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Editorial

Humanized Monoclonal Antibodies Against IgE Antibodies as Therapy for IgE-Mediated Coronary Syndromes: Are We There Yet?

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See article by Liu et al., pages 966.e5-966.e6 of this issue.

Immunoglobulin E (IgE) antibodies are synthesized and released by B lymphocytes as a result of a complex interplay between genes, cytokines, and environmental antigen exposure. IgE antibodies participate in atopic diseases and systemic anaphylaxis, constituting components of a protein network implicated in signalling response to antigens and allergens.[1] IgEs are very short lived in plasma (~ 1 day), but receptor-bound IgE can remain fixed to cells in tissues for weeks or months. Their biologic activity is mainly dependent on binding to specific fragment crystallisable region (FcR) receptors high-affinity FCεRI and FCγRI and low-affinity FCεRII and FCγRII situated on the surface, mainly of mast cells, but also of basophils, eosinophils, monocytes, and epithelial and dendritic cells.[2] The IgE binding to FcR increases cell survival and causes up-regulation of the above receptors. Interactions mediated by IgEs bound on mast cells with corresponding antigens/allergens on the surface of mast cells leads to mast cell degranulation and release of a variety of preformed and newly formed substances acting as mediators. Degranulation and mediator release occur when IgE antibodies bridged with antigens/allergens reach the critical number of 2000, forming 1000 bridges for a maximum of ~ 500,000-1,000,000 IgE antibodies on the cell surface![3]

Mediator release can induce coronary artery spasm, independently from the existence of underlying atherosclerotic disease, manifesting as Kounis type I syndrome (Table 1) and myocardial infarction with nonobstructive coronary arteries (MINOCA).[4] The mediators might contribute to the critical progression, erosion, and rupture of atherosclerotic plaque, inducing thrombotic complications resulting from platelet activation and fibrinolytic system impairment, and further promoting the development and growth of arterial aneurysms.[5]

Causes of IgE Release

Apart from up-regulation of IgE receptors, IgEs mediate prolongation of mast cell survival, enhancement of allergen uptake by B cells for antigen presentation, induction of T-helper 2 cytokine expression by mast cells, and amplification and further perpetuation of allergic responses.[6] Elevated serum IgE can be caused by allergic reactions, infections, and other immune conditions, including the hyper-IgE syndrome,[7] a rare primary immunodeficiency disease characterized by recurrent skin and pulmonary abscesses and extremely elevated IgE serum levels. In addition, IgEs might be increased in acute myocardial infarction, stable and unstable angina, further correlating with plaque destabilization and severity of acute myocardial infarction,[1,8] and elevated IgE levels may be a risk factor for increased cardiovascular mortality.[9]

Increased IgE Levels: Cause or Consequence of Acute Coronary Events?

In the Helsinki heart study,[10] among 270 initially healthy hyperlipidemic men who suffered myocardial infarction, the levels of IgE and other immunoglobulin classes, such as IgA and IgG, were significantly higher before the event compared with matched healthy control subjects. In that study, the risk of myocardial infarction increased as a positive function of immunoglobulin level, an effect that was independent from adjustment for confounding factors such as age, smoking, or blood pressure.

In another study using immunostained frozen sections of human atherosclerotic lesions, IgEs and their high-affinity receptors were concentrated in the microvessels of the shoulder atherosclerotic regions.[11] It is known that shoulder sites of coronary plaques are susceptible to erosion or rupture, meaning that IgEs, respective FcR receptors, and

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Table 1. Three types of Kounis syndrome

Type I (MINOCA type)	Type II	Type III
Normal or nearly normal coronary arteries.	Quiescent preexisting coronary disease.	Stent thrombosis (subtype IIIa) and/or stent restenosis (subtype IIIb).
Induced by histamine, chymase, arachidonic acid products (leukotrienes, PAF).	Induced by the same as type I plus platelet activation.	Induced by stent polymers, stent metals, eluted drugs, dual antiplatelets, environmental exposures.

PAF, platelet-activating factor; MINOCA, myocardial infarction with nonobstructive coronary arteries.

inflammatory cells might invade this area before an acute coronary event.[10]

Therefore, increased IgE levels appear to precede the coronary event and are not the result of inflammatory reaction from tissue damage occurring during the event.

