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REVIEW

NOVEL INSIGHTS INTO PEDIATRIC ALLERGY AND IMMUNOLOGY

Pidotimod in allergic diseases

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ABSTRACT

The rising incidence of allergic disease requires more specific, effective and safe therapeutic strategies. In this regard, several kinds of biologically active substances, commonly known as immunostimulants, have been introduced for the prevention and treatment of allergic diseases in pediatric population. Among the heterogeneous group of biologically active molecules to date available, pidotimod (Axil, Valeas S.p.A, Milan) is proved to be able to ameliorate both innate and adaptive immunity and enhances the immune system properties often impaired in patients with allergic disorders.

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KEY WORDS: Asthma; Dermatitis, atopic; Child; Chronic urticaria; Pidotimod; Rhinitis.

The rapid increase in the allergic diseases prevalence, their complexity and severity, the need of drug administration, the search for assistance by a general and specialist physician as well as the hospitalization rate result in high socio-economic burden to the affected patients and families as well as countries.[1-4] In light of these ever-increasing data, it is urgent the need for alternative therapeutic approaches. In this regard, several kinds of biologically active substances, commonly known as immunostimulants, have been introduced for the prevention and treatment of allergic diseases in the pediatric population.[5-8] Among the heterogeneous group of biologically active molecules to date available, pidotimod (Axil, Valeas S.p.A, Milan) is proved to be able to ameliorate both innate and adaptive immunity and enhances the immune system properties often impaired in patients with allergic disorders.[9, 10]

This review aimed to summarize the mechanistic and clinical evidence for the use of Pidotimod, a nonspecific oral immunomodulator, in the prevention and/or treatment of atopic dermatitis, allergic rhinitis, allergic asthma, food allergy, and chronic spontaneous urticaria.

Pidotimod: mechanism of action

In 1993, pidotimod (PDT, 3-L-pyroglutamyl-L-thiaziolidine-4-carboxylic acid), a synthetic dipeptide molecule with effects both on innate and adaptive immunity, has been approved as immunomodulatory agent for the treatment of respiratory and urinary tract infections in children (over 3 years of age) with weak immune response.[9] Currently, pidotimod is available as oral formulation; in the treatment of acute respiratory infections the recommended dosage is 400 mg twice for 10-15 days in addition to standard antibiotics. For prophylaxis, the dose used is 400 mg once daily for 60 days.[9, 10] Pidotimod is rapidly

absorbed in the gastrointestinal tract, and hepatic metabolism is minimal, then, it is excreted unchanged in the urine.[9] Pidotimod showed a good safety profile, and side effects or autoimmune disorders have been not reported in the pidotimod treated patients, except for a single report in the literature of Henoch-Schönlein purpura associated with pidotimod therapy.[11]

Pidotimod has shown to affect both the innate and adaptive immune response in multiple ways. By upregulating the expression of toll-like receptor (TLR) and inducing the expression of intercellular adhesion molecule (ICAM-1), as well as the release of pro- and anti-inflammatory cytokines, pidotimod help in identifying pathogen-associated molecular pathways and, indirectly, modulates airway epithelial cells functions, which play a crucial role in providing a defensive physical barrier.[9, 12, 13] The up-regulation of HLA-DR and other costimulatory molecules (CD83 and CD86) expression, T-cell differentiation toward Th-1 type as well as the increase in salivary immunoglobulin (Ig) IgA levels are other beneficial effects attributed to pidotimod administration.[9-14]

Lastly, in their observational study, Zuccotti *et al*. found that pidotimod, *via* preferential activation of complement-dependent pathways, was able to induce the up-regulation of multiple genes involved both in the activation of innate immunity and in antimicrobial activity.[15]

Pidotimod in allergic diseases

Pidotimod in atopic dermatitis

Atopic dermatitis (AD) is a chronic relapsing-remitting inflammatory skin disorder beginning usually in early childhood, featured by a skin barrier dysfunction resulting in epidermal damage and impaired permeability to allergens and microbes. Although the exact, an etiology of AD remains unknown, both genetic and environmental as well as immune factors have been proposed to play critical pathogenetic roles.[16, 17] From an immunological point of view, AD is characterized by the activation of pro-inflammatory cytokines, such as interleukin (IL)-17 and IL-23, and the suppression of the anti-inflammatory cytokine IL-10.[17, 18] In light of its ability to positively influence the immune response both *in vivo* models and in humans, authors suggested the use of Pidotimod as a treatment in mild to moderate AD.[19] When topically administered, pidotimod may be in the form of semi-solid or liquid formulations also containing at least an excipient and/or adjuvant and/or carrier. Moreover, pidotimod may be used in combination with immunosuppressive agents (methotrexate, azathioprine, cyclosporine, fumaric acid, tacrolimus or pimecrolimus), Vitamin D and analogues, Vitamin A and related compounds, and corticosteroids. In a clinical trial, pidotimod (800 mg/d) was topically administered both to pediatric and adult patients for 12 weeks. After the treatment period, a significant improvement in the erythema score compared to baseline was recorded ($P<0.001$). Moreover, the topical drug appeared well tolerated and side effects were not reported.[19]

