TOBI®: reducing the impact of pseudomonal infection

John Govan

Pseudomonas aeruginosa infection is associated with impaired lung function and reduced life expectancy in cystic fibrosis patients. Tobramycin nebulizer solution (TOBI®, Chiron Corporation Ltd, Hounslow) has been specifically formulated for use against P. aeruginosa infection in the lung.

Professor John Govan is Professor of Microbial Pathogenesis in the Department of Medical Microbiology, University of Edinburgh Medical School, Edinburgh EH8 9AG

An estimated 7500 people in the UK have cystic fibrosis (CF) and a further 2.4 million carry a mutation in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) – the protein that regulates salt and water movement across epithelial cell membranes. Within the airways, faulty salt and water regulation leads to a build up of tenacious mucus, resulting in impaired clearance of microorganisms, recurrent infection, bronchial damage, bronchiectasis and ultimately death as a result of respiratory failure. In recent years, a combination of improved infection control, regular physiotherapy, better nutrition and other supportive measures has led to significant improvements in life expectancy for people with CF, and there will soon be equal numbers of adults and children with the disease (*Figure 1*).

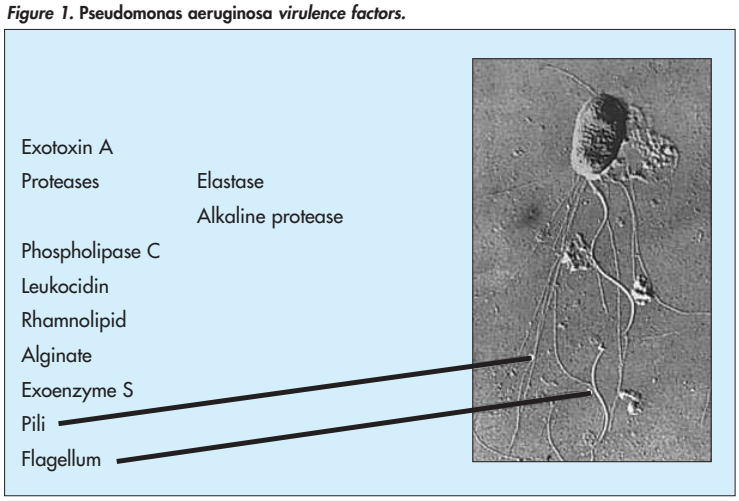
Continued improvements in the outlook for CF patients will depend largely on our detection of disease and on our ability to control and prevent the chronic infections, particularly those caused by *Pseudomonas aeruginosa* and *Burkholderia cepacia*, that lead to progressive inflammatory damage, impaired lung function and respiratory failure (Kerem et al, 1990; Hudson et al, 1993; FitzSimmons, 1996). A growing body of research is demonstrating that early intervention with nebulized antibiotics to prevent chronic infection, and prevention of cross infection with *P. aeruginosa* can have a significant impact on prognosis (Littlewood et al, 1985; Valerius et al, 1991; Frederiksen et al, 1997, 1999) (*Figure 2*).

THE *PSEUDOMONAS* PROBLEM

Recent data from the European Epidemiologic Registry of Cystic Fibrosis (ERCF) revealed an overall prevalence of *P. aeruginosa* of 54.2% in children aged 6–12 years, rising to 78.8% in those over 18 years (Navarro et al, 2001). Initial colonization is typically with a non-mucoid form of *P. aeruginosa* that is sensitive to antibiotic therapy. But the subsequent emergence of mucoid variants of a colonizing strain is associated with progression to chronic pseudomonal infection, which is hard to eradicate (Govan and Deretic, 1996). Chronic pseudomonal infection is linked to deteriorating lung function and increased respiratory morbidity and mortality (Henry et al, 1992; Pamukcu et al, 1995). Recent reports have highlighted the disturbing spread of multiresistant strains of *P. aeruginosa* in large CF clinics (Cheng et al, 1996; Jones et al, 2001) and the ability of such strains to superinfect patients already colonized with other *P. aeruginosa* (McCallum et al, 2001).

In its report on *P. aeruginosa* infection, the UK's Cystic Fibrosis Trust advised that all specialist CF centres and CF clinics should have a policy on cross-infection that addresses issues of surveillance, hygiene and segregation (Cystic

Figure 1.* Pseudomonas aeruginosa *virulence factors.



