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PRACTICAL ISSUES AND UPDATES

Look out for new treatment choices in chronic spontaneous urticaria

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Abstract

Chronic spontaneous urticaria (CSU), presenting with wheals and itch, usually persists despite therapy with approved second generation H1 antihistamines (sgAHs) and omalizumab. For refractory cases, recent approvals of dupilumab and remibrutinib in the USA and elsewhere offer new hope, as do several agents in clinical trials. Most of these, including the Bruton's tyrosine kinase inhibitors rilzabrutinib and TAS5315, and the anti-KIT antibody barzolvolimab, indirectly target mast cell activation. In phase 3 trials in sgAH-resistant CSU, these therapies improved itch and/or wheals from as early as week 1 and led to complete disease control. Long-term data are still needed.

Expanding choices in chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU), which affects about 1% of people, presents with angioedema and/or itchy wheals (hives) lasting at for least 6 weeks [1]. Its underlying cause is usually unknown or untreatable [1, 2]. Where chronic urticaria (CU) symptoms are inducible by cold or other known triggers, the disease is classified as chronic inducible urticaria [2]. However, patients may have both CU subtypes [2]. CSU may also coexist with other conditions. Autoimmune CSU (aiCSU), characterized by highly active disease, autoimmune comorbidities, and lack of (or delayed) response to first- and second-line therapies, may affect up to two-thirds of patients [1].

The goal of CSU treatment is complete disease control, defined as a score of 16 in the Urticaria Control Test (scale range 0–16), but in most cases symptoms persist for more than 1 year and respond imperfectly to established treatments [1]. First- and second-line options are second generation H1 antihistamines (sgAHs), sometimes at high dosages [2], and the anti-immunoglobulin (Ig)E monoclonal antibody (MAB) omalizumab [1]. The former control symptoms well in up to 21% of patients, with about 30% of poor responders to sgAHs achieving complete control with omalizumab [1]. Cyclosporin A is used off label as a third-line treatment, however, its use is limited by an unfavourable safety profile [1]. Innumerable other off-label options have been tried, with little proven benefit [2].

The dearth of effective therapies has left many CSU patients with unmet treatment needs and an often severely impaired quality of life [1, 2]. Dupilumab, was the first new treatment for a decade, is now approved in several countries, most recently in sgAH-refractory CSU in the USA and the EU [1, 3–5]. Shortly after, remibrutinib was also approved in this indication in the USA [6, 7] and China [8]. Several other promising agents are in advanced development [1]. This article summarizes new and emerging pharmacological CSU treatments, as reviewed by Kolkhir et al. [1], with additional information on CSU from an international expert consensus guideline [2].

Different inflammatory pathways can lead to chronic spontaneous urticaria

Urticaria is primarily driven by activated mast cells, which can release histamine as well as other inflammatory mediators causing nerve activation (itch), vasodilatation and plasma extravasation (redness and swelling) as well as cell recruitment to urticarial lesions that perpetuates inflammation [2]. However, the trigger for mast cell activation can be heterogeneous, and can involve helper T cell and autoreactive B cell pathways [2]. CSU with different underlying pathologies can affect the response to therapy. For example, patients with aiCSU, who have autoantibodies that can activate mast cells, tend to be less responsive to treatment with

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antihistamines and omalizumab [1]. New pharmacotherapies targeting different inflammatory pathways, and therefore the different causes of urticaria, may be of use for difficult-to-treat cases of CSU.

New therapies tend to target type 2 inflammation

Potential pharmacological therapies (Table 1) are emerging in line with an increasingly precise understanding of the pathogenesis of CSU [1]. Key to this is type 2 inflammation, involving: mast cells (MCs) in particular, plus activated Th2 cells, basophils and associated interleukins (ILs) (notably IL-4 and IL-13) and other cytokines. The IL-4/IL-13 pathway regulates the differentiation of naïve T cells to Th2 cells and is also key to the production of IgE and IgG antibodies in B cells; both these processes can contribute to MC activation, so makes an attractive target for therapy in CSU [1].

