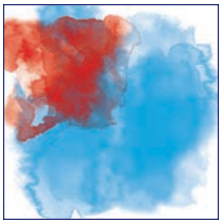

Efficacy and Safety of Up-dosed Second-generation Antihistamines in Uncontrolled Chronic Spontaneous Urticaria: A Review

by INDRASHIS PODDER, MD; ARUNIMA DHABAL, MD; and SANKHA SUBHRA CHAKRABORTY, MBBS
All authors are with the College of Medicine and Sagore Dutta Hospital, in Kolkata, West Bengal India.

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BACKGROUND: Oral second-generation antihistamines (sgAH) constitute the first-line treatment for chronic spontaneous urticaria (CSU), a debilitating dermatological condition. However, many patients respond incompletely, and up-dosing sgAHs up to four-fold their conventional dose is recommended for disease control. Many physicians refrain from up-dosing due to a paucity of efficacy and safety data, instead adding a second antihistamine or an immunomodulator. **OBJECTIVE:** With the aim of addressing this knowledge gap, we conducted a literature review to highlight efficacy and safety data on up-dosed sgAHs. **METHODS:** We conducted a comprehensive search of the literature across multiple databases (PubMed, EMBASE, MEDLINE and Google scholar) using the keywords (alone and in combination) and MeSH items as well as non-MeSH terms such as "chronic spontaneous urticaria", "chronic idiopathic urticaria", AND "updosing", "second-generation anti-histamines", "cetirizine", "fexofenadine", "levocetirizine", "desloratadine", "ebastine", "bilastine", and "rupatadine". **RESULTS:** Our review suggests bilastine, fexofenadine, levocetirizine, and cetirizine are recommended for up-dosing in non-responsive patients with CSU (Grade A recommendation), while desloratadine and ebastine can be recommended (Grade B recommendation). Among those with Grade A recommendation, bilastine and levocetirizine may be up-dosed safely to four times, while fexofenadine has been studied at three times the conventional dose. None of the drugs showed any dose-dependent increase of adverse effects; however, cetirizine up-dosing may increase the risk of dose-related sedation. There were no reports of systemic complications, including cardiotoxicity, at higher than licensed doses of these drugs. Only cetirizine and rupatadine up-dosing have been documented to be effective and safe in children, while there is lack of data on geriatric patients and pregnant or lactating females. **KEYWORDS:** Chronic spontaneous urticaria, second generation anti-histamines, up-dosing, effectiveness, safety

Chronic urticaria (CU) is a dermatological condition characterized by recurrent transient wheals, with or without angioedema, occurring daily or almost daily for more than six weeks.[1] There are two variants—chronic inducible urticaria (CIndU) or physical urticaria, which is triggered by certain physical stimuli like pressure, heat, or cold, and the more common chronic spontaneous urticaria (CSU), which develops without any known exogenous stimulus and accounts for 80 to 90 percent of cases.[2] This disease affects 0.5 to 1 percent of the global population, with female preponderance.[3] The recurrent symptoms often result in sleep disturbances and cause notable negative impacts on quality of life (QoL).[4]

Although the exact pathogenesis remains unclear, CSU is a mast cell-driven disease involving histamine as the predominant mediator. Thus, antihistamines form the first-line treatment for this condition, and second-generation antihistamines (sgAH) are recommended due to their minimal anti-cholinergic, sedative, and drug-interacting properties and longer half-lives.[1] However, almost 60 percent of patients remain uncontrolled with the standard licensed dose of sgAHs (Table 1).[3,5] In this subset of patients, up-dosing of sgAHs up to four times the licensed dose has been recommended by most guidelines, allowing 2 to 4 weeks for response at each dose.[1,6] Nevertheless, this recommendation is primarily based on expert opinions, and several studies concerning sgAH up-dosing have shown conflicting results. Additionally, the safety profile of up-dosed sgAHs needs to be considered carefully, as two of the earliest marketed sgAHs, astemizole and terfenadine, have been withdrawn because of their potential cardiotoxicity.[7]

The present article aims to review the effectiveness and safety of up-dosed sgAHs in an evidence-based manner, to promote their use in a more rational manner.

