

CF Guidelines - Nebulised Tobramycin

Nebulised Tobramycin:

Tobramycin is an aminoglycoside antibiotic with potent antipseudomonal activity. TOBI® is a pharmaceutical form of Tobramycin specifically formulated for nebulisation and is licensed for use in cystic fibrosis patients aged 6 years and older. Unlike other inhaled antibiotics, TOBI is taken in a continuous sequence of 8 week cycles – 4 weeks on treatment and 4 weeks off. It is delivered via a PARI LC PLUS nebuliser.

Indications for use:

Long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in CF patients aged 6 years and over.

Mechanisms of action:

When TOBI is administered by inhalation, high concentrations of antibiotic are achieved in the sputum. Levels achieved in the serum are extremely low; the ratio of serum to sputum concentration following TOBI administration is 0.010 (Geller et al, 2002). The dosing schedule for TOBI, 28 days on, followed by 28 days off, reduces the potential for decreased bacterial susceptibility due to continuous exposure to drug.

Evidence for efficacy:

Two large studies placebo-controlled studies have been conducted in the USA in 520 CF patients with *Pseudomonas aeruginosa* infection. Results showed that TOBI significantly improved lung function (FEV₁ % predicted) from 2 weeks onwards. Patients receiving TOBI demonstrated an average 10% increase in FEV₁ at week 20, compared to a 2% decline in those receiving placebo (a treatment effect of 12%, $p < 0.001$). At week 24 (the end of the third off-drug period), this treatment effect was 9%. (Ramsey et al, 1999)

Long-term efficacy and safety data were gathered during an open-label extension to the above 24 week studies. In the patients who continued with TOBI for the whole study, FEV₁ % predicted was 4.7% above pre-treatment at week 92 (the end of 9th on-drug period) and FEV₁ was maintained above pre-treatment value throughout the 96 weeks.

Sub-analyses of adolescent patients (aged 13-17 years) in the above 24-week and extension study found TOBI to be particularly effective in adolescents. The improvement in FEV₁ above pre-treatment was 15.9% at week 20, with a treatment effect compared with placebo of 23% ($p < 0.001$). In adolescents who were originally randomised to receive TOBI, an improvement in FEV₁ of 7.2% above pre-treatment value was noted at week 96. (Moss, 2002)

An open-label, randomised trial to evaluate the efficacy and safety of TOBI and colistin in CF patients chronically colonised with *Pseudomonas aeruginosa* has been conducted in the UK and Ireland. TOBI significantly improved lung function after four weeks of therapy (mean change in FEV₁ 6.7%). In contrast, there was no significant improvement in the colistin treated patients (0.37%). The between group differences proved to be statistically significant, with TOBI therapy producing significantly greater lung function improvement than Colistin. Both treatments were generally well tolerated, with no statistically significant differences in the overall incidence of adverse events or specific events. (Hodson et al, 2002)

Reduction in hospitalisation for infective exacerbations:

Inhalation of TOBI was associated with a significant reduction in hospitalisation (26%), compared to placebo over the 24 week period (Ramsey et al, 1999; Birnbaum et al, 1998). Reductions in hospitalisation rates, compared with placebo, were maintained throughout the 96-week extension study (Moss, 2001).

Reduction in IV antipseudomonal antibiotics:

TOBI therapy was also associated with a significant reduction in intravenous antipseudomonal therapy (36%), compared to placebo over the 24 week period (Ramsey et al, 1999; Birnbaum et al, 1998). Again, reduced requirement of IV antipseudomonal antibiotics, and oral quinolones, was reported in the 96-week extension study (Moss, 2001).

Quality of life (QOL):

For patients, use of TOBI may result in fewer exacerbations, fewer and shorter hospital admissions and reduced use of IV antibiotics. This, in addition, to the reduced number of days nebulising anti-pseudomonal antibiotic therapy (due to the 28 days on/28 days off regimen) may be associated with an improvement in quality of life. Physician assessments and a simple patient questionnaire attached to the 24-week placebo-controlled trials indicated that TOBI produced a significant improvement in QOL over placebo ($p < 0.05$) (Quittner et al, 2002).

