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# Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study

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**ABSTRACT: Bronchiolitis obliterans (BO) is a serious noninfectious pulmonary complication following allogeneic bone marrow transplantation (BMT). Azithromycin, a macrolide antibiotic, may have a beneficial effect in BO through its anti-inflammatory effect. The aim of the current study was to investigate the potential effect of azithromycin on pulmonary function tests (PFTs) in BO complicating BMT.**

**PFTs of 153 post-BMT patients were followed; eight patients out of 153 (12%) developed obstructive airway disease on their PFTs, along with characteristic findings of BO on high-resolution computed tomography of the chest. These patients were given azithromycin 500 mg *q.d.* for 3 days, followed by 250 mg three times a week for 12 weeks.**

**Clinically significant improvements were achieved both in forced vital capacity, where the mean (95% confidence interval) increase reported was 410 mL (0.16–0.65), which was an average improvement of 21.57%, and in the forced expiratory volume in one second, where the mean increase noticed was 280 mL (0.10–0.44), which was an average improvement of 20.58%.**

**In conclusion, the potential role of azithromycin in the treatment of bronchiolitis obliterans is intriguing and it warrants further testing.**

**KEYWORDS: Allogeneic bone marrow transplant, azithromycin, bronchiolitis obliterans, macrolides, pulmonary function tests**

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Bronchiolitis obliterans (BO) was first recognised as a serious and often fatal complication of allogeneic bone marrow transplant (BMT) in the 1980s [1, 2]. The pathogenesis of BO remains poorly understood. Graft *versus* host disease (GVHD), methotrexate use, hypogammaglobulinaemia and respiratory infections are commonly associated with development of BO, but the strongest association found is with chronic GVHD [3–7]. The diagnosis of BO is mainly based on pulmonary function tests (PFTs) revealing airflow obstruction. Chest radiography is usually normal. High-resolution computed tomography (HRCT) of the chest may show hypo-attenuated areas due to air trapping, especially on expiratory images [8, 9]. Transbronchial biopsy has low diagnostic yield, but thoracoscopic or open lung biopsy usually show typical features of small airway obliteration by fibrinous material [10].

Despite all measures, including prophylaxis against viral, bacterial and fungal infections, the incidence of BO remains 6–20% among the long-term survival of BMT patients, mostly associated with chronic GVHD. There are limited treatment options for BO; heavy immunosuppressive corticosteroids and cytotoxic medications have been tried with limited success. Most of these patients develop progressive respiratory failure [11–14].

Anti-inflammatory effects of macrolides are well established. The current observational open-labelled study investigates the effects on clinical symptoms and PFTs of azithromycin treatment in eight patients affected by BO secondary to allogeneic BMT. Some of the results of the current study were previously reported in collaboration with the John Hopkins University School of Medicine, Washington DC, USA [15].

## PATIENTS AND METHODS

### *Patients*

A total of 153 post-BMT patients were included in an initial review. The study protocol was approved by the hospital review board (King Faisal Specialist Hospital and Research Center,

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Riyadh, Saudi Arabia), and informed consent was obtained from all patients. PFTs were assessed in pre- and post-BMT. Three patients were excluded for existing obstructive airway disease (OAD) prior to BMT. In total, 20 patients (31%) developed OAD in their post-BMT PFTs. Eight patients (12%) with OAD had classical HRCT chest findings of mosaic pattern with airway trapping of BO. These patients were included in the current study. The current authors were comfortable with a clinical diagnosis of BO based on patients' clinical presentation, their PFT findings of newly developed OAD and the classical HRCT chest findings. No bronchoalveolar lavage or lung biopsies were performed to further substantiate the diagnosis.

The mean (range) age of the study group was 36 yrs (18–63). All patients had established diagnosis of GVHD. Patients receiving immunosuppressive medications, which included prednisone, cyclophosphamide, azathioprine and mycophenolate mofetil in different combinations, were maintained on these. Patients were questioned for the presence of cough and dyspnoea, and exercise tolerance. Objective exercise tolerance performance tests were not performed (table 1).

