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REVIEW

Immunological Antagonism Between Psoriasis and Atopic Dermatitis: Pathways, Clinical Implications, and Therapeutic Perspectives

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Abstract: Targeted biologics have proven to be highly effective treatments for both psoriasis and atopic dermatitis; however, they may occasionally induce the onset of the opposite disease phenomenon known as paradoxical reaction. The underlying mechanisms of these reactions remain largely unclear. This review summarizes all currently reported cases of paradoxical reactions and integrates findings from recent sequencing studies to elucidate the latest progress in this field, raising new concerns for dermatologists regarding the long-term use of biological therapies.

Keywords: psoriasis, atopic dermatitis, immune, cytokine pathways, targeted therapy

Introduction

Among dermatological disorders, psoriasis (PsO) and atopic dermatitis (AD) represent the two most prominent immune-mediated inflammatory skin diseases—one characterized primarily by Th17 dysregulation, and the other by Th2 imbalance. With the advent of biologic therapies, both diseases have entered a new era of targeted treatment, leading to remarkable clinical improvement.[1–3] However, this deliberate modulation of the immune system also raises important concerns regarding potential systemic risks, which dermatologists should remain vigilant about.

Interestingly, targeting the TNF/IL-17/23 axis in psoriasis or the IL-4/13 axis in AD can sometimes result in a phenotypic shift toward the opposite disease.[4] Such paradoxical transitions may necessitate treatment interruption or switching, thereby increasing the risk of disease exacerbation.

This review systematically summarizes the underlying mechanisms of both diseases and, for the first time, compiles all currently reported cases of paradoxical reactions. It further elucidates the potential causes of these phenomena and highlights how advanced sequencing technologies have deepened our understanding of their immunopathogenesis.

Contrasting Immunopathogenesis

Immunology of Psoriasis

Psoriasis is a chronic inflammatory disease driven by immune dysregulation, characterized by excessive proliferation and abnormal differentiation of keratinocytes. The inflammation in psoriasis is closely related to both innate and acquired immune responses, with its pathogenesis showing a significant genetic background.[5–7]

In the initial stages of psoriasis, antimicrobial peptide LL-37, released by keratinocytes under stress, forms complexes with DNA/RNA liberated from damaged cells,[8–10] The complex activates plasmacytoid dendritic cells (pDC) through

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Toll-like receptors (TLR9/TLR7), inducing them to produce large amounts of type I interferons (such as IFN α).[11,12] Subsequently, pDC activate myeloid dendritic cells (mDC).[13]

The axis of IL-23/Th17 cells is a central hub in the inflammatory loop of psoriasis.[8,14] IL-23, the most important upstream signaling factor driving the production of key effector molecules IL-17A and IL-17F, not only regulates the proliferation and maturation of Th17 cells but also plays a pivotal role in their function.[15–19] It is important to note that Th17 cells are not the only source of IL-17. Other immune cells, especially γδ T cells and type 3 innate lymphoid cells, are important sources of IL-17 in skin lesions. These cells, which can respond rapidly to IL-23, may play a "pioneer" role in the early initiation and acute exacerbation of the disease, making the inflammatory response more rapid and powerful.[20] Th17 cells, through surface homing receptors such as CCR6, recognize chemotactic signals like CCL20 produced in inflamed skin, migrating in a directed manner and infiltrating the dermis and epidermis, further exacerbate the inflammatory response.[21–25]

In the pathogenesis of psoriasis, an inflammatory environment centered on the IL-23/Th17 axis is formed under the reactivation of local antigens by skin-resident memory T cells and immune cells recruited to the site.[26] IL-17A has been confirmed as a key factor that directly causes the abnormal proliferation of keratinocytes, the production of chemokines, and the accumulation of neutrophils in the epidermis.[27] TNF-α and IFN-γ, on the other hand, amplify the inflammatory response, promoting the dilation of dermal blood vessels, congestion, and lymphocyte infiltration.[28] IL-22 is the key factor driving the excessive proliferation and abnormal differentiation of keratinocytes, leading to epidermal thickening and the formation of numerous silver-white scales.[29–32] while the self-amplifying inflammatory loop formed between these cytokines and keratinocytes causes the skin lesions to persist stubbornly, become chronic, and well-demarcated.[33,34]

