



# ABSTRACTS IN PERSPECTIVE

## **Addressing Future Risk and Exacerbations in Asthma Management Today**

### Editorial Overview

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**EDITORIAL OVERVIEW:****J. Mark FitzGerald, MB, MD,  
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**18<sup>th</sup> ANNUAL CONGRESS OF THE  
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A couple of decades ago, asthma management was mainly focused on the episodic nature of asthma exacerbations. Associated with this strategy were an over-reliance on symptom relief therapy with short-acting bronchodilators and intermittent use of inhaled corticosteroids (ICS) or systemic corticosteroids. This approach was associated with poor outcomes and in particular, an increased risk of asthma mortality and increased risk of side effects, especially with the use of repeated courses of oral corticosteroids. We now have a much broader range of therapeutic options, but of greater importance, the fundamental need to have anti-inflammatory therapy as the basis for asthma treatment. Coupled with this change in emphasis is the availability of long-acting beta agonists (LABAs) in combination with ICS and leukotriene receptor antagonists (LTRAs). In addition, for more severe allergic asthma, there is the option of monoclonal antibody therapy with omalizumab. Decisions about the management of asthma now take a broader perspective. Not only are we concerned about current control but we are also conscious of future risk in the context of preventing a decline in lung function, and reducing exacerbation rates and side effects of medication.

**The Importance of Control and Exacerbations**

Asthma control is a rather subjective concept, but an important one nevertheless, as in addition to influencing the patients' current quality of life, poor control has been associated with a higher rate of exacerbations, which in turn have been associated with a faster decline in lung function and represent a major source of anxiety for patients. In a

pooled analysis of six-month, randomized controlled trials, Bateman and O'Byrne reported a clear relationship between asthma control, defined in this case according to the score on the five-item asthma control questionnaire (ACQ-5; good control <0.5, uncontrolled  $\geq 1.5$ ) and exacerbations. Patients with well-controlled asthma experienced a mean of 0.180 exacerbations/patient/year compared to 0.664 for those with uncontrolled asthma. The relationship was even clearer for those on high-dose ICS (>1000  $\mu\text{g/day}$  beclomethasone dipropionate [BDP] equivalent) at study entry—0.263 for well-controlled asthma vs. 1.030 for uncontrolled asthma. This presumably reflects the fact that patients on high-dose ICS at study entry had more severe asthma, and so the differences between controlled and uncontrolled disease would be more marked.

**New Treatment Modalities**

Fixed-dose combinations of ICS and LABA are becoming increasingly popular as an alternative to increasing ICS dose in patients with uncontrolled asthma. For example, Gappa et al. reported a study of salmeterol/fluticasone (SAL/FLU) 50/100  $\mu\text{g}$  in a pediatric population whose asthma remained uncontrolled after a run-in phase with 100  $\mu\text{g}$  of FLU. These investigators reported superior efficacy of SAL/FLU compared to higher-dose ICS in terms of morning peak expiratory flow rate (PEFR)—the primary efficacy end point—in a randomized, double-blind study.

Budesonide/formoterol (BUD/FORM) is another fixed combination and one that also offers the possibility of being used as both maintenance treatment as well as rescue medication, with the obvious advantage to the patient that a separate short-acting beta<sub>2</sub>-agonist (SABA) inhaler is no longer needed.

The two studies included in the aforementioned analysis by Bateman and O'Byrne compared BUD/FORM maintenance and reliever therapy with SAL/FLU (50/250  $\mu\text{g}$  b.i.d) and with maximum-dose SAL/FLU (50/500  $\mu\text{g}$  b.i.d) (Bousquet et al. *Respir Med* 2007;101:2437-46, Kuna et al. *Int J Clin Pract* 2007;61:725-36). Bateman and O'Byrne's analysis suggests that the percentage of patients who failed to reach at least intermediate control was significantly lower for BUD/FORM maintenance and reliever therapy (26% vs. 30%,  $P=0.035$ ). This was achieved with lower mean ICS doses (BDP equivalent, 1000  $\mu\text{g/day}$  vs. 1341  $\mu\text{g/day}$ ). As discussed earlier, control is linked to exacerbation rates, and indeed, the seemingly better control achieved with BUD/FORM maintenance and reliever therapy was reflected by significantly lower exacerbation rates, both for all patients (0.25 exacerbations/patients/year vs. 0.35 for comparator,  $P<0.001$ ) and for those with high-dose ICS on entry (0.30 vs. 0.52,  $P=0.002$ ).

Six double-blind studies and one open-label study of BUD/FORM maintenance and reliever therapy were also analyzed

for safety by Sears and Radner. In total, 6648 patients received ICS/LABA maintenance and reliever therapy and 9833 received comparator treatment. None of the 15 deaths (11 in comparator groups and four in ICS/LABA maintenance and relieve groups) were considered related to the study drug by the investigators. The rates of non-fatal serious adverse events were similar, but importantly, asthma-related adverse events were significantly fewer for ICS/LABA maintenance and reliever therapy. Maintenance and reliever therapy also appeared to be better tolerated than comparators as discontinuations due to adverse events were reported in significantly fewer patients (1.53% vs. 2.15% for comparators).

The cost of treatment with ICS/LABA maintenance and reliever therapy was compared with usual practice in patients included in a Dutch open-label study. The analysis, presented by Goossens et al., in addition to medication costs and physician visits, also included societal costs such as absence from paid work. Although no significant differences in costs were observed, there was a trend towards lower costs for BUD/FORM maintenance and reliever therapy (€428 [95% CI, €382-480] vs. €561 [95% CI, €392-868]). This difference was mainly driven by lost productivity (cost of absence from paid work €94 [95% CI, €0-301] lower in ICS/LABA maintenance and reliever therapy group). As is often the case, the costs had a skewed distribution, and patients with worse control showed much greater variation.

## Towards Clinical Practice

We now consider asthma to be a chronic disease which requires regular anti-inflammatory treatment. This makes treatment adherence important. However, according to the results of a study by Price and colleagues presented at this year's European Respiratory Society (ERS) Meeting in Berlin, adherence is a major problem with asthma medication. In their "real-life" study of first-line therapy in mild asthma, they found adherence of 61% with LTRAs and 41% for ICS. Clearly, these figures are far from ideal. ICS, although in general safe, carry with them the stigma of an adverse-event profile to be expected with systemic corticosteroids. A Danish study presented by Elers and colleagues further highlighted the undertreatment of asthma patients. These authors distributed over 15,000 questionnaires to primary healthcare patients asking whether they suffered from respiratory symptoms. Patients with respiratory symptoms were invited for consultation and screened for asthma. It was striking that approximately half the patients were untreated and 20% were treated with beta agonists alone even though 19% of these suffered frequent asthma-related symptoms and 8% had nocturnal symptoms, the latter symptoms being indicative of relatively severe disease. Explicit evidence-based guidelines for asthma management are available, and the fact that they are not well adhered to indicates a need for

better physician and patient education. Another problem, as highlighted by the results of the study presented by Sera, is that often patients do not perceive symptoms, even in the presence of a significant loss of lung function. The problem of perception of symptoms was also reflected in the findings of a French study by Molimard et al. on the level of concordance between patients, their spouses, physicians and the guidelines. The authors found that 26.6% of patients considered asthma control unacceptable compared to 35.5% of physicians. The most striking difference, though, was between the percentage of patients with unsatisfactory control according to guidelines issued by the French National Agency for Accreditation and Evaluation in Health (85.2%) and physicians. This difference was largely driven by FEV<sub>1</sub>/PEF >85% of personal best, suggesting that monitoring of lung function is important in asthma patients.

Given that efficacy in randomized clinical trials corresponds to a closely monitored situation in which patients are more likely to be adherent, it is important to assess efficacy in a more real-world setting. This question was addressed with ICS/LABA maintenance and reliever therapy in a study reported by Søes-Petersen et al. conducted in Finland, Denmark and Norway (N=1835). After a run-in period, patients were randomized to conventional best standard treatment or ICS/LABA maintenance and reliever therapy and followed for six months. Tolerability was good with only 2.7% of patients in either group experiencing serious adverse events. The number of patients who dropped out due to adverse events was lower in the control group, possibly reflecting the fact that these patients could switch treatments if necessary. Significantly more patients were well-controlled (44.7% vs. 39.7%,  $P<0.01$ ) and the number of uncontrolled patients decreased with respect to the run-in phase by 42% with ICS/LABA maintenance and reliever therapy compared to 34% with conventional best standard treatment. Patients receiving ICS/LABA maintenance and reliever therapy also had 26% fewer exacerbations although this difference did not quite reach statistical significance (rate ratio 0.74; 95% CI: 0.54-1.01;  $P=0.058$ ). These findings reinforce the efficacy of ICS/LABA maintenance and reliever therapy in an everyday clinical setting.

