Review Article

Biologicals in Treatment of Chronic Urticaria: A Narrative Review

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Abstract

Chronic urticaria is a common inflammatory skin disease affecting around 0.5–1% of the world's population. The disease has a chronic indolent course which significantly affects the patient's quality of life. Urticaria pathogenesis involves cross-linking of immunoglobulin E (IgE) on mast cells causing degranulation which occurs by various pathways which leads to development of wheals and angioedema. The first-line treatment for chronic urticaria is non-sedating second-generation H1 antihistamines (AHs). After the advent of anti-IgE monoclonal antibody omalizumab, the response rate in resistant urticaria has improved significantly without any major adverse events. Other biologicals such as anti-IgE, anti-IL-5, anti-IL-1, anti-IL-17, and anti-CD20 monoclonal antibodies are under trial. These biologicals have better efficacy and safety profile as compared to conventional immunosuppressants. Even with the advances in the last decade, recurrence after stopping the therapy is common, and there is a need for better understanding of the pathogenesis and the drugs acting on the key pathways involved in urticaria. In this review, we provide the role of several biologicals in the treatment of chronic urticaria.

Keywords: *Biologicals, chronic urticarial, novel biologics, omalizumab, resistant urticaria*

Introduction

Urticaria is a common skin disease affecting up to 20% of world's population during lifetime, presents as itchy transient wheals lasting for minutes to hours.[1] In contrast, angioedema presents as painful swelling of lips, eyelids, tongue, pharynx, larynx, hands, feet, and genitals due to edema in dermis, submucosa, and subcutis lasting for 2–3 days. Acute urticaria is defined as urticaria episodes lasting for less than 6 weeks, episodic urticaria as urticaria episodes lasting for more than 6 weeks, but less than 2 episodes/week, and chronic urticaria as occurrence of at least 2 episodes of urticaria per week and lasting more than 6 weeks.[2] Chronic urticaria is further divided into chronic spontaneous urticaria (without specific stimulus, CSU) and chronic inducible urticaria (with specific stimulus, CIU). It significantly affects the quality of life, leading to sleep disturbances, decreased work efficiency, and social withdrawal. The 1-year, 3-year, and 5-year remission rates in CSU are 21%, 38%, and 45%, respectively.[3,4]

Pathogenesis

The key step in urticaria is complex immunological display after mast cell–basophil degranulation which can occur immunologically or nonimmunologically. Immunological activation can occur by type-I or type-IIa autoimmunity. Type-I autoimmunity is auto-allergen triggered, immunoglobulin E (IgE)-mediated mast cell degranulation involving cross-linking of IgE on mast cells and basophils. Type-IIa autoimmunity involves binding of IgG or IgM autoantibodies against IgE or FcεRI receptor on mast cell leading to degranulation.[5] Apart from FcεRI receptor, mast cell has many other surface receptors including C3a, C5a, toll-like receptor, cytokine, and chemokine receptors, and further activation of these receptors by their ligands can also lead to mast cell degranulation. In nonimmunological activation, drugs like codeine, food molecule, and neuropeptides such as substance *P* cause direct toxicity on the mast cells leading to degranulation.[4] Mast cell degranulation by above two mechanisms lead to cascade of immunological milieu starting with release of histamine which acts on H1 receptor on blood vessels leading to vasodilation and increases vascular permeability resulting in wheals and itching. Apart from histamine, mast cells also releases interleukin 5 (IL-5)

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and TNF-α, which also have a role to play in urticaria pathogenesis.[6]

Management

The first line of treatment for chronic urticaria is second-generation nonsedating antihistamines (AHs). The European Academy of Allergy and Clinical Immunology (EAACI/2021) recommends to increase the dose of AHs up to 4 times if there is unsatisfactory response after 2–4 weeks of standard doses of second-generation AHs. If there is no further improvement after 2–4 weeks of increasing the dose, omalizumab (up to 600 mg q2w) or ciclosporin (up to 5 mg/kg/day) can be added.[7]

Biologicals are large complex glycoproteins derived from living organisms such as microorganisms, humans, plants, or animals. Monoclonal antibodies (mAbs) are biologicals that target the specific antigen or epitope. The use of biologicals has revolutionized the management of chronic resistant urticaria (CRU) and are often preferred in CSU resistant to other treatment options. Omalizumab and ligelizumab are commonly used biologicals in urticaria because of their better efficacy and safety profile.

Biologicals in the Treatment of Chronic Urticaria

Anti-IgE therapy

Omalizumab

Omalizumab is a recombinant humanized IgG mAb that binds to C epsilon 3 (Cε3) domain of IgE.[8,9] It is the first US Food and Drug Administration (FDA)-approved biological in treatment of CSU. Autoantibodies in CSU patients bind to alpha-chain of high-affinity receptor FcεRI or to IgE leading to mast cell degranulation.[10,11] Omalizumab binds to free IgE, leading to decrease in free IgE and block the binding of IgE to FcεRI receptors on mast cells, dendritic cells, and basophils.[12,13] It also reduces mast cell degranulation by increasing the threshold of degranulation, reverses the basopenia, and improves basophil IgE receptor function.[14-16] It reduces IgG autoantibody activity against FcεRI and IgE and reduces IgE autoantibody activity against auto-allergen. The mechanism of omalizumab is summarized in Figure 1.

