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A Randomized Single Blinded Study Comparing the Efficacy of Bilastine Versus Cetirizine in Autoimmune Urticaria

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Abstract

Introduction

Autoimmune chronic spontaneous urticaria (aiCSU) is characterized by the presence of anti-FceR1 and anti-IgE autoantibodies. In this study we aimed to compare the efficacy and safety of bilastine versus cetirizine in aiCSU.

Methods

In a single blinded study, thirty-six patients with chronic spontaneous urticaria with positive autologous serum skin test (ASST) were randomly assigned to receive bilastine (20mg to 80 mg per day) or cetirizine (10mg to 40 mg per day) for 12 weeks. The disease activity score (UAS7) was documented at baseline, week 1, 2, 4, 8 and 12. The ASST and chronic urticaria quality of life scores (CUQ_2oL) were evaluated before and after treatment. Safety was assessed according to adverse events reported by patients during treatment period.

Results

A total of 14 male (38.9%) and 22 female (61.1%) patients aged between 21 to 70 years old (40.92 ± 13.59) were randomly assigned to receive bilastine (n=18) and cetirizine (n=18). Baseline UAS 7 scores improved significantly in both treatment groups; in the bilastine group from 20.50 ± 11.00 to 2.50 ± 5.00 ($p<0.01$) and in the cetirizine group from 16.50 ± 18.00 to 2.00 ± 4.00 ($p<0.01$). The evaluation of CUQ_2oL score revealed significant reduction in both groups; in the bilastine group from 43.50 ± 22.00 to 1.00 ± 2.00 ($p<0.01$) and in the cetirizine group from 41.00 ± 19.00 to 3.00 ± 11.00 ($p<0.01$).

Conclusion

Bilastine and cetirizine were similarly effective during a 12-week treatment period in patients with aiCSU.

Key words*: Autoimmune chronic spontaneous urticaria, autologous serum skin testing, bilastine, cetirizine*

Introduction

Urticaria is primarily a mast cell driven, heterogeneous group of disease characterized by sudden development of transient episodes of wheals, angioedema or both.[1] Urticaria can be classified based on its duration; acute if less than 6 weeks or chronic if more than 6 weeks.[1] Chronic urticaria (CU) is classified into two types based on the presence or absence of inducing factor; chronic spontaneous urticaria and chronic inducible urticaria.

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Chronic spontaneous urticaria (CSU) is defined as spontaneous occurrence of wheals and/or angioedema; occurring daily and persisting for more than 6 weeks without an obvious stimulus. CU is a highly prevalent disease with a point prevalence of 0.5 – 1.0 %.[2] Data on the current burden of urticaria in the Asia- Pacific region have yet to be reported, however it is suggested that the lifetime prevalence may be as high as 23%.[3]

The prevalence of urticaria among clinic attendees in a tertiary center in Malaysia is 4.13%.[4] Several factors could possibly contribute to underlying pathogenesis of CSU which includes autoimmunity, pseudo-allergy to food or drugs and infections.[1] In 30-50% of cases autoimmunity has been reported to be the causative factor.[5] Autoimmune chronic spontaneous urticaria (aiCSU) is defined by the presence of IgG autoantibodies to IgE or its high affinity receptor FceR1.[6] Two types of autoimmunity has been proposed; Type 1 autoimmunity (also known as autoallergy) is the presence of IgE against auto-allergens and Type IIb autoimmunity refers to presence of IgG autoantibodies against IgE or its receptor.[7]

The proposed diagnostic criteria for aiCSU is a positive in vivo autoreactivity (a positive Autologous serum skin test [ASST]), a positive in vitro basophil reactivity [a positive basophil histamine release assay(BHRA) or basophil activation test(BAT)] and a positive immunoassay for specific identification of IgG autoantibodies against FceR1 and/or anti-Ige (western blot or ELISA).[6] The PURIST study reported only 8% of its patients met the combined criteria for aiCSU. This study also suggested that a positive in vitro basophil reactivity has high predictive value for aiCSU.[8] However, Basophil reactivity test is not practical in clinical use as it is time consuming and difficult to standardize. Therefore, ASST is still used widely as a screening method to assess for autoreactivity as it is a simple clinical test that has a sensitivity of 70% and specificity of 80%.[6] A systematic review comparing ASST responses in patients with CSU suggests that patients with positive ASST responses had higher UAS and higher levels of serum total IgE than those of patients with negative ASST responses.[9]

The recent position paper on management of chronic urticaria recommended non-medical management such avoidance of allergic stimuli if known.[1] It also proposed the use of non-sedating second generation H1 antihistamines at conventional dose as the first-line management and increasing up to four-fold the recommended dose as second line management.[1] Subsequently, for the non-responders, the use of omalizumab or ciclosporin can be added as third line therapy.[1]

There are many second generation anti-histamine drugs available for the treatment of urticaria. However, only seven (cetirizine, loratadine, desloratadine, fexofenadine, levocetrizin rupatadine and bilastine) have been studied in detail for urticaria.[1] Bilastine is a non-sedating second generation H1-receptor inverse agonist, approved in many countries throughout the world and Malaysia for the treatment of allergic rhino-conjunctivitis and urticaria in adults and children over 12 years of age.[10-11]

