RESEARCH PAPER

Efficacy and Safety of Pidotimod in Persistent Asthma: A Randomized Triple-Blinded Placebo-Controlled Trial

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Objective: To study whether addition of pidotimod to inhaled corticosteroid (ICS) therapy enhances control in children with persistent asthma, as compared to ICS therapy alone.

Design: Triple-blinded, randomized controlled trial.

Setting: Allergy and Asthma Clinic, Department of Pediatrics, at a tertiary care hospital between May, 2018 and June, 2019.

Patients: 79 children (5-12 years) with newly diagnosed persistent asthma as per Global Initiative for Asthma guidelines.

Interventions: Children received 7 mL twice-a-day for 15 day, followed by 7 mL once-a-day for 45 days of either pidotimod (*n*=39) or placebo (*n*=40). In addition, both groups received inhaled budesonide via metered dose inhaler and spacer, throughout the study. Children were followed up every 4 weeks for a total of 12 weeks. At each follow-up visit, peak expiratory flow (PEF) and asthma symptom score and medicine adverse effects were recorded.

Main outcome measures: Change in PEF at 12 weeks compared to baseline. Secondary outcomes were PEF at each follow-up visit, asthma symptom score at each visit, change in asthma symptom score at 12 weeks, and adverse event profile.

Results: The median (IQR) change in PEF (from baseline to 12 weeks) was 13.0% (0.8%, 28.3%) in pidotimod group (*n*=35) vs 17.7% (4.3%, 35.2%) in placebo group (*n*=35) (*P*=0.69). All the secondary outcomes were also comparable between the two groups. There were no significant adverse effects observed.

Conclusions: Addition of pidotimod for 8 weeks to standard ICS therapy did not enhance asthma control compared to placebo.

Key words: *Immunostimulants, Management, Prophylaxis.*

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In children with asthma, inhaled corticosteroid therapy is the mainstay of pharmacologic management for reducing recurrent asthma attacks, preventing airway remodeling, and preserving lung function. Pidotimod, a synthetic immunomodulator, reportedly enhances innate and cell mediated immunity [1] by stimulating maturation of dendritic cells that activate natural killer cells, macrophages and neutrophils. It also increases T-helper 1 (Th-1) mediated release of Interferon-gamma (IFN-γ), thus increasing immuno-globulin-A (IgA) production, protecting the respiratory tract against microbes. In asthma, there is a reduction in regulatory T cells, which normally inhibit T-helper 2 (Th2) cells [2]. Pidotimod decreases Th2-mediated IL4 release, reducing IgE production, which could prevent asthma exacerbations [1]. Pidotimod also decreases the in vitro expression of CD30 affecting the Th-1/Th-2 balance in atopic asthma [3].

Pidotimod has been explored for the prevention of respiratory tract infection in children with allergic rhinitis [4], bronchopulmonary diseases [5], recurrent respiratory infections [6], Down syndrome [7], and even healthy toddlers [8]. Since respiratory tract infections often trigger asthma exacerbations, pidotimod could theoretically enhance asthma control, and perhaps reduce exacerbation severity or frequency. However, there is no well-designed study that has examined this hypothesis. This randomized controlled trial was conducted to evaluate whether the addition of pidotimod to inhaled corticosteroid therapy enhances asthma control in children with persistent asthma.

METHODS

This study was conducted in the Allergy and Asthma Clinic, Department of Pediatrics, PGIMER Chandigarh, from May, 2018 to June, 2019. All children aged 5-12 years, newly diagnosed with persistent asthma, defined as per the 2017 Global Initiative for Asthma (GINA) guidelines [9], were eligible. Those who had received inhaled corticosteroid preventer therapy for any duration more than 2 weeks during the preceding six months, those suffering from co-morbid conditions (cystic fibrosis, chronic lung disease or congenital lung dysplasia) and those prescribed immunomodulator therapy for any other condition, were excluded. The study was approved by the Institute Ethics Committee, and the trial was registered on the Clinical Trials

Registry India (CTRI) platform. Children were enrolled after written informed consent from their parents. Additional written assent was obtained from children older than 8 year.

Pre-trial analysis of approximately 600 children with persistent asthma in our institution showed that the mean (SD) PEF (% of predicted) in newly diagnosed children with asthma was 65.3 (12.7)%, increasing to 79.8 (11.7)% at the end of 4 weeks of ICS therapy, i.e., approximately 15% increase from baseline. In order to detect an additional 10% increase in PEF (% of predicted) in the intervention group, we estimated a sample size of 34 in each group i.e., total 68, with an alpha error of 0.05 and power of 80%. Anticipating 10% attrition, the sample size calculated was 75.

