CHAPTER 1
INTRODUCTION

Allergic rhinitis (AR) is a global health-care problem (1). It is a very common chronic inflammatory disease in developed countries and prevalence is increasing worldwide in both children and adults including developing countries (2). Although it is not life-threatening, AR symptoms result in sleep disturbance, fatigue, depressed mood, and cognitive function compromise that impair quality of life (QOL) and productivity (3). Unfortunately, some treatments for AR may also cause drowsiness and impair learning and memory (4). AR is also associated with a number of co-morbid diseases, including conjunctivitis, sinusitis, and asthma (5). Currently, AR is a major health concern associated with considerable economic and societal burdens (6). Treatment of AR includes allergen avoidance, pharmacotherapy, and immunotherapy. Intranasal corticosteroids (INCs) are recommended as first-line therapy for patients with moderate-to-severe AR, especially when nasal congestion is a major component of symptoms (2). INCs are highly effective in reducing both nasal and ocular symptoms of early- and late-phase AR, and improving health-related quality of life (3) without causing sedation and side effects associated with systemic corticosteroids (7). Furthermore, INCs are more cost-effective than non-sedating antihistamines, the most commonly prescribed AR medications (8). INCs can inhibit the onset of the inflammatory response and reduce nasal mucosa permeability, the number of inflammatory cells, and the release of mediators (9, 10). Since AR is a chronic disease and must be treated for long term, especially in persistent allergic rhinitis (PER), thus the effective drug with good safety profile and lower cost should be the best choice in order to reduce cost of the treatment and to improve quality of patient's lives. Currently, there are many different kinds of INCs available on the market such as mometasone furoate (MF), and the newest fluticasone furoate (FF) and each is different in potency, cost, and frequency of administration. Recent reviews have demonstrated similar efficacy among the available INCs in the treatment of AR symptoms, although differences have been shown in sensory attributes between

products (2). However, no such comparison of the efficacy and safety of these two INCs have been performed in Thai patients with PER.

1.1 ALLERGIC RHINITIS (AR)

1.1.1 Definition and classification of AR

Definition of AR

AR is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation (2). Symptoms of AR include rhinorrhea, nasal congestion, nasal itching and sneezing which are reversible spontaneously or with treatment. It is often associated with ocular symptom such as eye itching, tearing and redness (2). However, when nasal obstruction is the only symptom, it is very rarely associated with allergy. Patients with non-allergic rhinitis may have similar symptoms: infections, hormonal imbalance, physical agents, anatomical anomalies and the use of some drugs (11).

Classification of AR

Previously, AR was subdivided, based on the time of exposure, into seasonal, perennial and occupational diseases (12). Perennial allergic rhinitis (PAR) is most frequently caused by indoor allergens such as dust mites, moulds, insects (cockroaches) and animal danders. Seasonal allergic rhinitis (SAR) is related to a wide variety of outdoor allergens such as pollens or moulds. In 1999, the Allergic Rhinitis and its Impact on Asthma (ARIA) World Health Organization (WHO) group, has proposed the new classifications of AR as ‘mild’ or ‘moderate-severe’ depending on the severity of the symptoms and their impact on social life, school and work. AR has also been classified as intermittent (IAR) or persistent (PER) (1) (Figure 1).

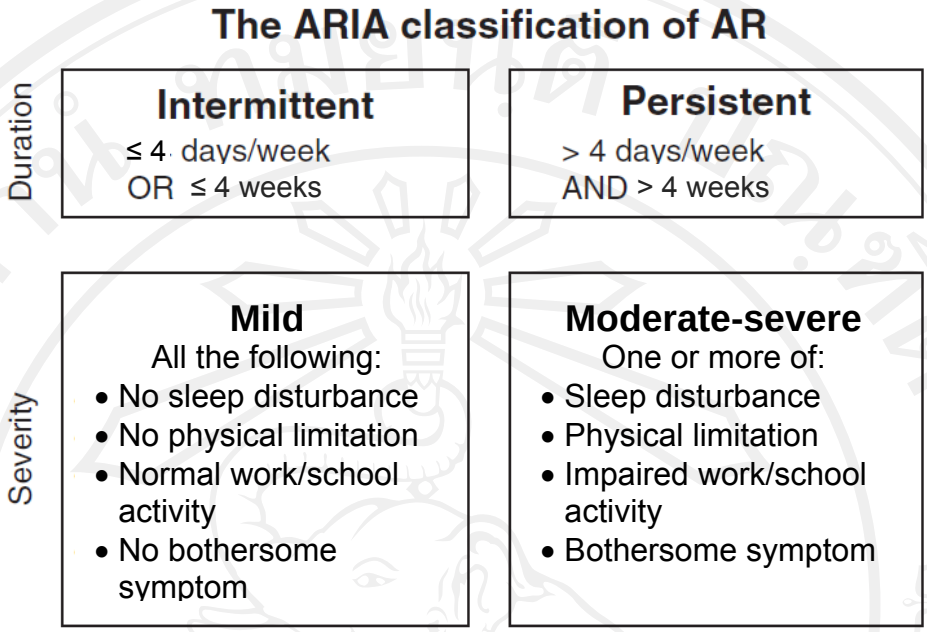

Figure 1 Classification of AR according to WHO's ARIA guidelines.

1.1.2 Epidemiology

AR is extremely common health problem, affecting 10-25% of the population worldwide (1). Patients from all countries, all ethnic groups and of all ages suffer from AR. In the United States, it affects approximately 10-30% of adults and up to 40% of children, or an estimated of 20-40 million patients, making it the sixth most common chronic illness (13). In Thailand, the prevalence of AR is as high as 20% (14) and increasing nearly 3 fold (from 17.9% to 44.2%) in children from 1990 to 2002 (15, 16) .

1.1.3 Risk factors for the development of AR

Risk factors for AR may intervene at all ages of life and epidemiology has greatly contributed in the exploration of these factors.

