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Experience-based advice on stepping up and stepping down the therapeutic management of chronic spontaneous urticaria: Where is the guidance?

To the Editor,

Patients with chronic spontaneous urticaria (CSU), a common disorder with a prevalence of 1%,[1] are treated in a wide range of healthcare settings, from primary care to specialized urticaria centers including Urticaria Centers of Reference and Excellence.[2] The past updates of the International Urticaria Guideline increasingly focused on adapting the diagnostic work up and treatment to individual patient needs, with the overall goal to "treat urticaria until it is gone." To achieve this, the most recent update of this guideline, the International EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI Urticaria Guideline, recommends an "as much as needed and as little as possible" approach, asking physicians to step up and step down the treatment of CSU patients based on levels of disease control assessed with the Urticaria Control Test (UCT).[3] Nevertheless, there remains a lack of studies and guidance on when and how to step up or step down the treatment in CSU patients. Here, we provide suggestions on how to step-up and step-down CSU treatment based on available evidence and clinical experience.

The use of a standard-dosed second-generation antihistamine (sgAH) is the recommended first-line treatment in all patients with CSU. Many, but not all patients, can be expected to benefit. Patients with high baseline disease activity, high CRP, and elevated D-dimer levels often show poor response to this treatment[4] and should be monitored closely. Patients who do not achieve complete control (UCT = 16 or UAS7 = 0) are recommended to use a higher dose (up to fourfold) of their sgAH (Figure 1). Complete control is the goal for both steps, and patients who do not achieve complete control within 2 to 4 weeks of high dose sgAH treatment should receive omalizumab, the second-line treatment option. This can also be done in patients where the disease activity is so high that waiting for 4 weeks cannot be tolerated.

If complete disease control cannot be obtained with the two steps of the first-line treatment, omalizumab, the only recommended second-line treatment, should be used. Omalizumab should be started at the standard dose of 300 mg every 4 weeks (Figure 1). Many, but not all patients, experience benefit. Patients with markers of type IIb autoimmune CSU, for example, a positive basophil test, low levels of baseline total IgE, and elevated levels of IgG-anti-TPO, should be expected to show slow and poor response and be monitored closely.[4] If the disease cannot be completely controlled with the standard dose, updosing of omalizumab up to a maximum dose of 600 mg every 2 weeks should be tried.[3] Treatment optimization with omalizumab is best done by interval shortening for patients with worsening of symptoms before the end of the interval and by updosing for patients with poorly controlled disease throughout the interval. Patients who experience partial response to high dose sgAH treatment before starting omalizumab should continue this treatment until completely controlled disease is achieved with omalizumab. Omalizumab has a good safety profile with a low frequency of side effects and is licensed for self-administration in some countries.[5]

If complete disease control cannot be obtained within 3 months of omalizumab updosing, treatment with cyclosporine, up to 5 mg/kg, should be started (Figure 1). Patients with markers of type IIb CSU, for example, a positive basophil test and low total serum IgE, can be expected to show better responses to cyclosporine.[4] In patients who achieve partial response to omalizumab, combining low-dose cyclosporine (1–3 mg/kg) with omalizumab should be considered.[5]

In patients who achieve complete disease control, with any therapy, stepping down their treatment should be considered, for two reasons: The first is to reduce the treatment burden and costs, without losing complete control, that is, to maintain complete control with as much therapy as needed and as little as possible. This is done by reducing the dose and/or the frequency of intake of medication. The second reason for stepping down treatment in patients with complete control is to assess patients for the need of further treatment. CSU is a disease with spontaneous remission. Furthermore, it must be acknowledged that CSU can fluctuate in disease activity (and also, though not the topic of this paper, in chronic inducible urticaria, for example, cold urticaria, the trigger can vary depending on season and individual exposure). Therefore, stepping up and down of the treatment should be regarded as a constant process of adjusting the therapy to the individual need with the aim of total symptom control. Once complete disease control is achieved, with any therapy, the need for treatment continuation should be assessed. This is done by treatment discontinuation. Currently, there is no other way to determine if the absence of signs and symptoms, in patients with complete response to treatment, is due to the effects of treatment or because spontaneous remission has occurred. Currently, there is

