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Randomized non-inferiority trial to compare trimethoprim/sulfamethoxazole plus rifampicin versus linezolid for the treatment of MRSA infection

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Objectives: The therapeutic arsenal for MRSA infections is limited. The aim of this study was to assess the non-inferiority of a combination of trimethoprim/sulfamethoxazole plus rifampicin versus linezolid alone for the treatment of MRSA infection.

Methods: We conducted a randomized, open-label, single-centre, non-inferiority trial comparing trimethoprim/sulfamethoxazole (160 mg/800 mg three times daily) plus rifampicin (600 mg once a day) versus linezolid (600 mg twice a day) alone in adult patients with various types of MRSA infection. Patients were allocated 1:1 to either regimen. The primary outcome was clinical cure at 6 weeks after the end of treatment (non-inferiority margin 20%) assessed by both ITT and PP analyses. Secondary outcomes included the microbiologically documented persistence of MRSA in clinical cultures, mortality and adverse events. The study protocol has been registered with ClinicalTrials.gov (NCT00711854).

Results: Overall, 150 patients were randomized to one of the two treatment arms between January 2009 and December 2013 and were included in the ITT analysis. Of these 56/75 (74.7%) in the linezolid group and 59/75 (78.7%) in the trimethoprim/sulfamethoxazole and rifampicin group experienced clinical success (risk difference 4%, 95% CI −9.7% to 17.6%). The results were confirmed by the PP analysis, with 54/66 (81.8%) cured patients in the linezolid group versus 52/59 (88.1%) in the trimethoprim/sulfamethoxazole and rifampicin group (risk difference 6.3%, 95% CI −6.8% to 19.2%). There were no statistically significant differences between the two groups in any of the secondary outcomes, including microbiologically documented failure. Four adverse drug reactions attributed to the study medication occurred in the linezolid group versus nine in the trimethoprim/sulfamethoxazole and rifampicin group.

Conclusions: Compared with linezolid, trimethoprim/sulfamethoxazole and rifampicin seems to be non-inferior in the treatment of MRSA infection.

Keywords: adults, Switzerland, humans, prospective clinical studies, staphylococcal infections, drug therapy, multidrug-resistant organisms

Introduction

Infections caused by *Staphylococcus aureus* represent an important therapeutic challenge. The treatment most frequently recommended for severe infection due to MRSA is a prolonged course of parenteral vancomycin.[1] However, vancomycin treatment increases healthcare costs because of the prolonged hospital stay and exposes patients to complications associated with venous lines, renal toxicity and the need for therapeutic drug monitoring. Alternative treatment regimens with oral antibiotics (e.g. fluoroquinolone and rifampicin for MSSA or linezolid for MRSA) have been proposed.[2,3] The use of older antimicrobial agents such as minocycline or trimethoprim/sulfamethoxazole, combined with rifampicin or fusidic acid, may represent particularly interesting treatment alternatives for both community- and healthcare-associated MRSA infections.[1,4,5] The only anti-MRSA antibiotic agent that has undergone in-depth clinical evaluation in its oral formulation is linezolid.[6] Its use is, however,

limited by its cost and the possible drug interactions and adverse events (AEs) associated with long-term therapy.[7,8] This leaves an unmet clinical need for the evaluation of other oral anti-MRSA therapies. Therefore, we performed a randomized non-inferiority trial to compare the efficacy and safety of therapy with trimethoprim/sulfamethoxazole plus rifampicin versus linezolid alone to treat MRSA infection.

Methods

Trial design

This was an investigator-initiated, open-label, single-centre, randomized clinical trial to demonstrate the non-inferiority of a combination of trimethoprim/sulfamethoxazole plus rifampicin versus linezolid in patients (allocation ratio 1:1) requiring antibiotic therapy for MRSA infection. The study protocol was approved by the local institutional review board (no. 08-59) and the Swiss agency for therapeutic products (SwissMedic no. 2008DR4305), and has been registered with ClinicalTrials.gov (NCT00711854). Written consent was obtained from all participants.

Setting and participants

This study was conducted at the Geneva University Hospitals, a Swiss tertiary care centre with 1915 beds, ∼48000 yearly admissions and hyperendemic MRSA transmission.[9] Antibiotic susceptibility data in 2011 revealed that MRSA isolates from clinical cultures were 97%, 97%, 11%, 97%, 100% and 100% susceptible to trimethoprim/sulfamethoxazole, rifampicin, clindamycin, fusidic acid, linezolid and vancomycin, respectively.

