Research Article ISSN 2768-6647

Medical and Clinical Case Reports

Real-World Experience of Pidotimod in Mexican Pediatric Patients

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Received: 05 Aug 2024; **Accepted:** 14 Sep 2024; **Published:** 21 Sep 2024

Citation: Ramírez Sandoval Ma de Lourdes Patricia, López Pérez Gerardo Tiburcio. Real-World Experience of Pidotimod in Mexican Pediatric Patients. Med Clin Case Rep. 2024; 4(2): 1-7.

ABSTRACT

Introduction: *Pidotimod is an immunostimulant molecule widely used to treat respiratory tract infections (RTIs) in children. It may also be useful for the treatment of allergic respiratory diseases. This real-world study evaluated the incidence of recurrent RTI after treatment with pidotimod in children with acute RTI or allergic disease in Mexico.*

Methods: *This observational, cross-sectional, retrospective, two-center study included medical records of children with active RTI or risk of recurrent RTI who were prescribed pidotimod for acute/subacute or chronic respiratory disease in two private clinics in Mexico City.*

Results: *Fifty children were included, (n=27, 54%) were girls, (n=39, 78%) were between 2 and 11 years of age and (n=10, 20%) were less than 2 years old, with a duration of follow-up that ranged between 11 and 384 days. The majority (n=36, 72%) received Pidotimod for both acute illness and prophylactic continuation; four children received Pidotimod only prophylactically. Forty children (80%) were prescribed Pidotimod for recurrent infection. The number of respiratory episodes decreased from 50 (100%) to 2 (4%), demonstrating an efficacy of 96%. Of the total patients treated with Pidotimod, 96% did not experience another infection during the follow-up period. No adverse events of Pidotimod were reported and almost all (n = 49, 98%) of the children found the taste of Pidotimod acceptable.*

Conclusions: *Pidotimod demonstrated 96% efficacy in recurrent respiratory infections and was well tolerated, supporting its continued use for the treatment of pediatric respiratory conditions, including recurrent RTIs and allergic diseases.*

Keywords

Synthetic immunoregulatory Pidotimod, Respiratory tract infections, Acute and recurrent respiratory infections, Infectious and non-infectious respiratory tract infections, Upper and lower respiratory tract infections in children.

Introduction

Respiratory tract infections (RTIs) are one of the most common infections in clinical pediatrics, especially in young children, although many RTIs have viral etiology, antibiotics are commonly prescribed as treatment, contributing to the development of microbiota selection and resistance to antibiotics, recurrent respiratory infections are associated with substantial morbidity, prevention is the ideal alternative, but the current pediatric vaccines that we have in the country only protect against a small number of respiratory pathogens, such as influenza, Streptococcus pneumoniae and Bordetella pertussis [1].

The frequency of RTIs in young children is thought to be influenced by an immature immune response involving defects of cells such as neutrophils, macrophages, dendritic cells, natural killer (NK) cells, B lymphocytes, and T lymphocytes [2,3]. Pidotimod (Adimod®) is a synthetic dipeptide molecule that exerts immunostimulating effects on both innate and adaptive immune responses, improving

the immune system's ability to combat infections such as RTIs [3,4], in addition to enhancing the beneficial effect of vaccines [5,6]. Pidotimod acts through multiple mechanisms. It positively regulates the expression of toll-like receptor (TLR) [2], leading to the release of cytokines and chemokines involved in response to bacterial and viral infections [7]. It also induces the maturation of dendritic cells, resulting in the activation of natural killer cells and T cells, and leading to a polarization towards a Th1 phenotype, which is responsible for defense against viruses and bacteria [4]. The resulting reduction in the Th2 response leads to a decrease in the production of immunoglobulin E (IgE), which gives Pidotimod potential usefulness for the treatment of allergies and infections [8].

Several clinical studies have evaluated the effectiveness of pidotimod in children, including children with recurrent respiratory tract infections and otorhinolaryngology [9,10], allergic rhinitis [11], and asthma [8]. Published studies in adults have evaluated pidotimod for chronic obstructive pulmonary disease. (COPD), urinary tract infection and vulvar papillomatosis, as well as recurrent respiratory tract infections [9,10,12]. Pidotimod has also been evaluated in people living with human immunodeficiency syndrome (HIV) [13].