## Treating the Entire Airway

Clinical trials for the management of asthma often exclude patients with allergic rhinitis or do not always monitor outcomes for this important symptom complex. This is unfortunate, in that untreated allergic rhinitis has been associated with less satisfactory treatment outcomes among asthma patients. Given the current trend towards considering the importance of both the upper and lower airways—the so-called unified airway theory—it is increasingly recognized that it is important to treat both asthma and rhinitis. Dao et al.

reported an interesting study in which asthma patients with allergic rhinitis were randomized to receive oral antihistamine agents or intranasal corticosteroids. In both groups, asthma control improved with respect to baseline as a result of treating the allergic rhinitis, but the improvement was particularly marked among patients treated with intranasal corticosteroids, which is the more effective treatment for allergic rhinitis. This suggests that airway inflammation can be more completely controlled by treating not only lower airway inflammation (asthma) but also the inflammation in the upper airways (allergic rhinitis).

### Summary

The goals of asthma management are evolving, with greater emphasis on recognizing asthma to be a chronic disease. While the importance of asthma control is currently

recognized, the influence on maximizing current control in preventing future exacerbations is only beginning to become fully apparent. Single-inhaler BUD/FORM maintenance and reliever therapy has been shown to be effective at achieving good asthma control and reducing the rates of exacerbations in randomized clinical trials, including those that attempt to mimic conditions in everyday practice. Pooled analyses of these trials presented at the ERS in Berlin further confirm the positive findings and failed to identify any safety issues. Other fixed combinations of ICS and LABA have also been shown to be superior to increasing ICS dose in patients with uncontrolled asthma. As part of the broadening scope of asthma management, a study of asthma patients with allergic rhinitis has also pointed to the benefit in terms of asthma outcomes of treating inflammation of the upper airway as well, and the unreliability of patients' perception of asthma symptoms is beginning to be recognized. 🌐

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## COMMENTAIRE ÉDITORIAL :

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## LE 18<sup>e</sup> CONGRÈS ANNUEL DE LA EUROPEAN RESPIRATORY SOCIETY

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Il y a une vingtaine d'années, la prise en charge de l'asthme était principalement axée sur la nature épisodique des exacerbations de la maladie. De cette orientation découlaient une trop grande dépendance à l'égard du traitement de secours au moyen de bronchodilatateurs à courte durée d'action et l'utilisation intermittente de corticostéroïdes pour inhalation (CSI) ou systémiques. Cette stratégie était associée à une issue défavorable, notamment un risque accru de mortalité par asthme et d'effets indésirables, surtout en situation de recours répété à la corticothérapie orale. Aujourd'hui, l'arsenal thérapeutique s'est considérablement étoffé, mais surtout, on a pris conscience de l'importance fondamentale du traitement anti-inflammatoire, devenu la pierre angulaire du traitement de l'asthme. Dans la foulée de ce recentrage, de nouveaux composés ont été commercialisés, tels les associations CSI et bêta-agoniste à longue durée d'action (BALA), les antagonistes des récepteurs des leucotriènes (ARL) et, pour le traitement de l'asthme allergique sévère, l'omalizumab, anticorps monoclonal. Les décisions de traitement s'inscrivent maintenant dans une perspective plus large. En effet, la prise en charge de l'asthme ne vise plus seulement le soulagement immédiat des symptômes mais tient compte du risque futur, ce qui implique de prévenir le déclin de la fonction pulmonaire, de réduire le taux d'exacerbations et d'atténuer les effets indésirables du traitement médicamenteux.

### Importance de la maîtrise de l'asthme pour prévenir les exacerbations

S'il est plutôt subjectif, le concept de maîtrise de l'asthme n'en est pas moins important : outre que l'absence de maîtrise suffisante se répercute sur la qualité de vie

immédiate des patients, elle est associée à un taux plus élevé d'exacerbations, évolution qui entraîne à son tour un déclin accéléré de la fonction pulmonaire et représente une source d'anxiété majeure pour les patients. Dans une analyse des données regroupées d'essais comparatifs randomisés d'une durée de six mois, Bateman et O'Byrne ont constaté une relation évidente entre la maîtrise de l'asthme — définie dans ce contexte en fonction du score au questionnaire de maîtrise de l'asthme à cinq items (ACQ-5 [*asthma control questionnaire*]; <0,5 : bonne maîtrise, ≥1,5 : absence de maîtrise) — et le taux d'exacerbations. Lorsque l'asthme était bien maîtrisé, le nombre moyen annuel d'exacerbations par patient était de 0,180 comparativement à 0,664 dans le cas contraire. La relation était encore plus évidente chez les sujets recevant au départ un CSI fortement dosé (>1000 µg/jour en équivalent de dipropionate de bécloéthasone [DPB]) (0,263 en cas de maîtrise vs 1,030 en l'absence de maîtrise). Cet écart prononcé reflète probablement le fait que les patients initialement sous CSI à forte dose présentaient un asthme plus sévère et donc plus difficile à maîtriser.

### Nouvelles modalités de traitement

Plutôt que d'augmenter la dose des CSI lorsque l'asthme n'est pas bien maîtrisé, on se tourne de plus en plus vers les associations fixes d'un CSI et d'un BALA. À cet égard, Gappa et al. ont fait état des résultats d'une étude randomisée à double insu au cours de laquelle l'association salmétérol/fluticasone (SAL/FLU) à 50/100 µg était administrée à des enfants dont l'asthme était demeuré réfractaire à un traitement préliminaire par la FLU à 100 µg. L'association SAL/FLU s'est avérée plus efficace que le traitement par une dose élevée de CSI au chapitre du débit expiratoire de pointe (DEP) matinal, paramètre d'efficacité principal de l'étude.

Le budésonide/formotérol (BUD/FORM), autre association fixe d'un CSI et d'un BALA, présente en outre l'avantage de pouvoir servir à la fois de traitement de fond et de secours, dispensant ainsi le patient de prendre un bêta<sub>2</sub>-agoniste à courte durée d'action (BACA) dans un inhalateur distinct.

Lors des deux études comprises dans l'analyse de Bateman et O'Byrne citée plus haut, on a comparé le BUD/FORM en traitement de fond et de secours avec le SAL/FLU à dose standard (50/250 µg deux fois par jour) et à dose maximale (50/500 µg deux fois par jour) (Bousquet et al. *Respir Med* 2007;101:2437-46; Kuna et al. *Int J Clin Pract* 2007;61:725-36). Selon l'analyse de Bateman et O'Byrne, le pourcentage de patients n'ayant pas obtenu de maîtrise au moins intermédiaire était significativement moins élevé dans le groupe BUD/FORM en traitement de fond et de secours (26 % vs 30 %, p=0,035). Ces résultats favorables ont en outre été obtenus avec une dose moyenne de CSI moins élevée (en équivalent DPB : 1000 µg/jour vs 1341 µg/jour). Comme on

l'a déjà dit, la maîtrise influence le taux d'exacerbations et, en effet, la maîtrise apparemment supérieure autorisée par le BUD/FORM en traitement de fond et de secours était associée à un taux d'exacerbations significativement moins élevé, tant chez l'ensemble des patients (0,25 exacerbation/patient/année vs 0,35 pour le traitement de comparaison,  $p < 0,001$ ) que chez ceux qui recevaient un CSI à forte dose au départ (0,30 vs 0,52,  $p = 0,002$ ).

Sears et Radner ont par ailleurs analysé les données d'innocuité provenant de six études à double insu et d'une étude ouverte sur le BUD/FORM utilisé en traitement de fond et de secours. Au total, 6648 patients avaient reçu ce schéma de traitement et 9833, un traitement de comparaison. Aucun des 15 décès signalés (11 dans les groupes témoins et quatre dans les groupes CSI/BALA en traitement de fond et de secours) n'était considéré comme lié au traitement à l'étude. Le taux d'événements défavorables graves non mortels était semblable d'un groupe à l'autre, mais, fait à souligner, les événements défavorables liés à l'asthme étaient significativement moins nombreux dans les groupes CSI/BALA en traitement de fond et de secours. L'association utilisée en traitement de fond et de secours a également semblé mieux tolérée que les agents de comparaison, si l'on en juge par le pourcentage significativement moins élevé de patients ayant abandonné le traitement en raison d'effets indésirables (1,53 % vs 2,15 % pour les groupes témoins).

Le coût du traitement par l'association CSI/BALA utilisée en traitement de fond et de secours a été comparé à celui du traitement standard chez les patients d'une étude ouverte menée aux Pays-Bas. En plus du coût des médicaments et des consultations médicales, les auteurs de l'analyse, Goossens et al., ont tenu compte du coût social, telles les pertes associées aux congés de maladie. Sans qu'il y ait de différence significative, on observait néanmoins une tendance à la baisse du coût du traitement par le BUD/FORM (428 € [IC à 95 %, 382-480 €] vs 561 € [IC à 95 %, 392-868 €]). Cette différence était principalement attribuable à la baisse moins marquée de la productivité (coût des congés de maladie : 94 € [IC à 95 %, 0-301 €] de moins dans le groupe CSI/BALA en traitement de fond et de secours). Comme c'est souvent le cas, on constatait une distribution asymétrique des coûts, la variation étant beaucoup plus importante dans les asthmes les moins bien maîtrisés.

