EDITORIAL

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New insights in the treatment of nontuberculous mycobacterial pulmonary disease

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“For both *Mycobacterium avium* complex and *M. abscessus*, tedizolid and clofazimine may help to improve the efficacy of treatment regimens.”

First draft submitted: 11 July 2017; Accepted for publication: 12 July 2017; Published online: 20 September 2017

Nontuberculous mycobacteria (NTM) are increasingly recognized as important opportunistic pathogens of humans. Chronic pulmonary infections are the most frequent diseases associated with NTM, particularly with *Mycobacterium avium* complex (MAC) and *M. abscessus* bacteria. This disease can manifest as a fibro-cavitary disease, mostly in patients with pre-existing pulmonary diseases or as a nodular/bronchiectatic disease, typically in elderly patients without underlying pulmonary diseases. In the latter group, subtle defects of mucociliary clearance and T-cell immunity have been suggested to underlie susceptibility to NTM disease [1].

Currently recommended antibiotic treatment regimens are presented in **Table 1**. On average, 50 (*M. abscessus*) to 70% MAC patients who tolerate recommended regimens achieve prolonged culture conversion [2]. This grave situation has recently led to a series of clinical and preclinical studies aiming to optimize antibiotic treatment of NTM pulmonary disease (NTM-PD).

Preclinical models have offered new leads to optimize antibiotic treatment. For both MAC and *M. abscessus*, tedizolid and clofazimine may help to improve the efficacy of treatment regimens. Tedizolid was recently shown to have MICs two- to four-fold lower than linezolid against both. Compared with linezolid, tedizolid has higher bioavailability, longer half-life, lower hematological and neurotoxicity rates, and it accumulates in the lung and macrophages [3]. The potential role of clofazimine became apparent in recent studies applying time-kill kinetic assays; clofazimine proved able to suppress the emergence of resistance to amikacin and clarithromycin, key drugs in NTM-PD treatment regimens [4].

For MAC bacteria, this rapid emergence of resistance was elegantly shown in hollow fiber pharmacodynamic models (HFM) by Schmalstieg *et al.*, who showed that macrolide resistance in MAC is based on continuous increase of efflux pump expression followed by chromosomal mutation [5].

KEYWORDS

- chronic pulmonary infections
- nontuberculous mycobacteria
- NTM

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Table 1. Currently recommended antibiotic treatment regimens.

Species	Recommended regimen
<i>Mycobacterium avium</i> complex	Rifampicin or rifabutin + ethambutol + macrolide
<i>M. abscessus</i>	First phase: cefoxitin or imipenem + amikacin + macrolide (+ tigecycline) Second phase: macrolide + two oral drugs based on AST (+ inhaled amikacin)
Drugs in brackets are optional. AST: Antimicrobial susceptibility testing.	

“What we need are safe, tolerable and highly effective short-course regimens, preferable with oral antibiotics only.”

From these data and Monte Carlo simulations, it appears that the macrolide antibiotic azithromycin, in its current recommended dose is ineffective in virtually all MAC patients [6]. The new antituberculosis drug bedaquiline proved bacteriostatic against *M. avium* in a mouse model, but it did not add to the activity of macrolides [7]. Perhaps, in synergistic combinations (like the bedaquiline–clofazimine combination already proven synergistic in mouse models of *M. abscessus* disease) [8] bedaquiline might still prove helpful in MAC pulmonary disease (MAC-PD) treatment.

For *M. abscessus*, preclinical studies reveal a dire picture which mirrors the clinical reality. Again using the HFM, Ferro *et al.* showed that moxifloxacin, which is currently recommended for *M. abscessus* treatment, is ineffective against it [9]. Also, the recommended initial regimen of amikacin–cefoxitin–clarithromycin fails to significantly reduce bacterial loads in the HFM and its limited activity is rapidly wiped out by the emergence of cefoxitin resistance [10]. This is in line with the earlier finding in a mouse model that cefoxitin alone, is as active as the full cefoxitin–amikacin–clarithromycin regimen [11]. More positive news was reported for tigecycline, which did prove effective against *M. abscessus* in HFM assays [12].