Each enrolled child underwent a detailed evaluation of demographic features, clinical history, history of atopy, family history, clinical examination, and asthma severity categorization, as per the GINA guidelines [9]. Computer generated, random sequence was created in blocks of 4, 6 or 8, by a faculty member not connected with the trial procedures. Transparent plastic bottles containing either pidotimod (400 mg per 7 mL) or placebo were used. The placebo was the vehicle in which pidotimod was dispensed, hence was identical to pidotimod in appearance, colour and taste. Each bottle was labeled with a sticker showing only the enrollment number and dosing instructions. This was done at a central location in our institution by personnel not connected with the study. Children were dispensed bottles as per the enrolment number; thereby assuring allocation conceal-ment. The randomization code was revealed only after data analysis.

At enrolment, baseline peak expiratory flow (PEF) and Asthma symptom score [10] were recorded. PEF was measured as per the American Thoracic Society recommendations [11], using mini Wright peak flow meter (mini Wright Cat No 3103001). Percentage was calculated against the predicted, as per Indian norms of Parmar, et al. [12] developed at our institution, and updated periodically. PEF measurements were performed by a single, trained technician. Each child performed the procedure thrice, and the best reading was used for analysis.

Asthma symptom score was measured using a tool validated in Indian children [10]. It comprised of six items, each item received a daily score of 0 for absence and 1 for presence; thus the weekly score could range from 0 to 42. An average score was calculated for four consecutive weeks by adding the weekly score of preceding four weeks and dividing it by 4.

All children were prescribed inhaled corticosteroid therapy (budesonide 200-600 µg/day), depending on the severity, delivered by metered dose inhaler through a spacer. In addition, children received bottles containing the study drug labeled with the enrolment number and dosing instructions. The dosage was 7 mL twice a day for the first 15 days, followed by 7 mL once a day for the next 45 days as per the manufacturer's instructions. Budesonide was continued throughout the study period and beyond, as per the GINA 2017 guidelines [9].

Children were followed up every 4 weeks, for a total of 12 weeks. At each follow-up visit PEF, asthma symptom score, and any adverse effects to the medication were recorded. The bottle from the previous visit was returned to the investigator, who measured the volume of syrup remaining, in order to determine the compliance.

The primary outcome was the change in PEF at 12 weeks, defined as PEF (% of predicted) at 12 weeks minus PEF (% of predicted) at baseline, expressed as a percentage of the baseline PEF (% of predicted). The secondary outcomes were PEF (% of predicted) at each follow-up visit, asthma symptom score at each visit, change in asthma symptom score at 12 weeks, and adverse event profile. The parents of the enrolled children were requested to record any perceived side effects, especially rash, abdominal pain, vomiting, nausea and headache. These data were reviewed at each follow-up visit.

Statistical analysis: Statistical analysis of data was performed using IBM SPSS software version 23. Inter group means were compared using the Student t test, whereas medians were compared using Mann-Whitney U test. Proportions were compared using Chi-square test. PEF (% of predicted) and asthma symptom scores were compared within each group using Wilcoxon signed rank test.

RESULTS

A total of 100 children were potentially eligible to participate in the trial during the study period. Of these, 21 were excluded on the basis of exclusion criteria and 79 children were randomized (pidotimod 39, placebo 40). Seventy children completed the study per protocol, as 9 children (pidotimod 4, placebo 5) did not attend the first follow-up visit (**Fig. 1).**

The baseline characteristics of children in both groups were similar with respect to age, duration of symptoms, type of symptoms, asthma severity, baseline PEF and Asthma symptom score as depicted in (**Table I)**. The most common associated comorbidities were allergic rhinitis (25.3%), allergic conjunctivitis (6.3%) and atopic dermatitis (5.1%).

The median (IQR) change in PEF at 12 weeks was 13.0% (0.8, 28.3) in the pidotimod group vs 17.7% (4.3, 35.2) in the placebo group (P=0.69). Similarly, PEF (% of

