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A Nonsteroidal Glucocorticoid Receptor Agonist Inhibits Allergen-induced Late Asthmatic Responses

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Abstract

Rationale: Effective antiinflammatory therapies are needed for the treatment of asthma, but preferably without the systemic adverse effects of glucocorticosteroids.

Objectives: We evaluated the effect of an inhaled nonsteroidal glucocorticoid receptor agonist, AZD5423, on allergen-induced responses.

Methods: Twenty subjects with mild allergic asthma were randomized to receive 7 days of treatment with nebulized AZD5423 (75 or 300 µg) once daily, budesonide 200 µg twice daily via Turbuhaler, or placebo in a double-blind, four-period, crossover design study. Allergen challenge was performed on Day 6.

Measurements and Main Results: FEV₁ was measured repeatedly for 7 hours after allergen challenge for early and late asthmatic responses. Sputum inflammatory cells was measured before and at 7 and 24 hours after allergen challenge, and methacholine airway responsiveness was measured before and 24 hours after allergen challenge. AZD5423 significantly attenuated the fall in FEV₁ during

the late asthmatic response (both doses led to an 8.7% fall) versus placebo (14% fall) ($P < 0.05$) with no effect of budesonide (12.5% fall) versus placebo ($P > 0.05$). There was no effect on the fall in FEV₁ during early asthmatic response. AZD5423 300 and 75 µg significantly attenuated allergen-induced sputum eosinophilia by 63 and 61% at 7 hours, respectively, and by 46 and 34% at 24 hours after allergen challenge, respectively, versus placebo (all $P < 0.05$). Budesonide did not reduce allergen-induced sputum eosinophilia versus placebo. AZD5423 at 300 µg significantly attenuated allergen-induced airway hyperresponsiveness at 24 hours after allergen challenge versus placebo ($P < 0.05$). Both doses of AZD5423 were well tolerated.

Conclusions: Seven-day treatment with inhalation of the nonsteroidal glucocorticoid receptor agonist AZD5423 effectively reduced allergen-induced responses in subjects with mild allergic asthma. Clinical trial registered with www.clinicaltrials.gov (NCT01225549).

Keywords: airway hyperresponsiveness; allergen inhalation challenge; AZD5423; late asthmatic response; sputum eosinophils

Glucocorticosteroids (GCSs) are clinically effective antiinflammatory therapies widely used for the treatment of inflammatory diseases. Inhaled corticosteroids (ICSs) are recommended as a first-line intervention for

the treatment of asthma, and early intervention can provide effective asthma control and reduce the risk of lung function decline.

The biological effects of GCSs are mediated through binding to the

intracellular glucocorticoid receptor (GR), causing dimerization and translocation to the nucleus. The antiinflammatory effects of GR agonists are mediated through transrepression and transactivation of

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At a Glance Commentary

Scientific Knowledge on the

Subject: Glucocorticosteroids are among the most effective therapies for the treatment of inflammatory diseases; however, they are associated with systemic adverse effects.

What This Study Adds to the

Field: A nonsteroidal glucocorticoid receptor agonist, AZD5423, was tested for efficacy and safety in a human model of asthma. Treatment with inhaled AZD5423 demonstrated significant inhibition of allergen-induced airway responses in subjects with mild allergic asthma. In this study, AZD5423 was effective, safe, and well tolerated.

genes (1), regulating immunosuppressive and antiinflammatory activities (2). However, GR agonists also have the potential to cause systemic adverse effects by affecting the hypothalamic–pituitary–adrenal axis and reducing bone mineral density and growth velocity (3). Side effects caused by GR agonists are mediated by the induction of genes encoding enzymes that are active in metabolic pathways and also possibly by a functional negative glucocorticoid response element in the promoter region (4).

