

REVIEW

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Review of biologics in allergic contact dermatitis

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Abstract

The resistant and recalcitrant nature of severe allergic contact dermatitis (ACD) makes its management challenging. With advances in the understanding of the cellular and molecular pathogenesis of ACD, newer therapeutic targets are becoming apparent. In particular, the use of biologics has gained momentum, given the specificity of their action. This article aims to review the presently available data on the use of biologics in ACD. English-language-based literature available on the use of biological therapy was thoroughly probed in the following databases as on October 14, 2019: PubMed, Google Scholar, The Cochrane library, Embase, Scopus, and EBSCO. The following keywords were used: “contact dermatitis”, “allergens”, “delayed-type hypersensitivity reaction”, “biologics”, “biological therapy”, “monoclonal antibodies”, “patch testing”, “TNF- α inhibitors”, “infliximab”, “adalimumab”, “etanercept”, “dupilumab”, “omalizumab”, “secukinumab”, “ustekinumab”, “rituximab”.

KEYWORDS

allergic contact dermatitis, biologics, review, treatment

1 | INTRODUCTION

Emerging biologic therapies with licensed indications for other eczematous and immunoinflammatory skin conditions, namely monoclonal antibodies inhibiting tumor necrosis factor α (TNF- α), interleukin 12 (IL-12), IL-17, IL-23, IL-4, and immunoglobulin E (IgE), may have a place in the treatment of recalcitrant cases of allergic contact dermatitis (ACD). These newer agents offer major promise in the treatment of contact dermatitis by targeting specific mediators or pathways of inflammation. Advances in the understanding of the cellular and molecular pathogenesis of ACD have led to the emergence of new pharmacologic targets.^{1,2} A summary of the studies pertaining to the use of biologics in allergic contact dermatitis is shown in Table S1.

2 | TNF- α INHIBITORS

TNF- α is known to play a crucial role during the sensitization process in contact dermatitis as part of the innate immune response and also during the amplification phase of elicitation.³ Hypodermal injection of TNF- α can induce histopathological changes similar to a contact hypersensitivity reaction such as local proliferation of fibroblasts and capillaries in the dermis and hyperplastic reaction of keratinocytes or massive necrosis in the epidermis.⁴ On the other hand, studies and individual human reports also exist on the development of contact dermatitis and failure of inhibition of patch test response while receiving therapy with TNF- α inhibitors.⁵⁻⁸ This suggests that in practice, TNF- α inhibitors are not sufficient to block contact allergic responses.⁷

- **Infliximab**

Limited literature is available on successful use of infliximab, an otherwise well-studied TNF- α inhibitor, in ACD. Reports exist on successful use of infliximab in contact dermatitis in patients with recalcitrant atopic eczema.⁹

- **Etanercept**

Although etanercept has not been studied in contact dermatitis, failure to inhibit the development of acute contact dermatitis to a strong allergen in a patient on etanercept therapy for psoriasis suggests that it may not affect delayed-hypersensitivity reaction.⁶

- **Adalimumab**

The exact response of the immune system when adalimumab is administered after allergen challenge is not clear. No reports are currently available on the use of adalimumab in ACD, although the mechanism may be the same as with other TNF- α inhibitors.^{8,10}

3 | OTHER BIOLOGICS

- **Dupilumab**

IL-4 is a signal for T_H2 pathway and important for type I hypersensitivity and adaptive humoral immunity. Although ACD is a manifestation of the T_C1/T_H1 response, some weaker allergens provoke T_H2-mediated responses during the elicitation phase. With this theoretical background, IL-4 may be regarded as a potential target for treating ACD.¹¹⁻¹⁵ Dupilumab, an IL-4/IL-13 inhibitor, disrupts the T_H2 pathway and has no known additional immunosuppressive activity.¹⁶ Dupilumab has thus been tried successfully in systemic ACD to nickel.¹⁷ It has proven to be of value in the management of recalcitrant ACD.^{18,19} These studies prompt the value of patch testing before considering dupilumab therapy in ACD, as a few antigens provoke a T_H2 response in certain individuals, including nickel, colophonium, *Myroxylon pereirae* (balsam of Peru), rubber, textile dyes, formaldehyde, and others.^{17,20-22}

- **Omalizumab**

Omalizumab acts by binding to the third constant domain of the IgE heavy chain, the site of binding to both high- and low-affinity IgE receptors, thus, omalizumab prevents interaction of IgE with these receptors.²³ This molecule has not been well studied in patients with ACD. It has however been tried successfully in recalcitrant protein contact dermatitis to wheat.²⁴ The positive response to omalizumab in case of wheat allergy can be accounted to the fact that wheat allergy is a combination of type I and type IV hypersensitivity reactions.²⁵

