Review Article

Review on the role of pidotimod in recurrent respiratory infections in children

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ABSTRACT

Background: Physiological immaturity of the immune system is the most common cause of recurrent respiratory infections (RRIs) in children. Drugs acting on the immunological pathways such as immunostimulants can be a very useful approach in the management of RRIs in children. Pidotimod (PDT) is an immunostimulant that acts on both innate and adaptive immunity. The immunostimulant activity of PDT has been firmly established in the management of RRIs in children with or without asthma. **Objectives:** This review was performed to summarize the available literature on the correlation of immunity and RRIs and current evidence of PDT in RRIs and pneumonia in children. **Methodology:** The literature search was performed in PubMed and Google Scholar databases using search terms such as pidotimod, children, RRIs, and pneumonia. **Results:** A total of 18 clinical studies with 10,704 children were included in this review. This includes 13 randomized controlled trials, two meta-analysis, and two observational studies. This review of current clinical evidence demonstrates that when added to the standard of care, PDT significantly reduces the number of recurrences of RRIs, severity, and duration of acute episodes in children and is safe in its prevention and treatment. This ultimately results in reduced visits to pediatric clinics and lesser absenteeism from school. It is also effective in improving the clinical outcomes in pneumonia patients. **Conclusion:** Pidotimod is effective and safe in the prevention and treatment of RRIs in children.

Key words: *Children, Pidotimod, Pneumonia, Recurrent respiratory infections*

Recurrent respiratory infections: A common occurrence in young children is of recurrent respiratory infections (RRIs). During the first 5 years of life, a child could develop 4–8 episodes of respiratory infections, which mainly affects the lower respiratory tract. There is no universal definition of RRIs and there are a lot of discrepancies about the same. Recurrence of three or more episodes of acute infections in a previous 6-month period suggests RRIs [1,2]. The most widely accepted definition is the occurrence of eight or more documented airway infections per year in pre-school-aged children (up to 3 years of age) or of 6 or more in children older than 3 years of age, in the absence of any underlying pathological condition [3]. As per one recently published Indian consensus statement, RRI should be considered in patients with three or more episodes of respiratory infection or more than 15 days of respiratory symptoms in the past 3 months [4].

Recurrent infections of the respiratory airways lead to significant morbidity and mortality among pediatric patients. Furthermore, RRIs in children warrant repeated visits to pediatric clinics and hospital admissions. Another important consequence of pediatric RRIs is the rampant and irrational use of antibiotics. Most of the respiratory infections are viral in origin and frequent irrational use of broad-spectrum antibiotics can lead to antibacterial resistance. Despite the use of antibiotics and vaccines, the incidence of RRIs is still high in children due to the deficiency of the immune system [5]. The use of immunostimulants can help to reduce RRIs and ultimately can result in better clinical outcomes [5]. There is a good amount of clinical evidence about the role of immunostimulants as an adjuvant in the prevention and treatment of respiratory diseases in children [6]. Pidotimod (PDT), an immunostimulant molecule has been studied extensively in RRIs.

METHODOLOGY

The literature search was performed using PubMed and Google Scholar databases, and search terms used were pidotimod, children, and RRIs. In additional, the Google search engine was used to identify any other studies of PDT in children. Clinical studies of PDT in the English language were included in this review. In this review, 18 studies in children were included in the study. Different indications studied in these studies were RRIs (n=16 studies) and pneumonia (n=2 studies).

Burden of RRIs

Acute respiratory infections (ARIs) are the most common cause of morbidity and mortality worldwide [7,8]. Approximately 1.3 million

children under 5 years die per year from ARIs worldwide [9]. In low-income countries, one-third of the deaths in <5 years of age, are due to ARIs [10]. According to the World Health Organization estimates, respiratory infections account for 6% of the total global burden of disease. Each year ARIs account for over 12 million hospital admissions in children <5 years worldwide [11]. In the year 2016, lower respiratory infections caused 652,572 deaths in children younger than 5 years worldwide [12].

