

Zafirlukast has no beneficial effects in the treatment of chronic urticaria

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Summary

Background Leukotriene receptor antagonists have shown some efficacy in the treatment of asthma. Injection of LTC₄, LTD₄ and LTE₄ into the skin leads to a weal-and-flare reaction, suggesting an involvement of leukotrienes in the pathogenesis of urticaria. Indeed, various reports have indicated a beneficial effect for leukotriene receptor antagonists in patients with chronic urticaria.

Objective To determine the therapeutic effect of the leukotriene receptor antagonist zafirlukast in patients with chronic urticaria.

Methods The study was a double-blind, placebo-controlled, cross-over study lasting for 12 weeks. Fifty-two patients with chronic urticaria were investigated at a university hospital. The patients were randomized to receive 20 mg zafirlukast b.i.d. or placebo and cross-over was scheduled after 6 weeks. The efficacy of the treatment was evaluated by a daily symptom score, six physical examinations, the requirement of rescue antihistamines (acrivastine) and an overall assessment by the patient and the investigating physician.

Results Forty-six patients completed the study: zafirlukast was well tolerated without alteration of the investigated laboratory parameters. In comparison with placebo, treatment with zafirlukast resulted in no significant positive effect for any of the efficacy measures. Moreover, we were unable to identify any subgroup of patients with chronic urticaria responding with a therapeutic benefit.

Conclusions The leukotriene receptor antagonist zafirlukast does not provide a significant therapeutic benefit at a dose of 20 mg b.i.d. in patients with chronic urticaria.

Keywords chronic urticaria, leukotriene receptor antagonist, zafirlukast

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Introduction

Chronic urticaria (CU) is a common skin disorder, which is thought to occur in at least 0.1% of the population [1]. CU is defined by the appearance of pruritic cutaneous weals recurring on most days for at least 6 weeks. Individual weals do not usually persist in a given location for more than 24 h. In many cases angioedema with infiltration and swelling at the lower dermal and submucosal levels coexists with CU. The course and duration of CU are highly variable and not predictable. Spontaneous remissions may often occur within 12 months but a substantial number of patients may have symptoms at least periodically for years [1, 2]. Therefore, CU often represents a seriously disabling condition with a considerable reduction in quality of life [3].

The management of CU may also present a therapeutic challenge. Except for some cases with an avoidable cause, patients with CU are usually treated symptomatically. The cornerstone of treatment is the use of antihistamines, but their therapeutic effect often remains unsatisfactory. Alternative therapeutic

regimens, including immunosuppressive agents such as glucocorticosteroids and cyclosporin, may be necessary in severe and refractory forms of CU. Furthermore, repeated plasmapheresis or intravenous immunoglobulin therapy have been reported to have some therapeutic effect in patients with circulating IgG autoantibodies to IgE or the high affinity IgE receptor [4].

In recent years some reports have also claimed a beneficial effect for the leukotriene receptor antagonists (LT-RA) zafirlukast and montelukast as well as the 5-lipoxygenase-inhibitor zileuton in the treatment of patients with CU [5–15]. The rationale for the treatment of CU with LT-RA is partly derived from the pathophysiology of urticaria, which is primarily caused by the degranulation of mast cells, releasing various mediators such as histamine, tryptase, prostaglandins and leukotrienes (LT) [2, 16]. Furthermore, intradermal injection of LT has been shown to induce a weal-and-flare reaction, providing further evidence that these mediators may participate in the formation of urticaria [17]. In contrast Onishi-Inoue reported an induction of urticaria in two patients with an aspirin-induced urticaria, giving low doses of an LT-RA [18]. However, besides some preliminary reports and one study on patients with intolerance to food and/or acetylsalicylic acid [14] the effects of LT-RA in CU have not yet been extensively studied in a controlled fashion. Due to the highly variable course of CU, with

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frequent spontaneous remissions, a randomized, double-blind, placebo-controlled trial is therefore warranted to obtain the required information of LT-RA efficacy in CU. In order to investigate the tolerability and efficacy of zafirlukast (Accolate®) in patients with CU, we used this LT-RA in the dose recommended for the treatment of asthma. Zafirlukast binds competitively and selectively to the Cys-LT₁ receptor (LTC₄ and LTD₄). It has proven its efficacy in patients with chronic asthma of all stages (mild to severe) as well as in patients with asthma, polyposis nasi and intolerance to aspirin [19].

