CHAPTER 6

DISCUSSION

The reason to take up the present study was to carry out a head to head comparison of various second-line medications commonly used by physicians in their clinical set up. The chosen ICS, budesonide was studied in combination with four different categories of drugs, namely formoterol, montelukast, doxofylline and tiotropium, to ensure specificity and uniformity in the efficacy assessment.

FEV₁ measurements which are done on clinician’s site with trained experts, always give accurate results than the peak expiratory flow (PEF) values by truly representing lung functions. PEF values are obtained directly from the patient’s records. Health outcome measures, such as patient reported day-time and night-time asthma symptom scores, frequency of rescue medications usage and specific HRQoL are important measures of clinical status in asthma. In the present study, subjective measurements were used in addition to objective measures of pulmonary function, such as spirometry FEV₁ measured in a clinical setting.

Patients were enrolled into the study, according to the scheduled plan and randomization was done after confirming the inclusion criteria. There were about 17.95% drop-out and this study was designed with a provision for offsetting the effects of 20% drop-out. The study analysis was performed using Per Protocol Analysis (PPA) method and not by Intention-To-Treat (ITT) analysis. Hence the drop-out patient’s data were not included in the statistical analysis.

Demographic data showed that, there was an equal distribution of gender among the study population. This equality in male and female ratio supports the significance of any population study results. The majority of the study subjects, irrespective of which group they belongs, had education up to school or college level and the number of illiterates was comparatively less. With respect to asthma severity,
it was observed that, the number of moderate persistent asthmatics was more than mild persistent asthmatics. The study included both mild and moderate persistent asthmatics and excluded severe persistent asthmatic patients due to an increased risk of exacerbations and subsequent hospital admissions. Generally, in intervention studies, patient cooperation is a key factor in obtaining enhanced results. As our study population had more number of educated people, it resulted in better patient cooperation.

Although National and International guidelines are framed and implemented over the last decade, many clinical studies have reported that, a significant proportion of asthma patients are not under control of symptoms [128]. Among the controller medications, ICS is the mainstay. Anti-inflammatory action of ICS in the lung is well established and ICS has proven its efficacy in improving pulmonary function and reducing exacerbations of asthma. The use of ICS is considered as one of the best treatment options for patients with mild to moderate asthma condition [88]. However, not all the patients achieve the asthma treatment goal with a single corticosteroid, since asthma is a multi-factorial disease, where inflammation alone is not playing a role. The pathophysiology of asthma is complicated. Leukotrienes and phosphodiesterase are also playing a major role in the progression of asthma. Unfortunately, corticosteroids do not have any effect on either synthesis or release of cysteinyll leukotrienes in the lungs and on phosphodiesterase enzyme control.

In the present study, we chose three different second-line medications, namely montelukast, doxofylline and tiotropium. Montelukast is a leukotriene antagonist (LTA). The cysteinyll leukotrienes especially LTC₄, LTD₄ and LTE₄ induce many pathological changes in lungs, including airflow obstruction, mucus secretion and inflammatory cell infiltration [129-132]. Thus, LTA agents have a beneficial action on controlling asthma. Doxofylline is a xanthine derivative, it has antitussive and bronchodilator activity by inhibiting phosphodiesterase activity [133-136]. Thus, it produces inhibition of lymphocyte, neutrophil, activation of monocyte and inhibition of inflammatory mediators.

Tiotropium is a potent inhaled LAMA. It has high potency as a selective antagonist at the muscarinic acetylcholine (Ach) receptors. It rapidly dissociates from
M₂ Ach receptors but slowly dissociates from M₃ Ach receptors. It acts mainly on M₃ muscarinic receptors located on bronchial smooth muscle cells and sub-mucosal glands. This reduces the smooth muscle contraction and mucus secretion and thus produces long lasting bronchodilator action [54, 137-139].

Several studies have reported that, the combined use of LABA with ICS provides greater clinical benefit [101, 120, 140-143]. Indeed, the use of ICS plus LABA is now the preferred treatment option and this combination is made available as fixed dose combination [144-146]. In the present study, ICS plus LABA treated group served as control (standard regimen) to compare the other three different treatment regimens.

The effect of montelukast and doxofylline on controlling asthma was studied by many authors [70, 72, 74, 147, 148]. But the study not only included ICS but also added LABA as third controller medication. Joos et al. [149] conducted a systematic review of montelukast as add on therapy to ICS in the treatment of mild to moderate asthma and they concluded that, montelukast may have a better long term safety profile and offer a treatment alternative for asthma patients. In the present study, among the second-line controller medications tested, montelukast was found to be clinically better than doxofylline and tiotropium.