Fibrosis Trust, 2001). It recommended that all centres and clinics should undertake surveillance to ensure that cross infection is rapidly detected, and put in place appropriate measures to limit spread. It also advised that every effort should be made to use appropriate antibiotic therapy to eradicate *P. aeruginosa* when it is first cultured in respiratory samples. When such a policy is practised successfully, deterioration of lung function is significantly less than in CF patients who become chronically infected with *P. aeruginosa* (Frederiksen et al, 1997). However, when chronic infection does occur antibiotic therapy is also essential to maintain lung function and prevent further pulmonary damage.

TOBI

Tobramycin is an aminoglycoside antibiotic that is active against both non-mucoid and mucoid strains of *Pseudomonas*. The minimum inhibitory concentration required to inhibit 90% of strains (MIC_{90}) in vitro ranged from 8–64 mg/litre (Lamb and Goa, 1999).

As direct delivery of antibiotics into the airways of CF patients has obvious potential advantages in terms of maximizing local concentrations while minimizing systemic exposure, a preservative-free, nebulized formulation of tobramycin has been developed that matches the pH and osmolarity of the lung.

TOBI (tobramycin nebuliser solution 300 mg/5 ml, Chiron Corporation Ltd, Hounslow) is licensed for the long-term management of chronic pulmonary infection caused by *P. aeruginosa* in CF patients aged 6 years and over. It is administered twice daily via a PARI LC Plus nebulizer (PARI Medical Ltd, West Byfleet) in a '28 days on, 28 days off' cycle of treatment.

Inhalation of a 300 mg dose of TOBI is associated with mean sputum concentrations (measured 10 minutes after administration) well above the MIC_{90} for *P. aeruginosa*: 1159±1150 mg/litre (Burns et al, 1999; Lamb and Goa, 1999). These are much higher than the levels achieved by intravenous administration and are necessary to achieve concentrations bactericidal for *P. aeruginosa*. As tobramycin is inactivated in purulent sputum, concentrations of 10–25 times the MIC are required for bacterial killing (Mendelman et al, 1985; LiPuma, 2001; Pai and Nahata, 2001).

At the same time, the drug has a low systemic bioavailability (11.7%) with a median serum concentration of 0.98 mg/litre 1 hour after inhalation (Lamb and Goa, 1999).

FORMULATION ISSUES

With a median particle diameter of 4 μm, TOBI has been formulated for delivery into the peripheral airways where infection is most likely to occur. Smaller particles (≤1 μm) may travel too deeply into the alveoli and may increase systemic absorption, while larger particles (>5 μm) are likely to be deposited in the central airways or oropharynx (Touw et al, 1995).

Some intravenous formulations of tobramycin may contain phenol as a preservative and, although these formulations have been used for aerosol therapy, the use of phenol can cause bronchoconstriction in CF patients (Nikolaizik et al, 1996). TOBI has therefore been formulated without the need for phenol as a preservative. Another preservative that is found in parenteral tobramycin solutions is sodium metabisulphite, which can also cause bronchoconstriction when inhaled (Nichol et al, 1989; Wright et al, 1990).

CLINICAL EFFICACY

TOBI 300 mg/5 ml, administered via a PARI LC Plus nebulizer, in a '28 days on, 28 days off' treatment cycle is associated with improved lung function in CF patients with confirmed *P. aeruginosa* infection (Ramsey et al, 1999).

