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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

APPENDIX 1

CHILD investigators include the following: Subbarao P (Director), The Hospital for Sick Children & University of Toronto; Turvey SE, University of British Columbia (co-Director), Anand SS, McMaster University; Azad M, University of Manitoba; Becker AB, University of Manitoba; Befus AD, University of Alberta; Brauer M, University of British Columbia; Brook JR, University of Toronto; Chen E, Northwestern University, Chicago; Cyr M, McMaster University; Daley D, University of British Columbia; Dell SD, The Hospital for Sick Children & University of Toronto; Denburg JA, McMaster University; Duan Q, Queen's University; Eiwegger T, The Hospital for Sick Children & University of Toronto; Grasemann H, The Hospital for Sick Children & University of Toronto; K HayGlass, University of Manitoba; Hegele RG, The Hospital for Sick Children & University of Toronto; Holness DL, University of Toronto; Hystad P, Oregon State University; Kobor M, University of British Columbia; Kollman TR, University of British Columbia; Kozyrskyj AL, University of Alberta; Laprise C, Université du Québec à Chicoutimi; Lou WYW, University of Toronto; Macri J, McMaster University; Mandhane PJ, University of Alberta; Miller G, Northwestern University, Chicago; Moraes TJ, The Hospital for Sick Children & University of Toronto; Paré, University of British Columbia; Ramsey C, University of Manitoba; Ratjen F, The Hospital for Sick Children & University of Toronto; Sandford A, University of British Columbia; JA Scott, University of Toronto; Scott J, University of Toronto; Sears MR, (Founding Director), McMaster University; Silverman F, University of Toronto; Simons E, University of Manitoba; Takaro T, Simon Fraser University; Tebbutt S, University of British Columbia; To T, The Hospital for Sick Children & University of Toronto.

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Updosing of bilastine is effective in moderate to severe chronic spontaneous urticaria: A real-life study

To the Editor,

We report an open-label study of the effects of bilastine at 20, 40 and 80 mg daily for 2 weeks on the signs and symptoms of chronic spontaneous urticaria (CSU) in patients who had not responded sufficiently to licensed doses of other H₁-antihistamines.

The study was designed to mimic the real-life situation in which the antihistamine dose is increased gradually up to fourfold the licensed dose, depending on the effectiveness of the previous dose. Its limitations include the relatively small number of patients and uncontrolled design.

Bilastine is an H₁-antihistamine with high selectivity for histamine H₁-receptors, undergoes negligible metabolism and does not interact with the cytochrome P450 metabolic system. Being a substrate for *p*-glycoprotein, its passage across the blood-brain barrier is limited making it a practically "nonsedating" H₁-antihistamine.¹ Bilastine is highly effective even when used at the standard dose of 20 mg daily.¹ In wheal and flare studies and in urticaria, up dosing to twofold and fourfold, as suggested by the EAACI/GA²LEN/EDF/WAO guideline for patients who are unresponsive to a single licensed dose,² showed bilastine to have increased effectiveness.³⁻⁵

Twenty-nine CSU patients, 23 females, median age 51 (range 20-85) years, were recruited. All had been referred to the Dermatology Department at Charité with moderate to severe CSU (UAS7 ≥ 14) that had not been treated successfully with an H₁-antihistamine (other than bilastine) in licensed dose. The mean ($\pm$ SEM) duration of their disease was 58.7 ± 94.1 months. This study was approved by the Berlin ethics committee (14/0150-EK 10). All volunteers gave written informed consent to be included in the study.

Following a 2-week baseline period, during which only rescue medication of bilastine 20 mg was allowed, there were 3 treatment periods each of 2 weeks. During the first treatment period, all 29 patients took 20 mg bilastine orally each day. At the end of this period, all patients with a complete response (UAS7 ≤ 3) were discontinued from further analysis. The remaining 23 patients went on to the second treatment period during which they took 40 mg bilastine daily. Again, at the end of this period, all patients with UAS7 ≤ 3 were discontinued from further analysis and the remaining 21 patients went on to the third treatment period during which they took 80 mg bilastine daily. During each period, patients made daily recordings of their urticaria activity score (UAS) and documented any adverse responses. At the end of each period, the patients underwent a physical examination and their UAS7² was calculated for the last 7 days. Rescue medication of 20 mg bilastine was allowed only during the baseline period.

