Monoclonal Antibodies for Chronic Spontaneous Urticaria

Subjects: Allergy

Contributor: Sara Manti, Alessandro Giallongo, Maria Papale, Giuseppe Fabio Parisi, Salvatore Leonardi

H1-antihistamines (H1AH) represent the current mainstay of treatment for chronic spontaneous urticaria (CSU). However, the response to H1AH is often unsatisfactory, even with increased doses. Therefore, guidelines recommend the use of omalizumab as an add-on treatment in refractory CSU. This paved the way for the investigation of targeted therapies, such as monoclonal antibodies (mAbs), in CSU. Omalizumab remains the best choice to treat refractory CSU.

Keywords: monoclonal antibodies ; biologics ; chronic spontaneous urticaria

1. Introduction

Urticaria is characterized by the development of wheals with or without angioedema. Chronic urticaria (CU) is defined as lasting for more than 6 weeks [1]. The prevalence of CU is estimated to be between 0.1 and 1.4% across different areas of the world [2][3].

Different triggers can elicit urticaria, such as cold, heat, contact, infections, and others. However, in 75% of the patients suffering from CU, the causal factor cannot be detected [4]. Accordingly, urticaria is defined as spontaneous when no specific trigger is identified [1].

Mast cells are primarily involved in the pathogenesis of chronic spontaneous urticaria (CSU) through the release of pro-inflammatory mediators, which, in turn, recruit neutrophils, eosinophils, and T lymphocytes [5][6]. Impaired intracellular signaling pathways, and type II and type I autoimmunity have been suggested as pathogenic mechanisms [7]. It has been found that 30–50% of patients with CSU produce immunoglobulin (Ig)G autoantibodies against IgE or its receptor (FcεRI), causing the degranulation of cutaneous mast cells and basophils, and thus histamine release [8][9]. Regarding type I autoimmunity, in a cluster of CSU patients, researchers reported evidence of IgG and IgE against thyroperoxidase (TPO), defining this mechanism as “autoallergy”. Patients with CSU had a six-fold higher risk of TPO antibodies positivity than controls (odds ratio (OR) 6.72; 95% confidence interval (CI) 4.56, 9.89). However, their pathogenic role is still under debate [10][11][12][13]. More recently, the activation of cascade coagulation has been proposed as an alternative pathogenic mechanism, initiated by tissue factors expressed on eosinophils in lesional skin. This event leads to thrombin-mediated increased vascular permeability and mast-cell degranulation [14].

CU can significantly affect the health-related quality of life (HRQoL) of patients, as it has been reported to interfere with sleep quality, and school and work performance, especially in patients with uncontrolled disease, with subsequent high health care and indirect costs [15][16]. Notably, it has also been associated with psychiatric disorders, such as anxiety and depression [15].

The treatment of CU has been based on the avoidance or elimination of triggering factors and, when identified, on the treatment of the underlying causes, such as infection. The treatment of CSU is based on symptomatic drugs and, among these, second-generation H1-antihistamines (H1AH) represent the current mainstay of treatment according to guidelines [1]. Nevertheless, the percentage of non-responders to H1AH is around 60%, which remains high, despite the possibility of increasing the dose to four-fold the licensed dose (40–45% of non-responders to standard dose) [17][18][19]. Furthermore, the up-dosing of H1AH is not free from potential adverse effects in children [19]. Therefore, in the last two decades, new treatment approaches, including monoclonal antibodies (mAbs) and immunosuppressants (e.g., cyclosporine), have been introduced to optimize symptom control and improve HRQoL [20]. The identification of different molecular pathways underlying CSU has made them potential therapeutic targets [6][8]. In this context, mAbs represent targeted therapies directed towards specific molecular pathways, being potentially more efficacious and avoiding toxicity and/or side effects of immunosuppressants [21]. They have proven to be effective in other inflammatory and allergic diseases, such as

rheumatoid arthritis and asthma [21][22][23]. In CSU, their use is currently restricted to moderate-to-severe forms refractory to standard treatment, and only omalizumab, an anti-IgE mAb, is labelled as an add-on treatment for CSU [24].

2. Monoclonal Antibodies

Although omalizumab still remains the only approved mAb in treating CSU, other biologics have shown promising results and are currently under investigation in several trials [24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57].

Regarding omalizumab, a number of performed trials with a consistent number of enrolled patients have shown that omalizumab is effective, improving disease control and QoL, and safe, thus representing a well-established add-on treatment in refractory CSU, as stated by the updated EAACI guidelines [1][58][59][60][61][62][63][64][65][66][67][68][69]. Nevertheless, a limitation is the lack of RCTs on children. The only data refer to adolescents (≥12 years of age), who have been included in RCTs with adults, where they represent a marginal percentage, and they are not analyzed separately. A prospective open-label research on 29 adolescents with refractory CSU confirmed the effectiveness of omalizumab, with 58% of patients reaching a complete response (UAS = 0) at week 12. Three patients had a relapse after several months (from 4 to 12) following omalizumab withdrawal [70]. A research including 13 children reported a complete response in 12 of them after omalizumab 150 mg or 300 mg [71].

Nevertheless, around 30–40% of patients do not achieve disease control (UAS ≤ 6) with omalizumab [59][60][72]. This might be due to the standard dose of omalizumab, not adapted to weight and IgE levels, as seen in asthma, and/or high IgE levels (>1500 IU/mL), and/or different pathogenic mechanisms [32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108][109][110][111][112][113][114][115][116][117][118][119][120][121][122][123][124][125]. Omalizumab up-dosing to 600 mg reduced the proportion of non-responders to 7% [126].

With the aim of optimizing a treatment, high total serum IgE levels have been suggested as a biomarker predictive of the response to omalizumab [127]. Indeed, patients who exhibited a poor response to omalizumab had lower pre-treatment IgE levels compared with responders, who also showed an increase in IgE levels at week 4, and the IgE level at week 4/IgE level at baseline ratio revealed its superiority as a predictor of the response to treatment [128]. Blood basophils and histamine, which both increased in patients treated with omalizumab 300 mg, could represent other biomarkers predictive of the response to treatment [129]. Serum transglutaminase-2 activity may be a more reliable monitoring biomarker of the response to omalizumab, being less influenced by other comorbidities than IgE [130].

