

INTERMITTENT ADMINISTRATION OF INHALED TOBRAMYCIN IN PATIENTS WITH CYSTIC FIBROSIS

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ABSTRACT

Background and Methods We conducted two multicenter, double-blind, placebo-controlled trials of intermittent administration of inhaled tobramycin in patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. A total of 520 patients (mean age, 21 years) were randomly assigned to receive either 300 mg of inhaled tobramycin or placebo twice daily for four weeks, followed by four weeks with no study drug. Patients received treatment or placebo in three on-off cycles for a total of 24 weeks. The end points included pulmonary function, the density of *P. aeruginosa* in sputum, and hospitalization.

Results The patients treated with inhaled tobramycin had an average increase in forced expiratory volume in one second (FEV₁) of 10 percent at week 20 as compared with week 0, whereas the patients receiving placebo had a 2 percent decline in FEV₁ (P<0.001). In the tobramycin group, the density of *P. aeruginosa* decreased by an average of 0.8 log₁₀ colony-forming units (CFU) per gram of expectorated sputum from week 0 to week 20, as compared with an increase of 0.3 log₁₀ CFU per gram in the placebo group (P<0.001). The patients in the tobramycin group were 26 percent (95 percent confidence interval, 2 to 43 percent) less likely to be hospitalized than those in the placebo group. Inhaled tobramycin was not associated with detectable ototoxic or nephrotoxic effects or with accumulation of the drug in serum. The proportion of patients with *P. aeruginosa* isolates for which the minimal inhibitory concentration of tobramycin was 8 µg per milliliter or higher increased from 25 percent at week 0 to 32 percent at week 24 in the tobramycin group, as compared with a decrease from 20 percent at week 0 to 17 percent at week 24 in the placebo group.

Conclusions In a 24-week study of patients with cystic fibrosis, intermittent administration of inhaled tobramycin was well tolerated and improved pulmonary function, decreased the density of *P. aeruginosa* in sputum, and decreased the risk of hospitalization. (N Engl J Med 1999;340:23-30.)

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PERIODIC exacerbations of *Pseudomonas aeruginosa* endobronchial infection in patients with cystic fibrosis have traditionally been treated with parenteral antipseudomonal antibiotics for 7 to 21 days.¹ Despite frequent intravenous therapy, patients continue to have a decline in pulmonary function of approximately 2 per-

cent per year, and eventually 90 percent of such patients die of lung disease.^{2,3} Thus, long-term antibacterial therapy may help maintain pulmonary function.

Other investigators have used inhalation to deliver antibiotics directly to the site of infection.⁴⁻⁷ However, these studies have been limited by small numbers of subjects, short duration, uncertain delivery of antibiotics to the airways, and the absence of a taste-masked placebo. In a multicenter, crossover study, a regimen of 600 mg of inhaled tobramycin delivered with an ultrasonic nebulizer three times a day for up to 56 days was effective and safe, but the regimen was cumbersome and costly.⁸ A formulation of tobramycin designed for efficient jet nebulization provides similar antibiotic concentrations in airway secretions.⁹

We report the results of two placebo-controlled, multicenter, randomized, double-blind trials of the efficacy and safety of inhaled tobramycin, delivered by a jet nebulizer, for the treatment of *P. aeruginosa* infection in patients with cystic fibrosis. We studied whether this regimen would improve pulmonary function, have an antimicrobial effect in sputum, and decrease hospitalizations and the use of intravenous antipseudomonal antibiotics over a period of 24 weeks. In addition, we assessed the safety of this regimen and its effect on the susceptibility of *P. aeruginosa* to tobramycin.

