

The BATTLE study: Effects of long-term tobramycin inhalation solution (TIS) once daily on exacerbation rate in patients with non-cystic fibrosis bronchiectasis. Study protocol of a double blind, randomized, placebo-controlled trial: study protocol

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ABSTRACT

Background: Patients with bronchiectasis typically suffer from chronic symptoms such as a productive cough with or without exacerbations leading to hospitalization, causing reduced quality of life (QoL) and mortality. Long-term inhaled antibiotics to treat chronic bronchial infection is registered for use in cystic fibrosis (CF) bronchiectasis. However, in patients with non-CF bronchiectasis data on long-term antibiotics are limited.

Objective: To investigate the effectiveness of maintenance tobramycin inhalation solution (TIS) in bronchiectasis patients without cystic fibrosis.

Study design: The BATTLE study is a randomized, double blind placebo controlled, multicenter study in the Netherlands performed in patients aged ≥ 18 -year-old with confirmed bronchiectasis, at least two exacerbations in the preceding year, and minimal one positive sputum culture with gram negative pathogens or *Staphylococcus aureus*, sensitive to tobramycin in the preceding year and at baseline. Patients will be treated with TIS once daily (OD) or placebo (saline 0.9%) OD for 52 weeks followed by a run-out period of 4 weeks after the last dose. The primary outcome is the yearly rate of pulmonary exacerbations. Among secondary outcome parameters are time to exacerbation, lung function, QoL, microbiological evaluation and safety.

Discussion: The BATTLE study is designed to determine the efficacy and safety of maintenance TIS OD in bronchiectasis patients colonized by different pathogens and could lead to important new evidence for TIS therapy in this population.

The BATTLE study is registered in Clinical [trials.gov](https://clinicaltrials.gov) with registration number: NCT02657473.

1. Background

Non-cystic fibrosis bronchiectasis (hereafter referred to as 'bronchiectasis') is chronic lung disease characterized by a vicious cycle of bacterial colonization, airway inflammation and airway structural damage, resulting in bronchial dilatation [1]. Patients commonly develop chronic symptoms of cough and sputum production, with recurrent infections, exacerbations and hospitalizations, accompanied by a reduced quality of life (QoL) [2,3]. The origin of bronchiectasis

varies, but the presence of microbial infection and a persistent inflammatory response are characteristic for the disease [4]. Bacteria isolated from the sputum of patients with bronchiectasis include *Streptococcus pneumoniae* (*S. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), *Haemophilus influenzae* (HI), and other gram-negative bacteria including *Pseudomonas aeruginosa* (PA) [5]. Chronic infections and colonization with these organisms, particularly with PA are associated with an increased number of exacerbations and hospital admissions, a reduced QoL and an increased morbidity and mortality [6–8].

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Reducing the number of exacerbations is the corner stone of long-term disease management, particularly for frequent exacerbating bronchiectasis patients [9–12]. Long-term systemic antibiotic treatment in bronchiectasis has shown favourable results, however antibiotic resistance may develop, relapse may occur when the antibiotics are stopped, and systemic antibiotics frequently fail to eradicate lung infections despite intensive therapy [6,13].

An attractive alternative is the use of inhaled antibiotics which can provide a consistent deposition of high antibiotic concentrations directly to the site of infection with a lower risk of systemic toxicity and systemic adverse events like gastrointestinal side effects [14,15]. Inhaled antibiotics are part of the standard care in cystic fibrosis (CF) with *PA* colonization [16–18]. Nowadays the international bronchiectasis guidelines recommend inhaled antibiotics in patients with *PA* colonization [9]. However this is based on limited and conflicting data and not much is known about the ideal dosage regimen and duration of treatment. In addition, the population of patients with bronchiectasis not due to CF is older, has different comorbidities, and the risk of adverse events may differ from the CF population [8,19,20]. A few small studies with aerosolized tobramycin inhalation solution (TIS) are conducted in bronchiectasis patients colonized with *PA*, and found a decrease in *PA* density in sputum, with improvement of the secondary outcomes respiratory symptoms and number of hospital admissions. In these studies, the duration ranged from 6 weeks to 13 months, TIS was given twice daily and the most common primary outcome was *PA* density in sputum [8,20–22]. No exact data is available of the effect of maintenance use of TIS once daily (OD) on exacerbation frequency, and especially in bronchiectasis patients colonized by *non-PA* Gram negative bacteria or *S. aureus*.