Patel et al. [70] observed a significant improvement in asthma symptoms and control with the combination of doxofylline and budesonide in moderate to severe persistent asthma patients. However, they added doxofylline as a third controller medication in ICS plus LABA combination and not only the combination of doxofylline and ICS.

Tiotropium is a long acting anticholinergic agent and its effect on COPD is well proven and it is in routine practice worldwide [61]. Whereas studies reporting the clinical benefit of tiotropium in asthma have been limited and only recently been a focus of systematic clinical investigation. Few cohort studies and case reports have demonstrated the clinical usefulness of tiotropium as a long term controller medication in asthmatic patients [58, 150]. Our findings were in line with these
studies and the present study is an evidence based report for the use of tiotropium in Indian adult asthmatic patients.

Peters et al. [71] portrayed the improvement in FEV$_1$ while adding tiotropium to low dose ICS in mild to moderate persistent asthmatic patients rather than doubling the dose of ICS. In this connection, Bateman et al. [151] reported that tiotropium was non-inferior to salmeterol in maintaining lung functions in moderate persistent asthma patients with the B$_{16}$-Arg/Arg genotype receiving regular ICS. Improvement in FEV$_1$ with tiotropium maintenance therapy in our study is of near similar magnitude to previous investigators. However, the present study documents a clear inferiority of tiotropium when compared with montelukast and doxofylline.

All the asthmatic patients were not responding to tiotropium treatment. Only some subgroups of asthmatics seem to respond this therapy. Though the pathophysiological reasons for these responders have not been clearly established [152], studies aimed to find the asthma sub-groups which respond better to tiotropium. Heterogeneity in airway inflammation in asthma has been demonstrated by several studies. Recent days, eosinophilic and non-eosinophilic asthma phenotypes are also recognized [153]. Iwamoto et al. [77] stated that a non-eosionophilic phenotype is associated with a better response to Tiotropium. In the present study, we chose mild to moderate persistent asthma patients regardless of their specific genotype or phenotype. This could be the reason for the inferiority of tiotropium than other controller medications in the present study.

Few studies have compared tiotropium with other controller medications like budesonide and doxofylline. Wang et al. [68] reported that tiotropium was slightly better than doxofylline with the statistically insignificant report. Um et al. [84] compared tiotropium alone with tiotropium/budesonide combination and stated combination therapy was superior. Those studies were carried out in COPD patients and no studies have compared tiotropium with other controller medications in asthmatic subjects.

The clinical measures provide valuable information only about the affected organ system, but not the functional impairment, which is also important to the
patients for their everyday life [154-158]. The physical, psychological and social consequences of chronic disease have detrimental and long term impacts on the QoL of affected individuals. The extent of this impact depends on the severity and prognosis of the disease as well as an individual’s personal values, attitudes and beliefs [159-161].

QoL is a subjective concept based on an individual’s perception of the impact that events and experiences have on his or her life. It encompasses the individual’s satisfaction or happiness in their life’ in key areas or domains that are important to the individual [162, 163].

It has been hypothesized that, complex entities such as adverse effects of medication use, anxiety and depression, patient satisfaction with care are captured by HRQoL measurements, but not by conventional physiological and clinical outcomes. These findings have led to the recommendation that HRQoL should be measured as an independent outcome [164, 165]. Nevertheless, the outcomes of efficacy and effectiveness in asthma clinical trials and in clinical practice have focused on improvement in asthma control, as measured by FEV$_1$ and peak flow, symptom scores and requirement for the use of reliever medication, with little attention to HRQoL [166-168].

HRQoL has become an important outcome in respiratory patients and it is proved by the development of several valid, reliable and responsive respiratory disease specific HRQoL questionnaires in recent years [157, 164, 165, 167]. Among them, SGRQ has become one of the most widely used instruments for assessing HRQoL in respiratory patients and has been translated into several languages.

In the present study, all the combinations of drugs significantly improved HRQoL. However, it was observed that, the improvement in SGRQ score was fairly rapid till day 60 and in further follow ups the same was gradual. This finding is in line with the results of Thomas et al. [169] a study in which a similar trend was observed for different classes of anti-asthma drugs. Our study shows that, the combination of budesonide plus montelukast resulted in better improvement in both % FEV$_1$ and SGRQ scores than budesonide plus doxofylline and budesonide plus tiotropium.
The effect of various parameters like age, gender, duration of asthma, smoking history and literacy levels of the efficacy variables was analyzed. This evaluation is particularly done in the study population to find out the role of these independent variables among the different sub-classes on study outcomes. The sub-group analysis was performed for the entire study population and not between the study groups. As the main treatment arms were separated by different medications, it would lead to misinterpretations of study results.

