Research Review Speaker Series™

Advances in Asthma and COPD Management

Making Education Easy

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He qualified at Cambridge and Oxford Universities (first class honours) and was appointed to his present post in 1987. He has published over 1000 peer-reviewed papers on asthma, COPD and related topics (h-index 150) and has written or edited over 50 books. He is the 7th most highly cited researcher in the world, has been the most highly cited clinical scientist in Europe and the most highly cited respiratory researcher in the world over the last 20 years.

He was elected a Fellow of the Royal Society in 2007, the first respiratory researcher for over 150 years. He is a member of the Scientific Committee of global guidelines on asthma (GINA) and COPD (GOLD). He also serves on the Editorial Board of over 30 journals and is currently an Associate Editor of Chest, Journal of COPD Foundation, Respiratory Editor of PLoS Medicine and Editor in Chief of Up-to-Date Pulmonary Medicine. He has given several prestigious lectures, including the Amberson Lecture at the American Thoracic Society, the Sadoul Lecture at the European Respiratory Society and the Croonian Lecture at the Royal College of Physicians, London. He has received honorary degrees from the Universities of Ferrara (Italy), Athens (Greece), Tampere (Finland), Leuven (Belgium) and Maastricht (Netherlands). He is a NIHR Senior Investigator and was elected a Master Fellow of the American College of Chest Physicians and a member of Academia Europaea in 2012. He was President of the European Respiratory Society 2013/2014. He co-founded an Imperial spin-out company RespiVert, which was acquired by Johnson & Johnson and has developed novel inhaled treatments for COPD and severe asthma.

Abbreviations used in this review
ICS = inhaled corticosteroid
COPD = chronic obstructive pulmonary disease
LABA = long-acting β_2-agonist
SABA = short-acting β_2-agonist
SMART = Single inhaler Maintenance And Reliever Therapy

This article summarises highlights from a lecture by world-renowned respiratory disease clinician and researcher, Prof. Peter Barnes (London), which was given to general practitioners in Auckland on 30th April 2015. The presentation, *Advances in Asthma and COPD Management*, emphasised the problem of poor asthma control and the benefits of budesonide/eformoterol SMART therapy in the treatment of asthma and COPD.

ASTHMA MANAGEMENT

Highly effective drugs are available for the treatment of asthma. ICSs revolutionised asthma therapy and combination ICS/LABA inhalers, which are even more effective, have become the gold standard for the treatment of asthma. Consequently, the general expectation is that all asthma patients should be well controlled. The INSPIRE study, however, revealed that half of nearly 3,500 asthma patients receiving effective maintenance therapy were poorly controlled and less than one-third were well controlled.[1] The explanation for this finding can only be that patients were not taking their treatment. It is now known that treatment non-adherence is the major barrier to attaining effective control of asthma.

The objective of asthma treatment is to:

I. Control current symptoms, i.e. minimise use of reliever medication and maximise lung function.
II. Reduce future risk, i.e. stabilise disease, prevent exacerbations, and preserve lung function over time.

These two approaches are inter-dependent; if you can achieve current control, you can reduce future risk. However, the INSPIRE study also demonstrated that asthma patients increase their SABA rescue medication early in response to exacerbations but they do not increase their ICS therapy until too late at the time of a worsening of symptoms.[1]

Adding a LABA to ICS therapy

The FACET study showed that adding the LABA, formoterol, to ICS therapy with budesonide in patients with severe persistent asthma produced a further improvement in lung function, which was superior to a 4-fold increase in the dose of budesonide.[2] Moreover, this add-on effect was maintained over the 12 month study period.[2] Similar results were produced in patients with mild persistent asthma in the subsequent OPTIMA study.[3] In summary, adding a LABA is better than increasing the dose of ICS when asthma is not controlled with low doses of steroids.

Chronic inflammation of the airways is responsible for the symptoms of asthma; therefore, suppression of the inflammation with steroids leads to a reduction in symptoms. Bronchoconstriction and the resulting symptoms are treated by the LABA component of the combination inhaler; however, LABAs provide an additional add-on effect that also contributes to symptom control.