Animal models gave further valuable insights into the *in vivo* efficacy of *M. abscessus* treatment. Lefebvre *et al.* showed inhibition of *M. abscessus* β -lactamase by avibactam. This increased efficacy of imipenem, *in vitro* and *in vivo*, in a zebrafish model [13]. These findings give hope to empowering β -lactam antibiotics as a potent treatment option by coadministering avibactam. Bedaquiline also showed activity in the lung tissue of *M. abscessus*-infected mice [11]. The combination of bedaquiline and clofazimine showed a stronger synergistic effect; this combination therapy significantly lowered bacterial burden of *M. abscessus* in organs of interferon-gamma knockout (GKO) mice [8]. These animal

models mimic disseminated rather than pulmonary NTM disease and like the HFM findings for MAC and *M. abscessus*, they still await confirmation in clinical trials.

Some very influential clinical studies have come out in the past 5 years. One of the major changes in the MAC-PD field is the arrival of the first industry-sponsored randomized clinical trial. Within this trial, addition of liposomal amikacin by inhalation, to previously failing treatment regimens led to a significantly higher rate of culture conversion compared with placebo [14]. Bedaquiline has now also been tried in patients with MAC-PD, but microbiological outcomes were poor, with failures related to rapid emergence of bedaquiline resistance [15]. Applying bedaquiline in rifamycin-free treatments (e.g., with clofazimine instead) will increase bedaquiline exposure and might improve its efficacy.

Also, several case series have reported the outcomes of guideline-compliant MAC-PD treatment. In patients with nodular-bronchiectatic MAC-PD, groups from the USA and South Korea have shown that intermittent treatment with the rifamycin–ethambutol–macrolide regimen is highly successful, leading to prolonged culture conversion in 70–85% of the patients. Also, intermittent treatment was well tolerated and required fewer regimen modifications than daily treatment [16,17]. Owing to these patients’ susceptibility to NTM-PD, recurrence rates remain high [17]. In a small fibro-cavitary MAC-PD cohort in The Netherlands, 57% of patients achieved prolonged culture conversion; addition of clofazimine and amikacin in patients with most severe disease yielded similar outcomes [18].

Clinical studies on *M. abscessus* treatment are fewer and consistently show poor outcomes, particularly for *M. abscessus* subspecies *abscessus* with its inducible macrolide resistance. The prognostic value of the detection of inducible or mutational macrolide resistance in the laboratory is now

evident and this should be a standard practice [19]. One of the many questions regarding optimal antibiotic treatment of *M. abscessus* pulmonary disease is how many intravenous drugs are needed in the initiation phase of treatment; this has now been addressed in a small retrospective study, which concluded that in its cohort there was no evident benefit of two intravenous drugs during the initiation phase over only one [20]. The efficacy of clofazimine in *M. abscessus* treatment regimens is another question that has now been addressed for the first time, albeit again in a retrospective study only. In a cohort of 42 patients in South Korea, clofazimine-containing regimens lead to significant decreases in bacterial loads in sputum. Overall, complete culture conversion only occurred in 24% of the patients, but up to 40% of patients who received clofazimine as part of their initial regimen converted to negative cultures [21]. Both topics clearly warrant prospective clinical trials. In fact, prospective clinical trials of the currently recommended regimens have never been performed. The advent of new drugs and *M. abscessus*-specific clinical trials could deliver these as a byproduct.

But treatment outside of trials and reference clinics is a different world. Recent surveys have shown that adherence to the rifamycin–ethambutol–macrolide regimen for MAC-PD is very poor. The percentage of patients with MAC-PD that received >6 months of treatment with this regimen amounted to 44% in Japan, 21% in the USA and a shocking 10% in five European countries [22].

Despite significant progress, we are nowhere near where we need to be. We know better what (not) to expect of currently recommended regimens. We have a few exciting new antibiotics but we still have no new regimens. Regimens including either liposomal amikacin inhalation, bedaquiline or clofazimine seem effective against MAC-PD and tigecycline, tedizolid, bedaquiline–clofazimine, amikacin–clofazimine combinations and β -lactam antibiotics (with avibactam) appear effective against *M. abscessus* in preclinical studies. But how many and which companion drugs do we need, to maximize the impact of these drugs and combinations?

What we need are safe, tolerable and highly effective short-course regimens, preferable with oral antibiotics only. Finding these requires combined efforts by pharmaceutical companies and academia and an inclusive mentality leading to multicenter, global, pro and retrospective clinical studies, fueled by solid preclinical data.

Financial & competing interests disclosure

J van Ingen has served on advisory boards for Insmed, Janssen and Spero Therapeutics. He is supported by a grant from the Netherlands Organization for Scientific Research (NWO/ZonMW grant Veni 016.176.024). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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