Methods

Patients

We recruited 52 adult patients (20 males, 26 females; age range 18–74 years) with CU from our outpatient clinic at the university hospital in Bern. CU was defined as the appearance of urticarial lesions for more than 6 weeks duration, with at least three episodes of weals a week. The presence of urticarial skin lesions was confirmed clinically by the investigating physician. The patients were recruited from a heterogeneous population of CU, in most patients no cause was found (idiopathic urticaria) but physical stimuli aggravated symptoms. Prior to the study most patients had received H1-antagonists and some of them additional medications including H2-antagonists and glucocorticosteroids.

The exclusion criteria of the study were the following: pregnancy, breast-feeding, significant general or psychiatric disease, and medication with astemizol, corticosteroids i.m. or LT-RA during the previous 2 months or oral corticosteroids in the last month. Furthermore, patients with an allergic urticaria or urticaria-vasculitis were also excluded from the study.

The ethical committee of the Medical Faculty of the University of Bern approved the study protocol. All patients gave their oral and written informed consent to participate in the study.

Study design

The study was a randomized, double-blind and placebo-controlled, cross-over study lasting for 12 weeks. All study medications were supplied by AstraZeneca, the provider of Accolate® (zafirlukast). They were also in charge of the blinding procedures. Study medication was allocated randomly by the investigating doctors.

Six clinical visits were carried out during the study. At visit 1 personal history was recorded, a physical examination, skin prick tests with common aeroallergens and food allergens and standard laboratory investigations for urticaria were performed, i.e. a full blood count, c-reactive-protein, biochemical profile, protein electrophoresis, total IgE, antinuclear antibodies, basal TSH, urine analysis. Thereafter a wash-out period of at least 1 week was started, in which all medical treatments except for the short-acting antihistamine acrivastine (up to 8 mg t.i.d.) were stopped. If required the patients were also allowed to take acrivastine as a rescue medication throughout the study. On visit 2 (day 0) the patients were randomized to receive either 20 mg zafirlukast b.i.d. or placebo. Subsequent visits were performed every 3 weeks, cross-over was scheduled at visit 4 (day 42). At this day patients didn't take any study medication,

having a wash-out period of 1 day, considering the short half-life of zafirlukast (about 8 h).

Laboratory analyses were done on visits 1, 4 and 6.

Efficacy measures

All patients recorded their symptoms, including itching, disturbance of sleep and daily activity, as well as the number of weals, in a daily diary. The number of study tablets and rescue medication taken were noted as well. At each clinical visit the patient's diary was reviewed and a physical examination was performed. The intensity of erythema, and the size, number and extension of the weals, were recorded. Furthermore, the overall clinical benefit of the treatment was assessed by the patient and the investigating physician at each of the visits. In addition, total serum tryptase ($\alpha + \beta$) (Unicap, Pharmacia, Uppsala, Sweden; normal range 1 to 13.5 µg/l) and methylhistamine in urine (RIA-Kit, Pharmacia; normal range 70 to 160 µg/g Crea) were measured as laboratory parameters.

Efficacy measures were scored according to the following scales. Itching, disturbance of daily activity and sleep: 0 (none), 1 (mild), 2 (moderate) and 3 (severe symptoms/disturbance). The intensity of erythema: 0 (absent), 1 (slight/pale), 2 (definite/red) and 3 (extreme/angry red). The number of weals: 0 (none), 1 (1 to 5 weals), 2 (6 to 15 weals), 3 (> 25 weals). The extension of weals: 0 (none), 1 (slight, 1 to 10% of body area involved), 2 (moderate, 11 to 30% of body area), 3 (severe > 30% of body area). The size of weals (greatest diameter): 0 (no lesions), 1 (small, < 0.5 cm), 2 (medium, 0.5 to 2 cm), 3 (large, > 2 to 4 cm), 4 (giant > 4 cm). The overall clinical benefit assessed by the patient and investigator: 0 (complete), 1 (marked), 2 (moderate), 3 (slight), 4 (no relief) and 5 (worse).