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, interventional studies were reported, one of which prescribed Pidotimod as an immunoregulator with good results [14,15].

There was also an increased need to treat patients with RTIs of viral and/or bacterial origin. In 2022, acute RTIs were the most common disease in Mexico, with almost 16 million cases reported [16], highlighting the need to strengthen immune responses in vulnerable populations. As a result, Pidotimod was frequently recommended for the treatment and prevention of RTIs in children during this period. However, real-world evidence on the characteristics of children with RTIs and allergy receiving Pidotimod is limited. The objective of the present study was to describe the characteristics of a series of pediatric patients with RTI or allergic disease who received Pidotimod in Mexico during the COVID-19 pandemic, and to evaluate the incidence of recurrent infection after treatment with Pidotimod.

Materials and Methods

This is an observational, cross-sectional, retrospective, two-center and non-interventional study. Clinical records of children <18 years of age who were prescribed pidotimod for acute/subacute respiratory disease or chronic respiratory disease of the upper and/or lower respiratory tract at two participating centers were included from February 28, 2020 to November 15, 2020. 2023. Children were prescribed pidotimod for acute illness (400 mg every 12 hours for 15 days), prophylaxis (400 mg per day for 60 days), or both consecutively.

Enrolled children had active RTIs or risk factors for recurrent RTIs. Active RTI was defined as the presence of fever ≥38°C (tympanic or axillary) and ≥2 of the following respiratory symptoms: cough, rhinorrhea, nasal congestion, pharyngeal pain, ear pain, respiratory distress, or wheezing. Risk factors for recurrent RTI included clinical signs of an immature immune system (e.g., <5 years of age, Down syndrome) or initiation of day care. Children were excluded if: i) their parents or guardians were unable to adequately administer pidotimod; ii) they did not complete the indicated number of days of treatment; iii) were hospitalized when pidotimod was first administered; iv) were lost to follow-up; v) had used immunosuppressants (for >14 days) or other medications that modify the immune system during the study period; vi) received other immunoregulators or immunostimulators during the study period. Ethical approval was not required as this was a retrospective study.

Baseline characteristics and demographic data collected included reason for pidotimod prescription. The diagnoses were made based on the doctor's impression guided by the conceptual definitions of the clinical practice guidelines for respiratory infections and allergies published by the Mexican government [17]. Acute respiratory diseases constituted a group of diseases that occur in the respiratory system, starting suddenly and lasting less than 2 weeks. Definitions: rhinosinusitis, inflammatory disease of the paranasal sinuses that is classified as acute <3 weeks, subacute from 3 to 10 weeks and chronic more than 3 weeks [18]. The common cold: disease of the upper respiratory tract with main symptoms of nasal obstruction and rhinorrhea, otitis media (AOM) without effusion, presence of erythema of the tympanic membrane, otalgia that interferes with activities or sleep and AOM with effusion due to bulging of the tympanic membrane, limitation or absence of mobility of the tympanic membrane, air-fluid level in tympanic membrane and otorrhea [19]. Abrupt-onset pharyngotonsillitis with the presence of high fever, headache, sore throat, attack on general condition and irritability, dysphagia or odynophagia, painful anterior cervical lymphadenopathy, occasional otalgia, erythema of the pharynx, pharyngotonsillar or tonsillar exudate yellowish, petechiae on the soft palate and isthmus of the fauces. Asthma crisis was an abrupt and/or progressive deterioration of asthma symptoms with shortness of breath, wheezing, respiratory distress, or a combination of these, associated with respiratory compromise. Bronchiolitis is the inflammation or obstruction of the small airways caused in most cases by a viral infection during the first years of life [20]. Allergic respiratory disease was chronic or recurrent respiratory symptoms caused by allergy, confirmed by skin testing to allergens. Recurrent respiratory infection the presence of more than 3 episodes in 6 months. The reason for Pidotimod prescription was classified as bacterial, viral or allergic based on previous diagnoses, or preventive for those without confirmed infection at the start of treatment.

