Long-term Benefits of Inhaled Tobramycin in Adolescent Patients With Cystic Fibrosis*

Richard B. Moss, MD, FCCP

Study objective: To determine the effect of long-term suppression of Pseudomonas aeruginosa on lung function and other clinical end points in adolescent patients with cystic fibrosis (CF).

Design: Two identical, randomized, placebo-controlled trials followed by three open-label follow-on trials.

Setting: Sixty-nine CF study centers in the United States.

Interventions: Active drug consisting of a 300-mg tobramycin solution for inhalation (TSI).

Patients: One hundred twenty-eight adolescent CF patients (aged 13 to 17 years) with P. aeruginosa and mild-to-moderate lung disease (FEV\textsubscript{1} percent predicted ≥ 25% and ≤ 75%).

Measurements: Pulmonary function, P aeruginosa colony forming unit density, incidence of hospitalization and IV antibiotic use, weight gain, and aminoglycoside toxicity were monitored.

Results: At the end of the first three 28-day cycles of TSI treatment, patients originally randomized to TSI and placebo treatments exhibited improvements in FEV\textsubscript{1} percent predicted of 13.5% and 9.4%, respectively. FEV\textsubscript{1} percent predicted was maintained above the value at initiation of TSI treatment in both groups. At the end of the last “on-drug” period (92 weeks), patients originally randomized to TSI and placebo treatments showed improvements of 14.3% and 1.8%, respectively. Improvement in pulmonary function was significantly correlated with reduction in P aeruginosa colony forming unit density (p < 0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. TSI treatment was associated with increased weight gain and body mass index. P aeruginosa susceptibility to tobramycin decreased slightly over time, but this was not correlated with clinical response.

Conclusions: TSI treatment improved pulmonary function and weight gain in adolescent patients with CF over a 2-year period of long-term, intermittent use. (CHEST 2002; 121:55–63)

Key words: aminoglycoside; cystic fibrosis; Pseudomonas aeruginosa; pulmonary function; tobramycin

Cystic fibrosis (CF) is an autosomal recessive disease that affects approximately 60,000 people worldwide. Mutations in the gene coding for a chloride-channel protein, called the CF transmembrane conductance regulator,\textsuperscript{1–3} result in reduced mucociliary clearance, leaving CF patients especially vulnerable to endobronchial infections, particularly with Pseudomonas aeruginosa. Chronic airway infections lead to progressive obstruction of the airways and loss of pulmonary function. In 1998, > 85% of CF patient deaths could be attributed to loss of pulmonary function.\textsuperscript{4} Relative lung function (expressed as a percentage of the patient’s predicted FEV\textsubscript{1} percent predicted) is a significant clinical predictor of mortality in patients with CF.\textsuperscript{5} After adjusting for age and gender contributions, the relative risk of death for CF patients doubles with each 10% loss of FEV\textsubscript{1} percent predicted.\textsuperscript{5}

P aeruginosa is the major infectious burden in the airway of CF patients,\textsuperscript{6} and this pathogen is present in the lower respiratory tract of nearly 70% of CF patients by the age of 17 years.\textsuperscript{7} Acquisition of P aeruginosa is a major event in the natural history of CF lung disease, as its presence is associated with

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increased rates of lung function decline and is a significant predictor of mortality. The relationship between chronic respiratory tract infection, decline in pulmonary function, and mortality has been described. Death rates for CF patients chronically infected with \textit{P. aeruginosa} increase slowly with age up to the teenage years, when rates increase more rapidly and then remain fairly constant from the late teens to beyond the age of 30 years. Similarly, mean FEV$_1$ percent predicted declines rapidly until early adulthood, when the rate of decline levels off. Kerem et al demonstrated an inverse relationship between age and risk of death for any given level of relative lung function. In patients with the same percentage of predicted FEV$_1$ but an age difference of 10 years, the relative risk of death is doubled for younger patients. These findings are consistent with those of Corey et al, who showed that patients who die earlier in life experience significantly higher rates of lung function decline than longer-living patients. In 1998, the median age of death in CF patients in the United States was 22.5 years.