## Regard sur la pratique clinique

L'asthme est maintenant considéré comme une maladie chronique qui nécessite un traitement anti-inflammatoire continu, ce qui fait de l'observance un enjeu clé. Or, selon une étude présentée par Price et ses collègues au congrès, l'observance représente un problème majeur eu égard aux anti-asthmatiques. L'étude qu'ils ont effectuée en conditions réelles sur le traitement en première intention de l'asthme

léger a mis en évidence un taux d'adhésion de 61 % pour les ARL et de 41 % pour les CSI. Ces chiffres sont évidemment loin d'être optimaux. Les CSI, bien que généralement sûrs, pâtissent de la réputation d'innocuité défavorable des corticostéroïdes systémiques. Une étude danoise présentée par Elers et ses collègues a fait ressortir encore plus crûment le traitement sous-optimal des patients asthmatiques. Les auteurs ont distribué un questionnaire à plus de 15 000 patients traités en soins primaires dans lequel il leur était demandé s'ils souffraient de symptômes respiratoires. Les patients présentant des symptômes respiratoires ont été invités à passer un examen médical et soumis à un dépistage de l'asthme. Il était frappant de constater qu'environ la moitié des patients n'étaient pas traités et que 20 % recevaient seulement un bêta-agoniste même si 19 % d'entre eux manifestaient des symptômes d'asthme fréquents et 8 % avaient des symptômes nocturnes, signe d'une relative sévérité de la maladie. Des recommandations de pratique clinique factuelles et explicites ont pourtant été formulées pour la prise en charge de l'asthme, et leur application médiocre souligne le besoin de mieux informer les médecins et les patients. Autre problème à prendre en compte et mis en lumière par les résultats de l'étude présentée par Sera, il est fréquent que les patients ne perçoivent pas de symptômes, même en présence d'un déclin notable de la fonction pulmonaire. Ce problème de perception des symptômes se reflétait également dans les résultats d'une étude française menée par Molimard et al. sur le taux de concordance entre les appréciations de la maîtrise de l'asthme faites par le patient, le conjoint, le médecin ou selon les recommandations de pratique clinique. Ainsi, 26,6 % des patients considéraient que la maîtrise obtenue était inacceptable vs 35,5 % des médecins. Toutefois, c'est entre le pourcentage de patients dont l'asthme était jugé insuffisamment maîtrisé selon les recommandations émises par l'Agence nationale française d'accréditation et d'évaluation en santé (85,2 %) et l'appréciation des médecins que la disparité était la plus frappante. Cette différence tenait principalement à l'utilisation du critère de maîtrise défini par un VEMS ou DEP >85 % de la meilleure valeur personnelle, ce qui tend à démontrer que la surveillance de la fonction pulmonaire est importante chez les patients asthmatiques.

Étant donné que l'efficacité mesurée dans les essais cliniques randomisés correspond à une situation de surveillance étroite qui favorise l'adhésion des patients au traitement, il est important d'évaluer l'efficacité dans un contexte plus proche de la réalité. C'est ce que visait une étude sur l'association CSI/BALA utilisée comme traitement de fond et de secours menée en Finlande, au Danemark et en Norvège par Søres-Petersen et al. (N=1835). Après une phase préliminaire, les patients ont été randomisés en vue de recevoir le traitement standard optimal ou le CSI/BALA en traitement de fond et de secours pendant six mois. Les traitements ont été bien tolérés, seulement 2,7 % des patients de chaque groupe ayant présenté des effets


indésirables graves. Le nombre d'abandons motivés par des effets indésirables était moins élevé dans le groupe témoin, ce qui s'explique peut-être par la possibilité qu'avaient les patients de ce groupe de changer de traitement au besoin. Le nombre de patients ayant obtenu une maîtrise suffisante était significativement plus élevé dans le groupe CSI/BALA en traitement de fond et de secours (44,7 % vs 39,7 %,  $p < 0,01$ ); de même, par rapport à la phase préliminaire, le nombre de patients dont l'asthme n'était pas maîtrisé a diminué de 42 % dans ce groupe vs 34 % dans le groupe traitement optimal standard. Le taux d'exacerbations était également 26 % moins élevé dans le groupe CSI/BALA en traitement de fond et de secours, bien que cette différence n'ait pas tout à fait atteint le seuil de signification statistique (ratio des taux : 0,74; IC à 95 : 0,54-1,01;  $p = 0,058$ ). Ces résultats corroborent l'efficacité de l'association CSI/BALA utilisée comme traitement de fond et de secours dans la pratique clinique quotidienne.

### Cibler la totalité de l'appareil respiratoire

La rhinite allergique est souvent un motif d'exclusion dans les essais cliniques sur la prise en charge de l'asthme, ou alors, elle n'est pas toujours prise en compte au titre de l'évaluation des résultats. Cela est regrettable dans la mesure où la rhinite allergique qui n'est pas traitée a été associée à des résultats thérapeutiques moins satisfaisants chez les patients asthmatiques. Étant donné l'opinion qui tend actuellement à s'imposer selon laquelle les voies respiratoires supérieures et inférieures sont interdépendantes — la théorie de l'unicité des voies respiratoires — l'importance de traiter à la fois l'asthme et la rhinite est de plus en plus reconnue. Dao et al. ont fait état d'une étude intéressante au cours de laquelle des patients asthmatiques souffrant de rhinite allergique ont été randomisés en vue de recevoir un antihistaminique oral ou un corticostéroïde intranasal. Par rapport au départ, le

fait de traiter la rhinite allergique a amélioré la maîtrise de l'asthme dans les deux groupes, mais l'amélioration était particulièrement marquée chez les patients recevant un corticostéroïde intranasal, traitement le plus efficace de la rhinite allergique. Il semble donc que l'on puisse maîtriser l'inflammation de façon plus complète en ciblant à la fois les voies respiratoires inférieures (asthme) et les voies respiratoires supérieures (rhinite allergique).

### Résumé

L'orientation de la prise en charge de l'asthme change et la chronicité de la maladie devient une donnée primordiale. Si l'importance de la maîtrise de l'asthme est aujourd'hui reconnue, on ne fait que commencer à pleinement saisir l'incidence favorable de l'optimisation de la maîtrise présente sur le risque futur d'exacerbation. On a démontré l'efficacité de l'association BUD/FORM en un seul inhalateur utilisée comme traitement de fond et de secours pour maîtriser l'asthme et réduire le taux d'exacerbations dans des essais cliniques randomisés, dont des études conçues pour simuler les conditions de la pratique quotidienne. Les analyses des données regroupées de ces essais présentées au congrès confirment les bons résultats observés et n'ont mis au jour aucun problème d'innocuité. D'autres associations fixes d'un CSI et d'un BALA se sont aussi révélées plus efficaces que l'augmentation de la dose du CSI chez les patients dont l'asthme n'est pas maîtrisé. Témoignant de l'élargissement des visées de la prise en charge de l'asthme, une étude effectuée chez des patients asthmatiques souffrant de rhinite allergique a en outre fait ressortir l'avantage, sur le plan de la maîtrise de l'asthme, à traiter l'inflammation des voies respiratoires dans leur totalité, et, autre découverte, on commence à reconnaître le manque de fiabilité de la perception des symptômes par les patients comme critère de maîtrise de la maladie. 

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## Is beta-agonist alone prescribed in case of uncontrolled asthma?

*J. Elers, L.M. Rasmussen, V. Backer (Respiratory Research Unit, Department of Respiratory Medicine, University of Copenhagen, Bispebjerg Hospital, Denmark)*

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**Background:** Mild asthma should, in accordance with guidelines, be treated with beta-agonist (SABA) alone, whereas uncontrolled asthma have inhaled steroid (ICS) prescribed. The aim has been to analyse the treatment pattern in uncontrolled asthma and whether particular symptoms lead to specific anti-asthmatic medication prescribed.

**Material:** All 793 asthmatics in the present survey were included on behalf of asthma symptoms and a positive test to methacholine provocation, inhaled SABA or day-to-day variation in PEF. Mean FEV<sub>1</sub> was 93% (15) and FEV<sub>1</sub>/FVC 81% (8). Furthermore, 45% smoked, 71% had rhinitis and 62% had atopy.

**Results:** Of the 793,345 asthmatics reported daily symptoms or more, of whom 54% had no treatment, 17% SABA alone and 29% ICS either alone or in combination with SABA or LABA; 31% had uncontrolled asthma. Treatment strategy was analysed in a multivariate regression including rhinitis, treatment, GINA classification, smoking, cough, wheezy, chest tightness, EIA, night symptoms, log DRS, atopy, FEV<sub>1</sub> % pred, FEV<sub>1</sub>/FVC%, age, sex and BMI. Among those treated, EIA ( $\beta$  .165  $p < 0.01$ ), night symptoms ( $\beta$  .128,  $p = 0.03$ ) and age ( $\beta$  .136,  $p = 0.01$ ) were found to be associated with specific selection of asthma treatment. Daily EIA were in 24% of the case prescribed SABA only (ICS 73%), night asthma 2-3 times per week were in 15% of the cases treated with SABA (ICS 82%). Daily EIA and 2-3 night symptoms of asthma per week, indicating partly controlled asthma, were untreated in 45% and 50% of the cases, respectively.

**In conclusion:** Partly controlled asthma was frequently untreated or treated with SABA alone, even symptoms as severe as night asthma, which indicate severe airway inflammation.

