Non-Tuberculosis Mycobacteria –
Difficult to treat infections that may present future opportunities for novel therapies

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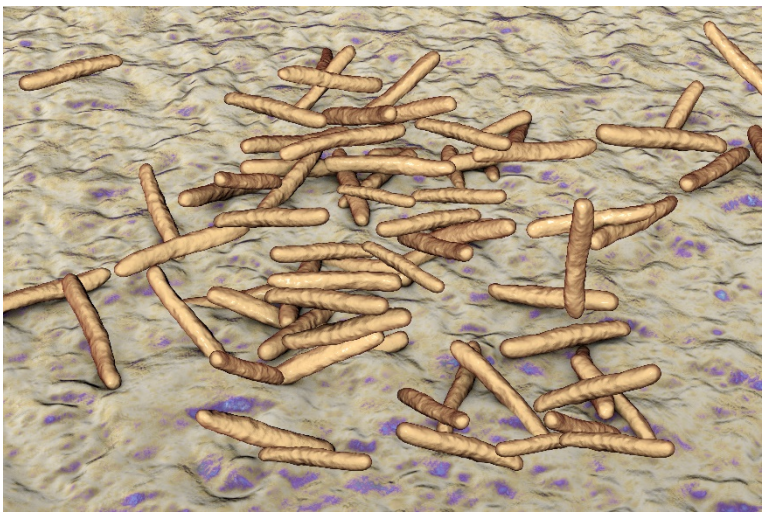
Introduction

Interest in Non-Tuberculosis Mycobacteria (NTM) has been steadily increasing over the last decades. Winthrop and workers noted an increase in prevalence of NTM in the United States (US) from 6.78 to 11.7/100,000 persons between 2008 and 2015[1]. The NTM indication is an attractive opportunity due to the ability to gain orphan drug status for treatments, long duration of therapy (>6 months) and premium pricing potential. This short review looks at some of the approaches in development.



NTM are common in the environment and cause disease in "at-risk" patients. NTM pulmonary disease requires an effective diagnosis and isolation of pathogenic species from at least two separate sputum samples taken a month apart. The treatment duration is long (>6 months), and the aim is for a sustained culture conversion (negative culture). At present, there are few approved (and off-label) options available for the treatment of NTM pulmonary disease. The 2020 update of the treatment guidelines[2] brings together the relevant respiratory (European Respiratory Society [ERS], American Thoracic Society [ATS]) and infectious disease (Infectious Disease Society of America [IDSA], European Society for Clinical Microbiology and Infectious Disease [ESCMID]) societies on both sides of the Atlantic to provide consistent guidance to treating physicians.

NTM traditionally have been categorised by their rate of growth and pigment production *in vitro* using the Runyon classification. However, with the advent of genetic techniques, species-specific identification by sequencing a number of target genes, including the 16S ribosomal RNA gene, has led to many new species of NTM being described. Currently, there are more than 125 NTM species listed which are classified into rapid-growing and slow-growing mycobacteria.[3]

- Rapid-growing mycobacteria produce non-pigmented, mature colonies on agar plates in less than 7 days of incubation and include *Mycobacterium fortuitum (M. fortuitum)* and the *M. chelonae-abscessus* group.

- Slow-growing mycobacteria require more than 7 days to produce mature growth *in vitro* and are further divided based on pigment production into three major groups: nonchromogens (e.g., *M. avium*, *M. intracellulare*, *M. chimaera*), photochromogens (e.g., *M. kansasii*) and scotochromogens (e.g., *M. scofulaceum*).

The treatment of rapid-growing NTM like *M. abscessus* is more problematic than for slow-growing species (e.g., *M. avium*, *M. kansasii*) as faster growing species tend to have more resistance mechanisms (e.g., Bla_{mtd} (beta-lactams), erm(41)(macrolides), AAC(2')(aminoglycosides)) to current standard of care agents.

The 2020 update of the ATS/ERS/ESCMID/IDSA guidelines recommend the early treatment of patients with risk of disease progression whereas 'watch and wait' may be appropriate in younger patients with limited disease, higher body mass index and lower NTM burden in the sputum.

Presentations and discussions at the recent July 2021 European Congress of Clinical Microbiology and Infectious Disease (ECCMID) covered a number of subjects related to NTM treatment. Highlighted by a number of speakers was the need to treat *M. abscessus* complex (MABc) with at least 3 active (proven *in vitro* susceptibility) agents to have a reasonable chance of culture conversion. However, the severity of infection, presence of resistance factors, and drug-drug interactions requiring changes of therapy, make adherence to these initial regimens a limited possibility for some patients, especially those with *M. abscessus* infections. Allied to this is a lack of prospective studies looking at defining the best maintenance therapy post-culture conversion for infections caused by the varied NTM species.

The guidelines recommend triple therapy using a macrolide, rifampicin and ethambutol for first line treatment of *M. avium* complex (MAC), with amikacin liposomal inhaled solution (ALIS) added on a once daily basis if culture conversion is not achieved after 6 months of treatment. A macrolide was chosen as this antibiotic class has demonstrated the best link between *in vitro* susceptibility and clinical outcomes. As macrolides are at increasing risk of inducible resistance, the need for adherence to triple/quadruple therapy to achieve sustained culture conversion becomes ever more important.

The commercial success of Insmed with their inhaled liposomal formulation of amikacin ($164M sales in 2020)[4] - in stark contrast to the commercial failure of Achaogen with plazomicin for multidrug resistant Gram-negative infections (both launched in 2018) - makes this an area of interest for a number of companies with agents in the Gram-negative infection space as well as those with a focus predominantly on NTM.