The central role of \textit{P. aeruginosa} in CF lung disease has led to testing of intensive therapy with antipseudomonal antibiotics to suppress infection. Ramsey et al reported significant increases in pulmonary function as well as decreases in hospitalization and IV antibiotic use following 6 months of long-term, intermittent therapy with tobramycin solution for inhalation (TSI) \cite{12} in a pair of double-blind, placebo-controlled, clinical trials. It is noteworthy that an age-stratified analysis of pulmonary function change showed a highly significant treatment effect in adolescents that was nearly three times greater than that observed in any other age subgroup. Here, the results reported by Ramsey et al are extended with an analysis of data obtained from adolescent patients (aged 13 to 17 years) who completed these controlled trials and received up to 24 months of treatment in a series of open-label, follow-on trials.

### Materials and Methods

The data presented here were collected during a 96-week series of clinical trials that consisted of a 24-week, double-blind, randomized, pivotal phase and 72-week, open-label phase. Figure 1, \textit{upper panel}, illustrates the two phases. In the pivotal phase, patients were randomized to treatment with either 300 mg of TSI bid or taste-masked placebo bid. In the open-label phase, all patients received TSI. The overall design of the open-label trials is identical to that of the controlled trials as described by Ramsey et al and illustrated in Figure 1, \textit{lower panel}. The study drug was administered in a series of cycles consisting of 28 days of treatment ("on-drug") followed by 28 days without treatment ("off-drug").

Study drug formulation and delivery have been described previously. Throughout the series, patients could receive any and all standard therapy for CF, with the exception of any inhaled antibiotics other than the study drug. The selection criteria were reported by Ramsey et al, but it is important to note that patients in this study series included only those with moderate-to-severe lung disease (FEV$_1$ 25 to 75% of predicted) uncomplicated by \textit{Burkholderia cepacia}. Therefore, this population represents a subset of the CF population as a whole.

### Assessments

There were a total of 27 scheduled visits during the series. During the screening period and the first treatment cycle (study

![Image](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21972/ on 06/25/2017)
weeks 4 to 8), visits occurred every 2 weeks. During the second to ninth treatment cycles (study weeks 8 to 72), visits occurred every 4 weeks and coincided with the end of each on-drug and off-drug period. During treatment cycles 10 and 11 (study weeks 72 to 88), visits occurred every 8 weeks and coincided with the beginning of each on-drug period. During treatment cycle 12 (study weeks 88 to 96) visits occurred every 4 weeks. Throughout the series, clinical evaluations and spirometry testing were performed at each visit. The frequency of other evaluations, including sputum cultures, safety laboratory assessments, and audiology testing, was greater during the controlled trials than during the open-label trials.

**Evaluations**

The primary evaluation in this series was change in lung function (FEV₁ percent predicted) from baseline. Other evaluations included change in *P. aeruginosa* susceptibility, change in serum creatinine concentrations, change in weight and body mass index (BMI), use of IV antipseudomonal antibiotics, and hospitalization. Spirometry testing (FEV₁) was performed according to American Thoracic Society standards. FEV₁ was expressed as a percentage of the value predicted based on age and height according to the methods of Knudson et al. Relative change in FEV₁ percent predicted was calculated as follows:

\[
\text{relative change} = \frac{\text{PFT \% predicted at end of on-drug period} - \text{PFT \% predicted at initiation of TSI}}{\text{PFT \% predicted at initiation of TSI}} \times 100
\]

where PFT = pulmonary function test. Sputum specimens were shipped on ice to the microbiology laboratory at Children’s Hospital and Regional Medical Center (Seattle, WA), where quantitative culture (controlled trial only) and susceptibility testing were performed. Susceptibility testing was performed using custom-made broth-microdilution trays for all *P. aeruginosa* morphotypes recovered from sputum. BMI was calculated as weight (in kilograms) divided by the square of height (in meters).

