Original article

Efficacy and safety of pidotimod as adjuvant in the treatment of recurrent upper respiratory tract infections (URTI) in children

Summary
The study evaluated the efficacy and safety of an immunomodulating drug, versus placebo, as an adjuvant during antibiotic therapy in paediatric patients affected by recurrent respiratory infections. The study enrolled 200 patients, randomly assigned to receive pidotimod or placebo, twice a day for 15 days, in addition to a standard antibiotic treatment. The evaluation of the severity of symptoms was recorded for the following parameters: fever, cough, nasal obstruction, otalgia, expectoration and rhinorrhoea. The improvement in the scores was statistically significant in pidotimod group in comparison to placebo group, showing therefore efficacy in reducing the rate of recurrent infections and in alleviating the symptoms related.

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Recurrent upper respiratory tract infections (URTI) are among the most common disorders in children[1]. As well as representing a challenge to paediatricians, they have significant socioeconomic implications and they are the major cause of morbidity and mortality in children in India[2]. From an epidemiological point of view, it has been shown that 57% of children with recurrent respiratory infections (three or more episodes per year during a period of at least two years) were deficient in one of the IgG subclasses and that 17% were IgA deficient[3]. IgG subclass deficiency is quite prominent in young children but rare in older children, suggesting a transient immaturity of the immune system as one of the possible pathogenic factors.
Defects in the immune system, such as common variable immunodeficiency and the more frequent selective IgA deficiency, are known to be linked to frequent respiratory infections by bacteria and viruses[4]. URTI are usually caused by viruses very often uncharacterized[5] and may involve bacterial super infection and subsequent complications, requiring various medical and surgical treatments. In the majority of cases, the increased susceptibility to infectious agents in the early years is probably the expression of the physiological immaturity of the immune system, as frequently reported in paediatric literature[6]. These are: inversion of the T-helper/T-suppressor ratio, reduced response of T lymphocytes to mitogens such as

PHA (phytohaemoagglutinin), reduced neutrophil chemotactic and phagocyte activity and impaired natural killer (NK) cell function. Moreover, repeated antibiotic therapy of such recurrent URTIs often fails to produce the desired response as the defects in the immune system remain unaffected. In this scenario, immunostimulant and immunomodulating drugs can help to improve the clinical outcomes in children by enhancing the capability of the immune system and reducing the need for repeated antibiotic therapy.

Pidotimod is an immunomodulating drug, acting through the stimulation and the regulation of cell-mediated immune response. By partially replacing or enhancing the thymus function and the phagocytic activity of human polymorphonuclear (PMN) leucocytes[7], pidotimod induces maturation of T cells and restores the complete immune competence of deficient T lymphocytes. Furthermore, pidotimod has an effect on the maturation of mucosal dendritic cells (DC), leading to the production of pro-inflammatory cytokines which can play an important role in T cell-mediated immune response; fully competent DCs can activate naïve T lymphocytes to induce adaptive immunity[8]. In addition, pidotimod stimulates macrophages, the main function of which is to ingest the antigens and present them on their membranes in association with the histocompatibility antigens. For this reason, the defence of the organism against pathogens depends on the efficiency of the specific immunity mechanism. Several studies have indicated that pidotimod positively influences T cells and granulocytes, thus modulating immune response[9].

The aim of the study was to evaluate the immunomodulatory effect of pidotimod, in comparison to placebo, as an adjuvant during antibiotic therapy, reducing respiratory symptoms/signs in URTI paediatric patients. A further aim was to evaluate the relapse of symptoms in a six-month follow-up period.

Materials and Methods

Study Design

This was a multicentre, prospective, randomized, comparative, double-blind, placebo-controlled, parallel group study, conducted in five Indian sites, approved by the Ethics Committee for Research on Human Subjects (Ethics Committee/IRB of K. J. Somaiya Medical College & Hospital, Mumbai) and conducted in compliance with the ethical principles of the Declaration of Helsinki. Eligible patients were children of both sexes, aged 1–12 years, with a history of recurrent respiratory infections (RRI), defined arbitrarily as ≥8 episodes of URTI for a child ≤3 years old and ≥6 episodes for a child >3 years old, as the definition of RRI is problematic and no clear consensus has yet been reached[10]. Patients were enrolled after obtaining informed consent from their parents/guardians/legally acceptable representative. The main exclusion criteria were long-term antibiotic therapy, treatment with other immune-stimulating drugs and immune-depression.

