

A review on the role of Pidotimod in prevention of acute exacerbations of chronic obstructive pulmonary disease

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Abstract

India contributes an extremely high percentage of chronic obstructive pulmonary disease (COPD) mortality estimated to be amongst the highest in the world; i.e. more than 64.7 estimated age standardized death rate per 100,000 amongst both genders. COPD is associated with recurrent periods of acute worsening of respiratory symptoms, termed as acute exacerbations (AE) of COPD. Though, conventional treatment for COPD including antimicrobial therapy, bronchodilators and inhaled corticosteroids (ICS) are available, however, no treatment except lung transplantation significantly improves the lung function or decrease mortality. Since COPD is associated with defective immune responses; therefore, management of COPD should be based on drugs which target the immunological pathways. Pidotimod is an immunostimulant that acts on the innate as well as adaptive immune system has been extensively studied in patients with AECOPD. Pidotimod has shown promising immunostimulatory effects in conditions with underlying cause of suppressed cell-mediated immunity to certain extent, such as chronic bronchitis and recurrent respiratory tract infection (RRTI) in both children and adults with a good tolerability profile. In this review article, we aimed to highlight and revisit the role of various immunostimulants with a special focus on clinical studies of Pidotimod and its beneficial effects in adults with exacerbations of COPD.

Keywords: Acute exacerbations (AE); Chronic obstructive lung disease (COPD); Pidotimod and Immunostimulants.

Introduction

Chronic obstructive pulmonary disease (COPD) is described by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as “a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases”. COPD comprises of chronic bronchitis, small airway disease, and emphysema, existing either separately or in combination [1-3].

COPD affects around 210 million people worldwide. According to the World Health Organization (WHO) fact sheet (2017), and the Global Burden of Disease Study report, a prevalence of 251 million cases of COPD was reported globally in 2016 [4]. The low and middle income countries contribute to >90% of COPD deaths with only India and China contributing to 66% deaths [5]. In different population based studies across India, the prevalence ranged between 2 to 22% among men and 1.2 to 1.9% among women [6, 7]. As per the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 2016 conducted from 1990 to 2016 in India, the contribution of chronic respiratory diseases to the total deaths and disability-adjusted life-years (DALYs) increased from 4.5% (95% UI 4.0–4.9) in 1990 to 6.4% (5.8–7.0) in 2016 [8].

COPD may be punctuated by recurrent periods of acute worsening of respiratory symptoms, called acute exacerbations (AE). It is an event characterized by an increase in dyspnea, sputum volume, and/or increase in sputum purulence. Viral (Rhinovirus, respiratory syncytial virus, and influenza viruses) or bacterial respiratory

infections (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*), followed by other infectious agents including *Pseudomonas aeruginosa*, *Gramnegative Enterobacteriaceae*, *Staphylococcus aureus*, and *H. parainfluenzae*) are identified in 78% of patients with AECOPD [9]. Tobacco smoking, genetic factors, ageing and environmental factors such as chronic infection and oxidative stress are also responsible for aggravating the disease [2, 10]. On an average, the patient experiences three exacerbations/year usually during the winter months. Exacerbations of COPD are associated with accelerated loss of lung function and quality of life and increased healthcare costs and mortality [4, 11].

Antimicrobial therapy, bronchodilators such as; long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), short acting beta agonists (SABA) and inhaled corticosteroids (ICS) are the conventionally prescribed treatment in the management of COPD [12, 13]. These conventional treatments are useful in improving the overall survival of patients; however, no treatment except lung transplantation significantly improves the lung function or decrease mortality.

In COPD, the components of innate immunity; airway epithelial barrier including alveolar macrophages and neutrophils are increased in number. However, their phagocytic and chemotactic properties are reduced [14]. Adaptive immune responses are elicited by the lung tissue antigens in the lungs of patients with COPD, with the participation of cytotoxic CD8+ T cells, T helper1 and Th17 CD4+ cells, and B-cell responses with antibody production aggravates the condition [6, 15]. Therefore, the

pathophysiology of COPD is majorly dependent on body's immune mechanism. Thus, better benefits can be obtained with the choice of treatment which have direct impact on the immunopathology of this disorder [16].

