Efficacy and Safety of Pidotimod in Childhood Wheezing: A Pilot Study

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Abstract

Background. Effective therapies for the management of wheezing in pediatric population are needed. We conducted a pilot, mono-centre, prospective, follow-up study to assess the efficacy and the safety of Pidotimod (PDT) in the treatment of wheezing in children.

Methods. Globally, 90 children (M:F=58:62, mean age 4.7 ± 1.64 years) with recurrent viral wheezing were enrolled in the study between October-November 2018. At baseline, children were receiving treatment with PDT as 1 vial of 400mg daily for 3 consecutive months. We evaluated the therapeutic efficacy of PDT treatment at the end of 3 (T3) months of therapy as well as the long efficacy and preventive efficacy of PDT treatment during a 3-months follow-up (T6) by using the following outcomes: (i) how many patients showed one or more episodes of viral wheezing, (ii) how many patients were taking concomitant medications (ICS, SABA, antibiotics), (iii) how many patients were requiring ED visits, and (iv) how many patients were requiring hospitalization.

Results. A significant decrease in number of patients with at least one or more episodes of wheezing and taking antibiotics was recorded after 3 months of treatment, and a further significant decrease for both outcomes was reported at 3-months follow-up period ($p < 0.05$). Differently, after 3 months of treatment, we found a significant decrease in number of patients taking ICS and SABA, in number of patients requiring ED visits and/or hospitalization ($p < 0.05$); however, for all these outcomes no further significant decrease was reported at follow-up period.

Conclusions. We firstly showed that administration of PDT is useful in the management of patients with recurrent viral wheezing because we found a reducing a number of patients requiring ED visits and/or hospitalization as well as number of patients taking drugs during the treatment period. Moreover, firstly to date, we found a long-term clinical effect over three months after treatment suspension counteracting the recurrence of disease.

Background

Wheezing is a common disorder in early life, affecting approximately 50% of children in the first years of life. It represents a significant cause of morbidity, decreased quality of life, and even increased health care services and economic costs, due to the frequent emergency department (ED) visits and hospitalizations [1]. Genetic factors and the environment are well recognized causative factors for wheeze although they may vary from child to child and within a child over time [2]. Whether in accordance of its temporal pattern, wheezing is classified into transient *versus* persistent wheeze, in accordance with the causative agents, wheezing is classified into multiple-trigger and episodic or viral wheezing. The latter appears to be most common in preschool children and usually associated with clinical evidence of a viral respiratory tract infection generally sustained by rhinovirus, respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, parainfluenza virus, and adenovirus [3]. The management for acute episodes of virus-induced wheezing in infants and preschool children was

established but the current therapeutic strategy on the clinical benefit is not evident. Due to the lack of a specific treatment, researchers on viral wheezing in childhood have increased in recent years not reaching, however, conclusive data.

Pidotimod (PDT), 3-L-pyroglutamyl-L-thiazolidine-4-carboxylic acid), a synthetic thymic dipeptide, influences both the innate and adaptive immune response. By causing maturation of mucosal dendritic cells, increasing antigen presentation, and promoting adaptive T helper (Th)1-mediated immunity, PDT induces the release of antimicrobial peptides and improves the mucociliary transport showing positive effects on the immune profile of children suffering recurrent respiratory tract infections (RTIs) [4–6]. In light of these immunological properties, PDT was approved in Italy as beneficial immunomodulator agent in treating RTIs. Following its marketing, several studies assessed both the good efficacy, expressed in terms of reduced number of RTIs, shortening the symptom duration, and decreasing signs and symptoms severity, as well as safety of PDT in treatment of recurrent RTIs [7].

Taking in account the aetiology of wheezing and the evidence of the effects of PDT as an adjuvant in the treatment of recurrent viral RTIs, we hypothesized that PDT could prove to be a new therapeutic option in children suffering for recurrent viral wheezing. To achieve this goal, we conducted a pilot, mono-centre, prospective study with PDT in the treatment of viral wheezing in childhood.

Methods

Study design

A mono-centre, prospective, follow-up study was designed.

Subjects and eligibility criteria

90 children with recurrent viral wheezing, documented by real-time reverse transcriptase polymerase chain reaction (RT-PCR) performed on nasal swab specimens, who had been referred to the Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, University of Catania, were enrolled in the study.

Patients were enrolled during October–November 2018. The treatment period started in December 2018 and ended in February 2019. The follow-up period started in March 2019 and ended in May 2019.

