Chronic spontaneous urticaria in the era of biologic therapy: a new hope

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Acknowledgement:

We would like to thank Karen Adamson of Chocolate Cow Design for the excellent Figure 1 graphic

Word count: 2668

1 figure and 1 table

Abstract

Chronic spontaneous urticaria (CSU) is a morbid condition associated with spontaneous urticaria, angioedema, or both for at least six weeks. CSU may persist for years, and until recently, the lack of effective disease-modifying therapies has been a heart-sink for patient and physician. A new hope has been provided with the registration of omalizumab – a targeted anti-IgE therapy which can be effective in up to 80% of CSU patients not adequately controlled with high dose antihistamine therapy. Access to omalizumab remains an obstacle; however, increasing use as standard-of-care in the public sector is encouraging. Excitingly, an improved understanding of the heterogeneous pathogenesis of CSU means there is a growing pipeline of new therapies, including biologics, under investigation. This review outlines novel therapies, either registered or under investigation for CSU, with detailed discussion of omalizumab use – at present the only registered biologic available in South Africa.

Background

Urticaria is edema involving only the superficial portion of the dermis, appearing as well-circumscribed wheals with raised erythematous serpiginous borders and blanched centers that sometimes coalesce to form large to giant wheals. Angioedema on the other hand is a well-circumscribed area of edema involving deeper layers of the skin and the subcutaneous tissue. Urticaria and angioedema can appear together or separately [1].

Clinically, the temporal classification includes acute urticaria (less than 6 weeks) - usually a result of a specific triggering allergen or infection; and chronic urticaria (persists more than 6 weeks) – where the likelihood of identifying specific offending triggers is significantly lower. Chronic urticarias are spontaneous, inducible or both. Chronic inducible urticarias (CIndU) can be secondary to friction (dermographism), deep pressure, cholinergic stimuli e.g. exercise, temperature (cold or hot), water, and sun [2].

Chronic Spontaneous Urticaria (CSU), also known as Chronic Idiopathic or Autoimmune Urticaria, is characterized by urticarial lesions, with or without associated angioedema for an overall period of more than 6 weeks. No identifiable trigger is found and symptoms are present most days of the week [3]. In this brief review we will outline novel CSU therapies, either registered or under investigation, presented in the context of the developing understanding of pathogenesis. A more detailed discussion of anti-IgE therapy with omalizumab is provided, as at present it is the only registered biologic available for CSU treatment in South Africa (SA).

Current understanding of pathophysiology

A complete pathophysiological picture of CSU remains elusive. Figure 1 provides an overview of the current major pathological drivers of a likely heterogeneous disease. The final common pathway driving the leakage of fluid into the cutaneous tissues involves a combination of site-of-disease mast cell, basophil and eosinophil activation, through either IgE or IgG autoantibodies. IgG autoantibodies against the FCεR1 and IgE have been long established in patients with CSU (type II hypersensitivity/autoimmunity), while IgE autoantibodies (type 1 hypersensitivity/autoallergy) against >200 cutaneous autoantigens has recently been demonstrated [4].

The presence of autoantibodies suggests roles for T and B-lymphocytes, as well as plasma cells in the immune pathogenesis. Other lines of evidence indicate contributory roles of the extrinsic coagulation cascade and systemic inflammation [5]. D-dimer has been proposed as a biomarker for CSU; increased d-dimer levels indicate turnover in the coagulation cascade. The extrinsic coagulation system is activated by increased expression of Tissue Factor on both activated site-of-disease eosinophils, and local endothelium with coagulation components having downstream effects through their protease-activated receptors (PARs) (Figure 1) [6].

In fact, warfarin therapy has even been studied as a therapy for CSU [7]. Non-specific systemic inflammation has been identified as a driver of CSU; for instance, both infection with Helicobacter Pylori [8] and the metabolic syndrome have been associated with CSU and disease severity [5]. A more detailed discussion of the etiopathogenesis of CSU is beyond the scope of

this article and readers are referred to other recent focused reviews by Kolkhir et al in 2016, and Asero et al. in 2017. Undoubtedly, increasing insights into the multiple activated cells and pathways continue to open up novel therapeutic targets [9].

