^+$ T lymphocyte subpopulations can then drive disease.

Based on the pathogenesis, immune drift can be regulated by restoring the dynamic balance of Th subpopulations. Targeting the Th1/Th2/Th17/Treg axis through biotargeted therapies—such as blocking IL-4Rα, IL-13, Janus kinase inhibitors/IL-17, TNF-α inhibition, IL-23 antagonists for atopic dermatitis/psoriasis, and PD-1/CTLA-4 inhibitors for enhancing anti-tumor immunity—reflects the translation from basic mechanisms to precision therapy. Therefore, biologics are commonly used for the treatment of atopic dermatitis/psoriasis. However, adverse skin reactions due to immune drift have been reported. Mechanisms of immune drift not only involve Th1/Th2 immune imbalance but also include imbalances between IL-17 isoforms, decreased expression of antimicrobial peptides leading to Staphylococcus aureus infections, and disruption of the skin barrier function, among other factors. As discussed in the above article, TNF-α inhibitors (etanercept, infliximab, adalimumab), IL-17 inhibitors (stuclizumab and ezekizumab), Th-12/23 inhibitors (ustekinumab) have been associated with eczematous lesions, atopic dermatitis, pemphigus herpetiformis, etc., in the treatment of psoriasis. Similarly, IL-4/13 inhibitors (duplejumab) have caused psoriasis-like lesions, rheumatoid polymyositis, and other manifestations in the treatment of atopic dermatitis, while psoriasis-like lesions have been reported with PD-1 inhibitors, among others, as shown in Table 1.[11–14,19,21–24,29,31-33,36–39,41,43–45]

Although mast cells, neutrophils, and other cells contribute to skin inflammation by releasing histamine, their activities are mostly regulated by cytokines (e.g., IL-4, IL-13) secreted by CD4$^+$ T cells. Existing studies have primarily focused on the core regulatory network of CD4$^+$ T cells, as they exhibit greater spatiotemporal heterogeneity and influence in immune drift, whereas other cellular mechanisms tend to be downstream or auxiliary.

Immune drift most commonly presents with the development of eczema-like and psoriasis-like lesions. However, studies have also shown that immune drift occurs with the use of biologics for treating other immune-inflammatory systemic disorders. A prospective study in the Danish Registry of Biological Agents found that 26.1% of patients with rheumatic disorders treated with infliximab or etanercept developed eczema.[48] Eczema-like lesions have also been reported in patients with Crohn's disease treated with TNF-α inhibitors.

Patients should be adequately questioned about their past medical history prior to the administration of biologics. A history of

diagnoses such as atopic dermatitis, asthma, or psoriasis may predispose them to immune drift.[11,49] Early identification of patients at risk for immune drift, along with thorough assessment and risk monitoring, is essential for personalized medicine. For patients who have already experienced immune drift, eczema-like or psoriasis-like skin lesions are commonly observed. Reviewing previous cases of successful treatment shows that mild skin lesions can be treated with topical glucocorticoid ointments or antimicrobial ointments.[12] If skin lesions do not improve with topical treatment, the biologic agent causing immune drift may be suspended or replaced. Treatment options include corticosteroids, immunosuppressants, or other biologics, such as glucocorticosteroids, cyclosporine, methotrexate, and dupliyuzumab.[13,25,36] Patients with psoriasis-like lesions may also benefit from phototherapy.[32] Traditional Chinese medicine may also be considered, as there have been no reports of immune drift in the treatment of these immunoinflammatory diseases.

