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Safety of Zafirlukast

Results of a Postmarketing Surveillance Study on 7976 Patients in England

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Abstract

Objectives: A prescription event monitoring (PEM) postmarketing surveillance study was carried out to examine the safety of zafirlukast as used in general practice in England.

Methods: Exposure data were obtained from the first National Health Service (NHS) prescription dispensed for patients whose prescription details were processed by the Prescription Pricing Authority between August 1998 and December 2000. Outcome data were obtained from 'green form' questionnaires sent to general practitioners (GPs) at least 6 months following the first prescription issued. Incidence densities (IDs) were calculated for events reported per 1000 months of patient exposure and ID differences between the first month of treatment and months 2–6 combined were analysed. Events of medical interest were followed up by postal questionnaire sent to GPs.

Results: 21 557 green forms were sent to 8051 doctors, of which 9124 (42.3%) were returned. Useful clinical data was obtained for 7976 patients of which 4664 (58.5%) were female and 3265 (40.9%) were male. The patient's sex was not specified in 47 (0.6%) forms. The median age of the cohort was 53 years (interquartile range 38–66 years). The most frequently reported primary indication was the licensed indication of asthma, but for a small proportion of the cohort it was prescribed 'off label'.

A total of 152 events in 120 (1.5%) patients were reported as adverse drug reactions (ADRs) by GPs on the green forms. ADRs with the highest reported frequency were headache and nausea. There were 3514 reasons for stopping zafirlukast in 3148 (39.5%) patients, the most frequently reported of which was that the drug was 'ineffective' (2008 patients; 25.2%). The most frequently reported specified clinical reason for stopping was headache (82 patients; 1.0%). There were 28 pregnancies reported in this cohort, 20 of which were reported to have exposure to zafirlukast during the first trimester. Nine live births with no recorded congenital abnormalities were reported for pregnancies with exposure in the first trimester. There were 151 deaths reported during the study period (1.9%). The most frequently reported causes of death were related to the respiratory system (57; 37.7%), including chronic obstructive pulmonary disease, asthma and bronchopneumonia.

Conclusion: This study showed that zafirlukast, as used in general practice in England, is a generally well tolerated drug with few associated adverse events.

The leukotrienes are biologically active lipids formed from the metabolism of arachidonic acid. The cysteinyl leukotrienes C_4, D_4 and E_4 are highly potent mediators of inflammation, involved in the activation of leukocyte chemotaxis, increased constriction and proliferation of bronchial smooth muscle, increased microvascular permeability, neuronal stimulation and hypersecretion of mucus.[1,2] Cysteinyl leukotrienes have been associated with the pathology of many inflammatory diseases and syndromes, including asthma.[1,3] They exert their physiological effect by binding to specific receptors, mostly mediated through the cysteinyl leukotriene 1 ($CysLT_1$) receptor found in smooth muscle in the airway.[4,5]

Zafirlukast is a highly selective $CysLT_1$-receptor antagonist,[6] which acts by antagonising the pro-inflammatory activities of the leukotrienes as well as by reducing smooth-muscle bronchoconstriction in a dose-dependent manner. Additionally, zafirlukast does not alter smooth-muscle response to β_2-adrenoceptor agonists, does not act on histamine, cholinergic prostaglandin or thromboxane receptors[7] and attenuates allergen-induced migration of inflammatory cells.[4,8,9]

Zafirlukast has been shown to be generally well tolerated.[10] The summary of product characteristics (SPC) reports that adverse events are usually mild and resolve following cessation of therapy. These include skin rash, gastrointestinal disturbance, hypersensitivity and headache. Haematological and musculoskeletal events, hepatitis, lower limb oedema and angioedema are listed as rare events in the SPC. The SPC also highlights the potential for zafirlukast to cause eosinophilic conditions, most notably Churg-Strauss syndrome.[11-14]

Prescription event monitoring (PEM) is a technique used to monitor the safety of newly marketed drugs. The Drug Safety Research Unit (DSRU) aims to carry out PEM studies on newly marketed drugs, as soon as possible after they are available on the market. Doctors are requested to report all significant 'events' that have been recorded in a patient's notes after treatment with the drug being monitored. By removing the need to give an opinion about the probability that any particular event might have been caused by the drug, PEM provides the possibility of identifying reactions which the reporters may not have suspected as being related to the monitored drug.