Pidotimod in allergic rhinitis

Allergic rhinitis, characterized by rhinorrhea, nasal obstruction, epiphora, and nasal itching, is a common pediatric condition affecting over one million children with a prevalence about of 14.6%. Evidence-based guidelines, advances in drug treatments, and novel specific immunotherapy have significantly improved the management of allergic rhinitis.[20-23] To the best of our knowledge, only one study evaluated the efficacy of Pidotimod in the treatment of allergic rhinitis.[24] Sixty children (age range, 5 to 14 years) with allergic rhinitis and also affected by allergic asthma were randomized in two groups: 1) treatment group, receiving routine symptomatic treatments, sublingual immunotherapy (SLIT) for dermatophagoides farinae and pidotimod; (2) control group, receiving only routine symptomatic treatments and SLIT for dermatophagoides farinae. After four-week treatment, the treatment group showed a significant reduction in inflammatory cytokine levels (C-reactive protein [C-RP], IL-8 and tumor necrosis factor-alpha [TNF-α]), and a significant improvement in the immunological function (assessed by an increase in Immunoglobulin, CD3+, CD4+, CD8+, CD4+/CD8+ levels) as well as in pulmonary function (expressed in terms of FEV1, PEF, PEF25, PEF50, and PEF75) when compared to

control group.[24] Thus, authors concluded that pidotimod in combination with the routine treatments was able to enhance the activity of the immune system in children affected by allergic rhinitis and accompanied by asthma, down-regulate the inflammatory reaction, and improve the pulmonary function.[24]

Pidotimod in allergic asthma

Allergic asthma is a highly heterogeneous disorder that accounts for 1.1% of the overall global estimate of "disability-adjusted life years" (DALYs)/100,000 for all causes.[25] Clinical phenotypes of asthma in children are characterized by an early onset and are usually associated with eosinophilia, increased serum total immunoglobulin E (IgE) levels, and multiple aeroallergens sensitization. Only a small subgroup of children presents with bronchial hyperresponsiveness and reduced lung function.[26-28] Each phenotype is linked to different pathobiological mechanisms or endotypes that, based on the type of airway inflammation, have been classified into type 2 and non-type 2.[29, 30] In regard to type 2- asthma, previous studies, have shown that CD30 cells play an important role in the development of Th2 cell-mediated allergic immune response.[31] A pioneering study conducted on 22 children with mild atopic asthma revealed that pidotimod was able to down-regulate the expression of CD30+ cells in asthmatic patients.[32] In light of the tight relationship between CD30+ levels, Th2-cells expression, and allergic asthma, further studies investigated the efficacy of pidotimod in the prevention and/or treatment of allergic asthma.[33-36] Zhai *et al*.[33] enrolled 100 asthmatic children treated with conventional treatment (N.=50) and with conventional treatment with addition of pidotimod (N.=50) for 12 weeks. Treatment with pidotimod resulted in a significant decrease in frequency, degree and duration of asthmatic attack. In parallel, authors reported that treatment with pidotimod was also associated to an increase in the phagocytic activity and chemotaxis of macrophages and neutrophils, a major number of circulating activate natural killer cells and restored normal values of low CD4+ and a normal CD4+/CD8+ ratio, assessing the immunomodulatory effects of pidotimod. Moreover, during the clinical observation period, none of the enrolled children experienced a serious adverse drug reaction, suggesting the good safety profile of pidotimod.[33]

The immunomodulatory effect of pidotimod in prevention and treatment of asthma was also investigated by Ma *et al*.[34] A clinical trial was designed in eighty asthmatic children aged 6-12 years and randomly assigned to pidotimod group (montelukast 5 mg/day, budesonide aerosol 200 mcg per day + pidotimod 400 mg per day) and control group (montelukast 5 mg/day, budesonide aerosol 200 mcg per day) for 30 days. A reduction in serum IL-4 and IgE levels as well as an improvement in lung function, assessed by forced expiratory volume in 1 second (FEV1%) and maximal peak expiratory flow (PEF%), were recorded in pidotimod group when compared to control group, suggesting that pidotimod, when administrated in addition to montelukast and inhaled steroid, can prevent asthma attacks and improve respiratory functions.[34] In a clinical trial, ninety patients with asthma were randomized to routine treatment (control group, N.=35) and routine treatment in combination with pidotimod (observation group, N.=55) for 2 months. Serum levels of IL-16, immunoglobulin, T-cell subsets were determined before and after pidotimod treatment. Authors reported a significant reduction in serum IL-16 levels with pidotimod treatment during the relief phase. Clinically, patients receiving pidotimod treatment also showed a significant decrease in acute asthmatic episodes, frequency of upper and low respiratory tract infections, and frequency of asthma attack.[35] Similarly, one hundred fifty children with asthma were enrolled and randomized to receive montelukast (control group, N.=75) or montelukast and pidotimod (observation group, N.=75). After three months of treatment, the cough symptom scores in day and night, the FEV1% and PEF% values, the average number of asthma attack, the duration and the number of respiratory tract infections were significantly lower in observation group than control group. Moreover, adverse effects were less in combination treatment when compared to monotherapy ($P<0.05$) and were restricted to skin rash, dyspepsia, nausea, vomiting, and diarrhea.[36]