This add-on effect can be explained in terms of how these drugs work in the asthmatic airways (**Figure 1**). LABAs act primarily as bronchodilators to reverse the bronchoconstriction induced by mast cell mediators, but also via non-bronchodilator effects including preventing mast cells from releasing bronchoconstriction mediators, reducing oedema, and inhibiting sensory nerves to reducing coughing. LABAs, however, are not able to deal with the chronic inflammation caused by the interactions among macrophages, T cells, eosinophils, and dentritic cells that produce the chronic hyperresponsiveness or 'twitchiness' of asthma. This makes LABAs potentially dangerous drugs because, although patients feel better due to the bronchodilation effect of LABAs, their underlying inflammation is not being treated. Consequently, they are at risk of complications of exacerbations or, in more serious situations, death. For these reasons, the use of a LABA without an ICS is believed to be unsafe for asthma patients. Therefore, it is vital to treat the underlying inflammation, which requires the use of ICS.

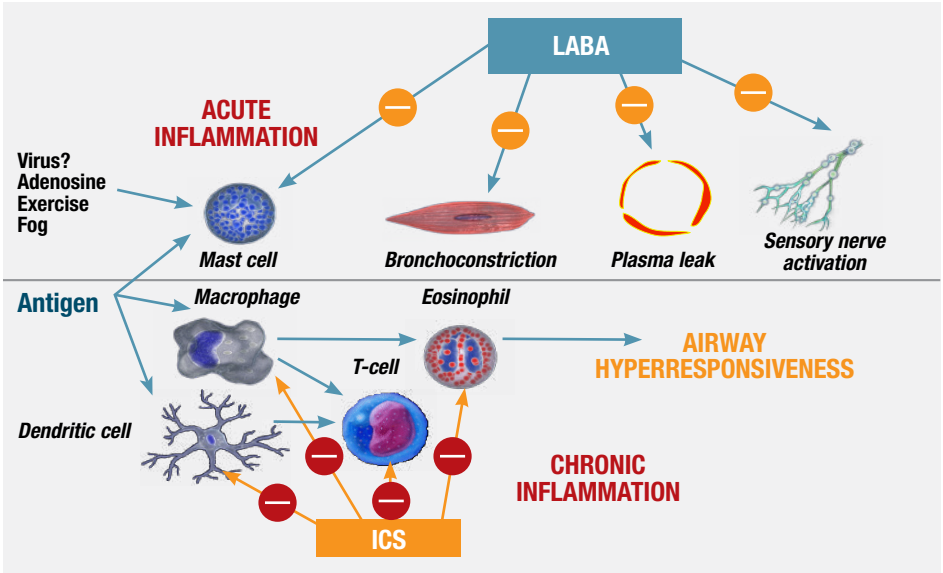

Figure 1. Rationale for the use of combination LABA/ICS therapy for treatment of asthma explained at a cellular level.

Evolution of asthma therapy

The complementary actions of LABAs and ICSs on the pathology of the cellular mechanisms of asthma provide the scientific rationale for the use of combination ICS/LABA inhalers, such as budesonide/eformoterol and fluticasone/salmeterol, in the treatment of asthma. These combination inhalers, given in a fixed dose twice-daily regimen, are equally effective in controlling asthma. Nevertheless, patients still experience symptoms from time to time, which they treat with rescue medication in the form of a SABA. This approach, i.e. ICS/LABA maintenance therapy plus as-needed therapy with a SABA, is better than giving an ICS and SABA which has been conventional therapy for many years. In the ongoing evolution of asthma therapy another strategy has emerged: a single ICS/LABA combination inhaler used twice per day for maintenance treatment and also as a reliever (instead of a SABA).

