OPTIMISING THE PATIENT JOURNEY IN CHRONIC SPONTANEOUS URTICARIA

Summary of Presentations from the Novartis-Supported Satellite Symposium, held at the 23rd EADV Congress, Amsterdam, the Netherlands, on 9th October 2014

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MEETING SUMMARY

Prof Marcus Maurer opened the symposium with an introduction to chronic urticaria (CU), as well as its two subtypes (chronic spontaneous urticaria [CSU] and chronic inducible urticaria [CIndU]), and the currently available therapeutic strategies. Dr Clive Grattan spoke about the burden of disease in patients with CSU and the specific effects it has on a patient's quality of life as well as the socioeconomic impact. Dr Donald Stull explained the importance of measuring the impact of disease using patient reported outcomes. Prof Ana Giménez-Arnau concluded the symposium by presenting the latest data on omalizumab for refractory CSU while touching on the recommendations in the latest urticaria guidelines. Interactive keypads were available throughout the symposium which allowed delegates to vote on different questions about their experience in treating patients with urticaria, posed by the speakers.

Introduction from the Chair

Professor Marcus Maurer

CU has a 1% global prevalence and is broadly divided into CSU and CIndU, with the spontaneous form being the more prevalent.[1] The latest EAACI/GA²LEN/EDF/WAO guidelines in urticaria now recommend treating the patient until they are completely symptom free.[1] However, non-sedating, second-generation antihistamines, used as first-line therapy, are not effective in approximately 50% of

CU patients. This was further confirmed by the audience responding to a question posed by the speaker, using the interactive keypads, indicating that only 50% of their patients remain symptom-free with antihistamines. The efficacy of omalizumab in CSU was first observed in individual cases and confirmed by an academia-driven proof of concept study and it was these results that drove the development of omalizumab as a treatment of CSU in patients inadequately controlled with antihistamines. This symposium will focus on the prevalence of the disease, its burden on patients, and the tools and therapeutic strategies now available for the management of CSU patients.

Burden of Disease and Unmet Needs in Patients with Refractory CSU

Doctor Clive Grattan

CU is characterised by itchy wheals, angioedema, or both, for 6 weeks or longer.[1] There are two main forms of CU: CSU and CIndU. The majority of patients present with CSU, which may be acute or chronic.[2] CSU affects females and males in a 2:1 ratio,[3] and peak incidence is between 20 and 40 years of age.[3] It is estimated that at any time 0.5–1.0% of the population suffers from the disease (point prevalence).[3-5] CSU is estimated to have a disease duration of between 1 and 5 years[3,6] but this is likely to be longer in more severe cases, such as those with concurrent angioedema and concurrent inducible urticaria or those with a positive autologous serum skin test.[3,7-9] Over 50% of CSU patients will experience at least one recurrence of symptoms after apparent resolution.[6] In terms of therapy, second-generation H_1-antihistamines are the first-line treatment.[1] Approximately 50% of patients treated with this option experience symptom improvement.[3] It has recently become common practice to treat the inadequately controlled patients with up to a 4-fold higher dose of second-generation H_1-antihistamines.[1,3] However, one-third of patients remain symptomatic,[3] highlighting that H_1-antihistamines do not provide symptom control in all CSU patients and there remains an unmet clinical need in CSU for more effective therapeutic strategies.

