

Comparing Antihistamines in Chronic Spontaneous Urticaria: Possible Future Directions



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In chronic spontaneous urticaria (CSU), the first-line treatment is licensed dose second-generation H1 antihistamines (2g-H1AHs). Although multiple 2g-H1AHs have shown to be effective at licensed doses in reducing symptoms of urticaria in approximately half of the patients, there exist only a few well-designed trials directly comparing the efficacy between the different 2g-H1AHs. In a recent issue of *Journal of Allergy and Immunology in Practice*, Phinyo and colleagues¹ used an elegant network meta-analysis to compare efficacy and acceptability of licensed-dose 2g-H1AHs in CSU. This is valuable information that adds to the knowledge we had in relation to 2g-H1AH in CSU treatment.

However, in doing so, the authors came across several obstacles inherent to doing meta-analysis that might reduce the credibility of their findings. A meta-analysis can only be as good as the quality of the original trials it is based on.

The most important issue that could be raised is the primary efficacy variable of the original trials.

Since almost a decade ago, the global urticaria guidelines have promoted the Urticaria Activity Score during 7 days (UAS7), more recently complemented by the Urticaria Control Test, as the official outcome measures in CSU.² These tools have been validated against other outcome variables including quality of life in patients with urticaria and are available in many languages. Even so, hardly any of the original trials used these tools. Instead, most studies used other nonvalidated outcome measures. The UAS7 classifies both number of wheals (0-3 points) and severity of pruritus (0-3 points) over a seven-day period, assigning zero points for no hives, one point for fewer than 20 hives, two for 20 to 50 hives and three for more than 50 hives within a time span of 24 hours. Most of the trials gave higher wheal scoring as one point was given to one to five wheals, but six to 10 wheals already got two points and so on, up to four points for more than 20

wheals. By scoring like this, a stronger reduction in score can more easily be obtained compared with scoring with the validated UAS7; however, what the importance of such a reduction in scoring is in a clinical setting is not clear. Whereas the minimal clinically important difference for UAS7 was demonstrated to range between 9.5 and 10.5,³ a minimal clinically important difference for these other scoring systems has not been established.

In addition, the patients recruited had variable severity of CSU and varied between the different trials included in the meta-analysis. Licensed-dose antihistamine therapy is the first-line therapeutic option in patients with CSU, but the majority are not controlled by a single tablet a day. In one patient-centered study, three-quarters of the patients reported they finally needed to take double or even quadruple dosing.⁴ When patients with milder symptoms are included, one could expect the outcomes to be better with licensed dosing; however, when patients with more severe symptoms are enrolled, normally a minority of them can be controlled with single daily dosing. A recent report from China indicated that this just close to a third of all CSU patients.⁵ Taken all these aspects together makes it difficult to produce a solid comparison between trials.

The meta-analysis by Phinyo et al¹ focused on the efficacy of 2g-H1AHs. This is adequate because only licensed doses were considered. However, both main urticaria guidelines, the EAACI/GA²LEN/EDF/WAO guideline² and the American one⁶ include other treatment options related to antihistamines and combinations in which safety analysis should be included. Both consider up-dosing in nonresponders to licensed doses of antihistamines. In addition, the American guideline still includes first-generation antihistamines as a second-line option. In both cases, safety is an important aspect when comparing antihistamines thus managed. Although up-dosing seems to enhance efficacy in urticaria control, for some 2g-H1AHs, up-dosing can result in a higher rate of side effects, especially sleepiness and sedation. These are directly related to the ratio of penetration of the antihistamine into the central nervous system (CNS) and occupancy of brain histamine receptors. Yanai et al⁷ developed a technique with radio-labelled doxepin to measure the degree of antihistamine CNS penetration and studied various H1-antihistamines with this procedure. Apart from the reported adverse events in the trials, this kind of tool can be very valuable in comparing the safety of different 2g-H1AHs, especially when up-dosing is proposed.

First-generation antihistamines, are not recommended by the EAACI/GA²LEN/EDF/WAO guideline² for the treatment of CSU, but they are still much used by the public at large and are considered an alternative treatment add-on by the American urticaria guideline from 2014.⁶ Apart from augmented sedation and sleepiness that carry over until the next day,⁸ due to their blood-brain-barrier passage without a G-protein-coupled carrier to

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facilitate their out-flux out of the CNS, they have several other side effects owing to their poor selectivity. As such, they also have an anticholinergic effect (dry mouth, urine retention) and act on the serotonin receptor (weight gain), as well as on the ion channels in the myocardium. However, apart from these well-known adverse effects, recently drugs with anticholinergic activity have been linked to dementia, making the case against the use of first-generation antihistamines in CSU probably more solid.

Finally, some studies have shown the superiority of multiple-dose over single-dose antihistamine therapy in CSU. Not all these trials have yet used the UAS7 as the primary efficacy variable.⁹ For future studies, it would be strongly recommended to use this tool to build a solid pool of evidence on CSU treatment with up-dosed 2g-H1AHs. Once more homogeneous trial designs and outcome measures have been adopted, the comparison of up-dosed regimens between different second-generation antihistamines could be possible. Thus, for the future, it might be interesting to have a comparative meta-analysis between up-dosed regimens of 2g-H1AHs once more robust up-dosing trails have been published, including both efficacy and safety variables.

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