PEM also allows the collection of information on large cohorts of patients using drugs prescribed under 'real-life' conditions, rather than clinical trials. The data are valuable not only in the assessment of the safety of new drugs but also because they provide information about the pattern of morbidity and mortality in patients treated with newly marketed drugs.

In the UK, zafirlukast is licensed for the treatment of asthma in adults and children >12 years of age; clinical experience is limited in elderly patients >65 years of age. This study included patients <12 years and >65 years of age. The aim of this study was to monitor the safety of zafirlukast used to treat a large cohort of patients in general medical practice in England.

Methods

An observational cohort study was undertaken using the technique of PEM.[15] The patients in this cohort were identified by means of data from dispensed National Health Service (NHS) prescriptions written by general practitioners (GPs) in England between August 1998 and December 2000. They were supplied to the DSRU in confidence by the Prescription Pricing Authority (PPA)[1]. Simple questionnaires ('green forms') were posted to the prescribing doctors between March 1999 and August 2001, at least 6 months following notification of the first prescription to the DSRU of individual patients. These forms requested information on the date of birth, indication for and duration of treatment, whether the drug had been stopped and reason for stopping (if applicable), and any event(s) that had occurred after zafirlukast was first prescribed. The term 'event' was defined as "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was

1 Now the Prescription Pricing Division of the National Health Service Business Services Authority.

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considered of sufficient importance to enter in the patient's notes".

All patients for whom a green form questionnaire containing clinical information was returned were included in the study cohort, irrespective of the reported indication for prescribing zafirlukast or the patient's age. There were no exclusion criteria. All events reported on green form questionnaires were coded onto the DSRU database using the DSRU Event Dictionary, which is arranged in a system-organ classification with specific 'lower' level terms grouped together under broader 'higher' level terms. For each event term included in the DSRU dictionary the PEM data provided a numerator (the number of reports of the event), a denominator (the number of patient-months of exposure) and a known time frame (the time between the start and stop dates of zafirlukast in individual patients). These data were assembled for each patient to give the number of reports for each month following start of therapy, for the entire cohort.

Follow-Up of Selected Events

Hypersensitivity reactions (such as urticaria, rash and itching) and any events considered to be medically important were followed up by sending an additional postal questionnaire to the prescribing GP. A list of Rare and Iatrogenic Adverse Drug Reactions (RAIDAR) events compiled by the DSRU[15] were also followed up if a more likely alternative explanation for their occurrence was not given.

Individual case reports were assessed for causality by research fellows at the DSRU, using the criteria of temporality, pharmacological plausibility, clinico-pathological nature and exclusion of other causes. Causality was graded as being probable, possible, unlikely or unassessable.[16] Pregnancies that occurred during treatment with, or within 3 months of stopping zafirlukast were also routinely followed up. If no clear cause of death could be established from a green form, the death certificate was requested from the Office of National Statistics (ONS).

Ethics

This records based study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organizations of Medical Science in collaboration with the World Health Organisation.[17] This method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians, for records based research.[18] PEM is stated in the 'Frequently asked questions' section of the General Medical Council booklet, *Confidentiality: Protecting and Providing Information*, as being a "professional organisation that monitors the safety of medicines to which doctors should provide relevant information from patients' records wherever possible".[19]

Considerable care was taken to preserve the confidentiality of patient data, and the DSRU databases are well protected. Medical reports and case histories were treated in the strictest medical confidence. To ensure patient anonymity, the name and address of the patient was deleted from the DSRU database when the green form questionnaire was returned. The GP completing the green form questionnaire was asked to enter a patient identification code on the return section of the form. Any request for follow-up information was possible only if a GP had provided this identification code.