METHODS

We conducted a comprehensive search of literature concerning up-dosing of second generation anti-histamines (sgAHs) across multiple databases (PubMed, EMBASE, MEDLINE and Google scholar) using the keywords (alone and in combination) and MeSH items as well as non-MeSH terms, such as "chronic spontaneous urticaria", "chronic idiopathic urticaria", AND "updosing", "second-generation anti-histamines", "cetirizine", "fexofenadine", "levocetirizine", "desloratadine", "ebastine", "bilastine", "rupatadine". We included all types of articles, but excluded articles not published in the English language. The references of relevant articles were further scanned for more articles.

The obtained articles were evaluated using two systems—"Oxford Centre for Evidence-Based Medicine (OCEBM)" AND "strength of

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CORRESPONDENCE: Indrashis Podder, MD; Email: ipodder88@gmail.com

recommendation taxonomy" (SORT). Oxford Centre for Evidence-Based Medicine (OCEBM) is based on an evidence-based approach for treatment benefit regarding the study quality, their imprecision and indirectness and categorized into the following: Level 1 (systematic review of randomized trials or n-of-1 trials); Level 2 (randomized trial or observational study with dramatic effect); Level 3 (non-randomized controlled cohort/follow-up study); Level 4 (case-series, case-control studies, or historically controlled studies); and Level 5 (mechanism-based reasoning).[8] The evidence in SORT, developed by editors of the United States Family Medicine and Primary Care journals (i.e., *American Family Physician, Family Medicine, Journal of Family Practice* and *British Medical Journal USA*) was graded using a three-point scale based on the quality of methodology, as follows: Level I=Good-quality, patient-oriented evidence; Level II=Limited-quality patient-oriented evidence; Level III=Other evidence, including consensus guidelines, opinion or case studies.[9] Clinical grade of recommendations were developed on the best available evidence and graded as follows: A=Recommendation based on consistent Level 1 evidence; B=Recommendation based on consistent Level 2 or 3 studies, or extrapolation from Level I studies; C=Recommendation based on Level 4 studies or extrapolation from Level II or III studies; and D=Level 5 evidence or inconsistent and inconclusive studies at any level.[8] For clinical implication, based on consensus, the grades of recommendation may be considered as: Grade A=is recommended; Grade B=can be recommended; Grade C=may be recommended; and Grade D=may be considered.

DISCUSSION

Several studies have been conducted to assess the utility and safety of sgAHs, when administered at higher than conventional dose with variable outcomes. Studies concerning individual drugs have been briefly mentioned below, along with their levels of recommendation (Table 2).[3,10–21]

Cetirizine. Cetirizine is one of the oldest sgAHs to be used for the treatment of CU. Kameyoshi et al[10] demonstrated more effective symptomatic control with doubled dose of cetirizine (20mg daily) in uncontrolled patients, compared to standard dose (10 mg daily). However, another study reported clinical improvement in only five percent of refractory patients when cetirizine dose was increased by three times (30mg daily). The authors recommended treatment with steroids and immunosuppressants in such patients for effective disease control.[11] A meta-analysis and a recent systematic review have also detected increased effectiveness on up-dosing of cetirizine (Table 2).[3,12]

There are variable reports regarding adverse effects of increased doses of cetirizine. Kameyoshi et al[10] reported increased sedation in 10 percent of patients on up-dosing (20mg daily), while Asero[11] reported increased tiredness and somnolence in 59% patients (30mg daily). No other systemic adverse effects were reported by either authors. Notably, higher dose of cetirizine (up to 3-times up-dosing or 30mg daily) has been found to be remarkably safe from a cardiovascular point of view, as it remains inactive on hERG channels, inhibition of which is responsible for antihistamine-related cardiotoxicity.[7]

Up-dosing of cetirizine has a Grade A recommendation and is recommended in uncontrolled CSU. However, evidence is limited, as studies show conflicting results and there is increased risk of sedation at higher dose (Table 2).