Efficacy

Phase II–IV clinical trials have demonstrated the efficacy of omalizumab among CSU patients who failed to respond to AHs. The complete response rate ranged from 34% to 70%.[17-21] The initial report on omalizumab efficacy in CSU came as early as in 2002.[22] The first prospective trial included 12 patients with chronic autoimmune urticaria resistant to AHs for at least 6 weeks. At week 16, there was a significant reduction in urticaria activity score (UAS) (7.5 ± 1.8 to 2.7 ± 3.3, −4.8 ± 2.9, $P = 0.0002$) and seven (58.3%) patients achieved complete remission.[23] The efficacy was confirmed in subsequent studies.[24-26] A meta-analysis of 67 studies on omalizumab with AHs has shown complete and partial response rates of 72.2% and 17.8%, respectively.[27] The summary of the important RCTs on omalizumab in CSU is given in Table 1. The

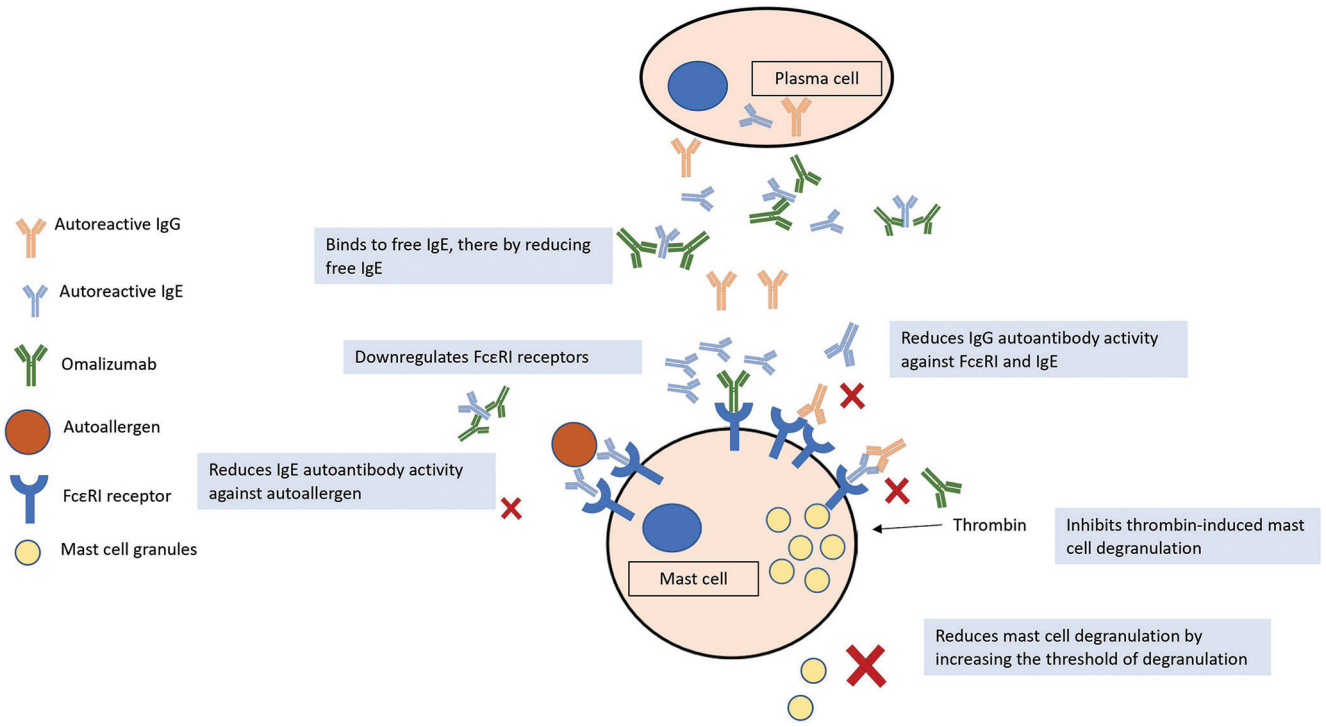

Figure 1: Mechanism of omalizumab in urticaria. FcεRI, high-affinity IgE receptor; IgE, immunoglobulin E; IgG, immunoglobulin G

Table 1: Summary of the major RCTs on omalizumab

Study	Sample size	Study design	Results	Conclusion
Maurer *et al*.[19]	323	RCT	Mean (SD)	Omalizumab is safe and effective in AHs-resistant CSU
		4 groups:	ΔWIS baseline to week 12	
		Placebo, 75 mg, 150 mg, and 300 mg omalizumab	Placebo: −5.1 (5.6)	
			75 mg omalizumab: −5.9 (6.5)	
			150 mg omalizumab: −8.1 (6.4)	
			300 mg omalizumab: −9.8 (6)	
Kaplan *et al*.[18]	336	RCT	Mean (95% confidence interval)	
		2 groups:	ΔWIS baseline to week 12	
		Placebo and 300 mg omalizumab	Placebo: −4.0	
			300 mg omalizumab: −8.6	
Saini *et al*.[30]	319	RCT	mean (SD)	
		4 groups:	ΔWIS baseline to week 12	
		Placebo, 75 mg, 150 mg, and 300 mg omalizumab	Placebo: −3.6 (5.2)	
			75 mg omalizumab: −6.4 (6.1)	
			150 mg omalizumab: −6.6 (6.2)	
			300 mg omalizumab: −9.4 (5.7)	

