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Role of bilastine in the management of allergic rhinitis and urticaria: an Asia-Pacific consensus statement

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The prevalence of allergic diseases is increasing globally, most particularly in middle- to low-income countries. This article examines the burden of allergic rhinitis and chronic urticaria in the Asia-Pacific region, unmet clinical needs, and the potential role of bilastine in the management of these conditions. An International Advisory Group meeting was convened in association with the Asian Pacific Society of Respirology Annual Congress in November 2014, followed by a literature review, and consensus-based outcomes from the meeting and literature review are described. Regional estimates of the prevalence of allergic rhinitis range from 10% to 50%, while little is known regarding the burden of urticaria in the Asia-Pacific region. A survey of allergy patients in the region identified fast, complete, and long-lasting symptom relief as the medication attributes most important to patients. International treatment guidelines for allergic rhinitis and urticaria advocate the first-line use of second-generation, no-sedating H_1-antihistamines, such as bilastine, over their first-generation counterparts and a range of these agents are available to Asia-Pacific patients. The newer agents possess many of the properties of an "ideal" antihistamine (once daily administration, rapid and complete symptom relief, limited potential for drug-drug interactions, minimal side effects). The burgeoning prevalence of allergic diseases in the Asia-Pacific region and the uncontrolled symptoms that these patients experience demand a new antihistamine that offers the highest number of positive features according to the international guidelines.

Key words: Rhinitis, Allergic; Urticaria; Histamine Antagonists; Asia; Consensus; Bilastine

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INTRODUCTION

There is growing evidence that the prevalence of allergic diseases is increasing globally [1], including in the Asia-Pacific region [2-5]. Estimates suggest that 20% to 30% of the world's population suffers from some form of allergic disease [1]. Allergy is a common and often unrecognized cause of respiratory illness among primary care patients. For example, data from China show that more than 50% of primary care patients with cough have a history of atopic illness [6]. Yet, cross-country studies show a consistent trend towards underdiagnosis of allergic diseases [7].

Although the causes of the worldwide "allergy epidemic" are not known, the growth in allergy prevalence is mainly centered in middle to low-income countries [2], which suggests that economic development may be driving the increase. In the Asia-Pacific region, this theory is borne out by data showing that allergy rates are higher in urban than in rural parts of Asian countries [8-11]. There is now emerging evidence of an interaction between irritants and allergens, whereby inhaled pollutants increase sensitization to allergens, and enhance airway hyperresponsiveness in susceptible people [12]. This may occur because pollutants compromise the barrier function of airway epithelial cells, or because they enhance the immune response to airborne allergens [12, 13]. The ability of pollutants to stimulate a nonallergic hypersensitivity reaction may explain the relationship between urbanization and rhinitis incidence in Asia and elsewhere [1, 8-11]. Climate change may also impact on the development of allergic disease, and the combination of declining air quality and increasing global temperatures is likely to be driving the increase in allergy prevalence in developing and developed countries alike [1].

Allergic diseases may include asthma, rhinitis, anaphylaxis, food allergy, eczema, urticaria and angioedema [1], and many patients with one type of atopic disorder often have another [14]. For example, up to 80% to 90% of patients with asthma also have allergic rhinitis, and 40% of patients with allergic rhinitis have asthma [1]. Almost half of patients (48%) with chronic urticaria also experience allergic rhinitis [15].

Allergic rhinitis and urticaria are common histamine-induced allergies that respond to treatment with antihistamines [16]. Although not life-threatening, the consequences of these conditions are not trivial. Patients with allergic rhinitis or urticaria report impaired quality of life [17-21]. Both of these conditions impact on patients' sleep [18, 20], and affect their daily activities such as work/school performance [19, 21]. Moreover, physicians frequently underestimate the impact of allergic conditions on the health and quality of life of afflicted patients [1].

