Review Article

Pidotimod: In-depth review of current evidence

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ABSTRACT

Pidotimod, an immunostimulant, is researched for over two decades. Current evidence indicates its utility in a variety of indications in children as well as in adults. Its immunostimulant activity has been firmly established in the management of recurrent respiratory infections in children with or without asthma. Compared to standard of care alone, addition of pidotimod to standard of care significantly prevents the recurrences and reduces the severity and duration of acute episodes, ultimately resulting in reduced visits to pediatric clinics and lower absenteeism at school. In adults, pidotimod is effective in the prevention and treatment of acute infectious exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD). Further, it has been evaluated in indications such as pneumonia, hand–food–mouth disease, bronchiectasis, and chronic idiopathic urticaria. From a total of 32 studies conducted in child (24 studies) and adult (8 studies) population, this in-depth review discusses the current evidence of pidotimod. With further exploration, the immunostimulant activity of pidotimod might be extended to different immunological disorders.

KEY WORDS: Adults, asthma, children, chronic obstructive pulmonary disease, pidotimod, recurrent respiratory infections

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INTRODUCTION

Acute respiratory infections (ARIs) are one of the most common infections in both adults and children. The Global Burden of Diseases Study (2015) reported that lower respiratory infections (LRIs) led to 2.74 million deaths and resulted in 103 million disability-adjusted life years. Over the past 10 years, the burden of LRIs has reduced in children below 5 years but increased in many regions in elderly people above 70 years worldwide.[1] This could be attributed to increased awareness in population, advances in antibiotics, and increased vaccination coverage. However, ARIs remain a significant cause of morbidity and mortality in developing countries.[2] Globally, the prevalence of ARIs is highest in South-East Asian region.[3] In children, recurrent respiratory infections (RRIs, ≥6 acute episodes year) are very common and often are the cause for frequent hospital visits.[4,5] Immaturity in immune response involving activities of immune cells such as neutrophils, macrophage, dendritic cells, natural killer (NK) cells, B-cells, and T-cells seen in early ages has been observed to be attributable to RRIs.[5,6] Immunological alterations in asthma with chronic inflammatory changes are known.[7] These may be associated with increased severity and often cause recurrences of asthmatic attacks. Further, immunological alterations in infections such as pneumonia can lead to more severe disease.[8,9] Therefore, modulation of immunity with pidotimod has emerged as a novel approach and has proven efficacy in the past two decades in both RRIs and asthma. Pidotimod is a synthetic dipeptide that exerts immunostimulatory effects by affecting both innate and adaptive immunity.[10] Multiple

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studies have evaluated the efficacy and safety of pidotimod in both adults and children across different indications such as RRIs, asthma, bronchitis, chronic obstructive pulmonary disease (COPD), and pneumonia. In this article, we reviewed the current clinical evidence of pidotimod in these different indications.

LITERATURE SEARCH METHODOLOGY

We performed literature search in PubMed and Google Scholar databases using search terms such as Pidotimod, children, recurrent respiratory infections, asthma, bronchitis, COPD, and pneumonia. Additionally, we also performed a general search in Google search engine to identify any relevant studies. Studies in English language were selected for the review. For studies in non-English language, relevant information available from the abstract was extracted. In this review, we included a total of 32 studies with 24 studies in children and 8 studies in adult population. Different indications analyzed in these studies were RRIs (n = 14 studies), RRIs with asthma (n = 2 studies), asthma (n = 4 studies), pneumonia (n = 2 studies), acute bronchitis (n = 1 study), and hand–foot–mouth (HFM) disease (n = 1 study) in children and chronic bronchitis (CB) or COPD (n = 5 studies), bronchiectasis (n = 1 study), pneumonia (n = 1 study), and chronic idiopathic urticaria (n = 1 study) in adults.

PIDOTIMOD

Chemistry

Chemically, pidotimod is 3-L-pyroglutamyl-L-thiaziolidine-4 carboxylic acid. It is a synthetic dipeptide molecule having immunostimulatory properties.[10]

Mechanism of action

The immunostimulatory activity of pidotimod is focused on both immune responses – adaptive and innate immunity. It has shown to affect the immune response in multiple ways as enumerated below.[10,11]

- Induction of maturation of dendritic cells
- Upregulation of HLA-DR and other co-stimulatory molecules (CD83 and CD86) expression
- T-cell differentiation toward Th-1 type (via release of pro-inflammatory molecules by stimulating dendritic cells)
- Increase in the activity of NK cells
- Inhibits thymocyte apoptosis
- Promoting phagocytosis
- Increase in salivary immunoglobulin (Ig) IgA levels
- Upregulation of TLR-7 and TLR-2 signaling pathway in respiratory epithelium (helps to assist in identifying pathogen-associated molecular patterns).

Pharmacokinetics

Pidotimod is a highly purified molecule and has high reproducibility among different batches. In the gastrointestinal tract, it is rapidly absorbed. It has an oral bioavailability of 43%–45%. The rate and extent of absorption of pidotimod are reduced significantly when consumed with food. The oral bioavailability is decreased by up to 50% in the fed state compared to its administration in the fasting state. To optimize absorption, pidotimod should be given 2 h before or 2 h after meals. Hepatic metabolism is minimal, and it is excreted unchanged renally.[11]

Dosing

In children

In the treatment of acute respiratory infections, pidotimod can be administered 400 mg twice daily for 15–20 days in addition to standard antibiotics. For prophylaxis against relapse, dose used is 400 mg once daily (before breakfast) for 60 days. Dosing in children with renal failure has not been established.[12]

In adults

In the treatment of bacterial exacerbations of CB, pidotimod can be administered 800 mg twice daily for 8 days in combination with antibiotics and 800 mg once daily for nearly 60 days for prophylaxis against acute exacerbations. Dose reductions may be necessary in patients with renal failure. However, in the elderly, dose reductions may not be necessary in the absence of renal dysfunction.[12]

Clinical evidence of pidotimod

Studies in children

Table 1 summarizes the evidence of pidotimod in different indications in children.