Additional outcomes included the number of respiratory infections after Pidotimod prescription, reports of adverse events due to Pidotimod, and taste acceptability of Pidotimod. Acceptability was reported by parents, according to clinical practice, by asking them if their child accepted (or seemed to accept) (yes/no). Data were

captured using Microsoft Excel and analyzed using SPSS version 26.0. Data are presented as mean (±SD) for continuous variables and mean (range) for categorical variables.

Results

Demographic data: of 120 clinical records reviewed, 43 (61%) were excluded because parents did not correctly administer Pidotimod, 27 (39%) did not complete the indicated days of treatment, and 50 (41%) met the inclusion criteria Therefore, they were included for the analysis, the majority of patients treated were in 2022 with 22 (44%) of the cases. By season, 14 (28%) were attended in spring and summer with the same percentage (Table 1).

Year of admission	Patients, n (%)	Winter (21 Dec–21 Mar)	Spring (22 Mar–21 Jun)	Summer (22 Jun–21 Sep)	Autumn (22 Sep–20 Dec)
2020	10 (20)	2	3	2	3
2021	10 (20)	3	2	2	3
2022	22 (44)	3	8	8	3
2023	8 (16)	4	1	2	1
Total	**50**	**12**	**14**	**14**	**10**

Table 1: Year and season of admission.

The follow-up of the patients ranged between 11 and 384 days, 27 (54%) of the patients were female, by age group, 39 (78%) were between 2 to 11 years of age and 10 (20%) were less than 2 years of age, 36 (72%) of patients received Pidotimod for acute illness and for prophylactic continuation (Table 2).

Characteristics	Study population (N=50)
Gender	
Female	27 (54)
Male	23 (46)
Age	
Median (range), years	6.5 (0.7–11.5)
<2 years	10 (20)
2 to 11 years	39 (78)
12 to 17 years	1 (2)
Pidotimod regimen	
Acute illness	10 (20)
Acute illness and prophylactic continuation	36 (72)
Prophylaxis	4 (8)
Recurrent infection	
Upper respiratory tract	38 (76)
Lower respiratory tract	2 (4)

Table 2: Demographic characteristics.

Data are n (%) unless otherwise indicated.

Forty children (80%) were prescribed Pidotimod for recurrent infection (Table 2).

The most common Diagnosis that warranted management with Pidotimod was acute rhinosinusitis in 16 (32%) followed by recurrent common cold with 6 (12%) cases (Figure 1).