METHODS

Study Design

Two identically designed trials, with a total of 520 patients enrolled at 69 cystic fibrosis centers in the United States, were conducted between August 1995 and October 1996. The base-line characteristics of the patients in the two studies were similar, permitting analyses of pooled data. The eligibility criteria included a

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documented diagnosis of cystic fibrosis, a respiratory tract culture yielding *P. aeruginosa*, an age of at least six years, an ability to perform reproducible pulmonary-function tests, and a forced expiratory volume in one second (FEV₁) that was at least 25 percent but no more than 75 percent of the predicted value. Criteria for exclusion were receipt of antipseudomonal antibiotics within the previous two weeks, known hypersensitivity to aminoglycosides, compromised renal function (serum creatinine level, ≥ 2 mg per deciliter [177 mmol per liter]), or recovery of *Burkholderia cepacia* from the respiratory tract within the previous two years. All patients or their guardians provided written informed consent, and the study was approved by the institutional review board at each participating center.

An adaptive-randomization procedure was used to assign patients in a 1:1 ratio to receive tobramycin or placebo, with stratification according to the ability or inability to produce sputum, the severity of disease as indicated by FEV₁ (<50 percent or ≥ 50 percent), age (6 to 12 years, 13 to 17 years, or ≥ 18 years), sex, treatment center, presence or absence of concurrent use of dornase alfa (Genentech, South San Francisco, Calif.), and susceptibility of *P. aeruginosa* to tobramycin (minimal inhibitory concentration [MIC], <8 μg per milliliter or ≥ 8 μg per milliliter).

Treatment Regimen and Monitoring

The treatment regimen consisted of 300 mg of aerosolized tobramycin or placebo twice daily in three cycles, with each cycle consisting of 28 days during which the drug was administered and 28 days during which it was not administered.

The active drug (tobramycin solution for inhalation, Pathogenesis, Seattle) is a sterile, pH-adjusted solution of 300 mg of preservative-free tobramycin in 5 ml of one-quarter strength normal saline. Taste-masked placebo, chosen to mimic the taste of the active drug, was 1.25 mg of quinine sulfate in 5 ml of one-quarter strength normal saline.⁸ The study drug was administered with a PARI LC PLUS jet nebulizer (Pari, Richmond, Va.) and a Pulmo-Aide compressor (DeVilbiss, Somerset, Pa.).

During the first cycle, the patients were evaluated every two weeks: at week 0 (the start of the first period of drug administration), week 2, week 4, and week 6. During the second and third cycles, the patients were evaluated every four weeks: at week 8 (the start of the second period of drug administration), week 12, week 16 (the start of the third period of drug administration), week 20 (the end of the third period of drug administration), and week 24 (the follow-up visit). Clinical evaluations and spirometry were performed, and sputum samples (or throat swabs if the patient could not expectorate) were obtained at each visit. At weeks 0, 4, 8, 12, 16, and 20, blood samples were obtained to evaluate drug safety, and auditory acuity was tested. Serum tobramycin levels were determined at weeks 0 and 20. All doses were administered by the patient, who was instructed to wear nose clips and perform normal tidal breathing. Patients were allowed to use their routine medications for the management of cystic fibrosis during the study. However, inhaled antibiotics other than the study drug were prohibited, and patients using dornase alfa or a pneumatic vest (ThAIRapy Vest, American Biosystems, St. Paul, Minn.), or both, were required to begin using them at least four weeks before week 0 and to maintain the same regimen throughout the study.

End Points

The primary end points of the study were lung function (FEV₁) and the density of *P. aeruginosa* in sputum at week 20. Secondary end points included hospitalization and treatment with intravenous antipseudomonal antibiotics.

Pulmonary-function testing was performed in accordance with American Thoracic Society standards.¹⁰ Lung function was expressed as the percentage of the value predicted on the basis of norms reported by Knudson et al.,¹¹ and changes were expressed as changes from values at week 0. The relative change in the percentage of the predicted value was calculated as follows:

$$\frac{\text{Percent predicted at week 20} - \text{percent predicted at week 0}}{\text{percent predicted at week 0}} \times 100.$$

Sputum samples were shipped on ice to a central laboratory (at Children's Hospital and Regional Medical Center, Seattle), where quantitative culture and subsequent tobramycin-susceptibility testing of each morphologically distinct *P. aeruginosa* isolate were performed.¹² The MIC of tobramycin for the isolate with the highest MIC cultured from each patient at week 0 and week 24 was documented. The density of *P. aeruginosa* in sputum was calculated as the log₁₀ value for the sum of all morphotypes (colony-forming units [CFU]) per gram of sputum.