Recurrent respiratory infections

Global estimates for severe acute LRIs in young children have been reported to be 11.9 million severe episodes with in-hospital mortality in 265,000 cases. Interestingly, 99% of the estimated deaths were from developing countries.[37] This clearly indicates that the standard of care in respiratory infections needs to be improved in developing countries. Recurrences in such respiratory infections are common in children. In developed countries, 25% of children aged below 1 year and 18% of children aged 1 to 4 years are reported to suffer from RRIs. In addition, 50% of pediatric consultations are observed to be due to RRIs.[4] In developing countries, RRIs are responsible for 30%–50% of the total pediatric outpatient visits and 20%–30% of admissions. Community-based estimates in children below 5 years report that 70% of the pediatric morbidities are due to ARIs.[3] RRIs in children are determined by various factors. Though these are seen even in normal, healthy children, atopic disease, chronic diseases, and immunodeficiency are instrumental in the development and progression of RRIs.[38]

Children between the age of 6 months and 6 years are probably the most at-risk population. A study from the United Kingdom observed the mean age of children with RRIs to be 24 ± 12 months.[39] Immune dysregulation

Table 1: Summary of efficacy and safety of pidotimod in different indications among children

Study (years)	Design	Population	Treatments	Follow-up duration	Efficacy%*	Safety
Children with RRIs without asthma						
Motta *et al*. (1994)[13]	RCT	Children with recurrent tonsillitis, 3-14 years	PD (*n*=177) versus PB (*n*=118) for 75 days	90 days	↓ Inflammatory episodes in upper airways↓Clinical S/S↓Antibiotic usage↓Absenteeism from school	Excellent safety
Burgio *et al*. (1994)[14]	RCT	Children with RRI, 2-13 years	PD (*n*=52) versus PB (*n*=49) for 60 days	60 days	↓ Clinical S/S of upper and lower RTIs↑Cells with CD25+ expression	Excellent safety
Caramia *et al*. (1994)[15]	RCT	Children with RRI, 2-8 years	PD (*n*=60) versus PB (*n*=60) for 75 days	-	Normalization of the immune response: Chemotaxis and leukocyte phagocytosis index↓Risk of relapses↓Hospitalizations↓Antibiotic use	Well tolerated AEs: 5 versus 7
Passali *et al*. (1994)[16]	RCT	Children with RRI, 3-14 years	PD (*n*=205) versus PB (*n*=211) for 60 days	90 days	↓ Duration and frequency of RRI episodes↓Fever duration↓Severity of clinical S/S↓Antibiotic need↓Absenteeism from school	Excellent safety AEs Diarrhea (*n*=0 vs. 4) Loss of appetite (n=1 vs. 1) Vomiting (*n*=1 vs. 1) Headache (*n*=1 vs. 1)
Aivazis *et al*. (2002)[17]	RCT	Children with RRI, 2.5-12 years	PD (*n*=32) versus no PD (*n*=18)	9 months	≤2 recurrences: 87.5% versus 33.3% Clearance time of respiratory epithelium after 6 months Reduced from 37 to 19.5 min	NR
Zhou and Dai (2012)[18]	RCT	Children with RRI	PD versus spleen aminopeptide (*n*=86) for 3 months	-	↓ Duration of symptoms Better clinical efficacy	-
Careddu (1994)[19]	RCT	Children with RRI, 3-14 years	PD (*n*=309) versus PB (*n*=327) for 60 days	90 days	↓ RRI incidence rate↓Symptoms↓School abstinence days↓Need of antibiotics	Well tolerated AEs Vomiting (*n*=6 vs. 4) Diarrhea (*n*=5 vs. 4) Abdominal pain (*n*=2 vs. 3)
Namazova-Baranova *et al*. (2014)[20]	RCT	Children with RRI, 3-6 years	PD (*n*=78) versus control (*n*=79) for 30 days	6 months	↓ Incidence of ARIs at 1, 2, and 3 months Development of ARI in the total 6 months: 92.3% versus 100% ↓ IgE↓IL-8 at 3 months Assists in the switch of immune response to Th1 (mature) type	NR
Licari *et al*. (2014)[21]	RCT	Children with RRI, 3-10 years	PD (*n*=50) versus PB (*n*=50) for 60 days	2 months	↓ Number of children with upper and lower respiratory symptoms↓Number of children with medication use↓Number of pediatric visits↑School attendance rate	NR
Walavalkar *et al*. (2014)[22]	RCT	Children with RRI, 1-12 years	Treatment phase: PD (*n*=96) versus PB (*n*=97) for 15 days; Maintenance phase: PD for 30 days	6 months	Improvement in clinical S/S↓Rate of relapse at 15 and 45 days of treatment	Good tolerability AEs: 2 versus 1
Mameli *et al*. (2015)[23]	RCT	Healthy children, 3 years of age	PD (*n*=24) versus PB (*n*=25), last 10 days of each month for 7 months	-	Nonsignificant but 22% decreased rate of acute RTIs Nonsignificant but 44% reduced usage of antibiotics	AE: Urticaria (*n*=1), resolved within 1 week after stopping the drug
Das *et al*. (2017)[24]	RCT	Children with RRIs, 2-10 years	PD (*n*=43) versus PB (*n*=20), for 75 days	6 months	↓ Recurrences in all children↓Recurrences in asthmatic children	None
Children with RRIs with Down's syndrome without asthma						
La Mantia *et al*. (1999)[25]	OB	Children with Down's syndrome and RRI, 3-13 years	PD (*n*=14) versus control (*n*=12) for 90 days	-	↓ Frequency, severity, and duration of infectious episodes↑Mucosal hyperemia, nasal secretions, and nasal respiratory obstructions	None

Contd...

Table 1: Contd...