This process, sustained by cytokines such as IL-23,[35] forms a self-amplifying inflammatory loop.[36] Immune cells in the lesions activate keratinocytes, while abnormal keratinocytes, in turn, sustain and amplify the immune response. The existence of this vicious cycle is considered the fundamental immunological basis for the chronic development and frequent relapse of psoriasis.[35,36]

Immunology of Atopic Dermatitis

Atopic dermatitis, which is commonly referred to as eczema, is a prevalent, chronic, and relapsing inflammatory skin disorder.[37,38] Similar to psoriasis, it is also an immune-mediated disease, but its immunological mechanisms are distinctly different.[39] The core of atopic dermatitis lies in a vicious cycle between skin barrier defects and immune dysregulation, involving multiple immune pathways that dynamically change across different stages and subtypes.[40]

The immune mechanism of AD, with the main characteristic being type 2 immune response, especially evident in the acute phase and in Asian populations or early-onset types.[41,42] After the damage to the epithelial barrier, alerting factors such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are first released by keratinocytes and others.[43] These cytokines directly activate type 2 innate lymphoid cells (ILC2s), causing them to rapidly produce IL-5, IL-9, and IL-13, The dendritic cells, which can also be activated, subsequently drive the differentiation of naive T cells into Th2 cells.[44–46] Finally, the activated ILC2s and Th2 cells work together to release a series of cytokines, including IL-4, IL-5, IL-9, IL-13, and IL-31, in large amounts.[40,47–49] This leads to an increase in eosinophils, the large production of immunoglobulin E (IgE), and associated inflammation, thereby causing the typical pathological changes of AD.[46,50]

IL-4 and IL-13, which have synergistic and complementary core functions in the Th2 immune response.[45,51] Specifically, IL-4 is the key inducer factor that drives the differentiation of naive T cells into Th2 cells.[52] At the same time, it is also the major cytokine that promotes class switching in B cells and the production of large amounts of IgE.[51] IL-13, on the other hand, primarily acts on tissue cells, directly damaging the integrity of the skin barrier by down-regulating the expression of key barrier proteins, such as filaggrin.[53] These two cytokines together form a self-reinforcing inflammatory loop: IL-4 ensures the continuous activation and proliferation of Th2 cells, while IL-13, by disrupting the epithelial barrier, creates conditions for the invasion of external allergens, thereby continuously stimulating the Th2 immune pathway.[54]

IL-31 plays a unique role in linking the immune system and the nervous system. IL-31, primarily produced by activated Th2 cells, directly activates itch-related neural pathways on sensory neurons,[41,44,55–57] This intense pruritic effect leads to the characteristic scratching behavior in patients, which further damages the already fragile skin barrier.[58]

This forms a vicious cycle of Th2 immune activation-IL-31 production-itching-scratching-barrier disruption-further Th2 activation.[59–62] It is worth noting that the production of IL-31 itself is also positively regulated by IL-4 and IL-13.[63]

The immune response in patients with AD can also manifest as the upregulation of Th1, Th17, and Th22 pathways, with Th1 particularly associated with chronic skin lesions, Th17 has more prominent characteristics in Asian populations.[64–66]

Antagonistic Mechanism

The Mutual Inhibition Between Th1/Th17 and Th2

Psoriasis and AD are two of the most common chronic inflammatory skin diseases, which exhibit significant differences in clinical presentation, immunological characteristics, and histopathology. Traditionally, psoriasis is defined as a disease dominated by Th1/Th17-type immune responses, while atopic dermatitis is defined as a disease dominated by Th2-type. A large body of clinical and basic research evidence suggests that there exists an antagonistic relationship between the immune pathways of these two diseases. A bidirectional inhibitory immune network is formed between Th1/Th17 cells and Th2 cells, along with their characteristic cytokines. There exists a dynamic balance between the Th1/Th17 and Th2 immune axes, with suppression of one side leading to dominance of the other.[67–70]

