Oral minocycline plus rifampicin versus oral linezolid for complicated skin and skin structure infections caused by methicillin-resistant *Staphylococcus aureus*: The AIDA open label, randomized, controlled Phase 4 trial

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eClinicalMedicine 2023;56: 101790
Published Online XXX
https://doi.org/10.1016/j.eclinm.2022.101790

Summary

Background The need for oral, cost-effective treatment for complicated skin and skin structure infections (cSSSIs) due to methicillin-resistant *Staphylococcus aureus* (MRSA) was addressed by the non-inferiority comparisons of oral minocycline plus rifampicin with linezolid.

Methods In the AIDA multicenter, open label, randomized, controlled clinical trial, hospitalized adults with cSSSI and documented MRSA were randomly assigned at a 2:1 ratio to either oral 600 mg rifampicin qd plus 100 mg minocycline bid or oral 600 mg linezolid bid for 10 days. The primary endpoint was the clinical cure rate in the clinically evaluable (CE) population at the test-of-cure visit (14 days). Non-inferiority was confirmed if the lower confidence limit (CI) did not fall below the accepted error margin of 15%. The study is registered with EudraCT number 2014-001276-56.

Findings 123 patients recruited between November 2014 and January 2017 were randomly assigned to treatment (81 patients to minocycline plus rifampicin and 42 patients to linezolid). Cure rates were 78.% (46/59, 90% CI 67.3–86.5) and 68.6% (24/35, 90% CI 53.4–81.3), respectively (P = 0.337). The percent difference in cure rates was 9.4% (90% CI –7.2 to 26.8%). Minocycline plus rifampicin combination was deemed non-inferior to linezolid as the lower CI was –7.2% i.e. smaller than the accepted error margin of –15%. Although statistically not significant, the overall rate of adverse events was higher in the linezolid group (47.6%, 20/42 versus 38.3%, 31/81).

Interpretation Oral minocycline plus rifampicin was non-inferior to oral linezolid treatment providing alternative oral treatment for cSSSI.

Funding The EU Seventh Research Framework Programme.

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Keywords: Minocycline; Rifampicin; Linezolid; MRSA; Clincal trial; cSSI

Research in context

Evidence before this study

Soft tissue infections are a frequent cause of hospitalisation accompanied by significant morbidity and mortality, with MRSA the leading isolated pathogen. There is a lack of clinical trial data regarding oral therapies in our therapeutic armamentarium. Linezolid is one treatment option, but its use is limited by both antimicrobial stewardship programmes and adverse events. Little evidence exists for the use of minocycline. Only five trials tested rifampicin as an adjuvant for MRSA treatment, none reporting a statistically significant difference between arms with or without rifampicin. Therefore, there is a clear clinical unmet need for solid data regarding oral MRSA treatment alternatives.

Added value of this study

To our knowledge this is the first study to compare the efficacy and safety of minocycline plus rifampicin versus linezolid treatment in patients who all had documented infection due to MRSA. Our results showed non-inferiority between the two treatments at the primary endpoint i.e., clinical cure in the clinically evaluable population at the test-of-cure visit.

Implications of all the available evidence

These clinical data demonstrate combination treatment with minocycline and rifampicin to be an evidence-based, well documented, safe alternative to linezolid in the treatment of MRSA cSSSI. Taking into consideration the urgent need for antimicrobial stewardship programs, our findings add pivotal information supporting the integration of minocycline plus rifampicin into everyday clinical practice when treating MRSA confirmed cSSSIs.

Introduction

Resistance of *Staphylococcus aureus* to methicillin (MRSA) remains a major hurdle in healthcare-associated infections.[1] Reported rates of resistance to methicillin vary between 1.0% and 44.4% across European countries while six countries (Malta, Cyprus, Greece, Portugal, Italy and Romania) reported rates above 30% in 2017.[2] Complicated skin and skin structures infections (cSSSIs) still remain a common cause of morbidity and are often caused by MRSA resulting in the need for management options without recourse to expensive newly introduced intravenous drugs like lipoglycopeptides. The suggested advantage of dalbavancin and oritavancin is the lack of need for hospitalization; however, cost of treatment remains a major concern.[3]

Linezolid is one alternative for oral treatment. Although reported cure rates for cSSSIs are ranging between 69 and 90%,[4] efficacy is often hampered by gastro-intestinal tract toxicity and myelotoxicity and drug interactions.[5,6] A combination of minocycline plus rifampicin may, however, be an adequate treatment alternative. There is enough published evidence that these two drugs may be effective treatment options for cSSSI caused by MRSA. Both drugs are well absorbed, with a long half-life and good tissue penetration and they act synergistically in vitro against MRSA.[7,8] Data from pre-clinical pharmacodynamic models also support the likely efficacy of the combination against tetracycline and rifampicin sensitive MRSA strains.[9] Two single-arm studies have been performed which have showed promising efficacy of tetracyclines for cSSSIs by MRSA.[10,11]

AIDA is an international consortium that has been supported by the European Union FrameWork 7. The idea was to provide non-inferiority evidence that lower-cost old drugs may be effective for targeting specific pathogens causing common infections. One arm of the project was to demonstrate non-inferiority of oral linezolid to the oral combination of minocycline and rifampicin for the management of cSSSIs. Results of this open-label, randomized Phase 4 clinical trial are presented here.