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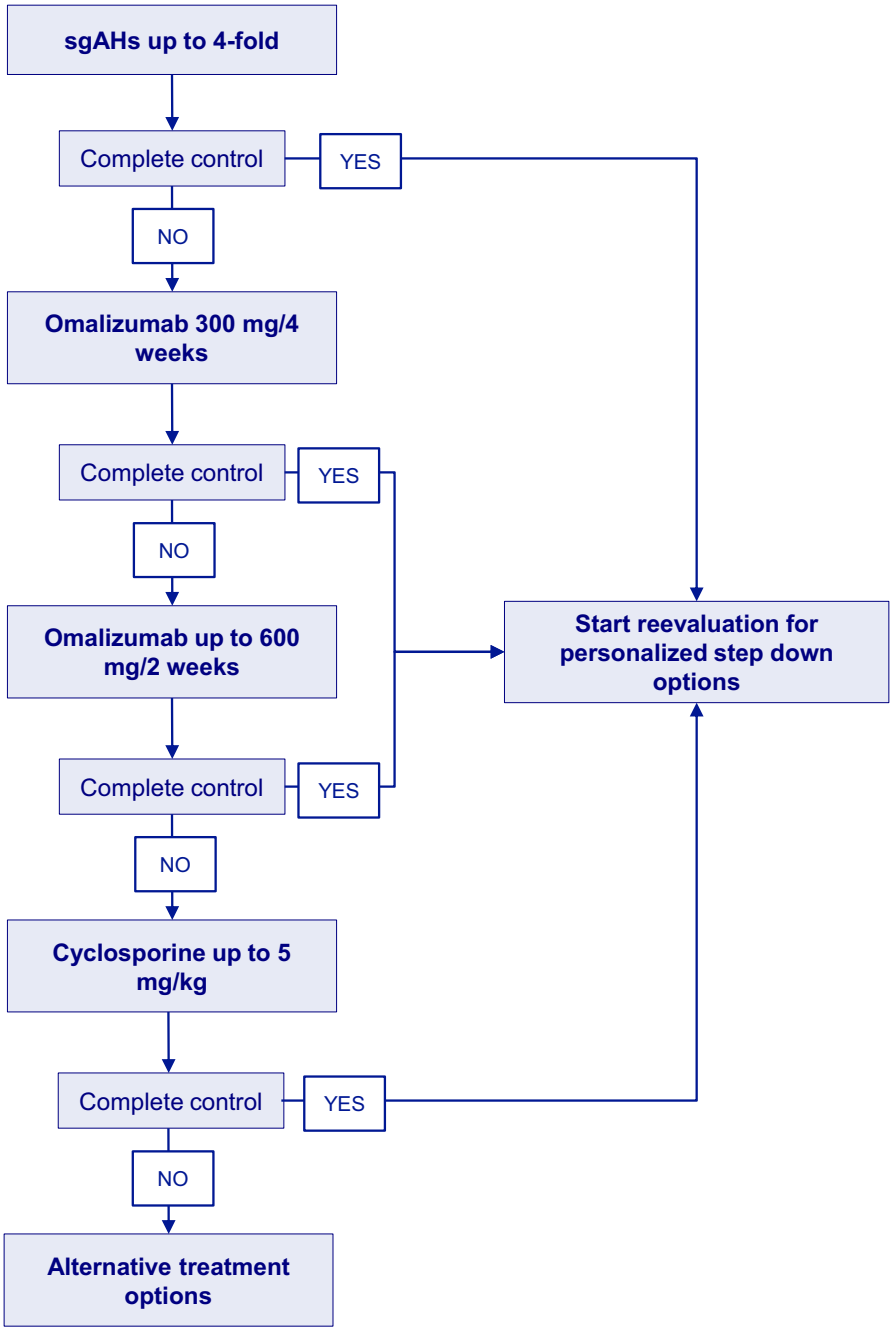