International evidence-based guidelines have been published for the management of allergic rhinitis [22] and chronic urticarial [23]. However, the extent to which these are applicable or followed in the Asia-Pacific region is unknown. In November 2014, an Advisory Group Meeting, sponsored by Menarini, was convened in association with the Asia-Pacific Society of Respirology Annual Congress in Bali, Indonesia. The aim of this Meeting was to identify unmet clinical needs in the management of allergic rhinitis and chronic urticaria in the region, and the role that bilastine may play in addressing these unmet needs. Unmet needs in Asia-Pacific were identified at the meeting by questionnaire. Once identified, literature searches relating to these unmet clinical needs were conducted, and an overview developed from those results, which was circulated electronically among all consensus group members. The current article describes the consensus-based outcomes of that meeting and the subsequent literature review.

BURDEN OF ILLNESS IN ASIA-PACIFIC

Allergic rhinitis

In Asia-Pacific, the prevalence of allergic rhinitis is variously reported as ranging from around 8–10% of the population (in Korea) to more than 50% (among adults in Vietnam and Thailand), depending on the method of assessment [9, 24-32]. The allergies in Asia-Pacific survey reported an adult prevalence of 9%, with 63% of patients having seasonal or intermittent allergies [33]. Studies consistently report that dust mites are the most common causative allergen in the region [34-37].

Patients with allergic rhinitis experience the three cardinal symptoms of sneezing, nasal obstruction, and rhinorrhea as a result of IgE-mediated inflammation of the nasal mucosa [38]. In addition, patients with allergic rhinitis can experience troublesome nonnasal symptoms, such as headache, thirst, and difficulty sleeping [17], as well as cough, snoring, wheezing, sinus pressure, sore throat, and ocular symptoms such as itchy, red or watery eyes [33, 39]. More than 70% of people with allergic rhinitis in Asia-Pacific suffer from sleep problems, which they rate as extremely troublesome, and many experience daytime fatigue related to sleep disturbance [33]. Comorbid asthma is common

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in allergic rhinitis, and many patients also experience sinusitis, depression and anxiety [39].

As described earlier, allergic rhinitis impairs quality of life [17, 21], and interferes with daily activities [33]. Patients with allergic rhinitis miss a substantial number of days of work or school because of their symptoms [33, 40, 41], and are less productive when at work because of their symptoms [33]. Direct and indirect costs of illness are high [40-42], to the health system as well as the patient, because many patients use over-the-counter products in addition to prescription medicines to manage their symptoms [41, 43]. An analysis of allergy-related medical costs among children in Thailand found that rhinitis was associated with higher per-patient costs than asthma [42].

Urticaria

Data on the current burden of urticaria in the Asia-Pacific region have yet to be reported. The lifetime prevalence may be as high as 23% [1]. Principal signs and symptoms are the development of wheals and/or angioedema. A single lesion usually lasts no more than 24 hours, but each episode is usually characterized by multiple lesions coming and going [1]. When severe (>50 lesions in 24 hours or large confluent areas of wheals), patients often experience intense pruritus, which can affect normal daily activity and sleep [23].

Urticaria may be classified as acute (episode lasting <6 weeks) or chronic (lasting ≥6 weeks). There is a high prevalence of emotional distress in patients with chronic urticarial [44].

The most common age for development of urticaria is early adulthood, a peak time for education, career development and starting a family; therefore, urticaria has the potential to negatively impact productivity at a crucial time in people's lives [1]. Because of the clear impact of urticaria on patient quality of life [19, 20, 45], guidelines recommend that physicians caring for patients with urticaria routinely assess their quality of life using a validated patient outcome measure such as the chronic urticaria questionnaire on quality of life [46].

PHARMACOLOGICAL TREATMENT: GUIDELINE RECOMMENDATIONS

Allergic rhinitis

The most widely used guidelines for allergic rhinitis are the Allergic Rhinitis and its Impact on Asthma (ARIA) evidence-based guidelines, which were last updated in 2010 [22]. Pharmacological treatment recommendations are summarized in Table 1 [22].

