

Accepted Manuscript

T-Cell Inhibitors for Atopic Dermatitis

W. James Tidwell, MD, Joseph F. Fowler, Jr., MD

PII: S0190-9622(17)32821-9

DOI: [10.1016/j.jaad.2017.12.020](https://doi.org/10.1016/j.jaad.2017.12.020)

Reference: YMJD 12181

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 10 November 2017

Revised Date: 8 December 2017

Accepted Date: 9 December 2017

Please cite this article as: Tidwell WJ, Fowler Jr JF, T-Cell Inhibitors for Atopic Dermatitis, *Journal of the American Academy of Dermatology* (2018), doi: 10.1016/j.jaad.2017.12.020.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



T-Cell Inhibitors for Atopic Dermatitis

- TSLP monoclonal antibody – AMG157/MEDI9929
- OX40 blocking antibody – GBR 830

W. James Tidwell MD^{1,2}, Joseph F Fowler Jr MD²

1 - Scripps Clinic, Micrographic Surgery and Cutaneous Oncology, La Jolla, CA.

2 – Division of Dermatology, University of Louisville, Louisville, KY.

Phone – 858-554-8646

Fax – 858-554-6271

10820 N. Torrey Pines Road, La Jolla, CA 92037, Mail Drop MS112A

Correspondence: W. James Tidwell, MD

Word count: 1135 (Not including abstract, figures, and references)

Abstract: The management of atopic dermatitis is changing with the development of novel biological agents to target specific molecules in the inflammatory cascade. Dupilumab has proven its ability to act on the IL-4 receptor in treating atopic dermatitis. Thymic stromal lymphopoietin (TSLP) monoclonal antibody (AMG157/ MEDI9929) and OX40 blocking antibody (GBR 830) were developed by target the same pathway as dupilumab. The clinical data on the efficacy for these drugs is not yet known. There is some early evidence that AMG157/ MEDI9929 attenuates most measures of allergen-induced asthmatic responses. However, there is no public data on its ability to treat atopic dermatitis. In a Phase 2a study, GBR 830 showed at least a 50% reduction in patient's Eczema Area and Severity Index (EASI) scores in 17 out of 23 patients, but it was not powered enough for statistical differences between GBR 830 versus placebo. Although there is potential for these two drugs to greatly improve the management of severe atopic dermatitis, there is not yet any available phase 3 clinical trials which are needed to truly evaluate their efficacy in affecting T-cells.

Capsule Summary:

- Multiple biological drugs are under development for severe atopic dermatitis
- Thymic stromal lymphopoietin (TSLP) monoclonal antibody (AMG157/ MEDI9929) and OX40 blocking antibody (GBR 830) target the same pathway as dupilumab
- The clinical efficacy and safety of these drugs are currently being studied

Introduction

Atopic dermatitis (AD) is a chronic condition with a significant burden in the United States and other countries. It has been reported that there is a two- to threefold increase over the past several decades in the prevalence of AD.¹ With that increase in prevalence, there has been increasing interest in new drug therapies beyond topical treatments. The new paradigm shift in atopic dermatitis is in aiming to treat pathways with the development of biological agents. The management of psoriasis has greatly improved with biological agents that target various pathways both up and down stream of various cells and cytokines described to be a part of the inflammatory process. The IL-4 receptor blocker dupilumab pioneered the AD biological pathway era. Thymic stromal lymphopoietin (TSLP) monoclonal antibody (AMG157/ MEDI9929) and OX40 blocking antibody (GBR 830) target the same pathway further upstream. These drugs are currently in phase 2 of development but show potential as novel agents to enhance treatment options for recalcitrant AD.

Mechanism of action

The current model of AD pathogenesis starts with a skin barrier deficiency that results in downstream immune dysregulation and triggers a chronic inflammatory cascade. This series of cytokines has allowed for a new generation of targets for drug development. TSLP has been identified as a “master switch” for allergic inflammation at the epithelial cell-dendritic cell interface in murine models.²

One trigger of the inflammatory cascade in AD begins with epidermal injury. Mutations in the epithelial barrier proteins filaggrin, serine peptidase inhibitor Kazal-type 5 (SPINK5) and corneodesmosin are associated with AD or atopic dermatitis – like syndromes.³ Once epithelial damage occurs, IL-33, IL-25 and TSLP are produced. IL-1 Beta may be an early key mediator towards the acquisition of an AD phenotype through the induction of TSLP.⁴ It has also been found that Δ Np73 regulates the expression of TSLP in keratinocytes by means of phosphorylation of NF- κ B with Toll-like receptor 3 increasing Δ Np73 production.⁵