Wijnhoven et al. [170] and Osborne et al. [171] conducted a detailed study to compare the effect of gender in the pulmonary functions and HRQoL and reported that, male gender was associated with a lower pulmonary function and a better HRQoL. The authors also stated that, gender remains a significant determinant of pulmonary function might indicate that, men are more affected by the disease, resulting in a lower pulmonary function when compared to women. This is in contrast with results from the present study in which it was found that, men with asthma reported better pulmonary functions and there were no significant differences in the HRQoL. The number of subjects in the present study might not be adequate to evaluate the gender wise impact on the efficacy variables. Still a further assessment with more emphasis on this objective is recommended in the Indian population.

Vignola et al. [172] stated that the elderly patients had responded poorer than the young asthmatics. They compared the asthmatics with normal subjects and found that the % FEV$_1$ of healthy people varies among the different age groups, i.e., elderly have lower % FEV$_1$ values than the youngsters, but in asthmatics such difference was not seen. However, in our study, younger asthmatics had better % FEV$_1$, day-time and night-time asthma symptom scores when compared to older patients. Sharma and Goodwin [173] stated that, there is a marked variation in the effect of aging on lung function. As the lung matures by the age 20 - 25 years, thereafter aging is associated with progressive decline in lung function. This could be the reason for better lung improvement in younger asthmatics.

Regarding HRQoL outcomes in the present study, there was no statistically significant difference between groups based on the selected age categories. As our study had a cut off age of 60 years, elderly people beyond this limit were excluded.
People below 60 years might have behaved like older adults and that may be the reason for HRQoL results of this study were not influenced by different age groups.

It is known that, asthma patients with shorter duration of the disease are expected to have better QoL, pulmonary functions and greater improvement when compared to those of longer duration of the disease. The statistically significant results obtained in this study confirmed the above fact and the same were reported by Cassino et al. [174]. In terms of day-time and night-time asthma symptom, the duration of disease did not have any reflection.

It was observed from a couple of studies which dealt with the effect of smoking on pulmonary functions and HRQoL [118, 175, 176]. The results of a study by Eisner and Iribarren, 2007 [175] indicated that, smokers exhibited poor outcome in the improvement of both the efficacy variables. The authors added that, smoking increases severity of asthma, worse asthma specific QoL, worse generic mental health status and greater longitudinal risk of hospitalization. The study done by Gallefose et al. [118] showed that, the negative effect of smoking on HRQoL, as measured by SGRQ scores, was found to be highly significant. The study team commented that, smoking would seem to decrease HRQoL as measured by the SGRQ.

Our study also observed the same that, a significant increase in the pulmonary functions of non-smokers than the smokers. But variables like HRQoL and symptom scores were not affected by the smoking status. The insignificance between the smokers and non-smokers in the improvement of these efficacy variables might be due to intensive patient education with respect to smoking cessation.

Patients of either school or graduate level education have shown statistically significant improvement in health outcomes, when compared to uneducated category. In a cross-sectional study by Williams et al. [177], it was found that, asthma patients with higher literacy had better metered dose inhaler technique. In addition to this, Dewalt et al. [178] in their review has analyzed the effect of low literacy levels on health outcome and concluded that, patients with low literacy levels were more likely to experience adverse health outcomes. Such findings support the present study results in this particular sub-group analysis.
A correlation between FEV\textsubscript{1} and SGRQ was analyzed and a direct correlation was not observed between these two parameters. Such observation was common in many of the reported studies. A number of studies have found either less or no correlation between QoL scores and lung function tests [179, 180]. It has been suggested, by the authors of such studies that, the perception towards health or disease would interfere with the relation between lung function and the results of psychometric tests. A generalization in the attitude towards health or disease may be the reason why lower lung function level is not necessarily accompanied by a lesser QoL. Westwood et al. [181] conducted a systematic review to assess the relationship between FEV\textsubscript{1} and health status change, as measured by the SGRQ. Their study analyses indicated that, improvement in mean trough FEV\textsubscript{1} is well associated with proportional improvements in health status. In contrast, in the present study, no significant correlation was obtained between % FEV\textsubscript{1} and SGRQ. Westwood et al. [181] study selection criteria were done on COPD patients but not for asthma patients.

Safety monitoring of the study drug was carried out with the help of recording adverse drug reactions in all the clinical visits. In addition to this, assessment of vital signs, changes in physical examination, intercurrent illness and concomitant disease and medications also helped in studying the safety related issues. Patients of all the study groups had adverse reactions. However, no serious ADRs were reported in any group of the study patients.

