Macrolide maintenance treatment for bronchiectasis
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CHAPTER 6
Changes of computed tomography features in patients with bronchiectasis following one year of azithromycin treatment.

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ABSTRACT

Background: Bronchiectasis (pathological dilatation of bronchi) is usually diagnosed by high resolution computed tomography (HRCT) and radiological severity has been found to correspond with clinical outcome. A beneficial effect of azithromycin maintenance treatment in patients with bronchiectasis and frequent exacerbations has lately been established in three randomized trials.

Aim: First, to evaluate longitudinal changes of radiological abnormalities in bronchiectasis; second, to explore whether azithromycin (AZM) maintenance treatment might revert some of these abnormalities.

Methods: The ‘BAT’ trial, a multicentre, randomized, placebo-controlled trial in the Netherlands (2008-2010) investigated the effect of 1 year of AZM treatment (250 mg OD) in bronchiectasis with frequent exacerbations. Chest HRCT-scans at baseline and after one year were scored by two radiologists according to a scoring system based on the Bhalla-system, but omitting three of the original item scores because of limited availability of two comparable imaging sets for each patient. CT scores were correlated to patient characteristics and longitudinal change was evaluated.

Results: Internal consistency for the 6 remaining items of the Bhalla score and interobserver agreement were sufficient (Cronbach’s α 0.71, ICC 0.89). Median baseline CT scores were 3.0 (IQR3.5) for AZM (n=31) and 2.0 (IQR2.25) for placebo (n=29; p=0.2), and decreased after one year of treatment to 2.5 (3.5) in the AZM group as compared to 2.0 (3.5) in placebo-treated patients (respectively, p=0.5 and 0.9). Higher baseline CT scores were found in pseudomonas-infected patients and in responders to treatment, with statistical significance in the former (p= 0.04) Moderate-good negative correlation was found between CT-score and lung function parameters at baseline (r=0.4–0.5).

Conclusion: CT severity in bronchiectasis reflects lung function impairment and Pseudomonas status but the beneficial effect of long-term azithromycin treatment on exacerbation frequency, lung function and quality of life in this randomized trial was not convincingly mirrored by radiological improvements.

Introduction

Non-cystic fibrosis bronchiectasis (hereafter referred to as ‘bronchiectasis’) is a chronic respiratory condition featuring dilated bronchi and known to cause chronic productive cough, fatigue and recurrent respiratory tract infections in affected patients. Key to development of the disease is a vicious circle of impaired ciliary clearance, chronic, predominantly neutrophilic inflammation and bacterial colonization, which results in irreversible, pathologic dilatation of the small and medium-sized bronchi. High resolution CT scanning is the method of choice in diagnosing bronchiectasis and radiological disease severity was disclosed as an independent predictor of both morbidity and mortality in these patients. Not surprisingly, two recently proposed scoring systems for disease severity in bronchiectasis have included CT-scores as one of their main variables.

The extent and type of radiological abnormalities in bronchiectasis has been found to correspond to FEV1 and other parameters of disease in some studies on the subject, but this relationship is disputed by other authors. In addition, bronchiectasis and its accompanying radiological features are traditionally considered irreversible. However, in 2012 Goeminne et al found a small but significant improvement of CT features when retrospectively investigating patients who received long-term macrolide therapy. The clinical benefits of long-term macrolide treatment as found in three recently performed trials, led to widespread use of this treatment modality for patients with bronchiectasis and frequent exacerbations. To date however, no prospective data was available on the effect of long term macrolide treatment on CT features of bronchiectasis and which CT features are predictive of a favourable effect of long term macrolide treatment.

The current study uses data from a recently performed randomized interventional trial to investigate the correlation between radiological disease severity and clinical outcome measures during one year of macrolide or placebo treatment.

We hypothesize that the severity of bronchiectasis as measured by a validated CT scoring system will correspond to exacerbation frequency and lung function, among other parameters of disease. In addition, we expect long term macrolide treatment to cause improvement of CT features of bronchiectasis, in particular of those indicative of active inflammation (e.g., airway thickness, mucus plugging).