Laboratory studies of safety and drug levels were performed at a central facility. Auditory acuity was tested at 39 centers by certified audiologists. The auditory threshold was determined at frequencies between 250 and 8000 Hz, with the use of a dual-channel audiometer. The criterion for hearing loss was a bilateral decrease of 15 dB or more in the auditory threshold at two consecutive frequencies, as compared with the findings on the first audiogram.

Spirometry was performed before and 30 minutes after administration of the study drug at weeks 0 and 20 to determine the risk of drug-induced bronchospasm. Changes in FEV₁ after administration of the study drug are expressed as percentages of the values obtained before administration of the study drug.

Statistical Analysis

Data from all patients who received at least one dose of the study drug were included in the analyses. Between-group comparisons of the mean relative change from week 0 in FEV₁ and forced vital capacity and the absolute change in the density of *P. aeruginosa* in sputum were performed with the use of analysis of variance. The relation between base-line characteristics and changes in FEV₁ was assessed with the use of multiple regression. Cox regression models were used to estimate the relative risks of hospitalization and the need for intravenous antipseudomonal antibiotic therapy. The number of days of hospitalization and intravenous antipseudomonal-antibiotic treatment were compared with a Wilcoxon rank-sum test. The number of adverse events was compared with Fisher's exact test. Values were not imputed for missing data.

RESULTS

Of 663 patients screened, 520 met the eligibility criteria and received at least one dose of study drug; 258 patients received tobramycin and 262 received placebo. The treatment groups were similar with respect to randomization strata, lung function, and the density of *P. aeruginosa* in sputum at week 0 (Table 1). Two hundred thirty-two of the 258 patients in the tobramycin group (90 percent) and 232 of the 262 patients in the placebo group (89 percent) completed the study. Compliance, as monitored by ampule count, was similar in the two groups, with 88 percent of the patients receiving tobramycin and 93 percent of those receiving placebo using at least 75 percent of the ampules that were dispensed.

Lung Function

In the tobramycin group, FEV₁, expressed as a percentage of the predicted value, improved during the first two weeks that the patients received the drug and remained above the value at week 0 throughout the remainder of the study, including

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS ACCORDING TO TREATMENT ASSIGNMENT.*

CHARACTERISTIC	TOBRAMYCIN (N=258)	PLACEBO (N=262)
Male sex — no. (%)	149 (58)	132 (50)
Age		
6–12 yr — no. (%)	55 (21)	61 (23)
13–17 yr — no. (%)	63 (24)	67 (26)
≥18 yr — no. (%)	140 (54)	134 (51)
Mean ±SD — yr	20.8 (9.5)	20.6 (10.0)
Use of dornase alfa — no. (%)	198 (77)	204 (78)
FEV ₁		
No. tested	257	262
Mean ±SD — % of predicted value	49.9±15.5	51.2±16.8
<i>P. aeruginosa</i> density		
No. tested	249	241
Mean ±SD — log ₁₀ CFU/g	7.6±1.2	7.3±1.6
MIC, ≥8 µg/ml — no./total no. (%)		
All patients	63/254 (25)	51/254 (20)
6–12 yr	11/54 (20)	14/60 (23)
13–17 yr	14/63 (22)	13/64 (20)
≥18 yr	38/137 (28)	24/130 (18)

*Percentages may not sum to 100 because of rounding. FEV₁ denotes forced expiratory volume in one second, CFU colony-forming units, and MIC minimal inhibitory concentration of tobramycin.

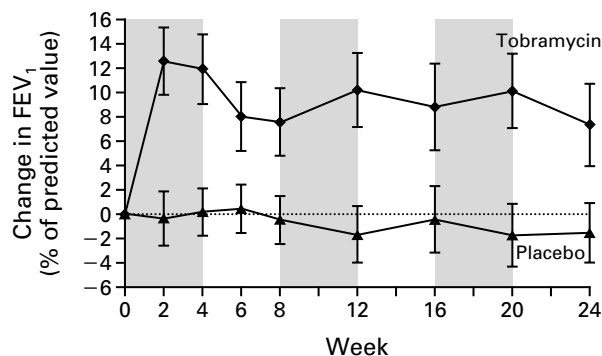


Figure 1. Mean Change in the Forced Expiratory Volume in One Second (FEV₁) in Patients Receiving Inhaled Tobramycin or Placebo.