SMART

The strategy of using an ICS/LABA combination inhaler for both maintenance and rescue therapy is known as Symbicort Maintenance And Reliever Therapy, i.e. SMART. It is a simpler way of treating asthma as well as being a more effective way of controlling the disease, in terms of reducing exacerbations versus regular dosing with a combination inhaler and separate SABA inhaler. Six randomised double-blind trials comparing SMART with conventional therapy in a total of 14,351 asthma patients, the AHEAD, COMPASS, SMILE, STAY, STEAM, and STEP studies, have clearly demonstrated that SMART produces significant improvements in lung function versus regular therapy and it is now an established way of controlling asthma.[4-9]

Severe exacerbations reduced

The most striking benefit of the SMART approach is that it reduces the number of severe exacerbations experienced by asthma patients compared with conventional approaches. Six key randomised double-blind studies have demonstrated that SMART i.e. budesonide/eformoterol maintenance plus reliever, reduces severe exacerbations more effectively than conventional therapy, which included high-dose budesonide/eformoterol or high-dose fluticasone/salmeterol plus SABA (**Figure 2**).[4-9] In the STAY study, for example, budesonide/eformoterol SMART halved the number of severe exacerbations versus conventional therapy using high-dose budesonide plus SABA and versus budesonide/eformoterol plus SABA in 2,750 patients with moderately severe asthma (0.19 vs 0.35 vs 0.40 events/patient/year).[6]

Severe exacerbations are the feature of asthma that patients dislike the most because these events can lead to courses of oral steroids, time off work, or, in more severe cases, hospitalisation or even death. Hence, prevention of severe exacerbations is a primary goal of therapy and SMART is the most effective strategy currently available for prevention of severe exacerbations.[10]

Steroid exposure reduced

The side effects of corticosteroids are a major concern for patients with asthma, and SMART is a way of reducing exposure to steroids. In the six randomised double-blind studies, the amount of oral steroids used was markedly reduced because patients experienced fewer exacerbations.[4-9]

The AHEAD study provided particularly compelling data of the benefit of SMART in reducing the requirement for corticosteroids; patients (n=2,309) with severe asthma treated with conventional therapy using high-dose fluticasone/salmeterol plus SABA used almost twice the amount of inhaled steroid versus SMART (2,000µg vs 1,238µg) and required more courses of oral steroids (139 vs 106).[4] The remarkable observation here is that better control of asthma was achieved with a lower dose of ICS, again reinforcing the effectiveness of budesonide/eformoterol SMART in reducing exacerbations at lower steroid load versus regular dosing with combination inhalers.