Materials and methods

The “BAT” trial, a multicentre, randomized, placebo-controlled trial was conducted at 14 sites in the Netherlands from 2008-2010 (Clinicaltrials.gov, registration no: NCT00415350).
Detailed study protocols are provided elsewhere. Participants were eligible for randomization if they had non-CF bronchiectasis and three or more lower respiratory tract infections treated with antibiotics in the preceding year, with sputum cultures showing evidence of chronic airways infection.

All participants gave informed consent and ethical approval was provided by the Institutional review board of Alkmaar Medical Centre: ‘METC Noord Holland’ (Approval no: M07-002, CCMO: NL16025.094.07).

Patients were randomized to receive either azithromycin (250 mg daily) or placebo for 12 months, during which the number of infectious exacerbations (the primary endpoint), lung function parameters, sputum bacteriology, inflammatory markers, adverse effects, symptom scores and quality of life (QoL) were recorded.

At baseline – with all study participants having stable disease, without recent or current exacerbation, and after one year of study treatment, HRCT scans were obtained with the radiological equipment available at the study sites at the time of study enrolment and according to the local CT-protocols. All HRCT’s were independently scored by two radiologists (radiology consultants with 15 (RW) and 10 (SG) years of experience in chest radiology, respectively, according to the scoring system Bhalla et al. The original, validated scoring system contains 9 items, representing key radiological features of bronchiectasis, which are independently scored to add up to a maximum total score of 25 (figure 1).

However, differences in scanning techniques and protocols between study sites caused the image quality to vary. Only a small minority of patients had 2 consecutive CT scans of sufficient quality to allow for proper use of the Bhalla CT scoring system. In many cases, slice thickness and intervals were too large to allow proper evaluation of lung tissue according to the segmental anatomy. This was particularly bothersome in items which required assessment of the exact number of segments/bronchial generations (Bhalla items no. 3, 4 and 6). We therefore decided to apply a modification to the Bhalla scoring system, omitting these 3 items (figure 1). The two observers were blinded to clinical severity of disease, spirometric findings and quality of life scores of all patients. The mean of the two readers was used for the total Bhalla score and also for score of the individual items.

All patients were familiar with routine spirometry measurements and these were performed according to European Respiratory Society standard criteria. Total lung capacity (TLC) and its subdivisions were assessed with body plethysmography (Master Screen Body, Care Fusion, San Diego, California, USA). Carbon monoxide transfer factor (TLCO) was determined by the single breath-hold method (Master Screen Diff, Care Fusion, San Diego, California, USA). Reference values for spirometry, static lung volumes and TLCO are from the European Coal and Steel Community.

Laboratory tests included measurement of serum C-reactive protein (CRP) and white blood cell count (WBC) and sputum samples were collected at each visit and sent for culture and susceptibility testing at Alkmaar Medical Centre.

Symptoms were measured using analogue scales (VAS) for dyspnoea, cough, fatigue, pain and sputum purulence. Each symptom was scored from 1 to 10 on the lower respiratory tract infections-visual analogue scale (LRTI-VAS), higher scores indicating more severe symptoms and domain- and total scores were provided.

Saint George’s Respiratory Questionnaire (SGRQ) was used to measure health related QoL (HRQoL). Its 76 items are partitioned into three sections (Symptoms, Activity, Impact), yielding domain- and total scores, ranging from 0 to 100%, zero indicating no impairment of quality of life. A difference of 4 points or more is considered clinically significant.

An infectious exacerbation was defined as an increase in respiratory symptoms, requiring antibiotic treatment. Exacerbation frequency was reported on diary cards by the participants, documented by the treating physicians and double-checked through chart review by the principal researcher.

Statistics

Nominal and ordinal variables were expressed using median and interquartile range (IQR). In those cases that IQR=0, the range from lowest to highest value was used, instead of the 25–75% range. Interval/ratio variables were expressed in terms of mean, SD and confidence intervals.