The mean change from week 0 in FEV₁ (expressed as the percentage of the value predicted on the basis of age, height, and sex) is shown for each study visit. The shading denotes the periods when the subjects received tobramycin or placebo. The I bars represent 95 percent confidence intervals. FEV₁ values were available for 257 patients in the tobramycin group and 262 in the placebo group at week 0 and for 232 patients in the tobramycin group and 231 in the placebo group at week 20.

the periods when the drug was not being administered. At week 20, the end of the third period of drug administration, the patients receiving tobramycin had an average 10 percent increase in FEV₁, as compared with a 2 percent decline in the patients receiving placebo (P<0.001) (Fig. 1). Multiple-regression analysis showed that treatment group,

age, and severity of disease were significant predictors of changes in FEV₁; sex, highest MIC of tobramycin, and use of dornase alfa were not. Improvements in forced vital capacity in the tobramycin group were similar to those in FEV₁ (data not shown), with an average increase of 8 percent from week 0 to week 20, as compared with a 1 percent decline in the placebo group.

Microbial Response

The density of *P. aeruginosa* in sputum samples from the tobramycin-treated patients decreased during each of the three 28-day periods when the drug was administered and approached week 0 values during the periods when the drug was withheld (Fig. 2). The treatment effects were greatest during the first two treatment cycles, with an average reduction of 2.2 log₁₀ CFU per gram of sputum at week 2, 1.9 log₁₀ CFU per gram at week 4, and 1.8 log₁₀ CFU per gram at week 12. By the end of the third period of drug administration (week 20), there was an average reduction of 0.8 log₁₀ CFU per gram of sputum, as compared with the value at week 0, whereas the density in the placebo group had increased by 0.3 log₁₀ CFU per gram (P<0.001). Resistance to tobramycin associated with drug administration did not account for the diminished microbial reduction in the third cycle (Fig. 2).

Hospitalization and Intravenous-Antibiotic Use

The patients receiving tobramycin were 26 percent (95 percent confidence interval, 2 to 43 percent) less likely to be hospitalized and 36 percent (95 percent confidence interval, 17 to 51 percent) less likely to require intravenous antipseudomonal antibiotics than the patients receiving placebo. The patients in the tobramycin group received intravenous antipseudomonal antibiotics for an average of 9.6 days and were hospitalized for an average of 5.1 days. Thirty-nine percent of the patients receiving tobramycin (100 of 258) received one or more courses of intravenous antibiotics, and 37 percent (95 of 258) were hospitalized at least once. The patients in the placebo group received intravenous antipseudomonal antibiotics for an average of 14.1 days and were hospitalized for an average of 8.1 days. Fifty-two percent of the patients receiving placebo (135 of 262) received one or more courses of intravenous antipseudomonal antibiotics, and 45 percent (117 of 262) were hospitalized at least once.

Subgroup Analyses

In each subgroup of patients (defined on the basis of age, sex, disease severity, and use or nonuse of dornase alfa), the FEV₁ increased from week 0 to week 20 in the patients receiving tobramycin and decreased in those receiving placebo (Table 2). The one exception was an increase in FEV₁ in patients re-