Between January 2009 and December 2013, we enrolled patients aged ≥18 years and able to provide informed consent, who had clinical signs and symptoms of MRSA infection according to clinical culture results (MRSA as the predominant or unique microorganism in culture) that was susceptible to trimethoprim/sulfamethoxazole, rifampicin and linezolid. Standard microbiology methods were used for MRSA identification and antimicrobial susceptibility testing, which was performed both phenotypically (using the disc diffusion method, interpreted with CLSI breakpoints) and genotypically (*femA* and *mecA* determination, using the BD GeneOhm MRSA assay).[10]

Various types of MRSA infection, including severe infections (e.g. pneumonia, bacteraemia), deep-seated infections requiring treatment for more than 14 days (e.g. osteoarticular infections) and non-severe infections (of skin and soft tissue) requiring shorter courses of treatment could be included. Potentially eligible patients were identified by daily surveys and an electronic alert of all MRSA-positive cultures generated by the clinical microbiology laboratory.[10]

Patients who had been treated for ≥72 h prior to study inclusion with antimicrobials active against MRSA (mostly vancomycin) were excluded. Additional exclusion criteria were: known hypersensitivity to linezolid, trimethoprim/sulfamethoxazole or rifampicin; pregnancy or breastfeeding; significant impairment of hepatic function; haemodialysis; severe thrombocytopenia (<50000 platelets/μL); chronic MRSA osteomyelitis without surgical debridement; a superinfected indwelling foreign body kept in place; severe sepsis or septic shock due to MRSA bacteraemia;[11] left-sided endocarditis; oral contraception; a history of phaeochromocytoma, carcinoid syndrome or untreated hyperthyroidism; or being in receipt of serotonergic agents.

Interventions

Patients randomized to the trimethoprim/sulfamethoxazole plus rifampicin arm received oral therapy or intravenous infusion (with a suggested maximum duration of 5 days) of 160 mg of trimethoprim and 800 mg of sulfamethoxazole three times daily and 600 mg of rifampicin once daily. Patients randomized to the linezolid arm received oral therapy (or an intravenous infusion) of 600 mg of linezolid twice daily. The treatment was administered for at least 7 days, depending on the type and severity of the MRSA infection. MRSA infection types were classified by the involved study physicians in agreement with the treating clinicians, based on clinical, bacteriological and radiological criteria. For each category, the minimum recommended duration of treatment was defined as follows: non-severe infections (e.g. urinary tract infections, soft tissue infections), 7–10 days; severe infections (e.g. pneumonia, bacteraemia), 14 days; and infections associated with deep-seated foci, 14–42 days. Any discontinuation or modification of antimicrobial therapy was left to the judgement of the treating physicians. In cases of polymicrobial infection not covered by the study treatment, physicians were able to add concomitant systemic antibiotic treatment without anti-MRSA activity if this was considered to be clinically indicated.

Outcomes

Assessments of bacteriological results, clinical signs and symptoms of infection, as well as clinical and laboratory safety evaluations, were made at study entry and at the end of the treatment (±48 h). Final evaluation was made by one of the study physicians 6 weeks (±1 week) after the patient had received the final dose of the trial treatment. If the patient could not be reached for the final assessment, telephone contact and evaluation by the general practitioner in charge were considered sufficient. The primary efficacy variable was the resolution of MRSA infection at 6 weeks after the end of treatment, defined as the resolution of all the clinical signs and symptoms of the infection that had been present at baseline;[2] failure was defined as no improvement or a deterioration in the clinical condition or a change of the allocated treatment regimen at any time or the death of the patient. We determined the final outcome using all the available information, including subsequent radiographic exams, microbiology results, surgical interventions and the patient's clinical course. Bacteriological cure as a secondary outcome was defined as the eradication of MRSA from the infection site. Bacteriological failure was defined as a microbiologically documented persistence or relapse of MRSA at the same site as the original isolate. Other secondary outcomes were all-cause mortality and length of hospital stay after randomization.

All included patients were monitored for AEs, serious AEs (SAEs) and adverse drug reactions (ADRs). An ADR was defined as harm causally related to the administration of the study medication at a normal dosage. Toxicity was reported to be causally related to the study antibiotics if it began when the drugs were first administered, abated after the discontinuation of drug use and was not clearly attributable to other causes.

