Review

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Pidotimod in pediatrics: new evidence and future perspectives

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ABSTRACT

Abstract: Pidotimod is a synthetic dipeptide that exerts immunomodulatory activity, modifying innate and adaptive immunity. Pidotimod firstly acts on Toll-like receptors, then on antigen-presenting cells and other immunocompetent cells. Pidotimod also affects immunoglobulin production and their switching. Evidence shows that pidotimod effectively and safely prevents respiratory infections, mainly in children with recurrent and frequent infectious episodes. In addition, pidotimod may be helpful as an add-on strategy in managing children with infections. Finally, there is evidence that pidotimod, thanks to its immunomodulatory activity and preventing respiratory infections (the main trigger for asthma exacerbation), may be beneficial in managing subjects with asthma and allergic diseases. The present review presents and discusses the most recent studies conducted in children with asthma, allergic rhinitis, recurrent respiratory infections and acute infections. Lastly, pidotimod is safe and well-tolerated in children.

Key words: add-on strategy, allergy, asthma, pidotimod, respiratory infections

Introduction

Allergic diseases, mainly concerning allergic rhinitis and asthma, and infections represent the most common medical conditions in childhood [1, 2].

Pediatric asthma is eminently recognized as a type 2 immunity, as most children with asthma are allergic [3]. Type 2 immune response derives from a functional and specific defect of immune regulation [4]. As a result, an expansion of type 2 immunocompetent cells occurs that promotes eosinophilic inflammation [5]. Moreover, allergic patients are prone to frequent infections as type 1 immunity (which defends against infections) is defective [6]. Therefore, a vicious cycle is created among altered immunity, allergies, inflammation, asthma and infections [7]. The last aspect is particularly relevant as most asthma exacerbations in children are preceded by an acute respiratory infection [8].

It has to be underscored that allergy is a state of hyperactivation of the immune system. Namely, allergic patients typically present with T and B helper cell expansion and activation, hyperproduction of immunoglobulin E (IgE), and proliferation of inflammatory cells [9].

On the other hand, infections are associated with immune response and inflammation [10]. Immune response to infections includes innate and adaptive immunity. However, defective immunity leads to frequent and severe infections, a typical characteristic shared by those from the extremes of life, namely childhood and senescence [11]. In other words, infancy and early childhood may be envisaged as "physiologic immunodeficiency" [12]. In addition, response to vaccinations is inadequate

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Authors' contributions: All authors contributed to the study conception and design. The first draft of the manuscript was written by Giorgio Ciprandi. Gian Luigi Marseglia commented and discussed the draft. All authors read and approved the final version of the manuscript.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

Acknowledgments: The authors would like to thank Carmen Innes who edited the manuscript before submission. The English editing and the publication costs were funded by unconditioned grant by Neopharmed Gentili SpA (Italy).

in these age groups because the immune system cannot mount an effective response to vaccines [13].

The practical consequence of these conditions is the compelling demand for compounds able to modulate immune response, such as immunoregulators. The class of immunoregulators includes many compounds (pharmacological and non-pharmacological) acting on the different steps of immune response to allergens and/or pathogens [7,14,15]. Notably, the coronavirus disease of 2019 (COVID-19) era significantly affected the need for suitable immunoregulators to prevent or sustain standard therapy for the infection [16,17].

In this regard, pidotimod is an effective and safe immunoregulator, as documented by several reviews [18-25]. As a recent in-depth review excellently reported the studies concerning pidotimod use in children [26], the present review presents and discusses the most recent evidence on this issue and proposes future perspectives in this field.

Pidotimod: pharmacological characteristics

Pidotimod is a synthetic dipeptide (3-L-pyroglutamyl-L-thiaziolidine-4 carboxylic acid), as represented in Figure 1.

Pidotimod was introduced in 1983, firstly in Italy and successively worldwide in many countries. Pidotimod has been approved as an immunomodulatory agent for treating respiratory and urinary infections in children (over 3 years of age) with weak immune responses [27]. Presently, pidotimod is available as an oral formulation. The recommended dosage for treating acute respiratory infections is 400 mg twice daily for 15–20 days as an add-on to standard therapies. For prevention, the proposed dose is 400 mg once daily for 60 days. As pidotimod exerts many immunoregulatory activities [28], it has also been suggested to manage children with asthma [29].