SD, Standard deviation; RCT, randomized control trial; ΔWIS, change in weekly itch score; AHs; antihistamines

relapse rates are high, seen in up to 61% of the patients.[28] Most of the adverse effects are benign which include upper respiratory tract infection, headache, injection-site inflammation, and rarely anaphylaxis.[29] Based on three good-quality RCTs on 733 patients, FDA has approved omalizumab at doses of 150 mg or 300 mg every 4 weeks.[18,19,30] A systematic review has shown promising results of omalizumab in cold urticaria, symptomatic dermographism, and solar urticaria.[18] In an open-label study by Chen *et al*.[31] in 23 normocomplementemic urticarial vasculitis patients, 17.3% and 56.5% had a complete and partial response, respectively. Apart from the CSU, inducible urticaria, and urticarial vasculitis, omalizumab is also effective in angioedema.[32,33]

Types of Responders

The onset of response to omalizumab in CSU patients varies, based on the onset of response, patients are divided into early responders (<1 week), late responders (>12 weeks), and nonresponders.[34] Patients with negative autoimmune serum skin test (ASST), normal-to-high IgE, and high expression of FcεRI respond early (<1 week) and patients with positive ASST, positive basophil histamine release assay, low IgE, and lower expression of FcεRI respond late (>12 weeks).

Dose and Frequency in Nonresponders

Factors predicting the response to omalizumab are summarized in Table 2. Patients with low IgE, positive ASST, basopenia, eosinopenia, low expression of FcεRI on basophils, IgG autoantibodies against FcεRI, and positive basophil activation test are associated with poor prognosis. Around 30% of patients fail to respond to standard regimen requiring a higher dose or increasing the frequency of administration. The dose can be increased from 450[35-37] to 600[38,39] mg every 4 weeks or the frequency can be increased to 300 mg to 600[40] mg every 2 weeks. Curto-Barredo *et al*.[39] used 300-mg omalizumab every 4 weeks; if insufficient response after five doses, updosing was done to either 450 mg or 600 mg q4w. If insufficient response after three doses of 600 mg, frequency was increased to every 2 weeks for two consecutive doses. A total of 286 patients on 300 mg were included, 27.6% required updosing (UAS >7). Among these, 65% had successful updosing (55% in 450 mg q4w and 25% in 600 mg q4w) and 25% had no improvement even at higher doses. Predictors of the poor responses were obesity, age >57, past treatment with cyclosporine. Changing from

Table 2: Prognostic markers for response to omalizumab in urticaria

Poor prognosis	Good prognosis
Eosinopenia (<50 cells/mL)[41]	Normal or high IgE
Basopenia (<10 cells/mL)[41]	High d-dimer[49]
Low IgE[42]	Very high expression of FcεRI on basophils
Positive basophil activation test[43]	Negative ASST
Positive CD63[44]	Negative basophil activation test
IgG autoantibodies against FcεRI[44]	
Lower expression of FcεRI on basophils[45]	
Positive ASST[43,46]	
High CRP >3 mg/mL[47]	
Low ratio of 4th-week IgE to baseline IgE[48]	

CRP, C-reactive protein; ASST, autologous serum skin test; IgE, immunoglobulin E

300 mg q4w to 150 mg q2w is also effective.[28] If no improvement is seen even after 6 months of omalizumab, it can be stopped.

Duration of Treatment and Tapering

There is no standard duration of therapy or standard method of weaning recommended by EAACI, it can be done as soon as remission is achieved. Possible methods are decreasing the frequency of administration or reducing the doses. Injection interval can be increased by 1 week (q5w) to 4 weeks (q8w) if urticaria is controlled. It can be stopped if it is controlled by q8w for 8 weeks and tapering [Figure 2].[50,51] After post-withdrawal relapse, retreatment with omalizumab can be done and is not associated with reduced efficacy but requires more number of doses (4–6) in some patients. During entire course of omalizumab, AHs will be continued.

Omalizumab in Children

There is paucity of controlled studies among children, but it is safe and effective.[52] Omalizumab dose in children ranges from 150 mg q4w to 300 mg q2w. RCTs are needed in children and adolescents.

Omalizumab in Pregnancy

Omalizumab crosses the placenta, but only a small amount (0.001–0.0001%) of omalizumab in the maternal serum is secreted into breast milk.[53] But no significant adverse effects are noted and FDA has categorized it as pregnancy category B. European Medicines Agency (EMA) has stated that omalizumab might be considered for use in pregnancy.[54]

Omalizumab and Risk of Malignancy

Allergies and serum IgE are associated with a reduced risk of malignancy.[55] Long-term omalizumab and other anti-IgE