TSLP then exerts its biological activity on mast cells, natural killer cells, and dendritic cells. In the latter cell type, it upregulates OX40L, CD 80, and CD86.⁶ This in turn drives the production of IL-4, IL-5, and IL-13 from naïve CD4 T cells forming a Th2 cell polarization.^{7,8} TSLP can also act directly on CD4+ T cells, CD8+ T cells, Treg cells, to induce proliferation of Th2 cells.^{9,10} IL-33 works as a positive regulator of TSLP-OX40 axis that initiates and maintains the Th2 cell-mediated inflammatory response.¹¹

Additionally, TSLP can directly stimulate T cell migration exclusively in filaggrin-deficient skin equivalents even in the absence of dendritic cells, indicating a potential role of TSLP in the pathogenesis of AD.¹²

A TSLP gene expression variant has been found to have a protective effect in patients and may be tied to reductions in TSLP protein activity.^{13,14} Furthermore, a clinical study found evidence that patients with a homozygous mutation in rs1898671 status may have milder overall disease and require less medications to manage their AD.¹⁵ In healthy skin, TSLP expression is normally undetectable but it has been found to be highly expressed in the lesional skin of individuals with atopic dermatitis.¹⁶

OX40 is a member of the TNF receptor superfamily.¹⁷ TSLP-activated dendritic cells express OX40L and are activated in the lymph nodes by OX40 which triggers a Th2 inflammatory cytokine production. OX 40 positive cells are greater in lesional than in non-lesional AD skin by an order of magnitude. There is however, no correlation between clinical severity of AD and OX40. It can be concluded that OX40 and OX40L may be involved in a complex interaction in the pathogenesis of AD.¹⁸

Safety and Efficacy

AMG 157 /MEDI9929 is a human anti-TSLP monoclonal immunoglobulin G2 gamma that blocks the binding of TSLP to its receptor and under joint development by Amgen and MedImmune LLC. It is also known as Tezepelumab and currently in phase 2 of development. Although not much evidence on treatment of AD is publically available, the data that has been published in asthma research shows potential. In a double-blinded placebo-controlled study, Tezepelumab attenuated most measures of allergen-induced early and later asthmatic responses. In addition, patients receiving Tezepelumab had significant decreases in levels of blood and sputum eosinophils.¹⁹ (NCT01405963) A current study is looking to see if Tezepelumab can promote lasting tolerance to cat allergen.²⁰ (NCT02237196) The estimated completion date of this study is February 2019. There is currently one ongoing phase II study on Tezepelumab in adults with moderate to severe AD (NCT02525094), but the results are not yet public. Besides atopic diseases, TSLP is considered to play a role in chronic obstructive pulmonary disease and eosinophilic esophagitis so the use of Tezepelumab in this conditions may have potential benefit.

GBR 830 is a monoclonal OX40 (CD134) blocking antibody under development by Glenmark Pharmaceuticals. In August 2017, Glenmark gave a press release that the Phase 2a study showed at least a 50% reduction in patient's Eczema Area and Severity Index (EASI) scores in 17 out of 23 patients. This study was not powered enough for statistical differences between GBR 830 versus placebo. The overall safety profile of GBR 830 was similar to that of the placebo. The most common adverse event was headache, but there was no meaningful difference between GBR 830 and the placebo. These findings have not yet been published in a peer review journal or presented at a scientific meeting.²¹ Phase 2b trial is planned to begin in the first half of 2018.

Of note, previous investigations in a phase 2 randomized controlled trial in mild asthma with an OX40L (CD252) inhibitor did not find an effect on allergen-induced airway responses.²² There are no published randomized controlled studies on OX40L and atopic dermatitis.

The safety of these T cell inhibitor biologics is under investigation. Like other biologics approved for psoriasis and AD, there is a theoretical risk of immunosuppression, infections, injection site reactions, and potentially lymphoproliferative disorders. Adverse effects from trial NCT01405936 included nasopharyngitis, headache, oropharyngeal pain, abdominal pain, and asthma. There were no serious adverse events and adverse effects were similar to the placebo agent.¹⁹

T cell inhibition was previously used in biologics treating psoriasis in two other agents. Efalizumab was removed from the market because of cases of progressive multifocal leukoencephalopathy (PML). The CD2/LFA3 inhibitor Alefacept was also used, but it caused a drop in CD4 T-cell counts. It was removed

from the market in 2011. There is no evidence at this time that the T cell inhibitors AMG 157/MEDI9929 or GBR 830 have similar adverse effects.

The cost of biologicals can be significantly more than conventional topical treatments such as corticosteroids. However, the total cost of a disease must be taken into account in an economic analysis. If the evidence shows that biologics can stop the atopic march to chronic conditions of asthma and rhinitis, the total cost of life long treatment may be less with prevention of disease.

