ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (9): 805-815
0114-5916/07/0009-0805/$44.95/0

Clinical Pattern of Zileuton-Associated Liver Injury

Results of a 12-Month Study in Patients with Chronic Asthma

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Abstract

Objective: Zileuton is a 5-lipoxygenase inhibitor approved by the US FDA in 1996 for the treatment of asthma in adults and children. During phase II/III clinical trials, zileuton was generally well tolerated, although elevations in ALT and AST levels were noted in some patients, and a single treated patient developed hepatocellular jaundice. To more fully characterise the hepatic effects of zileuton, and to establish appropriate monitoring guidelines, a 12-month open-label, safety surveillance study was conducted prior to FDA approval.

Patients and methods: In this study, 2458 patients with asthma received zileuton 600mg four times daily in addition to usual asthma care, and 489 patients were treated with usual asthma care only. All patients had their liver biochemistry checked monthly for the first 5 months, and at months 7, 10 and 12 thereafter.

Results: A total of 109 patients (4.4%) receiving zileuton treatment had elevations in ALT levels to ≥3 × the upper limit of normal (ULN), including 31 patients (1.3%) who had levels elevated to ≥8 × ULN, compared with 5 of 480 patients in the usual care alone group (1.0%) who had levels elevated to ≥3 × ULN, of whom 1 (0.2%) had levels elevated to ≥8 × ULN. Elevations in ALT levels were generally not associated with increases in alkaline phosphatase and/or total bilirubin levels. Therefore, the hepatic injury was predominantly hepatocellular. The majority of elevations in ALT level to ≥3 × ULN (64.2%) in the zileuton-treated group occurred within the first 3 months of treatment. There was no correlation between the time of onset of ALT level elevation and the height of the peak ALT level observed. There was no overall difference in the occurrence of elevations in ALT level to ≥3 × ULN between men (4.5%) and women (4.7%), but more women than men experienced an ALT level ≥8 × ULN (1.8% vs 0.5%). Women aged ≥65 years appeared to be at higher risk of elevated ALT levels than those aged <65 years (a rate of 10.1% compared with 4.1%). Patients who experienced ALT levels of ≥3 × ULN but <5 × ULN were allowed to remain on treatment and 52.5% of these patients were able to continue zileuton therapy and experienced resolution of the elevation (a reduction in level to <2 × ULN). In each of the patients who discontinued treatment because of elevated ALT levels, the ALT level returned towards baseline, with a mean time to resolution (defined as a reduction in levels to <2 × ULN) of 4 weeks. No patient in this study developed

clinically apparent jaundice or liver failure. Two patients (0.1%) experienced total bilirubin levels ≥1.5 × ULN in association with serum ALT levels exceeding 3 × ULN.

Conclusions: This study established that liver chemistry monitoring is most effective in detecting elevation of ALT levels during the first 3 months of zileuton therapy and that with appropriate monitoring the risk of irreversible liver injury appears to be low.

Introduction

Zileuton, a specific 5-lipoxygenase inhibitor, has been extensively studied in the treatment of inflammatory diseases that involve leukotrienes as mediators of inflammation, such as asthma, rheumatoid arthritis and inflammatory bowel diseases.[1,2] Zileuton tablets were approved by the US FDA in December 1996 for the prophylaxis and treatment of chronic asthma in adults and children ≥12 years of age.[3] In two phase III, placebo-controlled, clinical trials (of 3 months and 6 months duration),[4,5] patients with chronic asthma who were treated with zileuton had a statistically significant improvement in pulmonary function, required fewer doses of systemic corticosteroid rescue medication, used β-adrenoceptor agonist inhalers less often and had greater improvements in quality of life indices compared with patients given placebo. Zileuton remains the only approved leukotriene synthesis inhibitor; however, enthusiasm for expanding the indications for this drug has been tempered by concern regarding its potential to induce liver toxicity.