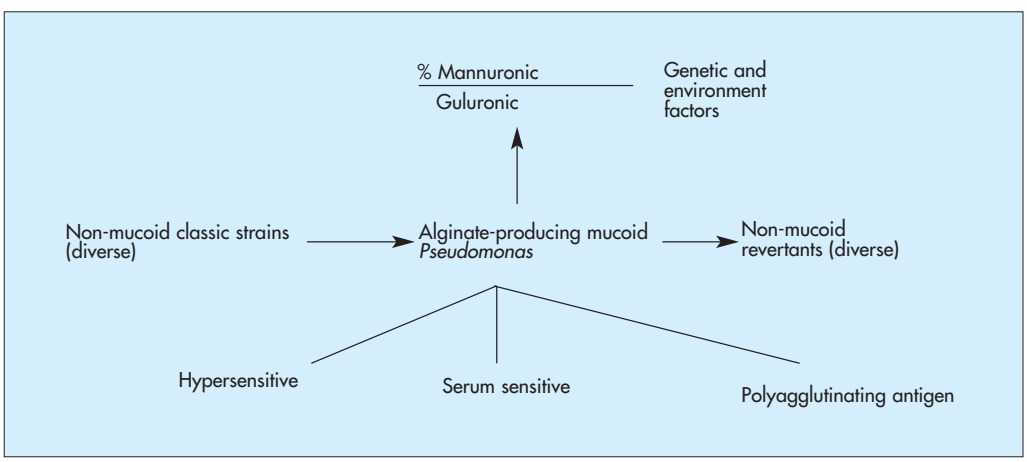


Figure 2. Heterogeneity of Pseudomonas within a single cystic fibrosis patient.

In two multicentre trials, 520 CF patients (mean age 21 years) were randomly assigned to TOBI 300 mg/5 ml administered twice daily or placebo in addition to their usual care for 4 weeks followed by 4 weeks with no study drug. Patients received treatment or placebo in three on–off cycles for a total of 24 weeks (Ramsey et al, 1999).

At week 20, forced expiratory volume in 1 second (FEV_1) in TOBI-treated patients had increased by 10% compared with baseline, whereas patients in the placebo group had a 2% decline in lung function ($P<0.001$). The greatest improvement was seen in adolescent patients, aged 13–17 years, who were in the TOBI group (*Figure 3*).

In the tobramycin group, there was an average reduction in *P. aeruginosa* density of 0.8 $\log_{10}$ colony forming units (CFU) per gram of sputum, compared to an increase of 0.3 $\log_{10}$ CFU/g with placebo ($P<0.001$).

In an extension to the 24-week trials, 242 CF patients completed open cyclical treatment with TOBI for a further 18 months (Moss, 2001). The improvement in lung function in patients who received TOBI throughout the trial was sustained throughout the 96 weeks of the study. At 92 weeks, mean FEV_1 was 4.7% above pre-treatment baseline.

The improvement was again most marked in the 13–17 years age group, where there was a 14.3% improvement in FEV_1 compared with baseline (Moss et al, 1999).

Patients who were switched from placebo to TOBI during the open phase of the study showed a marked improvement in FEV_1, but the loss in lung function that had occurred during placebo treatment was not entirely regained.

As with the earlier analysis, TOBI-treated patients continued to require less frequent hospitalization and intravenous antipseudomonal antibiotics than was required by patients in the placebo arm in the original 24-week studies.

CLINICAL SAFETY

In clinical trials, TOBI was well tolerated. In the 24-week studies described above (Ramsey et al, 1999), tinnitus and voice alteration were the only adverse events that were reported significantly more frequently in the TOBI than in the placebo-treated patients. Tinnitus was reported in eight TOBI-treated patients (3.1%) compared with none in the placebo group. It was transient, mild to moderate in severity, did not increase with subsequent cycles of treatment and did not necessitate withdrawal from the study.

Voice alteration was reported by 33 TOBI-treated patients (12.8%) and by 17 in the placebo group (6.5%). In most cases, it was minimal and did not increase with subsequent treatment cycles or require withdrawal from the study. As intravenous aminoglycoside treatment has been associated with ototoxicity, serial audiological tests were performed in 302 patients (148 in the tobramycin and 154 in the placebo group). No hearing loss was found in

