

Treatment preferences of adolescent patients with asthma

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The study objective was to assess whether asthmatic adolescents who were regular users of inhaled corticosteroids preferred treatment with zafirlukast tablets or inhaled beclomethasone dipropionate (BDP), and, secondarily, to assess adolescents' inhaler technique and their opinions about treatment. An open-label, randomized, two-period, crossover study was conducted in 18 centres (primary care to specialist asthma centres) in South Africa, the UK, Finland and the Czech Republic. One hundred and thirty-two adolescents aged 12–17 years with asthma for at least 1 year and $FEV_1 \geq 75\%$ of predicted, treated with short-acting bronchodilators and inhaled corticosteroids, entered the study. Patients received oral zafirlukast tablets (AccolateTM) 20 mg b.i.d. or inhaled BDP 100 or 200 μ g b.i.d., provided by a standard pressurized metered-dose inhaler, for 4 weeks each. One questionnaire was used to determine preference (the primary outcome measure) and a second questionnaire was used to determine patients' likes and dislikes of treatment.

Investigators also scored inhaler technique. Of 113 adolescents, 79 (70%) preferred zafirlukast compared with 31 (27%) who preferred the BDP inhaler ($p < 0.001$); three had no preference. Only 35 (29%) of 122 adolescents could use their inhaler correctly at study entry. Seventy-six patients (65%) rated zafirlukast tablets as 'very easy' to use, compared with 35 (30%) for the BDP inhaler. Both treatments were well-tolerated. This study shows that asthmatic adolescents prefer zafirlukast tablets by a ratio of 2.6:1 over inhaled BDP, and these results may have implications for improving adolescent patient compliance with asthma therapy.

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Asthma is a common disease of adolescence, and its prevalence in this age group is increasing (1,2), notwithstanding continuing evidence of underdiagnosis of asthma among adolescents (3,4). Although there are effective therapies for asthma, it continues to be a significant contributor to morbidity and mortality among adolescents. In the UK between 1990 and 1992, mortality rates were three times greater among patients 10–14 years of age and six times greater among those 15–19 years of age than among children 5–9 years of age (5). Many patients die because their asthma is poorly controlled despite the prescription of effective medications, while continuing high levels of morbidity account for 10.1 million days per year missed from school because of asthma in the USA alone (6). These data suggest

that the management of asthma in adolescents is suboptimal and that there is a need to address the issues of underdiagnosis and poor patient compliance with treatment in this age group (7).

Most asthma therapies are administered by inhalation and require multiple doses. Good technique is important for accurate dosing, and regular instruction is required to ensure the correct use of inhalers (8). Noncompliance and misreporting of inhaled steroid and β_2 -agonist dosing by adolescents and their parents have previously been linked with asthma exacerbations (9). In one study, compliance with inhaled corticosteroids among adolescents was only 30% compared with 57% for adults (10).

Compliance with oral medications is greater than with inhaled medications in both adoles-

cents and adults (10). The use of a safe and effective orally administered asthma therapy has great potential in improving compliance in adolescents.

Orally administered leukotriene-receptor antagonists have been shown to reduce asthma worsening in children, adolescents and adults with chronic asthma, and to reduce asthma symptoms and improve lung function and quality of life compared with placebo (11–15). In clinical trials in patients 12 years of age and older, zafirlukast 20 mg b.i.d. had a safety profile that was clinically indistinguishable from placebo (11,15).

The aim of this study was to assess whether asthmatic adolescents who were regular users of inhaled corticosteroids preferred treatment with oral zafirlukast or inhaled beclomethasone dipropionate (BDP) and to assess their opinions about these treatments. The study also investigated how well adolescents used their inhalers.

Subjects and methods

Subjects

Adolescents 12–17 years of age with a confirmed diagnosis of asthma of at least 1 year's duration and a forced expiratory volume in 1 s (FEV_1) $\geq$ 75% of the predicted value were recruited to the study. To qualify, their asthma had to have been stable for three or more months before starting the study. At entry, patients were treated with a short-acting β_2 -agonist bronchodilator and either fluticasone (50, 100 or 125 μ g bd), BDP or budesonide (100 or 200 μ g bd) administered by a metered-dose or dry powder inhaler. Patients had not taken oral corticosteroids in the 3 months before the study and had not suffered from an upper or lower respiratory tract infection within the previous 6 weeks.

