Novel Therapy in Treatment of Patients with Urticaria

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Changes:
- No further inclusion of H₂-AH and dapsone
- Omalizumab and cyclosporine A moved into 3rd line

1. Adapted from Zuberbier T, et al. Allergy 2009;64:1427–43
2. Proposal 4th International Consensus Meeting on Urticaria, Nov 28th-29th, 2012

*H₁-antihistamines are the only licensed treatment available for CSU
†Corticosteroids are not recommended for long-term treatment of CSU outside specialist clinics. nsAH, non-sedating antihistamine
<table>
<thead>
<tr>
<th>Patient population</th>
<th>Intervention</th>
<th>Quality of evidence</th>
<th>Strength of recommendation for use of intervention</th>
<th>Alternative interventions (for patients who do not respond to other interventions)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Chronic</td>
<td>ns sg H1-AH</td>
<td>High</td>
<td>Strong</td>
<td>ns sg H1-AH and ciclosporin</td>
<td>High</td>
</tr>
<tr>
<td>spontaneous</td>
<td>- Increase dosage if necessary up to four-fold</td>
<td>Low</td>
<td>Weak</td>
<td>ns sg H1 and H2-AH</td>
<td>Very low</td>
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<tr>
<td>urticaria</td>
<td></td>
<td></td>
<td></td>
<td>Cimetidine</td>
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- For treatment of CSU; **non sedating H1-AH** is the **first line** of treatment with **high quality of evidence**
• It is important to consider whether the antihistamine prescribed meets the patient’s expectations in terms of
  – Efficacy
  – Safety
  – Tolerability
• The consensus group conducted by Prof Holgate and colleagues under the auspices of the British Society of Allergy and Clinical Immunology, recommended that ideal antihistamine should have 6 properties.
Recommended Antihistamine

1. Anti-allergic/anti-inflammatory properties

2. Potency, efficacy and effectiveness
   (benefit-to-risk ratio = therapeutic index)

3. Lack of cardiotoxicity
   (QT prolongation, torsades de points, ventricular tachyarrhythmias etc.)

4. No drug interaction
   – should not affect any cytochrome P450 isoenzyme function
   – should not displace protein-bound medication
   – should not affect transport mechanisms (i.e. P-glycoprotein) important in drug absorption & excretion

5. Lack of CNS effects: **3 defined criteria for “non-sedative drug”**
   1. Incidence of subjective sleepiness
   2. Objective cognitive and psychomotor functions
   3. Positron emission tomography (PET) measurement of $H_1$ receptor occupancy

6. Pharmacological approach
   - A **new class** of antihistamine that may exhibit a **combination of $H_1$ receptor blockade and additional effect/s** but lack any side effects

Bilastine

- Bilastine is the newest second generation antihistamine
- Not structurally derived from any antihistamines currently on the market
- Not an active metabolite or enantiomer of another antihistamine
- Approved for symptomatic treatment of urticaria in adults and children over 12 years

Wolthers O. BioMed Res Int 2013;626837
• **Bilastine** showed potent antihistamine and weak antimuscarinic effects

• **Highly selective for the H$_1$-receptor** in both in vivo & in vitro studies

• **Poor or no affinity for other receptors** such as serotonin, bradykinin, leukotriene D$_4$, calcium, muscarinic M$_3$-receptors, alpha1-adrenoceptors, beta2-adrenoceptors, H$_2$- and H$_3$-receptors

