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Review Article

Pidotimod as an Immunomodulator: An Unsung Warrior to Restore Immune Dysregulation in Acute and Chronic Lung Disease

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Abstract: Immune dysregulation has been observed in the majority of the infective and non-infectious respiratory illnesses with impact on the natural course of illness in pediatric to geriatric age groups. Immune regulation between Th1 and Th2 is altered and reversal of proportion between these two differential cells and ultimately homeostasis, with predominance Th2 cells will increase susceptibility for recurrent illnesses; is typically documented in pediatric age groups with first respiratory infection during early neonatal period with respiratory viral etiologies. Apart from recurrent childhood infections, pediatric cases with immune dysregulation will have recurrent wheezing in childhood and are prone for development of childhood asthma in adolescent age groups; if immune dysregulation does not restore in time. In adults, respiratory illnesses due acute viral infective etiology will cause immune dysregulation as documented after coronavirus, influenza and respiratory syncytial virus infections. Immune dysregulation has also been documented in chronic respiratory illnesses such bronchial asthma, chronic bronchitis and COPD. Immune dysregulation will cause recurrent exacerbations in these inflammatory conditions. Pidotimod is an immunomodulator which will work as an immunostimulant molecule due to its unique pharmacological actions on antigen presenting cells, and have novel action on immune cell proliferation and differentiation. In spite of three decades of research of this novel drug Pidotimod, still; it is less used as of today for respiratory ailments in spite of need of a molecule with an immunomodulatory effect for prevention and or cure of illnesses; and modification of natural course of recurrent or relapsing course of chronic illnesses. COVID-19 pandemic has taught us many pathways of immune dysregulation which evolved during natural course of disease and now documented with respiratory viral illnesses such as RSV; and its long-term impact as long covid presenting due to immune dysregulation occurred as a natural course in recovered cases. It's unclear whether long covid is reversible as of now, but the majority of symptoms have been resolved and shown response to versatile molecules such as steroid, multivitamins, L-arginine, Paxlovid, beta blockers with variable results and long-term outcomes. Pidotimod can be used in acute COVID-19 illness without pneumonia and comorbidities in stable cases in outdoor settings, and also; considered as potential option in long covid cases with recurrent respiratory infections. In this review we have discussed basic aspects of Pidotimod, and its role in immunomodulatory effects in acute and chronic respiratory illness which have shown positive outcomes.

Keywords: Pidotimod, immunomodulatory, Th1 (T-helper cell), Th2, immunostimulatory, recurrent infections, corona virus, RSV.

INTRODUCTION

Since the early 90's more than a hundred papers have been published about Pidotimod, an immunostimulant drug. Due to its action mechanism and its potential, it has been used both in children and in adults, mostly for preventing respiratory tract infections, and asthma or chronic obstructive pulmonary disease exacerbations. Despite the use of antibiotics and vaccines, the frequency of respiratory tract infections is still high and these infections disturb a wide range of patients, from children to elderly, particularly these two extremes due to the deficiency of their immune system: immaturity in the first case and "immunosenescence" in the second one. For that reason, immunostimulant drugs steadily increased in the past few years, getting nowadays more importance and visibility in preventing the onset and reducing the duration of airway infections.

Immunostimulants are a heterogeneous group of compounds that act non-specifically on the immune system by inducing its activation, either upregulating it or by favoring the activity of one of its components. By understanding deeply their biological function, they may be implemented in the clinical practice to shape the immune system favorably according to the different processes that want to be enhanced or hampered. According to these peculiar characteristics they have also been called "Biological Response Modifiers" (BRMs) [1-3].

Acute respiratory infections (ARIs) are one of the most common infections in both adults and children. However, ARIs remain a significant cause of morbidity and mortality in developing countries. Globally, the prevalence of ARIs is highest in South-East Asian region [4]. In children, recurrent respiratory infections (RRIs, ≥6 acute episodes year) are very common and often are the cause for frequent hospital visits [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. Immunological alterations in asthma with chronic inflammatory changes are known [5]. 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. 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. Multiple 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 [6].

Pidotimod: Basic Aspects

Pidotimod is a synthetic dipeptide molecule (3-l-pyroglutamyl-l-thiazolidine-4carboxilic acid) endowed with immunomodulatory activity that affects both innate and adaptive immune responses. Higher expression of Toll Like Receptors (TLR) 2 and of HLA-DR molecules, induction of DC maturation and release of pro-inflammatory molecules, stimulation of T lymphocyte proliferation and differentiation toward a Th1 phenotype, as well as an increase in the phagocytosis have been demonstrated to be associated with Pidotimod in in vitro studies. Studies in different areas have demonstrated the benefit of Pidotimod, including its use in hepatitis C, HPV genital infection, Henoch-Schönlein Purpura, nephrotic syndrome, and immunodepressed individuals such as children and elderly [7]. The immunostimulatory activity of pidotimod is focused on both immune responses, adaptive and innate immunity.