Another unanswered question concerns the optimal duration of treatment. RCTs have reported CSU-relapses after the interruption of omalizumab, with a subsequent response when treatment was re-started [66]. Therefore, omalizumab cannot be defined as a disease-modifying drug, and long-term treatments seem to be needed to control the disease.

Ligelizumab (240 mg), another anti-IgE, drug has shown superiority to omalizumab, probably due to its slightly different mechanism of action and higher affinity to IgE [25]. However, at the end of 2021, Novartis announced that ligelizumab showed superiority to a placebo, but not versus omalizumab at week 12 in two ongoing trials (NCT03580369 and NCT03580356), although the data are not yet available [44][45][131]. Contrary to this, quilizumab did not improve symptoms [132].

Currently, several experimental and clinical research studies are ongoing with the aim to provide further evidence on the pathogenesis of CSU. Understanding the close relationship between pathogenic pathways and clinical features will allow the identification of novel predictive biomarkers helpful in selecting the best candidate to receive targeted therapies with mAbs, and, consequently, the achievement of better clinical outcomes.

In addition to IgE, other investigated targets have included IL-5/IL-5R, through the development of anti-IL-5 mAbs (mepolizumab, reslizumab, and benralizumab), showing efficacy in 14 patients [29][30][31][47][48]. The IL-4 and IL-17 pathways, targeted by dupilumab and secukinumab, respectively, seem to play a remarkable role in the pathogenesis of CSU; thus, they could be an additional therapeutic weapon in the treatment of refractory CSU [6][39][109]. Nevertheless, data on these mAbs, though encouraging, come from case series, thus no firm conclusions can be drawn about their efficacy [32][33][34][39]. Ongoing and future RCTs on larger populations will clarify their potential therapeutic role in CSU.

TSLP, IL-25, and IL-33, the so called “alarmins” probably represent one of the most intriguing targets because they are located upstream of the inflammatory cascade. Hence, blocking the alarmins pathway could potentially be more efficacious and modify the disease course [116]. Barzolvolimab, suppressing mast cells, could represent another disease-modifying drug [117]. Although it is not the purpose, it is necessary to mention that, among biologic drugs, small molecule

inhibitors such as remibrutinib (LOU064), a Bruton's tyrosine kinase (BTK) inhibitor with a potential role in the treatment of CSU, represent an alternative to mAbs [133]. Remibrutinib, similar to other BTK inhibitors (fenebrutinib, tirabrutinib, rilzabrutinib, and TAS5315), targets BTK, which is involved in B-cell differentiation and proliferation and mast-cell activation, mediated by B-cell receptor and FcεRI activation, respectively [133][134][135][136][137][138][139][140][141][142][143][144]. Remibrutinib at different doses showed superiority to a placebo in the NCT03926611 trial [133]. Similarly, the preliminary results of the NCT03137069 trial on fenebrutinib 150 mg daily and 200 mg twice a day showed a significant reduction from the baseline in UAS7 at week 8 compared with a placebo (−17.6 and −20.7, respectively, vs. −11.2) [145]. On the contrary, trials on tirabrutinib and etanercept, a TNF-α antagonist, have been stopped early [141][144]. Other trials are ongoing to investigate inhibitors acting on different targets, such as JAK1/TYK2 and prostaglandin D2 receptor 2 (DP2 or CRTH2) [146][147]. CRTH2 plays a role in the chemotaxis of Th2 cells and eosinophils, and Th2 cytokine synthesis. AZD1981, a CRTH2 antagonist, induced a significant reduction in UAS7 at the end of the drug wash out period compared with a placebo and with no safety concern [147]. To summarize, small molecule inhibitors may represent an alternative to mAbs as targeted therapies in refractory CSU, with the advantage for some of them of oral administration compared with mAbs. However, data on inhibitors, excepted for etanercept, whose use has been reported successfully in a case report of CSU, are limited to few trials, that, to date, do not allow researchers to draw conclusions on their efficacy and safety [40][135][141][147].

