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Eradication of *Pseudomonas aeruginosa* in cystic fibrosis patients with inhalation of dry powder tobramycin

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Abstract

Background: *Pseudomonas aeruginosa* (*Pa*) is the predominant pulmonary pathogen in patients with cystic fibrosis (CF). Tobramycin nebulization is used for the eradication of *Pa* infection. Nowadays, tobramycin dry powder inhalation (DPI) is available as well. This study reports the results of eradicating *Pa* with tobramycin DPI *versus* nebulization.

Methods: Adult CF patients with a *Pa* isolation between September 2010 and September 2017 from the University Medical Centre Groningen (UMCG), the Netherlands, were included in this retrospective study.

Results: In total 27 *Pa* isolations were recorded. In 13 of these, eradication was attempted with tobramycin, 7 with DPI and 6 with nebulization. DPI eradicated *Pa* successfully in six isolations (85.7%). Of these, one patient received additional oral ciprofloxacin and one received intravenous ceftazidime. Nebulization eradicated three *Pa* isolations (50.0%), in two of these, additional oral ciprofloxacin was given.

Conclusion: Eradication rates of DPI tobramycin are comparable with those for nebulized tobramycin reported in the literature. This study suggests that DPI tobramycin is an alternative to nebulized tobramycin for eradication of *Pa*.

Trial registration: The Medical Ethics Committee of the UMCG granted a waiver (METC2017-349), as they concluded that this study was not subject to the Medical Research Involving Human Subjects Act.

The reviews of this paper are available via the supplemental material section.

Keywords: cystic fibrosis, dry powder tobramycin, *Pseudomonas aeruginosa*

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Background

Pseudomonas aeruginosa (*Pa*) is the predominant pulmonary pathogen in adult patients with cystic fibrosis (CF), a chronic progressive disease of which the primary cause of death is respiratory failure resulting from chronic pulmonary inflammation and infection.[1] The presence of *Pa* is an unfavourable prognostic indicator and is associated with accelerated lung tissue destruction and decline in lung function, leading to increased morbidity and mortality.[2–4] In Europe more than half of the adult CF patients have a chronic *Pa* infection.[5] Once chronic infection is established, *Pa* is virtually impossible to eradicate. However, early infections with *Pa* usually have a low bacterial load, offering an opportunity for eradication.[6–9]

Different eradication strategies are available, including tobramycin or colistin inhalation or intravenous administration, sometimes combined with oral ciprofloxacin.[10,11] The advantage of inhaled antibiotics consists of facilitating high

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Table 1. Inclusion and exclusion criteria.

Inclusion criteria	- Patients diagnosed with CF with clinical signs consistent with CF and sweat chloride >60 mEq/l or two CF-causing mutations identified - An initial or new *Pa* isolation from sputum cultures during the study period, treated with tobramycin nebulization or tobramycin dry powder (DPI tobramycin)* - Multiple sputum cultures after the end of treatment
Exclusion criteria	- Chronic *Pa* infection - Patients receiving *Pa* suppressing therapy - Lung transplantation before *Pa* isolation - Incomplete exposure and/or outcome data

**Pa* isolation was defined as initial *Pa* isolation when the patient hadn't been infected with *Pa* prior to this *Pa* isolation. For new *Pa* isolation, patients had to be free of *Pa*, defined by the Leeds criteria, whereby all cultures taken in the last 12 months prior to *Pa* isolation had to be *Pa* negative.
CF, cystic fibrosis; DPI, dry powder inhalation; *Pa, Pseudomonas aeruginosa.*

drug concentrations at the target site in the lung, while minimizing systemic exposure and toxicity. The most frequently applied method of administration for inhaled antibiotics is by wet nebulization. Nowadays, dry powder inhalation of a few antibiotics is available in Europe since September 2010.[12–14] Hypothetically, these dry powder antibiotics have several advantages over nebulization: more effective lung deposition, reduced administration time and lower risk of auto-re-infection when used with a disposable inhaler. In daily practice, these dry powder antibiotics are now used to eradicate *Pa* infections. To the best of the authors knowledge, whether these dry powder antibiotics are equally effective in eradicating *Pa* compared with administration through nebulization has not been studied previously.