Data Analysis

Incidence densities (IDs) were calculated for all the events occurring during treatment with zafirlukast during a specified time period (t) for the entire cohort. IDs are expressed per 1000 patient-months of treatment (equation 1):

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period t}}{\text{Number of patient-months of treatment for period t}} \times 1000 \quad \text{(Eq. 1)}$$

IDs for events occurring in the first month of treatment (ID_1), during months 2–6 of treatment ($ID_{2–6}$) and for the overall treatment period (ID_A) were calculated for patients whose duration of treat-

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ment was known. The difference between the two IDs (ID_1–$ID_{2–6}$) was calculated to test the null hypothesis that the ID did not change over time. Where the arithmetic difference between ID_1 and $ID_{2–6}$ was statistically significant at the 1% level, this was considered to be a signal of a possible association between that event and initiating treatment with zafirlukast.

Results

Demographics

Of the 21 557 green forms posted, 9124 (42.3%) were returned and 7976 (37.0%) forms contained useful clinical data. Of the 7976 patients, 4664 (58.5%) were female and 3265 (40.9 %) were male. Sex was not recorded for 47 (0.6%) patients. The median age of the cohort was 53 years (interquartile range [IQR] 38–66 years). However, age was not recorded for 2978 patients, 37.3% of the total cohort. In this study, 27 patients (0.3%) who were prescribed zafirlukast were <12 years of age (ages 0–11 years), contrary to prescribing advice in the UK SPC.[7] Also, 1287 (16.1%) were aged ≥66 years.

Primary Indications

The most frequently reported primary indication for initiating zafirlukast therapy was the licensed indication asthma, accounting for 56.8% (4533) of the total cohort. For a small proportion of the cohort, the primary indication specified was not the licensed indication of asthma but included other indications; chronic obstructive pulmonary disease (COPD), for 255 patients (3.2%) and urticaria for 15 patients (0.2%). On 2861 (35.9%) green forms no indication was specified.

Effectiveness

6013 (75.4%) of the 7976 green forms included an opinion about the effectiveness of zafirlukast. Of these, zafirlukast was reported to have been effective by the GP on 3645 (60.6%) green forms, and ineffective on 2368 (39.4 %) forms. On 1963 (24.6%) green forms an opinion was not specified. At the end of the first month of treatment, 5466 (76.8%) of the 7118 patients whose duration of treatment was known continued taking zafirlukast, and 52.9% (3767) of the cohort (whose duration of treatment was known) remained on the drug at the end of 6 months' treatment.

Suspected Adverse Drug Reactions to Zafirlukast

152 events in 120 patients (1.5% total cohort) were reported by the GPs as ADRs to zafirlukast; 16 of these events were documented on the green form as having been reported to the Regulatory Authority. Table I shows the most frequently reported ADRs to zafirlukast.

Other ADRs reported on the green forms included asthma worse (5 events, 1 reported to the regulatory authority), dizziness (5), gastrointestinal unspecified (3), hepatitis (1) and jaundice (1 reported to the regulatory authority). Some ADRs of altered mental state were also reported, including confusion

Table I. Adverse drug reactions to zafirlukast reported frequently on the green forms

Event[a]	Total no. of events	Reported to Committee on Safety of Medicines
Unspecified side effects[b]	30	0
Nausea, vomiting	12	0
nausea	*10*	*0*
vomiting	*2*	*0*
Headache, migraine	11	3
headache	*11*	*3*
Malaise, lassitude	9	1
malaise	*5*	*0*
lassitude	*4*	*1*
Diarrhoea	8	0
Dyspepsia	7	2
dyspepsia	*4*	*0*
heartburn	*2*	*1*
oesophageal reflux	*1*	*1*
Pain abdomen	7	0
Upper respiratory tract infection	6	1
flu-like symptoms	*6*	*1*

a The events in italics are the 'lower level' event terms that are grouped under the 'higher level' term (given in the line above) within the Drug Safety Research Unit coding dictionary.

b General practitioner stated "side effects" or "adverse reaction" but provided no further details.

