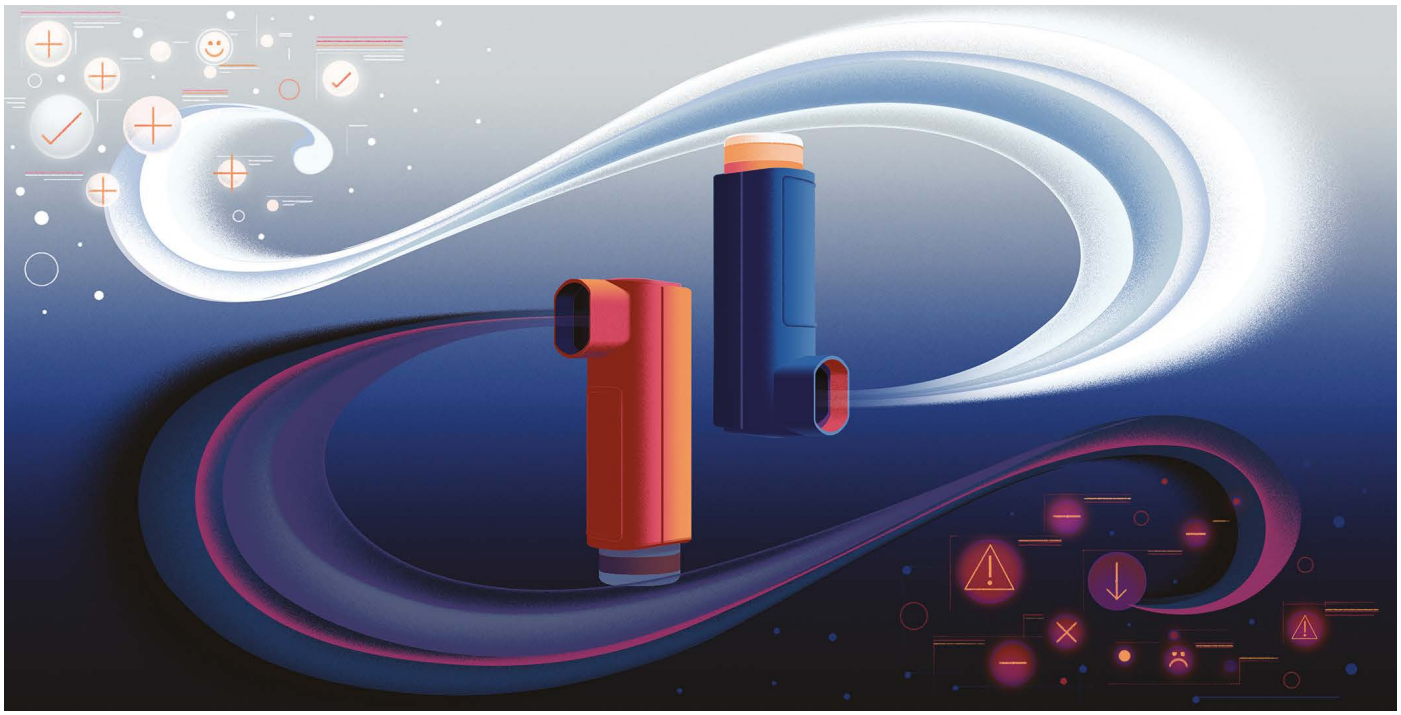

SAM CHIVERS

The steroid debate

Should physicians still be prescribing steroid inhalers as a first-line treatment? **By Julianna Photopoulos**

The first inhaled corticosteroids were developed in 1972 for use in people with asthma. The drugs, which tackle inflammation in the airways, were revolutionary in reducing the number of hospital admissions and deaths due to asthma.

It is little wonder, then, that physicians, faced with a paucity of treatment options for chronic obstructive pulmonary disease (COPD), would adopt the anti-inflammatory steroids that had proved so effective in managing asthma. The drugs became a common prescription – one of the first clinical trials to test inhaled steroids for COPD found that more than half of the people recruited between 1992 and 1995 were already receiving them[1]. Now, many estimates put the use at around 75%.

