CHAPTER 4
DISCUSSION AND CONCLUSION

4.1 DISCUSSION

This study was the first comparative efficacy study between MF with FF using both subjective and objective outcome measurements and also to compare their AEs and attributes preference profiles in Thai patients with PER. The results of the present study indicate that after 4 weeks of treatment both drugs provide comparable efficacy on improvement of TNSSs, TOSSs and individual symptom scores, NAR and in reducing the percentage of some inflammatory cells under study. AEs and attributes preference of both drugs were also comparable.

INCs are the most common and effective drugs for controlling symptoms and airway inflammation in respiratory diseases such as AR, rhinosinusitis, and nasal polyposis. The new INCs mometasone and fluticasone with furoate ester side chain come remarkably close to the pharmacokinetic/pharmacodynamic criteria for the ideal INCs: 1) a high degree of GR affinity, potency, and specificity; 2) low systemic availability; 3) high rate of hepatic first-pass clearance and rapid systemic elimination; and 4) once-daily dosing (117). Although, the pharmacokinetic properties of MF and FF are similar, but preclinical studies have demonstrated that FF has greater affinity for and slower dissociation from the GR than MF (115). Enhanced affinity for the target tissue may prolong residence time in the tissue, increase the duration of the anti-inflammatory effect at the target site, and also reduce the risk of systemic exposure caused by delayed transit from the target site. However, the present study demonstrated that both drugs were not different in the safety and efficacy for the symptoms of AR when treated with the recommended dose.

MF and FF are synthetic, lipophilic corticosteroids. Agents highly lipophilic will demonstrate a higher and faster rate of uptake by the nasal mucous membrane, a higher level of retention within the nasal tissue, and an enhanced ability to reach the GR (125). In this study, both drugs exhibited a rapid onset of action and higher efficacy after longer treatment period is prolonged. The improvement in TNSSs was

statistically significant within 24 h after the first application. In deed, if the evaluation TNSSs were to be done sooner, both treatments might demonstrate even more rapid effects than 24 h which was the first time point of TNSSs assessment. Because these agents are used primarily to control chronic symptoms, few studies focus the on onset of action (116). In previous study, the onset of action of MF and FF in patients with AR has been reported to be significantly greater effect on TNSSs compared with placebo as early as 7 (119) and 8 h (123), respectively. However, the onset of action in improving TNSSs of both drugs could not be elucidated in this study because we did not record intermediate time points. Further study to specifically determine the onset of action of INCs involved objective measurements at shorter time intervals is warranted.

Although no symptomatic worsening of symptoms were observed in this study, some patients presented the reduction in TNSSs of less than 50%. The reasons behind this unsatisfactory improvement include: 1) INCs do not reach the nasal mucosa because the nose may be extremely congested. However, this is a rare occurrence and can be overcome by pretreatment with rescue treatments (NSS irrigation and oral decongestant); 2) the appearance of respiratory infection may provoke more severe symptom. However, this study withdrew the patients who with respiratory infection that interfered evaluating the efficacy outcome and data of last observation were carried forward for ITT analysis; 3) prolonged duration of disease that continually exposed to perennial allergens in AR patients may give rise to chronic inflammation and these minimizes the improvement of symptoms.

Traditionally, clinical trials in AR have focused on nasal symptoms, however, recent studies have highlighted the significance of ocular symptoms. Although ocular symptoms are common in AR patients, their severity is variable, and baseline ocular symptoms have typically not been the criteria for eligibility. In this study, 87 of 140 patients presented with ocular symptoms, but only 28 patients had symptoms severity that met the inclusion criteria. Both drugs were effective against ocular symptoms (tearing, ocular itching and redness). Although FF produced slightly more improvement in TOSSs, tearing and ocular itching than MF but both changes were not significantly different. However, the small sample size of this study may reduce the likelihood of detecting statistically significant differences. Therefore, further study

should recruit more patients with ocular symptoms to boost the statistical power of test.

