

# Research letter

## Guidelines for the management of chronic spontaneous urticaria: recommendations supported by the Centre of Evidence of the French Society of Dermatology

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DEAR EDITOR, Chronic spontaneous urticaria (CSU) is an inflammatory disease characterized by spontaneous weals or angio-oedema for more than 6 weeks. The natural history of the disease is resolution within several months or years, and treatment is necessary to limit flares, reduce pruritus and improve quality of life (QoL). Numerous medical drugs are available, all having suspensive effects on CSU. International guidelines from the EAACI/GA<sup>2</sup>LEN/EDF/UNEV were published in 2018,<sup>1</sup> but practice remains heterogeneous, especially for CSU refractory to H<sub>1</sub> antihistamines and regarding states' official drug approval and reimbursement policies.

The Centre of Evidence of the French Society of Dermatology formulated recommendations on treatments for CSU based on evidence from the literature and on consensus expert opinion.<sup>2</sup> Firstly, a multidisciplinary working group, composed of eight health professionals including a biostatistician, with no conflicts of interest regarding the pharmaceutical industry, performed systematic reviews of all interventions, except for alternative treatments. The French National Health Authority performed the research of articles, including any therapeutic prospective study published between 2000 and 2017 found on MEDLINE, Embase, CENTRAL, LILACS and PsycINFO. Articles on diets and paediatric populations were included from 1995 because they were much fewer in number. Articles on H<sub>1</sub> and H<sub>2</sub> antihistamines were included after the inclusion periods of the systematic reviews from the Cochrane Collaboration, which were thus updated.<sup>3,4</sup>

The working group analysed the studies (two persons independently for each intervention) by describing the effect estimates, biases and harms, then graded the level of evidence (from D – no direct research evidence, to A – several multicentric double-blinded studies with concordant positive results and acceptable risks) after reaching unanimous consensus.<sup>5</sup> The comments from the eight experts who were secondarily interviewed were incorporated into the recommendations, then the synthesis was submitted to a multidisciplinary panel of 28 reviewers, including health providers and patients, who scored each recommendation from 1 to 9.

The main points from the recommendations are as follows.

- (i) A second-generation H<sub>1</sub> antihistamine at a single dose is the recommended first-line treatment for CSU.<sup>3</sup> There is no evidence to favour one drug over another. Some H<sub>1</sub> antihistamines should be avoided in individuals who present a known increase in QT interval or those on enzymatic inhibitors.
- (ii) In case of treatment insufficiency, the working group recommends a rapid increase in dosage (1 week to 2 months) until quadruple dosage of H<sub>1</sub> antihistamines, as a second-line treatment.<sup>3</sup>
- (iii) The working group does not recommend the adjunction of H<sub>2</sub> antihistamines or montelukast to H<sub>1</sub> antihistamines in CSU, owing to the lack of demonstrated efficacy.<sup>4</sup>
- (iv) No studies assessed the efficacy or safety of systemic steroids in CSU. The working group does not currently recommend using them.
- (v) As a third-line treatment, in case of decreased QoL of individuals linked to refractory CSU, the working group recommends the adjunction of omalizumab (300 mg every 4 weeks)<sup>6</sup> or ciclosporin (4–5 mg kg<sup>-1</sup> per day during a 6-month period) to H<sub>1</sub> antihistamines. Randomized controlled trials have shown that omalizumab is more effective than placebo, with good short-term tolerance. No head-to-head trials have compared omalizumab and ciclosporin.
- (vi) There is no evidence to indicate the optimal delay between the failure of quadruple dosage of H<sub>1</sub> antihistamines and initiation of omalizumab or ciclosporin; this would likely depend on the QoL of patients and the severity of the CSU.
- (vii) Isolated studies of hydroxychloroquine, dapsone, sulfasalazine, high-dose vitamin D, phototherapy and miltefosine for CSU have been published, but the working group does not recommend them because the data are too sparse.
- (viii) The working group does not recommend systematic food exclusion diets because of no evidence of benefit for individuals with CSU.<sup>7</sup> No prospective studies have been published to date on therapeutic education programmes and psychotherapy in CSU.
- (ix) For children < 12 years old with CSU, single-dose H<sub>1</sub> antihistamines can be used. The working group recommends favouring rupatadine and desloratadine in case of dosage escalation because more data are available than for other drugs. There is a real lack of evidence for third-line treatments in paediatric populations.<sup>8</sup>