The present double-blind randomized placebo-controlled trial is designed to answer whether maintenance treatment with TIS OD may reduce the number of exacerbations in bronchiectasis as compared to

placebo. This paper describes the study design of this randomized controlled trial: Effects of long-term ToBrAmycin InhalaTion SoluTion (TIS) once daiLy on Exacerbation rate (BATTLE study) in patients with non-cystic fibrosis bronchiectasis.

2. Methods

2.1. Objectives

The primary objective of the study is to determine whether maintenance use of TIS once daily (OD) as compared to placebo may reduce the number of exacerbations per year in patients with bronchiectasis. Secondary objectives are time to next exacerbation, lung function, QoL, laboratory test and microbiological evaluation in patients with bronchiectasis treated with TIS or placebo.

2.2. Study design

This study is a prospective, randomized, double-blinded, multi-center, placebo-controlled trial conducted in the Netherlands. The efficacy and safety of TIS OD will be evaluated as compared to placebo during a 52-week treatment period followed by a 4 weeks off-treatment follow up after the last study dose (Fig. 1). Patients with bronchiectasis with recurrent exacerbations (≥ 2 per year) colonized by Gram-negative bacteria or *S. aureus* will be included and evaluated. Whereby colonization is defined as at least two results of sputum culture separated by at least 3 months in a year. Subjects meeting all study eligibility criteria (Table 1), including a sputum culture with the predefined bacterial pathogens at baseline, are randomized 1:1 to receive OD treatment with either TIS or placebo at visit 1 (week 0).

At visit 1 (week 0) a tolerance test will be performed with lung function examination before and after the first dose of the study