Safety measures

The tolerability of zafirlukast was assessed by recording any adverse events and with laboratory tests (e.g. liver parameters) at visits 1, 4 and 6.

Statistical evaluation

The principal analysis was carried out on an intention-to-treat basis. Statistical analysis was performed using a simple two-sample unpaired *t*-test adjusting for the period effect as described by Senn [20]. The corresponding estimates for the treatment effect were calculated. A *P*-value of < 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics of the patients

Of the initial 52 patients enrolled, 46 completed the study. Six patients were excluded: two patients withdrew from the study (one after 19 days because of an exacerbation of urticaria, the other after 5 days due to starting alternative medicine), and one patient had to be excluded for taking oral corticosteroids as rescue medication because of a concurrent acute angioedema. All three patients were excluded during phase I, taking placebo. The other three patients had to be excluded at the end of the study because of poor compliance with filling out the daily diary.

Of the subjects completing the study, 24 patients were first randomized to receive 20 mg zafirlukast b.i.d., followed by placebo; 22 patients got the inverse treatment. The mean duration of CU was 31.4 months (range 3 to 338 months), in 25 patients (54%) the duration was less than 12 months, in five patients (11%) more than 5 years. According to their history, 31 of our patients experienced some aggravation of their symptoms by scratching or at pressure-exposed sites (67%). In 29 (63%) of these patients a positive dermatographism was found. Dermatographism was defined as an immediate itching linear red weal, drawing the tip of a blunt-pointed instrument firmly across the skin of the back [2]. Cold was identified as a trigger factor in two patients (both had a positive cold test and a negative family history for cold urticaria). Furthermore, 14 patients (30%) reported exacerbations after intake of acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs (NSAIDs). Pressure and intake of aspirine or NSAID showed an aggravation of the pre-existing disease and therefore were considered as triggers and not as physical, delayed pressure urticaria or aspirin sensitivity.

Laboratory evaluations showed an eosinophilia ($0.65 \times 10^9/L$, normal range 0.02 to $0.4 \times 10^9/L$) in one patient and an increased total IgE value in nine patients (228 to 2222 kU/L, normal range ≤ 200 kU/L). Three patients had slightly elevated antinuclear antibodies (1 : 320, negative ≤ 1 : 80), but no other signs of urticaria vasculitis: the weals were present for less than 24 h and did not cause residual pigmentation. All three patients had no other clinical or laboratory signs of a vasculitis. Two patients had decreased TSH values with normal fT3 and fT4 values. One patient suffered from chronic hepatitis B infection (anti-HBs and anti-HBc positive) with normal values for liver enzymes. Skin testing with autologous serum was not performed.

Efficacy measures

Statistical analysis of the efficacy measures showed no significant therapeutic effect for 20 mg zafirlukast b.i.d. compared with placebo for any of the analysed parameters. As a representative example for the lack of a therapeutic effect, the mean daily scores for itching in the placebo and the zafirlukast group during the trial are illustrated in Fig. 1. The intake of the rescue medication acrivastine (mean numbers of tablets per day), which did not differ significantly in both groups either, is shown as a further important parameter in Fig. 2: all patients (100%) required rescue medication in the form of acrivastine. Statistical analysis of the efficacy measures assessed daily by the patients and at the clinical visits by the investigating physician are demonstrated in Tables 1 and 2, respectively. No significant difference was found for any of these measures. Furthermore, no significant difference in the assessment of the overall clinical benefit of the treatment was observed by the patient (mean $\pm$ SD score in the placebo group, 2.93 ± 1.050 ; in the zafirlukast group, 3.62 ± 0.612 ; $P = 0.8086$) and the investigating physician (mean $\pm$ SD score in the placebo group, 2.86 ± 1.146 ; in the zafirlukast group, 3.52 ± 0.730 ; $P = 0.8294$).