In developing countries, every child has 5 episodes of ARI/year on an average, accounting for 30–50% of the total pediatric outpatient visits, and 20–30% of the pediatric admissions [13]. RTIs are a leading cause of childhood mortality, resulting in over 2 million deaths per year in developing countries [3]. Recent community-based estimates from the prospective study report that 70% of the childhood morbidities among children aged <5 years are due to ARI [13,14]. In India, ARIs are the most common cause of death among children <5 years [13].

Immune Dysfunction in Children with Recurrent Respiratory Tract Infections (RRTIs)

In children, immaturity in immune response involving activities of immune cells such as neutrophils, macrophage, dendritic cells (DCs), natural killer (NK) cells, B-cells, and T-cells has been observed and this contributes to RRIs in children [15].

The most common cause of RRIs in children are not severe immunodeficiency disorders, but low levels of immune parameters such as [4]: Defective phagocytosis and chemotaxis of macrophages and neutrophils, decreased toll-like receptor (TLR) function and ciliary function, and immaturity of DCs; decrease in immunoglobulins (Igs), namely, IgA, IgM, and IgG subclasses, decrease in the number of CD4+, CD8+, CD19+, and NK-cells, and alterations in the cytokine production by lymphocytes; and increased interleukin (IL) such as IL-4, IL-10, decreased interferon-gamma (IFN-γ), IL-12, and IL-2, and decreased Th1/Th2 ratio. According to a recent study in immunology, a functional disorder of Th1/Th2 cells or an immune hypofunction could result in the development of RRI in children [16].

Due to this immaturity of the immune system or reduced functioning of the immune cells, children including infants, pre-school children (3–5 years), and school-going children (5–14 years of age) are at risk of RRIs. Various studies from India also demonstrated that children <5 years of age suffer from RRI episodes up to 7–8/year until their immunity status reaches adult levels after 5 years of age. Even in school-going children, frequent RRIs were reported [4].

Risk Factors, Consequences, and Management of RRIs

In children, RRIs can be due to several risk factors like increased exposure to respiratory infectious agents during the first few years of life. This is very common, especially when the child is attending pre-school or school facilities, general immaturity of the immune system of children, environmental, and social factors, e.g., daycare attendance, family size, air pollution, and parental smoking [3].

RRIs in children can lead to the number of consequences such as frequent visits to pediatric clinics, school absenteeism, overuse of antibiotics and bacterial resistance, decreased quality of life, and economic burden on the family [3].

The children with RRIs represent a challenge to the pediatrician, both from the treatment as well as preventive aspect. Recurrence of respiratory infections can be attributed to host factors and environmental factors. Host factors may be immunological or non-immunological. Decreased immune function of the host is an important underlying factor for RRIs. Conventionally, the treatment of RRIs involves the use of antihistamines, antipyretics, and antibiotics. Recently, its prevention has gained focus as the overuse of antibiotics leads to antibiotic resistance and ineffectiveness of these medicines [17]. Drugs modulating the immune pathways are one of the new approaches in the management of RRIs in children. Immunostimulants which can stimulate both innate and adaptive immune system can be a very valuable therapeutic and preventive option in children with RRIs [3].

Pidotimod

It is a synthetic dipeptide molecule with immunostimulant properties. It acts on both innate and adaptive immunity [16]. It is indicated for treatment and prophylaxis of infections associated with immune deficiency [18].

Mechanism of Action

PDT induces the maturation of DC. These stimulated DCs further release pro-inflammatory molecules which drive T-cells proliferation and differentiation toward a Th1 phenotype [19]. Th1cells increase the activity of NK cells and promote phagocytosis. PDT directly increases levels of Th1-related cytokines and suppresses Th2 cytokines in children with frequent infections [18]. PDT also elicits adaptive immune responses by restoring the proliferative response of T lymphocytes, secretion of Th1 cytokines, and by protecting thymocytes from apoptosis. PDT upregulates the expression of TLR-2. These TLR-2s are present on airway epithelial cells. It can modulate the inflammatory cascade triggered by TLR ligands [16].

