

Comparative Study of Effectiveness of Oral Acyclovir with Oral Erythromycin in the Treatment of Pityriasis Rosea

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ABSTRACT

Background

Pityriasis rosea is an acute, self-limiting disease, probably infective in origin, affecting mainly children and young adults, characterized by distinctive skin eruptions and minimal constitutional symptoms. Both oral Erythromycin and oral Acyclovir have been used in its management.

Objectives

To compare the effectiveness of oral Erythromycin and oral Acyclovir in the treatment of Pityriasis rosea.

Method

Forty two patients with clinical diagnosis of Pityriasis rosea were enrolled. They were randomized into two groups. One group was given high-dose oral Acyclovir and another group oral Erythromycin in standard dose. The participants were evaluated one, two, four, six and eight weeks and six months after commencement of the study.

Results

Forty two patients including 26 males and 16 females completed the study. After 8th week, all patients showed complete response in both the groups. The response to oral Acyclovir compared with that to oral Erythromycin was better and was statistically significant in 1st, 2nd, 4th and 6th weeks.

Conclusion

Although it is a self-limiting disease which resolves within three weeks to three months, this study reveals that both oral Acyclovir and oral Erythromycin are helpful in decreasing the severity and duration of Pityriasis rosea. Moreover, the study also indicates that oral Acyclovir is more effective than oral Erythromycin in reducing the severity and duration of Pityriasis rosea.

KEY WORDS

Acyclovir, Erythromycin, HHV-6, HHV-7, Pityriasis rosea

INTRODUCTION

Pityriasis rosea (PR) is an acute, inflammatory, self-limiting, papulosquamous disease of the skin.¹⁻⁴ Its onset is usually marked by the appearance of a herald patch (Fig. 1) which is an asymptomatic, single, thin, oval plaque with peripheral scaling present over the torso. After a week or two, similar but smaller and multiple lesions appear in a fir-tree pattern of distribution over the trunk. It may also present atypically.¹ It is a common skin disease and is usually devoid of major constitutional symptoms but is presented to dermatology clinics with anxiety concerning the disease,

variable pruritus and cosmetic disfigurement.¹

An overall incidence of 0.68 per 100 dermatology patients was calculated with overall male to female ratio 1:1.43; the prevalence was reported to be 0.6% for young people aged between 10 and 29 years.⁵

Numerous studies suggest an infectious etiology for PR.^{6,7} Recent studies incriminate Human Herpes Viruses (HHV), mainly HHV7 and HHV6, as the causative agents.⁸⁻¹¹ Studies are now focused on implementing antivirals such

as Acyclovir, active against herpesviruses, in the treatment of PR.¹²⁻¹⁴ On the other hand, oral Erythromycin is a time-tested drug which is reported to be beneficial to patients with PR.¹⁵ However, recent clinical experiences suggest macrolides, including Azithromycin and Erythromycin, are of no value in the treatment of PR.^{16,17}

The aim of this study is to compare the effectiveness of empiric oral Erythromycin treatment with high dose oral Acyclovir targeting HHV7 and HHV6, in the management of PR.

METHODS

After approval from institutional review committee (IRC), an open randomized clinical trial was conducted in the Department of Dermatology, Dhulikhel Hospital, Kathmandu University School of Medical Sciences (KUSMS), from 18th April 2010 to 18th September 2011.

In all cases considered in this study, an informed consent was taken from every patient or patient's parent in case of minor.

The following diagnostic criteria of PR were used:¹⁸

Essential clinical features:

1. Discrete circular or oval lesions
2. Scaling on most lesions
3. Peripheral collarette scaling with central clearance on at least two lesions

Optional clinical features (at least one has to be present):

1. Truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh
2. Orientation of most lesions along direction of the ribs
3. A herald patch (not necessarily the largest) appearing at least two days before the generalized eruption

Exclusion clinical features:

1. Multiple small vesicles at the center of two or more lesions
2. Most lesions on palmar or plantar skin surfaces
3. Clinical or serological evidence of secondary syphilis

The peripheral collarette-scaling pattern of two or more lesions of PR in individual patients was observed and confirmed by Epiluminescence Dermatoscopy.¹⁹ Only patients with typical and generalized lesions of PR were included. Atypical presentation and cases with co-morbid skin conditions like psoriasis, eczema or mycosis were not included. Due to unavailability of internationally approved standardized scoring of severity of PR, the typicality and generalization of the disease was clinically judged. In each patient, the diagnosis and patient selection was agreed by two academic dermatologists.

