Comparative efficacy of bilastine, desloratadine and rupatadine in the suppression of wheal and flare response induced by intradermal histamine in healthy volunteers

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ABSTRACT
Objective: To compare the peripheral antihistaminic activity of bilastine, rupatadine and desloratadine in inhibiting the histamine-induced wheal and flare (W&F) response.

Research design and methods: Twenty-four healthy volunteers aged 18–40 years participated in this crossover, randomized, double-blind, placebo-controlled clinical study. Subjects received single doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo. W&F responses induced by intradermal injection of histamine 5 μg were evaluated before treatment (basal value) and at 0.5, 1, 2, 4, 6, 9, 12 and 24 hours after treatment. Fifteen minutes after histamine injection, W&F surface areas (cm²) were quantified using the Visitrak System. Itching sensation was evaluated using a 100 mm visual analog scale.


Main outcome measures: The primary outcome measure was the percentage reduction in W&F areas after each active treatment compared with corresponding basal values.

Results: Bilastine induced the greatest inhibition in wheal area and was significantly superior to desloratadine and rupatadine from 1 to 12 hours (both \( p < .001 \)). Rupatadine and desloratadine were better than placebo without differences between them. Maximum wheal inhibition occurred at 6 hours (bilastine 83%, desloratadine 38%, rupatadine 37%). Onset of action was 1 hour for bilastine and 4 hours for desloratadine and rupatadine. Bilastine was significantly superior to desloratadine and rupatadine for flare inhibition from 1–24 hours (both \( p < .001 \)) with an onset of action at 30 minutes. Bilastine was significantly better than desloratadine (2–12 hours; at least \( p < .001 \)) and rupatadine (2–9 hours; at least \( p < .01 \)) for reducing itching sensation. Neither desloratadine nor rupatadine significantly reduced itching compared to placebo. All active treatments were well tolerated.

Conclusions: Bilastine 20 mg induced significantly greater inhibition of the W&F response compared with desloratadine 5 mg and rupatadine 10 mg throughout the 24 hour study period, and had the fastest onset of action. Only bilastine significantly reduced itching sensation versus placebo.

INTRODUCTION
The prevalence of allergic diseases has increased considerably over the last few decades\(^1\) and, in parallel, many new treatment options have been introduced. Owing to their much more favorable pharmacokinetic and safety profiles, second-generation antihistamines have largely superseded their first-generation counterparts as treatment of choice to manage allergic rhinoconjunctivitis, urticaria, and other allergic skin disorders\(^2\)–\(^4\). The most frequently used second-generation antihistamines in clinical practice are bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine.

Besides their high selectivity for histamine H\(_1\) receptors and minimal central nervous system adverse effects, other characteristics second-generation antihistamines share in common are a rapid onset of effect within 1–4 hours of oral administration and a long duration of activity facilitating once daily dosing\(^5\). Nevertheless, chemical structure, physicochemical properties and pharmacological dissimilarities between molecules result in differences at the clinical level that may be relevant for special populations such as the elderly, pregnant women and individuals with compromised kidney and liver function\(^6\). An appreciation of the differentiating characteristics of second-generation antihistamines may assist in treatment selection.

The second-generation antihistamines approved most recently in Europe are desloratadine, rupatadine and bilastine. Desloratadine is the active metabolite of loratadine (and rupatadine)\(^6\)–\(^8\). Its elimination half-life of 24 hours\(^6\) is likely...
due to slow dissociation from the H₁ receptor. Desloratadine is presented at doses of 5 mg per day. The pharmacological profile of rupatadine includes dual affinity for histamine H₁ receptors and platelet-activating factor receptors. The recommended dose of rupatadine is 10 mg once daily, and the agent should not be administered concomitantly with known CYP3A4 inhibitors. Bilastine was approved by the European Medicines Agency in 2010 and is currently being introduced into clinical practice in 28 European countries for symptomatic treatment of allergic rhinoconjunctivitis (perennial and seasonal) and urticaria in adults and children over 12 years. Bilastine shows high specificity for H₁ receptors with little to no affinity for other receptors. It has no sedative or cardio-toxic effects at therapeutic doses, and is metabolized only negligibly in humans. The recommended dose of bilastine is 20 mg once daily. Although the efficacy and tolerability of each of these second-generation agents have been demonstrated repeatedly in extensive clinical trials programs, no study has directly compared all three antihistamines.