AZD5423 is an inhaled, nonsteroidal, potent, and selective modulator of GR among the nuclear hormone receptors. It modulates the GR in a novel way. The receptor–ligand binding profile of this modulator of GR shows a differential binding mode compared with reference GCSs. AZD5423 could confer the beneficial antiinflammatory effects of a conventional GR agonist, and it has been designed to reduce the adverse systemic effects of GR activation while promoting the suppression of proinflammatory proteins. The aim of this novel GR agonist is to provide an improved therapeutic window by reducing the incidence of adverse drug effects and maintaining or even improving antiinflammatory effects. AZD5423 shows antiinflammatory effects with lesser systemic unwanted effects as shown by investigators who used a rat model of pulmonary inflammation (5). Rats challenged intratracheally with Sephadex

beads (GE Healthcare Life Sciences, Pittsburgh, PA) developed an eosinophil-driven lung inflammation. AZD5423 administered via dry-powder inhalation demonstrated a dose-dependent inhibition of lung inflammation. In the same rat model, thymic involution (thymus weight decrease compared with vehicle-treated animals) is used to quantify systemic GR agonism. These data were then used to determine the ratio for AZD5423 for systemic effects (ED₂₅ thymus involution) and potency (ED₅₀ lung edema). AZD5423 showed an improved ratio for AZD5423, of approximately fivefold, as compared with a reference ICS, budesonide. Further, AZD5423 appears to interact preferentially with certain cofactors, including nuclear receptor-interacting protein 1, nuclear receptor coactivator 1, and peroxisome proliferator-activated receptor γ , coactivator 1 α (6, 7). A different coactivator profile generated by this novel GR ligand could lead to altered gene expression profiles and an altered profile *in vivo* (8).

The purpose of this study was to investigate the efficacy of AZD5423 in asthma using the inhaled allergen challenge model in subjects with mild allergic asthma. Inhaled allergen challenges induce the characteristic features of asthma, including bronchoconstriction, airway hyperresponsiveness (AHR) to direct stimuli, and airway inflammation (9). Furthermore, this model has been shown to have excellent negative predictive value and a moderate positive predictive value for assessing the efficacy of new compounds for the clinical treatment of asthma (10). Evaluating AZD5423 in this model may also provide information on how nonsteroidal agonists of GR can influence the pathophysiology of allergen-mediated immune responses and inflammation. Some of the results of this study have been reported previously in the form of an abstract (11).

Methods

Subjects

Twenty-seven subjects with mild, atopic, stable asthma and a history of episodic wheeze and shortness of breath were recruited for the study (NCT01225549). The subjects were nonsmokers, 18 to 60 years old, with a FEV₁ $\geq$ 70% of predicted, provocative concentration of methacholine

causing a 20% fall in FEV₁ (PC₂₀) $\leq$ 16 mg/ml, allergic to common aeroallergens, and documented asthmatic early- and late-phase responses after allergen inhalation (Table 1; see online supplement).

Study Design

In this study, we used a double-blind, double-dummy, randomized, placebo-controlled, multicenter, four-way crossover design consisting of 31 visits over the course of 16 to 21 weeks (Figure 1) to evaluate efficacy of two doses of AZD5423 on allergen-induced responses. Budesonide was used as an active control. The primary outcome was the change in maximum percentage fall in FEV₁ during the late asthmatic responses (LARs). The secondary outcomes were changes in maximum percentage fall in FEV₁ during the early asthmatic responses (EARs), AHR, and sputum eosinophils. The study was approved by the local research ethics boards at each participating center, and signed informed consent forms were obtained from all study participants before any study-related procedures took place.

Screening Period

The subjects underwent eligibility assessments, including measurement of airway responsiveness, allergy skin prick tests, blood chemistry and hematology, and airway responses to inhaled allergen. Randomized subjects had at least one positive aeroallergen sensitivity, and they developed EARs of at least 20% within 3 hours after allergen challenge and LARs of at least 15% between 3 and 7 hours after allergen challenge (Table 1).

Treatment Period

Each of the four treatment periods consisted of 7 days of treatment with inhaled budesonide 200 μ g twice daily via Turbuhaler dry-powder inhaler (AstraZeneca, Wilmington, DE), AZD5423 300 μ g once daily, AZD5423 75 μ g once daily, or placebo once daily via the I-neb AAD adaptive aerosol delivery system (Philips Respirics, Murrysville, PA) (see online supplement).