Immunostimulants are a new treatment approach for COPD. Various classes of immunomodulators (bacterial lysates, pre-probiotics, enzyme therapies, biologically active glucans, antibodies and herbal remedies) targeting immune cells such as T cells, antigen-specific Th2 and Th1, IgE and interleukins, CD4+ lymphocyte inhibitors have been studied in the past few decades in patients with COPD [17].

Pidotimod is a synthetic dipeptide molecule, which exhibits immunostimulatory properties. It's potential for immune-stimulation has been evaluated in conditions with underlying cause of suppressed cell-mediated immunity to certain extent, such as chronic bronchitis and recurrent respiratory tract infection (RRTI) in children and adults [18-21]. In this review article, we are focusing on the role of pidotimod in management of COPD and its benefits in reducing the AE-COPD. The article also reflects upon various clinical trials conducted in adult population and comparison of pidotimod with other immunostimulants.

Immunity and COPD Correlation

COPD is a complex disorder accompanied by chronic pulmonary inflammation. Chronic inflammation contributes to lung damage, compromises innate and adaptive immune responses, and facilitates the recurrent episodes of respiratory infection that punctuate and further contribute to the pathological manifestations of the stable disease. It involves the interplay of various defective immune responses that contribute to intermittent respiratory infections and increases

the disease severity [6]. Inflammatory cells such as neutrophils (usually found in sputum of smokers but increased in COPD and related to disease severity), and macrophages (present in airway lumen, lung parenchyma, and bronchoalveolar lavage fluid) play major role in COPD. Activation of these inflammatory cells results in producing more inflammatory mediators and proteases and may show defective phagocytosis. Possibly due to colonization and infection, B and T lymphocytes get increased in peripheral airways and within lymphoid follicles. There is seen increase in number of both CD4+ and CD8+ cells in the airway wall and lung parenchyma. The number of CD8+ T cells (Tc1) and Th1 cells also get increased which secrete interferon-γ and express the chemokine receptor CXCR3 [22, 23].

One of the key etiological factor of COPD pathogenesis is cigarette smoke (CS) that induces chronic lung inflammation is [6]. Exposure to inhaled irritants activates structural and inflammatory changes within the respiratory tract [24]. It leads to the production of potent inflammatory cytokines and chemo-attractant in the lung microenvironment that collectively induce a state of chronic inflammation [25]. Pathogenic microbes associated with acute and chronic infection also influence disease progression. Activation of signal transduction pathways such as nuclear factor kappa-B (NF-κB), phosphoinositide-3-kinase, p38 mitogen-activated protein kinases and IFN regulatory factors begins with recognition of pathogen-associated molecular patterns (PAMPs), by pattern recognition receptors (PRRs) which are expressed on epithelial and innate immune cells. This results in the production of proinflammatory mediators such as cytokines and chemokines [26]. Fig. 1 represents the pathophysiology of COPD.

