CHRONIC INFLAMMATORY LUNG DISEASE IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)-INFECTED CHILDREN. EPIDEMIOLOGICAL CONSIDERATIONS, AETIOLOGICAL DETERMINANTS AND THE EFFICACY OF LOW DOSE ERYTHROMYCIN IN BRONCHIECTASIS

R MASEKELA

MBBCh (Wits), MMed (Paeds) Pretoria, Cert Pulm (SA) Paeds, Dip Allerg (SA), FCCP

THESIS SUBMITTED IN THE FULFILMENT OF THE DEGREE OF PHILOSOPHIAE DOCTOR (PAEDIATRICS)

DEPARTMENT OF PAEDIATRICS

FACULTY OF MEDICINE

UNIVERSITY OF PRETORIA

PROMOTER: PROF RJ GREEN PRETORIA 2012

THE FOLLOWING ARTICLES BASED ON THE RESULTS OBTAINED IN SOME STUDIES REPORTED HEREIN; HAVE BEEN PUBLISHED IN SCIENTIFIC JOURNALS:

PEER REVIEWED JOURNALS

1. Masekela R, Moodley T, Mahlaba N, Becker P, Kitchin OP, Green RJ. Atopy in HIV-infected children in Pretoria, South Africa. *S Afr Med J* 2009;9:822-825.
2. Masekela R, Anderson R, Moodley T, Kitchin OP, Risenga SM, Green RJ. Human immunodeficiency virus-related bronchiectasis in children-an emerging spectre in high TB burden areas. *Int J Tuberc Lung Dis*. 2012;16:114-119.
3. Masekela R, Gongxeka H, Green RJ, Sathekge M. Positron emission tomography in the prediction of inflammation in children with human immunodeficiency virus-related bronchiectasis. *Hell J Nucl Med* 2012;15:23-27.
4. Masekela R, Green RJ. The role of macrolides in childhood non-cystic fibrosis related bronchiectasis. *Mediators Inflamm* 2012;ID134605:1-7.
5. Green RJ, Becker PJ, Labuschagne D, Kitchin OP, Masekela R. Disease progression unrelated to passive environmental tobacco smoke exposure in HIV-infected children. *Int J Collaborative Res Int Med Public Health* 2012;4:130-135.
6. Masekela R, Anderson R, Steel HC, Gongxeka H, Becker P, Green RJ. Lack of effect of erythromycin in children with human immunodeficiency virus-related bronchiectasis: A randomised, double-blind, placebo-controlled trial. *S Afr Med J;* submitted.

NON-PEER REVIEWEDJOURNALS

1. Masekela R. Prophylactic treatment in HIV infected children. *S Afr Paediatr Rev* 2007;3:15-19
2. Masekela R. Human immunodeficiency virus related bronchiectasis- not all abnormal x-rays are TB. *S Afr Respir J* 2010;16:17-20

ABSTRACT CONGRESS PRESENTATION

1. Masekela R, Moodley T, Mahlaba N, Wittenberg DF, Kitchin O, Becker P, Green RJ. Atopy in HIV-infected and non-infected children in Pretoria, South Africa. The Sky's The Limit Congress, 29 May-1 June 2008, Sun City, South Africa.(Oral presentation)
2. Masekela R, Labuschagne D, Moodley T, Kitchin OP, Green RJ. HIV staging and severity of AIDS in children in children exposed to environmental tobacco smoke. Chest 2008;134:139002S. (Poster presentation)
3. Masekela R, Moodley T, Kitchin OP, Risenga SM, Becker P, Green RJ. Bronchiectasis in children with human immunodeficiency virus infection. American Thoracic Society Congress, May 2010 New Orleans, USA. (Oral poster presentation) - Awarded the American Thoracic Society International Trainee Travel Award MECOR Graduate Travel Award: "Best of 2010" Achievement Award.

4. Masekela R, Gongxeka H, Green RJ, Sathekge M. ^{18}FDG-PET CT suggests that inflammation in HIV-related bronchiectasis is inconsistent and difficult to predict with current diagnostic modalities. International Congress of Paediatric Pulmonology 25-27 June 2011, Versailles, France. (Poster presentation)

In this research, the statistical planning and analyses, and recommendations arising from these analyses, have been done in consultation with Prof PJ Becker of the Institute of Biostatistics of the Medical Research Council of South Africa, as well as Prof P Rheeder of the Clinical Epidemiology Unit of the University of Pretoria.

DECLARATION

This thesis is the candidate's own original work, performed in the Department of Paediatrics and Child Health, University of Pretoria.

R. MASEKELA

ABSTRACT

Human immunodeficiency virus (HIV) infection has reached epidemic proportions in South Africa. The availability of highly active anti-retroviral therapy (HAART) prolongs life in HIV-infected persons, who may subsequently present with chronic manifestations of HIV-infection. The respiratory morbidity attendant to HIV-infection, even in the presence of HAART is high, the aftermath of which is lung tissue destruction and bronchiectasis. As a consequence of the political decision not to offer HAART to HIV-infected children, a number of children in South Africa have been left with severe consequences of uncontrolled HIV-infection. Bronchiectasis is one of those and because children with this devastating condition were numerous in the Pretoria region, the author and her colleagues began a Chronic Lung Disease Clinic in that region. This prompted the idea of investigating both the epidemiological profiles of these children and an attempt to intervene with both standard bronchiectasis guideline care and the use of a form of therapy commonly employed in other forms of bronchiectasis. This thesis explores those ideas.

