Oral streptogramins in the management of patients with methicillin-resistant Staphylococcus aureus (MRSA) infections

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Objectives: Chronic methicillin-resistant Staphylococcus aureus (MRSA) infections in debilitated patients are difficult to treat. We studied the clinical efficacy and safety of an oral streptogramin, pristinamycin, for these patients.

Patients and methods: Patients were admitted consecutively to receive pristinamycin, usually with doxycycline, for 7–21 days. Fifty-six patients (average age 75 years) from hospital and community were treated for skin, soft tissue, chest and other infections.

Results: The overall clinical response rate was 39 of 53 patients (74%; 95% CI: 60%, 85%) cured or substantially improved, from 53 of 56 (95%) patients clinically and 49 of 56 (87.5%) patients bacteriologically evaluable. Toxic effects comprised gastrointestinal disturbances in eight patients (14%) and one (2%) possible skin rash.

Conclusion: This study suggests that oral streptogramins may be useful in the management of debilitated patients with MRSA infections.

Keywords: oral streptogramins, MRSA infections

Introduction

Localized methicillin-resistant Staphylococcus aureus (MRSA) infections are difficult to manage in debilitated patients, since they do not usually warrant parenteral therapy and there are few oral alternatives. Systemic infections require parenteral antibiotics, which may be toxic and/or expensive.

Patients who remain untreated, or for whom treatment fails, are at risk of future sepsis since they remain a persistent source of MRSA. Many are condemned to long-term isolation because they reside in high-risk areas. Patients in the community are even less likely to receive therapy and can remain positive for months.

We identified an antibiotic called pristinamycin, an oral streptogramin, which is currently licensed in some European countries. Clinical indications include chest, skin and soft tissue infections caused by susceptible Gram-positive bacteria. In the absence of reported toxicity, an observational study was undertaken in order to help debilitated patients with MRSA infections. These patients were unable to tolerate any other agents. Known in vitro synergy between streptogramins and tetracycline led to the combination of pristinamycin and doxycycline, as dual therapy lessens the risk of selecting resistance. It was hoped that the combination might benefit patients who might not otherwise have received antibiotics for chronic MRSA infections.

Materials and methods

The study was conducted in a district general hospital and surrounding community with patients admitted consecutively over a 2 year period. Clinicians requested treatment advice for patients with MRSA infection, rather than colonization. Underlying medical conditions included peripheral vascular disease, diabetes mellitus, cancer, chronic obstructive airways disease, ischaemic heart disease, cerebral damage (stroke or

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trauma), rheumatoid arthritis, alcoholism, cardiac failure, dementia, epilepsy, psychoses and pernicious anaemia. Patients were excluded if septicemic, able to tolerate other appropriate antibiotics or if suspected of exhibiting a prior reaction to trial drugs. Concomitant isolation of other organisms was not a prerequisite for exclusion, nor was terminal illness. Consent for treatment was obtained according to Health Board guidelines for the use of unlicensed agents; formal ethical approval was not considered necessary since this was an observational study and not a trial. Admission was granted for compassionate reasons on a named patient basis only.

Pristinamycin 0.5–1.5 g three times a day, with or without doxycycline 50–200 mg once a day, was given for 7–21 days; this was extended in exceptional circumstances. Doxycycline was withheld if the patient’s strain was resistant. A test-of-cure was performed 48 h after treatment, with a clinical and bacteriological assessment.

The drugs were stopped if there were side effects. Treatment was initiated in all cases with a 3 day topical clearance regimen (nasal mupirocin, triclosan 2% and hexachlorophane), since eradication is far more likely if topical clearance is combined with antibiotics. Patients with mupirocin-resistant isolates received nasal Polyfax (polymyxin B/bacitracin) and fusidic acid for 5 days. In situ devices were removed or changed during therapy. Patients were monitored daily for clinical response and adverse effects, including overgrowth of resistant organisms not present at original sampling.5

Microbiology

Isolates were identified by standard laboratory methods and MRSA confirmed by detection of the mecA gene.6 MRSA strains were characterized by phage typing, biotyping and antibiograms.7

Susceptibility testing was performed by Stokes’ method (widely used in the UK at the time of the study) against erythromycin (5 µg), rifampicin (2 µg), fusidic acid (5 µg), tetracycline (5 µg), mupirocin (5 µg), clindamycin (2 µg), vancomycin (30 µg), gentamicin (10 µg) and quinupristin/dalfopristin (15 µg). The latter was used to assess pristinamycin susceptibility, as specific discs for pristinamycin were unavailable.8 Linezolid (10 µg) testing was introduced following its release in early 2001. Some strains were tested for macrolide–lincosamide–streptogramin B (MLSB)-type resistance.9

MICs of doxycycline (Sigma) were assessed by the NCCLS broth microdilution assay and of quinupristin/dalfopristin using a standard Etest (AB Biodisk) on Mueller–Hinton II agar containing 2% NaCl.