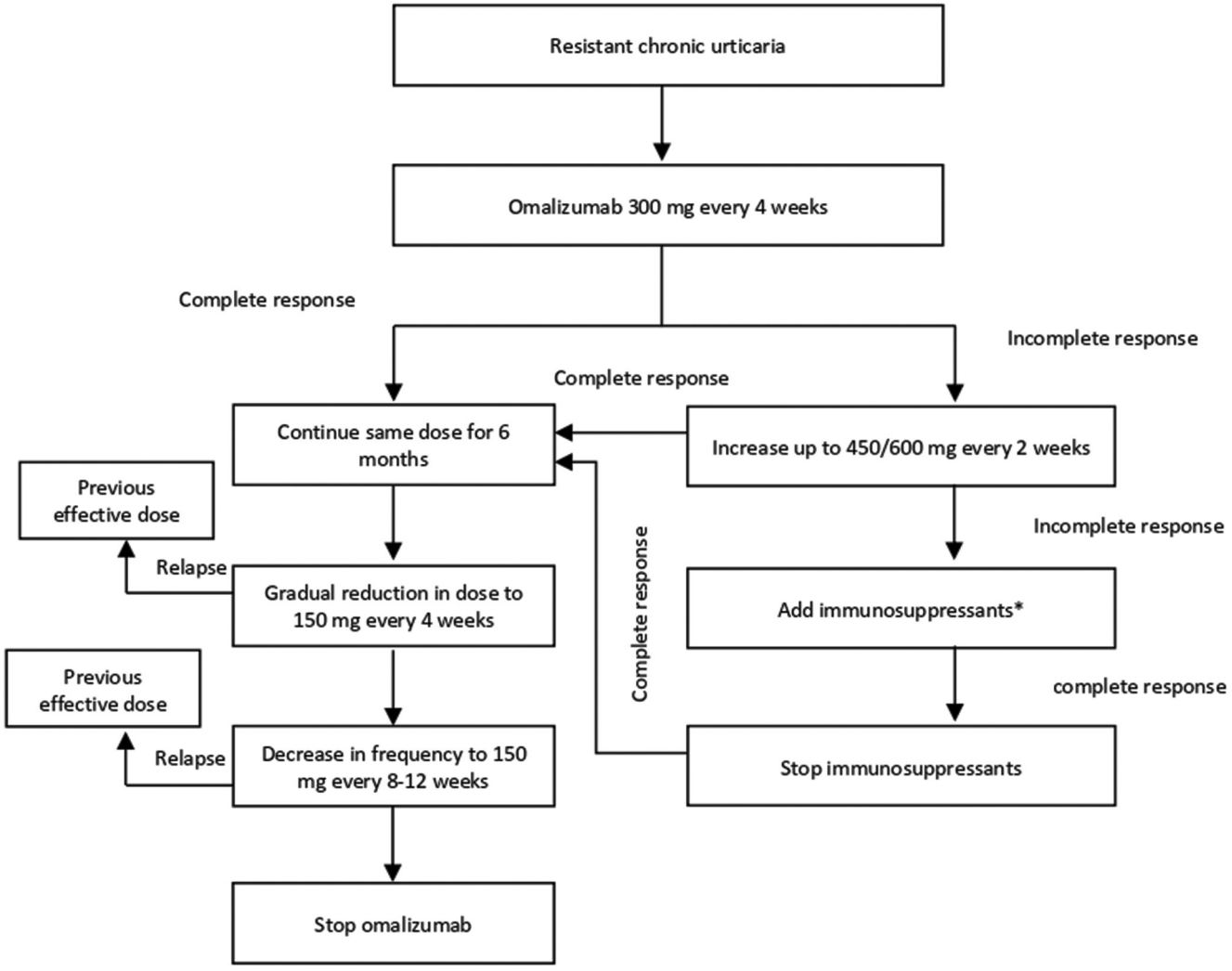

Figure 2: Tapering of omalizumab. *Treatment options include cyclosporine, methotrexate, and cyclophosphamide. A short course (less than 1 week) of oral steroids can be considered for severe exacerbation

treatment may disrupt this protective antitumor mechanism and increase the risk of malignancy. But systematic review and meta-analysis found no increased risk of cancer on long-term use.[56]

Omalizumab in Elderly

Not much data is available in the elderly >65 years, the dose is similar to young adults.[57]

Ligelizumab

It is recombinant humanized anti-IgE mAb which has similar mechanism of action to omalizumab and has 40–50 times higher affinity to IgE receptor than the omalizumab. The complete response rate range from 30% to 50%.[58,59] Maurer *et al*.[58] in a phase IIb RCT on 382 patients demonstrated ligelizumab to have rapid onset of action, better efficacy, and longer relapse time after discontinuation than omalizumab with similar safety profile. The complete control of symptoms in ligelizumab 24 mg, 72 mg, and 240 mg group were 30%, 44%, and 40%, respectively, as compared to 26% in omalizumab. Recently, FDA has approved ligelizumab in the management of CSU who have an inadequate response to H1 AHs, but ligelizumab in angioedema has shown inconsistent results.[58] Currently, phase III studies are under trial in patients with CSU, once cleared can be a boon for CRU.

Quilizumab

It is an afucosylated humanized IgG mAb against M1-prime segment of membrane-bound IgE on B cells. In contrast to omalizumab, it only binds to bound IgE but not free IgE. Harris *et al*.[60] in RCT has found no improvement in weekly severity itch score or UAS at the end of 20 weeks, but there was a decrease in serum IgE level by 30%. There is no evidence of quilizumab role in angioedema.

UB-221

It is a humanized IgG mAb with similar mechanism of action to omalizumab, has eightfold higher affinity to FcεRI than omalizumab, and also binds to CD23-bound IgE. In preclinical studies, UB-221 was better than omalizumab and phase-I trials are currently under investigation.