The wheal and flare (W&F) inhibition test is a well-established pharmacological model to assess the peripheral antihistaminic activity of antihistamines. The intensity of the antihistaminic effect is assessed objectively by measuring reduction of the W&F area induced by intradermal histamine injection after administration of study drug. It is regarded as a useful pharmacological test to assess the dose–response relationship of an antihistamine.

In the current study, the antihistaminic activities of bilastine, rupatadine and desloratadine in reducing histamine-induced skin reactivity (W&F response) were compared in healthy volunteers.

### Patients and methods

#### Study design

This phase IV, randomized, double-blind, placebo-controlled, crossover clinical study was conducted in the Drug Research Center (CIM, IIB Sant Pau), Barcelona, Spain. The study protocol was approved by the hospital’s Ethics Committee for Clinical Research and authorized by the Spanish Drug Agency (Ministry of Health) with EudraCT number 2015-000790-13.

#### Study population

The study enrolled young healthy male and female volunteers selected from a panel at the CIM, IIB Sant Pau. Subjects were aged between 18 and 40 years with a body mass index of 18–30 kg/m². Prior to inclusion, participants underwent clinical assessment (detailed medical history, concomitant medication, and questions regarding alcohol, stimulant beverage, drug, and tobacco use), complete physical examination (including vital signs), laboratory tests (hematology, biochemistry, serology for hepatitis B and C and HIV, serum pregnancy test for females), urine drug and alcohol screening, and 12-lead electrocardiography (ECG). Screening included assessment of skin reactivity to intradermal 5 µg histamine injection (0.05 ml of 100 µg/ml histamine solution), where wheal surface area had to be in the range of 55–260 mm².

Key exclusion criteria were: history of medical or psychiatric illness, allergy, idiosyncrasy or hypersensitivity to drugs; skin over-reactivity to histamine; rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption; consumption of stimulant drinks (coffee, tea, chocolate or cola drinks) > 5 cups/day; daily alcohol consumption >40 g for men and >24 g for women; use of medication within 2 weeks of study treatment other than paracetamol for short-term symptomatic treatment; smokers; pregnancy or lactation; positive dermatographism. Female volunteers of child-bearing potential were required to use contraceptive measures other than hormonal contraceptives.

All subjects provided written informed consent prior to any procedure. Subjects received economic compensation for time spent in the study and any expenses associated with study participation.

#### Study procedure

Subject who fulfilled all of the inclusion criteria and none of the exclusion criteria at the screening visit were allocated to a treatment sequence according to a previously generated randomization table. The experimental phase consisted of four treatment periods in which participants received a single oral dose of bilastine 20 mg (Faes Farma SA, Leioa, Bizkaia, Spain), desloratadine 5 mg (Merck Sharp & Dohme SA, Madrid, Spain), rupatadine 10 mg (Uricia & Cía SA, Barcelona, Spain) or placebo in crossover fashion, each separated by a 7-day washout period. Study medications were administered in the morning with 240 ml mineral water under fasting conditions. All tablets were over-encapsulated in opaque material to maintain double-blind conditions. During each treatment period, subjects were hospitalized from the day prior to until 24 hours after study drug administration. Study drugs were administered in the presence of an investigator to ensure compliance.

Before and after each drug administration, the following evaluations were conducted: objective skin reactivity test; subjective evaluation of itching perception after histamine inoculation; recordings of vital signs (systolic and diastolic blood pressure and heart rate). Concomitant medication and adverse events reported spontaneously by the subject or observed by the investigator were recorded.

The study was conducted in accordance with the latest revision of the Declaration of Helsinki (Brazil 2013), the International Conference on Harmonisation Guideline for Good Clinical Practice, and guidelines of the Spanish Ministry of Health (RD 223/2004) and European Directive (2001/20/EC), and followed standard operating procedures of the CIM, IIB Sant Pau.

