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Original article

Comparing the cost-effectiveness of linezolid to trimethoprim/sulfamethoxazole plus rifampicin for the treatment of methicillin-resistant *Staphylococcus aureus* infection: a healthcare system perspective

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ABSTRACT

Objective: Few industry-independent studies have been conducted to compare the relative costs and benefits of drugs to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infection. We performed a stochastic cost-effectiveness analysis comparing two treatment strategies—linezolid versus trimethoprim-sulfamethoxazole plus rifampicin—for the treatment of MRSA infection.
Methods: We used cost and effectiveness data from a previously conducted clinical trial, complementing with other data from published literature, to compare the two regimens from a healthcare system perspective. Effectiveness was expressed in terms of quality-adjusted life-years (QALYs). Several sensitivity analyses were performed using Monte Carlo simulation, to measure the effect of potential parameter changes on the base-case model results, including potential differences related to type of infection and drug toxicity.
Results: Treatment of MRSA infection with trimethoprim-sulfamethoxazole plus rifampicin and linezolid were found to cost on average €146 and €2536, and lead to a gain of 0.916 and 0.881 QALYs, respectively. Treatment with trimethoprim-sulfamethoxazole plus rifampicin was found to be more cost-effective than linezolid in the base case and remained dominant over linezolid in most alternative scenarios, including different types of MRSA infection and potential disadvantages in terms of toxicity. With a willingness-to-pay threshold of €0, €50 000 and €200 000 per QALY gained, trimethoprim-sulfamethoxazole plus rifampicin was dominant in 100%, 96% and 85% of model iterations. A 95% discount on the current purchasing price of linezolid would be needed when it goes off-patent for it to represent better value for money compared with trimethoprim-sulfamethoxazole plus rifampicin.
Conclusions: Combined treatment of trimethoprim-sulfamethoxazole plus rifampicin is more cost-effective than linezolid in the treatment of MRSA infection. **E. von Dach, Clin Microbiol Infect 2017;23:659**

Introduction

Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) represent a therapeutic challenge. The treatment most frequently recommended is a prolonged course of

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parenteral vancomycin or daptomycin [1]. Alternative treatment regimens with oral antibiotics (e.g. linezolid) have been proposed [2,3]. The use of older drugs such as trimethoprim-sulfamethoxazole, combined with rifampicin may represent a particularly interesting treatment alternative [1,4,5].

We previously performed a randomized, non-inferiority trial to compare the efficacy and safety of therapy with trimethoprim-sulfamethoxazole plus rifampicin versus linezolid to treat MRSA infection [6]. The principal findings of the study were: (a) compared with linezolid, the combination of trimethoprim-sulfamethoxazole plus rifampicin was not inferior for the treatment of MRSA infection; (b) there was no difference between the studied drugs in terms of total adverse events, serious adverse events or adverse drug reactions (ADR) [6]. Moreover, as trimethoprim-sulfamethoxazole and rifampicin are available as generic agents, this regimen may offer a substantial cost advantage over other agents such as linezolid and daptomycin [7]. As the launch of generic linezolid has recently been postponed in several countries and novel oxazolidinone agents (e.g. tedizolid) will be patent-protected against generic erosion for many years, the off-patent combination of trimethoprim-sulfamethoxazole plus rifampicin seems to be an attractive alternative oral treatment option for MRSA infection, though still underused because of safety concerns. Possibly, this combination therapy may generate substantial indirect costs due to rare, but costly severe ADRs. For all these reasons, we performed a cost-effectiveness analysis using data from our randomized controlled trial (RCT) and other sources to examine the economic impact of these treatment regimens from the perspective of the healthcare system.