1. Genetics and familial history

AR is a multifactorial disease with genetic as well as environmental factors influencing disease development. Allergic diseases such as asthma and rhinitis have closely related phenotypes and often occur with atopy (17). Atopy, the predisposition

to respond to environmental allergens with the production of specific IgE antibodies, occurs in only 13% of children for whom neither parent is atopic, but in 29% of children with one atopic parent or sibling and in 47% for whom both parents are atopic (18). The study of twins confirmed the hereditary transmission of atopy. The concordance of allergy in monozygotic, genetically identical twins is higher than in dizygotic twins (19). For the past decade, various antigens of the human leukocyte antigen (HLA) system have been identified as being responsible for SAR (17).

2. Early life risk factors

Sensitization to allergens may occur in early life. However, besides allergens, early-life risk factors have rarely been related to rhinitis (20). Young maternal age, multiple gestation, mode of delivery, low birth weight, growth retardation, hormones during pregnancy, prematurity and perinatal asphyxia are all inconstantly related to the risk of developing allergic diseases or rhinitis (21, 22).

3. Ethnic groups

In England, native people are at a lower risk of developing AR than those born in Asia or the West Indies (23). Similarly, Maori people suffered more from AR than New Zealanders from English origin. Migrants from developing to industrialized countries seem to be at risk of allergy and asthma development (24). It appears that lifestyle and environmental factors in western industrialized areas are more important than ethnicity.

4. Allergen exposure

Allergens are known risk factors for the development and the triggering of AR. They are proteins or glycoproteins that induce and react with specific IgE antibodies. They originate from a wide range of animals, insects, plants, fungi or occupational sources (25). Outdoor allergens appear to constitute a greater risk for SAR than indoor allergens, and indoor allergens a greater risk for asthma and PAR (26). Recently, new hypothesis has been raised on the effect of allergenic exposure, as early exposures to feather bedding, pillows and cats or dogs might have protective

effects in some individuals (27). However, although challenging, these hypotheses need to be confirmed by further studies.

5. Pollutants

The chronic effects of indoor and outdoor air pollutant such as tobacco smoke, ozone, acid rain, airborne toxics, and the chemical form of particulate matter (PM) (including diesel exhaust) are the possible pollutants of relevance in AR (28). In developing countries, automobile pollution in urban areas is becoming a major problem because of the increased traffic and the level of maintenance of vehicles which emit very large quantities of pollutants (29). Several studies have suggested that, people who live in urban areas tend to be more affected by AR than those who live in rural areas (30).

6. Social class

AR prevalence may have been associated with relative affluence in developed and developing countries. In the inner city of the USA, low social class is univariately associated with increases in total IgE, the number of allergen sensitizations and levels of specific IgE (31). It is not yet established as to what degree such differences in disease prevalence reflect patterns of sensitization and specific allergen sensitivities.

1.1.4 Pathophysiology of AR

AR is a type I hypersensitivity reaction, wherein the binding of allergen to mast cell-bound IgE results in rapid mast cell degranulation, increased levels of inflammatory mediators, local infiltration of inflammatory cells and, in many cases, a recurrence of symptoms several hours after initial allergen exposure (32). This response can be described as an initial allergen sensitization during which individuals with genetic and environmental risk factors develop hypersensitivity to specific allergens, followed by triggering of the acute response in which subsequent allergen exposure results in the rapid release of inflammatory mediators (33).

Sensitization

Atopy begins with the establishment of allergen sensitization. Initial sensitizing exposure may occur *in utero* (34), and sensitivity is often established very early in childhood (35). Intensity and persistence of exposure during the first years of life appears to influence whether the initial sensitization will progress to allergic disease or regress to a non-atopic phenotype (36). After sensitization has been established, interleukin (IL)-4 interacts with the class II antigen-major histocompatibility complex (MHC) on activated antigen-presenting cells (APC; macrophages, dendritic cells, Langerhans cells) to stimulate the differentiation of naive T cells [T helper type 0 (Th0)] into Th2 cells. Atopy-promoting Th2 cells release a number of proinflammatory cytokines (IL-2, IL-3, IL-4, IL-5, IL-9, IL-10, IL-13) and granulocyte–macrophage colony-stimulating factor (GM-CSF), whose effects include differentiation and localization of immune cells to the site of exposure; IgE-type class switching of B cells; and increased synthesis of IgE, which binds to high-affinity receptors on mast cells and basophils and to low-affinity receptors on other cells (37).

Early/acute-phase response

Asymptomatic up-regulation of inflammation occurring during the sensitization phase makes possible the symptomatic acute-phase response. Within minutes of inhalation of allergen in sensitized subjects, deposited allergens are recognized by IgE antibody bound to mast cells and basophils, causing degranulation and release of preformed mediators, such as histamine and tryptase, and the rapid *de novo* generation of mediators, including cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4) and prostaglandin D_2 (PGD_2). Mediators cause plasma leakage from blood vessels and dilation of arterioles, venules, arteriovenous anastomosis, with consequent edema, pooling of blood in the cavernous sinusoids (the principal cause of the congestion of AR), and occlusion of the nasal passages. Mediators also stimulate active secretion of mucus from glandular and goblet cells. Histamine elicits itching, rhinorrhea, and sneezing, whereas other mediators, such as LTs and PGD_2, likely have more important roles in the development of nasal congestion. Stimulation of sensory nerves results in the perception of nasal congestion and itching and can provoke

systemic reflexes, such as sneezing paroxysms (38). These subjective feelings correlate with physiologic changes that are measured after antigen provocation, such as increases in nasal secretions and nasal airway resistance (NAR) (39).