Bilastine has a rapid onset of action within 60 mins and it is sustained up to 24 hours. It undergoes minimal hepatic metabolism and is largely eliminated unchanged in both feces and urine. Studies in healthy volunteers and patients have shown that bilastine does not affect cardiac conduction, vigilance or driving ability, is free from antimuscarinic effects, and does not promote significant changes in laboratory tests, electrocardiograms or vital signs.[12] The most commonly reported side effects of bilastine are headache, somnolence and fatigue.[10] Cetirizine is a highly selective second generation H1-receptor antagonist and an active metabolite of hydroxyzine that is directly absorbed and not metabolized by the cytochrome P-450 enzyme system. The peak plasma concentration occurs approximately one hour after intake. It is mainly excreted in urine. Commonly reported side effects are headache, dry mouth, drowsiness and fatigue.[13] Cetirizine is widely used in our local setting for the treatment of urticaria due to its availability and cost.

In general, aiCSU is a disease which runs a prolonged and severe course that is difficult to control with conventional antihistamine and often third line of management is preferred. Many studies have been conducted looking into the effectiveness of various anti-inflammatory drugs, anti-leukotrienes, immunomodulators and biologics in aiCSU patients who failed second line treatment with antihistamines.[16-19] In this study we aim to look into the effectiveness and safety profile of bilastine versus cetirizine in aiCSU.

Materials and Methods

This was a randomised, single blinded study

comparing the efficacy of bilastine versus cetirizine in aiCSU. The study was conducted at the dermatology clinic in Hospital Tengku Ampuan Rahimah, Malaysia from April 2018 to December 2018.

Study Drugs

Bilastine (trade name Bilaxten) is a second generation anti-histamine. It was developed in Spain by FAES Farma and have been approved by European Union for the symptomatic treatment of allergic rhino-conjunctivitis and urticaria. Bilastine is recommended as one of the first-line antihistamines in the treatment of urticaria by the European Academy of Allergy and Clinical Immunology (EAACI)/WAO/EDF guideline and Malaysian guideline MARTEG.[1,11]

Cetirizine (brand name Zyrtec) is a second generation anti-histamine and has been approved by FDA US for the treatment of hay fever, allergies, angioedema and urticaria. Zyrtec was developed in Brussels by the company, UCB Pharmaceutical.
The study drugs were dispensed in its original packaging.

Disease severity assessment

UAS 7

UAS7 is a validated, unified and simple scoring system that is proposed for the assessment of disease activity in CSU by international guidelines.[1,24] The signs and symptoms are evaluated by the patient themselves. The subjects were taught on how to perform UAS 7 scoring. UAS was done every day once in the evening for 7 days prior to each clinic review. This tool assesses two items: daily intensity of pruritus and number of hives ratings (0: none to 3: severe). Assessment is done for seven days prior to appointment in order to build the UAS7 score (range 0-42). The UAS 7 scores are categorized into five categories to facilitate in disease severity monitoring. The five categories of disease state are; absent – 0, well-controlled – 1-6, mild – 7-15, moderate – 16-27, and severe – 28-42.

Chronic Urticaria Quality of Life Questionnaire (CUQ_2oL)

CUQ_2oL is a quality of life questionnaire specifically developed for CSU.[1] It is a validated questionnaire that assesses the physical, emotional, social and practical aspects characteristic of this condition. It is a self-administered 23-item questionnaire, where patients have to indicate, on a Likert scale with multiple options; (1: not at all, 2: a little, 3: somewhat; 4: a lot, 5: very much) how much they have been troubled by each problem, with higher scores indicating worse quality of life (range of the score from 23-115). There are six factors in the questionnaire; pruritus, swelling, impact of life activities, sleep problems, limitation, and looks.

Autologous serum skin testing (ASST)

ASST was performed following the recommendation by EAACI/GA^{2}LEN task force consensus report.[14] Briefly; 0.05 mL of autologous serum, 0.05 mL of normal saline 0.9% (as a negative control) and 0.05 mL of histamine diphosphonate (as a positive control) were injected intradermally. The wheal responses were measured at 30 mins. ASST is considered positive when autologous serum induced wheal was at least 1.5 mm greater than the negative control.[14]

Study population

Male and female patients aged 18 and above who are able to give consent with a clinical diagnosis of CSU were recruited. Eligible patients were additionally required to have a positive ASST. A total of 69 patients underwent ASST. Thirty-six CSU patients with positive ASST were diagnosed with aiCSU and were included in this study.