PDT improves the immunological response to inflammatory stimuli acting on different immunological pathways. There is evidence for its ability to prevent experimental viral and bacterial infections. PDT has been shown to affect cell-mediated immune responses [18].

Pharmacokinetics

PDT has an oral bioavailability of 43–45%. T_{max} is 1.5 h (range 1.3–1.8 h). The rate and extent of absorption of pidotimod are reduced significantly when given with food. Oral bioavailability is decreased up to 50% after administration with food, and peak serum levels occur up to 2 h later, compared to administration in the fasting state [18]. To optimize absorption, PDT should be given 2 h before or after meals. It has a low protein binding of 4%

with a volume of distribution of 30 L. It shows minimal hepatic metabolism. Approximately 45% of an oral dose (200–800 mg) of PDT is excreted unchanged in the urine within 24 h. The total plasma clearance after oral administration is approximately 11 L/h and elimination half-life is 4 h [18].

Indications and Usage

It is indicated as a part of treatment and prophylaxis in acute exacerbations of chronic bronchitis, RRIs such as rhinitis, sinusitis, otitis, pharyngitis, and tonsillitis. PDT has also been effective in conditions such as pneumonia and RRIs in children with Down's syndrome (DS) [18].

Dosage in Children

For 2–8 years of age: 400 mg orally twice daily for 15–20 days along with standard antibiotic therapy. The maintenance dose is 400 mg orally once daily without antibiotics for 60 days and the prophylaxis dose is 400 mg orally once daily for 60 days [18].

Clinical Evidence of PDT in RRIs

To date, numerous studies have proven the efficacy and safety of PDT in the prevention and treatment of RRIs in children [Tables 1-3]. Niu *et al*. conducted a meta-analysis of PDT randomized controlled trials (RCTs) in pediatric RRTIs to assess the effectiveness and safety of PDT in children <14 years. A total of 29 RCTs including 4344 pediatric patients were included in this meta-analysis. Ten RCTs out of 29 RCTs were from Italy, Russia, or Greece and 19 RCTs were published by Chinese groups.

Patients treated with PDT showed a significant reduction in the number of RRTIs compared with conventional treatment. PDT treatment also resulted in the remarkably reduced need for antibiotics, reduction in the duration of cough and fever, and an increase in the levels of serum Igs such as IgA, IgG, and IgM. There was no increased risk of adverse events (AEs) of any cause with the use of PDT. This recent meta-analysis concluded that PDT has good efficacy and safety in the treatment of pediatric RRTIs [20].

Acharya *et al.* conducted a study of PDT in children with RRIs. PDT was given in addition to standard of care for a period of 2 months (n=25) and follow-up was done for the next 3 months. Significant reduction in the mean number of ARI episodes (3.84±0.85 at baseline to 0.48±0.51 at follow-up, $p<0.0001$), duration of acute infectious episodes ($p<0.0001$), need of antibiotic courses ($p<0.0001$), and rates of hospitalization ($p<0.0001$) were observed. PDT was well tolerated [21].

Das *et al*. conducted a study in 63 children aged 2–10 years with RRIs. Participants were allocated to PDT (400 mg twice daily for 15 days and once daily for 2 months, n=43) and placebo (n=20) groups. All participants were followed up for 6 months. PDT resulted in a significantly lower number of recurrences in the overall study population as well as in those with existing asthma (44.2% in PDT and 25% in placebo groups). No AEs were reported in this study [22].

Walavalkar *et al*. divided 193 children aged 1–12 years, with a history of RRIs to PDT and placebo groups. PDT group received the drug 400 mg twice a day for 15 days and once a day for 30 days, (n=96) and the other group received matching placebo (n=97). All participants were followed for 6 months after the treatment. Significant improvement in clinical signs and symptoms was seen in the PDT group than the placebo group at 15 days and 45 days of assessment. Furthermore, significantly lower relapse rate was seen at 15 days (8.91% vs. 66.66%, $p<0.05$) and at 45 days (1.98% vs. 18.18%, $p<0.05$) assessments but non-significantly lower in 6-month follow up period (7% vs. 10%). Overall efficacy and safety rating by physicians and patients was excellent for PDT as compared to placebo (79.2% vs. 16.2% and 77.2% vs. 18.2%, respectively) [23].