In all patients, scales from a single PR lesion were subjected to KOH mount and were observed under low power and high power compound microscope for fungal elements and those cases in which such elements were seen were considered mycosis. All patients underwent Venereal Disease Research Laboratory (VDRL) test and those with positive results were subjected to Treponema Pallidum Haemagglutination Assay (TPHA) test.²⁰ Patients who were reactive to either VDRL or TPHA tests were considered to have secondary syphilis and were excluded from the study.

Patients already on antibiotics, antivirals or long-term medication (e.g. for hypertension, diabetes, hypothyroidism etc) and patients with renal or hepatic impairment were excluded from the study. Pregnant or lactating women were also excluded from the study and so were patients with a known history of sensitivity to Acyclovir or Erythromycin.

Patients with clinical diagnosis of PR, fulfilling the above criteria, were selected from outpatient department of dermatology, Dhulikhel Hospital, KUSMS. The patients were prescribed either oral Acyclovir (Adults: 800mg five times a day; Children: 20mg/kg/day in five divided doses; Maximum dose: four grams/day; Duration: seven days) or oral Erythromycin (Adults: 500 mg QID; Children: 40mg/kg/day in four divided doses; Maximum dose: two grams/day; Duration: seven days), randomly. All patients, with or without the complaint of pruritus, were also given oral antihistamine (Tab. Cetirizine 10mg OD HS for adults and children weighing more than 30 kg and Syrup Cetirizine 5mg/5ml OD HS for children weighing less than and 30kg; Duration: seven days) and topical Class 4 (mid-strength) glucocorticoid (ointment Fluocinolone acetonide 0.025% twice daily application over lesions for seven days), for symptomatic relief. All prescriptions were standardized and the drugs were written in generic name. The patients were required to buy the medication from Dhulikhel Hospital Pharmacy. The drugs were available in closed packs with brand name and generic name with dose, manufactured date and expiry date printed on it. Since the study was open, the patient had full access to the information of the drug he or she was taking.

The patients were consulted after one and two weeks and then fortnightly after commencement of the study to evaluate response to treatment and after six months to detect any recurrences.

The responses were categorized as per the study performed by Eshani et al¹³

- Complete response: No newer lesions. Disappearance of all previous lesions, with or without residual pigmentation.
- Partial response: Few newer lesions. Regression or disappearance of few previous lesions.
- No response: No improvement of older lesions. Appearance of newer lesions.

Table 1. Demographic Characteristics of Patients.

Parameters	Acyclovir group n=18	Erythromycin group n=24
Age		
< 25 years	11	13
25 – 35 years	6	9
>35 years	1	2
Sex		
Male	11	15
Female	7	9

In total, 42 patients completed the study. The patients who received oral Acyclovir were assigned Group A and those who received oral erythromycin Group B.

All the data were entered in MS Excel 2007. After transferring, data analysis was done by Statistical Package for Social Study (SPSS) version 16 utilizing Pearson chi square to find out the associations for significance at 0.05 level of confidence.

RESULTS

Forty two cases were included in the study. The mean age of the study group was 23.02±7.782 years. (table 1) The youngest patient was two years old whereas the eldest was 40 years of age. Out of the 42 patients, 26 (61.9%) were males whereas 16(38.1%) were females. Among the 42 patients included, 18 (42.9%) were given oral Acyclovir (Group A) and 24 (57.1%) were given oral Erythromycin (Group B). There was no significant difference between the demographic characteristics of the two groups. (Table 1)

Eight (19%) out of 42 patients suffered dyspepsia during the first week of therapy. All the eight patients were in Group B (Erythromycin). However, all patients completed the full course of allocated medication and no additional medication was added.

Table 2 tabulates the response to treatment in both the groups combined, at various time intervals. In total, 36(85.7%) patients showed partial response whereas six (14.3%) patients showed no response by the end of first week. No patient showed complete response by the end of the first week. However, by the end of second week, 10 (23.8%) patients had complete response. More than half the patients had complete response by the fourth week and all patients had complete response after eight weeks. On six months follow up, no patient had recurrence of the disease.