The exclusion criteria included pregnant or breast-feeding mothers; those who had severe angioedema; those with a history of hypersensitivity to antihistamine; those with urticarial vasculitis, chronic inducible urticaria, hereditary angioedema, or ACE-inhibitor induced angioedema or other dermatological disorder that could interfere in the evaluation of disease activity scoring (eg. psoriasis, endogenous or exogenous eczema); those who have hepatic, renal, cardiac, neurological, haematological, autoimmune, malignant diseases or any severe and uncontrolled disease; those who had received phototherapy, any systemic steroids/ systemic immunomodulatory medications, or on topical steroid within the last 4 weeks; those who had received drugs that are P-glycoprotein inhibitors (eg. amiodarone, ketoconazole/itraconazole, erythromycin/clarithromycin, verapamil, quinidine, protease inhibitors, tacrolimus) or P- glycoprotein inducers (eg. rifampicin, carmabazepine and phenytoin) in the last 30 days and patients who are involved in other on-going studies.

Randomization and blinding

Randomization codes were generated using the

'Research Randomizer' program. Two sets of 18 unique numbers per set were generated. Designated uninvolved staff were in-charge of maintaining the randomization code and dispensing the study drugs to study subjects during each clinic visit. Clinical outcome measurements were assessed by the clinical investigators who were blinded. The unblinding was carried out in the event of serious adverse event or pregnancy.

Study design

This was a randomized, investigator blinded study comparing efficacy of bilastine versus cetirizine in aiCSU. The study was conducted at the dermatology clinic in Hospital Tengku Ampuan Rahimah, Malaysia from April 2018 to December 2018. Subjects who were clinically diagnosed with CSU were approached and detailed information regarding the study was given by the clinical investigator. Each subject was then reviewed two weeks later. Subjects who provided informed consent for the study underwent physical examination and basic blood investigations (full blood count, renal profile and liver function test) to assess their eligibility to participate in the study. Those who met the inclusion/exclusion criteria underwent ASST. Subjects were required to withhold their anti-histamines 3 days prior to ASST. Subjects with positive ASST were included in the study and baseline UAS7 and CUQ_2oL scores were recorded. Subsequently, subjects were randomized to either the bilastine group or cetirizine group. Subjects were evaluated weekly for 2 weeks after initiation of treatment. Thereafter, the subjects were reviewed at week 4, 8 and 12. Subjects were provided with a diary to record UAS7 scores, adverse events and missed pills. Compliance to treatment was assessed by pill counting and direct questioning of subjects during follow-up visit. The dose of anti-histamine was increased based on the subjects UAS7 scores during each review. For subjects with absent or well-controlled symptoms, dose was maintained and for subjects with mild, moderate and severe symptoms, the anti-histamine dose were increased accordingly. The CUQ_2oL scores and ASST were repeated at the end of the study. The study end points are the objective changes in disease activity, quality of life scoring and ASST responses (Figure 1).

Efficacy measures

The study end points are the objective changes in clinical scorings (UAS7 and CUQ_2oL) and change in the diameter of serum induced wheal (ASST).

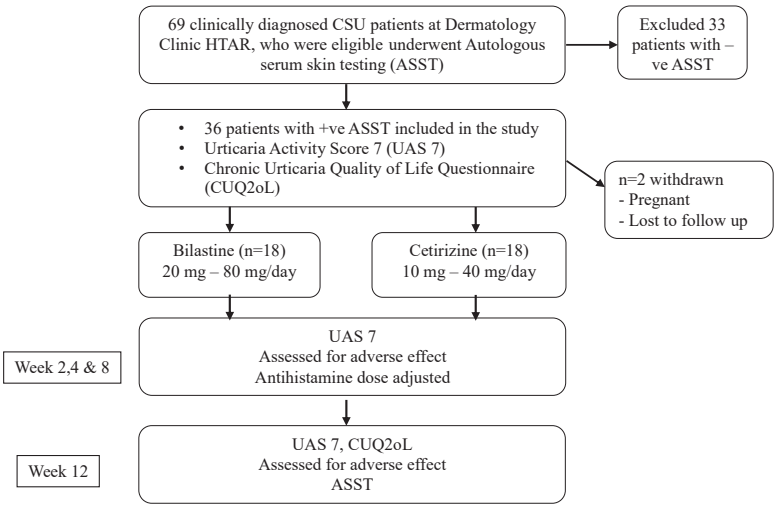
UAS7

The efficacy assessment was the change from baseline in the subjects' UAS7 score over the 12-week period. UAS7 was documented at baseline, week 1, 2, 4, 8 and 12. Subjects with UAS7 ≤ 6 was classified as responders and UAS7 > 7 was classified as non-responders.

Chronic urticaria quality of life score (CUQ_2oL)

The efficacy assessment was the change from baseline in the subjects CUQ_2oL score over the 12-week period. The validated English CUQ_2oL questionnaire was used. It was a self-administered questionnaire. CUQ_2oL was documented at baseline and week 12. The total score of CUQ_2oL (0-100) was calculated based on the sum of all completed items/total possible score of all completed items X 100.[15] Higher scores indicate greater impairment in the quality of life of the subjects.

Figure 1. Study flowchart



Autologous serum skin test (ASST)

ASST was done at baseline and repeated upon completion of study. The differences between the serum induced wheals and negative control were measured in millimeter. If the difference between serum induced wheal and negative control is more than 1.5mm, it was considered positive and less than 1.5mm was considered negative.

