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Lack of Efficacy of an Immunomodulatory Macrolide in Childhood HIV-Related Bronchiectasis: A Randomised, Placebo-Controlled Trial

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Abstract

Background: The epidemic of human immunodeficiency virus (HIV)-1 infection has resulted in a large number of children suffering from respiratory morbidity in South Africa. One of the outcomes of recurrent chest infections and TB is HIV-related bronchiectasis.

Introduction: We conducted a randomised, double-blind, placebo-controlled trial to assess the efficacy of low dose erythromycin in reducing the number of pulmonary exacerbations.

Methods: We randomly assigned 31 HIV-infected children with radiologically confirmed bronchiectasis, to receive either erythromycin (17) or matching placebo (14) for a period of 52 weeks. The primary outcome was the number of exacerbations documented over the 52 weeks, in each study arm, after randomisation.

Results: There was no difference in the number of exacerbations in the participants receiving erythromycin versus those receiving placebo (2.14 ± 1.29 *vs.* 2.18 ± 1.59 per year; p=0.17). There was an improvement (although not statistically significant) in both FEV_1 % predicted and FVC % predicted (56.0% predicted ± 15.1 to 68.0% predicted ± 21.0 and 53.5% predicted ± 13.6 to 62.5% predicted ± 13.6; p=0.31) in the erythromycin and placebo arm, respectively. Erythromycin did not impact the levels of pro-inflammatory and anti-inflammatory cytokines (all p>0.05).

Conclusion: Administration of HAART and adjunctive care, which includes airway clearance and treatment of exacerbations, in children with HIV-related bronchiectasis is associated with improvement in pulmonary function tests and IL-8, with no additional benefit from the use of erythromycin.

Keywords: Cytokine; Erythromycin; Chemokine; Exacerbations; Lung function

Introduction

Bronchiectasis is pathological bronchial dilatation occurring as a result of recurrent chest infections or destructive lung disease. Non-cystic fibrosis (CF)-related bronchiectasis is an "orphan" lung disease on which little research has been focused, especially in developing countries, where available data is mostly on the epidemiological and clinical features [1,2]. In South Africa, the epidemic co-infections of human immunodeficiency virus (HIV)-1 infection and TB, have become important drivers of recurrent pulmonary infections and increasing rates of bronchiectasis [3-5].

The natural history of bronchiectasis is characterized by periods of quiescence interspersed with intermittent exacerbations. Exacerbations result in airway inflammation, the end product of which is progressive lung tissue destruction, pulmonary function decline and poor quality of life [6]. In order for the infection-related inflammatory process to be halted, there is a need to correct underlying pathology, as well as prompt implementation of effective anti-inflammatory therapy [7].

Medical interventions to treat HIV-related bronchiectasis should incorporate immune system restoration with highly active antiretroviral therapy (HAART). In addition there is a strong evidence base for the use of macrolides as immunomodulatory agents in CF bronchiectasis subjects colonized with *Pseudomonas aeruginosa (Pa)* [8]. There is currently emerging evidence of the beneficial effects of macrolides in CF and non-CF bronchiectasis subjects without *Pa* [9,10]. The immunomodulatory effects of macrolides are thought to result in reduction in sputum volume, inhibition of virulence factor production by bacteria, diminished production of interleukin (IL)-8 and neutrophil influx and neutrophil elastase into the lung [11-13]. This in turn effects a reduction in pulmonary exacerbations, improved pulmonary function and improved quality of life. This therefore makes macrolides a natural choice for investigation as a candidate therapeutic intervention in bronchiectasis.

This study evaluated the efficacy of erythromycin compared to placebo, in reducing the number of pulmonary exacerbations in children with HIV-related bronchiectasis over a period of 52 weeks. The secondary end-points were to assess whether erythromycin could impact pulmonary function parameters, pro-inflammatory and anti-inflammatory chemokines and cytokines.

