REVIEW ARTICLE

Which anti-inflammatory drug should we use in asthma?

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KEY WORDS

asthma management, asthma treatment, glucocorticosteroids, leukotriene modifiers, pragmatic trials

ABSTRACT

Asthma is a chronic and heterogeneous inflammatory disorder of the airways defined by its clinical, physiological and pathological characteristics. Accordingly to currently available guidelines inhaled glucocorticosteroids (ICS) represent the most effective anti-inflammatory medication for the treatment of persistent asthma, and this class of drugs is recommended as the first-line controller therapy both in children and adults. Leukotriene modifiers (LTRAs) are usually used as a second line of add-on therapy, although they may be regarded as the first-line therapy in exercise induced bronchoconstriction, in patients with comorbid allergic rhinitis and in children with asthma and frequent viral infections. A recently published pragmatic (real-life) study showed that LTRAs provide an alternative treatment for asthma, which, at least for the evaluated endpoints, may be as effective as ICS in our every-day practice. To assess how the recent data may affect our every-day practice and current guidelines for clinical management of asthma, it needs to be clearly understood what pragmatic trials add to our knowledge. In our opinion, it is premature to change current guidelines. However, pragmatic and observational studies are clearly needed as they provide additional information to randomized controlled trials. The main goal of all those efforts is to improve asthma control and decrease the burden of the disease for patients and societies. It may be that the future approach will introduce several new strategies based on system biology studies for the treatment of asthma guided in a personalized medicine approach.

Introduction Asthma is a chronic and heterogeneous inflammatory disorder of the airways defined by its clinical, physiological, and pathological characteristics.[1] It is widely recognized that several different phenotypes[2] characterized both by clinical and physiological variables and biomarkers are grouped together based on a recognition of typical symptoms (airflow obstruction and airways hyperresponsiveness), and altogether form an umbrella-like definition of asthma. This heterogeneity is mirrored in the quite complex and descriptive definition of the disease and has a clear impact on our every-day clinical practice. In some difficult-to-treat, severe cases extensive diagnostic procedures, differential diagnosis, education and treatment on a personalized medicine level are necessary to obtain a clinical success and good control of the disease.

As clearly stated in the international guidelines on asthma diagnosis and management – Global Initiative for Asthma (GINA)[1] – there is good evidence that the clinical manifestations of asthma, including day and night symptoms, sleep disturbances, limitation of activity, impairment of lung function, and use of rescue medication, in most cases may be well controlled with appropriate treatment. Good control of the disease is the main goal of asthma management as it clearly improves patients' quality of life, reduces number of exacerbations, and decreases the cost of health care. Medications used to treat asthma are classified as controllers and relievers.[1] Relievers are limited mainly to rapid-acting inhaled β_2-agonists (short-acting β_2-agonists – SABAs), which act quickly to reverse bronchoconstriction and relieve symptoms. Controllers should be taken prophylactically and on a long-term basis to keep asthma in good control, which is believed mainly to be due to their anti-inflammatory effects. They include inhaled (ICS) and systemic glucocorticosteroids,

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leukotriene modifiers, long-acting β_2-agonists (LABAs, to be used only in combination with ICS), theophylline, and anti-immunoglobulin E.

The main strategy for asthma therapy may be summarized as a step-up/step-down approach. In those patients in whom asthma is not well controlled (as defined by frequency of symptoms, limitation of activities, need for rescue medications, lung functions, and exacerbations), an increase in dose of the currently used controller or adding another drug is the recommended action. On the other hand, in patients where asthma is well controlled, the dose or the number of controllers should be reduced to limit the possibility of side effects and decrease the costs. According to the GINA guidelines,[1] ICS represent the most effective anti-inflammatory medication for the treatment of persistent asthma, and this class of drugs is recommended as the first-line controller therapy both in children and adults. Leukotriene modifiers are usually used as a second line of add-on therapy, although they may be regarded as the first-line therapy in exercise-induced bronchoconstriction, in patients with comorbid allergic rhinitis, and in children with asthma and frequent viral infections.[3]

In current guidelines, recommendations regarding the choice of medications, prevention, and strategies for management are based almost exclusively on the results of double-blind, randomized controlled trials (RCTs). RCTs provide a good insight into mechanism of drug action, efficacy, and acute side effects. On the other hand, as a consequence of their strict scientific design, there are also some significant limitations of RCTs. The main issue is usually artificial selection of the study group. Strict inclusion criteria which guarantee that the patients' group is homogenous and the diagnosis of the studied disease is clear, at the same time lead to preselection of a cohort that does not mirror the real-life conditions which we face in our clinical practice. In addition, due to high costs, RCTs are usually relatively short-term studies, rarely exceeding 1 year of follow-up, and thus may be less powerful for evaluation of long-term factors such as variability of the disease, exacerbation-rate, compliance, tolerability, long-term adverse events, and patients' preferences. Other options to investigate the effects of treatment include observational (prospective and retrospective) studies and pragmatic trials. The main advantage of such real-life studies is that the study groups and therapeutic conditions are reasonably similar to those seen in every-day practice.

