ORIGINAL ARTICLE

Usefulness of a Short Course of Oral Prednisone in Antihistamine-Resistant Chronic Urticaria: A Retrospective Analysis

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Abstract

Background: The effectiveness of corticosteroids in antihistamine-resistant chronic urticaria (CU) is widely accepted although large studies on their use in this disease are lacking.
Objective: To assess the proportion of patients with antihistamine-resistant CU that respond to a course of corticosteroids.
Methods: We studied 750 adult patients with CU and prescribed a course of oral corticosteroids (starting with prednisone 25 mg/day for 3 days) to those who reported little or partial response to antihistamine treatment. The corticosteroid treatment was considered effective if it resulted in long-term control of the disease with antihistamines only. Patients showing a temporary response were offered a second course of prednisone, at the end of which temporary responders and nonresponders were offered ciclosporin therapy for 3 months.
Results: A total of 660 patients (88%) (male/female, 194/556) responded to antihistamine treatment. In 40/86 patients (47%), prednisone induced remission of the disease and subsequent control with antihistamines at licensed doses only. Thirty-five patients responded well but relapsed when prednisone doses were tapered or shortly after withdrawal. In all responders, the effect was appreciable as early as the day after the first 25 mg dose. In 8/23 temporary responders, a second course of prednisone induced remission of the disease; the other 15 patients responded well but only temporarily.
Conclusions: A single short course of prednisone induced remission in nearly 50% of patients with CU, and a second course induced remission in a further 9%. Less than 15% of patients did not respond at all to this treatment.

Key words: Chronic urticaria. Corticosteroids. Antihistamines. Therapy.

Resumen

Antecedentes: La eficacia de los corticoesteroides en la urticaria crónica (UC) resistente a los antihistamínicos está ampliamente aceptada a pesar de la ausencia de estudios importantes sobre su uso en esta enfermedad.
Objetivo: Determinar la proporción de pacientes con UC resistente a los antihistamínicos que responden a una tanda de corticoesteroides.
Métodos: Se prescribió una tanda de corticoesteroides orales (empezando con 25 mg/día de prednisona durante 3 días) a pacientes adultos con UC que notificaron una respuesta escasa o parcial al tratamiento con antihistamínicos. El número total de pacientes estudiados fue de 750. El tratamiento con corticoesteroides se consideró eficaz si daba lugar a un control a largo plazo de la enfermedad solo con antihistamínicos. A los pacientes que mostraron una respuesta temporal se les ofreció una segunda tanda de prednisona, al final de la cual a los pacientes que respondieron de forma temporal y a los que no respondieron se les ofreció un tratamiento con ciclosporina durante 3 meses.
Resultados: Un total de 660 pacientes (88%) (hombres/mujeres, 194/556) respondieron al tratamiento con antihistamínicos. En 40/86 pacientes (47%), la prednisona indujo la remisión de la enfermedad y el control posterior con antihistamínicos solo a dosis autorizadas. Treinta y cinco pacientes respondieron bien al tratamiento pero recayeron al reducir las dosis de prednisona o poco después de retirar el tratamiento. En todos los pacientes que respondieron, el efecto pudo apreciarse ya al día siguiente de la primera dosis de 25 mg. En 8/23 de los pacientes que respondieron de manera temporal, una segunda tanda de prednisona indujo la remisión de la enfermedad; los 15 pacientes restantes respondieron bien aunque solo temporalmente.
Conclusiones: Una única tanda corta de prednisona indujo la remisión en cerca del 50% de pacientes con UC, y una segunda tanda indujo la remisión de un 9% adicional. Menos del 15% de pacientes no respondieron a este tratamiento.

Palabras clave: Urticaria crónica, corticoesteroides, antihistamínicos, tratamiento.