Pearson’s correlation coefficient and the ICC (intra-class correlation coefficient) were used to calculate consistency between both observers. The final CT total- and item scores as used in the analysis was the mean score of both observers. Internal consistency of the Bhalla CT-score was measured by applying Cronbach’s alpha to each of the component scores at entry; accepting >0.7 as sufficient.

Between group differences were calculated with a student’s t-test in case of normally distributed variables and with Mann-Whitney U or Wilcoxon signed ranks test in case of a skewed distribution. Continuous variables were checked for normality by means of Kolmogorov-Smirnov test of equality.
Spearman’s correlation was used to examine the association between average CT scores and other parameters of disease severity (number of exacerbations, quality of life (QoL), symptom score, lung function (FEV1, FVC, TLCO, TLC, RV)).

When comparing two variables, P values of < 0.05 were considered statistically significant. The software package SPSS 20 for Windows (SPSS Inc. Chicago, IL, USA) was available for statistical analysis.

**Results**

After omitting three items of the original Bhalla CT-score, the 6 remaining items showed sufficient internal consistency (Cronbach’s Alpha 0.71).

The intraclass correlation coefficient between scoring results of the two observers was 0.89, and Pearson’s correlation coefficient 0.79, indicating good correlation and allowing us to take the average score of both observations. Only CT-scans that were scored by both observers were included in the analysis.

Although all 83 patients had CT-scans performed at baseline and at end of study treatment, due to logistical difficulties both observers were not able to score all CT’s for all patients. Observer SG had 2/83 (2.4%) missing scores at baseline and 8/83 (9.6%) at end of treatment. Observer RW had 16/83 (19.0%) of scores missing for both baseline and end of treatment. As such, total CT scores and item scores were available for 31/43 (72%) of azithromycin-treated and 29/40 (72%) of placebo-treated patients at baseline. At end of treatment CT scores were available for 36/43 (84%) azithromycin-treated patient and 30/40 (75%) patients in the placebo group.

Median total CT score at baseline for the whole group (n=60) was 2.25 (IQR 3.0). The scores on separate items of the CT score and other disease parameters for both the azithromycin and placebo group are depicted in table 1.

<table>
<thead>
<tr>
<th>Table 1. Baseline patient characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>BMI</td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>Current</td>
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<tr>
<td>Former</td>
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<tr>
<td>No. of exacerbations in year before study entry (median, IQR)</td>
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<tr>
<td>FEV1 (percentage predicted)</td>
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<tr>
<td>FVC (percentage predicted)</td>
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<tr>
<td>TLCO (percentage predicted)</td>
</tr>
<tr>
<td>TLC (percentage predicted)</td>
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<tr>
<td>RV (percentage predicted)</td>
</tr>
<tr>
<td>CRP mg/dL mg/L</td>
</tr>
<tr>
<td>WBC x10^9/L</td>
</tr>
<tr>
<td>CT total score* (median, IQR)</td>
</tr>
<tr>
<td>- Severity of bronchiectasis (median, IQR)</td>
</tr>
<tr>
<td>- Peribronchial thickening (median, IQR)</td>
</tr>
<tr>
<td>- Sacculation or abscesses (median, range)</td>
</tr>
<tr>
<td>- Bullae (median, range)</td>
</tr>
<tr>
<td>- Emphysema (median, IQR)</td>
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<tr>
<td>- Consolidation (median, IQR)</td>
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<tr>
<td>SGRQ total score</td>
</tr>
<tr>
<td>LRTI-VAS total score</td>
</tr>
<tr>
<td>Baseline sputum microbiology</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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</tbody>
</table>

All values are expressed as mean (SD) unless stated otherwise. *Mean score of two observers according to a modified Bhalla CT scoring system. (SD).