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Materials and Methods

Setting and study population

This study was conducted as a randomised, double-blind, placebo-controlled trial of erythromycin at the Paediatric Chest Clinic, Steve Biko Academic Hospital, Pretoria. The baseline characteristics of some of the participants have been previously described, as they form part of a larger study of children with HIV-related bronchiectasis [4].

Inclusion criteria: Children aged 6 to 18 years with confirmed HIV infection. The presence of bronchiectasis was confirmed on high resolution CT scanning, with exclusion of other causes of bronchiectasis including a sweat test to rule out CF. All children had to be able to perform reliable pulmonary function tests.

Exclusion criteria: Children were excluded if there was presence of the following: abnormal liver function tests (ALT/AST > 2.5 times normal) and abnormal urea/creatinine. Other exclusion criteria included the use of: carbamazepine, warfarin, cyclosporin or long-term midazolam.

All the participants were randomised to receiving either erythromycin (Adco erythromycin estolate) at a dose of 125 mg per os daily if ≤15 kg body weight or 250 mg per os daily if >15 kg body weight or a matching placebo daily. This erythromycin dose was chosen as a quarter of the expected daily dose in line with previous studies [14]. Enrolment occurred from January 2009 to June 2011, with monthly follow up for one year.

Randomisation and blinding

Participants were randomly assigned (1:1) to the erythromycin group (55%) or placebo group (45%). All study personnel performing the clinical evaluations were blinded to treatment assignment, with usual care treatment of exacerbations. An exacerbation was per protocol defined; as the presence of at least two of the following: increased tachypnoea or dyspnoea, change in frequency of cough, increase in sputum productivity, fever, chest pain and new infiltrates on the chest X-ray. Compliance was assessed with the use of a medication diary and verbal interviews.

Clinical investigations

Clinical information collected included: the age at HIV diagnosis, timing of initiation of HAART and growth parameters (according to World Health Organization (WHO) weight z-scores, height z-scores and BMI z-scores) [15]. Lung functions included % predicted values for (forced expiratory volume in one second {FEV_1}, forced vital capacity {FVC} and forced expiratory flow {$FEF_{25/75}$}) measured using the Viasys SpiroPro Jaeger Spirometer (Hoechberg, Germany).

Laboratory investigations

The pre-treatment cytokine data for this group of participants was described in an earlier study [4]. In the current study, the pre- and post-treatment serum and sputum cytokine specimens were analysed simultaneously using a modified, improved version of the original assay using the Bio-Plex Suspension Array System (Bio-Rad Laboratories, Inc. Hercules, Canada) and a Bio-Plex Pro™ assay kit (Bio-Rad Laboratories, Inc). The assay kit used included: interleukins (IL)-1β, IL-6, IL-8, tumour necrosis factor alpha (TNF-α) and interferon gamma-induced protein-10 (IP-10).

Serum immunoglobulins: Circulating concentrations of immunoglobulin (Ig)-G) were assayed by nephelometry (Siemens Healthcare Diagnostics, BN Prospec Nephelometer, Newark, NJ, USA).

Blood samples: Were also collected for total white cell count, C reactive protein (CRP), $CD4^+$ T lymphocytes and HIV-1 viral load.

Sputum elastase: Concentrations of the sputum elastase were measured using a commercial, capture, sandwich ELISA procedure (Hycult Biotechnology, Uden, The Netherlands).

Sputum samples: Sputum samples were collected at monthly intervals for microbiological testing including *Mycobacterium tuberculosis* where indicated.

CT scanning: High resolution CT scanning was performed. Two blinded radiologist carried out the CT scan scoring without viewing any clinical data, morphological testing and special investigations. The Bhalla scoring system was utilised to score the CT scans [14].