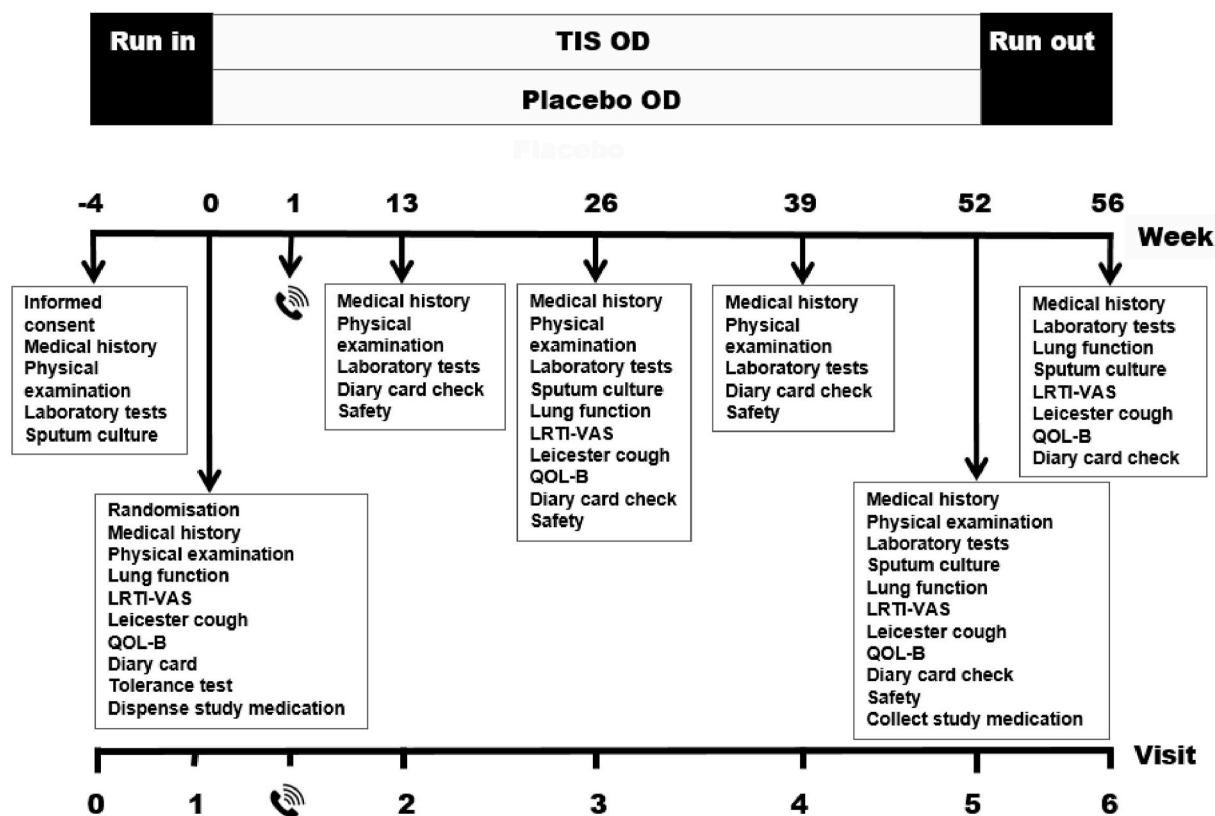


Fig. 1. Study schedule

Fig. 1. Study schedule. Abbreviations: Tobramycin inhalation solution (TIS); Once daily (OD); Lower respiratory tract infections – Visual Analogue Scale (LRTI-VAS); Leicester cough questionnaire (Leicester cough); Quality of life bronchiectasis questionnaire (QoL-B).

Table 1
In and exclusion criteria for the BATTLE study.

Inclusion criteria	Exclusion criteria
1 Age ≥ 18 years	1 Any exacerbation within the month prior to the start of the study
2 The presence of chronic respiratory symptoms such as cough, dyspnea, expectoration of sputum	2 Diagnosis of CF
3 Confirmed bronchiectasis by (HR) CT	3 Diagnosis of ABPA
4 Documented history of at least 2 pulmonary exacerbations treated with courses of antibiotics and/or prednisolone within 12 months before inclusion	4 Any oral, IV or inhaled antibiotics (except for macrolides) within 1 month prior to the start of the study
5 No course of antibiotics or maintenance antibiotics (except for macrolides) 1 month prior to the start of the study	5 Any IV or IM corticosteroids or change in oral corticosteroids (>10 mg) within 1 month prior to the start of the study
6 Minimal one documented sputum or BAL-fluid culture with gram-negative bacteria or <i>S. aureus</i> within 12 months	6 Any change/start treatment regimens of macrolides, hypertonic saline, inhaled mannitol or other mucolytics, or corticosteroids within 1 month prior to the start of the study
7 Growth of protocol defined pathogens (gram-negative bacteria or <i>S. aureus</i>) in sputum at randomization	7 Severe immunosuppression or active malignancy
	8 Active tuberculosis or NTM
	9 Chronic renal insufficiency (eGFR <30 ml/min)
	10 Use of loop diuretics, urea or mannitol
	11 Earlier diagnosed hearing impairment, balance disorders or neuromuscular disorders
	12 Serious active haemoptysis
	13 Have received an investigational drug or device within 1 month prior to the start of the study
	14 Serious or active medical or psychiatric illness
	15 Pregnancy and childbearing
	16 History of poor cooperation or non-compliance
	17 Unable to use nebulizers
	18 Allergic for tobramycin (or Saline 0.9%)

Table 1. In-and exclusion criteria. Abbreviations: Active allergic bronchopulmonary aspergillosis (ABPA); cystic fibrosis (CF); non-tuberculous mycobacterial infection (NTM); High resolution computed tomography (HRCT).

medication to assess the occurrence of local intolerance. Patients are instructed to use the diary card weekly to examine the respiratory symptoms and side effects, and if so, to notice an exacerbation. Patients are asked to contact the study staff if the experience shortness of breath, cough, tinnitus, or other side effects. If needed patients are referred to otolaryngologist for hearing examination. Study visits are planned at the outpatient ward and consists of an up to 4 weeks screening phase (run-in period), a treatment phase of 52 weeks, and a washout phase (run out period) of 4 weeks (Fig. 1). Throughout the study, visits are planned every 3 months, and clinical, QoL questionnaire's, bacteriological and laboratory examinations will be performed including lung function tests. Documented approval from the Independent Ethics Committees and Institutional Review Boards was obtained from all participating centers before start of the study, according to Good Clinical Practice and local laws and regulations. Written informed consent was obtained from all participants.

