Theme Editorial

Decoding the Enigma of Urticaria and Angioedema

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Sponte mea veniens varias ostendo figuras… (Symphosius, Anthologia Latina).[1] This Latin enigma refers to sleep and means "coming of my own accord I reveal varied forms," and could be applied to patients suffering from urticaria or angioedema, as illustrated on the cover of this issue of *J Allergy Clin Immunol Pract.* Deciphering the different forms is essential for the optimum management of such patients, and semiological clues help in defining the different clinical-pathophysiological entities encompassed by the terms urticaria and angioedema. As discussed in the 7 review articles[2-8] and 4 original reports[9-12] in this theme issue, advances in elucidating the pathogenic mechanisms of urticaria and angioedema are now providing opportunities for precision in diagnostics and therapeutics. Distinguishing histaminergic from nonhistaminergic causes of urticaria and angioedema is an essential first step in patient assessment and management (Figure 1). Urticaria, with or without angioedema, is usually histaminergic, mast cell-mediated, and associated with pruritis.[2,13,14] However, urticaria without angioedema or pruritis may be the consequence of nonhistaminergic autoinflammatory mechanisms involving the cryopyrin and IL-1 pathway.[7,15] Angioedema without urticaria may be either histaminergic or nonhistaminergic, and requires appropriate assessment for bradykinin and fibrinolytic dysregulation, as well as primary defects in vascular integrity.[8,16-21]

HISTAMINERGIC URTICARIA AND ANGIOEDEMA

Although the histaminergic urticarias and angioedemas share the mast cell as a common effector cell, the agonists for mast cell activation are diverse and span adaptive and innate immunity,[2,4,14,22-26] as illustrated in Figure 2. Signaling via the FcεR1 can occur by antigen crosslinking of IgE or by autoantibodies against the FcεR1 or anti-IgE autoantibodies[2] or by so-called superallergens (eg, Fv protein or various microbial peptides capable of antigen-independent crosslinking IgE).[27] There are also a variety of non-FcεR1 crosslinking mechanisms for mast cell activation that can cause urticaria. These include G-protein-linked receptors such as Mas-related G-protein coupled receptors (MRGPRX2),[25,26,28] N-formal peptide receptors (FPR),[29] and C3a and C5a receptors.[7] Ligands for the FPR are N-formyl oligopeptides generated by bacteria, including N-formyl-methionyl-leucyl-phenylalanine, which is the most potent and best known. MRGPRX2 ligands are basic molecules that include substance P, vasointestinal peptide, and a number of pharmaceutical drugs.[25,26,28] Toll-like receptors are also expressed on mast cells and may also serve as non-FcεR1 mechanisms for mast cell activation.[30] In addition, the skin-derived antimicrobial peptides, human beta-defensins and cathelicidin LL37, can activate mast cells to both degranulate and to express the pruritogenic cytokine IL-31.[31] Signaling through the C3a and C5a receptors links immune complex vasculitis with urticaria.[7] The mechanistic basis for the physical inducible urticarias remains elusive, and in some cases may be linked to allergen exposure as suggested for food-dependent exercise or cold-induced urticaria.[10,32] However, the mechanisms underlying mast cell sensitivity for activation with physical stimulation remain an enigma. Of future importance for managing urticarias will be refining our understanding of the role of phospholipid products on vascular permeability.

Appearance of pruriginous wheals, with or without angioedema, that are usually asymmetrical and transient, are the key elements of urticaria.[2,33] It is estimated that the prevalence of acute urticaria is approximately 15% to 20%. In 0.5% to 1.8% of the general population, the disease displays a chronic character by lasting for more than 6 weeks. Appearance of wheals and/or angioedema induced by specific triggers or occurring spontaneously configures the picture of chronic inducible urticaria (CIU) and chronic spontaneous urticaria (CSU), respectively.[2-4]