Statistical analyses

The sample size calculation was based on the number of pulmonary exacerbations requiring antibiotic therapy estimated at 3 per year. A sample size of 20 patients per study arm was determined to have a 90% power to detect a clinically relevant reduction in exacerbations of 30%, where a mean of 2 and a standard deviation of 1 exacerbation were assumed; with a presumed dropout rate of 10%, when testing was one-sided at the 0.05 level of significance. Analysis of variance (ANOVA) was used to compare medication groups with respect the mean number of exacerbations, as there was no baseline value. For the study variables, treatment arms were compared with respect to change from baseline to end of study using ANCOVA, with baseline values as covariates. Wilcoxon test was used to assess the pooled data for IL-8, TNF-α and lung function tests. The Spearman correlation test was used to assess correlations between the cytokines and markers of HIV disease activity. Data analysis was performed using Stata Release 11 (Statacorp LP, College Station, TX, USA).

Ethical approval was granted by the Research Ethics Committee of the University of Pretoria.

Results

As demonstrated in figure 1, a total of fifty-six children were screened with forty-three meeting all inclusion criteria. One child died prior to randomisation and in one child parents declined to participate. Ten (23%) participants (four in placebo arm and six in erythromycin

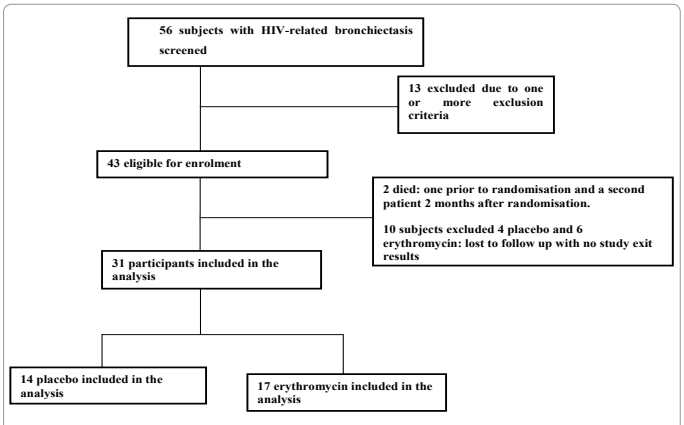

Figure 1: Enrolment and randomisation of participants included in the study.

arm) were lost to follow up during the 52-week follow up period. A total of thirty-one participants of whom 58% were male, were included in the final analysis. The baseline characteristics of the two treatment arms are reflected in table 1. The characteristics of the two study arms were generally balanced, with the exception of gender distribution with more males (55%) in the erythromycin arm and more females in the placebo arm.

All children were on HAART prior to enrolment. HIV virological suppression was achieved in 56% of participants with a geometric mean of (0.0 ± 22514.3 copies/ml and 80 ± 9635.2 copies/ml, p=0.97) in the erythromycin and placebo arms, respectively. The total $CD4^+$ T cell counts and percentage counts in the erythromycin arm were lower than in the placebo arm (650.9×10^9 ± 446.7 *vs.* 881.6×10^9 ± 505.8; p<0.01 and 16.3% ± 6.7 *vs.* 22.6% ± 11.9; p=0.01), respectively and this was statistically significant. The lower $CD4^+$ T cell counts were reflective of a shorter period on HAART when comparing the two study arms with the number of months on HAART being (12.0 months ± 12.8 *vs.*17.0 months ± 22.0), in the erythromycin arm when compared to the placebo arm, although this was not statistically significant.

There was no statistically significant difference in the mean number of exacerbations in the treatment versus the placebo arm (2.14 ± 2.28) *vs.* (2.18 ± 1.59) per year (p=0.17). However, 18% (erythromycin) *vs.* 0% (placebo) of study participants had no exacerbations during the study duration.

At study entry the growth parameters of children in both study arms were within the normal range. The compliance in both study arms was excellent, with more than 90% patients taking study medication.

There was no statistically significant change when comparing the Bhalla scores at baseline and study end in both treatment arms, indicating stability in the degree of bronchiectasis.

Of the microbiological cultures over the year only 2% of organisms cultured were *Pa* and 2% mycobacteria other than tuberculosis- *M. fortuitum* and *M. avium intracellulare,* with *one M.TB*.

