Short Communication

Non-inferiority of colistin compared with standard care for the treatment of ventilator-associated pneumonia

Giorgio Tulli a, Andrea Messori b,*, Sabrina Trippoli b, Claudio Marinai b

a Agenzia Sanitaria Toscana, Regional Health Service, Firenze, Italy
b HTA Unit, ESTAR, Regional Health Service, Firenze, Italy

A R T I C L E   I N F O
Article history:
Received 4 June 2016
Accepted 14 January 2017

Keywords:
Colistin
Ventilator-associated pneumonia
Meta-analysis
Aerosol

A B S T R A C T
This study examined the literature on the treatment of ventilator-associated pneumonia (VAP) using colistin or standard care (SC). Based on this clinical material, a meta-analysis was conducted and a non-inferiority test was performed. Studies were selected for inclusion based on the following criteria: (a) patients with VAP; (b) experimental arm based on intravenous or aerosolized colistin; and (c) control arm based on SC. The meta-analysis employed a fixed-effect model, and the endpoint was the rate of clinical response. No pre-specified non-inferiority threshold for the upper boundary of the 95% confidence interval was adopted; instead, the intention was to perform a retrospective evaluation of whether the threshold suggested by the results was acceptable on clinical grounds.

In total, eight controlled studies were included. The pooled risk ratio was 1.019 for colistin compared with SC (95% confidence interval 0.895–1.16); this result corresponds to a non-significant 1.9% increase in cure rate with colistin compared with SC (range +16% to −10.5%). Heterogeneity was minimal (0%). The post-hoc non-inferiority threshold for colistin compared with SC was −10.5% in terms of relative cure rate (pooled risk ratio = 0.895). This margin was considered to be acceptable on clinical grounds.

This analysis found that colistin can play a role in the treatment of VAP, particularly when given as a combination of aerosolized and intravenous drug.

© 2017 Elsevier B.V. and International Society of Chemotherapy. All rights reserved.

1. Introduction

Only 11 new antibiotics were approved between 1998 and 2014, and no new classes of antibiotics have been approved since 1987 [1]. In this framework, revisiting the therapeutic role of ‘old’ agents is worthwhile. At least two meta-analyses [2,3] have shown that aerosolized colistin [alone or in association with intravenous (IV) colistin] is more effective than the IV form given alone. On the other hand, no conclusive information is available regarding whether colistin (irrespective of its route of administration) is more or less effective for the treatment of ventilator-associated pneumonia (VAP) than other antibiotics compared with standard care (SC). In particular, two meta-analyses [3,4] found no significant difference between either aerosolized or IV colistin and SC in patients with VAP.

However, no evidence of difference is not the same as evidence of no difference [5]. As such, an equivalence analysis or a non-inferiority analysis is warranted to explore this issue further.

This study re-examined the literature on the treatment of VAP reported in the two meta-analyses by Florescu et al [3] (six trials) and Gu et al [4] (six trials). A non-inferiority study was undertaken based on this clinical material.

2. Methods

2.1. Study design

The analysis was designed to test the non-inferiority of colistin compared with SC. For this purpose, a series of clinical studies comparing colistin (IV or aerosolized) with SC was retrieved from two published meta-analyses [2,3]. The decision to rely on published papers [2,3] to identify the pertinent clinical studies was in line with the observation that an excessive number of overlapping meta-analyses are being published [6]. No pre-specified non-inferiority threshold for the upper boundary of the 95% confidence interval (CI) was adopted; instead, the intention was to perform a retrospective evaluation of whether or not the threshold suggested by the results was acceptable on clinical grounds.

2.2. Literature search and inclusion criteria

No original literature search was conducted. Eligible studies were those reported in the two meta-analyses mentioned above (fig. 2 of Reference 3 and fig. 2 of Reference 4). From an analysis of eligible

http://dx.doi.org/10.1016/j.ijantimicag.2017.01.013
0924-8579/© 2017 Elsevier B.V. and International Society of Chemotherapy. All rights reserved.

* Corresponding author. HTA Unit, ESTAR, Regional Health Service, Via San Salvi 12, 50100 Firenze, Italy.
E-mail addresses: andreamessori@interfree.it; andreamessori.it@gmail.com (A. Messori).