Patients fulfilling the inclusion/exclusion criteria were randomized by blocks of four (balanced 1:1) and ascribed to the following treatment schedule: one vial of pidotimod (400 mg)/matching placebo twice a day for 15 days in addition to standard amoxicillin + clavulanic acid at the dose and time required from individual cases (treatment phase); afterwards, one vial of pidotimod (400 mg) once a day for the following 30 days (maintenance phase). The study visits were at day 15 (end of treatment) and at day 45 (end of maintenance). After the maintenance phase, patients entered a six-month follow-up phase, with the last visit planned at the end of the six-month period.

The severity of the following RRI-related symptoms was recorded at each visit on a four-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe): fever, cough, nasal obstruction, otalgia, expectoration and rhinorrhoea. Hospitalization and absence from school, if any, were noted. Moreover, all patients (parents/guardians) were asked to complete a diary card to record the daily body temperature and symptoms/signs, the description of any adverse events and the eventual concomitant therapies during the whole study period. Treatment acceptability was judged by investigators and parents at the end of follow up. Laboratory investigations were performed at baseline, after the end of treatment (day 45) and at the end of the six-month follow-up period. Assessment of the safety of the study medication was performed at every visit.

Statistical Analysis

The statistical analysis was conducted by an institutional statistician, who provided descriptive summary statistics (mean, standard deviation, minimum and maximum values for quantitative data and absolute and relative frequencies for qualitative data) for all recorded variables at each planned examination, stratified by study device.

The homogeneity of patient distribution between groups was checked in a descriptive manner. Parametric efficacy variables were processed using ANOVA for repeated measures by measuring the effect of time, treatment and the time per treatment interaction. Non-parametric variables were measured using the Friedman Test. Concerning the tolerability analysis, the assessment of safety was performed on the safety population and based on the frequency of adverse events.
The data were analysed using the Microsoft Access database management system (Office 2007) and the Statistical Package for Social Sciences (SPSS) version 14. The Kruskal Wallis test and the chi-squared test were used to test the statistical significance of the findings. The significance level was set at 95%.

Results

Out of a total of 209 patients screened, 193 patients with a history of recurrent RRI were enrolled in the trial and subdivided, with 96 (49.7%) receiving pidotimod and 97 (50.3%) receiving placebo. In total, 177 (91.7%) patients completed the study (87 patients in the pidotimod group – 49.2%; 90 patients in the placebo group – 50.8%).

Demography and baseline characteristics

The patients' demographic characteristics are shown in Table 1. There was no statistically significant difference in gender, age, weight and number of RRI episodes in the previous 12 months at baseline between the two treatment groups. The mean temperatures of patients in the pidotimod and placebo groups were 37.98°C and 37.76°C respectively.
The RRI event had to be confirmed by the presence of fever, at least 37.5°C axillary and 38°C rectal, lasting at least 24 hours. The main duration of the episode of RRI leading to enrolment in the study was 5.15 ± 2.74 in the pidotimod group and 4.38 ± 2.71 in the placebo group.

Efficacy

Both groups showed statistically significant improvement after 45 days ($P<0.05$, Friedman Test). However, the improvement in scores for symptoms/signs of fever, cough, expectoration and rhinorrhoea in the pidotimod group gave statistically significant results in comparison to the placebo group ($P<0.05$, Kruskal Wallis Test) at the end of the pidotimod maintenance treatment period. Moreover, the scores for symptoms/signs of fever and otalgia were already statistically significant after the 15-day treatment period of 400 mg of pidotimod twice a day. In general, the improvement in scores for symptoms/signs in the pidotimod group was greater than for placebo group. The results of the symptoms/signs scores are summarized in Table 2.
RRI relapse was defined as the presence of any one or more of the following symptoms (irrespective of their severity): fever, cough, nasal obstruction, otalgia, expectoration and rhinorrhea. The numbers of patients with relapses occurring between 0–15 days (pidotimod treatment phase), 15–45 days (pidotimod maintenance phase) and during the six-month follow-up period were considered. If RRI relapse occurred during the follow-up period, the patients were considered to

Table 1. Demographic characteristics of patients at baseline.