Methods

Study design

The AIDA study was an investigator-initiated, prospective, open-label, randomized controlled clinical trial, to compare antimicrobial treatment with oral minocycline plus rifampicin with oral linezolid for complicated skin and skin structure infections (cSSSI) caused by MRSA. The study was conducted in 13 medical departments and in three surgical departments in Greece and in two medical departments in Italy.

The study protocol was approved by the National Ethics Committee of Greece (approval 87/14), by the National Organization for Medicines of Greece (approval IS-83/13), by the Agenzia Italiana del Farmaco (AIFA) and by the Ethics Committee of Istituti Ospitalieri di Cremona. This study was conducted in full

compliance with the principles of the Declaration of Helsinki, including all current amendments and with the laws and regulations in Italy and Greece, as part of the AIDA project. Written informed consent was provided by the patients prior to screening.

Participants

Study participants were adults with cSSSI caused by documented MRSA. Enrolled patients were to meet all following iinclusion criteria: i) isolation of MRSA from the lesion; ii) ulcers; or first or second degree burns involving less than 20% of body surface area with cellulitis; or major abscess; or deep or extensive cellulitis; or post-surgical trauma with purulent or seropurulent drainage; iii) at least three of: drainage and/or discharge; erythema extending at least one cm beyond the lesion; swelling and/or induration; warmth or pain or tenderness on palpation; and iv) at least one of: fever (oral temperature > 38 °C); total white blood cell count more than 10,000/mm^3; more than 15% bands; and isolation of MRSA from the lesion. Main exclusion criteria were: severe cSSSIs requiring intravenous antibiotics; diabetic foot infections; erysipelas; confirmed osteomyelitis; severe hepatic function impairment; end stage renal disease; and treatment with antimicrobials with activity against MRSA 24 h before inclusion in the study.

Following clinical evaluation for inclusion and exclusion criteria, two samples of draining pus were collected from each patient using sterile cotton swabs. Sampling was done after cleaning the skin surface with an alcoholic solution and by inserting the swab deeply towards the source of draining pus using Levine technique. The first swab was placed into transfer gel and was used for microbiological culture. The second swab was used for real-time polymerase chain reaction for the detection of *S. aureus*. Samples from all patients were transferred to the central laboratory located at the 4th Department of Internal Medicine of the ATTIKON University General Hospital for culture and susceptibility testing (see Supplementary Appendix).

Randomization and treatment

Eligible patients were 2:1 randomized into oral treatment with either minocycline plus rifampicin or linezolid. Randomization was performed by a central electronic system (see Supplementary Materials for minimisation details). The well-known efficacy of linezolid for cSSSIs[4–6] allowed to follow 2:1 randomization instead of 1:1. Neither patients nor treating clinicians were blinded as per protocol requirement. Rifampicin was administered as 600 mg once daily; minocycline as 100 mg twice daily and linezolid as 600 mg twice daily. Assessments of bacteriology, clinical signs and symptoms of infection including clinical and laboratory evaluations were made on baseline visit of day 1; during therapy on day 5 (±1 day) and on the test-of-cure (TOC) visit which was taking place on day 14 (±2 days). Clinical assessment was by a blinded clinical investigator, not involved in the patient's treatment, based on lesion size in mm and presence or absence of tenderness, erythema, oedema, purulent discharge, induration, ulceration, pain or chills. A follow-up call was done on day 30 to establish continued efficacy or other outcome. Clinical efficacy was defined as resolution of the signs and symptoms that were present at baseline day 1. Bacteriological efficacy was assessed in terms of eradication of MRSA from the site of infection. Safety was assessed at each visit by changes in laboratory parameters and patient vital signs.

Study endpoints

The primary study endpoint was clinical cure assessed by the size of the lesson in mm and the presence or absence of tenderness, erythema, oedema, purulent discharge, induration, ulceration, necrotic tissue pain and chills. Patients had to receive the study drugs for at least 4 days and were assessed among clinically evaluable (CE) patients at the TOC visit. This was the per protocol population. The secondary study endpoints were a) the comparison of oral linezolid to the combination of oral minocycline and rifampicin for clinical cure among the ITT patient populations; and b) the comparison of oral linezolid to the combination of oral minocycline and rifampicin for microbial eradication between evaluable CE patients at the TOC visit (see Supplementary Materials for definitions of the ITT, CE and ME populations). If the infection had completely cleared at the TOC visit and no sample could be obtained for culture, the infection was regarded as a microbiological success when included in the microbiologically evaluable (ME) group. One further sensitivity analysis was done excluding patients who received any other antimicrobial with potent activity against MRSA.

All serious and non-serious treatment-emergent adverse events (TEAEs) were captured in the CE population. The study adhered to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2D. As per the details given in E2D, the Marketing Authorisation Holders (MAH) of rifampicin, minocycline and linezolid were notified of any SAEs by the investigator.