Randomization

As soon as the results of antimicrobial susceptibility testing were available, and provided the enrolment criteria had been fulfilled, the patient and the medical staff responsible for the treatment were contacted by the study investigators. Patients who fulfilled the inclusion criteria were randomly assigned by sealed, opaque, numbered envelopes to one of the two treatment arms. The sequence was generated using an internet-based randomization generator with a block size of 30.

Sample size

This non-inferiority trial attempted to ascertain whether the clinical efficacy of treating MRSA infections with trimethoprim/sulfamethoxazole plus rifampicin was comparable to that of linezolid. The 95% CI for the difference in success rates (percentage cure at 6 weeks after the end of treatment in the trimethoprim/sulfamethoxazole plus rifampicin arm minus the percentage cure in the linezolid arm) was calculated on the basis of the normal approximation to the binomial distribution.[12] The non-inferiority test was based on the lower boundary of the 95% CIs for a

clinically important difference in success rates and settled within the non-inferiority margin of 20% and the upper boundary containing 0% (e.g. a difference of 20% in the clinical efficacy of the two antibiotic regimens would justify the use of one over the other). This margin was based not only on acceptable differences in cure rates, but also on considerations of treatment costs and study feasibility. Assuming a 75% efficacy in both treatment groups,[3,13,14] a statistical power of 80% and a one-sided significance level of 0.025, we estimated that 90 evaluable patients needed to be enrolled in each treatment group to test the null hypothesis (that the treatment success rates would differ by >20%).

Statistical methods

Two different patient populations were analysed: the ITT patient population and the PP population of completely evaluable patients. The ITT population included all the patients who had been randomized. For the ITT analysis, 13 patients lost to follow-up were assigned to the outcome 'failure'. Patients entered the PP analysis if they had received study drugs for at least 7 days and were fully clinically evaluable at the last follow-up visit.[2]

For hypothesis testing, we used the Student's *t*-test for normally distributed variables, the two-sample Wilcoxon rank-sum test for skewed distributions and the Fisher's exact test or χ^2 test for the homogeneity of proportions for categorical data. Statistical analyses were performed using Stata version 12 (Stata Corp., College Station, TX, USA).

Results

Participant flow and recruitment

The study groups and reasons for non-inclusion are shown in Figure 1. There were 1638 patients with at least one MRSA-positive clinical culture during the study period. Of these, 164 (10.0%) were deemed to be eligible after a chart review and were invited to participate; 150 (9.2%) agreed to participate in the study, provided written consent and were randomized, with 75 patients