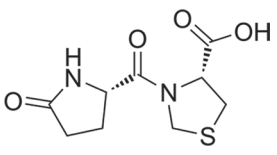

Figure 1. Chemical formula of pidotimod.

The pharmacokinetics of pidotimod are characterized by rapid absorption after oral ingestion, and the oral bioavailability is 43%-45% [30]. Food significantly diminishes the quality and quantity of pidotimod absorption. Accordingly, fasting doubles pharmacokinetics parameters of pidotimod. Therefore, optimal absorption requires administration 2 hours before or 2 hours after meals [26]. Hepatic metabolism is minimal; pidotimod is renally excreted unchanged [31].

Pidotimod has a very low acute toxicity: the intravenous (i.v.) 50% lethal dose (LD50) is > 4000 mg/kg in mice, >4000 mg/kg in rats, and >2000 mg/kg in dogs [32]. Chronic toxicity studies conducted in rats and dogs by the oral and parenteral routes with up to 6 months' treatment have shown no toxic effects up to 40–50 times the maximum therapeutic dose per kg per day. Pidotimod is not mutagenic or teratogenic in the rat and rabbit, and does not alter male and female fertility or have any peri- or post-natal toxicity in the rat [32].

Pidotimod: immunological effects

Pidotimod affects the innate and adaptive immune response, acting on multiple targets, including maturation of dendritic cells, upregulation of HLA-DR expression, modulation of co-stimulatory molecules (i.e. CD83 and CD86), T helper 1 expansion, down-regulation of T helper 2 polarization, promotion of phagocytosis, stimulation of natural killer cells, upregulation of Toll-like receptor (TLR) expression and promotion of secretory IgA (sIgA) production [33,34]. Detailed information on immunological activities provided by pidotimod has been extensively reported in previous reviews [20,21,23,25]. A schematic representation of the multifaceted effects on the immune system is shown in Figure 2. Pidotimod firstly acts on the main switcher of the innate immune response, such as the TLR machinery [23]. This stimulatory effect activates the immune response to antigens working on antigen-presenting cells. These effects provide an orientation of immunity towards a type 1 response [23], such as the physiological balance for fighting infections. In addition, type 1 polarization downregulates type 2 immunity and dampens eosinophilic inflammation.

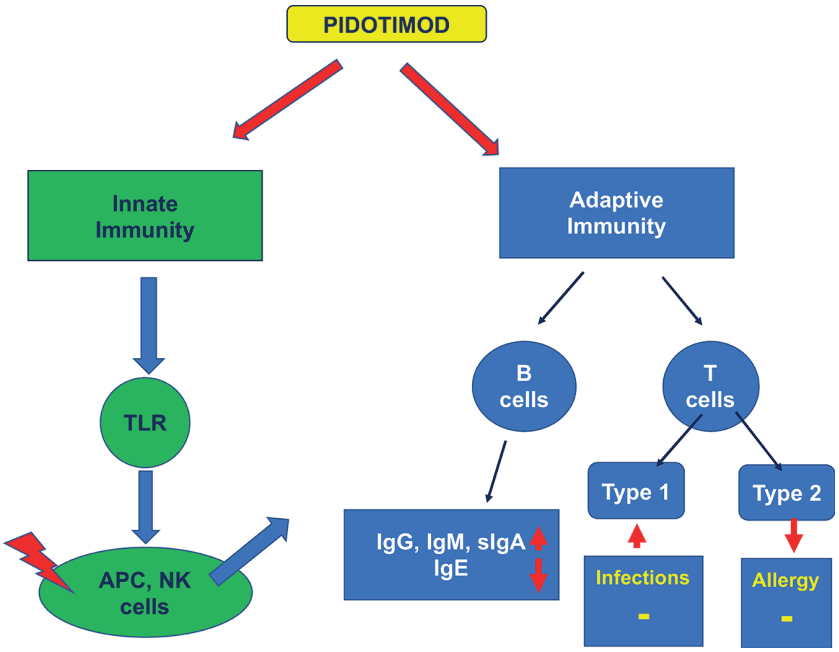

Figure 2. Schematic representation of the main immunological effects provided by pidotimod. APC, antigen presenting cells; Ig, immunoglobulin; NK, natural killer; sIg, secretory immunoglobulin; TLR, Toll-like receptor.