References

1. Zuberbier, T.; Abdul Latiff, A.H.; Abuzakouk, M.; Aquilina, S.; Asero, R.; Baker, D.; Ballmer-Weber, B.; Bangert, C.; Ben-Shoshan, M.; Bernstein, J.A.; et al. The international EAACI/GA²LEN/EuroGuiDerm/APAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022, 77, 734–766.
2. Sánchez-Borges, M.; Ansotegui, I.J.; Baiardini, I.; Bernstein, J.; Canonica, G.W.; Ebisawa, M.; Gomez, M.; Gonzalez-Diaz, S.N.; Martin, B.; Morais-Almeida, M.; et al. The challenges of chronic urticaria part 1: Epidemiology, immunopathogenesis, comorbidities, quality of life, and management. World Allergy Organ. J. 2021, 14, 100533.
3. Fricke, J.; Ávila, G.; Keller, T.; Weller, K.; Lau, S.; Maurer, M.; Zuberbier, T.; Keil, T. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy 2020, 75, 423–432.
4. Chow, S.K. Management of chronic urticaria in Asia: 2010 AADV consensus guidelines. Asia Pac. Allergy 2012, 2, 149–160.
5. Church, M.K.; Kolkhir, P.; Metz, M.; Maurer, M. The role and relevance of mast cells in urticaria. Immunol. Rev. 2018, 282, 232–247.
6. Kay, A.B.; Clark, P.; Maurer, M.; Ying, S. Elevations in T-helper-2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ('idiopathic') urticaria. Br. J. Dermatol. 2015, 172, 1294–1302.
7. Bracken, S.J.; Abraham, S.; MacLeod, A.S. Autoimmune Theories of Chronic Spontaneous Urticaria. Front. Immunol. 2019, 10, 627.
8. Hide, M.; Francis, D.M.; Grattan, C.E.; Hakimi, J.; Kochan, J.P.; Greaves, M.W. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N. Engl. J. Med. 1993, 328, 1599–1604.
9. Tong, L.J.; Balakrishnan, G.; Kochan, J.P.; Kinét, J.P.; Kaplan, A. Assessment of autoimmunity in patients with chronic urticaria. J. Allergy Clin. Immunol. 1997, 99, 461–465.
10. Kolkhir, P.; Metz, M.; Altrichter, S.; Maurer, M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. Allergy 2017, 72, 1440–1460.
11. Altrichter, S.; Peter, H.J.; Pisarevskaja, D.; Metz, M.; Martus, P.; Maurer, M. IgE mediated autoallergy against thyroid peroxidase—A novel pathomechanism of chronic spontaneous urticaria? PLoS ONE 2011, 6, e14794.
12. Çildağ, S.; Yenisey, Ç.; Ünübol, M.; Şentürk, T. Comparison of immunoglobulin E anti-thyroid peroxidase antibodies in patients with Hashimoto thyroiditis and chronic spontaneous urticaria. Med. Pharm. Rep. 2021, 94, 53–57.
13. Tienforti, D.; Di Giulio, F.; Spagnolo, L.; Castellini, C.; Totaro, M.; Muselli, M.; Francavilla, S.; Baroni, M.G.; Barbonetti, A. Chronic urticaria and thyroid autoimmunity: A meta-analysis of case-control studies. J. Endocrinol. Investig. 2022, 45, 45, 1317–1326.
14. Cugno, M.; Marzano, A.V.; Asero, R.; Tedeschi, A. Activation of blood coagulation in chronic urticaria: Pathophysiological and clinical implications. Intern. Emerg. Med. 2010, 5, 97–101.

15. Gonçalo, M.; Gimenéz-Arnau, A.; Al-Ahmad, M.; Ben-Shoshan, M.; Bernstein, J.A.; Ensina, L.F.; Fomina, D.; Galvàn, C.A.; Godse, K.; Grattan, C.; et al. The global burden of chronic urticaria for the patient and society. Br. J. Dermatol. 2021, 184, 226–236.
16. Maurer, M.; Abuzakouk, M.; Bérard, F.; Canonica, W.; Oude Elberink, H.; Giménez-Arnau, A.; Grattan, C.; Hollis, K.; Knulst, A.; Lacour, J.P.; et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy 2017, 72, 2005–2016.
17. Guillén-Aguinaga, S.; Jáuregui Presa, I.; Aguinaga-Ontoso, E.; Guillén-Grima, F.; Ferrer, M. Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: A systematic review and meta-analysis. Br. J. Dermatol. 2016, 175, 1153–1165.
18. Maurer, M.; Church, M.K.; Gonçalo, M.; Sussman, G.; Sánchez-Borges, M. Management and treatment of chronic urticaria (CU). J. Eur. Acad. Dermatol. Venereol. 2015, 29 (Suppl. S3), 16–32.
19. Manti, S.; Salpietro, C.; Cuppari, C. Antihistamines: Recommended Dosage–Divergence between Clinical Practice and Guideline Recommendations. Int. Arch. Allergy Immunol. 2019, 178, 93–96.
20. Kaplan, A.P. Chronic Spontaneous Urticaria: Pathogenesis and Treatment Considerations. Allergy Asthma Immunol. Res. 2017, 9, 477–482.
21. Andreakos, E.; Taylor, P.C.; Feldmann, M. Monoclonal antibodies in immune and inflammatory diseases. Curr. Opin. Biotechnol. 2002, 13, 615–620.
22. Licari, A.; Manti, S.; Castagnoli, R.; Marseglia, A.; Foiadelli, T.; Brambilla, I.; Marseglia, G.L. Immunomodulation in Pediatric Asthma. Front. Pediatrics 2019, 7, 289.
23. Licari, A.; Manti, S.; Marseglia, A.; De Filippo, M.; De Sando, E.; Foiadelli, T.; Marseglia, G.L. Biologics in Children with Allergic Diseases. Curr. Pediatr. Rev. 2020, 16, 140–147.
24. European Medicines Agency|(europa.eu). Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/xolair (accessed on 28 May 2022).
25. Maurer, M.; Giménez-Arnau, A.M.; Sussman, G.; Metz, M.; Baker, D.R.; Bauer, A.; Bernstein, J.A.; Brehler, R.; Chu, C.Y.; Chung, W.-H.; et al. Ligelizumab for Chronic Spontaneous Urticaria. N. Engl. J. Med. 2019, 381, 1321–1332.
26. Giménez-Arnau, A.; Maurer, M.; Bernstein, J.; Staubach, P.; Barbier, N.; Hua, E.; Severin, T.; Joubert, Y.; Janocha, R.; Balp, M.M. Ligelizumab improves sleep interference and disease burden in patients with chronic spontaneous urticaria. Clin. Transl. Allergy 2022, 12, e12121.
27. Maurer, M.; Giménez-Arnau, A.; Bernstein, J.A.; Chu, C.Y.; Danilycheva, I.; Hide, M.; Makris, M.; Metz, M.; Savic, S.; Sitz, K.; et al. Sustained safety and efficacy of ligelizumab in patients with chronic spontaneous urticaria: A one-year extension study. Allergy 2021, 77, 2175–2184.
28. Study to Investigate the Efficacy and Safety of QGE031 in Adolescent Patients with Chronic Spontaneous Urticaria (CSU)–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03437278 (accessed on 11 July 2022).
29. Magerl, M.; Terhorst, D.; Metz, M.; Altrichter, S.; Zuberbier, T.; Maurer, M.; Bergmann, K.C. Benefit of mepolizumab treatment in a patient with chronic spontaneous urticaria. J. Dtsch. Dermatol. Ges. 2018, 16, 477–478.
30. Maurer, M.; Altrichter, S.; Metz, M.; Zuberbier, T.; Church, M.K.; Bergmann, K.C. Benefit from reslizumab treatment in a patient with chronic spontaneous urticaria and cold urticaria. J. Eur. Acad. Dermatol. Venereol. 2018, 32, e112–e113.
31. Bernstein, J.A.; Singh, U.; Rao, M.B.; Berendts, K.; Zhang, X.; Mutasim, D. Benralizumab for Chronic Spontaneous Urticaria. N. Engl. J. Med. 2020, 383, 1389–1391.
32. Lee, J.K.; Simpson, R.S. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. J. Allergy Clin. Immunol. Pract. 2019, 7, 1659–1661.e1.
33. Staubach, P.; Peveling-Oberhag, A.; Lang, B.M.; Zimmer, S.; Sohn, A.; Mann, C. Severe chronic spontaneous urticaria in children—treatment options according to the guidelines and beyond—A 10 years review. J. Dermatol. Treat. 2022, 33, 1119–1122.
34. Errichetti, E.; Stinco, G. Recalcitrant chronic urticaria treated with dupilumab: Report of two instances refractory to H1-antihistamines, omalizumab and cyclosporine and brief literature review. Dermatol. Ther. 2021, 34, e14821.
35. Arkwright, P.D. Anti-CD20 or anti-IgE therapy for severe chronic autoimmune urticaria. J. Allergy Clin. Immunol. 2009, 123, 510–511.
36. Chakravarty, S.D.; Yee, A.F.; Paget, S.A. Rituximab successfully treats refractory chronic autoimmune urticaria caused by IgE receptor autoantibodies. J. Allergy Clin. Immunol. 2011, 128, 1354–1355.