Existing therapies and current recommendations

All registered non-sedating antihistamines are first-line treatment for urticaria. Second-line is high dose antihistamine therapy; up to 4x normal daily dosing. Safety and efficacy studies of high-dose antihistamine therapy are available for Cetirizine, Levocetirizine, Loratidine, Desloratidine, Fexofenadine, Rupatadine and Bilastine, with use for prolonged periods [7]. Up and down-titrating, as well as split and single dosing strategies are driven by provider preference without a solid evidence base justifying a particular approach.

Non-biologic third-line therapies include: i) Leukotriene receptor antagonists such as Montelukast 10mg daily and Zafirlukast 20mg twice daily (weak recommendation/low level of evidence) [7]; ii) Ciclosporine A, an immunosuppressant – six months course of 1.5-2mg/kg dosing is an alternative disease-modifier to biologic therapy but risk/benefits require consideration given the many adverse effects (strong recommendation/high level of evidence) [7]; iii) short-course corticosteroids for acute exacerbations (weak recommendation/low level of evidence); but long-term therapy is contraindicated due to adverse effects (strong recommendation/high level of evidence) [7].

Evidence is too low for current EAACI guidelines to make favorable recommendations for multiple other agents which have been attempted for the treatment of CSU including: H2-receptor antagonists e.g. ranitidine, Dapsone, sulfasalazine, methotrexate, interferon, plasmapheresis, high dose immunoglobulins, tranexamic acid, anti-TNF-α agents, and phototherapy; however, for some of these, responses to therapy have been promising [7].

Biologic therapy for CSU

There are a number of novel biologic based approaches to treatment of CSU; these include: i) registered biologic therapy e.g. Omalizumab; ii) off-licence exploratory use of available biologics targeting applicable pathways e.g. Canakinumab (IL-1 blockade); iii) clinical trials of new targeted biologic and small molecule drugs e.g. Ligelizumab (anti-IgE) or DP2 (CRTH2) receptor blockers e.g. Fevipiprant. A list of current and possible biologic therapies and their targeted pathway is provided in Table 1.

There are also some other interesting therapeutic targets under evaluation for novel drug approaches. Substance P (SP), a neuropeptide that binds mainly to neurokinin receptor 1 (NKR1), is a mast cell degranulator associated with itch and wheal formation. Recent case series show SP antagonists to have significant anti-pruritic effect in acute and chronic pruritus. DARPins (designed ankyrin repeat protein) are small oligonucleotides that exhibit highly specific and high affinity target protein binding; an IgE specific DARPin has been reported to bind IgE and suppress mast cell activation. Further details on these novel therapeutic approaches are available in an excellent recent review by Kocaturk and Zuberbier in 2018. The remainder of this review focuses on the use of omaluzimab, the only biologic registered for use in CSU in SA.

Table 1. Biologic therapies for CSU		
Drug	**Type of Drug**	**Pathway Target**
Registered in SA for CSU		
Omaluzimab	Humanized Anti-IgE	Suppression of free IgE, preventing Basophil degranulation.
Active in clinical trials for CSU/CIndU		
Ligelizumab	Humanized Anti-IgE (binds Cε3 domain of IgE)	Suppression of free IgE, preventing degranulation of Basophils.
Quilizumab	Humanized Anti-IgE (binds M1 prime segment of membrane expressed IgE on IgE-switched B cells/plasmablasts)	Suppression of free IgE, preventing degranulation of Basophils.
Canakinumab (or Rilonacept)	Humanized Anti-IL1	Suppression of Interleukin 1 beta, preventing innate inflammation.
Future biologics to consider in CSU		
Rituximab	Chimeric Anti-CD20	Antibody producing Memory B-lymphocytes depletion.
Adalimumab (or Infliximab or Etanercept)	Anti-TNF alpha	Suppression of TNF alpha, preventing inflammation.
Eculizumab	Humanized anti-C5 inhibitor	Suppression of complement, preventing inflammation.
Natalizumab (or vedolizumab)	Adhesion molecule inhibitor (alpha-4 integrin)	Inhibits cellular adhesion molecules, preventing a sustained late phase of CSU.
Benralizumab (or Mepolizumab, Reslizumab)	Anti-IL-5	Inhibits eosinophil activation and downstream inflammation
Dupilumab	Anti-IL-4	Reduction of IgE production

Abbreviations: IgE - Immunoglobulin E; CD20 - Cluster Differentiation 20; IL - Interleukin; TNF alpha - Tumor Necrosis Factor alpha; CSU - Chronic spontaneous urticaria; SA - South Africa; HUS - Hemolytic uremic syndrome; PNH - paroxysmal nocturnal hemoglobinuria; CIndU - Chronic inducible urticaria.