In this dynamic immune network with balance, IFN-γ, as one of the major cytokines of Th1 cells, not only directly inhibits the occurrence of Th2 immune responses but also further strengthens the immune activity of Th1/Th17.[71] The inhibitory effect is primarily manifested in the transcriptional level, IFN-γ, by activating the STAT1 signaling pathway, suppresses the expression of GATA3, a key transcription factor essential for Th2 differentiation, thereby preventing the differentiation of naïve T cells into Th2 cells at the source.[72,73] IFN-γ can also suppress the production of Th2 characteristic cytokines, thereby weakening the core components of Th2 inflammation.[74–77] IFN-γ even further enhances the Th1 immune response.[78] In addition, IFN-γ can also shape a local immune microenvironment unfavorable to Th2 responses by regulating the functions of macrophages and dendritic cells.[79–81]

Research has shown that IL-4 and IL-13, as typical Th2 cytokines, have a classic mutual inhibitory relationship with the Th17 pathway. IL-4 and IL-13 can inhibit the differentiation and function of Th17 cells through activating STAT6. It had been found in models of AD, psoriasis, and infections.[82–84] Further studies had shown that IL-4 can prevent the differentiation of naive T cells into Th17 cells by inhibiting STAT3 and the expression of RORγt.[85–88] Moreover, some scholars have hypothesized that in Th2-dominated diseases such as AD, IL-4 and IL-13 may indirectly alter the local cytokine milieu by suppressing the expression of keratinocyte terminal differentiation–related genes (eg, FLG, LOR, CDSN). This suppression could attenuate the tissue's responsiveness to IL-17 signaling. However, this assumption remains to be further validated through experimental evidence.[89] IL-13 induced by antigens like IPSE/α-1 may inhibit the Th17 pathway, though its pathological relevance in human diseases remains unclear.[86]

The Differences in Keratinocyte Response to Various Cytokines

In the classic mutual antagonism model, while the interaction between immune cells is central, keratinocytes can interpret and respond to various cytokine signals, thereby amplifying and accentuating the distinct immune features. In psoriasis, keratinocytes exhibit a proliferative response, promoting cell proliferation, inhibiting differentiation, and releasing chemokines through IL-17/IL-22.[90–93] In AD, keratinocytes exhibit a barrier-disruptive response to Th2 signaling, downregulating barrier proteins with IL-4/IL-13, impairing skin defense functions.[94–96] This differentiated response mechanism makes keratinocytes not only participants in immune responses but play a decisive role in the immunological opposition between the two diseases.[97]

Shared Pathways May Act as a Bridge

Although PsO and AD exhibit opposing immune responses, multiple shared immune pathways between them. The key bridges connect the two diseases. These overlapping mechanisms highlight the complexity of their pathogenesis and provide valuable insights into potential therapeutic targets.

The immune mechanism of AD is not a singular Th2 model. There are an immune pathway overlap driven by factors such as the IL-23/IL-17 axis and TSLP, similar to PsO. This contributes to disease heterogeneity and variability in treatment responses, which are particularly pronounced in Asian populations.[98] Moreover, TSLP secreted by