## Commentary

In this Danish study, the investigators sent out over 15,000 questionnaires to primary health care patients asking whether they suffer from respiratory symptoms. Sufferers were invited to come in for a visit where they were screened for asthma by spirometry. Those with a positive test formed the study sample and underwent an interview about the presence of exercise-induced symptoms and night symptoms and their current treatments. More than half were untreated and of those who were treated, 20% were treated with beta agonists even though 19% of these had frequent exercise-induced asthma symptoms and 8% had night symptoms. These findings suggest firstly that asthma is undertreated in Denmark, and secondly, that in cases of uncontrolled asthma (frequent exercise-induced symptoms and/or night symptoms), treatment is insufficient according to clear and widely distributed guidelines. The finding that some patients with night symptoms are untreated is particularly noteworthy, as this is an indication of severe airway inflammation.

### Questions and Answers with Dr. Jimmi Elers, Copenhagen, Denmark

**Q: Were you surprised by the results of this study?**

**A:** It is striking but perhaps not totally unexpected. This is something that we had suspected for some time based on anecdotal evidence. This study basically confirmed our suspicions in a more rigorous manner.

**Q: The main finding then is that both mild and uncontrolled asthma are undertreated. Do you have any suggestions as to why this is the case?**

**A:** This study was done in primary care. On the one hand, it may reflect a problem of physician education. There are clear guidelines out there and they are not implemented in clinical practice. Likewise, patients may be wary of treatment, and steroids in particular have a bad name. While this study didn't include children, there is also the problem that parents are uneasy about giving their children steroids.

**Q: So the way to improve the situation would be better education all round?**

**A:** Yes, in some ways it is a historical problem. Some of the earlier anti-inflammatory treatments had high doses and yes, they did have safety issues. The current asthma medications are safer, and this is something that needs to be transmitted.

E4272

## Does treatment of allergic rhinitis with intranasal steroids improve asthma control?

Deepak S. Rao, B.V. Muralimohan, S. Nanjundaiah

**Introduction:** Unified airway hypothesis suggests that treating co-morbid allergic rhinitis (AR) in asthmatic patients should improve asthma control. Evidence however is equivocal. This study aims to assess if AR treatment with intranasal steroids (INS) further improved asthma control.

**Objectives:** To determine in subjects with co-morbid AR-asthma, whether addition of INS to standard asthma care, improves asthma control and spirometric measurements, when compared to standard asthma treatment alone.

**Methodology:** Prospective, randomised, open study. After 4 weeks run-in period with ICS-LABA combination, 60 patients with asthma and AR were randomly assigned to 8 weeks of treatment with INS (standard doses of mometasone furoate - cases) or oral antihistamine (controls), while ICS-LABA treatment continued in both groups. AR and asthma symptoms were assessed by questionnaire, visual analogue scores (VAS) and spirometry, at baseline, after run-in period and after 8 weeks of treatment.

**Results:** 40 Cases (19F,21M); 20 Controls (8F,12M). Significant differences at baseline between cases and controls were abolished after run-in period. Cases further improved significantly both subjectively (VAS score) and objectively ( $FEV_1$ , PEF,  $FEF_{25-75}$ ) as compared with controls who showed no further improvement.

Change in spirometric values			
Parameters (%predicted)	Cases: mean (SD)	Controls: mean (SD)	P value*
$FEV_1$ change	13.68 (16.01)	5.17 (9.87)	0.03
PEF change	19.72 (14.90)	6.05 (12.84)	0.001
$FEF_{25-75}$ change	19.44 (24.01)	-0.64 (11.63)	0.000

\* Student's t Test

**Conclusions:** Asthma control improves significantly when INS are added to ICS-LABA combination in patients with combined AR and asthma.

## Commentary on abstract E4272

Many patients with asthma also suffer from allergic rhinitis. It is also known that the efficacy of asthma medication is often reduced in patients with concurrent allergic rhinitis. In view of this, it seems reasonable to hypothesize that treatment of allergic rhinitis would improve asthma control. To test this hypothesis, after a run-in phase with an ICS/LABA combination, asthmatic patients with allergic rhinitis were randomized to either intranasal steroids (n=40) or oral cetirizine (n=20) while continuing their asthma medication and followed for eight weeks in this double-blinded study. Allergic rhinitis and asthma symptoms were assessed by standard questionnaires and visual analogue scales, and all patients underwent spirometry. Improvements in lung function were significantly greater in the intranasal group compared to the cetirizine group (e.g. FEV<sub>1</sub> change, 13.7% vs. 5.12%,  $P=0.03$ ). In both groups, asthma symptoms improved significantly on starting treatment from allergic rhinitis, although that improvement was significantly larger in the case of intranasal steroids.

## Questions and Answers with Dr. Deepak S. Rao, Bangalore, India

### Q. Did any of the patients have seasonal rhinitis? If so, there would be no benefit of treating the rhinitis outside the season?

**A:** Interestingly, most patients had perennial allergic rhinitis (31 of the 40 cases, 14 of the 20 controls). The rest, although they had the seasonal type, behaved more or less like the perennial allergic rhinitis sufferers. It is known that perennial allergic rhinitis is much more common in India, due to the climatic conditions as well as the long pollination season. We classified allergic rhinitis patients purely on clinical grounds as per ARIA criteria, but didn't test for specific allergens. So far, there is substantial evidence to treat seasonal allergic rhinitis starting just prior to pollen season. Some studies suggest treating seasonal allergic rhinitis patients outside the pollination season improves asthma control but this evidence is not so compelling.

### Q: Control of allergic rhinitis was better in the intranasal steroid group. Do you think the better outcomes for asthma are more a result of the better outcome for allergic rhinitis, or is there some specific benefit to using a steroid?

**A:** We now have evidence linking upper and lower airways at various levels (pathophysiological, immunological, therapeutic and so on), the so-called "unified airway hypothesis." We also now know that a) bronchial hyperresponsiveness is common in people with allergic rhinitis, even if they have no asthma symptoms; b) asymptomatic airway hyperresponsiveness is associated with increased risk for developing asthma; and c) rhinitis is an independent risk factor for the subsequent development of asthma. Therefore, I think that better outcomes of asthma is due to the fact that the airway inflammation was more completely controlled by treating not only lower airway inflammation (asthma) but also the inflammation in the upper airways (allergic rhinitis). In our study, we did notice that there was improvement in both the groups in terms of asthma as well as allergic rhinitis, but the steroid group did significantly better. It is also evident from earlier studies that though antihistamines do control allergic rhinitis symptoms, they have very little effect on asthma control by themselves.

### Q: So the way to improve the situation would be better education all round?

**A:** Yes, in some ways it is a historical problem. Some of the earlier anti-inflammatory treatments had high doses and yes, they did have safety issues. The current asthma medications are safer, and this is something that needs to be transmitted.

E2797

## Control of severe asthma as assessed by guidelines, physician, patient and patient's spouse

*M. Molimard, D. Vervloet, V. Le Gros, A. Ponthieux (Bordeaux, Marseille, Rueil-Malmaison, France)*

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**Aim:** To compare 4 sources of asthma control assessment: physician, patient, patient's spouse and guidelines rules.

**Methods:** In patients with severe persistent asthma treated by high dose inhaled corticosteroid + long acting  $\beta_2$ -agonist, the global asthma control was simultaneously assessed by the patient, his (her) spouse and his (her) physician. The control was also assessed according to the rules of the ANAES French guidelines 2004, from control items noted by the physician. It was classified as unacceptable, acceptable or optimal.

**Results:** 169 pairs patient/spouse were included (patients gender: females 58.6%). Asthma control was found unacceptable in 85.2% of patients according to ANAES guidelines and assessed unacceptable by 26.6% of patients, 23.3% of spouses and 35.5% of physicians. The rate of concordance between the ANAES guidelines and the physician global assessment was low (50.3%,  $k=0.17$ ); physicians considered acceptable or optimal the control of 84 patients with ANAES criteria of unacceptable control. Patients and physicians had the same view in 77% of cases ( $k=0.47$ ), but 45% of patients assessed uncontrolled by the physician were self-assessed controlled. Concordance rates were high between patients and spouses (90%,  $k=0.74$ ) and between physicians and patients' spouses (82%,  $k=0.59$ ), but 36.6% of patients assessed uncontrolled by the physician were assessed controlled by the spouse.

**Conclusion:** Large differences between guidelines rules and physician global assessment were found. The concordance rates between spouses and patients and between spouses and physicians were better. Patients and spouses tended to minimize the poor control.

## Commentary on abstract E2797

Asthma patients and their partners have been reported to underestimate symptoms and control. This French study investigated these differences, and also assessed the degree of control determined according to the guidelines issued by the French National Agency for Accreditation and Evaluation in Health (ANAES). These guidelines contain eight items, and if at least one is not met, then control is considered unacceptable. The study included 169 patient/spouse pairs (58.6% of the patients were women). Asthma control was found to be unacceptable according to 26.6% of patients, 23.3% of spouses and 35.5% of physicians. However, according to the ANAES guidelines, 85.2% had unacceptable asthma control. In view of the large differences between the physician assessment and physician assessment based on the guidelines, the ANAES definition of unacceptable control might need revising for severe asthma. The results also confirm the impression that asthma patients and their partners may underestimate the severity of their disease.

