

A pilot study to compare tobramycin 80 mg injectable preparation with 300 mg solution for inhalation in cystic fibrosis patients

Wilfried H Nikolaizik MD¹, Delia Vietzke MD¹, Felix Ratjen MD PhD FRCPC^{1,2}

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BACKGROUND: Inhaled tobramycin has been shown to improve lung function in cystic fibrosis (CF) patients chronically infected with *Pseudomonas aeruginosa*. However, to date no comparative data are available for different dose regimens used in clinical practice.

OBJECTIVES: To compare the clinical efficacy of the two most commonly used treatment regimens of inhaled tobramycin in patients with CF.

METHODS: In an open crossover study of CF patients, subjects were randomly allocated to receive either 80 mg tobramycin twice-daily continuous treatment or 300 mg tobramycin twice daily in cycles of 28 days on and 28 days off treatment. After three months, patients were switched to the alternative treatment regimen.

RESULTS: A total of 32 patients with a mean (\pm SD) age of 18.5 ± 8.6 years were included in the study. Compared with the treatment period using colistin, forced expiratory volume in 1 s decreased by $-2.1 \pm 13.8\%$ in the 80 mg tobramycin group and increased by $+2.3 \pm 13.0\%$ in the 300 mg group. Similar changes were observed in forced vital capacity ($-2.5 \pm 12.9\%$ in the 80 mg tobramycin group versus $+2.5 \pm 9.6\%$ in the 300 mg tobramycin group). Variability in responses was large but the differences were not statistically significant. Personal preference indicated that the majority of patients preferred the high-dose cycle compared with the lower dose continuous inhalation, but this was not linked to objective data on efficacy.

CONCLUSIONS: The present trial fails to provide convincing evidence for superiority in efficacy of either of the two treatment regimens of inhaled tobramycin in CF patients.

Key Words: Antibiotics; Cystic fibrosis; Infection; Inhalation; Lung function; Tobramycin

Tobramycin originally formulated for intravenous use has been administered to cystic fibrosis (CF) patients off-label by inhalation for decades in Canada and Europe. In noncontrolled studies that include small numbers of CF patients chronically infected with *Pseudomonas aeruginosa*, improvements in lung function, partial pressure of O₂ and body weight (without significant nephrotoxicity or ototoxicity) were demonstrated (1,2). Despite these initial promising results, the efficacy of the 80 mg/2 mL twice-daily treatment regimen remained largely unproven (3). A 300 mg/5 mL preservative-free formulation of

Une étude pilote pour comparer une préparation injectable de tobramycine sous forme de solution en aérosol de 80 mg ou de 300 mg chez des patients atteints de fibrose kystique

HISTORIQUE : Il est démontré que la tobramycine en aérosol améliore la fonction pulmonaire chez les patients atteints de fibrose kystique (FK) et d'une infection chronique à *Pseudomonas aeruginosa*. Cependant, il n'existe encore aucunes données comparatives pour les diverses posologies utilisées en pratique clinique.

OBJECTIFS : Comparer l'efficacité clinique des deux schémas thérapeutiques de tobramycine en aérosol les plus utilisés chez les patients atteints de FK.

MÉTHODOLOGIE : Dans une étude transversale ouverte de patients atteints de FK, les sujets ont été divisés au hasard entre un traitement continu de 80 mg de tobramycine deux fois par jour ou de 300 mg de tobramycine deux fois par jour par cycle de 28 jours de traitement suivis de 28 jours sans traitement. Au bout de trois mois, les patients sont passés à l'autre schéma thérapeutique.