The Kounis Hypersensitivity-Associated Coronary Syndrome

Allergic, hypersensitivity, anaphylactic, or anaphylactoid reactions associated with cardiovascular symptoms were initially attributed to serum pathology and were characterized as acute carditis, morphologic cardiac reactions, or rheumatic carditis of unknown pathophysiology. The first comprehensive description of the allergic angina syndrome, as a coronary spasm representing a manifestation of endothelial dysfunction or microvascular angina leading to allergic acute myocardial infarction, was described in 1991[12] and later named the Kounis syndrome.[13] This syndrome is caused by inflammatory mediators released during an allergic insult, from degranulation of mast cells and other interacting cells, including T-lymphocytes, macrophages, eosinophils and platelets. Histamine, tryptase, and arachidonic acid products, in combination with chymase acting as a converting enzyme, can promote the acute ischemic event via coronary spasm, atheromatous plaque erosion/rupture, and platelet activation in the Kounis syndrome cascade. Potential inciting causes of the Kounis syndrome include drugs, metals, foods, environmental exposures, and clinical conditions. Kounis syndrome can affect not only the coronary arteries, but also the mesenteric, cerebral, and peripheral arteries, with an incidence ranging from 1.1% to 3.4% in patients who suffer an allergic, hypersensitivity, anaphylactic, or anaphylactoid insult.[14] Kounis syndrome was first thought to be a rare condition but appears rather to be an underdiagnosed disease. Three types of this syndrome have been described so far, as summarized in Table 1.

Humanized Monoclonal Antibodies as Therapeutics

In this issue of the *Canadian Journal of Cardiology*,[15] Liu et al. present the history of a 48-year-old previously atopic man, allergic to scallions and garlic, who underwent a polymer-free sirolimus-eluting stent implantation for recurrent angina attacks followed by systematic administration of dual-antiplatelet therapy (DAPT) with aspirin and clopidogrel. The patient developed Kounis type III syndrome (stent thrombosis) 1 year later, after consumption of scallions, accompanied by elevated levels of IgEs and chronic urticaria. An improvement in chronic urticaria, decrease in IgE levels, and reduction of the coronary ischemic episodes was reported after administration of omalizumab (150 mg subcutaneously every 4 weeks), a recombinant DNA–derived humanized IgG1k monoclonal antibody IgE reducer.

Omalizumab (sold under the trade name Xolair) blocks the binding of free IgEs to their high-affinity FcεRI receptors.[16] Unlike an ordinary anti-IgE antibody, it does not bind to IgE that is already attached to the high-affinity IgE receptor FcεRI on the surface of mast cells, basophils, and antigen-presenting dendritic cells. This mechanism clears free IgEs and suppresses IgE-mediated reactions. Following the

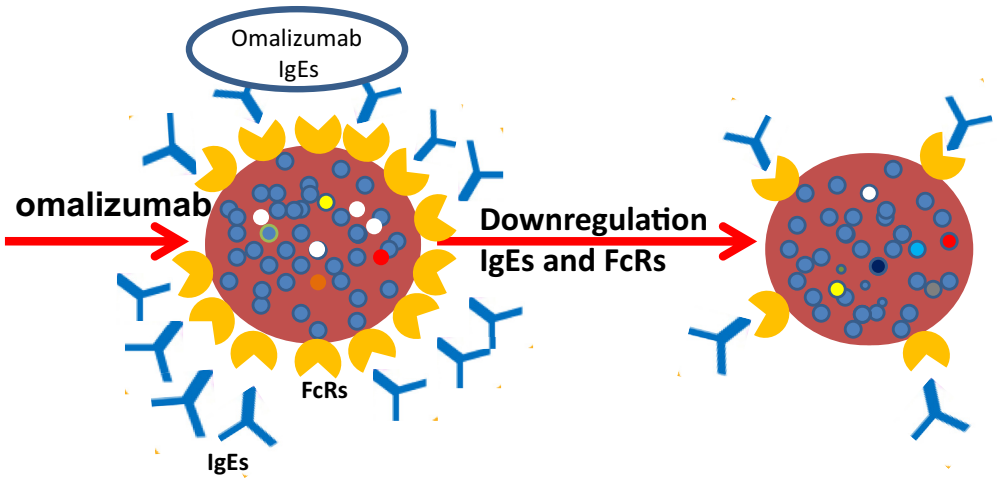

Figure 1. Omalizumab inhibits more than 96% of immunoglobulin E (IgE) from binding to the high-affinity fragment crystallisable region (FcR) receptors on mast cells, basophils, monocytes, and epithelial and dendritic cells.

