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REVIEW

Biologics in chronic urticaria

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Introduction

Chronic spontaneous urticaria (CSU) consists in the appearance of hives with or without angioedema for more than 6 weeks duration. It is a highly disabling disease, with a great impact on the patient's quality of life.[1] There are intermittent urticarias elicited by physical stimuli now classified as chronic inducible urticarias (CINDU) that comprise cholinergic urticaria, cold urticaria, dermatographism, local heat urticaria and aquagenic urticaria. This review will be focusing on CSU.

Up to the very moment, the pathophysiology of CSU remains elusive,[2] with several cells and mediators being involved thus possibly indicates that this medical condition affects not only one target. Antihistamines have been the mainstay treatment for CSU. Antihistamines can control the disease in 38% of cases and increasing its dose can control only up to 60% of cases.[3] Despite following the recommendation from the present guidelines that antihistamines can be given up to 4 times a day, a significant percentage of patients still remain symptomatic.[4] In uncontrolled cases with antihistamines, double blinded placebo controlled studies showed that cyclosporine is efficient to control urticaria and even improves after discontinuing the above mentioned medication.[5,6] However, it is an off-label treatment with serious systemic side effects such as the need of regular monitorization of blood pressure as well as renal function.

In the recent years, a number of biologics were developed that showed very good results to allergic diseases.[7] In this review, we will cover the biologic agents that were indicated and investigated for CSU most especially Omalizumab.

Biologicals are large molecular weight molecules produced in living organisms that bind to a specific determinant such as cytokines, receptors or other immunoglobulins. They allow the delivery of a personalized medication but at the same time, the knowledge of the exact mechanism to target specific players of each disease is vital. There is a recent published article with an excellent review on the updates of biologicals in allergic diseases.[8]

Rituximab

Rituximab is a chimeric monoclonal antibody that binds to the CD20 surface B cells receptor causing a depletion of B cells. It has been widely used for autoimmune disorders characterized by a high B cell number. The reason of using Rituximab for CSU is based on the presence of IgG against the FcεRII receptor, depleting B cells hence resulting to a decrease of IgG production.

There are two case reports: one in a 12-year-old and another in an adult patient[9,10] with severe and difficult to treat urticaria. Both patients received Rituximab. Corticosteroids or cyclosporine were not administered due its side effects. After four injections of Rituximab, both patients showed a very good response and were noted to be asymptomatic even on follow up after several months.

There is a negative case report outcome in a CSU patient associated with delayed pressure urticaria non-respondent to several immunosupressants such as cyclosporine or[11] methylprednisolone that neither responded to Rituximab.

In conclusion, further studies are needed in order to validate the effectivity of Rituximab in urticaria. We are not

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aware of ongoing clinical trials with Rituximab as of the moment.

TNF-alpha inhibitors

TNF-alpha has multiple actions in the immune system such as inducing secretion of several cytokines, adhesion molecules and T cell migration that offers a target for treatment of several inflammatory conditions like rheumatoid arthritis (RA), seronegative spondyloarthropathies and inflammatory bowel disease (IBD). There are several TNF-alpha antagonists available in the market: Etanercept, Infliximab, Adalimumab, Golimumab and Certolizumab Pegol that are reviewed elsewere.[12]

The group of inhibitors of TNF-alpha have been tried for urticaria based on reports that found higher levels of TNF-alpha in CSU lesions.[13,14] Mast cells are a source of TNF-alpha thus could possibly play a role. Its use in urticaria was first reported in a patient diagnosed with psoriasis with severe delayed pressure urticaria,[15] who showed a complete response after treatment with Etanercept and later on with Infliximab. The other study comprised six severe CSU patients who did not respond to multiple therapies.[16] Four were treated with Etancercept, one with Adalimumab and one with Infliximab with a very good response. Interestingly, three patients treated with Etanercept were free of lesions after 3 years, 2 years and 7 months respectively with no other add-on treatment needed. Another patient that did not respond to Etanercept switched to Infliximab plus Methrotrexate, still had occasional hives. The fifth patient was clear of lesions for 9 months after discontinuing Adalimumab. The sixth patient was still ongoing treatment with Etanercept, well controlled upon the publication of this article.