One recently published real-life pragmatic study was the paper by Price D et al.[4] The main goal of that trial was to evaluate real-world effectiveness of leukotriene-receptor antagonist (LTRA) as compared with either ICS as a first-line asthma controller, or LABAs as add-on therapy in patients already receiving ICS. More than 650 patients were included and followed up for up to 2 years by their primary care physicians and the main study outcome was asthma-related quality of life. Authors concluded that at 2 months LTRAs were equivalent to ICS both as a first-line controller therapy and as add-on to ICS compared with LABAs. At 2 years, the results were very similar although not meeting predefined criteria for equivalence. For another study outcome, improvement of lung function, there were equal improvements over the whole 2-year period between the compared treatment strategies whether LTRAs were given as first-line therapy or as addition to ICSs. This study has initiated much discussion as the results clearly question the current recommendations of asthma treatment.[1] To provide perspective, studies published to date have certainly documented that LTRAs have anti-asthmatic effects, which are undoubtedly better than those of placebo. However, most studies involving comparisons with other treatments have also suggested that LTRAs are less efficacious than ICS, although a few have been reporting similar asthma control with both approaches.[4] In order to conclude how the recent data may affect our every-day practice and current guidelines for clinical management of asthma, it needs to be clearly understood what pragmatic trials add to our knowledge.

Pragmatic and explanatory trials Differences between explanatory (mechanistic) and real-life (pragmatic) trials have recently been comprehensively reviewed by Sackett[5] and Ware et al.[6] Briefly, the two approaches differ with respect to the several main elements of a clinical treatment trial, namely, participant eligibility, administration of the therapeutic intervention, and compliance with study drug use, as well as adherence to protocols, follow-up intensity and outcome. The main goal of explanatory, RCTs is to evaluate the efficacy of specific intervention (a medication or other medical procedures) in a highly selected cohort of patients, under ideal circumstances, whereas pragmatic trials analyze potential role of studied intervention in a real-life condition, in a typical group of patients we meet in our every-day practice, suffering from other comorbidities, taking also other drugs, and allowing for natural variability in adherence to use of prescribed drugs. It is necessary to understand that both approaches are valid and add to our knowledge of the field; however, they address different clinical and scientific problems. Explanatory trials are designed to evaluate the efficacy of a studied drug in a mechanistic way, by answering the question "Does this medication work by affecting a particular mechanisms in the disease?" Pragmatic trials analyze the effectiveness of a drug which already is known to work under ideal conditions. The primary question here is whether this medication is efficacious in typical patients, in every-day settings, where several factors can influence the outcome of an intervention (TABLE). Results of such a study are of particular value for health care providers. Combined

TABLE Factors possibly influencing effectiveness of a therapeutic intervention in asthma in every-day clinical practice

Factor	Comments
comorbidities	allergic rhinitis, nasal polyps, sinusitis, cardiovascular diseases
socioeconomic status	education and income impact health care accessibility
smoking status	lung function is lower in smokers and exacerbations are more frequent
obesity	exacerbations are more frequent and lung function is lower in obese patients
compliance	with medications may be dependent on formulation (tablets vs. inhalers) and patients' preferences
adherence	with treatment plan (action in case of exacerbation) may be variable
follow-up	frequent and intense follow-up especially first months after diagnosis may improve compliance with treatment
inhalation techniques	differences between different inhalers: metered dose inhaler, dry powder inhaler
steroid phobia	not only for systemic but also corticosteroids in inhalations
age	compliance with treatment may be lower in adolescents
expertise of practitioner	may be different in those trained in allergic and lung diseases and those who are not trained
health care system	access to a specialist and medication

with pharmacoeconomy studies, pragmatic trials may help address the question of which medication is the most cost-effective in real-life conditions, and thus help create a health care policy.[5,6] There is no doubt that pragmatic trials give several interesting additional pieces of information. When results of RCTs are analysed, a message that a particular medication is more active than placebo is usually available. However, one can ask how does it add to our clinical practice as we do not treat our patients with placebos? This issue has been addressed by some regulators, and nowadays the approval of new medicines often requires proven effectiveness over and above the current "gold standard" treatment, or at least noninferiority. As stated by Ware et al.[6] "... pragmatic trials are designed to study real-world practice and represent less 'perfect' experimental design than efficacy trials". The challenge for health care providers and individual physicians is to assess how to integrate the information from these two types of studies, which in essence capture very different dimension of the evaluation of management strategies.

