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Treatment and outcome of non-tuberculous mycobacterial pulmonary disease in a predominantly fibro-cavitary disease cohort

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ABSTRACT

Background: The incidence of non-tuberculous mycobacterial pulmonary disease (NTM-PD) has increased in the Netherlands. The fibro-cavitary disease manifestation predominates, as elsewhere in Europe. We studied treatment and outcome of this disease manifestation, as such data are scarce.
Methods: We conducted a retrospective study of all patients diagnosed with NTM-PD according to the American Thoracic Society statement between 2008 and 2013 in a reference clinic.
Results: Sixty-three patients were included. Thirty-two (51%) were females and mean age was 60.8 years. Most patients had underlying COPD (73%). *M. avium* complex pulmonary disease (MAC-PD) was most frequent (n = 38, 60.3%), followed by *M. malmoense* (n = 7) and *M. kansasii* (n = 6). Twenty-two patients had fibro-cavitary MAC-PD, 14 had nodular-bronchiectatic MAC-PD and 2 had other manifestations. Thirty-two (94%) patients treated for MAC-PD received a rifamycin-ethambutol-macrolide based regimen. Microbiological cure rates were lower for fibro-cavitary (52.4%) than for nodular bronchiectatic MAC-PD (100%; p = 0.03). Sixty-nine percent of treated patients experienced adverse events, most frequently gastrointestinal discomforts (71%), tinnitus (18%), hearing impairment (16%) and hepatotoxicity (18%).
Conclusions: Fibro-cavitary NTM-PD remains predominant, but is now diagnosed more frequently in women. Fibro-cavitary disease is harder to cure than nodular-bronchiectatic disease. Adverse events are frequent and can necessitate cessation of treatment.

1. Introduction

Non-tuberculous mycobacteria (NTM) are opportunistic pathogens that are abundant in our environment, especially in water and soil [1]. NTM pulmonary disease (NTM-PD) is the most frequent disease manifestation [2]. NTM-PD is often seen in patients with predisposing pulmonary diseases, like COPD and bronchiectasis. In the last decade, NTM isolation frequency has increased in the Netherlands, as has the number of consultations at our mycobacterial reference clinic [2].

NTM-PD has two main radiographic manifestations, the fibro-cavitary and nodular-bronchiectatic disease. Fibro-cavitary disease predominated in previous studies in the Netherlands [2], in contrast to North America [3] and Australia [4]. The presence of cavities or consolidations at initial presentation is an independent factor associated with progression to treatment [5] as well as a predictor for treatment failure [6,7].

Guidelines for treatment of NTM-PD are mainly based on the results of cohort studies, as few randomized clinical trials have been performed [6]. There is also a notable lack of toxicity data, even for currently recommended treatment regimens. At our reference clinic, NTM patients are treated by a multidisciplinary team, consisting of several disciplines with at least respiratory physicians, clinical microbiologists and hospital pharmacists. We have conducted a retrospective medical file review to study treatment practices, outcomes and adverse events.

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Abbreviation list

MAC	Mycobacterium *avium complex*
MAC-PD	*M. avium* complex pulmonary disease
NTM	Non-tuberculous mycobacteria
NTM-PD	non-tuberculous mycobacterial pulmonary disease
PD	pulmonary disease
RE-macrolide	rifamycin-ethambutol-macrolide

2. Methods

We studied all patients with at least one positive NTM culture from 2008 to 2013 in our laboratory database, which was cross-checked with our local NTM-PD registry for completeness. From these, we selected all patients who met ATS diagnostic criteria for NTM-PD [8] and for whom data were available. Patients with Cystic Fibrosis were excluded from the analysis.

For all included patients, we registered clinical, microbiological and radiographic features. COPD was defined according to the GOLD-classification with pulmonary function testing at time of diagnosis [9]. The differentiation between nodular-bronchiectatic and fibro-cavitary disease was made by the pulmonologist based on available radiographic images. Culture results were registered at set times: at start of treatment, 3, 6, 12 and 24 months. All NTM isolates were identified using the Inno-LiPA Mycobacteria v2 line probe assay, supplemented with 16S rDNA or *hsp65* gene sequence analysis. Antimicrobial susceptibility test results of baseline isolates were retrieved from the laboratory database; susceptibility testing was performed by agar dilution (2008–2011) or broth micro-dilution (2012–2013). We used the following outcome definitions, based on assessment at the end of treatment: Microbiological cure was defined as clinical improvement with negative cultures at the end of therapy. Clinical cure was defined as reduction of symptoms and radiographic features in the absence of follow up cultures. Recurrence or therapy failure was defined as recurrence of positive cultures during treatment or persistent positive cultures despite 12 months of treatment. Death was defined as all-cause mortality during treatment. Treatment regimens were defined as all antibiotics used for the purpose of NTM disease treatment. Results were analysed using descriptive statistics; we used a Chi square test for the difference in outcome in the different treatment regimens and a two sided Fisher's exact test for the difference in adverse events between azithromycin and clarithromycin and the difference between microbiological cure rates in fibro-cavitary and nodular-bronchiectatic disease in *M. avium* complex (MAC).

