Pulmonary Mycobacterium abscessus infection treated in combination with inhaled tigecycline

Pedersen, Andreas Arnholdt; Fløe, Andreas; Løkke, Anders; Hilberg, Ole

Published in:
BMJ Case Reports

DOI:
10.1136/bcr-2023-255383

Publication date:
2023

Document version:
Final published version

OPEN ACCESS

Pulmonary *Mycobacterium abscessus* infection treated in combination with inhaled tigecycline

Andreas Arnholdt Pedersen ,[1,2,3] Andreas Fløe,[4] Anders Løkke,[1,2] Ole Hilberg[1,2,3]

[1]Department of Pulmonary Research, Lillebaelt Hospital, Vejle, Denmark
[2]Department of Regional Health Reserarch, University of Southern Denmark, Odense, Denmark
[3]Mycobacterial Centre for Research Southern Denmark, Odense, Denmark
[4]Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus N, Denmark

Correspondence to
Dr Andreas Arnholdt Pedersen; Andreas.Arnholdt.Pedersen@rsyd.dk

Accepted 30 November 2023

To cite: Pedersen AA, Fløe A, Løkke A, *et al*. *BMJ Case Rep* 2023;**16**:e255383. doi:10.1136/bcr-2023-255383

SUMMARY

Pulmonary disease caused by *Mycobacterium abscessus* is difficult to treat, as there is currently no reliable evidence-based treatment. Treatment is long, complex and has many side effects. In this case, we report a patient with treatment-refractory pulmonary *M. abscessus* disease, treated with inhaled tigecycline. Treatment with inhaled tigecycline lasted 15 months with comparably limited side effects. There were no positive mycobacterial cultures in the follow-up period of 2 years. Inhaled tigecycline is an option in the treatment of pulmonary *M. abscessus* when first-line treatment fails. Additional research should investigate this further.

BACKGROUND

More than 190 non-tuberculous mycobacteria (NTM) species have been identified and the incidence is increasing globally, ranging from 15.2/100 000 to 41.3/100 000 (USA and Canada).[1 2] The mortality is high (35.3%),[3] and the morbidity is significant.[4] The microbiological cure rate is as low as 45%.[5]

Mycobacterium abscessus belongs to the subgroup of rapidly growing NTM and is composed of three subspecies: *M. abscessus* susp. *abscessus*, *massiliense* and *bolletii*. In *M. abscessus* and *M. massiliense*, inducible resistance to macrolides is a common problem due to the expression of the *erm*(41) gene.[6]

There are currently no drugs or combinations thereof with reliable effects when treating pulmonary NTM infections of the *M. abscessus* complex subgroup. Multidrug regimens including a macrolide are suggested by the ATS/ERS/ESCMID/IDSA guidelines in the absence of inducible or mutational macrolide resistance.[6] Side effects are common, often severe and affect multiple organs, eg, the gastrointestinal tract, kidneys, liver and bone marrow.[7] Side effects from intravenous tigecycline are common and consist of nausea, vomiting, diarrhoea, hepatitis and pancreatitis. A study on intravenous tigecycline for the treatment of *M. abscessus* found the rate of dose reduction or discontinuation due to side effects was 57.1%.[8] Side effects of the more commonly used drugs are gastrointestinal, tinnitus/hearing loss, hepatotoxicity and prolonged heart rate–corrected QT interval (QTc) for macrolides. Ethambutol can cause ocular toxicity and neuropathy. Linezolid can cause peripheral neuropathy, optic neuritis and cytopenia. Rifampicin can cause hepatotoxicity, cytopenia and hypersensitivity. Side effects of aminoglycosides consist of vestibular toxicity, ototoxicity, nephrotoxicity and electrolyte disturbances. The liposomal inhalation suspension of amikacin can also cause cough, dysphonia and dyspnoea.[6] In the CONVERT trial of amikacin liposome inhalation suspension (for *M. avium* disease), 91.1% of the patients receiving only guideline-based therapy experiences treatment-emergent adverse events.[9] Thus, treatment of *M. abscessus* is difficult and often limited by the side effects.

CASE PRESENTATION

A female patient in her 60s presented initially with haemoptysis and was diagnosed with severe cylindrical and varicose bronchiectasis. Treatment for the bronchiectasis consisted of a combination of fenoterol and ipratropium as well as airway clearance. The patient had a prior history of breast cancer more than 30 years ago, successfully treated with mastectomy and radiation therapy, with no signs of recurrence. *M. abscessus* ssp. *abscessus* were subsequently cultured from expectorated sputum and the diagnosis of pulmonary NTM disease was made.