FIGURE 1 Personalized step-up therapeutic management plan of chronic spontaneous urticaria. The use of second-generation antihistamines (sgAH) starting from the standard dose up to fourfold is the recommended first-line treatment in all patients with CSU. If complete disease control cannot be achieved with this treatment, the second-line treatment option is omalizumab added-on to sgAHs, which should be started at the standard dose of 300 mg every 4 weeks, with updosing, in patients with inadequate response, until complete controlled disease is achieved. If complete disease control cannot be obtained within 3 months of omalizumab updosing, treatment with cyclosporine added-on to sgAHs should be started. In case of unresponsiveness to all these treatments, alternatives include several treatment options like doxepine, H2 antihistamines, leukotriene receptor antagonists, immunosuppressives, danazol, warfarin, tranexamic acid, IVIG, hydroxychloroquine, rituximab, anti-TNF-Alpha, colchicine, and more. Due to the low level of evidence in support of these treatments, the current international urticaria guideline recommends considering alternative treatment options only in special cases, those antihistamine treatment, omalizumab, and cyclosporine have failed. All treatment steps and recommendations in this figure are in line with the current international guideline[3]

no clear consensus exists on how to step down and discontinue CSU treatments. Treatment step-down protocols are different for first-line, second-line, and third-line therapeutics, and their implementation should bring on board individual patient needs (Figure 2).

Although cyclosporine is a drug with high efficacy in CSU,[6] care should be taken in its long-term use due to its side-effect profile. We use cyclosporine at the lowest effective dose and for not longer than 6 months. In patients who receive cyclosporine, antihistamines should be continued until completely controlled disease is achieved. Cyclosporine can be discontinued by reducing the dose gradually (e.g., 1 mg/kg per month) or all at once.

Nearly all patients who achieve complete control of their urticaria (UCT = 16 or UAS7 = 0) with omalizumab, at standard or higher dose, can stop their regular antihistamine use without loss of control[7,8]; however, this is off-label. After one to three months of complete control with omalizumab treatment, it can be considered to stop their daily antihistamine intake all at once or to reduce the dose gradually, over the course of a few weeks. Based on the short half-life of antihistamines the effect can be evaluated within 1–2 weeks after stopping the drug at latest. If patients still remain to have complete controlled disease after discontinuation of sgAHs, suitability for the stepping down and discontinuation of omalizumab treatment, which is explained below, should be evaluated. If this however results in the reoccurrence of signs and symptoms, antihistamine treatment should be started again, and discontinuation should not be attempted

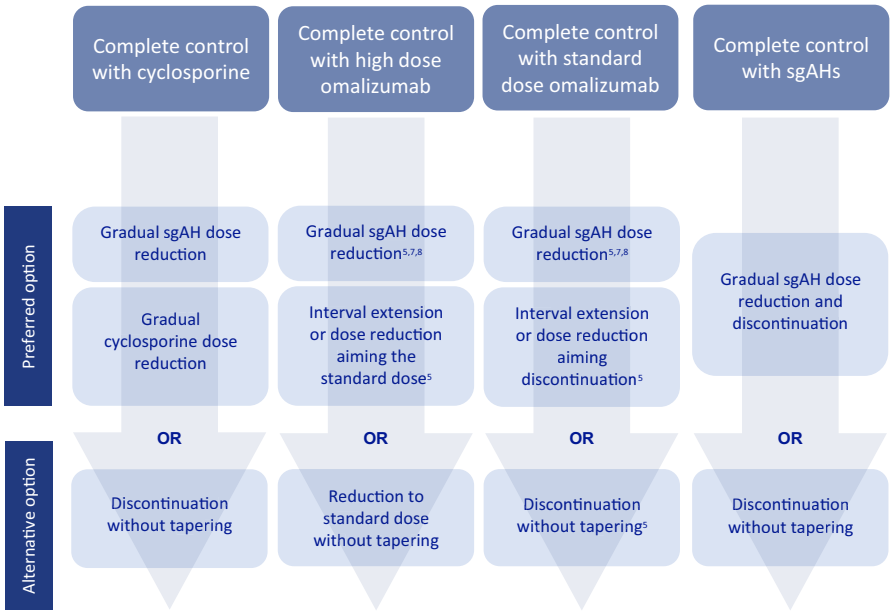

FIGURE 2 Treatment step-down protocols are different for first-line, second-line, and third-line therapeutics as shown in the figure separately in the direction of arrows and should be personalized based on individual patient needs, clinical experience, and legal limitations. Our preferred stepping down and discontinuation approach aims at reaching the lowest effective dose with gradual reduction of the treatment for all steps. An alternative option is an abrupt discontinuation of all treatments. It is important to note that, as of yet, there are no studies that compare our preferred stepping down options with alternative ones. Currently, there is no global consensus on when and how to step down and discontinue different CSU treatments, and recommendations in this figure are based on expert opinions and/or current literature

again until patients have achieved at least three consecutive months of complete control.