Fexofenadine. There are inconsistent results regarding up-dosing of fexofenadine. Magen et al. observed no significant clinical improvement in 31 percent of patients, even when fexofenadine dose was escalated to four times the conventional dose (720 mg daily). However, four-fold increased dose significantly reduced autologous serum-induced wheal size compared to standard dose.[14] In contrast, several authors have reported significant clinical improvement in uncontrolled patients when the dose was increased to 240mg, 360mg and 540mg daily at intervals of 1 to 2 weeks.[13,15] A meta-analysis also found fexofenadine up-dosing to be effective in 83.07 percent (95% CI 68.14-99.45) of non-responsive patients with CSU, the highest rate among all sgAHs.[12] This view is further corroborated by a recent systematic review which found two-fold up-dosing of fexofenadine to be effective in uncontrolled patients (Table 2).[3]

Fexofenadine has shown safety, even in increased doses (up to 540mg daily, or 3-times standard dose). The most common adverse effects with high doses are headache, followed by sedation, but no dose-dependent exacerbation has been reported. Concerning systemic side effects, no psychomotor or cognitive disruption has been reported at 360mg daily, as there is minimal transfer across the blood-brain barrier, while cardiac safety, including QT interval, has been maintained at even higher doses (800mg once daily to 690mg twice daily).[7,22]

TABLE 1. Standard/licensed dose of second-generation antihistamines evaluated in the review.[3]

SECOND GENERATION ANTI-HISTAMINE	MAXIMUM LICENSED DOSE
Cetirizine	10mg/day
Fexofenadine	180mg/day
Levocetirizine	5mg/day
Desloratadine	5mg/day
Ebastine	20mg/day
Bilastine	20mg/day
Rupatadine	10mg/day

Up-dosing of fexofenadine is recommended in uncontrolled patients with CSU at licensed dose, as there is Grade A recommendation. Dose may be escalated to three times the licensed dose (540mg daily) safely, without any significant dose-dependent increase of adverse effects (Table 2).

Levocetirizine. Several authors have reported increased clinical improvement and QoL with up-dosed levocetirizine (up to 4 times or 20mg daily), when administered sequentially to uncontrolled patients on standard dose, although the inter-group difference was not significant.[16-18] Notably, Sharma et al[18] reported no significant improvement in almost 30 percent of patients, even on four-fold up-dosing.[18] Furthermore, levocetirizine has been found to be more effective ($p<0.05$) compared to desloratadine, when both are escalated to four times their standard dose (20mg daily).[17] A meta-analysis and a recent systematic review have also detected increased effectiveness on up-dosing of levocetirizine.[3,12]

In all studies, sedative effects with increased doses of levocetirizine were mild and affected only a small percentage of the subjects. Sharma et al[18] found that more than 75 percent of the patients who experienced somnolence developed it on the standard 5mg dose, suggesting that up-dosing marginally increases the risk of sedation.[18] Staevska et al[17] reported no change/reduced sedation in 75 percent of

TABLE 2. Studies concerning up-dosing of second-generation antihistamines (sgAH) in uncontrolled chronic spontaneous urticaria (CSU)