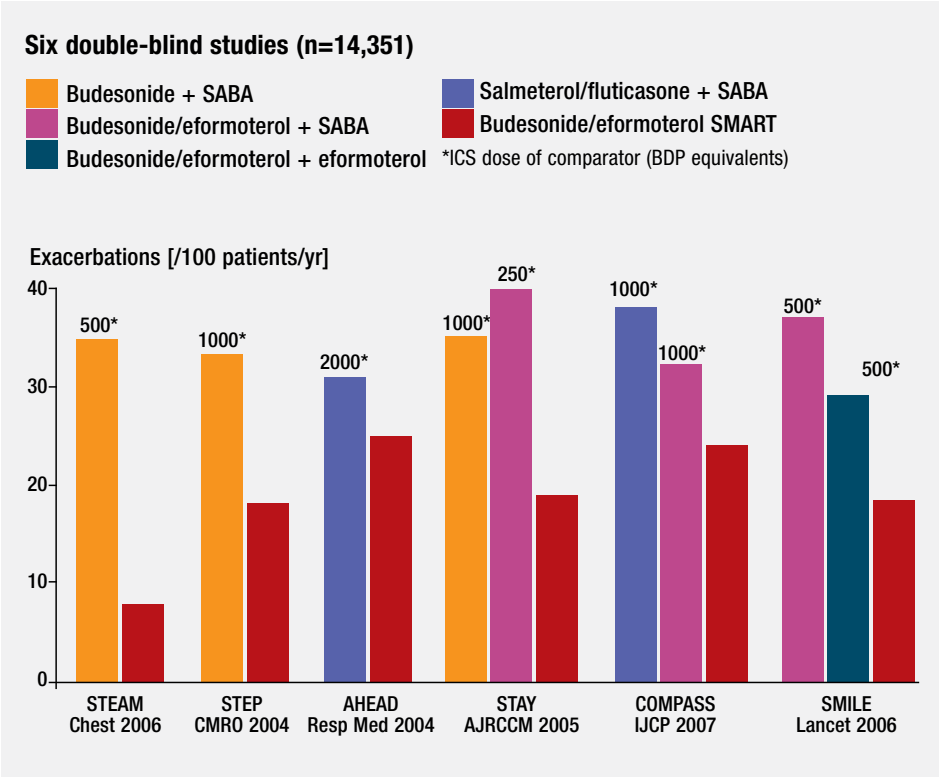

Figure 2. Six randomised double-blind studies demonstrated that budesonide/eformoterol SMART reduces the number of severe asthma exacerbations in patients with asthma versus conventional treatments.[4-9]

Real-world effectiveness

Venturing away from the contrived setting of controlled clinical trials, including the mitigation of poor adherence to treatment and highly selected patient populations, the EUROSMART study in >8,000 patients demonstrated that SMART is effective in reducing asthma exacerbations in a real-life setting, i.e. in patients more representative of those likely to be seen in daily clinical practice.[11] In EUROSMART, patients treated with budesonide/eformoterol SMART for one year experienced 90% fewer exacerbations versus the year before switching to SMART.[11] In comparison, the six randomised double-blind clinical trials showed a 50% reduction in exacerbations with SMART.[4-9] Professor Barnes believes the reason for the more dramatic effect of SMART in the real world is that most patients with asthma never take their ICS. This is mainly because they do not think that they need to take their ICS when their asthma is controlled. Herein lies the advantage of SMART: whenever a patient uses a reliever they are using an ICS, which would not normally be the case with conventional therapy.

How does SMART work?

A concern about SMART was that getting better control of asthma with a lower dose of ICS might result in the underlying inflammation being inadequately treated. However, this apprehension was allayed by a randomised controlled study that showed little difference in airways inflammation during one year of treatment with budesonide/eformoterol SMART at a quarter of the ICS dose versus high-dose budesonide/eformoterol plus SABA.[12]

SMART is not a new treatment; it is a new way of using an old treatment, i.e. the same fixed combination used twice daily for maintenance is also used for rescue treatment. The question is: how does it work so well, especially in reducing severe exacerbations?

The ICS/LABA fixed combination drugs, budesonide/eformoterol and fluticasone/salmeterol are markedly different. The difference is not due to the corticosteroid components – budesonide and fluticasone are similar in their ability to control asthma. There are, however, important differences in mechanism between eformoterol and salmeterol. The duration of action of both LABAs is approximately 12 hours so they need to be given twice per day, but eformoterol has a rapid onset of action (similar to that of the SABAs, salbutamol and terbutaline) whereas salmeterol has a slow onset of action. In addition, and more importantly, the duration of side effects with eformoterol is short (similar to that with salbutamol) whereas the side effects of salmeterol are much longer lasting. This difference is due to the LABAs working in a different way at the β_2-receptor. While eformoterol is a full agonist and stimulates β_2-receptors maximally, salmeterol is a partial agonist resulting in a flat dose-response, i.e. increasing the dose of salmeterol does not lead to further bronchodilation but does lead to more side effects. Hence, the side effects of salmeterol are cumulative. The practical consequence of these differences is that budesonide/eformoterol but not fluticasone/salmeterol can be used as rescue therapy.

Another question is: how does the budesonide/eformoterol combination work so well as a reliever in asthma and why is it better at reducing exacerbations than a SABA? The explanation is provided by a randomised double-blind study that compared a traditional SABA, terbutaline, eformoterol, and budesonide/eformoterol as relievers on top of budesonide/eformoterol maintenance therapy in asthma patients.[7] It demonstrated that both mono-components of budesonide/eformoterol contribute to the greater efficacy of SMART in preventing exacerbations.[7] The other factor contributing to the greater efficacy of SMART in preventing exacerbations is that exacerbations of asthma are not sudden events. They build up over time, with patients' asthma deteriorating over the course of about one week.[13] This means that there is a window of

opportunity to intervene at an earlier stage, i.e. before a patient's symptoms become serious or they require oral steroids.