Setting

The study was conducted at 18 centres in South Africa, the UK, Finland and the Czech Republic. These centres normally treated adolescents with asthma and were in varied locations from poor socio-economic to more affluent areas, and the adolescents enrolled in the study were from a range of social backgrounds. The study centres ranged from primary care to hospitals and specialist allergy units.

The study was designed and monitored to standards complying with the ethical principles of Good Clinical Practice and in accordance with the Declaration of Helsinki. Institutional review board approval was obtained at all participating

centres. The study was explained to the adolescents and their adult representatives and informed consent was obtained from both adolescents and their legal adult representatives before any study procedures were started.

Study design

This was an open-label study with a two-period crossover design following a 1-week screening period. Adolescents entering the study stopped taking their normal corticosteroid medication and were randomized to receive either oral zafirlukast tablets (AccolateTM, AstraZen, Zeneca Pharmaceuticals, UK) 20 mg b.i.d. or inhaled BDP (BecotideTM, Glaxo-Wellcome Pharmaceuticals, UK) 100 or 200 μ g b.i.d. (depending on their corticosteroid dose at study entry), provided as standard pressurized metered-dose inhalers (pMDI or 'brown inhaler'), for 4 weeks. Patients were instructed to take medications according to the label instructions. At the end of the first treatment period, patients switched to the alternate treatment which they received for a further 4 weeks. There was no washout period as the study assessed the patients' treatment preferences rather than drug therapeutic efficacy. Throughout the study, the patients continued to use their usual short-acting β_2 -agonist bronchodilator by inhalation when required.

Preference and opinions of treatment

All patients completed a questionnaire on preference and ease of use at the completion of the study or when they withdrew from the second round of treatment. This questionnaire assessed the patients' overall treatment preference which was the primary study endpoint.

The following questions were asked:

- 'Which was easier to use, the Accolate tablets or the brown inhaler?';
- 'Which did you prefer, taking the Accolate tablets or using the brown inhaler?'.

Patients who did not proceed to the second round of treatment, patients who used additional disallowed asthma medication at entry or during the trial or had other major protocol deviations or violations, were excluded from the primary per-protocol analysis of preference but were included in an intention-to-treat analysis. A second questionnaire that was administered after each treatment period included questions about how easy the treatment was to use (very easy to very difficult) and patients' likes and dislikes and worries about the treatment they had just received. Respondents could indicate their

agreement with statements regarding likes and dislikes and list any additional reasons for liking or disliking treatments. The question regarding worries was open-ended.

Inhaler technique assessment

To ensure that all patients could use the inhaler correctly, the clinical investigators assessed the ability of patients to use placebo pMDIs before and after instruction. The scoring system was based on that used by Taylor and Tunstall (16) and the instruction was adapted from Dompeling et al. (8). Ten steps were assessed, but patients were considered to have 'good' technique if they completed five key steps correctly. These steps were to correctly remove the cap, tilt the head back, inspire and actuate the inhaler, and continue inhaling slowly and hold the breath for 10 s. Instruction was given and repeated until patients completed all five steps correctly.

Other assessments

Compliance with zafirlukast therapy was calculated at the end of the zafirlukast treatment period (week 5 or 9) by dividing the actual number of tablets taken by the number of tablets prescribed. Compliance with inhaler medication was not assessed.

Safety assessments included adverse events recorded by the investigator, medical histories and physical examinations, hematology and clinical chemistry measurements. Adverse events were defined as new medical conditions or a deterioration of pre-existing conditions; deterioration of asthma requiring treatment was also classified as an adverse event. All clinical laboratory tests were standardized and conducted at the same center. FEV₁ and peak expiratory flow (PEF) were measured at each clinic visit (every 2 weeks at the same time $\pm$ 2 h) to ensure that any deterioration of the patient's asthma could be identified and treated.

