Azithromycin in Pityriasis Rosea: A Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Background: Pityriasis rosea is an inflammatory skin disorder with a known response to erythromycin. Considering similarities between erythromycin and azithromycin and lesser adverse effects of the latter, in a pilot study, we gave azithromycin to seven patients with pityriasis rosea and observed a noticeable improvement. The aim of this study was to evaluate the efficacy of azithromycin in patients with pityriasis rosea.

Methods: A double-blind, placebo-controlled clinical trial was performed in our clinic. Sixty patients over a period of 20 months were alternatively assigned to the treatment group or the placebo group. Patients in the treatment group received azithromycin, 250 mg/day, for 14 days. The response was categorized as complete response, partial response, or no response. All patients were followed up for 2 months.

Results: Age at presentation, sex, and average duration of the disease were comparable in both groups. Complete response was observed in 19 patients (63.3 %) in the treatment group and two in the placebo group ($p<0.0001$).

Conclusion: Oral azithromycin is effective in treating patients with pityriasis rosea. *(Iran J Dermatol 2008;11: 143-146)*

Keywords: azithromycin, pityriasis rosea, treatment

Introduction

Pityriasis rosea (PR) is an acute or subacute inflammatory skin disorder characterized by distinctive erythematous papulosquamous eruptions typically on the trunk and proximal parts of the limbs.[1] The disease is self-limiting and the eruptions usually disappear in less than 10 weeks without any treatment. The cause is uncertain but many epidemiological and clinical features suggest that an infective agent may be implicated.[1-4] in many patients, a respiratory tract infection precedes PR.[5] However, a correlation between bacterial or viral infectious agents and PR has not yet been clearly established.[6,7] There is some evidence that immune dysfunction plays an etiological role in PR.[8] Susceptibility to the disease appears not to be influenced by race or other genetic factors.[1,9,10]

Asymptomatic and self-limiting cases require no treatment but if the itching is troublesome or the appearance is distressing, topical steroids or UVB irradiation can be helpful.[1] Erythromycin has been successfully used in PR.[4] Azithromycin is a macrolide antibiotic with antibacterial and anti-inflammatory properties similar to erythromycin[11], but with less adverse reactions.[12-14] To the best of our knowledge, there is no published data on the usage of Azithromycin for the treatment of PR. To evaluate the efficacy and safety of azithromycin in patients with PR, we performed a double-blind placebo-controlled clinical trial.

Patients and Methods

The study included 60 patients with PR visited in our hospital from January 2004 to August 2005 (20 months). Pityriasis rosea was the diagnosis made clinically by an academic dermatologist and was proposed by the presence of typical erythematous papulosquamous lesions and their association with herald patch. Skin biopsy from the lesions was performed for two patients with atypical features, showing focal spongiosis and perivascular lymphocytic infiltrations well-matched with PR. Biopsy was not performed for the rest of the patients.

An informed consent was taken from all the patients or their parents. Cases assumed to have drug reactions, dermatophytic infection, secondary syphilis, eczema or psoriasis were excluded. Each patient was subjected to a meticulous review of

clinical history, sexual exposure, and similar diseases in their first degree relatives, drug intake, and a complete physical examination. Search for a herald patch was performed in each patient. We performed complete blood count with differential leukocyte count, erythrocyte sedimentation rate, anti streptolysin O titer, C-reactive protein and blood VDRL.

Patients were enrolled alternatively to either the treatment or the placebo group. All the doctors and patients were blinded to the group to which the patients belonged. Subjects in the treatment group were given oral azithromycin 250 mg daily, for 14 days. Those in the placebo group were given an analogous capsule not having azithromycin, once daily. The patients were also asked to report any side effects such as gastrointestinal upsets.

All patients were assessed clinically every two weeks for a period of two months. They were evaluated for improvement in symptoms, appearance of new lesions, regression or disappearance of lesions, increase or decrease of erythema, scaling, pigmentation, and atrophy. Response was categorized into three groups: 1) complete response: i.e. in less than 2 weeks after starting the treatment all the lesions cleared, no new lesions appeared, and redness in the existing patches disappeared; 2) partial response, if only a few of the lesions disappeared, or partial decrease in erythema in the first 2 weeks; 3) no response, if the lesions did not show any regression, or if new lesions appeared even after 2 weeks. We performed statistical analysis using SPSS ver. 12 and used chi-square test to analyze differences in proportion and the Student t test to evaluate differences in means.

Results

Comparability of the study groups

Table 1 shows the baseline characteristics of both groups. No significant difference was observed with respect to age at presentation, sex, average duration of disease at the time of first visit, and presence of upper respiratory tract infection before the appearance of skin lesions.

The mean age in both groups was 18 years and age ranged between 1.5 and 45 years in the treatment group and between 2 and 40 years in the placebo group. Four (13%) patients in the treatment group and 10 (33%) in the placebo group complained of pruritus.

Thirty_five patients (58.33%) out of 60 had raised C_reactive protein, 8 (13%) had raised leukocyte count, 36 (60%) had raised eosinophils count and 34 (56%) had raised anti_streptolysin O titer (table 2).

Response to treatment

Complete response was observed in 19 patients (63%) in the treatment group but not in any cases in the placebo group (table 3). This was statistically significant ($P<0.0001$). Similarly, partial response versus no response was compared between the groups (Fisher's exact test, $P=0.64$). This was not statistically significant.

On further follow-up of these patients for 18 months, there were no relapses in 19 patients in the treatment group who had shown complete responses. By the end of month 4, four more patients achieved complete disappearance of lesions in the treatment group. In the placebo group, only 5 patients (16%) showed complete disappearance of lesions by the end of month 2, and 10 (33%) showed partial improvement of their lesions. The only side effects noted were mild nausea in one patient in the treatment group.