Future therapeutic strategies should be revolutionized by studying the phenomena and mechanisms of immune drift induced by biologics leading to adverse skin reactions. The use of natural compounds and emerging alternative immunotherapies should also be emphasized. Recent studies have found that aryl hydrocarbon receptor dysfunction is implicated in the pathogenesis of atopic dermatitis due to its key role in regulating immune responses and maintaining skin barrier integrity. Natural compounds, such as curcumin, resveratrol, and quercetin, have been shown to activate aryl hydrocarbon receptor, inhibit Th2-type cytokines to modulate immunity, reduce inflammation, and promote skin barrier function. These natural medicines have fewer side effects than conventional treatments and could serve as a pharmacologic option for long-term treatment of atopic dermatitis.[50] It has also been shown that plasma rich in growth factors, due to its anti-inflammatory effects, may play a significant role in reducing inflammation and modulating the immune response.[51,52] Among these, high leukocyte content promotes the catabolic cascade response and expression of inflammatory cytokines, which have been shown to have favorable therapeutic effects on atopic dermatitis and other immunoinflammatory skin diseases, such as psoriasis.[53,54] The application of nanotechnology can significantly enhance drug delivery and efficacy by improving drug solubility, stability, and skin permeability.[55] Epidermal-targeted nanocarriers can enhance local drug concentration, precisely modulate the skin microenvironment, and reduce systemic exposure, thereby minimizing the risk of immune drift.[56]

Limitations

The molecular mechanisms of immune drift are still poorly understood, and there are gaps in the study of signaling pathways. Existing evidence overly relies on the classical Th1/Th2/Th17 differentiation pathway, while other potential etiological mechanisms remain insufficiently explored.

Conclusions

Skin adverse reactions due to immune drift not only exacerbate patient suffering and increase treatment costs but also place pressure on social healthcare resources and economic productivity. The underlying mechanisms may involve immune imbalances between Th1/Th2 cells, as well as imbalances between IL-17 isoforms, decreased expression of antimicrobial peptides leading to Staphylococcus aureus infections, and disruption of the skin barrier function, among other factors. By reviewing these phenomena and revealing the dual effects of biologic therapies, we can provide a theoretical basis for optimizing treatment strategies and strengthening risk management in the future through mechanism-based research. In the future, interdisciplinary cooperation will be essential to promote the development of safer immunotherapies. It is expected to achieve the therapeutic goal of "maximizing efficacy and minimizing toxicity" and to reshape the landscape of immunotherapy.

Acknowledgments

None.

Funding

This work was supported by Guangxi Zhuang Autonomous Region Administration of Traditional Chinese Medicine (GXZYZ20 210432).

Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Study conception, study design, writing of the manuscript (FYM, MZ), collection of documentary data (FYM, CL, JFC, CJS, ZCZ, LYY), review, and editing (MZ). All authors approved the final version and publication of the article.

References

[1] Forbes JD, Chen CY, Knox NC, Marrie RA, El-Gabalawy H, de Kievit T, *et al*. A comparative study of the gut microbiota in immune-mediated inflammatory diseases-does a common dysbiosis exist? Microbiome 2018;6(1):221. doi:10.1186/s40168-018-0603-4, PMID:30545401.

[2] Fitzgerald T, Melsheimer R, Lafeuille MH, Lefebvre P, Morrison L, Woodruff K, *et al*. Switching and Discontinuation Patterns Among Patients Stable on Originator Infliximab Who Switched to an Infliximab Biosimilar or Remained on Originator Infliximab. Biologics 2021;15:1–15. doi:10.2147/BTT.S285610, PMID:33442230.

[3] Cunliffe A, Gran S, Ali U, Grindlay D, Lax SJ, Williams HC, *et al*. Can atopic eczema and psoriasis coexist? A systematic review and meta-analysis. Skin Health Dis 2021;1(2):e29. doi:10.1002/ski2.29, PMID: 35664974.

[4] de Felici Del Giudice MB, Ravaglia G, Brusasco M, Satolli F. Managing the Overlap: Therapeutic Approaches in Patients with Concomitant Psoriasis and Atopic Dermatitis-A Case Series. J Clin Med 2025;14(3):796. doi:10.3390/jcm14030796, PMID:39941467.