#### Pharmacodynamic assessments

The antihistaminic activity of study medications was assessed by measuring the W&F area induced by a histamine skin test,
before and after each treatment. At each time point (predose, and at 0.5, 1, 2, 4, 6, 9, 12, and 24 hours after study drug administration), a skin test was performed by injecting 5 µg histamine intradermally into one of four randomly assigned zones on the ventral forearm, alternating arms each time and leaving a minimum distance of 2.5 cm between applications. Five minutes after each histamine injection, itching perception was evaluated by means of a 100 mm visual analog scale (VAS) where 0 = no itching and 100 = very much itching.

Fifteen minutes after intradermal injection, the W&F area was recorded by drawing the contours with a permanent marker pen onto a transparent film. Surface areas were quantified using the Visitrak System (Smith & Nephew Wound Management Inc., Largo, Florida) which automatically completes the area calculations in cm².

The primary endpoint was the percentage reduction from baseline in the W&F area. Secondary endpoints were: time of maximum inhibition of the W&F response; subjective itching sensation relative to baseline; and onset of action which was defined as the first evaluation time point at which the change in wheal surface was statistically significant compared with placebo.

**Tolerability assessments**

Tolerability assessments, including physical examination, 12-lead ECG, and laboratory tests (hematology and biochemistry), were performed at screening and final evaluation (24 hours after administration of last study dose). Vital signs were recorded at these same time points and during each treatment period at baseline and at 1, 2, 4, 6, 9 12 and 24 hours post-medicatin. In the 12 hours prior to each study drug administration, subjects underwent urine drug tests (cannabis, amphetamines, cocaine, opiates and benzodiazepines) and an alcohol breath test; women underwent a urine pregnancy test.

An adverse event was defined as any untoward medical occurrence irrespective of its association with the study drug. Adverse events occurring after the first dose of study medication were considered as treatment-emergent adverse events (TEAEs). Adverse events were either reported spontaneously by subjects or identified by the investigator. All adverse events were evaluated for seriousness, severity, relationship to study drug and outcome.

**Statistical analysis**

Primary and secondary pharmacodynamic outcomes were evaluated in the per-protocol population which included all subjects who completed the study without any major protocol deviations. The safety population consisted of subjects who received at least one dose of study medication.

A required sample size of 24 subjects was calculated to obtain a power of 80% to detect a minimum difference of 15% between treatments for inhibition of the histamine-induced W&F response, at a significance level of 5%. Statistical analyses were performed using IBM SPSS version 22.0, with the significance value (p) set at 0.05. Baseline conditions were analyzed by means of one-way ANOVA (treatment factor) with data expressed as direct values.

Variables obtained in objective skin reactivity evaluations and subjective evaluations of itching perception were evaluated by means of two-way ANOVAs (treatment factor and time factor) of repeated measures. Data was expressed as the percentage reduction relative to baseline values (effects of treatment) and as direct values (effect of interaction treatment by time). If statistically significant differences were detected, a detailed analysis was performed by means of paired t-test evaluating the differences between treatments at each evaluation time point and the differences between evaluation time points after each treatment.

Analyses of time of maximum inhibition and onset of action were descriptive. Analyses of adverse events, vital signs, ECG and laboratory test values were descriptive. Changes were evaluated in terms of their clinical relevance.

**Results**

Of 32 subjects selected for inclusion, 24 were randomized to a study treatment sequence. All subjects completed the study and were included in the pharmacodynamic and tolerability analyses. The main demographic characteristics of the final experimental sample (12 men and 12 women) expressed as mean (±SD) were: age 28.9 (±5.98) years, body mass index 23.1 (±3.07) kg/m². Compliance with study medication was 100% in all subjects. Eleven protocol deviations were committed throughout the study (four with placebo, two with bilastine, one with desloratadine, four with rupatadine); all were considered minor and to not have affected the integrity or validity of the results.

**Antihistaminic activity**

No significant differences were observed in values for W&F area or itching perception during assessments performed prior to the start of each treatment period. All active treatments induced a significant reduction from baseline in the W&F response (primary endpoint); however, the effect was most pronounced with bilastine.