Namazova-Baranova *et al*. performed a study in children aged 3–6 years with RRIs and randomized to PDT (400 mg once a day for 30 days, n=78) and control (antibiotic therapy, n=79) groups. Incidence of ARIs was significantly reduced at 1 (25.6% vs. 55.7%), 2 (33.3% vs. 77.2%), and 3 (64.1% vs. 98.7%) months of treatment. At the end of 6 month's treatment, 92.3% and 100.0% of patients from the two groups had developed ARI episodes. PDT also reduced the severity of ARIs as evidenced by a lesser number of moderate episodes (16.6% vs. 44.3%) and milder episodes (82.1% vs. 55.7%). IgE levels were decreased by 25.3% and 53.8% of patients from the two groups, respectively. Furthermore, PDT switched the immune response to Th1 type. Levels of IL-8 were significantly reduced with PDT at 3 months [24].

Licari *et al*. randomized children aged 3–10 years with RRIs to PDT 400 mg once a day for 60 days plus antibiotic and supportive treatment (n=45) and control (antibiotic and supportive treatment without PDT) (n=44) groups. All participants were followed up for 2 months. Significant improvement in upper and lower airway symptoms at day 30 and day 60 was seen in children who received PDT as compared to the control group. Furthermore, the number of children who required other rescue medications was significantly lower with PDT. School absenteeism and visits to pediatric clinics for RRIs were also reduced in the PDT group. There were no significant AEs reported in this study [25].

Del-Rio-Navarro *et al*. conducted a meta-analysis of studies of immunostimulants in children (age <18 years) with RRIs. The outcomes assessed were the mean number of ARIs and the percentage change in the rate of ARIs. It included a total of 35 placebo-controlled trials consisting of 4060 participants in the meta-analyses. Immunostimulant reduced the total numbers of acute respiratory tract infections (ARTIs) (mean difference [MD] −1.24; 95% confidence interval [CI] −1.54 –−0.94) and the difference in ARTI rates (MD −38.84%; 95% CI −46.37% –−31.31%) versus placebo. This confirms that the use of immunostimulants reduces ARIs incidence rate [26].

Aivazis *et al*. performed a study in children aged 2.5–12 years with RRIs. One group received treatment with PDT (400 mg twice daily for 15 days followed by once daily for 20 days, n=15) and the other group received broad-spectrum antibiotics without PDT (n=32). All participants were followed up for 9 months. Two or fewer recurrences were reported in 87.5% of children in the PDT