[5] Quaglino P, Bergallo M, Ponti R, Barberio E, Cicchelli S, Buffa E, *et al*. Th1, Th2, Th17 and regulatory T cell pattern in psoriatic patients: modulation of cytokines and gene targets induced by etanercept treatment and correlation with clinical response. Dermatology 2011;223(1):57–67. doi:10.1159/000330330, PMID:21865674.

[6] Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine 2015;74(1):5–17. doi:10.1016/j.cyto.2014.09.011, PMID:25458968.

[7] Barberis M, Rojas López A. T cell phenotype switching in autoimmune disorders: Clinical significance of targeting metabolism. Clin Transl Med 2022;12(7):e898. doi:10.1002/ctm2.898, PMID:35904141.

[8] An R, Deng YH. Advances in Cutaneous Side Effects and Treatment of Tumor Necrosis Factor Alpha Inhibitors. Chin J Dermatolvenereol 2020;34(9):1078–1082. doi:10.13735/j.cjdv.1001-7089.201911046.

[9] Menegatti S, Bianchi E, Rogge L. Anti-TNF Therapy in Spondyloar-

thritis and Related Diseases, Impact on the Immune System and Prediction of Treatment Responses. Front Immunol 2019;10:382. doi:10.3389/fimmu.2019.00382, PMID:30941119.
[10] Segaert S, Hermans C. Clinical Signs, Pathophysiology and Management of Cutaneous Side Effects of Anti-Tumor Necrosis Factor Agents. Am J Clin Dermatol 2017;18(6):771–787. doi:10.1007/s40257-017-0296-7, PMID:28597181.
[11] Al-Janabi A, Foulkes AC, Mason K, Smith CH, Griffiths CEM, Warren RB. Phenotypic switch to eczema in patients receiving biologics for plaque psoriasis: a systematic review. J Eur Acad Dermatol Venereol 2020;34(7):1440–1448. doi:10.1111/jdv.16246, PMID:31997406.
[12] Pagan-Leon S, Werbel T, Montanez-Wiscovich M. Tumor Necrosis Factor Inhibitor-Induced Eczematous Eruption: A Report of Two Cases and Review of the Literature. Cureus 2021;13(5):e15078. doi:10.7759/cureus.15078, PMID:34159000.
[13] Cleynen I, Van Moerkercke W, Billiet T, Vandecandelaere P, Vande Casteele N, Breynaert C, *et al*. Characteristics of Skin Lesions Associated With Anti-Tumor Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease: A Cohort Study. Ann Intern Med 2016;164(1):10–22. doi:10.7326/M15-0729, PMID:26641955.
[14] Magalhães CMC, Bartholo MR, Correa BHM, Ferrari MLA, Ferrari TCA. Dermatoses in patients with inflammatory bowel disease under tumor necrosis factor-alpha inhibitors treatment. Med Clin (Barc) 2025;164(4):173–177. doi:10.1016/j.medcli.2024.09.004, PMID:39516105.
[15] Zhu E, Zhang S, Zhang X. Pathogenesis of Th2-type Immune Phenotypic Switching Induced by Biologics for Plaque Psoriasis. Chin J Dermatolvenereol 2023;37(10):1099–1102. doi:10.13735/j.cjdv.1001-7089.202303087.
[16] Stoffel E, Maier H, Riedl E, Brüggen MC, Reininger B, Schaschinger M, *et al*. Analysis of anti-tumour necrosis factor-induced skin lesions reveals strong T helper 1 activation with some distinct immunological characteristics. Br J Dermatol 2018;178(5):1151–1162. doi:10.1111/bjd.16126, PMID:29143979.
[17] Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, *et al*. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014;371(4):326–338. doi:10.1056/NEJMoa1314258, PMID:25007392.