In addition, laboratory parameters measuring tryptase (mean $\pm$ SD of the log tryptase concentration in the placebo group, $1.85 \mu\text{g/L} \pm 0.514$; in the zafirlukast group, $2.03 \mu\text{g/L} \pm 0.610$; $P = 0.0705$) and methylhistamine in the urine (mean $\pm$ SD of the log methylhistamine concentration in the placebo group, $5.17 \mu\text{g/g Crea} \pm 0.484$; in the zafirlukast group, $5.14 \mu\text{g/g Crea} \pm 0.286$; $P = 0.3880$) showed no significant difference between the two study groups.

As no statistical significance was detectable in the collective patient group, analysis of subsets of patients with particular forms of CU was performed. However, neither the patients

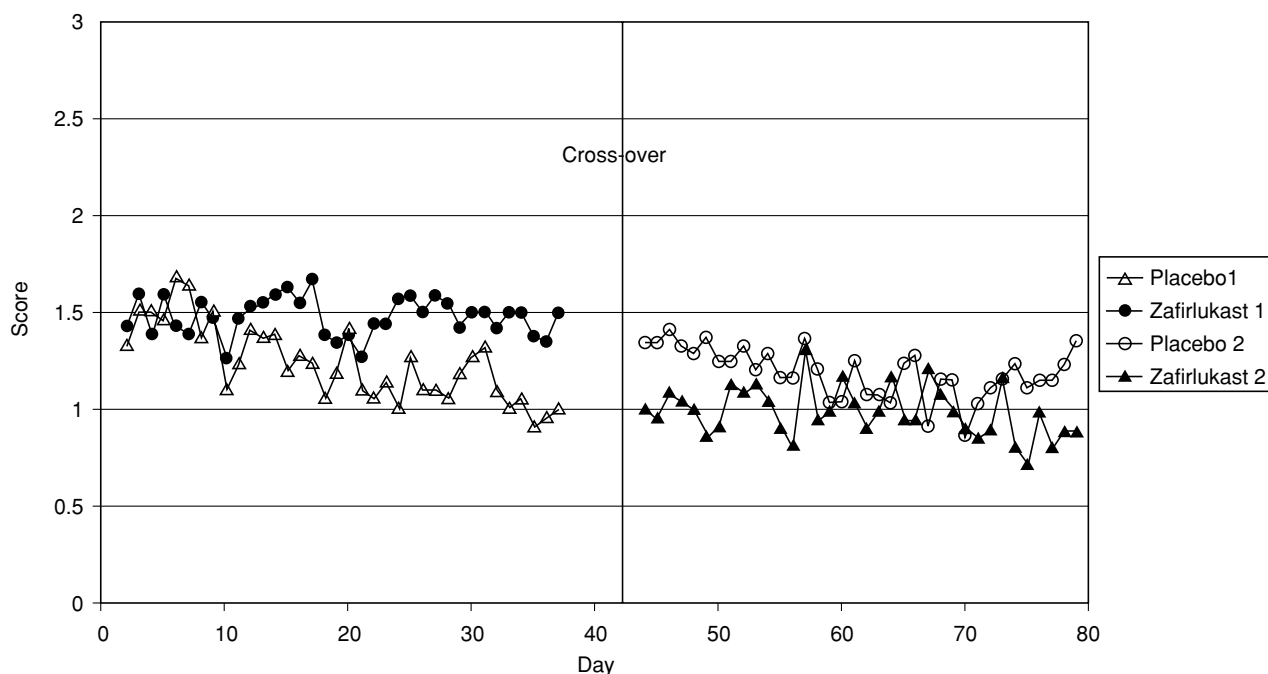


Fig. 1. Results of the itching score: 24 patients received 20 mg zafirlukast b.i.d. (zafirlukast 1), followed by placebo (placebo 2); 22 patients got the inverse treatment (placebo 1, zafirlukast 2). Daily mean values are shown.