Pidotimod with immunostimulatory pathway in figure 1, immunomodulatory pathway in figure 2 and Immunological activities shown in figure 3 [8]. Mechanisms are-

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

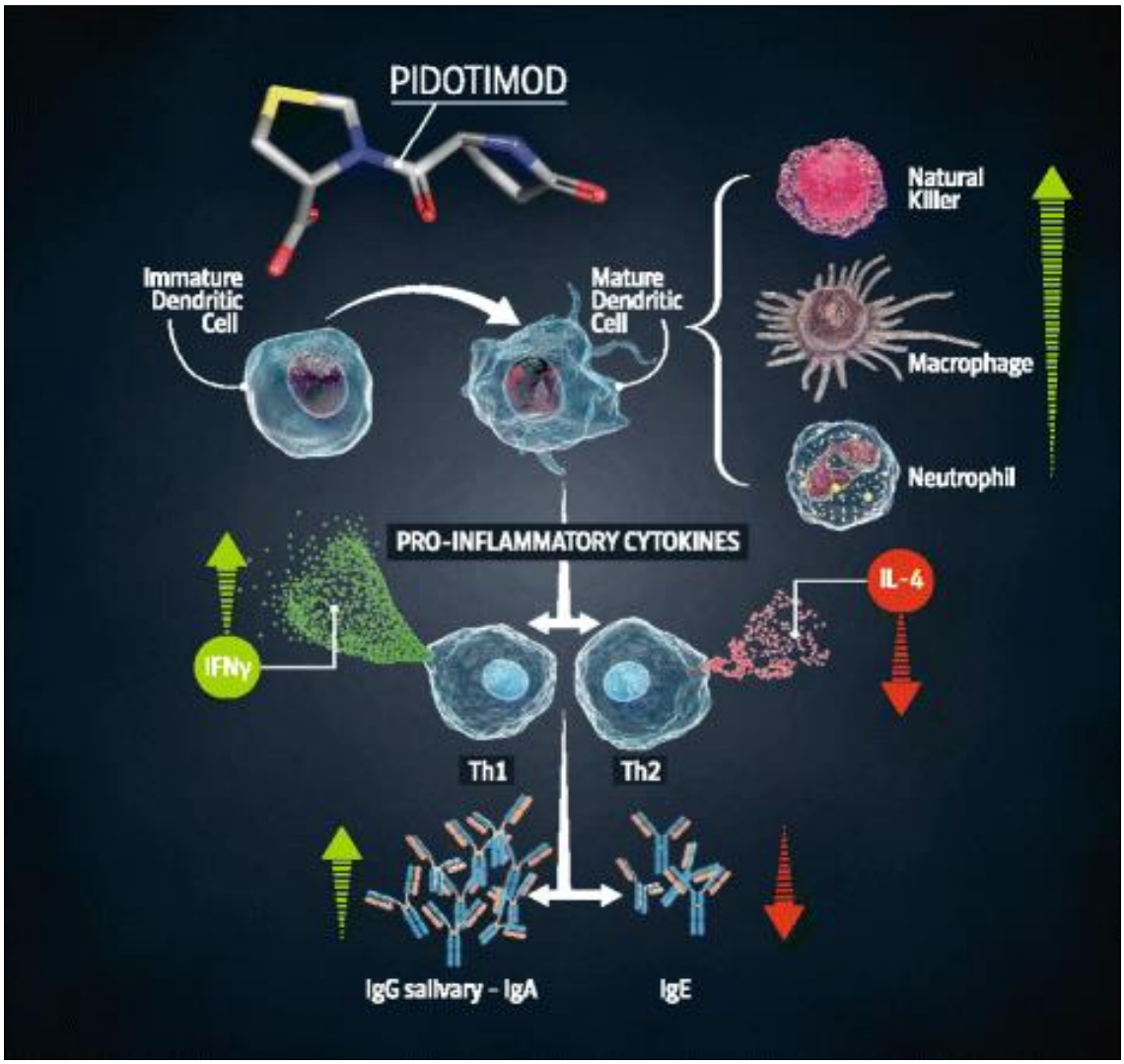

Figure 1: Pidotimod with immunostimulatory pathway

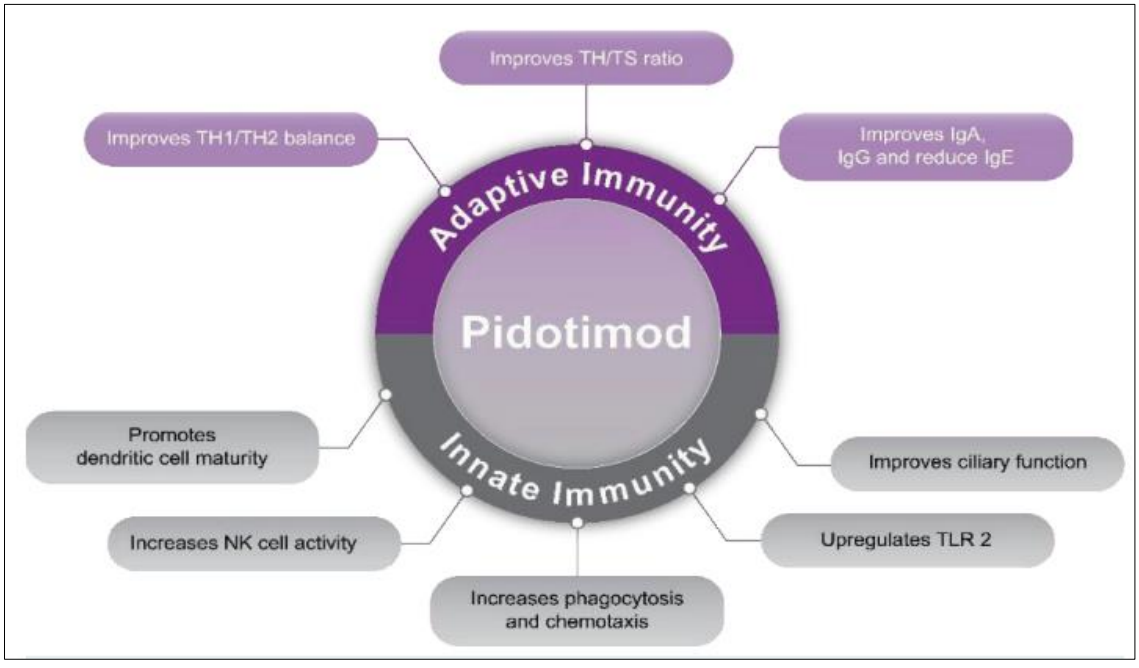

Figure 2: Pidotimod with immunomodulatory pathway

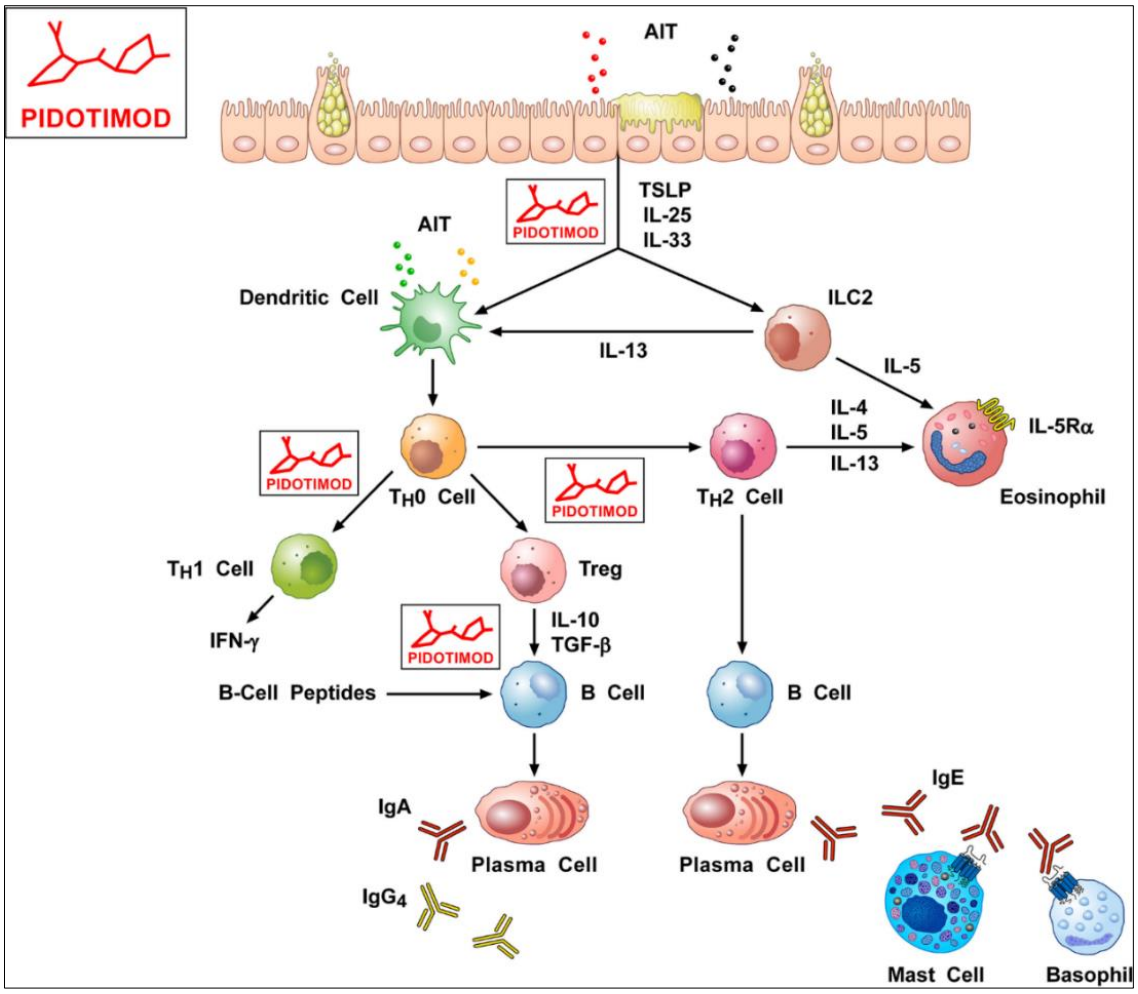

Figure 3: Showing Immunological activities of Pidotimod

The common end-point of these studies is that Pidotimod has an immunomodulatory activity which is able both to improve the clinical conditions of patients and to enhance and stimulate their immunity cells functions acting on both adaptive and innate immunity. Acute respiratory infections (ARIs) are still pandemics despite the introduction of new antibiotics and vaccines which contribute to reduce the risk of mortality and morbidity and they remain widespread and affect both young and elder people.

Dosing Frequency and Schedule of Pidotimod

***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.

***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.

Immune Dysregulation in COVID-19

