



An open labelled prospective clinical study to evaluate the efficacy, safety and cost analysis of Pidotimod as add-on drug for maintenance therapy in Paediatric Recurrent Acute Respiratory tract Infections

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ABSTRACT

Recurrent Acute Respiratory Tract Infections (ARTI) are the commonest form of infections affecting children irrespective of socioeconomic status and geographical limits. Immaturity of immune response involving neutrophils, NK cells, T and B cells, in the early childhood, is often cited as a reason for this RRTI. There is comparatively high incidence of ARTI in South East Asian countries when compared to global statistics. The possibility of using immune stimulation as a method of reducing the recurrence of ARTI prompted the use of Pidotimod as add-on drug. We tried to explore the safety, efficacy and cost benefit analysis of Pidotimod as add-on treatment for paediatric use. After registering for Clinical trial and getting IEC approval, we started an open labelled prospective single arm interventional study by recruiting 65 children between 2-12 years with ARTI to receive 800 mg daily for 15 days and 400 mg for 45 days and was followed up for 6 months. Study revealed a significant reduction in number and duration of RRTI as well as reduction in episodes requiring antibiotics and reduction in duration of treatment. The reduction in number of school days lost and treatment expenses were statistically significant. There was a significant increase in mean absolute count in CD45, CD3, CD4, CD8 and lymphocyte counts at 6 months follow-up. Hence, we conclude that 60day Pidotimod therapy has immune stimulatory activity preventing the RRTI in paediatric population when considered as an add-on therapy to standard treatment.



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INTRODUCTION

Acute respiratory tract infection (ARTI) forms the most common infection afflicting children worldwide. Irrespective of the socioeconomic and geographical conditions, children get at least 3-6 episodes of ARTI per year (Kamath *et al.*, 1969; Monto, 1974). In India, the incidence peaks in winter and autumn (Kumar *et al.*, 2015). The prevalence rate of ARTI was reported to be high (59%) among children less than 5 years in rural and urban areas of South India (Kumar *et al.*, 2015). There

is a higher incidence of ARTI in South East Asian countries when compared to global statistics (Selvaraj *et al.*, 2014). It is well known that smoke, pollution, dampness and passive smoking predispose children to ARTI (de Martino and Ballotti, 2007; Karevold, 2006; Zhang *et al.*, 2014). ARTI results in not only morbidity, but also considerable expenditure for medical consultations, treatments, emergency care and hospital admissions (Wheeler, 1995). Often indiscriminate use of routine antibiotics coupled with easy OTC availability in India complicates the issue further by inducing antibiotic resistance (van de Pol *et al.*, 2013; Del-Rio-Navarro *et al.*, 2006). In fact, 75% of prescriptions in ARTI contain antibiotics. The cost of management escalates as we consider the impact of loss of school days and loss of man-days for the working parents (McCutcheon and Fitzgerald, 2001). RRTI is facilitated by a decreased immune response in early life, both innate and adaptive. Various approaches have been tried to reduce the recurrence of ARTI (Dharnidharka *et al.*, 2014). Immaturity of immune response involving neutrophils, NK cells, T and B cells, in early childhood, is often cited as a reason for this RRTI (Raniszevska *et al.*, 2015).

Nonspecific enhancement of immune response is one among the functional approaches tried to prevent the recurrent ARTI (Zuccotti and Mameli, 2013). Both synthetic and natural sources of immune stimulant have been tried to prevent ARTI (Zuccotti and Mameli, 2013). One such synthetic immune stimulant- Pidotimod (3-l-pyroglytamyl-1-thiazolidine- 4-carboxylic acid) has both biological and immunological activity over adaptive and innate immune responses, and is authorised for use in children more than three years of age (Mameli *et al.*, 2015). However, in India, Drug Controller General of India has approved its use for children 2 years and above. Pidotimod is known to effect immune stimulatory activity via T cells and granulocytes (Zuccotti and Mameli, 2013). Mameli *et al* and Licari *et al* showed that Pidotimod may prevent recurrence of ARTI (Caramia *et al.*, 1994; Licari *et al.*, 2014).

The safety profile and efficacy of Pidotimod was upheld by a recent meta-analysis of 29 clinical trials on ARTI in children. It has been shown to be superior to conventional treatment in terms of reduction in recurrence, duration of symptoms and antibiotic usage (Niu *et al.*, 2019). It was shown to decrease the duration of cough and fever in ARTI. There was a significant increase in serum immune globulins (IgG,IgA,IgM) and T lymphocyte subtypes (CD3+,CD4+) in children who used pidotimod (Niu *et al.*, 2019).