Statistical analysis

The study outcome was a binary assessment of clinical cure (cured/not cured), and the test was for non-inferiority. For non-inferiority testing with a 5% significance level (one sided), and assuming a clinical cure rate of 87% for linezolid at a 2:1 ratio, and a non-

inferiority limit of 15 percentage points, it was calculated that a sample size of 130 patients in the minocycline plus rifampicin treatment group and 65 patients in the linezolid treatment group was required (80% power).

The analysis was a one-sided comparison of binomial proportions. Non-inferiority was confirmed with two methods; if the lower 90% confidence (CI) limit does not fall below the accepted error margin of 15%, then the study drug is regarded as non-inferior than the comparator. With the second method, the lower 90% CI limit of the cure rate for the test drug (minocycline plus rifampicin) must not fall below the percentage cure rate of the comparator (linezolid) minus the error margin (15%).

90% confidence limits were chosen for this study for pragmatic reasons, as this was not a study performed for regulatory purposes and related to the likely number of patients which could be reasonably recruited based on our initial feasibility work in Greece, Italy and the Balkans.

Results were provided as frequencies and confidence intervals (CIs) and compared by the Fisher exact test. All symptoms of infection were compared on days 5 and TOC using Cochran-Mantel-Haenszel test and the area of infection using the non-parametric Wilcoxon test.

External data monitoring committee was appointed. As part of the application process in the EU, details of the AIDA study were uploaded to the European clinical trials database which generated a EudraCT (European Union Drug Regulating Authorities Clinical Trials) number. The EudraCT number for this study, obtained on 20 March 2014 is: 2014-001276-56.

Role of the funding source

The funder had no role in the design, data collection, analysis, interpretation or report writing for the study.

Results

Study participants

Between 1 November 2014 and 31 January 2017, 1105 hospitalized patients were screened for eligibility and 123 patients were enrolled. The first patient was enrolled on 14 November 2014 and last patients were enrolled on 28 December 2016. The disposition of patients is shown in Fig. 1. It was decided to stop the study in January 2017 because of the slow enrolment rate which was associated with the high screening failure rate showing that the incidence of cSSSIs by MRSA was decreasing. This was particularly the case in Italy.

Of 123 patients enrolled, 81 were assigned to the minocycline plus rifampicin group and 42 to the linezolid group (total ITT population). Baseline characteristics between two groups were similar as shown at Table 1. A total of 94 patients were CE at the TOC visit; 59 patients in the minocycline and rifampicin arm; and 35 patients in the linezolid; 53 and 31 patients respectively were ME at the TOC visit.

As shown in Table 1, most patients in both groups had at least one comorbidity: 88.9% (72/81 patients) in

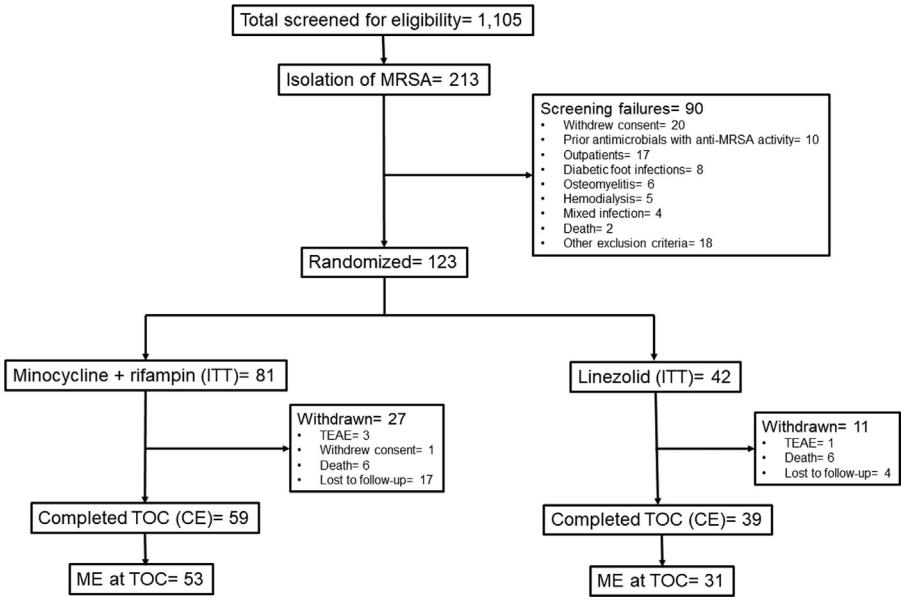

Fig. 1: **Study flow chart.** Abbreviations CE: clinically evaluable; ITT: intention to treat; ME: microbiologically evaluable; MRSA: methicillin-resistant *Staphylococcus aureus*; TEAE: treatment-emergent adverse event; TOC: test-of-cure visit.