Methacholine Inhalation Test

Methacholine challenge was performed using tidal breathing from a Wright nebulizer (12) (see online supplement). The test was terminated when a fall in FEV₁ of at least 20% of the lowest postsaline value occurred.

Table 1. Subject Demographics

Subject	Age (yr)	Sex	FEV ₁ % Predicted	Methacholine PC ₂₀ (mg/ml)	Allergen Inhaled	Highest Allergen Titration Inhaled	Screening EAR	Screening LAR	Drug Sequence
1	23	M	81.6	1.36	<i>Der F</i>	1:128	23.7	29.6	CAPB
2	26	M	82.5	2.78	<i>Der P</i>	1:128	31.5	18.6	BPCA
3	32	F	88.4	2.41	Grass	1:32	31.7	18.1	PBAC
4	27	F	88.3	0.23	Grass	1:4,096	15.6	19.3	APBC
5	28	M	77.4	0.31	Grass	1:1,024	38.3	26.3	CBPA
6	25	F	86.5	0.34	<i>Der F</i>	1:256	43.2	45.3	APBC
7	31	F	106.0	0.62	Grass	1:128	34.7	39.5	PCAB
8	27	F	84.1	0.32	Horse	1:512	42.5	12.0 [†]	BACP
9	20	M	73.9	1.17	<i>Der P</i>	1:512	33.5	23.5	CBPA
10	23	F	92.6	0.90	<i>Der P</i>	1:8	30.4	24.1	APBC
11	60	M	99.5	9.71	Cat	1:256	29.3	24.6	PCAB
12	31	M	85.6	0.66	<i>Alternaria</i>	1:2	48.7	32.1	BACP
13	18	M	84.4	0.08	Cat	1:128	25.4	45.9	BACP
14	29	M	115.9	12.86	<i>Der F</i>	1:8	35.0	26.6	CBPA
15	25	M	104.8	2.64	Ragweed	1:32	38.1	21.2	PCAB
16	50	M	103.7	10.08	<i>Der P</i>	1:64	39.3	20.4	ACBP
17	21	F	97.8	8.80	Ragweed	1:4	55.6	33.6	CBAP
18	21	M	116.9	14.55	<i>Der P</i>	1:16	36.1	17.9	PCAB
19	22	F	85.1	0.09	Cat	1:16	31.3	15.8	APBC
20	52	F	87.8	4.32	<i>Der P</i>	1:256	32.7	17.0	PCBA
Results	29.6 (11.3)	11 M/9 F	92.1 (12.1)	1.35 (0.08–14.55)*			34.8 (8.8)	25.6 (9.5)	10 sequences

Definition of abbreviations: A = AZD5423 75 µg; B = AZD5423 300 µg; C = budesonide; *Der P* = *Dermatophagoides pteronyssinus*; *Der F* = *Dermatophagoides farinae*; EAR = early asthmatic response (largest percentage fall in FEV₁ measured 0–3 hours after allergen challenge); LAR = late asthmatic response (largest percentage fall in FEV₁ measured 3–7 hours after allergen challenge); P = placebo; PC₂₀ = provocative concentration resulting in 20% fall in FEV₁.

Data are shown as mean (SD).

*Geometric mean (range).

[†]One subject did not reach 15% fall in FEV₁ during LAR.

Allergen Inhalation Challenge

Allergen challenge was performed as described previously (13, 14) (see online supplement). This same dose of allergen was administered at each of the treatment time points.

Sputum Analysis

Sputum was induced and processed using a variation of the method described previously (15) (see online supplement). Cell differential counting was performed at one investigation site.

Statistical Analysis

A sample size of 20 randomized patients was considered sufficient to achieve 90% power for a two-sided test at 5% to detect a 50% mean attenuation in LAR versus placebo. The prespecified comparisons of LAR, EAR, methacholine PC₂₀, and sputum eosinophils were based on analysis of covariance with patient, treatment, and period as factors and pretreatment value as a covariate (see online supplement). SAS software was used for calculations (SAS Institute, Cary, NC). Methacholine PC₂₀ and sputum cell

numbers were log-transformed prior to analyses. A *P* value < 0.05 was considered to be statistically significant.