Table 2. Conditions treated successfully with omalizumab

Allergic bronchopulmonary aspergillosis
Allergic rhinitis
Allergic uvula edema
Angioedema
Aspirin allergy
Atopic dermatitis
Bronchial asthma
Bullous dermatosis
Bullous pemphigoid
Cholinergic urticaria
Chronic spontaneous urticaria
Clopidogrel hypersensitivity
Eosinophilic chronic rhinosinusitis
Eosinophilic granulomatosis
Estrogen-induced dermatitis
Hereditary α-tryptasemia
Hymenoptera anaphylaxis
Hypersensitivity in oncological patients
Idiopathic anaphylaxis
Idiopathic mast cell activation syndrome
Indolent systemic mastocytosis
Insulin hypersensitivity
Morbihan syndrome (chronic erythematous edema of upper face)
Pediatric atopic dermatitis
Santer triad
Solar urticaria
Wells syndrome (eosinophilic cellulitis)
Wheat protein allergy

reduction of free IgEs, a down-regulation of FcεRI expression ensues (Fig. 1).

Omalizumab was approved by the United States Food and Drug Administration (FDA) in 2018 for therapy of moderate-to-severe allergic asthma and chronic idiopathic urticaria. During the past 2 years, omalizumab has been used for the treatment of other conditions not included in the FDA recommendations. Reports of off-label use of omalizumab include patient treatment with different types of mast cell disorders (Table 2).

The Liu et al. report appears to be the first in cardiologic clinical practice of the use of humanized monoclonal antibody for the treatment of Kounis syndrome, and it was associated with beneficial results. Although their report is for a case of type III Kounis syndrome, it is anticipated that such treatment might be beneficial for the other types of Kounis syndrome as well.

Too Many Cooks Spoil the Broth

Clinical studies support the idea that atopic patients simultaneously exposed to several allergens can present more symptoms than monosensitized individuals.[17] IgE antibodies with different specificities can convey additive effects and in small, even subthreshold, numbers can trigger cell mediators to release when a patient is simultaneously exposed to the corresponding antigens.[18]

In this case, the patient was exposed to aspirin and clopidogrel, while he had previously undergone deployment of a cobalt-chromium polymer-free metallic scaffold that also contains nickel and releases sirolimus. Aspirin[19,20] and clopidogrel[21] can induce Kounis syndrome, whereas metal anions and sirolimus can also act as antigens.[22,23] Surprisingly, omalizumab may be helpful to treat clopidogrel hypersensitivity without discontinuation of thienopyridine administration in patients requiring double-antiplatelet therapy after coronary stent implantation.[24]

Atopy and Kounis Syndrome

Atopy is defined as a genetic predisposition to produce excessive amounts of IgE antibodies.[25] Elevated total IgEs levels (562 IU/L compared with the reference level of < 165 IU/L) were demonstrated initially in Liu et al.'s patient; these decreased by 50% along with the abolition of signs and symptoms in response to omalizumab.

Despite the fact that omalizumab has shown beneficial effects on several allergic conditions (now including Kounis syndrome) its use might have some serious untoward effects that should not be overlooked. Omalizumab itself can cause anaphylaxis due to the potential antigenic properties of the antibody itself. In the observational study EXCELS (Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma),[26] the rates of cardiovascular and cerebrovascular events (comprising cardiovascular death, myocardial infarction, ischemic stroke, transient ischemic attack, and unstable angina) were higher in the omalizumab cohort compared with the nonomalizumab cohort (13.4 vs. 8.1 per 1000 person-years). Theoretically, indiscriminate blockade of IgE receptors might interfere with the immune system's recognition of cancer cells, affecting the genesis and treatment of malignancies.

Keeping in mind the corollary of the ancient Greek Stoic philosophers' dictum "ουδέν κακόν αμιγές καλού" ("ouden kakon amiges kalou," there is no pure evil, ie, every cloud has a silver lining) in today's cardiology practice, "ουδέν καλόν αμιγές κακού" ("ouden kalon amiges kakou," there is no pure good), we think that despite the above risks, the use of omalizumab in cardiac disorders associated with allergy, hypersensitivity, and anaphylaxis might be proven beneficial. However, before its wider therapeutic use, careful assessment of omalizumab risks based on the results of pooled analysis of randomized controlled trials and current meta-analyses should be taken into consideration.[27]

Conclusion

IgE antibodies can cause Kounis syndrome coronary events and might be implicated more broadly in acute myocardial infarction and stable and unstable angina. The use of humanized monoclonal antibodies to clear free IgEs and down regulate FcεRI expression might represent a new era for the treatment or prevention of such events. However, for now, omalizumab therapy should be reserved for dramatic refractory cases like that reported by Liu et al., pending the results of future prospective studies and/or convincing findings from large series of retrospective analyses.

Disclosures

The authors have no conflicts of interest to disclose.

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