For the characteristics of the participants at the end of the study period (summarised in table 2), there was an improvement in weight, which was more pronounced in the placebo versus the erythromycin arm, which was not statistically significant (p=0.45). There was a marginally significant improvement in the BMI z-scores when comparing the two study arms; more so in the placebo arm than the erythromycin arm (-0.6 ± 0.9 to -0.2 ± 1.0 *vs.* -0.5 ± 1.3 to -0.4 ± 1.6; p=0.08). The immunological status of the subjects improved in both study arms with increases in the $CD4^+$ T cell counts and decrease in the HIV viral load, although these differences were not statistically significant (p=0.88 and p=0.43), respectively.

For the pulmonary functions, there was an improvement (although not statistically significant) in FEV_1 % predicted (56.0 ± 15.1 to 68.0 ± 21.0, and 53.5 ± 13.6 to 62.5 ± 13.6; p=0.31) and FVC % predicted (49.0 ± 14.4 to 63.0 ± 17.9; 45.0 ± 14.3 to 58.0 ± 12.1, p=0.46); pre-and post therapy for the erythromycin and placebo groups, respectively. After pooling the data for the pulmonary functions, increases in both the FEV_1 % predicted and FVC % predicted, from baseline to end of study, were statistically significant (52.7 to 61.5; p=0.005 and 46.0 to 59.9; p<0.001), respectively. There was no change in the pooled data for $FEF_{25/75}$ % predicted at study entry compared to study end (53.4 ± 28.1 *vs.* 52. ± 25.2).

After intervention in both erythromycin and placebo study groups, there was a decrease in IgG. The change in IgG from baseline to study

Characteristic	Placebo (mean ± SD)	Erythromycin (mean ± SD)	P value
Gender (M:F)	5:9	13:4	
Age (years)	9.1 ± 2.1	8.4 ± 2.4	0.15
Exacerbations	2.1 ± 2.3	2.2 ± 1.6	0.47
Months on HAART	17.0 ± 22.0	12.0 ± 12.8	0.57
Weight z-score (kg)	-1.8 ± 0.9	-1.6 ± 1.6	0.77
Height z-score (cm)	-1.7 ± 1.4	-1.7 ± 1.5	0.50
BMI z-score (kg/m^2)	-0.6 ± 0.9	-0.5 ± 1.3	0.91
CD4 count (%)	22.6 ± 11.9	16.3 ± 6.7	0.01
CD4 (total$\times10^6$)	881.6 ± 505.8	650.9 ± 446.7	<0.01
HIV viral-load (copies/ml)*	80.0 ± 22514.3	0.0 ± 9635,2	0.97
FEV1 (% predicted)	53.5 ± 13.6	56.0 ± 15.1	0.54
FVC (% predicted)	45.0 ± 14.3	49.0 ± 14.4	0.94
$FEF_{25/75}$ (% predicted)	55.1 ± 25.3	56.0 ± 25.7	0.89
IgG (g/ml)	24.8 ± 15.4	26.2 ± 8.4	0.54
CRP (mg/l)	3.6 ± 16.1	9.4 ± 18.8	0.08
Bhalla score¶	11.5 ± 4.3	15.0 ± 4.0	0.02
Compliance (% medication)	91.0 ± 9.9	92 ± 9.9	0.87

SD: Standard deviation; BMI: Body mass index; HAART: Highly active antiretroviral therapy; CD4: Cluster differentiation cell; HIV: Human immunodeficiency virus; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IgG: Immunoglobulin G; CRP: C reactive protein; WCC: White cell count; ¶Bhalla score: Appendix D. *Geometric means reported.

Table 1: Baseline characteristics of children with HIV-related bronchiectasis treated with erythromycin or placebo.

end, was not attributed to the use of erythromycin (p=0.24). There was no correlation between IgG and FEV_1 at study entry and study end (p=0.75 and p=0.73) for the pooled data for the study population. CRP decreased from study entry when compared to the end of the study, although there was not statistically significant difference when comparing the treatment arms (p=0.98).