MATERIALS AND METHODS

This is a prospective, open label, non-comparative, single arm exploratory and interventional study conducted at Saveetha Medical college Hospital, Chennai between May 2018 to April 2019. The trial was initiated after prior approval from the Institutional Ethical Committee (013/05/2016/IEC/SU) and it was registered under the Clinical Trial registration No: CTRI/2018/02/011898. All children from 2 to 12 years of age of both sexes with recurrent ARTI (defined as ≥ 3 episodes per year or ≥ 15 days of respiratory illness in the past three months), (Paramesh *et al.*, 2017) were followed up for two months before inclusion in the study. Those patients who were allergic to the drug under study or had been vaccinated in the last three months for respiratory illness or diagnosed with congenital or acquired immune deficiency like HIV, or who were on antibiotic or steroids or any immune modulatory drugs or those with other co-morbid illness which could interfere with successful participation were excluded. 65 patients were enrolled after obtaining informed written consent. The uses, side effects, possibility of withdrawal from the study at any point of time were explained to the parents following the declaration of Helsinki (Figure 1).

All eligible children received Pidotimod 400 mg twice daily before meals for 15 days (800 mg/day) followed by 400 mg once daily for 45 days in addition to the standard therapy as per institutional protocol. Pidotimod was made available as liquid Immulina TM 200 mL (strength of 400 mg/7 mL) and as tablets Immulina (400 mg).

Each child was assessed at the beginning of the study (baseline data) with a medical history, physical examination, number and duration of ARTI episodes, episodes requiring antibiotics usage, average duration of antibiotic usage, rescue medications, number and duration of hospitalization, concomitant medications administered and adverse effects of Pidotimod. This was monitored at 2 months and at 6 months from the date of inclusion (Figure 1). Expenditure incurred prior to treatment with Pidotimod was analyzed from data obtained by parental recall and verifying the actual bills. The same was assessed during the trial also. As part of the exploratory approach, absolute count of CD markers (CD 45,3,4,8), Lymphocyte and total leucocyte count (TLC) were measured at baseline and after completion of therapy (at 6 months).

Statistical analysis

Table 1: Clinical & Health-economic outcomes in children treated with Pidotimod

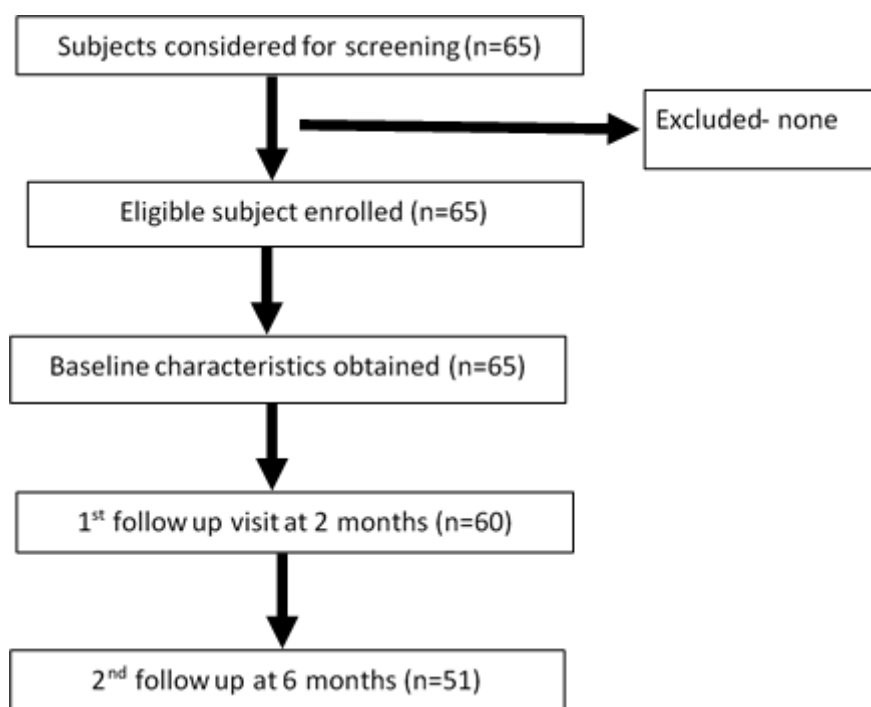
Parameter	Baseline	After 6 months follow up	P value
No. of ARTI episodes	7.67 ± 2.34	1.37 ± 1.23***	<0.001
Duration of ARTI episode in days	8.18 ± 3.58	2.46 ± 1.23***	<0.001
No. of ARTI episodes requiring antibiotics	7.07 ± 1.88	1.85 ± 1.20***	<0.001
Duration of antibiotics in days	6.59 ± 1.76	2.28 ± 0.98***	<0.001
No. of school days lost for the child	9.00 ± 3.35	5.35 ± 4.74***	<0.001
No. of work days lost for the parent	4.56 ± 1.83	4.47 ± 4.01	<0.832
Health-economic outcome (Mean)			
Treatment Expenses in INR	13748.25	554.39***	<0.001