Study (years)	Design	Population	Treatments	Follow-up duration	Efficacy%*	Safety
Children with RRIs with Down's syndrome without asthma						
Zuccotti *et al*. (2013)[26]	RCT	Children with Down's syndrome and ARIs, virosomal-adjuvanted influenza vaccine administered in all, 3-10 years	PD (*n*=9) versus PB (*n*=9) for 90 days	-	Upregulation of genes involved in the activation of innate immunity and in antimicrobial activity Increment in flu-specific IgG1/G3, suggesting activation of complement-dependent mechanisms	NR
Asthma						
Gourgiotis *et al*. (2004)[27]	In vitro	Children with atopic asthma (n=13) and normal children (n=9)	PD or no PD	-	Downregulated expression of CD30 in normal children and in those with atopic asthma	-
Vargas Correa *et al*. (2002)[28]	OB	Children with asthma, allergic rhinitis, or both with RRI, 2-16 years	PD (400 mg twice per day) (*n*=73)	6 months	↓ Number of RRI episodes↓Number of days affected in infectious event	NR
Ma and Sun (2011)[29]	RCT	Children with asthma, 6-12 years	Control (aerosol budesonide+ML) (*n*=40) versus control+PD (*n*=40) for 30 days	-	↓ IL-4 and IgE↑FEV_1% and PEF%	NR
Zhai and Liu (2011)[30]	OB	Children with asthma, 2-10 years	PD+conventional (*n*=50) versus conventional (*n*=50) for 12 weeks	-	Total effective rate: 94% versus 72% (P<0.05) ↑ IgA, IgM, and IgG↑CD3+, CD4+, CD8+, and CD4+/CD8+ratio	None
Sun *et al*. (2011)[31]	RCT	Children with asthma	PD+control (*n*=55) versus control (*n*=35) for 2 months	-	↓ IL-16	-
Ji and Liu (2016)[32]	OB	Children with asthma, 3-6 years	PD+ML (*n*=75) versus ML (*n*=75) for 3 months	-	Total effective rate: 94.67% versus 81.33% ↑ Cough symptom scores↑FEV_1% and PEF%	AEs: 6.67% versus 17.33% Nausea and vomiting (*n*=2 vs. 5) Diarrhea (*n*=1 vs. 2) Skin rash (*n*=2 vs. 0) Dyspepsia (*n*=0 vs. 3)
Pneumonia						
Esposito *et al*. (2015)[33]	RCT	Children with CAP, 3-14 years	PD+antibiotics (*n*=10) versus antibiotics (*n*=10) for 14 days	7 days	After pneumococcal polysaccharide stimulation↑DC expressing activation and co-stimulatory molecules↑TNF-α and IL-12 secretion↑TLR-2 expression in CD14+cells (monocytes) ↑ Release of pro-inflammatory cytokines from monocytes	
Ma *et al*. (2010)[34]	Unclear	Children with *Mycoplasma pneumoniae* pneumonia	PD versus general therapy (*n*=35) for 3-5 days	-	↑ CD4+cells↑CD4+/CD8+ratio	-
Acute bronchitis						
Wang *et al*. (2017)[35]	RCT	Children with acute bronchitis, 2-13 years	PD (*n*=65) versus PD+ML for 75 days	-	↓ CRP, haptoglobin, α-1 acid glycoprotein, cerocyanin↑CD3+, CD4+, and CD4+/CD8+cells	-

Contd...

Table 1: Contd...

Study (years)	Design	Population	Treatments	Follow-up duration	Efficacy%*	Safety
			HFM disease			
Guo and Luo (2016)[36]	OB	Children with HFM disease	Ribavirin+PD (*n*=78) versus ribavirin only (*n*=84) for 7 days	-	↑ Maculo-papule and herpes improvement↑CRP↑IL-6 and IL-10↑CD3+CD4+CD8-T cell, CD3+CD4-CD8+T cell, CD19+B cell, $CD14^{high}CD16$+monocyte, and $CD14^{low}CD16$+monocyte content in peripheral blood	NR

*Only statistically significant findings (exceptions mentioned as nonsignificant), RCT: Randomized controlled trial, OB: Observational, RRIs: Recurrent respiratory infections, PD: Pidotimod, PB: Placebo, ML: Montelukast, RTIs: Respiratory tract infections, S/S: Symptoms and signs, FEV1: Forced expiratory volume in 1 min, PEF: Peak expiratory flow, IL: Interleukin, AEs: Adverse events, NR: Not reported, CRP: C-reactive protein, ARIs: Acute respiratory infections, IgE: Immunoglobulin E, IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgG: Immunoglobulin G, TNF-α: Tumor necrosis factor-alpha, TLR: Toll-like receptor, ↑: Increase, ↓: Decreased, HFH: Hand-foot-mouth

is identified as an important contributor to RRIs. Atopy and allergies or reduced immune function and immunodeficiency have been reported with RRIs.[40,41]A study from India reported the association of family history of allergic disorder (odds ratio [OR]: 9.6) and family history of asthma (OR: 5.2) with RRIs.[42] Further, food allergy has also been observed to be implicated in the causation of RRIs.[43] These evidences provide a possible link of immune disruption with RRIs. Dysregulation of both humoral and cellular immunity has been reported in RRIs. The dysfunction of immune system is not severe, but low levels of immune parameters are observed as shown in Table 2.[44-46] Understanding the immune dysregulation in RRIs has led to the evolution of immunomodulator therapy.

Many studies (17 studies in this review) have proven the efficacy and safety of pidotimod in children with RRI with or without asthma. Among the initial studies that were conducted nearly two decades ago were the pathbreaking studies for describing the benefits of immunostimulation with pidotimod in RRIs. Studies have clearly established the role of pidotimod in reducing the recurrence and improving the clinical parameters such as antibiotic usage, visits to pediatric clinic, and absenteeism from school. The studies of pidotimod in RRI are described briefly below.