Introduction

Chronic ordinary urticaria (CU) affects up to 1% of the general population [1] and can seriously impair quality of life [2,3]. In most cases, the disorder can be sufficiently controlled with antihistamines at licensed doses or, in some cases, at higher-than-licensed doses, although this approach does not always seem to be effective [4]. When it fails, the disease can become challenging and frustrating for both the patient and the clinician. All of the guidelines published to date recommend systemic corticosteroids as the second-line treatment of choice in such cases [5-12]. It is generally accepted that corticosteroids are an effective treatment for CU, despite the shortage of large studies on their use in this disease. Furthermore, although there is general agreement that corticosteroids should be used for short periods and at the lowest effective dose, suggested treatment regimens differ greatly from one guideline to another, ranging from 5 mg of prednisone every other day until the urticaria subsides, to 30 mg/day to be reduced to 0 mg/day over 10 days, to longer and more complex therapeutic schedules characterized by alternate-day dose reductions, etc [5-12]. The present study aimed to assess the proportion of subjects with CU that are poorly controlled by antihistamines only and to analyze their response to a fixed-dose course of corticosteroids.

Methods

Patients

We studied adult patients (age, >17 years) with active CU (defined as the repeated occurrence of short-lived wheals accompanied by redness and itching, with or without angioedema, for more than 6 weeks) seen at the allergy outpatient clinic of the Clinica San Carlo in Paderno Dugnano, Italy from January 1, 2003 to May 31, 2009. Patients with physical urticaria were excluded. All those included in the study had negative skin prick tests to a large panel of commercial food extracts; furthermore, the results of the following laboratory tests in all cases were unremarkable: erythrocyte sedimentation rate, complete blood count, serum protein electrophoresis, complement fractions, and antinuclear antibodies.

Antihistamine Treatment and Assessment of Response

Patients who were not on medication at the time of the first visit were prescribed oral cetirizine 10 mg daily and asked to come back after 7 to 14 days to assess response to treatment.

Patients already taking antihistamines prescribed by general practitioners at the time of the first visit (cetirizine 10 mg, loratadine 10 mg, ebastine 10 mg, desloratadine 5 mg, or levocetirizine 5 mg daily) underwent an immediate assessment of the effectiveness of the treatment. The patients recorded the severity of their disease (number, size, and frequency of wheals, intensity of pruritus, occurrence of angioedema, and discomfort) on a visual analogue scale. Antihistamine treatment was considered effective if the patient reported the total or near-total disappearance of wheals, the total absence of angioedema, the disappearance of pruritus, little or no residual discomfort, and good quality of life while taking the drug. It was considered ineffective or only partially effective in the case of patients with persisting pruritus and recurrent wheals (with or without angioedema), significant discomfort, and poor quality of life despite antihistamine treatment. In such cases, a course of oral corticosteroids was prescribed (see the next section). No H_2 blockers were prescribed [13] and based on the results of a previous experience [4], H_1 blockers above the licensed dose were not routinely used in patients who had not responded to licensed doses prior to initiation of corticosteroid treatment.

Corticosteroid Treatment and Assessment of Response

Patients who did not respond to antihistamines were prescribed a course of oral prednisone as follows: 25 mg/day on days 1, 2, and 3; 12.5 mg/day on days 4, 5, and 6; and 6.25 mg/day on days 7, 8, 9, and 10. They were advised to take the drug in the morning and to continue their antihistamine treatment in the evening throughout the treatment period. Control visits were scheduled for weeks 1 and 4 after prednisone was stopped.

The oral corticosteroid course was considered effective if it resulted in long-term control of the disease with antihistamines only (see previous section). Long-term control was defined as the presence of minimal or no urticaria while taking antihistamines only for at least 1 month following the discontinuation of corticosteroid therapy. Patients showing a temporary response to prednisone (ie, those who responded well at higher doses but relapsed as soon as the doses were tapered, or soon after the withdrawal of the steroid) were offered a second course. Those who again showed a temporary response to this second cycle, together with patients who did not respond at all to prednisone, were offered ciclosporin 0.5 mg/kg/day for 3 months. Alternative treatments such as cyclophosphamide and low-molecular-weight heparin were offered in cases of ciclosporin failure or refusal.

Since the study was based on the routine management of CU patients who presented spontaneously at the allergy center asking for care, no institutional review board approval was needed. All the patients gave their oral informed consent before starting prednisone and written consent was obtained before subsequent treatments were started.