RÉSULTATS : Au total, 32 patients, d'un âge moyen (\pm ÉT) de $18,5 \pm 8,6$ ans, ont participé à l'étude. Par rapport à la période de traitement à la colistine, le volume expiratoire maximal par seconde (VEMS) a diminué de $-2,1 \pm 13,8\%$ dans le groupe prenant 80 mg de tobramycine et a augmenté de $+2,3 \pm 13,0\%$ dans celui en prenant 300 mg. On a observé des changements similaires de la capacité vitale forcée ($-2,5 \pm 12,9\%$ dans le groupe prenant 80 mg de tobramycine par rapport à $+2,5 \pm 9,6\%$ dans celui en prenant 300 mg). Les auteurs ont constaté une vaste variabilité des réponses, mais les différences n'étaient pas statistiquement significatives. Pour ce qui est des préférences personnelles, la majorité des patients ont préféré le cycle à fortes doses par rapport à l'inhalation continue à faible dose, mais cette observation n'était pas reliée à des données objectives d'efficacité.

CONCLUSIONS : Le présent essai ne fournit pas de données probantes convaincantes sur l'efficacité supérieure de l'un ou l'autre des schémas thérapeutiques de tobramycine en aérosol chez les patients atteints de FK.

tobramycin, designed and registered for inhalation, has been shown to improve lung function and reduce the rate of pulmonary exacerbations in a large placebo-controlled randomized trial (4). This latter preparation has been approved for twice-daily intermittent inhalation in four-weekly on-off cycles. However, so far no data are available comparing different doses of inhaled tobramycin in CF patients, and there has been no comparative trial between this treatment regimen and the lower dose continuous inhalation protocols used in many Canadian and European centres. The aim of the present study

¹Department of Pediatrics, University Hospital Essen, Essen, Germany; ²Division of Respiratory Medicine, The Hospital for Sick Children, Toronto, Ontario

Correspondence: Dr Felix Ratjen, Division of Respiratory Medicine, University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8. Telephone 416-813-6167, fax 416-813-6246, e-mail felix.ratjen@sickkids.ca

TABLE 1
Characteristics of the patients (n=32) at study entry

	Tobramycin 300 mg solution for inhalation	Tobramycin 80 mg intravenous preparation
Number of patients	14	18
Age, years, mean \pm SD	19.1 \pm 7.6	18.3 \pm 9.4
FVC, % predicted, mean \pm SD	68.8 \pm 17.7	76.7 \pm 17.4
FEV ₁ , % predicted, mean \pm SD	48.4 \pm 15.8	63.1 \pm 21.6
O ₂ saturation, %, mean \pm SD	95.6 \pm 1.9	95.2 \pm 1.4

FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity

was therefore to compare the efficacy and the patients' preferences between tobramycin 80 mg intravenous preparation used for continuous inhalation and tobramycin 300 mg administered intermittently in four-weekly on-off cycles for inhalation over a total period of 24 weeks.

METHODS

The present study was designed to compare the effect of continuous twice daily inhalation of 80 mg tobramycin intravenous preparation (Tiv80) with that of intermittent administration of 300 mg preservative-free tobramycin solution for inhalation (TIS300) in CF patients chronically infected with *P. aeruginosa* in an outpatient clinic setting. Because the four-week break in tobramycin inhalation is a characteristic feature of the latter regimen and the two solutions differ in quantity, it was not feasible to perform a double-blind trial. Therefore, an open crossover study design was chosen. All of the patients included in the present study had been on inhaled antibiotic therapy before enrolment in the study, because this is considered the standard of care. To achieve a similar baseline, all patients therefore received colistin (1 million units twice daily) during a washout phase for four or more weeks before being randomly allocated to receive either Tiv80 twice-daily treatment or TIS300 twice-daily treatment in four-weekly on and four-weekly off cycles. After 12 weeks of either treatment regimen, the patients were switched to the alternative treatment regimen.

Patients eligible for the present study had to have a confirmed diagnosis of CF substantiated either by the identification of two mutations known to cause CF (5) or by the sweat iontophoresis test (positive for CF if sweat Cl⁻ concentrations greater than 60 mmol/L in at least two samples of 100 mg sweat [6]), be clinically stable at the time of enrolment and have at least two positive cultures for *P. aeruginosa* within the past six months. Patients were excluded if there were any changes to their regular inhaled medications or systemic corticosteroids four weeks before the study or during the study period, and if they had acute or exacerbated allergic bronchopulmonary aspergillosis. During the study period, the patients were allowed to inhale beta-agonists as required. However, they had to withdraw the use of short-acting bronchodilators for more than 6 h, and long-acting bronchodilators for more than 12 h before lung function testing.