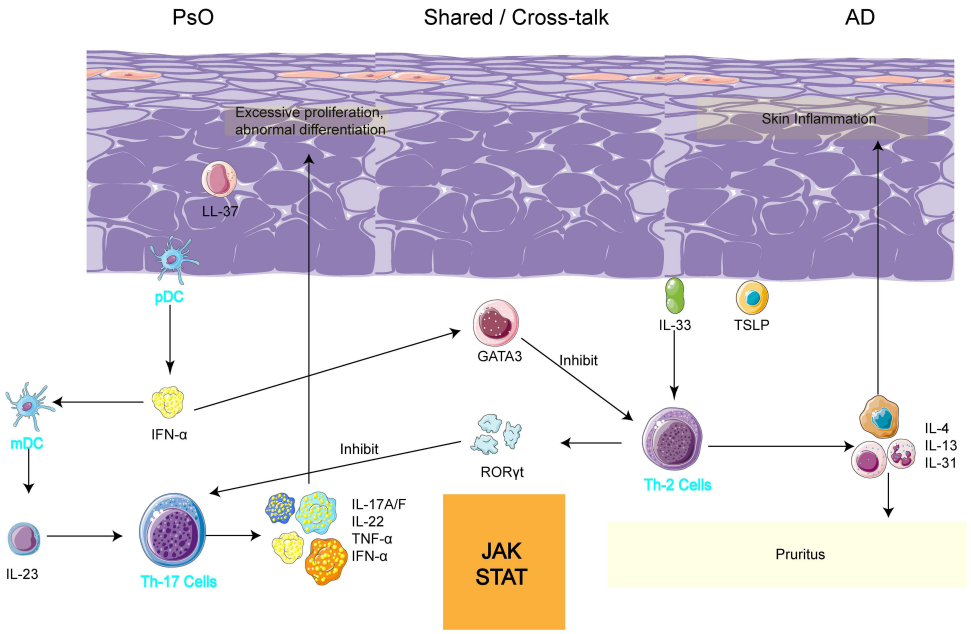

Figure 1 Psoriasis (left) is driven by IL-23/Th17 cytokines that cause keratinocyte excessive proliferation and abnormal differentiation. Atopic dermatitis (right) is mediated by Th2 cytokines (IL-4, IL-13, IL-31) leading to skin inflammation and pruritus. The center shows shared JAK-STAT signaling and mutual inhibition between Th17/Th1 and Th2 pathways.

keratinocytes not only drives Th2 responses but, in certain contexts, can also interact with IL-17–driven inflammation, thereby modulating the direction of the immune response.[99–101] Additionally, the JAK-STAT pathway, a downstream integration point for these signals, is capable of integrating various cytokine signals from psoriasis and AD.[102–104] IL-36, a potent pro-inflammatory factor, is also upregulated in severe subtypes of AD. It serves as a key link between skin barrier disruption and amplified inflammatory responses (Figure 1).

In summary, these shared immune pathways indicate that the immunological opposition between psoriasis and atopic dermatitis is not entirely independent. Rather, a complex and dynamic interplay exists between them, providing a new theoretical foundation for the development of cross-disease, broad-spectrum therapeutic strategies.[105]

Clinical Presentations and Epidemiological Support

AD and PsO, both common chronic inflammatory skin diseases, show an opposing trend in their pathogenesis, as demonstrated by extensive clinical observations and epidemiological studies. This negative correlation provides strong demographic and clinical support.

The Coexistence of Psoriasis and Atopic Dermatitis in a Single Patient is Exceedingly Rare

In clinical practice, it is relatively rare to encounter a patient simultaneously diagnosed with classic AD and PsO, a clinical observation supported by data from large-scale epidemiological investigations.[106] For instance, a cohort study demonstrated a significantly reduced risk of psoriasis among patients with AD compared to the general population.[107] And conversely, his inverse correlation suggests that the Th2-dominated immune microenvironment driving AD may suppress the establishment or development of the characteristic Th17 immune response in PsO, and, conversely, this immunological antagonism or deviation represents a key factor that constitutes their seemingly contradictory relationship.[108]

Epidemiological Data Showing a Negative Correlation in Patient Populations

This negative correlation becomes more evident when observed at the population level. Mendelian randomization analysis of genome-wide association studies (GWAS) provides strong evidence at the genetic level. Multiple studies have found that genetic loci associated with AD exhibit a slight protective effect against the development of PsO.[109–111]

This suggests that the individual's innate immune genetic background may predispose them to develop a specific type of inflammatory pattern. It may reduce the risk of developing immune diseases of the opposite type.[112]

Case Reports of Special Cases

Despite their exclusivity, there are indeed case reports of AD and PsO occurring concurrently or alternately in the same patient. These special cases provide valuable insights for understanding the complex interactions of their immune pathways.