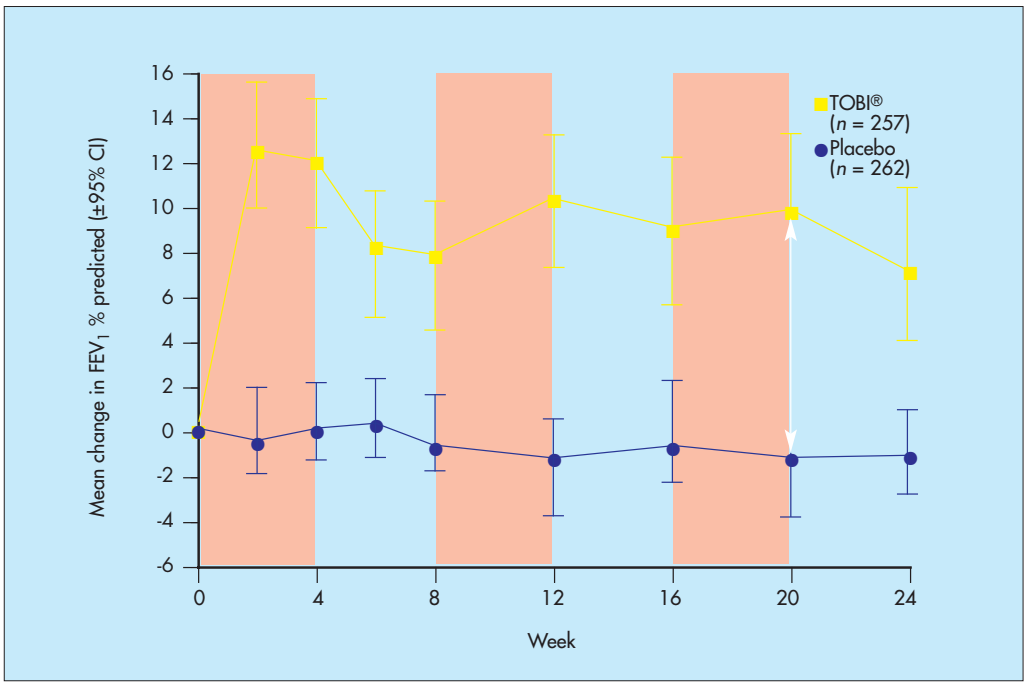


Figure 3. Mean change in forced expiratory volume in 1 second (FEV_1). From Ramsey et al (1999). CI = confidence interval.

either group. Mean serum creatinine levels were comparable in the two groups, with nine patients in each group experiencing a transient increase of 50% or more.

Long-term treatment with TOBI has also proved to be well tolerated. Safety data from the open label extension to the pivotal clinical trials of TOBI showed that most adverse events became less frequent with increasing exposure. At 96 weeks, the incidence of tinnitus in TOBI-treated patients was 3.5% and that of voice alteration had fallen to 3.9%. Once again, there was no evidence of oto- or nephrotoxicity associated with TOBI treatment.

MICROBIOLOGY

In common with other antibiotics, resistance to tobramycin is seen with increasing exposure to the drug. However, there is no evidence that the degree of resistance observed so far with either TOBI or colistin (a well-established antibiotic for the treatment of *P. aeruginosa* infections in CF patients) has an adverse effect on TOBI-related improvements in lung function (Govan, 2002). There is also some evidence that increases in in-vitro MICs should not preclude the subsequent effective usage of combination antibiotic therapy for exacerbations (Burns et al, 2000).

The parenteral breakpoint for tobramycin resistance is an MIC ≥16 μg/ml (National Committee for Clinical Laboratory Standards, 1998). Analysis of samples collected during the 24-week placebo-controlled trials of TOBI showed that the proportion of patients with at least one isolate with a tobramycin MIC ≥16 μg/ml increased from 13% at baseline to 26% at 20 weeks. It dropped back to 23% at 24 weeks (i.e. the end of the third 'off-drug' interval). Comparable figures in the placebo group were 10%, 17% and 8% respectively (LiPuma, 2001).

When clinical response was related to *P. aeruginosa* susceptibility to tobramycin at 20 weeks and 92 weeks, FEV_1 improvements were seen in all groups of TOBI-treated patients (MIC ≤8 μg/ml, MIC 16–64 μg/ml and MIC ≥128 μg/ml). Indeed, at 92 weeks, the proportions of patients with increases in FEV_1% predicted from baseline were similar across all pseudomonal susceptibilities to tobramycin.

These data provide evidence that MIC breakpoints based on parenteral therapy may not be relevant for nebulized TOBI because of the high sputum levels of tobramycin that are achieved with this formulation (Burns et al, 1999; Hodson et al, 2000; Moss, 2001; Govan, 2002).

FUTURE INDICATIONS

TOBI is the subject of a continuing international programme of research in non-CF indications.

Colonization with *P. aeruginosa* is a common feature of bronchiectasis, especially in patients with more extensive and severe disease, and antimicrobial therapy is an important aspect of disease management (Barker et al, 2000). As in CF, the opportunity to administer high concentrations of antibiotic directly to the site of infection, with minimal systemic effects, is attractive.

