CHAPTER 4

PATIENTS AND METHODS

4.1 PLAN OF WORK

The study was planned in the following steps to achieve the study objectives. The year wise plan is given in Table 4.1.

Table 4.1 Year wise plan of work

<table>
<thead>
<tr>
<th>Plan</th>
<th>1 to 6 months</th>
<th>7 to 12 months</th>
<th>13 to 18 months</th>
<th>19 to 24 months</th>
<th>25 to 30 months</th>
<th>31 to 36 months</th>
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<td>Literature review</td>
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<td>Sample size calculation</td>
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<td>Baseline evaluation</td>
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4.4 STUDY SITE

The study was carried out at the Pulmonary Medicine Out-Patient Department at SRM Medical College, Hospital and Research Center, Kattankulathur, 603 203. A formal consent letter was obtained from the clinical investigator before the commencement of the study (Appendix 2).

4.5 STUDY DESIGN

The study followed a prospective, randomized, open label, parallel study design.

4.6 INSTITUTIONAL ETHICS COMMITTEE APPROVAL

The Institutional Ethics Committee (IEC) approval was obtained prior to the commencement of the study (Appendix 3). Ethics committee’s composition, functions and operations are as per International Conference on Harmonization - Good Clinical Practice (ICH-GCP), Clause. 3.2. Study protocol, patient informed consent forms, data collection form and investigator’s consent form were submitted and discussed in the IEC meeting.
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4.7 CLINICAL TRIAL REGISTRY - INDIA

The present study was registered in the Clinical Trials Registry - India (CTRI). Trial No. CTRI/2012/08/002915 (Appendix 4). CTRI is an online public record system for registration of clinical trials being conducted in India. Since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General - India (DCGI), New Delhi.

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4.8 STUDY SUBJECTS

4.8.1 Inclusion Criteria

Patients fulfilling the following criteria were included in the study:

- Patients of either gender, aged ≥ 18 to ≤ 60 years
- Patients who gave their written informed consent for the study
- Patients with mild to moderate persistent asthma diagnosed according to GINA guideline
- Patients with mild persistent asthma for at least six months and had been treated with an inhaled glucocorticoid for at least three months
- Patients who are capable to perform spirometry test and shown improvement in FEV$_1$ greater than 12% after bronchodilator inhalation
4.8.2 Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Patients who are unable to undergo all the studies related procedures
- Patients with clinically significant renal, respiratory (other than asthma), cardiac, gastrointestinal, hepatic, endocrine disorders, hematological disorders, cancer, unresolved upper respiratory tract infection within past three weeks
- Patients who had any other concurrent illness or patients who had undergone major surgery
- Patients who had emergency treatment for asthma within past 1 month and/or had been admitted to hospital within past 3 months for the treatment of asthma
- Patients with oral steroid therapy during the month prior to the study
- Patients who smoke more than 10 packs per year
- Patients who were known or suspected hypersensitivity to study drugs
- Patients who were pregnant or lactating mother

4.9 RANDOMIZATION PROCEDURE

Randomization was adopted to ensure the even distribution of all the patients among the groups. It was informed to the clinical investigator to follow the randomization table for the allotment of patients among the treatment groups. Around 362 patients were randomized into 4 assigned codes which are given below:

- FB : Formoterol + Budesonide
- MB : Montelukast + Budesonide
- DB : Doxofylline + Budesonide
- TB : Tiotropium + Budesonide
4.10 ALLOCATION CONCEALMENT

Concealment of the randomization code was done to avoid selection bias. Third party randomization is the gold standard for concealment. Randomization list was prepared by a third person who was not involved in the recruitment of patients. Each allocation was written on paper and concealed in a serially numbered, opaque envelope.

4.11 STUDY MEDICATIONS

Commercially available brands of the study medications were used throughout the study period. All the patients entered into a run-in period received inhaled salbutamol at a dose of 200μg whenever necessary (total daily dose, 800 μg) as a rescue medication. At the end of 7 days run-in period, eligible patients were randomly assigned to receive one of the following treatments for a period of 6 months.

Group 1: Formoterol (12μg) + Budesonide (400μg)
Group 2: Montelukast (10mg) + Budesonide (400μg)
Group 3: Doxofylline (400mg) + Budesonide (400μg)
Group 4: Tiotropium (18μg) + Budesonide (400μg)

- **BUDAMATE**: It is a fixed dose combination of budesonide and formoterol. Each dosing consisted of one puff which was given twice daily (morning and night). One puff contains 200μg of budesonide and 6μg of formoterol in a metered dose inhaler (MDI).

- **BUDECORT**: It is a MDI of budesonide. Each dosing consisted of two puffs which were given twice daily (morning and night). One puff contains 100μg of budesonide.

- **TELEKAST - 10**: It is tablet montelukast. It was given once daily (Night). Each tablet contains 10mg.

- **DOXOBID**: It is tablet doxofylline. It was given once daily (Early morning). Each tablet contains 400mg.
• **SOLBIHALE - T**: It is a MDI of tiotropium. Each dosing consisted of two puffs. One puff contains 9μg.

### 4.13 PULMONARY FUNCTION TEST (PFT)

Spirometry is the most widely available and useful pulmonary function test (PFT), which takes only 15-20 minutes time, carries no risks and provides information about obstructive and restrictive diseases. Standard spirometer (Mini Wright Flow meter, Clement Clarke International, London) were used throughout the study. The spirometry was performed by well-trained pulmonary technicians. At least three spirometry maneuvers were done and the largest FEV$_1$ was considered for documentation.

The following procedures were implemented in performing the spirometry:

- Confirmed that the patient had no allergy to inhaled salbutamol
- Explained the purpose of the examination and the need for extra effort from the patient to get maximal results
- Explained the procedure in native language and demonstrated a deep inspiration, proper placement of the mouthpiece and forceful exhalation of air into the tube. Exhaled for at least 4 seconds to make the demonstration as realistic as possible
- Patients loosened any tight clothing and removed dentures (if not secure)
- Installed a new spirotube (mouthpiece) into the spirometer
- Asked patient to sit comfortably during the procedure
- Patients have elevated the chin and extended the neck slightly
- Placed nose clip on the nose. Clips removed between trials
- The patient did a trial exhalation

Measurements of FEV$_1$ were performed according to American Thoracic Society (ATS) criteria [122]. Spirometric analysis was carried out for the study patients at all visits (visit 1).
To undergo spirometric evaluation, in general, a patient should have reversibility of at least 12% in absolute value after inhalation of 2 puffs of salbutamol 100μg with a metered dose inhaler (MDI). All the patients were instructed to withhold the use of β2 agonist 6 hours prior to spirometric analysis. Bronchial reversibility was assessed by the measurement of spirometry before and 15 min after the inhalation of 200μg salbutamol from a MDI. Percentage reversibility was calculated using the following equation [123].

$$\frac{FEV_1 (Post Salbutamol) - FEV_1 (Pre Salbutamol)}{FEV_1 (Pre Salbutamol)} \times 100$$

A checklist with ten steps for proper use of the inhaler was developed with the standard procedure. The patients were checked for their inhaler techniques at baseline and at every follow-up until the end of the study. Patients were assessed individually for the appropriate use of inhalers. The steps which patients felt tough were identified for each patient and were educated and trained. Training was given using dummy inhaler.

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