Some patients experience AD in childhood that remits with age, followed by psoriasis appearing in adolescence or adulthood.[113,114] Biologic agents targeting the Th2 pathway, such as dupilumab (anti–IL-4Rα antibody), have also been reported to induce psoriasis-like eruptions or unmask previously undiagnosed psoriasis in a small subset of patients treated for AD. The underlying mechanism is thought to involve a rebound dominance of the Th1/Th17 immune response once Th2 inflammation is strongly suppressed, thereby inducing a psoriasis-like phenotype.[115–117] This proves the existence of a dynamic balance between the two pathways.[69,118]

In a very small number of patients, the lesions may appear typical AD and PsO lesions in different sites.[113,119–121] Such cases suggest the presence of a highly complex immune disturbance.[122]

Disparities Between Pediatric and Adult Populations

AD occurs predominantly in infancy and early childhood, while the peak onset of PsO occurs in adulthood.[123–125] However, the differential diagnosis in pediatric cases can be more challenging. Chronic and severe AD can lead to latensification which may clinically resemble the plaque-like lesions of PsO.[126] In addition, guttate psoriasis triggered by infections in children sometimes requires differentiation from AD exacerbated by infections.[127–129] These clinical overlaps highlight the importance of distinguishing based on the immunological nature.

In summary, clinical and epidemiological evidence strongly supports the existence of an immunological contradiction between AD and PsO. The low comorbidity rate and negative genetic correlation between them underscore their distinct innate immune predispositions, whereas the rare comorbid or alternating cases vividly illustrate the delicate equilibrium and reciprocal restraint between the two immune pathways within an individual. These findings are of significant clinical relevance, particularly for therapeutic choices and risk surveillance in the context of biologic treatments.

Antagonistic Responses from a Therapeutic Perspective

AD and psoriasis are two immune-pathologically opposing diseases. Clinical studies have found that highly effective biologics targeting a specific immune pathway may triggering or exacerbating another disease. This phenomenon is referred to as antagonistic responses in therapeutics.

Suppression of the Th2 Pathway and Induction of Psoriasis

Currently, most therapeutic approaches for atopic dermatitis primarily focus on suppressing the Th2-mediated immune response. However, Th2 cytokines such as IL-4 exert a physiological inhibitory effect on the Th1 and Th17 pathways. When the Th2 axis is strongly suppressed, this inhibition is lifted, potentially resulting in the reactivation or amplification of the previously restrained Th1/Th17 responses. This phenomenon, known as immune drift, represents a characteristic immune rebalancing side effect observed during biologic therapy.[130–132]

We summarized all currently reported cases in which biologic therapy for atopic dermatitis led to psoriasis-like manifestations, as shown in Table 1.

Inhibition of the Th17/Th1 Pathway and the Induction of Atopic Dermatitis

Similar phenomena have also been observed in psoriasis treatment, mirroring those seen in atopic dermatitis. Increasing clinical evidence indicates that inhibition of the Th17/Th1 pathway may disrupt immune homeostasis, resulting in a predominance of Th2 responses that can induce new-onset AD or exacerbate previously controlled disease—a typical paradoxical reaction.

We summarized all currently reported cases in which biologic therapy for psoriasis resulted in atopic dermatitis–like manifestations, as presented in Table 2.