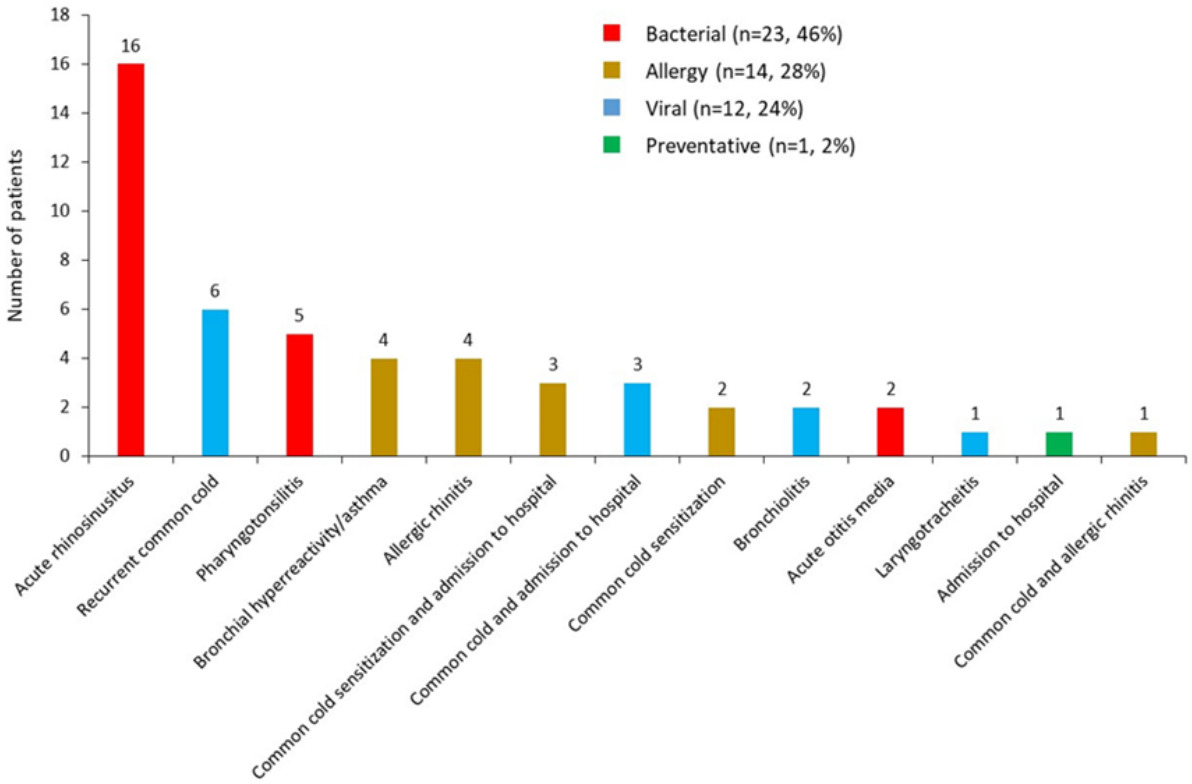

Figure 1: Diagnosis requiring treatment with pidotimod.

The majority of children had a previous respiratory infection during the last 6 months, 18 (36%) had 4 to 7 episodes, followed by 21 (42%) who had 1 to 3 episodes (Figure 2).

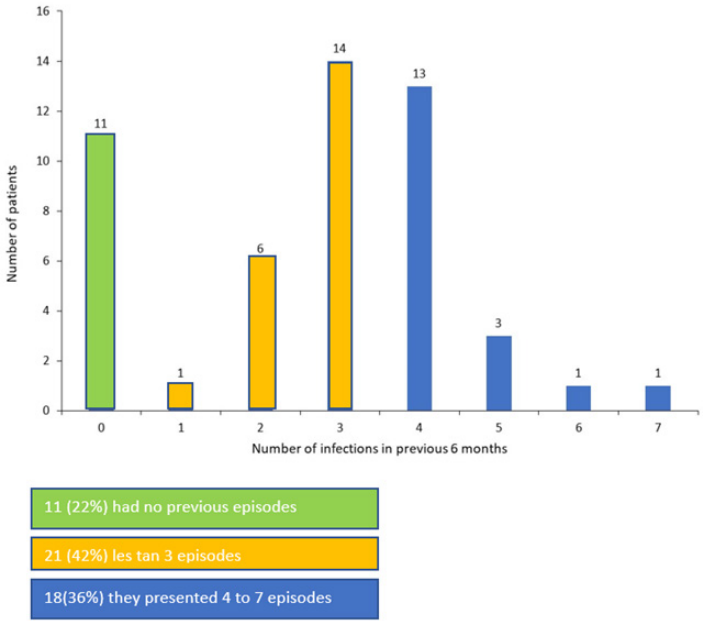

Figure 2: Number of infections during the previous 6 months.

The most common clinical manifestations of respiratory tract infection were rhinorrhea 47 (94%), cough 45 (90%), and nasal congestion 45 (90%) and the average duration was 4 days (Table 3).

Clinical manifestations	Patients, n (%) (N=50)	Duration of symptoms, median (range)
Rhinorrhea	47 (94)	3.7 days (1–8)
Nasal congestion	45 (90)	3.9 days (1–9)
Coughing	45 (90)	4 days (2–7)
Pharyngeal pain	31 (62)	4.8 days (1–9)
Fever	9 (18)	7.6 days (1–8) [38.3°C (38–39)]
Ear pain Unilateral ear pain Bilateral ear pain	12 (24) 6 (12) 6 (12)	7.3 days (1–8)
Wheezing	4 (8)	8.7 hours (2–7)
Respiratory difficulty	2 (4)	8 hours (3–6)

Table 3: Manifestations and duration of respiratory infection.