2.3. Intervention

TIS 300 mg (TEVA pharmaceuticals) OD and matched placebo (saline 0.9%) are provided in small plastic ampules of 5 ml and are packed in identical sealed boxes and will be dispensed on the regular visits every 3

months. The investigators are blinded for the content of the boxes. An OD dosing schedule, and not a twice daily (BID) dosing schedule is administered, which promotes adherence of the relatively intensive and time-consuming treatment schedule, whereby probably no increase in side effects or the development of tobramycin resistance. The study medication is delivered using the InnoSpire Deluxe air compressor (Philips Respironics) with a SideSteam Plus nebulizer with filter and mouthpiece (Fig. 2). Salbutamol aerosol with aerochamber is administered every day at a dose of 200mcg before the study medication. The nebulizer will be used for about 10 min until the reservoir is empty. The whole procedure: preparation of the nebulizer, inhalation and cleaning takes about 20 min to complete. Afterwards the patient should rinse their mouth three times. The study drug administration is performed OD in the morning after completion of the patient's regular bronchiectasis treatment.

2.4. Study population

Patients are included with proven bronchiectasis on high resolution computed tomography ((HR)CT), at least two exacerbations in the year prior to the study and a positive sputum culture for gram negative pathogens or *S. aureus* in the preceding year, as well as the screening visit (week 0, visit -4). The inclusion and exclusion criteria for the BATTLE study are shown in Table 1. Patients with known CF, active allergic bronchopulmonary aspergillosis (ABPA), tuberculosis or non-tuberculous mycobacterial infection (NTM) are excluded. All co-medications are allowed, except for any oral (except for macrolides), IV or inhaled antibiotics or corticosteroids (>10 mg) within 1 month prior to the start of the study. Other exclusion criteria are the use of immunosuppressive agents or any change or start of treatment regimens with macrolides, hypertonic saline, inhaled mannitol or other mucolytics within 1 month prior to the start of the study. Because of the potential interaction with tobramycin the use of loop diuretics or mannitol are prohibited during the study.

2.5. Sample size

We hypothesize that maintenance treatment with TIS reduces the number of exacerbations per patient by 50%. This reduction seems clinically relevant and assumes that maintenance treatment with TIS OD as well as intermittent TIS BID is comparable to that of maintenance AZM treatment. This assumption is derived from data of the BAT (Bronchiectasis and Long-term Azithromycin Treatment) trial (placebo: mean 2.1 exacerbations (Sd 1.6); azithromycin: mean 0.8 exacerbations (sd 1.1) [23]. The reduction in percentage is used for the determination of sample size. A Poisson regression model is used to determine group size [24]. For type I error and type II error 0.05 and 0.2 are used respectively. The hypothesis is tested two sided. With a baseline exacerbation rate of 2.1 in the placebo group and an expected response rate ratio of 0.5 with an exposure time of 1 year a total of 18 evaluable patients are required to be on each treatment arm. With a drop-out percentage of 30% we must include totally 48 (24 patients per group) patients [20,21]. Due to unforeseen reasons 2 extra patients per arm are included. So, a total of 52 patients are included in the study.

2.6. Interim analysis

After inclusion and follow up of 50% of the randomized patients, an interim analysis will be conducted.

The interim analysis will be used to calculate the predetermined effect size, and whether more patients should be included depending on this effect size. Depending on the frequency of exacerbations at baseline and the effect size, a power analyses will be performed by using the Poisson regression model [24].



Fig. 2. InnoSpire Deluxe with side stream plus with filter and mouthpiece
Fig. 2. InnoSpire Deluxe nebulizer with side stream plus with filter and mouthpiece.

2.7. Randomization

Block randomization of 4 will be performed centrally with an allocation ratio of 1:1 between groups. The numbers are anonymously dispensed in closed envelopes and stored at the pharmacy of the Northwest Clinics location Alkmaar and at an independent medical doctor. At visit 1 (week 0) patients receive the unique randomization number that allows subsequent identification of their randomized treatment group allocation. The study is blinded for treatment assignment and regimen.

3. Study assessments

3.1. Efficacy assessments

The primary efficacy endpoint of the BATTLE study is the number of exacerbations per year in patients with bronchiectasis. An overview of

the efficacy and safety assessments are shown in Table 2. Secondary efficacy endpoints of the study are time to next exacerbation, lung function (FVC% predicted, FEV₁% predicted) and QoL measurements based on Lower respiratory tract infections – Visual Analogue Scale (LRTI-VAS), Quality of Life-Bronchiectasis questionnaire (QoL-B) and the Leicester cough score [25–27]. In addition, laboratory assessments and bacterial load in sputum with the development of tobramycin resistance will be evaluated in both groups.

3.2. Safety assessments

Safety analysis include the occurrence of AE's and SAE's, with special interest to bronchospasm, hemoptysis, and hypersensitivity reactions. In addition, renal and liver function disorders, and the occurrence of hearing impairment and/or tinnitus probably due to the use of TIS will be evaluated.