TABLE I.—*Summary of efficacy and safety of pidotimod in allergic diseases.*

Pidotimod in allergic diseases	Authors (year)	Design Study	Population	Treatment
Pidotimod in atopic dermatitis	Mailland *et al*.[19] (2019)	OS*	Children Adult	Pidotimod 800 mg/d
Pidotimod in allergic rhinitis	Zhao *et al*.[24] (2017)	OS*	Children	Antihistamine Mometasone SLIT *vs.* Antihistamine Mometasone SLIT Pidotimod
Pidotimod in allergic asthma	Gourgiotis *et al*.[32] (2004)	*In vitro*	Children	Pidotimod *vs.* Not pidotimod
	Zhai *et al*.[33] (2011)	OS	Children	Conventional *vs.* Conventional+pidotimod
	Ma *et al*.[34] (2011)	RCT*	Children	Budesonide+montelukast *vs.* Budesonide+montelukast+pidotimod
	Sun *et al*.[35] (2011)	RCT	Children	Control *vs.* Control+pidotimod
	Ji *et al*.[36] (2016)	OB	Children	Montelukast *vs.* Montelukast+pidotimod
Pidotimod in chronic spontaneous urticaria	Wu *et al*.[38] (2012)	OB	Adults	Pidotimod

AEs: adverse effects; OS: observational study; RCT: randomized clinical trial; IL: interleukin; IgE: immunoglobulin E.

Pidotimod in food allergy

To the best of our knowledge, literature data on the efficacy of pidotimod in the treatment of food allergy are not reported. Currently, the only available management of food allergy is limited to strict dietary avoidance, education on prompt recognition of symptoms, and emergency treatment of adverse reactions.[37]

Pidotimod in chronic spontaneous urticaria

In adult population, Wu *et al*. assessed the efficacy of pidotimod in the treatment of chronic spontaneous urticaria. After four weeks of treatment, authors recorded a total effective rate of 92%.[38] There are not data on pediatric population with chronic idiopathic urticaria.[39]

Pidotimod and immunotherapy

Allergen immunotherapy (AI) is at present the only disease-modifying therapy, effective for the treatment of allergic rhinitis, allergic asthma, conjunctivitis as its target are the allergic inflammatory pathways.[40-42] It has been speculated that pidotimod may act as an adjuvant in case of concomitant treatment with immunotherapy for its ability to modulate the immune system through the modulation of the thymic stromal lymphopoietin (TSLP) and TNF-α.[43]

Conclusions

The rising incidence of the allergic disease requires more specific, effective and safe therapeutic strategies. In addition to standard therapy, pidotimod could represent a new and valid treatment option to influence positively the immune mechanisms underlying allergic diseases. The above-mentioned clinical trials show encouraging results with good clinical efficacy and satisfactory safety profile (Table I).[19, 24, 32-36, 38] However, further studies are required to better define the op-

Follow-up duration	Efficacy	Safety
12 weeks	Improvement in the erythema score	AEs were not reported[10]
4 weeks	Reduction in inflammatory cytokine levels Improvement in the immunological function Improvement in pulmonary function	Not stated
Not applicable	Reduced expression of CD30 both in normal children and asthmatic patients	Not applicable
12 weeks	Reduction in inflammatory cytokine levels Improvement in the immunological function	AEs were not reported
1 month	Reduced expression of IL-4 and IgE levels[14] Improvement in pulmonary function	Not reported
2 months	Reduction in inflammatory cytokine levels	Not evaluated
3 months	Improvement in pulmonary function	AEs: 6.67% *vs*.17.33% Skin rash (N.=2 *vs*. 0) Dyspepsia (N.=0 *vs*. 3) Nausea and vomiting (N.=2 *vs*. 5) Diarrhea (N.=1 *vs*. 2)
4 weeks	Clinical improvement	Not evaluated

timal dosage, duration treatment, and long-term effects of pidotimod, as monotherapy or in combination with standard therapy, in allergic diseases.

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