	Min + Rif (n = 81)	Linezolid (n = 42)	Total (n = 123)
Female sex, n (%)	38 (46.9)	18 (42.9)	56 (45.5)
Age (years, mean ± SD)	71.1 (15.1)	73.0 (15.6)	71.8 (15.2)
Type of cSSSI, n (%)			
Burn, n (%)	3 (3.7)	1 (2.4)	4 (3.3)
Cellulitis, n (%)	6 (7.4)	5 (11.9)	11 (8.9)
Major abscess, n (%)	6 (7.4)	3 (7.1)	9 (7.3)
Ulcer, n (%)	56 (69.1)	28 (66.7)	84 (68.3)
Wound, n (%)	10 (12.3)	5 (11.9)	15 (12.2)
At least one comorbidity, n (%)	72 (88.9)	40 (95.2)	112 (91.1)
Diabetes mellitus, n (%)	28 (34.6)	17 (40.5)	45 (36.6)
Coronary heart disease, n (%)	6 (7.4)	6 (14.3)	12 (9.8)
Chronic heart failure, n (%)	8 (9.9)	4 (9.5)	12 (9.8)
Atrial fibrillation, n (%)	10 (12.3)	4 (9.5)	14 (11.4)
Chronic obstructive pulmonary disease, n (%)	9 (11.1)	3 (7.1)	12 (9.8)
Dementia, n (%)	3 (3.7)	2 (4.8)	5 (4)
Parkinson disease, n (%)	5 (6.2)	5 (11.9)	10 (8.1)
At least one concomitant medication (n, %)	75 (92.6)	41 (97.6)	116 (97.6)
PPIs and antacids, n (%)	57 (70.4)	33 (78.6)	90 (73.2%)
Anti-coagulants[a], n (%)	50 (61.7)	31 (73.8)	81 (65.9)
Anti-hypertensives, n (%)	48 (24.7)	23 (26.2)	71 (57.7)
Diuretics, N (%)	28 (34.6)	14 (33.3)	42 (34.1)
Bronchodilators, n (%)	38 (46.9)	17 (40.5)	55 (44.7)
Beta blockers, n (%)	27 (33.3)	14 (33.3)	41 (33.3)
Oral anti-diabetics, n (%)	25 (30.8)	13 (30.1)	38 (30.9)
Psychiatric disorders drugs, n (%)	22 (27.2)	15 (35.7)	37 (30.0)
Corticosteroids, n (%)	14 (17.3)	4 (9.5)	18 (14.6)
Oral analgesics, n (%)	9 (11.1)	8 (19.0)	17 (13.8)
At least one concomitant antibiotic (n, %)	55 (67.9)	30 (71.4)	85 (69.1)
Aminopenicillins, n (%)	10 (12.3)	8 (19.0)	18 (14.6)
Cephalosporins, n (%)	8 (9.9)	5 (11.9)	13 (10.6)
Piperacillin/tazobactam, n (%)	27 (33.3)	17 (40.5)	44 (35.8)
Carbapenems, n (%)	12 (14.8)	10 (23.8)	22 (17.9)
Quinolones, n (%)	15 (18.5)	4 (9.5)	19 (15.4)
Teicoplanin, n (%)	1 (1.2)	4 (9.5)	5 (4.1)
Vancomycin, n (%)	9 (11.1)	2 (4.8)	11 (8.9)
Colistin, n (%)	3 (3.7)	5 (11.9)	8 (6.5)
Clindamycin, n (%)	5 (6.2)	4 (9.5)	9 (7.3)
Tigecycline, n (%)	4 (4.9)	0 (0)	4 (3.3)
Daptomycin, n (%)	2 (2.5)	0 (0)	2 (1.6)
Aminoglycosides, n (%)	1 (1.2)	4 (9.5)	5 (4.0)
Metronidazole, n (%)	14 (17.3)	7 (16.7)	21 (17.1)
Isolated pathogens, n (%) from skin lesions			
MRSA, n (%)	81 (100)	42 (100)	123 (100)
Alcaligenes faecalis, n (%)	1 (1.2)	0 (0)	1 (0.8)
Corynebacterium spp., n (%)	1 (1.2)	0 (0)	1 (0.8)
Enterococcus faecalis, n (%)	1 (1.2)	0 (0)	1 (0.8)
Proteus spp., n (%)	0 (0)	1 (2.4)	1 (0.8)
Providencia stuartii, n (%)	1 (1.2)	0 (0)	1 (0.8)
Pseudomonas spp., n (%)	0 (0)	1 (2.4)	1 (0.8)
Staphylococcus epidermidis, n (%)	1 (1.2)	0 (0)	1 (0.8)
Streptococcus agalactiae, n (%)	1 (1.2)	0 (0)	1 (0.8)

Abbreviations Min: minocycline; MRSA: methicillin-resistant *Staphylococcus aureus*; PPI: proton pump inhibitor; Rif: rifampicin. [a]This drug category involves acenocoumarone, aspirin, clopidogrel and low-molecular weight heparin.