**Statistical Methods**

The initial 24 weeks of the study series (controlled trials) included a placebo control group, allowing for statistical comparisons between 24 weeks of TSI treatment and 24 weeks of placebo treatment. Results from the controlled trial have been published previously. Results obtained following the beginning of the open-label trials (week 24, visit 11) are pooled and presented in one of the following three ways, depending on the requirements of the particular analysis: (1) by the number of cycles of TSI exposure, (2) by the number of weeks since the patient’s first dose of TSI (week 0 [visit 3] for patients originally randomized to TSI, and week 24 [visit 11] for patients originally randomized to placebo treatment), and (3) with all data for all patients randomized to placebo treatment, and (3) with all data for all patients since their first dose of TSI combined. In each case, data from the placebo experience during the controlled trials are presented for comparison. When relevant, the 96-week results are presented in the context of published controlled trial results.

Data from all patients whose age at entry into the controlled trial (visit 3) was between 13 years and 17 years (inclusive) and who received at least one dose of study drug were included in the analyses. Analysis of the relationship between changes in FEV₁ percent predicted and *P. aeruginosa* colony forming unit density was performed using a χ² test. The effect of recombinant human dornase α (rhDNase) on change in FEV₁ percent predicted was evaluated by means of a two-tailed t test. Changes in BMI and serum creatinine levels were performed using two-tailed, paired t test procedures.

**Results**

**Patient Population**

Patients were assigned to age subgroups (children, 6 to 12 years; adolescent, 13 to 17 years; adult, ≥ 18 years) according to their age at the first visit of the controlled trials (visit 3, week 0). One hundred twenty-eight adolescent patients were enrolled in the controlled trials. Of these 128 patients, 120 patients completed 24 weeks of randomized treatment. Ninety-three adolescent patients entered the open-label phase of the study and 65 adolescent patients completed the 96-week series.

Of the 63 adolescent patients who discontinued therapy at some point during the four consecutive 6-month trials, 39 patients (61.9%) completed at least one trial and chose not to enroll in the subsequent trial with no reason given for this decision. Of the remaining 24 adolescent patients (38.1%) who withdrew during trials, the primary reasons were nonmedical complaints (n = 11, 45.5%), medical complaints (n = 8, 33.3%), and protocol violations (n = 4, 16.7%). No adolescent patients withdrew due to adverse events associated with study drug.

The baseline characteristics of the adolescent patients showed no meaningful differences between treatment groups (Table 1). Examination of these characteristics by four three-cycle (24-week) blocks of TSI exposure demonstrates that despite attrition over the course of the series, there was no meaningful change in any of these characteristics over time.

**Pulmonary Function**

Pulmonary function increased dramatically following initiation of TSI therapy. At the end of the last on-drug period of the controlled trial (week 20),

**Table 1—Baseline Demographics of Adolescent Patients Enrolled in TSI Study**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>TSI (n = 61)</th>
<th>Placebo (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean yr (SD)</td>
<td>14.8 (1.4)</td>
<td>14.9 (1.4)</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>25 (21.9)</td>
<td>32 (25.0)</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>51.8 (16.4)*</td>
<td>54.3 (13.9)</td>
</tr>
<tr>
<td>≥ 50% predicted, No. (%)</td>
<td>32 (53.0)*</td>
<td>41 (61.0)</td>
</tr>
<tr>
<td>MIC ≥ 8 μg/mL, No. (%)</td>
<td>14 (23.0)</td>
<td>13 (20.3)†</td>
</tr>
</tbody>
</table>