An alternative approach in patients with a consistent complete response over 3 months is to first step-down omalizumab and keeping high dose antihistamine treatment (Figure 2). Up to date, no head-to-head trials exist comparing different stepping down approaches. The decision must be based on individual factors also including the costs as omalizumab is not reimbursed in all countries.

When updosing of omalizumab has resulted in complete response, patients should be considered for stepping down the treatment. We advise our patients to do this after at least 3 months of complete control. Patients on shorter than standard injection intervals extend their interval by 1 week at a time (until they reach the standard interval of 4 weeks), and patients who treat with 450 mg or 600 mg reduce by 150 mg every one to three months (until they reach the standard dose or 300 mg). Patients who treat with 450 mg or 600 mg at shorter than standard intervals should start to step down their treatment by interval prolongation or dose reduction, not both.

In some patients who achieve complete control of their urticaria with standard-dosed omalizumab, treatment intervals can be extended without the loss of control. This is usually done by extending the interval by 1 week at a time, if no signs and symptoms occurred. In patients who develop breakthrough signs and symptoms upon interval prolongation, omalizumab should be used at the last interval that previously provided complete control.

Discontinuation of omalizumab aims to establish the need for further treatment and to assess patients for possible spontaneous disease remission. Stopping of omalizumab should not be considered before patients have achieved 6 to 12 months of uninterrupted complete response, that is, in patients without any signs or symptoms of urticaria for at least half a year.[5] One approach is to increase injection intervals by 1 week each to 8 weeks and to then stop omalizumab. A second approach is to stop omalizumab treatment all at once, without tapering. If relapse occurs after the discontinuation of omalizumab, treatment should be reinitiated. Patients should have 6 to 12 months of complete response before another attempt of treatment discontinuation is considered.

When updosing of an antihistamine has resulted in complete response, patients should be considered for stepping down the treatment. This should be done after at least 3 months of complete control, by reducing the daily dose by one tablet every month. In patients who develop breakthrough signs and symptoms upon dose reduction, the antihistamine should be used at the last dose that previously provided complete control. Dose reduction should not be attempted before patients have achieved 3 months of complete control.

Discontinuation of antihistamine treatment aims to assess patients for possible spontaneous disease remission. Antihistamine discontinuation should not be considered before patients have achieved 3–6 months of uninterrupted complete response, that is, in patients without any signs or symptoms of urticaria for at least half a

year. If relapse occurs, treatment should be reinitiated, and patients should have 3–6 months of complete response before another attempt of treatment discontinuation is considered.

It is important to emphasize that the first and most important treatment aim, in chronic urticaria, is to provide patients with complete control of their disease. This requires, in most patients, step up of treatment, in line with the guideline algorithm.[3] Treatment step up should be done based on the information obtained by the use of PROMs, primarily the UCT.

The reduction of treatment burden is a secondary aim, achieved by stepping down treatment. Step-up and step-down decisions should be made together with patients (shared decision-making). Importantly, most of the statements and suggestions in this paper are based on the authors' clinical experience and expertise, rather than supported by randomized controlled trials or solid data from high-quality clinical registries. Further studies are needed to provide better guidance on how to step-up and step-down treatment in patients with CSU. Also, clinical decisions should be made by taking local regulations in consideration.

KEYWORDS

angioedema, chronic urticaria, guideline, treatment management, wheals

CONFLICT OF INTEREST

MT has no relevant conflict of interest in relation to this work. Outside of it, MT is or recently was a speaker and/or advisor for Novartis. İY has no relevant conflict of interest in relation to this work. Outside of it, İY is or recently was a speaker and/or advisor for AstraZeneca and Novartis. ÜMŞ has no relevant conflict of interest in relation to this work. Outside of it, ÜMŞ is or recently was a speaker and/or consultant for Expansiense Lab Mustela. EK has no relevant conflict of interest in relation to this work. Outside of it, EK is or recently was a speaker and/or advisor for Bayer, Novartis, and Sanofi. BEŞ has no relevant conflict of interest in relation to this work. Outside of it, BEŞ is or recently was a speaker and/or advisor for Abdi İbrahim, Novartis, Sandoz, Sanofi, and Synevo Laboratories. TZ has no relevant conflict of interest in relation to this work. Outside of it, TZ is or recently was a speaker and/or advisor for and/or reports personal fees from for AbbVie, ALK, Almirall, Astellas, AstraZeneca, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Henkel, Kryolan, Leti, L'Oréal, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, UCB, Takeda and Teva. MM has no relevant conflicts of interest in relation to this work. Outside of it, MM is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third HarmonicBio, UCB, and Uriach.