Airways inflammation in patients with severe asthma has been demonstrated to be associated with a loss of asthma control and a build-up in inflammation that precedes an increase in exacerbations.[14] Hence, inflammation needs to be treated at the first sign of asthma symptoms and, by using corticosteroids early, exacerbations can be prevented from becoming severe events. Furthermore, the belief that steroids take a long time to work has been disproved.[15] The mechanism appears to involve a rapid effect of corticosteroids on the airway epithelial cells that results in mast cells not being activated and consequently not releasing bronchoconstriction mediators.[15]

Cellular effects

The effectiveness of budesonide/eformoterol as a rescue medication can be explained at a cellular level. Eformoterol not only acts to relax airway smooth muscle but it also has an anti-inflammatory effect via inhibition of neutrophil inflammation and mast cell mediator release. At the same time, budesonide targets mast cells by preventing their activation and switching off production of eosinophil attractants in the airway wall. Budesonide also kills eosinophils and inhibits T lymphocytes and their ability to orchestrate eosinophilic inflammation.

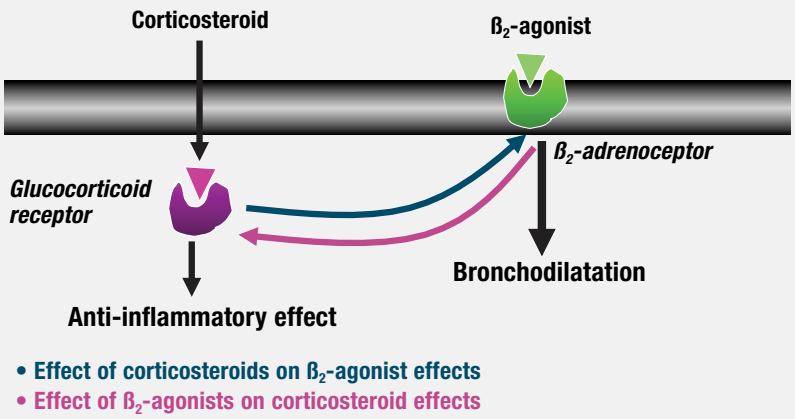

Figure 3. Depiction of the molecular interactions between corticosteroids and β_2-agonists that explain the additive effect of budesonide/eformoterol as a fixed-combination inhaler.

An advantageous molecular interaction between corticosteroids and LABAs also occurs (**Figure 3**). Steroids not only bind to glucocorticoid receptors inside airway cells to switch off inflammatory genes in the nucleus and supress inflammation, they also 'switch on' some genes including the gene for the β_2-adrenoreceptor. This dual action of corticosteroids increases the expression of β_2-receptors on the cell surface and enhances the effects of β_2-agonists, which act on β_2-receptors on the surface of airway smooth muscle leading to bronchodilation. β_2-agonists also act on glucocorticoid receptors and can enhance the anti-inflammatory effects of corticosteroids. Hence, additional benefits are obtained via these molecular interactions involving the steroid enhancing the effects of the β_2-agonist and the β_2-agonist enhancing the effects of the steroid when these treatments are combined.

What do patients want?

In a clinical practice context, it is important to know what patients want in terms of their asthma therapy. The Living and Breathing Study evaluated the treatment preferences and concerns of asthma patients in the UK.[16] The patients prioritised their concerns, which revealed that they wanted a treatment that was as simple as possible because they were confused by the different inhalers that they were taking at different times. They also wanted fewer inhalers, the lowest dose of corticosteroids possible due to concerns about steroid-related side effects, and to avoid hospitalisation and time off work (**Figure 4**).[16] Based on the evidence available, SMART addresses all of these patient needs. This is why SMART features in the latest GINA guidelines as an approach that can be used for treating patients at steps 3, 4, and 5 that are not controlled on a low-dose ICS.[1]

Living and Breathing Study

Patient preferences:	SMART
• Treatment as simple as possible	Yes
• Fewer inhalers	Yes
• Lowest dose of steroid to control symptoms	Yes
• Avoid hospitals when possible	Yes
• Minimise symptoms	Yes

Figure 4. Asthma patient treatment preferences as determined in the UK Living and Breathing Study,[16] and whether SMART satisfies these preferences.