	Pidotimod group	Placebo group
Gender		
Male (%)	50	59
Female (%)	46	38
Age (years)		
Mean ±SD	6.72 ± 3.55	6.5 ± 3.53
Weight (Kg)		
Mean ±SD	16.8 ± 6.45	15.67 ± 6.08
Temperature (°C)		
Mean ±SD	37.98 ± 0.32	37.76 ± 0.32
RRI episodes (12 months)		
Mean ±SD	6.6 ± 1.4	6.37 ± 1.34

Table 2. Symptom scores in the two groups at baseline, day 15 and day 45.

	Pidotimod group			Placebo group		
	Baseline (n=96)	Day 15 (n=89)¥	Day 45 (n=87)	Baseline (n=97)	Day 15 (n=92)	Day 45 (n=90)
Fever	1.26±0.78	0#	0*#	0.93±0.5	0.83±0.67	0.09±0.28*
Cough	1.43±0.65	0.04±0.20	0*#	1.16±0.49	1.17±0.84	0.22±0.46*
Nasal Obs.	0.17±0.45	0.02±0.14	0*	0.18±0.47	0.02±0.14	0.14±0.14*
Otalgia	0.75±0.5	0#	0*	0.74±0.44	0.52±0.5	0.01±0.1*
Expectoration	0.38±0.52	0.01±0.1	0*#	0.22±0.43	0.45±0.56	0.07±0.25*
Rhinorrhoea	1.4±0.62	0.06±0.23	0.03±0.23*#	1.05±0.60	1.09±0.91	0.17±0.43*

*Within-group analysis (Friedman Test): P<0.05. #Between-groups analysis (Kruskal Wallis Test): P<0.05. (¥ In the Fever group, n=88).

have completed the study at the onset of relapse. Figure1 shows the number of patients who reported RRI episodes over the course of the study. At the end of 15 days of treatment with 400 mg of pidotimod twice a day, nine patients (8.91%) in the pidotimod group and 66 patients (66.66%) in the placebo group reported an episode of RRI. The difference between the two groups was statistically significant (P<0.05, chi-squared test). Similarly, after 45 days of maintenance with 400 mg of pidotimod once a day, two patients (1.98%) in the pidotimod group and 18 patients (18.18%) in the placebo group reported an episode of RRI. The result in this case was also statistically significant (p<0.05, chi-squared test). During the follow-up phase, starting from the first month and throughout the follow-up period, the rate of recurrence ranged between 1% and 7% in the pidotimod group and between 0% and 10% in the placebo group, the difference not being significant.

At the end of follow up, both the investigators and the patients gave their opinions of the efficacy and the acceptability of the administration of pidotimod/placebo. The overall efficacy and acceptability of the treatment was rated by the investigators as "high" in 79.2% of the subjects in the pidotimod group and 16.2% of the subjects in the placebo group. The overall efficacy and acceptability of the treatment was rated by the parents/guardians as "excellent" in 77.2% of the subjects in the pidotimod group and 18.2% of the subjects in the placebo group. The results are shown in Figures 2 and 3.

Figure 1. Percentage of patients with episodes of RRI throughout the study (*P<0.05, Chi-squared test).

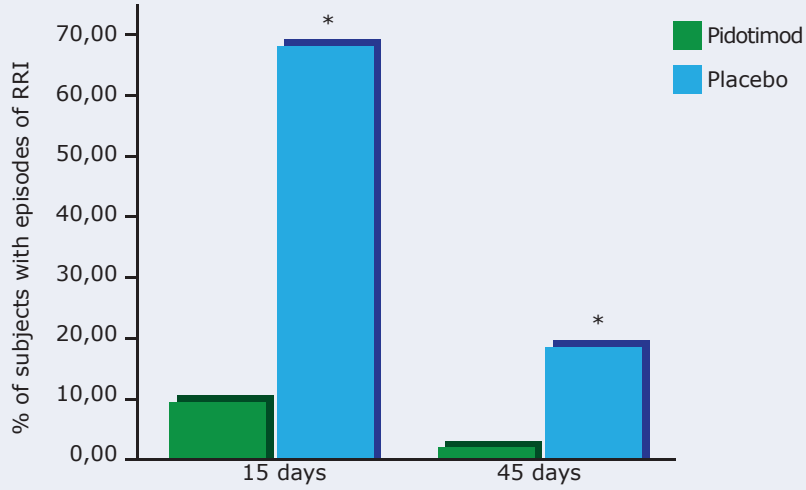


Figure 2. Percentage overall efficacy and acceptability assessed by Investigators.