Important new and novel findings that were consequent were; that bronchiectasis is diagnosed late in HIV-infected children at a mean age of 6.9 years. The predominant organisms cultured from the airways are *Haemophilus influenzae* and *parainfluenzae* in 49% of samples. *Pseudomonas aeruginosa* (PA), common in cystic fibrosis (CF)-bronchiectasis is an uncommon pathogen in HIV-related bronchiectasis; isolated in only 2% of specimens. Tuberculosis (TB), at least as reported, is a significant antecedent of bronchiectasis, reported in 48.5%of children. A further 21.2% of the patients had received more than two courses of anti-TB treatment. However, proof of TB infection has been lacking. Respiratory morbidity is significant with the mean forced expiratory flow in one second (FEV_1) of 53%, in this cohort at the time of presentation. Thirty-six percent of all children were exposed to environmental tobacco smoke, although this was not correlated with disease severity or HIV-disease progression. There is elevation of immunoglobulins in HIV-related bronchiectasis, with a mean IgE of 79 kU/l. This was not, though, associated with HIV disease progression as previously described in adult studies, nor with the presence of allergic bronchopulmonary aspergillosis (ABPA). The elevation in IgE

was also not associated with an elevation of T helper-2 mediated cytokines, confirming the lack of association with atopy.

The predominant cytokine, identified is interleukin (IL)-8, both systemically and locally (in airway secretions). There was elevation of other T helper-1 driven cytokines, reflecting an ability to mediate adequate inflammatory responses, which was independent of the level of immunosuppression. With the presence of HAART, there was a decline in the pro-inflammatory cytokines over time, which may be attributed to the ongoing effect of HAART that ties in to, or goes beyond the restoration of T cell numbers.

Soluble triggering receptor expressed on myeloid cells (sTREM), an innate immune marker, is elevated in children with HIV-related bronchiectasis when compared to a control group of children with cystic fibrosis-related bronchiectasis. sTREM is not associated with the presence of exacerbations and the level of immunosuppression. The use of an anti-inflammatory drug erythromycin also did not impact the sTREM values. There was also no relationship between sTREM and pro and anti-inflammatory cytokines and chemokines.

Fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) could not reliably predict the presence of pulmonary exacerbations. Its diagnostic value was limited to identifying disease activity in acute pneumonia. ^{18}F-FDG PET also had no significant correlation with CRP, inflammatory cytokines or markers of HIV disease activity.

In a randomised controlled trial of erythromycin, a cost-effective immunomodulatory drug, compared to placebo, erythromycin was ineffective in reducing the number of pulmonary exacerbations. Erythromycin also failed to demonstrate any effect on systemic and local pro- and anti-inflammatory cytokines/chemokines. With access to anti-retroviral therapy, airway clearance, nutritional rehabilitation and vigilant follow

up there was an improvement in pulmonary function parameters and stability of the degree of bronchiectasis that we propose is probably in keeping with an organ system disease modifying effect that may be, an as yet, undefined and undescribed byproduct of HAART.

Keywords

Paediatrics

Microorganisms

Biomass fuels

Highly active antiretroviral therapy

Atopy

Positron emission tomography

Macrolides

Cytokines

Chemokines

Soluble triggering receptor expressed on myeloid cells.

ACKNOWLEDGEMENTS

I wish to thank my supervisor Professor RJ Green for the encouragement, helpful criticism, unfailing support and advice throughout this project. This thesis would not have been possible without him.

These studies would not have been possible without the support of the following individuals who have all have contributed significantly to this work. Their dedication and hard work over the last four years is acknowledged.

Professor DF Wittenberg, Department of Paediatrics, University of Pretoria

Professor R Anderson, Department of Immunology, University of Pretoria

Professor M Sathekge, Department of Nuclear Medicine, University of Pretoria

Professor K de Boeck, Department of Paediatrics, University Hospital Leuven, Belgium

Dr H Gongxeka, Department of Radiology, University of Pretoria

Prof PJ Becker, Biostatistics Unit, Medical Research Council of South Africa

Dr H Fickl, Department of Immunology, University of Pretoria

Dr OP Kitchin, Department of Paediatrics, University of Pretoria,

Dr T Moodley, Department of Paediatrics, University of Pretoria

Dr SM Risenga, Department of Paediatrics, University of Pretoria

Mr R Sewnarain, Department of Immunology, University of Pretoria

Dr HC Steel, Department of Immunology, University of Pretoria

Mrs M Vreys, Department of Paediatrics, University Hospital Leuven, Belgium

Prof P Rheeder, Clinical Epidemiology Unit, University of Pretoria

Sr N Paulse, Pulmonology Outpatient Department, Steve Biko Academic Hospital

Mrs B Mnisi, Pulmonology Outpatient Department, Steve Biko Academic Hospital

DEDICATION

I would like to dedicate this thesis to my mother Dikeledi, who has been a constant source of support and has given me the faith that everything is possible if you work hard enough for it. Next I would like to thank my father David for the legacy to think outside the box and to be the best.

I would also like to thank my sisters Kedibone, Dimakatso, Mmasamo and Mabatho for their unfailing support over the years.

CONTENTS **Page**

CHAPTER V

CHAPTER VI

CHAPTER VII

Soluble triggering receptor expressed on myeloid cells in sputum of children with HIV-related bronchiectasis.

CHAPTER VIII

Positron emission tomography in the prediction of inflammation in children with HIV-related bronchiectasis.

CHAPTER IX

CHAPTER X

CHAPTER XI

APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF BOXES