Features and properties of bilastine (Bilaxten®; Ilaxten®)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Symptomatic treatment of seasonal or perennial allergic rhinoconjunctivitis or urticaria</th>
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<tbody>
<tr>
<td>Mechanism of action</td>
<td>H1-antihistamine</td>
</tr>
<tr>
<td>Dosage and administration</td>
<td>Dose: 20 mg, Frequency of administration: Once daily, Route of administration: Oral</td>
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<tr>
<td>Pharmacokinetic profile</td>
<td>Maximum plasma concentration ($C_{max}$) [median predicted interquartile value]: 220 ng/mL peak plasma conc. at 1 hr</td>
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<tr>
<td></td>
<td>Time to $C_{max}$: $\approx$ 1 h, Elimination half-life: $\approx$ 14 h</td>
</tr>
<tr>
<td></td>
<td>Apparent total plasma clearance: 18.1 L/h</td>
</tr>
<tr>
<td>Most frequently reported</td>
<td>Headache, somnolence, fatigue, dizziness</td>
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<tr>
<td>drug-related adverse events</td>
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- Rapidly absorbed
- **Not metabolized & not induces or inhibits activity of** cytochrome P450 isoenzymes
- No drug accumulation with repeated doses
- 84-90% bound to plasma proteins
- 95% of oral administered dose was recovered in **urine** (28.3%) and **feces** (66.5%) as unchanged bilastine

1. Anti-allergic/anti-inflammatory properties
2. Potency, efficacy and effectiveness
A phase IV, randomized, crossover, DBPC study

24 healthy volunteers

The study comprised 4 periods, placebo, bilastine 20 mg, rupatadine 10 mg, desloratadine 5 mg as a single oral dose, with a 7-day wash-out period between them.

A wheal & flare response was induced by intradermal histamine injection, and the area was measured (Visitrak system)

Assessment at 0.5, 1, 2, 4, 6, 9, 12 & 24 h after each treatment
Bilastine induced a significant reduction of wheal area VS RUP and DES from +1h to +12 h

Antonijoan R, et al.
Bilastine induced a significant reduction of flare area VS RUP and DES from +1h to +24 h
Bilastine significantly reduced itching perception
• as compared to placebo from +2h to +12h,
• and VS RUP and DES from +2h to +9h
Conclusions

• Bilastine 20 mg induced a statistically significant higher inhibitory effect on wheal and flare response compared to desloratadine 5 mg and rupatadine 10 mg throughout the 24 hours study period, with the fastest onset of action.

• Bilastine 20 mg better reduced itching perception than desloratadine 5 mg and rupatadine 10 mg.

• Safety: all active treatments showed a good safety profile
Comparison of the efficacy and safety of bilastine 20 mg vs levocetirizine 5 mg for the treatment of chronic idiopathic urticaria: a multi-centre, double-blind, randomized, placebo-controlled study

T. Zuberbier¹, A. Oanta², E. Bogacka³, I. Medina⁴, F. Wesel⁵, P. Uhl⁶, I. Antépara⁷, I. Jáuregui⁷, R. Valiente⁸ & The Bilastine International Working Group¹,*

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Allergy 2010; 65: 516–528.
• Multicenter RDPC study: 522 CIU aged 18-17 years
• Bilastine 20 mg, levocetirizine 5 mg or placebo once daily for 28 days
Both bilastine 20 mg, levocetirizine 5 mg were equally effective as compared with placebo.

Bilastine reduced mean TSS from baseline to a significant degree than placebo from day 2 onwards.
Both treatments were as equally safe and well tolerated as compared with placebo.

Up-dosing with bilastine results in improved effectiveness in cold contact urticaria

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• 20 patients with cold contact urticaria
• RDPC 12-wk study: placebo, 20, 40 or 80 mg of bilastine daily each for 7 days with 14-day washout periods
Critical temperature threshold of 80 mg bilastine was significant lower than those of 20 mg & 40 mg, illustrating the benefit of updosing.
Mean pruritus scores of all 3 doses were significantly different from placebo.
Dialysate levels of IL-6 & IL-8 during the 2- to -3-hour period after cold provocation in patients received 20 and 80 mg bilastine were significantly reduced, particularly with bilastine 80 mg.
A literature search of PubMed/MEDLINE:
- Look at studies investigated the effects of increased doses of non-sedating AH in patients with all types of CU
- For analysis of efficacy, only double-blinded placebo-controlled studies were included.
**Efficacy of increased doses of nonsedating antihistamines in patients with CU**

Statistical comparison of the data from PubMed/MEDLINE

Bilastine showed significant higher efficacy than desloratadine or levocetirizine.

3. Lack of cardiotoxicity
• Single doses of bilastine up to 220 mg and multiple doses up to 200 mg (10 times higher than therapeutic doses) during 7 days did not result in a statistically significant QT/QTc prolongation as compared with baseline & placebo.