Impact of pragmatic trials on clinical practice in asthma Some of the main weaknesses of the pragmatic trial strategy is thus the flexible study design, the uncertain compliance with treatment, and the losses of patients during follow-up. It is, therefore, difficult to identify which factor contributed most to the overall study result. The pragmatic study of Price et al.[4] is a good example of these inconsistencies. The main message of their study is that there is little, if any, difference between LTRAs and ICS in maintaining asthma control as first-line or add-on treatments. However, from the method section and the results of the trial, it is clear that several factors could have significant impact on the outcome. The intervention here was flexible, with significant crossover between treatment groups, possible use of concomitant therapies, possible enrolment of misdiagnosed patients, and possible spontaneous improvements. But attempting to assess the influence of different factors for the study outcome, we would suggest that the way of administration of the study drugs (tablets vs. inhalers) may have been the most important factor for the overall study outcome. Accordingly, adherence to LTRAs was significantly better than it was to the other drugs in the study (65% vs. 41% for ICS) and (74% vs. 46% for the LABA arm). It is well known that compliance with tablets (especially those taken once daily) is much better than with inhaled drugs.[7]

Conclusions The real-life study by Price et al.[4] showed that LTRAs provide an alternative treatment for asthma, which, at least for the evaluated endpoints, may be as effective as ICS in our every-day practice. Antileukotrienes may have several advantages in clinical practice. First, montelukast and zafirlukastare are available as generic medications in most countries, thus the cost of such treatment is decreasing. Second, many patients with asthma have rhinitis, and LTRAs may contribute to the treatment of rhinitis symptoms as well. Third, antileukotrienes have a very good safety profile. This may be contrasted to corticosteroids, where the common "steroid phobia" in many patients, as in fact suggested by the trial of Price et al.,[4] in addition may have a significant impact on adherence to therapy. On the other hand, ICS act broadly on several targets in the pathophysiological mechanisms of chronic inflammation, whereas LTRAs block only one pathway. Another therapeutic approach may be combining antileukotrienes with antihistamines, which has been proved to yield additional protection in allergen-challenge studies in atopic asthma.[8,9]

It needs to be made clear that the trial of Price et al.[4] has not proved that LTRAs are equal anti-inflammatory drugs to ICS, only that when used in the nonsupervised environment, in the primary care setting, there seems to be no major difference in overall treatment response. As mentioned above, the most plausible factor behind these somewhat surprising study results may be that the oral administration has advantages over inhaled medications more than pharmacologic differences between the two classes of drugs.

There are no doubts that the paper by Price et al.[4] has started an interesting discussion that may lead to an increase in our understanding of the clinical needs in asthma treatment. It is premature to change current guidelines but pragmatic and observational studies are clearly needed as they provide additional information to RCTs. The main goal of all those efforts is to

improve asthma control and decrease the burden of the disease for patients and societies. It may be that the future will introduce several new and personalized strategies for the treatment of asthma guided by patient specific patterns of changes in lung function[10] or biomarkers.[11] For example, new antagonists of prostaglandins or key cytokines present promising effects in animal and clinical models.[12] It is highly probable that future generation of therapies for asthma will combine several selective molecules, preferably given orally as a once-daily tablet, to block main proinflammatory pathways and significantly improve disease control. This scenario is similar to current medical practice in hypertension where the combination of several drugs gives a possibility to design a patient-oriented (depending on comorbidities, preferences, tolerance, etc.) effective therapeutic approach.

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ARTYKUŁ POGLĄDOWY

Jaki lek przeciwzapalny powinniśmy stosować w terapii astmy oskrzelowej?

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SŁOWA KLUCZOWE

astma oskrzelowa, badania pragmatyczne, glikokortykosteroidy, leki anty-leukotrienowe, postępowanie, terapia

STRESZCZENIE

Astma oskrzelowa jest przewlekłą zapalną chorobą dróg oddechowych, definiowaną przez typowe objawy oraz parametry patofizjologiczne. Według obecnych zaleceń glikokortykosteroidy (GKS) wziewne są najskuteczniejszymi lekami przeciwzapalnymi stosowanymi w terapii astmy przewlekłej. Tę grupę leków zaleca się jako terapię pierwszego rzutu kontrolującą przebieg choroby zarówno u dorosłych, jak i u dzieci. Leki antyleukotrienowe (*leukotriene receptor antagonist* – LTRA) są zwykle lekami drugiego rzutu, chociaż z powodzeniem stosowane są jako terapia podstawowa u pacjentów z obturacją dróg oddechowych indukowaną wysiłkiem, u chorych z towarzyszącym nieżytem nosa i u dzieci z astmą i częstymi infekcjami wirusowymi. W jednym z ostatnio opublikowanych badań pragmatycznych wykazano, że LTRA w terapii astmy, przynajmniej dla analizowanych w pracy punktów końcowych, mogą być równie skuteczne co GKS wziewne. Aby ocenić, jak przedstawione badanie może zmienić naszą codzienną praktykę i stosowane obecnie standardy postępowania w astmie oskrzelowej, niezbędne jest zrozumienie w jaki sposób badania pragmatyczne wpływają na wiedzę medyczną dotyczącą omawianych zagadnień. Naszym zdaniem jest za wcześnie na zmianę obecnych standardów i zasad postępowania w astmie. Bez wątpienia jednak badania obserwacyjne i pragmatyczne stanowią istotne źródło informacji uzupełniających dane zebrane w badaniach randomizowanych. Podstawowym celem wszystkich tych prac jest poprawa kontroli astmy oskrzelowej i zminimalizowanie obciążeń wynikających z tej choroby, zarówno dla pacjentów jak i całego społeczeństwa. Być może w przyszłości zostaną wprowadzone nowe metody postępowania w astmie, zgodne z zasadami medycyny personalizowanej.

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