37. Steinweg, S.A.; Gaspari, A.A. Rituximab for the Treatment of Recalcitrant Chronic Autoimmune Urticaria. J. Drugs Dermatol. 2015, 14, 1387.

38. Combalia, A.; Losno, R.A.; Prieto-González, S.; Mascaró, J.M. Rituximab in Refractory Chronic Spontaneous Urticaria: An Encouraging Therapeutic Approach. Skin Pharmacol. Physiol. 2018, 31, 184–187.

39. Sabag, D.A.; Matanes, L.; Bejar, J.; Sheffer, H.; Barzilai, A.; Church, M.K.; Toubi, E.; Maurer, M.; Vadasz, Z. Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. Clin. Exp. Allergy 2020, 50, 799–804.

40. Wilson, L.H.; Eliason, M.J.; Leiferman, K.M.; Hull, C.M.; Powell, D.L. Treatment of refractory chronic urticaria with tumor necrosis factor-alfa inhibitors. J. Am. Acad. Dermatol. 2011, 64, 1221–1222.

41. A Safety and Efficacy Study of Ligelizumab in the Treatment of CSU in Japanese Patients Inadequately Controlled with H1-Antihistamines–Full Text View–ClinicalTrials.gov. Available online: https://www.clinicaltrials.gov/ct2/show/NCT03907878 (accessed on 15 July 2022).

42. Study of Efficacy and Safety of Ligelizumab in Chronic Spontaneous Urticaria Patients Who Completed a Previous Study with Ligelizumab–Tabular View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/record/NCT04210843 (accessed on 15 July 2022).

43. Study of Mechanism of Action of Ligelizumab (QGE031) in Patients with Chronic Urticaria–Tabular View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/record/NCT04513548 (accessed on 15 July 2022).

44. A Phase III Study of Efficacy and Safety of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-Antihistamines–Tabular View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/record/NCT03580369?term=ligelizumab&draw=2&rank=8 (accessed on 15 July 2022).

45. A Phase III Study of Efficacy and Safety of Ligelizumab in the Treatment of CSU in Adolescents and Adults Inadequately Controlled With H1-Antihistamines–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03580356 (accessed on 15 July 2022).

46. Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of UB-221 as an Add-on Therapy in CSU Patients–Tabular View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/record/NCT03632291?term=ub-221&draw=2&rank=3 (accessed on 15 July 2022).

47. Mepolizumab for the Treatment of Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03494881 (accessed on 15 July 2022).

48. A Study to Investigate the Use of Benralizumab in Patients with Chronic Spontaneous Urticaria Who Are Symptomatic De-spite the Use of Antihistamines (ARROYO)–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04612725 (accessed on 15 July 2022).

49. Dupilumab in Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03749135 (accessed on 15 July 2022).

50. Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine and Who Are Naïve to, Intolerant of, or Incomplete Responders to Omalizumab (LIBERTY-CSU CUPID)–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04180488 (accessed on 15 July 2022).

51. Safety Study of Rituximab (Rituxan®) in Chronic Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT00216762 (accessed on 15 July 2022).

52. Study to Evaluate Tezepelumab in Adults with Chronic Spontaneous Urticaria (INCEPTION). Available online: https://clinicaltrials.gov/ct2/show/NCT04833855 (accessed on 15 July 2022).

53. A Study of CDX-0159 in Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://www.clinicaltrials.gov/ct2/show/NCT04538794 (accessed on 15 July 2022).

54. A Phase 2 Study of CDX-0159 in Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05368285 (accessed on 15 July 2022).

55. A Study of MTPS9579A in Participants with Refractory Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05129423 (accessed on 15 July 2022).

56. A Study of LY3454738 in Adults with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04159701 (accessed on 15 July 2022).

57. A Study to Assess the Efficacy and Safety of AK002 in Subjects with Antihistamine-Resistant Chronic Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03436797?term=Siglec-

8&draw=2&rank=1 (accessed on 15 July 2022).