Table 1: **Baseline characteristics of the ITT (intention to treat) patient population divided according to treatment groups.**

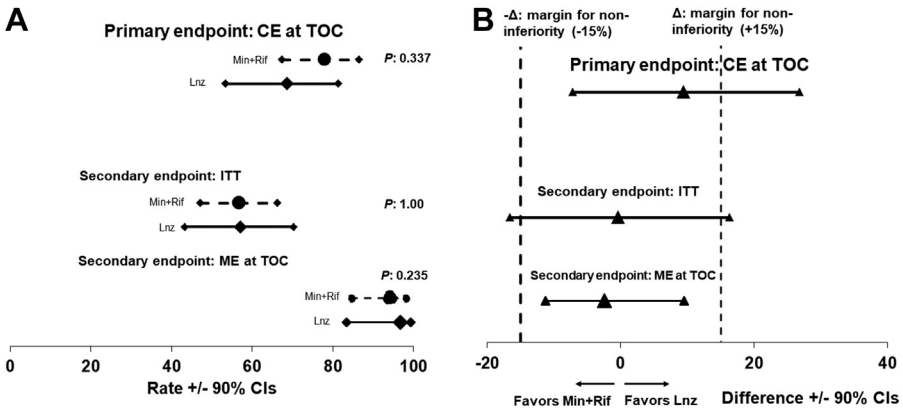

***Fig. 2:* Study endpoints.** A) Achievement of the primary endpoint and of the two secondary endpoints among study populations. The primary endpoint is clinical cure among clinically evaluable (CE) patients at the test-of-cure (TOC) visit. TOC visits were performed for 59 patients randomized to minocycline plus rifampicin and to 35 patients randomized to linezolid. The two secondary endpoints were: clinical cure among the entire ITT population (81 patients randomized to minocycline plus rifampicin and 42 patients randomized to linezolid) and microbiological eradication (ME) among CE patients at the TOC visit (53 patients randomized to minocycline plus rifampicin and 31 patients randomized to linezolid that is lower than the entire CE population since sampling for culture was not possible for all). The *P*-values of comparisons between groups are provided for each endpoint. B) Differences between groups for each endpoint. The lower and upper limits of the 15% of non-inferiority are shown. Abbreviations CI: confidence interval; Lnz: linezolid; Min: minocycline; Rif: rifampicin.

the minocycline plus rifampicin group and 95.2% (40/42 patients) in the linezolid group (Table 1). Most frequent comorbidities were cardiovascular and respiratory tract diseases. More than 90% of patients in each treatment group received concomitant medication (Table 1). The most common concomitant drugs were systemic antibiotics, antithrombotic agents and drugs for gastric acid related disorders. All drugs which were administered during the entire duration of the study including the drugs administered for the management of treatment-emergent adverse events were captured as concomitant medications. These medications were started after start of the study drug. Distribution of the type of cSSSI was similar between the two groups and the most frequent type of infection was skin ulcer without deep extension: 69.1% (56/81) in the minocycline plus rifampicin group and 66.7% (26/42) in the linezolid group. No clearly relevant other pathogens were isolated from wound swabs hence polymicrobial infection was rare in both groups.

The mean, median, standard deviation and minimum-maximum treatment period was the same for the two treatment groups: 11, 11, 2.3 and 5–15 days respectively for the minocycline plus rifampicin group and 11, 11, 2.0 and 7–16 days for the linezolid group. The median length of stay was 7 days in the minocycline and rifampicin group and 6 days in the linezolid group.

Endpoints

The analyses showed non-inferiority between the two arms of treatment in both the primary and secondary endpoints (Fig. 2). The primary endpoint of clinical cure at the TOC visit was achieved in 78.0% (46/59, CI 67.3–86.5%) of patients in the minocycline plus rifampicin group and 68.6% (24/35, CI 53.4–81.3%) of patients in the linezolid group. The percentage difference in cure rates was 9.39% in favor of minocycline plus rifampicin (CI –7.21 to 26.79%). Given that the lower CI did not fall below the accepted error margin of 15%, the combination of minocycline plus rifampicin was considered non-inferior to linezolid. In the ITT population cure was achieved in 56.8% (46/81, CI 47.1–66.2%) of patients in the minocycline plus rifampicin group and 57.1% (24/42, CI 43.3–70.2%) of those in the linezolid group, percentage difference –0.35%. In addition, in the ME population at the TOC visit, MRSA was eradicated from 94.3% (50/53) of patients receiving minocycline plus rifampicin and 96.8% (30/31) of patients receiving linezolid. The difference in percentages was –2.43% (CI –11.2 to 9.48%) meaning that minocycline plus rifampicin was non-inferior to linezolid.

There were 13 CE patients who received antimicrobials active against MRSA in addition to the study drugs: eight patients in the minocycline plus rifampicin arm and five patients in the linezolid arm. A sensitivity analysis of clinical cure at the TOC visit excluding these patients gave similar results to the primary analysis with 77.2% (24/57) in the minocycline plus rifampicin and 68.6% (24/35) of patients in the linezolid group reporting clinical cure. The overall conclusion was unchanged as the lower limit of the difference in cure rates was –8.2 so remained above –15%. Microbiological eradication (ME) among CE patients at the TOC visit (49