- **Secukinumab**

Secukinumab is a fully human IgG1 kappa monoclonal antibody against IL-17.²⁶ Levels of IL-17 were high in mice and human subjects that displayed positive patch test reaction to nickel. The higher levels of IL-17 in these test subjects indicated the involvement of IL-17 in the manifestation of ACD.^{27,28} Based on this finding, secukinumab was tried in ACD. However, in clinical practice, therapy with secukinumab failed to show any substantial clinical improvement.²⁹

- **Ustekinumab**

Ustekinumab is a human IgG1k monoclonal antibody that blocks the biologic activity of IL-12 and IL-23 by inhibiting receptors for these cytokines on T cells, NK cells, and antigen-presenting cells (APCs).³⁰ The likely role of IL-23 in ACD has recently come to light.³¹ When ustekinumab was administered to five patients with recalcitrant ACD, only one patient displayed clinical improvement. However, even this effect was not sufficient to prevent flaring of the disease during reexposure to the offending allergen.³²

- **Rituximab**

Rituximab is an IgG1 antibody, which targets CD20, a protein expressed on the surface of most B cells.³³ B cells cause complement activation and immune cell chemotaxis in allergic contact hypersensitivity (CHS).³⁴ The response of anti-CD20 antibodies on skin inflammation was studied in CHS murine models after challenging them with allergens. It was found, however, that despite causing a major B-cell depletion, anti-CD20 treatment exacerbated skin inflammation in the models.³⁵ Further scientific studies are necessary to verify the response of anti-CD20 antibodies in patients with ACD.

- **Anti IgD antibodies**

Anti IgD antibodies are known to deplete B cells and modulate both Th1 and Th2 response. This antibody has been found to inhibit apparent skin inflammation when administered in allergen-challenged murine models. This finding paves the way for anti-IgD antibodies to be tried as a therapeutic option in ACD.³⁵

4 | CONCLUSION

The management of ACD is based on the identification of the offending allergen, avoidance of exposure, use of safe alternatives, and treatment of symptoms. Although corticosteroids remain the first choice of therapy for many clinicians, the chronic nature of the disease and the many side effects associated with corticosteroids remain a major obstacle in their long-term use. Because ACD is an immunologically mediated disease, the role of biologics and other immunomodulators is undeniable. Further use and research of biologics,

especially in cases of recalcitrant contact dermatitis, will identify new treatment modalities.

CONFLICT OF INTEREST

None to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Online supplemental Table 1. Biologic medications in allergic contact dermatitis

STUDY	MOLECULE STUDIED	STUDY PURPOSE	STUDY DESIGN	SAMPLE SIZE	METHOD	OUTCOME MEASURES	RELEVANT FINDINGS / CONCLUSION
Cassano <i>et al.</i> , 2006 ¹⁰	Infliximab	Infliximab in recalcitrant severe atopic eczema associated with contact allergy	Case Report	1 Patient	Infliximab was administered in a case of atopic eczema with associated contact allergy that responded poorly to conventional treatments	Improvement in pruritus and decrease in number of lesions	Dramatic improvement in clinical lesions and pruritus
Myers <i>et al.</i> , 2006 ⁷	Etanercept	Ability to develop rhus allergic contact dermatitis in a patient with psoriasis receiving etanercept	Case Report	1 Patient	A psoriatic patient was noticed developing ACD to rhus while on etanercept therapy	Failure to inhibit the development of contact dermatitis in a patient on etanercept therapy for psoriasis	Etanercept cannot prevent delayed hypersensitivity reaction
Mease <i>et al.</i> , 2006 ⁸	Etanercept	Assessing the ability of the patient with psoriatic arthritis (PsA) treated with etanercept to produce antibodies on challenge with pneumococcal vaccine	Randomized placebo-controlled study	205 patients	Antibodies level to 5 antigens were measured by ELISA before and 4 weeks after vaccination in 184 patients. Vaccination was done 4 weeks after etanercept therapy	Proportion (%) of patients with 2- and 4- fold increase in antibody titres	Patients with PsA treated with etanercept were able to produce antibodies in response to pneumococcal vaccination
Puza <i>et al.</i> , 2018 ¹⁸	Dupilumab		Case Report	1 Patient	Patch Test Reaction to 129 allergens was observed in a Patient Taking Dupilumab	Ability to mount a positive patch test reaction	While being immunosuppressed with dupilumab, patient is able to mount a positive patch test response to allergens
Raffi <i>et al.</i> , 2019 ¹⁹	Dupilumab	To evaluate the reliability of patch testing on dupilumab	Non-randomized cohort study	48 patients	Patch test results before and after initiation of dupilumab therapy were compared	Ability to mount a positive patch test reaction	Dupilumab does not inhibit the ability to mount a positive patch test reaction
Raffi <i>et al.</i> , 2019 ²⁰	Dupilumab	To observe the	Case Report	1 Patient	Patch test results before	Ability to mount	Different contact allergens differ in