Interestingly, as allergy is associated with defective type 1 immunity, pidotimod restores a physiological immune response to pathogens [23]. Moreover, pidotimod stimulates the production of sIgA [23], such as the humoral counterpart of the immune response present on the mucosal surface. Namely, sIgA varnishes the respiratory tract, preventing pathogens' attachment to airway mucosa [35].

This schematic scenario supports the use of pidotimod for the prevention and treatment of infectious diseases and for immunomodulation in type 2 disorders, such as allergy and asthma, as represented in Figure 2.

This rationale has been substantiated by the number of studies conducted. This review discusses the most recent evidence (i.e. published successively to Mahashur's review concerning the effects of pidotimod in the model of type 2 disorders and infections) [26].

Pidotimod evidence in asthma and allergy

Recent evidence of pidotimod effects on type 2 disorders in children includes two studies: the first conducted in patients with asthma [36] and the second in children with allergic rhinitis [37], as summarized in Table 1.

Deglurkar and colleagues conducted a triple-blinded, randomized trial to investigate whether pidotimod add-on to inhaled corticosteroids (ICS) improved asthma control in children with persistent asthma, compared with ICS alone [36]. The study included 79 children (5-12 years) with newly diagnosed persistent asthma according to the Global Initiative for Asthma (GINA) guidelines. Children took either pidotimod (n=39) or placebo (n=40), initially 7 mL twice a day for 15 days and a further 7 mL once daily for 45 days. Both groups received inhaled budesonide using a metered dose inhaler and spacer for 60 days. Children were monitored every 4 weeks for 12 weeks in total. Data concerning peak expiratory flow (PEF), asthma symptom score and adverse reactions were collected during each visit. The primary outcome was the PEF change after 12 weeks; secondary outcomes included PEF value at each visit, asthma symptom score at each visit, asthma symptom score changes over time, and safety. The results showed

Table 1. Summary of recent evidence on efficacy and safety of pidotimod in asthma and allergic rhinitis in children.

Study	Design	Disease	Population	Treatment	Follow up	Efficacy	Safety
Deglurkar [36]	RCT	Asthma	79 children 39 Pidotimod 40 Placebo	7 mL twice daily × 15 days 7 mL once daily × 45 days	12 weeks	- PEF = Placebo - Symptoms = Placebo	Mild AR
Brindisi [37]	Pilot controlled open	AR/AH	76 children 57 ended Pidotimod for all	1 vial daily × 30 days	No	- Rhinomanometry = improved - Nasal symptoms = unchanged - Nasal microbioma = unchanged	ND

AH, adenoid hypertrophy; AR, allergic rhinitis; ND, not done; PEF, peak expiratory flow; RCT, randomized controlled trial.

that the 8-week pidotimod add-on did not improve asthma control. The authors declared two main limitations of the study: the short pidotimod course and the lack of objective lung function assessment. Moreover, this trial did not assess the asthma control level and biological variables [36]. The findings of this trial conflicted with outcomes reported by a recent narrative review (including four studies on asthma), suggesting that pidotimod may decrease some type 2 biomarkers (i.e. interleukin-4 [IL-4] and IgE) and improve lung function, such as increasing forced expiratory volume in 1 second (FEV_1) and PEF [26].

An Italian study evaluated the efficacy of pidotimod on nasal obstruction in children with allergic rhinitis and/or adenoidal hypertrophy [37]. The study also investigated whether pidotimod could affect nasal microbiota. The study included 76 children (aged 6–12 years) subdivided into four groups: i) children with allergic rhinitis; ii) children with adenoidal hypertrophy; iii) children with allergic rhinitis plus adenoidal hypertrophy; and iv) children without allergic rhinitis and adenoidal hypertrophy, who were considered as controls. Nasal fiberoptic endoscopy, anterior rhinomanometry and nasal swabs were performed at baseline and study end. A nasal symptom score was also measured using a 4-point scale (i.e. 0–3). Children with nasal obstruction (i.e. the allergic rhinitis, adenoidal hypertrophy and allergic rhinitis/adenoidal hypertrophy groups) started pidotimod treatment (1 vial daily for 30 days). The primary outcome was nasal obstruction assessment after treatment. Secondary outcomes included nasal symptoms and nasal microbiota changes. Pidotimod treatment significantly reduced nasal obstruction, measured by rhinomanometry ($p<0.001$). However, nasal symptoms and microbiota did not change [37].

