ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

A Review on Bilastine: A new H1-antihistamine

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Abstract

Bilastine, a novel H1-antihistamine of the second generation, was only recently given the green light for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU). Bilastine represents the development of studies on the effectiveness and safety of antihistamines. Multiple major controlled clinical studies have shown that AR therapy is effective in reducing nasal and ocular symptoms and improving quality of life for patients. Based on these findings, bilastine is a suitable medicine for the treatment of AR according to the latest EAACI/ARIA criteria. The literature study also shows that the 20 mg of bilastine given once day was beneficial in reducing symptoms and enhancing the quality of life for CU patients. Bilastine has a very safe and tolerable profile, almost identical to that of a placebo, with few negative effects on the central nervous system in particular. When higher-than-usual doses of antihistamines are required to manage symptoms, as is often the case in individuals with urticaria, the balance of effectiveness and safety offered by bilastine is especially useful.

Keywords: Antihistamines, Bilastine, Allergic rhinitis, Chronic urticaria, Efficacy, Safety

Introduction

Patients above the age of 12 may now use bilastine, a newer generation H1-antihistamine, for the symptomatic treatment of allergic rhinitis (AR) and chronic urticaria (CU). Asthma-related urticaria (AR-U) and urticaria are two of the most prevalent clinical disorders that bring patients to their family doctor or allergist. Ten percent to thirty percent of American adults and as much as forty percent of American youngsters suffer with AR [1, 2]. Acute urticaria has a lifetime incidence of around 20%, whereas CU has a prevalence of about 1.8% [3]. Despite their differences, these two clinical entities have the same negative impact on quality of life (QoL) and productivity [4-6]. Antihistamines are effective in treating AR and urticaria, and nonsedating second generation antihistamines are recommended as first line therapy for both conditions according to current international standards [3,7,8].

There is no doubt that histamine contributes to allergic inflammation. It has four different receptors that it acts on to produce its biological effects, with the H1-receptor being the most crucial in allergic disorders. Directly blocking H1 receptors, like H1 antihistamines do, reduces histamine's ability to cause allergic inflammation [9]. There are two types of H1-antihistamines, distinguished by whether or not they can cross the blood-brain barrier: first-generation antihistamines, like bilastine, bind to H1-receptors on neurons in the central nervous system, resulting in sedation and impaired mental status, and second-generation antihistamines, which typically cannot. In particular, bilastine from the second generation of antihistamines stands out due to its promising combination of extended duration of action, effectiveness, low-sedation impact, and low-performance impairment. In this article, we'll look at the clinical data supporting the use of bilastine to treat AR and urticaria.

ISSN PRINT 2319 1775 Online 2320 7876

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Pharmacodynamic and pharmacokinetic properties

Molecule-wise, bilastine is represented by the formula 2-[4-(2-(2-ethoxyethyl)-1Hbenzimidazol-2-yl) piperidin-1-yl] phenyl.-2-Propionic acid-2-methyl-. It is a member of the piperidine derivatives class and is structurally unrelated to other existing antihistamines. Bilastine has strong, H1-specific antihistamine properties.

Like other antihistamines, bilastine acts as an H1 receptor inverse agonist. In vitro and preclinical tests indicated that although bilastine has a high affinity for H1-receptors, it has almost little effect on the other 30 receptors tested (including sero- tonin, bradykinin, leukotriene-D4, muscarinic M3-receptors, alpha 1- and alpha 2-adrenoceptors, and histamine receptors H2 and H3) [10]. Compared to cetirizine and fexofena- dine, the H1 receptor affinity is increased by a factor of 3 and 6, respectively. Antiallergic properties, with similar potency to cetirizine and superior potency to fexo- fenadine [11], were confirmed by in vivo preclinical studies, which showed that bilastine reduced histamine-stimulated smooth muscular contraction, bronchospasms, endothelial permeability, and microvascular extravasation in rats.

By preventing human mast cells and granulocytes from releasing histamine, IL-4, and tumor necrosis factor (TNF)-, bilastine has been demonstrated to have anti-inflammatory effects [12].