CSU is a debilitating disease with a high socioeconomic burden and with an important negative impact on the quality of life of the affected patients.[34] Herein, Saini and Kaplan[2] reviewed, in detail, the pathogenesis, diagnostic workup, and therapeutic approaches to CSU. Ben-Shoshan and Grattan[3] also reviewed the clinical features of CIU in children, the differential aspects of urticaria mimickers, such as urticaria multiforme, and the natural history and therapeutic options for children. Importantly, their reviews reveal important gaps in the optimal management of children affected by CSU, especially those with more severe and refractory disease. Information about the proportion of pediatric patients not responding to standard doses of antihistamines are lacking, and studies about the percentage of failure with higher doses are scarce. As the authors highlight,

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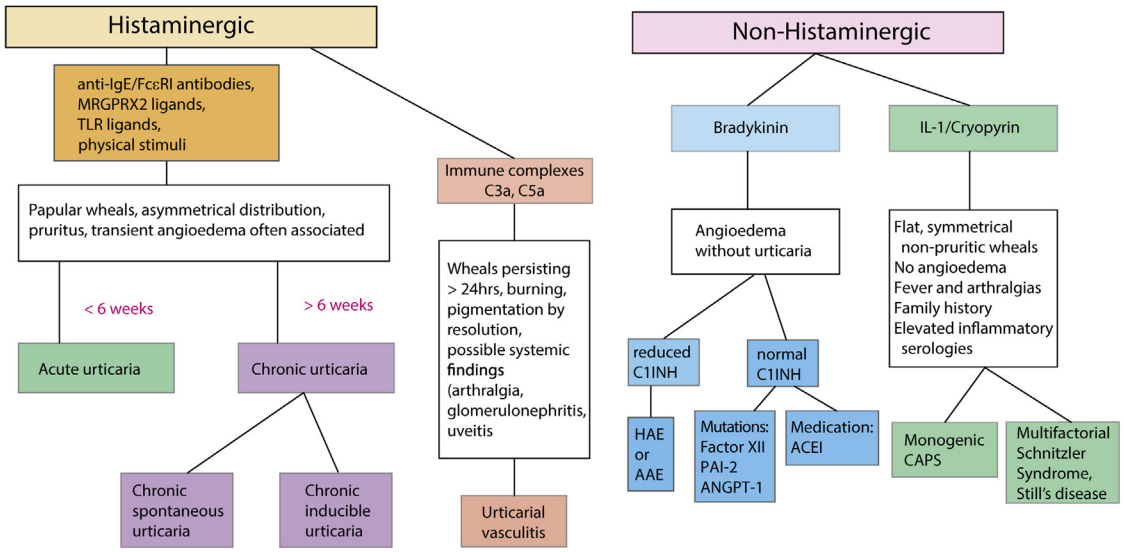

FIGURE 1. Algorithm for classification of urticaria and angioedema. *AAE*, Acquired angioedema; *ACEI*, angiotensin converting enzyme inhibitor; *ANGPT-1*, angiopoietin-1; *C1-INH*, C1-esterase inhibitor; *CAPS*, cryopyrin-associated periodic syndromes; *HAE*, hereditary angioedema; *PAI-2*, plasminogen activator inhibitor-2.