Inclusion criteria were: being out-patients of both sexes, 3–6 years of age, positive history for at least three episodes or more of viral wheezing in the last year (October 2017–May 2018), patients with at least one or more episodes of wheezing during October–November 2018.

Exclusion criteria included: children younger than 3 years, associate diseases (hepatic, infectious, or endocrine diseases, genetic syndromes, immunodeficiencies, neurological and psychiatric problems), pulmonary or cardiac congenital malformations, chronic pulmonary disease (broncho-pulmonary

dysplasia, cystic fibrosis, bronchiolitis obliterans post-infection), and congenital and/or acquired craniofacial anomalies. Patients receiving treatment with other immunomodulators were also excluded.

The investigator collected the symptoms recorded by the parent in the study diary during the treatment period.

Institutional Review Board of the University of Catania approved the study. Written informed consent was obtained from the parents and informed assent from the children and adolescents.

Study procedure and efficacy evaluation

The patients were receiving PDT as one vial of 400 mg daily. Treatment lasted for 90 consecutive days and followed by 3-months follow-up period.

All enrolled patients were compared at baseline (T0) and three months (treatment period) (T3), and after the subsequent 3-months follow-up (T6). We evaluated how many patients showed one or more episodes of viral wheezing, how many patients were taking concomitant medications (inhaled corticosteroid (ICS); short-acting beta-agonists (SABA), antibiotics), how many patients were requiring ED visits, and how many patients were requiring hospitalization during the period of therapy. After the subsequent 3-months follow-up (T6), we evaluated how many patients showed one or more episodes of viral wheezing, how many patients were taking concomitant medications (ICS, SABA, antibiotics), how many patients were requiring ED visits, and how many patients were requiring hospitalization.

Safety

Safety of PDT was evaluated as the number and the type (mild, moderate, and severe) of adverse events (AEs) recorded by a physician and/or parents children.

Data analysis

The data collected were statistically analyzed by the statistical computer software SPSS, version 15.0. Values were calculated as mean and standard deviation, T-student and χ^2 tests were adopted for comparisons between variables. A p-value less than 0.05 were considered statistically significant.

Results

All 90 children (M:F = 47:43, mean age 4.7 ± 1.64 years) completed the study and were considered in the final analysis. Clinical outcomes at T0, T3, and T6 were reported in Table 1.

Table 1

Clinical outcomes of the enrolled population at baseline (T0), after 3 months of treatment with Pidotimod (T3), and 3 months after follow-up period (T6).

Enrolled patients					
Outcomes	T0	T3	Pvalue	T6	Pvalue
N.* of patients with at least one or more episode of wheezing	90/90	43/90	< 0.05	19/90	< 0.001
N. of patients taking ICS*	74/90	42/90	< 0.001	27/90	n.s.
N. of patients taking SABA*	54/90	30/90	< 0.05	24/90	n.s.
N. of patients taking antibiotics	60/90	20/90	< 0.001	8/90	< 0.05
N. of patients requiring ED* visits	63/90	5/90	< 0.001	4/90	n.s.
N. of patients requiring hospitalization	15/90	7/90	< 0.05	4/90	n.s.
*N: number; ICS: inhaled corticosteroid; SABA: short-acting beta-agonists; ED: emergency department.					

Number of patients with at least one or more episodes of viral wheezing

A significant decrease in the number of patients with at least one or more episodes of viral wheezing was recorded after 3 months of treatment ($p < 0.05$; Table 1), and a further significant decrease was also reported at 3-months follow-up period ($p < 0.001$; Table 1).

ICS use

After 3 months of treatment, a significant decrease in the number of patients taking ICS was recorded ($p < 0.001$; Table 1); no further significant decrease was reported at follow-up period ($p = 0.60$; Table 1).

SABA use

After 3 months of treatment, a significant decrease in the number of patients taking SABA was recorded ($p < 0.05$; Table 1); no further significant decrease was reported at follow-up period ($p = 0.36$; Table 1).

Antibiotics use

A significant decrease in the number of patients taking antibiotics was recorded after 3 months of treatment ($p < 0.001$; Table 1), and a further significant decrease was reported at 3-months follow-up period ($p < 0.05$; Table 1).

Emergency department visits

After three months of treatment, a significant decrease in the number of patients requiring ED visits was recorded ($p < 0.001$; Table 1); no further significant decrease was reported at follow-up period ($p = 1.00$; Table 1).

Hospitalization

After 3 months of treatment, a significant decrease in the number of patients requiring hospitalization was recorded ($p < 0.05$; Table 1); no further significant decrease was reported at follow-up period ($p = 1.00$; Table 1).