Please cite this article in press as: Giorgio Tulli, Andrea Messori, Sabrina Trippoli, Claudio Marinai, Non-inferiority of colistin compared with standard care for the treatment of ventilator-associated pneumonia, International Journal of Antimicrobial Agents (2017), doi: 10.1016/j.ijantimicag.2017.01.013
<table>
<thead>
<tr>
<th>First author</th>
<th>Year/location</th>
<th>Study design</th>
<th>Population</th>
<th>No. of patients</th>
<th>Infecting organism</th>
<th>Colistin administration route</th>
<th>Treatment given to controls</th>
<th>Dosage of colistin</th>
<th>Type of nebulizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betrosian et al</td>
<td>2008/Greece</td>
<td>RCT</td>
<td>Adult ICU patients with MDR VAP</td>
<td>28 (15/13)</td>
<td>A. baumannii</td>
<td>IV colistin alone</td>
<td>IV ampicillin/sulbactam</td>
<td>9 MIU/day divided into three doses for 8–10 days</td>
<td>—</td>
</tr>
<tr>
<td>Garnacho-Montero</td>
<td>2003/Spain</td>
<td>PC</td>
<td>Adult ICU patients with MDR VAP</td>
<td>35 (21/14)</td>
<td>A. baumannii</td>
<td>IV colistin alone</td>
<td>IV mepenem/cilastatin</td>
<td>2.5–5.0 mg/kg/day divided into three doses with adjustment for renal function</td>
<td>—</td>
</tr>
<tr>
<td>Kallel et al</td>
<td>2007/Tunisia</td>
<td>CC</td>
<td>Adult ICU patients with PDR VAP</td>
<td>120 (60/60)</td>
<td>A. baumannii, P. aeruginosa</td>
<td>IV colistin alone</td>
<td>IV imipenem/cilastatin</td>
<td>6 MIU/day divided into three doses for 14 days</td>
<td>—</td>
</tr>
<tr>
<td>Lu et al</td>
<td>2012/France</td>
<td>PC</td>
<td>Adult ICU patients with MDR VAP</td>
<td>165 (43/122)</td>
<td>A. baumannii, P. aeruginosa</td>
<td>AS colistin alone</td>
<td>IV beta-lactam</td>
<td>6 MIU/day divided into three doses for 14 days or until successful weaning from mechanical ventilation</td>
<td>Vibrating plate nebulizer (Aeroneb Pro, Aerogen Nektar Corp., Galway, Ireland)</td>
</tr>
<tr>
<td>Rios et al</td>
<td>2007/Argentina</td>
<td>RC</td>
<td>Adult ICU patients with MDR VAP</td>
<td>61 (31/30)</td>
<td>A. baumannii, P. aeruginosa, K. pneumonia, S. maltophilia</td>
<td>IV colistin alone</td>
<td>IV imipenem/cilastatin</td>
<td>5 mg/kg/day for 14 days, doses were corrected in patients with renal failure</td>
<td>—</td>
</tr>
<tr>
<td>Zalts et al</td>
<td>2013/Israel</td>
<td>RC</td>
<td>Adult ICU patients with CR VAP</td>
<td>98 (66/32)</td>
<td>A. baumannii</td>
<td>IV colistin alone</td>
<td>IV ampicillin/subactam</td>
<td>6 MIU/day divided into three doses for 7–10 days; doses were corrected in patients with renal failure</td>
<td>—</td>
</tr>
<tr>
<td>Nakwan et al</td>
<td>2011/Thailand</td>
<td>RC</td>
<td>Neonates with MDR VAP</td>
<td>15 (8/7)</td>
<td>Drug-resistant A. baumannii</td>
<td>AS colistin (combined with IV colistin in two cases); concurrent IV antibiotics were given</td>
<td>IV cefoperazone/subactam or meropenem or ceftazidime/amikacin</td>
<td>8 mg/kg/day divided into two daily doses over 4–14 days</td>
<td>Servo Ultra Nebulizer in the SERVO-i ventilator (Maquet, Solna, Sweden)</td>
</tr>
<tr>
<td>Rattanaumpawan et al</td>
<td>2010/Thailand</td>
<td>RCT</td>
<td>Adults with Gram-negative VAP</td>
<td>100 (51/49)</td>
<td>A. baumannii, P. aeruginosa, K. pneumonia</td>
<td>AS colistin; concurrent IV antibiotics were given</td>
<td>IV standard antibiotics</td>
<td>4.5 MIU/day divided into two doses over 4 to 14 days</td>
<td>Jet or ultrasonic nebulizer</td>
</tr>
</tbody>
</table>