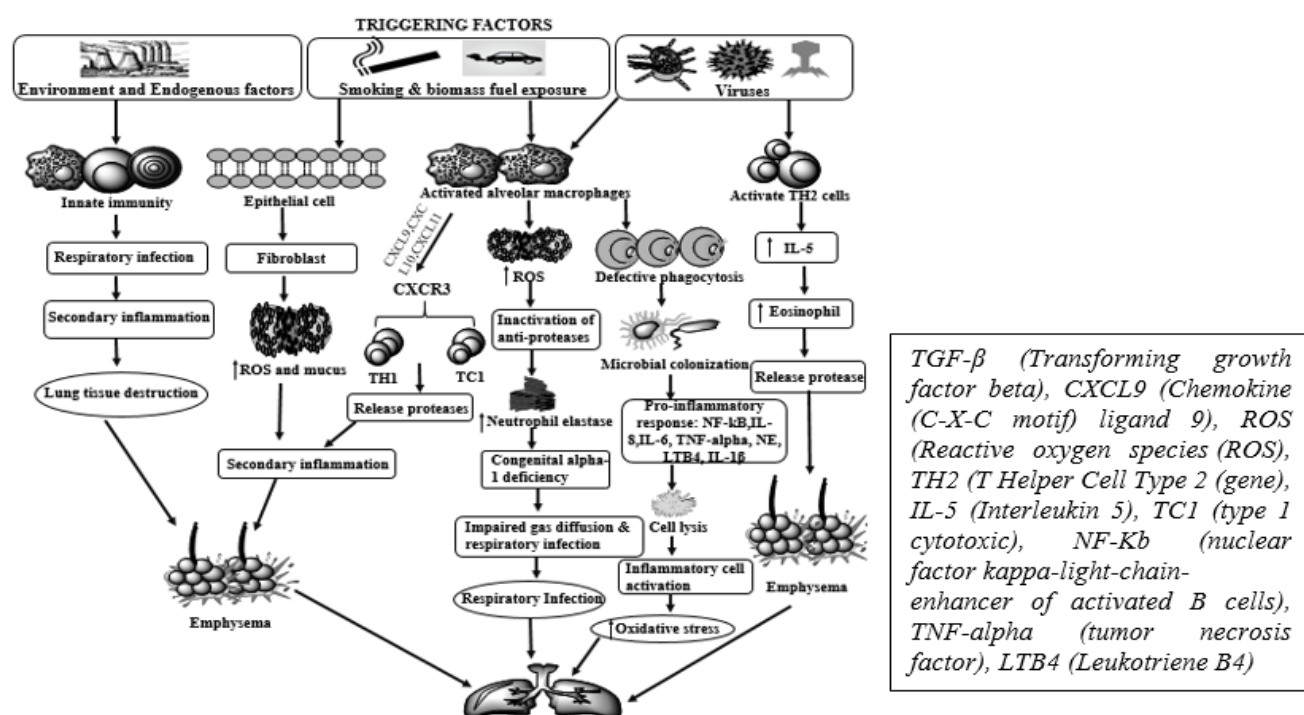


Fig. 1: Pathogenesis of COPD

Patients of COPD are prone to various respiratory infections which exacerbates the symptoms leading to AECOPD. In COPD, not only the initial response to pathogens but also the strength with which the adaptive immune system responds to such challenges is impaired [24]. Such weakened immune responses can lead to recurrent infections [27]. To counteract these over exuberant chronic inflammatory response, immunosuppressive pathways are augmented to prevent recurrent infections [28].

Role of Immunostimulants in Management of COPD

In the last few decades immunostimulants are extensively studied for the treatment of RRTI. These agents

help to restore the immunological activity that is partially suppressed [29]. Immunostimulants act by inhibiting inflammatory pathways including facilitation of antigen presentation to T cells, opsonization, enhancing the cellular secretions to neutralize bacterial toxins. These immune secretions stimulate cell differentiation and proliferation of lymphocytes, by inhibiting the effects of the released cytokine or mediators and interleukins [4]. There are different types of immunostimulants based on their mechanisms for the management of COPD. Various immunostimulants with their mechanism and clinical effectiveness are summarized in Table 1.