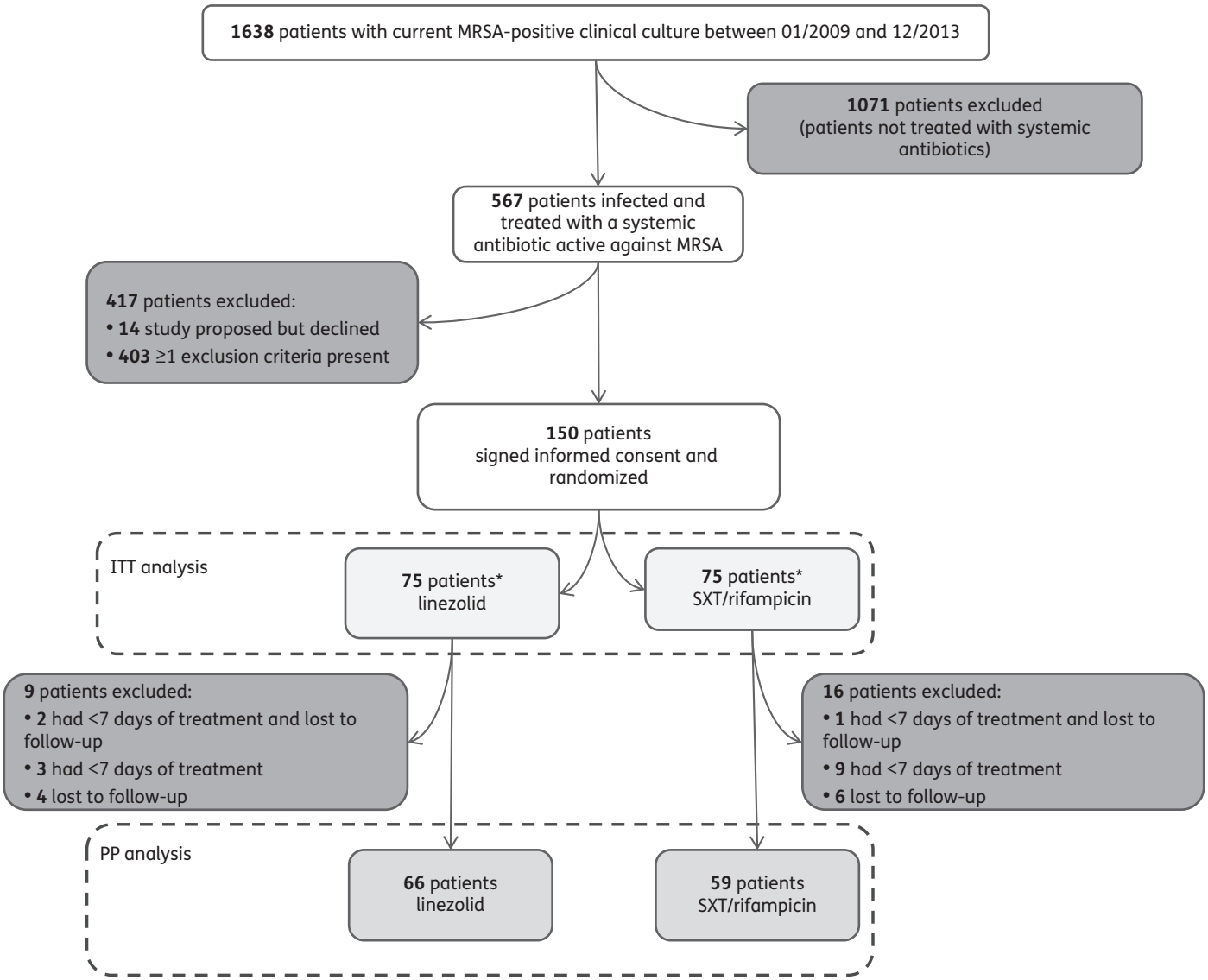

Figure 1. Trial profile. *All patients received the allocated regimen. SXT, trimethoprim/sulfamethoxazole.

Table 1. Baseline characteristics by treatment assignment (all randomized patients)

	Linezolid group ($n=75$)	Trimethoprim/sulfamethoxazole and rifampicin group ($n=75$)
Male, *n* (%)	50 (66.7)	52 (69.3)
Age (years), median (IQR)	69 (56–76)	67 (50–80)
Type of admission, *n* (%)		
emergency	47 (62.7)	51 (68.0)
elective	23 (30.7)	16 (21.3)
outpatient	5 (6.7)	8 (10.7)
Prior hospitalization in a long-term care facility, *n* (%)	20 (26.7)	25 (33.3)
Hospital unit at the time of inclusion, *n* (%)		
surgery	43 (57.3)	37 (49.3)
medicine	13 (17.3)	14 (18.7)
long-term and geriatric care	4 (5.3)	8 (10.7)
ICU	3 (4.0)	5 (6.7)
other	7 (9.3)	3 (4.0)
ambulatory	5 (6.7)	8 (10.7)
Comorbidities, *n* (%)		
cardiovascular	47 (62.7)	47 (62.7)
pulmonary	13 (17.3)	11 (14.7)
renal	16 (21.3)	14 (18.7)
metabolic	22 (29.3)	19 (25.3)
malignancy	20 (26.7)	18 (24.0)
digestive	9 (12.0)	3 (4.0)
immunological	1 (1.3)	4 (5.3)
other diseases	28 (37.3)	31 (41.3)
surgical interventions[a]	54 (72.0)	41 (54.7)
Degree of dependency on admission, *n* (%)		
independent[b]	55 (73.3)	42 (56.0)
semi-dependent	13 (17.3)	21 (28.0)
dependent	7 (9.3)	12 (16.0)
Charlson score, median (IQR)	5 (2–7)	4 (1–7)
McCabe score (underlying disease), *n* (%)		
non-fatal condition	58 (77.3)	58 (77.3)
ultimately fatal condition	13 (17.3)	13 (17.3)
rapidly fatal condition	4 (5.3)	4 (5.3)
Polymicrobial infection with MRSA as dominant pathogen, *n* (%)	23 (30.7)	13 (17.3)
History of known MRSA carriage, *n* (%)	59 (78.7)	51 (68.0)
MRSA infection source, *n* (%)		
skin and soft tissue infection	21 (28.0)	24 (32.0)
surgical site infection	19 (25.3)	15 (20.0)
bacteraemia	9 (12.0)	9 (12.0)
nosocomial pneumonia	8 (10.7)	9 (12.0)
osteoarticular	9 (12.0)	7 (9.3)
abdominal	4 (5.3)	3 (4.0)
urinary tract infection	2 (2.7)	5 (6.7)
other	3 (4.0)	3 (4.0)
Prior antibiotic treatment		
patients receiving at least one dose of empirical anti-MRSA antibiotic therapy before study inclusion, *n* (%)	40 (53.3)	29 (38.7)
time from start of empirical anti-MRSA antibiotic therapy to study inclusion (days), median (IQR)	1 (0–3)	0 (0–2)