Table 3 compares the response to treatment in group A (Acyclovir) with group B (Erythromycin) and highlights the statistical significance of the difference in the response between the two groups, at various time intervals.

All 18 patients in group A showed partial response within the first week whereas only 18 out of 24 patients in group B showed partial response. The remaining six patients in group B showed no response in the first week. The difference in response with Acyclovir and Erythromycin in the first week was statistically significant (<0.05). There was no complete response in either group, in the first week.

By the end of second week, seven out of 18 patients in group A showed complete response compared with only three out of 24 patients in group B. Eleven patients in group A were in partial response in second week and 21 patients in group B showed partial response in the second week. There was statistically significant difference in response to Acyclovir and Erythromycin in the second week as well (<0.05).

By the end of fourth week, 17 out of 18 patients in group A showed complete response compared with only 12 out of 24 patients in group B. Only one patient in group A remained in partial response as opposed to 12 patients in group B. There was high statistically significant difference in response to Acyclovir and Erythromycin in the fourth week (<0.01).

By the end of sixth week, all patients in group A had

Table 2. Response to treatment in both groups combined.

Follow up	1st week	2nd week	4th week	6th week	8th week	6 months
No response	6 (14.3%)	0	0	0	0	No recurrence
Partial response	36 (85.7%)	32 (76.2%)	13 (31.0%)	6 (14.3%)	0	
Complete response	0	10 (23.8%)	29 (69.0%)	36 (85.7%)	42 (100%)	

Table 3. Comparison of response to acyclovir versus erythromycin.

Follow up	1ST WEEK		2ND WEEK		4TH WEEK		6TH WEEK		8TH WEEK		6 MONTHS
N=42	NR	PR	PR	CR	PR	CR	PR	CR	PR	CR	RECURRENCE
Group A (18)	0	18	11	7	1	17	0	18	0	18	0
Group B (24)	6	18	21	3	12	12	6	18	0	24	0
p-value	0.022		0.047		0.002		0.022				

Group A: acyclovir, Group B: erythromycin, NR: no response, PR: partial response, CR: complete response, p-value: Pearson’s chi square value

complete response whereas only 18 out of 24 patients in group B had complete response. The remaining six patients in group B were still in partial response. There was statistically significant difference in response to Acyclovir and Erythromycin in the sixth week also (<0.05).

By the end of eighth week, all patients in both group A and group B had complete response.

All patients were followed up after six months of commencement of therapy and none of the patients from both group A and group B had recurrence of PR.

DISCUSSION

Most cases of PR occur between the ages of 10 and 35 years and it is uncommon in infancy, early childhood or old age.¹ Consistently, in this study, the mean age was 23.02 ± 7.782 years (table 1). PR is slightly more common in females but, in this study males outnumbered females (table 1).¹ This disparity may be due to limited sample size in our study. In a study done in Tehran, in which the sample size was 30, the male to female ratio was one.¹³

The skin lesions commonly fade after three to six weeks, but some clear in one or two weeks and a few persist for as long as three months.¹ In this study, by the end of two months, all patients had complete response (Table 2). This implies that both Acyclovir and Erythromycin does reduce the duration of the disease.

Second attacks of PR occur in about 2% of cases after an interval of a few months or many years, and rarely, a partial or complete relapse of a fading eruption may be seen.¹ In this study, no recurrence was seen by the end of six months suggesting that both Acyclovir and Erythromycin might prevent relapse of the disease. However, larger sample size and long term follow up studies are required to authenticate this statement.

In this study, oral Acyclovir was found to be superior to oral Erythromycin in reducing the severity and duration of PR (Table 3). Excepting one case, all patients taking oral Acyclovir had complete response within a month as opposed to two months for those taking oral Erythromycin. Similar results were seen in the study done by Eshani et al. who found that after eight weeks, the rate of complete response in patients who received high-dose Acyclovir was significantly higher than their matches who received oral Erythromycin.¹³ A placebo control trial done by Drago F, et al. found that 79% of patients treated with oral Acyclovir had complete response compared with 4% of the placebo group by the end of second week of therapy.¹² In the present study however, only 38.8% (7 out of 18) patients treated with oral Acyclovir had complete response by the end of second week of therapy. The disparity in earlier resolution may be due to the difference in inclusion criteria in the studies. Our study included only those patients who had full blown lesions of PR whereas the study by Drago F, et al. also included patients with initial or mild cases of