Results

The subjects were enrolled between November 2010 and December 2011 at four

academic centers in the AllerGen Canadian Clinical Investigator Collaborative. There were no imbalances in patient allocation among the four treatment periods. Of the 27 subjects enrolled in the study, 20 met the inclusion criteria and were randomized to treatment. Two of the 20 randomized subjects did not complete the study, owing to a need to receive disallowed medications.

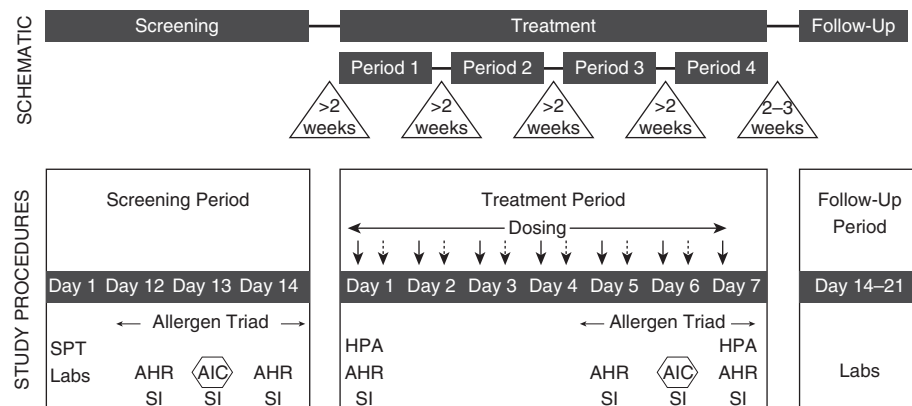


Figure 1. Study design. AHR = airway hyperresponsiveness measured by methacholine PC₂₀; AIC = allergen inhalation challenge; HPA = hypothalamic–pituitary–adrenal axis measurements; Labs = safety blood and urinalyses; SI = sputum induction; SPT = skin prick test.

One subject received inhaled and oral steroids for an exacerbation of asthma during the washout period after placebo treatment, and one subject was treated with clarithromycin for bronchitis during the washout period after budesonide treatment. One subject had to discontinue placebo treatment because of a need to receive a disallowed medication (clarithromycin) for an adverse event (AE), and thus allergen challenge was not conducted during this treatment period; however, this subject remained in the study.

Allergen-induced Asthmatic Responses

The mean maximum percentage falls in FEV₁ during the EARs and LARs measured during the screening period were -34.8% (SEM, 2.0) and -25.6% (SEM, 2.2), respectively (Table 1).

After treatment with AZD5423 300 and 75 μg , the maximum percentage decreases in FEV₁ during the LAR were -8.4% (SEM, 1.6) and -8.7% (SEM, 1.7) respectively, compared with placebo (-13.7% [SEM, 2.3]) ($P < 0.05$) (Figure 2). The mean maximum percentage fall in FEV₁ during the LAR was -12.1% (SEM, 2.3) for budesonide (see online supplement).

The geometric mean ratio of LAR compared with placebo was 1.06 (95% confidence interval [CI], 1.00–1.12) for AZD5423 300 μg ($P = 0.034$) and 1.06 (95% CI, 1.00–1.12) for AZD5423 75 μg ($P = 0.033$). The geometric mean ratio of LAR compared with placebo was 1.02 (95% CI, 0.96–1.08) for budesonide ($P = 0.56$). Compared with budesonide, the geometric mean ratio of LAR was 1.04 (95% CI, 0.99–1.10) for AZD5423 300 μg ($P = 0.12$) and 1.04 (95% CI, 0.99–1.10) for AZD5423 75 μg ($P = 0.13$). Similar results were found when LAR data were expressed as the area under the receiver operating characteristic curve. There were no significant differences in EAR in any of the four treatment periods ($P > 0.53$).