Discussion

In this study, we found that oral azithromycin is effective in the treatment of patients with PR. Sharma et al. reported the benefit of oral erythromycin, at the dose of 200 mg four times a day, in modifying the course of typical PR.[4] Complete response was observed in 73.3% of the patients in the treatment group and none in the placebo group.[4] The good response to erythromycin treatment could imply some involvement of etiological agents like Streptococcus, Chlamydia, Legionella and mycoplasma.[4,7] These etiological agents are sensitive to macrolide antibiotics such as erythromycin and Azithromycin and may be the

Table 1: *Baseline characteristics of patients with pityriasis rosea treated with azitromycin or placebo*

Variable	Azitromycin (N=30)	Placebo (N=30)	P value
Mean age in years (SD, range)	21.47 (9.87,9-41)	21.87 (9.85,9-44)	0.87
Sex Male (%)	11(36.7)	14(46.7)	0.43
Mean duration of disease at the time of presentation in days (SD, range)	13.43 (3.65,6-20)	13.93 (3.93,7-22)	0.61
History of previous upper respiratory tract infection (%)	13 (43.3)	15 (50)	0.6
Total leukocyte count	8633.33 (2146.4,5800-14000)	8326.67 (2188,5400-13200)	0.58
Mean anti-streptolysisn O titer (IU) (SD, range)	178.4 (30.98,129-253)	180.37 (32.06,126-243)	0.81

Table 2: *Laboratory investigations in the treatment and placebo group*

Indices	Treatment group No. 30 (%)	Placebo group No. 30(%)	Total No. 60 (%)
Leukocytosis	5(16.6)	5(16.6)	10(16.6)
Elevated anti-streptolysin titer(>200 IU)	6(20)	8(26.6)	14(23.3)
Elevated C3(>155 IU/mL)	13(43.3)	15(50)	28(46.6)
Elevated C4(>155 IU/mL)	10(33.3)	14(46.6)	24(40)

Table3: *Response of the patients in the treatment and placebo groups*

Response	Treatment group No. (%)	Placebo group No. (%)	P value
Complete response	19(63.3)	2(6.7)	<0.0001
Partial response	8(26.7)	6(20)	0.76
No response	3(10)	27(90)	-

cause of upper respiratory infections that are associated with PR in the literature.[5] Besides its antimicrobial effects, erythromycin has anti-inflammatory and immunomodulatory properties that may explain the positive response obtained throughout treatment.[7,15,16] In a case-control study of 13 patients with PR and 13 paired age-and-sex-matched controls, Chah and Chan failed to identify an association between PR and C. pneumoniae, C. trachomatis, L. longbeachae, L. micdadei, L. pneumophila, and M. pneumoniae infections. They concluded that infections caused by these bacteria are unlikely to play a significant role in the pathogenesis of PR.[7]

We used azithromycin in a pilot study of 7 patients with PR. Fading of lesions in 7 to10 days in these patients led us to undertake this double-blind, placebo-controlled clinical trial for evaluating the efficacy of azithromycin in PR.

There are many published reports on the anti-inflammatory effects of macrolides, some dating back to the introduction of erythromycin.[11, 17, 18] These antibiotics have been shown to affect a number of the processes involved in inflammation, including the migration of neutrophils, the oxidative burst in phagocytes and the production of various cytokines, although the exact mechanisms are not clear. Azithromycin and clarithromycin, macrolides with better pharmacokinetics than erythromycin, only show slight anti-inflammatory effects.[11] The anti-inflammatory properties of the macrolide antibiotic azithromycin are reported to be potentially beneficial in some diseases like cystic fibrosis[19] and diffuse panbronchiolitis.[20]

In a comparative study, Schonwald et al. observed side effects in one of 57 patients on azithromycin and in six of 44 patients on erythromycin and concluded that Azithromycin appears to be as effective as erythromycin in the treatment of atypical pneumonias, and better tolerated.[12]

Compared with erythromycin, azithromycin only needs to be taken once a day which is likely to improve patient compliance.[13] azithromycin is reported to have significantly fewer gastrointestinal side effects in pregnancy.[14]

Lower frequency of side effects along with the simplicity of administration and a possible comparable efficacy suggest that azithromycin should be suggested for the initial treatment of PR. Finally, we propose double-blind randomized clinical trials to compare azithromycin and erythromycin for the treatment of PR.

Most cases of PR occur between the ages of 10 and 35 years and the disease is uncommon in early childhood and old age.[1] In our study, a male predominance was observed in both the treatment and placebo groups, with a male/female ratio of 3:1 and 2.2:1, respectively. A male predominance is also noted by Sharma and his colleagues.[4] This is conflicting with earlier reports in which an equivalent involvement or a female preponderance was reported.[5,22]

Symptoms of upper respiratory tract infections were seen in 28 patients in both of the groups (46%), and acute phase reactants rose in many of the patients (Table 2). This might be in favor of an infectious origin for PR.

Sixty patients in the treatment group achieved complete response in two weeks of treatment with azithromycin compared with none of the patients in the placebo group ($P<0.0001$). Since they responded in the first two weeks, it is improbable that it was spontaneous remission. Our study showed that azithromycin was helpful in patients with PR.

In our study, eight patients in the treatment group did not respond to azithromycin. Assuming an infectious etiology for PR, it is possible that organisms resistant to azithromycin were responsible. In the absence of definitive origin of the disease, the present study cannot be assumed as an absolute answer to the treatment of PR.

However, we suggest that patients be given the profit of a trial of azithromycin which is a safe treatment.

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