The Simultaneous Inhibition of IL-4 and IL-13 by Dupilumab

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Abstract

Interleukins (IL) IL-4 and IL-13 are key players in diseases in which the Type 2 immune response is predominant, such as atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP), that are currently being treated with dupilumab. Dupilumab is a fully human IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain (IL-4Ra), preventing both IL-4 and IL-13 mediated signaling. This mini-review summarizes the IL-4 receptor system as well as the mechanism of action of dupilumab.

Keywords: IL-4; IL-13; dupilumab; Type 2 immunity

Abbreviations

AD: Atopic Dermatitis
CRSwNP: Chronic Rhinosinusitis with Nasal Polyps
DNA: Deoxyribonucleic Acid
JAK: Janus Kinase
IL: Interleukin
IL-4R: Interleukin 4 Receptor
IL-4Ra: Interleukin 4 Receptor alpha chain
IL-13Ra1: Interleukin 13 Receptor alpha 1 chain
IL-13Ra2: Interleukin 13 Receptor alpha 2 chain
STAT: Signal Transducer and Activator of Transcription
TGF-β: Transforming Growth Factor beta
TNF: Tumor Necrosis Factor
TYK2: Tyrosine Kinase 2
γc: Common gamma chain

Introduction

Cytokines are secreted glycoproteins that act as intercellular messengers to control the hematopoietic and immune systems along with the inflammatory response [1,2]. They are structurally distinct factors that bind cellular receptors belonging to at least seven families, which signal through very different pathways [1-3]. The major cytokine families are: the Type I/II cytokines, the Tumor Necrosis Factor (TNF) family, the IL-1 family, the IL-17 cytokines family, the stem cell factor/receptor tyrosine kinase cytokines, the Transforming Growth Factor Beta (TGF-β) family, and the chemokines family [1-3]. Type I/II cytokines signal through the Janus Kinase (JAK) and the Signal Transducer and Activator of Transcription (STAT) pathway [1-3].

Discussion

IL-4 and IL-13 Receptor Complexes

The specific cytokine-binding receptor chain for IL-4 is IL-4Ra while the specific cytokine-binding receptor chain for IL-13 is IL-13Ra1 [5-8]. IL-4Ra chain is widely expressed, with most cells carry in the very least, low numbers of it. Upon IL-4 binding to IL-4Ra, the IL-4/IL-4Ra-complex will bind to a secondary receptor chain to form a functional receptor complex. The secondary receptor chain can be the common gamma chain (γc) or the IL-13Ra1 chain [5-8]. The receptor formed by IL-4Ra dimerized with γc is the”Type I IL-4R” whereas the receptor formed by IL-4Ra dimerized with IL-13Ra1 is the “Type II IL-4R” [5-8]. The “Type II IL-4R” can also be used by IL-13. In this case, IL-13 first binds to IL-13Ra1 (its specific receptor). Then, the IL-13/IL-13Ra complex induces the recruitment of the IL-4Ra [5-8]. Therefore, IL-4Ra can pair with the γc chain to form the “Type I IL-4R” (IL-4 specific) as well as with the IL-13Ra1 to form the “Type II IL-4R” (IL-4 and IL-13 specific) (Figure 1) [5-8].

Once completely assembled, the functional IL-4R complex brings the two JAKs (associated with the intracellular receptor chains) close to one another [3,5-8]. Then, the trans-phosphorylation of the JAKs occurs, activating the JAK/STAT6 pathway [3,5-8]. In both Type I and Type II IL-4R, JAK1, JAK3, and JAK2 (or TYK2), are respectively associated with the IL-4Ra, γc and IL-13Ra1 [5-8].
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Figure 1: Structure of “Type 1 IL-4R” (IL-4Ra/γc; IL-4 specific) and “Type II IL-4” (IL-4Ra/IL-13Ra1; IL-4 and IL-13 specific). Cytokine binds to its specific receptor on the cell membrane (A1, B1, C1). Then, specific cytokine receptor subunit dimerizes with another receptor subunit (a receptor secondary chain) and the trans-phosphorylation (activation) of JAKs occurs (A2, B2, C2). IL-4R: interleukin 4 receptor; IL-4Ra: interleukin 4 receptor alpha chain; IL-13Rα1: interleukin 13 receptor alpha 1 chain; γc: common gamma chain; JAK: Janus Kinase; TYK2: Tyrosine kinase

Dupilumab: molecule overview and mechanism of action

Dupilumab is a recombinant, fully human IgG4 monoclonal antibody, with a molecular mass of 147 Kilodaltons, produced in Chinese Hamster Ovary cells via recombinant DNA technology.

The drug is administered through subcutaneous injections in doses of 200 or 300 mg. The maximum serum concentration is achieved one week after the initial injection, with a bioavailability of 64%. Following the administration of subsequent doses, steady-state concentrations are reached by week 16 and turns non detectable for about 10–13 weeks after last administration.

In relation to immunogenicity, the incidence of anti-drug antibodies is usually low. It was reported approximately 7% of patients using dupilumab for 16 weeks developed anti-drug antibodies, of which only 30% were classified as neutralizing.

Dupilumab binds specifically to IL-4Ra, the shared receptor subunit for IL-4 and IL-13. In Type I IL-4R, dupilumab inhibits IL-4 binding to IL-4Ra chain [4-10], and/or may inhibit the recruitment of γc to IL-4Ra chain [5]. In Type II IL-4R, it can inhibit IL-4 binding to IL-4Ra and/or inhibit the recruitment of IL-4Ra to IL-13Ra (Figure 2) [4-10].