Time to maximal plasma concentration after oral treatment is around 1 hour [13]. The medication is readily absorbed after oral administration. Approximately 60% oral bioavailability of bilastine was observed [14]. Half-life of 20mg bilastine was 14.5 hours, maximal plasma concentration was measured 1.3 hours after administration, and 84-90% of the drug was bound to proteins in the plasma [13,14]. Since bilas- tine is a substrate for P-glycoprotein, which limits its passage across the blood-brain barrier [15], no clinically relevant interactions have been reported to date. Approximately 95% of bilas- tine is excreted intact in feces (67%) or in urine (33%). Half-life for elimination was determined to be 14.5 hours on average in healthy volunteers, and the apparent total plasma clearance is 18.1 liters per hour [16,17]. The CYP450 family is not a substrate for biclastine [18].

Efficacy of bilastine

Wheal and flare inhibition

Antihistamine effects were tested against histamine-induced wheal and flare reactions in 21 healthy male volunteers over 24 hours in a phase 1, double-blind, randomised, placebo-controlled, single oral dosage, cross-over research [19]. Subjects were randomly assigned to receive either 20 or 50 milligrams of bilastine or 10 milligrams of cetirizine or a placebo orally before being pricked with 100 milligrams per milliliter of histamine at 1.5, 4, 8, 12, and 24 hours later to provoke wheal and flare reactions. Inhibition of wheal and flare at 1.5 h with bilastine was 89 3 versus 44 14% (P = 0.011) and 85 4 versus 45 14% (P = 0.016), respectively, but the authors found no significant differences between the overall inhibitions of wheal and flare by bilastine 20 mg and cetirizine10 mg. At 1.5 hours, 11/12 participants receiving bilastine and 3/11 volunteers taking cetirizine both showed a 70% reduction in wheals and flares, respectively (P = 0.003). In subsequent periods, the medications showed no discernible changes.

Bilastine efficacy in allergic rhinitis

Bilastine's effectiveness in treating seasonal and permanent allergic rhinitis is well established. The Vienna Challenge Chamber is used to compare various antihistamines since it is a well-established, standardized approach for the controlled exposure of patients

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

to identified allergens [20,21]. Patients with seasonal AR (SAR) participated in a double-blind, randomized, placebo-controlled, balanced four-treatment, four-period crossover phase II trial to examine the efficacy of bilastine, cetirizine, and fexofenadine in alleviating symptoms [22]. Adults having a history of grass pollen allergy were recruited to participate in the trial while they were not experiencing any symptoms related to their allergy. A single dosage of bilastine (20 mg), cetirizine (10 mg), fexofena- dine (120 mg), or placebo was given two hours after the commencement of the challenge, and their effects were compared using the Total Nasal Symptoms Score (TNSS). There was no significant difference between the three antihistamines during the first four hours after delivery, however all three were considerably more effective than placebo in lowering TNSS (p 0.001). When compared to cetirizine (10 mg) and fexofenadine (120 mg), bilastine (20 mg) was just as effective in relieving ocular symptoms 1 hour after ingestion. Bilastine's lengthy half-life was verified by the fact that it was still effective 26 hours after administration.

Two similar double-blind, placebo-controlled studies have been conducted to evaluate the efficacy of bilastine in patients with SAR [23,24]. These studies compared once-daily 20 mg of bilastine with placebo, 5 mg of desloratadine, and 10 mg of cetirizine over the course of two weeks, with the first also assessing quality-of-life. Table 1 provides information on the two studies. A total of 1404, ranging in age from 12 to 70 years old, with confirmed SAR owing to pollen allergens, participated in these two investigations. The major outcome measure of TSS was lowered in the bilastine group in both investigations, and this reduction was statistically significant compared to both the placebo and active comparator groups (table 1). As judged by the rhino-conjunctivitis quality of life questionnaire (RQLQ), bilastine was similarly effective as desloratadine in enhancing QoL; the administration of 20 milligrams of bilastine significantly enhanced both the overall RQLQ score and the majority of its single domains in comparison to placebo.

650 patients with symptomatic persistent AR (PAR) were included in a multicenter, randomized, placebo-controlled, double-blind, parallel-group research [25]. Over the course of 4 weeks of treatment, the authors found no statistically significant differences in efficacy outcomes between active treatments and placebo. However, in a post hoc analysis, bilastine 20 mg was found to be more effective than placebo and on par with cetirizine 10 mg in the population of patients from Europe and Argentina, though the difference was not statistically significant in patients from South Africa. Data on the effect of bilastine upon nasal obstruction and ocular symptoms from 7 phase II and phase III 2-4 week duration clinical trials were analyzed by Davila et al. and Bartra et al. [27,28]. The lack of efficacy throughout the whole group was likely due to the group great variability of symptom scores reported in different countries, particularly in South Africa [26]. After two weeks of treatment, the mean change in nasal obstruction symptom score was 0.66 with bilastine 20 mg and 0.57 with pla- cebo (p 0.001), and 0.67 with active comparators (cetirizine 10 mg and desloratadine 5 mg) (p 0.001 vs placebo; not statistically different vs bilastine) [27]. Bilastine was similarly more efficacious than placebo and comparable to active comparators in alleviating ocular symptoms [28].