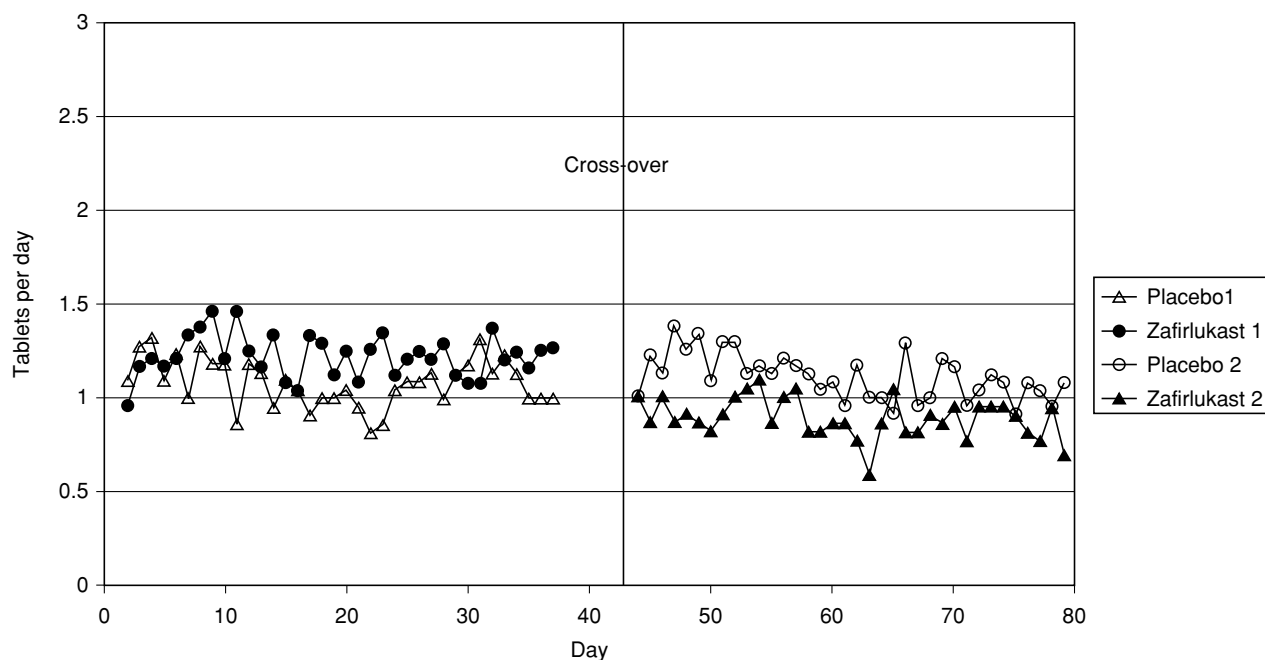


Fig. 2. Results of the use of rescue medication: the mean numbers of acrivastine tablets taken daily are shown in 24 patients who received 20 mg zafirlukast b.i.d. (zafirlukast 1), followed by placebo (placebo 2), and 22 patients who got the inverse treatment (placebo 1, zafirlukast 2). Daily mean values are shown.

Table 1. Assessments by the patient

	Zafirlukast (mean* $\pm$ SD)	Placebo (mean* $\pm$ SD)	P-value
Itching score	1.47 $\pm$ 0.647	1.24 $\pm$ 0.614	0.7994
Number of weals score	1.72 $\pm$ 0.776	1.27 $\pm$ 0.718	0.8319
Disturbance of daily activity score	1.18 $\pm$ 0.694	1.10 $\pm$ 0.779	0.4183
Disturbance of sleep score	0.50 $\pm$ 0.688	0.48 $\pm$ 0.540	0.8841
Intake of acrivastine (tablets per day)	1.23 $\pm$ 0.941	1.09 $\pm$ 0.924	0.6887

*Mean-value: mean of daily mean scores.

Table 2. Assessments by the physician

	Zafirlukast (mean* $\pm$ SD)	Placebo (mean* $\pm$ SD)	P-value
Intensity of erythema	1.02 $\pm$ 0.801	0.80 $\pm$ 0.797	0.5906
Extension of weals	1.20 $\pm$ 1.132	0.89 $\pm$ 0.987	0.4046
Size of weals	1.52 $\pm$ 1.165	1.02 $\pm$ 0.957	0.6808
Number of weals	1.50 $\pm$ 1.437	1.02 $\pm$ 1.220	0.2481

*Mean-value: mean of daily mean scores.

reporting aggravations after pressure ($n=31$), nor intake of ASA and NSAIDs ($n=14$), or after cold ($n=2$), showed a significant improvement of their symptoms.