Safety

PDT treatment was well tolerated and no significant adverse effects were reported.

Discussion

By conducting a pilot, mono-centre, prospective follow-up study, we firstly reported the therapeutic efficacy and safety of PDT in treating of childhood viral wheezing.

It is well known that wheezing is characterized by significant morbidity and represents a very common health problem in the first years of life, resulting in a high burden to the affected patients and families who have a greater need for primary care, specialist physician visits, ED visits, and hospitalization [1]. Currently, maintenance treatment with ICS and/or montelukast are recommended for episodic or viral and multiple-trigger wheeze, respectively, as well as SABA by metered-dose inhaler/spacer combination, are suggested for symptomatic relief [1]. However, although the daily use of ICS and/or montelukast significantly reduces wheezing exacerbations, they do not prevent virus-induced wheezing attacks, and, to date, shadows remain on their use [8, 9].

The shift of the immune balance to pro-/Th2/anti-Th1 direction, the increase both in the inflammatory response and Th2-related marker as well as in serum immunoglobulin (Ig)E levels and eosinophils infiltration are some of the mechanisms resulting in airway remodelling, wheezing, and asthma [1, 10, 11]. By acting on all these pathways [12–15], it has been hypothesized that PDT could prove to be a possible therapeutic approach in treating patients with wheezing. To the best of our knowledge, studies on the efficacy of PDT in patients affected by wheezing are relatively sparse and, the only studies identified did not report clear and exhaustive data since affected by methodological limitations including heterogeneity in enrolled population and some analysis, lack of sufficient details on the clinical outcomes, and absence of follow-up period [16, 17]. Firstly, in their papers, authors did not focus their investigations on wheezing as children with asthma and the related obstructive syndrome were enrolled; moreover, no data on number of patients with episodes of wheezing over time were described, thus, an objective outcome measure of PDT efficacy has not been reported [16, 17]. Secondly, both studies compared the data of children of such different ages (2–16 years) [16, 17]. In our pilot study, we restricted our investigations to children with the diagnosis of viral wheezing and restricted our investigation to children aged 3–6 years; further, all outcome measures of treatment efficacy were clearly stated.

Specifically, data on the number of patients with at least one or more episodes of wheezing, number of patients taking concomitant drugs (ICS, SABA, antibiotics), number of patients requiring ED visits and hospitalizations were collected and all these outcomes appeared to be significantly decreased by PDT administration.

ICS therapy has been widely adopted in treating wheezing with benefit. In our study, 3-months treatment with PDT was associated with a significant decrease in the number of patients taking ICS, an outcome measure of therapy efficacy. ICS use in children has lagged because of concerns about the potential for adverse effects related to the dose, the frequency, and duration treatment with which ICS are administered. High dosage (≥ 1.000 ug/day), frequent administration (≥ 4 times /day) are more likely to have local, such as oral candidiasis and dysphonia, as well as systemic adverse effects [1]. The potential for growth suppression and osteoporosis with long-term ICS use has been also a concern, especially in children who receive maintenance therapy with higher ICS doses because they are also likely to require systemic CS use. In this regard, PDT treatment reduced the number of patients taking routine ICS also preventing indirectly the side effects associated with a frequent ICS. The improvement of disease control has been indirectly assessed also by a significant decrease in the number of patients taking SABA after three months of treatment with PDT. Inhaled salbutamol is recommended in emergency management in children with wheezing, thus, a decrease in the number of patients taking SABA reflects the efficacy of PDT treatment in preventing wheezing exacerbations. In parallel, a significant decrease both in the number of patients requiring ED visits and in the number of patients requiring hospitalizations was recorded after three months of PDT treatment, further confirming an improvement in health status due to the PDT administration. Lastly, although we did not perform any estimate of the wheezing-related economic burden, we indirectly speculated on the evidence that PDT use, by decreasing significantly the use of concomitant drugs (ICS, SABA, antibiotics), ED visits and hospitalizations, can also contribute to reduce the economic burden of wheezing in the pediatric population.

Moreover, at 3-months follow-up period, a significant decrease in the number of patients taking antibiotics was also recorded. As viral agents are the causes of the episodic wheezing, they do not require antibiotic treatment. Nevertheless, antibiotic prescription occurs frequently. We explained the reduction in antibiotics use as an indirect sign of disease improvement; the patients and their parents perceived as less severe the episodes of wheezing, and, probably, a prescription of antibiotic was not required.