The use of LABA in the treatment of asthma was considered as a major advance in bronchodilator therapy, with evidence that, their use led to improved pulmonary function and QoL. However, the use of LABAs has raised safety concerns, such as their potential to provoke severe asthma exacerbations and death. Either monotherapy of LABA or its combination with ICS has been linked by the US Food and Drug Administration (FDA) to adverse outcomes. In reaction, the US - FDA recently mandated that the manufacturers of LABAs conduct randomized controlled trial (RCT) of the combination of LABA and ICS in asthmatic patients [182-186]. In the present study, no mortality was reported with the use of ICS and LABA combination.
In many developing countries, clinical pharmacy services are still in the budding stage, with pharmacists spending a predominant amount of time on distribution and manufacturing activities. In India, pharmacy practice is still in its infancy. The clinical pharmacist’s contribution to patient care through education is an approach being advocated to optimize drug therapy and improve patient’s HRQoL.

It is widely believed that, a patient who is educated about his or her health related problem will better adhere to treatment plans and have improved health outcomes. Patients also want information about their own health and management [89, 187-189]. Worldwide, numerous studies have evaluated the impact of patient education in various chronic disease conditions such as asthma, diabetes mellitus, cancer, HIV etc. Patient education should be an integral part of all interactions between health care professionals and patients [190-193].

Since asthma is a chronic but variable disease, patients and their families must be prepared to make lifestyle changes and adhere to drug therapy for long periods, even at times when symptoms are not evident. They must also be capable of making rapid decisions about symptom severity, self-medication and the need to seek medical advice. Educating the patients about their disease and medications will improve their knowledge, attitude towards disease and practice towards management and improve patients HRQoL [55, 73, 90, 194-196].

Studies have shown that, inadequate knowledge is identified as one of the leading causes influencing the adherence behavior. Various asthma treatment guidelines consider patient education to be an integral component of asthma management [1, 74, 197, 198]. The major components of health behavior and influence compliance concerning asthma management are the patients’ attitudes towards the disease and their belief, through which successful asthma care is achieved.

Many randomized, controlled trials with parallel groups have assessed the impact of asthma education on health care costs, patient well-being and environmental control [118, 199-204]. They suggest that, in addition to knowledge, patients gained such benefits as positive attitudes; greater family communication; increased physical
activity and feelings of control; increased use of objective measures of airflow obstruction (e.g., PEF) to determine asthma severity; improved treatment compliance, self-management, inhaler technique, HRQoL and pulmonary function and reduced asthma severity, school absenteeism, emergency room visits, admissions to hospital, health care use and health care costs.

As stated in previous studies, in the present study also many asthma patients were afraid of taking corticosteroid medications [205-207]. This is merely because of poor knowledge about the safety of corticosteroids. Using medicines without knowing some fundamental information about the treatment may lead to non-compliance. Education about asthma should be aimed at altering patient’s behavior rather than simply providing knowledge. In the present study, patients were not only taught with the validated educational material, but also counseled and corrected their misconception about the disease or medications.

KAP assessment is one of the most integral components of patient assessment of their actual knowledge of the given subject, attitude towards the established norms in the particular disease and the actual practice. This assessment helps the health care provider not only to evaluate the quality of an education program but also, quantitatively assess the impact of such program with KAP scores [64, 208-210].

KAP assessment was accepted by many researchers in studying the impact of educational intervention. In a study by Yang et al. [107], it was reported that education program significantly improved the knowledge as well as HRQoL scores in the asthma patients. Similar findings were observed by Yamaoka et al. [112] and Boulet et al. [211] in their studies. In contrast, Abdulwadud et al. [117] reported that, a limited asthma education program in a hospital outpatient setting had a positive impact on patient’s knowledge of asthma, but not on their HRQoL, self-management skills or attitudes and beliefs about asthma. The reason would be that, the patients had received education only at the beginning of the study and not in the follow up visits. Meszaros et al. [102] suggested that it is necessary to provide patient education on a regular and ongoing basis to achieve permanent improvements.
Validated KAP questionnaires are available in a number of languages, such as English, French, Portuguese and Spanish, but not in Tamil. In addition, the knowledge of asthma differs among various cultures and countries and specific questionnaires and programs should therefore be developed to meet different needs [60, 212-215]. Obviously, we could have translated an existing questionnaire. However, translating a questionnaire might not be suitable for all populations, since medical terminology and practices, as well as knowledge about asthma, differ among populations. In the present study, after patient education, a better improvement in all the components of KAP score was observed at the end of treatment period when compared to baseline values.