Seven patients (15%) had a complete resolution of symptoms during the study: four of them during the period of taking placebo, three during intake of zafirlukast. A marked improvement of symptoms was observed in 12 patients (26%): seven during treatment with placebo and five with zafirlukast. Thus, a slightly higher proportion of patients showed marked

improvement or resolution of their symptoms during treatment with placebo.

Safety measures

The therapy with zafirlukast was well tolerated: no clinical side-effects were reported and no substantial changes in laboratory parameters (i.e. eosinophils, liver enzymes) were observed.

Discussion

This is the first study to evaluate the efficacy of 20 mg zafirlukast b.i.d. in the treatment of CU in a double-blind and placebo-controlled cross-over fashion. Fifty-two adult patients were recruited, of which 46 completed the study. The majority of our patients reported an aggravation of their symptoms through pressure and some after the intake of ASA or other NSAIDs, which are well-known trigger factors of CU [21–23]. However, these factors were not the sole cause of the patients' symptoms, as weals also appeared without pressure and

NSAID intake, indicating the presence of an idiopathic form of CU in the majority of our patients.

Our results showed no significant difference between 20 mg zafirlukast b.i.d. daily and placebo for any of the efficacy measures analysed (i.e. daily symptom score, clinical assessment by the investigating physician, and overall assessment by patient and investigating physician). In particular, the consumption of rescue medication was also similar in both groups and did not alter after changing from verum or placebo or vice versa. Interestingly, a marked improvement or complete resolution of CU was found in 19 of the 46 patients. However, as this improvement occurred in placebo- and zafirlukast-treated patients, we attribute it to the spontaneous course of CU. It is well known that the spontaneous course of CU may be highly variable [22–25]. These spontaneous remissions might also be the main reason for the discrepant interpretation of the efficacy of LT-RA in open or double-blinded studies reported previously. Indeed, we obtained a positive effect of treatment (placebo and zafirlukast) in 40% of the patients, which in tendency resembles previously published data with open studies (53 to 60%) [11–13].

As a particularly noteworthy finding we were unable to identify any subgroup of patients with CU responding with a therapeutic benefit. One may have reasoned that those patients reporting an aggravation by ASA or NSAIDs might be better responders to LT-RA, as patients with aggravation of their asthma after ASA or NSAIDs are considered good responders to LT-RA [26]. Indeed, previous reports have suggested that patients with ASA or NSAIDs sensitivity and CU may be more likely to respond to LT-RA [5, 7, 14]. In particular, Pacor et al. have investigated the therapeutic effect of either montelukast 10 mg or cetirizine 10 mg daily with placebo in 51 patients with a positive challenge to additives and/or aspirin [14]. Thereby, montelukast showed a statistically better therapeutic effect compared with cetirizine and placebo regarding the patient's symptoms and their use of rescue medication ($P < 0.001$). However, none of our 14 patients, who had reported aggravation of their symptoms after intake of ASA or NSAIDs, responded with a significant improvement after treatment with zafirlukast.

One important difference to some of the previous reports is that many patients with an improvement of their symptoms had a constant contemporary therapy with antihistamines. Bensch and Borish reported a dramatic improvement of CU in 10 of 18 patients by adding zafirlukast, montelukast or zileuton to treatment with antihistamines [11]. Norris and Sullivan studied the therapeutic effects of zafirlukast in 15 patients with severe CU, who had been requiring systemic corticosteroids to achieve an acceptable quality of life [13]. In nine out of 15 patients (60%) an improvement was achieved by the addition of 20 mg zafirlukast b.i.d. to a combined H_1 - and H_2 -antagonist therapy. Thus, it cannot be ruled out that LT-RA may have a synergistic effect to antihistamines. Furthermore, it is also possible that higher doses of zafirlukast or other LT-RAs may have a better therapeutic effect in CU. Further controlled studies investigating the use of LT-RA in CU are thus warranted. Nevertheless, the missing therapeutic effect of LT-RA in our study indicates that the role of LT in the aetiology of CU is probably rather insignificant.