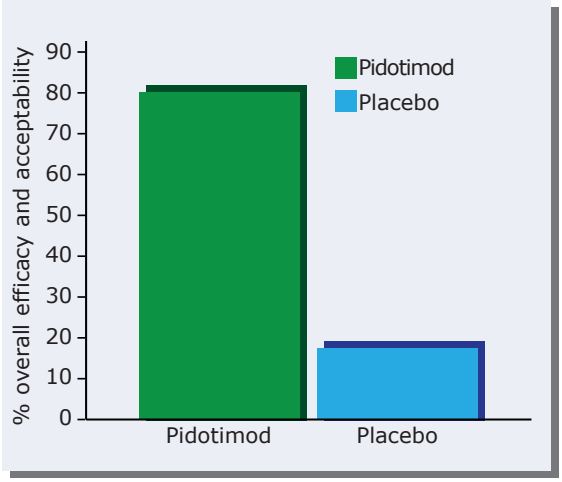
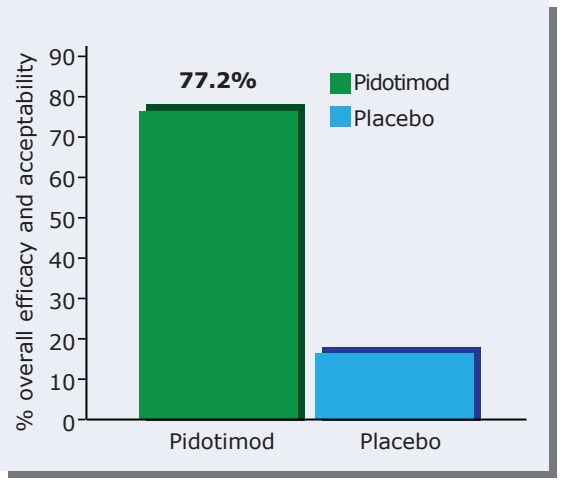


Figure 3. Percentage overall efficacy and acceptability assessed by parents/guardians.



Safety

The overall tolerability of the treatment was rated by the investigators as "good" in 86.1% of the subjects in the pidotimod group and 89.9% of the subjects in the placebo group. The overall tolerability of the treatment was rated by the parents/guardians as "good" in 86.1% of the subjects in the pidotimod group and 89.9% of the subjects in the placebo group. No serious adverse events occurred in this trial. Two patients in the pidotimod group and one patient in the placebo group reported mild itching during the follow-up period, which resolved itself spontaneously. There was no clinically significant difference between the laboratory investigations for safety at baseline and at the end of 45 days of treatment in both groups.

Conclusion

Children affected by recurrent upper respiratory tract infections (URTI) are increasingly susceptible to infectious agents due to the physiological immaturity of their immune systems, which has significant socioeconomic implications. Recurrent respiratory infections (RRI), usually caused by viruses, may involve bacterial super infection and subsequent complications requiring various medical and surgical treatments. In this scenario, it is necessary to have recourse to immunostimulant drugs, which stimulate and regulate the cell-mediated immune response, enhance the competence of the immune system and reduce the need for repeated antibiotic therapy. Pidotimod is an immunomodulating drug, acting through the stimulation and regulation of the cell-mediated immune response, inducing the maturation of T cells and restoring the complete immune competence of deficient T lymphocytes. The properties and the efficacy of pidotimod have also been demonstrated in recurrent infections of the urinary tract in children[11], as well as in the treatment of patients affected by bacterial exacerbations of chronic bronchitis[12,13]. These effects have been found to be more evident in the setting of immune defects, such as senescence, Down's syndrome and cancer[14].

In our study, pidotimod was effective in reducing the rate of recurrent infections of the upper respiratory tract; furthermore, pidotimod was superior to placebo in alleviating symptoms such as fever, cough, expectoration, rhinorrhoea and otalgia in our patients. Pidotimod showed its superiority in comparison to placebo in preventing episodes of respiratory tract infections during the 45-day treatment period. During the follow up, as there was also a decreased rate of relapses in the placebo group due to the seasonal variation, no statistical significant difference was found between the active drug and placebo.

No serious adverse events or changes in laboratory investigations were observed with the administration of either pidotimod or placebo. Pidotimod showed a better efficacy profile compared to placebo. The overall impressions of the investigators and parents/guardians also favour pidotimod over placebo.

Thus, we conclude that pidotimod is a safe and effective therapeutic option in the management of RRI in children. TiM

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