Table 1: Immunostimulants: classification, mechanism and clinical efficacy

Immunostimulant	Mechanism of Action	Clinical Effectiveness
<p>Monoclonal Antibodies</p> <p><i>Daclizumab</i> [42].</p> <p><i>Omalizumab</i> [43]</p> <p><i>Mepolizumab</i> [44]</p> <p><i>Reslizumab.</i> and <i>Benralizumab</i> [45]</p>	<p>The drug is specific for CD25 which are expressed by activated T-cells. It acts by inhibiting IL-2 stimulated proliferation by blocking the IL-2 receptor alpha chain.</p> <p>It is a recombinant humanized anti-IgE monoclonal IgG antibody.</p> <p>It is a humanized anti-IL-5 Mab.</p> <p>anti-IL5 Mabs</p>	<p>The drug showed 10% improvement in FEV1, 2/3rd reduction in asthma AE patients</p> <p>Studies with omalizumab treatment in adults with severe asthma, atopy, and an IgE level between 30 to 700 IU/mL, demonstrated a significant reduction in AE compared to placebo.</p> <p>The drug was tested in non-phenotyped mild intermittent and moderate persistent asthma subjects. It showed lacked favorable clinical outcomes also despite reduced eosinophil counts.</p> <p>These drugs were clinically evaluated in patients who had inadequately controlled asthma and elevated blood eosinophil levels. Both drugs showed significant reductions in AE</p>
<p>Immunostimulatory DNA molecules, CpG.</p>	<p>These are TLR-9 agonists which act by stimulating an antigen-specific Th2 to Th1 shift</p>	<p>It improves the safety margin of allergen immunotherapy by 50% reduction in symptoms with decreased rescue medication</p>
<p>Pleuran (1,3/1,6-β-glucan from <i>Pleurotus ostreatus</i>). [46]</p>	<p>Pleuran is an insoluble 1,3/1,6-β-glucan from mushroom <i>Pleurotus ostreatus</i>. It acts on immune cells of the Peyer's patches in the gut that stimulates innate and subsequently adaptive immune responses is initiated, mainly through release of pro-inflammatory cytokines (complement components, IL-1α/β, IL-6, IL-8, IL-12, TNF, eicosanoids, etc.) which improves the resistance to invading pathogens</p>	<p>The drug has shown reduction in incidence and duration of bacterial exacerbations in patients with AE COPD.</p>
<p>AM3 is an orally effective immunomodulator [47, 48]</p>	<p>It can normalize the defective antimicrobial functions of the immune system by altering the defective functions of peripheral blood natural killer and phagocytic cells of COPD patients</p>	<p>Various clinical studies have established the effectiveness of AM3. It improves health-related quality of life in COPD patients</p>
<p>OM-85 is a bacterial extract [49, 50].</p>	<p>It is an immunomodulator of interferon-β production and inflammasome activity. OM-85 induces interferon-β through the toll-like receptor adaptors Trif and MyD88 in bone marrow-derived dendritic cells</p>	<p>The drug has proved efficacy in RRTIs. Various studies have demonstrated the capacity of OM-85 to trigger immunomodulatory and protective immune mechanisms against diverse pathogens in vivo, including influenza and respiratory syncytial virus as well bacterial superinfection following influenza</p>

Pidotimod: Background and Mechanism of Action

Pidotimod is a synthetic dipeptide molecule with biological and immunological activity. It acts on both the adaptive and the innate immune responses [30]. The drug was formulated by PoliIndustria Chimica, an Italian pharmaceutical company in 1992. The drug is listed in the WHO indexed list of immunomodulators and is available in China, Italy, Mexico, Greece and Russia under different brand names [31]. In India, the drug was approved in 2011 by

the Drug Controller General India (DCGI) for respiratory infections in primary and secondary immune deficiencies with alteration of maturation in T cells. It is marketed under brand name Immulina400mg and 800mg tablets and Immulina200ml oral liquid formulation marketed by Wockhardt, Mumbai, India [32]. A brief overview on physical and pharmacokinetic properties and its dosage in different age groups is summarized in Fig. 2.

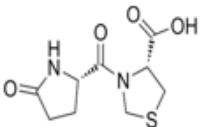
PHYSICAL PROPERTIES		PHARMAKOKINETIC PROPERTIES	DOSAGE
Molecular Weight	244.27	Oral Bioavailability: 43-45%	Adults 800 mg BD for 8 days in combination with amoxicillin/ clavulanic acid (1 gram twice daily). Prophylaxis: 800 mg orally once daily (before breakfast) for up to 2 months.
Molecular Formula	C ₉ H ₁₂ N ₂ O ₄ S	T_{max} - 1.5 hours (range 1.3 to 1.8 hours)	
Chemical Structure		Food Interaction: Food reduces the bioavailability up to 50%, therefore, pidotimod should be given two hours before or two hours after meals.	
Solubility	Soluble in water to 100 mM and in ethanol to 10 mM	Distribution: Low protein binding of 4% with a volume of distribution of 30 liters.	Children For 2 to 8 yr: 400 mg orally BD for 15 to 20 days +standard Ab therapy. Maintenance dose : 400 mg/day, without additional Ab for 60 days Prophylaxis (2 to 13 yr): 400 mg OD for 60 days.
Storage Instructions	Store at room temperature for up to 12 months	Metabolism : Undergoes minimal hepatic metabolism. Within 24 hours of administration, approximately 45% of an oral dose (200 to 800 mg) gets excreted unchanged in the urine.	Geriatrics No dose reductions in older patients are required
		Elimination Total plasma clearance after oral administration, is approximately 11 litres/hour.	
		Elimination half-life: 4 hours.	