Airway Hyperresponsiveness

The baseline methacholine PC₂₀ predose at Day 1 was similar for all treatment periods (Figure 3). Compared with Day 1 predose, the methacholine PC₂₀ after 5 days treatment increased by 0.5, 0.09, 0.39, and 0.29 doubling doses with AZD5423 75 μg , AZD5423 300 μg , budesonide, and placebo,

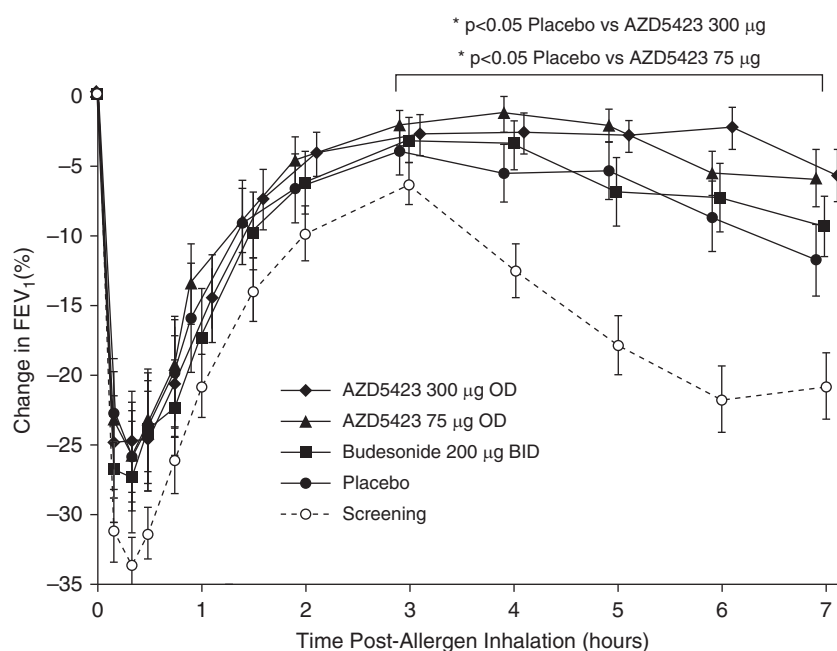


Figure 2. The effect of inhaled treatment on mean ($\pm$ SEM) percentage change in FEV₁ during allergen-induced early- and late-phase asthmatic responses. * $P < 0.05$ for maximum percentage fall in FEV₁ versus placebo.

respectively; however, the increase in methacholine PC₂₀ was not significantly different among any of the active treatments compared with placebo ($P > 0.05$).

Compared with the Day 5 preallergen PC₂₀ value, the methacholine PC₂₀ at Day 7 (24 hours after allergen challenge) fell by 0.05, 0.24, 0.31, and 0.43 doubling