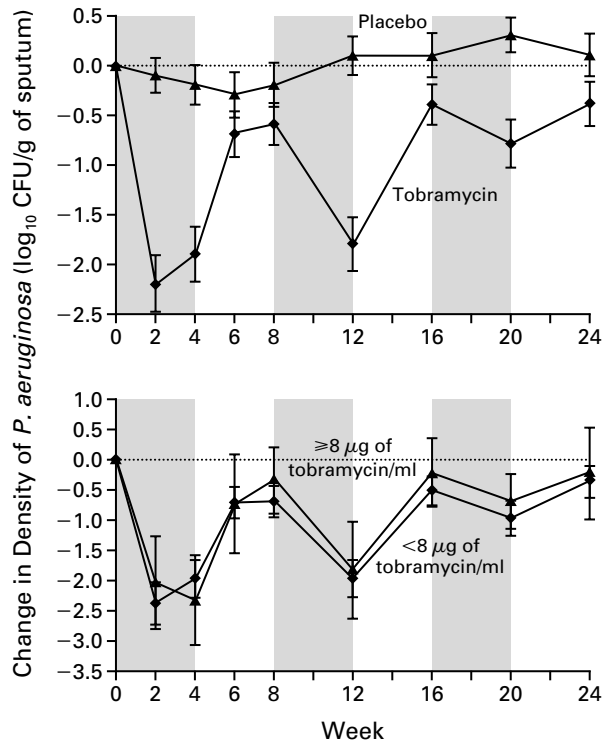


Figure 2. Mean Change in the Density of *P. aeruginosa* in Samples of Expectorated Sputum.

The upper panel shows the mean change from week 0 in the density of *P. aeruginosa* in samples of expectorated sputum at each visit for the 249 patients in the tobramycin group and the 241 in the placebo group. The lower panel shows the mean change from week 0 at each visit for the subgroup of patients in the tobramycin group whose most prevalent isolates had a minimal inhibitory concentration (MIC) of tobramycin of less than 8 µg per milliliter at week 0. The diamonds represent the 173 patients whose isolates continued to have an MIC of tobramycin of less than 8 µg per milliliter at week 20, and the triangles represent the 29 patients whose isolates had an MIC of tobramycin of 8 µg per milliliter or more at week 20. The I bars in both panels represent 95 percent confidence intervals.

ceiving placebo who were 6 to 12 years old. The difference in the change in FEV₁ between the treatment groups was significant in all subgroups except that of patients 6 to 12 years old ($P=0.08$).

Subgroup-treatment interactions were examined to determine whether the effect of inhaled tobramycin differed among the subgroups. There was no significant difference in the improvement achieved with inhaled tobramycin according to sex, disease severity, or use or nonuse of dornase alfa. However, patients who were 13 to 17 years old had a significantly greater increase in FEV₁ than those who were younger or older. The effect of treatment on *P. aeruginosa* density was also influenced by age, with the effect decreasing with increasing age ($P=0.01$, data not shown).

Adverse Events

Tinnitus and alteration of the voice were the only adverse events that were reported in a significantly greater percentage of the tobramycin group than in the placebo group. Tinnitus was reported by eight patients (3.1 percent) in the tobramycin group and by none of those in the placebo group ($P=0.003$). Tinnitus was transient, was mild or moderate in severity, and did not lead to withdrawal from the study. The number of episodes did not increase with increasing cycles of drug administration, and no hearing loss was documented on audiograms. Voice alteration was reported by 33 patients (12.8 percent) in the tobramycin group and by 17 (6.5 percent) in the placebo group ($P=0.02$). Voice alteration was minimal in most cases and did not increase with subsequent cycles of drug administration or lead to withdrawal from the study.

Hemoptysis occurred in 69 patients (26.7 percent) in the tobramycin group and in 81 (30.9 percent) in the placebo group. Pneumothorax occurred in one patient in the tobramycin group and in four in the placebo group. Four patients in the placebo group died during the study (in all cases, the cause of death was the underlying illness); none of the tobramycin-treated patients died.

Tobramycin and Creatinine Levels

Serum tobramycin levels were measured at the estimated time of the peak concentration, one hour after the inhaled dose (TDX, Abbott, Abbott Park, Ill.; detectable level, ≥ 0.18 µg per milliliter). These data were not disclosed to the study centers. Patients receiving concomitant intravenous tobramycin were excluded from this analysis. In the tobramycin group, the median serum level after the first dose had been administered was 0.94 µg per milliliter (range, 0.18 to 3.62). At week 20, the median serum level was 0.98 µg per milliliter (range, 0.18 to 3.41).