Although SARS-CoV-2 infection generally leads to a mild disease in a large proportion of infected individuals, 5-15% of COVID-19 patients develop a severe pathology that progresses to pneumonia and respiratory failure. Dysregulation in the immune system can lead to an unappropriated local and systemic immune responses and subsequently the rapid spread of the virus, leading to severe COVID-19 disease. Severity of illness increases with more lung parenchymal involvement as documented with chest imaging in proportion with inflammatory markers such as CRP [9-12], LDH [13-16], Ferritin [17-20], IL-6 [21-26], and D-Dimer [27-31]. Disease outcomes range from asymptomatic and mild to more severe and critical courses with pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and considerable risk of fatality. Inflammatory markers have been studied for predicting antigenic cross-reactivity and antigenic mimicry which has resulted in autoimmune and rheumatological manifestations. During COVID-19 pandemic antigenic cross reactivity has documented with dengue fever [32-36] COVID-19

related extrapulmonary manifestations have been reported secondary to dysregulated immune response and systemic effects on immunity & immunosuppression resulting into tuberculosis, central nervous system resulting into stroke and endocrinal effects resulting into hyponatremia [37-39]. Similarly, deregulated immune phenomenon has been documented after covid vaccination and transient autoimmune features have been reported in various studies [40-41].

Immune dysregulation is known to occur after natural COVID-19. Altered homeostasis between Th1 and Th2 interplay is a real issue of concern. Immune dysfunction as Th1 and Th2 dysregulation is usually restored after other respiratory viral infections by our own reboot system as in the "Tomorrow never dies" situation [42]. Composite index is combination clinical, radiological and laboratory inflammatory marker assessment. Combination of any two abnormalities were observed crucial role in early suspicion, diagnosis, monitoring, and recognition of complications, management and disposition of patients. Composite index rather than single biomarkers may provide more reliable information. Availability and cost issues cannot be ignored. It would be impossible for clinicians to consolidate and critically analyse the enormous data that is continuously added to the COVID-19 literature to extract practically useful information for the benefit of patients. Still, as of now Composite index should be considered as 'point of care test' to honour successful treatment outcome and prevent mortality and morbidity due to this "Dragon Pandemic" [43-44].