Follow-up completeness is a pre-requisite for reliable outcome assessment, and the lack of a follow-up period in the previous studies correlates inversely with the accuracy of outcome estimates, with the risk of selection bias, and with the credibility of study data [16, 17]. Conversely, by adopting a follow-up period study, we also firstly provided data on long-term effects of PDT and observed significant changes in the course of the disease as assessed by a further decrease of the number of patients with at least one or more episodes of wheezing also at 3-months PDT suspension. Although 60% of children with wheezing are expected to improve and/or be symptom-free at the age of 6 years [2], children with wheezing are at higher risk of developing asthma at school age, thus, thanks to PDT use, we also believe that is possible to interfere with long-term outcomes of disease, even if it will be not possible to prevent evolution of

wheezing in asthma. Further studies with a longer follow-up period are required to better define duration of drug effect over time.

Achieving the goal of primary prevention of viral wheezing both in healthy children and, even more, in patients with a positive clinical history for viral wheezing is still unsolved. In this scenario, PDT, thanks to its immune-modulatory effects, could be an innovative strategy, especially at our days sadly burdened by a new coronavirus (2019-nCoV) that also afflicts the pediatric population, resulting commonly in viral respiratory infection [18]. In this regard, our findings not only suggest the therapeutic effectiveness of PDT but also its preventive effectiveness, as assessed by the evidence that, after 3-months follow-up period, a decrease in the number of patients taking ICS and SABA, in the number of patients requiring ED visits and hospitalization was recorded.

The initiating and perpetuating factors of wheezing are multiple and their interactive processes are based on the interplay between genetic and environmental exposure which, in turn, influence the development of the immune system. Therefore, whether PDT affects significantly the immune response of children with wheezing, it cannot change or modulate other causes of wheezing, such as genetic predisposition and environmental exposure. On the other hand, the behaviour of the PDT as a symptomatic drug is in line with its properties; acting as an immunomodulator agent, PDT can modify the immune response until it is administered, and, although it cannot change the natural history of the disease, it can decrease the severity disease as assessed by a significant reduction in the number of patients taking ICS and SABA as well as in the number of patients requiring ED visits and hospitalizations. Thus, although PDT does not appear as a definitive treatment of wheezing our findings evidence that it can be considered as a valid and adjunctive therapeutic approach in treating wheezing.

Lastly, compared to the previous clinical studies [16, 17], we reported interesting findings on the safety profile of PDT and we showed that this immunomodulatory agent does not cause adverse effects neither at short- nor long-term.

Conclusion

Wheezing is characterized by significant morbidity and represents a very common health problem in the first years of life for abnormal use of drugs, increased health care services and economic costs, due to ED visits and hospitalizations [1]. Our pilot study highlighted the ability of PDT to modify the course of the disease during the period of treatment but, firstly to date, maintaining its clinical effect over three months after treatment suspension, counteracting the recurrence of disease.

Furthermore, PDT seems able to stabilize the severity disease, although the enrolled patients were not receiving PDT and they were still in winter virus season, the number of patients taking concomitant drugs (ICS and SABA) and the number of patients requiring ED visits and hospitalizations were maintained over time. Further studies are required to confirm this pilot study and future investigations with a longer follow-up period will better define the duration of drug effect over time. Interestingly, in light of our encouraging

findings, we suggest that PDT administration might prove useful also in treating multi-trigger wheezing, often requiring a more complex therapeutic management.

Abbreviations

PDT
Pidotimod
ED
emergency department
RSV
respiratory syncytial virus
RTIs
respiratory tract infections
RT-PCR
real-time reverse transcriptase polymerase chain reaction
ICS
inhaled corticosteroid
SABA
short-acting beta-agonists
AEs
adverse events

Declarations

Ethics approval and consent to participate Institutional Review Board of University of Catania approved the study. A written informed consent was obtained from the parents and informed assent from the children and adolescents. Consent for publication Not applicable Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Competing interests The authors have no conflicts of interest to disclose that could be perceived as prejudicing the impartiality of the research reported. Funding The authors did not receive any funding for the research. Valeas, s.p.s. Italia (Milano, Italy) covers the article-processing charge. Authors' contributions SL designed the study. SM wrote the initial draft of the manuscript. SL performed a critical revision of the manuscript and offered precious technical advice on how the study might be improved. GFP, MP, FM, AG enrolled the children and contributed to the data collection and follow-up. GFP reviewed and edit the manuscript. All authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the paper, revised the manuscript for important intellectual content, approved the final version, and agreed to be accountable for all aspects of the work. Acknowledgments We would like to thank all the participants and their families who took part in this research.

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