58. Saini, S.; Rosen, K.E.; Hsieh, H.J.; Wong, D.A.; Conner, E.; Kaplan, A.; Spector, S.; Maurer, M. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J. Allergy Clin. Immunol. 2011, 128, 567–573.e1.
59. Maurer, M.; Altrichter, S.; Bieber, T.; Biedermann, T.; Bräutigam, M.; Seyfried, S.; Brehler, R.; Grabbe, J.; Hunzelmann, N.; Jakob, T.; et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. J. Allergy Clin. Immunol. 2011, 128, 202–209.e5.
60. Kaplan, A.; Ledford, D.; Ashby, M.; Canvin, J.; Zazzali, J.L.; Conner, E.; Veith, J.; Kamath, N.; Staubach, P.; Jakob, T.; et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J. Allergy Clin. Immunol. 2013, 132, 101–109.
61. Maurer, M.; Rosén, K.; Hsieh, H.J.; Saini, S.; Grattan, C.; Gimenéz-Arnau, A.; Agarwal, S.; Doyle, R.; Canvin, J.; Kaplan, A.; et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N. Engl. J. Med. 2013, 368, 924–935.
62. Saini, S.S.; Bindslev-Jensen, C.; Maurer, M.; Grob, J.J.; Bülbül Baskan, E.; Bradley, M.S.; Canvin, J.; Rahmaoui, A.; Georgiou, P.; Alpan, O.; et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: A randomized, placebo-controlled study. J. Investig. Dermatol. 2015, 135, 67–75.
63. Staubach, P.; Metz, M.; Chapman-Rothe, N.; Sieder, C.; Bräutigam, M.; Canvin, J.; Maurer, M. Effect of omalizumab on angioedema in H1-antihistamine-resistant chronic spontaneous urticaria patients: Results from X-ACT, a randomized controlled trial. Allergy 2016, 71, 1135–1144.
64. Staubach, P.; Metz, M.; Chapman-Rothe, N.; Sieder, C.; Bräutigam, M.; Maurer, M.; Weller, K. Omalizumab rapidly improves angioedema-related quality of life in adult patients with chronic spontaneous urticaria: X-ACT study data. Allergy 2018, 73, 576–584.
65. Hide, M.; Park, H.S.; Igarashi, A.; Ye, Y.M.; Kim, T.B.; Yagami, A.; Roh, J.; Lee, J.H.; Chinuki, Y.; Youn, S.W.; et al. Efficacy and safety of omalizumab in Japanese and Korean patients with refractory chronic spontaneous urticaria. J. Dermatol. Sci. 2017, 87, 70–78.
66. Maurer, M.; Kaplan, A.; Rosén, K.; Holden, M.; Iqbal, A.; Trzaskoma, B.L.; Yang, M.; Casale, T.B. The XTEND-CIU study: Long-term use of omalizumab in chronic idiopathic urticaria. J. Allergy Clin. Immunol. 2018, 141, 1138–1139.e7.
67. Casale, T.B.; Murphy, T.R.; Holden, M.; Rajput, Y.; Yoo, B.; Bernstein, J.A. Impact of omalizumab on patient-reported outcomes in chronic idiopathic urticaria: Results from a randomized study (XTEND-CIU). J Allergy Clin. Immunol. Pract. 2019, 7, 2487–2490.e1.
68. Sussman, G.; Hébert, J.; Gulliver, W.; Lynde, C.; Yang, W.H.; Papp, K.; Gooderham, M.; Chambenoit, O.; Khalil, S.; DeTakacsy, F.; et al. Omalizumab Re-Treatment and Step-Up in Patients with Chronic Spontaneous Urticaria: OPTIMA Trial. J. Allergy Clin. Immunol. Pract. 2020, 8, 2372–2378.
69. Yuan, W.; Hu, S.; Li, M.; Yang, L.; Liu, L.; Zheng, M.; Guo, Z.; Song, Z.; Zhang, C.; Diao, Q.; et al. Efficacy and safety of omalizumab in Chinese patients with anti-histamine refractory chronic spontaneous urticaria. Dermatol. Ther. 2022, 35, e15303.
70. Ocak, M.; Soyer, O.; Buyuktiryaki, B.; Sekerel, B.E.; Sahiner, U.M. Omalizumab treatment in adolescents with chronic spontaneous urticaria: Efficacy and safety. Allergol. Immunopathol. 2020, 48, 368–373.
71. Al-Shaikhly, T.; Rosenthal, J.A.; Ayars, A.G.; Petroni, D.H. Omalizumab for chronic urticaria in children younger than 12 years. Ann. Allergy Asthma Immunol. 2019, 123, 208–210.e2.
72. Bérard, F.; Ferrier Le Bouedec, M.; Bouillet, L.; Reguiai, Z.; Barbaud, A.; Cambazard, F.; Milpied, B.; Pelvet, B.; Kasujee, I.; Gharbi, H.; et al. Omalizumab in patients with chronic spontaneous urticaria nonresponsive to H1-antihistamine treatment: Results of the phase IV open-label SUNRISE study. Br. J. Dermatol. 2019, 180, 56–66.
73. Maul, J.T.; Distler, M.; Kolios, A.; Maul, L.V.; Guillet, C.; Graf, N.; Imhof, L.; Lang, C.; Navarini, A.A.; Schmid-Grendelmeier, P. Canakinumab Lacks Efficacy in Treating Adult Patients with Moderate to Severe Chronic Spontaneous Urticaria in a Phase II Randomized Double-Blind Placebo-Controlled Single-Center Study. J. Allergy Clin. Immunol. Pract. 2021, 9, 463–468.e3.
74. Holgate, S.; Casale, T.; Wenzel, S.; Bousquet, J.; Deniz, Y.; Reisner, C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J. Allergy Clin. Immunol. 2005, 115, 459–465.
75. Metz, M.; Vadasz, Z.; Kocatürk, E.; Giménez-Arnau, A.M. Omalizumab Updosing in Chronic Spontaneous Urticaria: An Overview of Real-World Evidence. Clin. Rev. Allergy Immunol. 2020, 59, 38–45.

76. Spector, S.L.; Tan, R.A. Effect of omalizumab on patients with chronic urticaria. Ann. Allergy Asthma Immunol. 2007, 99, 190–193.

77. Kaplan, A.; Ferrer, M.; Bernstein, J.A.; Antonova, E.; Trzaskoma, B.; Raimundo, K.; Rosén, K.; Omachi, T.A.; Khalil, S.; Zazzali, J.L. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. J. Allergy Clin. Immunol. 2016, 137, 474–481.