The development of tobramycin resistant pathogens in sputum will be observed in both groups, including the occurrence of NTM and/or *Aspergillus fumigatus*.

A tolerance test will be performed with the first dose of study medication to evaluate the occurrence of inhalation induced bronchospasms. Defined as a decrease in FEV₁% of predicted of 20% following the study drug, and/or saturation <90%. A safety analysis will be performed by an independent expert every six months during the study and might recommend termination of the study if there are any safety concerns, outstanding benefit and/or futility.

3.3. Exacerbations

All participants are provided with 24-h contact details and invited to contact their respiratory physician or general practitioner and/or study staff when they experience worsening of respiratory signs and symptoms, to ensure that these symptoms are evaluated prospectively. In case of an exacerbation, participants are asked to provide a fresh sputum sample and are instructed to ensure that antibiotic and/or prednisolone prescriptions are provided by the own respiratory physician of the centers or the general practitioner. Criteria for a protocol defined pulmonary exacerbation (PDPE) are adjudicated prospectively by the treating respiratory physician. Deteriorations in respiratory symptoms that do not meet criteria for PDPEs will be termed non-protocol-defined pulmonary exacerbations (non-PDPEs). In these circumstances, participants are advised not require antibiotics, only if clinically indicated determined by the treating physician or the general practitioner. During an exacerbation, the study treatment is continued, if possible, unless the study medication is not tolerated, or the exacerbation is believed to be

Table 2
 Overview of the study assessments for the BATTLE study.

Primary assessment	Secondary assessments
1 Reduce in number of exacerbations	1 Time to next exacerbation 2 Change in lung function (FEV ₁ % and FVC%) 3 Change in QoL measurements (QoL-B, LRTI-VAS, Leicester cough)
Safety assessments	Additional assessments
1 Occurrence of any AE or SAE	1Development of tobramycin resistance in sputum (if possible, with MIC values) 2Bacterial load in sputum and pathogen eradication 3Occurrence of new pathogens
2 Occurrence of bronchospasm during the tolerance test	4Change in inflammatory markers in serum
3 Occurrence of bronchospasm, dyspnea, cough or other respiratory symptoms during the study	5Analyses of the use of inhaled medication (time consuming, treatment burden)
4 Occurrence of hearing impairment/tinnitus	
5 Change in safety laboratory values (renal and liver function)	

Table 2. Overview of the study assessments of the BATTLE study. Abbreviations: Adverse event (AE); Serious adverse event (SAE); non-tuberculous mycobacterial infection (NTM); Forced expiratory volume in 1 s (FEV₁); Forced vital capacity (FVC); Quality of life (QoL); quality of life bronchiectasis questionnaire (QoL-B); Lower respiratory tract infections – Visual Analogue Scale (LRTI-VAS); Leicester cough questionnaire (Leicester cough); Minimum Inhibitory Concentration (MIC).

related to the study drug.

3.4. Exacerbation definition

A PDPE is defined as the presence of three or more of the following symptoms or signs for at least 24 h:

1. Increased cough
2. Increased sputum volume and or/purulence
3. Haemoptysis
4. Increased dyspnoea
5. Increased wheezing
6. Fever ($>38.5^{\circ}\text{C}$) or malaise

AND the treating physician agreed that antibiotic and/or prednisolone therapy is required.

3.5. Study discontinuation

All participants who receive any study medication are encouraged to complete all the study assessments. However, participants can terminate the study at any time for any reason without any consequences. The investigator/treating physician can also decide to withdraw a subject from the study for urgent medical reasons. We estimate a drop-out of 30% patients based on previous studies with inhaled antibiotics.

4. Statistical analysis

4.1. Efficacy analysis

Efficacy analysis will be performed in the intention to treat (ITT) population, defined as all randomized patients, and the modified intention to treat population (mITT). The mITT population excludes the randomized patients who dropped out directly after the tolerance test, or in the first two weeks of study treatment (non-evaluable). Analysis in the per protocol population (PP), defined as all randomized patients who received and completed treatment according to the study protocol for at least nine months, will serve as supporting evidence.