AUTHOR, YEAR	TYPE OF STUDY	NUMBER OF UNCONTROLLED CSU PATIENTS	STUDY OUTCOME		LEVEL OF EVIDENCE	
			EFFECTIVENESS	SAFETY	SORT	OCEBM
Cetirizine						
Kameyoshi et al, 2007[10]	Open-label randomized, parallel-group trial	21	Doubled dose of cetirizine (20 mg daily) is more effective than licensed dose (10 mg daily) in uncontrolled patients, as evidenced by lower UAS score.	Minimal adverse effects reported, only 9.5% complained of increased drowsiness on double-dose.	II	2
Asero R, 2007[11]	Open-label longitudinal, single group	22	Only 1 patient (4.9%) demonstrated clinical benefit with up-dosed cetirizine (30 mg daily) after 2 weeks, Urticaria severity was assessed by visual analogue scale.	Tiredness and somnolence reported by 59% patients on higher dose, No other ADR reported.	II	3
Guillen-Aguinaga et al, 2016[12]	Systematic review and meta-analysis	20-418	Cetirizine up-dosing was effective in 53.8% (95% CI 33.3-79.2) non-responsive CSU patients. Up-dosing significantly improved pruritus, but not wheal number.	No dose-dependent increase of ADRs.	I	1
Iriarte et al, 2020[3]	Systematic review	20-439	Cetirizine showed increased effectiveness on up-dosing	No dose-dependent increase of ADRs.	I	1
Fexofenadine						
Godse et al, 2010[13]	Non-randomized, dose escalating, single group longitudinal trial	37	70% remained unresponsive to conventional dose but 97% became asymptomatic on up-dosing (up to 3 times or 540 mg daily). UAS7 score was used to assess effectiveness.	No significant ADR. Headache reported in 2 patients with higher dose; mild sedation in 1 patient with 540mg dose.	II	3
Magen et al, 2012[14]	Non-randomized, non-controlled clinical trial	67	UAS7 score improved significantly in 68.7% patients on standard dose (180 mg daily), while 31.3% had no significant improvement on 4-times updosing. Up-dosed fexofenadine significantly reduced autologous serum induced wheal size, compared to standard dose.	NA	II	3
Tanizaki et al, 2013[15]	Open-label, longitudinal, non-randomized, single group	20	Significant reduction in pruritus severity and histamine-induced flare and itch noted with 240 mg daily, compared to 120 mg daily.	No dose-dependent increased of ADR	II	3
Guillen-Aguinaga et al, 2016[12]	Systematic review and meta-analysis	15 publications following PRISMA guidelines	Among all sgAHs fexofenadine up-dosing has highest proportion of responders in 83.07% uncontrolled patients. Up-dosing significantly improved pruritus, but not wheal number.	No dose-dependent increase of ADRs.	I	1
Iriarte et al, 2020[3]	Systematic review	20-439	Fexofenadine up-dosing (up to 2 times) produced dose-dependent significant response and controlled CSU in majority patients	No dose-dependent increase of ADRs.	I	1

TABLE 2. (CONTINUED) Studies concerning up-dosing of second-generation antihistamines (sgAH) in uncontrolled chronic spontaneous urticaria (CSU)