78. Stull, D.E.; McBride, D.; Houghton, K.; Finlay, A.Y.; Gnanasakthy, A.; Balp, M.M. Assessing Changes in Chronic Spontaneous/Idiopathic Urticaria: Comparisons of Patient-Reported Outcomes Using Latent Growth Modeling. Adv. Ther. 2016, 33, 214–224.

79. Finlay, A.Y.; Kaplan, A.P.; Beck, L.A.; Antonova, E.N.; Balp, M.M.; Zazzali, J.; Khalil, S.; Maurer, M. Omalizumab substantially improves dermatology-related quality of life in patients with chronic spontaneous urticaria. J. Eur. Acad. Dermatol. Venereol. 2017, 31, 1715–1721.

80. Maurer, M.; Sofen, H.; Ortiz, B.; Kianifard, F.; Gabriel, S.; Bernstein, J.A. Positive impact of omalizumab on angioedema and quality of life in patients with refractory chronic idiopathic/spontaneous urticaria: Analyses according to the presence or absence of angioedema. J. Eur. Acad Dermatol. Venereol. 2017, 31, 1056–1063.

81. Arm, J.P.; Bottoli, I.; Skerjanec, A.; Floch, D.; Groenewegen, A.; Maahs, S.; Owen, C.E.; Jones, I.; Lowe, P.J. Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin. Exp. Allergy 2014, 44, 1371–1385.

82. Gasser, P.; Tarchevskaya, S.S.; Guntern, P.; Brigger, D.; Ruppli, R.; Zbären, N.; Kleinboelting, S.; Heusser, C.; Jardetzky, T.S.; Eggel, A. The mechanistic and functional profile of the therapeutic anti-IgE antibody ligelizumab differs from omalizumab. Nat. Commun. 2020, 11, 165.

83. Wedi, B. Ligelizumab for the treatment of chronic spontaneous urticaria. Expert. Opin. Biol. Ther. 2020, 20, 853–861.

84. Brightbill, D.; Hans, L.L.; Yuwen, L.Z.; Tan, M.; Meng, G.; Gloria, Y.; Balazs, M.; Chung, S.; Wu, C. Lawren, Quilizumab is an Afucosylated Humanized Anti-M1 Prime Therapeutic Antibody. Clin. Anti-Inflamm. Anti-Allergy Drugs (Discontin.) 2014, 1, 24–31.

85. Gauvreau, G.M.; Harris, J.M.; Boulet, L.P.; Scheerens, H.; Fitzgerald, J.M.; Putnam, W.S.; Cockcroft, D.W.; Davis, B.E.; Leigh, R.; Zheng, Y.; et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. Sci. Transl. Med. 2014, 6, 243ra85.

86. Kolkhir, P.; Elieh-Ali-Komi, D.; Metz, M.; Siebenhaar, F.; Maurer, M. Understanding human mast cells: Lesson from therapies for allergic and non-allergic diseases. Nat. Rev. Immunol. 2022, 22, 294–308.

87. Evaluating the Safety and Tolerability and Determining the PK and PD of Single Dose UB-221 in Chronic Spontaneous Urti-caria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04175704 (accessed on 12 July 2022).

88. A Study to Evaluate the Pharmacodynamics, Pharmacokinetics, Safety, and Efficacy of UB-221 IV Infusion as an Add-on Therapy in Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05298215?term=ub-221&draw=2&rank=1 (accessed on 12 July 2022).

89. Available online: https://pubchem.ncbi.nlm.nih.gov/pathway/WikiPathways:WP127 (accessed on 12 July 2022).

90. Adachi, T.; Alam, R. The mechanism of IL-5 signal transduction. Am. J. Physiol. 1998, 275, C623–C633.

91. Jackson, D.J.; Akuthota, P.; Roufosse, F. Eosinophils and eosinophilic immune dysfunction in health and disease. Eur. Respir. Rev. 2022, 31, 210150.

92. Farne, H.A.; Wilson, A.; Powell, C.; Bax, L.; Milan, S.J. Anti-IL5 therapies for asthma. Cochrane Database Syst. Rev. 2017, 9, CD010834.

93. Harvima, I.T.; Horsmanheimo, L.; Naukkarinen, A.; Horsmanheimo, M. Mast cell proteinases and cytokines in skin inflammation. Arch. Dermatol. Res. 1994, 287, 61–67.

94. Altrichter, S.; Frischbutter, S.; Fok, J.S.; Kolkhir, P.; Jiao, Q.; Skov, P.S.; Metz, M.; Church, M.K.; Maurer, M. The role of eosinophils in chronic spontaneous urticaria. J. Allergy Clin. Immunol. 2020, 145, 1510–1516.

95. Kay, A.B.; Ying, S.; Ardelean, E.; Mlynek, A.; Kita, H.; Clark, P.; Maurer, M. Elevations in vascular markers and eosinophils in chronic spontaneous urticarial weals with low-level persistence in uninvolved skin. Br. J. Dermatol. 2014, 171, 505–511.

96. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/nucala (accessed on 24 June 2022).

97. Antonicelli, L.; Tontini, C.; Garritani, M.S.; Piga, M.A.; Bilò, M.B. Efficacy of mepolizumab in patients with concomitant severe eosinophilic asthma and severe chronic urticaria: An example of personalized medicine? J. Investig. Allergol. Clin. Immunol. 2021, 32.