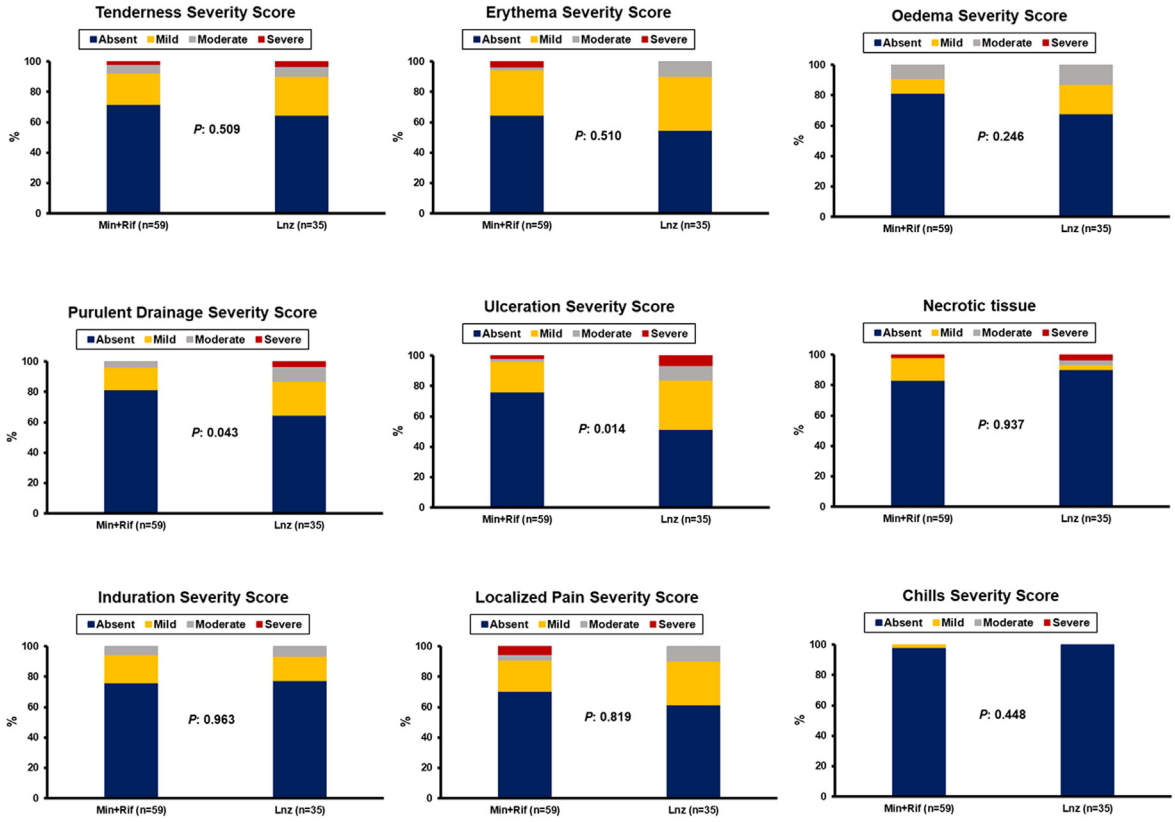

***Fig. 3:* Score of infection severity at the test-of-cure visit among clinically evaluable patient population.** The distributions of each of the sub-scores into absent, mild, moderate and severe for each of nine elements of the total score are provided for each group of treatment. The *P*-values of the comparisons for each of the nine elements are provided. Abbreviations Lnz: linezolid; Min: minocycline; Rif: rifampicin.

patients randomized to minocycline plus rifampicin and 29 patients randomized to linezolid) also showed non-inferiority (Supplementary Fig. S1). The systemic antibiotics with activity against MRSA (i.e., vancomycin, teicoplanin, tigecycline and daptomycin) which were recorded were administered for the treatment of serious infections captured as treatment-emergent adverse events and which presented long after start of the study drug.

Measures of symptom severity (tenderness, erythema, oedema, purulent drainage/discharge, induration, necrotic tissue, localized pain, chills) at baseline were similar between the two treatment groups (data not shown). On day 5 of follow-up, patients treated with the combination of minocycline plus rifampicin were distributed into less severe scores for oedema than patients treated with linezolid (Supplementary Fig. S2). This was also the case for purulent discharge and ulceration score at the TOC (Fig. 3). The area of the infection in the CE population did not differ between the two groups of treatment on either day 5 or at the TOC visit (Supplementary Table S1).

Safety

A total of 31/81 (38.3%) patients in the minocycline plus rifampicin group and 20/42 (47.6%) patients in the linezolid group experienced at least one TEAE (Table 2; $P = 0.340$). The most common adverse events in the minocycline plus rifampicin group were metabolism and nutrition disorders (16%). Infections (14.8%) and gastrointestinal disorders (13.6%) were the next most common. A total of 33 serious TEAEs were reported in 26 patients, 17/81 patients (21.0%) in the minocycline plus rifampicin group and 9/42 patients (21.4%) in the linezolid group (Supplementary Tables S2 and S3). The most common TEAEs in the linezolid group were gastro-intestinal disorders (14.3%), and metabolism and nutrition disorders (11.9%). The most frequently reported serious Treatment Emergent Adverse Events (sTEAEs) in the minocycline plus rifampicin group were septic shock and sepsis. In the linezolid group the most frequent sTEAE was cardiac arrest (7.1%). There were 10 TEAEs that were considered by the investigator to be possibly related to the study drug; 7/81 in the minocycline plus