Table 1 Double blind randomized trials in seasonal AR

Study	Patients N.	Duration	Treatment	Efficacy	Safety vs active comparator

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

Kuna P et al. [24]	683	14 days	Bilastine 20 mg Cetirizine 10 mgPlacebo	The mean TSS-AUC$_{0_14}$ days (score_day) was reduced in bilastine and cetirizine groups to a similar and significantly greater extent, compared with placebo (P < 0.001). Bilastine and cetirizine were comparable and significantly superior to placebo for all secondary outcomes	**Significantly fewer patients in the bilastine-treated group experienced somnolence (P < 0.001) and fatigue (P = 0.02) than patients in the cetirizine-treated group.**
Bachert C et al. [23]	**721**	**14 days**	**Bilastine 20 mg Desloratadine 5mg Placebo**	**The AUC of TSS was decreased to a significantly greater extent in the bilastine group compared with placebo group (P < 0.001). Total RQLQ score was significantly reduced from baseline by a value of 1.6 (1.2; 1.8–1.4) in the bilastine treated group compared with a value of 1.3 (1.3; 1.5–1.1) in the placebo-treated group (P < 0.005)**	**Safety profile of bilastine and desloratadine were comparable to placebo.**

TSS-AUC$_{0_14}$: area under the curve (AUC) of the reflective total symptoms score (TSS) from day 0 (D0) today 14; RQLQ: rhinoconjunctivitis quality of life questionnaire.

Bilastine efficacy in urticaria

Treatment of chronic idiopathic urticaria with bilastine 20 mg vs levocetirizine 5 mg was examined in a randomized, double-blind, placebo-controlled research including 525 adult patients [29]. Over a 28-day treatment period, all treatments lowered the TSS from baseline, however there were significant differences between the bilastine 20 mg and levo- cetirizine 5 mg-treated groups and the placebo-treated group starting on day 2. The primary efficacy measure, the mean change from baseline in patients' reflective daily TSS over the 28-day treatment period, was significantly higher for bilastine 20 mg and levocetirizine 5 mg treated groups compared with the placebo-treated group (P 0.001 for bilas- tine and levocetirizine vs. placebo), but there was no significant difference between the active treatment groups.

Activation of cutaneous mast cells and the subsequent release of pro-inflammatory mediators in response to cold exposure characterizes cold urticaria, a very rare type of inducible urticaria characterized by pruritic wheals and/or angio- edema [30]. Many

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

patients with cold urti- caria need substantial doses of antihistamines, often up to four times the daily recommended amount, in order to have symptom relief [31,32]. In a 12-week, randomized, crossover, double-blind, placebo-controlled research [33], Krause et al. compared the effectiveness of a regular 20 mg dosage of bilastine with up- dosing to 40 and 80 mg to reduce CU symptoms and inflammatory mediator production after cold exposure. Patients in this trial were randomly assigned to receive either a placebo, 20, 40, or 80 mg of bilastine once daily for 7 days, followed by a 14-day washout period if they did not respond to treatment. The critical temperature threshold (CCT, the highest temperature that produces a positive wheal response) and the number of patients who became symptom-free (P = 0.044) in the bilastine group were significantly different from the placebo group at 20 mg (median CCT value, 6°C in bilastine group and 18°C in placebo group, P 0.0001). Bilastine 80 mg was more effective than 20 mg (P = 0.003) and 40 mg (P = 0.04) in reducing the mean CTT, suggesting that the up-dosing was successful. The 80 mg dose of bilastine dramatically decreased inflammatory mediators.