98. Cinqaero|European Medicines Agency (europa.eu). Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/cinqaero (accessed on 16 July 2022).
99. Fasenra|European Medicines Agency (europa.eu). Available online: https://www.ema.europa.eu/en/documents/product-information/fasenra-epar-product-information_en.pdf (accessed on 24 June 2022).
100. Matsunaga, K.; Katoh, N.; Fujieda, S.; Izuhara, K.; Oishi, K. Dupilumab: Basic aspects and applications to allergic diseases. Allergol. Int. 2020, 69, 187–196.
101. Dupixent|European Medicines Agency (europa.eu). Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent (accessed on 24 June 2022).
102. Dupixent (Dupilumab) FDA Approval History–Drugs.com. Available online: https://www.drugs.com/history/dupixent.html (accessed on 15 July 2022).
103. Reff, M.E.; Carner, K.; Chambers, K.S.; Chinn, P.C.; Leonard, J.E.; Raab, R.; Newman, R.A.; Hanna, N.; Anderson, D.R. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994, 83, 435–445.
104. Taylor, R.P.; Lindorfer, M.A. Drug insight: The mechanism of action of rituximab in autoimmune disease--the immune complex decoy hypothesis. Nat. Clin. Pract. Rheumatol. 2007, 3, 86–95.
105. Rituxan (Genentech, Inc.). FDA Package Insert (medlibrary.org). Available online: https://medlibrary.org/lib/rx/meds/rituxan/ (accessed on 24 June 2022).
106. Delate, T.; Hansen, M.L.; Gutierrez, A.C.; Le, K.N. Indications for Rituximab Use in an Integrated Health Care Delivery System. J. Manag. Care Spec. Pharm. 2020, 26, 832–838.
107. Hauser, S.L.; Waubant, E.; Arnold, D.L.; Vollmer, T.; Antel, J.; Fox, R.J.; Bar-Or, A.; Panzara, M.; Sarkar, N.; Agarwal, S.; et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N. Engl. J. Med. 2008, 358, 676–688.
108. McAtee, C.L.; Lubega, J.; Underbrink, K.; Curry, K.; Msaouel, P.; Barrow, M.; Muscal, E.; Lotze, T.; Srivaths, P.; Forbes, L.R.; et al. Association of Rituximab Use With Adverse Events in Children, Adolescents, and Young Adults. JAMA Netw. Open 2021, 4, e2036321.
109. Lin, W.; Zhou, Q.; Liu, C.; Ying, M.; Xu, S. Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. Sci. Rep. 2017, 7, 17797.
110. Cosentyx|European Medicines Agency (europa.eu). Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx (accessed on 25 June 2022).
111. Dinarello, C.A. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011, 117, 3720–3732.
112. Hermes, B.; Prochazka, A.K.; Haas, N.; Jurgovsky, K.; Sticherling, M.; Henz, B.M. Upregulation of TNF-alpha and IL-3 expression in lesional and uninvolved skin in different types of urticaria. J. Allergy Clin. Immunol. 1999, 103 Pt 1, 307–314.
113. Sharma, P.; Sharma, P.K.; Chitkara, A.; Rani, S. To Evaluate the Role and Relevance of Cytokines IL-17, IL-18, IL-23 and TNF-α and Their Correlation with Disease Severity in Chronic Urticaria. Indian Dermatol. Online J. 2020, 11, 594–597.
114. Hammad, H.; Lambrecht, B.N. Barrier Epithelial Cells and the Control of Type 2 Immunity. Immunity 2015, 43, 29–40.
115. Ito, T.; Wang, Y.H.; Duramad, O.; Hori, T.; Delespesse, G.J.; Watanabe, N.; Qin, F.X.; Yao, Z.; Cao, W.; Liu, Y.J. TSLP-Activated Dendritic Cells Induce an Inflammatory T Helper Type 2 Cell Response Through OX40 Ligand. J. Exp. Med. 2005, 202, 1213–1223.
116. Wang, S.H.; Zuo, Y.G. Thymic Stromal Lymphopoietin in Cutaneous Immune-Mediated Diseases. Front. Immunol. 2021, 12, 698522.
117. Alvarado, D.; Maurer, M.; Gedrich, R.; Seibel, S.B.; Murphy, M.B.; Crew, L.; Goldstein, J.; Crocker, A.; Vitale, L.A.; Morani, P.A.; et al. Anti-KIT monoclonal antibody CDX-0159 induces profound and durable mast cell suppression in a healthy volunteer study. Allergy 2022.
118. Maun, H.R.; Jackman, J.K.; Choy, D.F.; Loyet, K.M.; Staton, T.L.; Jia, G.; Dressen, A.; Hackney, J.A.; Bremer, M.; Walters, B.T.; et al. An Allosteric Anti-tryptase Antibody for the Treatment of Mast Cell-Mediated Severe Asthma. Cell 2020, 180, 406.
119. Payne, V.; Kam, P.C. Mast cell tryptase: A review of its physiology and clinical significance. Anaesthesia 2004, 59, 695–703.
120. Blom, L.H.; Martel, B.C.; Larsen, L.F.; Hansen, C.V.; Christensen, M.P.; Juel-Berg, N.; Litman, T.; Poulsen, L.K. The immunoglobulin superfamily member CD200R identifies cells involved in type 2 immune responses. Allergy 2017, 72, 1081–1090.

121. Youngblood, B.A.; Brock, E.C.; Leung, J.; Falahati, R.; Bryce, P.J.; Bright, J.; Williams, J.; Shultz, L.D.; Greiner, D.L.; Brehm, M.A.; et al. AK002, a Humanized Sialic Acid-Binding Immunoglobulin-Like Lectin-8 Antibody that Induces Antibody-Dependent Cell-Mediated Cytotoxicity against Human Eosinophils and Inhibits Mast Cell-Mediated Anaphylaxis in Mice. Int. Arch. Allergy Immunol. 2019, 180, 91–102.

122. Agache, I.; Rocha, C.; Pereira, A.; Song, Y.; Alonso-Coello, P.; Solà, I.; Beltran, J.; Posso, M.; Akdis, C.A.; Akdis, M.; et al. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: A systematic review for the EAACI Biologicals Guidelines. Allergy 2021, 76, 59–70.

123. Tharp, M.D.; Bernstein, J.A.; Kavati, A.; Ortiz, B.; MacDonald, K.; Denhaerynck, K.; Abraham, I.; Lee, C.S. Benefits and Harms of Omalizumab Treatment in Adolescent and Adult Patients With Chronic Idiopathic (Spontaneous) Urticaria: A Meta-analysis of “Real-world” Evidence. JAMA Dermatol. 2019, 155, 29–38.