In the tobramycin group, the mean creatinine values were 0.91 mg per deciliter (80.44 µmol per liter) at week 0 and 0.89 mg per deciliter (78.68 µmol per liter) at week 20. In the placebo group, the mean creatinine values were 0.88 mg per deciliter (77.79 µmol per liter) at week 0 and 0.87 mg per deciliter (76.91 µmol per liter) at week 20. Nine patients in each group had transient increases of 50 percent or more in the creatinine value.

Audiologic Studies

Serial audiologic testing was performed in 302 patients (148 in the tobramycin group and 154 in the placebo group). No patients had hearing loss according to the prospectively defined criteria.

Bronchospasm

At week 0, the median change in FEV₁ 30 minutes after the first dose of the study drug had been

TABLE 2. CHANGE IN FEV₁ FROM WEEK 0 TO WEEK 20 ACCORDING TO SUBGROUP.*

SUBGROUP	NO. OF PATIENTS	MEAN CHANGE IN FEV ₁		TREATMENT EFFECT†	P VALUE‡
		TOBRAMYCIN	PLACEBO		
Age					0.005
6–12 yr	113	14.11	5.52	8.59	0.08
13–17 yr	120	15.88	–7.15	23.03	<0.001
≥18 yr	229	5.52	–2.64	8.16	<0.001
Sex					0.12
Male	246	8.67	–0.30	8.97	<0.001
Female	216	11.96	–3.24	15.20	<0.001
Disease severity					0.88
FEV ₁ <50% of predicted value	209	8.38	–3.83	12.21	<0.001
FEV ₁ ≥50% of predicted value	253	11.50	–0.12	11.62	<0.001
Use of dornase alfa					0.2
Yes	320	11.28	–2.28	13.56	<0.001
No	142	7.38	–0.68	8.06	0.02
All patients	462	10.08	–1.79	11.87	<0.001

*FEV₁ denotes forced expiratory volume in one second.

†The treatment effect was calculated as the difference between the mean changes in the tobramycin and placebo groups.

‡For each subgroup, the first P value is for the overall comparison of the two treatment groups by analysis of variance; the other P values are for subgroup–treatment interactions.

administered was –1.8 percent (range, –34.4 to +21.1) in the tobramycin group and –2.6 percent (range, –43.6 to +34.1) in the placebo group. At week 20, the median change in FEV₁ was –2.0 percent (range, –29.8 to +77.7) in the tobramycin group and –2.0 percent (range, –24.0 to +38.4) in the placebo group.

Microbiologic Findings

There was a trend toward an increase in the MIC of tobramycin in the *P. aeruginosa* isolates from the patients receiving tobramycin but not in the isolates from the patients receiving placebo (Fig. 3). The proportion of tobramycin-treated patients with *P. aeruginosa* isolates for which the MIC was at least 8 µg per milliliter increased from 25 percent (63 of 254 patients) at week 0 to 32 percent (72 of 224) at week 24, as compared with 20 percent (51 of 254 patients) at week 0 and 17 percent (38 of 223) at week 24 in the placebo group. A total of 171 patients in the tobramycin group had *P. aeruginosa* isolates for which the MIC was 4 µg or less per milliliter; in this group, the mean improvement in FEV₁ was 11 percent (95 percent confidence interval, –35 to +57 percent) at week 20 as compared with the value at week 0. In the 58 patients who had isolates for which the MIC was 8 µg or more per milliliter, the FEV₁ increased by 8 percent from week 0 to week 20 (95 percent confidence interval, –34 to +50 percent).

B. cepacia was newly isolated from respiratory tract secretions in two patients in the tobramycin group and three in the placebo group during the study. *Stenotrophomonas maltophilia* was newly iso-

lated from respiratory tract secretions in 41 patients in the tobramycin group and 58 in the placebo group.