There is a completed Phase I/II Open-label study with one anti-TNF-alpha, Abatacept however, results are not yet published.[17]

Unfortunately, TNF-alpha inhibitor has significant side effects mainly tuberculosis, neutropenia, serious infections, heart failure, and malignancy which places the indication of TNF-alpha for severe cases and unresponsive to other available therapies.

Omalizumab

Omalizumab (OmAb) is a recombinant humanized monoclonal antibody that binds to free immunoglobulin E on the C epsilon 3 locus[18–20] of the constant fragment. It recognizes an epitope that is masked when IgE is bound to its high-affinity receptor, Fc epsilon receptor I (FcεRI). Consequently, it inhibits mast cells and basophil activation and the allergic reaction and inflammation.[21] The reduction of circulating IgE causes a reduction of FcεRI in mast cells[22] and basophils.[23]

The rationale for utilizing Omalizumab for CSU is supported by the fact that sera from a subset of patients with chronic spontaneous urticaria (CSU) was demonstrated to activate normal basophils[24] and mast cells[25] through IgG antibodies against the alpha subunit IgE receptor[26,27] or against IgE.[27] Therefore, sequestering IgE would cause FcεRI endocytosis and antigen disappearance. FcεRI internalization occurs over several weeks.[28]

The first case report[29] on the efficacy of Omalizumab for CSU was done in 2007, establishing a very good response in CSU recalcitrant to conventional therapy. The first proof of concept was reported by Kaplan[30] in 2008 in a single blind and placebo controlled study with 12 autoimmune severe CSU patients, demonstrating a significant response in 11 among 12 patients with a response rate of 60%; remarkably, all patients had severe, prolonged and resistant to therapy of CSU. In 2011, two double blinded placebo controlled studies were performed. The first one[31] was a randomized study wherein patients received 75, 300 o 600 mg respectively of Omalizumab in addition to the antihistamine dose that they were taking. The patients showed a significant improvement in the UAS7 score with the 300 mg dose. Soon after, Ferrer reported in an observational study that Omalizumab was equally effective in patients with non autoimmune CSU subtype,[32] as it was reported for autoimmune. Shortly thereafter, two Phase III studies[33,34] reported a remarkable response in patients suffering CSU that did not respond to previous treatments. It was approved for CSU by the FDA and EMEA.

These findings were confirmed with real life reports[35–37] that find better results with higher percentage of response than in the clinical trials.

Omalizumab also showed effectivity upon reintroduction[38] so it signifies that it does not induce antibody production.

The exact mechanism of action is not well known. In contrast of what is believed, Eggel demonstrated that Omalizumab is indeed able to remove already bound to its receptor[39,40] causing a decrease in basophil activation. This was later confirmed by Serrano-Candelas et al.[41] demonstrating not only a decrease in basophil function and mast cells upon incubation with Omalizumab but also a downregulation of proximal and distal signaling molecules. However, clinical response could not be correlated with any in vitro parameter.

Other anti-IgE antibodies

There is a recent publication of the result of a clinical study with Quilizumab that included 45 CSU patients. Quilizumab is a monoclonal antibody that binds to the M1-prime segment of the IgE membrane that causes an IgE depletion and cell apoptosis. This clinical trial was not effective.[42]

Furthermore, there is an ongoing clinical trial involving another anti-IgE, Ligelizumab,[43] a humanised monoclonal IgG1κ antibody with a high avidity for IgE with no published result.

Conclusion

With the discovery of biologicals, specially Omalizumab, the CSU prospective has significantly changed thus offering better control of the disease as well as a better rate of response in real life reaching almost 85% of patients. However, there are many challenges ahead. We need to identify the predictive markers for the non-responders, generate the best administration protocol, define the non-responders and