*Baseline FEV₁ data available for 60 TSI-treated patients.
†Baseline MIC data available for 64 placebo-treated patients.
adolescent TSI patients had a mean improvement in FEV\textsubscript{1} percent predicted of 13.49\% relative to the start of TSI treatment (week 0). By the end of the last on-drug period of the open-label extension (week 92), FEV\textsubscript{1} percent predicted for the TSI group was 14.34\% above that at week 0 (Fig 2). In contrast to the TSI group, pulmonary function for adolescents in the placebo group declined by 8.95\% between weeks 0 and week 20; however, following initiation of TSI therapy (week 24), patients originally randomized to placebo treatment exhibited improvements similar to those observed in the TSI group. At the end of the first on-drug cycle of the open-label phase (week 28), mean FEV\textsubscript{1} percent predicted of these patients increased by 11.89\% relative to week 24; after three cycles of TSI treatment (week 44), mean FEV\textsubscript{1} percent predicted was increased by 9.4\%. At the end of the last on-drug period of the series (week 92), mean FEV\textsubscript{1} percent predicted for these patients was 1.84\% higher than at week 24 (Fig 2).

Following week 68, Figure 2 shows a decrease in the mean FEV\textsubscript{1} percent predicted improvement from baseline in the original placebo group. A review of patient rollover times from one 6-month trial to the next reveals that this decrease is most likely a result of implementing the study design. For those patients who completed the third 6-month trial and enrolled in the fourth trial, mean FEV\textsubscript{1} data at week 72 are derived from baseline data for the fourth trial. However, the baseline measurements for many patients were delayed beyond the 4-week study design interval shown in Figure 2. The average elapsed time between the week 68 and week 72 visits was 6.3 weeks (44.2 days), with one patient experiencing a delay of 13.1 week (92 days). This delay in treatment is reflected in the drop in lung function at week 72 shown in Figure 2. This effect is more pronounced in patients in the original placebo group because a much larger proportion of these patients (31 of 67 patients, 46.3\%) than those in the original TSI group (17 of 61 patients, 27.9\%) experienced a study rollover interval > 4 weeks between measurements.

In order to determine the relationship between change in pulmonary function and change in \textit{P} aeruginosa colony forming unit density, a correlation

![Figure 2](chart.png)

**Figure 2.** The mean relative change in FEV\textsubscript{1} percent predicted for the intent-to-treat adolescent population is shown over time. Baseline is the week that TSI therapy was initiated (week 0 for patients originally randomized to TSI treatment; week 24 for those originally randomized to placebo treatment). Shaded bars represent 28-day on-drug periods. Means at week 96 were derived from 27 TSI-arm and 37 placebo-arm patients who completed the trial. Ramsey et al\textsuperscript{12} reported a treatment effect of 23.03\% at week 20 (\(p < 0.001\)). † = End of on-drug period measurement not recorded.
analysis was performed using all available data points for adolescent patients from visit 3 to visit 11 (Fig 3). *P. aeruginosa* sputum density was calculated as the log10 value for the sum of all morphotypes. This analysis revealed a highly significant inverse relationship between the change in pulmonary function and change in *P. aeruginosa* colony forming unit density ($r = -0.34175$, $p = 0.0001$).

**Effect of rhDNase Use on Response to TSI**

When the adolescent patients in the original TSI group were categorized according to use (yes/no) of rhDNase (Pulmozyme; Genentech; S. San Francisco, CA) at baseline, generally greater FEV1 response among patients treated with rhDNase was observed between week 0 and week 92 (Table 2). However, the difference between groups was not significant, possibly due to the small number of patients who reported no rhDNase use at baseline.

**Hospitalization and IV Antibiotic Use**

Pooling the 96-week data according to cycles of TSI therapy received showed that the proportions of adolescent patients who were hospitalized or received IV antibiotics were not greatly affected after initiation of TSI therapy. During all four three-cycle blocks of TSI exposure, the average number of hospitalization and IV treatment days was generally comparable to that observed during placebo exposure. Table 3 shows the proportions of patients who were hospitalized or received IV antibiotics by cycles of TSI exposure. Cumulatively, over 96 weeks of TSI therapy, the number of hospital admissions and IV antibiotic courses per patient year were reduced by 19% and 32% respectively, compared to that observed during placebo exposure (Table 4).

