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Clinical evaluation and changes of the respiratory epithelium function after administration of Pidotimod in Greek children with recurrent respiratory tract infections

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Background. Several studies have been conducted on young children with recurrent respiratory infections using several compounds (synthetic derivates or lyophilized bacterial extracts) causing improvement in the clinical process.

Methods. We conducted a prospective, randomized study comparing the clinical results and the changes of the respiratory epithelium function after the administration of immunostimulating drug (Pidotimod) to children with respiratory infections over a 9 month period. A total of 32 children (group A) were randomly assigned to receive Pidotimod therapy while a second group of 18 children (group B) weren’t. All the children in group A received Pidotimod (400 mg x 2 daily) for fifteen days and 400 mg daily for the next twenty days. The proper function of the ciliary respiratory epithelium in all children was checked, using the Edicol Orange and CaH PO₄ 2H₂O, coloring method before the therapeutic intervention and after the first and the sixth month.

Results. 87.5% of group A, responded exceptionally well to treatment presenting two or less infections in the nine month period, whereas only 33.3% of group B showed improvement (p<0.001). In group A, the clearance of the respiratory epithelium, from a primary 36´4´´ to 34´2´´ and 31´ respectively (p=0.01).

Conclusions. Our results suggest that Pidotimod therapy is a reliable, simple and safe approach to treat children with recurrent respiratory infections and it can reduce the frequency of such infections as a result of improvement of the ciliary respiratory epithelium.

Key words: Respiratory tract infections, drug therapy - Epithelial cells - Mucociliary clearance.
compounds (synthetic derivatives or lyophilized bacterial extracts), which act as antigens, have been used in many studies with satisfactory results, causing a better clinical process.3-11

We decided to make this study because of several negative bibliographic opinions against the optimism for the action of these compounds. Our aim was to use a synthetic immunostimulating drug, used by other investigators before, to study the changes of the respiratory epithelium function, in children with frequent, persistent or recurrent respiratory tract infections.

**Materials and methods**

All the children who took part in our study had their parents approval. Thirty-two children (18 males and 14 females) aged 2.5-12 years (mean age 5.2 years), with three or more upper or lower respiratory tract infections during last six months, were the control (A) group and fifteen children (8 males and 7 females) with the same approximately age (mean age 5.6 years) and three or more respiratory tract infections during last six months, made up the comparison group (B) (Table I). Excluded from both groups were children with congenital respiratory defects, congenital heart defects, allergy and asthma, renal failure, diabetes mellitus, immunodeficiencies or immunosuppression caused by corticosteroids administration.

The proper function of the ciliary respiratory epithelium was checked using the "Edicol Orange 3% + CaHPO$_4$$\cdot$2H$_2$O" coloring method before the therapeutic intervention and one and six months after. A minimal quantity of a mixture composed of dibasic calcium phosphate (CaHPO$_4$$\cdot$2H$_2$O) 97% and Edicol Orange 3% was applied to the nasal mucosa covering the middle meatus. The time necessary for the orange-stained mucus to be detected in the pharynx represents the mucociliary clearance.

All the children in group A received the immunostimulator Pidotimod (\((R)-3-((S)-(5-oxo-2-pyrrolidinyl)carbonyl)thiazolidine-4-carboxylic acid, PGT1A,CAS 121808-62-6\) with the dose of 400 mg twice daily for fifteen days and 500 mg once a day for the next twenty days, while twenty-four of the thirty-two children received simultaneously broad spectrum antibiotics for 8-14 days, depending on the infection they suffered from before the onset of our study or during it. None of the children in group B received immune stimulants and thirteen of them received antibiotics at the onset, or when needed, during nine months follow-up.

The patients were clinically checked before the therapy initiation and during any other recurrence of infection until the last evaluation which took place nine months after the immunostimulating treatment.

**Results**

The results are presented in Table II and III. Table II shows that 87.5% (28/32 children) of group A responded exceptionally well to treatment with Pidotimod, presenting two or less infections in the nine month period, whereas 66.7% (10/15 children) of group B continued to have three or more infections during that period and only 33.3% of group B children showed improvement, having less than three infections. The difference between the two groups appears to be statistically very significant (p<0.001).