IL-4 and IL-13 share not only receptors but also biological activities, regulating the responses of lymphocytes, myeloid cells, and non-hematopoietic cells [4-8,12]. Acting on many kinds of cells (such as airway and skin epithelium, monocytes, dendritic cells, and B cells), IL-13 and IL-4 have pivotal roles in maintaining...
inflammation in Type 2 immune response [4-8,12]. Therefore, preventing both IL-4 and IL-13 mediated signaling, dupilumab has been useful in the treatment of several Type 2 immune-mediated diseases [4-19].

In moderate-to-severe AD, subcutaneous injections of dupilumab (as monotherapy or with concomitant topical corticosteroids) demonstrated improved AD skin lesions, symptoms, and quality of life, with a favorable safety profile, in adults and children (with 6 years old or more) [10,13-15]. Differences in gene expression following administration of dupilumab include downregulation of markers of epidermal proliferation, downregulation of inflammatory mediators, upregulation of structural proteins, upregulation of lipid metabolism proteins, and upregulation of epidermal barrier proteins resulting in normalization of skin [10]. The most common adverse events in all trials were nasopharyngitis, upper respiratory tract infection, injection site reactions, skin infections, and conjunctivitis [10,13-15].

Beyond AD, dupilumab is under investigation for several other dermatological conditions, including prurigo nodularis, chronic spontaneous urticaria, bullous pemphigoid, allergic contact dermatitis, chronic hand eczema, and alopecia areata [16,17], which indicates this drug can be, in a near future, an important player in the chronic skin diseases treatment arsenal.

**Conclusion**

Aberrant Type 2 immune responses underlie not only AD but also other diseases such as asthma and CRSwNP, which can be a challenge to treat [4,10,12-15,18,19]. IL-4 and IL-13 are key and central drivers of Type 2 immunity and the simultaneous inhibition of both cytokines carried out by dupilumab has shown significant clinical improvement in Type 2 immune-mediated diseases [4,5,9,10,12-19].

Specifically in dermatology, the sustained efficacy and favorable safety profile of dupilumab observed up to 3 years in adults with AD support the long-term continuous use of the drug for treating this chronic and debilitating disease [13]. There fore, Dermatologists should understand the mechanism of action of dupilumab, which besides to being used to treat moderate-to-severe AD [10,13-15], has great potential for the treatment of several other inflammatory skin diseases [16-17].

**Declarations**

Ana Paula Galli Sanchez has served as a speaker and/or consultant to AbbVie, Janssen, Lilly, Novartis, Pfizer, Sanofi, Lee-Pharma and Sandoz. Tatiane Ester Aidar Fernandes was Sanofi-Genzyme’s employee at the time of article writing.
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Reference

1. Schwartz DM, Boneilli M, Gadina M, O’Shea JJ. Type 1/II cytokines, JAKs, and new strategies for treating autoimmune diseases. Nat Rev Rheumatol. 2016;12(1):25-36. doi: 10.1038/nrrheum.2015.167.

2. Morris R, Kershaw NJ, Babon JJ. The molecular details of cytokine signaling via the JAK/STAT pathway. Protein Sci. 2018;27(12):1984-2009. doi: 10.1002/pro.3519.

3. Sanchez AP, Fernandes TEA, Palomino GM. The JAK-STAT Pathway and the JAK Inhibitors. Clin Res Dermatol Open Access. 2020;7(5):1-6. doi: 10.15226/2378-1726/7/5/001128.

4. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35-50. doi: 10.1038/nrd4624.

5. Harb H, Chatila T. Mechanisms of Dupilumab. Clin Exp Allergy. 2020;50(1):5-14. doi:10.1111/cea.13491.

6. Junttila I. Tuning the Cytokine Responses: An Update on Interleukin (IL)-4 and IL-13 Receptor Complexes. Frontiers in Immunology. 2018;9:888. doi: 10.3389/fimmu.2018.00888.

7. Bieber T. Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis. Allergy. 2020;75:1582–1605. doi:10.1111/all.14318.

8. Boatright PD, Arkwright PD, Bruggen MC, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75:1582-1605. doi: 10.1111/all.14318.

9. Beck LA, Thaçi D, Deleuran M. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-577. doi: 10.1007/s40257-020-00527-x.

10. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, Gooderham M. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282-1293. doi: 10.1016/j.jaad.2020.06.054.

11. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Huhtsch T, Davis JD, Zhang Y. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. Br J Dermatol. 2020;182(1):85-96. doi: 10.1111/bjd.18476.

12. Akdis CA, Arkwright PD, Brüggemann M, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75:1582-1605. doi: 10.1111/all.14318.

13. Beck LA, Thaçi D, Deleuran M. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-577. doi: 10.1007/s40257-020-00527-x.

14. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, Gooderham M. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282-1293. doi: 10.1016/j.jaad.2020.06.054.

15. Maloney NJ, Tegtmeyer K, Zhao J, Worswick S. Dupilumab in Dermatology: Potential for Uses Beyond Atopic Dermatitis. J Drugs Dermatol. 2019;18(10):S145-S156. doi:10.9549/s145-S156.

16. Akdis CA, Arkwright PD, Brüggemann M, et al. Type 2 immunity in the skin and lungs. Allergy. 2020;75:1582-1605. doi: 10.1111/all.14318.

17. Beck LA, Thaçi D, Deleuran M. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. Am J Clin Dermatol. 2020;21(4):567-577. doi: 10.1007/s40257-020-00527-x.

18. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, Gooderham M. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282-1293. doi: 10.1016/j.jaad.2020.06.054.

19. Maloney NJ, Tegtmeyer K, Zhao J, Worswick S. Dupilumab in Dermatology: Potential for Uses Beyond Atopic Dermatitis. J Drugs Dermatol. 2019;18(10):S145-S156. doi:10.9549/s145-S156.