When classifying respiratory infections by their clinical characteristics, 23 (46%) were of infectious origin (acute rhinosinusitis, AOM, Pharyngotonsillitis) followed by non-infectious "allergic" in 14 (28%) (Figure 1).

The number of upper respiratory tract infectious episodes before Pidotimod was 44 (88%) to decrease to 2 (4%) episodes after treatment with Pidotimod and for lower respiratory infections 6 episodes (12%) decreased to zero (Table 4).

Characteristics	Number of infections before Pidotimod	Number of infections after administering Pidotimod
Upper respiratory tract infections Acute rhinosinusitis	16 (32%)	0
Allergic rhinitis	4(8%)	0
Laryngotracheitis	1 (2%)	0
Recurring Common cold	6(12%)	2(4%)
Common cold and admission to day care	3(6%)	0
Common cold and sensitization and admission to day care	3(6%)	0
Common cold and sensitization	2(4%)	0
Entry to day care	1(2%)	0
Acute otitis media	2(4%)	0
Pharyngotonsillitis	5(10%)	0
Common cold and allergic rhinitis	1(2%)	0
Lower respiratory tract infection Bronquial hyperreaction	4 (8%)	0
Bronchiolitis	2 (4%)	0

Table 4: Episodes of respiratory infections before Pidotimod and after Pidotimod.

Almost all 49 children (98%) found the taste of Pidotimod acceptable.

Discussion

In this retrospective, observational, real-world study in pediatric patients with RTIs or allergic diseases in Mexico, low adherence to the treatment recommended to parents/guardians was observed, which is why only 50 patients were included, a situation that has been observed in other studies [21], however it is worth mentioning that parents/guardians were made aware of the importance of both giving the medication to their child according to the instructions and of monitoring.

The majority of patients seen were in 2022 with 22 (44%) of the cases and fewer cases in previous years likely due to the use of non-pharmaceutical interventions for COVID-19, resulting in an overall reduction in the transmission of respiratory pathogens. By season, 14 (28%) were attended in spring and summer with the same percentage (Table 1) without significant difference.

The follow-up of the patients ranged between 11 and 384 days, the extent of the follow-up was due to the fact that in the first visit the treatment in the acute phase when the child is sick and the prophylaxis phase are explained to the parents/guardians and They are given an appointment at 30 days and 60 days, but they do not return to their appointment, probably due to their financial situation, and they are seen again until another event. That is the moment in which it is verified whether (yes or no) Pidotimod

was administered. Therefore, it was not possible to determine the duration of protection of pidotimod after acute RTI or during prophylactic therapy in this study. However, a limitation of this study included the long follow-up time (11 days to >1 year).

27 (54%) of the patients were female, which had no statistical difference, and does not differ from other published studies. Due to age, 39 (78%) were between 2 to 11 years of age, and 10 (20%) were less than 2 years of age, other studies have been studied in the pediatric population [22]. However, in a study carried out in India in which children from 1 to 12 years of age with recurrent upper RTI participated, a statistically significant improvement in the severity of symptoms in patients treated with Pidotimod as an adjuvant to standard antibiotics, compared to placebo plus antibiotics [23], the decision to prescribe pidotimod as an immunoregulator to children under 2 years of age was individualized to the number of previous respiratory episodes of RTI and the clinical characteristics. Of each patient, all had a good clinical response. The younger the children, the more immature their immune system is [12,24], because they have not been in contact with multiple microorganisms and for this reason, the children present more viral respiratory infections. bacterial or allergic or a viral aggregation and bacterial over aggregation, providing with Pidotimod is to help the immune system. More studies would be needed to determine the efficacy and safety of pidotimod in children under 2 years of age.