On the other hand, it has to be noted that systemic and/or local corticosteroids and antihistamines or any other therapy in the last 4 weeks were not permitted during the study. These results were consistent with a recent study enrolling children with asthma and allergic rhinitis treated with allergen immunotherapy [38]. Children receiving pidotimod add-on to immunotherapy reported improved respiratory parameters and immunological biomarkers; consequently, pidotimod restored a physiological balance between type 1 and 2 immunity. Therefore, the Italian study provided evidence that pidotimod *per se* was able to affect nasal obstruction [37]. In this regard, it has to be considered that nasal obstruction reflects type 2 inflammation in children with allergic rhinitis [39]. As a result, this study indirectly supports the concept that pidotimod could affect type 2 inflammation by improving nasal obstruction. On the other hand, the findings of this pilot study require confirmatory trials, conducted with a robust methodology.

Pidotimod evidence in respiratory infections

Pidotimod has been extensively investigated in patients with frequent respiratory infections. As pidotimod positively modulates immune response toward a reinforced type 1 profile, many studies evaluated its

preventive and add-on activity in managing patients with defective immune responses due to an immature immune system (early childhood) or primitive or secondary immunodeficiency. Currently, children with recurrent respiratory infections (RRI) represent an ideal model for investigating the immunomodulatory activity provided by pidotimod. However, the definition of RRI is still controversial as precise criteria (based on a biostatistical background) still need to be defined. Italian studies used criteria to include children in RRI diagnosis, eminently based on expert opinion [40]. Also, a recent revision of these criteria did not consider a correct biostatistical approach based on the percentile incidence of respiratory infections [41]. Apart from this methodological consideration, the RRI model nevertheless represents an important scenario for evaluating the immunomodulating efficacy of pidotimod both because of its underlying immunopathological basis and the high prevalence of this medical condition.

Two types of intervention have been performed with pidotimod: as a preventive in children with RRI and as an add-on in children with acute respiratory infection.

Prevention of RRI

In this regard, Bozzetto and coworkers used metabolomics to evaluate the effects of pidotimod on children with RRI [42]. Metabolomics, a primary discipline of systems biology, is a high-dimensional method for biomarker profiling without needing to pre-define any particular hypothesis. Metabolomics simultaneously measures a broad number of metabolites and, thanks to bioinformatics, may generate a metabolite profile that identifies different "metabolomic-types" with specific pathophysiological characteristics [43]. Thus, metabolomics gives a complete snapshot of all the biochemical processes involved in a disease. Therefore, in the RRI context, metabolomics provides relevant information. A pilot study aimed to compare the metabolomic analysis of urine samples from 13 RRI children with 15 healthy children before and after a 3-month pidotimod treatment [42]. The results showed a significant difference between groups ($R2=0.92$, $Q2_{CV7\text{-}fold}=0.75$, $p<0.001$) at baseline. After pidotimod treatment, the metabolomic profile resembled that of healthy children apart from microbiome-related metabolites. As a result, the authors concluded that, as pidotimod did not affect gut microbiota, a possible synergic effect combining immunomodulating agents with probiotics is conceivable [42].

Li and colleagues performed a study to evaluate pidotimod's clinical and immunological effect in 132 children (aged 5–14 years) with RRI [44]. Patients were subdivided into two groups: 66 children took pidotimod oral solution (initially 400 mg twice a day for 2 weeks; then 400 mg, once a day, for 6 weeks) plus standard therapy for infections, and the other 66 children had standard treatment for infections alone. The parameters included clinical outcomes (fever, pulmonary rales, cough and tonsil swelling), duration of infection and antibiotic use. In addition, the study investigated the serum level of tumor necrosis factor (TNF)-α, procalcitonin, interferon (IFN)-γ, and IL-4. After 1 week, TNF-α and IL-4 decreased, whereas IFN-γ increased more significantly in the active group ($p<0.05$). Consistently, clinical parameters were better in the active group ($p<0.05$). Therefore, the authors concluded that pidotimod could efficaciously control infectious symptoms and re-balance the type 1 and 2 ratio.