*A. baumannii, Acinetobacter baumannii; P. aeruginosa, Pseudomonas aeruginosa; K. pneumoniae, Klebsiella pneumoniae; S. maltophilia, Stenotrophomonas maltophilia; RCT, randomized controlled trial; ICU, intensive care unit; MDR, multi-drug-resistant; VAP, ventilator-associated pneumonia; IV, intravenous; MIU, million international units; PC, prospective cohort; CC, case–control; PDR, pan-drug-resistant; AS, aerosolized; RC, retrospective cohort; CR, carbapenem-resistant.*
studies, studies for inclusion were selected based on the following criteria: (a) patients with VAP; (b) experimental arm based on IV or aerosolized colistin; and (c) control arm based on SC. Duplicate entries were excluded from the study.

2.3. Data extraction

The endpoint was the rate of clinical response assessed in patients receiving colistin compared with those receiving SC. Extraction was performed in duplicate by AM and ST.

2.4. Quality of included studies

The bias risk assessment was performed using the Cochrane Collaboration's risk of bias assessment tool [7]. In each domain, studies were given a rating of low, unclear or high risk. An automated tool was used for this purpose [8].

2.5. Statistical analysis

The outcome measure of the meta-analysis was the pooled risk ratio (RR) of clinical response with 95% CI. Statistical calculations were performed using Open Meta-Analyst, Version 4.16.12 (Tufts University, Medford, MA, USA; http://tufscaes.org/open_meta/). A random-effect model was adopted in the presence of significant heterogeneity, or a fixed-effect model if heterogeneity was not significant. Heterogeneity was assessed according to the I² index.

3. Results

In total, eight controlled studies [9–16] were included in this analysis (Table 1). In the experimental arm, five studies used IV colistin [9–11,13,14] and three studies used aerosolized colistin [12,15,16]; there was no treatment arm using a combination of aerosolized and IV colistin. As heterogeneity was minimal (0%), the fixed-effect model was employed for statistical calculations. In terms of the quality of the eight studies, the risk of bias was high/unclear in most cases (Fig. 1); only the trial by Rattanaumpawan et al [16] showed a low risk of bias score for four of the six domains.

Fig. 2 shows the results of the meta-analysis. The pooled RR was 1.019 for colistin compared with SC (95% CI 0.895–1.16), which indicates no significant difference between the two treatments. This result corresponds to a non-significant 1.9% increase in the cure rate for colistin compared with SC (range +16% to −10.5%). The posthoc non-inferiority threshold for colistin compared with SC was −10.5% in terms of relative cure rate (RR = 0.895). For practical purposes, this threshold can be rounded to −11%.

4. Discussion

Is a non-inferiority threshold of −11% for colistin compared with SC, or an equivalence interval ranging from −10.5% to +16%, acceptable? While, in the authors’ view, this equivalence interval does not allow exclusion of the hypothesis of the superiority of colistin, setting the non-inferiority threshold at −11% seems to be reasonable on clinical grounds; for example, a threshold of this
order of magnitude (i.e. at ±13%) was set by Florescu et al [3] in their power calculations.

One weakness of the present analysis is that the test treatment was ‘aerosolized or IV colistin’, whereas studying ‘combined aerosolized and IV colistin’ would have been more interesting. However, there were insufficient clinical data to perform the latter analysis. Furthermore, as sound evidence [2,3] supports the superiority of aerosolized colistin over IV colistin alone, demonstrating the non-inferiority of the less effective treatment (aerosolized or IV monotherapy with colistin) compared with SC permits the conclusion that the most effective route (combination of aerosolized and IV colistin) is non-inferior compared with SC. Another limitation of the present meta-analysis is that the quality of the eight included studies was low; this probably reflects difficulty in recruiting patients with VAP, so studies in this field are oversimplified in terms of methodology.

In conclusion, this analysis suggests that colistin can play a role in the treatment of VAP, particularly when given as a combination of aerosolized and IV drug.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

References