AUTHOR, YEAR	TYPE OF STUDY	NUMBER OF UNCONTROLLED CSU PATIENTS	STUDY OUTCOME		LEVEL OF EVIDENCE	
			EFFECTIVENESS	SAFETY	SORT	OCEBM
Levocetirizine						
Godse K, 2010[16]	Non-randomized, open label, dose-escalating trial	20	60% (12/20), 75% (6/8) and 100% (2/2) patients became asymptomatic (UAS7=0) with 5 mg, 10 mg and 20 mg daily levocetirizine respectively.	1 patient complained of mild sedation with 10 mg and 20 mg levocetirizine each. No significant ADR noted.	II	3
Staevska et al, 2010[17]	Randomized, double-arm (levocetirizine vs desloratadine).	40	22.5% (9/40) patients became symptom free with 5 mg, 25.8% (8/31) with 10mg and 21.7% (5/23) with 20 mg daily dose. 18 patients (45%) remained non-responsive to up-dosed levocetirizine. Increased dose also improved quality of life.	No dose-related increase in ADR (sedation) reported.	I	2
Sharma et al, 2017[18]	Open-label longitudinal/ cohort, single arm	113	18.6% became asymptomatic with 5 mg, proportion increased to more than twofold and threefold on doubling and quadrupling the standard dose respectively. Almost 30% unresponsive to four-times up-dosed levocetirizine	No notable ADR, no dose-related increase	II	3
Guillen-Aguinaga et al, 2016[12]	Systematic review and meta-analysis	20-418	Levocetirizine up-dosing was effective in 55.26% (95% CI 39.82-73.19) non-responsive CSU patients. Up-dosing significantly improved pruritus, but not wheal number.	No dose-dependent increase of ADRs.	I	1
Iriarte et al, 2020[3]	Systematic review	20-439	Levocetirizine showed increased effectiveness on up-dosing	No dose-dependent increase of ADRs.	I	1
Desloratadine						
Staevska et al, 2010[17]	Randomized, double-arm, cross-over (levocetirizine vs. desloratadine)	40	10% (4/40) patients became symptom free with 5 mg, 19.4% (7/36) with 10mg and 3.4% (1/29) with 20 mg daily dose. 28 patients (70%) remained non-responsive to up-dosed desloratadine. Increased dose also improved quality of life. 7/28 non-responders (25%) responded to 20 mg levocetirizine.	No dose-related increase in ADR (sedation) reported. One patient developed palpitation on 20 mg dose, without any ECG change.	I	2
Ebastine						
Godse K, 2011[19]	Non-randomized, dose escalating, single group longitudinal trial	30	33% remained uncontrolled with standard dose, but 100% patients responded on up-dosing (up to 4 times or 40 mg daily). UAS7 score was used to assess effectiveness.	No significant ADR. 1 patient reported mild sedation on 40 mg dose.	II	3
Bilastine						
Audicana et al, 2007[20]	Double-blind, randomized, placebo-controlled dose-ranging trial	222	Bilastine (10,20,30 mg) significantly better than placebo for disease control (reduced wheal number and itching). No significant difference between 10, 20 and 30 mg doses.	No ADR reported	I	2
Weller et al, 2018[21]	Open-label, non-controlled, longitudinal trial	31	Uncontrolled patients received bilastine in escalating doses (20, 40 and 80 mg) at 2-week intervals, if UAS7 >3 with preceding lower dose. Six patients (19%) gained complete (UAS7 ≤ 3) relief with bilastine 20 mg and a further 3(10%) bilastine 40 mg. Seven patients (23%) gained complete relief from itching with bilastine 20 mg and a further 3 (10%) with 40 mg. Urticaria became well-controlled (UAS7<6) in 26%, 6% and 3% patients with 20, 40 and 80 mg respectively.	No significant ADR reported.	II	3
Iriarte et al, 2020[3]	Systematic review	20-439	Bilastine showed increased effectiveness on up-dosing	No dose-dependent increase of ADRs.	I	1

subjects, possibly attributable to improved sleep-quality and daytime wakefulness and tolerance to the sedative property of drug.[17] Cardiac safety has been demonstrated with up to six-fold the standard dose without any QT-interval polongation or arrhythmia.[7]

There is Grade A recommendation and levocetirizine is recommended for up-dosing in refractory CSU. It may be safely up-dosed to guideline-recommended four times the standard dose (20mg daily) without any notable adverse effect. However, almost one third of patients may remain unresponsive to up-dosed levocetirizine.

Desloratadine. A single study has shown comparable rates of improvement of CSU when desloratadine was sequentially increased from 5mg to 20mg daily. However, 70 percent remained unresponsive to 20-mg dose. Twenty-five percent of the non-responders became asymptomatic with 20mg levocetirizine; on the contrary, none of the levocetirizine non-responders improved with 20mg of desloratadine. Overall, the authors found levocetirizine to be statistically superior to desloratadine in improving symptoms and quality of life.[17] Notably, Siebenhaar et al[23] have reported desloratadine 20mg to be more effective than the standard dose (5mg daily) in acquired cold urticaria (ACU), a type of CInDU.[23]

Neither study has reported any significant adverse effects with increased dose (up to 4-fold), without any evidence of dose-related increased somnolence.[17,23] Additionally, no significant risk of cardiac arrhythmias has been observed with up to four times the standard dose of desloratadine.[7]

Desloratadine has limited evidence regarding its up-dosing in uncontrolled CSU, although there is Grade B recommendation (based on a single study) and can be recommended. Although updosing is safe, a large proportion of patients may remain unresponsive. Such patients may be given an alternate antihistamine, such as levocetirizine or immune-modulators.