Initially, the patient was treated with clarithromycin and moxifloxacin. Due to persistent symptoms, doxycycline was added but had to be discontinued due to nausea. Subsequently, linezolid and amikacin were added because of the refractory nature of the disease. However, these medications were halted after 5 months as they did not lead to significant improvement in symptoms or cultures. Treatments and their duration are shown in figure 1. The treatment was switched to clofazimine 100 mg one time per day, inhaled amikacin 500 mg two times per day and azithromycin 250 mg one time per day due to treatment-refractory nature of the disease. However, clofazimine was stopped due to the development of a rash, photosensitivity and peripheral neuropathy, while azithromycin was discontinued due to loss of appetite.

A sputum sample obtained after 8 months revealed that *M. abscessus* ssp. *abscessus* was resistant to all tested agents except for intermediate susceptibility to sulfamethoxazole-trimethoprim. Consequently, sulfamethoxazole-trimethoprim 800 mg/160 mg two times per day was added to the treatment regimen alongside inhaled amikacin. Inhaled amikacin was halted after 42 months, which did not lead to clinical deterioration. Subsequently, the patient was administered inhaled interferon gamma-1b, but there was no subjective improvement and subsequent cultures continued to show the presence of *M. abscessus*.[10]

INVESTIGATIONS

The patient had a known prior medical history of bronchiectasis, a recognised risk factor for NTM