A further Italian study compared the effects of pidotimod with a probiotic mixture on RRI morbidity and urine metabolomics in preschoolers [45]. The study was a four-arm, exploratory, prospective, randomized, double-blinded and placebo-controlled trial that included 55 children (aged 3–6 years), stratified into four groups: i) A (the pidotimod + bifidobacterial group), who received pidotimod as a liquid suspension in 400 mg vial (one vial/day) + bifidobacteria mixture (*Bifidobacterium longum* BB536 [3×109 CFU], *B. infantis* M-63 [1x109 CFU] and *B. breve* M-16 V [1x109 CFU]) as powder in a 3-g sachet (one sachet/day); ii) B (the pidotimod group), who received pidotimod as a liquid suspension 400 mg vial (one vial/day) + an identical-looking and -tasting placebo of bifidobacteria mixture (one sachet/day); iii) C (the bifidobacteria group), who received an identical-looking and -tasting pidotimod placebo as a liquid suspension (one vial/day) + the bifidobacteria mixture (one

sachet/day); iv) D (the placebo group), who received identical-looking and -tasting placebos of pidotimod and bifidobacteria mixture at same posology. Patients received treatments for the first 10 days each month for 4 months. There was a 2-month follow up further. Pidotimod, alone or with probiotics, resulted in more symptom-free days (69 vs 44 days, p=0.003; and 65 vs 44 days, p=0.02, respectively) and a lower percentage of days with a common cold (17% vs 37%, p=0.005; and 15% vs 37%, p=0.004, respectively). Considering metabolomics, pidotimod (alone or in combination with bifidobacteria) provided a biochemical profile characterized by compounds related to the pathway of steroid hormones, hippuric acid, and tryptophan. Probiotics alone did not affect the metabolic profile [45].

Valentini and colleagues explored the possible pidotimod effects on RRI in a selected pediatric population of children with Down syndrome [46]. This model is attractive as children with Down syndrome exhibit raised susceptibility to contract frequent infections due to a defective immune response and airway anomalies [47]. Thus, pidotimod could be an ideal candidate to prevent the potential recurrence of infection. In this regard, a previous systematic review analyzed five randomized controlled studies on managing respiratory tract infections in Down syndrome [21]. One study in this review showed that pidotimod significantly reduced upper respiratory infections compared with no treatment (1.43 vs 3.82 infectious episodes) [21]. The retrospective study performed by Valentini included 33 children (mean age 6 years) [46]. Recruited children took pidotimod (400 mg daily) 20 days/month for 6 months. Clinical and immunological parameters were evaluated throughout the study. Pidotimod reduced the number of children with upper and lower respiratory infections and admissions for respiratory infections. In addition, pidotimod significantly increased B cell *in vitro* proliferation, peripheral B cell frequency, and serum IgM level [47].

A recent Chinese randomized trial compared the efficacy and safety of the traditional Chinese medicine Yupingfeng with pidotimod [48]. This study was conducted as a multicenter, randomized, double-blind, double-simulation and noninferiority clinical trial. The active treatment lasted 8 weeks, followed by a 52-week follow up. Oral pidotimod was administered at 400 mg once daily, 1 hour after dinner, for 8 weeks. Yupingfeng granules were prescribed at 2.5 g in children aged 2–3 years or at 5 g in children aged 4–6 years, once in the morning and once in the evening, for 8 weeks. The primary outcome was the reduction of RRI episodes until the standard level was reached throughout the follow up. Secondary outcomes included the number of RRI, symptom severity and safety. Both active treatments significantly reduced the RRI number compared to placebo (p<0.0001) [48].

These studies are summarized in Table 2.