Long covid is observed in selected group of patients and occurs irrespective of severity of covid, irrespective of hospitalization and interventions required during hospitalization. Long covid occurrence is observed in special class of patients which can be predicted early during course of illness by analysing markers. Biochemical markers will help in suspecting chance of occurrences but sequential markers will help in targeting interventions to prevent it and guide in management of long covid. Clinical presentation and immunological patterns are different during different waves due to either genetic makeup or immune pathway alterations resulting into long COVID [45-49]. Pathophysiology resulting into long COVID manifestations is still not completely validated. Researchers have reported 'immune dysregulation' and 'coagulation abnormalities' are probable pathophysiological mechanism for long COVID. Some of the long COVID effects shown complete reversibility including post COVID lung fibrosis [50-55]. Reboot system to restore immune dysregulation and recovery in long COVID is real concern. Long COVID symptoms cases are more health conscious and usually follows pattern of doctor shopping due to underestimation by family physicians either due to lack of suspicion or lack of knowledge regarding treatment protocol [56, 57]. Radiological phenotypes are radiological patterns or observable characteristics of COVID-19 pneumonia. Robust data is available regarding role of HRCT in COVID-19 pneumonia and authors have evaluated role of radiological phenotypes in assessing severity, predicting response to therapy and final outcome in COVID-19 pneumonia. Radiological patterns or phenotypes have documented important role in assessing disease severity in COVID-19 pneumonia [58-62]. Immune alteration is documented after natural infection & effect of vaccination in restoring Th1/Th2 interplay is not known. The 'reboot system' or time required to restore 'normalcy' is a real concern as documented as our immune phenomenon.

Role of Pidotimod in Viral Infections

Most common causes of respiratory tract infections have viral origin especially human rhinoviruses (HRV), adenovirus, parainfluenza virus, respiratory syncytial virus (RSV), enterovirus, human metapneumovirus and coronavirus in addition to influenza viruses. Impaired mucociliary escalator is a good media for bacteria proliferation and secondary infection (Particularly streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus), causing increase in disease severity, mortality and morbidity with progression to unfavored sequela such as pneumonia [63].

On the other hand, the host immune system tends to control viral infections via induction of apoptosis of infected cells using different mechanisms including: increasing TNF-alpha secretion, stimulation of natural killer (NK) cells to secrete perforin (making pores in the infected cells resulting in induction of cellular apoptosis) and stimulation of macrophages and neutrophils to produce reactive oxygen species causing oxidation of the infected host cell's proteins, lipids and DNA leading to its death [64].

Carta *et al.*, held a study to assess the ability of pidotimod to induce cellular changes enhancing the host immune system to defend infections. This study has documented that pidotimod is able to upregulate TLR2, with no increase in ICAM or IL8 levels, thus playing a protective role in decreasing susceptibility to HRV infection and from neutrophil-mediated damage to the airway surface [65].

Role of Pidotimod in 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 [66]. 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. 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. 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 [6].

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. Immune dysregulation is identified as an important contributor to RRIs. Atopy and allergies or reduced immune function and immunodeficiency have been reported with RRIs. 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. Further, food allergy has also been observed to be implicated in the causation of RRIs. These evidences provide a possible link of immune disruption with RRIs. Dysregulation of both humoral and cellular immunity has been reported in RRIs [6-67].

Possible Alterations in Immune System Function Associated with Recurrent Respiratory Infections

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

Many studies 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.

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. 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 [68].

Role of Pidotimod in Chronic Obstructive Pulmonary Disease (COPD)

COPD is a chronic inflammatory airway disease characterized by chronic fixed airway obstruction. It affects more than 5 % of the population and is associated with high morbidity and mortality. COPD results from complex interactions between environmental (mainly tobacco smoking and/or other pollutants) and molecular risk factors. Molecular risk factors for COPD include a plethora of gene polymorphisms, dysregulations of the antioxidants pool, metalloproteinase abnormalities and uncontrolled role of elastase. COPD exacerbations are triggered most often by respiratory viral infections, mainly rhinoviruses, even if bacterial component is present. Moreover, exacerbations tend to be more severe and prolonged if caused by viral pathogens [69].

In terms of immunological response, aside from the inflammation, there is usually a neutrophilic recruitment; sputum eosinophilia can be also relevant, in particular during viral infections [70]. Being the reduction of exacerbation frequency and intensity paramount for the disease control, it appears fundamental to act on the immune system in order to prevent infections and to reach the optimum of care.

Due to its role of potentiating and regulating both the innate and acquired immune systems, Pidotimod appears to be promising also in COPD. In two Italian double-blind randomized trials Pidotimod showed significant reduction in infective COPD exacerbations in Pidotimod treated patients [71]. This positive effect was not only present during the treatment period but also during the follow up, suggesting a protecting action of the drug and a possible use in cyclic regimen. The long-lasting effect of Pidotimod was furtherly confirmed as it demonstrated to potentiate the immune response up to 5 weeks after infection.