Zileuton did not produce liver toxicity in rats, dogs and monkeys during preclinical testing.[6] In the phase II and phase III controlled and uncontrolled studies of the clinical programmes for zileuton in the treatment of asthma (involving 1450 patients) and other inflammatory diseases (1067 patients), elevations in ALT levels to ≥3 × upper limit of normal (ULN) that were considered to be possibly or probably related to zileuton treatment were observed in 54 of the total 2517 patients (2.1%) in whom ≥1 post-baseline measurement was performed.[6] Thirteen patients (0.5%) had ALT levels ≥8 × ULN and four patients (0.2%) had ALT levels ≥15 × ULN. The rate of elevated ALT levels was similar between males (2.2%) and females (2.0%), and the mean age of the 54 patients who experienced elevated ALT levels was 37.5 years. In placebo-controlled studies, the rate of ALT levels of ≥3 × ULN was 1.9% in zileuton-treated patients versus 0.2% in placebo-treated patients.[3] A large proportion of patients (1602 of 2573) in the phase II/III studies were exposed to zileuton 600mg four times daily, whereas approximately 1074 patients received 1600 mg/day as either 800mg twice daily or 400 mg four times daily, with some patients receiving more than one regimen. As has been reported for several other drugs with a pattern of hepatocellular injury,[7-11] most patients with elevated ALT levels were asymptomatic. Only 15 of 54 (27.8%) patients with an ALT level ≥3 × ULN experienced symptoms such as nausea, influenza-like symptoms and right upper-quadrant abdominal pain, which may have been attributable to the liver injury.[6] None of the patients with elevated ALT levels presented with evidence of a hypersensitivity reaction (i.e. rash, fever and eosinophilia). However, a single individual developed severe liver injury and jaundice. This 28-year-old woman experienced fatigue, nausea, itching and influenza-like symptoms after being treated with zileuton 400mg four times daily for approximately 6 weeks. At the time of treatment discontinuation, this patient was jaundiced and had an AST level that was 19 × ULN, an ALT level that was 33 × ULN, an alkaline phosphatase level that was 1.3 × ULN and a total bilirubin level that was 6.6 × ULN. All viral hepatitis serology results were negative and no alternative aetiology was identified. Her total bilirubin levels reached 12.8 × ULN, 8 days after zileuton was stopped. Within 35 days of discontinuation of zileuton treatment, her ALT and AST levels had returned to normal and her total bilirubin level had decreased to 2.6 × ULN. The patient totally recovered, and her total bilirubin level was normal after 70 days.

Based largely on this single case, a long-term (12-month duration) surveillance study was conducted to further characterise the liver safety profile of zileuton and to determine an appropriate liver biochemistry monitoring schedule during treatment. In this study, 2458 patients with asthma in the US were exposed to zileuton 600mg four times daily in addition to the usual asthma care and 489 patients received usual asthma care only. The secondary objective of the study was to assess the clinical benefit of zileuton under conditions simulating actual clinical practice. The clinical efficacy outcomes of this study have been reported previously by Lazarus et al.[12] and will only briefly be described here.

Methods

Patients

Patients were non-smokers (for at least 6 months prior to enrollment) and were at least 16 years of age with a history of chronic asthma. Patients were required to have a baseline forced expiratory volume in 1 second (FEV_1) of ≥35% of the predicted value, measured at least 4 hours after salbutamol (albuterol) inhalation or 12 hours after salmeterol inhalation. Patients had a ≥15% increase in FEV_1 after salbutamol at screening, or a documented history of positive response to either a methacholine or histamine challenge, and could have no clinically significant abnormalities other than asthma. Women were required to be either postmenopausal, surgically sterile or using an effective method of contraception. Patients agreed to limit their alcohol consumption to ≤2 ounces per day during the study. Patients were allowed to continue their current asthma medications and other concomitant medications, excluding isotretinoin, methotrexate, systemic corticosteroids, gold salt, terfenadine, astemizole, carbamazepine and lipid-lowering agents, all of which had to be discontinued 2–4 weeks prior to starting zileuton.

All patients provided signed, informed consent prior to initiation of any study procedures, and the protocol was approved by the institutional review board of each participating centre.

Study Design

This was a 12-month, randomised, parallel-group, open-label study conducted at 233 sites throughout the US, including allergy and pulmonary clinics, private physician offices, research centres, and academic teaching institutions. Patients were randomly assigned to receive either zileuton (Zyflo®, [1] Abbott Laboratories) 600mg, four times daily plus usual asthma care, or usual asthma care alone in a ratio of approximately 5 : 1. Patients were allowed to continue using their usual asthma medications if the dose of the medication had been stable for at least 4 weeks before study entry.

In addition to an initial screening visit, study visits were scheduled on day 1 of treatment, at week 2 and at months 1, 2, 3, 4, 5, 7, 10 and 12. Safety assessments were performed at every visit, and incorporated both clinical and laboratory monitoring. Efficacy variables included the occurrence of asthma exacerbations, need for alternative treatment, systemic corticosteroid rescue medication use, emergency care or hospitalisation, and improvements in FEV_1 and symptom scores.

Liver Function Monitoring

The main objective of the study was to characterise the patterns and outcomes of zileuton-associated abnormalities in liver biochemistry (ALT, AST, γ-glutamyl transferase [GGT], alkaline phosphatase, lactate dehydrogenase and total bilirubin levels), including overall occurrence rates, the probability of first occurrence, severity of elevation, time to onset, and time to resolution, in patients with asthma treated with zileuton plus usual asthma care compared with patients treated with usual asthma care alone. Liver biochemistry was assessed at screening and at 1, 2, 3, 4, 5, 7, 10 and 12 months after the start of treatment. All post-randomisation test values ≥3 × ULN were required to be recorded as adverse events. Elevations of total bilirubin levels to ≥1.5 × ULN were recorded as adverse events. The protocol allowed asymptomatic patients with an ALT level ≥3 × ULN but <5 × ULN to continue taking zileuton; however, it required that such patients have their liver functions retested weekly until their

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ALT levels either returned to baseline levels or until they were withdrawn from the study because their ALT levels had reached ≥5 × ULN. Zileuton was discontinued in patients with ALT levels ≥5 × ULN, or in whom elevated ALT levels were was accompanied by symptoms consistent with liver disease (right upper quadrant discomfort, nausea, vomiting or fatigue). Patients in whom treatment was discontinued due to liver events were followed up every 2–7 days until resolution of the event (ALT level <2 × ULN).