The central role of MCs in CSU [2] make them a key target of several emerging agents (Table 1) [1]. These targets include the tyrosine kinase (TK) receptor, KIT, and its ligand, stem cell factor (SCF), which regulate MC differentiation and is required for their survival [9] (Table 1); Bruton's TK (BTK) which mediates, among other things, MC cytokine production via the high affinity IgE receptor (FcεRI) and B cell differentiation via the B cell receptor

Table 1 New and emerging pharmacological therapies for resistant/refractory chronic spontaneous urticaria, as reviewed by Kolkhir et al. [1]

Therapy (MOA)	Clinical trial comments
IL4-Rα inhibitor	
Dupilumab (MAB, inhibits IL-4 and IL-13 signalling)	In two 24-wk phase 3 RCTs in pts (aged ≥6 years) who were sgAH-refractory and OMZ-naïve [CUPID A ($n=138$); CUPID C ($n=151$)], dupilumab significantly ↓ UAS7[a] (−20.5 vs −12.0, $p=0.0003$ in CUPID A; −15.86 vs −11.21, $p=0.02$ in CUPID C) and ISS7[b] (−10.2 vs −6.0, $p=0.0005$ in CUPID A; −8.64 vs −6.10, $p=0.02$ in CUPID C) vs PL and ↑ CR[c] (31.4% vs 13.2% in CUPID-A and 30% vs 18% in CUPID C) at wk 24 [10, 11]
	In a 24-wk phase 3 RCT in pts (aged 12–80 years) who had no/incomplete response to OMZ or OMZ intolerance [CUPID B ($n=108$)], statistical significance was not reached for ↓ in UAS7[a] and ISS7[b], and ↑ in CR[c] vs PL [10]
	Injection-site reactions, accidental overdose, RTIs were treatment-emergent AEs that ↑ with dupilumab vs PL in CUPID A and C [11]
Bruton's tyrosine kinase inhibitors	
Remibrutinib (irreversible BTKi)	In two 24-wk phase 3 RCTs in pts (aged ≥18 years) with sgAH-resistant CSU [REMIX-1 ($n=470$); REMIX-2 ($n=455$)], ↓ UAS7[a] vs PL at wk 12 [LSM difference from BL of −20.0 vs −13.8 (REMIX-1) and −19.4 vs −11.7 (REMIX-2)], ↑ the proportion of pts with a UAS7[a] ≤6 vs PL [49.8% vs 31.1% (REMIX-1) and 46.8% vs 27.9% (REMIX-2)] and ↑ the proportion of pts with CRs[c] [31.1% vs 10.5% (REMIX-1) and 27.9% vs 6.5% (REMIX-2)] [12]
	↑ incidence of the AE petechiae vs PL [13]
Rilzabrutinib (reversible BTKi)	In the 12-wk phase 2 RCT in pts with sgAHs-resistant moderate-to-severe CSU (RILECSU; $n=160$), rilzabrutinib 1200 mg/d ↓ UAS7[a] vs PL (−17.95 vs −11.20) and ↓ ISS7[b] vs PL (−9.58 vs −6.31) [14]
	↑ incidence of the AEs diarrhoea, headache and nausea vs PL [14]
TAS5315 (irreversible BTKi)	In a 12-wk phase 2a RCT in pts with sgAH-refractory moderate-to-severe CSU ($n=126$), TAS5315 4 mg/d, 2 mg/d and 0.25 mg/d ↓ mean UAS7[a] compared with BL to a greater extent than PL (between-group difference −8.09, −6.95 and −8.78, respectively) [1, 15]
	Petechiae most common AE reported in TAS5315 recipients from clinical trials (0–33.3% vs 0% with PL) [1]
Anti-KIT MAB	
Barzolvolimab (MAB, inhibits KIT signalling)	In a 16-wk phase 2 RCT followed by a 36-wk OL phase in pts with sgAH-refractory CSU ($n=208$), barzolvolimab 150 mg 4-wkly (−23.02 vs −10.47) and 300 mg 8-wkly (−23.87 vs −10.47) ↓ UAS7[a] vs PL and increased the proportion of pts with CR[c] vs PL (37.5–51.1% vs 6.4%), with up to 71% of pts at wk 52 achieving a CR[c]; efficacy was unaffected by previous OMZ exposure [1, 16]
	↑ incidence of the AEs hair whitening, hypopigmentation and neutropenia vs PL [1]