Anti-interleukin 5

IL-5 is involved in the eosinophil development, migration, and activation.[61] Eosinophils numbers are increased in urticarial lesions which cause activation of coagulation cascade and subsequently cause mast cell degranulation.[62] Mepolizumab and reslizumab are IL-5 inhibitors, and benralizumab inhibits IL-5 receptor (IL-5Rα) present on eosinophils. In a single-blinded, repeated-measures study, Bernstein *et al*. treated 12 resistant CSU with benralizumab, 5 patients had complete remission (UAS = 0).[63,64] Mepolizumab and reslizumab also have been found to be effective in case reports.[65,66]

TNF-α Inhibitors

TNF-α is one of the important preformed mediators of urticaria present in the mast cells. Interestingly TNF-α is upregulated in both lesional and nonlesional skin. Anti-TNF-α agents bind to soluble and transmembrane TNF-α and inhibit its activity. Sand *et al*.[67] reported that treatment with adalimumab (n = 14) and etanercept (n = 4) in 18 patients with CSU had led to complete remission in 12 and partial remission in 3 patients. Another case series by Bangsgaard *et al*.[68] of nine patients with CSU treatment with adalimumab had led to complete remission in three and partial remission in four. Currently, TNF-α can be considered in CSU resistant to anti-IgE therapy.[68]

Anti-CD20

Rituximab is a mAb against CD20 which depletes memory B cells by antibody-dependent and complement-dependent cellular cytotoxicity, apoptosis, and antibody-dependent phagocytosis, which subsequently cause a reduction in the autoantibodies. The dose of rituximab is 375 mg/m^2 or 1 gm 2 weeks apart. Rituximab has been tried in five case reports in the literature, four patients had complete remission, and one patient did not respond.[69-73] Because of the risk of serious adverse effects, currently rituximab can be considered only in severe CSU resistant to other treatment options.

Anti-IL-1

IL-1 is implicated in the development of urticaria in Schnitzler syndrome, Muckle–Wells syndrome, and other autoinflammatory syndromes. Canakinumab is an IL-1β inhibitor, in an open-label study by Krause *et al*.[74] in 10 patients with urticarial vasculitis, 70% of the patients had >50% improvement. A double-blinded RCT by Maul *et al*.[75] in 20 patients showed no significant difference as compared to placebo. Anakinra is an IL-1 receptor antagonist and is effective in cold urticaria and refractory delayed pressure urticaria in individual patients.[76,77] Rilonacept is a recombinant IL-1 antagonist which binds to IL-1β and blocks binding of IL-1 with its receptor. A phase-II placebo-controlled study is undergoing on cold contact urticaria (NCT02171416).

Bruton Tyrosine Kinase Inhibitors

Bruton tyrosine kinase (BTK) is an important protein of the downstream signaling pathway of FcεRI and B-cell receptor. Fenebrutinib binds to BTK noncovalently and inhibits BTK leading to inhibition of the FcεRI signaling pathway. In a phase-II RCT in 93 patients, fenebrutinib at a dose of 150 mg and 200 mg showed a significant reduction in UAS7 and no significant difference in adverse events as compared to placebo.[78] In contrast to fenebrutinib, remibrutinib binds to BTK covalently; hence, it has faster onset of action and long-lasting inhibition.[79] There is an ongoing phase-II trial on remibrutinib (NCT03926611, NCT04109313) in resistant CSU.

Dupilumab

CSU is a Th2 (T-helper 2 cells)-mediated disease with elevated IL-4 and IL-13. Dupilumab is a human mAb that binds to the alpha subunit of IL-4 receptor (IL-4Rα) and blocks IL-4 and IL-13 action. Dupilumab has shown significant improvement in six patients with omalizumab-resistant CSU.[80] There are ongoing phase-II and phase-III clinical trials (NCT03749148, NCT03749135) assessing the safety and efficacy of dupilumab in resistant CSU.

Anti-IL-17

There is a dense infiltration of IL-17 expressing $CD4^+$ T cells and increased expression of IL-17A on mast cells in CSU patients. Secukinumab blocks IL-17 produced by mast cells. In a case series by Sabag *et al*.[81] on eight severe AHs and omalizumab-resistant CSU, secukinumab 150 mg q4w led to 55% and 82% reduction in UAS7 after 1 month and 3 months of therapy and significant improvement in angioedema in all patients.

Other Newer Biologics

Anti-siglec-8 therapy

Siglec-8 is a cell surface receptor present on the eosinophils and mast cells which is involved in the apoptosis of eosinophils and inhibition of FcεRI-mediated histamine release. Antolimab and lirentelimab are monoclonal anti-siglec-8 antibodies that deplete eosinophils and can be utilized as therapeutic options in CSU. In phase-IIa open-label study by Altrichter *et al*.,[82] lirentelimab has been found to be effective in both omalizumab naive and resistant spontaneous and inducible urticaria. The dose of lirentelimab was 0.3 mg/kg and gradually increased to 3 mg/kg every month if tolerated. The complete remission in omalizumab-naive, omalizumab-resistant, chronic inducible urticaria and symptomatic dermographism was 92%, 36%, 82%, and 40%, respectively. The common side effects included infusion reactions, nasopharyngitis, and headache. There is an ongoing phase-IIa clinical trial (NCT03436797) assessing the safety and efficacy of antolimab in resistant CSU.