And yet the evidence underpinning the efficacy of steroids for COPD is surprisingly inconclusive. "Inhaled steroids have turned out to have very little clinical benefit in COPD," says Peter Barnes, a respiratory scientist at the National Heart and Lung Institute in London. Although the drugs might be beneficial to some people with COPD, many researchers think that the upsides are often outweighed by the risk of side effects. As that point of view has become more widespread, guidelines on prescribing inhaled steroids for COPD are changing. The aim now is to give the drugs only to those who stand to benefit.

Balance of evidence

Inhaled steroids are commonly prescribed in combination with drugs known as bronchodilators. The main examples used for COPD are long-acting β2-agonists (LABAs) that widen airways by causing lung muscles to relax, and long-acting muscarinic antagonists (LAMAs) that prevent nerves from releasing chemicals that cause the airways to tighten. Used daily, bronchodilators help to manage symptoms, improve lung function and – through processes that are not well understood – prevent flare-ups, known as exacerbations.

For asthma, LABAs can be given only alongside inhaled steroids, says Leonardo Fabbri, a respiratory researcher at the University of Ferrara in Italy – on their own, the bronchodilators increase the risk of a life-threatening asthma attack. LABA and steroid combination inhalers are also commonly used to manage COPD, but including a steroid, rather than a combination of LAMA and LABA bronchodilators, has been called into question.

The efficacy of the two drug combinations has been extensively tested, and the findings are conflicting. In 2016, the FLAME trial, involving around 3,000 people, reported an 11% lower rate of COPD flare-ups when people used a combination of LAMA and LABA for a year, than when they used a LABA and steroid inhaler[2]. But in 2018, the larger IMPACT study, which involved more than 10,000 people with moderate-to-severe COPD, found the opposite – a combination of LABA and steroid was associated with fewer exacerbations[3].

The apparent disagreement could be because steroids work better for some forms of COPD than for others, says Daiana Stolz, a respiratory researcher at University Hospital Basel in Switzerland. Although the FLAME study suggested that steroid inhalers were outperformed by LABA and LAMA treatment, Stolz says that people who had previously experienced frequent exacerbations did respond positively to inhaled steroids. And a clinical practice study led by pharmacoepidemiologist Samy Suissa at McGill University in Montreal, Canada, found that roughly 10% of participants benefited from using inhaled steroids rather than dual bronchodilators[4].

Suissa's study also found that people with COPD who started on LABA and inhaled steroid treatment were more likely to develop pneumonia than were those who did not receive a steroid treatment. This is a common safety concern associated with inhaled steroids.

People with COPD are already more prone to developing pneumonia than are healthy people, Fabbri says. But several studies have suggested that inhaled steroids increase the risk — nearly doubling it in some cases[5].

New recommendations

Although there is still some debate as to who can benefit from inhaled steroids, researchers agree that the drugs have long been overprescribed. "It's important that we only give drugs to patients who are likely to benefit from them," says James Chalmers, a respiratory researcher at the University of Dundee, UK.

Since 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has published a strategy for diagnosing and managing COPD, which is often used as the basis for national and regional guidelines. For many years, GOLD recommended that inhaled steroids be broadly prescribed for people with frequent exacerbations and severe loss of lung function. But over time, that advice has changed. In 2011, LAMA bronchodilators were recommended over combinations of LABA and inhaled steroids, following research that showed that the two had a similar effect on the rate of flare-ups. And in 2017, following the FLAME findings, GOLD recommended that LABA and steroid inhalers be given only when LAMA and LABA therapy fails to control symptoms.

In 2019, GOLD highlighted a biomarker — blood eosinophil count — that could be used to identify which people experiencing frequent exacerbations are most likely to benefit from inhaled steroids. Eosinophils are white blood cells that fight infection, and can contribute to airway inflammation. Ian Pavord, an airway-disease researcher at the University of Oxford, UK, found that the higher the eosinophil levels in people with COPD, the more effective steroids are at managing exacerbations[6]. In people with low eosinophil counts, steroids had little effect. In a later study, he showed that people with low cell counts are also at greater risk of pneumonia[7].