Pidotimod was found effective also in a particularly susceptible population: elderly COPD patients; a population patient with severe COPD with different degrees of immunological signs of “immunosenescence” achieved a reduced number of exacerbations by the concomitant use of Pidotimod with flu vaccination compared to those treated with vaccine only [72].

In terms of bacterial exacerbations, another study showed that patients treated with Pidotimod plus amoxicillin/ clavulanic acid, had a faster remission of symptoms compared to those treated with antibiotics only. Moreover, Pidotimod was seen able to increase the production of secretory IgA in patients with COPD, contributing in defining Pidotimod as a potential strategy to prevent infections [73].

Role of Pidotimod in Bronchial Asthma

Asthma phenotypes and endotypes based on inflammatory airway involvement have nowadays

increasing medical interests thanks to the development of targeted therapies that aim to hamper directly the mechanism of the underlying pathologic processes. At least two big groups of endotypes have been so far identified: an endotype characterized by Th2 cytokines overexpression (particularly IL5, IL4 and IL13) with concomitant airway eosinophilic inflammation, and a Th2-low inflammatory endotype in which neutrophils are the predominant inflammatory cells within the airways [74].

Th2-high endotypes of asthma can be further distinguished in allergic and non-allergic but eosinophilic asthma [90]. The former is the result of an allergic reaction and more typically has a childhood onset, while the latter is the result of an eosinophilic inflammation toward an unknown trigger, it has typically an adult onset and is often associated to chronic rhinosinusitis with nasal polyposis and aspirin hypersensitivity. All the above mentioned endotypes can present in a wide range of severity, and about 5–10% of all asthmatics are classified as affected by severe asthma as they require high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic glucocorticoids to prevent asthma from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy [75].

One of the peculiar features of severe asthma is the high frequency of exacerbations, often associated with respiratory tract infections, and accounting for the major fraction of the total health-care related costs of asthma. Moreover, a personalized approach to asthma cannot prescind from the diagnosis and treatment of comorbidities, in particular rhinitis and chronic rhinosinusitis with (CRSwNP) or without nasal polyps (CRSsNP). Recently, a cross-sectional study showed that CRS-related exacerbations is associated to lost productivity in asthmatics assessed as number of lost days of work or school [76]. Another common comorbidity of severe asthma is bronchiectasis that it is estimated to be present in up to 25% of patients; bronchiectasis is as an irreversible enlargement of the airways, which brings about a predisposition to develop recurrent and often severe lower respiratory tract infections, triggering asthma exacerbations. Into this complex context in which patients with asthma, particularly if severe, are clearly more prone to develop exacerbations linked to upper and/or lower airway infections, an immunostimulatory approach with Pidotimod may be beneficial.

Pre-clinical evidence is already available: in a study investigating the ability of Pidotimod to affect in vitro the phenotype and cytokine profile of blood cells in relation to atopic asthma showed that it was able to down-regulate the expression of CD30 on mononuclear cells isolated from both atopic asthmatic children and healthy controls [77]. Because CD30 has been associated with Th-2 cells, this observation supports the possibility of Pidotimod being able to affect the Th-1/Th-2 balance in atopic asthma.

T2-low asthma endotype patients tend to not react to targeted therapies for pathologic type 2 inflammation, such as glucocorticosteroids. Some, recent studies support the theory that NK cell cytotoxic function is disabled in part by steroids in severe asthma. These NK cells express specialized pro-resolving mediators (SPMs) that are pivotal signals for the resolution of tissue inflammation; nevertheless, SPM abundance or signaling receptors are disrupted in chronic inflammatory disease. SPM receptors and SPMs can in some instances counter the deleterious effects of corticosteroids on the effector function of NK cells. Together, these findings suggest that some severe asthma, patients already refractory to the beneficial actions of corticosteroids, may be harmed by the steroids, increasing susceptibility to viral infection and asthma exacerbations. Thus, leaving an unveiled indication for the use of Pidotimod in these patients once its acts in the prevention of viral infections and asthma exacerbations [78].

Role of Pidotimod in Allergy

In Europe, approximately 23% of the population is affected by allergic rhinitis (AR) that is frequently accompanied by allergic asthma (AA), the prevalence of which increases from less than 2% in individuals without AR to 10–40% in those with AR; this combination of upper and lower respiratory symptoms increases the overall impact on the patient. There is now considerable evidence that the symptoms of AR and AA negatively affect patients' health related quality of life [79]. Allergen immunotherapy (AIT) is nowadays the only treatment specifically targeting the allergic inflammatory pathways and it represents a prototype of personalized medicine approach to respiratory disease patients. AIT is highly effective and may induce long-term remission of symptoms. However, ongoing problems include the duration of treatment, the safety of immunotherapy, its cost and accessibility [80]. Adjuvants have the potential to modify the pharmacological and immunological effects of allergen vaccines. They may modulate allergen delivery, act as a depot, stimulate immune responses or limit antibody responses in order to reduce unwanted side effects. Adjuvants may be used in combination with potentially cumulative effects. Therefore, since Pidotimod action pathways include an effect against TSLP and TNF-α action (Fig. 3), it could open an interesting and unexplored option of adjuvant treatment in allergen immunotherapy depending on the choose route of administration.