Following 20 mg bilastine daily for 2 weeks, the mean ($\pm$ SEM) UAS7 (Figure 1A) fell from a baseline value of 24.3 ± 1.5 to 15.3 ± 2.1 . This fall of 37% was highly significant ($P < .001$). The corresponding falls in the pruritus and wheal components were 44% and 29%, respectively. Figure 2A shows that before treatment 26 patients (84%) had moderate or severe disease activity and only 5 (16%) had mild disease activity. Following 20 mg bilastine, 18 patients (58%) had minimal-activity urticaria or mild-activity urticaria and 3 were completely symptom-free (UAS7 = 0). The number of patients with minimal urticaria or mild disease activity was significantly ($P = .0001$) higher following 20 mg bilastine daily than at baseline (Fisher's exact test).

Updosing to 40 mg bilastine (Figure 1B) produced a further mean UAS7 fall from 18.7 ± 1.8 to 14.4 ± 1.5 (Figure 1B). This 23% fall was statistically significant ($P = .002$). The corresponding falls in the pruritus and wheal components were 24% and 17%, respectively. Figure 2B shows that, after taking 40 mg bilastine for 2 weeks, there were no patients with severe disease activity ($P < .01$ compared with 20 mg). Furthermore, 3 patients became symptom-free.

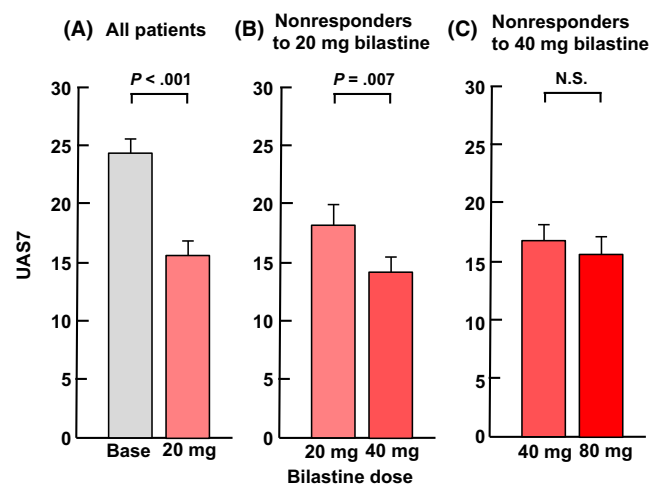


Figure 1. UAS7 levels illustrating the beneficial effects of bilastine in CSU. Panel A, shows mean $\pm$ SEM for UAS7 in 29 untreated CSU patients and following 2-wk treatment with 20 mg bilastine. Panel B, shows mean $\pm$ SEM for UAS7 following 2-wk treatment with 40 mg bilastine of 23 patients who were nonresponders (UAS7 ≥ 3) with 20 mg bilastine. Panel C, shows mean $\pm$ SEM for UAS7 following 2-wk treatment with 80 mg bilastine of 21 patients who were nonresponders (UAS7 ≥ 3) with 40 mg bilastine [Colour figure can be viewed at wileyonlinelibrary.com]