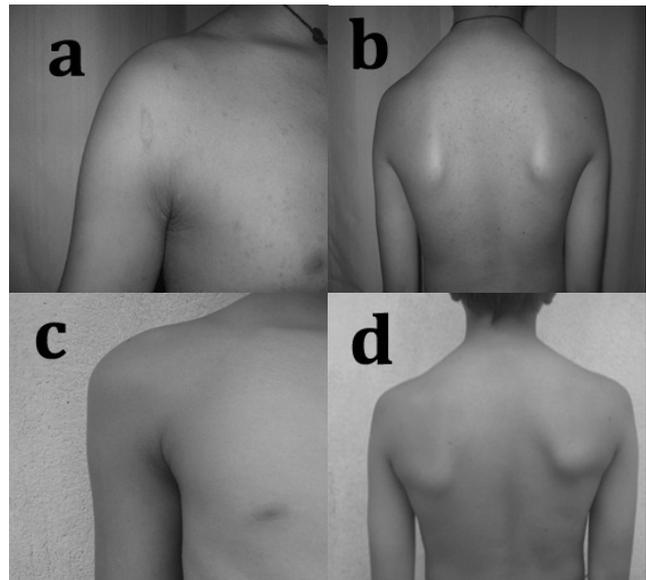


Figure 1. a) Papulosquamous lesions of Pityriasis rosea along with the herald patch. b) Fir tree pattern of distribution of the lesions over the back. c) Complete response after taking oral Acyclovir d) Complete response after taking oral Erythromycin.

PR.¹²

Many microorganisms have been incriminated for causing PR. Various fungi, bacteria like Streptococci, Spirochaetes (*Borrelia* spp), Legionella (*L. longbeachae*, *L. micdadei*, *L. pneumophila*), Chlamydia (*C. pneumonia*, *C. trachomatis*), Mycoplasma (*M. pneumonia*) and viruses such as Cytomegalovirus (CMV), Epstein Barr Virus (EBV), parvovirus B19, picornavirus, influenza virus, parainfluenza virus have been studied but there is no evidence relating them with PR.^{1,2}

Newer studies are focused on HHV7 and HHV6. Though no virus has been cultured from affected skin, virus-like particles were detected ultrastructurally over 40 years ago.²¹ Recent studies have found herpesvirus-like particles in 71% of PR lesions.²² Viral DNA of HHV7 and HHV6 is reported to be present in the peripheral blood mononuclear cells and lesional and unaffected skin of the majority of individuals with acute PR.²³ With these scientific observations, PR can be considered as a viral disease caused by HHV7 and HHV6.

Acyclovir is an antiviral agent which works by inhibiting DNA synthesis and is variably active against different HHV. In practice, it is used in herpes simplex, chickenpox and herpes zoster. Besides dosage adjustment in renal failure, it is a well-tolerated drug. With the new knowledge that HHV7 and HHV6 are herpes viruses causing PR, it is logical to use oral Acyclovir for the condition.¹²

Erythromycin is a macrolide antibiotic primarily used as an antibacterial agent. It is also known to have anti-inflammatory and immunomodulatory properties. Erythromycin has been used in PR after incidental observation of improvement in some patients with PR while receiving erythromycin.¹⁵

The main limitation to the study was the small sample

size. Double blind studies, considering the effect size of the two therapies, following the instructions guided by the flowchart provided by CONSORT (Consolidated Standards of Reporting Trials) with larger sample size would further authenticate the results.

CONCLUSION

PR is nowadays considered a papulosquamous viral exanthema most probably caused by HHV7 and 6. Although it is a self-limiting disease which resolves within three weeks to three months, this study reveals that both oral Acyclovir and oral Erythromycin are helpful in decreasing

the severity and duration of PR. Moreover, the study also indicates that oral Acyclovir is more effective than oral Erythromycin in reducing the severity and duration of PR. In this study, no untoward effect to oral Acyclovir was seen however, eight out of 24 patients taking oral Erythromycin complained of dyspepsia. Since oral Acyclovir is an antiviral agent effective against HHV and has high safety profile, its use in PR is strongly advisable.

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