Materials and methods

We constructed a stochastic decision tree model from a Swiss healthcare system perspective, using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA, USA). The model was developed using data from the previously published RCT comparing trimethoprim-sulfamethoxazole plus rifampicin to linezolid for the treatment of any type of MRSA infection (Fig. 1). This trial was an investigator-initiated, open-label, single-centre RCT to evaluate the efficacy of a combination of trimethoprim-sulfamethoxazole (160/800 mg thrice daily) plus rifampicin (600 mg once daily) versus linezolid (600 mg twice daily) in 150 patients (allocation ratio 1 : 1) requiring antibiotic therapy for MRSA infection at the Geneva University Hospitals. Patients who were treated for ≥72 h before study inclusion with antimicrobials active against MRSA (mostly vancomycin) were excluded. We included all types of MRSA infection except chronic MRSA osteomyelitis without surgical debridement, a super-infected indwelling foreign body kept in place, severe sepsis or septic shock due to MRSA bacteraemia, and left-sided endocarditis. Patients were followed throughout the duration of antibiotic therapy until 6 weeks after the end of treatment. A full description of the RCT is available elsewhere [6].

Probabilities and duration of study treatment

All effectiveness probabilities used in the model were based on the previous RCT (Table 1), including the efficacy of the study drugs stratified by type of MRSA infection, the cumulative incidence of death and the rate of ADR observed in each study arm. Data surrounding duration of treatment (days) were obtained from the RCT and then stratified by mode of administration (oral versus intravenous). Of note, the overall length of hospital stay was similar between the two treatment groups [6].

Costs

In this analysis, we used only direct costs in 2016 Swiss francs (CHF) and Euro (€) (1CHF = €0.92, December 2016) for the study drugs and ADR costs (Appendix 1). Drug costs were obtained from the Swiss medicines agency (Table 1). In the base case the highest unit price was used where there was variation due to packaging or

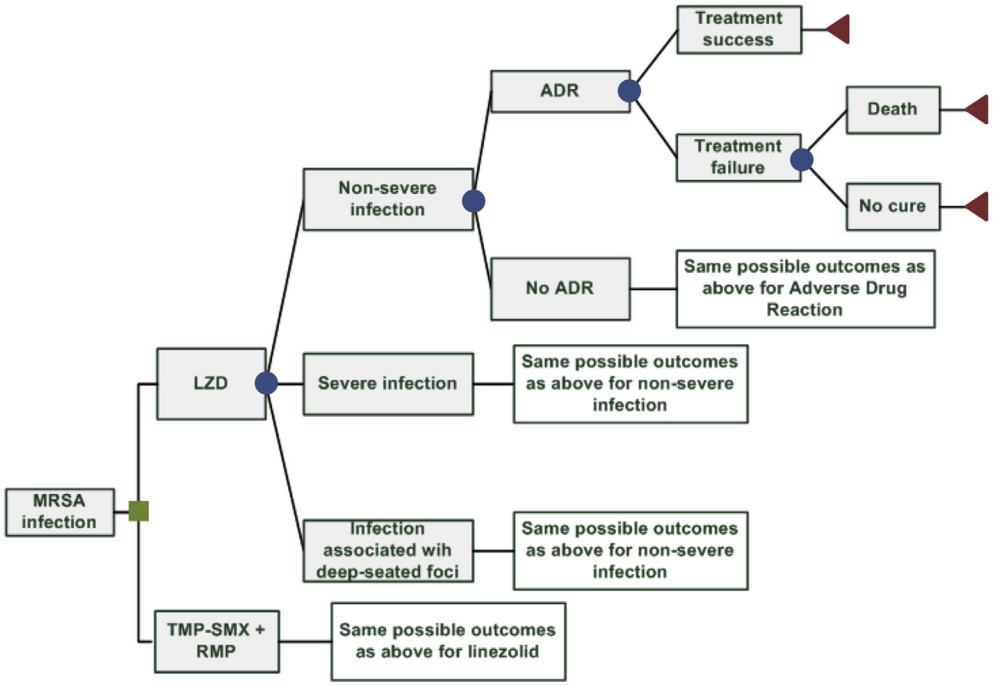

Fig. 1. Decision tree model. Abbreviations: LZD, linezolid; TMP-SMX, trimethoprim-sulfamethoxazole; RMP, rifampicin; ADR, adverse drug reaction; MRSA, methicillin-resistant *Staphylococcus aureus*.