System organ class and preferred term	Min + Rif (n = 81)	Linezolid (n = 42)
At least one TEAE, n (%)	31 (38.3)	20 (47.6)
Metabolism and nutrition disorders, n (%)	13 (16.0)	5 (11.9)
Hypoalbuminemia, n (%)	1 (1.2)	4 (9.5)
Hyponatraemia, n (%)	5 (6.2)	0 (0.0)
Hypernatremia, n (%)	2 (2.5)	0 (0.0)
Hypokalaemia, n (%)	2 (2.5)	0 (0.0)
Fluid retention, n (%)	0 (0.0)	1 (2.4)
Gastrointestinal disorders, n (%)	11 (13.6)	6 (14.3)
Nausea, n (%)	7 (8.6)	2 (4.8)
Constipation, n (%)	0 (0.0)	2 (4.8)
Diarrhoea, n (%)	2 (2.5)	0 (0.0)
Gastrointestinal haemorrhage, n (%)	2 (2.5)	0 (0.0)
Vomiting, n (%)	1 (1.2)	1 (2.4)
Haematochezia, n (%)	0 (0.0)	1 (2.4)
Infections and infestations, n (%)	12 (14.8)	3 (7.1)
Septic shock, n (%)	6 (7.4)	2 (4.8)
Sepsis, n (%)	5 (6.2)	0 (0.0)
Lung infection, n (%)	0 (0.0)	1 (2.4)
Respiratory – thoracic and mediastinal disorders, n (%)	5 (6.2)	3 (7.1)
Dyspnoea, n (%)	3 (3.7)	2 (4.8)
Pulmonary oedema, n (%)	1 (1.2)	1 (2.4)
Cardiac disorders, n (%)	1 (1.2)	5 (11.9)
Cardiac arrest, n (%)	0 (0.0)	3 (7.1)
Cardiorenal syndrome, n (%)	1 (1.2)	1 (2.4)
Tachycardia, n (%)	0 (0.0)	2 (4.8)
Renal failure acute, n (%)	1 (1.2)	1 (2.4)
Renal impairment, n (%)	0 (0.0)	1 (2.4)
Investigations, n (%)	4 (4.9)	1 (2.4)
Prothrombin time prolonged, n (%)	1 (1.2)	1 (2.4)
Vascular disorders, n (%)	3 (3.7)	0 (0.0)
Endocrine disorders, n (%)	1 (1.2)	1 (2.4)
Hypothyroidism, n (%)	0 (0.0)	1 (2.4)
Psychiatric disorders, n (%)	0 (0.0)	2 (4.8)
Confusional state, n (%)	0 (0.0)	1 (2.4)
Depression, n (%)	0 (0.0)	1 (2.4)
Blood and lymphatic system disorders, n (%)	0 (0.0)	1 (2.4)
Anaemia, n (%)	0 (0.0)	1 (2.4)
Nervous system disorders, n (%)	0 (0.0)	1 (2.4)
Epilepsy, n (%)	0 (0.0)	1 (2.4)

Abbreviations Min: minocycline; n: number; Rif: rifampicin.

Table 2: **Treatment-emergent adverse events (TEAEs) reported for ≥2% of patients in either treatment group, by system organ class and preferred term.**

rifampicin group (8.6%); and 3/42 in the linezolid arm (7.1%) (Supplementary Table S4).

Overall, there were 22 deaths during the study, 15/81 (18.5%) in the minocycline plus rifampicin group and 7/42 (16.7%) in the linezolid group (Supplementary Table S5).

Discussion

The AIDA study was uniquely designed to test the non-inferiority of the two oral treatments; the combination of minocycline plus rifampicin and linezolid against cSSSIs caused by documented MRSA. The terminology cSSSI is preferred here to the newly introduced of ABSSIs since cSSSI was the term commonly used when the AIDA project was funded by the European Union. The study fully met the primary endpoint of non-inferiority both for the primary endpoint of clinical cure among CE patients at the TOC visit and for the secondary endpoints. These results are important since they indicate that patients with staphylococcal CSSSIs can be effectively and economically treated with a

combination of older antimicrobials. The MRSA eradication rates were similar between the two treatment groups at 96.8%.

The clinical cure rates in the CE population were 78% in the minocycline plus rifampicin group and 68.6% in the linezolid group. The cure rate in the linezolid group was lower than anticipated. In designing the trial, a clinical cure rate of 87% was estimated, based on the cure rates for *S. aureus* infections treated with linezolid reported by Falagas et al.[5] in their systematic review. However, it is reported that the clinical cure rates of linezolid may vary considerably between 66% and 90%.[12] The lower cure rate of linezolid in the present study may be explained by patients' characteristics, especially older age and by the higher incidence of MRSA in our study. In addition, different definitions of failure may also have an impact. Comparing studies in the literature suggest that patient age may play a role in clinical success. In a non-inferiority trial of MRSA infection, which corroborates our results comparing the combination of trimethoprim-sulfamethoxazole plus rifampicin to linezolid, the mean age of the two patient groups were 67 and 69 years respectively; clinical cure rates were 83.3% and 76.2% respectively.[13] Cenizal et al.[10] reported a clinical cure rate in the treatment of cSSSIs by MRSA exceeding 90% using trimethoprim-sulfamethoxazole or doxycycline but their patient population was young with a mean age of 38 years. Further to this study, a study in Japan reported success rate of 77.8% of linezolid for cSSSIs by MRSA; the mean age of their patient population was 68.4 years.[6] Elderly patients have a greater number of underlying comorbidities which impact on infection resolution. In fact, 95% of patients in the linezolid group of our study had at least one ongoing medical condition. Contrary to our trial, reported comorbidities were substantially lower in previous studies and they involved 60% of the participants.[13] It should also be noted that most study participants had cSSSIs presenting with ulcers which is associated with poor clinical outcomes.[14] Although designed to study drug efficacy of primary treatment, results encourage the use of the minocycline plus rifampicin combination as de-escalation for an early switch/early discharge policy in order to decrease the prolonged hospitalization with parenteral antimicrobials. This strategy is supported by the results of two retrospective studies from Europe,[15,16] but the current prospective study is further enhancing the concept.