The majority of children 36 (72%) of the patients received Pidotimod, both for the acute illness and for prophylactic continuation (table 2), 4 children did not have infection at the time of prescription and received Pidotimod prophylactically, this study is consistent with other previous clinical studies [9,10,17,18] Forty children (80%) were prescribed. Pidotimod for recurrent infection (Table 2) A systematic analysis demonstrated that Pidotimod reduced reinfection rates among people with acute RTI compared to placebo without safety concerns [9]. The most common diagnoses that led to the prescription of Pidotimod were acute rhinosinusitis (n = 16, 32%) followed by recurrent common cold (n = 6, 12%) and pharyngotonsillitis with (n = 5, 10%), (figure 1) This is not unexpected, given the high incidence of acute RTIs in children and in Mexico during the COVID-19 pandemic. Furthermore, it has been reported that almost the entire world population (99%) breathes air that exceeds the quality limits recommended by the World Health Organization (WHO) [22], which may predispose to recurrent acute respiratory infections. This highlights the need to improve air quality to reduce the incidence of RTIs and support global health goals.

The majority of children had a previous respiratory infection during the last 6 months, 18 (36%) had 4 to 7 episodes, followed by 21 (42%) who had 1 to 3 episodes (Figure 2). 6 to 8 infections a year when they are cared for at home and up to 15 episodes when they go to daycare, with a maximum incidence in children under 2 years of age 2, a situation that occurs in young children under 5 years of age, especially in those under 2 years of age. years who have an immature immune system and who have not been exposed to multiple microorganisms as has been reported in other studies [2,25-27]. Since the number of infections has an inverse relationship with age, there is no doubt that it is a problem of the greatest quantitative importance, to which a significant percentage of care time is dedicated, despite its theoretical banality.

The most common clinical manifestations of respiratory tract infection were rhinorrhea 47 (94%), cough 45 (90%) and nasal congestion 45 (90%) and the average duration was 4 days (Table 3). Considering the clinical characteristics to label a patient with respiratory disease, it remains a challenge for the first contact doctor to identify whether he or she is facing an infectious or non-infectious process due to the clinical similarity between both conditions. When classifying respiratory infections by their clinical characteristics, 23 (46%) of the children treated with Pidotimod due to bacterial infection (acute rhinosinusitis, AOM, Pharyngotonsillitis) followed by non-infectious "allergic" 14 (28%) (bronchial hyperreaction/ASMA, allergic rhinitis) and 12 (24%) due to infection of viral origin (bronchiolitis, laryngotracheitis, common cold) (Figure 1). Uncomplicated infectious RTIs generally respond within 10 days of evolution, however the possibility of complicating with bacteria usually occurs as a complication of a viral respiratory infection of the upper airways. The most important agents are the rhinoviruses, with more than 100 different serotypes, the coronavirus and the respiratory syncytial virus A and B, the four types of parainfluenza virus (PIV 1-4), the influenza viruses A;B;C and the group of adenoviruses, in a study published by Brindisi G et al. 11 reports efficacy in reducing nasal obstruction and improving symptoms, without changes in the microbiota, after treatment with Pidotimod in the treatment of allergic rhinitis in children. Other studies conclude that pidotimod prevents RRTI in children [28,29].

When the duration of the condition is greater than ten days, bacterial superinfection is assumed, however 90% of cases are caused by bacteria such as H. influenzae, S. pneumoniae, M. catarrhalis mainly. A study carried out by Puggioni F et al. 4 showed that pidotimod is useful to reduce the need for antibiotics in respiratory tract infections, increasing the level of immunoglobulins (IgA, IgM, IgA) and subsets of T lymphocytes (CD3+ CD4+) endowed with immunomodulatory activity that affects to both the innate and adaptive immune responses [4]. Recent consistent studies have reported the effect of Pidotimod on asthma [3]. In adults Pidotimod is effective in the prevention and treatment of acute infectious exacerbations, chronic and chronic obstructive bronchitis, and COPD lung disease [3].