Maximum percentage reduction in wheal area was greatest with bilastine (83.1%), followed by desloratadine (38.0%), rupatadine (37.3%) and placebo (7.3%). Maximum percentage reduction in flare area was greatest with bilastine (86.9%), followed by desloratadine (53.9%), rupatadine (52.5%) and placebo (24.2%).

Significant differences in percentage reduction of the wheal response versus placebo were observed from 1 to 24 hours (all p < .001) with bilastine; from 4 to 12 hours (p < .001) and at 24 hours (p = .022) with rupatadine; and at 4 hours (p = .002), 6 hours (p < .001) and 12 hours (p = .001) with desloratadine. Desloratadine did not show a significant difference relative to placebo at 24 hours (p > .05), indicating a duration of activity less than 24 hours (Figure 1). Significant differences in percentage reduction of the flare response versus placebo were observed at 0.5 hours (p = .023) and all
time points to 24 hours (p < .001) with bilastine; at 4 hours and all time points to 24 hours with rupatadine (p < .001); and at 4 hours (p = .002) and all time points to 24 hours (p < .001) with desloratadine (Figure 2).

The maximum reduction in itching scores was obtained with bilastine (Figure 3). Compared with baseline, VAS scores were significantly lower with bilastine at all time points from 1 to 24 hours (1 hour: p = .007; 2 to 9 hours: p < .001; 12 hours: p = .001; 24 hours: p = .008). Desloratadine significantly reduced itching scores versus baseline from 1 to 12 hours (1 hour: p = .041; 2 hours: p = .002; 4 hours: p = .003; 6 hours: p = .012; 9 hours: p = .040; 12 hours: p = .045). Rupatadine significantly decreased itching perception with respect to baseline at 4 hours (p = .032), 6 hours (p = .038) and 12 hours (p = .030). Compared with placebo, significant differences in VAS scores were observed from 2 to 12 hours with bilastine (2 hours: p = .001; 4 and 6 hours: p < .001; 9 hours: p = .001; 12 hours: p = .018), whereas scores with desloratadine and rupatadine did not differ significantly from placebo at any evaluation time point (Figure 3).

The time to maximum reduction in wheal area was strictly 6 hours with all active treatments and 24 hours with placebo. From 2 to 12 hours, the percentage reduction with bilastine was between 72% and 83%. The time to maximum reduction in flare area was 2 hours with bilastine, 9 hours with desloratadine, and 24 hours with rupatadine and placebo. From 2 to 24 hours, the percentage reduction with bilastine was between 74% and 87%.

Wheal area remained significantly reduced from baseline at 24 hours with all active treatments, although the effect was greatest with bilastine (41.7%; p < .001) compared with rupatadine (28.5%; p < .001) and desloratadine (19.8%; p = .003). Likewise, the reduction from baseline in flare area at 24 hours was significant for all active treatments but was most pronounced with bilastine (74.6%; p < .001) compared with rupatadine (52.5%; p < .001) and desloratadine (51.0%; p < .001).

Bilastine showed a faster onset of action. Compared with placebo, a significant reduction in wheal area was observed from 1 hour with bilastine (p < .001) versus 4 hours with rupatadine (p = .001) and desloratadine (p = .002). A significant reduction of flare area versus placebo was observed from 0.5 hours (30 min) with bilastine (p < .05) versus 4 hours with rupatadine (p < .001) and desloratadine (p < .01).

Safety

No serious adverse events were recorded during the study. Four subjects recorded a total of six TEAEs, all of which were mild to moderate in intensity (Table 1). Four events (three reports of headache, one report of vomiting) were considered by investigators as possibly related to study medication; two episodes of dysmenorrhea were deemed not related. All adverse events resolved without sequelae.

There were no clinically relevant alterations in laboratory tests (hematology, biochemistry), vital signs, ECG assessments, or physical examinations during the study.

Figure 1. Percentage inhibition of wheal area (mean ± SEM) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo.

Figure 2. Percentage inhibition of flare area (mean ± SEM) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo.

Table 1. Safety summary by treatment group

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Bilastine 20 mg</th>
<th>Desloratadine 5 mg</th>
<th>Rupatadine 10 mg</th>
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<tr>
<td>Headache</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
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<tr>
<td>Abdominal pain</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
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<tr>
<td>Vomiting</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
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<tr>
<td>Dizziness</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Other</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
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<tr>
<td>Other</td>
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Figure 2. Percentage inhibition of flare area (mean ± SEM) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo.