This study compares the results of eradicating *Pa* with dry powder tobramycin (DPI tobramycin) with nebulized tobramycin from our own experience and in comparison with reported results from the literature.

Methods

This was a retrospective study from September 2010 until September 2017 concerning adult CF patients from the CF centre University Medical Centre Groningen (UMCG) in the Netherlands. Inclusion and exclusion criteria are listed in Table 1. We focused on incident *Pa* cases; thus, patients were included more than once when they had more than one *Pa* infection during the study period if they were declared free from *Pa* according to the Leeds criteria. Patients treated with DPI tobramycin received 112 mg twice daily for 28 days, for tobramycin nebulization dosage consisted of 300 mg twice daily for 28 days. The Medical Ethics Committee of the UMCG granted a waiver (METC2017-349), as they concluded that this study was not subject to the Medical Research Involving Human Subjects Act.

The primary outcome was the eradication of the *Pa* infection, defined as at least three *Pa* negative sputum cultures over 6 months. Secondary outcome parameters were time to recurrence of *Pa* after successful eradication, and development of chronic *Pa* infection.

Results

All 113 adult CF patients were assessed for eligibility. Of these, 69 (61.1%) were excluded. Reasons for exclusion were chronic *Pa* (53; 76.8%), lung transplantation before start of study (15; 21.7%) and one person had no sputum cultures taken due to mild CF (1.5%). Of the 44 included patients, 18 (40.9%) were found to have one or more *Pa* infection during the study period. In total 27 incident *Pa* isolations were recorded. A total of 14 were excluded due to receiving treatment other than tobramycin inhalation; too many missing data (in three patients too few sputum cultures were available after treatment); or not meeting Leeds criteria for early/new *Pa* isolation (two patients). In the end, 13 *Pa* isolations were found eligible for analysis, of which 7 were treated with DPI tobramycin, and 6 with tobramycin nebulization. Treatment with DPI tobramycin consisted of 112 mg twice daily for 28 days (Podhaler®). Patients treated with tobramycin nebulization received 300 mg twice daily for

Table 2. Clinical characteristics.

	Dry powder tobramycin (*n* = 7)	Nebulization tobramycin (*n* = 6)
Gender, *n* (%)		
Male	3 (42.9)	1 (16.7)
Female	4 (57.1)	5 (83.3)
Age in years, mean (range)	33.8 (23.8–51.5)	28.4 (18.6–39.3)
BMI, mean (range)	24.7 (20.8–29.5)	21.7 (16.6–29.1)
CFTR mutation, *n* (%)		
Homozygote_Phe508del	6 (85.7)	4 (66.7)
Heterozygote_Phe508del	–	2 (33.3)
Other	1 (14.3)	–
Unknown	–	–
Comorbidities, *n* (%)		
Cystic fibrosis-related diabetes	2 (28.6)	3 (50.0)
Cystic fibrosis-related liver disease	1 (14.3)	2 (33.3)
Pancreas insufficiency	7 (100.0)	5 (83.3)
Osteoporosis	1 (14.3)	1 (16.7)
Forced Expiratory Volume in 1 second		
Percentage of predicted, mean (range, ±SD)	80.7 (58–100, ±18.5)	78.8 (29–106, ±33.5)
Absolute, mean (range, ±SD)	2.9 (1.88–4.1, ±0.8)	2.9 (0.99–4.76, ±1.4)
***Pa* infection new/first**	4/3	6/0
Coinfection with pathogens, *n* (%)		
Staphylococcus aureus	7 (100.0)	4 (66.7)
Haemophilus influenza	2 (28.6)	2 (33.3)
Streptococcus pneumoniae	0	0
Aspergillus	5 (71.4)	4 (66.7)
Acinetobacter	2 (28.6)	0
Stenotrophomonas maltophilia	0	1 (16.7)
Burkhholderia	0	0
Nontuberculosis Mycobacteria	0	0

BMI, body mass index; CFTR, Cystic fibrosis transmembrane conductance regulator; *Pa, Pseudomonas aeruginosa*; SD, standard deviation.