Results

The results are summarized in the Figure. A total of 750 patients with chronic urticaria (male/female, 194/556) were studied; of these 660 (88%) responded satisfactorily to antihistamine treatment. The remaining 90 (12%) (male/female, 16/74; age range, 22-85 years; mean age, 51 years) showed poor or insufficient response to antihistamines and were prescribed the scheduled corticosteroid course. Four of the 90 patients that did not respond to antihistamines were

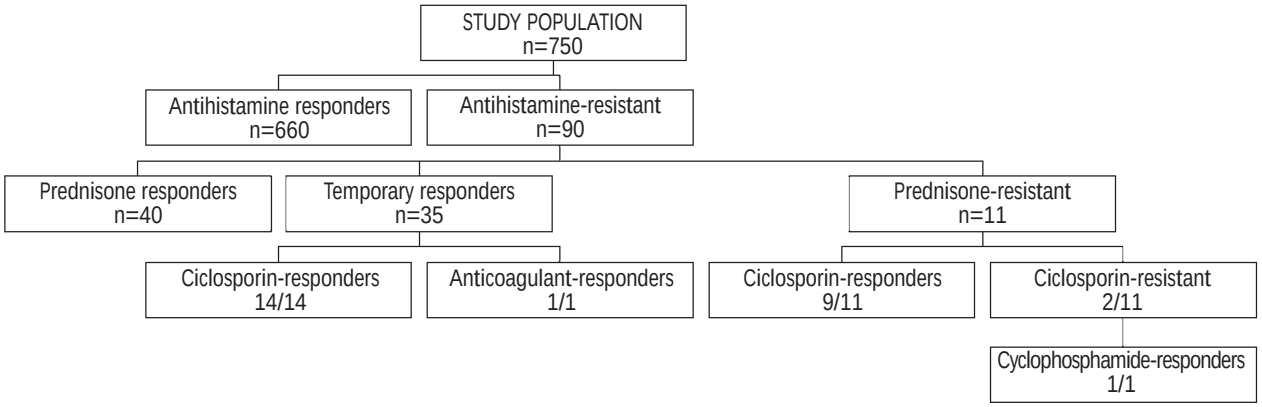

Figure. Response to antihistamines, oral corticosteroids, ciclosporin, and other drugs in 750 patients with chronic urticaria.

lost to follow-up, leaving 86 patients in whom to assess the effectiveness of the prescribed corticosteroid regimen.

In 40/86 patients (47%), the recommended oral prednisone course induced remission of the disease, which was then adequately controlled with antihistamine treatment at licensed doses alone. The effect of the prednisone seemed to be persistent, as it was still appreciable 4 weeks after the drug had been stopped. An additional 35 patients responded well to the corticosteroid treatment but experienced relapse when the doses were tapered or shortly after cessation of therapy. In all corticosteroid responders (both full and temporary responders) the effect of prednisone was clearly appreciable as early as the day after the first 25 mg dose. Of the 35 temporary corticosteroid responders, 23 agreed to undergo a second prednisone course, at the end of which 8 had achieved stable disease control with antihistamines only (still in remission 1 month after steroid treatment was stopped); the remaining 15 patients showed a good but temporary response. Fourteen of the 15 temporary responders along with 11 patients who showed little or no response to oral prednisone agreed to undergo ciclosporin treatment, which induced remission in 14/14 and 9/11 cases, respectively. The remaining temporary steroid responder had very elevated plasma D-dimer levels and was offered a 2-week treatment with subcutaneous nadroparin 11 400 IU once a day [14], which led to complete control of the disease, which was still present 3 months after anticoagulant withdrawal. Finally, one patient that did not respond to ciclosporin achieved good control after undergoing a course of oral cyclophosphamide [15].