AUTHOR CONTRIBUTION

MT conceived the presented idea. MT and MM wrote the manuscript with input from all authors. All authors reviewed, provided critical feedback, and approved the final version of the manuscript. MM and TZ supervised the manuscript.

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Comparative assessment of allergic reactions to COVID-19 vaccines in Europe and the United States

To the Editor,

Among the rare complications that may compromise vaccine acceptance are allergic reactions.[1–3] Recently, we demonstrated that anaphylaxis rates associated with COVID-19 vaccines are within the range of those observed earlier with other vaccines, as indicated by passive reporting systems.[4] Herein, we aimed to comparatively assess the incidence and potential underlying causes of the most common allergic reactions post-COVID-19 vaccination in Europe and the United States (US). To our knowledge, such a comparison has not been performed before.

Allergic reaction data following COVID-19 vaccination reported from Week 52/2020 to Week 39/2021 were collected from EudraVigilance for the European Economic Area (EEA) and from Vaccine Adverse Event Reporting System (VAERS) for the United States and analyzed for all licensed vaccines. These included mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), AD26.COV2.S (Janssen/Johnson & Johnson), and the not yet licensed in the US ChAdOx1-S (Oxford/AstraZeneca). Incidence rates were calculated using the corresponding administered vaccine doses as denominators. Vaccine composition was examined to identify potential allergic triggers.

The most common allergic reactions after COVID-19 vaccination were anaphylactic reactions, with an overall incidence of 9.91/million doses (EEA: 13.69/million/US: 4.44/million, Figure 1). Anaphylactic shock followed, with much lower rates (overall incidence: 1.36/million, EEA: 2.01/million/US: 0.41/million). Other allergic symptoms post vaccination, which were infrequently reported in the two databases, included, among others, "anaphylactoid reactions" and "allergic edema." Sampath et al. and Alhumaid et al. also reported a similar spectrum of allergic and possibly non-allergic reactions post vaccination.[2,5]

Higher anaphylactic reaction rates have been reported after the first than the second dose, especially when prior anaphylaxis was present, but that was not always the case.[5,6]

The incidence of anaphylactic reactions reported in EudraVigilance varied considerably by vaccine and was threefold to fourfold higher for BNT162b2 or mRNA-1273 compared with VAERS. AD26.COV2.S-associated anaphylaxis did not differ between databases. The very low incidence of anaphylactic shock also varied by vaccine, particularly as captured in EudraVigilance.

Considering vaccine platforms, the incidence of anaphylactic reactions post adenovirus-vectored vaccination was higher compared with mRNA-based vaccines (EudraVigilance: 15.62/ vs. 13.36/million and VAERS: 6.79/ vs. 4.34/million doses). Anaphylactic shock incidence rates were also higher for vectored compared with mRNA vaccines (EudraVigilance: 3.14/ vs. 1.81/million and VAERS: 1.20/ vs. 0.38).

Detailed demographic data and outcomes of anaphylactic reaction and anaphylactic shock cases post-COVID-19 vaccination are presented in Tables S1 and S2, respectively. The vast majority of cases affected females (82% of anaphylactic reaction/75% of anaphylactic shock reports). The reasons why women have been implicated more frequently in hypersensitivity reactions throughout cohorts remain unknown.

With regard to age, different patterns are evident. In EudraVigilance, both types of anaphylaxis were more common among working age (18–64 years) and older individuals; in VAERS, anaphylactic reactions were more frequent among subjects aged 30–59 years (69%), while the very rare anaphylactic shock cases were distributed across age groups.

Regarding outcome, the vast majority of cases were resolved or resolving (90.0% of anaphylactic reaction/81.7% of anaphylactic