Statistical Analysis

Comprehensive analyses of liver biochemistry test results were performed to characterise possible zileuton-induced increases in hepatic enzyme levels. For patients with ALT levels ≥3 × ULN, additional analyses were performed, including classification by demographic characteristics, time to first occurrence of an abnormal elevation in ALT level, time to resolution (defined as a reduction in ALT level to <2 × ULN), and type of liver injury as defined by the standard criteria[13] used to assess patterns of liver biochemistry abnormalities. Comparisons between the zileuton plus usual care group and the usual care alone group, with respect to the proportions of patients with abnormally high post-baseline ALT levels, were made using Fisher's Exact test. Life table methods were used to compare the times to the first occurrence of an ALT level ≥3 × ULN between the treatment groups.

Results

A total of 2947 patients were enrolled at 233 centers in the US, with 2458 randomised to treatment with zileuton 600mg four times daily plus usual asthma care and 489 to usual care alone. Patient demographics are provided in table I.

There were no statistically significant differences between the treatment groups with regard to gender, race, age, height or weight. Approximately 61% of patients were female and 39% were male; 91% of patients were Caucasian, 7% were Black and 2% were other ethnicities. The mean age of patients was approximately 43 years.

Of the 2947 patients randomised to treatment, a total of 1196 (40.6%) withdrew prematurely from the study, 1069 patients (43.5%) randomised to treatment with zileuton plus usual care and 127 patients (26.0%) randomised to usual care alone. In the zileuton plus usual care group, 486 patients (19.8%) discontinued as a result of adverse events and 583 (23.7%) discontinued for other reasons (i.e. non-compliance, lack of efficacy, personal reasons, moving). The most common adverse events associated with premature discontinuation in the zileuton group were asthma exacerbations (3.7%), nausea (2.4%) and dyspepsia (1.6%).[12] In the zileuton group, 68 patients (2.8%) with abnormal liver function tests were prematurely withdrawn from the study per protocol as they had ALT levels that were ≥5 × ULN or ALT levels that were 3–5 × ULN in conjunction with symptoms of liver disease.

Of the 489 patients in the usual care group, 11 (2.3%) discontinued treatment due to adverse events and 116 (23.7%) discontinued treatment for other reasons.

Table I. Patient demographics

Variable[a]	Zileuton + usual care (n = 2458)	Usual care (n = 489)
Gender [n (%)]		
female	1490 (60.6)	308 (63.0)
male	968 (39.4)	181 (37.0)
Race [n (%)]		
Caucasian	2236 (91.0)	449 (91.8)
Black	185 (7.5)	31 (6.3)
other	37 (1.5)	9 (1.8)
Age (years)[b]	43.3 ± 0.3	42.7 ± 0.7
Height (cm)[b]	169.2 ± 0.3	168.7 ± 0.5
Weight (kg)[b]	77.0 ± 0.3	77.9 ± 0.7

a There were no significant differences between groups with regard to gender (p = 0.327), race (p = 0.574), age (p = 0.426), height (p = 0.772) or weight (p = 0.277).

b Values are presented as means ± standard error of the mean.

Elevations in Liver Function Tests

Most elevations in liver biochemistry results were mild (>1 × ULN to <1.5 × ULN for total bilirubin levels and >1 × ULN to <3 × ULN for other tests), and the frequencies of mild elevations were generally similar between zileuton-treated patients and patients receiving usual care only. Mild (>1 × ULN to <3 × ULN) elevation in ALT levels occurred in 20.5% of patients in the zileuton group and

19.6% of patients in the usual care group (table II). A total of 109 patients (4.4%) in the zileuton group had ALT levels ≥3 × ULN compared with 5 (1.0%, $p < 0.001$) in the usual care alone group. Maximum reported ALT levels were ≥3 × ULN to <8 × ULN in 78 patients (3.2%) in the zileuton group and four patients (0.8%) in the usual care alone group, and ≥8 × ULN in 31 patients (1.3%) in the zileuton group and 1 patient (0.2%) in the usual care alone group (table II). Eleven patients (0.4%) in the zileuton group had an ALT level ≥15 × ULN, while no patients in the usual care group experienced such an elevation. The time courses of ALT elevation in the 11 patients who experienced ALT levels >15 × ULN, either while on treatment or shortly after treatment discontinuation, are illustrated in figure 1.