### *Azithromycin dosing schedule*

Azithromycin was given in a loading dose of 500 mg *q.d.* for 3 days, followed by 250 mg three times a week for 12 weeks.

Patients who responded to azithromycin were maintained on similar doses of azithromycin beyond the 12-week study period. Complete blood count, renal profile (serum creatinine, urea and electrolytes) and liver enzymes were checked at a 6-week follow-up, along with information on drug tolerance and clinical side-effects.

### *Pulmonary function tests*

PFTs were done before starting the treatment with azithromycin in the PFT laboratory (King Faisal Specialist Hospital and Research Centre) by an experienced technician using a standard protocol, according to American Thoracic Society guidelines [16]. Lung volumes were measured by the nitrogen wash-out method. Repeat PFTs were performed at the end of the 12-week trial of azithromycin therapy. OAD was defined as decrease in forced expiratory volume in one second ($FEV_1$) to $<80\%$ of the predicted value, and $FEV_1$/forced vital capacity (FVC) to $<70\%$ of predicted value [17]. Chest HRCTs were read and reported by an experienced pulmonary radiologist. A decline in $FEV_1$ of $\geqslant 20\%$, as set out by the International Society of Heart and Lung Transplantation [18], and evidence of air trapping on expiratory HRCT of chest were used to diagnose BO. A change of 12% and 200 mL in FVC and $FEV_1$, respectively, was considered significant.

### *Statistical methods*

Paired t-tests were used to compare pre- and post-treatment values. A p-value of $<0.05$ was considered significant.

## RESULTS

All patients tolerated the treatment well and there were no dropouts. Seven patients showed significant improvement in FVC and $FEV_1$ after azithromycin treatment. One patient showed partial improvement in PFTs. The mean (95% confidence interval) change in FVC after treatment was 410 mL (0.16–0.65; $p<0.0052$). This represents an average improvement of 21.57%. The mean increase in $FEV_1$ was 280 mL (0.10–0.44; $p<0.0067$), representing an average increase in $FEV_1$ of 20.58%. Patients with improved PFTs also showed significant improvement in shortness of breath and exercise tolerance. One patient showed decline in PFTs, and later needed oxygen supplementation after discontinuing azithromycin. Reinstitution of azithromycin caused improvement in the clinical status and PFTs, and the patient was taken off oxygen supplementation. All patients tolerated azithromycin well. No significant clinical side-effects or any abnormalities in laboratory testing were noticed. Tables 2 and 3 demonstrate individual and mean pre- and post-treatment PFT values. The overall results show significant improvement in PFTs, after azithromycin treatment in patients with BO following BMT.

## DISCUSSION

The beneficial effect of macrolides in patients with BO after BMT has not been studied before. This is the first study on the use of azithromycin in patients with BO following BMT. It was found that the addition of azithromycin to the treatment regimen of these patients improved pulmonary functions

**TABLE 1** Patients' clinical data

| Patient No. | Diagnosis | BMT/type | GVHD | | Immunosuppression |
|---|---|---|---|---|---|
| | | | Liver | Skin | |
| 1 | CML | BMT/allogeneic | Yes | Yes | None |
| 2 | AML | BMT/allogeneic | Yes | Yes | MMF + steroid |
| 3 | AML | BMT/allogeneic | Yes | Yes | None |
| 4 | CML | BMT/allogeneic | Yes | Yes | CSA |
| 5 | AML | BMT/allogeneic | Yes | No | CSA + prednisone + MMF |
| 6 | ALL | Allogeneic/PBSCT | Yes | Yes | CSA + MMF + prednisone |
| 7 | NHL | PBSCT/autologous | No | No | None |
| 8 | ALL | BMT/allogeneic | No | Yes | Prednisone |

BMT: bone marrow transplant; GVHD: graft *versus* host disease; CML: chronic myeloid leukaemia; AML: acute myelocytic leukaemia; ALL: acute lymphoblastic leukaemia; NHL: non-Hodgkin's lymphoma; PBSCT: peripheral blood stem cell transplant; MMF: mycophenolate mofetil (cellcept); CSA: cyclosporine.