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(2), aggression (1), agitation (1 reported to the regulatory authority) and anxiety (1).

Reasons for Discontinuing Zafirlukast

GPs recorded 3514 reasons for stopping zafirlukast therapy in 3148 (39.5 %) patients. The most frequently reported reasons are provided in table II.

Other reasons for withdrawing treatment included dizziness (18 events), oedema (12), palpitation (10), abnormal liver function tests (9), angioneurotic oedema (4), depression (3), hepatitis (2), jaundice (2) and anxiety (2).

Table II. Frequently reported reasons on the green forms for discontinuing zafirlukast

Reason for stopping (higher level term)	Number (%)[a]
Not effective	2008 (25.2)
Patient request	196 (2.5)
Condition improved	181 (2.3)
Headache, migraine	86 (1.1)
Nausea, vomiting	81 (1.0)
Non-compliance	74 (0.9)
Malaise, lassitude	61 (0.8)
Hospital referrals – no admission	59 (0.7)
Rash	53 (0.7)
Intolerance	43 (0.5)
Non-surgical admissions	39 (0.5)
Abdominal pain	39 (0.5)
Diarrhoea	36 (0.5)
Unspecified side effects[b]	30 (0.4)
Pruritus	30 (0.4)
Asthma worse	26 (0.3)

a Percentage of total cohort (7976 patients).

b GP stated "side effects" or "adverse reaction" but provided no further details.

Events in Children <12 Years of Age

The most frequently reported events in the 27 children <12 years of age recorded on the green forms were chest infection (three patients) and 'not effective' (six patients). There were 12 reasons for withdrawing zafirlukast in 11 children <12 years of age. Four of the reasons for discontinuation of zafirlukast were specified adverse clinical events including hypoaesthesia (one event), paraesthesia (one event), intolerance (one event) and nausea (one event). The most frequently reported reason for stopping zafirlukast therapy in children of this age group was poor clinical efficacy (six events).

Events in Patients >65 Years of Age

Seven of the 34 (20.6%) hepatic events reported during treatment were in patients aged ≥66 years. In this study, there were 255 events of upper respiratory tract infection (URTI) and 323 events of lower respiratory tract infection (LRTI) reported in 529 patients (for some patients more than one event was reported) during treatment with zafirlukast. Thirty-four events of URTI and 65 events of LRTI were reported in 92 (15.9%) patients aged ≥66 years (where age was specified). Overall, only three of the above events (3.3%) were reported as the reason for withdrawing zafirlukast, and two were reported as an ADR to zafirlukast. In the first case reported as an ADR, the GP reported that the patient felt "as though getting flu after taking the tablets" and zafirlukast was stopped because it was not effective. In the second case, zafirlukast was stopped because it "caused flu like symptoms". In addition, three of the 21 reports of palpitations occurred in patients ≥66 years of age.

Incidence Densities

Table III summarises events that were amongst those most frequently reported in the first month of treatment in this study and produced a significant positive ID difference. Excluding indication-related events, clinical events included in this table are listed in the SPC for zafirlukast. The only other non-indication-related events for which ID_1 was significantly greater than $ID_{2–6}$,were dizziness ($N_1 = 21$; $N_{2–6} = 15$: $ID_1=3.12$; $ID_{2–6} = 0.69$) and palpitations ($N_1 = 12$; $N_{2–6} = 5$: $ID_1= 1.78$; $ID_{2–6} = 0.23$). Neither of these events is listed in the SPC for zafirlukast.

