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ANTILEUKOTRIENS IN MANAGEMENT OF PAEDIATRIC ASTHMA: EFFICIENCY OF „ADD-ON" THERAPY

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REZUMAT

ANTILEUKOTRIENE ÎN MANAGEMENTUL ASTHMULUI PEDIATRIC: EFICIENŢA TERAPIEI „ADD-ON"

Cuvinte-cheie: copii, astm, corticosteroizi, antileucotrien, eficienţă

Rezultatele studiului clinic randomizat „dublu-orb", placebo-controlat au confirmat faptul că includerea modificatorului leucotrienelor *Montelukast* (*Zespira*®) în tratamentul complex de bază la copiii cu astm bronşic cu severitatea moderată, asigură un efect clinic aditiv, ceea ce permite obţinerea controlului asupra astmului bronşic la 75,0±6,8% din pacienţi (comparativ cu 47,0±7,9% la copiii cu monoterapie 200 μg de Fluticazonă (*Flixotide*®, p<0,01).

РЕЗЮМЕ

АНТИЛЕЙКОТРИЕНЫ В ЛЕЧЕНИИ ПЕДИАТРИЧЕСКОЙ АСТМЫ: ЭФФЕКТИВНОСТЬ «ADD-ON» ТЕРАПИИ

Ключевые слова: дети, астма, кортикостероиды, антилейкотриенs, эффективность

В ходе двойного „слепого", плацебо-контролируемого клинического испытания было доказано, что подключение модификатора лейкотриенов *Montelukast* (*Zespira*®) в комплекс базисной терапии детей с БА среднетяжелого течения обеспечивает аддитивный клинический эффект, что позволяет достичь полный астма-контроль у 75,0±6,8% пациентов (по-сравнению с 47,0±7,9% на фоне 200 мкг/кг *Фликсотида*, p<0,01).

Introduction. Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation (*GINA*). The „golden standard" of asthma control in children is inhaled corticosteroids (ICS) [2]. However, multicenter epidemiological studies (*GOAL, AIRE, INSPIRE*) indicate failure of asthma control in the vast majority of patients (approx. 70%). There is ample reliable published data on the antiasthmatic efficiency and safety of leukotriene receptor antagonists (LTRA) (*MOSAIC,* et al) [3, 4]. However, LTRA have no anti-inflammatory effect.

The character of interaction of LTRA with ICS is not fully determined. Our earlier research indicates that the level of LTC4 in exacerbations of asthma in children increases 10 times (31.0±0.9 ng/ml versus 2.2±0.2 ng/ml in the control group, p<0.001) [5]. Therefore, *add-on* therapy could be sufficient to achieve asthma control without increasing the dose of corticosteroids [1, 3, 4].

Objective/Aim: Explore the additive effect of the antileucotriene *Montelukast* (*Zespira*®) in children with mild-to-moderate asthma.

Methodology. This is 12-week, placebo-controlled, double blind, randomized trial in parallel groups (ZPA-007-01) in 40 children, aged 5-15 years, with mild-to-moderate asthma and poor symptom control despite 2 weeks of treatment (*run-in period*) with low dose of ICS (*Fluticasone propionate* ≤200μg daily).

The study used LTRA *Montelukast sodium* 5 mg (*Zespira*®, produced by *„Bilim Pharmaceuticals", Turkey*). Identically looking and packaged tablets (produced by *„Farmaco", Moldova*) were used as *Placebo*. According to the *add-on* design, all patients continued treatment with ICS *Fluticasone* 100 μg twice daily and used *short-acting beta2-agonist (*SABA*)* „as-needed". The response profile was estimated after 4, 8 and 12 weeks by:

- Assessing asthma symptom control (number of exacerbations, daytime asthma symptoms, nocturnal awakenings, reliever needed, percentage of asthma-free days);
- Lung function testing (spirometry);

- Assessing safety and tolerance (complaints, transaminases AST, ALT).

Protocol of clinical trial was sanctioned by the National Ethics Committee of RM. Patients' parents signed the *Informed Consent* beforehand.

Statistical analysis was done with the use of *EpiInfo 3.5* and *RevMan 5.0 (ANOVA,* Fisher's exact test, *Cochran-Mantel-Haenszel* test).

Results. Assessing asthma symptom control**.** After 4 weeks of treatment with *Montelukast+ICS* the following were significantly reduced from baseline: asthma symptoms (p<0.05), percentage of asthma-free days (p<0.01) and, coresponding, use of SABA (p<0.01), fig. 1, 2.

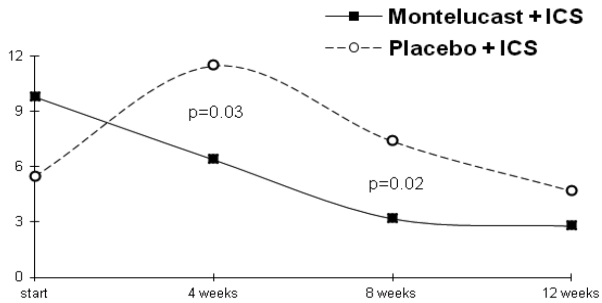


Fig.1. Frequency of asthma symptoms (daily and nighttime symptoms /month)

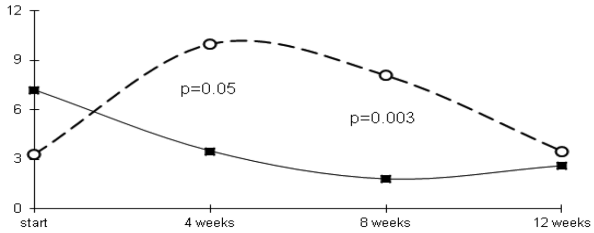


Fig.2 „As-needed" SABA use (puffs/month)

After 12 weeks of treatment with *Montelukast+ICS* the following have dropped:

- the frequency of daytime asthma symptoms – 3 times from baseline (p<0.05)
- the frequency of nocturnal awakenings – 4 times (p<0.001)
- the need for bronchodilators – 3 times (p<0.01).

