



Pidotimod for the prevention of acute respiratory infections in healthy children entering into daycare: A double blind randomized placebo-controlled study



Chiara Mameli^a, Angela Pasinato^b, Marina Picca^c, Giorgio Bedogni^d, Stefania Pisanelli^e, Gian Vincenzo Zuccotti^{a,*}, for the AX-Working group¹

^a Department of Pediatrics, Ospedale dei Bambini V. Buzzi, University of Milan, Milan, Italy

^b Center for Research and Education of Family Pediatricians (CESPER), Padova, Italy

^c Pediatric Society of Primary Health Care (SICuPP), Milan, Italy

^d Clinical Epidemiology Unit, Liver Research Center, Basovizza, Trieste, Italy

^e Department of Pediatrics, Luigi Sacco Hospital, University of Milan, Milan, Italy

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ABSTRACT

Acute respiratory tract infections (ARTIs) are very common in pediatric age and reach a peak in the first 4 years of life, especially in children attending daycare. Pidotimod, a synthetic immunostimulant, may reduce the incidence of ARTIs in children with predisposing risk factors. Nevertheless studies on healthy children are presently lacking. We performed a double-blinded randomized placebo-controlled trial study to assess the efficacy of Pidotimod in a population of 3-year-old healthy children who just entered kindergarten. The main outcome was the incidence of respiratory infections in this population and the secondary outcome was the prescription of antibiotics.

The study group consisted of healthy 3-year-old children who had not yet attended day-care centers. Patients were enrolled by a convenience sample of 17 family pediatricians (FP). Children were randomized to receive either Pidotimod 400 mg *per os* or placebo twice daily for the last 10 days of each month from October 2013 to April 2014. Any time a child presented to his/her FP with fever and ARTI was diagnosed, clinical and therapeutic data were collected.

A total of 800 children were pre-screened, 733 did not meet the inclusion criteria and 10 refused to participate. Of the 67 eligible subjects, 57 were successfully enrolled within the study recruitment period and randomized to receive Pidotimod ($n = 29$) or placebo ($n = 28$). Eight children were lost to follow-up. In the final analysis were thus included 24 children who received Pidotimod and 25 who received placebo. The incidence rate ratio for respiratory infections was 0.78 (95%CI 0.53 to 1.15, $p = 0.211$) for Pidotimod vs. placebo. The corresponding risk ratio for antibiotic usage was 0.56 (95%CI 0.27 to 1.16, $p = 0.120$).

In our trial, Pidotimod did not prove to be statistically superior to placebo for the prevention of ARTI in a population of healthy children who entered kindergarten. However, Pidotimod showed some potential as a means for reducing antibiotic usage in these children.

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Abbreviations: ARTIs, acute respiratory tract infections; CI, confidence interval; IRR, incidence rate ratio; NK, natural killer; PI, principal investigator; SD, standard deviation.

* Corresponding author at: Department of Pediatrics, Ospedale dei Bambini V. Buzzi, University of Milan, Via Castelvetro 32, Milan, Italy. Tel.: +39 02 57995322.

E-mail address: gianvincenzo.zuccotti@unimi.it (G.V. Zuccotti).

¹ List of members of 'AX-working group' are listed in Appendix.

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1. Introduction

Worldwide acute respiratory tract infections (ARTIs) are the most common forms of infections in children. In temperate countries, ARTIs have higher incidence in colder seasons such as autumn and winter [1]. During childhood, ARTIs incidence peaks in the first 4 years of life, especially in children attending daycare [1].

Given the increasing proportion of working mothers during the past decades, day care centers constitute an important common childhood environment, where children are exposed to conditions that may influence their respiratory health. Compared to their home-attended pairs, children attending day care centers are exposed to a larger variety and amount of pathogens, given their closer contact with other children every day. Upon entry to day care, the youngster are the most vulnerable and more susceptible to develop respiratory infections [2]. A tendency toward hyporesponsive immune responses in early life, characterized by both reduced innate and adaptive immune responses, plays an important role in ARTIs recurrence in the first 6 years of life [3]. Moreover exposure to dampness, molds, parental smoke and pollution are known environmental risk factors for ARTIs [1,4–7].

ARTIs contribute to healthcare expenses up to 20% of medical consultations, emergency room admittance, hospitalization and prescription of symptomatic treatments and antibiotics [7,8]. ARTIs are responsible of 75% of antibiotics prescription in pediatric age and may contribute substantially to the rise in antibiotic resistance [8,9]. ARTIs also lead to indirect costs such as parental absence from work and loss of productivity: up to 30% of parental work-days are lost because of their child's respiratory infection [9,10].

Current epidemiological and socio-economical data, call for alternative approaches to the most well-studied and known therapies. Non-specific enhancement of the antimicrobial immune responses or the innate immunity mechanisms are functional approaches to prevent and treat ARTIs considering the immaturity and naivety of childhood immune system [3,9].