STUDY	MOLECULE STUDIED	STUDY PURPOSE	STUDY DESIGN	SAMPLE SIZE	METHOD	OUTCOME MEASURES	RELEVANT FINDINGS / CONCLUSION
		differential effect of dupilumab therapy on positive patch test reaction to certain allergens			and after initiation of dupilumab therapy were compared	positive patch test reaction after dupilumab therapy to allergens previously tested positively	their immune responses and dupilumab may block certain molecular pathways and not others
Joshi <i>et al.</i> , 2018 ²¹	Dupilumab	Use of dupilumab in treating allergic contact dermatitis	Case Report	1 Patient	Dupilumab was administered in a case of recalcitrant ACD	Improvement in dermatitis	Dupilumab can be effective in selective cases of ACD that show predominance of Th2 pathway
Chipalkatti <i>et al.</i> , 2018 ²²	Dupilumab	Use of dupilumab in treating allergic contact dermatitis	Case Report	2 Patients	Dupilumab was administered in two cases of recalcitrant ACD	Improvement in pruritus, rash	Dupilumab may be used as an off-label therapy in ACD
Machler <i>et al.</i> , 2018 ²³	Dupilumab	Use of dupilumab in treating allergic contact dermatitis	Retrospective case study	15 Patients	Effectivity of dupilumab was observed in patients with recalcitrant and systemic ACD with a background of atopic dermatitis	Improvement in dermatitis	Dupilumab can be effectively used in cases of ACD to weaker allergens that elicit a Th2 response
Collantes-Rodriguez <i>et al.</i> , 2018 ²⁴	Dupilumab	Recall dermatitis at the patch test site in patient of atopic dermatitis treated with dupilumab	Case Report	1 Patient	Patch test was performed in a case of suspected ACD while patient was on dupilumab therapy for atopic dermatitis	Exaggerated patch test response	Dupilumab can inhibit Th2 mediated response that may exaggerate the response of memory Th1 leading to recall dermatitis
Hoot <i>et al.</i> , 2018 ²⁵	Dupilumab	Effect of dupilumab on patch testing	Case Report	1 Patient	Patch test was performed in a patient while on dupilumab therapy when the rash kept worsening despite dupilumab therapy	Positive patch test reaction	Exaggerated patch test reactions can occur in patients while on dupilumab therapy
Mur Gimeno <i>et al.</i> , 2013 ²⁷	Omalizumab	Use of omalizumab in a case of wheat contact dermatitis	Case Report	1 Patient	Omalizumab was administered to case of wheat contact dermatitis after	Improvement in skin lesions and in Skin Quality of life Questionnaire	Omalizumab can be used in occupational protein contact dermatitis when other therapies

STUDY	MOLECULE STUDIED	STUDY PURPOSE	STUDY DESIGN	SAMPLE SIZE	METHOD	OUTCOME MEASURES	RELEVANT FINDINGS / CONCLUSION
					other therapies such as corticosteroids and ciclosporin were contraindicated		cannot be administered. IgE could be a participant in the complementary immune pathways involving protein contact dermatitis
Todberg <i>et al.</i> , 2018 ³²	Secukinumab	To study the effect of anti-IL-17 on ACD in humans	Prospective cohort study	4 patients	Patients with ACD were treated with 300 mg of secukinumab at weeks 0, 1, 2, 3, 4 and 8.	Physician Global Assessment (PGA) (range 0-4), the Patient Global Assessment (PaGA) (range 0-5), and the Dermatology Life Quality Index (DLQI), and bphotography of the skin were noted at weeks 0, 2, 4, 8, 12 and 16	There was minimal or no improvement in ACD with secukinumab
Bangsgaard <i>et al.</i> , 2011 ³⁵	Ustekinumab	To evaluate the clinical efficacy of ustekinumab in ACD	Retrospective, case cohort study	5 patients	Patients of ACD were administered ustekinumab at weeks 0 and 4 and followed up at week 16	Improvement in clinical picture of ACD based on photographic evidence	Significant improvement in ACD is not achieved by ustekinumab
Nguyen <i>et al.</i> , 2018 ³⁸	Anti CD-20 antibody	Effect of anti-IgD and anti-CD20 antibody on skin inflammation in CHS murine models	Phase 1 clinical trial	-	Mice were treated with anti-IgD or anti CD-20 after allergen challenge at specific time points	Ear swelling as a measure of increased or decreased inflammation, measured with a digital micrometre calliper	Anti- CD20 antibodies may exacerbate skin inflammation to certain allergens
Nguyen <i>et al.</i> , 2018 ³⁸	Anti-IgD antibodies	Effect of anti-IgD and anti-CD20 antibody on skin inflammation in CHS murine models	Phase 1 clinical trial	-	Mice were treated with anti-IgD or anti CD-20 after allergen challenge at specific time points	Ear swelling as a measure of increased or decreased inflammation, measured with a digital micrometre calliper	Anti-IgD induced immunomodulation can suppress allergic skin inflammation in murine models