**Changes in Weight**

From week 0 to week 20, adolescent TSI-treated patients had greater absolute mean weight gain (1.78 kg) than did patients receiving placebo (0.51 kg). When individual variations in weight were adjusted for height and expressed in terms of BMI, it was observed that between week 0 and week 24, the mean BMI of TSI-treated patients increased by 0.44 kg/m² compared to baseline ($p = 0.0015$), whereas that of placebo patients actually decreased by 0.018 kg/m² ($p = not significant$; Fig 4). At week 24, the mean BMIs of TSI-treated and placebo-treated patients was 18.6 kg/m² and 17.9 kg/m², respectively ($p = not significant$). During the 24 weeks following the switchover from placebo to TSI (week 24 to week 48), the mean BMI for the original placebo group increased 0.69 kg/m² ($p = 0.0002$).

**Microbiology**

To evaluate changes in the susceptibility of the entire population of *P. aeruginosa* recovered during the study series, data for all *P. aeruginosa* morphotypes isolated from adolescents over 96 weeks were collected and the change in distribution of minimum inhibitory concentration (MIC) values at initiation of TSI therapy to the end of each three-cycle treatment period was examined. Figure 5, *left panel*, illustrates the shift in MIC values over time; the changes observed in adolescents were consistent with those observed in the patient population as a whole. At the end of 12 cycles, the proportion of isolates with MIC $\geq 16 \mu g/mL$ increased from 5 to 19%. Over 96 weeks of TSI therapy, the tobramycin MIC for 50% of isolates of *P. aeruginosa* increased from 1 to 2 $\mu g/mL$, and the MIC for 90% of isolates (MIC$_{90}$) increased from 8 to 32 $\mu g/mL$ (Table 5). A similar shift toward higher tobramycin MICs was observed for the most resistant morphotype isolated from each patient. At the end of 12 treatment cycles, the

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**Table 2—Mean Change (%) From Baseline in FEV$_1$ Percent Predicted by rhDNase Use**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>RhDNase Use</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 32)</td>
<td>No (n = 7)</td>
</tr>
<tr>
<td>44</td>
<td>5.8</td>
<td>2.4</td>
</tr>
<tr>
<td>68</td>
<td>2.3 (n = 27)</td>
<td>-0.8 (n = 7)</td>
</tr>
<tr>
<td>92</td>
<td>5.9 (n = 21)</td>
<td>-2.6 (n = 5)</td>
</tr>
</tbody>
</table>

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![Figure 3](http://journal.publications.chestnet.org/pdfffaccess.ashx?url=/data/journals/chest/21972/)
percentage of patients whose most resistant isolate had an MIC of $\geq 16 \mu g/mL$ increased from 10 to 41% (Fig 5, right panel).

**Antibiotic Susceptibility and Clinical Response**

Change in pulmonary function was used to determine the relationship of tobramycin MIC and response to TSI. For all patients, the change in FEV$_1$ percent predicted was measured from initiation of TSI treatment to the end of the on-drug periods of the third, sixth, ninth, and 12th treatment cycles. Patients were grouped into three MIC categories ($\leq 8 \mu g/mL$, 16 to 64 $\mu g/mL$, and $\geq 128 \mu g/mL$) according to the MIC value of their most-resistant *P. aeruginosa* isolate obtained at any start-of-treatment visit prior to the end of that TSI exposure period. As was observed for the entire study population, neither the percentage of adolescent patients with a positive clinical response, nor the magnitude of the observed response appeared to be related to tobramycin MIC (Fig 6).