Of the 109 zileuton-treated patients with ALT levels ≥3 × ULN, 70 (64.2%) had their first significant elevation in ALT level noted within the first 3 months of treatment, and 89 (81.7%) had their first elevation within the initial 6 months of treatment. Twenty patients (18.3%) had their first elevation in ALT levels noted after >6 months of treatment. The probability of first occurrence (i.e. the risk) of abnormally high ALT levels by time period is shown in figure 2. The probability has been calculated using intervals, which account for the unequal distribution of days between visits; therefore, months 6 and 7; months 8, 9 and 10; and months 11 and 12 were combined because there were no scheduled visits at months 6, 8, 9 and 11.

For the zileuton group, the probability of an ALT levels ≥3 × ULN decreased from a maximum of 2.06% at month 1 to 0.35% at month 3, and then fluctuated in the range of 0.38–0.67% during months 4 through to 12; for the group receiving usual care alone, the probability fluctuated in the range of 0–0.54% throughout the entire study period. After 3 months, the risk of ALT elevation in zileuton-treated patients appeared to remain fairly constant and reflected a rate only marginally higher that that observed in patients receiving usual asthma care.

Table II. Peak ALT levels from baseline

ALT level (multiples of ULN)	Zileuton + usual care (n = 2458) [n (%)]	Usual care (n = 489) [n (%)]
≤1	1744 (71.0)	345 (70.6)
>1 to <3	505 (20.5)	96 (19.6)
3 to <5	45 (1.8)	2 (0.4)
5 to <8	33 (1.3)	2 (0.4)
8 to <15	20 (0.8)	1 (0.2)
≥15	11 (0.4)	0

ULN = upper limit of normal.

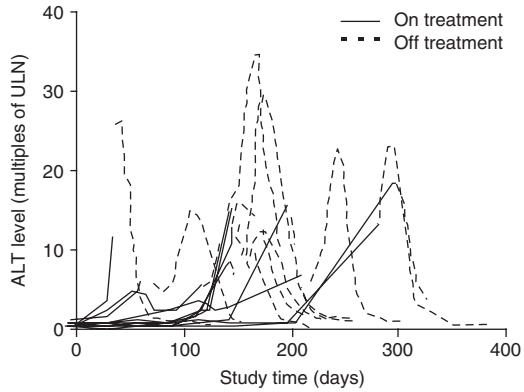
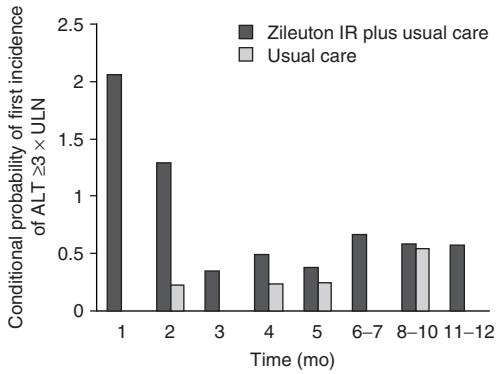


Fig. 1. Serum ALT levels (in terms of the upper limit of normal [ULN]) vs time in the study.

Of the 31 patients with elevations of ALT levels to ≥8 × ULN, 16 (51.6%) experienced these extreme elevations during the first 2 months of treatment. Twenty-four patients (77.4%) had their first elevation in ALT level to ≥8 × ULN during approximately the first 6 months (169 days) of zileuton treatment and 7 patients (22.6%) experienced such an event after 6 months of treatment. There was no apparent pattern to suggest a clinically meaningful relationship between the time of onset and the magnitude of elevation in ALT levels at onset (figure 3). Patients were no more likely to develop very high ALT levels after longer drug exposure than shorter exposure.

There was no overall difference between men and women in the rates of ALT levels ≥3 × ULN (4.7% women vs 4.5% men), but more women than men experienced ALT levels ≥8 × ULN (1.8% vs 0.5%). The rate of elevations in ALT levels among women appeared to increase with age. Women aged ≥65 years appeared to be at higher risk of developing elevated ALT levels (10.1% compared with 4.1% in women <65 years of age). The rate of ALT elevation by race showed no clear trends. The rate of ALT levels ≥3 × ULN was 4.5% and 5.4% in the Caucasian and Black race groups, respectively. No



Patients at risk

Zileuton IR + usual care	2213	1922	1787	1686	1604	1527	1431	1331
Usual care	446	434	425	417	408	397	379	360

Fig. 2. Conditional probability of the first incidence of an ALT level ≥3 × the upper limit of normal (ULN). **IR** = immediate release.

other clinical or laboratory factors appeared useful for the identification of patients at risk of developing an ALT level ≥3 × ULN during treatment with zileuton.

