

Applications of the GOAL study in childhood asthma

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Considering recent epidemiologic data we find strong evidence suggesting the advantage of starting the asthma therapy with controllers or preventive drugs very early on life, better in the first 5 years of age. The epidemiologic studies supporting that idea are: first able around 80% of asthmatics start their disease in the first 12 years of age¹, second the cohort study from Melbourne² shows that asthma is a “tracking disease” in symptoms and pulmonary function, meaning that a person that as a child have certain severity of disease and pulmonary function compromised will have the same compromise when he or she become an adult and third the cohort study from Tucson³ demonstrates that the asthmatic suffer the major loosing in pulmonary function in the first 5 years of age.

Besides those epidemiologic data, studies in asthmatic children where bronchoalveolar lavage were done demonstrated the presence of inflammation in the air way in children 8 years old⁴ and even in infants as little as 15 months of age with persistent wheezing⁵. There are also studies which demonstrate airway remodeling in asthmatic children⁶⁻⁷ and the most amazing finding is the fact of the thickness of the basal membrane of the airway in asthmatic children without controlled of their disease is very similar to severe asthmatic adults and it is not related either with the duration of the disease⁸. Therefore, we end up once more to the same conclusion that is essential to start the treatment of asthma with controllers or preventing drugs at infancy.

The only drugs which have been demonstrated to be useful to stop the airway remodeling in humans are the inhaled corticosteroids (ICS) like beclomethasone⁹, budesonide¹⁰ and fluticasone¹¹ and the long active beta agonists like salmeterol¹². The ICS that needs lower doses and less time to decrease the thickness of the basal membrane of the airway in asthmatics was fluticasone¹¹. There is no evidence in the scientific literature that other type of drugs use for asthma like chromones, theophyllines or leukotriene receptor antagonists have any effect in stop-

ping the airway remodeling in humans. These anti-inflammatory and anti-remodeling effects that the ICS has demonstrated besides their already well know utility in improving symptoms and pulmonary function¹³ make ICS become the first controller drug in asthma. This should be use very early on life (in the first 5 years) otherwise the results will not be satisfactory, like Childhood Asthma Management Program (CAMP) study¹⁴ demonstrated. In that study the children did not improve their pulmonary function maybe because the ICS treatment started after that age.

The problem is that in the first 5 years of age coexisting at least three phenotypes of wheezing in children (transitory, late and persistent or classic asthmatic). One way to differentiate which infant with recurrent wheezing will become asthmatic in order to early start ICS therapy is using the asthma predictive value (API)¹⁵. Those infants with recurrent wheezing in the Tucson cohort who had a positive API had 7 times more risk to become asthmatic at school age. In other words, if an infant with recurrent wheezing come to the office and we apply the API and the result is positive we can tell the mother with 77% of certain that the infant will became asthmatic at school age and start controller drugs will be more effective. In the other hand, if the API is negative we can tell the mother with 70% of certain that the child will stop wheezing when he or she reaches school age.

All of us who are involve in asthma management try to have our asthmatic children free of exacerbations, emergency consults, symptoms with exercise, improved their pulmonary function and quality of life, in other words, stop feeling asthmatic or have a normal life. However, epidemiologic questionnaires done in several parts of the world¹⁶⁻¹⁸ have shown that around 95% of the asthmatic do not reach the control of their disease according to international guidelines^{19,20}.

One of the more remarkable issues is that most of the clinical trials done to investigate the efficacy of different

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drugs in asthma consider as the outcome only one parameter (either clinical, laboratory or pulmonary function) and therefore, besides overestimating the level of asthma control²¹. They do not consider that an asthmatic patient like other chronic patient need to be controlled in not only one parameter but also in a group of several parameters.

Few months ago, Bateman et al²² published the results of the GOAL study (*The Gaining Optimal Asthma Control Study*). GOAL was a 1-year, stratified, randomized, double-blind, parallel-group study comparing the efficacy and safety of individual, predefined, stepwise increases of salmeterol/fluticasone with fluticasone alone in achieving two predefined composite measures of asthma control ("well control" and "total control"). Those outcomes are new and involve many clinical and pulmonary functions criteria as a whole.