### Questions and Answers with author Vincent le Gros, Rueil-Malmaison, France

**Q: What are the definitions of asthma control in the French ANAES guidelines based on?**

**A:** There are eight items defining acceptable control. These include an assessment of daytime symptoms, nighttime symptoms, physical activity, exacerbations, absence from work or school, use of SABAs, lung function, and diurnal variation in PEF. If at least one is not met, the control is considered unacceptable.

**Q: Why do you think there is such a large and striking difference between control according to the guidelines and the physician's assessment?**

**A:** In our study, the two items most frequently not met were physical activity and  $FEV_1/PEF > 85\%$  of personal best, explaining the gap between control according to the guidelines and the physician's assessment.

**Q: Does this imply that the physicians (in primary care) are relatively unaware of the asthma guidelines?**

**A:** I think this suggests that the ANAES definition of unacceptable control should be reconsidered.

E4649

## Assessing overall asthma control with budesonide/formoterol maintenance + relief in moderate/severe asthma

*E. D. Bateman, P. M. O'Byrne (Cape Town, South Africa; Hamilton, Canada)*

**Background:** The ability to achieve current clinical control and reduce the future risk of exacerbations with moderate-to-high dose ICS/LABAs or budesonide/formoterol (B/F; Symbicort®) maintenance and reliever therapy (SMART) in patients symptomatic on moderate-to-high dose ICS is unknown.

**Methods:** This post-hoc analysis, examined the percentage of patients with  $\geq 1$  exacerbation (hospitalisation/emergency room visits or oral steroid use) and the percentage of controlled and uncontrolled asthma patients assessed by a validated questionnaire (ACQ-5 scores  $\leq 0.75$  and  $\geq 1.5$ , respectively) in symptomatic asthmatics ( $\geq 12$  years) from 2 double-blind randomised studies  $\geq 6$ -months duration that compared these treatment strategies. Data were pooled for SMART-treated patients using B/F 160/4.5 $\mu$ g 1 or 2 inh bid + prn or higher fixed-dose ICS/LABA-treated patients, using double the maintenance dose (B/F 329/9 $\mu$ g bid or salmeterol/fluticasone (Seretide™) 50/250 or 50/500 $\mu$ g bid) plus SABA prn.

**Results:** The mean dose of ICS used in each of the groups ( $\mu$ g/d beclomethasone equivalent) was: SMART (1000 $\mu$ g/d) vs higher fixed-ICS/LABA + SABA (1341 $\mu$ g/d).

**Conclusions:** SMART reduces the risk of exacerbations and uncontrolled asthma with a similar probability of achieving clinical control vs fixed higher dose ICS/LABA plus SABA in moderate/severe asthma.

Treatment (N, Exacerbations/ACQ-5)	Percentage of patients		
	$\geq 1$ exacerbation	Uncontrolled	Controlled
SMART (2254/2173)	9 <sup>a</sup>	26 <sup>b</sup>	44
Higher fixed-ICS/LABA + SABA (3371/3246)	12	30	43

<sup>a</sup> $P=0.001$ , <sup>b</sup> $P=0.035$  vs fixed ICS/LABA

## Commentary on abstract E4649

Several randomized controlled trials have been conducted with the BUD/FORM maintenance and reliever therapy. In this analysis, data were pooled from two randomized, double-blind, six-month studies. The first study compared BUD/FORM maintenance (160/4.5 µg b.i.d.) and reliever therapy with BUD/FORM 320/9 µg b.i.d. or SAL/FLU 50/250 µg/b.i.d. The second compared BUD/FORM maintenance (320/9 µg b.i.d.) and reliever therapy with maximum-dose SAL/FLU 50/500 µg b.i.d. Asthma control was assessed using the five-item asthma control questionnaire (ACQ-5). Of note was the higher percentage of patients with uncontrolled asthma (ACQ  $\geq$  1.5) in the pooled comparator group (30 vs. 26,  $P=0.035$ ), even though the mean daily ICS dose was higher (1341 µg vs. 1000 µg in BDP equivalent). Asthma control showed a clear relationship with exacerbation rates (0.180 exacerbations/patient/year for well-controlled asthma vs. 0.664 for uncontrolled asthma). The relationship was even more evident for patients on high-dose ICS (>1000 µg/day BDP equivalent) at study entry (0.263 vs. 1.030, respectively).

## Questions and Answers with Prof. Eric Bateman, Cape Town, South Africa

### Q: How arbitrary is the definition of asthma control?

A: Including three levels of control is now common to most of the recent guidelines: GINA, EPR3, the Australian and Canadian guidelines. There is not much difference in the terms used to denote control—some prefer “well,” others “good,” and others “complete.” Also, there is not much difference about what is unacceptable control. The main differences come in this area in between.

### Q: Why include an intermediate definition of control in the guidelines?

A: This is a recognition that in many patients, we cannot achieve ideal control, and in many patients, we might have to settle for something that is close but not there. So the concept of partial control is really an admission that although we would like to move everybody to have complete control, this is not always attainable. We wouldn't want to push treatment too far, and end up with worse long-term outcomes.

P3632

## Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials

M.R. Sears, F. Radner (Hamilton, Canada; Lund, Sweden)

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**Background:** Long-acting  $\beta_2$ -agonists (LABAs) used without inhaled corticosteroids (ICS) have been associated with an increase in asthma-related serious adverse events (SAEs). Budesonide/formoterol (Symbicort<sup>®</sup>) maintenance and reliever therapy (Symbicort SMART<sup>®</sup>) increases LABA and ICS doses simultaneously, which may improve the benefit/risk ratio.

**Methods:** Seven asthma trials (6 double-blind) all  $\geq 6$  months duration were examined to compare the odds ratios (OR) for deaths, SAEs and discontinuations due to adverse events (DAEs) with SMART (n=6648) vs controls (n=9833) treated with a 2–4 fold higher regular dose of budesonide + short-acting  $\beta_2$ -agonist (SABA) prn, or ICS/LABA + SABA prn (formoterol prn in one study).

**Results:** Death was reported for 4 (0.06%) SMART patients and 11 (0.11%) controls, OR 0.54 [95% CI, 0.12–1.81]; 2 deaths were asthma-related (1 per group), 4 were cardiac-related (all controls). Non-fatal SAEs with SMART were 292 (4.4%) vs controls 455 (4.6%), OR 0.95 [0.81–1.1]. Asthma-related SAEs were reduced with SMART; 51 (0.8%) vs 136 (1.4%), OR 0.55 [0.39–0.77]. Cardiac-related SAEs were uncommon; 30 (0.5%) vs 29 (0.3%), OR 1.53 [0.89–2.65]. All cause DAEs were reduced with SMART: 102 (1.5%) vs 211 (2.1%); OR 0.71 [0.55–0.91], and primarily related to fewer asthma-related DAEs: 28 (0.4%) vs 96 (1.0%); OR 0.43 [0.27–0.66]. Cardiac-related DAEs were uncommon, with 15 (0.2%) in each group.

**In conclusion:** In this trial database of 16481 patients, the risk of asthma-related SAEs and DAEs were 45% and 57% lower, respectively, in patients on Symbicort SMART compared with controls. No increase in mortality was seen with Symbicort SMART.

## Commentary on abstract P3632

Management of asthma with BUD/FORM maintenance and reliever therapy has been extensively studied. This paper presents the pooled analysis from seven randomized controlled trials (six with a double-blind design) that enrolled a total of 16,481 patients and that lasted between six and 12 months. Comparators corresponded to standard practices in asthma management (BUD + SABA, BUD/FORM + SABA, BUD/FORM +FORM, SAL/FLU + SABA). Analysis of adverse events considered at least possibly related to  $\beta_2$ -agonists or ICS did not reveal any noteworthy differences between comparator and BUD/FORM maintenance and reliever therapy (e.g. tremor, 0.7% vs. 0.7%; dysphonia, 1.2% vs. 1.1%). Deaths were reported in 11 patients on comparator therapy and four patients on BUD/FORM maintenance and reliever therapy (not attributed to the study drug); only one death in each group was asthma-related. Analysis of non-fatal serious adverse events suggested that asthma-related serious adverse events were significantly less common for BUD/FORM maintenance and reliever therapy, as were discontinuations due to adverse events.

## Questions and Answers with Dr. Franz Radner, Lund, Sweden

**Q: This analysis includes a large number of patients, and the results do not seem to have identified any safety issues. Could you comment on what you see as the most interesting aspect of these findings?**

**A:** One of the hot topics with BUD/FORM maintenance and reliever therapy has been the asthma-related adverse events. Because the dose of steroids is lower, there have been worries that asthma-related events might be more frequent. This does not happen, in fact the opposite is the case; there were significantly fewer serious asthma-related events and asthma-related events leading to discontinuation.

**Q: Do you believe this may also be a reflection of better efficacy demonstrated in the clinical trials?**

**A:** Of course, a clinical study has rigorous inclusion and exclusion criteria and it is difficult to say how representative they are. However, the comparators by and large corresponded to standard treatment. These patients would have been treated anyway and we compared the treatment they would normally get with BUD/FORM maintenance and reliever therapy.