Role of Pidotimod in Lower Respiratory Tract Infections

Lower respiratory tract infections (LRTIs), such as acute bronchitis and pneumonia, represent the most common cause of death from infectious diseases and the

fourth overall most common cause of death worldwide. In 2016, it has been estimated that LRTIs have caused 2 million and 370 thousand deaths, among which more than 1 million where due to S. pneumoniae infection. Even if the incidence of LRTIs has decreased in the last decade in the pediatric population, LRTIs remain a leading, albeit preventable, cause of death among elderly patients [81].

Two different studies were planned to evaluate the in vivo immunomodulatory effect of pidotimod during acute community-acquired pneumonia (CAP) [82, 83]. One was held on children and the other was held on adults. In both studies, the patients were divided in two groups, one group receiving antibiotics only while the other antibiotics plus Pidotimod. Pidotimod induced the enforcement of the immune system stimulating some proteins such as lactoferrin, cathepsin G and myeloperoxidase, known to be endowed with potent antibacterial; similarly important is the finding that Pidotimod was associated with a reduced production of TNF-alpha, a proinflammatory cytokine whose excessive production is known as a negative prognostic factor in CAP. Finally, the finding that Pidotimod increased the expression of CD80 and CD86 on DC, confirms its role in triggering the adaptive immunity response [83]. Both studies indicated that pidotimod significantly increased the natural immune system response to an infectious stimulus via stimulation of DC maturation and increased TNFα and IL12 secretion.

A recently published meta-analysis assessed a total of 29 RCTs consisting of 4,344 pediatric patients. Ten RCTs were published from Italy, Russia or Greece, and 19 RCTs were published by Chinese groups. Nonetheless, appropriate randomization methods were only used in 15 trials. Only one study had explicit allocation concealment. Since only eight RCTs were double-blind and placebo controlled, the evidence was not assessed as high quality. The meta-analysis indicates that treatment with Pidotimod resulted in a significant increase in the proportion of participants who had lower respiratory tract infections compared with the conventional treatment. Pidotimod could significantly decrease the duration of cough and fever. The number of patients using antibiotics was also remarkably decreased in the Pidotimod treatment group. Moreover, Pidotimod administration improved the levels of serum immunoglobulin (IgG, IgA, or IgM) and T-lymphocyte subtypes (CD3+, CD4+). Besides, Pidotimod administration did not increase the risk of adverse events of any cause [84].

Potential Role of Pidotimod in Stable COVID-19, Without Comorbidity and Pneumonia in Outdoor Setting

In humans, SARS-Cov-2 entry occurs via the host cell surface enzyme angiotensin-converting enzyme 2 (ACE2) receptor. Specifically, downregulation of ACE2 leads to compensatory overproduction of angiotensin II by ACE. Angiotensin II, in turn, stimulates its type Ia receptor, leading to an increased pulmonary vascular permeability. Moreover, both lung injury and symptoms are associated with host response to viremia. Notwithstanding immune response appeared fundamental for SARS infection resolution, SARS-Cov-2 disease present increased levels of plasma pro-inflammatory mediators, as a consequence of an induced dysregulated cytokine storm. Furthermore, Covid-19 patients' CD4 T-cells arbor enhanced transcription of both IL-6 and GM-CSF favoring symptoms' duration and disease progression. For these reasons, drugs rebalancing the host immune system, such as pidotimod, could to theoretically useful to prevent SARS-COV-2 clinical worsening.

Several studies reported pidotimod regimens as adjuvant therapy in several conditions. In elderly subjects, it enhances cell proliferation and secretion of IFN-γ and decrease of IL-6 production.4 Similarly, immune host modulation has been reported in decreasing susceptibility to rhinovirus infection, and neutrophil-mediated pulmonary parenchymal injury via TLR-2 upregulation without any IL-8 levels increase. In vitro study demonstrated that pidotimod is able to down-regulate MCP-1, which is a master regulator in the inflammatory response associated with severe recurrent viral bronchiolitis [85]. Finally, pidotimod promoted maturation of mucosal dendritic cells, thus playing a putative role in the expression of HLD-DR and T cells. All these translated effects could represent a new approach on COVID-19 infection management. Recent data report a dysregulated activation of macrophage compartment could contribute to a hyper inflammation state in COVID19 patients [86], as confirmed by high concentrations of monocyte recruiting chemokines and of mononuclear phagocytes sampled in SARS-CoV-2 bronchoalveolar cytology specimens. In an ambulatory adult patient with SARS-Cov2 infection without pneumonia, in outdoor settings; pidotimod could be considered an option, well tolerated and associated with a rapid reduction of systemic symptoms of disease [87].

