Emerging Therapies in Hereditary Angioedema

Meng Chen, MD*, Marc A. Riedl, MD, MS

KEYWORDS

• Angioedema • Emerging therapies • C1 esterase inhibitor • Bradykinin • Kallikrein • Factor XII

KEY POINTS

- Although significant therapeutic progress has been made in hereditary angioedema (HAE), current treatments are still limited by access, cost, and side effects.
- Multiple new therapies are being investigated for the treatment of HAE due to C1 esterase inhibitor deficiency.
- Novel mechanisms of action and drug delivery include subcutaneous complement component 1 esterase inhibitor (C1INH) concentrates, a monoclonal antibody inhibitor of kallikrein, oral kallikrein inhibitors, RNA-targeted antisense against prekallikrein, RNA interference drugs against factor XII, monoclonal antibody inhibitor of factor XIIa, and gene therapy.
- Studies are ongoing to expand the number of drugs available for pediatric patients with HAE due to C1 esterase inhibitor deficiency.

INTRODUCTION

Angioedema occurs due to the transient movement of fluid from the vasculature into the interstitial space leading to subcutaneous (SC) or submucosal swelling, which can have life-threatening consequences. Current evidence suggests that most angioedema conditions can be grouped into 2 categories: histamine-mediated or bradykinin-mediated angioedema. Although effective therapies for histamine-mediated angioedema have existed for decades, effective therapies for bradykinin-mediated angioedema have only more recently been developed, studied rigorously, and approved by regulatory agencies. As such, the treatment options for hereditary angioedema (HAE) have increased substantially over the last decade.

In the United States, therapy for HAE angioedema attacks was largely supportive a decade ago. Currently, 4 effective HAE-specific acute treatment options are available.[1] In addition, advances in HAE-specific prophylactic treatment have been

Division of Rheumatology, Department of Medicine, Allergy & Immunology, University of California San Diego, 8899 University City Lane, Suite 230, San Diego, CA 92122, USA
* Corresponding author.
E-mail address: mec079@ucsd.edu

Immunol Allergy Clin N Am 37 (2017) 585–595
http://dx.doi.org/10.1016/j.iac.2017.03.003
immunology.theclinics.com

realized and continue to evolve. This article primarily focuses on emerging treatments for bradykinin-mediated angioedema, specifically HAE due to complement component 1 esterase inhibitor (C1INH) deficiency, because most recent research and therapeutic development has focused on improved prevention of HAE symptoms. To provide context for therapeutic strategies, this article provides a cursory review of the pathophysiology of angioedema (Fig. 1).

HISTAMINERGIC VERSUS BRADYKININ PATHWAYS

As detailed in other articles of this issue, angioedema is generally caused by 1 of 2 mechanisms: through a mast cell–mediated pathway (histaminergic angioedema) or through a nonhistaminergic pathway. Current evidence strongly supports bradykinin as the predominant mediator responsible for nonhistaminergic forms of angioedema. Clinically distinguishing between these 2 pathways is paramount in selecting the appropriate agents for both acute and preventative treatment because these 2 categories respond to completely different classes of medications.

Histaminergic angioedema is mediated by mast cell activation with release of histamine, leukotrienes, and other mast cell–associated mediators. This form of angioedema is often accompanied by urticaria or pruritus and is seen in immunoglobulin (Ig)-E–mediated allergic reactions due to food, medication, or venom allergy, though a substantial portion of recurrent histaminergic angioedema is idiopathic in nature.

Nonhistaminergic angioedema seems to be primarily mediated by bradykinin dysregulation wherein symptoms result from the overproduction of bradykinin, which causes vasodilatation and vascular permeability by binding to the bradykinin B2 receptor on endothelial cells.[2] Bradykinin is generated through the activation of the kallikrein-kinin (contact) system, although the precise mechanisms are still poorly understood. Angioedema episodes are believed to be initiated by activation of the contact system, prekallikrein and factor XII, forming factor XIIa and kallikrein. Bradykinin is formed by cleavage of high molecular weight kininogen by plasma kallikrein. C1INH is a serine protease that inhibits proteases involved in this pathway. HAE due to C1INH

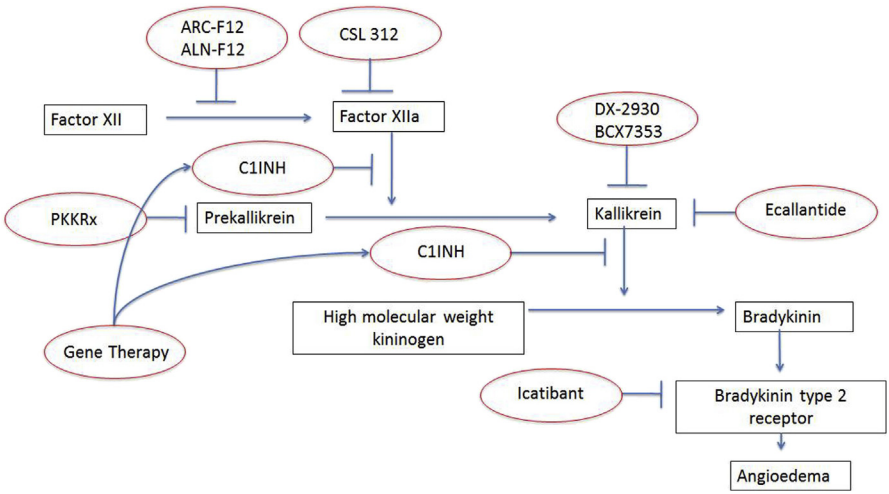

Fig. 1. Pathogenesis of bradykinin-mediated angioedema with targets for existing and developing therapies. C1INH, complement component 1 inhibitor.