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Treatment of *Mycobacterium avium–intracellulare* complex: a great leap forward

Jan-Willem C. Alffenaar[1]* and Jakko van Ingen[2]

[1]*University of Groningen, University Medical Center Groningen, Groningen, Department of Clinical Pharmacy and Pharmacology, The Netherlands;* [2]*Radboud University Medical Center, Department of Medical Microbiology, Nijmegen, The Netherlands*

*Corresponding author. University of Groningen, University Medical Center Groningen, Department of Hospital and Clinical Pharmacy, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel: +31503614070; Fax: +31503614087; E-mail: j.w.c.alffenaar@umcg.nl

Mycobacterium avium complex (MAC) bacteria are the most frequent causative agents of non-tuberculous mycobacterial pulmonary disease. MAC pulmonary disease has two main manifestations: a fibrocavitary disease, which is diagnosed in patients with underlying lung pathology such as chronic obstructive pulmonary disease; and a nodular/bronchiectatic disease, which is diagnosed in elderly patients without significant underlying disease or in younger patients with cystic fibrosis. The severity of MAC pulmonary disease can range from mild to extensive cavitation and destruction of lung tissue, leading to respiratory failure. Today, the recommended treatment consists of a combination of macrolides, ethambutol and a rifamycin continued for at least 12 months after conversion to negative cultures.[1] In general, MAC treatment is lengthy and results are poor with a pooled treatment success of 40%.[2] More recently, successful treatment was reported in 84% of patients, but relapse occurred in about 12% of these patients.[3] In addition, gastrointestinal adverse events significantly compromise treatment tolerance.[4] Therefore, novel drug regimens that are able to shorten treatment duration are urgently needed. Gumbo and colleagues have accepted this challenge. The series of articles in this Supplement of the Journal provides insight into why the current regimen is failing, and how we might identify optimal candidates using pharmacokinetic and pharmacodynamic science and determine the required dosage needed for short-course treatment.[5]

In the second article, Pasipanodya *et al.*[6] performed a meta-analysis, using sputum conversion as the endpoint, after 6 months of therapy, at the end of therapy, or on follow-up after stopping therapy. Treatment was lengthy, about 18 months for a macrolide-containing regimen and about 23 months for macrolide-free regimens. The number needed to be treated to benefit one patient using a macrolide-containing regimen was five, this rose to eight for a macrolide-free regimen. In their meta-analysis of prospective clinical studies, Pasipanodya *et al.*[6] found that the standard regimen is associated with a poor success rate of only 55%. Strikingly, the main findings of the meta-analyses were the poor quality and heterogeneity of the studies, showing that current recommendations are based on weak evidence.

The third article by Srivastava *et al.*[7] aimed to identify the performance of two drugs in the standard regimen, 15 mg/kg ethambutol and 500 mg azithromycin daily for 28 days, in the hollow-fibre system model of pulmonary MAC. They showed that the combination was effective for 7 days, but by day 28 treatment failed with the emergence of acquired drug resistance. The authors confirmed the current clinical data that the combination of only a macrolide and ethambutol is not very active and a rifamycin should be added.

In the fourth[9] and fifth[10] articles, Deshpande and colleagues studied two oxazolidinones, linezolid and tedizolid, to identify the pharmacokinetic/pharmacodynamic (PK/PD) parameters for human drug exposure. They used human pharmacokinetics, i.e. linezolid and tedizolid concentration–time profiles achieved in adult human lungs treated for 28 days, and then performed 10000 patient Monte Carlo simulations to identify the optimal dose for clinical use. Tedizolid was more active than linezolid, as reflected by a bactericidal effect at standard dose (200 mg), whereas linezolid required a higher dose (1800 mg) to reach optimal microbial kill in 90% of the patients. Breakpoints were determined to be 16 mg/L and 1 mg/L for linezolid and tedizolid, respectively. Moreover, clinically significant mitochondrial inhibition was noticed to a greater extent with linezolid than with tedizolid. It seems likely that tedizolid may be more suitable as a new backbone drug than high-dose linezolid.

In the sixth article, Deshpande *et al.*[11] explored whether ceftaroline and ceftazidime/avibactam were efficacious against intracellular and extracellular pulmonary MAC disease. Ceftaroline and ceftazidime/avibactam both had substantial activity. Ceftazidime/avibactam showed optimal efficacy at free drug $fT_{>MIC}$ of 50% at clinical doses. The authors advocate that these results should encourage exploration of the activity of other cephalosporins in combination with the latest β-lactamase inhibitors for their effect against MAC.

In the seventh article, Srivastava *et al.*[8] investigated whether the efflux pump inhibitor thioridazine combined with moxifloxacin would kill bacteria faster than drugs in the standard treatment regimen using the *in vitro* hollow-fibre system. The combination regimen of thioridazine with moxifloxacin was highly active, providing an option for a short-treatment regimen for pulmonary MAC; however, the toxicity of thioridazine is likely to limit its use.

In the eighth paper, Deshpande *et al.*[12] explore the efficacy of ceftazidime/avibactam, tedizolid, rifabutin and moxifloxacin for the treatment of pulmonary MAC disease. In this situation the authors used drug exposure related to the standard dose of the drug for a period of 28 days. The four-drug regimen showed adequate kill but started to fail by day 28. Although kill rates were promising, further dose optimization needs to be performed.

Finally, Deshpande *et al.*[13] have outlined how to develop a programme within 5 years to design a combination therapy regimen for pulmonary MAC to be administered for $\leq$6 months with efficacy in >90% of patients. They used a stepwise PK/PD approach consisting of a rapid screen to identify drugs with activity against MAC followed by setting targets for monotherapy using hollow-fibre models and a PK/PD approach for the combination therapy and a subsequent approach to translate results to daily practice by means of Monte Carlo simulations. Such a programme would help leapfrog treatment of pulmonary MAC a considerable distance. In the end, if the goals and targets are met, treatment would change for the better for patients suffering from this difficult-to-treat disease.

Transparency declarations

None to declare.

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