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Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial

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Abstract

Objective To assess the efficacy and safety of oral pristinamycin versus intravenous then oral penicillin to treat erysipelas in patients in hospital.

Design Multicentre, parallel group, open labelled, randomised non-inferiority trial.

Setting 22 French hospitals.

Participants 289 adults admitted to hospital with erysipelas.

Results At follow up (day 25-45) the cure rate (primary efficacy end point) for the per protocol populations was 81% (83/102) for pristinamycin and 67% (68/102) for penicillin. The planned interim analysis (global one sided type I error 5%) showed that the one sided 97.06% confidence interval of the observed difference (pristinamycin – penicillin) between cure rates (3.3% to ∞) exceeded the –10% non-inferiority threshold. For the intention to treat populations the cure rate at follow up was 65% (90/138) for pristinamycin and 53% (79/150) for penicillin, with the one sided 97.06% confidence interval of the observed difference between cure rates (1.7% to ∞) exceeding the –10% non-inferiority threshold. That the lower limit of the confidence interval exceeded the –10% threshold and was also >0 supports the hypothesis that pristinamycin is significantly superior at the 5% level. More adverse events related to treatment, as assessed by the investigators, were reported in the pristinamycin group than in the penicillin group. Most adverse events involved the gastrointestinal tract (nausea, vomiting, and diarrhoea) but were minor and usually did not require discontinuation of treatment.

Conclusion Pristinamycin could be an alternative to the standard intravenous then oral penicillin regimen used to treat erysipelas in adults in hospital, with the advantages of oral first line therapy.

Introduction

Erysipelas is an acute superficial dermal-hypodermal infection (cellulitis) usually affecting the legs and commonly caused by streptococci.¹⁻⁶ Although regimens vary, the standard treatment is intravenous penicillin G.^{3 5 7 8 9 10-12} To date, only a few studies have evaluated the efficacy of oral penicillin¹⁰ or macrolides¹² versus standard penicillin to treat erysipelas or acute cellulitis. Pristinamycin, a natural streptogramin, is especially active against *Streptococcus pyogenes*.

Methods

Study design

The study was a randomised open label, parallel group clinical trial designed to assess the non-inferiority of oral pristinamycin versus a standard intravenous then

oral penicillin regimen. It took place from August 1998 to November 2000 in 22 dermatology centres in France. We used a non-inferiority approach to investigate whether pristinamycin is not less effective than the reference treatment. Patients were randomly assigned to 14 days' treatment with either oral pristinamycin or benzylpenicillin until their temperature was normal and then oral phenoxymethylpenicillin.

Patients

All adults with erysipelas who were admitted to hospital in each of the participating centres were eligible for the study (see bmj.com for clinical characteristics of eligible patients). The local severity of the infection was calculated with a clinical score describing the oedema, erythema, and pain of cutaneous plaque (0=absent, 1=moderate, 2=severe). To be included, each patient had to have a total clinical score ≥ 3 .

Baseline and follow up assessments

Assessments were carried out at enrolment, 48-72 hours after starting treatment, during treatment (days 4-10), at the end of treatment (days 14-17), and at follow up (days 25-45). At each visit participants underwent a complete physical examination, and we calculated a severity score. Patients whose local or general status had deteriorated could be withdrawn from the trial and the treatment was considered to have failed. A blood sample and swabs were tested at enrolment.