Pulmonary function tests, including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁), were performed before and after each treatment cycle using a body plethysmograph (Viasys Healthcare GmbH, Germany). The

results were expressed as a percentage of the predicted values according to Polgar and Promadhat (5) and Morris (6). A minimum of three forced expiratory manoeuvres were performed for every recording, and data were used from the best manoeuvres according to the guidelines of the American Thoracic Society (7,8). The study medication was administered with a Pari LC Plus nebulizer and a Pari Master compressor (Pari GmbH, Germany). Adherence to medication was assessed at regular visits to the clinic by checking the prescriptions and asking the patients to return the unused drugs. At the end of the second treatment period, the patients were asked about their individual preferences for the different treatment regimens, which was then documented.

Statistical analysis

In a large multicentre, double-blind, placebo-controlled trial (4), patients with intermittent administration of inhaled tobramycin had an average increase in FEV₁ of 10% at week 20. To yield 80% coverage probability so that a difference of 10% is detected between the two study groups, a target sample size of 32 patients per group was chosen assuming an SD of 14% FEV₁ or FVC, respectively.

The data were analyzed using ANOVA with the following factors: treatment group, cycle, sequence and patient-within-sequence. All statistics were calculated using SAS version 8.2 (SAS Institute Inc, USA). ANOVA was calculated using PROC GLM of SAS version 8.2. A value of $P < 0.05$ was considered significant.

RESULTS

A total of 32 patients (17 women) with CF, mean (\pm SD) age 18.5 \pm 8.6 years, completed the study. Eighteen patients were initially treated with Tiv80, and 14 patients were treated with TIS300. There was no significant difference in sex, age, FVC, FEV₁ or O₂ saturation at baseline between the groups (Table 1).

In patients initially treated with 80 mg tobramycin, the mean FEV₁ decreased by $-2.5 \pm 16.8\%$, and increased by $+2.8 \pm 14.2\%$ when switched to the TIS300 group. In the patients initially treated tobramycin with TIS300, the mean FEV₁ increased by $+1.5 \pm 11.6\%$, and decreased by $-1.5 \pm 9.0\%$ when switched to Tiv80 (Figure 1). In patients initially treated with 80 mg tobramycin, mean FVC decreased by $-2.5 \pm 15.7\%$, and increased by $+3.9 \pm 11.0\%$ when switched to TIS300. In the patients initially treated with 300 mg tobramycin, the mean FVC increased by $+0.6 \pm 7.3\%$, and decreased by $-2.5 \pm 8.6\%$ when switched to Tiv80 (Figure 2).

An ANOVA analysis revealed no significant influence of the four factors – treatment group, cycle, sequence and patient-within-sequence – on the response in FVC, FEV₁ and O₂ saturation after each treatment period; therefore, all data were pooled for analysis. No change in O₂ saturation was observed ($-0.0 \pm 2.9\%$ Tiv80 group versus $+0.1 \pm 1.8\%$ TIS300 group). Compared with the treatment period with colistin, the mean FEV₁ decreased by $-2.1 \pm 13.8\%$ in the Tiv80 group and increased by $+2.3 \pm 13.0\%$ in the TIS300 group. Similar changes were observed for FVC ($-2.5 \pm 12.9\%$ Tiv80 group versus $+2.5 \pm 9.6\%$ TIS300 group). A post hoc sample size calculation was performed based on the study data, which revealed that a population of more than 140 patients would have been required to demonstrate that the trend in pulmonary function observed in the present study reflects a significant difference between the two treatment regimens in FEV₁.