4.2. Methods of analysis

Descriptive statistics for patients treated with TIS or placebo will be calculated at baseline in the ITT population. Discrete variables will be presented as counts (percentage) and continuous variables as means with standard deviation (sd) if normally distributed and medians with interquartile range (IQR) if not normally distributed. Between groups differences will be tested using the students T-test or the Mann-Whitney U Test depending on the distribution. The effect of TIS as compared to placebo on exacerbation frequency will be analyzed by using the Poisson regression analysis. Linear mixed model analysis will be used to analyze the effects on lung function and QoL over the time. The minimal important difference (MID) of the QoL-questionnaires in bronchiectasis is previously reported only for the QoL-B respiratory symptom scale, with an increase of 8 points representing clinical relevance. The MID for the total score of the Leicester cough questionnaire is 1.3 points [25,27]. Time to first exacerbation during the treatment period, as well as during the wash-out period, will be assessed using Cox proportional hazards regression. A p-value <0.05 is considered statistically significant. The data will be collected in the online Electronic Case Report Form (ECRF) of Castor EDC – Medical Research and the analysis will be conducted by using IBM SPSS 25 for Windows.

5. Discussion

The BATTLE study is designed to determine the efficacy and safety of maintenance TIS OD in bronchiectasis patients infected by tobramycin

sensitive pathogens, with an expected reduction in number of exacerbations of 50% as compared to placebo (saline 0.9%). Secondary objectives of the study are time to next exacerbation, change in lung function, QoL measurements and safety assessments.

As mentioned, in CF bronchiectasis; a more homogenous and younger population; long-term inhaled antibiotics are part of the standard care with sufficient evidence, especially in PA colonized patients [17]. In bronchiectasis not due to CF, previous studies of inhaled TIS are small and limited, but showed some promising results with a decrease of PA density in sputum and improvement of respiratory symptoms [8,20,21]. Other studies with inhaled antibiotics in bronchiectasis found also trends towards clinical benefit of the inhaled treatment regime, however the primary endpoints were not met [28–30]. Though, a recently published meta-analysis of inhaled antibiotics demonstrated a significant reduction in exacerbations with no significant improvement of respiratory symptoms or QoL [14]. The results of this BATTLE study can complement the current evidence in this heterogeneous and older population of bronchiectasis patients, with different etiologies and more comorbidities.

The strengths of our RCT are the multicentre study design, with the strict inclusion and exclusion criteria, and a predefined clear definition of an exacerbation, whereby the impact of variability between the clinical assessments should be reduced. Safety will be monitored closely, and all patients underwent a tolerance test with the randomized study medication at visit 1, to observe the development of bronchospasms.

In addition, not only patients with PA colonization will be included, but also patients colonized with other gram-negative and gram-positive pathogens. Beside PA, also other pathogens often colonize bronchiectasis patients and may also be associated with poorer outcomes [2]. It is therefore important to determine the effect of inhaled tobramycin on different pathogens, and could provide insight into treatment with TIS in non-PA. All aetiologies are included in our study, excluding the bronchiectasis patients diagnosed with ABPA or active tuberculosis or NTM, which reflects the daily patient population of non-CF bronchiectasis.

A unique feature of our BATTLE design is the OD maintenance treatment with TIS or placebo.

Twice daily on/off dosing was originally chosen for TIS in CF with the underlying idea to maximize the treatment effect and reduce the development of tobramycin resistance pathogens, however there is a lack of evidence for this specific treatment schedule [31]. During daily practice, a decrease in adherence to therapy developed due to the BID cycle of this intensive therapy, with an increase of treatment burden. The use of antibiotic inhalation solution is time consuming and will take about 20 min a day, including preparation of the InnoSpire and the cleaning protocol afterwards.

Intravenous administration of aminoglycosides have shown that OD dosing is equivalent in terms of antimicrobial efficacy compared to more frequent dosing [35–37]. And in addition, the OD dosing is supported by knowledge that its bactericidal activity is concentration-dependent with a long post-exposure antibiotic effect [32–34].

A possible disadvantage of this continuous OD treatment instead of the on/off schedule is probably an earlier development of tobramycin resistance or an increase of side effects, for example the occurrence of local intolerance.

In conclusion, the BATTLE study is designed to determine the efficacy and safety of maintenance TIS OD in bronchiectasis patients infected by different pathogens and could lead to advances in the treatment of bronchiectasis, including an optimal treatment regime for TIS therapy in this population.

Ethics approval and consent to participate

Approval of Independent Ethics Committees and Institutional Review Boards was obtained from all the participating centers. Clinical trials.gov number of the BATTLE study: NCT02657473. EudraCT number of the BATTLE study: 2016-000166-35. Written informed consent

was obtained from all the participants at the screening visit.