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References

- 1 Greaves MW. Chronic urticaria. *N Engl J Med* 1995; 332:1767–72.
- 2 Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000; 105:664–72.
- 3 O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; 136:197–201.
- 4 Wanderer AA, Bernstein LI, Goodman DL et al. The diagnosis and management of urticaria. *Ann Allergy Asthma Immunol* 2000; 85:521–44.
- 5 Ellis MH. Successful treatment of chronic urticaria with leukotriene antagonists. *J Allergy Clin Immunol* 1998; 102:876–7.
- 6 Spector S, Tan RA. Antileukotrienes in chronic urticaria. *J Allergy Clin Immunol* 1998; 101:572.
- 7 Asero R. Leukotriene receptor antagonists may prevent NSAID-induced exacerbations in patients with chronic urticaria. *Ann Allergy Asthma Immunol* 2000; 85:156–7.
- 8 Berkun Y, Shalit M. Successful treatment of delayed pressure urticaria with montelukast. *Allergy* 2000; 55:203–4.
- 9 Hani N, Hartmann K, Casper C et al. Improvement of cold urticaria by treatment with the leukotriene receptor antagonist montelukast. *Acta Derm Venereol* 2000; 80:229.
- 10 Tedeschi A, Suli C, Lorini M, Airaghi L. Successful treatment of chronic urticaria. *Allergy* 2000; 55:1097–8.
- 11 Bensch G, Borish L. Leukotriene modifiers in chronic urticaria. *Ann Allergy Asthma Immunol* 1999; 83:348.
- 12 Chu TJ, Warren MS. Zafirlukast in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1998; 101:155.
- 13 Norris GJ, Sullivan TJ. Leukotrienes and cytokines in steroid dependent chronic urticaria. *J Allergy Clin Immunol* 1998; 101:128.
- 14 Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria. A double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001; 31:1607–14.
- 15 Nettis E, Dambra P, D'Oronzio L, Loria MP, Ferrannini A, Tursi A. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol* 2001; 137:99–100.
- 16 Wedi B, Novacovic V, Koerner M, Kapp A. Chronic urticaria serum induces histamine release, leukotriene production and basophil CD63 surface expression-inhibitory effects of anti-inflammatory drugs. *J Allergy Clin Immunol* 2000; 105(3):552–60.
- 17 Maxwell DL, Atkinson BA, Spur BW, Lessof MH, Lee TH. Skin responses to intradermal histamine and leukotrienes C4, D4 and E4 in patients with chronic urticaria and in normal subjects. *J Allergy Clin Immunol* 1990; 86:759–65.
- 18 Ohnishi-Inoue Y, Mitsuya K, Horio T. Aspirin-sensitive urticaria: provocation with a leukotriene receptor antagonist. *Br J Dermatol* 1998; 138:483–5.
- 19 Adkins JC, Brogden RN. Zafirlukast: a review of its pharmacological and therapeutic potential in the management of asthma. *Drugs* 1998; 1:121–44.

- 20 Senn S. Cross-Over Trials in Clinical Research. New York: John Wiley, 1993.
- 21 Greaves MW, Sabroe RA. ABC of allergies: allergy and the skin. I. Urticaria. *Br Med J* 1998; 316:1147–50.
- 22 Henz BM, Zuberbier T. Urtikaria. *Hautarzt* 2000; 51:302–8.
- 23 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; 104:369–81.
- 24 Humphreys F, Hunter JA. The characteristics of urticaria in 390 patients. *Br J Dermatol* 1998; 138:635–8.
- 25 Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema. *Br J Dermatol* 1969; 81:588–97.
- 26 Dahlen B, Nizankowsk E, Szczeklik A et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin intolerant asthma. *Am J Crit Care Med* 1998; 157:1187–94.