Statistical analysis

The primary endpoint, overall treatment preference, was analyzed using Mainland–Gart and Prescott's tests. The Mainland–Gart test is independent of randomization and uses only information from patients who expressed a preference for either therapy. Prescott's test investigates additional information that randomization provides and also uses data from adolescents who showed no preference for either the BDP inhaler or zafirlukast tablets. Odds ratios, 95% confidence intervals and

p values were calculated using each statistical method for the primary endpoint. No formal statistical analyses were performed on the secondary endpoints (the likes and dislikes questionnaire, ease of use, and inhaler technique), other descriptive analyses, or the subset descriptions of preference.

Results

Patient demographics

One hundred and thirty-two adolescents (66 males and 66 females) aged 12–17 years (mean $\pm$ SD, 14.0 years $\pm$ 1.64) were randomized into the study. Most of the adolescents were Caucasian (105 patients, 80%) with the other adolescents being of Afro-Caribbean ($n = 10$, 7.5%), Asian ($n = 6$, 4.5%) and mixed ($n = 11$, 8%) ethnic origins. On study entry, FEV₁ ranged from 75% to 173% of predicted (mean 97.3% $\pm$ 16.6%). The mean duration of asthma was 7.4 $\pm$ 4.1 years, and the mean duration of inhaled corticosteroid therapy was 23.1 $\pm$ 20.2 months. Previous use of pMDIs varied from 0% in Finland to 70% in the UK, 76% in the Czech Republic and 97% in South Africa.

Of the 132 adolescents randomized into the study, 113 completed the study according to the protocol and were included in the per-protocol analysis of the primary endpoint. Four patients withdrew from the study during the first round of treatment: three patients receiving zafirlukast (one patient lost to follow-up and two patients with worsening asthma) and one patient receiving BDP (worsening asthma). In the second round of treatment, three patients taking zafirlukast withdrew (one patient with worsening asthma, one patient lost to follow-up, and one patient with urinary tract and skin infections as well as an adverse event of moderate nausea and mild headaches). One patient who withdrew from the study, but completed all questionnaires, was included in the analysis, and two patients did not complete the preference questionnaire. An additional 11 patients completed the questionnaire but were excluded from the per-protocol analyses: eight patients started new asthma therapies other than the trial treatments during the study due to asthma worsenings (five while receiving zafirlukast, three while receiving BDP), two patients were taking disallowed oral asthma medications (ketotifen) and one patient had an upper respiratory tract infection during the screening period. Inhaler technique was assessed

before treatment in 122 patients and after treatment in 119 patients.

Preference

Seventy-nine of 113 patients (70%) preferred zafirlukast tablets, compared with 31 patients (27%) who preferred the BDP inhaler ($p < 0.001$ for both Mainland–Gart and Prescott's tests) (Fig. 1). Three patients had no preference. Zafirlukast was preferred to BDP with a Mainland–Gart test-based odds ratio of 5.63 and a 95% confidence interval of 2.66–11.92. Fifty-six per cent of the patients preferred the treatment taken first and 44% preferred the treatment taken last. However, 71% of patients who preferred their first treatment and 73% of patients who preferred their last treatment preferred zafirlukast. Therefore, it was reasonable to combine periods for the overall determination of preference. Among all patients who completed the preference questionnaire (intention-to-treat), 84 (68%) stated a preference for zafirlukast tablets compared with 35 (28%) who preferred the inhaler ($p < 0.001$ for both Mainland–Gart and Prescott's tests). Five patients had no preference.

Preference varied somewhat by the inhalation device used before trial entry, by inhaler technique, and by country. Among the 30 patients who were using dry powder inhalers before entering the study, 80% preferred zafirlukast tablets, 17% preferred the BDP inhaler and one patient

expressed no preference. Among those patients who were using pMDIs before trial entry, 66% preferred zafirlukast tablets, 31% preferred inhaled BDP and two patients (2%) had no preference (Fig. 1). Of 32 patients who were considered to have 'good' inhaler technique, 63% preferred zafirlukast tablets to inhaled BDP, 34% preferred the inhaled BDP, and one patient did not express a preference (Fig. 1). Zafirlukast tablets were preferred to inhaled BDP by 10 of 11 patients (91%) in Finland, 31 of 38 patients (82%) in the Czech Republic, 21 of 30 patients (70%) in the UK and 17 of 34 patients (50%) in South Africa.