The outcomes of all ALT level elevations to ≥3 × ULN in patients treated with zileuton in this study are shown schematically in figure 4. Patients were not required to discontinue study drug treatment if ALT values were ≥3 × ULN and <5 × ULN, in the absence of symptoms. Therefore, patients with ALT levels ≥3 × ULN and <5 × ULN had the opportunity to experience resolution while remaining on the drug. The majority of patients with ALT levels ≥3 × ULN experienced these elevations while taking zileuton. In a few cases (8 of 109 [7.3%]), the initial elevation was first detected after zileuton treatment was stopped, usually within a few days of discontinuation. It is possible that the onset of the elevation may have occurred while on study drug but treatment was stopped before the patients returned for testing.

Of the 109 patients who experienced ALT levels ≥3 × ULN (figure 4), 104 were followed to resolution (defined as an ALT level <2 × ULN) while remaining on zileuton treatment or after discontinuation of therapy (one patient completed the study with an ALT level of 3.1 ULN and could not be consider resolved). The remaining five patients were followed until their ALT level was ≤3 × ULN; however, they were lost to follow-up before reaching an ALT level of <2 × ULN. Of the 61 patients who experienced modest elevations in ALT (≥3 × ULN but <5 × ULN) while receiving zileuton, 32 (52.5%) experienced spontaneous resolution while continuing zileuton treatment. The mean time to spontaneous resolution for these patients was between 3 and 4 weeks. Of the remaining 29 patients (47.5%), one patient remained on study drug with an ALT level between 3 and 5 × ULN and completed the study with an ALT level of 3.1 × ULN. The remaining 28 patients discontinued the study drug per protocol, as their ALT levels increased to ≥5 × ULN. For the 66 patients who experienced an ALT elevation of ≥5 × ULN while taking zileuton, discontinued study drug and were followed to resolution, the mean time to resolution (<2 × ULN) of the ALT elevation was 1 month after discontinuation. There was no apparent relationship between the magnitude of first elevation and time to resolution. For the five patients in whom the initial ALT elevation ≥3 × ULN was detected after stopping zileuton treatment (either because they finished the study or because they discontinued treatment prematurely) that were followed until resolution, the mean time to resolution was between 2 and 3 weeks (table III),

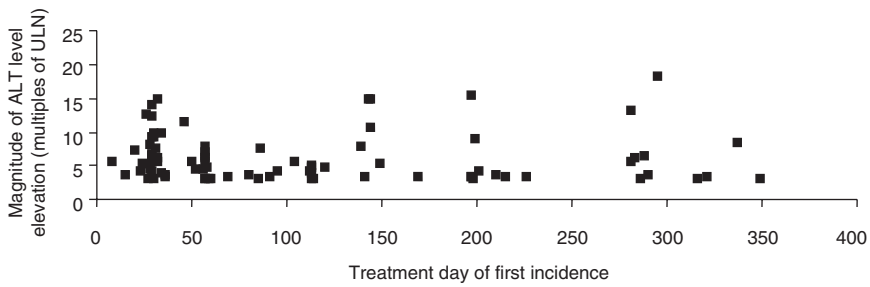


Fig. 3. Magnitude of first ALT level ≥3 × the upper limit of normal (ULN) by the duration of therapy with zileuton.

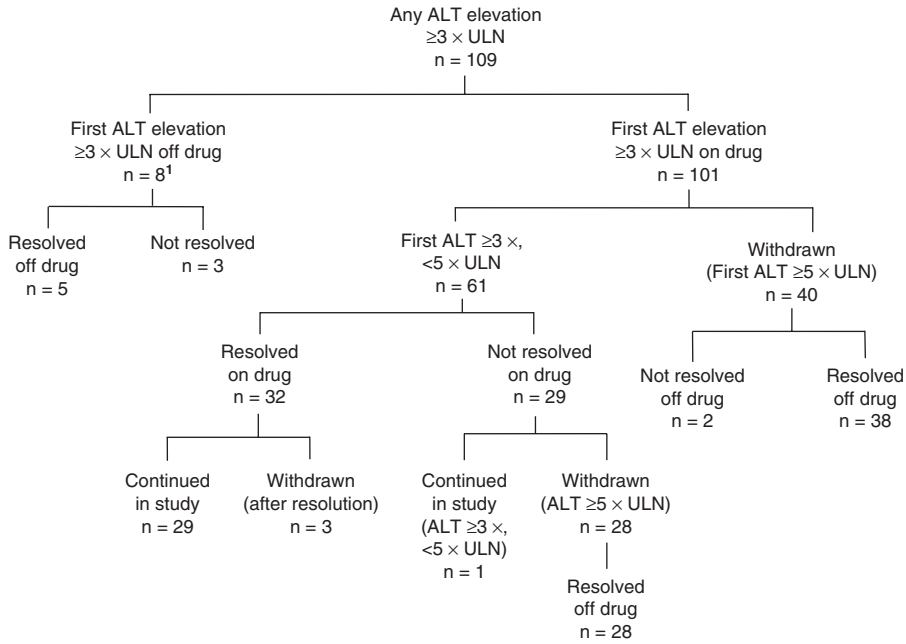


Fig. 4. Schematic diagram of the outcomes of ALT levels ≥3 × upper limit of normal (ULN) for patients treated with zileuton. **1** Four of eight cases were detected 2–4 days after stopping zileuton, while the remaining four were detected at the next follow-up visit 1–2 weeks after discontinuation.

although resolution may have started when zileuton was discontinued before the actual detection time.