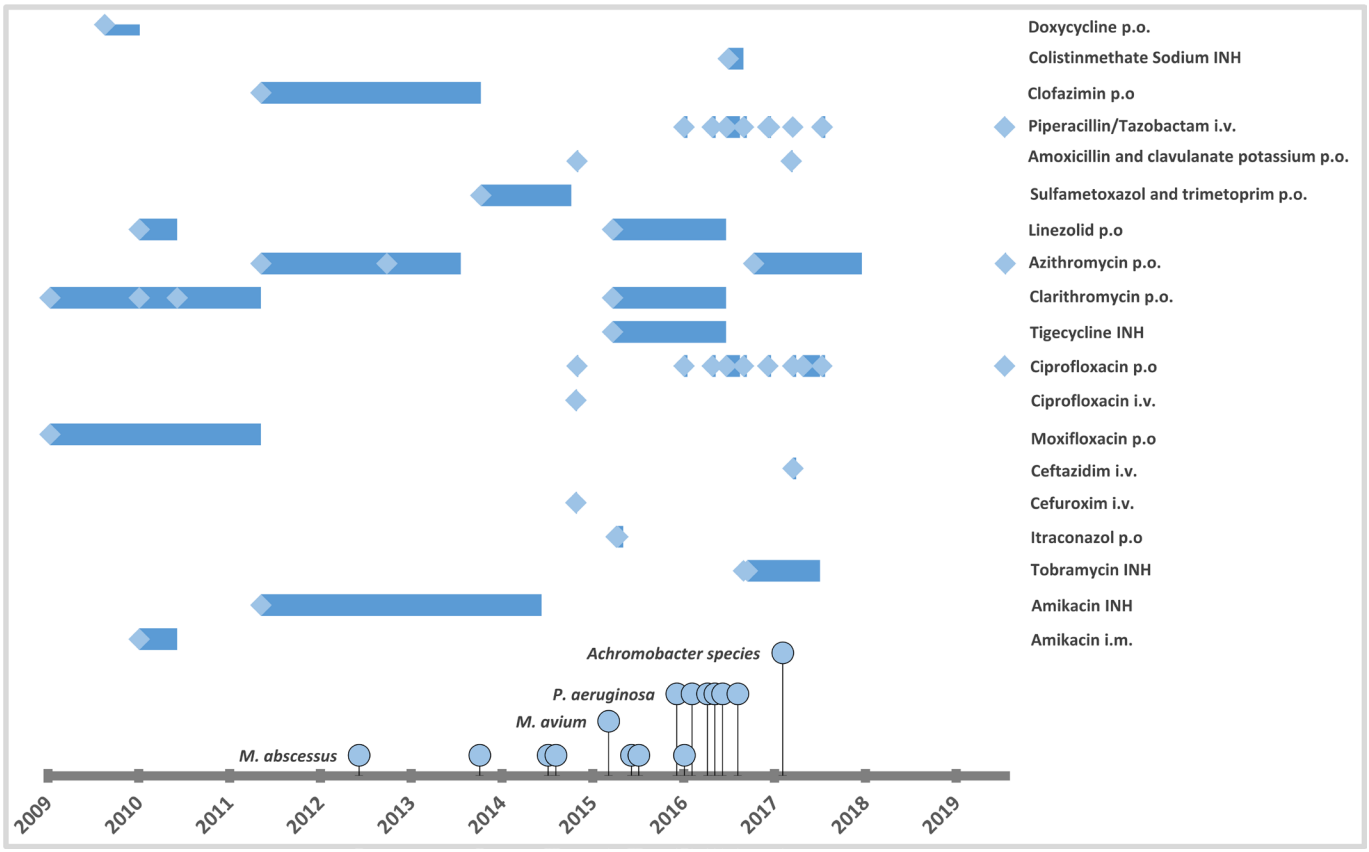

Figure 1 Diagram of treatment regiments from 2009 through 2019. The duration is denoted by the bars. Note the long timescale. Notable culture results from 2012 to 2019 are added below. i.v., intravenous; p.o, orally; INH, inhalation; i.m., intramuscular application. Created by AAP.

infection. Further diagnostic evaluations included screening for immunodeficiency, which encompassed HIV, hepatitis B and C, immunoglobulin levels, including IgG subtypes, antinuclear antibodies, antineutrophil cytoplasmic antibodies, alfa-1-antitrypsin, haemoglobin A1c, cytomegalovirus and Epstein-Barr virus antibodies, mannan-binding lectin, assessment of vaccine response to *S. pneumoniae*, M-component disease and lymphocyte subset quantitation (TBNK). All of these screening tests yielded unremarkable results. There were no signs of solid or haematological malignancies detected. An investigation of the interferon-gamma–IL-12 pathway revealed normal interferon gamma receptors, production of T-lymphocytes, interferon gamma stimulation and normal function of interleukin 12 receptors.

All cultures of *M. abscessus* were reported as resistant to tigecycline with a minimum inhibitory concentration (MIC) of 4 mg/L, linezolid (MIC >32 mg/L) and clarithromycin (MIC >16 mg/L).

TREATMENT

Nebulised treatment with inhaled tigecycline 25 mg two times per day was initiated, despite the reported resistance to tigecycline, as the reported in vitro resistance may not translate to a clinically relevant resistance and no clinical breakpoints are available for *M. abscessus*. Additionally, the treatment regimen included linezolid 600 mg two times per day as well as clarithromycin 500 mg two times per day. To prepare the nebulised tigecycline solution, 50 mg tigecycline dry powder was dissolved in 5 mL sterile saline and kept in a refrigerator for a maximum of 48 hours. For each dose, 2.5 mL of this solution was transferred to a Pari Boy Classic nebuliser, mixed with 2 mL sterile saline and then administered.

At the time of initiation of inhaled tigecycline, the patient complained of severe cough, expectoration, chest pain and weight loss. Her body mass index was 19.2 kg/m^2. On auscultation, low-frequency rhonchi were detected in both lungs. Her oxygen saturation was 94% without the need for oxygen supplementation. The FEV1 was 1.39 L (59% of the expected value), and the FEV1/FVC ratio was 71%. A high-resolution CT scan revealed severe bronchiectasis affecting all lobes, as well as consolidations and tree-in-bud phenomena, but no cavitary lesions.

After 12 days of treatment, the patient developed aphthous stomatitis, which was suspected to be an adverse event associated with inhaled tigecycline. Treatment was paused for 5 days because the stomatitis was mild and self-limiting. Initially, the patient reported improvement of symptoms, but after 1 month of treatment, she was admitted to the hospital due to increased coughing, nausea and discomfort. During the admission, the patient was treated with continuous positive airway pressure (CPAP), and the antibiotic treatment was continued. Therapeutic bronchioalveolar lavage (BAL) was performed to aid mucus clearance and was repeated 12 times over the following 29 months. This was considered an exacerbation of her mycobacterial disease rather than an adverse event, as assessed by the treating physician.