Safety assessment

The number and severity of adverse events were assessed at each visit (weeks 1, 2, 4, 8 and 12) by the investigators. Subjects had patient's diary to document events and the investigator's emergency contact number. All adverse events were judged clinically, and subjects were dropped out from the study if deemed necessary.

Statistical analysis

Data were compiled, entered into a dataset and analysed using Statistical Package for Social Sciences version 20.0 (SPSS). Descriptive analysis included using frequencies, means (standard deviations) and medians (interquartile range) for dependent variables i.e. UAS7 at baseline, week 1, 2, 4, 8 and 12 and CUQ_2oL and ASST at baseline and at week 12. Mean and standard deviation were used for normally distributed data whereas median and interquartile range were used when data was not normally distributed.

The significant differences within bilastine and cetirizine groups (at week 0, 1, 2, 4, 8 and 12) and between bilastine and cetirizine groups (at week 0, 2 and 4) were tested using Wilcoxon signed rank test and Mann Whitney Test respectively with *p*-value of less than 0.05 used as the levels of significance.

Ethical approval was obtained from the Medical Research and Ethics Committee with research code of NMRR-18-414-39554.

RESULTS

Demographics

A total of 69 clinically diagnosed CSU subjects who were eligible underwent ASST. 36 subjects with positive ASST were randomized to bilastine and cetirizine group, 18 subjects in each group. One subject was withdrawn from study at week 9 because of pregnancy and another subject was lost to follow up at week 10. However, all of the subjects were included in the intention to treat population. The demographic and baseline clinical characteristics are as shown in table 1. Mean age of subjects were 40.92 years ± 13.59. There were 61.1% females in total. The male to female ratio is 1:1.6 in both groups. The mean duration of disease for the entire study population is 29.33 months ± 27.82. The mean disease duration is 24.17 ± 23.87 in the bilastine group and 34.50 ± 31.10 in

Table 1. Demographic data and clinical characteristics

Characteristics	Bilastine (n = 18)	Cetrizine (n = 18)	Total (n = 36)	p-value
Mean age in years (mean±SD) Age range	39.67 ± 14.33 21 – 71	42.17 ± 13.09 25 – 63	40.92 ± 13.59 21-71	[a]0.606
Gender, *n* (%)				
Male	7 (38.9)	7 (38.9)	14 (38.9)	[b]0.633
Female	11 (61.1)	11 (61.1)	22 (61.1)	
Race, *n* (%)				
Malay	7 (38.9)	9 (50.0)	16 (44.4)	[b]0.723
Chinese	6 (33.3)	4 (22.2)	10 (27.8)	
Indian	5 (27.8)	5 (27.8)	10 (27.8)	
Months since diagnosis (mean±SD) Disease duration (range in months)	24.17 ± 23.87 5 – 84	34.50 ± 31.10 3 – 120	29.33 ± 27.82 3 – 120	[a]0.719
UAS 7 score (95% CI) at baseline				
Pruritus	11.44 (9.23-13.66)	10.00 (7.32-12.68)	10.72 (9.06-12.39)	[a]0.521
Wheals	10.11 (7.90-12.32)	7.83 (5.24-10.43)	8.97 (7.31-10.63)	[a]0.143
Total	21.56 (17.62-25.49)	17.83 (13.22-22.45)	19.69 (16.75-22.64)	[a]0.279
CUQoL scores, mean (SD)	47.64 ± 17.29	45.52 ± 20.57	42.86±16.96	[a]0.542
Pre study ASST in mm, mean (SD)	5.89 ± 2.54	5.26 ± 1.71	5.58±2.16	[a]0.563

[a]Mann Whitney test
[b]Fisher's Exact test

the cetirizine group. The mean total UAS7 score at baseline was 21.56 ± 7.91 in the bilastine group and 17.83 ± 9.28 in the cetirizine group. At baseline 66.7% of the total subjects had moderate to severe disease activity. The mean CUQ_2oL score is 47.64 ± 17.29 for the bilastine group and 45.52 ± 20.57 for the cetirizine group. The mean baseline ASST is 5.89 ± 2.54 in the bilastine group and 5.26 ± 1.71 in the cetirizine group. Both groups were similar with respect to demographics and baseline clinical characteristic, there were no significant differences noted between the groups (p>0.05) (Table 1).

Efficacy

The disease severity score improved significantly in both groups with reduction of total UAS7 score (median ± IQR) from 20.50 ± 11.00 at baseline to 2.50 ± 5.00 (p<0.01) in the bilastine group and from 16.50 ± 18.00 at baseline to 2.00 ± 4.00 (p<0.01) in the cetirizine group. Significant improvement was observed as early as week 1, with a trend of rapid improvement seen in the bilastine group when compared to the cetirizine group. However, these differences were not statistically significant (p=0.293). Similar significant reduction was also noticed in both pruritus and wheal components of UAS 7 score. Pruritus score reduced from 11.00 ± 6.00 to 1.50 ± 2.00 (p<0.01) in bilastine group and 9.00 ± 10.00 to 1.00 ± 2.00 (p<0.01) in the cetirizine group. The wheal score improved from 10.50 ± 7.00 at baseline to 1.00 ± 3.00 (p<0.01) in the bilastine group and 7.50 ± 9.00 at baseline to 0.50 ± 2.00 (p<0.01) in the cetirizine group. Both groups showed a statistically significant improvement in quality of life with reduction of scores from 43.50 ± 22.00 at baseline to 1.00 ± 2.00 (p<0.01) in the bilastine group and from 41.00 ± 19.00 at baseline to 3.00 ± 11.00 (p<0.01) in the cetirizine group. There was no significant inter-group difference in the UAS7 and CU_2QoL (p=0.211 and p=0.273 respectively) between the bilastine and cetirizine groups at the end of treatment (Table 2, Figure 2 & 3).