Late-phase response

While acute symptoms often disappear within 1 h, these early-phase mediators also initiate a complex network of late phase inflammatory phenomena in the nasal mucosa involving adhesion molecules, Th_2 cells, cytokines and other inflammatory mediators (38) that evolve over several hours following allergen provocation (37). Components of this inflammatory cascade, including cytokines, chemokines and leukotrienes, stimulate proliferation and inhibit apoptosis of immune cells (1). They also act as chemoattractants, promoting migration and infiltration of immune cells at the challenge site (1). In addition, early-phase mediators increase expression of cell-surface adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1)] on endothelial and epithelial cells in the nasal mucosa (40), which promote migration of inflammatory cells (eosinophils, basophils and neutrophils) from the circulation and cell adhesion to the inflammation site (38). Inflammatory cell infiltration and accumulation of activated eosinophil products are credited with inducing the late-phase response (37), characterized by a recurrence of symptoms 3–11 h following initial challenge, in up to 80% of patients with AR (41). Although clinical symptoms during the late phase might be clinically similar to those of the acute reactions, nasal congestion is more prominent. Subjects who develop late-phase symptoms have been found to have significantly higher numbers of eosinophils and neutrophils in nasal lavage samples (42). Activated eosinophils secrete eosinophil cationic protein (ECP) and other mediators that stimulate eosinophil proliferation, migration and adhesion (37); amplify production of Th_2 cytokines (1); and damage endothelial cells. ECP levels in nasal lavage samples have also been shown to correlate with symptoms 24 h later (43).

Priming effect

The amount of allergen necessary to elicit an acute response becomes less when allergen challenges are given repeatedly, a phenomenon called the priming

effect (44). During ongoing, prolonged allergen exposure and repeated late phase inflammatory responses, the nasal mucosa becomes progressively more inflamed and responsive to allergen (33). Clinically, the priming effect can explain why patients might have increasing symptoms despite decreasing aeroallergen levels as a season progresses and also provides the rationale for initiating effective anti-inflammatory rhinitis therapies before a pollen season or before other chronic or repetitive aeroallergen exposures. In addition, the priming effect from allergen is also associated with mucosal hyperresponsiveness to non-antigenic triggers, such as strong odors and cigarette smoke.

Neuronal Contribution

Sneezing and itching during the early response to allergen provocation involve the nervous system. Unilateral intranasal antigen challenge experiments have supported the role of the nervous system in amplifying the allergic response as challenge leads not only to an increase in sneezing, rhinorrhea, nasal secretions, histamine, NAR (45), and PGD_2 (46) on the side of challenge but also to an increase in rhinorrhea, secretion weights, and PGD_2 contralateral to the challenge (46). The contralateral secretory response is rich in glandular markers and is inhibited by atropine, an anticholinergic (45), suggesting that the efferent limb is cholinergically mediated. It has also become clear that the nasal response to allergen accompanied by an ocular response can be explained by a neural reflex. Monitoring ocular symptoms and secretions after unilateral allergen challenge has shown an ocular symptomatic and secretory response that is inhibited by pretreatment with an intranasal antihistamine, suggesting that histamine's action on nasal afferent nerves initiates this reflex (47). This nasal ocular reflex has also been shown to be potentiated by repeated allergen challenges, which leads to priming, a process inhibited by pretreatment with INCs because of their anti-inflammatory actions (48).

Several neuropeptides in addition to sympathetic and parasympathetic nerves and their transmitters are found in the nasal mucosa. These neuropeptides are secreted by unmyelinated nociceptive C fibers (tachykinins, calcitonin gene-related peptide [CGRP], neurokinin [NK], gastrin-releasing peptide), parasympathetic nerve endings (vasoactive intestinal peptide [VIP], peptide histidine methionine), and

sympathetic nerve endings (neuropeptide Y). Substance P (SP), a member of the tachykinin family, is often found as a co-transmitter with neurokinin A and CGRP; it has been found in high density in arterial vessels and, to some extent, in veins, gland acini, and epithelium (49). Several studies support the concept that neuronal mechanisms mediated by these peptides amplify the inflammatory allergic reaction (50).

1.1.5 Co-morbidities of AR

Untreated AR can lead to impaired quality of life and the development of chronic inflammatory obstruction and infection. Worse still, patients can suffer from mucosal damage, and other diseases of the upper and lower respiratory airways. Epidemiological survey data suggest that AR is closely associated with, and is possibly a causative factor for co-morbidities such as otitis media, rhinosinusitis, and asthma. The link between AR and other inflammatory diseases possibly exists because of the common airway passages affected by these disorders (51).

1. Otitis media

Otitis media is defined as an infection of the middle ear with acute onset, presence of middle ear effusion (MEE), and signs of middle ear inflammation.

A hypothesis to describe how nasal inflammation in AR can lead to otitis media has been proposed: prolonged nasal inflammation can induce inflammation of the Eustachian tube, which subsequently imposes negative pressure on the middle ear. Owing to reduced ventilation resulting from the forced pressure exerted on the middle ear, the middle ear cavity can be filled with nasopharyngeal secretions that contain bacteria, viruses, and/or allergens. The presence of these unwanted bacteria can give rise to acute bacterial otitis media (51).

2. Rhinosinusitis

Rhinosinusitis, also termed sinusitis, is a condition with increasing prevalence (52). It is defined as inflammation of the paranasal mucous membranes, which leads to nasal obstruction, poor drainage, and nasal infection.

The co-existence of AR and rhinosinusitis probably arises because of the fact that both inflammatory disorders involve mucociliary dysfunction, tissue edema, and increased mucous production (53). A potential model has been proposed to explain the progression of AR to rhinosinusitis: nasal congestion arising from AR can obstruct the sinus passages making it difficult for nasal secretions to pass through. Accumulation of these secretions can lead to further obstruction and mucosal swelling, thereby creating the ideal environment for the growth of infective agents that can lead to acute rhinosinusitis.

3. Asthma

Asthma is a chronic, debilitating disease characterized by life-threatening symptoms. Compelling evidence from a number of epidemiological surveys suggests that AR is an important risk factor in the development of asthma (53). AR and asthma are often found to co-exist; indeed, 40% of AR patients also have lower airway disease (54).