Table 1: Clinical studies of PDT in children with RRIs

Study (year)	Study design	Study population	Treatments	Follow-up duration	Efficacy%*	Safety
Acharya *et al.* [21]	Observational study	Children with RRIs, 2–15 years	Pidotimod in addition to standard of care (n=25)	3 months	↓Number of RRI episodes, duration of acute episodes, antibiotic course, and hospitalization	Well tolerated
Das *et al*. [22]	RCT	Children with RRIs, 2–10 years	PDT (n=43) versus placebo (n=20), for 75 day	6 months	↓RRI episodes in all children ↓Recurrences in asthmatic children	None
Walavalkar *et al*. [23]	RCT	Children with RRI, 1–12 years	Treatment: PDT (n=96) versus placebo (n=97) 15 day; Maintenance: PDT 30 day	6 months	Improvement in clinical symptoms ↓Relapse rate at 15 and 45 day of treatment	Good tolerability AEs: 2 versus 1
Namazova-Baranova *et al*. [24]	RCT	Children with RRI, 3–6 years	PDT (n=78) versus control (n=79) for 30 days	6 months	↓Incidence of ARIs at 1, 2 and 3 month ARI in total 6 month: 92.3% versus 100% ↓IgE, IL-8 at 3 month	NR
Licari *et al*. [25]	RCT	Children with RRI, 3–10 years	PDT (n=50) versus placebo (n=50) for 60 days	2 months	↓Number of children with respiratory symptoms, drug use, pediatric visits and school absenteeism	NR
Aivazis *et al*. [27]	RCT	Children with RRI, 2.5–12 years	PDT (n=32) versus no PDT (n=18)	9 months	≤2 recurrence: 87.5 versus 33.3% Clearance time of respiratory epithelium after 6 m reduced from 37 to 19.5 min	NR
Careddu (2014) [28]	RCT	Children with RRI, 3–14 years	PDT (n=309) versus placebo (n=327) for 60 day	90 days	↓RRI incidence, symptoms school abstinence, and need for antibiotics	Well tolerated AEs
Yue and Yu, 2017 [29]	RCT	Children with RRI	PDT versus spleen aminopeptide (n=86) for 3 month	-	↓Duration of symptoms	-
Passali *et al*. [30]	RCT	Children with RRI, 3–14 years	PDT (n=205) versus placebo (n=211) for 60 day	90 days	↓Duration and frequency of RRIs, fever, severity of symptoms, antibiotics, and school absenteeism	Excellent safety
Caramia *et al*. [31]	RCT	Children with RRI, 2–8 years	PDT (n=60) versus placebo (n=60) for 75 day	-	Normalization of chemotaxis and leukocyte phagocytosis index, ↓Risk of relapses, hospitalization, antibiotics	Well tolerated AEs: 5 versus 7
Burgio *et al*. [32]	RCT	Children with RRI, 2–13 years	PDT (n=52) versus placebo (n=49) for 60 days	60 days	↓Symptoms, cells with CD25+expression	Excellent safety
Motta *et al*. [33]	RCT	Children with recurrent tonsillitis, 3–14 years	PDT (n=177) versus placebo (n=118) for 75 days	90 days	↓Inflammatory episodes, clinical symptoms antibiotic use, absenteeism from school	Excellent safety

***Only statistically significant findings (exceptions mentioned as nonsignificant), RCT: Randomized controlled trial, PDT: Pidotimod, AEs: Adverse events, NR: Not reported, RRI: Recurrent respiratory infection, ARIs: Acute respiratory infections**

Table 2: Clinical studies of PDT in RRIs in children with DS

Study (year)	Study design	Study population	Treatment	Efficacy%*
La Mantia *et al*. [34]	Observational study	DS and RRI, 3–13 years	PDT (n=14) versus control (n=12) for 90 days	↓Frequency, severity and duration of infectious episodes, ↓Mucosal hyperemia, nasal secretions and obstructions
Zuccotti and Mameli [35]	RCT	DS and ARIs, virosomal-adjuvanted influenza vaccine administered in all, 3–10 year	PDT (n=9) versus placebo (n=9) for 90 days	Upregulation of genes involved in activation of innate immunity and antimicrobial activity, increment in flu-specific IgG1/G3 suggesting activation of complement-dependent mechanism

***Only statistically significant findings (exceptions mentioned as non-significant), RCT: Randomized controlled trial, PDT: Pidotimod, AEs: Adverse events, NR: Not reported, DS: Down's syndrome, RRI: Recurrent respiratory infection, ARIs: Acute respiratory infections, Ig: Immunoglobulin**

Table 3: Clinical studies of pidotimod in RRIs in children with pneumonia

Study (year)	Study design	Study population	Treatment	Follow-up	Efficacy%*
Esposito *et al.* [36]	RCT	Children with CAP, 3–14 years	PDT+antibiotics (n=10) versus antibiotics (n=10) for 14 d	7 days	↑DC expressing activation and costimulatory molecules, ↑TNF-α and IL-12 secretion, ↑Release of pro-inflammatory cytokines from monocytes, ↑TLR-2 expression in CD14+cells
Hong-Qiu *et al.* [37]	Unclear	Children with *Mycoplasma pneumoniae* pneumonia	PDT versus general therapy (n=35) for 3–5 d	-	↑Number of CD4+ cells, ↑ and CD4+/CD8+ ratio