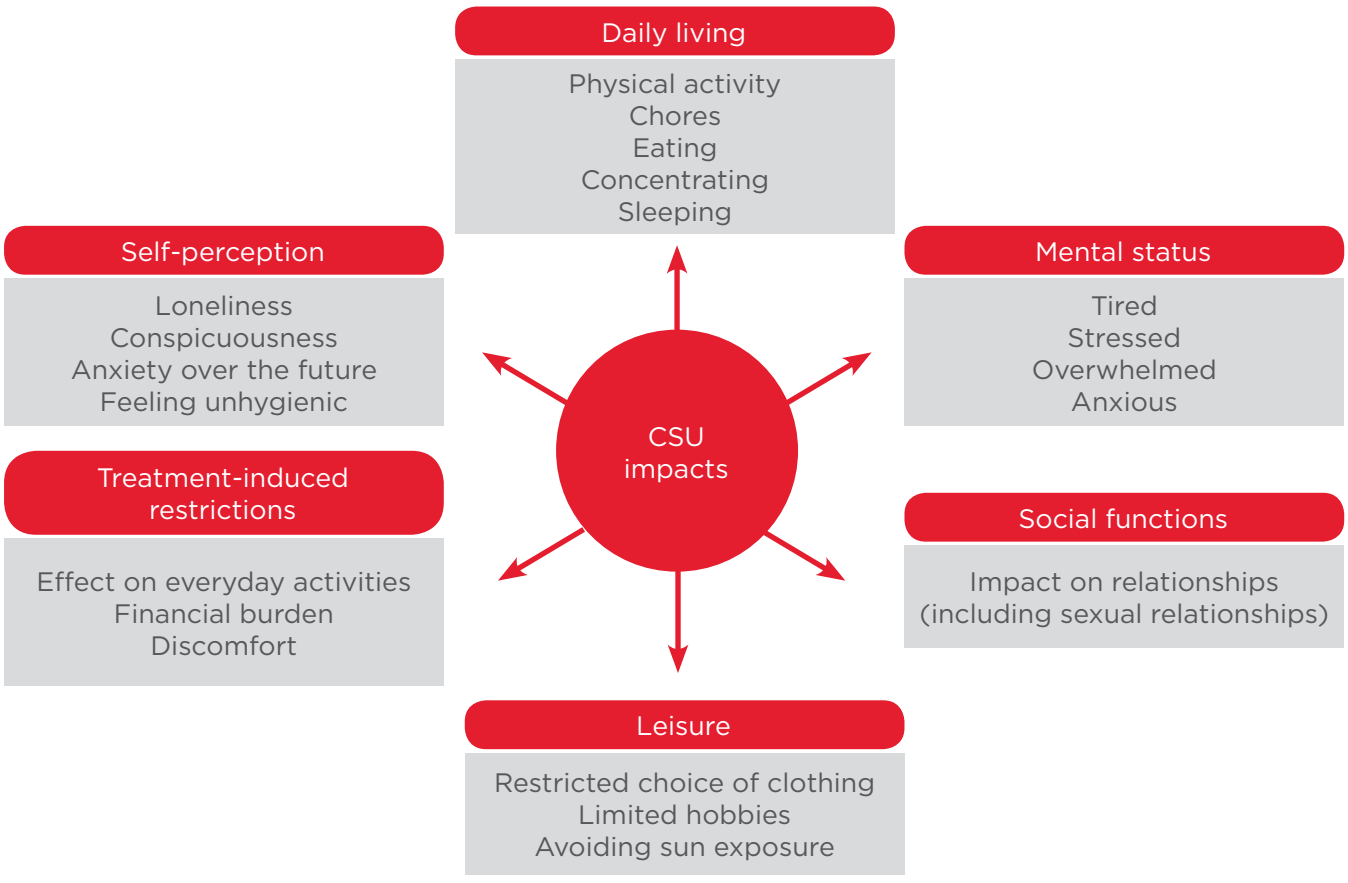

Figure 1: Chronic spontaneous urticaria (CSU) has a negative impact on health-related quality of life.

Patients with inadequately controlled CSU experience a significant burden of disease (Figure 1). Sleep deprivation due to itch impairs the patient's quality of life (QoL), physical and emotional wellbeing, work performance, and social functioning.[3] Patients with CSU also often experience depression and anxiety, with studies showing a positive correlation between itch intensity and severity of depression.[10] Such psychiatric comorbidities impair a patient's QoL.[11]

Another factor that can increase disease burden is delayed referral. Studies suggest that patients see an average of two physicians before being referred to a specialist.[12] This can lead to a delay in diagnosis and appropriate treatment, and consequently extend disease burden. A study conducted in Germany showed that 69% of CSU patients are not referred by their practitioner to tertiary care centres,[13] thereby potentially limiting access to more effective treatment since dermatologists are more aware of the management and treatment guidelines for CSU.[14]