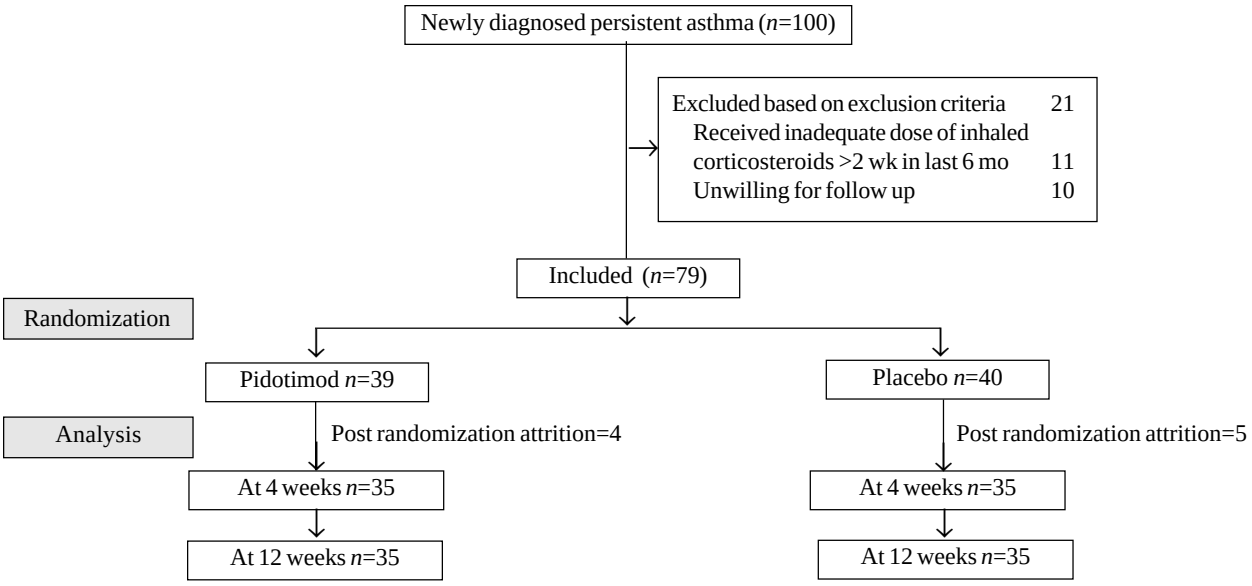

Fig. 1 Flow of participants through each stage of the trial.

predicted) at each follow-up visit was comparable between the groups (**Table II**). The median Asthma symptom score declined from 21.0 to 1.75 in the pidotimod group and 21.0 to 0.0 in the placebo group at the end of 4 weeks, and the difference was not statistically significant. The score was also comparable between pidotimod and placebo groups at other time-points (**Table II**).

Only two children in each group (5.7%) complained of mild abdominal pain during the first week of enrolment. This was observed for one day in those in the pidotimod group, and for two days in those in the placebo group. The pain resolved spontaneously and did not require discontinuation of the medication. None of the other children complained of any other side effects. Three children in each group experienced a mild exacerbation within the first four weeks. These were managed with addition of inhaled salbutamol for 2-3 days, and none required oral steroids or hospital admission. The highest Asthma symptom scores (out of 42) of these six children on any given day were 7, 9, 10 (Pidotimod group) and 7, 7, 8 (Placebo group).

Table I Baseline Characteristics of Children With Persistent Asthma Enrolled in the Study

Characteristics	*Pidotimod group (n=39)*	*Placebo group (n=40)*
Age (y), mean (SD)	7.95 (2.33)	8.20 (2.42)
Male sex[a]	30 (77)	32 (80)
Duration of cough (mo)	32.0 (8,61)	36.5 (11,72)
Wheeze on auscultation[a]	18 (46.2)	22 (55.0)
Asthma classification[a]		
Mild persistent	17 (43.6)	17 (42.5)
Moderate persistent	21 (53.8)	19 (47.5)
Severe persistent	1 (2.6)	4 (10)
PEF (% of predicted)[b]	76 (66,87)	73 (60,89)
Asthma symptom score[b]	21 (21,28)	21 (21,28)

Values in median (IQR) or [a]no. (%).[b]Values at baseline. PEF: Peak expiratory flow.

DISCUSSION

This placebo-controlled trial showed that the addition of pidotimod (for 8 weeks) to inhaled corticosteroid therapy did not enhance asthma control. Even though pidotimod

Table II Primary and Secondary Outcomes in Children in the Pidotimod and Placebo Groups

Outcome measures	*Pidotimod group (n=35)*	*Placebo group (n=35)*	*P value*
Change in PEF[a]	13% (1, 28)	18% (4, 35)	0.69
PEF (% of predicted)			
At 4 wk	84 (79, 97)	95 (77,105.5)	0.61
At 8 wk	87 (79, 100)	94 (82, 103)	0.52
At 12 wk	93 (78.5, 104)	98 (92, 103)	0.43
Asthma symptom score			
At 4 wk	1.75 (0, 8.0)	0 (0, 7.0)	0.59
At 8 wk	0 (0, 2)	0	0.24
At 12 wk	0 (0, 2)	0	0.41

Values in median (IQR). [a]change from baseline after 12 wk of treatment. PEF-peak expiratory flow.

was safe compared to placebo, there was no additional benefit.

A Chinese trial in 60 children with allergic rhinitis and asthma, comparing pidotimod plus symptomatic treatment, versus only symptomatic treatment, showed that pidotimod improved mean PEF as compared to controls, but this benefit was observed only after one year of treatment [13]. In contrast, our study was limited to only 8 weeks of therapy and 12 weeks of follow-up. Another placebo-controlled rando-mized trial in 60 children with allergic rhinitis accompanied by asthma, suggested that pidotimod decreased the inflam-matory reaction, and improved pulmonary function parameters [14]. However, the details of this study in terms of enrollment criteria, case definitions, dosing, etc. were not available, hence the results could not be compared to the present study.