28 days. Different nebulizers were used by the various patients. Table 2 liststhe clinical characteristics of the 13 *Pa* infections.

Of the seven *Pa* isolations treated with DPI tobramycin, eradication was successful in six cases (85.7%), however in one case only two sputum cultures were available in the year after treatment instead of three. In only one case, *Pa* infection was not eradicated with DPI tobramycin. In five of the seven isolations, DPI tobramycin was used without comedication. In one of the six eradicated cases, oral ciprofloxacin (20 mg/kg twice daily, with a maximum total dosage of 1500 mg per day for 2 weeks) was added to DPI tobramycin; in one case, DPI was combined with intravenous ceftazidime (in a dosage of 8 gram/24 h, for 14 days).

In the group with nebulized tobramycin, eradication was achieved in three out of six cases (50.0%); in two of them, tobramycin nebulization was combined with oral ciprofloxacin. Statistical analysis using Fisher's exact test showed no significant difference in eradication rate between treatment with DPI and nebulization ($p = 0.266$).

Mean time to reinfection or end of study for those without recurrence during the study period in the group treated with DPI tobramycin was 552.8 days *versus* 123.0 days in the nebulization group. The log-rank test showed a significant difference ($p = 0.018$). No patients treated with DPI tobramycin developed chronic infection *versus* two patients in the nebulization group. Fisher's exact test showed no significant difference ($p = 0.192$).

Discussion

Treatment with DPI tobramycin appears to be at least as effective as nebulization in achieving *Pa* eradication, since 85.8% of *Pa* was eradicated with DPI compared with 50.0% with nebulization. In the literature, numbers of eradication success from nebulized tobramycin vary widely.[15] Gibson found an overall eradication efficacy of 74%, evaluated 1–3 months after ending treatment.[16] In the first ever *Pa* isolations, 14 out of 15 persons (93%) remained free of *Pa* after 1 year of treatment with tobramycin nebulization.[17] Proesmans found an eradication success of 79.3%, evaluated at the end of treatment with nebulized tobramycin for 28 days. At 1 year follow-up, 44.8% were still free of *Pa*.[18] A study by Taccetti recorded an eradication success of 65% with nebulized tobramycin for 28 days combined with oral ciprofloxacin, eradication defined as three negative cultures over 6 months.[19]

The lower eradication success by nebulization of 50% in our study may be owing to the fact that only adults were included in contrast with most other studies, causing the presence of not only first *Pa* isolations but also new *Pa* isolations. The acquisition of *Pa* at an older age negatively affects eradication success.[9] For DPI tobramycin, we showed that its success rate of 85.7% is comparable with the numbers reported in the literature. As soon as treatment success is similar, other benefits such as ease of use, time burden and convenience become more important.

The main limitation of this study was the small population size, preventing us from drawing firm conclusions. Furthermore, it prevented us from performing statistical analyses corrected for confounding factors, such as forced expiratory volume in 1 second and body mass index, to reflect health status. Moreover, administration of either DPI tobramycin or nebulization was not randomized. However, looking at the characteristics of the 13 incident *Pa* infections, the clinical condition of the patients treated with DPI tobramycin seems to be similar to those treated with nebulized tobramycin.

In conclusion, the present study suggests that DPI tobramycin might be a good alternative to nebulized tobramycin for the eradication of *Pa.* Further research is needed to evaluate DPI tobramycin as an eradication strategy, as it can potentially increase treatment effectiveness and patient convenience, ultimately improving clinical outcome.

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Conflict of interest statement

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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