E4651

## Overall asthma control with budesonide/formoterol maintenance and relief vs. conventional best practice

*P. Demoly, R. Louis, U. Søres-Petersen, H. Worth, J. Almeida, M. R. Sears (Montpellier, France; Liege, Belgium; Roskilde, Denmark; Fürth, Germany; Porto, Portugal; Hamilton, Canada)*

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**Background:** Budesonide/formoterol (B/F; Symbicort<sup>®</sup>) maintenance and reliever therapy (Symbicort SMART<sup>®</sup>) reduces asthma exacerbations and symptoms vs alternative fixed-dose regimens plus short-acting  $\beta_2$ -agonist (SABA) in double-blind trials. More information is needed on the efficacy of SMART vs local guideline-based conventional best practice (CBP).

**Methods:** This pooled analysis examined clinical control and risk of exacerbations in asthmatics ( $\geq 12$  yrs) during 6-month open-label studies, performed to the same core protocol. Patients ( $n=7855$ ) symptomatic on ICS or stable/symptomatic on existing ICS/long-acting  $\beta_2$ -agonists (LABA) were randomised to SMART (B/F 160/4.5 $\mu$ g bid and prn) or CBP, which could include ICS or ICS/LABA at any dose  $\pm$  other agents, e.g. leukotriene antagonists, and prn SABA. Outcomes were exacerbations (oral steroid use or hospital/ER visits) and the percentage of controlled/uncontrolled patients at all visits, defined using the asthma control questionnaire (ACQ-5 score  $\leq 0.75/\geq 1.5$ ).

**Results:** The risk of a first exacerbation (primary variable) was not significantly reduced with SMART (HR 0.86; 95% CI 0.74, 1.01;  $P=0.062$ ) but SMART-treated patients experienced 15% fewer exacerbations (0.20 vs 0.24 patient/year;  $P=0.02$ ) and fewer exacerbation days (totals 2753 vs 3801;  $P<0.0001$ ). Exacerbations defined by oral steroid use were 0.15/year with SMART and 0.18/year with CBP ( $P=0.01$ ). Well controlled asthma was achieved by 45% with SMART vs 41% with CBP (OR 1.29;  $P<0.01$ ). Uncontrolled asthma was reduced (25% vs 29%, OR 0.81;  $P<0.01$ ).

**In conclusion:** Symbicort SMART, 160/4.5 $\mu$ g bid and prn, resulted in improved asthma control and fewer exacerbations compared with CBP.

### Commentary on abstract E4651

Double-blind randomized clinical trials represent the gold-standard methodology for demonstrating clinical efficacy. However, patients in clinical trials often correspond to an ideal situation in that the sample is highly selected and often highly adherent to treatment. It is therefore important to confirm the results of these rigorous trials in “real life” situations. This pooled analysis of six randomized, six-month, open-label national studies conducted in several European countries, Chile and Canada went some way towards confirming that the real-life effectiveness of BUD/FORM maintenance and relief mirrors efficacy in comparison with local conventional best practice. Patients were randomized to best practice according to local guidelines or BUD/FORM maintenance and relief and followed for six months. Patients in the latter group had a 29% greater chance of being well-controlled ( $P<0.01$ ), a 19% lower risk of remaining uncontrolled ( $P<0.01$ ) and experienced 15% fewer exacerbations (rate ratio 0.85, 95% CI: 0.737-0.975;  $P=0.02$ ). These encouraging outcomes were achieved with a lower steroid dose.

**PAPER HAS BEEN SUBMITTED TO ALLERGY JOURNAL BY AUTHOR DEMOLY**

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P3508

## Budesonide/formoterol maintenance and reliever therapy compared with conventional best standard treatment

*U. Soes-Petersen, R. Dahl, T. Kava, Y. Lei, N. Dam (Roskilde, Copenhagen, Denmark; Fredrikstad, Norway; Joensuu, Finland; Mississauga, Canada)*

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**Aim:** To compare the effect of budesonide/formoterol (B/F; Symbicort®) Maintenance and Reliever Therapy (Symbicort SMART) with conventional best standard treatment (CBST) in patients with persistent asthma.

**Methods:** In this 6-months open-label, parallel group study 1835 patients recruited from Denmark, Finland and Norway (mean age 42,5 years) were randomised to B/F 160/4,5 mg twice daily plus B/F 160/4,5 mg as as-needed therapy or CBST according to GINA guidelines. The study was designed to reflect real life asthma management with only a few scheduled clinic visits. The prescribed study medication was dispensed by the local pharmacy and was free of cost to the patient. Efficacy was assessed by time to the first severe asthma exacerbation, number of severe asthma exacerbations (defined as hospitalisations, emergency room visits or use of oral steroids), use of as-needed medication and average dose of inhaled corticosteroid (ICS).

**Results:** There was no statistically significant difference between Symbicort SMART and CBST in time to first severe asthma exacerbation (hazard ratio 0,794;  $P=0,189$ ). A trend towards a reduction in the rate of severe exacerbations in the Symbicort SMART arm (16 vs. 22 events/100 patient years;  $P=0,058$ ) was observed. The total mean daily ICS dose was significantly reduced by 31% (752 vs. 1092 mg daily (BDP equivalent);  $P<0,0001$ ), while no difference in mean as-needed medication use was seen ( $P=0,98$ ). All treatments were well tolerated.

**Conclusion:** Budesonide/formoterol maintenance and reliever therapy resulted in similar or better asthma control compared with conventional best standard treatment with a significant lower daily ICS dose.

## Commentary on abstract P3508

This was another study that aimed to investigate the efficacy of BUD/FORM maintenance and reliever therapy in a real-world setting, this time in Finland, Norway and Denmark. As in the study presented by Demoly et al., patients with a prescribed ICS dose of  $\geq 320 \mu\text{g}$  were randomized to conventional best standard treatment or BUD/FORM maintenance and reliever therapy and followed for half a year. Neither the time to first severe exacerbation nor the cumulative number of severe exacerbations over time showed any significant differences over time, though in both cases, there were trends in favour of the maintenance and reliever therapy vs. comparator. However, there were significant benefits in terms of asthma control; 44.7% vs. 39.7% were well controlled ( $P < 0.01$ ). The total mean daily dose of ICS (BDP equivalents) was significantly lower with BUD/FORM maintenance and reliever therapy (500  $\mu\text{g}$  maintenance + 253  $\mu\text{g}$  as needed vs. 1082  $\mu\text{g}$  maintenance in the comparator group,  $P < 0.0001$ ).

### Questions and Answers with Ragnar Dahl, Fredrikstad, Norway

**Q: The comparator in this study was conventional best standard treatment, but presumably that varies from country to country.**

**A:** Yes, but in the Scandinavian countries Finland, Denmark, and Norway, where this study was carried out, the standard treatment is similar. Of course, outside Scandinavia, standard treatment does vary. That is why other studies are necessary, such as the one presented by Demoly et al.

**Q: The results are encouraging; do you think that conventional standard treatment will change in time?**

**A:** Oh yes, and I think we are already seeing that. Use of BUD/FORM maintenance and reliever therapy is already included in some guidelines and is beginning to form part of conventional best standard treatment. Furthermore, it is difficult to get patients who have taken BUD/FORM maintenance and reliever therapy to go back to using two or three different inhalers. It is also difficult to persuade the physician to change in view of the reduction in number of exacerbations and the reduced ICS dose demonstrated in this and other studies.

E4650

## Preventing asthma exacerbations with budesonide/formoterol maintenance + relief: a pooled analysis

P. M. O'Byrne, E. D. Bateman (Hamilton, Canada; Cape Town, South Africa)

**Background:** Uncontrolled asthmatics on inhaled corticosteroids (ICS) benefit from stepping up to a higher ICS dose, the addition of along-acting  $\beta_2$ -agonist (LABA), or both. In reducing asthma exacerbations and emergency treatment for asthma, these options have been compared with budesonide/formoterol (Symbicort®) maintenance + reliever therapy (SMART).

**Methods:** This pooled analysis examined exacerbation rates in ICS-treated adults ( $\geq 18$  years) from six double-blind studies all  $\geq 6$  months induration. SMART was compared with: A) 2-to 4-fold higher maintenance ICS; B) maintenance budesonide/formoterol equal to SMART; C) higher maintenance ICS/LABA (budesonide/formoterol or salmeterol/fluticasone [Seretide™]). All comparators used short-acting  $\beta_2$ -agonists (SABA) as needed. Exacerbations requiring oral steroids and/or hospitalisation/emergency room (H/ER) visits were analysed (Poisson regression), and the number needed to treat (NNT) to prevent one of each type of exacerbation was estimated.

**Results:** Estimated annual exacerbation rate/100 patients for SMART vs comparators A-C.

SMART vs comparator (n per stratum)	All events SMART vs comparator	% $\Delta$ with SMART	NNT (95% CI)	H/ER events SMART vs comparator	% $\Delta$ with SMART	NNT (95% CI)
A (n=3765)	19 vs 34	43***	7 (6–9)	2 vs 3	27	–
B (n=3390)	21 vs 40	47***	5 (4–7)	4 vs 7	35**	42 (30–71)
C (n=4680)	28 vs 39	29***	9 (6–15)	13 vs 17	28**	20 (14–37)

$\Delta$  = change, \*\*\* $P < 0.001$ , \*\* $P < 0.01$  vs comparator

**In conclusion:** Compared with all traditional fixed-dose regimen plus SABA comparators, SMART reduced the rate of asthma exacerbations and H/ER visits.