TAKE-HOME MESSAGES

- For achieving asthma control and reducing future risk, SMART is more effective than conventional approaches.
- SMART achieves control of asthma at lower doses of both ICS and oral steroids compared to regular combination therapy, i.e. it reduces total steroid exposure.
- Use of a single inhaler simplifies the treatment regimen, making it convenient for patients, and remedies the problem of real-world patient behaviour, i.e. not taking their maintenance treatment and only using their reliever medication.
- Corticosteroids and LABAs have complementary and additive effects in controlling asthma.
- SMART using the combination of budesonide/eformoterol for maintenance and reliever in a single inhaler is particularly effective in controlling asthma and preventing exacerbations.

COPD MANAGEMENT

COPD is also an important respiratory disease, especially as there is a greater unmet need in COPD than in asthma. COPD is a very different disease from asthma in terms of clinical presentation, which is primarily because the underlying inflammation is different (**Figure 5**). In asthma, the inflammation is characterised by eosinophilia with mast cell activation, good responsiveness to corticosteroids, and generally high reversibility. COPD, in contrast, is predominated by the presence of neutrophils and macrophages, poor responsiveness to steroids, and generally low reversibility.

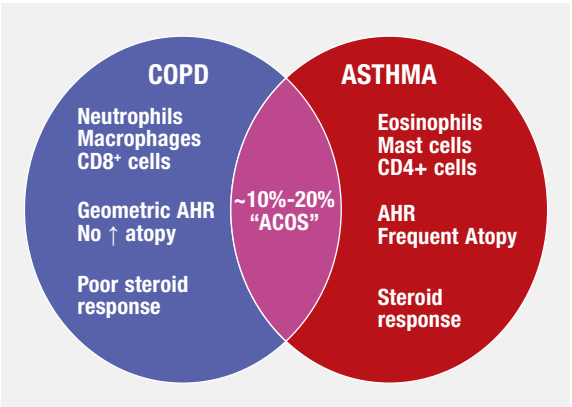

Figure 5. Differentiating features of COPD, asthma, and the Asthma-COPD Overlap Syndrome (ACOS). AHR = airway hyperresponsiveness

Asthma-COPD overlap

Between 10% and 20% of COPD patients also have features of asthma and have been termed Asthma-COPD Overlap Syndrome (ACOS) patients. These patients either have co-existing asthma or a variant of COPD with increased eosinophils. ACOS patients also have greater reversibility than other COPD patients. COPD patients with reversibility is explained by the presence of eosinophilic inflammation, which is not present in other COPD patients.[18] Also, because eosinophils respond to steroids, it predicts that ACOS patients should respond to corticosteroid treatment in a way similar to patients with asthma. This prediction has been confirmed in a controlled clinical trial in which exacerbations in COPD patients were prevented by a management strategy using ICS therapy that aimed to minimise eosinophilic airway inflammation.[19]

Rationale for ICS/LABA inhalers

Treating COPD patients with a budesonide/eformoterol combination inhaler has been demonstrated in two randomised double-blind trials to be more effective in controlling lung function, reducing exacerbations, and improving quality of life than giving eformoterol or steroids alone.[20,21] The efficacy of this combination in treating COPD can be explained by the cellular mechanisms of the mono-components (**Figure 6**). As in asthma, the LABA acts as a bronchodilator so it reduces air trapping. It may also have some non-bronchodilation effects, including neutrophil killing and reducing plasma leak and sensory nerve activation. In contrast, it appears that ICSs are less effective against the inflammation in conventional COPD. Corticosteroids may, however, be of benefit in COPD via a non-anti-inflammatory mechanism.