***Only statistically significant findings (exceptions mentioned as nonsignificant). RCT: Randomized controlled trial, PDT: Pidotimod, CAP: Community-acquired pneumonia, DC: Dendritic cell, TNF-α: Tumor necrosis factor-alpha, IL: Interleukin, TLR: Toll-like receptor**

group whereas three or more recurrences seen in 33.3% children in the control group in 9 months follow-up period ($p<0.0001$). Mucociliary clearance time of respiratory epithelium decreased significantly with PDT (from 37–19.5 min, $p<0.001$) than the control group (from 36.4–31 min, $p>0.05$) at 6 months follow up. This improved functioning ciliary epithelium contributes to improved clinical outcomes in RRIs [27].

Careddu conducted a study in 671 children (3–14 years) with RRI. PDT (n=329) significantly reduced number of RRI episodes (no episodes: 55.3% vs. 34.8%, $p<0.01$) compared to placebo (n=342). Furthermore, PDT significantly reduced associated clinical signs and symptoms, school absenteeism, use of antibiotics, and other treatments. The study population was followed up for 3 months after completion of therapy. During the follow-up period too, PDT group reported a significantly fewer number of recurrences. Both treatments were well tolerated (number of patients with AEs: 22 vs. 15) [28].

Yue and Yu did a comparative study of PDT with spleen aminopeptide in 86 children with RRIs for 3 months. PDT significantly improved clinical symptoms and decreased its duration. Furthermore, the levels of IL-4 and IFN-γ were significantly improved with PDT than control [29]. Passali *et al*. conducted a study on 416 children with RRIs. Treatment with PDT (n=205) and placebo (n=211) was given for 60 days and then followed up for 3 months. The recurrence rate was significantly lower in PDT group than placebo (56.1% vs. 68.8%, $p=0.014$). The median time for relapse was greater in PDT than placebo (48 vs. 24 days) groups. Similarly, a significant reduction in clinical signs and symptoms and use of antibiotics were observed with PDT with an excellent safety profile [30].

Caramia *et al*. conducted RCT in 120 children with RRIs. PDT 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 quicker recovery (10.8 vs. 13 days, 2.2 days, $p<0.01$), shorter duration of antibiotics (7.6 vs. 10 days, $p<0.01$) and hospitalization (6.4 vs. 8.5 days, $p<0.01$), and clinical signs and symptoms as compared to placebo (n=60). Furthermore, the normalization of chemotaxis and leukocyte phagocytosis index was observed which indicates improved immune response by PDT. A significant decrease in relapse rate (39 vs. 60, 35% reduction, $p<0.05$) was observed and it was well tolerated [31].

Similarly, Burgio *et al*. performed a study of 101 children aged 2–13 years with RRI. Treatment given was either PDT or placebo for 60 days and followed for 60 more days. PDT treatment resulted in a significant reduction in clinical features of both lower and upper respiratory infections ($p<0.05$). During follow-up, only 16% and 18% of patients in PDT presented with lower and upper respiratory symptoms than 42.5% and 62.5% of patients in placebo group ($p<0.05$). Further, the need for antibiotics and supportive treatment and medical assistance was significantly reduced. PDT was well tolerated in the study. Immunological assay with phytohemagglutinin stimulation in 18 patients has shown that PDT significantly increased cells with expression of CD25+ (7 out of 8) than placebo (3 out of 10) (88% vs. 30%, $p<0.05$) [32].

Motta *et al*. randomized 235 children (3–14 years) with recurrent tonsillitis to PDT or placebo group. Treatment was given for 75 days and all participants were followed up for the next 90 days. Numbers of inflammatory upper airway episodes were significantly reduced during treatment as well as follow-up period. One, two, three, and four episodes or recurrences were seen in 35.7%, 21.4%, 8.9%, and 0.9% patients in PDT group and in 20.7%, 24.3%, 17.1%, and 9.9% in placebo group, respectively ($p<0.001$). It was observed that the median time for the appearance of the first relapse was higher in PDT than in the placebo group (41 vs. 24 days). PDT group reported a significant reduction in clinical signs and symptoms, antibiotic usage, and school absenteeism with an excellent safety [33].