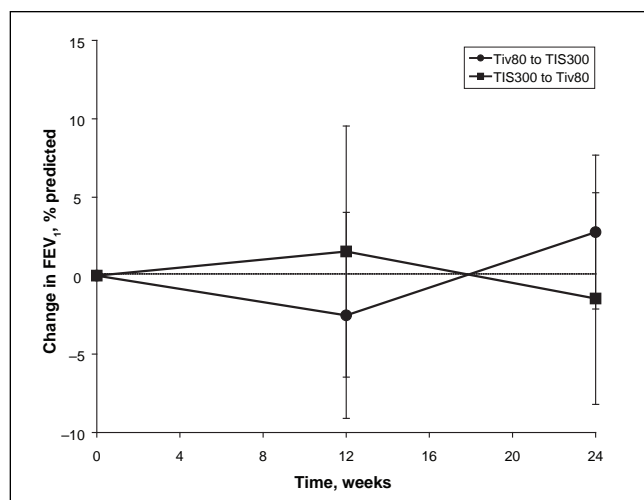


Figure 1 Change in forced expiratory volume in 1 s (FEV_1) in per cent predicted from baseline by treatment arm. Data are presented as mean per cent predicted with 95% CI. Tiv80 represents the 80 mg tobramycin intravenous preparation whereas TIS300 refers to the 300 mg tobramycin solution for inhalation. Differences between groups are not significant

The individual preferences were assessed by an open questionnaire asking the patients to rank the three inhaled preparations, colistin, Tiv80 and TIS300. Of the 32 patients, 19 (59%) favoured TIS300, seven (22%) favoured the Tiv80 preparation, three (9%) favoured colistin and three had no preference. This reflected a significant difference in preference between the two tobramycin solutions in favour of TIS300 ($P < 0.01$; Fisher's exact test). The individual preference was not related to changes in lung function parameters such as FVC, FEV_1 or O_2 saturation (data not shown).

DISCUSSION

The present study is the first trial to compare two different treatment regimens of inhaled tobramycin: 300 mg tobramycin (twice daily) administered intermittently in four-weekly on and four-weekly off cycles versus low-dose tobramycin (80 mg, twice daily) administered continuously in CF patients with chronic *P. aeruginosa* infection. The first preparation has been developed and approved for inhalation, while the latter has been developed for injection and used off-label for decades. We found large variability in lung function over time in both treated groups, but no significant difference in FEV_1 and FVC between the two treatment regimens.

A post hoc analysis suggested that the initial sample size calculation underestimated the required number of patients to demonstrate differences between TIS300 and Tiv80 in the present study. Therefore, it was not possible to show superiority of one or the other treatment regimen. Our original sample size calculation was based on the results of a large multicentre, double-blind, placebo-controlled trial by Ramsey et al (4), showing an average increase in FEV_1 of 10% compared with placebo. This study assumed that the preparation used during the washout phase (colistin) as well as the Tiv80 preparation do not have efficacy in excess of placebo. The present study provides indirect evidence that this assumption was incorrect. In another randomized clinical trial (9), TIS300 produced a mean 6.7% improvement in FEV_1 , while there was a small, nonsignificant increase of 0.37% in the colistin-treated group.

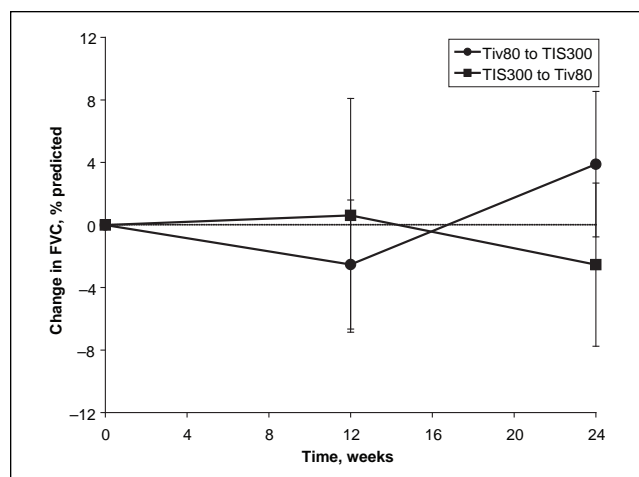


Figure 2 Change in forced vital capacity (FVC) in per cent predicted from baseline by treatment arm. Data are presented as mean per cent predicted with 95% CI. Tiv80 represents the 80 mg tobramycin intravenous preparation whereas TIS300 refers to the 300 mg tobramycin solution for inhalation. Differences between groups are not significant

