PITYRIASIS ROSEA – A REVIEW OF THE SPECIFIC TREATMENTS

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Objectives: To evaluate the evidence for using 'specific' treatments in pityriasis rosea (PR), to discuss mechanisms of their action and to recommend a strategy for using them.

Methods: MEDLINE search for specific treatments for PR, with ranking of evidence into four levels and sub-levels.

Results and discussion: Six specific treatments (erythromycin, artificial ultraviolet radiation, systemic corticosteroids, dapsone, rivanol and streptomycin) were reviewed. Their possible mechanisms of action were discussed. A strategy of using specific treatments is recommended.

Conclusions: Most specific treatments for PR are not supported by adequate evidence. Mechanisms of action of these treatments are largely unknown. Most patients do not require specific treatments. Erythromycin should be reserved for patients with severe pruritus unresponsive to non-specific treatments, and systemic corticosteroids should only be used as a last resort.

BACKGROUND

The cause of PR is unknown. Up to 50% of all patients with PR experience pruritus, which can be severe in some cases. Treatment can be specific or non-specific. Specific treatments aim at modifying the course of the disease; non-specific treatments such as emollients and anti-pruritic agents are mainly prescribed for symptomatic relief.

A recent double-blind controlled trial reported the potential benefit of the macrolide erythromycin in modifying the course of the disease.[1] Apart from erythromycin, several other specific treatments have been tried and although most of these treatments are not being routinely used, an understanding of the level of evidence for their benefit may shed light on the underlying pathogenesis of the condition itself, thus paving the way for further investigations.

OBJECTIVES

The objectives of this article are to evaluate the evidence for using specific treatments in PR, to discuss the possible underlying mechanisms for their action and to recommend a strategy for using them in PR.

METHODS

'Specific treatments' are defined as 'treatments administered with the intention of shortening or modifying the course of the disease (i.e. the rash in the case of PR), not merely for temporary symptomatic relief (mainly pruritus for PR)'. MEDLINE was searched for mentions of 'pityriasis rosea' with unlimited entrez date limit; all articles in which specific treatments are discussed were studied and the specific treatments ranked into levels (modified from other sources):[2, 3]

- I evidence available from a systemic review of all relevant randomised controlled trials;
- II evidence available from at least one properly designed randomised controlled trial;
- III-1 evidence available from at least one well-designed pseudo-randomised controlled trial (alternate allocation or some other method);
- III-2 evidence available from comparative studies with concurrent controls and allocations not randomised (cohort studies), case-control studies, or interrupted time series in a control group;
- III-3 evidence available from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group;
- IV evidence available from case series or case reports.

RESULTS

Our results are summarised in Table 1. Six specific treatments were reviewed: erythromycin,[1, 4, 5] artificial ultraviolet (UV) radiation,[6-10] systemic corticosteroids,[11, 12] dapsone,[13] rivanol[14] and streptomycin.[15]

Sunlight has been advocated for PR,[7, 8] although the rationale for this treatment is not specifically to modify the disease's course. Sunlight was therefore considered non-specific therapy and was not reviewed as a specific treatment.

No specific treatment modality was ranked in Levels I or II. Erythromycin was ranked at Level III-1. Artificial UV radiation, systemic corticosteroids, dapsone, rivanol and streptomycin were ranked at Level IV. The rationale for such ranking is discussed below.

DISCUSSION

Evidence in modifying disease course

Our results indicate that apart from erythromycin and artificial UV radiation, benefits of other specific treatments have not been evaluated with controlled clinical trials.

For erythromycin, a double-blinded, placebo-controlled clinical trial was published in 2000. Ninety patients with PR attending the out-patient dermatology department at one hospital in India from 1996 to 1998 were recruited. The diagnosis was made clinically. Secondary syphilis was excluded by a serological test. The patients were alternatively assigned to the treatment and placebo groups. Thirty-three (66·0%) patients in the treatment group achieved complete response after two weeks of treatment with erythromycin while none did so in the control group ($p < 0{\cdot}0001$). Sharma *et al.* thus concluded that erythromycin was effective in treating patients with PR.[1]

The severity of pruritus, the most prominent symptom

TABLE 1
Levels of evidence of specific treatments in pityriasis rosea (PR).