Inhaler technique

Even though the patients participating in the study were experienced in using inhaled corticosteroids, only 35 of 122 patients (29%) could perform all the essential steps correctly before the study investigators gave them instruction. Among patients who were regular users of the pMDI inhaler at study entry, only 29 of 90 patients (32%) could perform all the essential steps correctly before instruction. After the first instruction session, 51 of 87 patients (59%) could use their inhalers correctly, but patients received repeated instruction and assessment until they all demonstrated 'good' inhaler technique. After 4 weeks' BDP treatment, 14% of patients were unable to perform all essential steps correctly. The essential steps that caused the patients the greatest problems were 'holding breath for 10 s' and 'tilting the head back at dosing'.

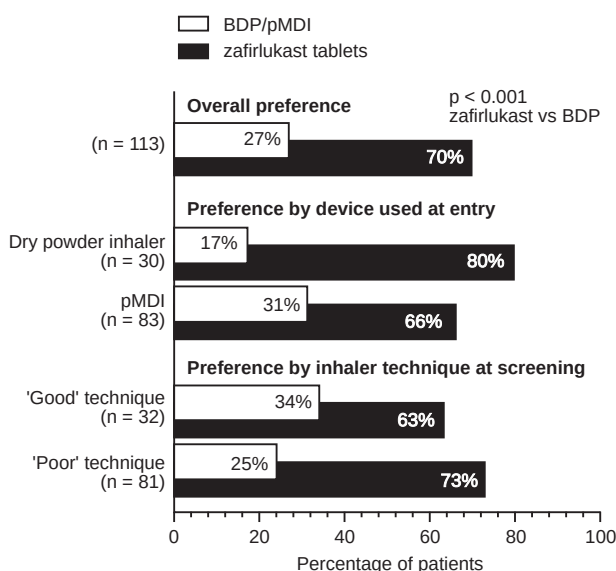


Fig. 1. Percentage of adolescents preferring beclomethasone dipropionate (BDP) by pressurized metered-dose inhaler (pMDI) or zafirlukast tablets. Preference is shown for all patients, for subsets divided by device used at study entry and by inhaler technique at screening (see text for definition of 'good' and 'poor' inhaler technique). *Statistical analyses were not performed on subset data.

Ease of use and likes and dislikes questionnaire

Eighty out of 113 patients (71%) preferred zafirlukast tablets for ease of use compared with 33 (29%) who preferred the BDP inhaler for ease of use. In the likes and dislikes questionnaire, 76 of 117 adolescents (65%) rated zafirlukast as 'very easy to use' and 35 (30%) said the inhaler was 'very easy to use' (Table 1).

The most common reasons adolescents liked their medication were that it was easy to take (88% for zafirlukast tablets versus 69% for inhaled BDP), they knew they had taken the drug correctly (74% versus 35%, respectively), it was quick to take (72% versus 69%, respectively) and they knew how much they had taken (72% versus 26%, respectively) (Table 2).

Seventy-eight per cent of adolescents indicated no dislikes for zafirlukast tablets compared with 28% for inhaled BDP (Table 2). The most common dislike about the zafirlukast tablets was adjusting dosing to meals (9%). The most common dislikes for the BDP inhaler were that

Table 1. Results of questionnaires given after zafirlukast or beclomethasone dipropionate (BDP) treatment asking how easy the treatment was to use (total n = 117)

Ease of use	Number (%) of patients	
	Zafirlukast tablets	BDP inhaler
Very easy	76 (65)	35 (30)
Easy	29 (25)	52 (44)
Neither easy nor difficult	6 (5)	23 (20)
Difficult	4 (3)	5 (4)
Very difficult	2 (2)	2 (2)

they did not know how much was left in the inhaler (54%) and it was difficult to check whether they had taken it (57%).

Overall, few patients expressed worries about either treatment (13% for zafirlukast tablets compared with 9% for inhaled BDP). The greatest worry about inhaled BDP was possible side-effects (six patients, 5%), and for zafirlukast tablets, it was the fear that their asthma might worsen (six patients, 5%).