The clinical response was assessed as cure, improved, failure or indeterminate; bacteriological outcome was assessed as eradicated, presumed eradicated, persistence, presumed persistence or indeterminate, as defined previously. The overall response rate was derived from both clinical and bacteriological responses and reflected the number of patients with a clinical response of cured or improved plus a bacteriological response of eradicated or presumed eradicated, divided by the total number of patients, including those with indeterminate responses.5 The criteria for clinical and bacteriological evaluable are summarized in Table 1.

Statistics

Confidence intervals (CI) were calculated using exact binomial methods, and Fisher’s exact test was used to compare the rates in the MRSA carriers and non-carriers.

Results

Fifty-six patients were treated for localized MRSA infections: forty-three (77%) in hospitals, nine (16%) in community hospitals or nursing homes and four (7%) in their own

Table 1. Criteria for clinical and bacteriological evaluabilities

(a) Clinical evaluable

(i) Signs and/or symptoms of localized infection and not colonization.
(ii) Clinical response of cure, improved or failure.
(iii) Clinical assessment performed within 1 week after finishing therapy.
(iv) No concomitant medical condition confounding clinical response.
(v) Pristinamycin administration for at least 7 days.
(vi) No more than 5% pristinamycin doses missed, and no scheduled dose missed on two or more consecutive days.
(vii) 0.5–1.5 g pristinamycin three times a day prescribed.

(b) Bacteriological evaluable

(i) MRSA isolated from infection site.
(ii) At least one set of screening swabs or samples taken 48 h or more after finishing therapy, including a sample from the original site.
(iii) Confirmation of methicillin and quinupristin/dalfopristin susceptibilities by the Scottish MRSA reference laboratory.
Oral streptogramins for MRSA

The mean age was 75 years (range 35–100), with eight patients (14%) aged >90 years. There were 33 (59%) females and 23 (41%) males, all white Caucasian. Infection sites are shown in Table 2. Two patients (4%) had had MRSA septicaemia previously. Twenty-eight (50%) patients were nasal carriers and thirty-five (62.5%) carried MRSA at sites other than those thought to be infected.

Six patients received intravenous vancomycin initially (0.5–2 g once a day) for 2–5 days, but toxicity or lack of response forced the physicians to abandon therapy in favour of pristinamycin and doxycycline. Similarly, one received rifampicin and fusidic acid for 2 days before toxicity precipitated enrolment. Six patients with doxycycline-resistant strains and two with doxycycline intolerance were treated with pristinamycin alone; one received pristinamycin and rifampicin.

Fifty-three of 56 patients (95%) were clinically evaluable; 49 (87.5%) of 56 were bacteriologically evaluable. Forty-six (82%) of 56 were cured, four (7%) improved and three (6%) failed treatment. MRSA was eradicated from 27 (51%) patients, presumed eradicated in 12 (23%) and persisted in 14 (26%), of which 11 (21%), despite persistence, showed cure or improvement. The overall response was 39 of 53 patients (75%; 95% CI: 60%, 85%), with no indeterminate responses. Eight patients (14%) died within a month of treatment but this was not attributed to study drugs; six of these were already known to be terminal.

Non-clinically evaluable patients included one who died during therapy, one who disappeared from follow-up and one with an exfoliative skin rash after 4–5 days of treatment. The latter was receiving multiple other drugs and it was unclear whether study antibiotics caused her rash.

Eighteen of 31 (58%) MRSA carriers were cured as opposed to 16 of 22 (73%) non-carriers (P = 0.39). Ten of ten patients with erythromycin-susceptible strains were cured, in contrast to 26 of 33 (79%) with strains showing clindamycin resistance induction (P = 0.14). Similarly, 12 of 12 patients with EMRSA-16 did better than patients with EMRSA-15 (31 of 38; 82%) (P = 0.138). These differences were not significant.

There was little difference in outcome between patients receiving pristinamycin alone (seven of eight; 87%) and those receiving both drugs (39 of 44; 89%) (P = 0.71). Five of eight (62%) (monotherapy), however, showed persistence of the organism at one or more sites, in contrast to eight of 44 (18%) in the dual group (P = 0.018).