The association between AR and asthma could involve a number of mechanisms. Clearly, IgE is the common initiating step that gives rise to inflammation in both diseases with differences between the two conditions largely being due to the structural differences between the nose and the lungs (55). Another hypothesis is that dysfunction of the nose could negatively impact the lower airways; for example, allergen provocation in the nose of patients can lead to decreased pulmonary function (56). Furthermore, it has been proposed that interaction between the systemic pathway, including the bloodstream, between the upper and lower respiratory tracts can contribute to asthma signs and symptoms (54).

Recent ARIA guidelines characterize AR and asthma as manifestations arising from one syndrome and/or shared airway. Thus, it is felt that a combined strategy should be employed to treat both the upper and lower airways to combat the occurrence and symptoms of both disorders (1). Although guidelines help practitioners and patients make appropriate decisions, a study of the medications used in the treatment of AR and asthma suggested that guidelines should be simple, with methodologies being the main focus of concern (57).

1.1.6 Diagnosis of AR

The diagnosis of AR is based on the coordination between a typical history of allergic symptoms and diagnostic tests. Interviewing the patient with AR is of emphasis in the diagnosis of rhinitis, co-morbidities and allergy. The frequency, severity, duration, persistence or intermittence and seasonality of symptoms should be determined. Nasal itching and rhinorrhea is more suggestive of AR than non-allergic rhinitis (58). Since AR is frequently associated with allergic conjunctivitis, the presence of eye itching and tearing is a helpful indication that a patient's rhinitis has an allergic basis. Immediate hypersensitivity skin tests are widely used to demonstrate an IgE-mediated allergic reaction of the skin and represent a major diagnostic tool in the field of allergy (1). The wheal and erythema response 15 to 20 min after the "prick" or intradermal application of the allergen is compared with negative (saline) and positive (histamine) controls. In alternative procedures, *in vitro* tests for serum IgE antibody to allergens estimate the amount of allergen-specific IgE antibody in a patient's serum, with sensitivity and specificity equal to that of skin testing. As many as 50% of patients with AR have normal level of total IgE, while 20% of non-affected individuals can have elevated total IgE levels. Thus, this test is generally not used alone for diagnosis of AR but used the results combined with other factors. However, the skin testing carries a very small risk of a systemic allergic reaction (1). This technique is use to identify allergen responsible for triggering symptoms in allergic disease.

1.1.7 The management of AR

The increasing recognition of AR as a systemic inflammatory disorder has many implications for its management. Treatment should be directed not only at relieving nasal symptoms but also at the underlying inflammatory processes; options consist of allergen avoidance, pharmacotherapy, and immunotherapy.

1. Allergen avoidance

Allergen exposure leads to symptoms. Thus allergen avoidance is a logical approach that is recommended by all asthma and rhinitis guidelines (1). Avoidance studies are limited, however, especially with respect to rhinitis, and the amount of

allergen reduction needed to reduce symptoms effectively is unknown (1). Allergen-impermeable covers might reduce allergen levels, but as a single intervention, they fail to cause clinically significant improvement (59). Furthermore, individuals frequently are sensitized to multiple allergens, making it difficult, if not impossible, to limit allergen exposure adequately. As a result, pharmacotherapy is required frequently.

2. Pharmacotherapy

Antihistamines

Oral or intranasal antihistamines act by blocking the histamine (H1) receptor, thus inhibiting the resultant inflammatory cascade. They act within 1–2 h of administration and remain effective for up to 12–24 h (2). Unlike their first-generation counterparts, second-generation antihistamines do not impair performance, and offer an improved safety profile (60). However, while symptoms of rhinorrhea, sneezing, and itching are relieved (61), antihistamines only have a limited effect on preventing or alleviating nasal congestion (2).

Decongestants

Oral decongestants are alpha-adrenergic-agonist drugs that function by constricting capacitance vessels in the turbinates. By reducing blood flow to the nasal mucosa, decongestants prevent nasal edema and congestion. Antihistamines and decongestants are often used in combination to treat the entire portfolio of symptoms seen in AR, including ocular symptoms of itching (2). However, oral decongestants are associated with numerous side effects, including insomnia and irritability Furthermore, the fact that oral decongestants exert non-selective vascular constriction means they have limited use in patients with hypertension and ischemic heart disease (62).

The intranasal (topical) forms of decongestants have a more rapid onset of action compared with the oral formulations (61). However, they are often associated with rhinitis medicamentosa – a phenomenon whereby the efficacy of the drug is progressively reduced with continued application (62). Ultimately, symptoms of nasal congestion are exacerbated. This indicates that intranasal decongestants are a

poor choice of therapy in patients where nasal congestion is a predominant and long-lasting symptom (61).

Leukotriene receptor antagonists (LTRAs)

LTRAs are currently indicated for the treatment of asthma (63). The idea that asthma evolves as a continuum of AR-mediated inflammation of the same airway suggests a potential for LTRAs in the treatment of AR (1). It is hypothesized that LTRAs function by inhibiting the binding of LTs to the LTC_4 receptors (63).

Evaluation of data in a review paper by Meltzer (64) suggests a role for LTRAs as either initial or adjuvant therapy (to antihistamines) for the treatment of AR. Furthermore, Storms (65) suggested that LTRAs could be used as prophylactic treatment for the persistent minimal inflammatory symptoms of AR during asymptomatic periods. This could delay or prevent the onset of inflammatory symptoms during the allergy seasons. LTRAs, however, prove less effective than INCs (63).

Mast-cell stabilizers

Mast cell stabilizers may function by preventing dissolution of the mast cell wall and hence degranulation and subsequent induction of inflammatory mediators, although the mode of action is not proven (2). The most commonly used mast cell stabilizer is cromolyn sodium (62). It is recommended that cromolyn sodium be used four to six times daily and this dosing regimen could hinder compliance (60). Furthermore, efficacy is reduced if the drug dosing is not adhered to. Moreover, mast cell stabilizers have a very marginal effect, much less than that of antihistamines or INCs, on nasal symptoms. The duration of their action is relatively short-lived (66).