Although statistically not significant, the rate of adverse events was higher in the linezolid group (47.6%) than in the minocycline plus rifampicin group (38.3%). In a meta-analysis of randomized controlled trials linezolid was associated with more adverse events than comparator antibiotics although the difference was not statistically significant.[5] The most common TEAEs in this study were most likely to be related to the underlying comorbidities of the participants such as the reported metabolism and nutrition disorders and predisposition for subsequent infections.

The major strength of the study is the focus on the pathogen. All participants were infected not only by the same pathogen but also of the same resistance pattern of this pathogen, that is, resistance to methicillin. This has been rarely reported in randomized trial of infectious diseases to date and provides unique validity to this trial in the area of skin infection.

Four main limitations of the trial need discussion. The first is the inability to enrol the total number of participants based on the original power calculation. However, the range of the confidence intervals of the difference of the endpoints between the two groups are narrow and they make highly unlikely that the non-inferiority would cease if more patients were enrolled. The second is the primary endpoint which is focused on the CE participants at the TOC visit and not to early response after 72 h as reported for new drugs like tedizolid, dalbavancin and oritavancin.[17–19] The severity scorings on nine variables shows improvement for most of participants by day 5 of follow-up and this may be equivalent to early response. On day 5 of follow-up both regimens achieved more than 20% decrease of the affected skin area from baseline which is the criterion for achieving early response. In addition, the use of combination therapy with minocycline plus rifampicin though supportable from a microbiological viewpoint may have resulted in increased drug–drug interactions given that rifampicin can interact with many non-antibiotic drugs. That said, TEAEs were not increased in the rifampicin group. The third limitation is that oral management of cSSSI may introduce lack of compliance when patients have to receive two drugs. The fourth limitation is the high rate of co-administration of antibiotics for Gram-negative coverage despite the low rate of isolation of Gram-negative pathogens. In addition, a small number of patients received intravenous antibiotics with anti MRSA activity. This is due to the characteristics of the enrolled population which were elderly with comorbidities that is, factors increasing the likelihood for co-infection.

The AIDA randomized clinical trial managed has shown, subject to a number of limitations, that for cSSSIs caused by MRSA the oral administration of minocycline plus rifampicin is safe and non-clinically inferior to oral linezolid treatment. Taking into consideration the worldwide need for reducing costs for hospital care these results should be received with enthusiasm.

Contributors

A.K. drafted the manuscript, performed monitoring of the study and review and editing of the manuscript. N.T., T.K., I.M.K., S.S., Z.A., H.S., K.T., K.A. and M.L. contributed to patient recruitment and assessment, collection of data and review and editing of the manuscript. V.R. contributed to the statistical design, formal pre-defined analysis, post

hoc analysis and made comments on manuscript. M.O'H. contributed to the protocol methodology, project management and administration, supervision of data collection, review and editing published outputs. E.J.G.-B. contributed to drafting the manuscript, monitoring the study and reviewing and editing the manuscript. A.M. contributed to the conception of study, design of protocol, project management, over saw data analysis, discussion of research findings and review and editing of published outputs. M.O'H. and E.J.G.-B. accessed and verified the underlying data. All authors have read and approved the final version of the manuscript.

Data sharing statement

The Clinical trial report and all supporting tables and listings were uploaded to the EMA website https://clinicaldata.ema.europa.eu/web/cdp/home and are available under the study EudraCT number: 2014-001276-56. Patients are identified by study number only.

Declaration of interests

Helen Sambatakou has received honoraria from MSD Greece, Elpen Hellas, Mylan Hellas and Pfizer Greece. E.J. Giamarellos-Bourboulis has received honoraria from Abbott CH, bioMérieux, Brahms GmbH, GSK, InflaRx GmbH, Sobi and XBiotech Inc; independent educational grants from Abbott CH, AxisShield, bioMérieux Inc, InflaRx GmbH, Johnson & Johnson, MSD, Sobi and XBiotech Inc.; and funding from the Horizon2020 Marie Skłodowska-Curie International Training Network "the European Sepsis Academy" (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grants ImmunoSep and RISCinCOVID (granted to the Hellenic Institute for the Study of Sepsis). Alasdair MacGowan has research grants/activities with the following: Merck, Shionogi, Venatorx, InfectoPharm, GSK, Bioversys, MRC (UK), NIHR (UK). All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101790.

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