With respect to the pro-inflammatory cytokines, the chemokine IL-8 was most significantly elevated in the sputum, with a moderate non-statistically significant different decrease post-intervention in both the erythromycin and placebo arms (p=0.99) (Table 3). After pooling the data for sputum IL-8 for the whole study population, there was a statistically significant decrease of log values of sputum IL-8 from baseline to study end (geometric means 1234.5 to 434.5; p=0.04). Sputum IL-1β was elevated with a modest decline in the erythromycin arm and a moderate elevation in the placebo arm. The change of IL-1β from baseline to study end was not statistically significant in the treatment arms (p=0.99). Although TNF-α levels declined in both treatment arms, the decline could not be attributed to the use of erythromycin. The pre- and post treatment serum TNF-α levels were independent of $CD4^+$ T cell percentage counts (p=0.74 and p=0.62) and

Characteristic	Placebo (SD)		Erythromycin (SD)		P Value
	Entry	End	Entry	End	
Weight z -score (kg)	-1.8 ± 0.9	-0.9 ± 0.8	-1.6 ± 1.6	-1.7 ± 1.7	0.45
Height z-score (cm)	-1.7 ± 1.4	-1.6 ± 1.4	-1.7 ±1.5	-1.9 ± 1.4	0.97
BMI z-score (kg/m^2)	-0.6 ± 0.9	-0.2 ± 1.0	-0.5 ± 1.3	-0.4 ± 1.6	0.08
CD4 count (%)	22.6 ± 11.9	29.3 ± 11.4	16.3 ± 6.7	21.7± 7.8	0.88
CD4 (total×10^6)	881.6 ± 505.8	939.3 ± 530.6	650.9 ± 446.7	1036.7 ± 461.8	0.47
HIV viral load (copies/ml)	80.0 ± 22514.3	0.0 ± 26685.9	0.0 ± 9635.2	0.0 ±19231.2	0.34
FEV_1 (% predicted)	53.5 ± 13.6	62.5 ± 13.6	56.0 ± 15.1	68.0 ± 21.0	0.31
FVC (% predicted)	45.0 ± 14.3	58.0 ± 12.1	49.0 ±14.4	63.0 ±17.9	0.46
IgG (g/ml)	24.8 ± 15.4	22.7 ± 6.9	26.2 ± 8.4	19.0 ± 5.4	0.24
CRP (mg/l)	3.6 ± 16.1	2.4 ± 21.0	9.4 ± 18.8	4.0 ± 73.9	0.98
Bhalla score	11.5 ± 4.3	12.5 ± 4.1	15.0 ± 4.0	15.0 ± 3.3	0.62

Z-scores according to WHO growth charts [2,19]; CD4: cluster differentiation 4 cells; HIV: Human immunodeficiency virus; FEV_1: Forced expiratory flow in 1 second; FVC: Forced vital capacity; IgG: Immunoglobulin G; CRP: C-reactive protein.

Table 2: Characteristics of children with human immunodeficiency virus related bronchiectasis pre- and post- treatment with erythromycin and placebo.

