

Detection of Heterogeneity in the Treatment of Atopic Dermatitis with T2-Specific Agents

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Abstract. Atopic dermatitis (AD) is a complex and heterogeneous chronic inflammatory dermatosis with significant individual differences in pathological mechanisms and treatment response. In recent years, the use of T2-specific drugs in the treatment of AD has attracted widespread attention, but the treatment response varies widely among patients. This review focuses on the heterogeneity of therapeutic responses of T2-specific drugs in patients with atopic dermatitis. By systematically combing relevant studies in recent years, this paper summarises a variety of methods for detecting patient heterogeneity, including clinical data-based analysis tools and biomarker detection techniques. The literature suggests that clinical indicators such as baseline lung function, acute exacerbation (AE) frequency, oral glucocorticoid use, and eosinophil count play an important role in the assessment of heterogeneity. This paper further discusses the impact of individual differences on T2-specific drug efficacy and points out the limitations of current studies and directions for future research, especially potential applications in the field of personalised therapy. The results aim to facilitate the optimisation of precision treatments for atopic dermatitis and contribute to the further investigation of heterogeneity detection tools.

Keywords: Atopic Dermatitis, T2-Specific Agents, Treatment Heterogeneity, Detection Methods, Clinical Efficacy.

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a complex and remarkably heterogeneous etiology. In recent years, the central role played by the T2 immune response in the pathological mechanisms of AD has been widely recognised, and T2-specific drugs such as dupilumab have become an important treatment for AD. However, the efficacy of T2-specific drugs exhibits considerable inter-individual variability, with individual immune profiles exerting a significant influence on patients' responses to these drugs. Despite the favourable outcomes observed in clinical trials, the efficacy of T2-specific drugs is not guaranteed in real-world settings, with some patients still failing to achieve the desired therapeutic effect. This phenomenon serves to illustrate the considerable heterogeneity of the immune system in AD patients, particularly with regard to the pivotal role played by genetic characteristics, immune status and other biomarkers in determining the individual treatment response. Identifying and quantifying these heterogeneous features is therefore essential to optimise personalised treatment strategies. Existing studies have typically used clinical metrics such as baseline

lung function, acute exacerbation incidence, and eosinophil count to assess disease status and treatment response in AD patients. However, these metrics have limitations in the detection of heterogeneity and fail to adequately reveal the deeper impact of individual immune characteristics on treatment response. Therefore, the development of more accurate heterogeneity detection tools that can better reflect the immune characteristics of patients has become the focus of current research. The paper aims to explore the heterogeneity performance of T2-specific drugs in the treatment of AD patients and to sort out the existing heterogeneity detection methods by reviewing the relevant literature in recent years. And it also analyzes the limitations of these methods and suggest directions for future research, especially the potential for application in the field of personalised therapy.

2. Mechanisms and Classification of T2-Specific Agents

2.1. Biological Basis of T2-Type Immune Response

The T2 immune response is a central driver in the pathomechanism of AD and is mainly mediated by a series of T2-associated cytokines, such as interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-5 (IL-5). This involves a wide range of immune cells and cytokines, whose main function is to protect against parasitic infections and to participate in the regulation of allergic reactions [1]. These cytokines induce skin inflammation, IgE production, and eosinophil recruitment, thus driving the role of the T2 immune response in AD. However, although T2-specific drugs such as the IL-4 receptor antagonist dupilumab have shown efficacy in the majority of AD patients, there are still significant differences in the response to these drugs between patients. Significant heterogeneity in the intensity and persistence of the T2-type immune response in different AD patients was found. Some patients showed higher levels of IL-4 and IL-13 expression, while others may have relatively weak T2 responses or show activation of other immune pathways. This heterogeneity not only affects the patients' clinical symptom presentation, but is also directly related to the efficacy of the response to T2-specific drugs. For example, overexpression of IL-13 may be associated with more severe skin inflammation, whereas the efficacy of treatment may be correspondingly reduced in patients with lower IL-13 expression. Therefore, accurate assessment of the expression of T2-associated cytokines in patients can provide the basis for personalised treatment regimens. In addition, the heterogeneity of the T2 immune response is reflected in the response of different patients to environmental and genetic factors. Some studies have shown that specific gene polymorphisms may regulate the expression levels of T2-associated cytokines, which in turn affects the response of AD patients to immunotherapy. This further suggests that the heterogeneity of T2-type immune responses is not limited to the strength of the immune response, but also involves more complex biological mechanisms. Therefore, identifying the characteristics of T2-type immune responses in different patients is essential for understanding the heterogeneity and developing precise treatment strategies. In this context, the expression levels of biomarkers targeting T2 responses, such as IL-4 and IL-13, have become important indicators of heterogeneity detection, which can help to further resolve the individualised responses of AD patients to T2-specific drugs.