Abbreviations: CRP, C-reactive protein; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; IQR, interquartile range; LRTI-VAS, lower respiratory tract infection–visual analogue score; SGRQ, St George’s Respiratory Questionnaire; WBC, white blood cell. SI conversion factor: To convert CRP levels to nmol/L, multiply by 9.524.
**Relation between CT-scores and other parameters of disease severity.**

At baseline, the modified Bhalla total score correlated well with lung function parameters (FEV\(_1\) = -0.4, FVC = -0.4 and TLCO = -0.4). Poor correlation was found between CT scores and exacerbation frequency, BMI, CRP, WBC, RV, TLC, reversibility of FEV1 and SGRQ and VAS total scores.

When discerning patients with respect to pseudomonas status at baseline, pseudomonas-infected patients (n=10, 17%) had a median total CT score of 4.25 (IQR 5.63) as compared to 2.0 (2.5) in non-pseudomonas patients (n=50, 83%), (p=0.3). Pseudomonas-infected patients scored significantly higher on the 'consolidation' item score (0.75 (1.0) versus 0.0 (0.5), p=0.04) and the 'peribronchial thickening' item score [1.0 (1.5) versus 0.0 (1.0) p=0.04] in non-pseudomonas-infected patients.

**Change of CT-scores during treatment**

CT total scores and item scores at baseline and after one year of study treatment are shown in table 2.

**CT scores in responders and non-responders to azithromycin treatment**

In the BAT trial protocol, response to treatment was defined as reduction of one exacerbation or more during study treatment as compared to the number of exacerbations in the year before study inclusion. In the current study we explored radiological severity in responders and non-responders. Since no fixed definition of 'treatment response' exists for the evaluation of azithromycin maintenance treatment, we also looked at between-group differences when using a stricter definition of response, that is, a reduction of two or three exacerbations during treatment.

When using the less strict definition of a reduction of at least one or two exacerbations during treatment, only 2 participants qualified as non-responders. When treatment response was defined as a reduction of at least three exacerbations, 7 non-responders were identified.

At baseline, CT total scores for responders were consistently higher than for non-responders and this was true for both response definitions, but the difference between both groups did not reach statistical significance (p=0.12 and 0.25 respectively) (figure 2a+b). The between group difference could mainly be explained by differences in the 'severity' and 'peribronchial thickening' item scores which were 1.5 (2.5) and 0.5 (2.5) in responders and 1.0 (0.0) and 0.0 (0.0) in non-responders (median IQR p=0.47 and 0.13 respectively) for patients with a reduction of one or two exacerbations.

**Discussion**

This is the first study in patients with bronchiectasis to prospectively evaluate changes in CT features during azithromycin maintenance therapy. Our main finding was that although the CT score did not change significantly, a trend towards an improvement (=reduction) of CT scores was noted in the azithromycin group, as compared to stability in the placebo group. Radiological disease severity corresponded very well with dynamic lung function parameters and CO-diffusion capacity and proved to be a tool for discerning pseudomonas-infected patients, who had higher scores for 'consolidation' and 'peribronchial thickening'.

In addition, responders to azithromycin treatment could be discriminated, based on their baseline CT scores which were higher as compared to those that did not respond favourably.

**Table 2. CT scores and item scores (average score of two observers) for baseline and at one year for azithromycin- and placebo treated patients.**

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin group (n=31)</th>
<th>Placebo group (n=29)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End of treatment</td>
</tr>
<tr>
<td>CT total score</td>
<td>3.0 (3.5)</td>
<td>2.5 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Delta baseline</td>
<td>Delta end-baseline</td>
</tr>
<tr>
<td></td>
<td>-0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Severity of bronchiectasis</td>
<td>1.5 (0.9)</td>
<td>1.25 (1.0)</td>
</tr>
<tr>
<td>Peribronchial thickening</td>
<td>0.5 (1.0)</td>
<td>0.5 (1.0)</td>
</tr>
<tr>
<td>Sacculation or abscesses (median, range)</td>
<td>0.0 (0.9)</td>
<td>0.0 (0.0-2.0)</td>
</tr>
<tr>
<td>Bullae (median, range)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0-1.5)</td>
</tr>
<tr>
<td>Emphysema</td>
<td>0.0 (1.0)</td>
<td>0.0 (1.0)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>0.25 (0.5)</td>
<td>0.0 (1.0)</td>
</tr>
</tbody>
</table>

* Wilcoxon signed ranks test. All values are expressed using median (IQR) unless stated otherwise.
The favourable effect of azithromycin maintenance treatment in bronchiectasis has been demonstrated in two randomised trials 8,9, showing a significant reduction of exacerbations (number needed to treat = 3). Other beneficial effects included preserved lung function and better quality of life in patients on azithromycin treatment.