Safety of bilastine

Table 2 summarizes tolerability results from four phase III studies ranging in length from two to four weeks. Bilastine was well tolerated in these studies, with the majority of adverse events described as mild or moderate and no reports of serious adverse events or deaths; additionally, bilastine 20 mg was not associated with any statistically or clinically significant changes in laboratory tests, ECGs, heart rate, or systolic or diastolic blood pressure. Headache, somnolence, and weariness were the most often reported negative effects, however they were reported less frequently than in individuals taking cetirizine at 10 mg once day. Patients with SAR had these side effects at a rate similar to that seen with desloratadine. Unlike second-generation antihistamines, which typically do not cross the blood-brain barrier and have fewer sedative effects, first-generation antihistamines are able to enter the brain and bind the H1-receptors on the membranes of postsynaptic neurons in the central nervous system, leading to sedation and impaired mental status. Histamine 20mg bilastine. Since bilastine met both the objective and PET requirements to be characterized as a non-sedating antihistamine [34], positron emission tomography (PET) was used to assess H1-receptor occupancy in healthy participants. Furthermore, studies showed that bilastine had little to no effect on performance. Twenty healthy volunteers participated in a crossover, randomized, double-blind, placebo-controlled trial in which they were given bilastine (20, 40, or 80 mg) and hydroxyzine (25 mg), a first-generation antihistamine, for 7 days in a row [35]. Although a dosage of 40 mg bilastine was associated with a subjective perception of drowsiness, objective impairment was not apparent until doses of 80 mg bilastine were compared to placebo. Similar results were seen when testing single and multiple doses of bilastine up to 40 mg [36]. Objective impairment induced by bilastine 80 mg + alcohol (0.8 g/Kg) was of similar magnitude to that induced by hydroxyzine 25 mg + alcohol [37]. The combination of bilastine and alcohol at the therapeutic dose of 20 mg does not produce greater central nervous system (CNS) depressant effects than al- cohol alone. Cardiovascular safety at therapeutic and supratherapeutic levels was also demonstrated. The QTc was not significantly altered by 20 mg or 100 mg of bilastine. Clinically significant prolongation of the QT interval (QTc) was seen after concomitant treatment of 20 mg of bilastine and ketoconazole [38]. Furthermore, neither therapeutic nor supratherapeutic doses of bilastine (up to 100 mg) induced any changes in T-wave shape [39].

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

Table 2 AEs in patients receiving bilastine 20 mg inclinical trials

Study	Patients N. Duration	Disease	AEs in bilastine- treated group
Kuna P et al. [24]	683	SAR	**Any 24.7%**
	14 days		
			Headache 10.6%
			Somnolence 1.8%
			Fatigue 0.4%
			Dyspnoea 0.9%
Bachert C et a. [23]	721	SAR	**Any 28.3%**
	14 days		**Headache 12.0%**
			Somnolence 3.9%
			Fatigue 2.6%
Sastre J et al. [25]	650	PAR	**Any 23.4%**
	4 weeks		
			Headache 10.7%
			Somnolence 13.7%
Zuberbiert T et al. [29]	525	CIU	**Any 30.1%**
	28 days		**Headache 12.1%**
			Somnolence 5.8%
			Fatigue 2.9%

SAR: seasonal allergic rhinitis; PAR: persistent allergic rhinitis, CIU: chronicidiopatic urticarial, AEs: adverse event.

Conclusions

Bilastine represents the development of knowledge about the effectiveness and safety of antihistamines throughout time [40]. Several big controlled clinical studies have shown its effectiveness in treating AR [26]. In 2012, Bousquet et al. summarized the research to conclude that 20 mg of bilastine once day significantly reduced nasal and ocular symptoms of AR and enhanced quality of life, a crucial result in allergic disorders. The authors reasoned that because of this, bilastine should be used to treat AR according to the current EAACI/ARIA criteria [41]. In a similar review of the medical literature, Jauregui et al. [42] concluded that once-daily treatment with bilastine 20 mg was effective in managing symptoms and improving patient quality of life in chronic urticaria. This was true for both spontaneous and inducible urticarial syndromes. In all Phase I, II, and III clinical studies, bilastine had a safety and tolerability profile equivalent to placebo. Bilastine, in contrast to other antihistamines, does not amplify the CNS depressive impact of lorazepam [43]. Neither does it, in contrast to other second-generation antihistamines like cetirizine, amplify the effects of alcohol on the CNS. Bilastine's optimal effectiveness and tolerability profile is especially useful when non-standard doses are required for symptom management. Patient safety is a major need when selecting a specific antihistamine [44]. This is especially true when the dosages are substantially greater, as is often the case in patients with urticaria, when antihistamines doses up to four times the usual dose are delivered.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022

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Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 1,Jan 2022