Treatment of asthma: roles of different classes of drugs

Dr. Paul O'Byrne in an interview with Dr. Roman Jaeschke: part 1

Prof. Paul O'Byrne, MB, FRCPI, FRCPC, FRCPE, FRCP(Glasg), FAPC, FCCP, FERS, FRSC

Professor at the Division of Respirology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; Dean and Vice-President of the Faculty of Health Sciences, McMaster University; member of the Executive Committee of the Global Initiative for Asthma; Associate Editor of *Chest, Thorax,* and *International Archives of Allergy and Immunology;* his current research activity focuses on the mechanisms and treatment of asthma, specifically the regulation of environmental allergen-induced airway inflammation and the development of new anti-inflammatory asthma treatments

In a previous interview,[1,2] you talked about the history of asthma, use of inhaled corticosteroids (ICSs), and use of short- and long-acting ß$_2$-agonists. Specifically, in part 2 of the interview,[2] you mentioned the use of muscarinic antagonists, both short- and long-acting, and I wonder if we could now reflect on something different which is the place of different drugs in management of asthma, including those muscarinic antagonists.

The information we now have about asthma management, asthma control, and particularly the more acute severe events, exacerbations, hospital admissions, and so forth, is actually very encouraging. In Ontario, where I work, the risk, for example, of children being admitted to an emergency room and into a hospital setting for acute severe asthma is reduced by half compared to 10 years ago. That is a very dramatic change, and it is because of the—in my view—almost certainly increased use of ICSs, at low doses; we do not need high doses to manage most patients.

I think it is widely accepted now that with inhaled steroids as a monotherapy or ICSs together with a long-acting ß$_2$-agonist (LABA) in the same device, we can manage really well, probably 90% of patients with asthma or even more. The challenging piece is getting the patient to use the medications regularly, particularly when they are feeling well. That is another topic for discussion. We do, however, have a subset of patients who are on optimal inhaled therapies with ICS/LABA at the optimal doses or highest doses in whom asthma is not well controlled. The treatment recommendations are now indicating that we should, as the next step, add a long-acting muscarinic antagonist (LAMA), to the combination of ICS/LABA. That is because of 2 large studies, published again in the *New England Journal of Medicine* a couple of years ago, showing that adding a LAMA in that clinical setting does 2 things: it improves lung function and it further reduces severe exacerbation rates. The evidence is very compelling, and now that approach is approved in Canada and many other countries as a third-line therapy for patients.

However, even with adding the LAMA, we are still left with a subset of patients in whom you have assured that adherence is adequate or done your best to do that, tried to rule out other comorbidities that can make asthma worse, like rhinosinusitis, gastroesophageal reflux, and so on, and you are left with people who have what is now called severe refractory asthma. And it turns out that about 60% of these patients have a persisting

airway—and sometimes blood—eosinophilia, despite being on all of this inhaled therapy. Some of those patients are allergic, and it is appropriate to consider treatment with an anti-IgE monoclonal antibody, omalizumab, but that has to be in patients with severe asthma, who have had exacerbations, and who have evidence of allergy as a driving factor for their asthma.

More recently, in the past couple of months, we have had approved here in Canada and in the United States and many other countries a second approach with a monoclonal antibody, which is directed against interleukin 5 (IL-5). That is important because IL-5 is essential for eosinophil production in the bone marrow, for eosinophilopoiesis, and for its survival in tissues. If you block IL-5, you essentially get rid of eosinophils. The evidence—going back a little bit—and a number of very, very good publications, very good, well-designed studies, is that giving this anti-IL-5 approach to patients with severe eosinophilic refractory asthma markedly reduces exacerbation rates, by more than half, 60% probably, as well as improving lung function. So that is yet another new approach as a fourth-line therapy, when added on to the high doses of inhaled therapy.

Two questions. Probably quite expensive, I suspect.

Yeah.

And the second question is, you mentioned LAMAs. Any place for a short-acting muscarinic antagonist (SAMA)?

So the second question first. SAMAs have been used in asthma actually for many years but in the acute care setting. Again, there are studies going back more than 20 years showing that adding a SAMA, ipratropium (which was the sort of the standard drug used) to a short-acting ß$_2$-agonist (SABA) in acute severe asthma in the emergency room improved outcomes. And that has been the gold standard of treatment for acute severe asthma in an emergency setting, and it is still the case. We do not have good evidence in fact that the LAMA is as effective in that acute setting. Those studies just have not been done so we do not know that yet. So still, as of today, when you look at treatment recommendation guidelines, the combination of SABA and SAMA in an emergency room setting is what is recommended. But not for the regular maintenance use in asthma.

The second question you asked is about cost in relation to the biologics that are being used. And you are absolutely right. This is a very expensive class of medication, just as any biologic is for any chronic disease. However, fortunately, we have very clear evidence of what phenotype we should use these drugs in and the magnitude of benefit. So this is, I think, a tremendous example of personalized medicine, where you select an effective biologic therapy, which is only going to work in a very specific patient population. And those patients are those with severe refractory eosinophilic asthma, where you can eliminate the eosinophils in the airway and in the blood, and that is associated with a very clear outcome, which is reduction in exacerbation rates and, in the studies that we conducted here in Canada, withdrawal of oral corticosteroids, which had been up to now the only viable option for these patients, long-term maintenance oral corticosteroids.

Great, very useful. Two more historical questions. In the acute asthma setting, or in chronic in fact, is there a place for aminophylline-type drugs and for magnesium?

Second question first: magnesium, yes. Magnesium given as a single bolus dose has been shown to improve outcomes, to improve the likelihood of patients being discharged from the emergency room rather than being admitted to the hospital. So magnesium is in treatment guidelines, usually in patients who are not responding well to the conventional treatment approaches with high doses of bronchodilators, short-acting; in some settings, formoterol, which is a rapid-onset but longer-acting SABA, is used, but with high doses of ß$_2$-agonists used and the antimuscarinics that I have talked about. If those are not providing rapid improvement, then magnesium is considered to be a viable option.

1, 2, 4 grams?

1 gram as a bolus. The second question about aminophylline: There is essentially no role for aminophylline today in management of asthma in most health care settings. Aminophylline is a modestly effective bronchodilator, not nearly as effective as an inhaled ß$_2$-agonist. It has no direct anti-inflammatory properties; it is oral or intravenous use, which is different to the other approaches. It does have many more side effects than the inhaled treatment approaches I have mentioned already. The only situation where potentially one could consider it is in a health care setting in a developing country, particularly, where costs of the inhaled medications are potentially an issue. So what I am trying to say: it is better than nothing, but not nearly as good as the newer medications we have.

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2 O'Byrne P, Jaeschke R. Safety of long-acting ss2-agonists: current state of knowledge. Dr. Paul O'Byrne in an interview with Dr. Roman Jaeschke: part 2. Pol Arch Med Wewn. 2016; 126: 912-913.