The when, how much and how long of omalizumab

Omaluzimab is a recombinant humanized anti-IgE monoclonal antibody licensed to Novartis, and registered in 2015 for use in South African CSU patients. Omalizumab targets the C3 domain of the Fc region of IgE, reducing levels of free IgE by sequestration. Postulated mechanisms include: raising degranulation thresholds of mast cells and basophils; reducing pro-inflammatory mediator release and cell recruitment e.g. eosinophils; and reducing free IgE; see Chang et al for a detailed report on proposed mechanisms of action [10].

The evidence-base for the use of omalizumab in patients with antihistamine refractory CSU is high quality, with a series of randomized, placebo-controlled, multicenter studies including proof-of-concept study X-CUSITE, phase II study MYSTIQUE, and then three pivotal phase III studies ASTERIA I, ASTERIA II, and GLACIAL [11]. In all studies, omalizumab provided rapid and sustained improvement in symptoms of CSU, with the studies meeting all primary and secondary efficacy endpoints at week 12 and exploratory efficacy endpoints at week 24 in ASTERIA I and GLACIAL (300mg dose only) – end points included itch severity score, urticaria activity score 7 (UAS7), and the dermatology life quality index.

Three doses (75mg, 150mg and 300mg) administered subcutaneously every 4 weeks were studied, with only the 300mg dose meeting all efficacy end-points across all the studies. Notably, only the GLACIAL study enrolled patients with CSU refractory to high dose antihistamines and adjunctive therapies e.g. H2-antagonists and LRTA, thus more closely resembling difficult-to-control patients in clinical practice [11]. Omalizumab is safe; across allergic asthma and CSU programs there is an estimated 5890 patient treatment years with very few adverse effects. Common minor side-effects include headache, arthralgia, injection site reactions and upper respiratory tract infections [11]. Importantly, the safety profile is better than the only other guideline recommended step 3 treatment – cyclosporine A. Real-life efficacy studies suggest that omalizumab is effective in between 60-80% of CSU patients. Studies are ongoing for CIndU and other unusual conditions such as urticarial vasculitis [11].

Considerable interest is now focused on early identification of biomarkers that predict responses to omalizumab; as well as variables to predict relapse following discontinuation of omalizumab after 24 weeks. Regression models applied to the three phase III RCTs indicate that higher baseline disease severity (as measured by UAS7) and slower response to therapy (low UAS7 area above the curve, AAC determined by plotting the UAS7 scores across time-points) predicted relapse [12]. Promising proposed biomarkers of poor treatment response include: i) low pre-treatment levels of FCεR1 expression on basophils [13]; ii) lower D-dimer levels [14]; and iii) lower pre-treatment total IgE, and perhaps more importantly limited increase in total IgE at week 4 after treatment initiation [15]. There remains an urgent need for easily accessible biomarkers to predict treatment response to anti-IgE therapy.

Prescribing in the South African context

Omalizumab is registered and available to patients, with a monthly cost for 300mg of ~R10 000. CSU is unfortunately not a prescribed minimum benefit condition meaning that with such a high price tag, many medical schemes continue to decline funding motivations. Fortunately, certain schemes have put in place funding policies of omalizumab in CSU that include: i) refractory to second-line guideline therapy (high dose antihistamines), ii) UAS7≥16 and iii) Dermatology quality of life index score >=11. In addition, specialist allergy centres have successfully motivated in the public sector for omalizumab on a named patient basis indicating that this is guideline-driven standard of care for CSU patients.

Patient advocacy around the severe morbidity of CSU, continued efforts for price reductions from Novartis, and ongoing motivation by allergy specialist and centres of excellence to

individual schemes is required to ensure that our CSU patients are able to access this and other future targeted therapies. Finally, three centres in SA have been identified as clinical trial sites for the next generation anti-IgE therapy – Ligelizumab (see table 1), and this remains a method for severe patients to access biologic treatments.