TOBI should be considered for use in patients who:

- Are chronically colonised with *Pseudomonas aeruginosa*.
- Are over 6 years of age.
- Have had > 3 courses of IV antibiotics in the last 12 months.
- Have had an annual rate of loss of lung function >3% per year.
- Have tried nebulised colomycin and either failed to respond or been sensitive to it.
- Have previously been treated with intravenous tobramycin.
- Are compliant with other medications.

Trial Period:

Local practice may vary but TOBI should initially be tried for a period of 6 months (3 months of drug treatment). At the end of this period, if the drug has been tolerated, an assessment of efficacy should be undertaken to decide on further prescribing. This should/can involve:

- Comparison of FEV₁ decline with historical data over 6-12 months pre treatment.
- Use of IV antibiotics/hospitalisations compared to 6-12 months pre treatment.
- Other measures of health improvement such as weight/BMI.
- A measure of Quality of Life.
- Likelihood of continued adherence to treatment.

Side-effects:

- Bronchospasm can occur with inhalation of medicinal products and has been reported with nebulised Tobramycin. The first dose of TOBI® should be given under supervision. If bronchospasm occurs, try using a bronchodilator prior to each dose of Tobramycin.
- Tinnitus - transient and resolves without discontinuation of TOBI® therapy, and is not associated with permanent loss of hearing on audiogram testing.
- Sputum discolouration.

- Respiratory tract infection.
- Myalgia.

Other rare side-effects include:

- Gastrointestinal system:
 - Nausea.
 - Anorexia.
 - Mouth ulceration.
 - Vomiting.
- Nervous system:
 - Dizziness.
- Respiratory system:
 - Voice alteration.
 - Dyspnoea.
 - Increased cough.
 - Pharyngitis.
 - Lung disorder.
 - Increased sputum.
 - Haemoptysis.
 - Decreased lung function.
 - Laryngitis.
 - Epistaxis.
 - Rhinitis.
 - Asthma.
- Senses:
 - Taste perversion
 - Hearing loss
- Skin:
 - Rash
- General:
 - Chest pain.
 - Asthenia.
 - Fever.
 - Headache.
 - Pain.

In the double-blind randomised controlled trials, only tinnitus and voice alteration were significantly more common with TOBI than with placebo administration [3.1% vs. 0 and 12.8% vs. 6.5%, respectively]. No instances of hearing loss or renal dysfunction were recorded (Moss, 2001). In open-label studies some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. TOBI should be used with caution in patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis.

Contradictions:

Known sensitivity to any aminoglycoside.

Cautions:

- Nephrotoxicity - TOBI® should be used with caution in patients with known or suspected renal dysfunction and serum concentrations of Tobramycin should be monitored. Tobramycin levels need only to be measured in patients with known or suspected renal disease.
- Ototoxicity - In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy, it may be necessary to consider audiological assessment before initiating TOBI® therapy.
- Neuromuscular disorders - TOBI should be used with at caution in patients with neuromuscular disorders such as parkinsonism or other conditions characterised by Myasthenia, including Myasthenia gravis, as aminoglycosides may aggravate muscle weakness due to a potential curare-like effect on neuromuscular function.
- Haemoptysis - Inhalation of nebulised solutions may induce a cough reflex. The use of TOBI® in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

References:

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- 5, Hodson M.E, Gallagher CG, Govan, JR. A randomised clinical trial of nebulised Tobramycin or colistin in Cystic Fibrosis. Eur Respir J 2002; 20: 658-664.
- 6, Birnbaum H, et al. Analysis of hospitalization and IV anti-pseudomonal antibiotic use in Cystic Fibrosis patients on Tobramycin solution for inhalation (TOBI). Presented at 12th Annual North American Cystic Fibrosis Conference: Montreal, Canada, 1998.

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