

LETTER TO THE EDITOR

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# Once daily aerosolised tobramycin in adult patients with cystic fibrosis in the management of *Pseudomonas aeruginosa* chronic infection

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## Abstract

It is estimated that about 60–70% of Cystic Fibrosis patients develop *Pseudomonas aeruginosa* chronic infection, with progressive loss of lung function, as well as increased antibiotic resistance and mortality. The current strategy is to maintain lung function by chronic suppressive antipseudomonas antibiotic therapy. Tobramycin inhalation solution was the first approved aerosolised antibiotic to be used against *P. aeruginosa*; inhalatory tobramycin frequency of administration is twice daily and inhalation time is estimated to be 15 to 20 min. From the pharmacokinetic point of view, aminoglycosides are dose-dependent antibiotics and therefore once-daily dosing intravenous regimens have shown to be superior to the conventional multiple daily dosing. Therefore, there is no pharmacological reason to prefer the b.i.d administration as it is usually performed in current clinical practice. Should this be confirmed also for inhalatory route, the use of once-daily dosed aerosolized tobramycin could be an important step in making treatment burden easier in CF patients. The aim of this proof of concept study was to explore the effectiveness of treatment with once daily inhaled tobramycin in reducing *P. aeruginosa* density in sputum of chronically infected patients.

**Keywords:** *P. aeruginosa* chronic infection, Tobramycin, Aerosolised antibiotic therapy, Cystic fibrosis

It is estimated that during their lifetime about 60–70% of Cystic Fibrosis patients develop *P. aeruginosa* chronic infection, with progressive loss of lung function, as well as increased morbidity and mortality [1]. In addition, the massive use of antibiotics during bronchial exacerbations is associated with the selection of antibiotic resistance [2].

Commonly, a period of intermittent colonization by *P. aeruginosa* precedes the establishment of chronic infection and, in this window, efforts are made to obtain bacterial eradication by means of standardized antibiotic strategies.

Once infection is established, the current strategy is to maintain lung function by chronic suppressive antipseudomonas antibiotic therapy. Alongside the more traditional

routes of administration (oral or IV), aerosol delivery has become a notable complementary strategy [3, 4].

Tobramycin inhalation solution (TIS) was the first approved aerosolised antibiotic to be used against *P. aeruginosa* (FDA, 1998). TIS frequency of administration is twice daily and inhalation time is estimated to be 15 to 20 min (excluding time for maintenance and disinfection of the nebulizer). Given the heavy burden of care in CF, attempts to reduce the time of administration have been discussed and a great number of studies addressing new delivery strategies have been reported [5, 6].

From the pharmacokinetic point of view, aminoglycosides are dose-dependent antibiotics and therefore once-daily dosing regimens have shown to be superior to the conventional multiple daily dosing [7]. Therefore, there is no pharmacological reason to prefer the b.i.d administration as it is usually performed in current clinical practice. Pharmacokinetic data on sputum concentration of tobramycin following aerosol administration are inconclusive

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[8] and recent data seems to indicate the possible efficacy of using once daily tobramycin in reducing *P. aeruginosa* bacterial load in chronic sinusitis in CF [9]. Should this be confirmed, the use of once-daily dosed aerosolized tobramycin could be an important step in making treatment burden easier in CF patients.

The aim of this proof of concept study was to explore the effectiveness of treatment with once daily inhaled tobramycin in reducing *P. aeruginosa* density in sputum of chronically infected patients.

A once daily dose regimen of 300 mg aerosolised tobramycin [Bramitob<sup>®</sup>, Chiesi Farmaceutici] was administered for one month in adult CF patients with chronic *P. aeruginosa* infection, after a 4-week wash-out period of antisepedemonal therapy.

Patients were evaluated at T1, at the end of wash-out period, at T2, after 7 days of treatment, at T3, after 21 days of treatment and at T4, at the end of the 28-day treatment period.

The following parameters were analysed:

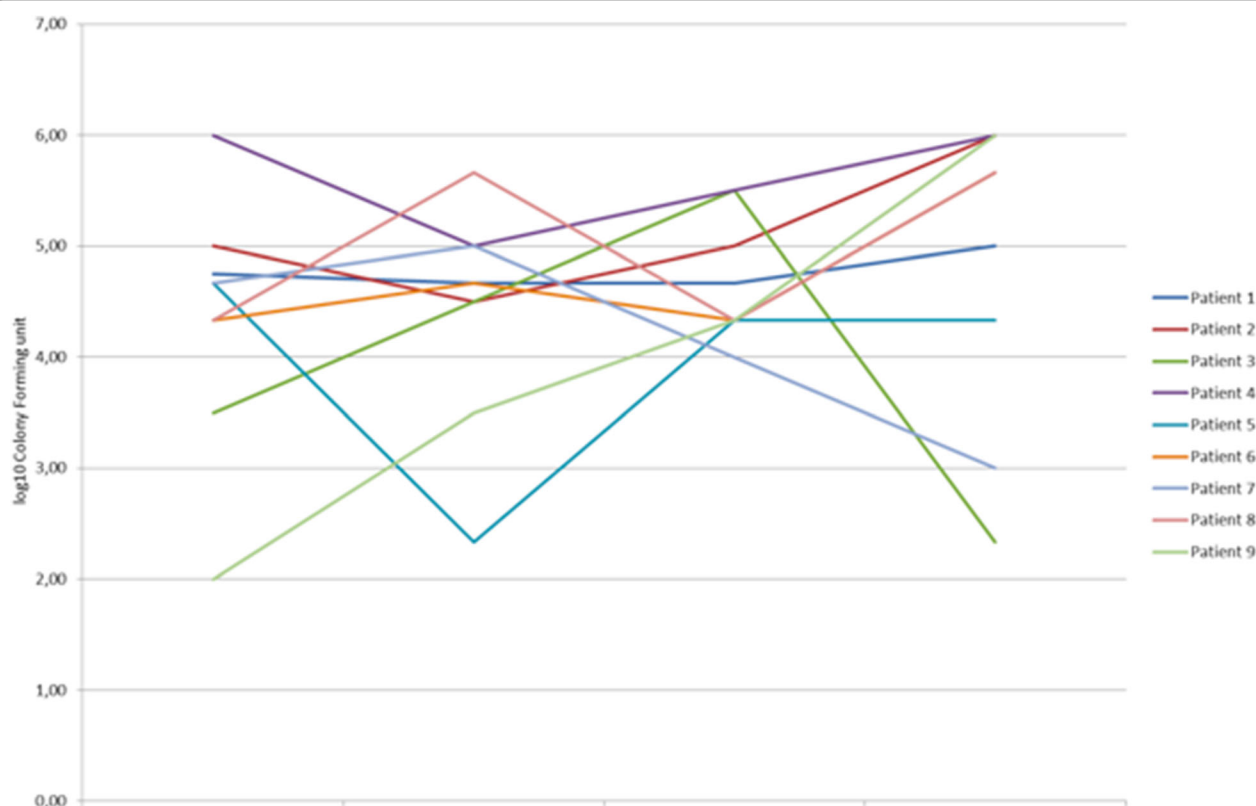
- Maximum bacterial load in sputum. (Max load)
- Mean bacterial load in sputum. (Mean load).
- Tobramycin-resistant *P. aeruginosa* strains (n°).
- Tobramycin-resistant *P. aeruginosa* strains (%).

- change in daily sputum amount.
- change in Forced Expiratory Volume in the first second (FEV<sub>1</sub>).
- change of systemic inflammatory markers, C-Reactive Proteine (CRP) and Procalcitonin (PCT).
- change in serum cytokines profile; Interleukin 2; (IL2), Interleukin 4 (IL4); Interleukin 6 (IL6); Interleukin 8 (IL8); Interleukin 10 (IL10); Vascular Endothelial Growth Factor (VEGF); Interferon Gamma (INF $\gamma$ ); Tumor Necrosis Factor Alfa (TNF $\alpha$ ); Interleukin 1a (IL1a); Interleukin 1b (IL1b); Monocyte Chemoattractant Protein 1 (MCP1); Epidermal growth factor (EGF).

A comparison between data obtained at basal time (T1) and at T2, T3 and T4 was performed.

A total of 12 patients [7 males/2 females, mean age (SD) 35.1 (8.1) years] with chronic *P. aeruginosa* infection were enrolled. Nine patients completed the study, 2 were excluded from the study because sputum culture tests resulted negative for *P. aeruginosa* before the first dose of tobramycin, and 1 patient withdrew consent.

No statistically significant differences in the Max and Mean bacterial load expressed as median and inter quartile range (IQR) at the different time points, were found;



**Fig. 1** Mean bacterial load trend for each patient. T1: end of wash-out period; T2: 7 days after the beginning of treatment; T3: 21 days after the beginning of treatment; T4: end of the 28-day treatment

respectively 5.0 (4.5–5.5) log 10 CFU at T1, 5.0 (4.5–5.5) log 10 CFU at T2, 5.0 (5.0–6.0) log 10 CFU at T3 and 6.0 (5.0–6.0) log 10 CFU at T4;  $p$  (ANOVA) = 0.27 and 4.7 (3.9–4.9) log 10 CFU at T1, 4.7 (4.0–5.0) log 10 CFU at T2, 4.3 (4.3–5.3) log 10 CFU at T3 and 5.7 (3.7–6.0) log 10 CFU at T4  $p$  (ANOVA) = 0.50. No difference in the mean (IQR) percent of predicted FEV<sub>1</sub> at the different time points was found, 64 (60.50–80.00)% at T1 68.00 (59.00–79.50)% at T2, 69.00 (58.50–83.50)% at T3 and 67 (57.00–77.50)% at T4  $p$  ANOVA = 0.97. Despite this, no increase in the number of resistant bacterial strains was registered and no difference in the mean (IQR) sputum 24-h production at the different time points were found, 25 (11.25–27.00) ml/day at T1, 20.00 (8.70–27.50) ml/day at T2, 15.00 (11.25–25.00) ml/day at T3 and 25.00 (11.25–30.00) ml/day at T4  $p$  ANOVA = 0.93.