Anti-IL-31

IL-31 is one of the mediators of Th2 response elevated in CSU. IL-31 is expressed on mast cells, eosinophils, macrophages, and basophils. It is one of the key mediators of itch in urticaria, atopic dermatitis, psoriasis, and prurigo nodularis. The levels of IL-31 are significantly elevated in CSU patients as compared to psoriasis and healthy individuals. Nemolizumab can be another treatment alternative for CSU.[83]

Anti-oncostatin M receptor

Oncostatin M receptor (OSMR) is upregulated in chronic autoimmune urticaria and inhibition of OSMR leads to a decrease in inflammatory factors (IgE, IL-1, IL-6, and IFN-γ) and eosinophils. Vixarelimab is a mAb against oncostatin M receptor beta (OSMRβ) which mediates the IL-31-signaling pathway and might be a treatment option in CSU.[84] Currently, there is an ongoing phase-II trial on vixarelimab (NCT03858634) in chronic urticaria including CSU.

Anti-C5a

Complement 5a (C5a) is a complement agonist that enhances IgG-mediated mast cell degranulation and basophil-mediated inflammation. Eculizumab is a mAb against C5a and has been used in the treatment of paroxysmal nocturnal hemoglobinuria and asthma. Avdoralimab is mAb against C5a receptor, currently under investigation in the treatment of bullous pemphigoid. Avacopan is a small-molecule against C5a used in antineutrophilic cytoplasmic antibody associated vasculitis. Anti-C5a therapy can be future treatment option in CSU.[85]

Anti-KIT antibodies

Mast cells are the key cells involved in the pathogenesis of urticaria. KIT is a cell surface receptor present on mast cells. Stem cell factor is a ligand for this receptor, a potent activator of mast cells. Treatment with anti-KIT antibody CDX-0159, a mast cell depletor leads to significant reduction in the mast cells and tryptase without any major side effects.[86] In an open-label study by Molawi *et al*.[87] in chronic inducible urticaria, single dose of intravenous CDX-0159 led to significant improvement in UAS and response was maintained at the end of 12 weeks.

Spleen tyrosine kinase inhibitors

Spleen tyrosine kinase (SYK) is a protein-tyrosine kinase involved in allergen-mediated mast cell degranulation through IgE-signaling pathway. In an phase-Ia/Ib randomized double-blind placebo-controlled study by Disckson *et al*.,[88] treatment with GSK2646264 (topical inhibitor of SYK) has led to significant reduction in critical temperature threshold of cold urticaria as compared to placebo. Due to the small number of patients with CSU, no conclusion was drawn on the same. There were no serious adverse effects or dose-limiting toxicity noted.

CRTh2 inhibitors

CRTh2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) is a surface receptor present on eosinophils and basophils and is involved in eosinophil chemotaxis and degranulation. AZD1981 is an oral reversible antagonist of CRTh2 which inhibits prostaglandin D2 (PGD2)-mediated eosinophil shape alteration, chemotaxis, and degranulation. In a randomized, placebo-controlled study by Oliver *et al*.[89] on 28 patients of AH-resistant CSU, treatment with AZD1981 led to significant reduction in UAS and itch score compared to placebo in resistant CSU. There was also increase in

the circulating eosinophils due to altered recruitment of eosinophils into skin. AZD1981 was well tolerated without any major side effects. The improvement of urticaria with CRTh2 inhibitor, AZD1981, supports the role of PGD2/CRTh2 pathway in the pathogenesis of urticaria.

Designed ankyrin repeat protein

DARPins (designed ankyrin repeat protein) are antibodies that have high specific and high-affinity binding property. IgE-specific DARPins bind to IgE and cause unbinding of IgE from its receptor, which inhibits mast cell degranulation. DARPins can be potential therapeutic options in the management of FcεRI-induced allergic reactions. The major limitations of DARPins are immunogenicity and increased risk of parasitic infections.[90]

Anti-IL-6

IL-6 is elevated in CSU making IL-6 receptor antagonist tocilizumab, a potential alternative for CSU. In a case report by Makol *et al*.[91] treatment with tocilizumab led to significant improvement in lupus-associated urticarial vasculitis which was resistant to methotrexate, anakinra, etanercept, and intravenous immunoglobulin therapy. Apart from urticarial vasculitis, there was significant improvement in arthritis, cutaneous lesions, and fever.

MRGPRX2 inhibitors

MRGPRX2 is a cell surface receptor present on mast cells, eosinophils, and basophils and activation of MRGPRX2 leads to mast cell degranulation independent of IgE. MRGPRX2 levels are significantly elevated in CSU. MRGPRX2 inhibitors directly inhibit the receptor and downstream signaling pathway and could be a future target in the treatment of urticaria.[92]

Neurokinin receptor antagonists, aprepitant, and tradipitant are under investigation for pruritus, which can be a potential alternative for CSU.[93] Thymic stromal lymphopoietin (TSLP) is a Th2 response promoter which is elevated in CSU; TSLP inhibitor tezepelumab could be future treatment option in CSU.[86] Natalizumab is a cell adhesion inhibitor that inhibits α_4-integrin and endothelial activation and can be future therapeutic option. Vedolizumab is mAb against $\alpha_4\beta_7$ integrin which inhibits release of proinflammatory meditators from blood monocytes and also inhibits endothelial activation.[94] Although most have been utilized in urticaria management, still larger studies are required to assess the efficacy and safety profile. The emerging biologicals for urticaria are summarized in Tables 3 and 4 and Figure 3.