Fig. 2: Pidotimod: General properties and dosage

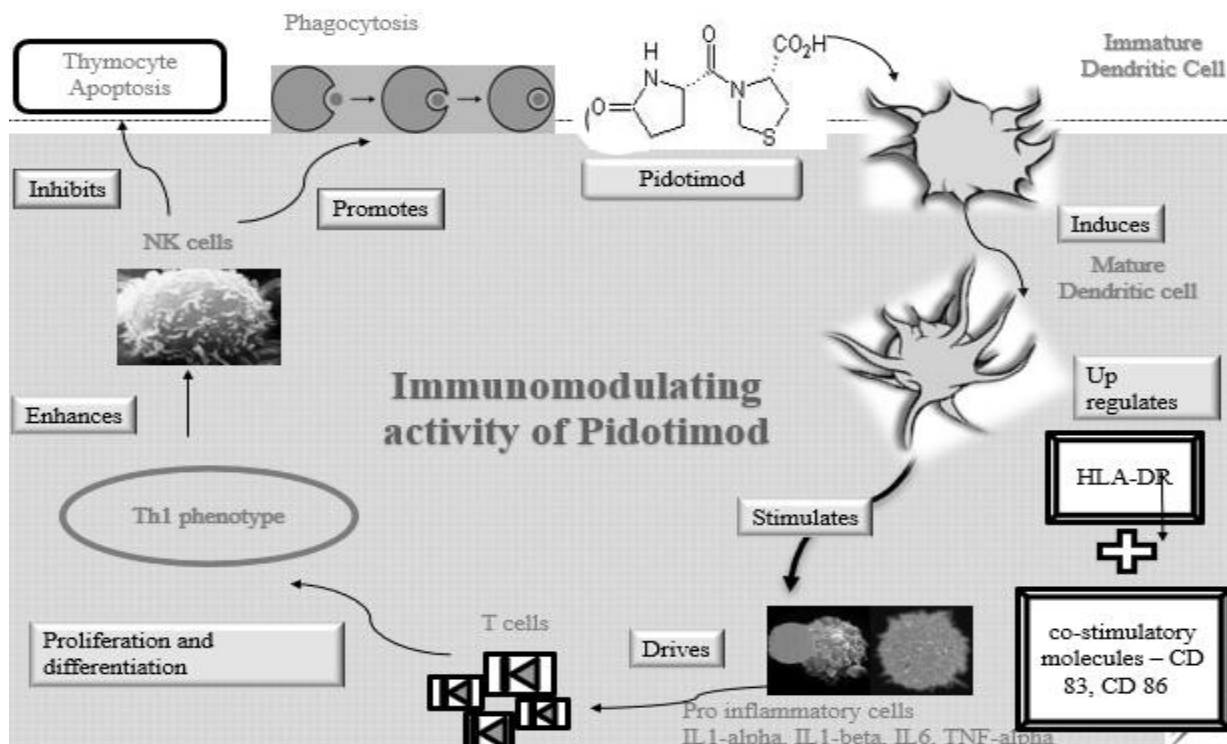
Pidotimod’s immunological activity initiates by acting on dendritic cells (DCs). It induces DCs’ maturation and also up-regulates the expression of HLADR and of co-stimulatory molecules. The stimulated DCs further release pro-inflammatory molecules which drives T-cells proliferation and differentiation towards a Th1 phenotype that enhances natural killer (NK) cells and promotes phagocytosis [18, 30]. Pidotimod directly increases levels of Th1-related cytokines and suppresses Th2 cytokines in children with frequent infections [33]. The drug was earlier tested in preclinical models to understand its immunostimulating activity. In mice previously treated with steroids, cyclophosphamide or methotrexate as immunosuppressant agents, Pidotimod showed the elicited adaptive immune responses by restoring the proliferative response of T lymphocytes, secretion of Th1 cytokines and by protecting thymocytes from apoptosis [34].