[a]$P=0.028$.
[b]$P=0.026$.

included in each study arm (the ITT population). Of note, the study was stopped after 150 patients because of recruitment problems due to the substantially decreased incidence of MRSA infections at our institution.

Overall, 25 patients were excluded from the PP analysis: 12 patients because of <7 days of study treatment, 10 patients for not having a complete follow-up and 3 patients for both reasons (Figure 1).

Baseline data

Baseline characteristics were comparable between the two study groups, except that patients in the linezolid group underwent statistically significantly more surgical interventions (54/75 versus 41/75) and were more likely to be living independently at home (55/75 versus 42/75; Table 1). The mean age of the patients was 64 years (range 18–95 years), and 102/150 (68.0%) were male. A majority of patients (53.3%) were hospitalized in the surgical department. The leading primary sites of MRSA infection were skin and soft tissue (30%) and surgical sites (23%), which were equally distributed in the two study arms.

Antibiotic treatment

In both treatment groups, similar proportions of patients received empirical anti-MRSA antibiotic therapy for up to 72 h before study inclusion (Table 1). After study inclusion, 32 patients received concomitant non-investigational antimicrobial therapy without anti-MRSA activity, with comparable frequencies between the study arms (Table 2).

The total duration of study treatment was similar in the two study groups (Table 2). Only 29 patients (19.3%) received ≥1 dose of intravenous study treatment. The proportion of patients who prematurely discontinued the assigned study medication, as well as the reasons for their premature withdrawal, were comparable between the treatment groups (Table 2).

Efficacy

The clinical response rates provided by the ITT and PP analyses demonstrated that trimethoprim/sulfamethoxazole and rifampicin produced success rates comparable to those of linezolid treatment (Table 3). In the ITT analysis, 56/75 (74.7%) linezolid-treated patients and 59/75 (78.7%) of patients receiving trimethoprim/sulfamethoxazole and rifampicin achieved clinical success, with an absolute difference in success rates of +4% (95% CI −9.7% to 17.6%). Since the lower boundary (−9.7%) was within the predefined margin (−20%), the non-inferiority of trimethoprim/sulfamethoxazole and rifampicin could be demonstrated.

The PP analysis confirmed the ITT results, with 54/66 (81.8%) of patients in the linezolid group achieving clinical success versus 52/59 (88.1%) in the trimethoprim/sulfamethoxazole and rifampicin group (risk difference +6.3%, 95% CI −6.8% to 19.2%). The microbiological success rates among the 58 patients with available follow-up cultures were also similar in the two groups in the PP analysis, with proven eradication of MRSA in 26/33 (78.8%) patients in the linezolid group and 22/25 (88.0%) in the trimethoprim/sulfamethoxazole and rifampicin group (risk difference +9.2%, 95% CI −12.0% to 28.4%; $P=0.09$). No selection of resistance to the study drugs was observed among the follow-up MRSA cultures.

Table 4 shows the *post hoc* subgroup analyses by site and severity of MRSA infection, revealing small differences in success rates except for pneumonia and osteoarticular infection.

Mortality and length of stay

Eight patients in the linezolid group and six patients in the trimethoprim/sulfamethoxazole and rifampicin group died before end of follow-up ($P=0.78$). Among the 18 patients with MRSA bacteraemia, 4 died (2 in each arm). One death in the linezolid arm was directly attributable to MRSA bacteraemia and subsequent therapeutic withdrawal. There was no significant difference