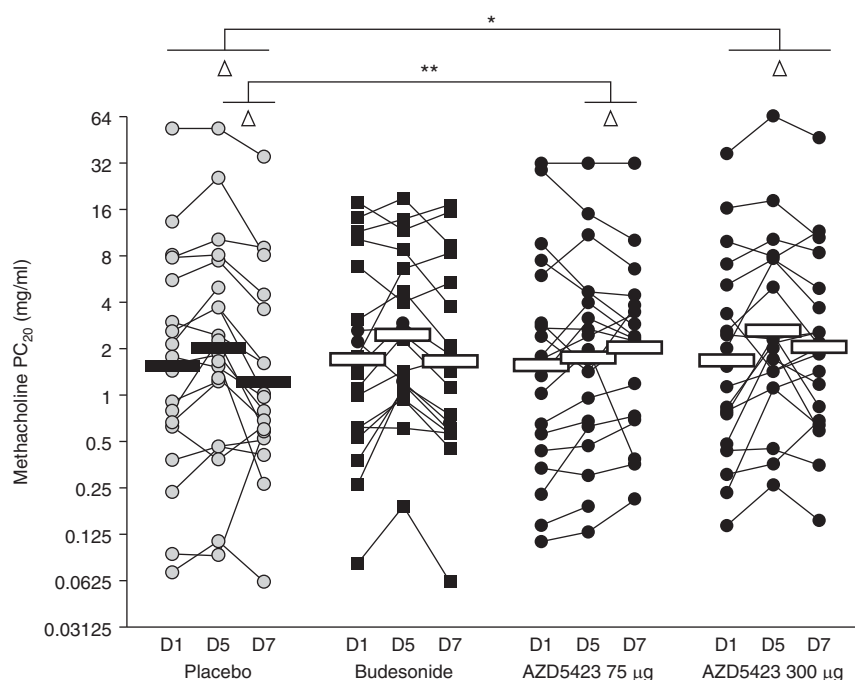


Figure 3. The effect of inhaled treatment on geometric mean provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀). * $P < 0.05$ for change in PC₂₀ from Day 1 at the beginning of treatment to Day 7 at the end of treatment, versus placebo. ** $P < 0.05$ for change in PC₂₀ from Day 5 before allergen challenge to Day 7 after allergen challenge, versus placebo.

doses with AZD5423 75 μg , AZD5423 300 μg , budesonide, and placebo, respectively. Compared with placebo, AZD5423 75 μg significantly inhibited the allergen-induced fall in PC_{20} ($P = 0.012$). The PC_{20} measured after allergen challenge after AZD5423 300 μg treatment inhibited the allergen-induced fall in PC_{20} by 34% compared with placebo, but did not achieve statistical significance ($P = 0.13$). From Day 1 to Day 7, AHR improved significantly with AZD5423 300 μg treatment compared with placebo ($P = 0.016$) (Figure 3).

Sputum Cells

Complete sputum data were available from 10 subjects during screening and from more than 14 subjects during the treatment periods. The baseline sputum eosinophils predose at Day 1 were similar for all treatment periods, and there was no significant change in the level at Day 5 after any of the treatment periods compared with placebo ($P > 0.05$). Allergen inhalation increased sputum eosinophils from 1.7% (SEM, 0.8) before allergen challenge to 22.7% (SEM, 6.4) and 19.6% (SEM, 5.1) at 7 and 24 hours, respectively, after allergen challenge during the screening period, and from 1.8% (SEM, 0.9) at Day 5 (before allergen challenge) to 13.2% (SEM, 3.6) at Day 6 (7 hours after allergen challenge) and 7.1% (SEM, 1.6) at Day 7 (24 hours after allergen challenge) in the placebo arm (Figure 4). Compared with placebo, the percentage of sputum eosinophils measured 7 and 24 hours after allergen challenge was significantly lower after treatment with AZD5423 75 μg ($P = 0.002$ and $P = 0.02$, respectively) and with AZD5423 300 μg ($P = 0.002$ and $P = 0.005$, respectively). Compared with budesonide, the percentage of sputum eosinophils measured 24 hours after allergen challenge was significantly lower after treatment with AZD5423 300 μg ($P = 0.04$). In line with the findings for percentage of the sputum eosinophils, treatment with AZD5423 300 and 75 μg was associated with lower absolute count of sputum eosinophils at 7 and 24 hours after allergen challenge compared with placebo (Figure 4).

Hypothalamic–Pituitary–Adrenal Axis

Treatment with AZD5423 and budesonide did not change the serum concentrations of dehydroepiandrosterone sulfate or osteocalcin as compared with placebo ($P > 0.05$).