Motta *et al*. randomized 235 children (3–14 years) with recurrent tonsillitis to pidotimod or placebo for 75 days' treatment period and 90 days' follow-up period, leading to a total duration of 165 days of assessment. Pidotimod (400 mg) was administered as two oral vials for 15 days followed by a single vial for 60 days. Significant reduction in inflammatory upper airway episodes was observed during the total period of assessment. One, two, three, and four episodes of recurrences were seen in 35.7%, 21.4%, 8.9%, and 0.9% patients in pidotimod group and in 20.7%, 24.3%, 17.1%, and 9.9% in placebo group, respectively ($P < 0.001$). Furthermore, the median time for appearance of the first relapse was higher in pidotimod than in placebo group (41 vs. 24 days, respectively). The study also reported significant reduction in clinical signs and symptoms; antibiotic and other drugs' usage; frequency of number of days with fever, rhinorrhea, and earache in relapse episodes; and number of days absent from kindergarten or school. Safety was observed to be excellent. The frequency of adverse events (AEs) was no greater than placebo ($n = 11$ vs. 12). Diarrhea ($n = 8$ vs. 5) was the most frequent side effect in pidotimod and placebo groups.[13] Similarly, Burgio *et al*. randomized 101 children aged 2–13 years with RRI to pidotimod or placebo for 60 days and followed for 60 more days. In the first 2 months of treatment, a significant reduction in the clinical features of both lower and upper respiratory infections was reported with pidotimod ($P < 0.05$). During follow-up, only 16% and 18% of patients in pidotimod than 42.5% and 62.5% of patients in placebo group ($P < 0.05$) presented with lower and upper respiratory symptoms, respectively. Further, significant reduction in the usage of antibiotics and supportive treatment, medical assistance during study, and improvement in attendance at school was reported with pidotimod. Safety of pidotimod was found to be excellent. In 18 patients undergoing immunological assay with phytohemagglutinin (PHA) stimulation, increase in cells with expression of CD25+ was seen in a significant higher proportion of children with pidotimod (7 out of 8) than placebo (3 out of 10) (88% vs. 30%, $P < 0.05$).[14] Another randomized controlled trial (RCT) from Caramia *et al*. assessed 120 children with RRIs. Compared to placebo ($n = 60$), pidotimod treatment (400 mg twice a day for 15 days [acute phase] and once a day for 60 days [maintenance phase], $n = 60$) was associated with quick recovery of acute episodes (10.8 vs. 13 days, 2.2 days early, $P < 0.01$), shorter duration of antibiotic (7.6 vs. 10 days, $P < 0.01$) and hospitalization (6.4 vs. 8.5 days, $P < 0.01$), and clinical signs and symptoms. Further, the study observed significant trend toward normalization of immune response evidence by chemotaxis and leukocyte phagocytosis index. A significant decrease in the risk of relapse (39 vs. 60, 35% reduction, $P < 0.05$) was reported along with rapid response in patients with relapse after treatment with pidotimod. It was well tolerated, and the frequency of AEs was similar to placebo ($n = 5$ vs. 7).[15] Passali *et al*. assessed 416 children with RRIs. Treatment period with pidotimod ($n = 205$) and placebo ($n = 211$)

Table 2: Possible alterations in immune system function associated with recurrent respiratory infections

↓ IgA, IgM, and IgG
↓ CD4+, CD8+, CD19+, and NK-cells
↑ IL-4, IL-10
↓ IFN-γ, IL-12, and IL-2
↑ T-reg/Th ratio
↓ Th1/Th2 ratio
Defective phagocytosis and chemotaxis of neutrophils
↓ TLR function and ciliary function
Dendritic cell immaturity

NK: Natural killer, TLR: Toll-like receptor, IgA: Immunoglobulin A, IgM: Immunoglobulin M, IgG: Immunoglobulin G, IL: Interleukin, IFN-γ: Interferon gamma