Table 2. Study treatment description

	Linezolid group ($n=75$)	Trimethoprim/sulfamethoxazole and rifampicin group ($n=75$)	P
Total study treatment duration (days), median (IQR)	12 (8–15)	11 (8–15)	0.48
oral study treatment duration (days), median (IQR)	12 (8–15)	10 (7–14.5)	0.63
Intravenous study treatment			
patients receiving at least one dose of intravenous study treatment, *n* (%)	11 (14.7)	18 (24.0)	0.21
delay before intravenous–oral switch (days), median (IQR)	1 (1–11)	6 (3–7)	0.84
intravenous study treatment duration (days), median (IQR)	6.5 (5–7)	12.5 (1–24)	0.14
Patients with concomitant systemic antibiotic treatment without anti-MRSA activity, *n* (%)	14 (18.7)	18 (24.0)	0.55
Patients who prematurely discontinued study therapy, *n* (%)	7 (9.3)	12 (16.0)	0.33
Reason for premature discontinuation, *n* (%)			
drug toxicity	3 (4.0)	6 (8.0)	0.49
clinical failure	1 (1.3)	2 (2.7)	1.00
death	2 (2.7)	4 (5.3)	0.68
protocol violation	1 (1.3)	0 (0.0)	1.00

Table 3. Analyses of clinical and microbiological efficacy

	Linezolid group	Trimethoprim/sulfamethoxazole and rifampicin group	Risk difference	95% CI
Clinical follow-up				
ITT analysis				
success, *n* (%)	56 (74.7)	59 (78.7)	4.0	−9.7 to 17.6
relapse/failure, *n* (%)	19 (25.3)	16 (21.3)		
PP analysis				
success, *n* (%)	54 (81.8)	52 (88.1)	6.3	−6.8 to 19.2
relapse/failure, *n* (%)	12 (18.2)	7 (11.9)		
Microbiological follow-up				
PP analysis				
success, *n* (%)	26 (78.8)	22 (88.0)	9.2	−12.0 to 28.4
persistence, *n* (%)	7 (21.2)	3 (12.0)		

Table 4. ITT outcome analysis by site and severity of MRSA infection

Clinical outcome	Linezolid group	Trimethoprim/sulfamethoxazole and rifampicin group	Risk difference	95% CI
Skin and soft tissue infection				
success, *n* (%)	16 (76.2)	20 (83.3)	7.1	−17.0 to 31.8
relapse/failure, *n* (%)	5 (23.8)	4 (16.7)		
Surgical site infection				
success, *n* (%)	15 (78.9)	11 (73.3)	−5.6	−35.6 to 23.2
relapse/failure, *n* (%)	4 (21.1)	4 (26.7)		
Bacteraemia				
success, *n* (%)	6 (66.7)	7 (77.8)	11.1	−31.2 to 50.0
relapse/failure, *n* (%)	3 (33.3)	2 (22.2)		
Pneumonia				
success, *n* (%)	6 (75.0)	5 (55.6)	−19.4	−57.9 to 26.8
relapse/failure, *n* (%)	2 (25.0)	4 (44.4)		
Osteoarticular infection				
success, *n* (%)	5 (55.6)	6 (85.7)	30.1	−18.0 to 65.4
relapse/failure, *n* (%)	4 (44.4)	1 (14.3)		
Abdominal				
success, *n* (%)	4 (100.0)	3 (100.0)	0	−59.9 to 52.8
relapse/failure, *n* (%)	0 (0.0)	0 (0.0)		
Urinary tract infection				
success, *n* (%)	2 (100.0)	5 (100.0)	0	−47.3 to 69.1
relapse/failure, *n* (%)	0 (0.0)	0 (0.0)		
Other				
success, *n* (%)	2 (66.7)	2 (66.7)	0	−65.3 to 65.3
relapse/failure, *n* (%)	1 (33.3)	1 (33.3)		
Non-severe infection ($n=62$)[a]				
success, *n* (%)	22 (81.5)	30 (85.7)	4.2	−14.6 to 24.8
relapse/failure, *n* (%)	5 (18.5)	5 (14.3)		
Severe infection ($n=53$)[a]				
success, *n* (%)	22 (71.0)	17 (77.3)	6.3	−18.9 to 29.1
relapse/failure, *n* (%)	9 (29.0)	5 (22.7)		
Infection associated with deep-seated foci ($n=35$)[a]				
success, *n* (%)	12 (70.6)	12 (66.7)	−3.9	−33.8 to 26.9
relapse/failure, *n* (%)	5 (29.4)	6 (33.3)		

[a]Categories determined by site of infection and duration of therapy, as defined in the Methods section.