No difference in inflammatory markers was found, CRP expressed as median and IQR, at the different time points were 0.29 (0.21–0.44) mg/dl at T1, 0.39 (0.25–0.83) mg/dl at T2, 0.31 (0.25–0.56) mg/dl at T3 and 0.32 (0.20–1.36) mg/dl at T4  $p$  ANOVA 0.86; PCT expressed as median and IQR was 0.05 (0.03–0.06) µg/ml at T1, 0.05 (0.04–0.06) µg/ml at T2, 0.31 (0.25–0.56) µg/ml at T3 and 0.32 (0.20–1.36) µg/ml at T4  $p$  ANOVA = 0.86.

No difference in the cytokine profile was found at the different time points.

The analysis of the mean bacterial load showed reductions in some patients, but not in others, see Fig. 1.

The main finding is that none of the selected outcomes (lung function, bacterial load, inflammation and cytokine profile) significantly changed during and at the end of the study, but some response may be observed in selected patients.

## Conclusion

These results may be related to the small sample size, but the lack of any positive trend suggests that the use of 300 mg of once daily aerosolised tobramycin is insufficient in treating the majority of CF patients with chronic *P. aeruginosa* infection. However, individual patients did benefit from once daily aerosolized tobramycin. Moreover, no increase in inflammatory and cytokine profile was found and no evidence of resistant strain selection emerged showing that in all patients some form of control of infection and inflammation was attained.

This leads us to conclude that it would be interesting to further explore the use of tobramycin with a phase II study with a dose-finding design and to confirm the existence of patients who are responders to once daily aerosolised tobramycin.

## Abbreviations

ANOVA: Analysis of variance; CF: Cystic fibrosis; CFU: Colony forming units; CRP: C-Reactive protein; EGF: Epidermal growth factor; FEV<sub>1</sub>: Forced expiratory volume in 1 s; IL: Interleukin; INFγ: Interferon gamma; IQR: Inter-quantile ranges;

MCP1: Monocyte chemoattractant protein 1; PCT: Procalcitonin; TIS: Tobramycin inhalation solution; TNFα: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor

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## Availability of data and materials

All materials described in the manuscript will be freely available to any scientist wishing to use them for non-commercial purposes.

## Authors' contributions

FB and GP contributed to conception, design and interpretation of data, as well as in drafting and revising the manuscript. MM and AG contributed to the design, analysis and interpretation of data, as well as in drafting and revising the manuscript. All authors read and approval the final manuscript.

## Authors information

Not applicable.

## Competing interests

GP has received personal fees from Chiesi and Vertex; FB has received personal fees from Bayer, Novartis, Menarini, Guidotti, Almirall, AstraZeneca, Dompè, Glaxo-SmithKline, and TEVA, and grants and personal fees from Pfizer, Chiesi, and Zambon. No competing interests for all other authors.

## Consent for publication

All authors gave their consent to publication in this journal.

## Ethics approval and consent to participate

Research has been performed in accordance with the Declaration of Helsinki and has been approved by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethics on nov 4, 2011 (prot. 180/2011 det. 2614/2011). Informed consent to participate in the study has been obtained from all participants. This trial was prospectively registered on EU Clinical Trial Register: EUDRACT 2011–001821–26 (<https://www.clinicaltrialsregister.eu/ctr-search/search?query=2011-001821-26>).

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## References

- Li Z, Kosorok MR, Farrell PM, Laxova A, West SE, Green CG, et al. Longitudinal development of mucoid *Pseudomonas aeruginosa* infection and lung disease progression in children with cystic fibrosis. *JAMA*. 2005; 293(5):581–8.
- Steinkamp G, Wiedemann B, Rietschel E, Krah A, Gielen J, Bärmeier H, et al. Prospective evaluation of emerging bacteria in cystic fibrosis. *J Cyst Fibros*. 2005;4:41–8.
- Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176(10):957–69.
- Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest*. 2001;120(3 Suppl):107S–13S.
- Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. *Pediatr Pulmonol*. 2002;33(4):269–76.
- Murphy TD, Anbar RD, Lester LA, Nasr SZ, Nickerson B, VanDevanter DR, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol*. 2004;38(4):314–20.
- Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med*. 1996;124(8):717–25.

8. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic fibrosis inhaled tobramycin study group. *N Engl J Med*. 1999;340(1):23–30.
9. Mainz JG, Schädlich K, Schien C, Michl R, Schelhorn-Neise P, Koitschev A, et al. Sinonasal inhalation of tobramycin vibrating aerosol in cystic fibrosis patients with upper airway *Pseudomonas aeruginosa* colonization: results of a randomized, double-blind, placebo-controlled pilot study. *Drug Des Devel Ther*. 2014;8:209–17.

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