The majority (71 of 109 [65.1%]) of the 109 zileuton-treated patients who experienced elevations in ALT level to ≥3 × ULN also had an elevation in their AST level, although usually of lower magnitude. AST levels exceeded 3 × ULN in 25 (22.9%) of the patients with elevated ALT levels. In a few cases, elevations in ALT levels were associated with alkaline phosphatase levels that were ≥3 × ULN (seven patients [6.4%]) and/or total bilirubin levels that were ≥1.5 × ULN (two patients [1.8%]). A pattern of cholestatic injury, associated with alkaline phosphatase levels ≥2 × ULN and mild elevations in ALT levels, was observed in <5% of the 109 zileuton-treated patients with who had elevated ALT levels in this long-term study.

Most patients with elevated ALT levels were asymptomatic. Only 17 (15.6%) of the 109 patients with ALT levels ≥3 × ULN experienced symptoms such as nausea, vomiting, influenza-like symptoms and right upper-quadrant abdominal pain, which may have been attributable to liver injury.

Two of 2458 zileuton-treated patients experienced an elevation in ALT level to ≥3 × ULN associated with a total bilirubin level ≥1.5 × ULN. The first patient, a 35-year-old Asian woman, was prematurely withdrawn from the study after 5 months of treatment with zileuton because of abdominal pain; she had an ALT level of 7.9 × ULN and an AST level of 3.6 × ULN with normal total bilirubin and alkaline phosphatase levels at the time of withdrawal. This patient's ALT levels kept increasing after discontinuation of zileuton treatment and reached 29.8 × ULN on post-treatment day 31. Her total bilirubin levels had increased to 1.5 × ULN by post-treatment day 28. A prolonged rise in serum ALT level after stopping treatment has not been previously associated with zileuton treatment. A liver biopsy, performed on post-treatment day 35, revealed moderate centrilobular (Zone III) necrosis, which is consistent with paracetamol (acetaminophen)-induced injury. The patient reported taking paracetamol during that time period but the amount and actual timing relative to the liver event could not be documented. The consulting hepatologist could

not rule out the possibility that zileuton initiated a hepatic reaction but, in view of the zonal distribution of the injury detected by biopsy, he felt it likely that paracetamol had contributed to the unusual course observed. This case would just meet the conservative criteria for Hy's law (ALT level ≥3 × ULN with total bilirubin level ≥1.5 × ULN).[14]

The second patient, a 57-year-old man, experienced moderate elevations in ALT (up to 6.3 × ULN), AST (up to 3.3 × ULN) and total bilirubin levels (up to 1.8 × ULN), together with severely elevated GGT level (up to 16 × ULN) and an elevated alkaline phosphatase level (2 × ULN) after 1 month of treatment with zileuton. All liver function tests returned to baseline within 29 days after discontinuation. Since this patient had a substantial elevation in the serum alkaline phosphatase level, this can not be considered to be hepatocellular injury and this patient would not qualify as a Hy's law case. In addition, one patient had an ALT level of >12 × ULN and a total bilirubin level of 1.43 × ULN at the final study visit at month 12; however, the borderline increases in total bilirubin levels (1 × ULN) at screening and on day 58, without increases in other liver biochemistry parameters, and the normalisation of liver enzyme levels (ALT and AST) post-treatment without a corresponding normalisation in bilirubin level suggest potential undiagnosed Gilbert's syndrome, and did not meet the conservative definition of Hy's law. Although no cases of jaundice were reported in this long-term study of zileuton, one patient of 2458 (0.1%) exposed to zileuton would meet the conservative definition of Hy's law.

Discussion

Drug-induced liver injury has been and remains the single most common adverse effect of concern for compounds in all phases of clinical development, and is the most frequent cause of post-marketing regulatory actions including withdrawal, labeling restrictions and warnings.[7,14-16] Most drug-induced liver injury presents as acute elevations in the levels of serum aminotransferases (ALT and AST) with minimal or no elevation in serum alkaline phosphatase and bilirubin levels. This is termed a 'hepatocellular' pattern of injury. The majority of drugs capable of causing severe liver injury are well tolerated in most patients taking them and produce progressive liver injury in only a very small proportion of the treated population. The injury is therefore termed 'idiosyncratic', and the assumption is that certain patients with rare combinations of inherited and environmental factors are predisposed to developing hepatotoxicity. Examples of drugs that can cause idiosyncratic hepatocellular injury include troglitazone, trovafloxacin, multiple antibacterials and NSAIDs.[8,9,16-19]