Moreover, as preventing RRI is a compelling task in clinical practice, a recent meta-analysis evaluated 29 randomized controlled trials using pidotimod to prevent RRI [49]. Notably, 19 trials were performed in China, whereas 10 were derived from Italy, Russia or Greece. However, only 15 studies complied with the correct methodology. The meta-analysis demonstrated that pidotimod significantly reduced the number of children with lower respiratory tract infections (relative risk [RR] 1.59; 95% confidence interval [CI] 1.45–1.74, p<0.00001). In addition, pidotimod significantly diminished the duration of cough and fever and antibiotic use. From an immunological point of view, pidotimod increased serum IgG, IgA and IgM levels and CD3+ and CD4+ cells. Pidotimod was also associated with few adverse reactions (RR 1.05, 95% CI 0.72–1.54, p=0.80) [49]. However, the authors underlined the need for further studies with robust methodology to confirm the current evidence.

Finally, a recent cost-utility analysis investigated the ability of pidotimod to decrease RRI probability in children [50]. The decision tree model demonstrated that pidotimod could be a cost-effective option for reducing the incidence of RRI in children.

Add-on treatment

A Chinese study investigated the use of pidotimod combined with azithromycin in 149 children with *Mycoplasma pneumoniae* pneumonia [51]. All children were treated with i.v. azithromycin (10 mg/kg/day) for 3–5 days. This course was stopped if the clinical condition stabilized. After that, two to four 3-day oral azithromycin (10 mg/kg/day) courses were

Table 2. Summary of recent evidence on efficacy and safety of pidotimod in children with recurrent respiratory infections.

Study	Design	Population	Treatment	Follow up	Efficacy	Safety
Bozzetto [42]	Pilot, open	15 RRI 13 healthy	Pidotimod × 3 months	No	Metabolites similar to controls	ND
Li [44]	RCT	66 RRI 66 RRI	Pidotimod 1 vial twice daily × 14 days; then 1 vial once daily × 45 days Standard treatment	No	Reduction of fever, cough, duration Reduction of serum TNF-α and IL-4; Increase of IFN-γ	ND
Santamaria [45]	RCT	55 children 13 pidotimod + probiotics 13 pidotimod 13 probiotics 16 placebo	1 vial daily × 3 months	12 months	Metabolites Changes compatible with pathway of steroids hormones, hippuric acid and tryptophan	Well tolerated
Valentini [46]	Retrospective	33 children	1 vial daily for 20 days/ month × 6 months	No	Reduction of upper and lower respiratory infections and hospitalizations Increased B cell frequency and proliferation IgM increase	ND
Xu [48]	RCT	140 children 141 children 70 children	Pidotimod for 8 weeks Yupingfeng for 8 weeks Placebo	12 months	No difference between active groups Significant reduction vs placebo for number of infections	Well tolerated

ND, not done; RCT, randomized controlled trial; RRI, recurrent respiratory infections.

administered. Seventy-nine children also took pidotimod (400 mg/twice daily for 2 weeks). Pidotimod significantly ($p<0.05$) reduced serum IL-10 and granulocyte colony-stimulating factor (G-CSF) concentrations. In addition, pidotimod increased antibiotic curative activity and was associated with a low adverse reaction rate [51].

Mononucleosis model

Mononucleosis represents a valuable model of secondary immunodeficiency consequent to initial infection [52]. Namely, mononucleosis, by weakening immune response, may increase subsequent co-infections. As a result, immunomodulators could help manage patients with mononucleosis. In this regard, two recent studies investigated the preventive activity exerted by pidotimod.

Lyu and coworkers enrolled 76 children hospitalized for mononucleosis and randomly stratified them into two groups: standard treatment (ganciclovir + symptomatic support); or add-on pidotimod [53]. The treatment course lasted 2 weeks. Outcomes included clinical parameters and immunological biomarkers. Pidotimod significantly shortened fever duration, hastened disappearance of palpable lymph nodes and hepatosplenomegaly, and reduced hospitalization days ($p<0.05$). Also, pidotimod reduced peripheral CD3+ and CD8+ T cell levels more significantly than standard treatment ($p<0.001$). Therefore, the authors concluded that pidotimod provided advantageous clinical effects and positive immunological changes as adjunctive therapy in managing mononucleosis [53].

A further Italian study recruited 40 children (aged 7–16 years) with symptomatic mononucleosis [54]. Investigators subdivided children into two groups: i) group A were treated with pidotimod (400 mg or 800 mg daily, depending on age) for 30 days and successively 10 days/month for 6 months; and ii) group B were treated only with symptomatic drugs. The resolution time of the infection was the primary outcome.