Follow-Up of Specific Events

Follow-up questionnaires were sent for 105 of the events that occurred in 96 patients. Eighty-six of the 105 forms sent were returned (81.9%). Each case followed up was assessed for any possible relationship between the event and the use of the drug. Some events of interest assessed as probably related

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Table III. Significant positive incidence density (ID) differences (99% CI) for the most frequently reported events occurring during treatment with zafirlukast

Higher level term	No. of events		ID		ID difference (99% CI)			Totals	
	1mo	2–6mo	ID_1	$ID_{2–6}$	$ID_1–ID_{2–6}$	CI min	CI max	N_A	ID_A
Not effective	880	876	130.73	40.40	90.33	78.45	102.21	2006	39.95
Asthma worse	105	205	15.60	9.45	6.14	1.87	10.42	435	8.66
Condition improved	91	101	13.52	4.66	8.86	5.02	12.70	233	4.64
Headache, migraine	80	48	11.88	2.21	9.67	6.15	13.19	159	3.17
Corticosteroid short course	80	134	11.88	6.18	5.70	2.02	9.39	488	9.72
Nausea, vomiting	67	48	9.95	2.21	7.74	4.50	10.98	130	2.59
Patient request[a]	59	83	8.77	3.83	4.94	1.81	8.07	191	3.80
Non-compliance	44	18	6.54	0.83	5.71	3.12	8.29	89	1.77
Malaise, lassitude	41	40	6.09	1.84	4.25	1.68	6.81	94	1.87
Rash	40	38	5.94	1.75	4.19	1.66	6.72	95	1.89
Diarrhoea	34	26	5.05	1.20	3.85	1.54	6.16	76	1.51
Abdominal pain	34	46	5.05	2.12	2.93	0.56	5.30	95	1.89
Intolerance	31	11	4.61	0.51	4.10	1.93	6.26	46	0.92

a Patient requested to stop the drug or be changed to another medication.

ID_1 = incidence density for 1mo; **$ID_{2–6}$** = incidence density for 2–6mo; **ID_A** = incidence density for each event for the total treatment period; **N_A** = total number of first reports of each event during total treatment period.

to zafirlukast by medical staff at the DSRU are shown in table IV.

There was one case of erythema multiforme reported in this study. The patient had been receiving zafirlukast for 2 months at the time of the event. Zafirlukast was stopped as a result of the event, which resolved a few days later. However, during the week prior to the event, the patient had completed a different course of medication, which has been associated with erythema multiforme. The event was assessed as possibly related to zafirlukast.

One case of urticaria was assessed as probably related to zafirlukast. In this case, the patient developed a severe urticarial rash 2 weeks after starting zafirlukast. The urticaria resolved after the drug was stopped.

There were 21 cases of palpitation recorded during treatment with zafirlukast, 12 of which were reported to have occurred during the first month of treatment. Two events were reported as possible ADRs by GPs on the green form. Only 3 of the 21 cases reported during treatment with zafirlukast occurred in patients ≥66 years. Ten cases were followed up for further information (available for eight cases). Three events were assessed as probably related to zafirlukast and three events were assessed as possibly related to the use of the drug.

There were 34 hepatic events reported during treatment with zafirlukast in this cohort, seven of which (20.6 %) were in patients ≥66 years of age. Of the 11 cases that were followed up, there were two events of jaundice and one event of abnormal liver function tests that were assessed as probably related to the use of zafirlukast. There was no history of alcohol abuse or other known relevant factors predisposing the patient to the event in any of these cases. None of the events were serious, and all cases resolved after the drug was discontinued.

Pregnancies

There were 28 pregnancies reported on the green forms during the study period. Twenty of these patients took zafirlukast during the first trimester. Of the 20 women exposed to zafirlukast during this period, there were 9 live births without any reported congenital abnormalities, 4 spontaneous abortions, and 1 therapeutic termination. The outcomes of the remaining six cases were not known.

Deaths

There were 151 deaths reported on the green forms, of which 117 (77.4%) had a specified cause for death. The most frequently reported causes of

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death related to the respiratory system (57 patients, 37.7% deaths), including COPD (32), asthma (9) and bronchopneumonia (4). Other causes of death were cardiovascular (74 patients) and cancer (23, including 10 patients with carcinoma of the lung). There were 15 deaths reported during the first month of treatment with zafirlukast; these deaths were due to respiratory causes (6 deaths, including 4 from COPD), 2 were due to carcinoma of the lung, 3 to cardiovascular causes and 1 to carcinoma of the ovary. A cause of death could not be ascertained by the GP for the remaining three deaths reported during the first month of treatment with zafirlukast. There were 55 deaths reported >6 months after treatment with zafirlukast was commenced.