was for 60 days with 3-month follow-up. Recurrence after treatment was seen in significantly lower proportion of children in pidotimod treatment than placebo (56.1% vs. 68.8%, $P = 0.014$). The median time for relapse was greater in pidotimod than placebo (48 vs. 24 days) groups. Similarly, significant reduction in clinical signs and symptoms and antibiotic courses was observed with pidotimod compared to placebo. More than one episode of recurrence were reported in 17% and 48% patients in two groups, respectively. Safety was observed to be excellent and comparable to placebo. Gastrointestinal disturbances such as nausea, vomiting, diarrhea, and lack of appetite were the common AEs in both groups and were rapidly reversible. Physician assessment of efficacy of pidotimod was excellent to good in 80% of cases compared to that of 49% in cases receiving placebo.[16] A randomized study from Zhou and Dai compared pidotimod and spleen aminopeptide in 86 children with RRIs for 3 months. Pidotimod was associated with significant improvement in clinical symptoms and their decreased duration and significantly better interleukin (IL) IL-4 and interferon gamma levels than controls, suggesting its effect in modulating the balance of Th1/Th2 cytokine.[18] In a RCT similar to the above designs, Careddu assessed children (3–14 years) with RRI. Among 671 children, 57% and 43% were preschool (3–5 years) and school going (6–14 years), respectively. Compared to placebo ($n = 342$), significant reduction in the number of RRI episodes (no episodes: 55.3% vs. 34.8%, $P < 0.01$), associated clinical signs and symptoms, absence from school or kindergarten, consumption of antibiotics, and other symptomatic treatments were reported with pidotimod ($n = 329$). During 90 days of follow-up period also, there were significantly lesser recurrences in pidotimod group. Safety was also comparable (number of patients with AEs: 22 vs. 15), with most AEs being GI disturbances. Vomiting ($n = 6$ and 4) and diarrhea ($n = 5$ and 4) were the most frequent AEs in two groups, respectively.[19] A prospective, randomized study by Aivazis *et al*. enrolled children aged 2.5–12 years with RRIs and received treatment with pidotimod (400 mg twice daily for 15 days followed by once daily for 20 days, $n = 15$) and the other group continued broad-spectrum antibiotic without pidotimod ($n = 32$). During the 9-month follow-up, 87.5% of children in pidotimod group developed two or lesser recurrences, whereas 33.3% of children in the control group developed three or more recurrences. The difference in proportions was statistically significant ($P < 0.0001$). At 6-month follow-up, the mucociliary clearance time of respiratory epithelium decreased significantly with pidotimod (from 37 to 19.5 min, $P < 0.001$) than control group without pidotimod (from 36.4 to 31 min, $P > 0.05$). This indicates that improvement in the functioning of ciliary epithelium contributes to improved outcomes in RRIs.[17] Licari *et al*. enrolled children aged 3–10 years with RRI who were randomized to pidotimod 400 mg once a day for 60 days ($n = 45$) and control (antibiotic and supportive treatment without pidotimod) ($n = 44$) groups. Over 2-month follow-up, significantly higher proportion of children in pidotimod treatment showed improvement in upper and lower airway symptoms at day 30 and day 60. Furthermore, the number of children who required other medications was significantly lower in the pidotimod group. There was increased attendance in school with reduced visits to pediatrician. No adverse effects were reported.[21] In another RCT, Namazova-Baranova *et al*. enrolled children aged 3–6 years with RRIs and randomized to pidotimod (400 mg once a day for 30 days, $n = 78$) and control (antibiotic therapy, $n = 79$) groups. Significant reduction was reported in the incidence of ARIs at 1 (25.6% vs. 55.7%), 2 (33.3% vs. 77.2%), and 3 (64.1% vs. 98.7%) months of treatment. At 6 months, 92.3% and 100.0% of patients from the two groups, respectively, had developed ARI episode. Severity of ARIs was also reduced with pidotimod as evidenced by lesser number of moderate episodes (16.6% vs. 44.3%) and more milder episodes (82.1% vs. 55.7%). Reduced rate of complications (15.4% vs. 43%, $P < 0.05$) and antibiotic usage (17.9% vs. 53.2%, $P < 0.05$) was also reported. Importantly, levels of IgE were decreased in 25.3% and 53.8% of patients from the two groups, respectively. In addition, pidotimod was associated with a switch of immune response of more mature type, i.e., Th1 type. Reduction in IL-8 with pidotimod was significant at 3 months. These results indicate the immunostimulatory effects of pidotimod which provide better outcomes in children with RRIs.[20] A study from India by Walavalkar *et al*. randomized 193 children aged 1–12 years with RRIs to pidotimod (400 mg twice a day for 15 days and once a day 30 days, $n = 96$) and placebo ($n = 97$) groups and were followed up for 6 months after the treatment was over. Pidotimod was associated with significant improvement in clinical signs and symptoms than placebo at 15 days' and 45 days' assessment. RRI relapse rate was significantly lesser at 15-day (8.91% vs. 66.66%, $P < 0.05$) and at 45-day (1.98% vs. 18.18%, $P < 0.05$) assessments but nonsignificantly lower in 6-month follow-up period (7% vs. 10%). Physician and patients rated the overall efficacy and safety of treatments to be high/excellent for pidotimod and placebo at 79.2% vs. 16.2% and 77.2% vs. 18.2%, respectively.[22]

Mameli *et al*. enrolled healthy children aged 3 years who entered kindergarten who were randomized to pidotimod (400 mg twice daily for the last 10 days of each

month for 7 months, $n = 24$) or placebo ($n = 25$). The incidence rate ratio for ARIs was 0.78 ($P = 0.211$), suggesting no significant difference in the prevention of ARIs. Rate of antibiotic prescription was lower with pidotimod than placebo (0.29 vs. 0.52). Tolerability was excellent with only one AE of urticaria in pidotimod group which resolved within 1 week of discontinuation. Although not effective in reducing ARIs in healthy children, pidotimod offers the advantage of lesser need of antibiotics.[23] A recent study by Das *et al*. on 63 children aged 2–10 years with RRIs randomized to pidotimod ($n = 43$) and placebo ($n = 20$). Dose of pidotimod was 400 mg twice daily for 15 days and once daily for 2 months. In 6-month follow-up period, pidotimod resulted in significantly lower number of recurrences in the overall study population as well as in those with existing asthma (44.2% in pidotimod and 25% in placebo groups). There were no AEs in any of the children.[24]

Del-Rio-Navarro *et al*. performed a meta-analysis of studies with immunostimulants in children (aged <18 years) with RRIs. The outcomes assessed were mean number of ARIs and percentage change in the rate of ARIs. They included 35 placebo-controlled trials enrolling 4060 participants in the meta-analyses. Compared with placebo, the use of immunostimulant reduced the total number of ARTIs (mean difference [MD] −1.24; 95% confidence interval [CI] −1.54 to −0.94) and the difference in ARTI rates (MD −38.84%; 95% CI −46.37% to −31.31%). Thus, in nearly 40% of children, the incidence rate of ARIs was reduced with the use of immunostimulant, and ARI-susceptible children can derive benefits from immunostimulant treatment.[47]

With a hypothesis that immunological alterations in Down's syndrome (DS) may predispose to different infections, some investigators conducted studies with pidotimod in these special population suffering from RRIs. La Mantia *et al*. performed a study in children with DS suffering from RRIs. The study group received pidotimod 400 mg once a day for 90 days ($n = 14$) and control group ($n = 12$) was without pidotimod. Besides reducing the frequency of RRIs (2.71 vs. 6.82, $P < 0.001$), pidotimod significantly reduced the severity and duration of infectious episodes. Pidotimod therapy was also associated with significant improvement in mucosal hyperemia, nasal secretions, and nasal respiratory obstructions. The study reported no AEs with the pidotimod treatment.[25] In another study, Zuccotti *et al*. randomized DS children aged 3–10 years with ARIs to pidotimod 400 mg once a day for 90 days ($n = 9$) or placebo ($n = 9$). All patients had received virosomal-adjuvanted influenza vaccine. Pidotimod treatment was associated with the upregulation of various genes involved in the activation of innate immune responses and in antimicrobial activity. The flu-specific IgG1 was increased, whereas IgG3 was reduced after 90 days than baseline. These results were suggestive of the stimulation of complement-dependent effector mechanisms.[26]

