Most but not all 2nd generation H_1-antihistamines have been tested specifically in urticaria, and evidence supports the use of bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine. We recommend the use of a standard-dosed modern 2nd generation H_1-antihistamines as the first-line symptomatic treatment for urticaria. However, no recommendation can be made on which to choose because, to date, well-designed clinical trials comparing the efficacy and safety of all modern 2nd generation H_1-antihistamines in urticaria are largely lacking.

Should modern 2nd generation H_1-antihistamines be used as first-line treatment of urticaria?

We **recommend** a 2nd generation H_1-antihistamine as first-line treatment for all types of urticaria.

↑↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] 100% agreement

Is an increase in the dose to up to fourfold of modern 2nd generation H_1-antihistamines useful and to be preferred over other treatments in urticaria?

We **recommend** updosing of a 2nd generation H_1-antihistamine up to fourfold in patients with chronic urticaria unresponsive to a standard-dosed 2nd generation H_1-antihistamines as second-line treatment before other treatments are considered.

↑↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] ≥90% agreement

Should modern 2nd generation H_1-antihistamines be taken regularly or as needed?

We **suggest** 2nd generation H_1-antihistamines to be taken regularly for the treatment of patients with chronic urticaria.

↑

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

Should different 2nd generation H_1-antihistamines be used at the same time?

We **suggest against** using different H_1-antihistamines at the same time.

↓

Consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1] ≥70% agreement

Several studies show the benefit of the use of a higher than standard-dosed 2nd generation H_1-antihistamines in urticaria patients[86–88] corroborating earlier studies with 1st generation H_1-antihistamines that came to the same conclusion.[89,90] Studies support the use of up to fourfold standard-dosed bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, and rupatadine.[86,87,91–94]

If there is no improvement, should higher than fourfold doses of 2nd generation H_1-antihistamines be used?

We **recommend against** using higher than fourfold standard-dosed H_1-antihistamines in chronic urticaria

↓↓

Strong consensus[1]

Evidence- and consensus-based (see Evidence Report)

[1]≥90% agreement

In summary, these studies suggest that some patients with urticaria, who show insufficient response to a standard-dosed 2nd generation H_1-antihistamine, benefit from updosing which is preferred over mixing different 2nd generation H_1-antihistamines as their pharmacologic properties are different. We, therefore, recommend to increase the dose up to fourfold, in such patients (Figure 4). Patients need to be informed that 2nd generation H_1-antihistamine updosing is off-label and higher than fourfold is not recommended as it has not been tested. However, updosing has been suggested in the guidelines for urticaria since the year 2000 and so far no serious adverse events have been reported, nor has a side effect ever been reported in the literature attributed to long-term intake and potential accumulation.

5.4.3 | Omalizumab treatment

Omalizumab is the only other licensed treatment in urticaria for patients who do not show sufficient benefit from treatment with a 2nd generation H_1-antihistamine, and therefore the next step in the algorithm. Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of CSU.[95-100] Omalizumab has also been reported to be effective in CIndU[101–103] including cholinergic urticaria,[104] cold urticaria,[105,106] solar urticaria,[107] heat urticaria,[108] symptomatic dermographism,[109,110] and delayed pressure urticaria.[111] In CSU, omalizumab prevents wheal and angioedema development,[112] markedly improves quality of life,[113,114] is suitable for long-term treatment,[115] and effectively treats relapse after discontinuation.[115,116] The recommended initial dose in CSU is 300 mg every 4 weeks. Dosing is independent of total serum IgE.[117]

Patients with urticaria who do not show sufficient benefit from treatment with omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher doses, shorter intervals, or both. Studies support the use of omalizumab treatment at doses up to 600 mg and intervals of 2 weeks, in patients with insufficient response to standard-dosed omalizumab.[118-121] Patients need to be informed that omalizumab updosing is off-label.

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