Macrolide maintenance treatment for bronchiectasis
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CHAPTER 1
Introduction and outline of the thesis
Already in the early 19th century physicians have been fascinated by the main object of this thesis; bronchiectasis. Dr René de Laennec (1781-1826), a French doctor, pathologist and inventor of the stethoscope wrote down his post mortem observations of this disease in a very lively and illustrative way, able to captivate even 21st century readers:

“the organic lesion which I am now about to notice seems to have been hitherto entirely overlooked (...). It can only be detected by tracing the individual bronchial tubes to their ultimate ramification, a thing which is rarely done in our examination of the lungs”.

“ramifications which in their natural state would scarcely admit a fine probe, acquire a diameter equal to that of a crow-quill, or goose-quill or even of the finger”

A pathology specimen of a lung segment of a child with severe varicose bronchiectasis (courtesy of J. Haas, Clinical Professor of pathology, University of Washington School of Medicine).

mistakenly attributed to smoking habits or labelled as ‘chronic bronchitis’. In addition, affected patients are often reluctant to seek medical advice for their condition, which may be cause for embarrassment when being out in public. Because bronchiectasis is not usually life threatening, many patients probably go undetected.

Doctors frequently believe bronchiectasis to be a near-extinct or ‘orphan’ disease, due to the evident decline in incidence since antibiotic treatment for tuberculosis and pneumonia – in earlier days the primary causes of bronchiectasis- became widely available. In addition, researchers are frustrated by the vast array of underlying conditions and causes.

In the last two decades, there has been a renewed interest in bronchiectasis, for various different reasons. First, the detection of bronchiectasis was importantly facilitated by the ubiquitous availability of CT scanning. Bronchography, bronchial examination via X-ray following the coating of the inside of the bronchial tree with a radiopaque substance, has been the method of choice for diagnosing bronchiectasis for a long period of time. This rather patient-unfriendly and time consuming procedure, is now considered obsolete. Due to the increase in the number of chest-CT scans, which were obtained for various reasons, one came to realise that the true incidence of bronchiectasis was much higher than expected, particularly in the rapidly expanding elderly population.

Further, developments in cystic fibrosis (CF) research, inspired scientists to look again at “non-CF” bronchiectasis as a field of interest. At first, trials in bronchiectasis were mainly small, non-randomized and involved medication that was first tested in CF. But in the last ten years, larger and better designed trials were executed in bronchiectasis, and the last ten
Chapter 1

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Bronchography of both sides with deformed, ectatic bronchi of the lingula (chestradiology.net).

years, larger and better designed trials were executed in bronchiectasis, and the research pipeline contains a growing number of trials with agents specifically developed for bronchiectasis treatment.

The research described in this thesis focuses on macrolide treatment in bronchiectasis by combining clinical, pharmacological and immunological data. Our aim is to add to the understanding of the mechanism of action of long term azithromycin treatment and to take a step forward in defining patients who are expected to benefit from this treatment modality, while at the same time trying to balance advantages and disadvantages.

Chapter 2 reviews the available literature on epidemiology, clinical presentation, diagnostic work up and evidence-based treatment options in bronchiectasis. Bronchiectasis is depicted as the result of a final common pathway of bacterial colonization, infection and an exaggerated inflammatory response, which may be present in a variety of disorders, mainly infection (pneumonia, tuberculosis) and immunodeficiency. In order to facilitate the finding of the underlying cause, a protocol-driven workup is proposed. We also propose a protocol-driven stepwise treatment schedule.

An overview of the available evidence on macrolide maintenance treatment in chronic inflammatory respiratory tract disorders and its mode of action is presented in Chapters 3 and 4.

The clinical efficacy and safety of long term azithromycin treatment in bronchiectasis was studied in the BAT trial, a multi-center, randomised clinical trial, described in Chapter 5.

The effect of long term macrolide treatment on radiological abnormalities and the correlation between CT findings and clinical parameters in bronchiectasis are addressed in Chapter 6.

The relationship between azithromycin sputum and serum levels and its clinical efficacy during long-term treatment in bronchiectasis is explored in Chapter 7. We correlate sputum concentrations of azithromycin with respiratory symptoms and inflammatory markers.

Chapter 8 reports on the validation of a newly developed tool for convenient symptom measurement in bronchiectasis patients. Validity, responsiveness and reliability of the 'Lower respiratory tract infections – visual analogue scale' (LRTI-VAS) are assessed.