Other assessments

Based on returned tablet count, compliance data for zafirlukast tablets were available for 129 patients. Ninety-five per cent (n = 122) of these patients showed compliance with therapy of greater than 85%.

Adverse events were reported in 44 of 131 patients (34%) when receiving zafirlukast and 41 of 129 patients (32%) when receiving inhaled BDP. None of the adverse events were considered serious. The most common adverse event during either treatment was pharyngitis, which occurred in 17 of 129 patients (13%) while they were receiving BDP and 12 of 131 patients (9%) while they were receiving zafirlukast. The event term describing worsening of asthma, allergic reactions and rhinitis was the next most common event, occurring in five of 129 patients (4%) during the inhaled BDP treatment periods and nine of 131 patients (7%) during the zafirlukast treatment periods. Otherwise adverse event profiles were similar between treatments. The percentage of patients experiencing infection was the same for each treatment (5%).

There were no clinically relevant changes in PEF or FEV₁ during either treatment period. Mean $\pm$ SD clinic PEF was 371 ± 78 l/min before the study, 364 ± 79 l/min after zafirlukast treatment and 373 ± 77 l/min after BDP treatment. Clinic FEV₁ averaged 2.81 ± 0.76 l before the study and was 2.74 ± 0.78 l after zafirlukast treatment and 2.86 ± 0.83 l after BDP treatment.

Table 2. Percentage of patients who agreed with statements on questionnaires regarding what they liked and disliked about treatment with zafirlukast or beclomethasone dipropionate (BDP)

	Zafirlukast (n = 117) %	Beclomethasone (n = 115) %
What do you like about taking this treatment?		
It is quick to take	72	69
I would remember to take it	52	45
I know how much I have taken	72	26
It is easy to take	88	69
I know I have taken the drug correctly	74	35
I do not have to be trained how to take it	62	21
I know how much is left	72	8
Nothing	6	19
Other*	9	6
What do you not like about taking this treatment?		
It is complicated to take	5	22
I sometimes found it difficult to take	6	22
It is difficult to check that I have taken it	2	57
I have to be trained how to take it	4	43
I could not tell how much was left	0	54
Nothing	78	28
Other statements*	16	12

*Patients could list any other likes or dislikes they could think of. The most common likes written in related to effectiveness (e.g. 'It made me feel better' or 'It works better'), which were listed by 4% of the patients for zafirlukast and 3% for beclomethasone. The most common dislike written in for zafirlukast was avoiding dosing with meals (9%), and the most common dislike written in for beclomethasone was the taste (3%).

Discussion

In this study, adolescents with asthma preferred zafirlukast tablets over the BDP inhaler by a ratio of 2.6:1 even though all the patients had previously been taking inhaled corticosteroids. Most patients were experienced in the use of inhaled corticosteroids and had been taking these medications for an average of about 2 years before enrolling in the study. This is the first preference study to show that adolescents prefer an oral medication for asthma over an inhaled treatment. This study, by showing a greater preference for the oral medication, supports the generally held, but previously unproven view, that an oral drug regimen might be better than an inhaled drug regimen in improving compliance or adherence with drug regimens (17).

Few similar studies have been conducted in children or adolescents to assess their preference for asthma therapies. In one study, children had no preference between two types of inhaler (18). A similar preference study to ours conducted with 167 adults with asthma showed a 2:1 preference for tablet zafirlukast compared with inhaled BDP (19). This two-fold preference for zafirlukast is less than that observed in our study with adolescents.

A study in adults and adolescents assessed compliance with oral theophylline and inhaled

corticosteroids using pharmacy claims data (10). In adults, mean compliance with theophylline was 79% of expected usage compared with 54% for inhaled corticosteroids, and, in adolescents 12–17 years of age, mean compliance with theophylline was 73% of expected usage compared with only 30% for inhaled corticosteroids (10). These results suggest that adolescents in particular are less likely to comply well with inhaled therapies compared with oral treatment. In our preference study, compliance was not compared. However, compliance with oral zafirlukast therapy was measured, and appeared to be high as assessed by returned tablet count. Usage was not available for the returned pMDIs. Use of an electronic monitoring device that recorded inhaler actuations would have allowed an assessment of compliance (20), but altering the inhaler presentation would have complicated the assessment of treatment preference and introduced a possible bias in favor of the tablet therapy.