↑ increase(d), ↓ decrease(d), *AE(s)* adverse event(s), *BL* baseline, *BTKi* Bruton's tyrosine kinase inhibitor, *CR* complete response, *CSU* chronic spontaneous urticaria, *IL* interleukin, *IL4-Rα* IL-4 receptor alpha, *ISS7* itch-severity scale over 7 days, *LSM* least-squares mean, *MAB(s)* monoclonal antibody(ies), *MCID* minimal clinically important difference, *MOA* mechanism of action, *OL* open-label, *OMZ* omalizumab, *PL* placebo, *pt(s)* patient(s), *RCT* randomized controlled trial, *RTI* respiratory tract infection(s), *sgAH(s)* second generation H1 antihistamine(s), *UAS7* urticaria activity score over 7 days

[a]Scale range 0 to 42; with 0 = no symptoms (itch and hives) over 7 days, and a MCID of 9.5–10.5 points [17]

[b]Scale range 0 to 21; with 0 = no itch over 7 days, and a MCID of 5 points [17]

[c]Defined as UAS7 = 0

(BCR) (Table 1); and receptors associated with IgE-independent MC activation pathways, such as the Mas-related G protein-coupled receptor X2 (MRGPRX2) [1].

Rapid action and potential autoimmune benefits of new treatments

Agents targeting MC activity via the mechanisms described above often appear to act rapidly in CSU, based on clinical trial reports [1]. Overall, dupilumab, BTK inhibitors and barzolvolimab demonstrated efficacy in alleviating symptoms of CSU in patients who are refractory/resistant to first-line treatment (Table 1). Additionally, remibrutinib, rilzabrutinib and barzolvolimab were all associated with rapid CSU improvements, with measurable changes occurring within a week [1]. Of these treatments, dupilumab and remibrutinib have been approved in the USA, as well as other countries, for adults with symptomatic CSU despite treatment with H1 antihistamines [3, 18]. The relative positioning of these newly approved treatments is currently unclear; however, a clinical trial has been initiated comparing the efficacy of dupilumab and remibrutinib as add-on treatments in adult with moderate to severe CSU inadequately controlled by sgAHs (NCT06868212).

There may also be good news for the large subset of patients with confirmed or likely aiCSU [2]. Remibrutinib displayed similar efficacy in patients with and without signs of aiCSU, and aiCSU markers decreased with rilzabrutinib treatment [1]. Phase 3 development of rilzabrutinib is planned [1]. Agents still progressing through phase 1b/2 trial stage in CSU include the anti-KIT MAB briquilimab, the Janus kinase inhibitors povorcitinib and TLL018, and the MRGPRX2 inhibitor EVO756 [1].

As a cautionary note, more long-term safety data in developing options are needed [1]. Several important adverse events were more common in active agents than placebo in phase 2 and 3 trials (Table 1). Amongst the BTK inhibitors, bleeding events (including petechiae) is an adverse event of special interest. However, no severe bleeding events occurred in the pivotal phase 3 trials of remibrutinib [18]. Additionally, trials in the BTK inhibitor fenebrutinib (due to the increase in the incidence of elevated blood levels of transaminases) and the MRGPRX2 inhibitor EP262 were terminated or paused for safety reasons [1, 19]. Increases in the levels of transaminases were not observed in trials of the approved BTK inhibitor remibrutinib in CSU [12], although a long-term extension study investigating the continued safety of remibrutinib is currently ongoing (NCT05513001).

Take home messages

- The debilitating hives and itch of CSU often persist despite treatment with established therapies, including sgAHs and omalizumab, leaving many patients with a poor quality of life
- Mast cells are a key target of therapy of CSU
- Consider dupilumab and remibrutinib in patients with refractory CSU
- Be aware of emerging therapies for CSU, including the BTK inhibitors remibrutinib, rilzabrutinib and TAS5315, and the KIT inhibitor barzolvolimab

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Declarations

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