Immunotherapy

Immunotherapy should be considered in patients with a constant need for pharmacotherapy, patients with adverse effects from pharmacotherapy, and patients with refractory symptoms. Immunotherapy decreases the severity of AR, reduces the need for pharmacotherapy, and significantly improves QOL (67). It is an effective part of the treatment plan and should be administered by an allergy specialist (1). Subcutaneous immunotherapy involves the administration, in gradually increasing doses of allergen to induce a degree of immune tolerance to the specific allergen. Although this treatment has been shown to be very effective and safe, with beneficial

effects persisting for years after treatment, immunotherapy requires a high degree of patient commitment (68) as treatment typically lasts for several years. Patients need to be aware of their commitment and of the very small but real risk for anaphylaxis following injection (69).

Corticosteriods

Corticosteriods are among the most potent and effective agents available for the treatment of AR. National and international guidelines recommend INCs as first-line therapy when nasal congestion is a major component of the patient's AR (2). Initially available as systemic agents, the well-documented side effects and therefore restricted use of corticosteroids led to the development of intranasal formulations (62). A further rationale for the development of topical formulations was to achieve and maintain high drug concentrations at the receptor sites within the nasal mucosa, which would help improve efficacy, while minimizing the risk of systemic adverse effects (2).

Corticosteriods are defined as anti-inflammatory drugs. The mechanisms by which corticosteriods inhibit allergic inflammation are complex and not understood completely; however, efficacy is thought to attribute to their effects on regulating expression of proteins associated with inflammation (70). In the cytoplasm, corticosteriods bind to and activate glucocorticoid receptors (GR). This GR complex regulates DNA transcription by binding to positive and negative glucocorticoid response elements in promoter activator regions of target genes (70). Inhibition of gene expression also occurs via interactions between the GR complex and cytoplasmic transcription factors such as nuclear factor (NF)-κB and activator protein-1 (AP-1) (70, 71).

Although the exact target genes are unknown (71), the downstream effect of INCs appears to be down-regulation of the expression of a number of cytokines [IL-1, IL-3, IL-4, IL-5, IL-6, Il-10, IL-13, tumor necrosis factor (TNF)-α, granulocyte macrophage colony stimulating factor (GM-CSF)] and chemokines [IL-8, regulated upon activation normal T cell expressed and secreted (RANTES) and eotaxin] that promote the proliferation, infiltration and activation of inflammatory cells (70). However, differences in cytokine inhibition have been demonstrated among INCs agents, with greater potency *in vitro* against atopy promoting Th_2 cytokines (IL-4, IL-

5) observed with MF compared with older agents such as beclomethasone dipropionate (BDP), budesonide (BUD) and triamcinolone (72). In addition, the impact of INCs on inflammatory mediators and cells that are the basis for nasal priming and hyperresponsiveness has been well described. In clinical trials of subjects with AR, MF inhibits allergen-induced expression of ICAM-1 on nasal epithelial cells. Nasal airway infiltration, activation and survival of inflammatory cells such as eosinophils, basophils and mast cells are also reduced with MF (73). Moreover, INCs also decrease specific and non-specific sensitivity in atopic nasal tissue, suggesting inhibition of the underlying inflammation. INCs inhibit the allergen-induced release of histamine and other mast cell-derived mediators in patients with AR (9). INCs also increase the threshold dose of allergen (10) and histamine required to elicit allergic symptoms. In addition, INCs dramatically reduce or eliminate APCs in the nasal epithelia which may, in part, explain the effect of INCs to eliminate the increased sensitivity seen in untreated, allergen-primed subjects with AR (10).

Two large meta-analyses found superior efficacy for INCs compared with oral or topical anti-histamines in reducing nasal symptoms and at least equal efficacy at relieving ocular symptoms (74, 75). Although the mechanism of action of INCs in relieving ocular symptoms is not understood, several mechanisms have been proposed. By decreasing nasal inflammation, INCs may modulate or normalize the excess stimulation of reflex neural activity that occurs during allergic reactions, thereby reducing ocular symptoms. In addition, by inhibiting local nasal inflammation (production of cytokines and infiltration of inflammatory cells), INCs may have indirect systemic effects that reduce the recruitment of inflammatory cells in other tissues, including the eyes. This effect would be observed on the late response to ocular challenge with antigen. Some authors have suggested that INCs increase drainage in inflamed nasolacrimal ducts, thereby reducing conjunctival exposure to allergens and inflammatory mediators. However, duct patency has been found to be maintained in subjects who have symptomatic allergic responses following ocular challenge (76). It has been suggested that INCs might travel through the nasolacrimal duct, exerting their anti-inflammatory effect directly on the conjunctiva. However, the lack of steroid-related side effects such as glaucoma and

cataracts suggests that movement of INCs through the nasolacrimal duct is not a common mechanism for the ocular effects of these agents. Baroody *et al*, (48) performed a double-blind, placebo-controlled, crossover experiment in 20 subjects with SAR to elucidate a mechanism by which FF could affect the nasal-ocular reflex. The result showed that repeated nasal allergen challenges lead to priming and augmentation of nasonasal and nasal-ocular reflexes and that FF decreases inflammation and subsequently inhibits both reflexes thereby resulting in reduction of eye symptoms.

Common local side effects of INCs include dryness, stinging, burning, and epistaxis, the frequencies of which are similar in the various compounds. Nasal mucosal atrophy is a concern with chronic INCs use. A long-term study with MF and FF found no evidence of atrophy or metaplasia following 12 months of intranasal use (77, 78). In addition, the major concern over the use of INCs is their potential to affect the hypothalamic–pituitary–adrenal (HPA) axis–an established side effect of systemic oral steroids that can manifest as growth suppression in children, bone thinning, skin thinning, and fat redistribution. However, in clinical trial of patients receiving MF and FF at recommended doses appear not to have a significant effect on the HPA axis because of the negligible systemic bioavailability of these drugs (78, 79).