Discussion

This study, which was a retrospective analysis of a large group of patients with clinically defined CU, has certain limitations that are characteristic of field investigations, namely a lack of randomization and blinding. Nonetheless, it should be considered that all the patients treated with prednisone had severe urticaria that was not sufficiently controlled by antihistamines alone and had come to the clinic for an effective treatment that would improve their quality of life. A short course of corticosteroid therapy was offered since corticosteroids are considered an effective treatment for CU, although this belief is based more on clinical experience than on large clinical studies. It would be desirable to conduct a double-blind, placebo-controlled study on the effect of steroid therapy on CU uncontrolled by antihistamines, but performing such a study in patients with a severely impairing disease poses ethical problems.

The present study aimed to estimate the proportion of patients with CU at an outpatient allergy clinic that do not respond to antihistamines and to determine how many of these respond to standard corticosteroid treatment. In order to minimize the risk of adverse effects (particularly in view of the fact that the majority of the patients were women and the mean age of the population was over 50 years), the prednisone course employed was shorter and involved lower doses than several of the steroid courses suggested by various experts [5-12]. Nonetheless, the treatment induced remission in nearly 50% of the patients after a single course, and in a further 9% after a second course. Many of the other patients also responded well to oral prednisone therapy, but the effect was shortlived. Less than 15% of the patients did not show any response to oral corticosteroid treatment. Most patients whose disease was insufficiently controlled with oral prednisone subsequently responded well to alternative drugs such as ciclosporin. Based on these findings, it is possible to conclude that the suggested oral corticosteroid course was quite effective in antihistamine-resistant CU patients.

Another interesting aspect is the speed with which CU patients respond to oral prednisone. It is generally accepted that the anti-inflammatory effect of corticosteroids is primarily based on a complex genomic mechanism leading to the switch-off of many inflammatory genes and to the activation of anti-inflammatory genes encoding for anti-inflammatory proteins [16-18]. However, it seems rather unlikely that genomic-based effects would be rapid enough to induce a marked clinical effect as early as 24 hours after the first dose

of prednisone. On the other hand, it has to be considered that corticosteroids do not exert any effect on cutaneous mast cell degranulation [19] or on complement activation [8]. It has been suggested that the clinical effects of corticosteroids in CU might be the result of their influence on inflammatory cell infiltrates [8], but the rapid clinical response observed in CU patients also makes it unlikely that this is a primary mechanism. In contrast, an inhibitory effect on the functions of infiltrating cells might be one possible explanation for the rapid onset of action of these drugs. A direct inhibitory effect on the release of mediators from eosinophils (notably, a cell type recently found to be activated in CU [20,21]) has been reported [22]. Similarly, an effect on histamine release from basophils was reported many years ago [23]. An effect based on nontranscriptional mechanisms resulting in the inhibition of vasodilation and vascular permeability, 2 typical features of urticaria/angioedema [24], might also be involved in the rapid response to systemic corticosteroids in CU patients, although such a putative mechanism lacks sound scientific evidence.

The last aspect worth considering is that this study was carried out in a peripheral secondary level outpatient allergy clinic to which patients are referred by their general practitioners for a first-line evaluation. It is therefore possible that the average severity of disease differs from that observed in patients referred to highly specialized tertiary academic clinics (possibly after a number of visits to other centers). Accordingly, the response rate to antihistamine or corticosteroid treatment would be higher in this population than in more severely affected CU patients seen in other settings. On the other hand, it is very likely that the population included in this study is more representative of the general population with CU.

In conclusion, while our study was not randomized, double-blind, or placebo-controlled, it is one of the first studies to deal with oral corticosteroids in refractory CU in a large population of outpatients with CU that might be representative of patients with CU seen every day in allergy outpatient clinics. The very recent EAACI/GA2LEN/WAO guideline on management urticaria states that the quality of evidence supporting the use of corticosteroids in refractory CU is “very low” [13]. Nonetheless, clinical experience with steroid use is “very high” worldwide, suggesting that guidelines based only on quality of evidence measurements may not sufficiently reflect real-life situations. In effect, the same guideline suggests the use of corticosteroids to control urticaria exacerbations at step 3, after the use of nonsedating antihistamines at higher-than-licensed doses. It is the excess of corticosteroids, in terms of both quantity and duration, rather than the drugs per se that is a problem. This study provides new data on the proportion of CU patients that are expected to respond to the various therapeutic options, including corticosteroids.

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