The GOAL²² study defined that a patient reaches "total control" of asthma if in 7 out of 8 weeks fulfills all of the following criteria: without symptoms in the day, no rescue medication use, normal pulmonary function (peak expiratory flow [PEF] am > 80%), no wake-ups at night, no exacerbations, no emergency visits and without secondary effects. We can say that "total control" means clinical remission of asthma and that objective was more stringent than the one that Global Initiative for Asthma (GINA)¹⁹ proposed. The "well control" was defined as the fact that in 7 out of 8 weeks the patient fulfills the criteria: no wake-ups at night, no exacerbations, no emergency visits and no secondary effects *PLUS* at least more than two of the follows criteria: ≤ 2 days with light symptoms, use of rescue medications in ≤ 2 days and ≤ 4 times/week and normal pulmonary function (PEF am > 80%).

From a total of 5068 patients (between 12 and 80 years of age) recruited in 44 countries, 3421 patients fulfilled the inclusion criteria. Interesting 10% of them were adolescents (12-17 years-old). At the beginning of the study the patients were separate in three strata- according to the ICS uses- and were randomized to received salmeterol/fluticasone or fluticasone alone. In each strata, the percentage of patients who reached the "well control" and the "total control" definition were statistical more frequent in the salmeterol/fluticasone group vs. fluticasone. And at the end of the year considerable proportion of patients (41%; all strata) in the salmeterol/fluticasone group reach the "total control". Moreover, those patient in the salmeterol/fluticasone group reach the "total control" with 60% less dose of ICS and earlier than those in the fluticasone group. In the other hand, the patients in the salmeterol/fluticasone group had better quality of life - according to Asthma Quality of Life Questionnaire (AQLQ) scale- than those in the fluticasone group and without differences in adverse events. This study demonstrated, for the first time, the fact that "total control" in asthma can be reach and that is a challenge that physicians and patients have to struggle for.

According to the evidence mentioned at the beginning of this editorial, the main question in pediatrics is if the GOAL results can be apply to asthmatic children under 12 years of age. Unfortunately, there is no clinical trial done for that age with the same design, however institutions like NAEPP²³ in the US and in the British Thoracic Society in UK have has in their guidelines the uses of ICS plus long active beta agonist for asthmatic children under 5 years of age with moderate to severe persistent asthma.

Moreover, there are some clinical trials which proved the efficacy of salmeterol/fluticasone in asthmatic children less than 12 years of age. For example, Van der Berg et al²⁴ in a multicenter, randomized, double blind and parallel-group study compared the clinical efficacy of salmeterol (50 μg bid) plus fluticasone (100 μg bid) administered in one single inhaler (combination therapy with Accuhaler®) vs. concurrently in two separate Accuhaler® inhalers. From a total of 257 asthmatic children (aged 4-11 years) who remained symptomatic on ICS alone (200-500 μg beclomethasone or budesonide) were randomized to one of each group. After 12 weeks of treatment both groups of children (combination and separate therapy) were similar in improve PEF, clinical score, less use of rescue drugs, well tolerate therapy and few secondary effects. Bracamonte et al²⁵ in a multicenter, randomized study compared 428 asthmatic children (4-11 years) who remained symptomatic on moderate doses of ICS (≤ 500 μg beclomethasone or budesonide). One group received salmeterol/fluticasone in a MDI free of CFC (25/50 μg two inhalations bid) and the other salmeterol/fluticasone in Accuhaler® device (50/100 μg one inhalation bid) for 12 weeks. Clinical improve was reached in 90% and 86% of the children in each group, respectively. Finally, Sekhsaria S. et al²⁶ in a retrospective study with 50 children (5-60 months of age) with recurrent wheezing demonstrated clinical improve (decrease emergency visits, hospitalization and exacerbations) when they started the treatment with salmeterol/fluticasone.

Even though these clinical trials with salmeterol/fluticasone in children under 12 years of age are not big in number of children enrolled and have different design to the GOAL study, their results are promising.

Competing interest statement

JACR: in the past five years has been received reimbursement for attending conferences from Grünenthal, Merck, GlaxoSmithKline and Andromaco, at the present he is medical advisor for GSK. The position of this paper is a personal opinion and does not express the opinion of any pharmaceutical company

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