One diabetic patient with a stump infection required 5 weeks of pristinamycin before the infection healed. Two others receiving extended courses included one that required two 14 day courses of both drugs (cured), and one with a mixed S. aureus and MRSA elbow osteomyelitis, who received 3 months of therapy. This patient improved despite persistence of S. aureus, but needed further flucloxacillin and fusidic acid

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**Table 2. Clinical infections with MRSA in the treated population**

<table>
<thead>
<tr>
<th>Clinical Infection</th>
<th>No. of patients (n = 56)</th>
<th>No. cured or improved (n = 53)</th>
<th>No. eradicated or presumed eradicated (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>post-surgical wound</td>
<td>20</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>ulcer</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>bedsore</td>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>cellulitis</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>eye</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>mouth</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. of patients (n = 56)</td>
<td>20</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>No. cured or improved (n = 53)</td>
<td>19</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>No. eradicated or presumed eradicated (n = 49)</td>
<td>15</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
before achieving a cure. The patient receiving pristinamycin and rifampicin failed therapy and died 6 months later.

Adverse events included diarrhoea or loose stools (eight cases; 14%) and one possible rash (2%). The latter patient and one with severe diarrhoea had therapy curtailed, although neither of these conditions was life threatening. Another patient had *Clostridium difficile* more than a month after therapy. There were no adverse events regarding the usual haematological and biochemical parameters.

Microbiology

Fifty-six isolates were confirmed MRSA. Fifty-three were phage typed: 40 (75%) were EMRSA-15, 12 (23%) were EMRSA-16 and one was non-typeable. All were susceptible to quinupristin/dalfopristin, fusidic acid, linezolid and glycopeptides. The quinupristin/dalfopristin MIC90 was 0.38 mg/L (range 0.125–0.75 mg/L) and the doxycycline MIC90 was 4.0 mg/L (range 0.5–>64 mg/L). Six (11%) isolates were resistant to doxycycline (MIC > 64 mg/L). Forty-five (80%) isolates were resistant to erythromycin, 13 (23%) to neomycin, five (9%) to mupirocin, six (11%) to clindamycin and four (7%) to rifampicin. Thirteen of 45 (29%) erythromycin-resistant isolates showed mild and 20 (44%) moderate to high induction of clindamycin resistance.9 There was no evidence that persistent strains became resistant to either of the study drugs.

Other isolates included groups B, C and G β-haemolytic streptococci, *S. aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. These were all eradicated, except for the patient with MRSA and *S. aureus* osteomyelitis already mentioned.

Discussion

There is a real need for more agents against MRSA, particularly non-toxic oral drugs suitable for elderly or debilitated patients with chronic low-grade infections. Pristinamycin, with or without doxycycline, appears to be effective in these patients. Overall, 39 of 53 (74%) patients were cured of MRSA, with a further seven demonstrating clinical cure despite persistence of MRSA.

Whilst patients receiving pristinamycin and the combination achieved similar outcomes, it was noted that those given both drugs responded more rapidly (data not shown) and had significantly less chance of persistent MRSA. It is possible that the combination is synergic in vivo, reflecting in vitro findings, but this should be clarified with a larger comparative trial.

Adverse events requiring termination of therapy were rare. Most patients tolerated the drugs well, including the very elderly and those weighing <50 kg. Only two patients demonstrated enterococcal overgrowth, in contrast to reports following the use of intravenous quinupristin/dalfopristin.5 Besides clinical benefits, patients could be moved out of isolation and rehabilitated with much less risk to others. It is possible that eradication of these chronic infections from long-stay patients has helped to control MRSA in this hospital.

Strains with MLSB-type resistance may reduce the therapeutic potential of pristinamycin despite persisting synergy between group A and B streptogramins.10 There was a suspicion that patients with inducible strains did less well. There have been reports of clinical failures, and resistance to pristinamycin, although there was no evidence for the latter in this study.

In conclusion, we have found that pristinamycin, with or without doxycycline, provides effective treatment for patients with chronic MRSA infections. The regimen is well tolerated with minimal toxicity. We believe that a randomized clinical trial is now required in order to evaluate further the role of oral streptogramins in the management of patients with MRSA infections.

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A pilot study of this work (first 10 patients) was presented to the Federation of Infection Societies Annual Conference, Manchester, UK, in December 1999 (Abstract P57a), and a poster summarizing the results in this paper was shown at the Fifth International Conference of the Hospital Infection Society, Edinburgh, UK, September 2002.

References

Oral streptogramins for MRSA