The ARIA group grades their recommendations as "strong" (i.e., most individuals should receive this intervention, and adherence to this guideline could be used as a quality criterion or performance indicator), or "conditional" (i.e., applying to most individuals but recognizing that different choices will be appropriate for different patients) [22]. Most ARIA recommendations on pharmacological therapy are conditional, but several are strong recommendations. These include the recommendation that, for first-line treatment, patients receive new-generation oral H_1-antihistamines that do not cause sedation or interact with cytochrome P450 enzymes [22]. In these guidelines, new-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines [22].

Urticaria

Joint guidelines for the management of urticaria have been developed by the Asian Academy of Dermatology and Venereology (AADV), European Academy of Allergy and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA^{2}LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) [23]. These guidelines were last updated in 2013 [23].

The goal of treatment in urticaria is complete symptom control [23]. Similar to ARIA, these guidelines strongly recommend that modern second-generation H_1-antihistamines are preferred over first-generation H_1-antihistamines in the treatment of urticaria, based on a high level of evidence [23]. In addition, the EAACI/GA^{2}LEN/EDF/WAO guidelines recommend that modern second-generation H_1-antistamines be used first-line for the treatment of urticaria, and be taken continuously at the lowest effective dose rather than on-demand [23].

Another key recommendation in the EAACI/GA^{2}LEN/EDF/WAO guidelines is that the dose of modern second-generation H_1-antistamines can be increased up to 4 folds, and this approach is preferred to combining different H_1-antistamines at the same time [23]. If patients have persistent symptoms despite a 4-fold increase in the dose of second-generation antihistamine, then a trial of add-on therapy (with omalizumab or cyclosporine) is recommended, rather than trying to increase the dose of antihistamine further [23]. Montelukast is an alternative third-line agent, but this is a weak recommendation based on a low level of evidence [23]. A short course of oral corticosteroids may

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Table 1. Allergic Rhinitis and its Impact on Asthma recommendations for the pharmacological treatment of allergic rhinitis [22]

Recommendation	Strength	Evidence quality
Oral antihistamines		
Recommend use of new-generation oral H_1-antihistamines that do not cause sedation and do not interact with CYP450	Strong	Low
Suggest use of new-generation oral H_1-antihistamines that do cause sedation and/or interact with CYP450	Conditional	Low
New-generation oral H_1-antihistamines are recommended over old-generation oral H_1-antihistamines	Strong	Low
New-generation oral H_1-antihistamines are recommended over intranasal H_1- antihistamines in adults with persistent or seasonal AR, and in children with intermittent or persistent AR	Conditional	Very low
New-generation oral H_1-antihistamines are recommended over oral leukotriene receptor antagonists in patients with seasonal AR, and in preschool children with persistent AR	Conditional	Low
Do NOT use oral H_1-antihistamines to treat wheezing in preschool children with other allergic diseases	Conditional	Very low
Intranasal antihistamines		
Suggest use of intranasal H_1-antihistamines for symptoms of seasonal allergic rhinitis in adults and children, but NOT for persistent allergic rhinitis	Conditional	Very low
Suggest use of intranasal H_1-antihistamines over intranasal chromones in patients with AR	Conditional	Low
Oral leukotriene receptor antagonists		
Can use oral leukotriene receptor antagonists in adults and children with season AR and in preschool children with persistent AR, but NOT in adults with persistent AR	Conditional	High
Intranasal glucocorticosteroids		
Recommend use of intranasal glucocorticosteroids in adults	Conditional	Moderate
Suggest use of intranasal glucocorticosteroids in children	Conditional	Low
Suggest use of intranasal glucocorticosteroids over oral H_1-antihistamines in adults with seasonal AR	Conditional	Low
Suggest use of intranasal glucocorticosteroids over oral H_1-antihistamines in children with seasonal AR	Conditional	Very low
Recommend use of intranasal glucocorticosteroids over intranasal H_1-antihistamines in patients with AR	Strong	High
Recommend use of intranasal glucocorticosteroids over oral leukotriene receptor antagonists in patients with seasonal AR	Strong	Low
Intranasal chromones		
Suggest use of intranasal chromones in patients with AR	Conditional	Moderate
Intranasal ipratropium bromide		
Suggest use of intranasal ipratropium bromide to treat rhinorrhea in patients with persistent AR	Conditional	Moderate
Decongestants		
Suggest a very short course (≤5 days) of intranasal decongestant in combination with other treatments in adult patients with AR and severe nasal obstruction, but do NOT use in preschool children	Conditional	Very low
Do NOT use oral decongestants regularly in patients with AR	Conditional	Low
Suggest NOT to use a combination of an oral H_1-antihistamine and oral decongestant compared with an oral H_1-antihistamine alone	Conditional	Moderate
Ocular treatments		
Suggest use of an intraocular H_1-antihistamine in patients with AR and symptoms of conjunctivitis	Conditional	Low
Suggest use of an intraocular chromone in patients with AR and symptoms of conjunctivitis	Conditional	Low