Discussion

A PEM study was carried out to evaluate the safety profile of zafirlukast as used in general practice in England. This study describes a cohort of 7976 patients prescribed zafirlukast by GPs in England. Events that occurred after starting treatment were recorded and analysed for any possible safety signals of interest, and the incidence of all events experienced in patients prescribed zafirlukast was quantified. PEM methodology facilitated collection of data on a wide range of patients prescribed zafirlukast in general practice in England with characteristics likely to be representative of the general population who are prescribed this drug, as there are no exclusions for this study cohort, and the only inclusion criteria are that the green form questionnaire is returned and contains clinical information. Also, the patients are identified from dispensed prescriptions; hence, PEM methodology does not interfere with the GPs' prescribing practices. It was found that for a small proportion of the study cohort, patients had been prescribed the drug 'off label', with respect to the indication. The ability to collect data on all events experienced by these patients

Table IV. Selected specific events for which further information was obtained

Event (lower level term)	No. events reported during treatment	No. events followed up (valid forms returned)	Follow-up events assessed as probably related to zafirlukast	Time to onset (days)[a]	Other risk factors or relevant concomitant medication	Dechallenge
Skin						
Erythema multiforme	1	1 (1)	0			
Rash	95	19 (15)	4	1.5–14	None	Positive
Urticaria	24	2 (1)	1	15	None	Positive
Cardiovascular						
Oedema face	7	2 (1)	1	2	None	Positive
Palpitation	21	10 (8)	3	1–13	1- None; 2- H/O anxiety[b]	Positive
Respiratory						
Churg-Strauss syndrome	1	1 (1)	0			
Flu-like symptoms	23	3 (3)	3	1–27	None	Positive
Alimentary						
Jaundice	4	3 (3)	2	3; 129	None	Positive
Hepatitis	2	1 (1)	0			
Liver function test abnormal	16	7 (6)	1	219	None	Positive
Haemopoietic						
Eosinophilia	4	2 (2)[c]	0			
Immunological						
Angioneurotic oedema	5	5 (5)	1	4–5 hours	None	Not specified

a For events assessed as probably related to zafirlukast.

b History of anxiety; palpitations not pre-existing and re-challenge positive.

c One event detected after zafirlukast treatment stopped.

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during the study period increased the possibility of identifying events not previously suspected by GPs to be related to zafirlukast.

The average response rate was 55.9% for 90 previous PEM studies.[15] The response rate for this study (42.3%) was lower than expected. This may be a reflection of increased workload demands on GPs.[20] The results of this cohort may have contained selection biases, as it was not determined whether the characteristics of patients whose GP completed the questionnaire differed from those of patients whose GPs did not return the green form. Nevertheless, the number of patients included in this study is much higher than the number normally included in clinical trials. Also, because PEM is dependent on the GPs transcribing information from the patient's medical record, there may be underreporting of events, including that of serious or fatal events.

The results of this study showed good agreement with other reported literature that zafirlukast is an effective and generally well tolerated drug with few associated adverse events. In this study, the drug was reported to have been effective by the GP on 3645 (60.6 %) green forms (where the GP specified an opinion), and 52.9 % (3767) of the cohort (where the duration of treatment was known) remained on the drug at the end of 6 months' treatment. There were 3459 events reported throughout the study period, 3226 of which were reported during treatment with zafirlukast. The events with the highest ID in the first month of treatment were generally as expected and listed in the SPC.