Asthma

Multiple studies proved the utility of pidotimod in children with asthma. Among studies included in this review, one was in asthma with RRIs and four were only in asthmatic children. In the first study, to understand whether pidotimod affects the T-cell in asthmatic children, Gourgiotis *et al*. enrolled 22 children of which 13 had atopic asthma. Peripheral blood mononuclear cells were isolated from both groups of children and were incubated and stimulated with PHA in the presence or absence of pidotimod. The only significant observation from the study was downregulation of CD30 expression on cells in both groups of children in the presence of pidotimod. CD30 is associated with Th2 lineage of T-cells, suggesting that pidotimod may affect the immune balance by promoting Th1 immune response.[27] Vargas Correa *et al*. studied 73 children aged 2–16 years with allergic rhinitis and asthma with RRIs who were treated with pidotimod 400 mg twice a day and reported a significant reduction in the mean number of acute infectious episodes than that were before treatment (5.7–4.04, $P < 0.005$). This resulted in the reduction in the number of days with infectious event from 6.10 days per patient to 4.21 days per patient ($P < 0.0001$).[28] A study from China by Ma and Sun enrolled eighty asthmatic children aged 6–12 years and randomly assigned to control group (montelukast 5 mg/day, budesonide aerosol 200 mcg per day; $n = 40$) and observation group (control + pidotimod 0.4 g per day; $n = 40$) for 30 days. Compared to control group, reduction of IL-4 and IgE levels was significant in pidotimod group. Furthermore, improvement in respiratory function assessed by forced expiratory volume (FEV_1%) and maximal peak expiratory flow (PEF%) was significant with pidotimod treatment than that of control group. These results indicate that pidotimod can potentially lower asthmatic recurrences and improve lung functions when used in addition to montelukast and inhaled steroid.[29] Zhai and Liu from China studied 100 children with asthma treated with conventional treatment ($n = 50$) and with addition of pidotimod to conventional treatment ($n = 50$) for 12 weeks. In their study, treatment with pidotimod resulted in significant increase in IgA, IgG, and IgM antibodies. Furthermore, the levels of CD3+, CD4+, CD8+, and CD4+/CD8+ cells increased significantly. The total effective rate was significantly higher in pidotimod treatment (94% vs. 72%, $P < 0.05$).[30] Sun *et al*. reported significant reduction in IL-6 levels with pidotimod treatment during relief phase (after acute phase of asthma was over) in Chinese children with asthma.[31] Another study by Ji and Liu from China compared pidotimod and montelukast (0.4 g two times/day and 10 mg/day) combination ($n = 75$) against montelukast (10 mg/day) monotherapy ($n = 75$) in children with asthma. After 3 months of treatment, total clinical efficacy rate (defined on the criteria of improvement in symptoms, FEV1% and PEF%) was significantly higher in combination treatment (94.67% vs. 81.33%, $P < 0.01$). Combination treatment was also associated with significant improvement in daytime and nocturnal cough symptom score as well as in FEV1 and

PEF rates than montelukast monotherapy. Asthma attacks were significantly lower (3.64 vs. 6.77, $P < 0.05$) and so were the number of respiratory infections (4.53 vs. 8.61, $P < 0.01$). AEs were also less in combination group (6.67% vs. 17.33%, $P < 0.05$) and were restricted to nausea and vomiting ($n = 2$ vs. 5), diarrhea ($n = 1$ vs. 2), skin rash ($n = 2$ vs. 0), and dyspepsia ($n = 0$ vs. 3).[32]

Pneumonia

We found two studies of pidotimod in children with pneumonia. The first was in children with community-acquired pneumonia (CAP) and other was with *Mycoplasma pneumoniae* pneumonia. Both studies demonstrated effective immunostimulation with pidotimod. In a study by Esposito *et al*., twenty children hospitalized for CAP were randomized to pidotimod (800 mg/day in two daily doses) plus antibiotic therapy and antibiotic therapy alone (cefotaxime [100 mg/kg/day in three daily doses, intravenous] plus clarithromycin [15 mg/kg/day in two daily doses, orally]) for 14 days' treatment. Evaluation of immunological markers was done at day 3, day 5, and day 21 of treatment. Peripheral blood mononuclear cells were isolated and were stimulated with pneumococcal polysaccharide for 18 h. The percentage of CD11c+ cells expressing HLA-DRII, CD80, or CD86 significantly increased in the pidotimod group compared to the antibiotic alone group on days 5 and 21 of therapy initiation, suggesting maturation and activation of dendritic cells. Furthermore, percentage of CD11c+ cells secreting tumor necrosis factor alpha (TNF-α) or IL-12 became higher in the pidotimod group. The activation and maturation of monocytes as suggested by CD14+ cells expressing toll-like receptor 2 (TLR2) were significantly higher in pidotimod group than that of controls. Secretion of TNF-α and IL-12 was also higher in pidotimod group. Upregulation of antibacterial response with pidotimod was evidenced by mRNA expression of antimicrobial peptides reaching peak at day 5 followed by decreased levels at day 21. Increase in mRNA was more pronounced in pidotimod group. Further, genes involved in inflammatory response were also augmented by treatment with pidotimod. This confirms that pidotimod exerts persistent immunostimulatory effects in addition to antibiotics in patients with CAP.[33] Another study in children with *M. pneumoniae* pneumonia by Ma *et al*. enrolled 35 patients. The patients received azithromycin only or azithromycin plus pidotimod for 3–5 days. Nine healthy controls were also enrolled for comparisons. Patients receiving only azithromycin had low levels of CD4+ cells and low ratio of CD4+/CD8+ cells than healthy controls. Treatment with pidotimod resulted in significant increment in the number of these cells ($P < 0.05$). This proves that pidotimod upregulates T-lymphocyte subsets that may help in early recovery from pneumonia by *M. pneumoniae*.[34]