Patient satisfaction can adversely affect treatment compliance (80). In a cross-sectional study involving 120 patients (81), aftertaste has been reported to be the most adverse attribute (28%), followed by taste (19%), throat rundown (18%), nose run out (12%), smell (11%), and feel of spray (7%). However, a further study indicated that MF is preferred by a significantly greater number of patients over fluticasone propionate (FP) ($p < 0.05$), based on sensory attributes such as odor, taste, and aftertaste (82). The severity of the sensory factors also decreased patients' adherence to therapy. Thus, patient preferences for specific attributes of INCs can play an important role in treatment selection and adherence.

1.2 RHINOMANOMETRY (RMM)

RMM has been well established as a useful clinical method for objective evaluation of NAR. It can generally be differentiated into active and passive methods

that can be differentiated further into anterior and posterior techniques. Active anterior RMM has been recommended as a standard method by an International Committee on Rhinomanometric Standard at the 8th Congress of the European Rhinologic Society in 1980 (83). In this model, transnasal pressure and airflow are measured across the left and right nostrils during normal breathing and NAR is measured in one side of the nasal cavity only because the contralateral cavity is occluded.

Pressure difference (Δ P) and flow data obtained during respiration are usually represented as a variable derived from pressure and flow differential in the curve. Principle of measurement: synchronous measurement of 2 parameters (Figure 2);

X: Δ P (Pascal or Pa) between nasal opening and choana.

Y: Flow V (cm^3/s) = volume of air flowing through each cross section per sec or per min.

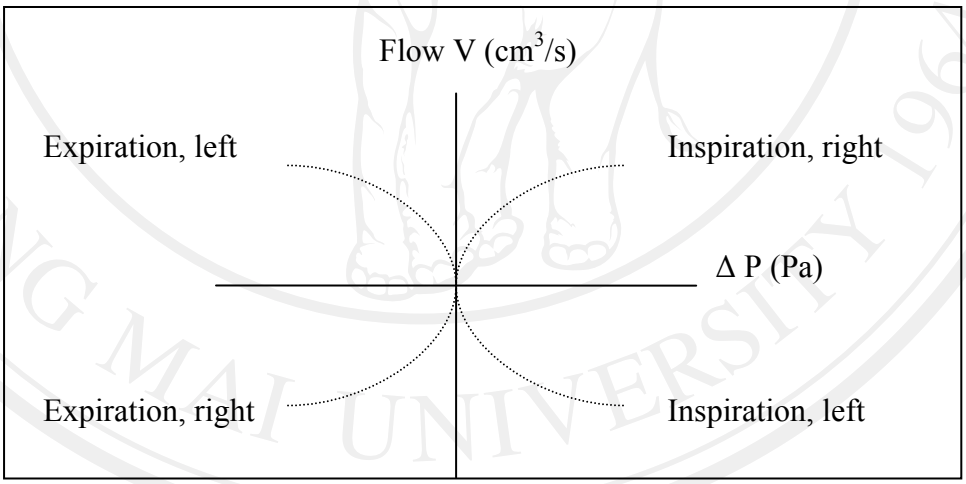

Figure 2 Diagrammatic representation of pressure-flow curve during a breath.

The most suitable flow is that at transnasal pressure of 150 Pa (84) but studies evaluated NAR in Thai people usually use transnasal pressure of 75 Pa for standard value (85). Because the figure and the size of the nose in each race are different.

Mathematically, the NAR then can be calculated according to the following formula (86):

$$R = \Delta P/V$$

When R = Nasal airway resistance (Pa/ cm^3/s)

ΔP = Transnasal pressure gracient (Pa)

V = Nasal flow rate (cm^3/s)

The total NAR can be calculated according to the parallel resistance formula (87):

$$\text{Total NAR} = \frac{NAR^R \times NAR^L}{NAR^R + NAR^L}$$

When total NAR = Total nasal airway resistance

NAR^R = Left nasal airway resistance

NAR^L = Right nasal airway resistance

The measurement of NAR by active RMM is influenced by nasal cycling (the cyclically constriction of sinusoidal vessels) that has been found around 80% of the healthy population (88). The nasal cycling results in significant variability in the measurements of the airflow on the unilateral side of nose. Nevertheless, the total NAR remains relatively constant. Therefore, it is important to measure resistance on both sides of the nose several consecutive time to eliminate this effect. Other factors such as changes in posture, exercise, and cold air also influence NAR (89, 90). However, it is possible to demonstrate the effects of medication on nasal resistance in patients with AR. The total NAR of normal Thai people at 75 Pa is 0.22±0.1 Pa/ cm^3/s (85).

1.3 NASAL CYTOLOGY

The objective evaluation is the examination of nasal cytology. The method includes sampling, processing and evaluating techniques. In the sampling technique, nasal scraping is an easy one with a specificity of sampling site, minimal trauma and no need for anesthesia, ease of repetition, and adequacy of specimens at any age in all nasal conditions. After processing with histological staining, nasal cytogram then is viewed at high power (x1000) light microscope to estimate the number of inflammatory cell in nasal mucosa. In the study of patients with SAR using scraping

technique, eoinophils have been found 81%, basophils in 42% and neutrophils in 64 % in patients enrolled (91).

1. Eosinophils

The most prominent effector cell in AR and in the late-phase reaction of the nose to allergen challenge is the eosinophil (92). Eosinophils are a kind of leukocyte with coarse round granules of uniform size within its cytoplasm and typically a bilobate nucleus. Granules stain a bright reddish-orange with Wright's giemsa stains. Eosinophils derive from the bone marrow from a progenitor cell (CD34+) that may develop into either eosinophils or basophils. The number of eosinophils, particularly activated eosinophils, increases substantially in the epithelium and lamina propria during the allergic response (93). The cytokines and chemokines involved in migration and activation of eosinophils include (1) IL-4 and IL-13, which up-regulate VCAM-1 on the vascular endothelium, (2) IL-1 and TNF-α, which induce ICAM-1 on the vascular endothelium (a contributor to eosinophil migration), (3) the chemokines RANTES, which are chemotactic for eosinophils, and (4) IL-3, IL-5, and GM-CSF, which promote eosinophil activation and survival (94). Once activated, products from eosinophils increase vascular permeability and mucous secretion. Eosinophils are also deleterious in rhinitis by the release of highly toxic products major basic protein (MBP), ECP, eosinophil-derived neurotoxin (EDN) and oxygen free radicals which induce instability of the surface epithelium. In the study of AR with nasal scraping found that 43% of patients has over 20% of sample cells that are eosinophils (95).

