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Home spirometry as early detector of azithromycin refractory bronchiolitis obliterans syndrome in lung transplant recipients

Claudia de Wall [a,*], Dettmer Sabine [b], Warnecke Gregor [c], Greer Mark [a], Haverich Axel [c], Fuehner Thomas [a], Welte Tobias [a], Gottlieb Jens [a]

[a] Department of Pulmonary Medicine, Hannover Medical School, Hannover, Germany
[b] Department of Radiology, Hannover Medical School, Hannover, Germany
[c] Department of Cardiothoracic, Transplantation and Vascular Surgery, Hannover Medical School, Hannover, Germany

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Summary
Background: To evaluate the utility of home spirometry (HS) versus office spirometry (OS) in assessing treatment response to azithromycin in bronchiolitis obliterans syndrome (BOS).
Methods: 239 Lung transplant recipients were retrospectively studied. $\Delta FEV_1 \pm 10\%$ from FEV_1 at azithromycin initiation for $\geq$7 consecutive days in HS or $\geq$2 measures in OS were taken as cut-off for response or progression.
Results: Based upon HS, 161/239 (67%) patients were progressive despite macrolide, 19 of who exhibited transient improvement in FEV_1 (11%). Time to progression was 29 (13–96) days earlier with HS than in OS. Forty-six (19%) recipients responded in HS after median 81 (22–343) days, whilst 22% remained stable. Concordance in azithromycin treatment response between OS and HS was observed in 210 of 239 patients (88%). Response or stabilization conferred significant improvement in survival ($p = 0.005$). Transient azithromycin responders demonstrated improved survival when compared to azithromycin refractory patients ($p = 0.034$).
Conclusions: HS identified azithromycin refractory patients significantly earlier than OS, possibly facilitating aggressive treatment escalation that may improve long-term outcome.

Abbreviations: BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in one 1 s; HS, home spirometry; IQR, interquartile ranges; LTx, lung transplantation; OS, office spirometry; RAS, restrictive allograft syndrome.

* Corresponding author. Hannover Medical School, Department of Respiratory Medicine, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany. Tel.: +49 511 532 3560; fax: +49 511 5328094.
E-mail addresses: dewall.claudia@freenet.de, dewall.claudia@mh-hannover.de, claudia.andre@arcor.de (C. de Wall).

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Treatment response to azithromycin should be assessed 4 weeks after initiation. Responders demonstrated best survival, with even transient response conferring benefit. Macrolide-refractory BOS carried the worst prognosis.

Introduction

Lung transplantation (LTx) has become an accepted therapeutic option for selected patients with end-stage lung disease. Post-transplant survival continues to improve, but mean 5-year survival remains disappointingly low at 53% [1]. Bronchiolitis obliterans syndrome (BOS) remains the leading cause of death beyond the first year after transplantation [1], affecting almost half of all patients within 5 years. BOS is characterized by its unpredictable and variable clinical course, ranging from an insidious onset with gradual loss of pulmonary function over months to years, to an abrupt and severe decline in pulmonary function within a matter of weeks [2—4]. Whilst obliterative bronchiolitis is the presumed histopathological correlate, it is not consistently detectable by transbronchial biopsy and spirometry is routinely used as the agreed surrogate marker to diagnose and stage BOS [5]. Current treatment strategies for BOS include aggressive management of known risk factors as well as early identification of BOS and initiation of proposed treatments or re-transplantation.

Long-term azithromycin has been shown to improve FEV_1 and survival in up to 40% of BOS patients in various single-center studies [6—10]. Current data however, does not provide insight beyond initial response, with little being known about whether initial responders relapse later or whether non-responders stabilize after azithromycin initiation. Early azithromycin initiation prior to development of BOS stage 2 has been associated with a significant reduction in risk of death [9], suggesting the possibility of critical therapeutic windows for efficacy of some treatment options.

Given these issues, prompt assessment for therapeutic response with a view to treatment escalation in progressive patients is vital. Previous studies involving lung transplant recipients have demonstrated the benefits of daily home spirometry (HS) in detecting early changes in graft function [11—16]. In the current study, home spirometry data was used to evaluate treatment response after commencing azithromycin in LTx patients with BOS to evaluate if macrolide-refractory progression could be identified earlier than the present system of office spirometry (OS).

Materials and methods

A single-center retrospective analysis of all adult lung transplant recipients between 2003 and 2011 commenced on long-term azithromycin for bronchiolitis obliterans was performed.

Only patients with adequate adherence to home spirometry ($\geq$50% prescribed measures) and at least one follow-up visit after azithromycin initiation were included. Recipients with severe airway complications, unknown start or interrupted azithromycin treatment were excluded (Fig. 1). All patients were followed-up from azithromycin initiation until death, re-transplantation or to completion of the study on May 31, 2011.

Home spirometry (HS)

Patients were instructed on using a home spirometry device and asked to perform daily testing, ensuring that attempts were made at the same time each day. All patients used a handheld electronic spirometry system (VIASYS® Healthcare, Hoechberg, Germany) that collected and stored relevant expiratory flow—volume parameters including FEV_1. Following each attempt, a digital display on the spirometer indicated the current FEV_1 value along with a direct comparison to the patient's pre-programmed best FEV_1. Based on a "traffic light" system, the device displays green when $\geq$90% best FEV_1 is achieved, yellow for $<$90% but $\geq$80% and red for $<$80% best FEV_1. The device stores up to 450 measurements, which were routinely downloaded at each outpatient attendance and stored centrally in an electronic database. Patients were instructed to contact the transplant center within 24 h following a change in "colour" on the spirometer, regardless of symptoms.

Routine follow-up

Patients were followed-up at our specialized outpatient clinic with scheduled visits at 2- to 4- month intervals. Standard immunosuppression consisted of a triple-drug regimen including a calcineurin-inhibitor, prednisolone and either a cell-cycle-inhibitor or mTOR (mammalian target of rapamycin) inhibitor. After excluding alternate causes, azithromycin (as the standard neo-macrolide therapy) was commenced in all patients demonstrating a persistent deterioration in lung function below 80% baseline, with most patients receiving an initial loading dose of 500 mg daily for 3 days before continuing with 250 mg three times per week thereafter. Routine follow-up attendances included clinical examination, spirometry, capillary blood gas analysis and a chest x-ray. Bronchoscopy was routinely performed, based on interpretation of these findings to investigate suspected rejection, infection or airway complication.

BOS staging complied with the International Society of Heart and Lung Transplantation classification of bronchiolitis obliterans syndrome (BOS) [17]. Baseline FEV_1 was defined as the average of the two highest measurements obtained at least 3 weeks apart during postoperative course.

Restrictive allograft syndrome (RAS) was defined according to Sato et al. [18]. If TLC data were not available, RAS was defined by imaging (presence of parenchymal