Table 1 The Contradictory Reactions That Occur During the Treatment of AD

	Inducing Drugs	Types of Induced Skin Lesions	Occurrence Time	Reporting Country	Reference
1	Dupilumab	Pustular Psoriasis	Ten days after taking the medicine	China	[133]
2	Dupilumab	Psoriasiform Erythema	After 20 weeks of medication	China	[134]
3	Dupilumab	Follicular Psoriasis	One month after taking the medicine	China	[135]
4	Dupilumab	Pustular Psoriasis	One day after taking the medicine	China	[136]
5	Dupilumab	Alopecia area-like psoriasis, psoriasis lesions	Five months after taking the medicine	Brazil	[137]
6	Dupilumab	Pustular psoriasis	Ten days after the first injection	China	[138]
7	Dupilumab	Plaque Psoriasis	Two years after taking the medicine	Canada	[139]
8	Dupilumab	Psoriasiform Erythema	After 20 weeks of medication	China	[134]
9	Dupilumab	Plaque Psoriasis	Two months after taking the medicine	France	[140]
10	Dupilumab	Guttate Psoriasis	One month after taking the medicine	Italy	[141]
11	Dupilumab	Plaque Psoriasis	Two months after taking the medicine	Italy	[142]
12	Dupilumab	Plaque Psoriasis	4 weeks after taking the medicine	America	[143]
13	Dupilumab	Scalp Psoriasis & AA	One year after taking the medicine	France	[144]
14	Dupilumab	Psoriasiform Dermatitis	(Median) After 8 months of medication	America	[117]
15	Dupilumab	Guttate Psoriasis	After 16 weeks of medication	Italy	[145]
16	Dupilumab	Plaque Psoriasis	Eight weeks after taking the medicine	America	[146]
17	Dupilumab	Reverse Psoriasis	54 days after taking the medicine	China	[147]
18	Dupilumab	Palmoplantar Psoriasis	Not specified (within one year)	Korea	[148]
19	Dupilumab	Plaque Psoriasis	Three months after taking the medicine	Italy	[149]
20	Dupilumab	Plaque Psoriasis	Five months after taking the medicine	America	[150]
21	Dupilumab	Psoriasis	Eight weeks after taking the medicine	Italy	[151]
22	Dupilumab	Pustular Psoriasis	One day after taking the medicine	China	[136]
23	Dupilumab	Pustular Psoriasis	One week after taking the medicine	China	[152]
24	Dupilumab	Psoriasiform Eruption- scalp	Four months after taking the medicine	Italy	[153]
25	Dupilumab	Psoriatic Plaques – body	Several weeks after receiving the third dose of the COVID-19 vaccine (about 2 years and 7 months after the first dose)	Italy	[153]
26	Dupilumab	Psoriatic Plaques - scalp	Four months after taking the medicine	Italy	[153]
27	Tralokinumab	Psoriasis Vulgaris rash	About 7 months after taking the medicine	Germany	[154]
28	Tralokinumab	Plaque psoriasis (confirmed by biopsy)	Three months after taking the medicine	Italy	[155]
29	Dupilumab	Psoriasis	After taking the medicine for several months	America	[132]
30	Tralokinumab	Psoriasis	Unspecified	Germany	[156]

Table 2 The Contradictory Reactions That Occur During the Treatment of Psoriasis

	Inducing Drugs	Types of Induced Skin Lesions	Occurrence Time	Reporting Country	Reference
1	Secukinumab	Eczematoid	One year after taking the medicine	China	[157]
2	Secukinumab	AD	Ten days after taking the medicine	Italy	[158]
3	Ixekizumab	AD	Two years after taking the medicine	America	[159]
4	Secukinumab	AD	Four months after taking the medicine	Brazil	[160]
5	Ustekinumab	AD	After 172 weeks of medication	Japan	[161]
6	Ustekinumab	AD	After 4 weeks of medication	Japan	[161]
7	Secukinumab	AD	4 days after each injection of the medication	Italy	[162]
8	Secukinumab	Eczema-like dermatitis	After 16.9 weeks of medication (on average)	Italy	[163]
9	Ixekizumab	Eczema-like dermatitis	After 16.9 weeks of medication (on average)	Italy	[163]
10	Secukinumab	AD	After 6 months of medication	China	[164]
11	Brodalumab	AD	Eczematous Eruption	Italy	[165]

