

Original Research Article

Effectiveness and safety of pidotimod in recurrent respiratory infections in children: a pilot study

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ABSTRACT

Background: Recurrent respiratory infections (RRIs) are common in children especially in age 1 to 6 years. Pidotimod, an immunostimulant has been found to lower the recurrences of RRIs and improve the quality of life. The Objective of this study was to assess the efficacy and safety of pidotimod in children with recurrent respiratory infections (RRIs).

Methods: In this single-centre, prospective, observational study, children aged 2 to 15 years diagnosed with RRIs were included. RRIs were defined as occurrence of 3 or more episodes of acute respiratory infections (ARIs) or more than 15 days of respiratory symptoms in the past 3 months. These children were treated with pidotimod in addition to standard care treatment. Treatment duration was two months and the follow-up continued for three months. Number of RRIs and severity of RRIs, antibiotic courses and rate of hospitalization before and after treatment were compared.

Results: In total 25 children included in the study, mean age was 7.34 ± 3.63 years. Among them, 68% were males. After treatment with pidotimod, there was significant reduction in mean number of ARI episodes (3.84 ± 0.85 at baseline to 0.48 ± 0.51 at follow-up, $p < 0.0001$). Also, there was significant reduction in the duration of acute infectious episodes ($p < 0.0001$), need of antibiotic courses ($p < 0.0001$) and rates of hospitalization ($p < 0.0001$). No safety concerns were identified and pidotimod was well tolerated.

Conclusions: Addition of pidotimod to the standard treatment in children with RRIs significantly reduces the recurrence, duration of repeat infectious episodes, need of antibiotic treatments and future rates of hospitalizations. These findings support previous data.

Keywords: Children, Immunostimulant, Pidotimod, Recurrent respiratory infections

INTRODUCTION

In developing countries, respiratory infections are responsible for significant morbidity and mortality.^{1,2} Recurrent respiratory infections (RRIs) are common in children especially in age 1 to 6 years. These RRIs are responsible for frequent hospital visits and increased economic burden.³ Among various factors, immaturity of immune functions involving activities of neutrophils,

macrophage, natural killer (NK) cells, B-cells and T-cells are observed to be linked with RRIs.^{4,5} A synthetic dipeptide, Pidotimod, exerts immunostimulatory effects on both innate and adaptive immune systems.⁶ Use of pidotimod in children with RRIs is associated with reduction in the recurrences, and severity of the infectious episodes, improvement of clinical features, rapid clinical recovery, reduced need for the antibiotics and other symptomatic treatments and decrease in school

absenteeism and visits to paediatric clinics.⁶⁻⁸ Pidotimod is in research for over two decades in other parts of the world, and it is now being used in India since nine years. Two previous studies have reported excellent overall efficacy and safety of pidotimod in RRIs.^{9,10} Authors performed this study to assess the efficacy and safety of Pidotimod in addition to standard of care in children with RRIs from India.

METHODS

Study setting

This study was performed at specialty paediatric clinic in Western part of India. The study was conducted between September 2018 to March 2019.

Study design

This was a single-centre, prospective, observational study.

Study population

In this study, children with RRIs were recruited. RRI was defined as recurrence of three or more episodes of ARIs or more than 15 days of respiratory symptoms in the past 3 months.¹¹ Inclusion criteria was children aged two to fifteen years, either gender, diagnosed with RRIs and receiving treatment on out-patient basis. Patient with prior history of pidotimod hypersensitivity and critically ill children were excluded.

Also, children who were diagnosed with immune deficiency disorders or acquired immunodeficiency states, having known systemic illness, receiving drugs or other agents affecting immune responses and those who had received any immunization within 3 months before enrolment were excluded.

Study treatments

Children were treated with standard therapy plus pidotimod. Pidotimod was administered in a dose of 400 mg/day twice-a-day for 15 days during an active episode followed by once-a-day for 2 months. Patients were followed for three months after completion of pidotimod therapy to check for the recurrence of acute infectious episode. Standard therapy included antibiotics (amoxicillin/clavulanic acid) for maximum of 7 days and oral antihistamines and antipyretics.

Outcomes assessed

Primary outcome assessed was the reduction in number of acute infectious recurrences. Secondary assessments were the duration of acute infectious episode, concomitant antibiotic use and hospitalization. All parameters during overall five months (2 months treatment and 3months follow-up) were evaluated.

Statistical analysis

The data was captured in a case record form. Data was entered into the Microsoft excel sheet version 2016 and was analysed with the same. Categorical data was presented as frequency and percentages whereas continuous data was presented as mean and standard deviation. Outcome parameters before and after treatment were assessed for significant differences using paired student t-test. P value <0.05 was considered significant for all comparisons.

RESULTS

Baseline characteristics

In total authors included 25 children with RRIs who were treated with pidotimod in addition to standard care. Table 1 describes the baseline characteristics. Mean age of the patients was 7.34±3.63 years. Among the children, 68% (17/25) were males and 32% (8/25) were females.

Table 1: Baseline characteristics.

Parameter	Observation (n=25)
Age (years)	7.34±3.63
Gender (%)	
Male	17 (68.0)
Female	8 (32.0)
Weight (Kg)	18.74±5.14
Symptoms/signs (%)	
Cold	7 (28.0)
Cough	11 (44.0)
Cold and cough	7 (28.0)
Other comorbidities	
Restrictive airway disease	
Asthma	1 (4.0)
Allergic rhinitis	1 (4.0)
History of respiratory allergy (%)	21 (84.0)
Antibiotic treatment (%)	18 (72.0)

Mean weight was 18.74±5.14 kg. Among symptoms, cold, cough and cold with cough were seen in 28%, 44% and 28% children. In addition to RRIs, history of respiratory allergies was found in 84% cases. Among respiratory comorbidities, restrictive airway disease was seen in 8%, asthma and allergic rhinitis were present in 4% each. Overall, 72% of the children had received antibiotics in the past for the treatment of RRIs.