CSU adversely affects many aspects of QoL[15] with the presence of angioedema further impairing QoL.[16] A survey of CSU patients, using the Nottingham Health Profile, showed that swelling, itch, and pain were the worst aspects of urticaria for patients.[17] The impact of CSU on QoL, in comparison to psoriasis and atopic dermatitis, was investigated using the VQ-Dermato French QoL instrument.[18] Assessment across different domains (e.g. daily living activities, self-perception, social functioning, leisure activities, and physical discomfort) showed that the impact on health-related quality of life (HRQoL) was similar for each of the three skin disorders.[18] CSU was found to have a significantly greater impact on daily living and physical discomfort than psoriasis ($p<0.001$).[18] Refractory CSU not only impacts QoL but also has a high socioeconomic burden, with the majority of direct costs being attributable to medication and indirect costs being caused by absences from work.[19]

In conclusion, CSU is a common disease with a prevalence estimated to be 0.5–1% of the population; however, duration of the disease lasts 1-5 years in the majority of cases.[6] Not all patients achieve adequate control with first-line therapy, highlighting the need for new therapeutic strategies that will reduce disease burden and socioeconomic impact.

CSU from a Patient Perspective – What can we Learn?

Doctor Donald Stull

CSU has a significant negative impact on patient QoL, affecting daily activities, mental and emotional status, self-perception, and social functions to name a few.[3] Patient-reported outcomes (PROs) are increasingly recognised as valuable instruments to assess the impact of the disease on patients and their response to treatment. This is also applicable to CSU for which validated PROs exist to assess burden of disease and response to treatment. The US FDA defines PROs as: "A report of the status of a patient's health condition that comes directly from the patient, without interpretation of their response by a physician or anyone else."[20] For example, signs and symptoms of disease severity would only be obtainable from the patient. Similarly, HRQoL, adverse events (AEs), and treatment satisfaction or preference can only be provided by the patient.

The latest urticaria guidelines now recommend the use of PROs in CSU patients to measure and monitor disease activity and QoL.[1] There are many different kinds of PROs that assess QoL impairment, which can be used to measure the impact of disease. These can be divided into three broad categories: CU-specific questionnaires, general dermatologic questionnaires, and generic HRQoL questionnaires.

Urticaria Activity Score (UAS), one example of a specific CSU PRO, is a simple validated daily diary to assess itch severity and number of hives in urticaria.[1,21] It is composed of two questions that ask patients to rate the severity of their itch and the number of hives. The daily scores are summed to create a weekly UAS value (UAS7), with a score ranging from 0 (no itch, no hives) to 42 (severe itch, many hives)[1,21] (Figure 2[22,23]).

The UAS7 has been used in CSU clinical trials alongside other PRO assessment measures. In the ASTERIA-I, II, and GLACIAL trials, which were Phase III trials investigating the effects of omalizumab in patients with inadequately controlled CSU, four PRO tools were used: UAS7, the Chronic Urticaria and Quality of Life questionnaire (CU-Q2oL), the Dermatology Life Quality Index (DLQI), and the Medical Outcomes Survey (MOS) Sleep Scale.[24-26] The CU-Q2oL is a patient questionnaire designed to assess CU-specific QoL, including the physical, psychosocial, and practical aspects of the

condition,[27] whereas the DLQI is a dermatological measure that is used to measure HRQoL in patients with a variety of skin conditions, including CSU.[21,28] The MOS Sleep Scale is a generic measure used to assess impairment of key aspects of sleep.[29] For each of the three trials, QoL scores were collected at baseline, week 4, and week 12. UAS7 scores were reported every 4 weeks. The primary endpoint was change from baseline in weekly itch severity score (component of UAS7) at week 12. At baseline in each of the trials, the disease burden for patients with inadequately controlled CSU was high in terms of UAS7 scores and low HRQoL.[24-26] This was reflected in the PRO scores from the three studies: the mean UAS7 score was 30/42, mean DLQI score was 12–14.6/30, mean somnolence score was 40/100, and mean sleep disturbance score was 47/100.[24-26] In the GLACIAL trial, for example, administration of 300 mg omalizumab resulted in a significant decline ($p<0.001$) in UAS7 scores (omalizumab versus placebo, -19.0 versus -8.5), indicating a substantial improvement in patient symptoms.[25]