The mechanism of action by which INCs relieving nasal symptoms of AR is their potent anti-inflammatory effects to suppress the production of multiple pro-inflammatory mediators such as cytokines and LTs and also to inhibit the action, recruitment, and migration of inflammatory cells (1). However, the mechanism of action of INCs in relieving ocular symptoms is not well understood. Recent study proposed that the INCs could affect the nasal-ocular reflex to reduce ocular symptoms. The nasal-ocular reflex is described as chemical and mechanical stimulation of the nasal mucosa leading to lacrimation (126). Philip *et al* (127) found that nasal application of capsaicin produces lacrimation within 10 sec. Furthermore, nasal and ocular responses diminish with repeated capsaicin application, which supports the concept of a nasal ocular reflex pathway. In a more recent study, Baroody *et al* (48) performed a double-blind, placebo-controlled, crossover experiment in 20 subjects with SAR. They demonstrated that unilateral nasal provocation with ragweed or grass pollen results in ocular symptoms (itching and watery eyes) and increases in ocular secretions bilaterally in SAR patients. Pretreatment with FF, on the other hand, reduces sneezing, the nasonasal and nasal-ocular reflexes, and the amount of eosinophils in nasal secretions. Although, the present study did not evaluate the mechanism, both drugs not only reduced TNSSs but also TOSSs in patients with both symptoms when used continually.

RMM is generally accepted as the standard technique of measuring NAR and assessing the patency of the nose and provides a sensitive and functional measure of nasal patency during normal breathing. This measurement is easy to perform and is not time-consuming. RMM has been used to demonstrate the efficacy of medications such as INCs in alleviating nasal obstruction by measuring changes in NAR. Although RMM can be used to measure both unilateral and total NAR, the total NAR remains relatively constant and gives an overall measure of nasal function due to a reciprocal relationship between the nasal passages. The unilateral NAR is unstable as a result of spontaneous and often reciprocal changes in resistance associated with the so-called nasal cycle (128). This physiologic phenomenon is associated with AR (129) and is also found in healthy subjects (88). The duration of the nasal cycle, as

shown in previous studies, varies from 30 min to 6 h and has been demonstrated in 13% to 80% of adults (128). In the present study, although only FF but not MF significantly reduced the left nostril NAR, mean total NAR also declined after week 2 and week 4 of treatment with both MF and FF. RMM has major disadvantage that it is impossible to make any measurement if one of the nasal passages is completely obstructed, and patients with AR often have obstruction of one nasal passage. Other factors such as exercise, cold air, and changes in posture also can influence NAR. Patients with AR after have symptom aggravated in the morning or evening. During measurement, the presence of mucus in the nose, a leak around the face mask, application of a nozzle to the nostril might cause discomfort to the inflamed mucosa that there is a significant difference in mean values between NAR with mask compared to mean values without mask. In contrast, no significant difference has been found between values with or without nozzle (130). At present, NAR obtained by anterior RMM with a nasal nozzle and a face mask is the most frequently employed method of study. To minimize these confounding factors, patient were asked to sit in upright position and to rest for 15 min in an air conditioning room and NAR measurements were done in the afternoon when they usually were less symptomatic or asymptomatic. Some patients who had their noses completely obstructed were asked to getting blow their noses and their NAR were repeated over a period of 10 – 15 min until their readings were consistent. Anterior RMM with nasal nozzle and face mask was used for measurement of NAR in this study.

The clinical symptom of AR is considered to be the result of the accumulation and activation of infiltrating inflammatory cells, and releasing mediators and cytokines. The infiltration of granulocytes, specifically the eosinophils, is typical of the late phase response (131) and eosinophils have been recognized as pro-inflammatory cells active during allergic reactions, through the release of granule proteins. The accumulation of eosinophils and their products are cytotoxic to the respiratory epithelium (132). The evaluated eosinophil count in the nasal cytology can be used to predict whether the patients develop AR. The number of basophilic cells also correlates with nasal eosinophilia in AR (133). The finding of these cells and/or eosinophils increases the sensitivity of the test for confirming an allergic

diagnosis to nearly 80% (134). The frequency of neutrophil-positive and bacteria-positive specimens in patients with allergy are also noteworthy.

Nasal cytology done by scraping the surface in the middle-third of the inferior turbinate to obtain nasal specimen of both the secretions and the surface epithelium is cheap, simple, and safe technique, which is quite useful for the differentiation of nasal inflammation in allergic and non allergic rhinitis (135). This method has the advantage of adequacy of specimen but may cause slight irritation. In this study, patients had eosinophils, basophils and neutrophils approximately 74%, 68% and 64%, respectively before treatment. Some patients (56%) had both eosinophils and basophills increased and some patients (4%) had no nasal inflammatory cells before treatment. The percentage of eosinophils and basophils decreased significantly after week 2 and 4 of treatment with both MF and FF. These responses indicate the anti-inflammatory effect of INCs. However, changes in the percentage of eosinophils and basophills at 2 and 4 weeks of both treatments were not statistically significant different. Both MF and FF also decreased the percentage of neutrophils, but they were not significantly different from baseline. Furthermore, approximately 30-40% of patients with no upper respiratory infection in both treatment groups had their neutrophils increased after treatment. Concerning neutrophils, it is worth noting that neutrophils appear to have a short life span in tissue and that the true cellular load of neutrophils is very difficult to assess (136).