Primary outcome

Mean number of respiratory infectious episodes in children in the past 6 months before enrolment into the study was 3.84±0.85. After treatment, mean number of respiratory episodes reduced significantly to 0.48±0.51 episodes by end of study (p<0.0001) (Figure 1).

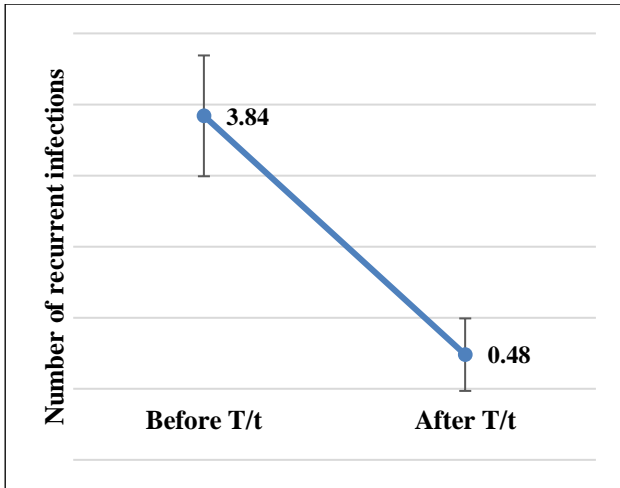


Figure 1: Change in number of RRI episodes after pidotimod treatment.

Error bar represents standard deviation

Secondary outcomes

In addition to number of RRI episodes, authors evaluated other parameters (Table 2).

Table 2: Change in secondary outcome parameters after treatment.

Parameter	Before treatment	After treatment	P value
Duration of acute infectious episodes (days)	5.84±2.38	2.04±2.37	<0.0001
Antibiotic courses	3.88±0.90	0.12±0.33	<0.0001
Hospitalizations	1.36±1.41	0.08±0.28	<0.0001

The duration of acute infectious episodes reduced significantly after treatment with pidotimod from 5.84±2.38 days before treatment to 2.04±2.37 days after treatment (p<0.0001). This was also accompanied by the significant reduction in need of antibiotic courses from 3.88±0.90 to 0.12±0.33 (p<0.0001) after treatment with pidotimod. These improvements culminated in reducing the rates of hospitalizations significantly in patients treated with pidotimod (from 1.36±1.41 to 0.08±0.28, p<0.00001).

Safety

No adverse effects were observed in any of the children who were given pidotimod. No tolerability issues were identified.

DISCUSSION

Worldwide, 11.9 million severe acute lower respiratory infections are reported in young children. Among these

children, in-hospital mortality was reported in 2,65,000 cases. Among the children who died, 99% were reported to be from developing countries.¹² RRIs are common in children and are reported in 25% children <1 year and 18% children of 1 to 4 years in developed nations. It has also been observed that RRIs are a cause for nearly 50% of paediatric consultations.³ This has been reflected in figures such as 30%-50% of the total paediatric outpatient visits and 20%-30% of admissions being due to RRIs in developing nations.¹³ Thus, effective management and prevention of RRIs is necessity around the globe. Immuno-stimulation has been observed to lower the risk of RRIs.

A meta-analysis from Del-Rio-Navarro et al, involving studies with immunostimulants in children (age <18 years) reported that compared with placebo, the use of immunostimulant is associated with reduction in the total numbers of acute infectious episodes (mean difference (MD) -1.24; 95%CI -1.54 to -0.94). The difference in rates of acute infectious recurrences was also significant (MD -38.84%; 95% CI -46.37% to -31.31%). this points towards the fact that in nearly 40% of children, incidence rate of acute respiratory infections is reduced with use of immunostimulant.¹⁴

Another recent metanalysis from Niu et al, reported that compared to conventional treatment, pidotimod was associated with significant increase in the proportion of participants who had lower RTIs (RR 1.59; 95% CI 1.45-1.74, p<0.00001). Reduction in duration of cough and fever was also significant whereas use of antibiotics was reduced remarkably. These benefits were seen without an apparent increase in adverse events of any cause (RR = 1.05, 95% CI 0.72-1.54, p=0.80) establishing efficacy as well as safety of pidotimod in RRIs.¹⁵ These findings also corroborated with the findings of these meta-analyses. There was significant reduction in mean number and duration of acute episodes.

Multiple previous studies have reported such observations with reduction in number of recurrences and the duration of recurrent acute infectious episodes with Pidotimod.⁷⁻¹⁰ Two reports from India also confirm the similar outcomes with reduction in recurrences in children with or without asthma.^{9,10}

Overall, clinical evidence from these studies affirmatively confirms that pidotimod in children with RRIs is associated with reduction in RRI recurrences, duration of episodes, antibiotic use, visits to paediatric clinics, and reduced rate of hospitalizations.

All these contribute to the improved attendance at school or kindergarten.⁷⁻¹⁰ The observed benefits with pidotimod in RRIs are because of modulation of both innate and adaptive immunity contributing to improved outcomes in RRIs.^{8,16} These findings therefore consolidate the role of pidotimod as one of the first-line therapies that can be considered in children with RRIs to improve the rate and

duration of recurrences and future hospitalization rates in these children.

CONCLUSION

Pidotimod by virtue of its immunostimulant activity improves the outcomes in RRIs. Pidotimod reduces the number and duration recurrences, usage of antibiotics and rates of hospitalizations for repeat episodes. Overall, this may contribute to reduced absenteeism from school and thereby improved quality of life in children with RRIs.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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