[18] Yang X, Zhou J, Dong Y, Zhao Z. Literature analysis of adverse drug reactions induced by IL-17A inhibitors: secukinumab and ixekizumab. Chin J New Drugs 2022;31(10):1027–1032.
[19] Caldarola G, Pirro F, Di Stefani A, Talamonti M, Galluzzo M, D'Adamio S, *et al*. Clinical and histopathological characterization of eczematous eruptions occurring in course of anti IL-17 treatment: a case series and review of the literature. Expert Opin Biol Ther 2020;20(6):665–672. doi:10.1080/14712598.2020.1727439, PMID:32045273.
[20] Napolitano M, Megna M, Fabbrocini G, Nisticò SP, Balato N, Dastoli S, *et al*. Eczematous eruption during anti-interleukin 17 treatment of psoriasis: an emerging condition. Br J Dermatol 2019;181(3):604–606. doi:10.1111/bjd.17779, PMID:30768788.
[21] Yatsuzuka K, Muto J, Shiraishi K, Fujisawa Y, Murakami M. Paradoxical eczema associated with interleukin-17A inhibitor use in a patient with generalized pustular psoriasis accompanied by asthma. Cureus 2024;16(7):e64680. doi:10.7759/cureus.64680.
[22] Mi W, Li M, Li F, Xiao Y, Wang J, Khalik BNA, *et al*. Secukinumab-induced Eezema-like Dermatitis in Patients with Plaque Psoriasis Successfully Treated with Ustekinumab: Two Cases Report. Chin J Dermatolvenereol 2024;38(5):522–525. doi:10.13735/j.cjdv.1001-7089.202307050.
[23] He J, Wang R, Zhang X, Li C. Local Eczema-Like Dermatitis Caused by Secukinumab in the Treatment of Nail Psoriasis: A Case Report. Chin J Dermatolvenereol 2024;38(6):644–647. doi:10.13735/j.cjdv.1001-7089.202305106.
[24] Potestio L, Ruggiero A, Martora F, Megna M. Long-term efficacy and safety of bimekizumab in real-world setting: a 52-week prospective study. Arch Dermatol Res 2024;317(1):102. doi:10.1007/s00403-024-03594-w, PMID:39666087.
[25] Napolitano M, Gallo L, Patruno C, Fabbrocini G, Megna M. Eczematous reaction to ixekizumab successfully treated with dupilumab. Dermatol Ther 2020;33(2):e13218. doi:10.1111/dth.13218, PMID:31912951.
[26] Megna M, Caiazzo G, Parisi M, Ruggiero A, Capasso G, Mascolo M, *et al*. Eczematous drug eruption in patients with psoriasis under anti-interleukin-17A: does interleukin-22 play a key role? Clin Exp Dermatol 2022;47(5):918–925. doi:10.1111/ced.15052, PMID:34862807.
[27] Paolino G, Di Nicola MR, Brianti P, Bianchi VG, Mercuri SR. New onset atopic dermatitis and psoriasis in the same patients under biologic treatments: The role of systemic treatments as a possible trigger. Dermatol Ther 2022;35(11):e15814. doi:10.1111/dth.15814, PMID:36088634.
[28] Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, *et al*. The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. Nat Immunol 2018;19(12):1286–1298. doi:10.1038/s41590-018-0256-2, PMID:30446754.
[29] Guttman-Yassky E, Krueger JG. IL-17C: A Unique Epithelial Cytokine with Potential for Targeting across the Spectrum of Atopic Dermatitis and Psoriasis. J Invest Dermatol 2018;138(7):1467–1469. doi:10.1016/j.jid.2018.02.037, PMID:29941097.