124. Jia, H.X.; He, Y.L. Efficacy and Safety of Omalizumab for Chronic Spontaneous Urticaria: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Am. J. Ther. 2020, 27, e455–e467.

125. Salman, A.; Comert, E. The Real-Life Effectiveness and Safety of Omalizumab Updosing in Patients with Chronic Spontaneous Urticaria. J. Cutan. Med. Surg. 2019, 23, 496–500.

126. Curto-Barredo, L.; Spertino, J.; Figueras-Nart, I.; Expósito-Serrano, V.; Guilabert, A.; Melé-Ninot, G.; Cubiró, X.; Bonfill-Ortí, M.; Garcias-Ladaria, J.; Villar, M.; et al. Omalizumab updosing allows disease activity control in patients with refractory chronic spontaneous urticaria. Br. J. Dermatol. 2018, 179, 210–212.

127. Marzano, A.V.; Genovese, G.; Casazza, G.; Fierro, M.; Dapavo, P.; Crimi, N.; Ferrucci, S.; Pepe, P.; Liberati, S.; Pigatto, P.D.; et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: A study of 470 patients. J. Eur. Acad Dermatol. Venereol. 2019, 33, 918–924.

128. Ertas, R.; Ozyurt, K.; Atasoy, M.; Hawro, T.; Maurer, M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy 2018, 73, 705–712.

129. Saini, S.S.; Omachi, T.A.; Trzaskoma, B.; Hulter, H.N.; Rosén, K.; Sterba, P.M.; Courneya, J.P.; Lackey, A.; Chen, H. Effect of Omalizumab on Blood Basophil Counts in Patients with Chronic Idiopathic/Spontaneous Urticaria. J. Investig. Dermatol. 2019, 139, 496–497.

130. Bae, Y.; Kang, S.H.; Park, J.O.; Park, G.H.; Choi, J.H. Serum transglutaminase 2 activity as a potential biomarker of disease severity and response to omalizumab in chronic spontaneous urticaria. Allergol. Int. 2020, 69, 304–306.

131. Novartis Provides an Update on Phase III Ligelizumab (QGE031) Studies in Chronic Spontaneous Urticaria (CSU)|Novartis. Available online: https://www.novartis.com/news/media-releases/novartis-provides-update-phase-iii-ligelizumab-qge031-studies-chronic-spontaneous-urticaria-csu (accessed on 20 July 2022).

132. Harris, J.M.; Cabanski, C.R.; Scheerens, H.; Samineni, D.; Bradley, M.S.; Cochran, C.; Staubach, P.; Metz, M.; Sussman, G.; Maurer, M. A randomized trial of quilizumab in adults with refractory chronic spontaneous urticaria. J. Allergy Clin. Immunol. 2016, 138, 1730–1732.

133. Gabizon, R.; London, N. A Fast and Clean BTK Inhibitor. J. Med. Chem. 2020, 63, 5100–5101.

134. This Was a Dose-Finding Study to Evaluate Efficacy and Safety of LOU064 in Patients with CSU Inadequately Controlled by H1-Antihistamines–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03926611 (accessed on 20 July 2022).

135. Open-Label, Multicenter, Extension Study to Evaluate Long-Term Safety and Tolerability of LOU064 in Subjects with CSU–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04109313 (accessed on 20 July 2022).

136. A Safety and Efficacy Study of Remibrutinib in the Treatment of CSU in Japanese Adults Inadequately Controlled by H1-Antihistamines–Full Text View–ClinicalTrials.gov. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05048342 (accessed on 20 July 2022).

137. A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-Antihistamines–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05032157?cond=chronic+spontaneous+urticaria&draw=5&rank=32 (accessed on 20 July 2022).

138. Global Managed Access Program Cohort for Remibrutinib in Adult Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://www.clinicaltrials.gov/ct2/show/NCT05170724 (accessed on 20 July 2022).

139. Metz, M.; Sussman, G.; Gagnon, R.; Staubach, P.; Tanus, T.; Yang, W.H.; Lim, J.J.; Clarke, H.J.; Galanter, J.; Chinn, L.W.; et al. Fenebrutinib in H1 antihistamine-refractory chronic spontaneous urticaria: A randomized phase 2 trial. Nat. Med. 2021, 27, 1961–1969.

140. A Study to Evaluate the Long-Term Safety and Efficacy of Fenebrutinib in Participants Previously Enrolled in a Fenebrutinib Chronic Spontaneous Urticaria (CSU) Study–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT03693625 (accessed on 20 July 2022).
141. Study to Evaluate the Efficacy, Safety, and Tolerability of Tirabrutinib in Participants with Antihistamine-Resistant Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT04827589 (accessed on 20 July 2022).
142. Rilzabrutinib for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05107115 (accessed on 20 July 2022).
143. A Phase 2a Study of TAS5315 in Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05335499 (accessed on 20 July 2022).
144. Etanercept for the Treatment of Chronic Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT01030120 (accessed on 20 July 2022).
145. A Study of GDC-0853 in Participants with Refractory Chronic Spontaneous Urticaria (CSU). Available online: https://clinicaltrials.gov/ct2/show/NCT03137069 (accessed on 20 July 2022).
146. Safety and Efficacy of TLL018 in Patients with Chronic Spontaneous Urticaria–Full Text View–ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT05373355 (accessed on 20 July 2022).
147. Oliver, E.T.; Chichester, K.; Devine, K.; Sterba, P.M.; Wegner, C.; Vonakis, B.M.; Saini, S.S. Effects of an Oral CRTh2 Antagonist (AZD1981) on Eosinophil Activity and Symptoms in Chronic Spontaneous Urticaria. Int. Arch. Allergy Immunol. 2019, 179, 21–30, Correction in Int. Arch. Allergy Immunol. 2019, 179, 320.