The difference between the two active treatment regimens was measured after one month following a two-week screening period of no antipseudomonal antibiotics by any route. The mean change in FEV_1 observed after TIS300 in our population of patients was much smaller (+2.3%), which may reflect the fact that we did not take patients off inhaled antibiotics before initiation of tobramycin treatment, but rather elected to use colistin during the washout period. Presuming that colistin has a benefit for treatment of chronic *P. aeruginosa* airway infection, it cannot necessarily be assumed that lung function will increase with a change in inhaled antibiotics. The results of the present study failed to demonstrate either impressive changes from baseline or significant differences between the two doses of tobramycin, indicating that differences in clinical efficacy between these inhaled antibiotic regimens may be small. This finding may be relevant to the decision process of choosing a given treatment in CF patients, when other factors such as availability and cost of the different preparations also play an important role.

In our study, Tiv80 contained EDTA and sodium metabisulphite as antioxidants and phenol as a preservative, while TIS300 was free of antioxidants and preservatives. In a previous study (10), we have shown that there was no significant difference in bronchial reactions to the inhalation of tobramycin formulations with and without antioxidants or preservatives. Therefore, it is unlikely that the different formulations used in our study had an effect on the outcome of the trial.

When patients were asked about their individual preferences, 59% preferred the preservative-free tobramycin compared with only 22% favouring the intravenous preparation. This difference in preference may be related to perceived efficacy of treatment or to the preference of using an on-and-off regimen, with the possibility to take a break from the time-consuming inhalation of antibiotics. The individual preference for TIS300 did not correlate with any other outcome measure such as lung function and had no effect on patient self-reported adherence. It is, therefore, unlikely that the

patients who preferred TIS300 experienced greater improvement on treatment. In addition, data on treatment preference in an open trial have to be interpreted with caution.

The present study has a number of important limitations. As pointed out earlier, all patients had previously been treated with inhaled antibiotics (mostly the intravenous tobramycin preparation), which may affect the expected effect size of the new treatment regimen (TIS300) in the present study. However, the lack of impressive superiority of TIS300 in the present study may reflect efficacy of the lower dose tobramycin preparation. We cannot exclude the fact that our study was of insufficient duration because the change in FEV₁ and FVC might not have reached a plateau, and thus the final difference between the groups might not have been discerned. The study was performed unblinded because of the difficulties in blinding two treatments that vary in schedule (on and off versus continuous) and volume of nebulized solution. We also did not use a washout period both at the beginning of the trial and before crossover to the other treatment regimen. While a carryover effect between treatments cannot be completely excluded, the sequence of therapy had no detectable effect on efficacy. A small statistically insignificant difference between TIS300 and Tiv80 was observed in patients receiving TIS300 as initial treatment or during the second cycle.

Because the present trial failed to provide evidence for a marked increase in FEV₁ in response to treatment in patients previously treated with inhaled antibiotics, an alternative approach to evaluate the efficacy of different treatment

strategies could be to compare the rate of decline in lung function of patients receiving different doses of inhaled tobramycin. In addition, it may be meaningful to assess the effect of treatment on the development of antibiotic resistance, which may potentially occur at a higher rate in patients receiving continuous inhalation with lower doses of tobramycin. This would require a long-term prospective study in a large patient population or, alternatively, the analysis of a large database containing patients treated with these two antibiotic regimens. It would also be possible to investigate other important outcome parameters such as exacerbation rate and the potential for organism antibiotic resistance. The results of such a study could serve as a basis for a more evidence-based approach to weigh the cost-benefit ratio of different tobramycin preparations that are available to treat chronic *P aeruginosa* infection in CF patients.

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