[30] Chang J, Qi M, Wang Y, Li Y, Shi T. Bullous pemphigoid occurred in a patient with severe plaque psoriasis treated with secukinumab: a case report. China J Lepr Skin Dis 2024;40(3):199–201. doi:10.12144/zgmfskin202403199.
[31] Cui Y, Yang Q, Wu W, Liu Y, Sun Y. Bullous Pemphigoid in a Psoriasis Patient After Secukinumab Treatment: A Case Report. Dermatology Bulletin 2024;41(2):209–213.
[32] Ishiuji Y, Umezawa Y, Asahina A, Fukuta H, Aizawa N, Yanaba K, *et al*. Exacerbation of atopic dermatitis symptoms by ustekinumab in psoriatic patients with elevated serum immunoglobulin E levels: Report of two cases. J Dermatol 2018;45(6):732–734. doi:10.1111/1346-8138.14295, PMID:29569296.
[33] Shi W, Zhao Z, Zhai Y, Ye X, Xu F. Adverse events associated with IL-23 and IL-12/23 inhibitors in the clinical management of psoriasis: a comprehensive pharmacovigilance analysis. BMC Pharmacol Toxicol 2025;26(1):11. doi:10.1186/s40360-025-00837-y, PMID:39833957.
[34] Pernet C, Guillot B, Bessis D. Eczematous drug eruption after ustekinumab treatment. Arch Dermatol 2012;148(8):959–960. doi:10.1001/archdermatol.2012.586, PMID:22911203.
[35] Harb H, Chatila TA. Mechanisms of Dupilumab. Clin Exp Allergy 2020;50(1):5–14. doi:10.1111/cea.13491, PMID:31505066.
[36] Tracey EH, Elston C, Feasel P, Piliang M, Michael M, Vij A. Erythrodermic presentation of psoriasis in a patient treated with dupilumab. JAAD Case Rep 2018;4(7):708–710. doi:10.1016/j.jdcr.2018.05.014, PMID:30128344.
[37] Mirza FN, Wang A, Ramachandran SM, Damsky W, Cohen JM. Dupilumab-induced phenotype switch from atopic dermatitis to psoriasis is characterized by de novo interleukin-17A expression: a case report. Br J Dermatol 2021;185(2):432–434. doi:10.1111/bjd.20064, PMID:33730377.
[38] Safa G, Paumier V. Psoriasis induced by dupilumab therapy. Clin Exp Dermatol 2019;44(3):e49–e50. doi:10.1111/ced.13901, PMID:30656722.
[39] Cirone KD, Lovegrove FE. Dupilumab-induced psoriasis in a patient with atopic dermatitis successfully treated with Upadacitinib: A case report. SAGE Open Med Case Rep 2025;13:2050313X251317811. doi:10.1177/2050313X251317811, PMID:39906475.
[40] Matsuda T, Yamada H, Hida N, Nakaizumi T, Yamada E, Satoh H, *et al*. An asthmatic case of psoriasiform eruption caused by administration of dupilumab. Allergol Int 2020;69(3):478–479. doi:10.1016/j.alit.2020.02.004, PMID:32178985.
[41] Yang Z, Pan M, Zhao X. Dupilumab-induced immune drifting from atopic dermatitis to polymyalgia rheumatica: a case report. China J Lepr Skin Dis 2023;39(7):508–511. doi:10.12144/zgmfskin202307508.
[42] Chen Y, Ni J, Li M, Hong Y, Zhu K, Hong R, *et al*. Safety of dupilumab in Chinese pediatric patients aged 6 months and older: a prospective real-world study. Front Pediatr 2024;12:1524962. doi:10.3389/fped.2024.1524962, PMID:39895989.
[43] Bonigen J, Raynaud-Donzel C, Hureaux J, Kramkimel N, Blom A, Jeudy G, *et al*. Anti-PD1-induced psoriasis: a study of 21 patients. J Eur Acad Dermatol Venereol 2017;31(5):e254–e257. doi:10.1111/jdv.14011, PMID:27739129.
[44] Eshaq AM, Flanagan TW, Ba Abbad AA, Makarem ZAA, Bokir MS, Alasheq AK, *et al*. Immune Checkpoint Inhibitor-Associated Cu-