DS is characterized by alterations in immune functions, which makes these children more susceptible to different infections. To test this hypothesis, some investigators conducted studies with PDT in children with DS suffering from RRIs. La Mantia *et al*. conducted a study in children with DS suffering from RRIs. One group received PDT 400 mg once a day for 90 days (n=14) and the control group (n=12) did not receive PDT. It significantly reduced the frequency of RRIs (2.71 vs. 6.82, $p<0.001$), severity, and duration of infectious episodes. Furthermore, there was a significant improvement in mucosal hyperemia, nasal secretions, and nasal respiratory obstructions with PDT therapy. There were no AEs with the PDT treatment [34].

Another study by Zuccotti and Mameli enrolled DS children aged 3–10 years with ARIs to PDT 400 mg once a day for 90 days (n=9) or placebo (n=9). The upregulation of genes involved in the activation of innate immune responses and in antimicrobial activity was observed with PDT treatment. In additional, flu-specific IgG1 was increased whereas levels of IgG3 were reduced

after 90 days of treatment with PDT. These results suggest that PDT stimulates complement-dependent effects or mechanisms [35].

Esposito *et al*. randomized 20 children with community-acquired pneumonia (CAP) into two groups. One group received antibiotic therapy plus PDT (800 mg/d in twice daily) and other group received standard antibiotic therapy alone for 14 days. The levels of tumor necrosis factor-alpha and/or IL-12 and expression of TLR-2 were significantly increased in PDT group as compared to controls. The study concluded that PDT has immunomodulatory effects in children with CAP when administered along with antibiotics [36].

Hong-Qiu *et al*. conducted a study in 35 children with *Mycoplasma pneumoniae* pneumonia divided into two groups. One group received azithromycin only and the other group received azithromycin plus PDT for 3–5 days. Nine healthy controls were also enrolled for comparisons. Azithromycin group had low levels of CD4+ cells and a low ratio of CD4+/CD8+ cells than healthy controls. PDT group demonstrated a significant increase in the number of CD4+ cells ($p<0.05$). This study concluded that PDT upregulates T-lymphocyte subsets which may help in early recovery from *M. pneumoniae* pneumonia [37].

Recently, Shi *et al*. conducted one study of PDT in children with *M. pneumonia*. Of 149 children, 79 were treated with PDT and azithromycin, and 70 controls were treated with azithromycin sequential therapy. After treatment, serum IL-10 and granulocyte colony-stimulating factor (G-CSF) levels were significantly lower in cases than in controls. Furthermore, a significant positive correlation was observed between IL-10 and G-CSF levels before and after treatment in PDT group ($p<0.05$), and a significant positive correlation between expression levels of IL-10 and G-CSF before and after treatment in the control group ($p<0.05$). Improved curative effect and reduced occurrence of adverse reactions were observed in the observation group as compared to the control group [38].

Place in Therapy

Current clinical evidence of PDT in the treatment and prevention of RRIs in children is very robust and it suggests that PDT is an effective and safe treatment strategy in the management of RRIs. Compliance with recommended therapy of PDT for a period of 2 months is essential for the prevention of further episodes of RRIs. It not only reduces the RRIs but it also reduces the duration of cough and fever and also the need for antibiotic therapy. PDT therapy results in faster recovery and reduces school absenteeism. Reduced antibiotic usage can further help to prevent the problem of antibiotic resistance in RRI management. PDT improves immune function in children with immune dysfunction or physiological immaturity of the immune system and reduces RRIs. Thus, PDT can be a very good treatment option along with the standard of care in RRI patients.

CONCLUSION

PDT acts on both innate and adaptive immune systems and improves the overall functioning of the immune system. It is safe and effective in the treatment and prevention of RRIs in children. Available clinical evidence strongly supports its use in the management of RRIs in children.

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