Table 5. Mortality and time to discharge

	Linezolid ($n=75$)	Trimethoprim/sulfamethoxazole and rifampicin ($n=75$)	Risk difference	95% CI
Death, *n* (%)	8 (10.7)	6 (8.0)	−2.7	−12.8 to 7.2
death before discharge, *n* (%)	8 (10.7)	3 (4.0)	−6.7	−16.3 to 1.9
death after discharge, *n* (%)	0 (0.0)	1 (1.3)	1.3	−3.7 to 7.2
death among outpatients, *n* (%)	0 (0.0)	2 (2.7)	2.7	−2.6 to 9.2
Time from inclusion to discharge (days), median (IQR)[a]	16 (8–36)	12 (6–31)		

[a]Among non-deceased, hospitalized patients ($n=125$; $P=0.83$).

Table 6. Safety features in the ITT population

	Linezolid group ($n=75$)	Trimethoprim/sulfamethoxazole and rifampicin group ($n=75$)	Risk difference	95% CI
AEs, *n*	192	169		
patients with at least one AE, *n* (%)	49 (65.3)	50 (66.7)	1.4	−13.8 to 16.4
Type of AE, *n* (%)				
gastrointestinal	72 (37.5)	61 (36.1)	−1.4	−11.3 to 8.6
cardiovascular	23 (12.0)	24 (14.2)	2.2	−4.8 to 9.5
fever	23 (12.0)	18 (10.7)	−1.3	−8.0 to 5.5
pulmonary	16 (8.3)	7 (4.1)	−4.2	−9.5 to 0.9
dermatological	15 (7.8)	14 (8.3)	0.5	−5.3 to 6.5
haematological	14 (7.3)	10 (5.9)	−1.4	−6.7 to 4.1
neurological	12 (6.3)	16 (9.5)	3.2	−2.4 to 9.3
fall	6 (3.1)	5 (3.0)	−0.1	−4.1 to 4.0
urological	3 (1.6)	4 (2.4)	0.8	−2.4 to 4.5
liver	0 (0.0)	1 (0.6)	0.6	−1.4 to 3.3
nephrological	2 (1.0)	3 (1.8)	0.8	−2.2 to 4.2
rheumatological	1 (0.5)	0 (0.0)	−0.5	−2.9 to 1.7
orthopaedic	1 (0.5)	1 (0.6)	0.1	−2.4 to 2.8
others	4 (2.1)	5 (3.0)	0.9	−2.7 to 5.0
SAEs, *n*	15	16		
number of patients with at least one SAE, *n* (%)	15 (20.0)	15 (20.0)	0.0	−13.0 to 13.0
Type of SAE, *n* (%)				
death	8 (53.3)	6 (37.5)	−15.8	−47.3 to 19.1
rehospitalization	6 (40.0)	10 (62.5)	22.5	−13.0 to 52.9
invalidity	1 (6.7)	0 (0.0)	−6.7	−30.3 to 13.9
ADRs[a], *n*	4	9		
number of patients with at least one ADR, *n* (%)	4 (5.3)	9 (12.0)	6.7	−2.6 to 16.7
Type of ADR, *n* (%)				
gastrointestinal	1 (25.0)	4 (44.4)	19.4	−37.8 to 61.0
haematological	1 (25.0)	0 (0.0)	−25.0	−71.2 to 12.3
nephrological	1 (25.0)	2 (22.2)	−2.8	−55.4 to 41.0
tongue discoloration	1 (25.0)	0 (0.0)	−25.0	−71.2 to 12.3
dermatological	0 (0.0)	2 (22.2)	22.2	−29.3 to 54.7
neurological	0 (0.0)	1 (11.1)	11.1	−38.7 to 44.0

[a]No SAE or suspected unexpected serious adverse reaction.

between the treatment arms concerning the time to discharge among hospitalized patients (excluding ambulatory and deceased patients), as shown in Table 5.

Safety and toxicity

The frequencies of AEs reported, regardless of the causality and type of AE, were comparable between the treatment arms

(Table 6). A total of 192 AEs were documented in the linezolid group versus 169 in the trimethoprim/sulfamethoxazole and rifampicin group, with similar proportions of patients who experienced ≥1 AE in both treatment groups (linezolid, 65.3%; trimethoprim/sulfamethoxazole and rifampicin, 66.7%). The most common type of AE in both groups was of gastrointestinal origin.

SAEs were reported in 15 patients in the linezolid group and 16 in the trimethoprim/sulfamethoxazole and rifampicin group (Table 6). Four ADRs directly attributed to the study medication occurred in the linezolid group versus nine in the trimethoprim/sulfamethoxazole and rifampicin group ($P=0.16$).