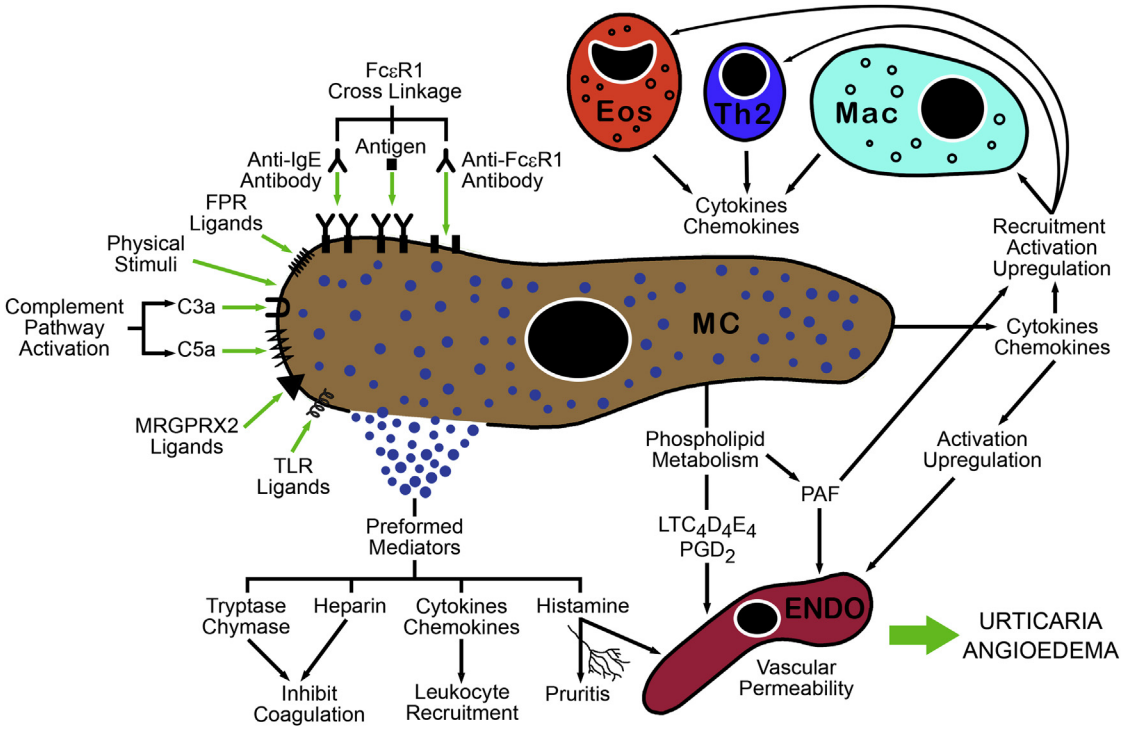

FIGURE 2. Mechanisms for mast cell activation in histaminergic urticaria and angioedema. *FPR*, N-formal peptide receptor; *MRGPRX2*, Mas-related G-protein coupled receptor; *TLR*, Toll-like receptor.

there is a need for randomized controlled trials in establishing the role of omalizumab and cyclosporine in the pediatric age group, and the importance of educational programs to limit the use of corticosteroids for the management of those children.

Available data about the natural history of CSU in adults indicate that this is usually a self-limited disease, with approximately 50% of patients undergoing resolution of symptoms within 6 months from onset.[33] Approximately 20% of patients will experience resolution within 3 years and another 20% within 5 years. In <2% of affected individuals, resolution will happen within 25 years. Importantly >50% of patients experience relapse, and the natural history does not seem to be