In a phase II trial, 74 stable bronchiectasis patients with *P. aeruginosa* infection were randomized to TOBI or placebo twice daily for 4 weeks, followed by a 2-week off-drug phase (Barker et al, 2000). Sixty patients completed the study. At week 4, there was a mean decrease in *P. aeruginosa* density of 4.54 $\log_{10}$ CFUs per gram of sputum in the TOBI group, compared with no change in the placebo group. At week 6, *P. aeruginosa* was eradicated in 35% of TOBI-treated patients but was detected in all of those in the placebo group. Interestingly, these results highlight the greater opportunity to reduce the bacterial load in the bronchiectactic lung compared with the CF lung. Tobramycin-resistant strains of *P. aeruginosa* were detected, according to current intravenous breakpoints, in 11% of the TOBI group and 3% of the placebo patients (P=0.36).

There was no improvement in lung function in the TOBI compared with the placebo group, but investigators indicated that 62% of patients taking TOBI showed an overall improved medical condition compared with 38% of placebo patients. Cough, dyspnoea, wheezing and non-cardiac chest pain were more common in the TOBI-treated patients but these symptoms did not limit therapy.

This phase II study was designed and powered to determine the microbiological efficacy of TOBI in bronchiectasis patients with *P. aeruginosa* and further trials are now needed to confirm determine clinical efficacy and safety.

CONCLUSIONS

P. aeruginosa is a major cause of morbidity and contributes to increased mortality in CF patients as a result of lung function deterioration. Antibiotic therapy that can effectively target *P. aeruginosa* is essential, and should not only prevent further loss of lung function, but improve lung function.

TOBI is a ready-to-use, preservative-free formulation of tobramycin that has been developed specifically for nebulizer administration to treat *P. aeruginosa* infection in the lung.

In clinical trials of CF patients with *P. aeruginosa* infection, intermittent (1 month on, 1 month off) twice-daily treatment with TOBI was associated with significant reductions in *P. aeruginosa* density, accompanied by sustained improvements in lung function over a 2-year period. Hospitalization and need for intravenous antibiotics were also reduced in TOBI-treated patients.

Adolescent CF patients, aged 13–17 years, showed the greatest benefit from TOBI treatment, in terms of sustained improvements in lung function.

Extensive experience has shown that TOBI is well tolerated with no evidence of oto- or nephrotoxicity with long-term treatment. **HM**

Conflict of interest: Professor John Govan wrote this article at the invitation of Chiron Corporation Ltd.

Barker AF, Couch L, Fiel SB et al (2000) Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med* **162:** 481–5

Burns JL, Van Dalfsen JM, Shawar RM et al (1999) Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbial flora in patients with cystic fibrosis. *J Infect Dis* **179:** 1190–6

Burns JL, Ramsey BW, Fiel SB (2000) In vitro antibiotic susceptibility testing of CF Pseudomonas isolates does not predict FEV1 response to combination intravenous antibiotic therapy [Abstract]. XIIIth International Cystic Fibrosis Congress, 4–8 June, Stockholm, Sweden

Cheng K, Smyth RL, Govan RJW et al (1996) Spread of a beta-lactumlactam-resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. *Lancet* **348:** 639–42

Cystic Fibrosis Trust (2001) *Pseudomonas aeruginosa* infection in people with cystic fibrosis. Suggestions for Prevention and Infection Control. Cystic Fibrosis Trust, Bromley, Kent

FitzSimmons S (1996) The Cystic Fibrosis Foundation Registry Report. *Pediatr Pulmonol* **21:** 267–75

Frederiksen B, Koch C, Hoiby N (1997) Antibiotic treatment of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* **23:** 330–5

Frederiksen B, Koch C, Hoiby N (1999) Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974–1995). *Pediatr Pulmonol* **28:** 159–66

Govan JRW (2002) Insights into cystic fibrosis microbiology from the European tobramycin trial in cystic fibrosis. *J Cystic Fibrosis* (in press)

Govan JR, Deretic V (1996) Microbial pathogenesis in cystic fibrosis: mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. *Microbial Rev* **60:** 539–74

Henry RL, Mellis CM, Petrovic L (1992) Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol* **12:** 158–61

Hodson ME, Gallagher CG, Govan JRW et al (2000) Randomised UK/Eire clinical trial of the efficacy and safety of tobramycin 300mg/5ml nebuliser solution or nebulised colistin. [Abstract]. *Pediatr Pulmonol* **2**(suppl): 269

Hudson VL, Wielinski CL, Regelman WE (1993) Prognostic implications of initial oropharyngeal bacterial flora in patients with cystic fibrosis diagnosed before the age of two years. *J Pediatr* **122:** 854–60