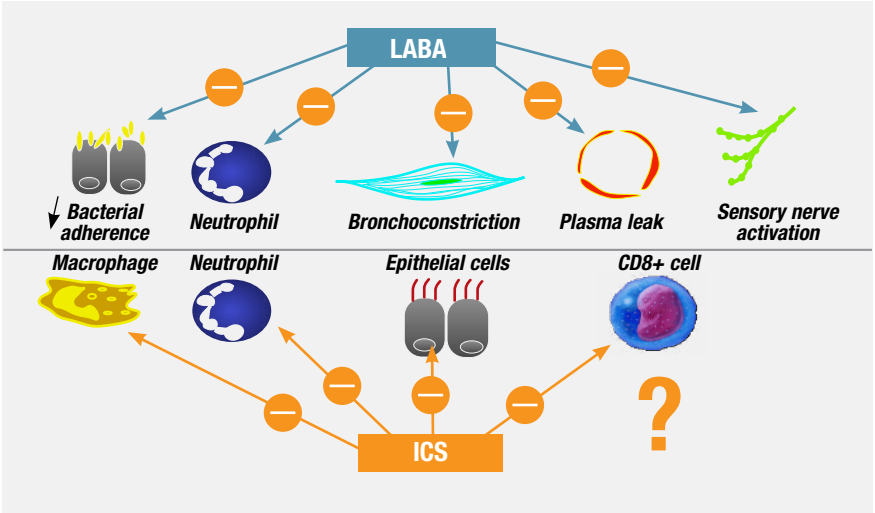

Figure 6. Proposed cellular effects of LABAs and ICSs in the treatment of COPD.

A critical component of COPD is small airway fibrosis because it relates to the loss of lung function and accounts for the irreversibility of airway obstruction in COPD. This scarring is caused by transforming growth factor beta-1 (TGF-β1) mediator, which is produced by airway epithelial cells and macrophages. TGF-β1 reduces the number of β_2-receptors in airway smooth muscle by switching off the β_2-receptor gene. Hence, beta-agonists used alone have less effect in COPD. Corticosteroids, however, increase the expression of β_2-receptors, which may overcome the suppressive effect of TGF-β1 and allow beta-agonists to exert a larger effect. This mechanism appears to explain the greater efficacy of budesonide/eformoterol than eformoterol alone in patients with COPD demonstrated in clinical studies.[20,21]

Risk of steroid-related side effects

Because corticosteroids might not work very well in COPD, patients tend to receive them at high doses leading to an increased risk of steroid-related side effects.

One of these side effects is osteoporosis, which is of particular relevance because COPD patients are already at high risk of osteoporosis due to their lack of physical mobility, advanced age, and likelihood that they have a poor diet and are smokers. Another major concern in COPD patients treated with high doses of ICSs is an increased risk of lung infections, primarily pneumonia. For example, a post hoc analysis of the large (n=6112), randomised, double-blind, 3-year TORCH study showed a progressive increase in the number of cases of pneumonia in COPD patients treated with fluticasone/salmeterol versus the mono-components.[22] This risk may not be the same for all ICS/LABA combinations. Two subsequent real-world evidence studies using observational data obtained from patients' electronic health records concluded that fluticasone/salmeterol was associated with a higher risk of pneumonia, including more hospitalisations and deaths from pneumonia, than treatment with budesonide/eformoterol in COPD patients.[23,24] In addition, meta-analyses of clinical study data have demonstrated budesonide/eformoterol to be associated with fewer pneumonia events than salmeterol/fluticasone in patients with COPD,[25] and budesonide treatment (with or without eformoterol) over a period of 12 months not to increase the risk of pneumonia in patients with COPD.[26]

Given the increased risk of corticosteroid-related side effects, and particularly pneumonia, in patients with COPD, it is suggested that ICS/LABA therapy should only be used in patients with severe COPD and frequent exacerbations (>2 per year).

TAKE-HOME MESSAGES

- ACOS patients benefit from ICS/LABA therapy because the corticosteroids treat the asthmatic component of the syndrome.
- ICS/LABA is also effective in the treatment of normal COPD:
  - eformoterol acts on the small airways to reduce air trapping.
  - budesonide may enhance β_2-receptors and increase ICS response.
  - budesonide is associated with a lower risk of pneumonia than fluticasone.

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