DISCUSSION

Our study shows that long-term, intermittent administration of inhaled tobramycin in conjunction with standard therapy for cystic fibrosis improves pulmonary function, decreases the density of *P. aeruginosa* in expectorated sputum, and reduces the need for intravenous antipseudomonal antibiotics and hospitalization. Pulmonary function is the best predictor of morbidity and mortality in patients with cystic fibrosis and is the most widely used clinical end point in therapeutic trials.^{13,14} Treatment with tobramycin improved lung function in all subgroups defined at the start of the study on the basis of age, sex, severity of lung disease, and concurrent use or nonuse of dornase alfa. The improvement in patients using dornase alfa suggests that tobramycin has an additive effect.¹⁵

We used bacterial density in sputum as a long-term microbiologic end point. The decrease of 1 to 2 log₁₀ (i.e., 90 to 99 percent bactericidal activity) in the density of *P. aeruginosa* in sputum during the first two treatment cycles is similar to the bactericidal effect reported in a previous study of high-dose inhaled tobramycin⁸ after 28 days of therapy. During each period when the drug was not being used, the improvement in lung function was maintained, whereas the density of *P. aeruginosa* in sputum returned toward base-line values. In addition, the magnitude of bacterial reduction was smaller with the third cycle of therapy, although the improve-

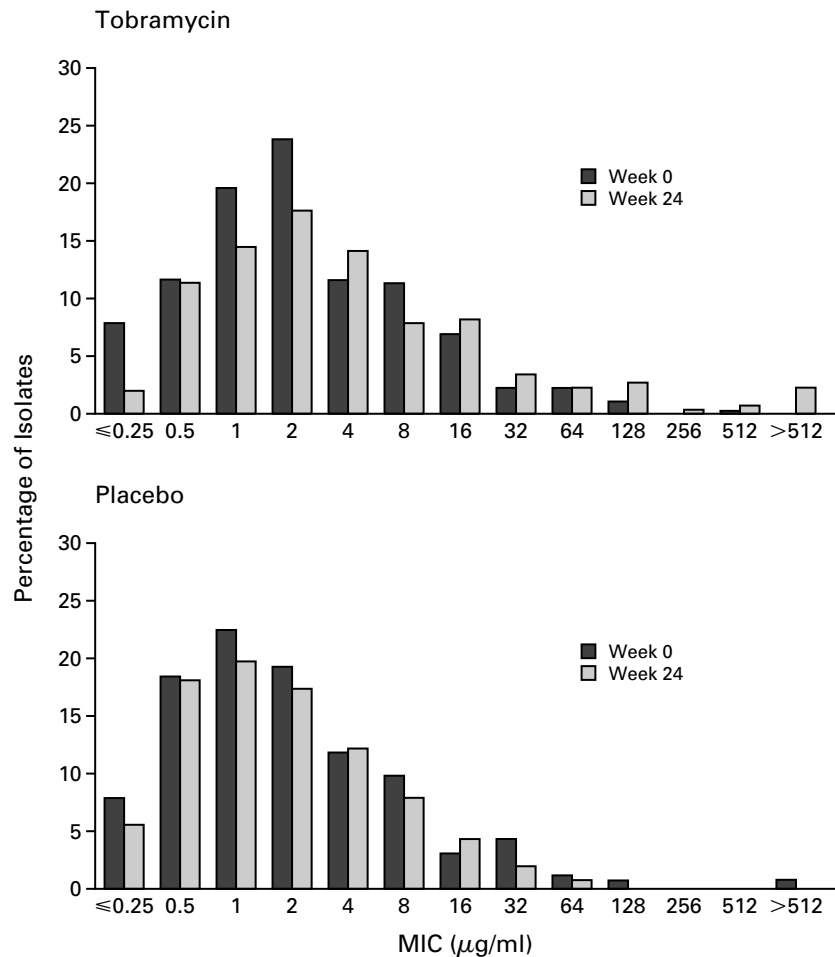


Figure 3. Changes in the Minimal Inhibitory Concentration (MIC) of Tobramycin in *P. aeruginosa* Isolates from Patients in the Tobramycin Group (Upper Panel) and the Placebo Group (Lower Panel). For each patient, the MIC for the *P. aeruginosa* isolate with the highest value at week 0 was compared with the MIC for the isolate with the highest value at week 24.