In the bilastine group 8 subjects had responded with standard dose of 20 mg per day, 8 subjects responded while on 40mg per day and 1 subject was on 60mg per day. 1 subject remained having mild disease activity (UAS7 =15) despite being on bilastine 80 mg per day. Meanwhile in the cetirizine group, 7 subjects responded with standard dose of 10 mg per day throughout the study, 5 subjects responded at 20 mg per day and 4 subjects responded at 30 mg per day. 2 subjects were on maximum dose of 40 mg per day. One of the 2 subjects who required 40 mg of cetirizine per day remained having moderate disease activity.

Table 2. Pre-treatment and post-treatment scores for bilastine and cetirizine at week 12.

Total scores	Bilastine (n=18)			Cetrizine (n=18)		
	Pre-treatment	Post- treatment	*p-value	Pre- treatment	Post- treatment	*p-value
Total Median±IQR Range	20.50±11.0 27	2.50±5.00 15	<0.01	16.50±18.00 28	2.00±4.00 16	<0.01
CUQ_2oL Median±IQR Range	43.50±22.00 57	1.00±2.00 28	<0.01	41.00±19.00 73	3.00±11.00 17	<0.01
[a]ASST Mean±SD	5.89 ± 2.54	6.14 ± 2.05	0.566	5.26 ± 1.71	5.34 ± 2.58	0.756

[a] ASST, the difference between serum induced wheal – saline induced wheal
*Wilcoxon Signed rank test.

Figure 2. Total reduction in mean scores of UAS 7 & CUQ2oL for Bilastine & Cetirizine group from baseline to week 12

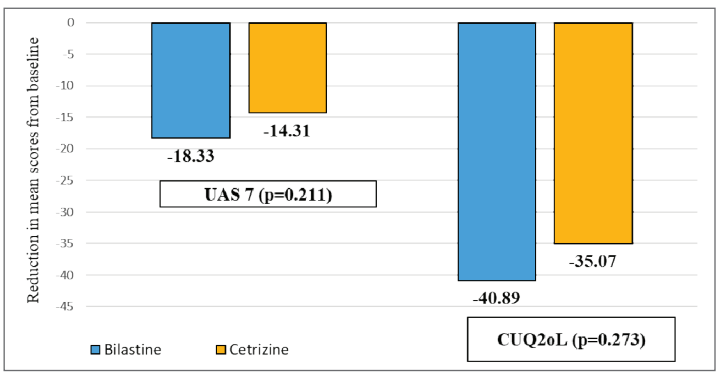
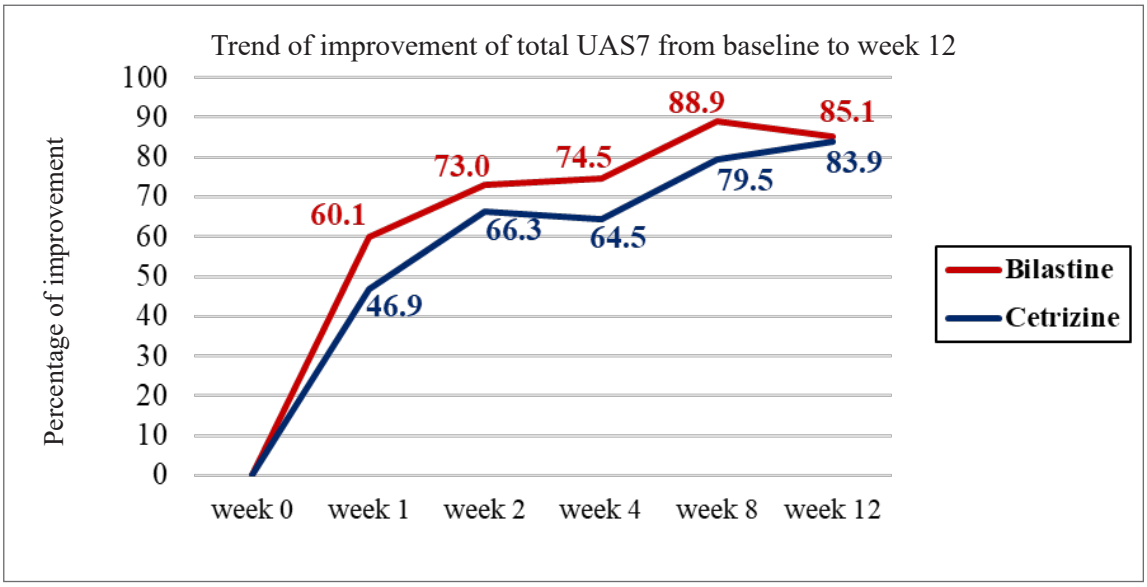