Pidotimod upregulates the expression of toll-like receptor-2 (TLR-2) that are present on airway epithelial cells. It has important effects on intercellular adhesion molecule (ICAM-1), IL-8 release and others. Pidotimod has the ability to modulate the inflammatory cascade triggered by TLR ligands via up-regulation of the nucleotide binding and oligomerization domain receptor (NOD-like receptor)

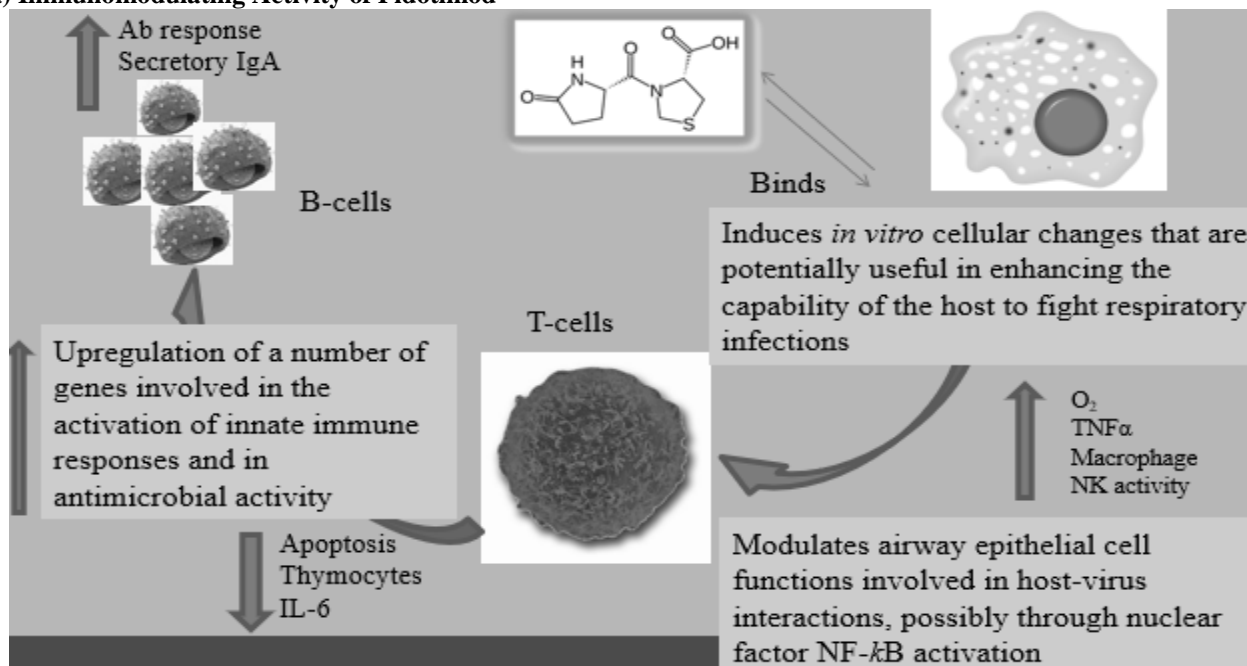
NLRP12 [18]. Fig. 3 explains the immune-stimulating activity of Pidotimod. Based on the receptors and target-based mechanisms of pidotimod on body’s immune system, it has also been studied for specific biomarkers for which the effectiveness of drug could be evaluated. A study by Carta et al., evaluated if Pidotimod could stimulate the inflammatory and immune effector cells. The study explained the immunomodulatory effect of Pidotimod. It described how it modulates the functions of airway epithelial cell on NF-kB cytoplasmic expression and its nuclear translocation associated with an increased TLR-2 expression. Using the Western blot analysis, it was reported that the constitutive TLR-2 expression was significantly increased after exposure to all the stimuli. Finally, while a remarkable inhibition of TNF-α -induced ERK1/2 phosphorylation was observed in the presence of pidotimod. Both TNF-α and pidotimod were found to be effective in inducing NF-kB protein expression in the cytoplasm and its nuclear translocation [35].

Results from one of the recent studies performed with pidotimod to determine its effectiveness on mouse bone marrow-derived macrophage polarization and its function showed a significant increase of M2 marker gene expression (Arg1, Fizz1, Ym1, MR) (p < 0.01) in IL-4-induced M2 macrophage treated mice[36]. Similarly, in other studies such

as in a model of *Mycoplasma pneumoniae* infection, NK cell markers were down regulated; however, data suggested that this might improve resistance to further infection [37].