**TABLE 2** Pre- and post-treatment forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) values for individual patients

| Patient No. | Pre-treatment FVC L | Post-treatment FVC L | Percentage change % | Pre-treatment $FEV_1$ L | Post-treatment $FEV_1$ L | Percentage change % |
|---|---|---|---|---|---|---|
| **1** | 2.23 | 2.22 | -0.44 | 1.10 | 1.18 | 7.27 |
| **2** | 2.41 | 3.30 | 36.9 | 1.11 | 1.25 | 12.61 |
| **3** | 1.25 | 1.61 | 28.80 | 1.25 | 1.59 | 27.20 |
| **4** | 1.06 | 1.46 | 37.7 | 0.60 | 0.84 | 40.00 |
| **5** | 2.77 | 3.05 | 10.10 | 2.50 | 2.79 | 11.60 |
| **6** | 2.11 | 2.89 | 37 | 1.68 | 2.40 | 42.9 |
| **7** | 1.03 | 1.40 | 35.9 | 0.69 | 0.79 | 14.5 |
| **8** | 2.38 | 2.61 | 9.7 | 2.0 | 2.28 | 14 |

**TABLE 3** Mean change in forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) after azithromycin treatment

| Variables | Mean pre-treatment value L | Mean post-treatment value L | Change$^{\#}$ L | 95% CI | Percentage change % | p-value |
|---|---|---|---|---|---|---|
| **FVC** | 1.90 | 2.31 | 0.41 | 0.16–0.65 | 21.57 | 0.0052 |
| **$FEV_1$** | 1.36 | 1.64 | 0.28 | 0.10–0.44 | 20.58 | 0.0067 |

CI: confidence interval. $^{\#}$: mean post-treatment – mean pre-treatment value.

significantly, and improved their respiratory symptoms and exercise tolerance. The anti-inflammatory role of macrolide antibiotics is well established. The mechanism by which macrolides act as anti-inflammatory agents is not well understood at present. There are several reports indicating the role of macrolides as modulators of neutrophil activity by suppressing chemotactic activity at the inflammatory sites. Macrolides also inhibit superoxide generation by human neutrophils *in vitro*, and have an anti-cytokine effect by inhibiting the generation of nitric oxide, prostaglandin E2, interleukin (IL)-1β, IL-8, IL-6 and tumour necrosis factor both *in vivo* and *in vitro* [19–23].

The potential anti-inflammatory effect of macrolide antibiotics is well described in panbronchiolitis [24]. A steroid-sparing effect of macrolides has also been shown in asthmatics [25]. A maintenance oral azithromycin therapy in BO after lung transplantation has shown promising results [26]. Recent studies have shown a potential role for macrolides in treating patients with cystic fibrosis, especially those who are colonised with *Pseudomonas aeruginosa* [27].

The current observational study shows a beneficial role of azithromycin in improving lung functions in patients with bronchiolitis obliterans after bone marrow transplant. This is probably due to its anti-inflammatory effects through mechanisms described previously. Although the majority of the current patients were not microbiologically screened for possible airway infection using sputum cultures and bronchoalveolar lavage, the beneficial response of azithromycin due to an antimicrobial effect could not be ruled out. Future studies should be designed with this consideration. This is a preliminary study with few limitations; however, *in lieu* of the current authors' promising results and the grim prognosis of bronchiolitis obliterans in this category of patients with conventional treatment, a large-scale placebo-controlled randomised trial is warranted to further assess the beneficial response of azithromycin in post-bone marrow transplant bronchiolitis obliterans.

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