Analysis of the changes in the three PROs found that changes in the UAS7 were highly correlated with changes in both the DLQI and the CU-Q2oL ($r=0.94$ in both cases for ASTERIA I).[30] This finding demonstrates that changes in the signs and symptoms of CSU, as measured by UAS7, show equivalent changes in HRQoL as measured by the CU-Q2oL and DLQI score. This very strong correlation indicates that information on changes in a patient's condition can be obtained using either the DLQI or CU-Q2oL, if a daily diary is not convenient.[30]

The EAACI/GA²LEN/EDF/WAO guidelines on urticaria now recommend the use of PROs to measure and monitor disease activity; furthermore, the acceptance by regulatory bodies of PRO data in product label claims is also increasing. PROs add the patient's perspective to disease management and give an indication of the success of the treatment.

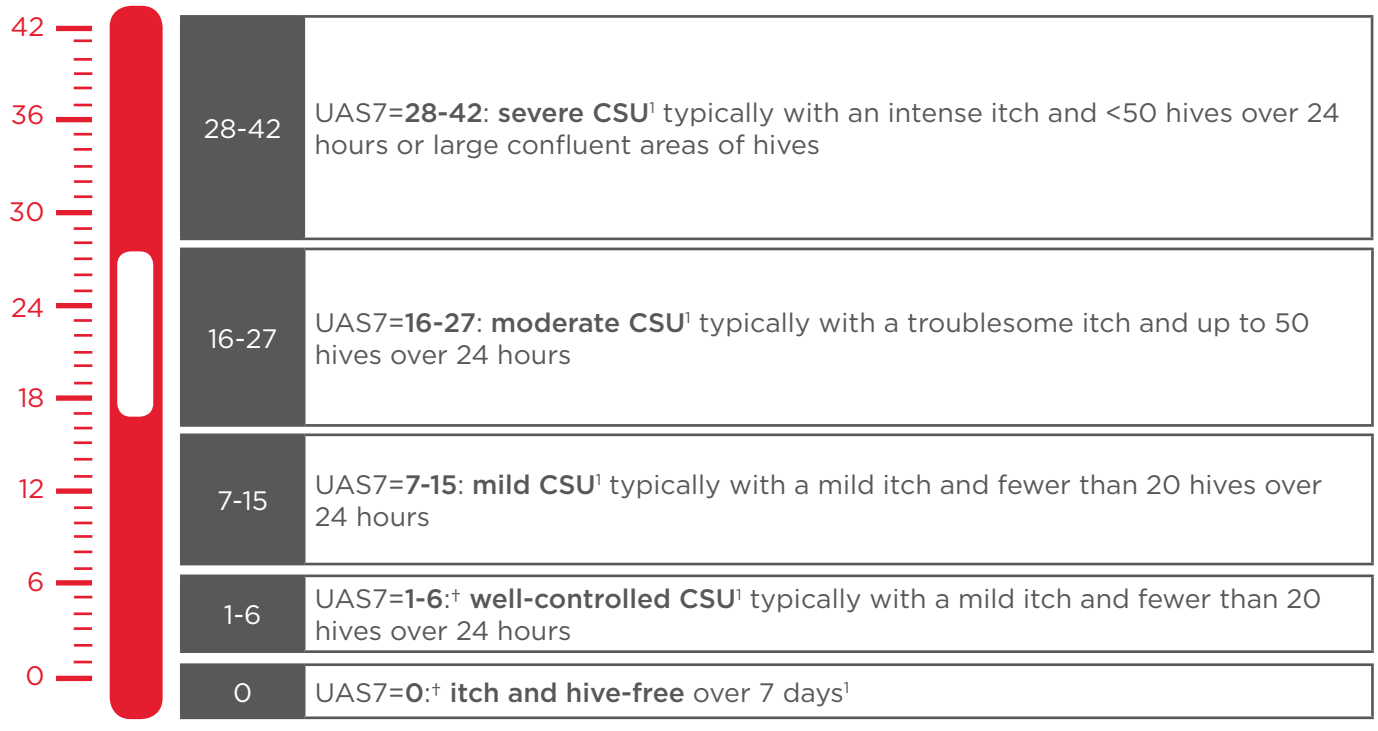

Figure 2: Categorising the weekly Urticaria Activity Score (UAS7) into ranges efficiently describes chronic spontaneous urticaria (CSU) health states.[22,23]

*UAS7≥16 was an inclusion criterion for Phase III clinical trials of omalizumab in patients with refractory CSU; †UAS7≤6 (well-controlled disease) and UAS7=0 (complete response) were key secondary endpoints in these trials.

