Doxycycline In Pityriasis Rosea: Placebo-Controlled Clinical Trial

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Summary

Background: *Pityriasis rosea is an acute, self-limiting skin disease, probably of infective origin. Doxycycline is a broad-spectrum antibiotic, and most probably has an immunomodulator and an anti-inflammatory effect.*
Objective: *To assess the efficacy of doxycycline in the treatment of pityriasis rosea in patients evaluated between January 2001 and May 2002.*
Patients and methods: *This was a placebo-controlled clinical trial. One hundred and twenty patients with pityriasis rosea were included in the study; all of them were above 12 years of age. They had been divided into 2 groups, the treatment group consisted of 60 patients and received doxycycline capsule. 100,mg orally for 14 days and the placebo group consisted of 60 patients and received glucose capsules for 14 days, all the patients were followed up clinically for 4 weeks after treatment, the responses were categorized into excellent, partial and no response.*
Results: *forty-six patients from the treatment group completed the study. Excellent response was achieved in 30 patients (65%), partial response in 15 patients (33.5%) and no response in I patient (1.5%). Forty patients from the placebo group completed the study. Excellent response was achieved in 4 patients (10%), partial response in 20 (50%) and no response in 16 patients (40%). The results were statistically significant.*
Conclusions: *we concluded that doxycycline was effective in the treatment of pityriasis rosea, with very few adverse effects.*
Key words: Pityriasis rosea, doxycycline.

Introduction:

Piutyriasis rosea is an acute self-limiting disease, probably of infective origin, characterized by a distinctive skin eruption and minimal constitutional symptoms (1). Most patients being in the age of 10-43 years (2), it affects both sexes equally (3), although some studies showed either female or male preponderance (4, s)

Etiology of pityriasis rosea is unknown, infection had been suggested as one of the etiological factors. HHV-7 and HHV-6 had been blamed as a causative microorganism of pityriasis rosea (6, 7), other etiological factors include drugs e.g. arsenic, bismuth, barbiturate, gold, metronidazole, clonidine, isotretinoin, omeprazole (2), also ketotifen was reported to cause pityriasis rosea-like rash in one case (g) .Oral corticosteroids had been reported to cause exacerbation of the disease, especially if received in the beginning of the eruption and in larger doses (9).

A pityriasis rosea-like eruption was described after bone marrow transplant (10), and after interferon alpha 2A in a patient with Behcet disease (11).

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Suggestion of an autoimmune pathogenesis based on statistical interpretation data, has not been supported by any more direct evidence (1)
Various treatment modalities have been used in the management of pityriasis rosea with varying results. These include : topical steroid (1), zinc oxide or calamine lotion (2), oral antihistamine, and prednisolone (12), dapsone (2), gammaglobulin (13), erythemogenic dose of UVB (14), natural sunlight (12), and recently erythromycine orally was effective in the treatment of pityriasis rosea (5) .

The current work was designed to assess the efficacy of doxycycline in the treatment of pityriasis rosea.

Patients And Methods:

A total number of 120 patients were included in this study. Patients were attending the Department of Dermatology and Venereology of Baghdad Teaching Hospital during the period from January 2001 to may 2002. Only 86 patients completed the course of the study. Diagnosis of pityriasis rosea was made clinically, any case of suspected fungal infection, psoriasis, eczema, or secondary syphilis was excluded from the study.
All patients were above 12 years of age, pregnant and lactating women were not included. Each

patient was subjected to a detailed review of clinical history and a complete physical examingtjon including the skin, relevant information obtained included preceding history of fever, cough, throat pain, nasal discharge, sexual exposure, similar disease in the family and drug intake.

Examination of the skin was conducted to locate a herald patch, the number, distribution and pattern of the secondary rash were also noted. The following tests were conducted for the patients: ESR, VDRL, and complete blood count.

The disease was divided in ~q 3 groups according to its severity:

I . Severe: if the lesions were inflamed antinvolved much of the trunk and/or extending onto the extremities, the lesions may become confluent.

2. Moderate: if the lesions though numerous, not extensively erythematous or edematous.

3. Mild: if the lesions are scanty, less easily perceptible. Pruritus was also divided according t its severity to the following:

1. Negative: if not present.

2. Mild: if not interfere with work or rest.

3. Moderate: if present much of the day but tolerable.

4. Severe: if interfere with the activities or sleep and the patient is notably uncomfortable.

The patients were divided into 2 groups, treatment group (TG) and placebo group (PG). TG consisted of 46 patients, all of them received doxycycline capsules 100 mg daily for 14 days with topical emollient. PG consisted of 40 patients, all received glucose capsule once daily for 14 days with topical emollient.

