Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients

Nancy R Porhownik MD[1], Wael Batobara MD[1], Wayne Kepron MD FRCPC[1], Helmut W Unruh MD FRCSC[2], Zoheir Bshouty MD PhD FRCPC[1]

NR Porhownik, W Batobara, W Kepron, HW Unruh, Z Bshouty. Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. Can Respir J 2008;15(4):199-202.

BACKGROUND: Bronchiolitis obliterans syndrome (BOS), the main cause of late mortality following lung transplantation, is defined as an irreversible decline in forced expiratory volume in 1 s (FEV_1). Previous studies using azithromycin for BOS in lung transplant patients have demonstrated a potential reversibility of the decline in FEV_1.

OBJECTIVES: To examine whether initiating azithromycin reverses decline in FEV_1 in lung transplant recipients with established BOS of at least three months.

METHODS: Pulmonary function tests were performed every three months in seven lung transplant recipients with established BOS of at least three months. FEV_1 was recorded at six and three months before initiation, at time of initiation, and three, six, nine and 12 months postazithromycin initiation. The primary end point was change in FEV_1. During the study, no immunosuppressive medication changes or acute rejection episodes occurred.

RESULTS: Mean time from transplant to azithromycin initiation was 64 months (range 17 to 117 months). Mean time from BOS diagnosis to azithromycin initiation was 22 months (range three to 67 months). Rate of FEV_1 decline from six months before azithromycin initiation, and rates of FEV_1 increase from initiation to three and 12 months post-treatment initiation, were not statistically significant (P=0.32, P=0.16 and P=0.18, respectively). Following a trend toward improvement in the first three months after treatment initiation, FEV_1 tended to stabilize.

DISCUSSION: Although several studies address the possible benefit of maintenance azithromycin in lung transplant patients with BOS, the role of the drug remains unproven in these patients, and would best be addressed by a large randomized controlled trial.

Key Words: *Azithromycin; Bronchiolitis obliterans syndrome; Lung transplant*

L'effet de l'azithromycine d'entretien sur le syndrome de bronchiolite oblitérante chez des patients ayant subi une greffe pulmonaire

HISTORIQUE : Le syndrome de bronchiolite oblitérante (SBO), la principale cause de mortalité tardive après une greffe du poumon, se définit par une diminution irréversible du volume expiratoire maximal par seconde (VEMS). Les études antérieures faisant appel à l'azithromycine pour soigner les patients atteints de SBO ayant subi une greffe du poumon ont démontré la réversibilité potentielle de la diminution du VEMS.

OBJECTIFS : Examiner si le fait d'amorcer l'azithromycine supprime la diminution du VEMS chez les patients greffés du poumon atteints d'un SBO établi depuis au moins trois mois.

MÉTHODOLOGIE : Sept greffés du poumon atteints d'un SBO établi depuis au moins trois mois ont subi des explorations fonctionnelles respiratoires tous les trois mois. Les auteurs ont enregistré le VEMS six mois et trois mois avant le début du traitement, au début du traitement, puis trois, six, neuf et 12 mois après le début du traitement à l'azithromycine. Le point ultime primaire était une modification du VEMS. Pendant l'étude, aucun changement aux immunosuppresseurs ou épisode de rejet aigu n'a eu lieu.

RÉSULTATS : Le délai moyen entre la greffe et le début du traitement à l'azithromycine était de 64 mois (plage de 17 à 117 mois). Le délai moyen entre le diagnostic de SBO et le début du traitement à l'azithromycine était de 22 mois (plage de trois à 67 mois). Le taux de diminution du VEMS à compter de six mois avant le début du traitement à l'azithromycine et le taux d'augmentation du VEMS entre le début du traitement et le troisième et le douzième mois suivant le début du traitement n'étaient pas statistiquement significatifs (P=0,32, P=0,16 et P=0,18, respectivement). Après une tendance à l'amélioration au cours des trois premiers mois suivant le début du traitement, le VEMS avait tendance à se stabiliser.

EXPOSÉ : Bien que plusieurs études portent sur les bienfaits potentiels d'un traitement d'entretien à l'azithromycine chez les greffés du poumon atteints de SBO, le rôle du médicament demeure non démontré chez ces patients et serait mieux examiné par un grand essai aléatoire et contrôlé.