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Author's contributions

Conceptualization of the manuscript was done by WG. Boersma, J. Altenburg and L.C. Terpstra. Formal analysis, methodology and writing the original draft were done by LC. Terpstra and WG. Boersma. The funding acquisition for the BATTLE study was conducted by LC. Terpstra and WG. Boersma. The Project administration was done by L.C. Terpstra.

All authors, L.C. Terpstra, J. Altenburg, I. Bronsveld, H.J. Doodeman, W. Rozemeijer, H.G.M. Heijerman, W.G. Boersma reviewed the manuscript and has given final approval of the version to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Not Applicable.

References

- [1] M.P. Murray, A.T. Hill, Non-cystic fibrosis bronchiectasis, *Clin. Med.* 9 (2) (2009) 164–169, <https://doi.org/10.7861/clinmedicine.9-2-164> ([doi]).
- [2] J.D. Chalmers, P. Goeminne, S. Aliberti, et al., The bronchiectasis severity index: an international derivation and validation study, *Am. J. Respir. Crit. Care Med.* 189 (5) (2014) 576–585, <https://doi.org/10.1164/rccm.201309-1575OC> ([doi]).
- [3] L.C. Terpstra, S. Biesenbeek, J. Altenburg, W.G. Boersma, Aetiology and disease severity are among the determinants of quality of life in bronchiectasis, *Clin. Respir. J.* 13 (8) (2019) 521–529.
- [4] P.J.P.J. Cole, Inflammation: a two-edged sword—the model of bronchiectasis, *Eur. J. Respir. Dis. Suppl.* 147 (1986) 6–15.
- [5] P.J. McShane, E.T. Naureckas, G. Tino, M.E. Streck, Non-cystic fibrosis bronchiectasis, *Am. J. Respir. Crit. Care Med.* 188 (6) (2013) 647–656.
- [6] J.D. Chalmers, W. Boersma, M. Loneragan, et al., Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis, *Lancet Respir. Med.* 7 (10) (2019) 845–854.
- [7] M.A. Martínez-García, J. Soler-Cataluña, M. Perpiñá-Tordera, P. Román-Sánchez, J. Soriano, Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis, *Chest* 132 (5) (2007) 1565–1572.
- [8] P. Scheinberg, E. Shore, PC-TNDS-008 study group, A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis, *Chest* 127 (4) (2005) 1420–1426.
- [9] E. Polverino, P.C. Goeminne, M.J. McDonnell, et al., European respiratory society guidelines for the management of adult bronchiectasis, *Eur. Respir. J.* 50 (3) (2017), <https://doi.org/10.1183/13993003.00629-2017>. Print 2017 Sep. doi: 1700629 [pii].
- [10] D.J.D. Chalmers James, Mechanisms of immune dysfunction and bacterial persistence in non-cystic fibrosis bronchiectasis, *Mol. Immunol.* 55 (1) (2013-8) 27–34.
- [11] D.J.D. Chalmers James, Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis, *Am. J. Respir. Crit. Care Med.* 186 (7) (2012-10-01) 657–665.
- [12] P. Mandal, M. Sidhu, L. Donaldson, et al., Eight-weekly intravenous antibiotics is beneficial in severe bronchiectasis, *QJM: Int. J. Med.* 106 (1) (2013) 27–33.
- [13] C. Rayner, G. Tillotson, P. Cole, R. Wilson, Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis, *J. Antimicrob. Chemother.* 34 (1) (1994) 149–156.
- [14] I.F. Laska, M.L. Crichton, A. Shoemark, J.D. Chalmers, The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis, *Lancet Respir. Med.* 7 (10) (2019) 855–869.
- [15] A.M. Brodt, E. Stovold, L. Zhang, Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review, *Eur. Respir. J.* 44 (2) (2014) 382–393, <https://doi.org/10.1183/09031936.00018414> ([doi]).
- [16] M.N. Hurley, D.L. Forrester, A.R. Smyth, Antibiotic adjuvant therapy for pulmonary infection in cystic fibrosis, *Cochrane Database Syst. Rev.* (6) (2013).
- [17] C. Castellani, A.J. Duff, S.C. Bell, et al., ECFS best practice guidelines: the 2018 revision, *J. Cyst. Fibros.* 17 (2) (2018) 153–178.