Figure 1: Mechanism of action for TSLP and OX40 in inducing a Th2 cytokine inflammatory response related to the development of atopic dermatitis.

Table 1: Summary of T-cell inhibition drugs AMG157-MEDI9929 and GBR 830. TSLP, Thymic stromal lymphopoietin.

Drug	Target	Name of Antibody	Phase of Development
AMG 157/ MEDI9929	TSLP	Tezepelumab	Phase 2
GBR 830	OX40	Not yet named	Phase 2

References

1. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicounty cross-sectional surveys. *Lancet*. 2006;368:733-43.
2. Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med* 2006;203:269-73.
3. Han H, Roan F, Ziegler S. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. *Immunological Reviews*. 2017;278:116-130.
4. Bernard M, Carrasco C, Laoubi L, et al. IL-1B induced thymic stromal lymphopoietin and an atopic dermatitis-like phenotype in reconstructed healthy human epidermis. *J Pathol* 2016;242:234-245.
5. Kumagai A, Kubo T, Kawata K. Keratinocytes in atopic dermatitis express abundant Δ Np73 regulating thymic stromal lymphopoietin production via NF- κ B.
6. Wang L, Li HY, Zhang MS, et al. Thymic stromal lymphopoietin: a promising therapeutic target for allergic disease. *Int Arch Allergy Immunol*. 2013;160(1):18-26.
7. Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 3 cell response through OX40 ligand. *J Exp Med*. 2005;202:1213-1223.
8. Liu YJ, Soumelis V, Watanabe N, et al. TSLP: An epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol*. 2007;25:193-219.
9. Omori M, Ziegler S. Induction of IL-4 expression in CD4(+) T cells by thymic stromal lymphopoietin. *J Immunol*. 2007;178:1396-1404.
10. Kitajima M, Lee HC, Nakayama Ziegler SF. TSLP Enhances the function of helper type 2 cells. *Eur J Immunol*. 2011;41:1862-1871.
11. Murakami-Satsutani N, Ito T, Nakanishi T, et al. IL-33 promotes the induction and maintenance of Th2 immune responses by enhancing the function of OX40 ligand. *Allergol Int*. 2014 Sep;63(3):443-55.
12. Wallmeyer L, Dietert K, Sochorova M, et al. TSLP is a direct trigger for T cell migration in filaggrin-deficient skin equivalents. *Sci Rep*. 2017 Apr 4;7(1):774.
13. Goa PS, Rafaels NM, Mu D, et al. Genetic variants in thymic stromal lymphopoietin are associated with atopic dermatitis and eczema herpeticum. *J Allergy Clin Immunol*. 2010;125(6):1403-1407.e4.

14. Margolis DJ, Kim B, Apter AJ, et al. Thymic stromal lymphopoietin variations, filaggrin loss of function, and the persistence of atopic dermatitis. *JAMA Dermatol.* 2014;150(3):254-259.
15. Chang J, Mitra N, Hoffstad O, Marolis D. Association of filaggrin loss of function and thymic stromal lymphopoietin variation with treatment use in pediatric atopic dermatitis. *JAMA Dermatol.* 2017;153(3):275-281.
16. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol.* 2002;3:673-680.
17. Godfrey WR, Fagnoni FF, Harara MA, et al. Identification of a human OX-40 ligand, a costimulatory of CD4+ T cells with homology to tumor necrosis factor. *J Exp Med* 1994;180:757-762.
18. Ilves T, Harvima IT. OX40 ligand and OX40 are increased in atopic dermatitis lesions but do not correlated with clinical severity. *J Eur Acad Dermatol Venereol.* 2013 Feb;27(2)e197-205.
19. Gauvreau GM, O'Byrne PM, Boulet LP, et al. Effects on an anti-TSLP antibody on allergen-induced asthmatic response. *N Engl J Med.* 2014;370:2102-2110.
20. National Institute of Allergy and Infectious Diseases (NIAID), Immune Tolerance Network(ITN). Anti-TSLP (AMG 157) Plus Antigen-Specific Immunotherapy for induction of tolerance in individuals with cat allergy. Bethesda, MD: National Library of Medicine (US); 2014. [Http://clinicaltrials.gov/show/NCT02237196](http://clinicaltrials.gov/show/NCT02237196). Accessed August 13, 2017.
21. Glenmark Pharmaceuticals Ltd. "Glenmark pharmaceuticals reports positive data in a phase 2a study of GBR 830 for the treatment of patients with atopic dermatitis. Released August 1, 2017. www.glenmarkpharma.com/media/newsroom. Accessed August 13, 2017.
22. Gauvreau GM, Boulet LP, Cockcroft DW, et al. OX40L blockade and allergen-induced airway responses in subjects with mild asthma. *Clin Exp Allergy.* 2014;44:29-37.a