Cytokine	Erythromycin N (95% CI)		Placebo N (95% CI)		P value
	Entry	End	Entry	End	
Serum					
IL-1β	3.3 (1.1-9.7)	4.0 (2.3-7.0)	4.1 (2.1-8.0)	5.3 (2.1-13.3)	0.31
IL-6	6.9 (3.0-15.9)	6.1 (3.0-12.5)	18.4 (4.9-69.2)	14.9 (4.6-47.8)	0.31
IL-8	18.9 (9.0-39.6)	18.1 (7.4-44.2)	24.2 (7.0-83.7)	39.4 (12.9-119.8)	0.26
IL-10	3.9 (3.0-5.2)	3.9 (2.5-6.1)	4.8 (3.3-6.9)	4.3 (3.0-6.0)	0.51
IP-10	4667.9 (2620.9-8613.5)	3636.9 (2420.0-5465.8)	2734.6 (2341.7-5956.0)	3235.4 (2311.7-4528.3)	0.24
TNF-α*	101.9 (-70.3-274.1)	78.2 (-63.5-219.8)	55.0 (-27.2-137.2)	51.7 (3.8-99.7)	0.74
TNF-R1	111.8 (94.7-132.0)	106.9 (92.5-123.6)	119.5 (103.8-137.5)	115.4 (100.8-132.1)	0.95
Sputum					
IL-1β	544.8 (198.0-1499.1)	575.3 (177.1-1869.1)	870.3 (366.8-2064.9)	823.2 (434.5-1559.6)	0.99
IL-6	5.6 (2.5-12.6)	2.9 (1.4-6.2)	5.6 (2.4-13.1)	4.6 (92.2-9.9)	0.39
IL-8	932.7 (341.1-2550.2)	268.4 (81.0-888.9)	1476.6 (537.5-4056.6)	808.3 (274.7-2378.3)	0.99
IL-10	0.6 (0.5-0.9)	0.6 (0.4-1.0)	0.8 (0.4-1.33)	0.7 (0.5-0.9)	0.93
IP-10	16.7 (4.1-68.5)	7.8 (5.9-10.5)	9.1 (6.9-11.9)	11.2 (6.3-19.7)	0.32
TNF-α*	15.0 (8.2-21.8)	10.5 (5.7-19.4)	17.0 (9.9-24.2)	10.9 (6.2-19.0)	0.97
Elastase	17.6 (13.2-23.4)	18.9 (13.0-66.6)	17.9 (13.1-24.6)	20.3 (16.5-25.0)	0.92

All mean reported as geometric means unless indicated; *Arithmetic means reported; sTREM: Soluble triggering receptor expressed on myeloid cells; IL- Interleukin: TNF-α: Tumour necrosis factor alpha, IP-10: Interferon gamma induced protein -10; Units of all the cytokines in picograms per millimetre except elastase in nanograms per litre. ANCOVA test used to obtain p-values for mean change from post treatment to mean change pre-treatment.

Table 3: Summary of serum and sputum cytokines in children with human immunodeficiency virus related bronchiectasis before and after treatment with erythromycin or placebo.

HIV viral load (p=0.48 and p=0.90), respectively. Sputum elastase did not change at baseline or studies end in the two treatment arms.

For the anti-inflammatory cytokine IL-10, the values were not elevated in both serum and sputum, with no statistically significant change in the levels after intervention with erythromycin or placebo (p=0.51 and p=0.93), respectively.

The chemokine IP-10 was elevated in serum and less so in sputum at baseline. There was a modest decline in serum IP-10 in the erythromycin arm and an increase in the placebo arm, although the change from baseline was not statistically significant (p=0.24). There was no correlation between IP-10 and $CD4^+$ T cell percentage count (p=0.34) and HIV viral load (p=0.11). IP-10 was not correlated with FEV_1 % predicted (p=0.55) or FVC % predicted (p=0.15).

Discussion

The use of macrolides for their immunomodulatory properties in CF-bronchiectasis is currently regarded as standard of care in those with *Pa* colonisation. In paediatric non-CF bronchiectasis, there is need for more robust data on the role of macrolides in a form of bronchiectasis where *Pa* is rarely cultured. The current study showed no additional benefit of erythromycin relative to placebo on the reduction of exacerbations in a cohort of HAART treated children with HIV-related bronchiectasis, although there was a statistically significant difference in the CD4 T^+ cell counts with higher levels in the placebo arm may have influenced the outcome of the study, Erythromycin had no effect on local and systemic pro-inflammatory and anti-inflammatory cytokines. This is consistent with findings in a group of HIV-positive women on HAART [16]. Pulmonary functions and sputum IL-8 improved, although this cannot be attributed to the use of erythromycin.