- [18] H.G. Wiesemann, G. Steinkamp, F. Ratjen, et al., Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of pseudomonas aeruginosa colonization in cystic fibrosis, *Pediatr. Pulmonol.* 25 (2) (1998) 88–92.
- [19] M.J. McDonnell, S. Aliberti, P.C. Goeminne, et al., Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study, *Lancet Respir. Med.* 4 (12) (2016) 969–979.
- [20] A.F. Barker, L. Couch, S.B. Fiel, et al., Tobramycin solution for inhalation reduces sputum pseudomonas aeruginosa density in bronchiectasis, *Am. J. Respir. Crit. Care Med.* 162 (2 Pt 1) (2000) 481–485, <https://doi.org/10.1164/ajrccm.162.2.9910086> ([doi]).
- [21] M.E. Drobnic, P. Sune, J.B. Montoro, A. Ferrer, R. Orriols, Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with pseudomonas aeruginosa, *Ann. Pharmacother.* 39 (1) (2005) 39–44.
- [22] R. Orriols, J. Roig, J. Ferrer, et al., Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by pseudomonas aeruginosa, *Respir. Med.* 93 (7) (1999) 476–480.
- [23] J. Altenburg, C.S. de Graaff, Y. Stienstra, et al., Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial, *JAMA* 309 (12) (2013) 1251–1259.
- [24] D.F. Signorini, Sample size for Poisson regression, *Biometrika* 78 (2) (1991) 446–450.
- [25] A.L. Quittner, A.E. O'Donnell, M.A. Salathe, et al., Quality of life questionnaire-bronchiectasis: final psychometric analyses and determination of minimal important difference scores, *Thorax* 70 (1) (2015) 12–20, <https://doi.org/10.1136/thoraxjnl-2014-205918> ([doi]).
- [26] J. Altenburg Josje, Validation of a visual analogue score (LRTI-VAS) in non-CF bronchiectasis, *Clinical Respiratory Journal*, The. 10 (2) (2016-3) 168–175.
- [27] M.P. Murray, K. Turnbull, S. MacQuarrie, J.L. Pentland, A.T. Hill, Validation of the leicester cough questionnaire in non-cystic fibrosis bronchiectasis, *Eur. Respir. J.* 34 (1) (2009) 125–131, <https://doi.org/10.1183/09031936.00160508> ([doi]).
- [28] T. Aksamit Timothy, RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis, *Eur. Respir. J.* 51 (1) (2018-1).
- [29] A. De Soysa, T. Aksamit, T.J. Bandel, et al., RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis, *Eur. Respir. J.* 51 (1) (2018), <https://doi.org/10.1183/13993003.02052-2017>. Print 2018 Jan. doi: 1702052 [pii].
- [30] C.S. Haworth, D. Bilton, J.D. Chalmers, et al., Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials, *Lancet Respir. Med.* 7 (3) (2019) 213–226.
- [31] B.W.B.W. Ramsey, Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. cystic fibrosis inhaled tobramycin study group, *N. Engl. J. Med.* 340 (1) (1999-1-07) 23–30.
- [32] D. Maglio, C.H. Nightingale, D.P. Nicolau, Extended interval aminoglycoside dosing: from concept to clinic, *Int. J. Antimicrob. Agents* 19 (4) (2002) 341–348.
- [33] G.L. Drusano, Antimicrobial pharmacodynamics: Critical interactions of bug and drug, *Nat. Rev. Microbiol.* 2 (4) (2004) 289–300.
- [34] F. Scaglione, L. Paraboni, Influence of pharmacokinetics/pharmacodynamics of antibacterials in their dosing regimen selection, *Expert Rev. Anti-infect. Ther.* 4 (3) (2006) 479–490.
- [35] R.D.R.D. Bates, Pharmacokinetics and safety of tobramycin after once-daily administration in patients with cystic fibrosis, *Chest* 112 (5) (1997-11-05) 1208–1213.
- [36] R. Hatala, T.T. Dinh, D.J. Cook, Single daily dosing of aminoglycosides in immunocompromised adults: a systematic review, *Clin. Infect. Dis.* 24 (5) (1997) 810–815.
- [37] D.G. Contopoulos-Ioannidis, N.D. Giotis, D.V. Baliatsa, J.P. Ioannidis, Extended-interval aminoglycoside administration for children: a meta-analysis, *Pediatrics* 114 (1) (2004) e111–e118, <https://doi.org/10.1542/peds.114.1.e111> ([doi]).