• Bilastine, at **therapeutic & supratherapeutic dosage**, does not induce any effects on **T-wave morphology** or **QTcF**.

• Results confirm **absence of effect for bilastine on cardiac depolarization**
Consensus group on new-generation antihistamines (CONGA): present status and recommendations

S. T. Holgate (chairman)
This Consensus Group was convened under the auspices of the British Society for Allergy and Clinical Immunology.

4. No drug interaction
Bilastine undergoes **no hepatic metabolism or interaction with cytochrome P450**, hence has **minimal potential for drug-drug interactions.**
Consensus group on new-generation antihistamines (CONGA): present status and recommendations

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5. Lack of CNS effects
Histamine activity inhibition at BrH1R level may cause unfavourable effects for example increased somnolence, decreased cognitive functions (memory and learning).

Histamine can be found in the brain and peripheral organs.

Oral first generation antihistamines can cross BBB to reach the CNS and provoke adverse effects.
Bilastine has **low penetration into CNS** due to:
- Bilastine is a substrate of P-glycoprotein (p-gp)
- The relatively high molecular weight
- The relatively lower lipophilicity
- The chemical structure with the hydrophilic carboxy substituent

*Figure 1. Chemical structure of Bilastine. The hydrophilic carboxylic substituent, contribute to the low penetration into CNS.*

Compared with other second-generation H₁-antihistamines, bilastine has one of the lowest cerebral H₁-receptor occupancy.
Bilastine 20 mg did not affect psychomotor scores compared with alcohol plus placebo.

Single or multiple administration of bilastine 20 mg for 8 consecutive days did not potentiate the central depressant effects of lorazepam 3 mg.

• **Objective psychomotor test** in healthy volunteers
• Using **alcohol in combination with** placebo, bilastine 20, 80 mg, cetirizine 10 mg & hydroxyzine 25 mg
• Compared with **placebo alone**

• Study the effect of bilastine 20 mg on the **central depressant effects of lorazepam 3 mg**
• Assessed by **subjective & objective psychomotor tests** in healthy volunteers

Bilastine: a new antihistamine with an optimal benefit-to-risk ratio for safety during driving

Ignacio Jáuregui†, Johannes G Ramaekers, Kazuhiko Yanai, Magí Farré, Esther Redondo, Román Valiente & Luis Labeaga
†Allergy Department, Basurto University Hospital, Bilbao 48013, Spain

Bilastine has an optimal benefit-to-risk ratio for safety for driving.
Standard deviation of lateral position (SDLP)

- Method used for evaluation of driver performance after drug administration by assessing the weaving of a car
- The higher the SDLP, the greater the drug-induced driving performance
• Effects of bilastine 20, 40 mg compared with hydroxyzine 50 mg and placebo in 22 healthy volunteers on actual driving performance
• Assessed by mean SDLP on day 1 and day 8

No effects on actual driving performance after single and repeated doses of bilastine, confirming its safe use in traffic at doses up to 40 mg

The efficacy of bilastine in relation to HRQoL in 525 CU has been evaluated versus levocetirizine & placebo.

Improvement in the global DLQI score and all of its individual domains, with no differences between the two active drug groups.
CASE 1
Patient Profile

• 70 year-old Thai male
• Business man

• **Chief complaint:** spontaneous wheals for 1 year
• 1 year:
  • Spontaneous wheals; 20-50 wheals/day (20% BSA); >2.5 cm; 7 days/week
  • Dermographism: positive
  • Sometimes; angioedema (lips)
  • Pruritus: 3 (severe) (scoring 0-4; 4 = very severe)
  • Usually exacerbated at night
  • Symptoms interfered his work, physical activities and sleep

CSU: moderate severity
Past History

• No other comorbid conditions

• Previous treatment
  – Fexofenadine 180 mg once daily
  – Levocetirizine 5 mg once daily
  – Chlorphenamine 4 mg before bedtime
Physical Examination