The apparent greater preference for zafirlukast tablets in adolescents (2.6-fold preference in favor of zafirlukast tablets compared with a 2:1 preference by adults) may be a chance finding but also may be due in part to the greater concerns of adolescents and their parents about corticosteroid therapy (7,10,21), or the fact that oral treatment is less obtrusive, which would be important to adolescents who do not wish to appear different from their peers. However, only 5% of the regular corticosteroid users recruited to our study volunteered their concerns regarding possible side-effects of the inhaled corticosteroid and none indicated the obtrusiveness of the pMDI as a concern or dislike. The most common dislikes of the inhaler were responses to statements provided and included uncertainties over whether or not they had taken the inhaled treatment sufficiently. One could speculate that swallowing a pill provides feedback that the drug has been taken, and that feedback is not as obvious for an inhaled controller medication that does not give immediate benefits.

It is common to use self-reported data from questionnaires to assess preference (17). However, there is little research into the reliability and validity of measures used to assess preference and the appropriate design of such studies. Because preference cannot be determined until patients have completed all treatments, one treatment would have been completed 4 weeks before completing the preference questionnaire, which could potentially affect the patients' reporting of preference, and our results seemed to show a tendency for patients to prefer the first treatment received. However, the randomization

process ensured that approximately equal numbers of patients received each drug as their final treatment, and there was no apparent effect on the overall results.

The 2.6-fold preference in favor of zafirlukast tablets may not reflect what the preference would be in newly treated asthmatic adolescents, because preference was influenced, as would be expected, by inhaler technique and previous experience with a pMDI. However, even patients with 'good' inhaler technique preferred zafirlukast tablets over inhaled corticosteroids by a 1.9:1 ratio. Patients with 'poor' inhaler technique preferred zafirlukast tablets by a 3.2:1 ratio. Patients who were using dry powder inhalers at study entry, for whom both treatments may have been new, had an even stronger preference for zafirlukast tablets over the inhaled corticosteroids by a ratio of 4.7:1, which was greatly increased compared with the preference by a 2.1:1 ratio in favor of zafirlukast among patients who were already using pMDIs.

The type of inhaler which the adolescents had used previously varied between countries, and these differences are likely to have influenced the differences in preference expressed. In South Africa, where there was no clear preference between treatments, almost all patients had previous experience with pMDIs. By contrast, the largest preference difference in favor of zafirlukast was seen in Finland, where all patients were using dry powder inhalers before entering the study. Previous device use cannot explain all the differences in preference between countries and other factors such as the amount of education and information about asthma and inhaled corticosteroid treatment that each adolescent had received before entering the study may have influenced patients' perceptions of the two treatments.

Good compliance and correct inhaler technique are essential if correct dosing is to be achieved with inhaled corticosteroids (22). In a study of 50 adults, inhaler technique was adequate in 73% of patients, but only 7% completed all steps correctly (8). In another study in adults, almost half of patients (44%) failed to complete all essential steps in using the inhaler correctly (19). In the current study, less than one third of the adolescents used their inhaler correctly when first assessed, even among those who were using a pMDI at study entry, which suggests that incorrect inhaler use may be more common among adolescents than adults. These observations further highlight the need for regular checks of inhaler technique in adolescent asthma patients.

To overcome the many barriers that exist in achieving good compliance with treatment in adolescents, it is becoming increasingly apparent that there is a need to view and treat adolescent patients with asthma as a special group (23). This approach needs to reflect the adolescents' need for greater autonomy and personal decision making in determining their healthcare. The greater patient preference for zafirlukast tablets (20 mg b.i.d.) and the simplicity of using tablets over inhaled BDP (100 or 200 µg b.i.d.) observed in this study, suggests that treatment of adolescent asthma with zafirlukast could lead to improved compliance with regular asthma medication.

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