Biologic Therapy in the Treatment of Chronic Skin Disorders

James M. Fernandez, MD, PhD[a], Anthony P. Fernandez, MD, PhD[b], David M. Lang, MD[a,*]

KEYWORDS

• Urticaria • Angioedema • Psoriasis • Atopic dermatitis • Biologic agents • Omalizumab • Dupilimab

KEY POINTS

- Understanding of immune pathways involved in the pathogenesis of chronic urticaria, atopic dermatitis, and psoriasis is growing.
- Biologic therapies targeting specific immune-related targets are rapidly becoming viable options for patients with severe or refractory dermatologic diseases.
- Biologic agents allow a safe and efficacious alternative in some refractory skin diseases.

INTRODUCTION

Chronic immune-related skin diseases continue to affect patients throughout the world. In many instances the diseases are refractory to first-line therapy. As clinicians uncover immunologic pathways involved in the pathogenesis of these diseases, therapeutic agents targeting specific molecular pathways are being developed. This article reviews the use of such agents in chronic urticaria (CU), atopic dermatitis, and psoriasis.

Chronic Urticaria

Understanding of the pathogenesis of CU has improved in recent years.[1,2] Despite this, many patients affected with CU experience poor control of their disease and

Disclosure: J. Fernandez, no disclosures; A. Fernandez, speaker's bureau, research, consulting for AbbVie, consulting for Novartis; D.M. Lang (PI: ClinicalTrials.gov Identifier: NCT00555971), clinical research with, received honoraria from, and/or has served as a consultant for Adamis, AstraZeneca, Genentech (PI: ClinicalTrials.gov Identifier: NCT00555971), GlaxoSmithKline, Merck, Novartis.

[a] Department of Allergy and Clinical Immunology, Respiratory Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA; [b] Departments of Dermatology and Pathology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA
* Corresponding author.
E-mail address: langd@ccf.org

Immunol Allergy Clin N Am 37 (2017) 315–327
http://dx.doi.org/10.1016/j.iac.2017.01.006
immunology.theclinics.com

impaired quality of life.[1] An estimated 50% or more of patients with CU do not achieve satisfactory control with antihistamine treatment alone.[2]

Urticaria and pruritus are generated primarily by the action of histamine on H1 receptors located on endothelial cells (wheal) and on sensory nerves (flare). The nonnecrotizing infiltrate in CU consists of CD4+ (CD, cluster of differentiation) lymphocytes, monocytes, neutrophils, eosinophils, and basophils, which may be refractory to antihistamine pharmacotherapy, even when advanced to higher than US Food and Drug Administration (FDA)–approved doses.[2] Patients with CU who do not improve with H1 and H2 antihistamine therapy, including dose advancement of a potent antihistamine (eg, doxepin or hydroxyzine) as tolerated are candidates for alternative therapies.[1] Several biologic agents have been studied in patients with antihistamine-resistant CU.

Omalizumab

Omalizumab is a chimeric human-mouse recombinant antibody, produced in a Chinese hamster ovary cell line that binds to the domain at which immunoglobulin (Ig) E binds to FCεRI (the high affinity IgE receptor) on mast cells and basophils.[3] Its mechanism of action in patients with CU has not been determined. In clinical trials of omalizumab in subjects with CU, most adverse events (AEs) were mild or moderate in severity, and did not differ remarkably compared with placebo. Severe thrombocytopenia, eosinophilic conditions, serum sickness, and hair loss have been reported.[3] The rate of anaphylaxis observed in patients with moderate-severe allergic asthma receiving omalizumab is approximately 1 in 1000.[1,3] Whether the rate of anaphylaxis will be similar in patients with CU, and whether the same precautions for omalizumab are appropriate for a population of patients with CU, is unclear. In clinical studies, malignancies were observed in clinical trials in a small number of subjects with asthma receiving omalizumab and in subjects receiving placebo.[1,3] Of 4127 subjects who received omalizumab, 20 (0.5%) developed malignancy; of 2236 who received placebo injections, 5 (0.2%) developed malignancy. A recent study,[4] with a median follow up time of approximately 5 years, compared the safety of omalizumab in 5007 asthmatics receiving omalizumab with 2829 asthmatics not receiving omalizumab. Rates of malignancy were similar: 12.3 per 1000 patient years for omalizumab, compared with 13.0 per 1000 patient years in asthmatics who did not receive omalizumab. This finding implies that omalizumab is not associated with an increased risk for malignancy. This study also found a higher rate of cardiovascular events in asthmatics receiving omalizumab (13.4 per 1000 patient years), including myocardial infarction and cerebrovascular events, compared with non–omalizumab-treated asthmatics (8.1 per 1000 patient years). Although these results suggest that omalizumab is associated with an increased risk of cardiovascular events, there were aspects of the design of this study that imply this is not the case, including baseline differences in cardiovascular risk factors. An analysis of 25 randomized controlled trials found no remarkable difference in the rate of cardiovascular events in 3342 omalizumab-treated asthmatics compared with 2895 subjects with asthma who did not receive omalizumab.[3] Efforts to further understand possible risks for malignancy and for cardiovascular disease are continuing during postmarketing surveillance.

There is evidence from case reports and case series, and high-quality evidence from randomized controlled trials, supporting the therapeutic utility of omalizumab for patients with refractory CU.[1,5–7] A recent meta-analysis[8] identified 7 randomized, double-blind, placebo-controlled studies of omalizumab, with 1312 subjects with CU. Omalizumab was administered at doses of 75 mg, 150 mg, 300 mg, or 600 mg. The 7 studies showed a low risk of bias. All used allocation concealment, and there