ment in lung function was maintained. Resistance to tobramycin during treatment was not responsible for this reduction in the antimicrobial effect. Follow-up studies will determine whether the reduced bactericidal effect in the third cycle is a harbinger of reduced lung function in subsequent cycles of therapy. However, an interim analysis of a subgroup of 128 patients treated with this regimen for 11 months has shown that the improvement in lung function is maintained (increase in FEV₁ at week 44 as compared with week 0, 9.8 percent; data not shown). These findings suggest that, in addition to its known bactericidal activity, inhaled tobramycin may have an antiinflammatory effect or may inhibit the production of factors that influence the virulence of pseudomonas,¹⁶ allowing improved lung function even with smaller reductions in the density of *P. aeruginosa*.

The role of inhaled antibiotics in altering the susceptibility of airway microbes to antibiotics is an important clinical issue. In our studies, the proportion of tobramycin-treated patients who had *P. aeruginosa* isolates for which the MIC was at least 8 µg per milliliter increased from 25 percent to 32 percent over a period of 24 weeks. In comparison, the proportion of patients treated with intravenous tobramycin for 14 days who had isolates for which the MIC was at least 8 µg per milliliter increased from 29 to 43 percent.¹⁷ Our rationale for intermittent administration of tobramycin was based on the observation that “drug holidays” allow susceptible pathogens to repopulate the airways in patients with cystic fibrosis.¹⁸ The threshold of susceptibility to tobramycin with parenteral therapy may not be relevant to inhalational therapy, since the concentration of inhaled drug can be 100 times as high as the systemic concentra-

tion. In our patients treated with inhaled tobramycin, the improvement in FEV₁ at week 20 was similar whether the MIC of tobramycin in *P. aeruginosa* isolates was above or below the threshold of susceptibility to the drug when it is administered parenterally.

In our studies, tobramycin was administered by means of a jet nebulizer (mean particle size, 4 μm). This device was chosen to deliver the drug to the site of infection in the airways rather than the alveoli. Minimizing delivery to the alveolar surface area may help limit systemic absorption.¹⁹ The formulation of tobramycin that we used did not increase airway reactivity. In contrast, preparations intended for intravenous use may contain phenol or metabisulfites, which are known to irritate the airways.²⁰ The results with the drug–nebulizer combination we used may not be applicable to other formulations or devices, and other devices have not been formally tested.

The widespread use of antibiotic therapy since the 1940s for lung infections in patients with cystic fibrosis has contributed to improvement in survival.²¹ The use of inhaled tobramycin in combination with current treatment for patients with cystic fibrosis who have *P. aeruginosa* infection with airway obstruction may provide an additional benefit. Further refinements in treatment, such as optimizing the regimens of current antibiotics, developing new antibiotics, and developing new modes of delivery, may result in even greater benefits in the future for patients with cystic fibrosis.

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Drs. Ramsey, Montgomery, and Smith hold a patent for the formulation of tobramycin used in the study. PathoGenesis, where Dr. Montgomery, Dr. Quan, Ms. Otto, and Mr. Vasiljev-K are employees, has licensed this invention through Children's Hospital and Regional Medical Center in Seattle, which owns Drs. Smith and Ramsey's contributions to the invention.

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APPENDIX

In addition to the authors, the following investigators participated in the Cystic Fibrosis Inhaled Tobramycin Study Group: *Writing Committee* — M. Aitken, G. Albers, S. Fiel, G. Marelich, T. Murphy, N. Eid, H.W. Parker, J. Van Dalen, and B. Nickerson; *Children's Hospital and Regional Medical Center* — J. Burns, T. Standaert, C. Clausen, M. Cohen, and S. McNamara; *participating investigators* — I. Abdulhamid and C. Van Wagnen, Children's Hospital of Michigan; A. Adler and P. Tosta, Children's Hospital, Oakland; G. Albers and P. Lewis, Saint Louis University–Cardinal Glennon Children's Hospital; S. Aronoff and L. Baer, West Virginia University; J. Biller and M. Freeman, Children's Hospital of Wisconsin, Medical College

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