In contrast to asthma, there is more data available on the effect of pidotimod on acute respiratory infections. In a multicentric placebo-controlled randomized trial, children who received pidotimod had fewer acute respiratory infection (ARI) episodes as compared to controls, and pidotimod use was not associated with significant adverse effects [15]. A clinical trial in children aged 2-10 year with >6 annual respiratory infections showed that pidotimod (used in the same regimen as in our study) significantly reduced the incidence of infections, and of asthma episodes [16]. However, the authors did not explore the frequency of asthma episodes.

Another prospective study in children with frequent episodes of ARI, where pidotimod was taken for 6 months, showed reduced frequency of ARI episodes [4]. However, the absence of a control group makes interpretation difficult. Since respiratory tract infections trigger exacerbations, and/or vitiate asthma control in many children with asthma, it follows that reduced frequency of infection should result in better asthma control. Although, we did not examine the frequency of ARI episodes (home-based, self-reporting of acute respiratory infections can be unreliable), we did not observe any benefit of pidotimod on asthma control. In yet another recent trial, pre-school children (3-6y) with recurrent respiratory infections, were randomized to four arms viz., pidotimod plus bifidobacteria, pidotimod plus placebo, bifidobacteria plus placebo or double placebo, administered during the first 10 days of the month for four consecutive months. Those who received pidotimod (with or without bifidobacteria) had less frequent colds and more symptom-free days [17].

A recent meta-analysis [18] to assess the effects of pidotimod on recurrent respiratory infection in children <14 years, identified several low-quality trials, mostly from China. Those receiving pidotimod had less frequent respiratory tract infection, shorter durations of fever and cough during episodes, and reduced antibiotic usage. However, there were several methodological issues compromising the credibility of the systematic review [18].

A narrative review of 32 studies (24 in children including four studies in asthma), suggested that pidotimod decreased IL-4, and IgE levels, resulting in improved FEV1% and PEF. Those receiving pidotimod also had lesser days with infection compared to the control group [19]. However, the variability in definitions of asthma in these studies, methodological differences, and duration of follow-up, made them incomparable with our study. Another review in children with acute respiratory infections, suggested that pidotimod reduced reinfection (odds ratio 0.20, CI 0.12, 0.33), duration of antibiotics (mean difference -2.65, CI -3.68, -1.6) and absenteeism [mean difference (-2.99, CI -4.03, -1.95) [20].

Although the body of evidence on a potential role for pidotimod in various childhood respiratory conditions is growing, the evidence pool is compromised by poorly-designed trials, inappropriate methodology, and a gap between laboratory results and clinical results. This calls for well-designed studies to address the knowledge gaps.

The strengths of this study were a triple-blinded randomized control design minimizing the risk of bias. Considerable precautions were taken to ensure allocation concealment and blinding. Objective parameters of asthma control were used to assess immediate, short-term as well as longer-term asthma control. These objective parameters included patient-centric observations by parents (recorded in the home-based asthma symptom diary), physicians (performing clinical examination) and respiratory technician (performing PEF). Each type of outcome assessor was unaware of the outcomes recorded by the others. Thus, the combination of patient reported observations combined with professional assessments, minimized observer bias. Frequent follow-up visits ensured that outcome data were collected at least thrice after enrolment. The study was adequately powered to detect statistically significant differences in the primary outcome. Children were enrolled all-round the year, minimizing season bias.

The study limitations include a relatively short period of pidotimod use (8 weeks). This regimen was chosen based on the manufacturer's dosing recommendation, and the absence of sufficient prior data supporting benefit or harm. Spirometry could not be performed in most children, as the instruments available in our institution provide reliable results in those above 8 years of age. Determination of safety was based on parental report of a pre-defined set of symptoms, rather than telephonic or home-based active surveillance.

WHAT IS ALREADY KNOWN?

- Pidotimod is an immunomodulator that improves innate and cell-mediated immunity and helps mount an immune response, thus potentially preventing recurrent respiratory tract infections.

WHAT THIS STUDY ADDS?

- This trial showed that addition of pidotimod for 8 weeks to standard ICS therapy did not enhance asthma control, compared to placebo.

Our study concluded that addition of pidotimod for 8 weeks to standard inhaled corticosteroid therapy did not enhance asthma control, compared to placebo. There were no remarkable safety issues observed.

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Ethics Clearance: Institute's Ethics Committee, PGIMER; No. NK/4232/MD/481 dated 20 March, 2018.

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