Ebastine. A single study (n=30) has demonstrated the effectiveness of sequentially up-dosed ebastine in unresponsive CSU patients starting from 10mg (standard dose) to 40mg (4-times up-dosing), over four weeks. They reported 20mg to be more effective than 10mg, and two patients who remained symptomatic with 20mg, improved with 40mg dose.[19]

The author reported no significant adverse effect with increased doses; only mild sedation was reported by one patient at the maximal dose of 40 mg.[19] Additionally, *in-vivo* studies have confirmed good cardiovascular tolerability without any QT prolongation, even when the dose is increased by five times.[24]

Ebastine can be recommended for up-dosing in uncontrolled CSU (Grade B recommendation; single study), although there is limited evidence. There is no risk of significant ADRs at higher dose.

Bilastine. Bilastine is a relatively new long-acting, sgAH, recently approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria. It does not cross the blood brain barrier and is free of any sedative effect (non-sedative), apart from being devoid of any systemic adverse effects or drug interactions.

A randomized dose-ranging trial studied bilastine in doses of 10, 20, and 30 mg versus placebo to assess disease control in CSU based on the number of wheals and itching. All doses were statistically better than placebo, however no significant difference was observed between the doses, despite showing a dose-related trend.[20] Weller et al[21] may be credited to perform the first authentic up-dosing study with bilastine in patients with uncontrolled CSU at licensed doses of other sgAHs such as loratadine, cetirizine, rupatadine, ebastine, fexofenadine anddesloratadine. They administered bilastine in gradually escalating doses (20, 40 and 80mg daily) at two-week intervals, to patients not responding to the preceding lower dose (UAS7>3). They concluded that licensed dose of bilastine is effective in moderate to severe CSU patients not responding sufficiently to other sgAHs, and there is definite benefit of up-dosing to double or four times the licensed dose in terms of reduction in mean UAS7.[21] A recent systematic review has also found increased effectiveness for up-dosed bilastine.[3] In addition to CSU, up-dosing to four times the dose has also been found to be effective and safe in cold contact urticaria.[25]

Bilastine is a safe antihistamine without any sedative effects or cognitive impairment, and this property is maintained even on up-dosing up to four times the licensed dose.[21,25,26] No systemic adverse effects, including cardiac complications, have been reported even with doses up to five times the licensed dose.[7,27]

Bilastine has Grade A recommendation and is recommended for up-dosing in uncontrolled CSU. It may be up-dosed safely to four times its licensed dose without any sedation or cognitive impairment.

Rupatadine. Rupatadine is a sgAH with a higher receptor affinity than levocetirizine and fexofenadine, along with additional anti-platelet activating factor (PAF) effects.[28] PAF is a recognized mediator in CSU, and rupatadine was proposed to be a significant addition to the existing array of antihistamines.[29]

To the best of our knowledge, there are no studies on rupatadine up-dosing in uncontrolled CSU. Studies have been conducted to determine its dose in naïve patients with CSU, with conflicting results. Dubertret et al[30] observed faster and longer-lasting symptomatic relief with rupatadine 10 and 20 mg; however, a clear dose-response was observed for 20-mg dose.[30] Contrarily, Giménez-Arnau et al[31] observed no significant difference between the two doses (10 or 20 mg daily) with respect to pruritus severity, number of wheals, and total symptoms scores.[31] However, in a pooled data analysis including both trials (n=538), 20 mg daily resulted in a higher proportion of patients with a 75-percent or greater response for all three parameters assessed (Mean Pruritus Score, Mean Number of Wheals, and Mean UAS) than 10-mg dose.[32] Thus, in CSU the maximum studied dose remains 20mg daily, although up-dosing up to four times (40mg daily) is supported in cold urticaria with better response than 20mg daily dose.[33] Recently, a post-hoc analysis of a Phase III clinical trial has indicated increased efficacy of up-dosed rupatadine (up to 20mg) in Japanese patients with CSU, dermatitis, or pruritus.[34] However, this study included patients without exclusive CSU, and there was no definite criteria or timing for up-dosing (patients simply up-dosed during the earlier Phase III study due to lack of efficacy, or later due to aggravation of symptoms), and thus not considered while generating evidence for the current review.