CYP450, cytochrome P450; AR, allergic rhinitis.

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be also used third-line or for acute exacerbations, but long-term treatment with systemic steroid is not recommended [23].

The AADV consensus guidelines (2012) are in general agreement with the EAACI/GA^{2}LEN/EDF/WAO guidelines in stating that second-generation H_1-antihistamines should be used first-line in most patients [47]. However, they also note that updosing of H_1-antihistamines can be undertaken in smaller dose increments in Asian patients, because they are generally of smaller build [47].

APPLICABILITY OF ANTIHISTAMINE TREATMENT RECOMMENDATIONS IN ASIA-PACIFIC

The clinical attributes of allergy medications that are important to patients include good efficacy, a rapid onset of action, a long duration of action, and a lack of unwanted effects [48]. Second generation H_1-antihistamines are recommended first-line because of their proven efficacy and good tolerability, in particular a low rate of sedative effects [48].

In the Asia-Pacific allergies survey, the medication attributes rated as most important were fast onset (30%), complete (26%), and long-lasting (25%) symptom relief [33]. Specifically, 72% of patients expected relief within 3 hours, and 21% expected symptom relief to last for >24 hours [33].

As new agents become available, the clinical profile of these agents approaches those defined by the EAACI and ARIA as the attributes of the 'ideal' antihistamine [49, 50]. Most are taken once daily; the exception is fexofenadine, which is cleared more quickly from the body because it is actively secreted into the intestine and urine [48]. Cetirizine, and to a lesser extent levocetirizine, have the potential to cause sedating effects, because they are capable of crossing the blood-brain barrier [48].

The consensus group believes that physicians in Asia-Pacific have access to a range of suitable second-generation H_1-antihistamine options and are therefore well placed to follow international guideline recommendations for first-line treatment of allergic rhinitis and urticaria.

ROLE OF BILASTINE IN ALLERGY MANAGEMENT

Bilastine, a novel second-generation H_1-antihistamine, is approved for the symptomatic treatment of allergic rhinoconjunctivitis and urticaria in adults and children over 12 years of age. Current AR and urticaria guidelines recommend second-generation antihistamines as first-line therapy for both conditions [22, 23], and bilastine has the highest number of positive attributes of such agents using the criteria defined by the EEACI/GA^{2}LEN/WAO guidelines [23]. Bilastine has a favourable pharmacokinetic profile, being rapidly absorbed resulting in an onset of clinical effect within one hour of administration, and has a long duration of action, exceeding 24 hours, which allows for once-daily dosing [49]. In a comparison versus cetirizine, bilastine had a significantly greater beneficial effect on wheals and flares at the earliest postdose measurement (89% vs. 44%, $p = 0.011$ and 85% vs. 45%, $p = 0.016$, respectively, at 1.5 hours after administration), suggesting a faster onset of antihistaminergic action [51]. The duration of action of bilastine has also proven to be significantly longer than that of fexofenadine [52]. The route of bilastine elimination is independent of the liver, and therefore this agent has limited potential for metabolic drug-drug interactions [49].

In clinical trials, bilastine has shown efficacy equivalent to cetirizine and desloratadine in allergic rhinitis [53-55], and equivalent to levocetirizine in urticarial [56], and was shown to improve the quality of life of patients with allergic rhinitis [54] or chronic urticarial [56]. The cumulative quality of life data from the major bilastine clinical trials demonstrate significant improvements with bilastine relative to placebo in patients with allergic rhinitis or urticaria, with quality of life improvements consistent with symptom relief in these conditions [57].