### Commentary on abstract E4650

Nowadays, there is increasing emphasis in asthma management on preventing future exacerbations. In addition to the risk entailed, exacerbations are also a source of anxiety for patients and their families and have been linked to accelerated decline in lung function, particularly early on in the course of the disease. A number of randomized controlled trials have hinted that BUD/FORM maintenance and relief can reduce the rate of exacerbations compared to other treatment approaches such as stepping up the ICS dose and adding SABAs (comparison A), same fixed-dose BUD/FORM + SABA (comparison B), or higher fixed-dose LCS/LABA + SABA (comparison C). In this analysis, six clinical trials based on these comparisons (two per comparison) were pooled in an attempt to further elucidate the effect of BUD/FORM maintenance and relief on exacerbation rate. In all cases, the mean annualized rate of exacerbations was significantly lower for all comparisons (comparison A: decrease 43%,  $P < 0.001$ ; comparison B: decrease 47%,  $P < 0.001$ ; comparison C, decrease 29%,  $P < 0.001$ ).

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P3509

## Budesonide/formoterol maintenance and reliever therapy for asthma in general practice: is it cost-effective?

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**Background:** Symbicort Maintenance And Reliever Therapy (SMART) implies that asthma patients take a low daily dose of budesonide/formoterol, with the option to take more puffs for symptom relief. No additional short-acting  $\beta_2$ -agonist is needed. SMART has been shown to be cost-effective in patients with relatively severe asthma who were mainly treated by pulmonologists in hospital clinics.

**Aim:** This study assesses the cost-effectiveness of SMART compared to usual care for mild-moderate asthma patients treated by general practitioners in the Netherlands from a societal perspective.

**Methods:** The economic evaluation was linked to a one-year randomised, active-controlled, open-label, multi-centre clinical trial, including 102 patients  $\geq 18$  years who daily used inhaled corticosteroids prior to the trial. Costs included asthma medication, physician visits and absence from paid work. Outcomes were measured as change from baseline in symptom-free days, well-controlled patients, Asthma Control Questionnaire (ACQ) score, and additional number of patients with relevant ACQ improvement.

**Results:** Mean costs were €426 (95%CI: €382-€480) for SMART and 561 (CI: €392-€868) in the control group, a decrease of €135 (CI: -€45-€439). Medication costs were €36 (CI: -€71-€161) lower and production losses were €94 (CI: €0-€301) lower in SMART. Outcome differences (SMART vs. usual care) were -3.8 pp/py (CI: -36.9-30.9) for symptom-free days, 12.6% (CI: -6.5-32.3%) for well-controlled patients, 0.049 (CI: -0.22-0.30) for ACQ improvement, and -5.8% (CI: -27.0-15.9%) for patients with ACQ improvement.

**In conclusion:** SMART was as effective as usual care. Treatment is simplified at potentially lower cost.

## Commentary on abstract P3509

The results of other studies presented at the ERS suggest that BUD/FORM maintenance and reliever therapy effectively reduces exacerbation rates and visits to the hospital/emergency room. It would therefore be expected that an economic analysis would reflect the cost-effectiveness of this approach. In this study, the authors took patients from a large open-label trial comparing BUD/FORM maintenance and reliever therapy with usual practice as defined by the Dutch general practice guidelines (patients  $\geq 18$  years who used daily ICS prior to study entry) and added up the costs for each group. The analysis included medication costs and physician visits, but also societal costs such as absence from paid work. Although no significant differences in costs were observed, there was a trend towards lower costs for BUD/FORM maintenance and reliever therapy (€428 [95% CI: €382-480] vs. €561 [95% CI: €392-868]). This difference was mainly driven by lost productivity (cost of absence from paid work €94 [95% CI: €0-301] lower in BUD/FORM maintenance and reliever therapy group).

### Questions and Answers with author Lucas Goossens, Rotterdam, Netherlands

**Q: Has the study on which this economic analysis is based been published?**

**A:** The study has been submitted for publication. It is currently being reviewed.

**Q: Were hospitalizations due to exacerbations included in the analysis?**

**A:** Hospitalizations were included in the analysis, but none of the patients had to be admitted to the hospital. This may not be surprising, since these patients had mild to moderate asthma.

**Q: What was the “usual care”? If there were a number of different “usual cares,” was BUD/FORM maintenance and reliever therapy compared to each different therapy and if so, were there any differences?**

**A:** “Usual care” was defined as the care that patients received prior to the study and driven by Dutch General Practice guidelines, which prescribe low or medium daily doses of ICS ( $\leq 800$   $\mu\text{g}$  BUD/BDP or  $\leq 500$   $\mu\text{g}$  FLU) plus a SABA if needed. A LABA is added if asthma is not under control with this medication. (The study included only patients who used ICS.) Patients in the control group were treated according to guidelines, but doses and specific medication vary.

**Q: The lower confidence intervals were similar, but the higher ones were different. Can you comment on that?**

**A:** Costs usually have a skewed distribution: many patients have relatively low costs and some have very high costs. This affects the confidence intervals. Patients with poorer control show more variation. In this case, the statistical uncertainty was increased by one patient in the control group who had especially high productivity costs. This is, of course, discussed in our paper. Excluding this patient altered the results somewhat, but did not lead to a different conclusion.

P1149

## Use of methacholine test to improve maintenance and reliever therapy in mild-moderate asthma

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The maintenance and reliever therapy described by Barnes (*Eur Respir J* 2007; 29) can fail if the patients have a low perception of their symptoms, and the reliever drug is under used. To understand when the asthmatic patients really use bronchodilators "as needed", we compared the functional parameters with the subjective symptoms during Metacholine Bronchoconstriction Test (MTCH) in 132 subjects. Bronchial Hyper Responsiveness was Positive in 99 patients according with clinical diagnosis of asthma (40 stade I, 40 stade II, 8 stade III, 11 unclassified); 48 male & 51 female, mean age 34 (range 16-61), 66 (67%) were atopics. In 57 patients (control group C) we stopped as usually at PD20FEV<sub>1</sub>: patients were poor-or asymptomatic or had only cough, or light troubles; nobody needed Bronchodilator. In 42 patients we added supplementary doses of methacoline until symptoms were reached. In 24 subjects (group A) we stopped when dyspnoea or symptoms similar to those referred at home appeared; all patients needed Bronchodilator. In other 18 cases (group B) we stopped for cough and breathing trouble, not truly dyspnoea; only 6 people asked for inhalation of Bronchodilator. The average fall of FEV<sub>1</sub> was: 38% (range 30-46) in group A, 29% (25-32) in group B, 23% (20-29) in group C. In this study we noticed that in the lower stades of asthma the dyspnoea is perceived (and reliever drug is used) only when the obstruction is fairly important (fall of almost 30% of the FEV<sub>1</sub>). Making the simulation with MTCH test we can help the patient's awareness and we can advise/order an early and more efficacious use of the drug, improving the asthma control.

## Commentary on abstract P1149

There is often a mismatch between patients' perception of symptoms and decline in lung function. In such cases, it is possible that maintenance and reliever therapy can fail because patients do not perceive the need for reliever therapy. In this study, patients underwent a bronchoconstrictor challenge test with methacholine while spirometry was measured and subjective symptoms were reported, with a view to investigating discrepancies. In 57 patients—the control group—the test was stopped after a 20% decline in FEV<sub>1</sub>. In the remaining patients, the test was continued and stopped in 24 patients on reaching the subjective dyspnea experienced at home (all required  $\beta_2$ -agonists) and in 18 patients on coughing but without actually experiencing dyspnea (six required  $\beta_2$ -agonists). The decline in FEV<sub>1</sub> was 38% in those who stopped because of dyspnea and 23% in those who stopped because of cough. The results suggest that lung function has often declined substantially before patients perceive symptoms that require reliever medication.

## Questions and Answers with author Giuseppe Sera, Turin, Italy

**Q: Your study suggests that in order to educate patients about the need to take reliever therapy, the methacholine dose should continue to be administered until the patients experience symptoms, rather than when FEV<sub>1</sub> decreases by 20%. This would then enable the physician to indicate that lung function had declined substantially even though the patient had not experienced excessive symptoms. Is that interpretation correct?**

**A:** Basically yes, although the methacholine dose needn't necessarily be administered until the patients experience symptoms, I tend to do so in the poorly compliant patients. So often a single dose is sufficient: I use a dosimetric protocol starting from 50  $\mu$ g of methacholine with steps of 50-100-150-300-450-600-900-1200-1500-1800  $\mu$ g, and sometimes even 2400  $\mu$ g when I want to be sure the test is negative.