2.2. Pharmacological Effects of Various T2-Specific Agents

T2-specific drugs (e.g. dupilumab, benralizumab, and mepolizumab) inhibit the T2-type immune response by targeting key T2-associated cytokines or their receptors, thereby attenuating the inflammatory response in AD. These drugs have demonstrated significant efficacy in clinical trials, but the differences in their therapeutic responses in different patients demonstrate the significant heterogeneity of patients with AD. Dupilumab is currently the most widely used T2-specific drug, inhibiting T2 inflammation primarily by blocking the IL-4 and IL-13 signalling pathways. Although dupilumab is effective in many AD patients, some patients have limited efficacy, which is closely related to their levels of T2-associated cytokines and activation of other immune pathways. Dupilumab blocks the binding and signalling of IL-4 and IL-13 to their receptors by binding to the IL-4 receptor alpha subunit (IL-4R α). IL-4R α is a common receptor component in the IL-4 and IL-13 signalling pathways, so dupilumab's action effectively blocks signalling for both cytokines. Related studies have shown that

the efficacy of dupilumab tends to be less pronounced in patients with low IL-13 expression or high activation of non-T2 pathways, such as IL-17 and IL-22, than in patients with high T2 responses. Therefore, by detecting T2-associated biomarkers, such as IL-4 and IL-13 levels, in patients, it could help to predict treatment response to dupilumab and optimise personalised treatment regimens. Other T2-specific drugs such as benralizumab and mepolizumab inhibit eosinophil activation and recruitment by targeting IL-5 or its receptor, respectively. These drugs are more effective in some AD patients, especially in those with high eosinophil levels. Nevertheless, therapeutic response has been less favourable in those patients with low eosinophil levels or who are primarily driven by other immune pathways. Therefore, testing patients' eosinophil levels could be a potential way to assess the efficacy of these drugs. In short, the efficacy of different T2-specific drugs varies depending on the immune profile of individual patients. A better understanding of the mechanism of action of these drugs and the heterogeneity of patient responses can be achieved by assessing the immune status of the patient, the levels of T2-related cytokines and the activity of other inflammatory pathways [2-3].

3. Clinical Studies and Their Efficacy

3.1. Clinical Trial Data Analysis

Clinical trials have provided a wealth of data for assessing the efficacy of T2-specific drugs in patients with AD; however, these data have also revealed significant heterogeneity in patients' therapeutic responses to the same drug. To gain a deeper understanding of this heterogeneity, multiple metrics in clinical trials, such as differences in gene expression, levels of immune markers, and the underlying immune status of patients, must be systematically analysed to reveal the underlying factors that contribute to different treatment responses. In multiple clinical trials for dupilumab, researchers found that levels of IL-4 and IL-13 were strongly associated with treatment response [4]. Those patients with higher expression of T2-associated cytokines in baseline assays typically showed stronger efficacy, while for patients with lower baseline levels, efficacy was relatively poor. This difference may be related to the different gene expression profiles of the patients, particularly in the pathways that control the inflammatory response. Further genetic analysis revealed that high expression of the IL-13 signalling pathway is a potential predictor of treatment response. Therefore, future clinical trials should focus more on genetic testing to help predict patients' response to treatment. In addition, eosinophil levels are an important indicator of heterogeneity. In trials of mepolizumab and benralizumab, patients with higher eosinophil levels tended to show more significant improvement. This suggests that eosinophils, as the primary effector cells of the T2 response, may have an important role in assessing drug efficacy. In contrast, different therapeutic strategies may need to be explored for those patients with lower eosinophil levels, further highlighting the need for a more precise categorisation of individual immune status. Notably, the genetic background of patients is also an important source of heterogeneity. Studies have shown that patients of different races, ages, and genders differ markedly in their response to T2-specific drugs. For example, some trials have found that patients of Asian descent respond more slowly to dupilumab than other races, while older patients are less tolerant of the treatment, which may be related to the decline of their immune system [5-6]. Tralokinumab can induce remission and normalize skin conditions in some patients, demonstrating significant efficacy even in the later stages of treatment (Phase 3). The ECZTRA 3 study (NCT03363854) suggests that combining tralokinumab with topical corticosteroids (TCS) may enhance its clinical applicability in routine practice. Among patients achieving clinical remission with tralokinumab administered biweekly (Q2W) at week 16, over 50% maintained remission for an additional week. Notably, 52 cases required no rescue medications, including TCS, while 39-51% of patients sustained remission with tralokinumab given every four weeks (Q4W). Interestingly, at week 16, a subset (21-47%) of tralokinumab responders was re-randomized to the placebo group yet continued to maintain their response at week 52, with response lasting over 36 weeks without active maintenance therapy or TCS [7].