An important advantage of bilastine is that it has a very favourable tolerability profile with minimal effect on sedation, psychomotor performance and driving competence [58, 59]. Bilastine is truly nonsedative. A study using positron emission tomography found that bilastine 20 mg occupied almost none of the cerebral H_1-receptors, compared with about 54% occupancy with hydroxyzine 25 mg ($p < 0.01$) [60]. This means that bilastine has one of the lowest reported rates of central nervous system H_1-receptor occupancy of the available antihistamines [60]. In addition, and unlike cetirizine, bilastine does not augment the CNS effects of alcohol [61].

In addition to being nonsedative, bilastine is not associated with weight gain, anticholinergic effects, or cardiac side effects [49]. Even at supratherapeutic doses, bilastine has no significant effect on QT interval, even when administered with ketoconazole

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[62]. In comparative analyses, bilastine was associated with significantly lower rates of somnolence and fatigue relative to cetirizine [55]. These features mean that bilastine has many of the characteristics of the optimal H_1-antihistamine as recommended for first-line treatment of allergic rhinitis or urticaria in current international guidelines [23, 49].

UNMET NEEDS IN ALLERGY MANAGEMENT IN ASIA-PACIFIC

The consensus group identified a number of barriers to the optimal management of allergic conditions in Asia-Pacific. These include underdiagnosis and undertreatment of allergies, diverse treatment practices, patient perceptions of allergy treatment options, and physicians' attitudes to guidelines and treatments.

Diverse treatment practices

Anecdotal evidence suggests that allergic rhinitis and urticaria are managed differently in different countries with variable use of international guidelines [63]. Specialist care of allergy patients differs between countries. For example, in Singapore, adults requiring specialist care for allergic disease tend to be referred to rheumatologists with a subinterest in allergy, whereas in Malaysia, referral is mainly to otolaryngologists or dermatologists. While some variation between countries is unavoidable in health care, a more consistent approach to allergy management within countries should be the goal. Consistent and structured approaches to disease management in allergic conditions can reduce morbidity, improve patient well-being and reduce costs to both the healthcare system and the patient [1]. In addition, treatment according to accepted guidelines results in better symptom control and improved quality of life for patients with allergy compared with treatment based on physician free choice [63].

Suboptimal use of evidence-based guidelines in allergy is also a concern. For example, sedating antihistamines are frequently used in Malaysia. The reason for this is not clear, but it may involve primary care physicians' lack of awareness of current recommendations, patients self-medicating with over-the-counter treatments, or patients/physicians opting for this treatment because of issues related to cost.

A recent initiative in Europe has been the development of integrated care pathways (ICPs) to standardize the management and referral of patients with chronic respiratory disease, including allergic rhinitis, with or without concomitant asthma [64]. It is hoped that, by providing a common framework for guideline-directed care in these conditions, not only will the evidence-based management of patients improve, but there will be a reduction in the healthcare burden associated with these diseases, e.g., fewer emergency room visits or hospitalizations, less patient disability, and reduced costs [64].

Physicians need to be aware of the potential adverse effects of first-generation H_1-antihistamines, including CNS effects and anticholinergic effects (e.g., dry mouth, urinary retention), when making prescribing choices [48]. If first-generation H_1-antihistamines are prescribed, patients need to be fully aware of the potential CNS side effects of these agents, and the impact they may have on their ability to drive and to use machinery.

In addition, there is variable use of updosing of second-generation H_1-antihistamines as recommended in the international urticaria guidelines [23], probably because this practice is not used in the management of other allergic conditions.

Patient perceptions of treatment

Asia-Pacific data show that the most common reasons for patients to be dissatisfied with treatment for allergic rhinitis are inadequate efficacy and bothersome side effects [21]. Moreover, these are also reasons cited for nonadherence, along with symptom relief that does not last 24 hours and safety concerns with intranasal corticosteroids [65]. Poor adherence or inadequate treatment efficacy may explain why, in the Asia-Pacific allergies survey, only 42% of patients with allergic rhinitis reported that their symptoms were completely or well controlled [33].