**Q: Do you have any measurement of use of reliever therapy at home in the patients in whom the test continued after a 20% decrease in FEV<sub>1</sub>, as I suppose such information might indicate whether those without dyspnea were underusing their reliever medication?**

**A:** I have only anecdotal reports of use of reliever therapy at home and no systematic measurement in these patients.

E3057

## Superior efficacy of the salmeterol/fluticasone 50/100 mcg combination compared to fluticasone 200 mcg in children with uncontrolled asthma – the VIAPAED trial

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**Background:** In asthmatic children uncontrolled on standard doses of inhaled corticosteroids (ICS), guidelines recommend to either increase ICS dose or add a second controller, e.g. a long acting  $\beta_2$ -agonist (LABA). We compared efficacy and safety of the salmeterol/fluticasone propionate combination (SFC) with that of fluticasone propionate (FP) in children aged 4 to 16 years.

**Methods:** Multicentre, double-blind, parallel-group study. During a 14 day run-in, participants inhaled FP 100 mcg b.i.d. If the 24 h symptom score was  $\geq 2$  on  $\geq 7$  of 14 days, they were randomised to inhale for 8 weeks via Diskus<sup>®</sup> either SFC 50 mcg/100 mcg b.i.d. or FP 200 mcg b.i.d. Primary endpoint was the mean change in a.m. PEFR from baseline. The initial stat. hypothesis of non-inferiority of SFC versus FP was confirmed in an adaptive interim analysis, and the study was terminated prematurely.

**Results:** 441 patients entered run-in, 64% of these were randomized to treatment (N=138 SFC; N=145 FP). After 8 weeks, patients on SFC had significantly better results for primary and secondary endpoints (ITT groups, covariance analysis):

Change during treatment	SFC	FP	Results
a.m. PEFR [L/min] (Per protocol group)	+29.6	+18.3	11.3 [3.4; $\infty$ ]
a.m. PEFR [% predicted]	+9.2	+6.3	3.0 [0.5; 5.5]
% days without asthma symptoms	+41.5	+33.3	8.7 [1.2; 16.3]
% days without salbutamol	+39.9	+32.4	8.0 [0.6; 15.3]

Both treatments were well tolerated.

**In conclusion:** In children with uncontrolled asthma, SFC was more effective than doubling the FP dose. These results support the GINA recommendation of low-dose ICS plus LABA as the preferred controller option for children  $\geq 5$  yrs.

## Commentary on abstract E3057

Fixed combinations of ICS and LABAs in a single inhaler for maintenance are becoming increasingly widespread because they are thought to improve adherence and reduce the overall dose of ICS, without compromising efficacy. In this randomized, double-blind study, the combination SAL/FLU (50/100 µg) was compared to FLU 200 µg in children with uncontrolled asthma. At the end of a run-in phase with 100 µg of FLU, patients who reported symptoms were randomized to the fixed combination or higher-dose ICS and followed for eight weeks. The primary end point was mean change in morning PEF from baseline. An interim analysis was planned and the study was terminated prematurely given that this showed non-inferiority of the combination treatment ( $30.4 \pm 34.1$  L/min for the combination therapy vs.  $16.7 \pm 35.8$  L/min for control [ $P < 0.0004$ ]). Secondary end points such as days without asthma symptoms and days without rescue therapy also favoured the fixed combination.

### Questions and Answers with author Lucas Goossens, Rotterdam, Netherlands

**Q: The primary end point was analyzed according to the per-protocol group. How was “per-protocol” defined?**

**A:** Per-protocol was defined as patients who fulfilled all predefined criteria and completed the study.

**Q: In the conclusions, you mention that these fixed combinations may improve adherence, but that this would have to be addressed in a different study. Nevertheless, did you collect any data that might give an idea of adherence?**

**A:** According to the protocol, the only measure of adherence came from completion of diary card entries. It was not the aim of this study to address adherence.

**Q: No patient discontinued due to a clinical adverse event although one patient (in the combination group) experienced severe tachycardia considered drug-related. Why did this patient continue in the study?**

**A:** The patient made a full recovery. It was the decision of the investigator for the patient to continue in the study.

4429

## Should asthma guidelines be rewritten for initial controller therapy: a 2-year randomized pragmatic equivalence trial of leukotriene antagonists (LTRAs) and inhaled corticosteroids (ICS) in primary care

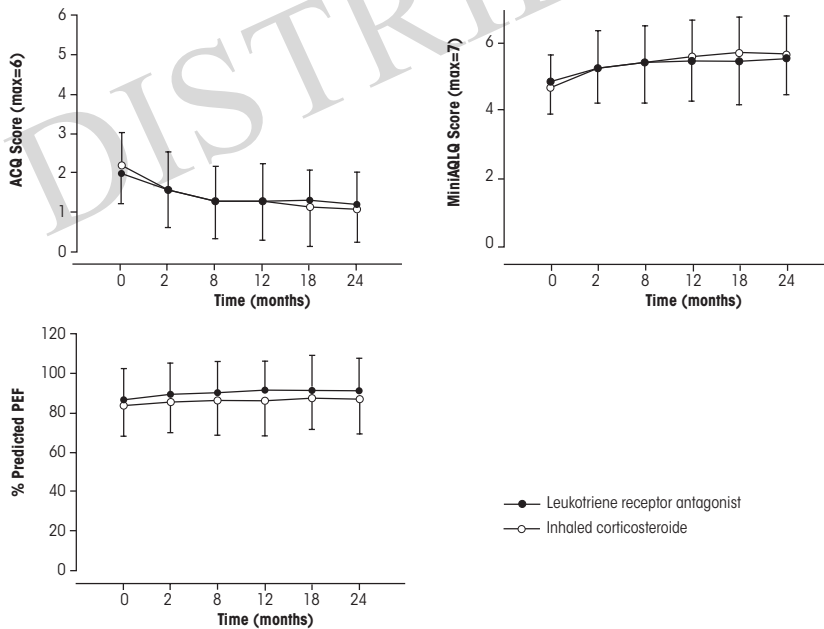
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**Background:** The role of leukotriene receptor antagonists (LTRA) as initial controller therapy for managing asthma is unclear.

**Aim:** To test if LTRA provides equivalent improvements in asthma quality of life and control at least equal to prescribing ICS in uncontrolled asthmatic patients in primary care aged >11 years.

**Study Design and Methods:** Pragmatic, single-blind (to study staff), randomised controlled trial comparing LTRA and ICS as initial controller therapy with Drug/device choices according to normal practice. Outcomes (Juniper Mini Asthma Quality of Life Questionnaire (mAQLQ), Asthma Control Questionnaire, % predicted PEF, asthma exacerbations, respiratory tract infections (RTIs) and consultations for RTIs) were measured at baseline (time 0), 2, 6, 12, 18 and 24 months post-randomisation. Study was powered for equivalence based on mAQLQ difference of <0.3. Analysis of covariance (fixed effect: treatment; covariates: baseline value and time to follow-up) was used to compare all outcomes except % PEF, where Mann-Whitney test was used.

**Results:** 294 of 306 recruited patients (% PEF mean (SD):84.65 (15.99)) completed. No differences were found in any outcomes at 2 or 24 months.



**In conclusion:** Guidelines merit review to reflect equivalence of LTRA to ICS as initial controller therapy in primary care.

## Commentary on abstract 4429

Most of the current asthma guidelines indicate that first-line therapy in mild asthma should be ICS, and LTRAs are not contemplated except in some pediatric guidelines. This UK government-funded study aimed to compare LTRAs and ICS in a situation as close to “real life” as possible, while maintaining the rigorosity of a clinical trial. Thus patients, including smokers and those with active rhinitis, were randomized to either ICS or LTRAs (the choice of actual ICS or LTRA was left at the discretion of the physician) and followed for two years. All assessments were done blinded; the primary outcome measure was quality of life, and no differences were found between the two groups. Indeed, the only real differences were reported for adherence—61% for LTRAs and 41% for ICS. This suggests that LTRAs are as clinically effective as ICS, though this is not to say that they are as pharmacologically efficacious.

## Questions and Answers with Prof. David Price, Aberdeen, UK

### **Q: In the subgroups of smokers, were there any differences between LTRAs and ICS?**

**A:** We are going to have to wait until next year for those results as we are in the process of analyzing it. What is interesting, though, is that we have just been looking at a different population with more severe asthma in the general practice research database, and we have looked at people having an increase in ICS, a LABA added, or an LTRA added. For in-dose comparison, in the group with ICS, the likelihood of success is halved in smokers; in the LABA group, the success is 30% less likely; and in the group with LTRA added, it is 10% less likely to be successful.

### **Q: How much do you think the results are due to adherence? If adherence were better with ICS, would the findings be different?**

**A:** We are hitting ceiling effects in both populations. I am sure that if the ICS were taken with the same adherence as LTRAs in this study, it would probably on average be a bit more efficacious. That is what we have seen in the moderate asthma trials. If you think that most people in this study had a 15% decrement in lung function, an LTRA increases lung function by about 10%, that is, enough to bring most people under control.

### **Q: How many patients in each group required a change in therapy?**

**A:** I can't answer that question properly. About half the patients in each group had a change in therapy, though the reasons why are hard to ascertain from the study design. Sometimes, there was a locum physician in the office who said that they weren't going to prescribe a LTRA because that is not what the guidelines say. Probably about one in six patients had a change because it was clinically necessary.



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