'Specific treatments'	Levels of evidence of effectiveness in modifying course of disease	Remarks
Erythromycin	III-1	One report in 1954[5] documented partial response in 12 patients treated with erythromycin (form unspecified) 200 mg four times daily for three weeks. A double-blind, placebo-controlled clinical trial[1] reported 90 patients alternately assigned to treatment or placebo control groups. Thirty-three (73.33%) patients receiving treatment (erythromycin stearate 250 mg four times daily for two weeks for adults, 25–40 mg/kg in four divided doses for two weeks for children) showed response defined as complete disappearance of lesions six weeks after commencement of therapy. No patient in the placebo group achieved response ($p < 0.0001$). The intensity of pruritus was not documented.
Artificial ultraviolet	IV	It was generally believed that artificial UV radiation can alter the course of PR.[6-8] In a bilateral (UV) radiation comparison study,[9] the right side of 20 patients received UV-B at 80% of minimal erythema dose (MED) on day one with a 17% increase daily for five days. The left side was shielded. Of 19 patients with initial pruritus, 15 noted improvement of symptoms, with nine reporting significantly greater improvement on the treated side. Two reported no change in pruritus, and two reported worsening of pruritus. The extent of rash improved in 16 out of 20 patients, with greater improvement on the treated side in ten patients. Improvement was most beneficial if treatment was received within the first week of eruption. Although the investigators intentionally recruited only patients with pruritus, it is not clear why a patient without pruritus was recruited. No placebo treatment was given to the left side. In another bilateral comparison study,[10] the right side of 17 patients with extensive PR received UV-B at 80% of MED on day one and dosage was adjusted according to degree of erythema daily five days per week for two weeks. 1J of UV-A was given to the left side as placebo. The overall reduction in Pityriasis Rosea Severity Score (PRSS) was significantly more for the treated side after the third treatment. During follow-up at 14 and 28 days after commencement of therapy, no significant difference in severity score and pruritus was noted between the two sides.
Systemic	IV	No clinical trial was available. A one year review from a national skin centre[11] reported short-decreasing courses of oral prednisolone given to 30 patients with very extensive PR. Most improved. A clinical report[12] documented exacerbation of PR in 18 patients treated with systemic corticosteroids.
Dapsone	IV	One case report[13] documented improvement in a case of vesicular PR.
Rivanol	IV	An uncontrolled trial[14] reported improvement in 33 out of 36 patients treated with rivanol 0.05 g twice daily for ten days.
Streptomycin	IV	An uncontrolled trial[15] of 66 patients, of whom 53 completed treatment, reported rapid disappearance of scaling and pruritus on varying doses of intramuscular streptomycin.

in PR, was not documented in the trial.[1] It cannot be assumed that persistence or disappearance of the rash exactly parallels the persistence or disappearance of pruritus. Moreover, many patients do not have pruritus in the first place. Only two patients in the treatment group experienced mild nausea. This contrasts significantly with incidence of gastrointestinal side-effects of 25·0%[16] and 51·4%[17] in other studies using erythromycin stearate. The drop-out rate of 0·0% for both treatment and control groups has been criticised as being unlikely,[4] although such compliance is, of course, still possible to attain in the appropriate environment and with good follow-up strategies.

Strictly speaking, the alternate allocation of treatment and control groups is pseudo-randomisation.[2, 3] Erythromycin was therefore graded as Evidence Level III-1.

For artificial UV radiation, the available data reveals conflicting results. The bilateral comparison study by Arndt *et al.*[9] reported favourable results. However, their 20 patients were aware that their right sides were being exposed to UV-B while their left sides were shielded. After five treatment days, they were asked whether the pruritus increased, decreased or stayed unchanged for both sides: a source of bias is thus evident. The extent of the rash was judged by the investigators according to subjective standards, and, since they knew that the right side had been exposed, bias is again possible.

The methodology is more scientific in the bilateral comparison study by Leenutaphong *et al.*[10] UV-B was given to the right side of 17 patients with the left side shielded. UV-A was then given to the left side as placebo treatment. Before, during and after the two weeks of treatment, the

distribution and severity of the rash were assessed by the Pityriasis Rosea Severity Score (PRSS) to achieve a higher standard of objectivity. The score was found to decrease during the treatment period; pruritus was unchanged. Two and four weeks after the treatment, the treated and untreated sides were indistinguishable in regard to PRSS and pruritus. The final outcome of the disease was thus not modified.