Primary and secondary end points

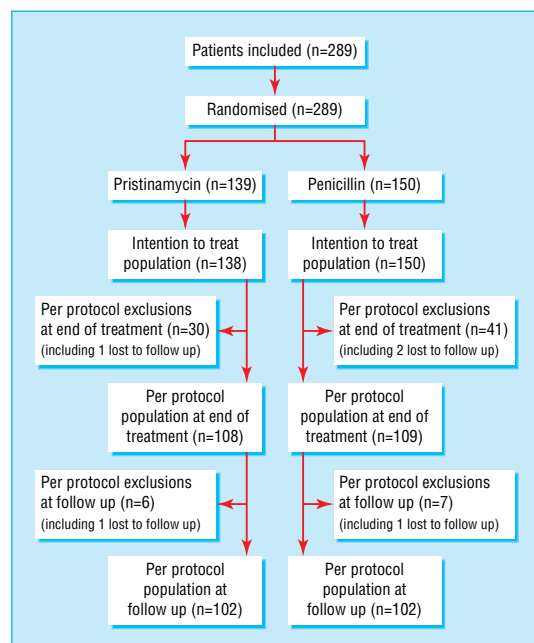
All randomised patients were included in the intention to treat analysis. Patients without any major protocol violation were included in the per protocol population.

The primary end point was the clinical cure rate determined at follow up (days 25-45) for the per protocol population. The secondary end points were the clinical cure rate determined at follow up for the intention to treat population and the clinical success rate determined at the end of treatment (days 14-17) for the intention to treat and per protocol populations.

Statistical analyses

Our main objective was to assess the non-inferiority of pristinamycin versus penicillin. The calculation of sample size was based on the primary end point and was calculated as 420 patients, with a planned interim analysis once about 2 \times 95 assessable patients had been enrolled.

We compared primary and secondary efficacy variables between the two treatment groups using a one sided non-inferiority test: the lower limit of the confidence interval of the difference in cure rates between pristinamycin and penicillin had to exceed the predefined threshold of –10%.¹³ The non-inferiority margin for all criteria was set at 10%.



Trial regimen (*one patient randomised twice in error but was included only once in efficacy analysis). Exclusions from per protocol at end of treatment were because of non-compliance with treatment, prohibited treatment used during study, discontinuation of treatment due to adverse event, or missing data (patient may have had one or more major protocol violation). Exclusions at follow up were because of missing data or prohibited treatment used during study (patient may have had one or more major protocol violation)

Results

Patients

We performed the interim analysis when we had included 289 patients (figure). With the exception of one patient wrongly included twice, all randomised patients were included in the intention to treat population and received at least one dose of the study medication.

Efficacy

Treatment

For the pristinamycin and penicillin groups the mean duration of treatment and mean duration of hospital stay were similar. Mean clinical severity scores were also similar for both groups.

Primary efficacy variable

At follow up the respective cure rates for the pristinamycin and penicillin per protocol populations were 81% (83/102) and 67% (68/102) (table), with the lower limit of the one sided 97.06% confidence interval for the observed difference between them exceeding the -10% non-inferiority threshold. For the per protocol popula-

tion, the pristinamycin effect was estimated to be $+14.7$ (SE 6.1%) (estimation of the difference).

Secondary efficacy variables

For the pristinamycin and penicillin intention to treat populations, the respective cure rate at follow up was 65% (90/138) and 53% (79/150), with the lower limit of the one sided 97.06% confidence interval for the observed difference between them exceeding the -10% non-inferiority threshold (table). For the intention to treat population, the pristinamycin effect was estimated (as above) to be $+12.6$ (SE 5.9%).

Because this interim analysis established the non-inferiority of pristinamycin compared with penicillin, it became the final analysis. Moreover, the 14.7% difference in favour of pristinamycin over penicillin on the principal assessment criterion and the confidence interval support the hypothesis of the superiority of pristinamycin.

The clinical success rates at the end of treatment for per protocol and intention to treat populations also showed the non-inferiority of pristinamycin (table).

Safety

Adverse events related to treatment were more common in the pristinamycin group ($P=0.034$), were mostly mild or moderate, and involved the gastrointestinal tract. The proportions of adverse events necessitating discontinuation of the study medication were similar for the two groups ($P=0.174$).

Two patients in the penicillin group experienced a severe adverse event—leucopenia or erythema multiforme—that was possibly related to the study medication.