For urticaria patients, a GA^{2}LEN Task Force report indicates that <50% of patients respond to standard doses of second-generation H_1-antistamines [66], supporting the EAACI/EDF/GA^{2}LEN/WAO recommendation that the dose be increased up to 4 folds to achieve relief [23]. If physicians are unwilling to updose H_1-antihistamines for these patients, many will be dissatisfied with treatment.

Taken together, these data suggest that much can be done to improve the treatment (and treatment satisfaction) of allergy patients in Asia-Pacific. Choosing a treatment with a rapid onset of action, good efficacy and tolerability, and proven effects on quality of life would help to improve patient satisfaction with treatment in the region.

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CONSENSUS GROUP RECOMMENDATIONS

The Consensus Group encourages and endorses regional initiatives to raise awareness of allergic diseases as a common cause of respiratory problems among patients attending primary care physicians [1, 6]. They also endorse all regional activities that will optimize treatment outcomes for allergy patients in Asia-Pacific through physician education, guideline adherence, and improved awareness of burden of illness. Consideration should be given to the development of ICPs, similar to those being introduced in Europe, in the Asia-Pacific region, on either a national or a regional basis.

The Consensus Group recommends that further research be undertaken, specifically in Asia-Pacific, into various aspects of allergic disease, including patient attitudes to treatment and factors affecting adherence in both urticaria and allergic rhinitis. The data on the relationship between pollutants and allergy, and the differences between 'true' allergic rhinitis and a non–IgE-mediated hypersensitivity phenotype (also called local allergic rhinitis), highlight the need for more research into the classification of rhinitis subtypes, which may eventually help physicians to better tailor treatment for individual patients. Unlike most other forms of nonallergic rhinitis, which are treated with topical corticosteroids, local allergic rhinitis can respond to oral antihistamines [67].

They also endorse all efforts to improve the use of guideline-recommended therapies for allergic rhinitis and urticaria in the Asia-Pacific region. The Consensus Group recommends that more effort is made by regional organizations to raise awareness and drive medical education on guidelines for optimal disease management in allergic rhinitis and urticaria. This education should reinforce the importance of using second-generation H_1-antihistamines in preference to first-generation agents, because of their improved CNS safety profile. There are no significant barriers to the optimal prescription of nonsedating H_1-antihistamines in Asia-Pacific, and therefore the Consensus Group recommends that more activities are undertaken at a regional and national level to raise awareness of international guidelines, and to encourage adherence to these guidelines through continuing medical education, and quality assurance endeavours.

The Consensus Group also urges physicians, when prescribing, to keep in mind those treatment-related factors that are likely to achieve the greatest patient adherence: convenient treatment regimen, rapid symptom relief, long-lasting effects, and a good tolerability profile. The availability of newer second-generation H_1-antihistamines, such as bilastine, allows the use of agents that have these features and which closely meet the criteria for the ideal agent outlined by the EAACI and ARIA [50].

CONCLUSIONS

Because of the growing prevalence of allergic disease in Asia-Pacific, more research is needed in the region on the experience and attitudes of patients with allergies, and on the prevalence of urticaria, in order to fully define the burden of illness in the region. Currently, these conditions are underdiagnosed and undertreated, and much can be done at a regional and national level to improve awareness of the burden of illness, and adherence to international guidelines, in order to optimize treatment for patients. One of the key guideline recommendations is for nonsedating antihistamines to be used first-line in the treatment of allergic rhinitis and urticaria. Physicians in Asia-Pacific have access to a range of suitable second-generation H_1-antihistamine options and are therefore well placed to follow international guideline recommendations for first-line treatment of allergic rhinitis and urticaria. International guidelines have defined a number of features for the ideal antihistamine. Of the available agents, bilastine has the highest number of these features, with good efficacy, excellent tolerability, rapid onset and long duration of action, as well as being truly nonsedative, with minimal CNS penetration.

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