Omalizumab and the Latest Data for Refractory CSU

Professor Ana Giménez-Arnau

Current guidelines for the treatment of patients with CU recommend complete symptom control as safely as possible as a goal.[1] They also state that second-generation H_1-antihistamines remain the first-line option of treatment, with their use recommended at up to 4-times the licensed dose as second-line treatment.[1] Omalizumab, cyclosporin A, and montelukast are all third-line therapy options.[1] Omalizumab is a humanised monoclonal IgG that binds to the Cε3 domain of IgE, forming trimers or hexamers and preventing it from binding to FcεRI on the surface of mast cells and basophils.[31] As a result, omalizumab neutralises the IgE-mediated response, preventing IgE-mediated histamine release.[31]

Evidence of the efficacy of omalizumab for CSU was first reported in academic case reports in 2006.[32] Following this, the promising results of an academia-driven proof of concept trial[33] and a dose finding trial[34] eventually led to the initiation of a Phase III programme in 2011 which was completed in 2013, the results of which led to the approval of omalizumab in Europe and the USA in 2014 as an add-on therapy for CSU in adult and adolescent patients 12 years of age and above with inadequate response to H_1-antihistamines.[24-26]

The Phase III programme included three trials: ASTERIA I and II, and GLACIAL.[24-26] Each trial included approximately 300 patients who were refractory to licensed doses of second-generation H_1-antihistamines. The GLACIAL study also investigated patients who were refractory to higher doses of H_1 and H_2-antihistamines and leukotriene receptor antagonists. Inclusion criteria included a UAS7 score of ≥16 and a weekly itch score of ≥8. The primary endpoint for the ASTERIA trials was a change in baseline to week 12 in weekly itch severity score.[25,26] The primary objective of the GLACIAL study was to evaluate the overall safety of omalizumab compared with placebo.[24] The results showed that omalizumab had a rapid onset of effect causing a decrease in the weekly itch severity score with a sustained response throughout the treatment period.[24-26] Symptoms returned upon withdrawal of omalizumab; however, there was no rebound effect and symptoms did not reach baseline levels.[24-26] Complete symptom control (i.e. UAS7=0) at week 12 was achieved in 40% of patients in the ASTERIA I/II trials ($p<0.0001$ versus placebo) and 33.7% in the GLACIAL trial ($p<0.0001$ versus placebo).[35] A total of 58.8% and 52.4% of patients had well-controlled symptoms (UAS7≤6) at week 12 ($p<0.0001$) in the ASTERIA I/II and GLACIAL trials, respectively.[35] Omalizumab significantly improved HRQoL as measured by the DLQI scale in all three studies across all domains assessed (ASTERIA I versus ASTERIA II versus GLACIAL; $p<0.0001$; $p=0.0004$; $p<0.001$).[24-26]

Overall, the incidence and severity of AEs were similar for omalizumab and placebo.[36] AEs considered to be related to the study drug were higher in the omalizumab group compared to the placebo group (11.9% versus 7.4%).[36] However, the majority of AEs were mild or moderate in severity and there were no deaths related to omalizumab across the studies. In another retrospective clinical analysis based in real-life use, 57% of complete responder patients achieved complete response with omalizumab in the first week of treatment and 86% during the first 4 weeks.[37] Similarly, a retrospective study conducted in Spain, consisting of 110 patients who received omalizumab therapy, showed that 81.8% of patients exhibited a significant or complete response.[38] Collectively these data show that omalizumab is efficacious and safe in clinical trials, and offers potential benefits for real-life practice.

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