Discussion

This study is the first large scale trial to show clearly that oral treatment can replace intravenous then oral penicillin to treat erysipelas in patients in hospital. At present, the reference treatment for erysipelas is penicillin, usually administered intravenously for at least 10 days.^{3 5 7-10 12 14 15} Randomised prospective trials to assess the efficacy of intravenous penicillin against erysipelas are rare.^{10 12 14} Other than those trials, penicillin regimens for erysipelas have been derived from retrospective studies.^{3 7 8 9}

Although we would have preferred to use a double blind, double placebo design, this study is the first in erysipelas or cellulitis in which the design corresponds to that of a non-inferiority trial. As recommended for non-inferiority trials, the analysis was conducted on both per protocol and intention to treat populations.^{13 16} As the study design was more explanatory than pragmatic and our main aim was to assess the

Clinical responses at follow up (day 25-45) and at end of treatment (day 14-17)

Response	Pristinamycin	Penicillin	97.06% CI (one sided)	94.12% CI (two sided)
Cure rate at follow up*:				
Per protocol population	81% (83/102)	67% (68/102)	(3.3% to ∞)	(3.3% to 26.1%)
Intention to treat population	65% (90/138)	53% (79/150)	(1.7% to ∞)	(1.7% to 23.4%)
Clinical success rate at end of treatment†:				
Per protocol population	89% (96/108)	74% (81/109)	(4.8% to ∞)	(4.8% to 24.3%)
Intention to treat population	74% (102/138)	63% (95/150)	(0.3% to ∞)	(0.3% to 20.8%)

*Primary end point.

†Cure and lesion regression.

What is already known on this topic

The reference treatment for erysipelas is intravenous penicillin, which requires admission to hospital

Few studies have evaluated the efficacy of oral treatment for erysipelas

What this study adds

Oral pristinamycin is at least as effective as intravenous then oral penicillin to treat erysipelas in adult inpatients, with the advantage of oral first line treatment

non-inferiority of pristinamycin versus penicillin, the primary end point relies on the per protocol analysis.¹³ Full application of the intention to treat analysis will be possible only once complete outcome data become available for all randomised patients.¹⁷ Most of our non-assessable patients were excluded from the per protocol analysis because of adverse events leading to premature withdrawal, missing data, or use of prohibited treatment. Intention to treat analysis also confirmed the non-inferiority of pristinamycin as inclusion of non-compliers decreased the cure rates to similar extents in both groups.

Currently, pristinamycin is marketed only in some European countries. It is commonly used in France to treat erysipelas¹⁸ and superficial pyodermas¹⁹ in outpatients. Our results show that pristinamycin could be an alternative to intravenous then oral penicillin to treat erysipelas in adult inpatients. Whether this therapeutic strategy is valid for outpatients needs to be investigated.

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Effect of general hospital management on repeat episodes of deliberate self poisoning: cohort study

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Provision of services in the United Kingdom for patients who deliberately poison themselves is variable, and many patients leave hospital without adequate assessments.¹ This may reflect the equivocal research evidence on the effectiveness of interventions.² In this cohort study, we aimed to investigate whether aspects of routine hospital management—such as admission, psychosocial assessment, and referral for follow up—had an impact on the repetition of deliberate self poisoning.

Participants, methods, and results

Over eight weeks, we prospectively identified patients aged over 16 years who attended six general hospitals

(three teaching; three district) in north west England for deliberate self poisoning. We examined the notes in accident and emergency departments for all patients (regardless of presenting complaint) to ensure that we did not miss any episodes. We also looked at databases held in wards and emergency departments and copies of specialists' self poisoning assessments, and we retrospectively checked the patient administration system in each hospital. We collected information about patients' characteristics, clinical details, and the management of the current episode, including whether the patient had received a psychosocial assessment (as defined by the Royal College of Psychiatrists).³ We followed participants for 12 weeks after their index episode, because half of those who poison themselves again do so within