As far as data analysis is concerned, the unpaired two-tailed Student-"t"-test was used to compare the mean changes in the two groups.
rehabilitation of the cilia destroyed. Table III shows that the mean time (MT) of the mucociliary clearance of group A children before therapy was 37 minutes (38’ in males and 35’ 5” in females) and of group B children was 36’ 4” (37’ in males and 36” in females). The difference is not statistically significant.

One month after the initiation of therapy the clearance mean time improved mildly to both groups, and the time decreased to 33 minutes (group A) and 34’ 2” (group B), which is a statistically insignificant difference. After six months treatment, group A children showed a great decrease of the mean time to 19’ 5” (20’ 2” in males and 18’ 5” in females) whereas group B mean time remained to 31 minutes (32” in males and 30” in females). This difference between the two groups was statistically significant (p<0.001).

**Discussion and conclusions**

The normal ciliary function represents a primary defense mechanism of the respiratory tract. During the acute phase of viral or bacterial infections several transient, non-specific and reversible ciliary structural abnormalities as well as quantitative and qualitative mucus changes, take place leading to impaired respiratory epithelium function, defective local defense and infections recurrences.\(^1,2,12-17\)

Many previous researches have proved the relation between respiratory ciliary abnormalities and frequent infections.\(^13-17\)

The time of the dye transfer in all group A and group B children initially, and in group B children who continued to suffer from frequent infections afterwards, was greater than thirty minutes. The clearance in group A children, who showed better clinical process and reduction of infections, improved, demonstrating a relative structural and functional rehabilitation of the ciliary epithelium.

The statistically significant difference of the epithelium function between the two groups six months after treatment and the reduction of the respiratory infections frequency induce to the conclusion that Pidotimod helped the children to avoid recurrent respiratory infections, making their local defense better.

The way of action of immunostimulating or immunoamplifying drugs has not been absolutely established yet. According to bibliographic data, after their oral administration, they get absorbed from the gut mucosa passing through the Gut Associated Lymphoid Tissue (GALT) which is connected to the Payer’s plaques, they get transferred through the lymphoid circulation to the lymphoid tissue connected to the bronchus, so called BALT (Bronchus Associated Lymphoid Tissue), where they act. Their local effect is...
associated with an increase of IgA secretory immunoglobulin, of the macrophages phagocytic ability, of the interleukin and interferon release and of the T-lymphocytes number as well as restoration of the balance of T-helper(CD4):T-suppressor(CD8) lymphocyte ratio.8, 18, 19

The infections diminution results to a) less antibiotics administration and reduction of the bacteria resistance improvement as well as the patients hypersensitivity reactions; b) less hospitalization days that leads to less days of school absence for the pupils and days of work missing for their parents; c) decrease of financial cost due to limited antibiotics and other drugs administration and to less days-off of parents work; d) support of children and parents mental health.

Although our study took place during seasons where children infections are more frequent and more severe (autumn-winter-spring), the results were remarkably satisfactory. The percentage of children with good clinical process in Pidotimod’s group was 87.5 against 33.3 of the comparison group. Another research reported similar results, with the percentages of 68 and 8% respectively.20

All of the children tolerated the treatment well and there were no side effects observed. Bibliographic data mention only a few side effects in cases of simultaneously administration of Pidotimod and broad spectrum antibiotics such as nausea, vomit, headache and skin rush, mainly attributed to concomitant antibiotic therapy.

The parents made a remarkable note, which was confirmed from us, that the Pidotimod’s group children showed improvement of their appetite and gained weight. This is a considerable fact, having in mind that most of these children have reduced body weight due to frequent infections they suffer from.

It is obvious from our findings that Pidotimod has a positive influence on the immunobiological defense mechanism of the children with recurrent respiratory tract infections, giving another dimension to their therapy and allowing us to show temperate optimism. Thus, we consider that more extensive and long term researches are necessary for the pediatricians in order to confirm the accurate and detailed way of action of the specific drug and its similar ones, improving in this way children’s living.
References