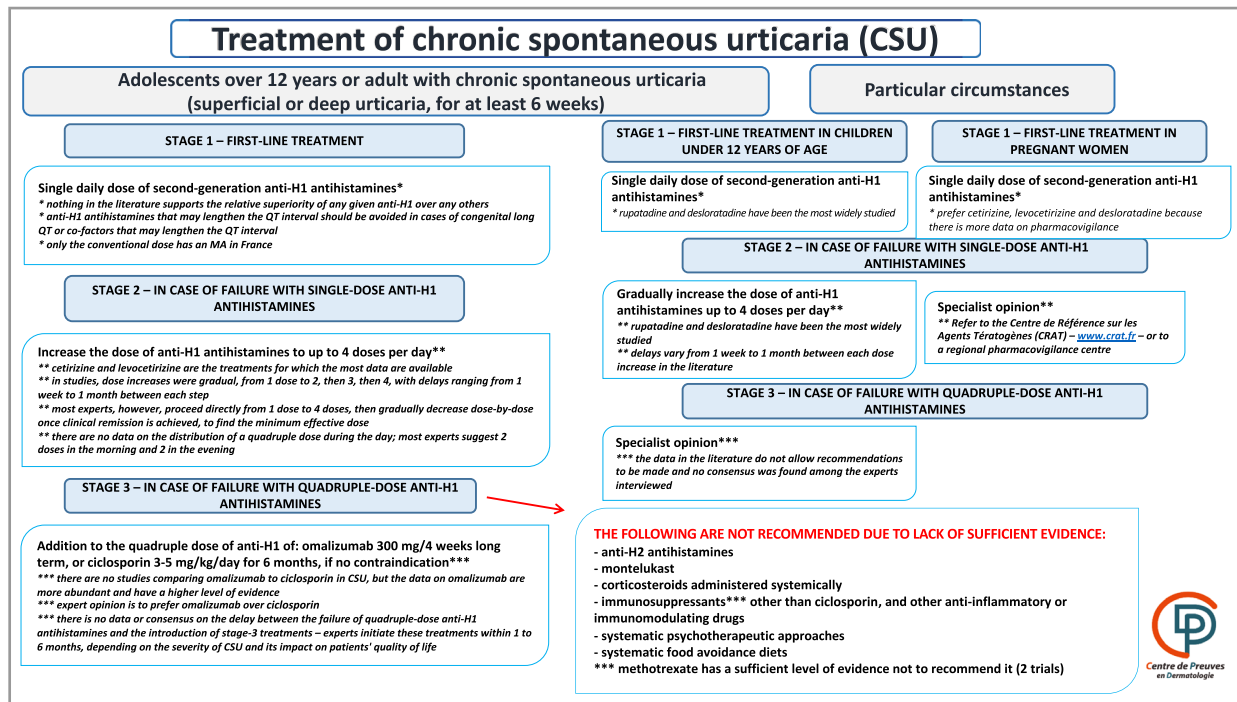


Figure 1 French guidelines for chronic spontaneous urticaria: treatment algorithm. MA, marketing authorization.

- (x) During pregnancy and breastfeeding, a single dose of cetirizine, levocetirizine or desloratadine is preferred because more safety data for these H<sub>1</sub> antihistamines are available. In case of refractory CSU, a specialized consultation is required.

In conclusion, several drugs are considered effective for CSU. The impact on QoL should guide any therapeutic escalation. There is a need for randomized controlled trials (i) comparing omalizumab to immunosuppressive drugs, (ii) in paediatric individuals with CSU, and (iii) evaluating the usefulness of systemic steroids.

On behalf of the French Center of Evidence, these data led to a practical decision-making algorithm (Figure 1) and are included on a dedicated website to provide an easy-to-use tool with a fast step-by-step navigation according to clinical situations (<https://reco.sfdermato.org/en/guidelines-chronic-spontaneous-urticaria>).

Further methodological information is available upon direct request.

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