3 (a) Immunomodulating Activity of Pidotimod



3 (b) Pidotimod Binding Site and Cascading Effect

Fig. 3: Mechanism of action of Pidotimod

CD: complementary driven, IL: Interleukin, TNF: tumour necrosis factor, NK: natural killer cells, HLA DR: human leukocyte antigen (major histocompatibility complex (MHC) class II isotypes)

Clinical Studies of Pidotimod in Management of COPD (Table 2)

Table 2: Clinical studies for pidotimod in acute exacerbations in chronic bronchitis (AECB)

Author and Year	Study Title	Study Design	Key Findings
Pozzi et al., 1994	Pidotimod in treatment of patients affected by bacterial exacerbations of chronic bronchitis	Multicentre, double-blind, placebo controlled, parallel group study; N = 137, Length = 45 days <i>Pidotimod Group:</i> N = 68 (50 males, 18 females, aged 40 to >69 years) <i>Placebo Group:</i> N = 69 (53 males, 16 females, aged 40 to >69 years)	<i>Pidotimod Group:</i> Sputum volume decreased by 36.8%. Changes of potentially pathogenic bacteria in sputum – 30.6% at Day 0 to 8.1% at Day 8. <i>Placebo Group:</i> Sputum volume decreased from 22.6% to 9.7%. <i>Pidotimod Group:</i> Decrease in symptoms relevant to exacerbations Total number of positive responses were increased at the end of treatment (D15) in Pidotimod Group (+12.2%) more than in the Placebo Group (+6.8%)
Benetti et al., 1994	Ex vivo Evaluation of Pidotimod activity in patients with chronic obstructive pulmonary disease	Multicentre, placebo controlled, parallel group study; N = 52, Length = 30 days. <i>Pidotimod Group:</i> N = 26 (13 males, 13 females, aged 45 to 82 years) <i>Placebo Group:</i> N = 26 (10 males, 16 females, aged 29 to 80 years) Dose: <i>Pidotimod Group:</i> 800mg twice daily <i>Placebo Group:</i> Matching placebo	Significant increase of Stimulation Index (SI) was observed in Pidotimod group on Day 15 and Day 30 Increase of T-cell blastogenesis appeared after 15 days of treatment and lasts for 5 weeks after therapy withdrawal
Ciaccia et al, 1994	Pidotimod activity against chronic bronchitis exacerbations	Multicentre, placebo controlled, double blind study; N = 181, Length = 120 days (Treatment Phase – 2 months; Follow-up – 3 months). <i>Pidotimod Group:</i> N = 251 <i>Placebo Group:</i> N = 263 Dose: <i>Pidotimod Group:</i> 800mg twice daily <i>Placebo Group:</i> Matching placebo	Pidotimod group had lesser exacerbations even in winter season as compared to placebo (p <0.05) Pidotimod group had lesser antibiotic days as compared to placebo (p <0.05)
Chen et al., 2010	Innate Immune deficiency in the elderly with chronic obstructive pulmonary disease at acute exacerbations and medication intervention to it	Randomized trial <i>Trial Group:</i> N=35 <i>Control group</i> N=35 with a additional health control group of 20 elderly people. Dose <i>Trial Group:</i> Pidotimod was prescribed for 30 days, For the first 15 days, 800 mg (two tablets), twice a day; and for the second 15 days 800 mg as maintenance dose, once a day.	The levels of CD14, CD158b and HLA-DR of the patients in both trial and control groups were lower than those in the health group (p=0.05). Prior to treatment, the elderly COPD intervention group showed lower levels of CD14, CD158b, HLA-DR, as compared with the 30 days of pidotimod treatment (p=0.05). At the 10th day the clinical symptoms such as cough, amount of expectoration, pulmonary wet rales were obviously improved, with a significant difference as compared with in the control group (p=0.05).
Cogo R et al., 2014	Pidotimod activity in patients affected by COPD	Randomized trial N= 85 <i>Treated group:</i> Pidotimod (800mg) once a day for 15 days/month for 2 months). <i>Study period:</i> 4 months including 2 months follow-up.	In the 16 patients from the treatment group, one or more exacerbations were registered, compared to the 29 patients in the control group. No significant difference was observed in the symptoms between the two groups of patients.