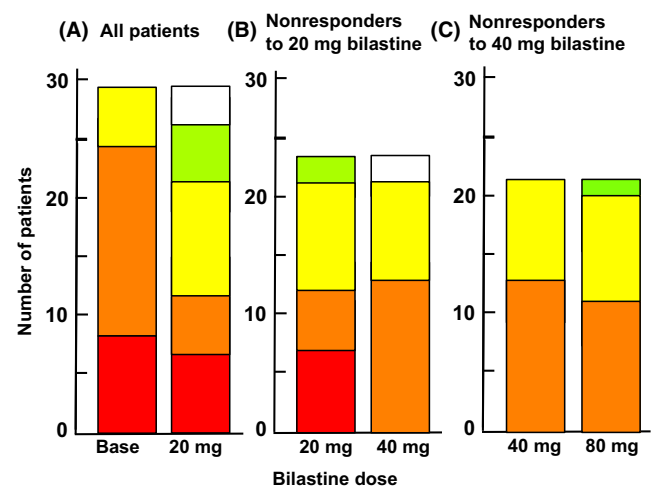


Figure 2. CSU patients' symptom severity levels following treatment with bilastine. Panel A, shows results from 29 untreated CSU patients and following 2-wk treatment with 20 mg bilastine. Panel B, shows results following 2-wk treatment with 40 mg bilastine of 23 patients who were nonresponders (UAS7 ≥ 3) with 20 mg bilastine. Panel C, shows results following 2-wk treatment with 80 mg bilastine of 21 patients who were nonresponders (UAS7 ≥ 3) with 40 mg bilastine. Colours for patient severity are as follows: red = severe-activity urticaria (UAS7 28-42); orange = moderate-activity urticaria (UAS7 16-27); yellow = mild-activity urticaria (UAS7 7-15); green = minimal-activity urticaria (UAS7 1-6); and white = urticaria-free (UAS7 = 0) [Colour figure can be viewed at wileyonlinelibrary.com]

Further up dosing to 80 mg bilastine produced a small fall in mean UAS7 from 16.7 ± 1.2 to 15.5 ± 1.4 (Figure 1C). This 7% fall was not statistically significant. The corresponding falls in the pruritus and wheal components were 0% and 12%, respectively.

Figure 2C shows that following 80 mg bilastine 1 patient had minimal-activity urticaria and 2 additional patients only mild-activity urticaria. Interestingly, 11 patients still had moderate-activity urticaria showing them to be poor responders to H₁-antihistamine therapy. This has been noted in previous up dosing studies in CSU.⁶⁻⁹

Bilastine appeared to be safe and well tolerated confirming previous studies.^{1,4} No treatment-related serious adverse reactions occurred in the study. Tiredness was reported by 6 patients on 20 mg bilastine but only by 1 each at 40 or 80 mg suggesting that this is unlikely to be drug-related but rather an effect of the disease itself. This is in line with the fact that undertreatment of urticaria has an effect on performance and that a modern H₁-antihistamine like bilastine can restore these cognitive functions.

The effectiveness of 20 mg bilastine confirms previous CSU studies in Europe, South America and Japan.³ The benefit of up dosing to 40 mg bilastine confirms the results of a cold urticaria study.⁴ Interestingly, pruritus appeared to be more sensitive to bilastine with 55% inhibition being reached at 40 mg with no increase thereafter. In contrast, wheal inhibition was only 42% at 40 mg and increased to 51% at 80 mg. Post hoc analysis of the ten worst affected patients (UAS7 $\geq$ 18) showed the mean UAS7 to fall 25% on increasing bilastine from 40 to 80 mg ($P = .02$) indicating that severely affected patients are most likely to benefit from up dosing to 80 mg bilastine.

In conclusion, bilastine at standard dose is an effective H₁-antihistamine in relieving the symptoms of CSU in difficult-to-treat patients who had not responded to licensed doses of H₁-antihistamines. Up dosing to double the licensed dose of bilastine appeared to be sufficient for the majority of CSU patients with only a proportion of the more severely affected patients benefiting from a four-fold increase in dose.

CONFLICT OF INTERESTS

Karsten Weller is or recently was a speaker and/or advisor for Dr. Pflieger, Uriach, UCB, Moxie and Novartis. Martin Church has been a speaker or consultant for Almirall, FAES FARMA S.A., Menarini, Moxie, MSD, Novartis, UCB Pharma, Sanofi-Aventis and Uriach. Tomasz Hawro has no conflict of interest. Sabine Altrichter has conducted studies for Allakos, GSK, Moxie and Novartis. Luis Labega is a member of the medical department of FAES FARMA S.A. Markus Magerl is or recently was a speaker and/or advisor for Moxie and Novartis. Martin Metz has been a speaker and/or consultant for Bayer Pharma, Moxie, Novartis and Uriach. Torsten Zuberbier has consulted and had research grants and/or honoraria from AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES FARMA S.A, HAL, Henkel, Kryolan, Leti, L'Oréal, Meda, Menarini, Merck, MSD, Novartis, Pfizer, Sanofi, Stallergenes, Takeda, Teva and UCB. Marcus Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, Genentech, GSK, Menarini, Merckle Recordati, Moxie, Novartis, Sanofi, MSD and Uriach.

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