Currently, there are a number of interesting, ongoing, pre-clinical and clinical studies looking at treatment of MAC and MABc that may improve outcomes for patients in the future:

1. Omadacycline (NUZYRA®) – Paratek Pharmaceuticals announced on 18 Aug 2021 that the U.S. Food and Drug Administration (FDA) has granted the orphan drug designation for omadacycline for the treatment of infections caused by NTM, including infections caused by MABc, which is the focus of an ongoing Phase 2b study initiated by Paratek.[5]

   This move by Paratek into the NTM indication is an example of expansion of the approach by companies with antimicrobials that have utility in both large indications like community acquired pneumonia and an orphan strategy – (of which NTM and Cystic Fibrosis are examples) – where the funding and commercial opportunities are much more attractive.

2. Arikayce – Insmed, following FDA approval in September 2018 (for refractory MAC) and recent European Medicines Agency approval of Arikayce (ALIS, October 2020) for refractory MAC, are now progressing with a Phase 3 study for use as a first line treatment of MAC.[6]

   The results of this Phase 3 study and subsequent submission for expansion of the ALIS approved indication will greatly expand the potentially accessible MAC patient population and help to cement the use of inhaled adjunctive therapy for MAC. This endorsement of inhaled therapy for treatment of a pathogen may help drive research into use of inhaled therapeutic agents in bronchiectasis and possibly ventilator associated pneumonia. It will be interesting to see whether there is major push back from payers on annual cost of ALIS (~$80,000 per year in US) once first-line use for MAC is approved.

3. SPR720 – This is a novel class of oral antibacterial agent for the treatment of NTM being developed by Spero. However, Spero have decided to pause their Phase 2a clinical trial as a precautionary measure based on a recommendation from Spero's Safety Review Board following review of data from an ongoing toxicology study of SPR720 in adult non-human primates in which mortalities with inconclusive causality to treatment were observed. These studies are to support longer-term treatment with SPR720 beyond the 28 days currently supported by IND-enabling toxicology studies. No serious adverse events have been observed in any human study participants.[7]

   As SPR720 is the first of a new class of NTM treatments, hopefully, when the animal toxicology data is fully analysed, the trials can restart and help provide a novel alternative to repurposed antibacterials and showcase another indication of interest to companies developing novel approaches to difficult-to-treat bacterial infections.

4. Dual beta-lactams – The concept of using beta-lactams to treat NTM (especially *M. abscessus*) is well established. Over the last 5-10 years, the approval of novel beta-lactams (BLs, e.g., ceftaroline) and BL/beta-lactamase inhibitors (BL/BLi), e.g., ceftazidime-avibactam, imipenem-relebactam) opens the potential for new treatment

approaches to be investigated. Pandey and colleagues have investigated the activity of a range of single BLs, BL/BLi combinations and dual BLs against MABc. Their work indicates that there may be potential new avenues for treatment as the BL combinations and BL/BLi approaches both demonstrated good activity in *in vitro* tests.[8]

If proven in clinical practice, the use of BL combinations may accelerate the options for treatment and use of approved BL/BLi combinations and/or standalone BLis may ultimately improve the currently poor long-term outcomes for these patients.

5. Inhaled tigecycline – Tigecycline is active against *M. abscessus*, but severe toxicity and the need for intravenous administration limit its use in clinical practice. Inhaled tigecycline is being assessed as a potential treatment for *M. abscessus* pulmonary disease. Van Ingen and co-workers have measured its efficacy in a mouse model of chronic *M. abscessus* pulmonary disease. They have also both established the intracellular activity of tigecycline against *M. abscessus* in human macrophages and measured the activity of tigecycline in the sputum of cystic fibrosis patients. Tigecycline showed potent activity against *M. abscessus* in macrophages and retained most of its activity in the presence of sputum from cystic fibrosis patients. A stable and safe formulation of inhaled tigecycline has been achieved allowing pharmacokinetic/pharmacodynamic studies and clinical trials to be performed. This approach may represent a future treatment option for *M. abscessus* pulmonary disease.[9]

6. Inhaled clofazimine – Banaschewski and co-workers have investigated the tolerability and efficacy of a novel clofazimine inhaled suspension (CIS) formulation in various mouse models of NTM disease. The minimum inhibiroty concentrations (MICs) for *M. avium* and *M. abscessus* were evaluated *in vitro*, and tolerability of CIS was determined in naïve mouse models over various durations. CIS demonstrated antimycobacterial activity *in vitro*, with MIC values between 0.125 and 2 µg/ml for MAC and *M. abscessus*. CIS was well tolerated over 28 consecutive treatments. *In vivo*, CIS significantly improved bacterial elimination from the lungs of both acute and chronic NTM-infected mice compared to negative controls and oral clofazimine administration. Clofazimine concentrations in lung tissue were approximately four times higher using CIS compared to the concentrations achieved by oral dosing, making CIS a potential choice for further development as a treatment for MAC and MABc.[10]

The interest in looking at alternate inhaled formulations of known efficacious products, but whose use is restricted by toxicity or drug-drug interactions, mirrors prior development for exacerbations of cystic fibrosis caused by *Pseudomonas aeruginosa* and could be another avenue for development of effective treatments by a range of companies specialising in alternate drug delivery and/or bacterial infections/respiratory disease.

Summary

In summary, the NTM space is seeing an increase in interest from companies driven by the increasing incidence of these respiratory infections worldwide, by the demonstrable attractiveness of orphan drug designation and long-term treatments, and the proven commercial success of Insmed's ALIS. This can only bode well for improved outcomes for patients and may provide a commercially viable route into the antibacterial space for novel developmental agents currently focused on multidrug-resistant Gram-negative infections.

Contact Us

To discuss any aspects of NTM that may relate to current developmental compounds or future exploration of the potential of the NTM space, please contact us on 0118 963 7846 or email us at info@transcrip-partners.com.

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