taneous Adverse Events: Mechanisms of Occurrence. Int J Mol Sci 2024;26(1):88. doi:10.3390/ijms26010088, PMID:39795946.
[45] Zhou Y, Xu F, Chen XY, Yan BX, Wang ZY, Chen SQ, *et al*. The epidermal immune microenvironment plays a dominant role in psoriasis development, as revealed by mass cytometry. Cell Mol Immunol 2022;19(12):1400–1413. doi:10.1038/s41423-022-00940-8, PMID:36348078.
[46] Sibaud V. Dermatologic Reactions to Immune Checkpoint Inhibitors : Skin Toxicities and Immunotherapy. Am J Clin Dermatol 2018;19(3):345–361. doi:10.1007/s40257-017-0336-3, PMID:29256113.
[47] Saggau C, Bacher P, Esser D, Rasa M, Meise S, Mohr N, *et al*. Autoantigen-specific CD4(+) T cells acquire an exhausted phenotype and persist in human antigen-specific autoimmune diseases. Immunity 2024;57(10):2416–2432.e8. doi:10.1016/j.immuni.2024.08.005, PMID:39226901.
[48] Yosef N, Shalek AK, Gaublomme JT, Jin H, Lee Y, Awasthi A, *et al*. Dynamic regulatory network controlling TH17 cell differentiation. Nature 2013;496(7446):461–468. doi:10.1038/nature11981, PMID:23467089.
[49] Napolitano M, Scalvenzi M, Fabbrocini G, Cinelli E, Patruno C. Occurrence of psoriasiform eruption during dupilumab therapy for adult atopic dermatitis: A case series. Dermatol Ther 2019;32(6):e13142. doi:10.1111/dth.13142, PMID:31664761.
[50] Lee J, Choi HK, Shin HS, Kim GD. Natural Products as Modulators of Aryl Hydrocarbon Receptor Signaling in Atopic Dermatitis Management. Molecules 2024;29(24):5951. doi:10.3390/molecules29245951, PMID:39770040.
[51] Anitua E, Tierno R, Martínez de Lagrán Z, Alkhraisat MH. Bioactive Effect of Plasma-Rich in Growth Factors (PRGFs) on Cell-Based In Vitro Models of Skin Inflammation in Relation to Inflammatory Skin Disorders. Cureus 2024;16(11):e74252. doi:10.7759/cureus.74252, PMID:39712761.
[52] Lynch RI, Lavelle EC. Immuno-modulatory biomaterials as anti-inflammatory therapeutics. Biochem Pharmacol 2022;197:114890. doi:10.1016/j.bcp.2021.114890, PMID:34990595.
[53] Vafaei-Nodeh S, Kabiri-Abyaneh S. Long-term control of atopic dermatitis with platelet-rich plasma. JAAD Case Rep 2021;7:54–56. doi:10.1016/j.jdcr.2020.10.036, PMID:33319006.
[54] Bunjaj A, Brandao L, Siracuse K, Soti V. Platelet-Rich Plasma for the Treatment of Plaque Psoriasis: A Systematic Review. Cureus 2023;15(12):e50356. doi:10.7759/cureus.50356, PMID:38089952.
[55] Lee YI, Lee SG, Kim J, Choi S, Jung I, Lee JH. Proteoglycan Combined with Hyaluronic Acid and Hydrolyzed Collagen Restores the Skin Barrier in Mild Atopic Dermatitis and Dry, Eczema-Prone Skin: A Pilot Study. Int J Mol Sci 2021;22(19):10189. doi:10.3390/ijms221910189, PMID:34638528.
[56] Slavkova M, Lazov C, Spassova I, Kovacheva D, Tibi IP, Stefanova D, *et al*. Formulation of Budesonide-Loaded Polymeric Nanoparticles into Hydrogels for Local Therapy of Atopic Dermatitis. Gels 2024;10(1):79. doi:10.3390/gels10010079, PMID:38275852.