2. Basophilics (Basophils and mast cells)

Mast cells and basophils are effector cells in IgE-associated immune responses. These cells contain many large, rough-looking, special cytoplasmic granules that stain black and blue or deep purple with basic dye, such as Wright's stain. The nucleus has 2 or 3 lobes but usually is obscure by granules under the microscope. Both mast cells and basophils are derived from hematopoietic progenitor cells but that the two cell types differ importantly in other aspects of their natural history. With rare exceptions, mature mast cells are not identifiable in the blood. By contrast, basophils typically complete their differentiation in the bone marrow or other

hematopoietic tissues and then enter the circulation; unlike mast cells, basophils are identifiable in peripheral tissues primarily after they have been recruited to sites of inflammatory or immune responses. Moreover, apparently "mature" mast cells in peripheral tissues can express proliferative ability, whereas this has not been shown to occur with basophils (96).

Basophillic cells are known to be in an activated state as shown by degranulation evident by electron microscopy and increased levels of the mast cell mediators histamine and tryptase in nasal lavage fluid (97). Mast cell degranulation results in histamine, tryptase, PGD_2, $PGF_{2,}$ and bradykinin release with the subsequent induction of nasal symptoms of sneezing, rhinorrhea and transient nasal blockage. Mast cell degranulation contributes to the eosinophilic mucosal inflammation seen in rhinitis since mast cells contain preformed pro-eosinophilic cytokines and mRNA for IL-4, IL-5, IL-6 and TNF-α. They also release IL-4 and IL-3 in response to FcRI-dependent activation (98).

The basophilic cell content of the nose is normally between 200-400 cells/mm^3 of mucosa (99). The number of these cells correlates with the severity of the disease. An influx of basophilic cells characterize the late-phase reaction to nasal allergen challenge, whereas the less intense and more prolonged allergen exposure with SAR and PAR results in an increase in mucosal mast cells and perhaps basophils in the nasal mucosa. Therefore, some patients with chronic rhinitis may have more than 2000 basophillic cells/mm^3 (100).

3. Neutrophils

Neutrophils are polymorphonuclear (PMN) leukocytes that play an essential role in the immune system, acting as the first line of defense against bacterial and fungal infections. Their role in the inflammatory process once thought to be restricted to phagocytosis and the release of enzymes and other cytotoxic agents, but it is now known that these cells can release diverse mediators that have profound effects on the airways of asthmatic individuals. The granules of neutrophil are very tiny and light staining. The nucleus is frequently multi-lobed. Neutrophils are the most abundant leukocyte in blood, accounting for 33% to 75% of all circulating leukocytes. The numbers of these cells and eosinophils in nasal secretions increase during both early

and late phases of allergic response (101). However, the nasal scraping specimens which have neutrophils number greater than 1.1 per high-power field along with the present of bacteria usually represent the infectious rhinitis (102).

4. Monocytes and macrophages

Monocytes play multiple roles in immune function. Such roles include: (1) replenish resident macrophages and dendritic cells under normal states, and (2) in response to inflammation signals, monocytes can move quickly to sites of infection in the tissues and differentiate into macrophages and dendritic cells to elicit an immune response (103). These cells are an important aspect of innate immunity, can function independently of adaptive (acquire) immunity, serve to alert the immune system of new pathogens, can dictate the character of new immune response by varying the expression of co-stimulatory molecules during antigen presentation, are functionally activated by allergic responses and the mediators released, are a rich source of inflammatory mediators, cytokines, and direct inflammogens. Although this traditional role remains critical, these cells have a much wider function in biology and pathology. By virtue of their specialized plasma membrane receptors and versatile biosynthetic and secretory responses, macrophages play a major role in inflammation (104) and repair (105). Macrophages are capable of secreting growth factors and cytokines such as IL-1, TNF-α, transforming growth factor (TGF)-β and interferons (IFN), depending on their state of maturation and elicit immune modulatory functions. It has long been known that macrophage function is controlled by activated T-cell (106). Macrophages also have a role in specific immunity by their accessory cell function. However, compared to dendritic cells, macrophages do not fuction efficiently as APC for T-cells. In SAR and PAR, a significant increase in macrophages has also been found in the nose (107).

5. Lymphocytes

T-lymphocytes are among the principal factors that regulate and co-ordinate immune responses in allergic diseases. Two helper T-cell subsets have been identified in humans: Th1 T-cells which mainly release IFN-γ and IL-2 and are involved in the delayed hypersensitivity immune reactions, Th2 T-cells, which mainly

release IL-4 and IL-5 are involved in IgE-mediated allergic inflammation. An imbalance of Th1 and Th2 cells has been proposed in various diseases. In atopy, Th_2 cells are thought to predominate regulating IgE synthesis and cell recruitment at the sites of inflammation. T-cell differentiation, activation and cytokine production is determined by several factors including cytokines, growth factors, inflammatory mediators and hormones (108).

There is growing evidence that Th1 and Th2 subsets can be differentially recruited into tissues to promote different types of inflammatory reaction (109). Th1 but not Th2 cells are recruited through P and E selectin into inflamed tissues, where they induce delayed-type hypersensitivity reactions. The human eotaxin-receptor, originally described on eosinophils and basophils, has also been found on Th2 cells. The attraction of Th2 cells by eotaxin could represent a key mechanism in allergic reactions because it promotes the allergen-driven production of IL-4 and IL-5 necessary to activate basophils and eosinophils. Other chemokines are important in the recruitment of Th1 and Th2 cells (110).