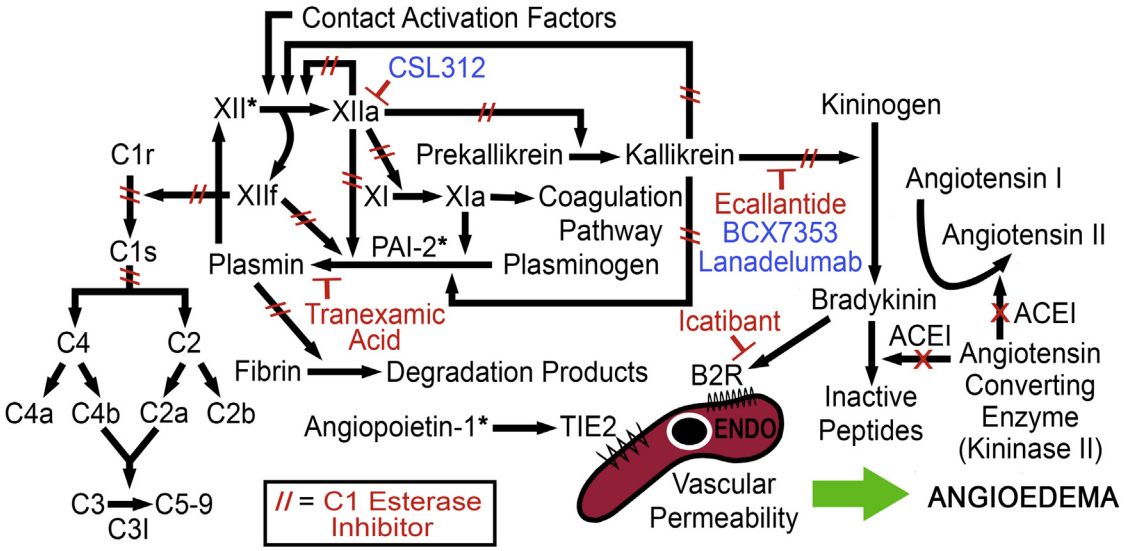

FIGURE 3. Mechanisms for nonhistaminergic angioedema. // indicates sites at which C1INH regulates the fibrinolytic and complement cascades, and the rationale for C1INH replacement therapy. XII* indicates mutated factor XII, resulting in increased susceptibility to activation by plasmin. PAI-2* indicates mutated plasminogen activator inhibitor, resulting in impaired inhibition of plasminogen activation into plasmin. Angiopoietin-1* indicates mutation of angiopoietin-1, resulting in impaired binding to its receptor (TIE2) on endothelial cells, which results in loss of vascular integrity. X indicates how angiotensin converting enzyme inhibitors (ACEI) impair bradykinin degradation. T indicates sites in the bradykinin generation pathway that are being targeted for therapy; available therapies are denoted in red; therapies in development are denoted in blue.

influenced by treatment. Deza et al[5] discuss the most promising biomarkers related to disease. The authors conclude that C-reactive protein (CRP), IL-6, mean platelet volume (MPV), D-dimer, and prothrombin fragment 1+2 are the most promising biomarkers to evaluate disease activity. However, as the authors pointed out, those markers are not specific and their elevation could reflect comorbidities or underlying diseases. Another important question is whether particular biomarkers of disease differ in adults versus children. For example, in adults profound basopenia may be associated with autoimmune (anti-IgE or anti-FcεR1) reactivity and a severe clinical phenotype, and that in turn could also be used as a biomarker for longer disease duration.[3] However, basopenia in children is associated with shorter disease duration. Further studies are needed to resolve this question. As reviewed by Deza et al,[5] preliminary observations suggest the potentials of RNAseq, microarrays, proteome, or metabolome strategies for the identification of reliable biomarkers for CSU.

Deza et al[5] summarize that more than 90% of patients with CSU respond to antihistamines or omalizumab or cyclosporine, and review the therapeutic pipelines for CSU, namely alternative anti-IgE treatment (ligelizumab and quilizumab), rituximab, intravenous IgG (IVIG), anti-TNFα, and investigational agents such as spleen tyrosine kinase (Syk), Bruton tyrosine kinase (BTK), and chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2) inhibitors. As the authors highlight, further studies are needed to establish whether IL-6 contributes to the pathogenesis of CSU and whether IL-6 antagonists could expand the therapeutic pipeline in CSU. Regarding the use of omalizumab in CSU, enigmas remain, such as when to stop, taper, or adjust the interval of treatment, and the appropriate concomitant medication use. An exploratory analysis reported in this theme issue by Ferrer et al[9] indicated that baseline UAS7 and the kinetics of treatment response could predict relapse of symptoms after omalizumab discontinuation. Still lacking is insight into the exact mechanisms by which omalizumab is effective for treating CSU.