Figure 3. Trend of improvement of (a) total UAS 7, (b) pruritus and (c) wheals scores in the Bilastine & Cetirizine groups from baseline to week 12.

a)



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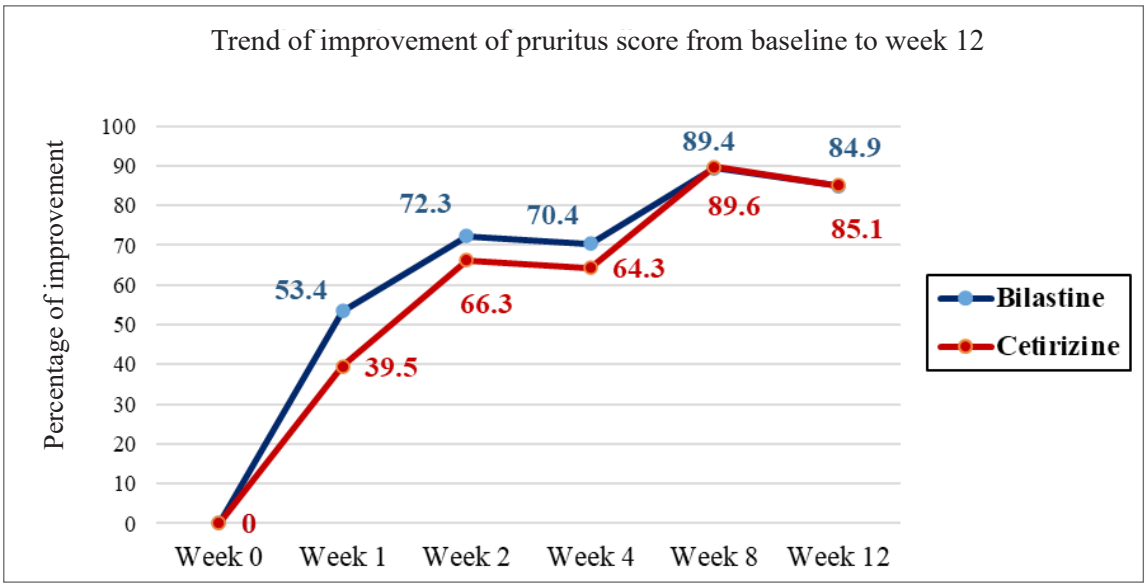
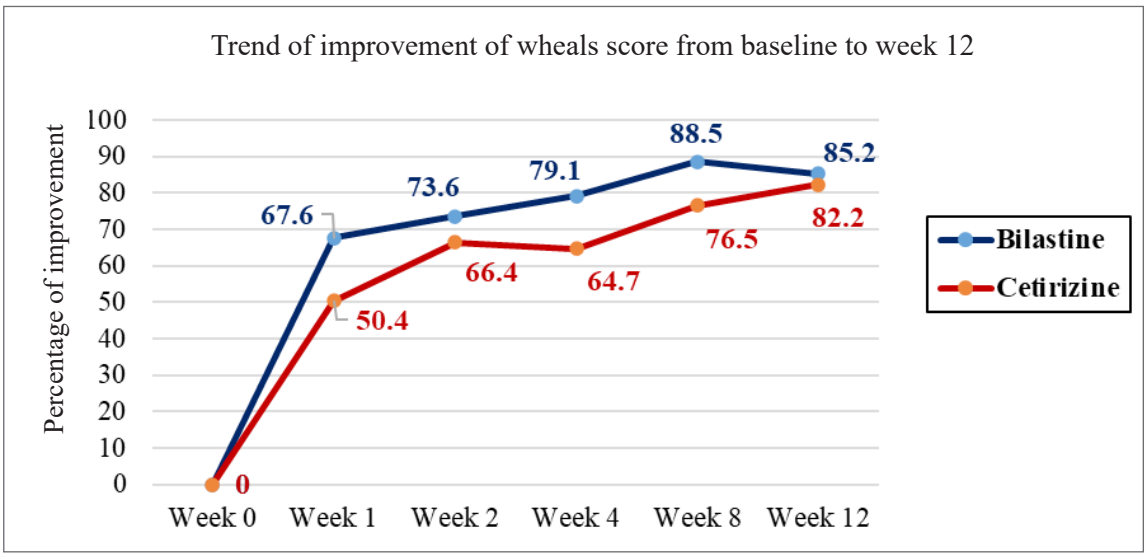


c)



There was no significant change in the ASST responses before and after treatment in both the bilastine and cetirizine groups. Although not statistically significant, there was a slight increase in the mean diameter of serum induced wheal at the end of treatment; in the bilastine group it increased from 5.89 ± 2.54 to 6.14 ± 2.05 (p = 0.556) and in the cetirizine group from 5.26 ± 1.71 to 5.34 ± 2.58 (p= 0.756). One subject from the cetirizine group showed negative ASST response at the end of the study.