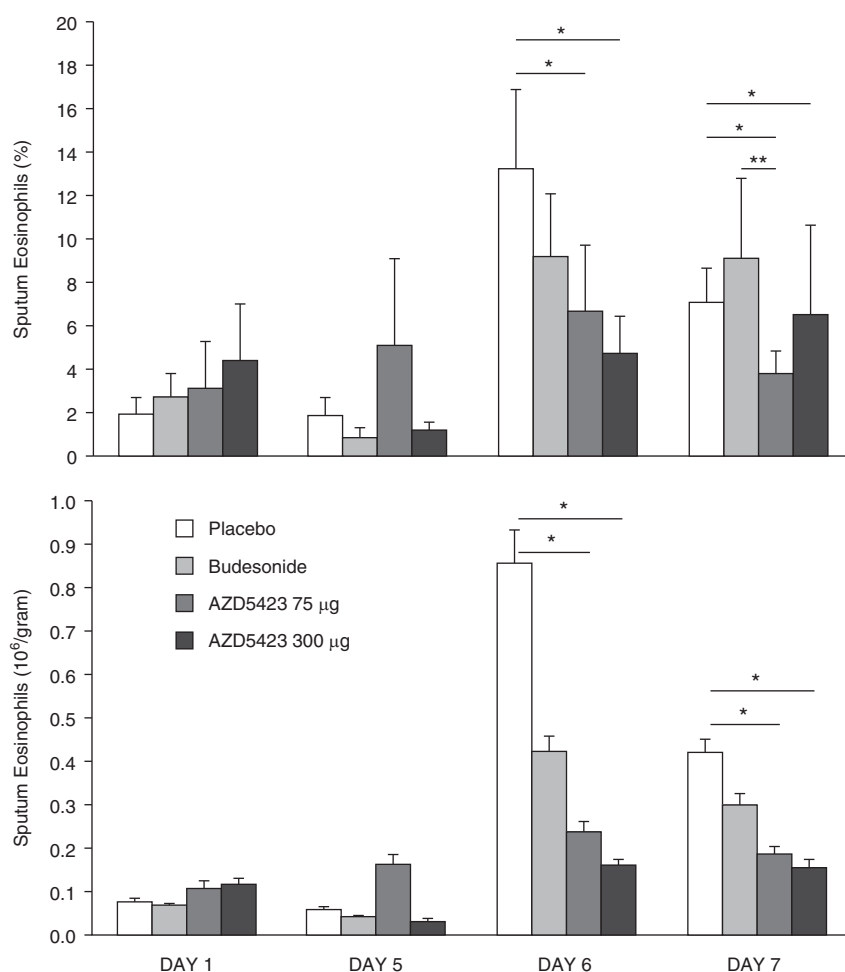


Figure 4. The effect of inhaled treatment on mean ($\pm$ SEM) percentage sputum eosinophils (top panel) and number of eosinophils per gram of sputum (lower panel). * $P < 0.05$ versus placebo. ** $P < 0.05$ versus budesonide.

Safety

There were no deaths, serious AEs, or discontinuation of study drug due to AEs. The most commonly reported AEs during each treatment period were nasal congestion and oropharyngeal pain (two subjects each) during placebo treatment; bronchitis (two subjects) during budesonide treatment; headache and oropharyngeal pain (two subjects each) during AZD5423 75 μg treatment; and drug eruption after treatment for *Helicobacter pylori* infection (one subject), which occurred during washout from AZD5423 300 μg . Causally related AEs, as judged by the investigators, were dry mouth, dysphagia, and oropharyngeal pain. One AE of oropharyngeal pain reported during placebo treatment was of severe intensity. No clinically important differences were seen between any of the treatment periods

with regard to the total number of AEs. The lowest frequency of AEs was reported during the 300- μg AZD5423 treatment period.

Discussion

This is the first study to assess the efficacy of a nonsteroidal glucocorticoid receptor agonist, AZD5423, in a randomized crossover trial using a human model of allergic asthma. Seven days of once-daily inhaled AZD5423 300 μg significantly inhibited allergen-induced LARs compared with placebo in subjects with mild allergic asthma. This observation was further validated by inhibition of AHR and sputum eosinophilia. Inhaled AZD5423 75 μg attenuated the allergen-induced LARs and the increase in sputum eosinophils, but not

the allergen-induced AHR. Neither dose of AZD5423 had an effect on the EAR, other sputum inflammatory cells such as neutrophils and lymphocytes, or circulating leukocytes ($P > 0.05$).

Surprisingly, the effect of budesonide 200 μg twice daily did not achieve statistical significance over placebo treatment. Attenuation of LAR by budesonide and other ICSs has been reported in most studies (16–18), but occasionally ICS treatment fails to attenuate the LAR (19). When compared with the LAR during the screening period, it is evident that the LAR with placebo treatment in our present study was smaller (Figure 3), thus providing less room for therapeutic improvement. Despite this large placebo effect, both doses of AZD5423 attenuated most of the allergen-induced airway responses.