The anti-inflammatory effect of azithromycin is in part attributable to its anti-neutrophilic mode of action as depicted by lower levels of neutrophil chemo-attractants (e.g. IL-8, TNF-alpha) and markedly decreased airway neutrophilia after macrolide treatment. Besides, other anti-inflammatory effects of azithromycin are proposed; from a direct anti-bacterial effect through inhibition of bacterial protein synthesis in Gram-positive pathogens to other anti-inflammatory effects of azithromycin. Besides, the anti-inflammatory effect of azithromycin is in part attributable to its anti-neutrophilic activity. The latter trial demonstrated significant changes in bronchiectasis, mucous plugging, peribronchial thickening and total Brody score, a CT scoring system used in CF.

In our exploratory analyses we made the observation that participants who showed a reduction of exacerbations during treatment had higher baseline CT total scores as compared to non-responders. The difference between both groups was mainly accounted for by higher scores on ‘peribronchial thickening’ and ‘severity’ item scores in the responders. These findings have to be interpreted with care since, even with the somewhat ‘liberal’ definition of response, only a small number of non-responders could be identified which importantly limited the reliability of our statistical analyses.

In the current study, CT total scores showed good correlation to dynamic lung function parameters and the gas transfer factor. A good (negative) correlation between FEV1 and CT scores has been demonstrated earlier; this finding can be interpreted as air flow limitation caused by thickening of the bronchial mucosa and an increase in bronchial secretions 5,6,22. Correlation between TLCO and CT score was only investigated in one other study, which also found a negative correlation between the two parameters. 23 Small airways disease, often present in bronchiectasis, might account for the reduced CO-diffusion capacity in patients with high radiological severity scores.

Interesting, although not completely surprising, findings in the current study were the higher CT scores in patients colonized with \( P. \) aeruginosa as compared to those without, indicating more severe disease in the former group. Despite the fact that total CT scores showed no more than a trend towards more severe disease in patients infected with \( P. \) aeruginosa, the item score for consolidation and peribronchial thickness in this group was significantly higher. \( Pseudomonas \) presence is traditionally linked to faster lung function decline and worse prognosis in both CF and non-CF bronchiectasis.

There are certain limitations to a wider applicability of the findings in this study. In this analysis we focused on those items in the Bhalla score for which we had two comparable imaging sets. By limiting our analysis to the sub-set of items of the Bhalla score, we did not use the validated scoring system as such. However, because internal consistency of the score was still sufficient after omission of the three items and because we found a good interobserver agreement between the results on the remaining 6 items, we still felt confident using this shortened version of the Bhalla score. The study is further limited by the fact that almost one quarter of participating patients did not have their CT’s scored, which might influence the results, although missing scans were evenly distributed between azithromycin- and placebo treated patients.

These limitations imply that the findings of the current study must be interpreted with care and that further research is necessary to confirm these results.

Despite these limitations, this study is the first prospective attempt to evaluate longitudinal...
CT changes during azithromycin treatment in non-CF bronchiectasis and generates interesting material for further contemplation. In the current study, one year of treatment with azithromycin did not result in a statistically significant improvement of CT features. An interesting finding which needs further study, is the radiological finding of more severe disease in patients who were responsive to azithromycin treatment. If this finding is replicated in larger series with the same CT settings, CT scores, which include items indicative for bronchial inflammation might be useful tools to select patients with a potency to a favourable response to macrolide treatment.

Reference list