The reinfections number was the secondary outcome. Pidotimod significantly shortened the recovery time and reduced the reinfections number ($p<0.0001$ for both). In addition, pidotimod reduced the reinfection duration [54].

Autoinflammation model

Autoinflammatory disorders represent a large category of non-suppurative inflammatory diseases characterized by immunopathological mechanisms. In this context, periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome belongs to the "periodic diseases" group [55]. This syndrome is relatively frequent, affecting about 2.3 per 10,000 children aged <5 years each year. The diagnosis is clinical. Oral corticosteroids significantly relieve PFAPA episodes [56]. However, no medication can modify the disease outcome. Therefore, a team of Italian researchers hypothesized that pidotimod could attenuate the inflammatory cascade in children with PFAPA [57]. They designed a pilot, prospective, controlled, open and cross-over trial to test this hypothesis. The study included 30 children with a diagnosis of PFAPA. Pidotimod was prescribed as 800 mg daily for 3 months. Betamethasone (0.5–1 mg daily) was administered as needed for 6 months. Outcomes included the number of episodes of fever, pharyngitis or aphthous stomatitis, as well as the need for on-demand corticosteroids. Pidotimod significantly decreased the frequency of fever ($p=0.002$), pharyngitis ($p=0.049$), aphthous stomatitis ($p=0.036$) and on-demand corticosteroid use ($p=0.007$) [58].

Global considerations

First, these recent studies confirm the continued interest in updating the knowledge on pidotimod and exploring new research areas. Indeed, in the last few years, 11 studies have been conducted on children to investigate the effects of pidotimod. RRI prevention remains at the core of the research on pidotimod, as this model represents the best way to demonstrate and confirm its immunomodulatory activity. Most children with RRI usually present with a relative defect in the immune response to pathogens, mainly sustained by the physiological immaturity of the immune system in early childhood. However, this para-physiological condition commonly disappears with growth. Effectively, pidotimod could represent a safe and effective option in managing children with RRI as evidence confirms its ability to reduce infectious episodes' number and severity. This aspect has relevant clinical outcomes as respiratory infections commonly precede asthma exacerbations. Consequently, children with asthma and frequent respiratory infections could benefit from immunomodulation by using effective and safe medications, such as pidotimod. Moreover, thanks to its ability to modulate the impaired immune response, pidotimod could also help restore physiological type 1 immunity and dampen type 2 inflammation in allergic subjects.

Future perspective

The possible implementations of pidotimod may include its use as an adjuvant in vaccinations. Vaccinations greatly affected the outcome of many epidemic infections. COVID-19 represents a paradigmatic example of the irreplaceable role played by vaccination in containing its spread and especially in reducing its severity. However, an excellent response to a vaccine is closely linked to a fully functioning immune system, as it should guarantee an adequate humoral and cellular response to the administered antigen. Unfortunately, frail subjects, including infants and younger children, frequently respond poorly to vaccines [58]. As a result, enhancing immune response using immunomodulators may represent a valuable strategy for improving vaccine effectiveness. Accordingly, pidotimod has been proposed as a worthy option for enhancing response to vaccines [59], or as a beneficial adjunctive approach in managing patients with active COVID-19 [60-66].

Moreover, pidotimod may be a potential candidate for improving response to allergen immunotherapy to inhalants and foods [38]. Its use could enhance response to allergens and reduce adverse reactions.

Conclusive remarks

There is robust and updated evidence that pidotimod may effectively and safely contribute to preventing respiratory infections, mainly if recurrent, by modulating immune response. In addition, pidotimod may positively exert synergistic activity when combined with the standard therapy for infectious diseases. These interactions depend on its mechanism of action based on stimulation of innate immunity and regulation of adaptive immunity. Moreover, thanks to its immunomodulatory properties, pidotimod may be a valuable option in managing patients with asthma and allergic disorders.

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Received for publication: 22 May 2024 - Accepted for publication: 25 June 2024

Multidisciplinary Respiratory Medicine 2024; 19: 986
doi: 10.5826/mrm.2024.986