Acute bronchitis

Children with acute bronchitis ($n = 180$) were randomized to control (pidotimod, 400 mg two times a day for 2 weeks and then 400 mg once a day for 2 months, $n = 65$) and observation (pidotimod plus montelukast, $n = 63$) groups by Wang *et al*. Addition of montelukast to pidotimod resulted in significant reduction of acute-phase proteins such as C-reactive protein (CRP), haptoglobin, a1-acid glycoprotein, cerocyanin (CER) and significant improvement in the number of CD3+, CD4+, and CD4+/CD8+ cells.[35]

Hand–foot–mouth disease

Guo and Luo enrolled children with HFM disease who were treated with ribavirin alone ($n = 84$) or ribavirin and pidotimod ($n = 78$) for 7 days. In combination treatment, significant improvement in maculopapule and herpes was reported than monotherapy treatment. Increase in CRP, IL-6, and IL-10 levels was significantly greater in combination group. On the 7th day after treatment, CD3+CD4+CD8-T cell, CD3+CD4-CD8+T cell, CD19+B cell, CD14^{high} CD16+ monocyte, and CD14^{low} CD16+ monocyte content in peripheral blood of combination group were significantly higher than those in monotherapy with ribavirin.[36]

STUDIES IN ADULTS

It is known that COPD is the chronic inflammatory state which results in lung damage. There is also immune dysfunction involving innate and adaptive immune responses, which is probably responsible for the recurrent acute infectious episodes.[48] This further compromises the lung function and adds to disease progression. Presence of chronic inflammation has proved the substantial utility of steroids in the management of COPD and bronchitis. However, risk of serious adverse effects, especially with oral steroids in the long term, may restrict their use. Thus, immune modulation with pidotimod provides an opportunity to understand its benefits in COPD. Pidotimod has shown promise in such patients. In this review, we included studies of pidotimod in adults with COPD or bronchitis, bronchiectasis, and CAP [Table 3]. Five studies included in the review highlight its efficacy in COPD and bronchitis.

Chronic bronchitis/chronic obstructive pulmonary disease

Ciaccia enrolled adults of age 45 years and above who had CB in stable phase with a history of CB for at least 5 years. Patients were randomized to pidotimod (800 mg once a day, $n = 251$) or placebo ($n = 263$) for 2 months and were followed up for an additional 3 months. Pidotimod was found to exert positive effect on exacerbation with significantly reduced number in all patients, as well as in patients who had up to three recurrences in the previous year. Time elapsed in appearance of the first exacerbation was also significantly higher in pidotimod (105 vs. 98 days, $P < 0.01$). Duration of infectious episodes was also significantly lower in pidotimod than placebo (5.6 vs. 7.8 days, $P < 0.01$). Antibiotic therapy duration ($P < 0.01$) and day of daily work activities suspended ($P < 0.05$) were significantly lesser in pidotimod than placebo. All these changes were also significant in those patients with less than three exacerbations before trial. Pidotimod was

Table 3: Summary of efficacy and safety of pidotimod in different indications among adults

Study (years)	Design	Population	Treatments	Follow-up duration	Efficacy%*	Safety
CB or COPD						
Ciaccia (1994)[49]	RCT	Adults with stable CB, 45 years and above	PD (*n*=251) versus PB (*P*=263) for 2 months	3 months	↓ Exacerbations in all patients and in those with <3 or ≥3 recurrences in previous year↓Time elapse before appearance of the first exacerbation in all patients and in those with<3 recurrences in the past↓Duration of infectious episodes↓Total days of antibiotic therapy↓Days of daily activities or work suspended in all patients and in those with <3 recurrences in the past	Well tolerates AEs: 6.1% versus 5.6%
Pozzi *et al*. (1994)[50]	RCT	Adults with CB	PD (*n*=68) versus PB (*n*=69) for 15 days	30 days	↓ Recovery time of infectious exacerbations	AEs: 6 versus 4
Bisetti *et al*. (1994)[51]	RCT	Adults with CB	PD (*n*=93) versus PB (*n*=88) for 60 days	60 days	↓ Rates of relapse during treatment and follow-up period	Well tolerated AEs: 5 versus 9
Benetti *et al*. (1994)[52]	RCT	Adults with COPD	PD versus PB for 30 days (*n*=52)	5 weeks	↑ T-cell functions: Increment in both SI ratio and SI difference determined by the mean values of spontaneous and stimulated blastogenesis	AEs: 3 versus 3
Cogo (2014)[53]	Unclear	Adults with COPD	PD versus no PD (*n*=85) for 2 months	2 months	↓ Rate of one or more exacerbations in 4 months: *n*=16 versus 29#	-
Bronchiectasis						
D'Amato *et al*. (2017)[54]	Unclear	Adults with noncystic fibrosis bronchiectasis without obstructive airflow limitation	PD versus no PD (*n*=20) for 20 days per months for 6 months	-	↑ FeNO with PD and↓without PD	-
Community-acquired pneumonia						
Trabattoni *et al*. (2017)[55]	RCT	Adults with CAP	PD + levo (*n*=9) versus levo (*n*=7) for 5 days	-	↑ Immunomodulatory proteins↑Percentage of TLR-2 and TLR-4, and of CD80- and CD86-expressing immune cells	NR
Chronic idiopathic urticaria						
Wu and Liang (2012)[56]	Unclear	Adults with chronic idiopathic urticaria	PD (DT) + fexofenadine (*n*=50) versus fexofenadine (*n*=50) for 4 weeks	-	Total effective rate: 92% versus 76%	-