Early survival of lung transplant recipients in the first 12 months has improved over the past decade as surgical techniques and perioperative care have advanced. However, the subsequent rate of decline in survival is virtually unchanged (1). Bronchiolitis obliterans (BO) is the main cause of late mortality in lung transplant patients. The International Society for Heart and Lung Transplantation, recognizing that histological diagnosis of BO is limited by poor sensitivity of transbronchial biopsies, devised a clinical description for BO, termed BO syndrome (BOS). BOS is defined clinically as a progressive decline (20% or greater) in forced expiratory volume in 1 s (FEV_1) from 'best' FEV_1 that cannot be explained by another process (2). This standard nomenclature has been adopted by transplant centres internationally. Once physiological decline has begun, no treatment has proven successful in halting or reversing the process.

[1]*Department of Respiratory Medicine;* [2]*Department of Thoracic Surgery, University of Manitoba, Winnipeg, Manitoba*
Correspondence: Dr Nancy R Porhownik, Section of Respiratory Medicine, 810 Sherbrook Street, Winnipeg, Manitoba R3A 1R8. Telephone 204-787-1848, fax 204-787-1433, e-mail umporho0@cc.umanitoba.ca

Azithromycin is postulated to have anti-inflammatory properties that may be effective for treatment of lung transplant patients. The anti-inflammatory mechanisms, including reduced interleukin 8 levels, 8-isoprostane release from airway smooth muscle cells (3,4) and reduced airway neutrophilia (4), are currently under investigation. Previous studies using maintenance therapy with low-dose azithromycin in lung transplant recipients have demonstrated potential reversibility of BOS. Gerhardt et al (5) demonstrated improvement in FEV_1 in five of six lung transplant recipients receiving maintenance azithromycin therapy for a mean of 3.5 months. Verleden and Dupont (6) found a similar improvement in FEV_1 in patients treated with azithromycin for three months. Yates et al (7) demonstrated an improvement in FEV_1 with maintenance azithromycin, and noted that the increase in FEV_1 at three months persisted in 12 of 17 patients, up to 11 months of follow-up. However, not all of the previous studies support the reversibility of BOS with azithromycin. In 11 patients treated with maintenance azithromycin with a mean follow-up of 10 months, Shitrit et al (8) found no reversibility of BOS. The authors did note, however, a trend toward slowed progression of BOS following drug initiation.

In the present study, we prospectively examined the effect of maintenance, low-dose azithromycin therapy in seven lung transplant recipients with established BOS of at least three months. Compared with the previous studies mentioned above, the present study did not initiate azithromycin therapy when patients met the diagnostic criteria of BOS (20% decline in their FEV_1 from best FEV_1). Instead, we examined the effectiveness of initiating azithromycin in patients with established BOS (ie, patients who have had ongoing decline in lung function for at least three months after meeting the diagnostic criterion of BOS). We also examined the relationship between response to azithromycin and both time to development of BOS and duration of BOS.

METHODS

Induction therapy was not used in the present study. Instead, patients were started on triple therapy, which usually included a steroid, azathioprine and cyclosporine, immediately postlung transplantation. Episodes of acute rejection were treated with pulse steroid therapy followed by a high-dose steroid for at least two weeks before weaning. Following two episodes of acute rejection, patients were usually switched to mycophenolate and tacrolimus. All patients performed home spirometry twice daily following lung transplantation. Patients with an acute drop in FEV_1 of 10% or greater on two consecutive measurements were seen by a respirologist with expertise in lung transplantation. In addition, patients underwent chest x-ray and pulmonary function testing, including spirometry with measurements of lung volumes and, at times, gas transfer. If acute rejection was suspected, arrangements were made for bronchoscopy and transbronchial biopsy. Treatment of acute rejection was initiated without delay irrespective of the lung biopsy findings. Patients with progressive decline in FEV_1 (even when the decline was less than 10%) underwent frequent pulmonary function assessments, ranging from every week to every several weeks (not to exceed every three months) based on the time from transplant and the degree of decline from best FEV_1. Patients with BOS underwent bronchoscopy to rule out central airway problems (eg, tracheobronchomalacia, anastomotic stenosis, etc). Transbronchial biopsy was not routinely performed in this group of patients. Specimens collected at every bronchoscopy were routinely sent for Gram staining, culture and sensitivity testing, and direct fluorescent antibody staining for *Legionella* species, acid fast bacilli, fungi cultures and viral cultures. Specimens were also sent for cytological analysis to look for tumour cells, *Pneumocystis jirovecii* pneumonia and cytopathic changes secondary to *Cytomegalovirus* (CMV) species. In addition, blood was collected for CMV polymerase chain reaction.

All patients with a diagnosis of BOS were included in the study, unless deceased before initiation of azithromycin. Because of the emphasis on established BOS in the present study, patients with potential BOS – defined by the International Society for Heart and Lung Transplantation as a 10% to 19% decrease in FEV_1 from baseline – were excluded. All study patients had persistent physiological decline in lung function, despite negative investigations for other causes and no evidence of anastomotic complications on bronchoscopy. CMV status was documented for both donor and recipient.