Conclusion

An estimated one in five people will experience urticaria in their lifetime; it is a debilitating symptom. Chronic spontaneous urticaria carries serious morbidity, impact on quality of life and indirect costs. The condition has a complex etiopathogenesis that we are slowly unraveling; and our improved understanding together with an exploding array of immune targeting biologics heralds a new hope for diverse treatments. A robust evidence-base supports the efficacy and safety of omalizumab, and it is being accessed for CSU patients in SA. Allergy and Dermatology specialists should be encouraged and feel comfortable to prescribe omalizumab, especially given the support available for its use. However, ongoing efforts are required to raise CSU awareness, and continue to encourage lower prices and wider access through private and public health funders.

References

1. Terhorst D, Koti I, Krause K**. In chronic spontaneous urticaria, high numbers of dermal endothelial cells, but not mast cells, are linked to recurrent angioedema.** Clin Exp Dermatol. 2018 Mar;43(2):131-136. DOI: 10.1111/ced.13254.

2. Zuberbier T, Asero R, Bindslev-Jensen C et al. **EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria.** Allergy. 2009 Oct;64(10):1417-1426. DOI:10.1111/j.1398-9995.2009.02179.x.

3. Webster L, Rider NL, Archambault ME. **Evaluating and managing chronic idiopathic urticaria in adults.** JAAPA. 2018 Jul;31(7):22-26. DOI:10.1097/01.JAA.0000534976.46365.11.

4. Kolkhir P, Church MK, Weller K et al. **Autoimmune chronic spontaneous urticaria: What we know and what we do not know.** J Allergy Clin Immunol. 2017 Jun;139(6):1772-1781.e1. DOI: 10.1016/j.jaci.2016.08.050.

5. Asero R, Tedeschi A, Marzano AV et al. **Chronic urticaria: a focus on pathogenesis.** F1000Res. 2017 Jul 11;6:1095. DOI: 10.12688/f1000research.11546.1.

6. Yanase Y, Takahagi S, Hide M. **Chronic spontaneous urticaria and the extrinsic coagulation system.** Allergol Int. 2018 Apr;67(2):191-194. DOI: 10.1016/j.alit.2017.09.003.

7. Zuberbier T, Aberer W, Asero R et al. **The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria.** Allergy. 2018 Jul;73(7):1393-1414. DOI: 10.1111/all.13397.

8. Zheleznov S, Urzhumtseva G, Petrova N et al. **Gastritis Can Cause and Trigger Chronic Spontaneous Urticaria Independent of the Presence of Helicobacter pylori.** Int Arch Allergy Immunol. 2018;175(4):246-251. DOI: 10.1159/000487669.

9. Kocatürk E, Zuberbier T. **New biologics in the treatment of urticaria.** Curr Opin Allergy Clin Immunol. 2018 Jul 13. DOI: 10.1097/ACI.0000000000000466.

10. Chang TW, Chen C, Lin CJ et al. **The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria.** J Allergy Clin Immunol. 2015 Feb;135(2):337-342. DOI: 10.1016/j.jaci.2014.04.036.

11. Zuberbier T, Maurer M. **Omalizumab for the treatment of chronic urticaria.** Expert Rev Clin Immunol. 2015 Feb;11(2):171-180. DOI: 10.1586/1744666X.2015.993971.

12. Marta Ferrer. **Immunological events in Chronic Spontaneous Urticaria**. Clin Transl Allergy (2015) 5:30. DOI 10.1186/s13601-015-0074-7.

13. Deza G, Bertolin Colilla M, Pujol RM. **Basophil FCeRI expression in chronic spontaneous urticaria: A potential immunological predictor of response to Omaluzimab**

therapy. Acta Derm Venereol. 2017 Jun 9;97(6):698-704. DOI: 10.2340/00015555-2654.

14. Cugno M, Genovese G, Ferrucci S et al. **IgE and D-dimer baseline levels are higher in responders than nonresponders to omalizumab in chronic spontaneous urticaria.** Br J Dermatol. 2018 Mar 27. DOI: 10.1111/bjd.16593.

15. Ertas R, Ozyurt K, Atasoy M. **The clinical response to omaluzimab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change**. Allergy. 2018 Mar;73(3):705-712. DOI: 10.1111/all.13345.