A bilateral comparison study can be considered pseudo-randomised.[18] However, significant sources of bias exist in the study by Arndt,[9] while the study by Leenutaphong[10] reported no change in the overall disease course. Artificial UV radiation was thus graded Evidence Level IV. In the present climate of increasing awareness of long-term adverse effects of UV radiation, its routine use for this self-limiting condition cannot be recommended.

For systemic corticosteroids, only case reports are available for study, demonstrating conflicting data with a potential of aggravating the rash. We are aware that they are accepted as conventional therapy for exceptionally recalcitrant cases by some dermatologists.[19] They were graded Evidence Level IV. Their use might lead to many short- and long-term adverse effects, and is potentially dangerous for special groups of patients such as those with co-existing liver disease or who are pregnant. There is also a possibility of inadvertent administration of systemic corticosteroids for cases with undiagnosed secondary syphilis.[19]

The benefits of dapsone, rivanol and streptomycin are supported by uncontrolled trials or case reports only. They were graded Evidence Level IV. These agents are too toxic to be used for a self-limiting condition.

Mechanisms of action

The potential benefit of erythromycin might shed light on the underlying pathogenesis of PR. Apart from its effects on streptococci and atypical bacteria as suggested by Sharma,[1] erythromycin also has anti-inflammatory and immunomodulatory effects,[20] and it is suggested that such effects might also contribute towards its action in PR.

Epidemiology data[21] and microbiological studies in general support a viral aetiology for PR, and therefore the question has to be asked whether the benefit of erythromycin is compatible with the role of viruses.

Drago *et al*.[22, 23] reported the detection of human herpesvirus 7 (HHV-7) DNA by nested polymerase chain reaction in the skin, peripheral blood mononuclear cells (PBMC) and plasma of all of their 12 patients with PR. They failed to detect it in the plasma and skin of 11 control specimens, though finding weaker signals in 44% of the control PBMC specimens. Subsequent studies on the role of HHV-7 in PR reported conflicting results.[24-26]

The hypothesis that can be put forward is that immune dysfunction might be a relatively primary event in PR, leading to occasional reactivation of latent viruses, including, but not specific, for HHV-7. This could explain the occasional detection of active HHV-7 infection in PR. As such, reactivations rather than primary infections occurred, and seroconversion could not be documented. This was found to be the case by Kosuge *et al*.[26] Immune dysfunction as a relatively primary event can also explain the apparent benefit of erythromycin as an immunomodulatory agent.

Another virus not recently focussed upon that might play a role in PR is Epstein-Barr virus (EBV). Bonafe *et al*.[27] conducted, in 1982, a study of the roles of influenza A, B, parainfluenza 1, 2, 3, adenovirus, respiratory syncitial virus, *Mycoplasma pneumoniae*, ornithosis-psittacosis, Q-fever, herpes-virus, herpes-virus varicellae, cytomegalovirus and EBV in PR. They reported that while all other viral investigations had a negative result, a large number of patients had antibodies against EBV early antigen.[27]

It has long been known that EBV infection has immunomodulatory effects. The age distribution of patients with primary EBV infection also matches that of patients with PR. Should EBV really play a part in the pathogenesis of PR? Two possibilities exist: EBV may be the primary offending agent leading to cellular immune modulation, or immune dysfunction, by yet undiscovered cause, might lead to EBV reactivation. Both are compatible with the reported benefit of erythromycin therapy in PR.

Since immune dysfunction and deficiency are aetiological factors in PR, PR will be expected to be seen in patients on immunosuppressive agents or in immunocompromised states. It has long been known that gold[28-31] and other immunosuppressive agents[32] can precipitate PR. Four cases of histologically confirmed PR have been reported in bone marrow transplant recipients.[33] A PR-like rash with macular red oval lesions extending onto the face, palms and soles has been documented for patients with HIV infection and AIDS.[34, 35]

Apart from viruses, the role of atypical bacteria may also explain the action of erythromycin. A case-control study[36] reported that *Legionella micdadei* antibodies were detected in 12 (33·3%) PR cases and in only one (5·2%) control ($p = 0{\cdot}020$). Studies on *Mycoplasma spp* however yielded inconclusive results.[27, 37, 38]

The mechanism of action of artificial UV radiation in PR is unknown. Similar to its actions in psoriasis, specific[39] and non-specific[40] lymphocytotoxic effects may be involved. It has been argued that the truncal distribution of the rash, with relative sparing of face and distal extremities, is indirect evidence that PR lesions are improved by UV radiation.[41] However, this cannot explain cases of atypical acrally-distributed PR.[11, 42-44] Moreover, many other dermatoses are well known to improve by UV radiation such as plaque psoriasis, which are not necessarily truncally distributed.