Nearly all drugs capable of causing severe idiosyncratic hepatocellular injury have been associated with an increased incidence (relative to placebo) of serum ALT levels ≥3 × ULN in patients during clinical studies. An ALT level ≥3 × ULN has been identified as a sensitive, but not necessarily specific, signal of liver toxicity, and is not always predictive of more severe outcomes such as overt toxicity (symptoms and jaundice).[7-11,14,15]

Table III. Time to resolution of elevated ALT level in affected patients receiving zileuton

Magnitude of initial elevated ALT level	Elevation and resolution on drug[a]		Elevation on drug, resolution off drug[b]		Elevation and resolution off drug[a]	
	n	mean days	n	mean days	n	mean days
Any elevation ≥3 × ULN	32	25.3	66	31.6	5	15.8
3 × ULN ≤ALT <5 × ULN	32	25.3	28	29.4	2	21.0
5 × ULN ≤ALT <8 × ULN	0		19	38.0	3	12.3
8 × ULN ≤ALT <15 × ULN	0		17	27.8	0	
ALT ≥15 × ULN	0		2	33.0	0	

a Time to resolution = number of days from first abnormally high level (≥3 × ULN) to the first measurement of a level <2 × ULN, after which the level did not subsequently reach or exceed 2 × ULN during monitoring.

b Time to resolution = number of days from discontinuation of study drug to the first measurement of a level <2 × ULN, after which the level did not subsequently reach or exceed 2 × ULN during monitoring.

ULN = upper limit of normal.

The principal objective of this long-term surveillance study was to characterise the clinical pattern of liver injury associated with zileuton in order to better assess the true risk of severe injury and to provide data upon which to propose to physicians the most appropriate patient monitoring schedule. This long-term study was also conducted to assess the clinical benefit of zileuton as an adjunctive treatment to usual asthma care. The results from the clinical efficacy outcomes[12] demonstrated that smaller proportions of patients treated with zileuton plus usual care than usual care alone required corticosteroid rescue medication (23.0% vs 30.3%; $p \leq 0.001$), emergency care (7.7% vs 11.5%; $p \leq 0.05$), or hospitalisation (3.2% vs 4.1%, not significant) and that zileuton-treated patients had greater improvements in FEV_1 (0.28L vs 0.21L; $p \leq 0.05$). In addition to significant improvements in objective measures, including a reduction in health resource utilisation, the zileuton-treated group showed significant improvements in asthma symptoms compared with the group that received usual care alone. Overall, the data from the study indicated that zileuton, when added to an existing therapeutic regimen, improves asthma control in many patients.

Among the 2458 patients treated with zileuton, 4.4% (109 patients) experienced elevations in ALT levels to $\geq 3 \times$ ULN compared with 1.0% (5 patients) of the 489 in the usual care group. This is higher than the rate of ALT levels $\geq 3 \times$ ULN reported in the Zyflo® labeling, which was taken from placebo-controlled studies with zileuton (1.9% with zileuton and 0.2% with placebo).[3] This higher rate is probably accounted for, in part, by the longer duration of this study (12 months compared with 3–6 months for the placebo-controlled studies) and perhaps by the less restrictive inclusion criteria in terms of patient population and use of concomitant medications. As seen in the phase II/III studies, most elevations in ALT levels were mild, asymptomatic and usually not associated with elevations in alkaline phosphatase and/or total bilirubin levels. The characteristic biochemical pattern of zileuton-associated liver injury is therefore hepatocellular. In this study, all episodes of ALT elevation resolved, with a mean resolution time of 4 weeks.

The majority (64.2%) of elevated ALT levels occurred during the first 3 months of treatment. After 3 months, the risk of elevated ALT levels in zileuton-treated patients fell toward that observed in patients receiving usual asthma care. However, it seems likely from our data that zileuton-associated liver injury can occur after 3 months of treatment, as the rate of elevated ALT levels did not quite fall to the rate observed in the usual care group. This provides the rationale for the current guidelines for monitoring zileuton-treated patients: the approved package insert for zileuton IR (Zyflo®)[3] recommends that the ALT level be monitored before starting therapy; once a month for the first 3 months of zileuton therapy; every 2–3 months for the remainder of the first year of treatment; and periodically thereafter.

Although there was a clear reduction in risk of ALT level elevation after the first 3 months of treatment, there was no clear correlation between the time of onset of elevated ALT levels and the severity of liver injury. This may in part reflect the less frequent blood sampling (every 2–3 months) that occurred after the first 5 months of treatment. Except for a higher risk of elevated ALT levels in women aged ≥65 years, no other risk factors appeared to be helpful for the identification of patients at risk of developing an ALT level $\geq 3 \times$ ULN during treatment with zileuton. This suggests that some caution should be used when prescribing zileuton to elderly women; however, the data suggest that approximately 90% of such patients will not experience elevated ALT levels during treatment.

