# On-demand use of $\beta_2$-agonists led to better asthma control than did regular use in moderate-to-severe asthma

## QUESTION

In patients with moderate-to-severe asthma, is on-demand use of $\beta_2$-agonists as effective and safe as regular use?

## DESIGN

Randomized {allocation concealed*}†, blinded (outcome assessors and statistician),* crossover trial with 24-week follow-up for each treatment condition.

## SETTING

Outpatient clinic at Düsseldorf University Medical Center in Germany.

## PATIENTS

80 patients (mean age 48 y, 74% women) with moderate-to-severe asthma on regularly scheduled $\beta_2$-agonist (minimum daily intake of 6 puffs) and inhaled corticosteroids (ICS) for $\geq$ 2 years. Exclusion criteria were nonrespiratory illnesses or pregnancy. 73 patients (91%) completed the study.

## INTERVENTION

Two 24-week periods in which patients were allocated to on-demand inhalation (salbutamol or fenoterol) or regular use of $\beta_2$-agonist (2 inhalations 4 times daily plus salbutamol or fenoterol on demand) and crossed over to the other regimen after completion of the first period. All patients used constant doses of inhaled corticosteroids.

## MAIN OUTCOME MEASURES

The primary outcome measure was asthmatic episodes defined as an asthma attack that could only be treated by $\beta_2$-agonist inhalation. Secondary outcome measures were safety and consequences of reducing $\beta_2$-agonist.

## MAIN RESULTS

The treatment groups did not differ for asthmatic episodes and exacerbations (66% of symptom-free days in on-demand–treated patients vs 62% in regularly treated patients). However, daytime use of $\beta_2$-agonist was lower in on-demand–treated patients than in regularly treated patients (3.3 vs 7.9 puffs/d, $P < 0.001$). Patients in the on-demand group also had fewer days of prednisone use for asthma exacerbations than did those in the regular-use group (mean of 44 vs 52 d, $P = 0.001$). $FEV_1$, FVC, and midexpiratory flow rate at 25% to 75% of FVC were all higher in patients in the on-demand group than in those in the regular-use group (2.53 vs 2.42 L, $P = 0.008$; 3.66 vs 3.54 L, $P = 0.003$; 1.85 vs 1.74 $Ls^{-1}$, $P = 0.02$, respectively). The groups did not differ for immunoglobulin E, peripheral blood eosinophils, or other blood chemistry values or for changes in unwanted effects in concomitant medications.

## CONCLUSION

In patients with moderate-to-severe asthma, on-demand $\beta_2$-agonist inhalation led to better asthma control than did regular $\beta_2$-agonist inhalation.

## COMMENTARY

The β-agonist controversy revolves around the question of whether sustained and regular use of inhaled β-adrenergic agents results in decreased bronchodilator responsiveness over time and has been addressed in epidemiologic and controlled prospective trials (1, 2). Most recently, the Asthma Clinical Research Network study found no difference between patients with mild asthma who were randomly allocated to regularly scheduled or as-needed albuterol over a 16-week period (3). Richter and colleagues compared the effects of short-acting inhaled bronchodilators over 24 weeks in a more symptomatic patient population.

Several design and methodologic issues deserve comment. First, although patients were required to have used ICS for a minimum of 2 years before enrollment, no protocol was provided for titrating to a minimum effective dose of ICS before randomization. This would have increased the potential for patients to destabilize during the study and thereby show a difference between treatment groups. Second, medication compliance was not directly assessed but was extrapolated from adherence to scheduled clinic visits and completeness of diary cards. Third, the crossover design did not include a wash-out period between treatments, which is inappropriate if the hypothesis being tested is that extended exposure to β-agonists results in down-regulation of the receptor. Finally, patients in this study were not blinded. For such a disease as asthma with subjective and effort-dependent end points, this is clearly suboptimal.

What should the practitioner take from this study? At the least, this study and others show that regular use of short-acting inhaled β-agonists do not confer added benefit over those used on an as-needed basis. The addition or optimization of ICS therapy with subsequent addition of other therapies as required is a preferable management strategy (4).

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### References

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