Differences in therapeutic recommendations for CSU have existed between expert opinion guidelines. Zuberbier and Bernstein[6] reviewed the differences between US and European Guidelines and noted that recent efforts to refine these guidelines were toward a unified and consistent set of recommendations.[14] The major differences among the guidelines are the stepwise treatment strategy for patients resistant to standard antihistamine dosage, including the place of omalizumab in this approach. However, the most important controversies are the dietary management, that lacks sufficient scientific evidence, and the use of first-generation antihistamines. A better mechanistic understanding of CSU will hopefully lead to greater precision in treatment.

As detailed by Maurer et al,[4] the spectrum of CIU is quite diverse, yet specific to the inducing physical stimulus. Of note, patients suffering from cold or cholinergic CIU may experience systemic symptoms, including anaphylaxis, based on the extent of the stimulus. Despite the precision in identifying the physical stimulus responsible for clinical symptoms, the molecular mechanisms responsible for this histaminergic response remain an enigma. Therefore, management is primarily limited to avoidance of the offending stimulus and treatment with antihistamines. Although controlled trials are in favor of efficacy of omalizumab in cold urticaria and dermographism, its use is off-label. Although the mechanism by which such efficacy occurs in these CIU is not clear, the molecular tools for identifying potential mast cell activation pathways in CIU are available and will hopefully facilitate decoding these enigmas.[5] Perhaps clues can be derived from the observation that some CIU can be food

dependent,[10,32] or a manifestation of multisystem disease such as autoinflammatory disease or PLAID (PLCG2-associated antibody deficiency and immune dysregulation).[7] Another potential clue is that vibratory urticaria can occur as part of the clinical picture of familial hypertryptasemia.[35] Further studies are needed to identify reliable biomarkers and to identify effective therapeutic options for the various forms of CIU.

URTICARIA MIMETICS

When urticaria is present, the clinical features are of utmost help in the differential diagnosis. The clinical cases presented in this theme issue by Davis and van der Hilst[7] provide clinical clues to assist in differentiating autoinflammatory disorders and urticarial vasculitis from spontaneous or inducible urticaria.

In autoinflammatory disorders, such as cryopyrin-associated periodic syndrome and Schnitzler syndrome, the wheals are usually symmetrical and nonpruritic and angioedema is mostly absent. The clinical picture is also accompanied by systemic symptoms (eg, fever attacks, arthralgia) and sign of inflammation (elevated CRP). These diseases are usually characterized by a diagnostic delay of years and are not only debilitating but also carry the risk of AA amyloidosis. Symptoms do not respond to antihistamines but require anti-IL1 treatment.[7]

In urticarial vasculitis wheals usually persist for more than 24 hours and are associated with a burning sensation more than itching and may have residual discoloration. This nosological entity usually occurs in young women and may be manifest as only skin lesions to severe systemic or organ-specific manifestations of immune complex disease, with or without hypocomplementemia. Treatment depends on the severity. Moderate-severe disease requires immunosuppressive therapy.[7]

NONHISTAMINERGIC ANGIOEDEMA

When angioedema without urticaria is the clinical presentation, evaluation for dysregulation of bradykinin metabolism and the fibrinolytic pathways is indicated. Rapid progress has been made in unraveling the pathobiology of bradykinin dysregulation, reviewed by Cicardi and Zuraw.[8] As illustrated in Figure 3, in addition to the well-defined type 1 and 2 C1INH deficiency hereditary angioedemas (HAEs) with impaired C1INH production or function, mutations in factor XII,[18,19] plasminogen activation inhibitor-2 (PAI2),[20] or angiopoietin-1[21] have been implicated in the pathobiology of HAEs with normal C1INH. The factor XII mutations make it more readily activated, whereas PAI-2 mutations impair control of plasminogen cleavage to plasmin. The recent identification of angiopoietin-1 mutations that impair binding to its TIE2 receptor on endothelial cells provides a mechanistic basis for an additional HAE with normal C1INH that is not directly linked to bradykinin, but rather is due to impaired maintenance of vascular integrity. Based on these advances in defining distinct mechanisms underlying a shared clinical phenotype of HAEs, it is reasonable to anticipate that additional molecular mechanisms will be identified in the future to explain nonhistaminergic angioedema of unknown origin.[11] It is also important to recognize that all patients with a genetic basis for angioedema may not have a known positive family history or may represent a de novo mutation.