*Only statistically significant findings (exceptions mentioned as nonsignificant), #Statistical significance uncertain. RCT: Randomized controlled trial, PD: Pidotimod, PB: Placebo, AEs: Adverse events, NR: Not reported, CB: Chronic bronchitis, COPD: Chronic obstructive pulmonary disease, FeNO: Exhaled nitric oxide, DT: Dispersible tablet, SI: Stimulation index, CAP: Community-acquired pneumonia, TLR: Toll-like receptor, ↑: Increase, ↓: Decreased

well tolerated with AEs in 6.1% and 5.6% of patients from the two groups, respectively. Heartburn (n = 9 vs. 6) was the most common AE observed.[49] A similar study by Pozzi *et al*. randomized patients of CB with bacterial exacerbation to pidotimod and placebo. In the first 8 days of treatment, 68 patients received 800 mg twice-daily pidotimod and 69 received placebo in addition to antibiotics. During the next 7 days, antibiotics were stopped, whereas study treatments were continued. This was followed by 30 days of follow-up. Assessments were done at baseline and at days 4, 8, 15, and 45. Significantly quicker relief of symptoms of exacerbations with lower recovery time was noted in pidotimod treatment compared to placebo (8.9 vs. 10.7 days, $P < 0.01$). Rates of AEs were low (n = 6 vs. 4).[50] In another study involving patients with exacerbation of CB, Bisetti *et al*. randomized patients to pidotimod 800 mg/day and placebo for 60 days' treatment. Patients were followed up for another 60 days. There was significant reduction in infectious relapse rates 1st (9% vs. 39.5%, $P < 0.001$) and 2nd (1.2% vs. 46.1%, $P < 0.001$) months of treatment as well in follow-up (0 vs. 50%, $P < 0.001$). Pidotimod was well tolerated.[51] In another RCT, Benneti *et al*. enrolled 52 patients with COPD who received pidotimod 800 mg twice daily and placebo for 30 days and were followed up for 5 weeks. Stimulation indexes (SIs) were used to determine the effect

on immunological parameters. SI ratio and SI difference of the mean values of spontaneous and stimulated blastogenesis were considered. Compared to placebo, pidotimod treatment resulted in significant improvement in T-cell functions, demonstrated by significant increment in both SI ratio and SI difference at day 15 and day 30. AEs were minimal and comparable (n = 3 vs. 3).[52] In a study by Cogo, 85 Italian patients with exacerbations of COPD who were subjected to influenza vaccination were randomized to receive treatment with pidotimod 800 mg/day for 15 days per month for 2 months or placebo. After treatment, patients were followed up for an additional 2 months. During the total of 4 months, one or more exacerbations were reported in 16 and 29 patients from the two groups, respectively. This may contribute to better quality of life and reduce visits to clinic.[53]

Bronchiectasis

D'Amato *et al*. enrolled twenty adult patients with noncystic fibrosis bronchiectasis in two or more lobes with a history of four or more bronchial infections without any obstructive flow limitation. The patients were randomized to receive pidotimod 800 mg once a day for 20 days per month or no pidotimod for 6 months. Exhaled nitric oxide (FeNO) was improved significantly with pidotimod and worsened without it. Furthermore, there was a significant reduction in exacerbation rate with pidotimod. The improvement in FeNO suggests that pidotimod may result in lower airway inflammation.[54]

Community-acquired pneumonia

Trabattoni *et al*. randomized 16 patients of CAP to pidotimod (800 mg twice daily), standard antibiotic (levofloxacin 500 mg BID) (n = 9), and standard antibiotic alone (n = 7). Immunological assessments performed on day 5 of treatment revealed that pidotimod addition to standard treatment upregulated antimicrobial and immunomodulatory proteins. Further, there was increase in the percentage of cells expressing molecules such as TLR2 and TLR4 and CD80 and CD86. Furthermore, a robust reduction of TNFα-producing cells was seen. There were no significant differences in the clinical parameters. These results point that pidotimod potentially modulated innate immunity against different infections.[55]

Urticaria

In China, Wu and Liang assessed the efficacy of fexofenadine and pidotimod dispersible tablets in the treatment of chronic urticaria. Among 100 patients randomized, 50 received combination treatment (800 mg once a day and 60 mg twice a day), whereas 50 received only fexofenadine. After 4 weeks of treatment, total effective rate was 92% and 76% (P < 0.05) in the two groups, respectively.[56] Thus, the study proves the efficacy of pidotimod in chronic idiopathic urticaria.

PLACE IN THERAPY

Based on the current evidence, pidotimod should be considered during acute attacks of respiratory infections in children as well as in bacterial exacerbations in adults with CB. For prophylaxis of recurrences in both age groups, pidotimod needs to be continued for at least 2 months after the acute attack. Besides reducing the rate of recurrence, pidotimod reduces the severity of infectious episodes, improves clinical features, results in rapid recovery, reduces the need for antibiotic and other symptomatic treatments, and decreases school absenteeism and visits to pediatric clinics. It improves lung function and airway epithelial clearance, suggesting its potential to lower the rates of asthma in children. Immunostimulation with pidotimod has also paved way for its use in different indications such as CAP, *M. pneumonia*, acute bronchitis, and HFM disease in children. This indicates that, in major infectious disease where there is immune dysregulation, immunostimulation with pidotimod will be useful. In adults, efficacy in reducing acute exacerbations of CB or COPD with improvement in T-cell function suggests that pidotimod should be considered in the treatment armamentarium of acute exacerbation of bronchitis and COPD. Further consideration in indications such as bronchiectasis suggests its ability to reduce the lower-airway inflammation. Thus, pidotimod can be considered in children and adults with acute and chronic respiratory conditions. Stimulation of innate and adaptive immune responses helps in reducing disease severity in acute phase, and prophylactic use can effectively reduce the recurrences.

CONCLUSION

Immune dysregulation involving innate and adaptive immune responses has been identified in a variety of diseases in children and adults. Being able to positively affect these immune responses, pidotimod proved to be effective in improving the outcomes. Current evidence convincingly established its efficacy in children with RRIs with or without asthma and in adults experiencing acute exacerbations of CB. Understanding its role in immune stimulation has led to exploration in immune dysregulation conditions such as HFM disease in children and urticaria in adults. With expanding indications of pidotimod, it may further be explored in a wide range of immunological conditions as an additional agent to conventional therapies.

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Conflicts of interest

Authors Kundan Nivangune, Snehal Muchhala, and Rishi Jain are salaried employees of the Wockhardt Ltd., Mumbai, India. Other authors declared no conflicts of interest.

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