A person's eosinophil count can vary — levels are higher in the morning than they are in the evening, says Stolz, suggesting that multiple tests might be needed to ensure physicians have an accurate picture of their patients. But even so, the measure has turned out to be a "surprisingly good indicator" of whether people with severe COPD will respond to steroids, says Barnes. GOLD now recommends that a blood eosinophil count of more than 300 cells per microlitre is a sign that people with frequent exacerbations and severe symptoms will benefit from inhaled steroids. If a person's eosinophil count is under 100 cells per microlitre, inhaled steroids are discouraged owing to lack of efficacy and the increased risk of pneumonia, even if the person is experiencing frequent exacerbations.

Disparate worlds

In 2017, Chalmers and his colleagues estimated that more than 60% of people in the United Kingdom with COPD were receiving steroids as a first-line treatment[8]. Pavord hopes that including blood eosinophil count as a biomarker in the GOLD recommendations will lead to inhaled steroids being prescribed more selectively (only around 10–20% of people with COPD have eosinophil counts greater than 300 cells per microlitre). But clinical practice does not always follow GOLD recommendations to the letter. One 2019 study found that many Europeans at low risk of COPD exacerbations were still being prescribed inhaled steroids[9].

"It's important that we only give drugs to patients who are likely to benefit from them."

What happens in research labs and what is done in clinical practice are different things, says Suissa. "These are two completely disparate worlds." In some countries, he says, long-acting bronchodilators are either available only with an inhaled steroid — as would be required for asthma — or can be prescribed without a steroid only by specialists. Until this year, primary-care physicians in Israel gave patients combined LABA and steroid inhalers because they could not prescribe LABA alone, he explains.

Some researchers are also concerned that the ready availability of triple-combination inhalers that contain both bronchodilators and a steroid might lead to more people receiving steroids.

The IMPACT study found that the rate of flare-ups in people using triple therapy was 25% lower than in those using LAMA and LABA combination inhalers. The rate of pneumonia, however, was 50% higher. Several other trials have also reported lower rates of exacerbations associated with triple therapy than with dual-bronchodilator therapy, says Fabbri. He thinks that there are cases in which triple therapy could be beneficial as a first-line treatment, despite current guidelines, and says that most people with COPD will end up using it eventually. Barnes agrees that this is likely, albeit inappropriate in his estimation, simply because triple therapy is "the easiest way to manage COPD".

While researchers and clinicians debate the best prescriptions for people with COPD, a thornier issue looms: what to do about the millions of people already receiving inhaled steroids. "There is clearly no point" in administering medicines that could do more harm than good, Pavord says. But, he admits, "it's quite hard withdrawing treatment in very symptomatic patients", which most are. Fabbri thinks that if the treatment seems to be working and there aren't any other complications, it should be continued — even if it includes a steroid.

Take it away

Some evidence suggests that steroids can be safely withdrawn from people with COPD who are used to taking them. For example, an observational study in Japan found that older people with COPD who had the steroid component of their treatment withdrawn after a flare-up were less likely to die or be admitted to hospital than were those who stayed on the steroid[10]. The 2014 WISDOM study also found that gradually discontinuing inhaled steroids did not affect flare-ups in people who had been using triple therapy, although the results did suggest that continuing to use inhaled steroids was beneficial for lung function[11] — the importance of which has divided researchers.

As things stand, there are no international recommendations about withdrawing steroids from people with COPD. But Chalmers expects guidelines from the European Respiratory Society on who it is appropriate to withdraw inhaled steroids from, and how best to do it, to be published in May. "Hopefully it'll start to reverse some of the overuse of steroids across Europe," he says.

For Chalmers, it is time to move on from the inhaled-steroid debate. Even in people who do see a benefit, steroids are not very effective treatments, he argues. "We have spent too much time talking about steroids," he says. "We need to invest more energy into finding better treatments."

Julianna Photopoulos is a science journalist near Thessaloniki, Greece.

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