The pipeline of approved and experimental treatments for the HAEs is rapidly expanding and offers hope for effective, safe, and convenient patient management.[8] As illustrated in Figure 3 and reviewed by Cicardi and Zuraw,[8] rational approaches for therapeutic intervention of bradykinin dysregulation or abnormalities in vascular integrity can be derived from understanding the relevant pathophysiologic mechanisms leading to clinical disease. Gene therapy strategies may someday provide a curative intervention.[36]

In addition to the HAEs is the challenge of the type 1 and type 2 acquired angioedemas, due to either C1INH consumption associated with an underlying tumor, and often with an underlying monoclonal gammopathy, or C1INH inactivation by autoantibodies, and for which treatment of the underlying tumor or autoantibody production can be efficacious.[37] Angioedema associated with angiotensin converting enzyme inhibitors (ACEI) is due to impaired degradation of bradykinin by ACE, and hence is best managed by discontinuation of ACEI.[8]

CONCLUSIONS

The spectrum of articles on urticaria and angioedema in this issue of *J Allergy Clin Immunol Pract* illustrate the significant advances that have been made in elucidating the pathobiology underlying these clinical conditions and in translating that mechanistic insight into novel and precise diagnostic and therapeutic applications. The authors also highlighted the gaps that remain in our understanding of these conditions. However, the pipeline is rich with exciting new tools with which to further decode the enigma of urticaria and angioedema and establish more effective therapies.

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REFERENCES

1. Leary TJ, editor. Symphosius The Aenigmata: An Introduction, Text and Commentary. London: Bloomsbury; 2014.
2. Saini SS, Kaplan AP. Chronic spontaneous urticaria: the devil's itch. J Allergy Clin Immunol Pract 2018;6:1097-106.
3. Ben-Shoshan M, Grattan C. Management of pediatric urticaria with review of the literature on chronic spontaneous urticaria in children. J Allergy Clin Immunol Pract 2018;6:1152-61.
4. Maurer M, Fluhr JW, Khan DA. How to approach chronic inducible urticaria. J Allergy Clin Immunol Pract 2018;6:1119-30.
5. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging biomarkers and therapeutic pipelines for chronic spontaneous urticaria. J Allergy Clin Immunol Pract 2018;6:1108-17.
6. Zuberbier T, Bernstein JA. A comparison of the American and International perspective on chronic urticaria guidelines. J Allergy Clin Immunol Pract 2018; 6:1144-51.
7. Davis M, van der Hilst J. Mimickers of urticarial: urticarial vasculitis and autoinflammatory diseases. J Allergy Clin Immunol Pract 2018;6:1162-70.
8. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. J Allergy Clin Immunol Pract 2018;6:1132-41.
9. Ferrer M, Giménez-Arnau A, Saldana D, Janssens N, Balp M-M, Khalil S, et al. Predicting chronic spontaneous urticaria symptom return after omalizumab treatment discontinuation: exploratory analysis. J Allergy Clin Immunol Pract 2018;6:1191-7.
10. Kulthanan K, Tuchinda P, Chularojanamontri L, Maurer M. Food-dependent cold urticaria: a new variant of physical urticaria. J Allergy Clin Immunol Pract 2018;6:1400-2.
11. Andrási N, Veszeli N, Kőhalmi KV, Csuka D, Temesszentandrási G, Varga L, et al. Idiopathic non-histaminergic acquired angioedema vs. hereditary angioedema. J Allergy Clin Immunol Pract 2018;6:1205-8.
12. Wu MA, Ippolito S, Zanichelli A, Perego F, Cicardi M. Recurrent retroperitoneal angioedema. J Allergy Clin Immunol Pract 2018;6:1384-5.
13. Bernstein JA, Lang DM, Khan DA. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270-7.