Data is represented as Mean ± Standard Deviation *P< 0.05, ** P< 0.01,*** P< 0.001

Table 2: Effect of Pidotimod on Blood CD Markers

Parameter	Pre-treatment	Post-treatment	P value (t-test)	% change
CD 45	3934.80 ± 1945.13	4587.47 ± 1745.45**	0.010	+ 16.6
CD 3	2569.67 ± 1263.60	3066.20 ± 1186.21**	0.005	+ 19.3
CD 4	1376.00 ± 642.32	1614.82 ± 620.39**	0.006	+ 17.4
CD 8	1066.61 ± 616.07	1285.16 ± 610.05*	0.020	+ 20.5
Lymphocyte	3939.20 ± 1917.06	4539.82 ± 1659.43**	0.014	+ 15.2
TLC	10301.18 ± 4281.70	10292.16 ± 2426.82	0.988	- 0.10

Data is represented as Mean ± Standard Deviation and percentage change. *P< 0.05, **P< 0.01, *** P< 0.001

**Figure 1: Flow diagram of the study**

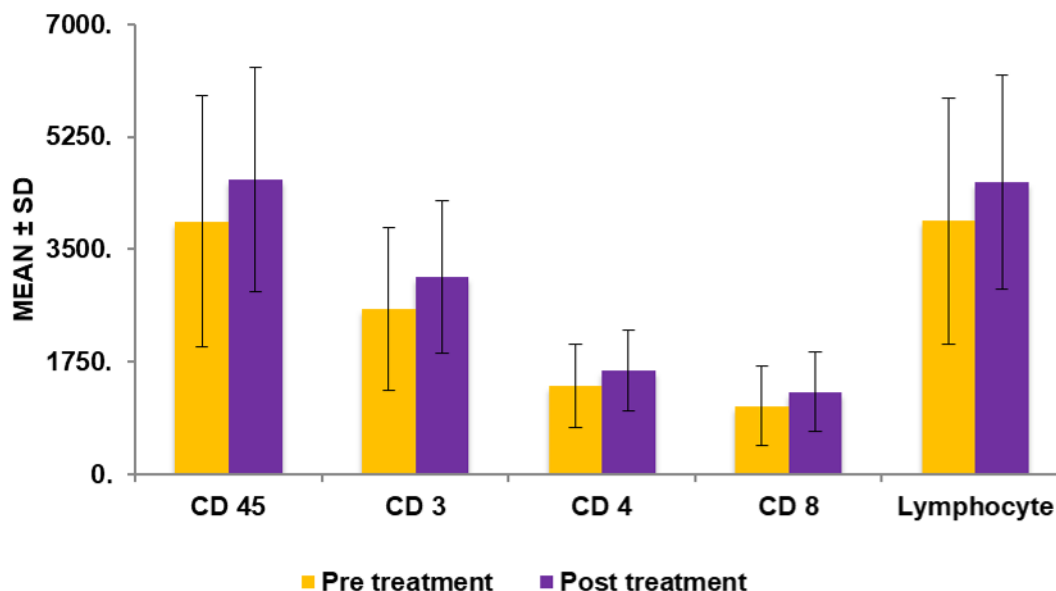


Figure 2: Changes in mean CD count before and after treatment

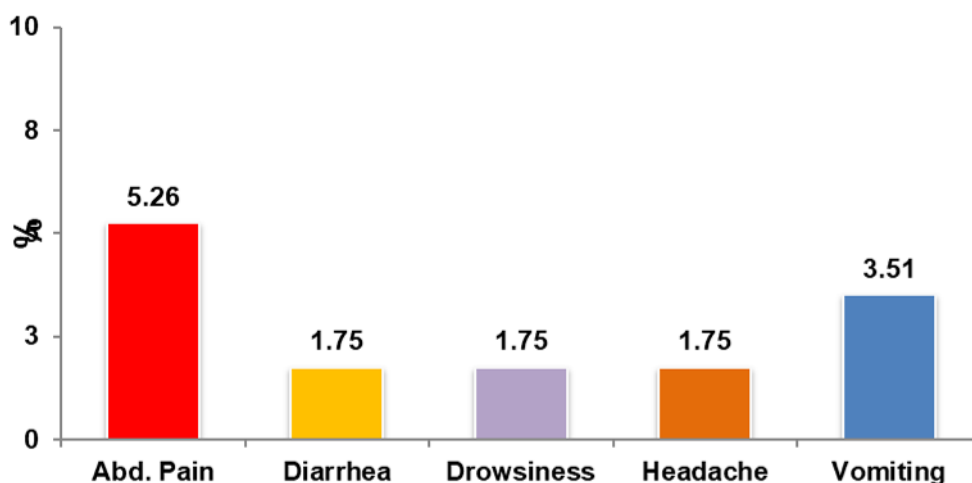


Figure 3: Adverse reactions to pidotimod

The number and duration of ARTI episodes, episodes requiring antibiotics along with their average duration, number and duration of episodes of hospitalizations were analysed by paired t-test /Wilcoxon signed Rank test. The analysis of safety data and exploratory analysis was done using descriptive statistics. P-value<0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Out of the 65 children who enrolled after valid consent, 14 discontinued (n=5 logistical reasons, 7 shifted residence and 2 for unknown reasons) and 51 completed the study. (Figure 1. Follow-up). 61.4% were males with a mean age of 4.6 ± 2.09 years. There was a significant reduction in the mean number of episodes of ARTI in the 6 months follow-up period (7.67 ± 2.34 vs 1.37 ± 1.23 ; $p < 0.001$). Fur-

ther, 31.6% children remain ARTI free throughout this period.

Mean duration of ARTI episode also reduced significantly (8.18 ± 3.58 vs. 2.46 ± 1.23 ; p value<0.001) with none of the episodes requiring hospitalization during the follow-up period compared to 22.8% episodes requiring hospitalization (hospital stay 5 ± 2.06 days) prior to Pidotimod therapy. The health care expenditure during this period reduced significantly from INR 13748.25 to 554.39 ($p < 0.001$) after Pidotimod therapy.

The number of ARTI episodes requiring antibiotics (7.07 ± 1.88 vs 1.85 ± 1.2 ; $p < 0.001$) and mean duration of antibiotic usage (6.59 ± 1.76 vs 2.28 ± 0.98 ; $p < 0.01$) were significantly reduced during follow-up period of 6 months following Pidotimod use. The mean school days lost for children due to ARTI also reduced significantly ($p < 0.001$)

(Table 1). Changes in Absolute lymphocyte count and CD markers (CD45,3,4,8) were found to be statistically significant though TLC showed an insignificant reduction after Pidotimod use (Table 2; Figure 2). 14% reported adverse reactions though most of them were mild and self-limiting. (Figure 3).