While asthma-free days increased nearly 2 times (p<0.001).

In the *Placebo*+ICS group significant diffrence from baseline has not been noted (p>0.05)

The impact on the lung function. *Montelukast* together with inhaled corticosteroids, possesses a pronounced additive effect, certainly improving lung function in children with mild-to-moderate asthma. During the 12-week period the average increase of dynamic parameters of spirometry was 20-30%, in comparison with 3-7% in *Placebo*+ICS group (p<0.05), fig. 3.

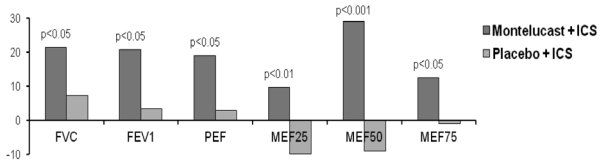


Fig.3 Percentage of change inf spirometry parameters (%)

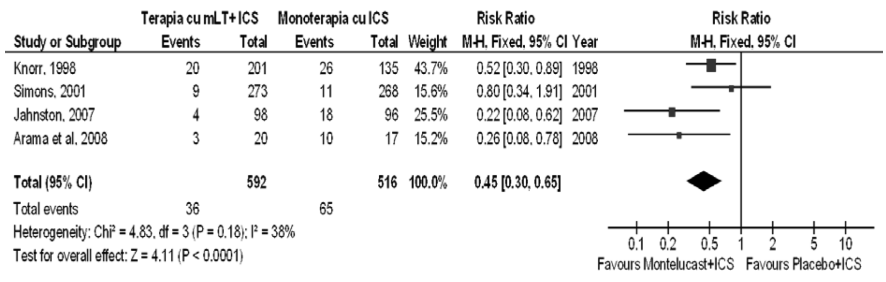
After 12 weeks of treatment with *Montelukast* 2/3 of children had normal values of pulmonary function (>80% of predicted) in comparison with the 35.0% at the beginning (p<0.05).

Out of the monotherapy with ICS group only 1/3 of children had normal lung function at the end of study (in comparison with 17.6% at the beginning, p>0.05; in comparison with *Montelukast+ICS* group – p<0.05).

As a result**,** complete asthma control (according to international protocol GINA) was achieved in 75% of patients who underwent *Montelukast* together with ICS, in comparison with the 47% among those who underwent monotherapy with ICS (p<0.01).

Thus, alongside therapy with LTRA *Montelukast* in children with mild-to-moderate asthma and poor symptom control on treatment with low dose of ICS induction of clinical improvement was noticeable already during the first days of treatment, reaching its peak on the 8th week and remaining stable. The phenomenon of therapeutic selectivity was observed: in 15% of children on combination therapy with *Montelukast* asthma symptoms disappeared completely after 4 weeks and asthma control was maintained with only ¼ of initial doses of ICS (*Fluticasone* 50 µg/day), however, 25% of patients did not attain asthma control after 12 weeks of combination *Montelukast* with *Fluticasone* 200 µg daily.

To strengthen the statistical significance and to position our research among similar studies we ran a ***meta-analysis*** *(Cochrane unique ID: 713209011917161246).* Using evidence-based data sources we have identified 31 paediatric studies on effectiveness of additive treatment with antileucotrienes (yrs. 1996–2007), 10% were considered eligible based on methodological compatibility with our research. Endpoint: number of exacerbations. The sample size – 1108 children. The methodological quality of included studies (GRADE) was ≥4 (Jadad, 1996).



Thus, additive treatment with the use of the antileucotriene *Montelukast* in children with asthma leads to a double reduction in number of exacerbations (RR=0.45; 95%CI:0.30-0.65; p<0.0001).

Conclision. The data collected in the randomized trial and the statistics from the meta-analysis, demonstrate that the efficiency and safety of *Montelukast* (Zespira®) allows for it to be recommended as a controller medication for children with mild-to-moderate persistent asthma in combination with inhaled corticosteroids as a „add-on therapy". The question for following studies: what asthma-phenotype in children is the most sensitive to antileukotrienes?

References:

1. DUCHARME FM, Di SALVIO F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Systematic Reviews*, 2004.
2. CHAUHAN BF, DUCHARME FM Addition to inhalated cotrticosteroids of long-acting beta2-agonists versus antileucotriena for cronic asthma. Cochrane Database Syst Rev 2014; 1:CD003137.
3. Global srtategy for asthma management and prevention (GINA), 2019, p. 210. Available from http://www.ginasthma.org.
4. JEREMY D., MARK H. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics*, 2006, vol.118, p.344-345.
5. RAM F., CATES C., DUCHARME F. Long-acting beta2-agonists versus antileukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database of Systematic Reviews*, 2005.
6. VASILOS Liubov, COJOCARU Ala, GORELCO Tatiana, CULEȘIN Tatiana, ARAMĂ Marina, HORODIȘTEANU-BANUH Adela. *Actualităţi în diagnosticul, tratamentul şi prevenţia maladiilor alergice la copii*. Chișinău, Grafema Libris, 2007, -30 p.