Follow up of the patients and assessment of the outcome: Patients were evaluated clinically every week for 4 weeks, the evaluation included: improvement in symptoms, appearance of new lesions, regression or disappearance of lesions, increase or decrease of erythema, scaling, pigmentation and atrophy.

1. Responses were categorized into 3 groups :Excellent response : in less than 2 weeks after starting the treatment, more than 75% of the lesions disappeared, and the remaining regressed, no new lesions appeared, the erythema disappeared, with or without pigmentation and scaling.

2. Partial response: if the lesions regressed or only few of them disappeared, some decrease in erythema or few new lesions appeared in the 2 weeks after starting the treatment.

3. No response: if the lesions did not show any regression or no lesions still appear even after 2 weeks of treatment and no improvement of symptoms.

RESULTS:

A total number of 86 patients were completed the study. Their ages ranged from 13-55 years with a mean of 28.03 ± 9.2. Number of females was 52 (60.5%) and the number of males was 34 (39.5%) with female to male ratio was 1.5: 1. Duration of the disease at time of presentation ranged from 3-30 days with a mean of 10.4 + 5.8.

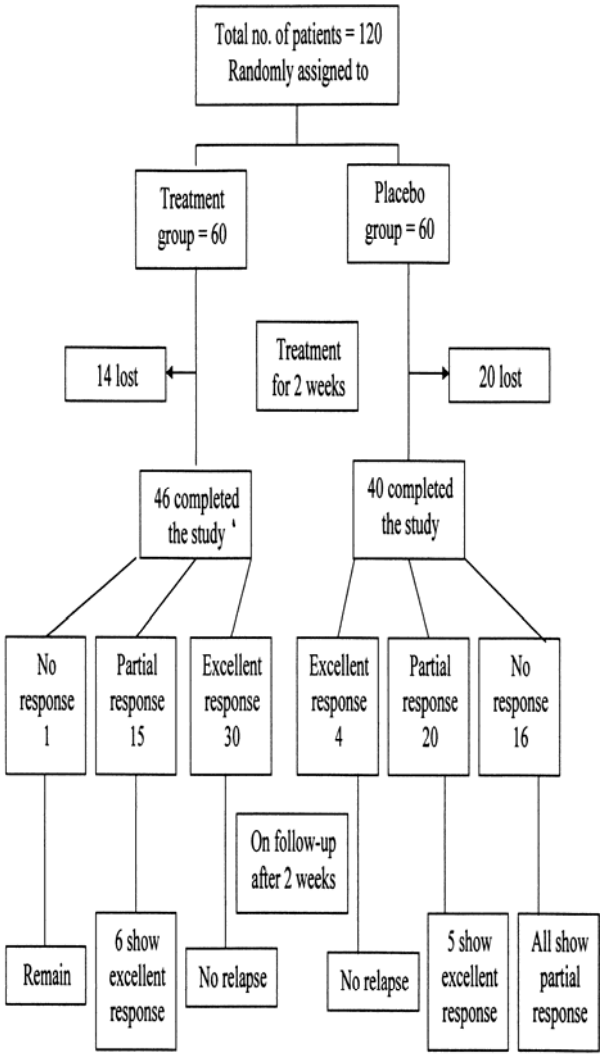
Other clinical criteria of the disease were shown in (Table 1). Response to treatment. (Table 2):

Table 1: Different Clinical criteria of patients with PR included in the study

Clinical criteria	Number (%)
*Disease severity	
Severe	10 (11.6%)
Moderate	60 (69.7%)
Mild	16 (18.6%)
*Itching	
Severe	6 (6.9%)
Moderate	12 (13.9%)
Mild	60 (69.7%)
Negative	8 (9.3%)
*History of upper respiratory tract infection preceding PR	16 (18.6%)
*History of atopy	15 (17.4%)
*Presence of herald patch	46 (53%)
*Presence of oral lesion	10 (11.6%)
*Scalp involvement	11 (12.7%)
*Family history of PR	2 (2%)
*Investigations	Normal

Table 2: responses of the patients in TG and PG

Response	TG No. (%)	PG No. (%)	P value
ER	30 (65%)	4 (10%)	P = 0.00081 significant
PR	15 (32%)	20 (50%)	P = 0.28 NS
NR	1 (1.5%)	16 (40%)	P = 0.00085 significant



Flow chart showing study protocol and response to treatment

Excellent response was achieved in 30 patients (65%) of the treatment group and this was statistically significant when compared with placebo group in which 4 patients (10%) achieved excellent response.

Partial response was achieved in 15 patients (33.5%) of the treatment group and in 20 patients (50%) of placebo group. This was statistically not significant when compared with the placebo group.