The highest ranking clinical events reported during treatment with zafirlukast were headache (140; 1.8 %), rash (95; 1.2 %) abdominal pain (95; 1.2 %), nausea (92; 1.1 %) and depression (79; 1.0 %). The events (with the exception of depression) were reported with a lower or comparable incidence than those reported in the SPC.[7] These events all produced significant positive incidence density differences, indicative of an event associated with the start of treatment with zafirlukast. Other frequently reported events during treatment were worsening asthma (447; 5.6 %), chest infection (281; 3.5 %) and upper respiratory tract infection (97; 1.2 %).

Twenty-seven patients (0.3%) who were prescribed zafirlukast were <12 years of age in this study, contrary to the prescribing advice in this country (because of limited information in children of this age group). However, zafirlukast is recommended for use in children >5 years of age in the USA. In this cohort, there were no serious events reported in children aged <12 years related to zafirlukast therapy. Although based on small numbers, the results of our study are in agreement with other clinical studies[21] that have shown that zafirlukast is generally well tolerated in children.

The SPC states that clinical trial data have shown that the use of zafirlukast may predispose elderly patients to mild infections (normally in the respiratory tract).[7] It was not feasible in our study to elucidate whether these events may have been related to use of the drug, as there were many contributory factors, which would have predisposed patients to this kind of event.

The most frequently reported reason for discontinuation of zafirlukast (and most frequently reported event) was that the drug was 'ineffective' (2008; 25.2%). This highlights the difficulty in establishing an effective treatment regimen in patients with asthma. Asthma is a heterogeneous syndrome, and individuals respond differently to the various treatments, depending on their phenotype.[22,23] Some evidence suggests that some drugs work better in some patients with certain genetic polymorphisms, probably related to their leukotriene metabolism.[10,22]

There are some literature reports that suggest that zafirlukast may be an effective treatment for other inflammatory conditions, such as urticaria, nasal polyps, sinusitis and eczema.[4] In our cohort there were some 'off-label' uses of zafirlukast (urticaria 15 patients; nasal polyp 4; eczema 3; and sinusitis 3). The benefits of zafirlukast for these indications is debatable, with conflicting reports in the literature.[4,24] In this study, GPs reported that zafirlukast was ineffective on 9 of the 15 green forms that reported urticaria as a primary indication. It was reported on three of these green forms that zafirlukast was effective. Similarly, zafirlukast was reported to be effective in only one of three patients with sinusitis. According to entries in the green forms, zafirlukast was not effective for the treatment of patients with eczema or nasal polyp. These results suggest that GPs did not find zafirlukast effective

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for 'off-label' use of other inflammatory conditions; it must be stressed that this study was not designed to evaluate 'off-label' use of zafirlukast.

The rate of events occurring during the first month of treatment (ID_1) was compared with the rate of events reported during months 2–6 ($ID_{2–6}$) of treatment with zafirlukast. There were two events (dizziness and palpitations) with a significant positive incidence density difference not already listed in the SPC for zafirlukast. There were no unexpected serious events reported in this cohort that were associated with use of zafirlukast. Rare events listed in the SPC were followed up for further information.

Three cases of palpitation were assessed as probably related to zafirlukast. In all three cases, the event was not a pre-existing condition and zafirlukast was stopped as a result of the event. In all three cases, the palpitations ceased after drug withdrawal. Six of eight cases of palpitation for which follow-up information was available were in patients who received other anti-asthma medications, such as β_2-adrenoceptor agonists, which are known to cause palpitations.[25] Three of these six patients were also reported to experience anxiety/stress, which has been associated with the asthma syndrome.[26] In 2005, there had been only five events of palpitation reported to the Regulatory Authority on the yellow-card system (this does not imply causality).[27] Palpitation is recorded in the SPC of montelukast (another antileukotriene receptor antagonist) as an adverse event,[28,29] but has not been listed as an adverse event in the SPC for zafirlukast.