Conclusion

Chronic urticaria is significantly associated with poor quality of life and forms a major cause of economic burden for those who suffer with it for a long time. With the development of biologicals, management of AHs refractory urticaria has been eased with a good success rate in up to 80–90% patients. Omalizumab is the most commonly used biologic which is safe and effective, but less effective in autoimmune urticaria. Ligelizumab is a newer anti-IgE

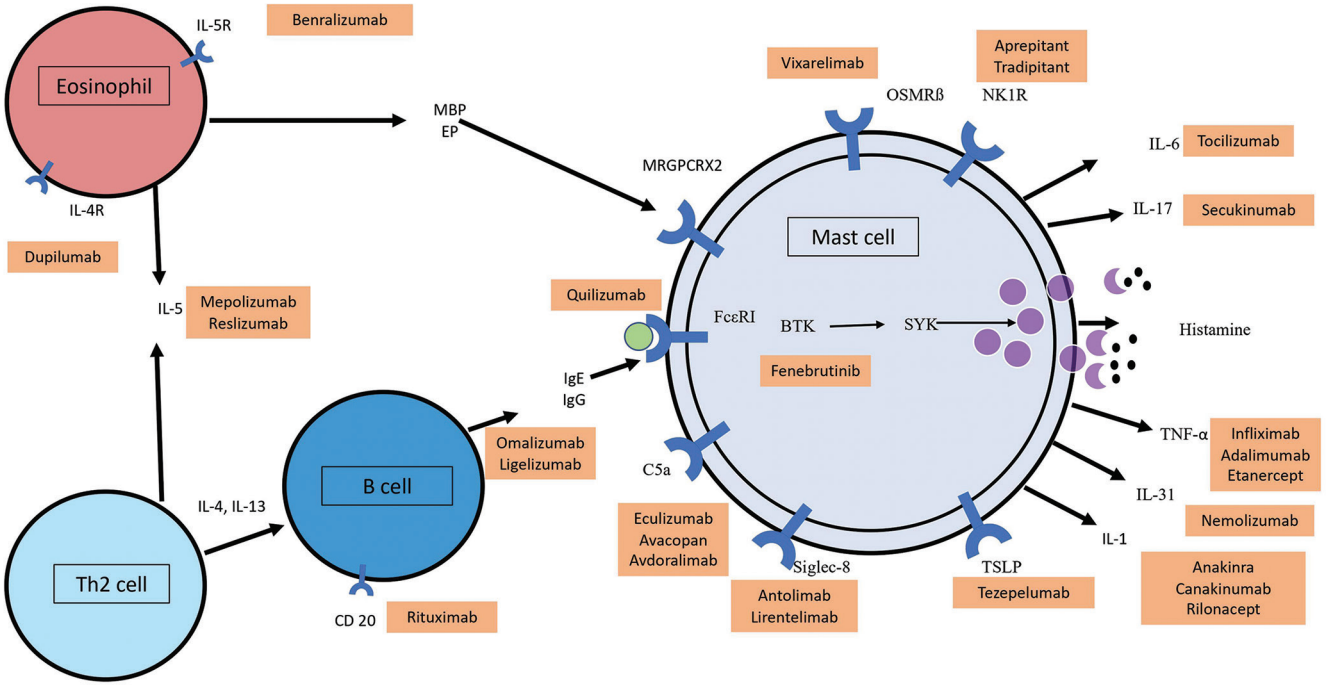

Figure 3: Biological targets in urticaria. BTK, Bruton tyrosine kinase; TNF-α, tumor necrosis factor-alpha; C5a, complement 5a; NK1R, neurokinin-1 receptor; SYK, spleen tyrosine kinase; EP, eosinophil peroxide; EBP, eosinophil binding protein; FcεRI: high-affinity IgE receptor; TSLP: thymic stromal lymphopoietin; IL-4R, IL-4 receptor; IL-5R, IL-5 receptor; MRGPCRX2, Mas-related G protein-coupled receptor X2