OUTCOME AND FOLLOW-UP

The treatment was complicated by three episodes of culture-confirmed infections with *Pseudomonas aeruginosa*. Each

episode was treated with 2 weeks of piperacillin/tazobactam 4 g/0.5 g three times per day and ciprofloxacin 500 mg two times per day. The third episode was followed by inhaled colistin 80 mg two times per day. Before discontinuing the tigecycline treatment, a BAL sample revealed a low quantity of *M. abscessus* ssp. *abscessus*. However, inhaled tigecycline was stopped before receiving the culture result. All subsequent cultures were negative for mycobacteria in the 2-year follow-up period, with no evidence of recurrence or relapse.[11] The duration of treatment with inhaled tigecycline lasted 15 months.

DISCUSSION

In this report, we present a case of a patient treated with inhaled tigecycline for *M. abscessus* pulmonary infection. The treatment was well tolerated for 15 months with limited side effects compared with other antimycobacterial treatments, mainly causing nausea and aphthous stomatitis. During the 2-year follow-up period, no relapse of infection with *M. abscessus* or any other pulmonary NTM was observed.

A study by Pearce *et al* demonstrated promising results with inhaled tigecycline in a laboratory setting. In this study, mice were infected with *M. abscessus* (with inducible macrolide resistance) by a pulmonary route and treated with inhaled tigecycline in different concentrations for 4 weeks. The results showed a significant reduction in colony-forming units of *M. abscessus* in a dose-dependent manner. Furthermore, tigecycline exhibited significant effects against *M. abscessus* in human macrophages.[12]

Antibiotic inhalation treatment is not a novel idea. Inhaled amikacin has been studied for *Mycobacterium avium complex* (MAC) disease since 2007.[13] A liposomal formulation of amikacin is recommended as a second-line add-on therapy in MAC disease.[6] Treatment of *M. abscessus* with inhaled amikacin has also been investigated but with no clear benefit. However, it is suggested as a continuation treatment after induction phase.[14] The rationale behind using antibiotic inhalation therapy is to maximise the local therapeutic effect while minimising the often severe side effects.

During the treatment, the patient consistently produced culture-negative sputum samples. However, a solitary sputum sample showed slow growth of *M. abscessus* after an extended culture duration, shortly before discontinuing treatment, and symptoms persisted throughout the duration of tigecycline therapy. Thus, it is not possible to definitively attribute the subsequent stabilisation solely to the treatment with inhaled tigecycline.

The isolated *M. abscessus* ssp. *abscessus* in this case was in vitro resistant to all the agents in the final treatment combination (tigecycline, linezolid and clarithromycin). Linezolid and clarithromycin were attempted early in the disease course, but culture conversion only occurred with the addition of tigecycline. It is important to note that a high MIC in vitro for tigecycline may not translate to clinically relevant resistance. Currently, there are no clinical breakpoints available for *M. abscessus* and the value of antimicrobial susceptibility testing has therefore been subject to debate.[12] We suggest that inhaled tigecycline can be considered as a treatment option for pulmonary *M. abscessus* infections when first-line treatment fails. While we cannot definitively conclude that inhaled tigecycline alone caused the culture conversion based on a single patient case, the timing of tigecycline treatment and subsequent culture conversion warrant further investigations of this treatment approach.

Patient's perspective

My cough started in 2006. I retired the same year. I was sent for a scan to be examined for lung cancer. No cancer was observed, but the examination revealed bronchiectasis in the lungs. I was referred to the hospital. Sputum samples were sent to the national reference laboratory who established the presence of *Mycobacterium abscessus*. It seemed uncertain if the bronchiectasis was colonised by mycobacteria or if the mycobacteria caused the bronchiectasis. Treatment started at department. I received different kinds of antibiotics. I usually received two to three different medications simultaneously. The medication was either inhaled, given intravenously or given as tablets. The treatments often resulted in severe side effects such as nausea, headache, oral candida or malaise. Sometimes, the treatment had to be put on hold for a few days, for me to recover my strength. I was seen at the hospital as a patient from 2007 until 2018. Additionally, I received intravenous medication administered three times a week. The medication that seemed to finish off the mycobacteria was inhaled tigecycline which I received with linezolid in 2015 and 2016. The last 2–3 years, I also had bronchoscopies done when my cough was too severe. That happened 12–13 times from 2016 until the end of 2018. It was some very tough years where you start to doubt if you can return to a normal life. Eventually, I did. No mycobacteria were found in the samples sent for culture and test in 2017 and 2018. I got through 10–12 tough years because I have a helpful and loving family. At the end of 2018, my affiliation with the hospital ended, and I was transferred to a new clinic. Here, my lung function is tested 3–4 times a year. To keep my lungs functional, I use CPAP in the morning and evening. My medication is prednisolone, alvesco and spiolto. The patient's perspective has been translated and anonymised by the authors.