No response was observed in 1 patient in the treatment group (1.5%), while in 16 patients (40%) of the placebo group showed no response, and this was statistically significant.

On further follow-up of the patients, 6 of 15 patients (40%) with partial response of treatment group showed complete disappearance of the lesions.

In addition, patients with excellent response showed no relapse of the disease. In placebo group, 5 of 20 patients (25%) with partial response showed complete disappearance of the lesions, and the partial response was noticed in all patients with no response (16 patients).

Discussion:

Pityriasis rosea is a common dermatological disease affecting mainly children and young adults. In our study, all the patients with pityriasis rosea were above 12 years of age, their ages ranged from 13-55 years and this was similar to the age range of pityriasis rosea that documented in studies before (2).

In the current worn, females were affected more frequently than males (female to male ratio was 1.5: 1), and this in agreement with previous report (4); however, other studies showed either equal occurrence of the disease in males and females or slightly more common in males (3, 5,15)

The disease severity varies from mild, moderate and severe (14) Itching is severe in 25% of cases and slight to moderate in 50% (2). The majority of our patients were of moderate type of disease (69.7%). The severe type was found in 11.6% of our patients.

Pruritus was of mild type in 69.7% and severe in 6.9% only. This may depend on patients' threshold rather than the severity of the disease because many patients with severe type of the disease had only mild to moderate itching.

According to certain evidences, pityriasis rosea supposed to be an infectious disease [(1)]. In this study, we found the following points which may support infectivity of the disease:

1. Simultaneous appearance of pityriasis rosea in 2 members of the same family and this was the same finding of other reports (16)
2. History of upper respiratory tract infection preceding pityriasis rosea in 18% of our patients. Upper respiratory tract infection preceding pityriasis rosea was said to be significantly commoner among pityriasis rosea patients than controls in one study [(17),] and it occurred in 68.88% in other study (5).
3. History of appearance of herald patches and followed by the secondary eruption in 53% of our patients. As mentioned, the presence of primary lesion with a disseminated secondary rash after an interval might support the infective cause
4. No history of recurrence in all our patients during the period of follow-up.
5. Spontaneous improvement of our placebo group

patients, although slight, at the end of the follow-up period. Pityriasis rosea is unknown to be a self-limiting disease and this might support the infective cause

For these points mentioned above, we tried to use oral doxycycline, which is a broad spectrum antibiotic for the treatment of pityriasis rosea.

The results were interesting. P-value was strongly significant in comparison between responders and non-responders in the 2 groups of patients (P value = 0.00081 in excellent response group and 0.00085 in non-responder group).

The response achieved by doxycycline is slightly less than that achieved by erythromycin in a previous study (5), but doxycycline has better compliance as it has taken once daily with little side effects, also we should take in consideration that all age group were included in that study i.e. better response may be achieved by children and this may affect the outcome.

Because the response was achieved within the first 2 weeks, it is unlikely that this was spontaneous remission of the disease.

The exact mechanism of action of doxycycline in these patients is unknown it has a wide spectrum of activity against many bacteria, and pityriasis rosea may be caused by one of these bacteria that are sensitive to doxycycline, the six patients who responded later at the end of the study may have other types of bacteria which are less sensitive to doxycycline or represent slow response or may be explained by spontaneous remission of the disease.

Doxycycline may act in a mechanism other than its antimicrobial action. It may work as an anti-inflammatory or immunomodulator.

Tetracyclines have recently been shown to exert a number of antiinflammatory and immunomodulatory activities, independent of their antibiotic properties. These include the ability to inhibit metalloproteinases (MP), a class of enzymes involved in crucial cellular functions such as the shedding of soluble mediators and their receptors from the cell surface, as well as interaction with, and remodeling of, the extracellular matrix (18).

Doxycycline at therapeutic concentrations (1-5 microgram ml"') significantly suppresses immunoglobulin (Ig) secretion and class switching by in vitro activated murine B-cells

In another study, they evaluated the effect of doxycycline on the regulation of interleukin-I (IL-I) expression and activity in human cultured corneal epithelium. They found that doxycycline can suppress the steady state amounts of mRNA and protein of IL-beta and decrease the bioactivity of this major inflammatory cytokine (19)

These data may explain the action of doxycycline as an antiinflammatory and immunomodulator.

Excellent response was achieved mainly if the patient received the treatment during the first week of the disease (77.7%). This may be explained that the disease activity is at its maximum during the first week and when give the treatment, we can suppress this activity or at least, we can decrease it and ultimately we can decrease the severity of the disease or its duration. This finding was also observed in previous studies (13, 14), as improvement of pityriasis rosea achieved if the treatment received during the first week of the disease.

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