**Nephrotoxicity and Ototoxicity**

There were no clinically or statistically significant changes in mean serum creatinine levels in either treatment group during the controlled trials. During the 96-week study period, mean serum creatinine levels remained within normal limits and exhibited no clinically relevant changes (data not shown). The ototoxic effects of TSI were evaluated with serial audiograms obtained throughout the study series. These evaluations revealed no evidence of aminoglycoside-induced hearing loss, as defined by bilateral hearing loss > 15 decibels, in this patient group. Two adolescent patients experienced tinnitus during the course of the study series: one patient had multiple episodes of tinnitus considered possibly related to study drug, and the other patient had transient tinnitus attributable to another known cause. Neither of these patients showed objective evidence of ototoxicity as measured by serial audiograms.

**DISCUSSION**

Pulmonary function is the single best predictor of morbidity and mortality in patients with CF. Adolescent CF patients are at a particularly vulnerable stage in their life cycle when they are susceptible to rapid decline in pulmonary function and high rates of death through early adulthood. The 2-year TSI results show long-term improvement in pulmonary function in adolescent CF patients. The substantial improvements in FEV$_1$ percent predicted and the

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**Table 3—Hospitalization and IV Antibiotic Use**

<table>
<thead>
<tr>
<th>Variables</th>
<th>0 Cycles (n = 67)</th>
<th>1–3 Cycles (n = 111)</th>
<th>4–6 Cycles (n = 90)</th>
<th>7–9 Cycles (n = 74)</th>
<th>10–12 Cycles (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients hospitalized, No. (%)</td>
<td>29 (43.3)</td>
<td>40 (36.0)</td>
<td>32 (35.6)</td>
<td>40 (54.1)</td>
<td>7 (23.3)</td>
</tr>
<tr>
<td>Mean hospitalization, d</td>
<td>17.3</td>
<td>15.1</td>
<td>16.3</td>
<td>14.7</td>
<td>18.4</td>
</tr>
<tr>
<td>Median hospitalization, d</td>
<td>12.0</td>
<td>14.0</td>
<td>13.5</td>
<td>12.0</td>
<td>14.0</td>
</tr>
<tr>
<td>IV antibiotic use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients treated, No. (%)</td>
<td>36 (53.7)</td>
<td>46 (41.4)</td>
<td>38 (42.2)</td>
<td>41 (55.4)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Mean IV course, d</td>
<td>25.9</td>
<td>33.7</td>
<td>24.7</td>
<td>24.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Median IV course, d</td>
<td>16.0</td>
<td>17</td>
<td>20.5</td>
<td>19</td>
<td>24.5</td>
</tr>
</tbody>
</table>

**Table 4—Hospitalizations and IV Courses per Patient-Year**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Hospitalizations</th>
<th>IV Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-treated group</td>
<td>1.48</td>
<td>1.80</td>
</tr>
<tr>
<td>Following TSI exposure</td>
<td>1.20</td>
<td>1.23</td>
</tr>
<tr>
<td>Change, %</td>
<td>$-18.9$</td>
<td>$-31.7$</td>
</tr>
</tbody>
</table>

**Figure 4.** The mean change in BMI from the beginning to the last visit of each 24-week study period is shown. BMI was calculated as weight in kilograms/height in meters squared. * = Patients in the original placebo group received TSI after week 24.
maintenance of lung function above baseline for 96 weeks in adolescents represent a clinically significant benefit of treatment for this group. Notably, delay in initiation of TSI therapy was associated with reduced long-term improvement over baseline, suggesting an irreversible component to lung function decline.