Mucosal inflammation in AR is characterized by the tissue infiltration of T-lymphocytes (CD4+ T-cells and CD25+ (activated) T-cells) both in the submucosa and the epithelium (111). There is a significant correlation between the increase in CD4+ T-cells during the late-phase allergic reaction following an allergen challenge and the number of infiltrating eosinophils in the mucosa. This is associated with an increased expression of IL-3, IL-4, IL-5, GM-CSF at mRNA levels in the nasal mucosa (112). In PAR, there is an increase in CD4+ T memory cells, CD4+ T cells and B-cells in the nasal mucosa (111). This is associated with an increase in the number of IL-4, IL-5 and IL-13 positive cells suggesting a Th2 pattern. B-cells can be found in the epithelium and the lamina propria of the nasal mucosa. In the nasal mucosa of patients with PAR, B-cells comprise about 20% of the total lymphocyte population (111). Recent studies have shown that in SAR, B-cells can undergo class switch to IgE locally in the nasal mucosa (113).

1.4 BACKGROUND OF MEDICATIONS

MF and FF are potent lipophilic glucocorticoid agonists displaying once-daily efficacy on both nasal and ocular symptoms of AR. MF is available as an aqueous

pump spray and FF is administered via a unique, side-actuated device with recommended starting dose of 200 µg and 110 µg, respectively. Both have been developed for the treatment of AR in patient 2 years of age and older. The 17-furoate ester group on their structure improves anti-inflammatory activity and enhances molecular affinity for the GR binding site (114) (Figure 3). Previous studies on the human GR binding kinetics of MF and FF have shown a very fast association and a slow dissociation resulting in a relative receptor affinity (RRA): MF = 2,244 and FF = 2,988 vs. dexamethasone (RRA =100) (115). However, it is not evident that the compound with the highest receptor affinity will have superior clinical efficacy.

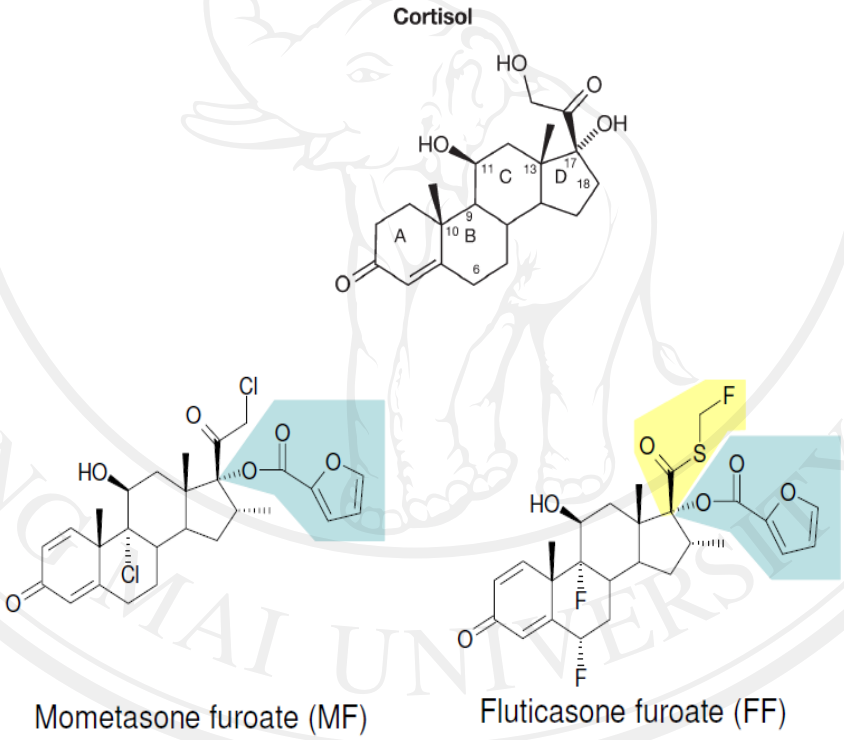

Figure 3 Structural formulae of FF and MF with 17-furoate ester group.

MF and FF with high lipophilicity are absorbed more quickly and thoroughly by the nasal mucosa, and retained longer in nasal tissue, increasing exposure to the GR (116). Lipophilicity also contributes to increased plasma protein binding. In the event of systemic absorption, lipophilicity may contribute to the accumulation of drug in other tissues, possibly contributing to unwanted side effects (117).

MF has a bioavailability of less than 0.1% and also undergoes extensive first-pass metabolism in the liver to inactive metabolites (6β-OH MF) after absorption from the gastrointestinal tract. Plasma half-life is from 18.4 to 24 h. It has rapid hepatic clearance and high plasma protein binding (~ 99%) (118). In subjects with SAR, MF significantly improves nasal symptom scores compared with placebo in as little as 7 h after a single 200 μg dose (119). It also significantly improves ocular symptom versus placebo in SAR patients (120).

FF has an average absolute bioavailability of 0.5% and half-life after single intravenous dose is 15.1 h. The levels of free drug are further minimized by the very high plasma protein binding (>99%) (121). Clearance of FF is primarily by hydrolysis in the liver by the cytochrome P450 isozyme (CYP) 3A4 that converts the drug to the 17[beta]-carboxylic acid metabolite (M10), which displays low GR agonist potency. The drug is excreted mainly in the feces (122). In the clinical trial in AR patients with both nasal and ocular symptoms, the onset of therapeutic effect occurs at 8 h after initial administration, and provides 24-h symptom control (123). It also significantly improves nasal airflow versus placebo in PAR patients (124).

1.5 HYPOTHESIS

MF is as effective as FF in relieving nasal and ocular symptoms, in reducing inflammatory cells, and in improving nasal airflow.

1.6 PURPOSE OF THE STUDY

To compare the efficacy, tolerability and safety of the two INCs, MF and FF in the treatment of patients with PER, by using both subjective (nasal and ocular symptom scores) and objective (RMM and nasal cytology) assessment.