The number of upper respiratory tract infectious episodes before Pidotimod was 44 (88%) to decrease to 2 (4%) episodes after administering Pidotimod and for lower respiratory infections 6 episodes (12%) decreased to zero (table 4). In this study, children with allergies and RTIs of bacterial and viral origin were enrolled, including allergic rhinitis and asthma. In this study, cases of non-infectious "allergic" etiology were confirmed by skin tests to allergens. In recent decades, the prevalence of allergic diseases has

increased in all ages as well as other chronic non-communicable diseases. At the same time, many environmental changes have occurred. Currently, 75% of the earth's surface and 66% of the oceans have been altered. which suggests a close relationship between climate changes and the development of chronic allergic and inflammatory pathologies in people with genetic susceptibility [27]. None of the children with allergies experienced recurrent infections after treatment with pidotimod. Allergic rhinitis in children leads to an impairment of natural immunity with reduced TLR expression, which favors the survival and replication of pathogens and makes patients more susceptible to viral and bacterial RTIs [11]. Therefore, the increase in the expression of TLR2 induced by pidotimod may be beneficial in these patients [7]. In support of this, a previous study in children with allergic rhinitis demonstrated beneficial effects of pidotimod on nasal obstruction [11] and others show that pidotimod prevents ITRR [27,28]. The hypothesis has been raised that the reduction of the Th2 response and the subsequent reduction of IgE induced by pidotimod improves asthma control [8]. However, a previous study in children with persistent asthma did not detect any effect of pidotimod in addition to inhaled corticosteroid therapy on peak expiratory flow. Esposito S et al. reported the immunomodulatory activity of Pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia, favoring recovery [22].

A meta-analysis study of randomized controlled trials concludes the efficacy and safety of Pidotimod as an immunostimulant in the treatment of pediatric recurrent respiratory tract infections, significantly reducing the duration of cough, fever, and the number of patients using antibiotics, Pidotimod improved serum immunoglobulin levels (IgA, IgG, IgM) and lymphocyte subtypes (CD3+ CD4+) [8,10].

No adverse events were reported to Pidotimod, which supports the safety profile of Pidotimod in the clinical setting, a situation that has been reported in other studies [10]. Almost all children (49 (98%)) found the taste of the Pidotimod formulation acceptable, as determined by parents or guardians. The unpleasant taste can be a challenge to treatment compliance, especially among children. 19 This may have benefits for conditions other than RTIs and allergy, as pidotimod has other potential indications in both children and adults, including urinary tract infections and vulvar papillomatosis [10,12].

Conclusion

1. Respiratory infections are the most frequent pathology in humans, their impact on health will be given by age, immunity, and vaccines that the individual has, being the group of those under 5 years of age and those over 65 years of age are the most affected, these extreme categories are due to the deficiency of the immune system due to immaturity in children and immunosenescence in older adults, in addition to the potential participation of the environment, pollution and precarious socioeconomic level that influence our health.
2. In Mexico, respiratory infections continue to be one of the most important health problems, however, they are the first cause of morbidity consultation, predominated in children, with the common cold being the most common disease and also the most frequent one treated. a pediatrician in primary care.
3. The main results of this clinical experience study are the reduction in the number of infectious episodes, less severity of the signs and symptoms and consequently, a reduction in the use of antibiotics and symptomatic drugs, fewer work and school days, lower mortality and morbidity.
4. Pidotimod is an immunoregulator that acts both in patients with active, recurrent, allergic and prophylactic disease.
5. Pidotimod, a synthetic immunostimulant, reduces the incidence of RTI in children with predisposing risk factors, especially children who enter daycare, in addition to the fact that it can improve family costs by reducing respiratory tract infections.
6. This prolonged use of pidotimod demonstrates that the medical community in Mexico is aware of the need to protect this vulnerable population.
7. More studies are warranted to evaluate the impact of pidotimod in children with asthma.
8. More studies are warranted to evaluate treatment with pidotimod in children under 2 years of age.

Final Conclusion

96% of children with acute and recurrent RTIs and allergic respiratory disease in this study did not experience recurrent infections after treatment with pidotimod.

The taste of Pidotimod was well accepted and tolerated, it can be considered as a positive predictor that would help promote adherence to treatment regimens, supporting optimal treatment efficacy.

Clinical use in Mexico and other places is based on the fact that pidotimod has an immunomodulatory activity that is capable of both improving the clinical conditions of patients and improving and stimulating their cellular immunity functions, which act on adaptive and innate immunity. But it can also increase the concentration of salivary IgA directed against bacteria, and it can also modulate the functions of airway epithelial cells by positively regulating the expression of Toll-like receptors and acting on adhesion molecules.

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