The reliability of nasal cytology depends on the sampling technique and sample analysis. In adults with SAR using the Rhino-probe scraping technique, the following cytologic patterns have been reported: eosinophils in 81%, basophilic cells in 42%, neutrophils in 64%, and bacteria in 28% of those with at least a 1+ grading (91). In this study, the percentage of inflammatory cells per total cells (20 high power fields) found at baseline were approximately 4% for eosinophils, 3-5% for neutrophils, and 1-2% for basophils. Therefore, grading method may not be appropriated because the finding of these cells corresponded to a 1+ grading at baseline that was insubstantial to detect statistically significant differences.

Drug formulation and delivery device may affect the efficacy, tolerability, drug retention and deposition in nasal tissue, safety, patient preference and adherence to treatment (137). Sensory attributes are an important factor in patient preference

and adherence to INCs treatment. Patients consider several sensory attributes during INCs therapy: aftertaste, taste, scent/odor, run out of nose, throat rundown, irritation, and urge to sneeze (82, 137). Additives and preservatives are included in INCs formulations to prevent bacterial growth, confer both taste and smell, absorb extra water, and maintain appropriate moisture levels. Some of these agents may irritate or dry nasal tissue and, rarely, lead to hypersensitivity. There is benzalkonium chloride, polysorbate, and carboxymethylcellulose in the MF and FF formulations. A study showed that benzalkonium chloride has a bitter taste that can be unpleasant (80). However, in our study, both drugs were well tolerated, with similar preference rates for the taste and odor. FF is administered via a unique, side-actuated device with a shorter delivery nozzle that is a new trigger mechanism that presents low risk for nasal tissue damage and minimizes potential variation in the dose delivered of drug by the device (138). This device delivers a lower spray volume (50 µL) when compared with MF (100 µL), which minimizes the amount of drug available to run down the back of the throat or run out of the nose. However, both drugs were also similar in preference rating scores such as less running out the nose and feeling less invasive. Although postnasal drip in the FF group was less than the MF group, but this difference was not significant. Further study may determine other preference of attributes that are not included in this study.

In both groups, use of rescue treatments decreased significantly at week 4 of treatment when compared with week 2. NSS irrigation can reduce nasal symptom of AR but its mechanism of action is not known (139). Pseudoephedrine hydrochloride is an oral decongestant that can relieve only nasal congestion (1). The patients were instructed to use the rescue treatment only when symptoms were intolerable. In this study, TNSSs continued to decline at week 4 and the decline in the use of rescue treatments was so remarkable at week 4 when compared with week 2. The fast onset of action and lesser need for rescue treatments after initiation of MF or FF treatments confirm the effectiveness of these drugs on nasal symptoms of AR.

This study demonstrated that MF and FF was safe and free from serious AEs. The overall incidence of AEs with both drugs was similar. Although, burning or stinging in the nose, and cough and dry/sore throat were common, but they might result from additives and preservatives of drug formulations and usually disappeared

after some days with continuous use. Symptoms of upper respiratory infection (e.g., fever, cough, sore throat, rhinorrhea, nasal congestion and headache) are similar to AR symptom and when these symptoms interfered with evaluating of treatment, these patients were withdrawn. However, upper respiratory infections are common by found in AR patients that may be associated with the symptoms of the disease rather than true side effects. None of the patients in this study developed nasal septum perforation.

4.2 CONCLUSION

MF and FF produced equal efficacy by subjective measurement of TNSSs and TOSSs. The improvement in TNSSs reached statistically significant within 24 h by both treatments. Moreover, nasal symptoms were more improved when used continually. The proportion of remaining responders after 4 weeks of treatment was similar in both treatment groups. No patient reported no relief of TNSSs. FF improved total NAR more than MF but with no statistically significant difference between both drug treatments. In unilateral NAR, only FF but not MF produced significantly decrease in NAR of the left nostril. Nasal cytology mainly found eosinophils, basophills and neutrophils. Both drugs significantly reduced eosinophils and basophills but not neutrophils after week 2 and week 4 of treatment. These results confirm the anti-inflammatory effects of INCs. Preferences of MF and FF attributes were similar; however, patients preferred FF slightly over MF with respect to odor and taste but less preferred to ease of use. Both treatments were well tolerated. They produced similar AEs profile in the present study.