Discussion

The principal findings of this study were: (i) compared with linezolid, the combination of trimethoprim/sulfamethoxazole and rifampicin seems to be non-inferior in the treatment of MRSA infection; (ii) the clinical success rates in both groups were comparable to those reported in previous clinical trials;[15–18] (iii) there was no difference between the studied medications regarding total AEs; and (iv) serious drug-related AEs were rare.

Three systematic reviews have summarized the evidence supporting the use of trimethoprim/sulfamethoxazole for treating MRSA infections.[19–21] All have suggested that trimethoprim/sulfamethoxazole may be a useful alternative to vancomycin or linezolid for the treatment of MRSA infection. The combination of rifampicin plus trimethoprim/sulfamethoxazole is a theoretically even more attractive regimen for the treatment of MRSA infections for a number of reasons, including enhanced and intracellular antistaphylococcal activity, excellent bioavailability and favourable pharmacodynamics.[22,23] The combination is widely used in several European countries, especially for osteoarticular infections, although published evidence supporting its use remains sparse.[24,25] Moreover, since these antibiotics are available as generic agents, they offer substantial cost advantages over other agents such as linezolid and daptomycin.[26] As the launch of generic linezolid has recently been postponed to late 2016 and tedizolid will be patent-protected against generic erosion for many years, the off-patent combination of trimethoprim/sulfamethoxazole plus rifampicin will remain an attractive and inexpensive alternative oral treatment option for MRSA infections.

There was no selection of resistance to the study medication among patients with follow-up cultures. Nevertheless, we observed a non-significant trend towards a higher rate of MRSA eradication in the combination arm. This is in agreement with one controlled trial that demonstrated the efficacy of trimethoprim/sulfamethoxazole plus rifampicin for MRSA decolonization.[27] In the present study, the number and nature of AEs was similar in both arms and consistent with the known safety profile of the study drugs.[7,28,29] However, five more drug reactions occurred in the combination arm, although this was statistically non-significant.

Our study has several strengths. First, our study population included patients with various types of MRSA infection, allowing us to make comparisons not previously reported.[1] Interestingly, we found a clinically important variation in the success rates for pneumonia and osteoarticular infection; however, this study was underpowered to detect statistically significant differences. Second, following EMA policy, we chose a clinically unambiguous outcome (clinical cure at 6 weeks after the end of treatment) and did not focus on earlier primary endpoints, such as 'cessation of lesion spread' or 'time to clinical stability'.[30] Third, our study was investigator-initiated and did not receive industry sponsoring, decreasing an important source of potential bias.[31]

This study also has several limitations. First, the chosen non-inferiority margin is too wide by current standards (10%–15%) and the predefined sample size ($n=180$) was not reached due to enrolment challenges despite 5 years of recruitment. Consequently, the study lost statistical power. Furthermore, the sample size of this study is too small to determine efficacy advantages based on secondary outcomes such as bacteriological cure, mortality or length of stay. Nevertheless, we believe that our findings can be used in practice to inform therapeutic decision-making, since the estimates of treatment effect that were obtained and the corresponding CIs are robust and clinically meaningful, supporting the idea that trimethoprim/sulfamethoxazole and rifampicin is a suitable alternative compared with linezolid for a variety of MRSA infections. Second, the study was open-label and hence subject to the inherent limitations of this type of study design. Third, the trial was confined to a highly selected patient population from a single institution in Switzerland with a specific hyperendemic MRSA strain,[32] possibly limiting the generalizability of the results. Fourth, microbiological follow-up cultures were performed for only 58 patients, limiting the evaluation of microbiological failure as a secondary outcome.

In summary, our results suggest that both trimethoprim/sulfamethoxazole and rifampicin combination therapy and linezolid monotherapy are equally effective for treating patients with MRSA infection. However, the lower daily cost of the combination treatment renders it an attractive alternative to oxazolidinones.

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Author contributions

Agree with the manuscript's results and conclusions: all authors. Developed the original idea for the study: S. H. Oversight of study integrity and guarantor of data validity as Chief Investigator: S. H. Designed the study: S. H., S. E. and I. U. Had access to and analysed the entire dataset: E. v. D. and S. H. Collected data/did experiments for the study: E. v. D., M. M.-V., L. P. and F. O. Enrolled patients: E. v. D., M. M.-V., L. P., B. H., F. O. and I. U. Wrote the first draft of the paper: S. H. and E. v. D. Contributed to the writing of the paper and interpretation of study findings: all authors.

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