A major concern with long-term use of inhaled antibiotics in CF patients is decreased antibiotic susceptibility of *P aeruginosa*. CF patients frequently receive IV aminoglycosides for the treatment of acute exacerbations, and the potential risk of reducing the effectiveness of these agents must be weighed carefully against the benefits of aerosol administration. When considered in these terms, the threefold increase in MIC50 and the nearly 40% increase in patients whose most-resistant isolate had an MIC exceeding the traditional parenteral break point warrant concern. However, withholding long-term inhaled tobramycin therapy to preserve the effectiveness of IV antibiotics may present risks even greater than those posed by decreased antibiotic susceptibility. Treatment of exacerbations with IV antibiotics is a symptom-driven strategy that by itself fails to address the progressive decline in lung function experienced by Pseudomonas-infected CF patients. Lung function decline occurs even in the absence of exacerbations, and for each 10% decline in relative lung function, a patient's risk of death doubles. This is a particularly salient point for adolescent CF patients and their caregivers. As a group, adolescents can have high rates of pulmonary function decline and, consequently, high rates of death. This high death rate is a substantial contributor to the 22.5-year median age of death for Pseudomonas-infected patients. Management strategies that fail to reduce the inexorable decline in lung function in these patients serve only to maintain the status quo of disease progression and death by early adulthood.

The data presented here demonstrate that long-term, intermittent TSI therapy can not only preserve but can actually improve lung function for at least 2 years in adolescent patients with CF, and that clinical response is not affected by tobramycin MIC. This finding is consistent with that of Ramsey et al, who showed that improvement in FEV1 percent predicted at the end of the last on-drug period of the controlled trials was similar regardless of whether the patient’s most-resistant isolates were above or below the parenteral break point. Continued pulmonary response, even in patients with tobramycin-resistant strains of *P aeruginosa*, suggests that the traditional parenteral break point for tobramycin (MIC ≥ 16 µg/mL) does not apply to inhaled tobramycin. This is most likely because sputum tobramycin concentrations (mean, 1,000 µg/g) far exceed the MIC values of most strains considered resistant using the parenteral break point.

Analysis of secondary study end points of hospitalization and IV antibiotic use also supports the long-term effectiveness of TSI. The primary cause of hospitalization in CF patients is for treatment of exacerbations with IV antibiotics. In 1998, nearly 50% of all CF patients in the United States were hospitalized at least once, with an average stay of 9.8 days. The finding that both hospitalization and IV antibiotic use were reduced in CF adolescents fol-

Table 5—Susceptibilities of all *P aeruginosa* Morphotypes at the End of Each Three-Cycle Exposure Periods*

<table>
<thead>
<tr>
<th>Tobramycin MIC</th>
<th>Cycles</th>
<th>Cycles</th>
<th>Cycles</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC50</td>
<td>1-3</td>
<td>4-6</td>
<td>7-9</td>
<td>10-12</td>
</tr>
<tr>
<td>MIC90</td>
<td>8</td>
<td>8</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>

*MIC50 = MIC for 50% of isolates.
following initiation of TSI therapy is consistent with the substantial improvements observed in pulmonary function. The number of exacerbations leading to hospitalization and IV antibiotic treatment clearly did not increase over time, although this could be expected in a population of patients with rapidly declining lung function. Furthermore, the hospitalization and IV treatment data suggest that changes in the susceptibility of \textit{P. aeruginosa} did not affect the severity of the underlying exacerbations, or the efficacy of treating them. Finally, body weight is an important prognostic factor in CF patients and has been associated with survival.\textsuperscript{15-18} Results from this study series strongly suggest that long-term suppression of \textit{P. aeruginosa} with TSI therapy can significantly improve weight gain in growing adolescents.

In conclusion, the long-term results obtained from adolescent patients participating in the TSI study series confirm and extend those previously reported.\textsuperscript{12} The adolescent subgroup analyses illustrate that this vulnerable group of patients can gain substantial benefit from long-term TSI treatment, including improved lung function, reduced hospitalization and IV antibiotic use, and increased weight gain. They also strongly suggest that in order to be maximally effective, TSI treatment should begin earlier rather than later, since lung function decline in patients with CF appears to be in part irreversible.

![Figure 6. The relationship of MIC value and clinical response is shown. Upper panel: the percentage of patients in each MIC category who had improved FEV\textsubscript{1} percent predicted by MIC category. Lower panel: the mean relative change in FEV\textsubscript{1} percent predicted for patients in each MIC category.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21972/ on 06/25/2017)
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