The present study clearly demonstrates that Pidotimod has good efficacy in the management of recurrent ARTI in children of 2 to 12 years of age. Das et. Al. in their study had also concluded that Pidotimod significantly decreases the RRTI (Das et al., 2017). This study reports that Pidotimod is cost effective in the management of recurrent ARTI since the intervention demonstrates a reduction in average treatment cost, number and duration of ARTI episodes, hospitalizations, antibiotic use and days lost due to illness, which is similar to other studies reported.²⁰ Present study also reports that there is a significant reduction in antibiotic use following Pidotimod treatment, reducing the possibility of antibiotic resistance. All these findings are similar to some studies reported recently. One study involving 100 children with a mean of 4.9 years with history of at least 6 episodes in 1 year found that Pidotimod treatment improved symptoms of ARTI along with concomitant reduction of use of medication including antibiotics and loss of school days (Caramia et al., 1994).

It was also observed that in the present study, that 60-day Pidotimod therapy resulted in, significantly decreased antibiotic usage and gave a 2-fold reduction rate of ARTI recurrence within a 3-month period. They also had milder ARTI with early recovery as found in similar study (Namazova-Baranova et al., 2014).

Current study also shows an increase in absolute CD count and lymphocyte count at completion of 2 months of treatment, suggesting that Pidotimod might significantly increase the activity of immune system. This enhancement of immune response may be the reason for better reduction in RRTI which was also corroborated in another study (Zhang et al., 2014).

Significant reduction in health care expenditure in the present study after Pidotimod therapy is similar to the findings of Asha Goyal et .al., although it was performed in adults (Goyal, 2018). Current study is the first of its kind showing cost effectiveness of using Pidotimod in ARTI in children.

The adverse events reported were mild and self-limiting and were within reasonable limits (14%). This is congruent with a recent meta-analysis which shows only 5% mild and transient adverse reactions while using Pidotimod. There was no statistically

significant increase in adverse effects with the use of Pidotimod (Namazova-Baranova et al., 2014).

This is also the first Indian study which gauges the use and effects of Pidotimod for 6 months and also evaluates the immune stimulant nature through an objective measurement of immune markers.

Though the absence of use of a placebo or randomization can be explained by the fact that it is a study done on an experimental drug on compassionate grounds, and being a non-blinded study by itself may be considered as limitations of the present study. Further we are not ruling out the possibility of a recall bias. Hence there is a need for a randomized controlled trial to generate confirmatory data on efficacy, cost benefits and safety of Pidotimod therapy.

CONCLUSIONS

The role of Pidotimod in prevention and treatment of recurrent ARTI in children is reinforced by the present study with opportunities for significant health care cost benefits in developing nations. The immune stimulant activity further supports the potential use of Pidotimod along with the current standard care in the management of ARTI in children.

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