Among those zileuton-treated patients who experienced an initial elevated ALT level of between 3 and $5 \times$ ULN, more than half were able to continue zileuton treatment with resolution of the elevation. An 'adaptation' phenomenon has been reported for several other drugs associated with idiosyncratic hepatocellular injury.[15] The currently accepted interpretation of this observation is that the majority of patients who experience elevated ALT levels due to a drug are not at risk of developing significant liver injury, and in most of these patients the elevation will resolve with continued drug exposure. Patients who develop progressive liver injury may therefore be a subset of patients who experience elevated ALT levels but lack the ability to adapt. The mechanisms underlying adaptation to liver toxicity are not known.

The mechanisms underlying zileuton-induced liver injury are also unknown. All patients in this study received the same dose of zileuton (600mg, four times daily) and plasma levels of zileuton were not routinely measured. However, in the phase II/III clinical studies, the incidence and severity of liver injury did not appear to be related to total daily dose. In addition, when plasma-level data were available, toxicity was not associated with zileuton blood levels ≥7.5 μg/mL, which are considered to be higher than expected in patients receiving zileuton at dosages ≤600mg four times daily.[6] It is important to note that, in this study, elevated ALT levels were not associated with rash, fever or peripheral eosinophilia. Hence, there is no evidence that any liver injury associated with zileuton is the result of an allergic response.

The absence of a relationship between zileuton-associated hepatotoxicity and drug dose, systemic exposure and clinical signs of hypersensitivity is consistent with the observations made with most drugs that are associated with idiosyncratic hepatocellular injury.[8,15,16] The assumption is that the liver injury results from, at least in part, aberrant metabolism of the drug or an unusual response in rare susceptible individuals. Therefore, the mechanism underlying this form of liver toxicity has been termed 'metabolic idiosyncrasy'.[20]

Although it is not possible to accurately estimate the zileuton-associated risk of severe liver injury from the current study, some comments can be made. The late Hyman Zimmerman[20] first noted that patients presenting with the combination of hepatocellular injury (elevated serum ALT levels) and clinically apparent jaundice (associated with a total bilirubin level >3 mg/dL) had a mortality rate of approximately 10%. Therefore, Zimmerman's observation would predict that if 1 in 1000 treated patients in a clinical study presented with hepatocellular jaundice, fatal injury could be expected to occur in approximately 1 in 10 000 treated patients. This has been referred to as 'Hy's law' and has withstood the test of time.[20,21] In an effort to cast the widest net possible and capture the most sensitive (though not the most specific) predictive value of biochemical markers, Hy's law has come to be defined as any ALT level ≥3 × ULN with a total bilirubin level of 1.5 to 2 × ULN in the absence of a substantial elevation in the serum alkaline phosphatase level. These more restrictive criteria have been invoked as a potential predictor of acute liver failure from pre-approval data, even in the absence of any documented cases of acute liver failure or hepatocellular jaundice in the clinical trial database.[21,22]

As previously mentioned, a single patient developed hepatocellular jaundice among the 2517 patients who received treatment with zileuton in the phase II/III clinical trials. There were no cases of jaundice in this long-term study of 2458 zileuton-treated patients, but one patient met a conservative definition of Hy's law. For the total zileuton experience in over 6000 patients, these two cases would predict a risk of liver failure of 1 : 30 000 treated patients. However, the duration of treatment in the clinical trials varied and, without knowing the incidence of liver injury as a function of time on treatment, it is not possible from the phase II and phase III clinical studies to assess the true risk of liver failure.

It should be noted that our study was not designed to prove the value of monitoring, which would have required a study arm in which patients received treatment without monitoring. Nonetheless, it seems reasonable to assume that terminating treatment when the serum ALT level exceeded 5 × ULN prevented progression to clinically important liver injury in at least some patients.

Conclusions

In summary, this prospective study defined a characteristic presentation, or 'signature' of zileuton-associated liver injury as a hepatocellular injury generally occurring within 3 months of starting therapy and resolving within 1 month of discontinuing therapy. It is generally asymptomatic and treatment can often be continued with careful monitoring in asymptomatic patients with low-level elevations in serum enzyme levels (between 3 and 5 × ULN). With liver enzyme monitoring, the risk of irreversible liver injury appears to be low.

Acknowledgements

This study was funded by a grant from Abbott Laboratories, North Chicago, Illinois. Abbott Laboratories was responsible for the design and conduct of the study, and for the analysis and reporting of the results.

Dr Watkins has acted as a consultant for Abbott Laboratories and Critical Therapeutics Inc. regarding zileuton, but has not received compensation for the preparation of this manuscript. Dr Dube was employed by Abbott Laboratories at the time this study was conducted, is currently acting as a consultant for Critical Therapeutics Inc. and has received stock options from Abbott Laboratories and Critical Therapeutics Inc. Dr Walton-Bowen is currently an employee of and has received stock options from Critical Therapeutics Inc. Drs Cameron and Kasten have no conflicts of interest that are directly relevant to the content of this study.

The authors thank Drs Willis, C Maddrey and Steven Schenker for their critical review of this manuscript.

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