Lung transplant recipients with documented BOS of at least three months (n=7) were started on maintenance azithromycin therapy and studied prospectively. Patients were treated with a loading dose of 1 g azithromycin orally, followed by 500 mg on days 2 to 4, and 250 mg three times a week thereafter. Pulmonary function tests, as outlined above, were measured at least every three months using GS 4G, CPL or BOXII pulmonary function equipment (Collins Medical Inc, USA) (9). Qualified, registered cardiopulmonary technologists performed testing and calibration according to American Thoracic Society guidelines. Calibrations were performed daily before subject testing. FEV_1 was recorded for each patient at six and three months before treatment initiation, at time 0 (treatment initiation), and three, six, nine and 12 months post-treatment initiation. The primary end point was change in FEV_1. Statistical significance of change in FEV_1 was determined using ANOVA for repeated measures with specific comparisons. A value of $P<0.05$ was considered statistically significant.

RESULTS

Four men and three women participated in the study. Patient demographics are shown in Table 1. Most patients (n=5) had chronic obstructive pulmonary disease (COPD) as their primary diagnosis. Four patients received double-lung transplants. All patients were CMV positive, were treated with triple immunosuppressive therapy and were administered trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis. During the study period, no changes in immunosuppressive medications occurred and there were no episodes of acute rejection.

Length of time from transplantation, best postoperative FEV_1 and BOS diagnosis to initiation of azithromycin therapy is shown in Table 2. The mean time from transplant to initiation of azithromycin was 64 months, with a range from 17 to 117 months. The mean time from diagnosis of BOS to initiation of azithromycin was 22 months, with a range from three to 67 months. Best postoperative FEV_1 is included in the graph to demonstrate the overall drop in lung function before treatment initiation, although the time axis from this point to six months (before initiating azithromycin) is not to scale.

The mean rate of decline in FEV_1 from six months before treatment to time 0, and the mean rate of increase in FEV_1

TABLE 1
Demographics of patients with established chronic rejection of at least three months

Patient number	Sex	Age, years	Diagnosis	Transplant type	BOS stage at azithromycin initiation	Immunotherapy	Antibiotics	CMV
1	F	65	COPD	DLT	3	MMF, FK, Prd	TMP-SMX	+
2	M	42	CF	DLT	3	MMF, FK, Prd	TMP-SMX	+
3	M	66	COPD	DLT	3	MMF, FK, Prd	TMP-SMX	+
4	F	57	COPD	Left SLT	1	Imuran, CsA, Prd	TMP-SMX	+
5	M	55	COPD	Redo DLT	1	Imm, FK, Prd	TMP-SMX	+
6	F	61	COPD	Right SLT	1	Imm, FK, Prd	TMP-SMX	+
7	M	58	IPF	Left SLT	3	Imm, CsA, Prd	TMP-SMX	+
	Men, n=4; Women, n=3	Mean (± SE) age of 57.71±3.04 years	COPD, n=5; IPF, n=1; CF, n=1	DLT, n=4; SLT, n=3	Stage 1, n=3; Stage 2, n=0; Stage 3, n=4	All patients had triple therapy	All patients	All patients

CF Cystic fibrosis; CMV Cytomegalovirus*; COPD Chronic obstructive pulmonary disease; CsA Cyclosporine A; DLT Double-lung transplant; F Female; FK Fujimycin; Imm Imuran (GlaxoSmithKline, Canada); IPF Idiopathic pulmonary fibrosis; M Male; MMF Mycophenolate mofetil; Prd Prednisone; SLT Single-lung transplant; TMP-SMX Trimethoprim-sulfamethoxazole*

TABLE 2
Length of time to initiation of azithromycin therapy

Patient number	Time from transplant, months	Time from best post FEV_1, months	Time from BOS, months
1	117	29	7
2	111	77	67
3	82	49	40
4	66	64	3
5	23	19	13
6	32	25	13
7	17	13	12
Mean ± SE	64.00±15.63	39.43±9.18	22.14±8.72