<table>
<thead>
<tr>
<th>Treatment vs. Placebo</th>
<th>Bilastine vs. Desloratadine</th>
<th>Bilastine vs. Rupatadine</th>
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<tr>
<td>$^* p &lt; .05$</td>
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<td>$^{**} p &lt; .01$</td>
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<td>$^{***} p &lt; .001$</td>
<td>$^{***} p &lt; .001$</td>
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</table>

Figure 3. Itching perception scores recorded on a 0–100 mm visual analog scale (mean ± SEM) after crossover treatment with single oral doses of bilastine 20 mg, desloratadine 5 mg, rupatadine 10 mg and placebo.

<table>
<thead>
<tr>
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* $^* p < .05$  ** $^{**} p < .01$  *** $^{***} p < .001$
Table 1. Summary of treatment-emergent adverse events.

<table>
<thead>
<tr>
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<th>Rupatadine</th>
<th>Placebo</th>
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</thead>
<tbody>
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<td>1 (mild)</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
<td>1 (mild)</td>
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</table>

Discussion

Modern second-generation antihistamines play a key role in the treatment of allergic rhinoconjunctivitis and urticaria, offering benefits to patients such as convenient once daily dosing and improved tolerability including no sedation at therapeutic doses. However, the wide range of available products can make choosing a treatment for an individual patient difficult. Treatment selection is further complicated by the absence of readily discernible differences between second-generation antihistamines during routine clinical use and by the lack of comparative data from controlled clinical trials for all possible comparisons.

Bilastine, desloratadine and rupatadine are the newest second-generation antihistamines to be approved for use in Europe. Although clinical trials of seasonal allergic rhinoconjunctivitis have shown similar efficacy and tolerability between bilastine 20 mg and desloratadine 5 mg, and between rupatadine 10 mg and desloratadine 5 mg, to date no studies have compared all three antihistamines directly. In the absence of such clinical data, we have used a standard method for measuring the pharmacodynamic effects of antihistamine drugs in healthy volunteers in order to compare the peripheral antihistaminic activity of bilastine, desloratadine and rupatadine at their approved doses.

All active treatments significantly suppressed the W&F response induced by intradermal histamine relative to placebo, but the level of activity was consistently greater with bilastine. At the time of maximum inhibition from baseline of the wheal area (6 hours post-administration with all active treatments), the percentage reduction was two-fold greater with bilastine than with desloratadine and rupatadine. At 24 hours, the wheal response remained significantly inhibited with bilastine and desloratadine but not with rupatadine. Maximum reduction from baseline of flare area was significantly greater with bilastine than with desloratadine and rupatadine and occurred much earlier: at 2 hours post-administration with bilastine compared with 9 hours for desloratadine and 24 hours for rupatadine. Bilastine significantly reduced itching sensation from 2 to 12 hours relative to placebo, with reductions of about 75% to 82% compared with the baseline value. In contrast, neither desloratadine nor rupatadine had a significant effect on itching perception versus placebo. Bilastine also showed an earlier onset of action, recording significant reductions from baseline relative to placebo in wheal and flare areas at 1 hour and at 0.5 hours after administration, respectively, compared with 4 hours for desloratadine and rupatadine.