A possible causal relationship between Churg-Strauss syndrome and the use of $CysLT_1$-receptor antagonists, including zafirlukast, has been highlighted in the literature.[12,30-36] In many (but not all) cases, the event has been associated with an 'unmasking effect' as a consequence of reducing corticosteroid therapy following initiation of antileukotrienes. There was one case of Churg-Strauss in this cohort, but the event was not assessed as being related to zafirlukast. In this case, the patient was found to have eosinophilia during a hospital admission, and subsequently Churg-Strauss syndrome was diagnosed. The condition was reported to be pre-existing and did not resolve after withdrawal of zafirlukast. In this study, there were five cases of eosinophilia, four of which were reported during treatment. Two cases were followed up, but neither case was found to be attributable to the use of zafirlukast.

The SPC for zafirlukast states that there are rare cases of increased levels of liver enzymes associated with zafirlukast use in controlled clinical trials and rarely, cases of hepatotoxicity associated with the drug at the recommended doses.[7,37-40] Of the 11 cases with hepatic events followed up, there were 2 events of jaundice and 1 event of abnormal liver function tests that were assessed as probably related to the use of zafirlukast. There was no history of alcohol abuse or other known relevant factors predisposing the patient to the event in any of these cases. None of the events were serious, and all cases resolved after drug withdrawal. This is also the case with most literature reports, although in very rare instances, patients have gone on to develop subfulminant liver failure requiring a transplant.[37] It is well known that zafirlukast is extensively metabolised by cytochrome P450 (CYP) isoenzyme CYP2C9.[4] However, the mechanism of zafirlukast hepatotoxicity is not yet understood. In some patients, there appears to be an underlying immune reaction, but in other cases, liver injury appeared to be idiosyncratic. The earliest cases of hepatotoxicity reported in the literature occurred in women and after several months of treatment.[37,39] Most cases of hepatotoxicity reported in the literature are similar in their time to onset (over several months), idiosyncratic liver injury, poor response to corticosteroid therapy and the severity of damage.[37-40] Actis et al.[38] suggested that patients who no longer received corticosteroids as part of their therapy were most at risk of hepatic injury because of reduced protection from allergic reactions as a result of corticosteroid withdrawal. They also argued that there may be some precipitating factor, such as an interaction between zafirlukast and other drugs, mediated by CYP and leading to increased levels of a concurrent drug or production of a toxic zafirlukast metabolite. Several drugs are already known to interact with zafirlukast, including theophylline,[41] warfarin, erythromycin, terfenadine and aspirin.[7] The case reports of liver injury have occurred predominantly (but not exclusively) in females. It has been suggested that CYP may be more active in females than males,[37,39] and thus females are more at risk of

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zafirlukast-induced hepatotoxicity. However, Actis et al.[38] thought that the clustering of cases in females was probably due to chance. Nevertheless, they agree that interaction between zafirlukast and CYP may result in the formation of a toxic metabolite. The results from this PEM study indicate that more females than males had hepatic events reported; 11 of the 16 (68.8 %) patients had abnormal liver function (during treatment), both cases of hepatitis, and 3 of the 4 (75.0%) cases of jaundice occurred in female patients.

Depression showed a (non-significant) negative incidence density difference (ID difference −1.1; 99% CI −2.4, 0.3). Depression in this study was reported with an incidence of 1% of the total cohort, but is not listed in the company's SPC as occurring at an incidence of ≥1%.[7] In a number of cases, depression was reported along with concurrent illnesses, or worsening asthma (14 green forms) or was associated with lack of efficacy (11 green forms). There were ten cases where depression was the only reported event on the green form, and two cases where depression was recorded along with 'condition improved' only. There is a high prevalence of anxiety disorders in people with asthma.[26] Asthmatics with psychological distress tend to have feelings of lack of control, and have a decreased physical health status.[42] There are no adverse events listed in the zafirlukast SPC referring to psychological disorders,[7] although the montelukast SPC lists agitation and insomnia as undesirable effects.[29]

Conclusion

Zafirlukast was a generally well tolerated drug, when used in general practice in England. For 60% of patients for whom the GPs expressed an opinion, zafirlukast was reported to be effective. The most frequently reported events, and events with significant positive ID differences (early-onset signal) were events also listed in the SPC for zafirlukast. The results of this study should be considered along with results from other postmarketing studies.

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