JAK Inhibitors, as Intermediate Modulators, May Simultaneously Act on Th1/Th2

The JAK–STAT signaling pathway, a central hub mediating the actions of numerous cytokines, plays a pivotal role in regulating multiple immune axes, including Th1, Th2, and Th17 responses. JAK inhibitors can block the activation of downstream STAT proteins through targeting JAK family proteins (such as JAK1, JAK2, JAK3, TYK2). This mechanism

of action endows it with the ability to simultaneously modulate both Th1 and Th2 immune responses, making it a promising option for correcting immune imbalances induced by targeted therapies, such as paradoxical reactions (Table 3).

In summary, JAK inhibitors act on the common downstream of multiple cytokines signaling pathways through their unique mechanism of action. By doing so, they serve as versatile immune modulators capable of rebalancing dysregulated immune responses. Clinical practice has demonstrated that JAK inhibitors offer an effective, rapid, and relatively safe approach for managing paradoxical reactions induced by biologic therapies that disrupt immune balance.

Molecular and Transcriptomics Evidence

The specific mechanisms underlying these paradoxical reactions remain poorly understood by clinicians. Single-cell RNA sequencing offers a powerful approach to decoding the immunological signatures of inflammatory diseases. By integrating skin transcriptomic data with clinical phenotypes, it becomes possible to delineate local inflammatory processes and broader immune interactions in greater detail. Therefore, we have summarized the current genomic and transcriptomic studies investigating paradoxical reactions to provide an updated overview of this emerging field.

A recently published single-cell sequencing study compared PBMCs from psoriasis patients who developed dermatitis after biologic therapy with those from psoriasis patients without such adverse reactions. Compared with the psoriasis control group, the case clusters exhibited a global upregulation of TNF and IFN-γ expression. In addition, IFN-α expression was increased within both B-cell and T-cell populations, whereas Th2 cytokine signaling was not enriched. These findings suggest that the pathogenesis of paradoxical eczema does not simply represent an inflammatory shift from Th1/Th17 to Th2 polarization.[70]

Another study conducted proteomic and genomic analyses comparing serum samples from psoriasis patients who developed dermatitis after biologic therapy with those from psoriasis patients without such changes. The study found that STAMBP expression was reduced in cases of paradoxical eczema and demonstrated that, at the gene set level, the systemic inflammatory profile of patients with paradoxical reactions tended to resemble that of AD.[175]

Although genomic data on paradoxical reactions remain limited at present, we believe that this emerging approach will help elucidate the underlying mechanisms in the future. As more sequencing studies are conducted, the molecular landscape of these reactions will become clearer, paving the way for targeted experimental validation and mechanistic exploration.

Future Research Directions and Clinical Implications

From Genetic Background to Immune Endotype

Although PsO and AD are generally considered mutually exclusive diseases in most populations, there are still a few clinical cases of patients suffering from both conditions simultaneously. This phenomenon suggests that the two may share certain susceptible genetic backgrounds. Studies indicate that the HLA gene, FLG mutations, and GWAS may play key roles in the pathogenesis of both diseases.[176,177] Especially in the immune genetic factors that regulate the balance between Th17 and Th2 responses.[178–180] In addition, FLG mutations have also been identified in some psoriasis patients, suggesting a shared genetic basis underlying the barrier dysfunction observed in both diseases.[181]