Learning points

- Pulmonary disease caused by *Mycobacterium abscessus* is difficult to treat, often resulting in significant side effects and poor outcome.
- First-line treatment involves a combination of at least three active drugs guided by susceptibility testing. However, there is no reliable standard treatment regimen.
- Inhalation therapy offers increased local effect of the drug and limits the often severe side effects.
- Inhaled tigecycline can be considered as a potential option for treating pulmonary *M. abscessus* infection when first-line treatment is insufficient.

Contributors This study was conceptualised and designed by AAP, OH, AF and AL. Data acquisition was performed by OH, AAP and AF and analysed by all authors. Figure was made by AAP. The draft was written by AAP and critically revised by OH, AF and AL. All authors contributed significantly to this paper as per the Vancouver guidelines.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests The authors declare the following competing interests: AAP and AF participate in an Advisory Board to Nordic Infucare. The remaining authors declare no competing interests.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD
Andreas Arnholdt Pedersen http://orcid.org/0000-0003-0751-6918

REFERENCES

1 Adjemian J, Olivier KN, Seitz AE, *et al*. Prevalence of Nontuberculous Mycobacterial lung disease in US medicare beneficiaries. *Am J Respir Crit Care Med* 2012;185:881–6.
2 Marras TK, Campitelli MA, Lu H, *et al*. Pulmonary Nontuberculous Mycobacteria-associated deaths, Ontario, Canada, 2001-2013. *Emerg Infect Dis* 2017;23:468–76.
3 Wang P-H, Pan S-W, Wang S-M, *et al*. The impact of Nontuberculous Mycobacteria species on mortality in patients with Nontuberculous Mycobacterial lung disease. *Front Microbiol* 2022;13:909274.
4 Mehta M, Marras TK. Impaired health-related quality of life in pulmonary Nontuberculous Mycobacterial disease. *Respir Med* 2011;105:1718–25.
5 Chen J, Zhao L, Mao Y, *et al*. Clinical efficacy and adverse effects of antibiotics used to treat Mycobacterium Abscessus pulmonary disease. *Front Microbiol* 2019;10:1977.
6 Daley CL, Iaccarino JM, Lange C, *et al*. Treatment of Nontuberculous Mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline: executive summary. *Clin Infect Dis* 2020;71:905–13.
7 Egelund EF, Fennelly KP, Peloquin CA. Medications and monitoring in Nontuberculous mycobacteria infections. *Clin Chest Med* 2015;36:55–66.
8 Kwon Y-S, Levin A, Kasperbauer SH, *et al*. Efficacy and safety of Tigecycline for Mycobacterium abscessus disease. *Respir Med* 2019;158:89–91.
9 Griffith DE, Eagle G, Thomson R, *et al*. Amikacin Liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium Avium* complex (CONVERT). A prospective, open-label, randomized study. *Am J Respir Crit Care Med* 2018;198:1559–69.
10 Hallstrand TS, Ochs HD, Zhu Q, *et al*. Inhaled IFN-gamma for persistent Nontuberculous Mycobacterial pulmonary disease due to functional IFN-gamma deficiency. *Eur Respir J* 2004;24:367–70.
11 van Ingen J, Aksamit T, Andrejak C, *et al*. Treatment outcome definitions in Nontuberculous Mycobacterial pulmonary disease: an NTM-NET consensus statement. *Eur Respir J* 2018;51:1800170.
12 Pearce C, Ruth MM, Pennings LJ, *et al*. Inhaled Tigecycline is effective against Mycobacterium Abscessus in vitro and in vivo. *J Antimicrob Chemother* 2020;75:1889–94.
13 Raaijmakers J, Schildkraut JA, Hoefsloot W, *et al*. The role of amikacin in the treatment of Nontuberculous Mycobacterial disease. *Expert Opin Pharmacother* 2021;22:1961–74.
14 Henriette Zweijpfenning SM, Chiron R, Essink S, *et al*. Safety and outcomes of amikacin Liposome inhalation suspension for Mycobacterium Abscessus pulmonary disease: a NTM-NET study. *Chest* 2022;162:76–81.