• Erythematous wheals on
  - Chest
  - Back
  - Arm

• Dermographism: positive
Diagnosis

• Chronic spontaneous urticaria
Treatment and follow up

Baseline UAS7 before starting bilastine was 28

Prior to consult

Chronic spontaneous urticaria

Fexofenadine (180) 1X1
Levocetirizine (5) 1X1
CPM (4) 1X1 hs

Stop medication 1 wk

Wk 0

• Started bilastine 20 mg/day
• Lesions resolved within 1 hr

Wk 1

Bilastine 20 mg/day

Wk 2

Completely controlled by day 2

Wheal: 20-50 lesions/day everyday no angioedema

No urticarial lesions No angioedema

No urticarial lesions No angioedema
Total CU-Q2oL scores decreased significantly from baseline when the patient took bilastine.
After taking bilatine
• Improved ability to do work and physical activities
• But with some persistent difficulty in sleeping because of stopping long-term sedating antihistamine
CU-Q_{20}L Scores of Each Question

- **Scores**
- **Items**
  - (Difficulty in../ Interfere with..)

- **Significant improvement of medication side effects**

*Graph showing scores for various items, with a notable improvement in medication side effects from Week 0 to Week 2.*
A 17 year-old woman

CC: chronic urticaria for 8 months, sometimes with angioedema

Wheals: 7 days/week; 10 - 20 lesions/day; ≥ 4 cm

No history of atopy

No histories that suggested food & drug reactions, physical urticaria etc.

PE: WNL

CBC, ESR, U/A, stool exam: WNL

ANA, anti-thyroglobulin Ab, antithyroid peroxidase Ab = Negative

ASST positive
Previous treatment: combination of
- cetirizine 10 mg/day; loratadine 10 mg/day; fexofenadine 180-360 mg/day, desloratadine 10-20 mg/day
- Montelukast 10 mg/day
- Prednisolone 10 mg/day (interval)
- Partial improvement

Then added bilastine 20 mg/day; 4 weeks = still partially improved
Updose bilastine to 40 mg/day; within 2 months, only bilastine 40 mg/day alone could completely control the symptoms.
Main benefits of bilastine

- Fast symptom relief in urticaria, reducing the number of wheals, relieving pruritus, and improving patients’ QoL
- Rapid onset of action, with peak plasma concentration occurring at 1.29 hours

- No induction of cytochrome P450 enzymatic activity
- No hepatic metabolism

- No clinically relevant cardiovascular effects

- Close to zero occupancy of brain $H_1$-receptor
- No sedative effects or impact on psychomotor performance

- Good safety profile, with no severe adverse events observed even at higher doses (80 mg) of bilastine
Thank you for your attention
Special precaution for use

- Efficacy and safety of bilastine in children under 12 years old have not been established.

- Limited data are available in subjects older than 65 years.

- No or limited data in pregnant women (Animal studies do not indicate direct or indirect effects; preferable to avoid the use during pregnancy)

- Unknown whether bilastine is excreted in human breast milk.
Interaction

• Concomitant intake of bilastine 20 mg and grapefruit juice decreased bilastine bioavailability by 30%
  – This effect may also apply to other fruit juices

• In patients with moderate or severe renal impairment
  – Coadministration of bilastine with P-glycoprotein inhibitors, such as ketoconazole, erythromycin, ciclosporin, ritonavir or diltiazem, may increase plasma level of bilastine and therefore increase the risk of adverse effects of bilastine.
• Double-blind crossover study
• 24 healthy subjects received a single oral dose of bilastine 20 mg, hydroxyzine 50 mg, or placebo

• On test days, pre-dose (baseline) levels and post-dose levels at selected time points of alertness & performance were determined with the use of objective (vigilance, complex tasks) and subjective tests (tailored to the specific tasks of aircrew)

• Under hypobaric conditions as in intact cockpit
Conclusion: A single oral dose of bilastine 20 mg did not cause sleepiness and did not impair the performance of tasks associated with flying ability. It is anticipated that a single oral dose of bilastine 20 mg will not affect flying performance. This finding might also have implications for the treatment of allergic disorders of personnel involved in other highly skilled jobs.