14. Zuberbier T, Aberer W, Asero R, Latiff AHA, Baker D, Ballmer-Weber B, et al. The EAACI/GA LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2017 revision and update. Allergy 2018;69:868-87.
15. Cush JJ. Autoinflammatory syndromes. Dermatol Clin 2013;31:471-80.
16. Zuraw BL. Hereditary angioedema with normal C1 inhibitor: four types and counting. J Allergy Clin Immunol 2018;141:884-5.
17. Kaplan AP, Ghebrehiwet B. The plasma bradykinin-forming pathways and its interrelationships with complement. Mol Immunol 2010;47:2161-9.
18. de Maat S, Björkqvist J, Suffritti C, Wiesenekker CP, Nagtegaal W, Koekman A, et al. Plasmin is a natural trigger for bradykinin production in patients with hereditary angioedema with factor XII mutations. J Allergy Clin Immunol 2016;138:1414-23.
19. Björkqvist J, de Maat S, Lewandrowski U, Di Gennaro A, Oschatz C, Schönig K, et al. Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. J Clin Invest 2015;125:3132-46.
20. Joseph K, Tholanikunnel BG, Wolf B, Bork B, Bork K, Kaplan AP. Deficiency of plasminogen activator inhibitor 2 in plasma of patients with hereditary angioedema with normal C1 inhibitor levels. J Allergy Clin Immunol 2015;137:1822-9.
21. Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. J Allergy Clin Immunol 2015;141:1009-17.
22. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias—the EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy 2016;71:780-802.
23. Sanchez J, Amaya E, Acevedo A, Celis A, Caraballo D, Cardona R. Prevalence of inducible urticaria in patients with chronic spontaneous urticaria: associated risk factors. J Allergy Clin Immunol Pract 2017;5:464-70.
24. Dressler C, Werner RN, Eisert L, Zuberbier T, Nast A, Maurer M. Chronic inducible urticaria: a systematic review of treatment options. J Allergy Clin Immunol 2018;141:1726-34.
25. Azimi E, Reddy VB, Seadi Pereira PJ, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein-coupled receptors to induce itch. J Allergy Clin Immunol 2017;140:447-53.
26. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast cell specific receptor crucial for pseudo-allergic drug reactions. Nature 2015;519:237-41.
27. Marone G, Rossi FW, Detoraki A, Granata F, Marone G, Genovese A, et al. Role of superantigens in allergic disorders. Chem Immunol Allergy 2007;93:195-213.
28. Ali H. Mas-related G protein coupled receptor-X2: a potential new target for modulating mast cell-mediated allergic and inflammatory diseases. J Immunobiol 2016;1:115.
29. Migeotte I, Communi D, Parmentier M. Formyl peptide receptors: a promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth Factor Rev 2006;17:501-19.
30. Sandig H, Bulfone-Paus S. TRL signaling in mast cells: common and unique features. Front Immunol 2012;3:1-29.
31. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, et al. Antimicrobial peptides human beta-defensins and cathelicidin LL37 induce the secretion of a pruritogenic cytokine IL-31 by human mast cells. J Immunol 2010;184:3526-34.
32. Romano A, Di Fonso M, Giuffreda F, Papa G, Artesani MC, Viola M, et al. Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. Int Arch Allergy Immunol 2001;125:264-72.
33. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. Clin Exp Dermatol 2010;35:869-73.
34. Beltrani VS. An overview of chronic urticaria. Clin Rev Allergy Immunol 2002;23:147-69.
35. Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. J Allergy Clin Immunol 2014;133:1471-4.
36. Pagovich OE, Qiu T, Whaley AS, Nelson C, Wisch L, O'Brien M, et al. One-time gene therapy for hereditary angioedema. Molecular Therapy 2016;24(S1):S298.
37. Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. J Allergy Clin Immunol Pract 2017;5:1307-13.