BOS Bronchiolitis obliterans syndrome; FEV_1 Forced expiratory volume in 1 s

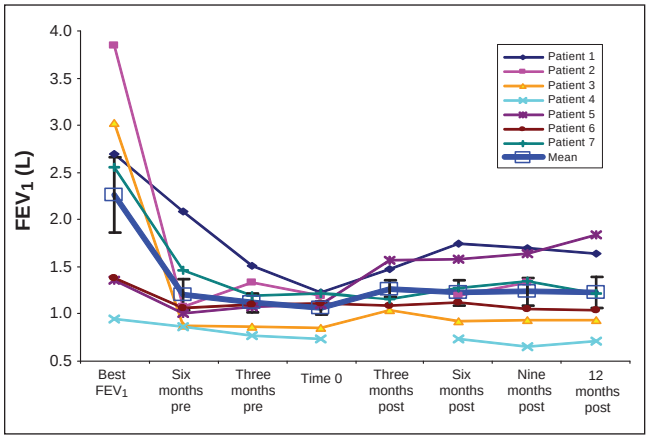

Figure 1) *Forced expiratory volume in 1 s (FEV_1) before (pre) and after (post) initiation of azithromycin*

from time 0 to three and twelve months post-treatment initiation, were not statistically significant (P=0.32, P=0.16 and P=0.18, respectively). Although not statistically significant, FEV_1, as evidenced by the graph, appeared to stabilize postinitiation of azithromycin.

DISCUSSION

The results of the present study show that initiation of azithromycin in patients with established BOS does not improve FEV_1. Nevertheless, as shown in Figure 1, mean FEV_1 demonstrates an upward trend at three months following treatment initiation, and this improvement was sustained at 12 months (P not significant). When individual data were examined, two patients appeared to have a clinically significant improvement in FEV_1 (Figure 1). Patient 1 was a 65-year-old female double-lung recipient for underlying COPD. Although azithromycin was initiated approximately 10 years following her lung transplant, she had only met the criteria for diagnosis of BOS seven months before treatment initiation. Patient 5 was a 55-year-old male redo double-lung recipient for underlying COPD who began treatment with azithromycin approximately two years following his second transplant. He met the criteria for BOS 13 months before treatment initiation. As evidenced by these patients, a clear relationship between the response to azithromycin and the time to development of BOS, as well as the duration of rejection, was not identified.

Our results are similar to those reported by Gerhardt et al (5), who followed patients for a similar length of time. Although a statistically significant improvement was not demonstrated in our study, it is possible that earlier studies showing improved lung function at three months would have shown a similar plateau had their follow-up period been extended.

The effect of treatment for a disease with variable natural history such as BOS is better studied with a randomized, controlled trial. However, given the limited number of patients, the approach we undertook (repeated measures – ie, before and after intervention in the same group of patients) increases the likelihood of identifying a treatment effect, if present, by minimizing variance. Our study adds a new perspective to previously published studies, because it only enrolled patients with well-established BOS at various stages and it followed these patients for an extended period (one year).

During the study period, none of the patients underwent an episode of acute rejection, nor were any major changes made to their management. Such episodes or interventions could have significantly affected FEV_1 and would have made our results uninterpretable. Hence, the lack of acute rejection and modifications in immunosuppressive therapy in our group of patients may be considered an advantage. The inclusion of lung function data before treatment initiation, which documents a progressive

deterioration in lung function consistent with established BOS in all patients, allows a clear comparison of lung function before and after treatment. This study does not examine the effect of initiating azithromycin at the time of diagnosis of BOS on FEV_1. It is possible that if treatment were started earlier (eg, at the time of BOS diagnosis), the results would have been more favourable. Limitations of the study include the small patient population, the absence of blinded investigators, and no random assignment of patients to treatment and control groups.

Although several studies address the possible benefit of maintenance azithromycin in lung transplant patients with BOS, the role of the drug remains unproven. However, with a clinically significant improvement in two of seven patients and only minimal side effects associated with azithromycin, a treatment trial with azithromycin, even in patients with established BOS, is quite reasonable. A multicentre randomized controlled trial addressing the role of azithromycin in patients with BOS is needed.

REFERENCES

1. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twenty-second official adult lung and heart-lung transplant report – 2005. J Heart Lung Transplant 2005;24:956-67.
2. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. J Heart Lung Transplant 2002;21:297-310.
3. Vanaudenaerde BM, Wuyts WA, Geudens N, et al. Macrolides inhibit IL17-induced IL8 and 8-isoprostane release from human airway smooth muscle cells. Am J Transplant 2007;7:76-82.
4. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2006;174:566-70.
5. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: Results of a pilot study. Am J Respir Crit Care Med 2003;168:121-5.
6. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2004;77:1465-7.
7. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2005;172:772-5.
8. Shitrit D, Bendayan D, Gidon S, Saute M, Bakal I, Kramer MR. Long-term azithromycin use for treatment of bronchiolitis obliterans syndrome in lung transplant recipients. J Heart Lung Transplant 2005;24:1440-3.