A reduction of the LAR with placebo treatment could have been caused by a variety of factors. It is possible that the length of the washout period was not sufficient to prevent drug carryover. The washout period rarely exceeded 30 days. The mean durations (ranges) before placebo, budesonide, AZD5423 75 μg , and AZD5423 300 μg were 21.9 days (13–29 days), 21.6 days (13–36 days), 19.7 days (14–30 days), and 21.9 days (14–51 days), respectively. In our study's four-way crossover design with only 20 subjects, it was not feasible to confirm period effects with any of the treatment arms; however, dividing subjects into groups of those who received treatment with placebo first or AZD5423 first provided data consistent with carryover of AZD5423 into the placebo and budesonide treatment periods (see online supplement). Variability was also generated by unpaired data from subjects who did not undergo all allergen challenges: one subject during placebo treatment, one subject during AZD5423 75 μg treatment, and one subject during budesonide and AZD5423 300 μg treatment. In addition, unmatched allergen

concentrations occurred five times when lower doses were administered during inhalation challenges (two with budesonide, two with AZD5423 75 μg , and one with placebo). It is unlikely that these deviations could account for the large placebo effect observed. Although improvement in AHR could affect the EAR and LAR, there is no evidence that AHR systematically increased in subjects compared with baseline during screening (Table 1, Figure 3).

Glucocorticoids act on the GR to reduce inflammatory gene expression, which explains the clinical effectiveness of ICSs in mild to moderate asthma. There is a clinical need to identify improved antiinflammatory GR ligands with the potential to be used as a well-tolerated and efficacious antiinflammatory therapy. AZD5423 is a highly potent and selective inhaled nonsteroidal GR agonist. Receptor–ligand binding studies have indicated differential binding of this ligand to the GR compared with reference GCSs and different cofactor affinity profiles (7). Modulating the receptor in a novel way by extending into a volume that natural ligands do not enter may produce antiinflammatory effects that are at least as effective, if not greater. The existence of GR-inducible genes that could be induced to a greater extent than by conventional GCSs may provide additional therapeutic benefits (8, 20). Furthermore, the favorable lung pharmacokinetic properties and high clearance of this inhaled molecule may result in low systemic exposure and fewer systemic unwanted effects, of lesser intensity, from GR agonism. Hence, AZD5423 has been designed to improve selectivity for GR over other NHRs and to reduce the adverse systemic effects of GR activation while maintaining or improving effects on suppression of proinflammatory proteins. The pharmacokinetics of inhaled AZD5423, both after single doses and at steady state, are characterized by rapid

absorption from the lung and fast overall elimination. In previous studies, there was no consistent deviation from dose-proportional pharmacokinetics of inhaled AZD5423; the results did not indicate time-dependent pharmacokinetics; and the accumulation ratio was low (≤ 1.5). Clearance indicates that AZD5423 is a high hepatic extraction drug. The major contribution to the systemic availability of AZD5423 comes from the lung, because the oral bioavailability of AZD5423 was low (approximately 3%).

Because of the pleiotropic effects of the glucocorticoid receptor on multiple signaling pathways, treatment with ICSs can cause systemic side effects (21–23). Treatment with budesonide and both doses of the nonsteroidal glucocorticoid receptor agonist AZD5423 were all found to be safe and well tolerated. There were no significant changes in serum concentrations of dehydroepiandrosterone sulfate or osteocalcin in patients treated with AZD5423 or budesonide as compared with placebo. Furthermore, there were no clinically relevant findings in laboratory evaluations, vital signs, electrocardiograms, or spirometry tests. However, the study treatments were too short to properly evaluate the systemic effects that are characteristic of GR agonists.

This study demonstrates that the inhaled nonsteroidal GR agonist AZD5423 administered once daily at doses of 75 and 300 μg attenuates allergen-induced responses in subjects with allergic asthma. Furthermore, AZD5423 is at least as efficacious as the ICS budesonide, which was administered at a dose of 200 μg twice daily. The duration of action of AZD5423 is not known and requires further evaluation to determine the onset and offset, as well as minimum dosing requirements, for control of asthma. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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