Few studies have been conducted in adult patients with chronic bronchitis of stage I, II and III. One of the study by Pozzi *et al.* evaluated the effect of pidotimod (800 mg twice a day) in combination with antibiotics (amoxicillin and clavulanic acid) in comparison to placebo and antibiotic group for a period of 45 days in adults. Within 8 days of treatment, there was a decrease in sputum volume by 36.8% in the pidotimod group. There were reduced levels of potentially pathogenic bacteria in sputum; 8.1% in the pidotimod group and 9.7% in the placebo group. A faster and higher decrease in other clinical parameters like cough, dyspnea, lung sounds, anorexia, and asthenia in group treated with pidotimod as compared with the placebo group was observed. At the end of study, all patients treated with pidotimod had normal body temperature and two patients on placebo still had hyperpyrexia [38]. Similarly, Benetti *et al.* demonstrated pidotimod to be clinically effective in 52 adult patients with COPD treated with 800mg Pidotimod or placebo twice a day for 30 days. A significant increase of lymphocyte stimulation index was seen in treated patients on day 15 and even more at the end of treatment. No changes were reported in the placebo group [21]. In another study conducted to evaluate the efficacy of pidotimod in infectious exacerbations of chronic bronchitis, there were reported fewer and shorter infectious episodes in the pidotimod group. It was a double-blind, placebo-controlled study of parallel groups conducted over a period of 5 months (60 days of treatment and 90 days of follow-up) in 580 patients. There was a significant difference during the follow-up period in all patients and also during the treatment period in subjects with a less severe history, as compared with placebo [39]. Another study by Chen *et al.*, investigated the role of pidotimod in elderly patients (n=70) who were immune deficient and had AECOPD. Patients were randomized in three groups; trial (n=30), control (n=28) and healthy (n=20). At the end of treatment, it was reported that the levels of CD14, CD158b and HLA-DR of the patients in the trial and control groups were lower than those in the healthy group (p=0.05). At the Day 10 of treatment, there was seen significant improvement in clinical symptoms such as cough, amount of expectoration, pulmonary wet rales as compared with the control group (p=0.05). The results favored pidotimod administration for 30 days; 800 mg (two tablets), twice a day for first 15 days followed by 800 mg as maintenance dose (once a day) for the rest 15 days [40].

Another study by Cogo *et al.*, evaluated the role of Pidotimod in reducing the frequency of physicians visits and number of prescriptions. The study enrolled 85 patients affected by COPD (GOLD III) subjected to influenza vaccination. The patients were randomly divided in two groups. Treated group was administered (Pidotimod (800mg) once a day for 15 days/month for 2 months). The patients were evaluated for AECOPD for a total period of 4 months including 2 months follow up. The results showed that Pidotimod is an efficacious drug as immunostimulant. In the 16 patients from the treatment group, one or more exacerbations were registered, compared to the 29 patients in the control group. There was no significant difference

reported in the symptoms observed between the two groups of patients. There were minor incidence of exacerbations in the treatment group. The results concluded that Pidotimod offers better quality of life, including less physician visits and/or drugs prescriptions and finally a reduction in the disease progression [41].

All the above studies favor Pidotimod as safe and cost-effective therapy for the clinical management of exacerbation of COPD. The drug provides better quality of life. It helps in faster and better remission of symptoms by restoring and improving immune responses. It is effective in improving the clinical symptoms like cough, dyspnea, asthenia, anorexia and reduced sputum volume and also reduce the episodes of AE in COPD [38, 39].

Conclusions

Pidotimod is a safe, well tolerated and provides a valuable treatment option in prevention of recurrence of AECOPD. Since, it is also effective in patients prone to infectious exacerbations, it can be a suitable treatment approach for prophylactic treatment in such patients. There are few studies available on the cost effectiveness of drug.

Conflict of Interest: The authors Kundan Nivangune, Snehal Muchhala and Rishi Jain are full time employees in medical affairs team of Wockhardt Ltd.

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