Table 3: Summary of the biologicals for urticaria

Biologic agent	Dosage	Mechanism	Onset of action	Adverse events
Anti-IgE therapy				
Omalizumab	US FDA approved: 150 or 300 mg Q4W Off label: 300 mg Q2W to 600 mg Q4W	Reduce free IgE and downregulates FcεRI receptor No effect on receptor-bound IgE	1–2 weeks	Headache, upper respiratory tract infection, black box warning for anaphylaxis
Ligelizumab	24 mg Q4W or 72 mg Q4W or 120 mg Q4W or 240 mg Q4W US FDA approved	Similar to omalizumab, has greater affinity to free IgE	1 week	Headache, upper respiratory tract infection
Quilizumab	450 mg Q4W	Binds to membrane-bound IgE at M1-prime segment No effect on free IgE	NA	Headache, arthralgia, and injection-site inflammation
UB-221	Dosing yet to be finalized	Similar to omalizumab	NA	
TNF-α inhibitors				
Infliximab	5 mg/kg IV over 2 hours Q8W	Inhibit TNF-α elevated in lesional and nonlesional skin	Within a month	Reactivation of tuberculosis and hepatitis B, neutropenia, leukopenia, injection-site reactions, demyelinating disease
Adalimumab	40 mg SC Q2W			
Etanercept	50 mg SC weekly			
Anti-IL-5				
Mepolizumab	100 mg SC Q4W	IL-5 inhibitor, no effect on eosinophil	Within a week	Headache, injection-site reaction, backache, fatigue
Reslizumab	3 mg/kg IV over 15–20 min Q4W	IL-5 inhibitor, no effect on eosinophil	Within days	Upper respiratory tract infection, headache, back pain
Benralizumab	30 mg SC Q4W	Inhibits IL-5Rα present on eosinophil	NA	Headache, fever
IL-1 inhibitors				
Anakinra	100 mg SC per day	Binds to interleukin-1 type I receptor and inhibits IL-1 action	1–2 days	Upper respiratory tract infection, headache, fever, and arthralgia
Canakinumab	150 mg SC Q4W	Bind to IL-1β and prevents its interaction with IL-1 receptor	NA	Upper respiratory tract infection and headache
Rilonacept	320 mg f/b 160 mg weekly	Binds to IL-1β and prevents interaction with its receptor	NA	Injection-site infection and upper respiratory tract infection
Bruton tyrosine kinase (BTK) inhibitors				
Fenebrutinib	150 mg or 200 mg PO per day	Inhibits BTK a crucial enzyme for FcεRI-mediated mast cell degranulation	Within a week	Upper respiratory tract infection, transaminitis, headache
Anti-IL-4 and IL-13				
Dupilumab	600 mg f/b 300 mg Q2W	Binds to IL-4Ra and inhibit IL-4 and IL-13-induced inflammation	Within 3 months	Injection-site reaction, conjunctivitis, upper respiratory tract infection
Anti-CD20				

Contd...

Table 3: Contd...

Biologic agent	Dosage	Mechanism	Onset of action	Adverse events
Rituximab	375 mg/m² BSA IV weekly for 4 weeks or 1 gm IV 2 weeks apart	B cell depletion by apoptosis, complement, and antibody-dependent cellular cytotoxicity, and antibody-dependent phagocytosis	1–6 weeks	Infusion reactions, Hepatitis B reactivation, bacterial infection (pneumonia, pyelonephritis), arrhythmia, PML, bowel perforation and obstruction, neutropenia
Anti-IL-17				
Secukinumab	150 mg weekly for 4 weeks f/b 150 mg Q2W	Inhibit IL-17 produced by activated mast cells	Slow onset	Headache, upper respiratory tract infection
Anti-siglec-8				
Lirentelimab	0.3-3 mg/kg IV every 4 weeks	monoclonal anti-siglec-8 antibody which depletes eosinophils	3-5 months	Infusion-related reaction, nasopharyngitis, and headache

US FDA, United States Food and Drug Administration; TNF-α, tumor necrosis factor-alpha; PML, progressive multifocal leukoencephalopathy; BTK, Bruton tyrosine kinase; IL1RI, interleukin 1 receptor, type I; IgE, immunoglobulin E

Table 4: Future targets for chronic spontaneous urticaria

Drugs	Mechanism of action
Antolimab and lirentelimab	Monoclonal anti-siglec-8 antibodies which deplete eosinophils
Nemolizumab	Monoclonal antibody against IL-31, one of the key mediators in the pathogenesis of urticaria
Vixarelimab	Monoclonal antibody against OSMRβ which mediates the IL-31 signaling pathway
Eculizumab and avdoralimab	Monoclonal antibody against C5a and C5a receptor, respectively
Avacopan	Small-molecule against C5a
CDX-0159	Anti-KIT antibody
GSK2646264	Spleen tyrosine kinase inhibitor
AZD1981	Reversible antagonist of CRTh2
DARPins	Bind to IgE and cause unbinding of IgE from its receptor, which inhibits mast cell degranulation
Tocilizumab	Monoclonal antibody against IL-6 receptor
Aprepitant and tradipitant	Neurokinin receptor antagonist
Tezepelumab	TSLP (Th2 response promoter) inhibitor
Natalizumab	Cell adhesion inhibitor which inhibits α_4 integrin and endothelial activation
Vedolizumab	Monoclonal antibody against $\alpha_4\beta_7$ integrin which inhibits release of proinflammatory meditators from blood monocytes and also inhibits endothelial activation

IL-31, Interleukin 31; OSMRβ, oncostatin M receptor beta; KIT, stem cell receptor; Th2 cells, T-helper 2 cells; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; TSLP, thymic stromal lymphopoietin; IgE, immunoglobulin E

biologic which is more effective and has rapid onset of action as compared to omalizumab. Even with good success rate in resistant CSU with biologicals, treatment of CSU is challenging, because of high rate of recurrence after stopping the therapy. Further studies are required to understand the key mediators involved in the pathogenesis of urticaria, to target these mediators to achieve higher success rate and reduce the recurrence rate. Robust RCTs are required to assess the efficacy of newer biologicals such as anti-IL-5, anti-TNF-α, and anti-IL-1 drugs in the management of urticaria.

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Conflicts of interest

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