Emerging Therapeutic Target: Dual-Pathway Regulation

Emerging therapies are moving from single-pathway blockade toward dual or upstream regulation to more precisely modulate the shared immune network of PsO and AD. TSLP inhibitors can inhibit both Th2 and IL-23/IL-17 pathways, proving particularly effective for severe mixed-type patients.[182] IL-36R inhibitors, show potential in the AD subtype with IL-36 signaling activation.[183,184] JAK inhibitors have become representatives of dual-pathway regulation through blocking multiple inflammatory pathways. In the future, targeting skin-resident memory T cells (TRM) and innate lymphoid cells (ILCs) may offer new opportunities for achieving sustained remission or even cure.[185–187]

Table 3 The Efficacy of JAK Inhibitors in Managing Paradoxical Reactions Induced by Biologic Therapies

	Protopathy	Inducing Drugs	Types of Paradoxical Skin Reactions	Occurrence Time	JAK Inhibitors and Dosing Regimens	Cure/Relief Time	Reporting Country	Reference
1	Plaque psoriasis	Ixekizumab	Eczematous	After 16 doses	Abrocitinib (100mg/d,2 week); Upadacitinib (15mg/d, 4week)	Significant improvement in 2 weeks; 90% clearance in 4 weeks	China	[166]
2	Atopic dermatitis (head and neck type)	Dupilumab	Psoriasis-like dermatitis	One year later	Baricitinib (4mg/d)	It will be completely cleared within three months	Switzerland	[167]
3	AD	Dupilumab	Psoriasis-like dermatitis	Unspecified	Upadacitinib (45mg/d)	Improvement in 4 weeks; It will be completely cleared in four months	Italy	[168]
4	Plaque psoriasis	Anti-TNF-α preparations	Eczema-like rash	1 to 18 months	Upatinib (15mg/d)	Effective	Multinational	[156]
5	Plaque psoriasis	Secukinumab	Psoriasis-like dermatitis	Eight months later	Tofacitinib (5mg bid, 4 weeks; then 5mg qd, 2 weeks)	6 weeks	China	[169]
6	AD	Dupilumab	Psoriasis-like dermatitis	Two years later	Upatinib (30mg/d)	Effective	Japan	[170]
7	AD	Dupilumab	Psoriasis-like dermatitis	Unspecified	Upatinib (15mg/d)	Effective	Italy	[171]
8	AD	Dupilumab	Psoriasis-like dermatitis	Unspecified	Upatinib (15mg/d)	Effective	The United States	[172]
9	AD	Dupilumab	Psoriasis-like dermatitis	Three years later	Baricitinib (4mg/d)	Effective	Britain	[173]
10	AD	Upadacitinib	Plaque psoriasis	After three weeks of treatment	Upadacitinib 30 mg/d	Remission occurred after the treatment was interrupted	Italy	[174]

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From the Perspective of Precision Medicine: Treatment Selection Guided by the Patient's Immune Phenotype

Future dermatologic therapies are expected to move beyond the traditional disease name–based approach toward precision models defined by immune subtyping. At the core of this transition is biomarker-driven, stratified treatment tailored to individual immune profiles.[188] Patients can be stratified into distinct immune endotypes by analyzing cytokine profiles in serum, skin transcriptomic signatures, or immune cell subset compositions. For instance, in patients with AD who show inadequate responses to Th2-targeted therapies, improved outcomes may be achieved with JAK inhibitors or combination approaches.[112] This immune phenotype-guided treatment strategy will maximize treatment efficacy and promote the development of precision medicine.

The Significance of Basic Research in Skin Immunology and Clinical Management

The research of the contradictory phenomenon is significant for skin immunology and clinical management. It is a challenges for the traditional Th1/Th17 and Th2 dichotomy model, highlighting the dynamics and plasticity of the skin immune system,[189] It provides a new perspective for understanding immune tolerance and immune memory. In clinical practice, this understanding can drive innovation in diagnostic and treatment strategies. It remind doctors to pay attention to atypical dermatitis presentations and make individually adjust treatment plans.[188] Collectively, this research expands current knowledge in skin immunology and fosters the translation of mechanistic discoveries into precision-based clinical applications.

Consent for Publication

All authors consented to publication of the manuscript in its current form.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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