A dose-related increase in adverse effects was reported in both trials, with somnolence and headache being most frequent. Rupatadine 10mg was tolerated better than 20mg; however, the differences between the incidence or type of adverse effects noted with the two doses were not significant.[30,31] The cardiac safety of rupatadine has been studied and no significant

changes in cardiac repolarization were noted with doses up to tenfold higher than the recommended dose.[7]

Currently, rupatadine has no evidence for up-dosing in uncontrolled CSU. However, based on previous studies, two-fold up-dosing (20mg) may be attempted in unresponsive patients, taking into account the increased risk of somnolence and headache in a dose-dependent manner.

Up-dosing in special populations. Until recently, there was no literature concerning up-dosing of antihistamines for treating CSU in special populations, such as pediatric and geriatric age groups, and pregnancy or lactating patients. However, recently, Gabrielli et al[35] and Sarita et al[36] documented the effectiveness and safety of up-dosed second generation antihistamines in children. Gabrielli et al demonstrated only 10 percent of children to be unresponsive to maximally updosed sgAHs (up to four times), compared to 50 percent of adults, and they attributed this discrepancy to varying pathogenic mechanisms. Sarita et al[36] found up-dosed cetirizine and rupatadine (up to four times standard dose) to be tolerable and safe in children with refractory CSU, however efficacy appeared to be limited to double the standard dose. To the best of our knowledge, there is no data yet concerning geriatric patients and pregnant or lactating patients. The authors recommend up-dosing of cetirizine and rupatadine in children with CSU not responding to standard does as per current guidelines, however the same cannot be extrapolated to elderly, pregnant and lactating patients due to a dearth of quality evidence.

CONCLUSION

Although several studies have been conducted concerning the up-dosing of sgAHs in uncontrolled CSU, the results are not uniform for all drugs. Bilastine, fexofenadine, levocetirizine and cetirizine have grade A recommendation for up-dosing, while desloratadine and ebastine have Grade B recommendation. Up-dosing possibly exerts a significant impact on pruritus, but not on wheal number.[12] Besides urticaria control, these drugs also improve the QoL and sleep quality of affected individuals. Bilastine and levocetirizine may be safely up-dosed to four times their licensed dose, consistent with guidelines, while fexofenadine has been safely up-dosed to three-fold. Cetirizine up-dosing may result in increased dose-dependent sedation, while a considerable proportion of patients may respond inadequately to higher doses of levocetirizine and desloratadine. No drug is associated with systemic complications including cardiotoxicity, even at higher doses. No statistical difference has been noted regarding occurrence of unwanted effects and sedation with standard or higher dose. However, patients tend to have a negative perception towards up-dosing of sgAHs being concerned about their long-term harmful effects, loss of effectiveness and dependence.[37] Cetirizine and rupatadine may be considered for up-dosing in children, while increasing the dose is not yet recommended in elderly, pregnant, or lactating patients. Thus, adequate counseling is necessary to motivate these patients for up-dosing if they remain uncontrolled at standard doses. We also noted considerable heterogeneity in the evidence with respect to study designs, sample-size, study duration and interval between dose-escalations. Further large-scale and well-designed trials adhering to the current treatment guidelines are necessary to validate or refute our evidence-based recommendations.

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