The mechanisms of action of systemic corticosteroids in some patients with PR are likely to be anti-inflammation and immune modulation. One study did report that 28% of patients with PR have T lymphocytotoxic antibodies,[45] an autoimmune marker present in 82% of systemic lupus erythematosus patients. However, since systemic corticosteroids can sometimes paradoxically exacerbate PR, this observation does not support hypersensitivity or autoimmunity as being the sole components of the immunopathogenesis of PR.

The mechanisms of action of these specific therapies are therefore largely unknown in the present state of knowledge, and further investigations related to EBV, atypical bacteria and cellular immune dysfunction should be set up.

Strategy for using specific treatments

Apart from pruritus, transient cosmetic problems and disease-related psychosocial stress, PR does not lead to scarring or other complications. It has thus been suggested

that many patients, especially those without pruritus, do not need any treatment at all.[4] For patients with severe pruritus, some might respond to non-specific treatments. Apart from the bilateral comparison study of UV-B by Arndt[9] with significant sources of bias, there is no direct evidence that specific treatments are more beneficial when given as early as possible.

As PR rarely involves the face, and the extensiveness of the rash has not been documented to exactly correlate with severity of pruritus, the extensiveness of the rash *per se* is not a good guideline for commencement of specific therapy. Assessments of symptom severity and how these affect the patient psychosocially are more important. These assessments can be quite subjective, and quality of life (QOL) indexes can be useful tools in the decision making process.

The possibility of secondary syphilis is an additional issue to be considered. It has been suggested that to reach a diagnosis of PR for adolescents and young adults, secondary syphilis should always be excluded with apposite serology tests.[46] However, a prospective study does not support routine syphilis serology tests for all PR patients with no suspected history or feature of syphilis.[47] It is extremely rare, although possible,[48] for PR to co-exist with secondary syphilis.

The following strategy is recommended for using specific treatments in PR:

- for patients with no pruritus, no treatment needs to be given, unless the rash is extensive and the patient is psychologically distressed by the presence of the rash despite adequate counselling and explanation on the benign and self-limiting nature of the rash;
- for patients with mild pruritus which is not significantly affecting their QOL, non-specific treatments such as emollients or sedating anti-histamines, as a single night-time dose, should be given;
- for patients with pruritus severe enough to disturb their QOL, a trial of non-specific treatments can be given for one to two weeks; should there be little or no symptomatic relief after the trial, a course of erythromycin can be given; a VDRL test should be considered before commencement of therapy, and lesional biopsy should be considered in the presence of any atypical feature; these patients should be informed of the uncertainty for the benefit of erythromycin in modifying the course of PR, the potential gastrointestinal adverse effects of erythromycin, and given free choice to have other non-specific treatments;
- the use of systemic corticosteroids should be restricted to adult patients with exceptionally recalcitrant and symptomatic PR which is resistant to other treatments; a VDRL test result should be available before commencement of therapy; lesional biopsy should be considered in the presence of any atypical feature; contraindications, including pregnancy, should be actively excluded; the patients should be informed of the uncertainty of the benefit of systemic corticosteroids in modifying the course of PR, data relating to potential aggravation of the rash and the potential adverse effects of systemic corticosteroids should be discussed with the individual patient who should be given free choice to have other treatments; and
- in assessing the symptom severity and effects on daily life, QOL indexes such as the Dermatology Life Quality Index (DLQI)[49, 50] and Children's Dermatology Life Quality Index (CDLQI)[51] can be helpful adjuncts in the decision-making processes.

CONCLUSIONS

Most specific treatments for PR are not supported by adequate evidence, and by and large the mechanisms of action of these treatments are largely unknown. Further investigation of the roles of EBV, atypical bacteria and cellular immune dysfunction may prove helpful.

Many patients with PR do not require any treatment, and most do not require specific treatments; the use of erythromycin as a specific treatment for PR in particular is still controversial. Its use should be reserved for patients with severe pruritus unresponsive to non-specific treatments. Systemic corticosteroids should be kept as a last resort for exceptionally recalcitrant and symptomatic adult cases with a definite diagnosis and no contraindication to their use.

Assessments of symptom severity and the effects of PR on QOL are more important than assessment of extensiveness of rash in deciding the use of specific treatments; the use of QOL indexes is recommended to assist in reaching such a decision.

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