3. Results

Sixty-three (33%) of 191 patients with positive cultures from respiratory samples met ATS diagnostic criteria for NTM-PD.

Of 63 patients with NTM-PD, 32 (50.8%) were female and the mean age was 60.8 ± 12.9 years. *Mycobacterium avium* complex (MAC) was the predominant causative agent (n = 38, 60.3%; 23 *M. avium*, eight *M. intracellulare*, three *M. chimaera*, four untypeable/MAC-X); *M. malmoense* and *M. kansasii* were seen in seven and six patients, *M. abscessus* in four, *M. simiae* in three and *M. xenopi* in two patients; three patients had mixed infections.

The baseline characteristics of patients with MAC-PD, *M. malmoense*-PD and *M. kansasii*-PD are presented in Table 1. The predominant radiographic disease manifestation was fibro-cavitary disease (n = 37, 58.7%); 20 patients (31.7%) had nodular-bronchiectatic disease and 6 patients had other radiographic features (3 had dense airspace opacities, 2 had nodules only, 1 had atelectasis and bronchiectasis). Severe COPD (Gold III-IV) was more frequent in patients with fibrocavitary disease than in those with nodular bronchiectatic disease (58% vs 33%). Two patients had proven immunodeficiencies; one had interferon gamma deficiency and one idiopathic CD4 lymphopenia.

Sputum culture conversion rates differed per species. After 6 months of therapy 41.2% MAC-PD had converted, compared to 66.7% with *M. malmoense*-PD and 83.3% with *M. kansasii*-PD (Table 2). The cure rates obtained for the different NTM species and radiographic manifestations are outlined in Table 3. In MAC-PD patients the rifamycin-ethambutol-macrolide (RE-macrolide) regimen was the most frequently used regimen (32/34; 94.1%). Of these 32, five patients received additional clofazimine, 7 received additional clofazimine and amikacin. The microbiological cure rates did not differ significantly between the MAC- PD treatment regimens.

The average treatment duration was 17 ± 10.5 months in fibrocavitary disease and 13 ± 7.6 months in nodular bronchiectatic disease. Thirty-five patients were treated for fibrocavitary disease, with different species of NTM. Twenty-one patients were treated for fibrocavitary MAC disease with the rifamycin-ethambutol-macrolide regimen. Of these, 7 received additional amikacine and clofazimine and 3 patients received additional clofazimine only. Of 11 patients with fibrocavitary MAC-PD who only received a rifamycin, ethambutol and a macrolide, 4 reached microbiological cure (36%) and 1 reached clinical cure (9%). Of the 7 patients with additional clofazimine and amikacin, 4 patients reached microbiological cure (57%), 3 patients were not cured. All 3 patients who only received additional clofazimine reached microbiological cure.

Overall, in the fibro-cavitary MAC-PD group, 12 of 21 patients with macrolide-susceptible strains attained microbiological or clinical cure (57.2%). No deaths were attributable to mycobacterial disease. In the nodular-bronchiectatic group with macrolide-susceptible strains, all 7 patients attained microbiological cure. Microbiological cure differed significantly between fibro-cavitary and nodular bronchiectatic disease ($p = 0.03$).

We found no significant correlations between Gold stages, gender and treatment outcomes.

Four patients had macrolide-resistant MAC isolates at baseline. These patients received a rifampicin-ethambutol regimen, with amikacin and clofazimine (n = 1), or with a macrolide (n = 3); one achieved clinical cure, two had therapy failure and one died of an unrelated cause. Four of seven *M. malmoense*-PD patients received RE-macrolide. Two patients received rifampicin and ethambutol alone due to macrolide intolerance. Four *M. kansasii*-PD patients received a regimen of rifamycin-ethambutol-isoniazid. Two patients only received rifampicin and ethambutol.

Overall, at least four patients who attained microbiological cure had recurrence of positive cultures during further follow up.

Side effects were common. In the 55 treated patients, adverse events were reported by 38 patients (69.1%). Gastrointestinal side effects were predominant, reported by 71.1% of all patients reporting any adverse event; hearing impairment (15.8%) and tinnitus (18.4%), hepatotoxicity (18.4%) and decreased vision (5.3%) were other commonly reported adverse events. In 7 patients treatment had to be ceased and 15 patients stopped temporally or stopped at least one drug due to adverse events. Overall 6 out of 7 patients were treatment had to be ceased, did have negative cultures despite short treatment regimens due to adverse events. One had persistent positive cultures. There is a trend towards more gastro-intestinal and haematological side effects in MAC-PD patients receiving azithromycin than in those receiving clarithromycin-based regimens, although not statistically