A variety of biologically active substances of natural and synthetic origins – known as immunostimulants have been introduced in some countries for the prevention of ARTIs in children [11]. Pidotimod (3-L-Pyroglyutamyl-L-thiazolidine-4-carboxylic acid) is a synthetic immunostimulant authorized for use in subjects 3 years of age or older [11]. Pidotimod has been shown to improve the maturation of dendritic cells, the functioning of natural killer (NK) lymphocytes phagocytosis, and the differentiation of T-cells toward the Th1 phenotype [11–15]. A recent study in children with Down syndrome showed that Pidotimod can up-regulate genes involved in the innate immunity activation [16]. However, the efficacy of immunostimulants in preventing ARTIs is still debated [9]. Some studies reported a reduction of ARTIs following the administration of immunostimulants [9,16–18]. Of note, these studies were all performed in small and heterogeneous populations, and potential confounding factors such as age, concomitant disorders, daycare attendance, parental smoking and seasonality of infections were often not taken into consideration [9]. On the other hand, a more recent study by Licari et al. showed that Pidotimod may prevent respiratory infections in children with an history of recurrent respiratory infections [19].

To date, the preventive effect of Pidotimod on ARTIs incidence in healthy children entering daycare is unknown.

We aimed to assess the efficacy of Pidotimod in preventing ARTIs in a cohort healthy children entering into daycare.

2. Materials and methods

2.1. Study protocol

This double-blinded randomized placebo-controlled trial study was first designed to assess the incidence of ARTIs in the study

population. The secondary outcome was to assess the prescription of antibiotics. The study was performed on a convenience sample of 17 family pediatricians (FPs) working for the Italian National Health System in two cities, Milan and Vicenza. FPs were enrolled by word of mouth by the Center for Research and Education of Family Pediatricians, the Pediatric Society of Primary Health Care and the principal investigator (PI). Recruitment took place from October 1 to October 19, 2013. Eligible for the study were healthy Caucasian 3-years old children entering into daycare in fall 2013. Children were excluded if had history of: (1) exposure to passive smoking, (2) one or more siblings attending a day-care center, (3) congenital abnormalities of the respiratory tract, (4) congenital or acquired immunodeficiency including cystic fibrosis, (5) cardiovascular disease, (6) neurological disease, (7) hematological disease, (8) renal diseases, (9) Down syndrome and (10) previous use of immunostimulants. Each FP provided the PI with a anonymous list of potentially eligible children, in which the pediatrician code, an arbitrary patient number and the gender and birthdate of each child. Children were randomized using permuted-block randomization (4:1) to receive Pidotimod (Axil® – Valeas, Milan) 400 mg *per os* or placebo twice daily for the last 10 days of each month from October 2013 to April 2014. An alpha numeric string was generated by a statistician for the randomization; numbers were printed on a random assignment card and placed in an opaque envelope.

Pidotimod and placebo pills were prepared in order that they were of the same number, size, appearance and taste by Valeas S.p.A and they were administered to the participant children by their FP. Blindness of patients and pediatricians was ensured by using packages that reported only the progressive number of the subject. Subjects were followed-up from October 20, 2013 to May 31, 2014. Any time a child presented to his/her FP with fever (defined as axillary temperature $>38^{\circ}\text{C}$), a complete clinical examination was performed. Were considered ARTIs: common cold, influenza, tonsillitis, pharyngitis, bronchitis and otitis media. If the diagnosis of ARTI was made, a case report form including the specific diagnosis and the prescription of any drug was completed. Upon enrollment, FPs were instructed to perform phone calls follow up every 15 days, to remind the study procedures to the parents and monitor participants' adherence to the protocol, documenting the number of missed doses if any. The study was performed in accordance with the declaration of Helsinki and was approved by the Ethical Committee Luigi Sacco Hospital of Milan. The parents of each child gave their written consent to participate.

2.2. Statistical analysis

We considered 0.30 to be the minimally clinically relevant difference in the rate of respiratory infections between the Pidotimod and placebo groups. Considering that an average of 5 respiratory infections per year are reported for 3-year-old children and that they are expected to occur mostly during the autumn–winter season of interest, here [20], we calculated that a number of 40 children per group gives a power of 93% to detect an incidence rate ratio (IRR) of 0.70 at an alpha level of 0.05 [21]. The main outcome (IRR of respiratory infections) was evaluated using a Poisson regression model having the number of infections developed during the study as response variable and the treatment group (0 = placebo; 1 = Pidotimod) as predictor [22]. The secondary outcome (risk ratio [RR] of use of antibiotics) was evaluated using a binomial regression model having the use of antibiotics at any time during the study (0 = no; 1 = yes) as response variable and the treatment group (0 = placebo; 1 = Pidotimod) as predictor [21]. Statistical analysis was performed using Stata 13.1 (Stata Corporation, College Station, TX, USA).

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