Potential Role of Pidotimod in Recurrent Respiratory Infections Following COVID-19 Illness Related Immune Dysregulation Presenting as Long Covid

Immune dysregulation is known to occur after natural COVID-19 disease. Altered homeostasis between Th1 and Th2 interplay is a real issue of concern. We are in 'great peace of life' as COVID-19 pandemic is in its end phase or 'waning phase' and has observed a significant drop in active cases in the last few months across the globe. Authors have documented immune dysregulation in cases with rheumatological manifestations post-covid, cases with recurrent seasonal viral infections post-covid (never experienced before covid-19 infection), cases with persistent fever in TB and disseminated TB in post covid, and asymptomatic or minimally symptomatic cases with covid vaccination in recent past [88-92]. Authors have documented that

Th1/Th2 homeostasis desynchrony (categorised as Th1/Th2 normal, Th1 hyperactive/Th2 suppressed, Th1Supressed and Th2 hyperactive) has been documented in all four study groups [88-92]. Immune dysregulation after COVID-19 is lingering longer than the natural trend as documented with other viral infections and time trends for normalcy is a real concern. Immune dysregulation persisting post covid should be considered as 'Disease of global concern'. Effect of vaccination in maintaining harmony between Th1-Th2 needs further research. Immune alteration is documented after natural infection & effect of vaccination in restoring Th1/Th2 interplay is not known. The 'reboot system' or time required to restore 'normalcy' is a real concern as documented as our immune phenomenon [88-92].

Pidotimod can be theoretically used in management of immune dysregulation related recurrent viral infections due to seasonal and sporadic respiratory viral illnesses due to influenza, RSV, coronavirus, Rhinovirus, and adenovirus. Probable rational for use in these conditions would be the same as observed in RRN in paediatrics and adults. Role of this molecule in other conditions related to long covid such as rheumatological, non-specific generalised and specific or topographical or systemic manifestations is not known.

Learning Points

1. Immune dysregulation involving innate and adaptive immune responses has been identified in a variety of diseases in children and adults. Pidotimod enhances both innate and adaptive immune responses such as it restores T-lymphocytes balance with a possible additional anti-allergic activity in allergic conditions such rhinitis with or without asthma, Reduces the severity of infectious episodes in pneumonia and chronic lung disease in adults, Rapid recovery in acute and chronic illnesses, Reduces the need for antibiotic and other symptomatic treatments in deterioration of allergic and chronic lung disease, and lastly; it improves lung function and airway epithelial clearance which is the most important pathway for bronchiectasis and RRNs.
2. Pidotimod is indicated and proved effective in paediatric cases with recurrent respiratory infections (RRIs), Childhood Asthma, Pneumonia, and Acute bronchitis. Immature immune response is one of the causative factors for RRIs and it also worsens outcomes in obstructive airway diseases.
3. In cases with RRIs, Pidotimod restores Th1/Th2 balance, confers faster disappearance time for fever, clearance of pulmonary rale and cough, and reduces incidence of RRIs and the need for frequent use and also longer course antibiotics for current and future illnesses by improving innate immune response and restoring adaptive immune response.
4. Pidotimod is indicated and proved effective in adults with chronic bronchitis, chronic obstructive pulmonary disease, Bronchiectasis, Community-acquired pneumonia, and Urticaria. A vicious circle of 'infection, inflammation, injury and subsequent infection' is modified with use of pidotimod and observed to play an important role in recurrent respiratory infections, and exacerbations of bronchiectasis and chronic bronchitis. 'Vicious circle hypothesis' as it relates to interaction between bronchial epithelial cells and bacterial products in the amplification of neutrophil induced epithelial damage.
5. Immunological alterations in respiratory diseases worsens disease outcomes. Lung-specific and systemic immune dysfunction facilitate disease exacerbations and thus it needs to be combated with the help of immunomodulators. We recommend the use of this 'novel immunomodulator' Pidotimod to have successful treatment outcome, with impact on mortality and morbidity in RRNs in paediatrics and COPD, bronchiectasis in adults.

Conflicts of Interest: NIL

Research Funding: NIL

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