Figure 1. Intersecting components underlying CSU pathophysiology

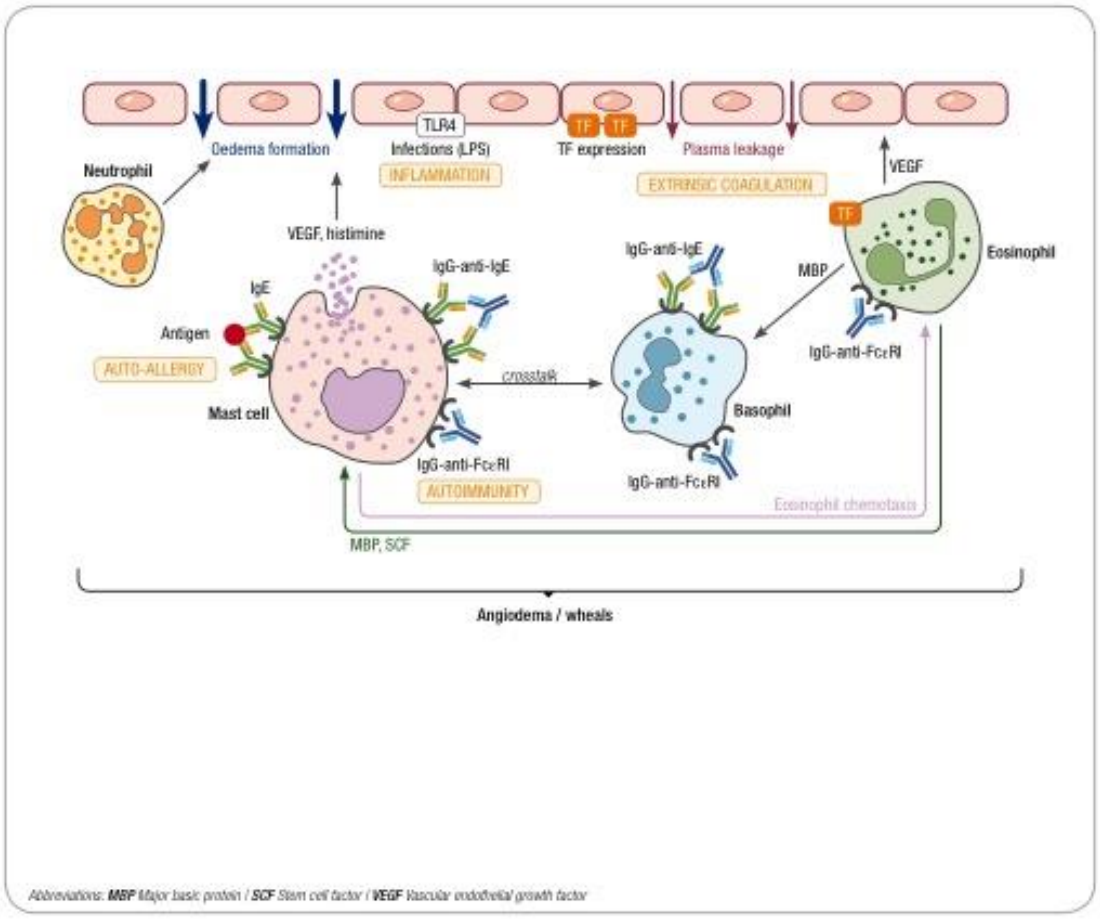

Figure Legend

Mast cells, basophil and eosinophils are the effector immune cells involve in CSU pathology. Current understand groups four major upstream contributors to mast cell degranulation, basopenia, and eosinophilic activation. These are: i) auto-allergy – IgE antibodies directed against cutaneous autoantigens (>200), such as IL-24 (Schmetzer et al., 2017); ii) auto-immunity – IgG antibodies directed against IgE and FCεR1; iii) inflammation – elevated cytokines e.g. IL-6 & TNF-α or inflammatory molecules e.g. lipocalin-1 are produced in response to either metabolic or infective stimuli and lead to endothelial activation and signaling through innate pattern recognition receptors e.g. TLR4; iv) coagulation – activation of the extrinsic coagulation cascade predominantly via increased TF expression on activated eosinophils with downstream signaling through protease-activated receptors (PARs). These mechanisms are suggested to work synergistically to differing extents in individuals.