3.2. Comparison of Efficacy and Safety

In assessing the efficacy and safety of T2-specific drugs, while existing studies provide comparative data on general effects, in-depth analyses of inter-individual differences in response are lacking. Therefore, this paper will focus on differences in efficacy and safety across individuals and explore how biomarkers can guide personalised treatment. Firstly, studies have shown that eosinophil levels are an important biomarker of efficacy. Among patients treated with dupilumab, those with higher baseline eosinophil levels typically showed more significant improvement in skin symptoms. This suggests that eosinophils are not only strongly associated with T2 immune responses, but may also play a key role in predicting treatment efficacy. In contrast, patients with lower eosinophil levels may fail to fully realise the efficacy of a drug during treatment, suggesting that in clinical practice, the detection of eosinophil levels can help identify patient groups that may benefit from specific drugs. In addition, individual differences in drug safety should not be ignored. Factors such as the underlying disease, age and genetic background of different patients may influence the adverse effects of a drug. For example, older patients may face higher safety risks when using T2-specific drugs due to more comorbidities. Therefore, future clinical trials should take these individual differences into account to ensure drug safety and efficacy. It is also important to compare the performance of different drugs in specific patient populations in order to more fully understand the relationship between efficacy and safety. In a comparative study of mepolizumab and benralizumab, results showed that patients with higher eosinophil levels responded more significantly to mepolizumab, whereas benralizumab demonstrated a better safety profile in the low eosinophil population. This difference suggests that patient biomarkers may not only influence efficacy, but also have an important impact on drug safety as well [8].

4. Detection of Heterogeneous Responses

4.1. Identification of Biomarkers and Prediction of Treatment Response

In the treatment of atopic dermatitis, the identification of biomarkers and the prediction of treatment response are crucial to understanding the heterogeneity among patients. The specific detection methods of different biomarkers and their application in clinical practice will provide us with important information to optimize personalized treatment plans. For eosinophils, commonly used detection methods include peripheral blood smears, flow cytometry, and ELISA. These methods can quantitatively assess the level of eosinophils in the blood, thereby helping us understand the intensity of the patient's T2 immune response. Clinical studies have shown that patients with higher baseline eosinophil levels usually achieve better efficacy when treated with T2-specific drugs (such as dupilumab), which provides an important biomarker basis for predicting treatment response. In addition, the detection of IL-4 and IL-13 is also widely used to evaluate T2 immune responses. Specifically, the levels of these cytokines can be measured by immunohistochemical staining or ELISA technology. In some clinical cases, the patient's IL-4 and IL-13 levels significantly affected their response to biologics. For example, in one study, patients with higher IL-13 levels showed significant symptom improvement after treatment with specific biologics, which further supports the importance of biomarkers in personalized treatment. Strengthening the discussion of clinical cases will help to better understand the application of biomarkers in predicting treatment response. For example, in a multicenter clinical trial of T2-specific drugs, researchers analyzed the relationship between patients' baseline eosinophil levels and treatment response. The results showed that the proportion of patients with high eosinophil levels who improved symptoms after treatment was significantly higher than that of patients with low eosinophil levels. And this finding underscores the potential of biomarkers as effective predictive tools in clinical practice, aiding physicians in selecting optimal treatments for patients. To detect heterogeneity, it is recommended to integrate analyses of genetic factors and personalized immune responses. Utilizing technologies such as genomics, transcriptomics, and proteomics enables researchers to gain deeper insights into the variations in T2 immune responses among patients. For instance, genetic polymorphisms may influence the expression of specific immune markers, leading to differential responses to T2-specific medications among patients [9-10].