Jones AM, Govan JRW, Doherty CCCJ et al (2001) Spread of multiresistant strain of *Pseudomonas aeruginosa* in an adult cystic fibrosis clinic. *Lancet* **358:** 557–8

Kerem E, Corey M. Gold R et al (1990) Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonization with *Pseudomonas aeruginosa*. *J Pediatr* **116:** 714–9

Lamb HM, Goa KL (1999) Management of patients with cystic fibrosis. Defining the role of inhaled tobramycin. *Dis Manage Health Outcomes* **6:** 93–108

LiPuma JL (2001) Microbiological and immunological considerations with aerosolized drug delivery. *Chest* **120:** 118S–23S

Littlewood JM, Miller MG, Ghonheim AT, Ramsden CH (1985) Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. *Lancet* **i:** 865

Mendelman PM, Smith AL, Levy J et al (1985) Aminoglycoside penetration, inactivation and efficacy in cystic fibrosis sputum. *Am Rev Respir Dis* **132:** 761–5

McCallum SJ, Corkhill J, Gallagher M et al (2001) Superinfection with a transmissible strain of *Pseudomonas aeruginosa* in adults with cystic fibrosis chronically colonised by *P. aeruginosa*. *Lancet* **358:** 558–60

Moss RB (2001) Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest* **120:** 107S–13S

Moss R, Kylstra JW, Gibson R (1999) Who benefits more? An analysis of FEV_1 and weight in adolescent (ages 13-15) CF patients using TOBI (Tobramycin Solution for Inhalation). 13th North American Cystic Fibrosis Conference, October 7–10, Seattle, USA

National Committee for Clinical Laboratory Standards (1998) *Performance Standards for Antimicrobial Susceptibility Testing.* Eighth Information Supplement. National Committee for Clinical Laboratory Standards, Wayne, Pennsylvania

Navarro J, Rainisio M, Harms HK et al (2001) Factors associated with poor pulmonary function: cross-sectional analysis of data from the ERCF. *Eur Respir J* **18:** 298–305

Nichol GM, Nix A, Chung KF et al (1989) Characterisation of bronchoconstrictor responses to sodium metabisulphite aerosol in atopic subjects with and without asthma. *Thorax* **44**(12): 1009–14

Nicolaizik WH, Jenni-Galovic V, Schoni MH (1996) Bronchial constriction after nebulised tobramycin preparation and saline in patients with cystic fibrosis. *Eur J Pediatr* **155:** 608

Pamukcu A, Bush A, Buchdal R (1995) Effects of *Pseudomonas aeruginosa* colonisation on lung function and anthropomorphic variables in children with cystic fibrosis. *Pediatr Pulmonol* **19:** 10–15

Pai VB, Nahata MC (2001) Efficacy and safety of aerosolised tobramycin in cystic fibrosis. *Pediatr Pulmonol* **32:** 314–27

Ramsey BW, Pepe MS, Quan JM et al (1999) Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* **340:** 23–30

Touw DJ, Brimcombe RW, Hodson ME et al (1995) Inhalation of antibiotics in cystic fibrosis. *Eur Respir J* **8:** 1594–604

Valerius NH, Koch C, Hoiby N (1991) Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. *Lancet* **338:** 725–6

Wright W, Zang YG, Salome CM et al (1990) Effect of inhaled preservatives on asthmatic subjects. I sodium metabisulfite. *Am Rev Respir Dis* **141**(6): 1400–4

KEY POINTS

- TOBI (tobramycin, Chiron Corporation Ltd, Hounslow) is a 'ready to use' aminoglycoside antibiotic that is active against both non-mucoid and mucoid strains of *Pseudomonas*.
- TOBI 300 mg/5 ml, administered via a PARI LC Plus nebulizer (PARI Medical Ltd, West Byfleet), in a '28 days on, 28 days off' treatment cycle is associated with improved lung function in cystic fibrosis patients with confirmed *Pseudomonas aeruginosa* infection.
- In trials at week 20, forced expiratory volume in 1 second in TOBI-treated patients had increased by 10% compared with baseline, whereas patients in the placebo group had a 2% decline in lung function ($P<0.001$).
- The improvement in lung function in patients who received TOBI throughout the trial was sustained throughout the 96 weeks of the study.
- Long term treatment with TOBI has proved it is well tolerated with no evidence of oto- or nephrotoxicity.