Tolerability

Both the study drugs were safe and well tolerated by all the subjects of this study. Table 4 lists the adverse events reported by subjects. Sleepiness was reported in both groups however it was significantly lesser in bilastine group when compared to cetirizine group, with 11.1 % in bilastine group and 38.9% in the cetirizine group. Only one subject experienced headache in the bilastine group as compared to 4 subjects in the cetirizine group. Incidences of giddiness were reported by 2 subjects in the cetirizine group and none in the bilastine group. Other adverse events reported were lethargy (11.1% in the bilastine group and 5.6% in the cetirizine group) and dryness of mouth/eyes (5.6% in the bilastine group and 22.2% in the cetirizine group). (Table 3)

Table 3. Adverse events reported by subjects

Side effects	Bilastine n (%)	Cetirizine n (%)	[a]p value
Sleepiness	2 (11.1)	7 (38.9)	0.054
Headache	1 (5.6)	4 (22.2)	0.148
Lethargy	2 (11.1)	1 (5.6)	0.546
Dryness	1 (5.6)	4 (22.2)	0.148
Giddiness	0 (0)	2 (11.1)	0.146

[a]Mann Whitney test

Discussion

There is general understanding that aiCSU presents with severe symptoms and a long disease duration which often requires a third line of management with immunomodulatory or anti-inflammatory drugs for control of symptoms. Previous studies on aiCSU had looked into the effectiveness of various immunomodulatory and anti-inflammatory drugs such as omalizumab[16], cyclosporin[17], dapsone[18] and prednisolone[19] in subjects who had failed to respond to anti-histamines. A meta-analysis had proven the efficacy of standard and higher doses of anti-histamine in CSU, however there was no mention of the effectiveness of these anti-histamines in the subgroup of aiCSU.[20] This study was done to compare the effectiveness of bilastine and cetirizine in aiCSU patients.

aiCSU is more prevalent among females around the world as reported by many studies in Western and Asian countries[19,21-22]. Similar female predominance is seen in our cohort with a ratio of 1:1.6, however the distribution was not as remarkable as shown in other studies.[19,21-22] The mean age at diagnosis in our study was 40.92 years, which was comparable to studies done in Thailand and Korea which reported a mean age of 37.[21-22] The prevalence of positive ASST varies between 35%-58% in patients with chronic urticaria.[14,23,25] In our study the ASST prevalence was high at 52.2% of the CSU patients studied. This is likely because our center is a tertiary center where the more severe and persistent CSU patients are given follow ups.

In our study we found that both bilastine and cetirizine were equally effective in controlling the symptoms and improving the quality of life in patients with aiCSU. There was significant reduction in disease activity scores ($p<0.01$) and chronic urticaria quality of life scores ($p<0.01$) from baseline to week 12 in both the bilastine and cetirizine group. There were no significant differences in the disease activity scores & chronic urticaria quality of life scores reduction over the 12 weeks when both the groups were compared (p-values were 0.211 & 0.27 respectively). In a study comparing efficacy and safety of bilastine versus levocetirizine in the treatment of CSU, it was shown that bilastine is equivalent to levocetirizine in relieving symptoms and improving quality of life in CSU patients.[26] A one-year study done in Japan, evaluating safety and efficacy of bilastine in the treatment of CSU revealed that bilastine improved disease symptoms of CSU early in the treatment and efficacy was maintained throughout the treatment.[27] Recent studies have proven bilastine to be effective in treating pruritus and difficult to treat CSU that did not respond to other antithistamines.[28-29]

Although the mean total UAS7 score was higher in the bilastine group (21.56 ± 7.91) when compared to the cetirizine group (17.83 ± 9.28) at baseline, the rate of improvement was more rapid in the bilastine group and it was sustained till the end of the study (Figure 3a). In a randomized double-blinded study in 21 healthy volunteers evaluating the effect of 2 different bilastine doses (20 and 50mg) versus

cetirizine 10mg on histamine-induced wheal/flare over a period of 24 hours, Chruch MK et al. found that there was no significant difference between overall inhibitions of wheal/flare by 20 mg bilastine & 10 mg cetirizine.[30] However, bilastine had more rapid onset of action when compared to cetirizine.[30] It was also proven in previous studies that bilastine had a rapid onset of action in reducing histamine induced wheals and controlling pruritis in comparison to cetirizine, desloratadine or rupatadine.[30-31] A meta-analysis reported that up-dosing of anti-histamines did not significantly improve response control or reduce number of wheals. However, up-dosing did show significant improvement in pruritus control.[20] The current study shows that there is a significant improvement in both pruritus and number of wheals in both cetirizine (change in mean of pruritus; 8.19 ± 5.49 and number of wheals; 6.13 ± 5.19, $p<0.05$) and bilastine (change in mean of pruritus ; 9.72 ± 4.11 and number of wheals; 8.61 ± 4.54, $p<0.05$) groups (Figure 3b,c).