4.2. Patient Heterogeneity and Personalized Treatment Strategies

The response to T2-specific drugs varies significantly between patients, and this heterogeneity may be related to the patient's genetic background, comorbidities, and environmental factors. For example, high levels of inflammatory markers (e.g., eosinophils and exhaled nitric oxide) are often associated with a better therapeutic response. The severity of atopic dermatitis varies from person to person, which influences drug dosage and treatment regimen. In milder cases, lower doses can be started and adjusted based on response to treatment, whereas more aggressive interventions in combination with other treatments may be needed in patients with severe disease. Differences in biomarkers in patients also have an important impact on the response to T2-specific drugs. By testing for specific biomarkers (e.g., eosinophils and FeNO), physicians can more accurately select drugs and adjust treatment regimens to improve outcomes. In addition, many patients may have other coexisting allergic diseases (e.g., allergic rhinitis), which requires that the management of multiple diseases be considered together in the development of a treatment plan. Individual differences in patient response to T2 medications may also contribute to the development of side effects. For patients who do not respond well or experience significant side effects, it may be necessary to change medications or combine them with other therapies (e.g., phototherapy or immunotherapy). Studies have shown that the efficacy of benralizumab and mepolizumab differs when treating different patient populations. Relevant studies have shown that mepolizumab, benralizumab and reslizumab are effective in reducing the incidence of disease exacerbations and improving lung function (FEV1). Benralizumab's effect on FEV1 may be higher than some minimal clinically important difference (MCID), whereas mepolizumab showed statistically significant changes but did not reach the MCID. In addition, while benralizumab had an effect on FEV1, its effect on FeNO was not significant. These findings suggest that there may be differences in therapeutic efficacy in different patient phenotypes, and future studies should explore these differences in more depth to further optimise personalised treatment strategies [11].

5. Difficulties in clinical practice and countermeasures

Despite research showing that the safety profile of T2-specific drugs is comparable to that of a placebo, the occurrence of adverse effects like upper respiratory tract infections, nasopharyngitis, and injection-site reactions raises concerns about their long-term use. Efficacy studies of these drugs have focused on short-term and generally small sample sizes, leading to a poor understanding of patient heterogeneity. Particularly in patients with AD, individual response to treatment may be influenced by a variety of factors, such as biomarkers, stage of disease and comorbidities. Therefore, future studies need to design large-scale, long-term randomized controlled trials to systematically assess the efficacy and safety of T2-specific drugs and their correlation with different biomarkers [12]. This will help identify the best treatment population and provide a basis for clinical decision-making, optimizing the treatment regimen and improving patients' quality of life. In addition, exploring new therapeutic combinations, such as pairing with other immunomodulators, could further boost efficacy and overcome the limitations of current treatments. Through the in-depth research, the application of T2-specific drugs in AD treatment will have a broader prospect.

6. Conclusion

T2-specific drugs show good potential in the treatment of AD. However, the heterogeneity of patient responses when applying these drugs highlights the complexity and diversity of the disease, hence emphasizing the need for personalized treatment. Genetic susceptibility, environmental factors, and individual immune profiles influence treatment efficacy and tolerability, showing significant differences between patients. Advances in biomarker research offer promising avenues to tailor treatment to the individual and improve the precision of T2-specific interventions. Identifying biomarkers associated with treatment response enables clinicians to more accurately predict which patients will benefit from specific therapies, thereby optimizing clinical outcomes. Moreover, gaining a deeper understanding of the interactions between T2-specific pathways and other immune mechanisms is crucial for enhancing therapeutic results. Future studies should aim to integrate multi-omics approaches to unravel the

complex biological networks in AD. This process may lead to the development of combination therapies targeting multiple pathways, thereby improving efficacy and minimizing side effects. Meanwhile, exploring novel T2-targeted drugs and their mechanisms of action will enhance our understanding of AD heterogeneity. Further research will focus on identifying biomarkers that predict efficacy and evaluating long-term

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