The antihistaminic activity of these newer second-generation agents has previously been evaluated in numerous randomized, crossover studies which used the same pharmacodynamic model. Single and repeated doses of bilastine 20, 40 and 80 mg were compared with hydroxyzine 25 mg, and a single-dose study compared bilastine 20 and 50 mg with cetirizine 10 mg. Whereas no major differences were observed in either study between bilastine and active comparator in the magnitude or duration of W&F suppression, similar to our findings, bilastine had a more rapid onset of activity (1 hour vs. 2 hours with hydroxyzine; 1.5 hours vs. 4 hours with cetirizine). In single-dose studies of desloratadine, maximal inhibition of histamine-induced W&F area was consistently of a lesser magnitude and generally occurred later with desloratadine than with active comparators, which included cetirizine, ebastine, fexofenadine, and levocetirizine. In single-dose studies especially, pharmacological characteristics such as bioavailability, receptor binding affinity, volume of distribution and protein binding are known to be major determining factors of differential peripheral H₁-blocking activity. The inferior activity of desloratadine versus bilastine and the approximately equivalent activity of desloratadine versus rupatadine observed in the current study may reflect at least in part their relative volumes of distribution (>100 vs. 1.3 vs.143 L/kg) which influence the amount of drug available in the extracellular space. In pharmacodynamic studies of rupatadine, a potent dose-dependent inhibition of the W&F response compared to placebo was observed after single escalating doses of 10, 20, 40 and 80 mg, with the magnitude of effect greatest and of a similar size between rupatadine 80 mg and hydroxyzine 25 mg. A single oral administration of high-dose rupatadine (40 mg) was associated with early (2 hours) and long-lasting (up to 72 hours) inhibition of histamine- and PAF-induced dermal flares. Similar to our own observations, maximal W&F inhibition with rupatadine generally occurred between 4 and 8 hours after administration in both studies.

In this four-way comparison inclusive of a placebo arm, primary and secondary endpoints were consistently in favor of bilastine 20 mg over desloratadine 5 mg and rupatadine 10 mg. Bilastine produced the greatest inhibition of wheal and flare response, had the fastest onset of action (1 hour for wheal inhibition and 30 minutes for flare inhibition), maintained the greatest level of antihistaminic activity at 24 hours, and was the only active treatment to reduce the subjective perception of itching compared with placebo. In hindsight, we consider that the doses of desloratadine and rupatadine may have been too low to produce optimal antihistaminic efficacy in a skin model of allergic disease, and may explain the frequent need to up-dose (by 2-4 times the therapeutic dose) some second-generation antihistamines when treating patients with urticaria. By comparison, significant and sustained peripheral H₁-blocking effects have been observed after single and repeated administrations of bilastine at its therapeutic dose, with no clinically relevant differences in activity noted between 20 mg and 40 mg doses or between 20 mg and 80 mg doses.

The argument against using the W&F model to predict or compare the clinical efficacies of antihistamines has been well iterated in the literature. The lack of correlation between pharmacodynamic effects and clinical responses is thought to relate to the involvement of multiple mediators other than histamine in the allergic response and the relatively short duration of pharmacodynamic studies compared
with usual clinical treatment\textsuperscript{35}. This line of thinking has recently been challenged, however, especially as it applies to urticaria. After reviewing direct comparative data for desloratadine and levocetirizine in W\&F studies and in chronic spontaneous urticaria, Church and Maurer described the W\&F response as the “best indicator we have of effectiveness of H\textsubscript{1} antihistamines in clinical practice”, although they called for the conduct of studies without pharmaceutical company sponsorship\textsuperscript{17}. To this end, an independent, randomized, triple-blind study evaluating cetirizine, fexofenadine, bilastine, desloratadine and ebastine over 8 weeks in patients with chronic spontaneous urticaria found that a strong clinical response to antihistamine could be predicted by >75% inhibition of the histamine wheal at 24 hours after administration\textsuperscript{36}.

Conclusions

At their approved therapeutic doses, the antihistaminic profile of bilastine 20 mg was shown to be different from that of desloratadine 5 mg and rupatadine 10 mg. Bilastine had an earlier onset of activity (1 vs. 4 hours) and a more prolonged effect. Maximum wheal inhibition with bilastine was more than twice that of desloratadine and rupatadine. Bilastine, but not desloratadine or rupatadine, significantly reduced itching sensation compared with placebo between 2 and 12 hours. Pharmacodynamic evidence of a greater inhibitory effect of bilastine on objective and subjective measures of the histamine-induced W\&F response may reflect differences in the basic pharmacokinetics of the active treatments at authorized doses. Within the context of a four-way, single-dose, crossover study, all active treatments were safe and well tolerated.

Transparency

Declaration of funding

This study was funded by Faes Farma SA.

Declaration of financial/other relationships

C.C., LL. and R.V. have disclosed that they are employees of Faes Farma SA. R.A., J.C., C.G.-G., M.P. and I.G. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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