The same meta-analysis reported that the response rate to standard doses of antihistamine in CSU patients was 38.6%.[20] Among the antihistamines, cetirizine had a lower proportion of responders, at 41.98%.[20] The response rate to up-dosing in CSU patients who were non-responders to standard doses was 63.2%.[20] In our study, the response rate to standard dose of bilastine was 44.4% and standard dose of cetirizine was 38.8%. In both groups, 94.4% responded to up-dosing. However, direct comparison cannot be made between current study and previous studies because the definition of responder differs; one study defined responders as UAS7 less than 3[29] and another defines as more than 30% improvement in symptoms[28]. One patient in the bilastine group and two patients in the cetirizine group required a fourfold increase in the dose of antihistamine.

Both bilastine and cetirizine were generally well tolerated in our study. All reported adverse events were mild. More subjects in the cetirizine group complained of sleepiness. Among these 7 subjects who reported sleepiness, 5 of them were on higher than standard dose of cetirizine, at a dose of 20-30mg per day. This finding confirms the findings of previous studies that reported bilastine to be non-sedative as it does not cross the blood brain barrier.[32-33]

A research testing the effect of bilastine on the ability to perform tasks related to flying found that bilastine did not cause sleepiness or impaired performance on tasks related to flying.[34] Second generation anti- histamines (SGAH) ,which are highly selective for H1 receptor, have limited blood brain barrier penetration as their translocation across the central nervous system are under the control of active transporter proteins (ATP-dependent efflux pump, Pgp).[35] Pgp is essentially a cell detoxification mechanism where it helps to clear SGAH from the body.[35]

As such, the SGAH is minimally sedating or non-sedating with almost no adverse effect. Bilastine shows negligible H1 receptor occupancy in the brain, hence they do not have CNS effects even at higher doses.[35] However, single oral doses of 10 and 20 mg of cetirizine caused 12.5 and 25.2% occupancy of H1 receptors in prefrontal and cingulate cortices and subsequently causing drowsiness.[35] This explains the higher incidence of sleepiness experienced by subjects in the cetirizine group who were on higher doses.

ASST indicates the presence of functional circulating autoantibodies to FceR1 and/or to IgE and a positive ASST only suggest 'autoreactivity'. However, combining a positive ASST with characteristic clinical features (severe symptoms and anti-thyroid antibodies) may increase the sensitivity (94%) and specificity (86%) of this test.[36] In Malaysia, sophisticated tests like basophil histamine release assay(BHRA) or basophil activation test(BAT) and immunoassay for specific identification of IgG autoantibodies against FceR1 and/or anti-Ige (western blot or ELISA) are not available, hence our diagnosis of aiCSU mainly relies on a positive ASST and established clinical characteristics. In our cohort, only 1 subject had a negative ASST at week 12 and was completely symptom free at the end of the study. Keeping in mind the natural progression of the disease, this could possibly be due to spontaneous remission of disease activity. The remaining 33 subjects had positive ASST at the end of the study. A negative ASST serves as a good predictor for achieving urticaria remission within 2 years.[9] Positive ASST at week 12 in most of our patients suggests they have not achieved remission.

There were two drop outs in this study and both were in the cetirizine group. One subject was lost to follow up at week 8 and the other subject was withdrawn from study due to pregnancy. The subject informed of her pregnancy (6 weeks of amenorrhea) at week 10 of the study. She was taking 40mg of cetirizine per day when she was withdrawn and

referred to the obstetric team for further care. We are happy to report that she had an uneventful antenatal follow up and delivered a healthy full-term baby. Contrary to our concerns, an observational cohort study and a meta-analysis concluded that cetirizine was not associated with an increased risk of major malformations or other adverse fetal outcomes.[37]

In the era of biologics, with the availability of effective anti-IgE monoclonal antibodies like omalizumab and upcoming novel anti-IgE monoclonal antibodies like Ligelizumab and UB-221[38], it is important to have a clearer idea on the efficacy of antihistamine in aiCSU management. This study concludes that both bilastine and cetirizine at standard or higher dosing are equally effective and safe in controlling the symptoms of autoimmune urticaria, although bilastine has proven to have lesser side effects. Since cetirizine of more than 10mg causes drowsiness in more than one third of our patients, we need to be cautious when prescribing to a patient especially higher dosage eg 20 to 40mg to patients who will drive or handle machinery at work.

We feel that this study was limited as it only involved a small cohort of patients. It was also a single blinded study where the investigator was blinded but the subjects were aware of the drugs consumed. This could have let to response biasness, whereby subjects are aware of the expected findings and adapt their responses to suit. The diagnosis of autoimmune urticaria was based on positive ASST alone as other tests were not available in Malaysia. Nevertheless, there was careful selection of the patients before enrolment into this study. The patients were followed up closely only by the primary investigator and the primary outcome measures were patient-reported. Future studies should be multicenter, double-blind placebo-controlled and designed with a larger number of patients.

Conclusion

Autoimmune chronic spontaneous urticaria is more prevalent among female patients with a prolonged course of disease and severe symptoms which significantly affect patients' quality of life. Both bilastine and cetirizine at standard or higher dosing are equally effective and safe in controlling the symptoms of autoimmune chronic spontaneous urticaria.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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