Medical interventions to treat HIV-related bronchiectasis should incorporate immune system restoration with HAART, physiotherapy and adequate nutrition. There is currently no data on the effect of HAART on lung disease progression. One adult study suggested possible decline in pulmonary functions in patients on HAART, although this was confounded by more than half of the subjects being smokers [17]. The restoration of the immune system with the use of HAART is accompanied by a reduction of pro-inflammatory cytokines, with its effect on the $CD4^+$ T cell population continuing for the first three to five years [16,18]. Although physiotherapy forms a fundamental part of current guidelines for bronchiectasis treatment, its effect is mainly on reduction of cough frequency and improved quality of life [19,20].

The newer macrolides (clarithromycin and azithromycin) and erythromycin have been studied in non-CF bronchiectasis for their immunomodulatory effects, but erythromycin has the added benefit of being cheap and freely available. Previous studies of macrolides have shown a reduction in pulmonary exacerbations and modest improvements in lung functions, although this is limited by lack of long-term randomised controlled trials [21-23]. A small study by Serisier and Martin demonstrated a reduction in the number of exacerbations observed over 12 months (from four to two per year) [21]. A one-year retrospective review by Anwar et al, showed a reduction in exacerbations with the use of azithromycin, but in this study 32% of participants had a previous culture or were colonized with *Pa* [10]. The lack of efficacy in the current study may be attributed to the fact that there were no participants colonized with *Pa.* The data on the effect of macrolides on pulmonary functions is conflicting. Tsang et al. found a significant improvement in FEV_1 and FVC, over 8 weeks in 11 patients treated with erythromycin, whilst Yalcin et al. found no effect of clarithromycin on 17 children [22,24]. We found no effect of erythromycin on either FEV_1 or FVC in this study. However, on pooling the data a significant increase in both pulmonary function parameters was evident at the end of the study period. This finding we postulate could be attributable to either "continued" sub-clinical immune restoration from HAART or improved overall care of subjects, which includes physiotherapy and early treatment of exacerbations.

In vitro data has shown declines in cytokines with the use of macrolides in bronchiectasis [11]. One randomised study assessed cytokines as an end-point after three months of clarithromycin and found a decrease in IL-8, but not TNF-α [24]. This study did not replicate this finding, possibly due to the superior tissue penetration of clarithromycin when compared to erythromycin or the waning effect of the beneficial effect of the macrolides over time.

Serum IP-10- a cytokine, involved in the trafficking of monocytes and activated T helper cells was significantly elevated in the serum. Elevated levels of IP-10 were previously found to be associated with HAART failure or TB [25,26]. These associations were, however, excluded in our cohort of children who were screened for TB and found to be un-infected and there was actually improvement in HIV disease activity markers.

Elastase, a protease released by disrupted neutrophils, has been found in CF to be responsible for 90% of the protease activity resulting in damage to the extracellular components such as elastin, collagen and proteoglycans with subsequent pulmonary destruction [27-29]. Values in CF, greater than 500 ng/ml have been found in adults in stable state CF [28]. In the current study, the levels were significantly lower than those previously described in CF and did not change over time. One explanation for this may be the low prevalence of *Pa,* which can be an independent source of proteases. Downey et al. demonstrated no change in soluble and free elastase levels in a group of CF participants after a course of antibiotic therapy [30].

Prior studies in CF reveal a correlation between elevated IgG levels and respiratory morbidity [31,32]. In the current study there was a decrease in the IgG levels in both treatment arms, but this was not correlated to pulmonary function parameters.

The strengths of this study are that preliminary evidence of the effect of HAART and adjunctive care on pulmonary functions and sputum IL-8 in children with HIV-related bronchiectasis. The limitations of this study are that the number of patients was small. In addition, quality of life assessments were not conducted. The study was also confounded by the fact that the CD4 T^+ cell count levels were higher in the placebo group when compared to the active study arm. It is, however, very unlikely that even a larger study, would find benefit from erythromycin on exacerbations as no numerical difference in exacerbations was seen and patients would have to be followed up for many years to detect the slightest benefit.

Conclusion

Administration of HAART and adjunctive care, which includes airway clearance and treatment of exacerbations, in children with HIV-related bronchiectasis is associated with significant improvement

in pulmonary function tests and IL-8, with no additional benefit from the use of erythromycin.

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