Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial

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ABSTRACT
Rationale Antibiotic therapy for early Pseudomonas aeruginosa infection in patients with cystic fibrosis (CF) is effective, but the optimal therapeutic regimen and duration for early treatment remains unclear. The Early Inhaled Tobramycin for Eradication (ELITE) study was designed to assess the efficacy and safety of two regimens (28 and 56 days) of tobramycin inhalation solution (TIS) 300 mg/5 ml twice daily for the treatment of early onset P aeruginosa infection in patients with CF.

Methods In this open-label randomised multicentre study, patients with CF (aged ≥6 months) with early P aeruginosa infection were treated for 28 days with TIS twice daily administered by the PARI LC PLUS (PARI GmbH, Starnberg, Germany) jet nebuliser. After 28 days, patients were randomised 1:1 to either stop TIS (n=45) or to receive a further 28 days of TIS (n=43). The primary endpoint was the median time to recurrence of P aeruginosa (any strain). Secondary endpoints included the proportion of patients free of P aeruginosa infection 1 month after cessation of therapy and safety assessments.

Results The median time to recurrence of P aeruginosa (any strain) was similar between the two groups. In total, 93% and 92% of the patients were free of P aeruginosa infection 1 month after the end of treatment and 66% and 69% remained free at the final visit in the 28-day and 56-day groups, respectively. TIS was well tolerated.

Conclusions Treatment with TIS for 28 days is an effective and well tolerated therapy for early P aeruginosa infection in patients with CF.

Trial registration number NCT00391976.

INTRODUCTION
Cystic fibrosis (CF) is a hereditary disorder that significantly reduces a patient’s life expectancy. Individuals with CF are highly susceptible to early endobronchial infections and chronic Pseudomonas aeruginosa infection has a major negative impact on the course of lung disease in these individuals.1 2 Once chronic infection with a mucoid phenotype of P aeruginosa is established, eradication is rarely possible even with intense treatment. Studies have shown, however, that antibiotic therapy initiated shortly after a new detection of P aeruginosa is effective in preventing or delaying the onset of chronic infection.3–6 This is now considered the standard of care in European CF centres.7 8

Antibiotics administered via parenteral, inhaled and oral routes are efficacious; however, the optimal regimen and duration of therapy remains unclear. Inhaled antibiotics are an attractive option, delivering high concentrations of antibiotic directly to the infection site while minimising systemic exposure.9 10 Several small studies have shown that eradication of P aeruginosa infection can be achieved with early inhaled tobramycin treatment.6 11 12 A bronchoalveolar lavage-based study using 28 days of tobramycin inhalation solution (TIS) 500 mg/5 ml (TOBI; Novartis Pharma AG, Basel, Switzerland) twice daily suggested a high rate of efficacy whereas previous studies have used lower doses of tobramycin and longer treatment periods.5 6 11 These positive results have prompted further large-scale investigations into the use of inhaled tobramycin. The present Early Inhaled Tobramycin for Eradication (ELITE) trial was designed to assess the short- and long-term efficacy and safety of TIS 500 mg/5 ml twice daily for 28 and 56 days in the treatment of early onset P aeruginosa infection in patients with CF.

METHODS
Patients who regularly attended outpatient clinics, had microbiological testing at least every 3 months and a first or early positive P aeruginosa culture at a routine hospital visit were eligible for enrolment. Patients were enrolled from 21 centres in Germany, France, The Netherlands, UK, Spain and Austria.

Study design and patients
This was an open-label two-arm randomised multicentre study (figure 1) conducted between November 2003 and January 2008. Patients aged ≥6 months with confirmed CF (clinical signs consistent with CF and a sweat chloride >60 mEq/l by quantitative pilocarpine iontophoresis or genotype with two identifiable mutations consistent with CF) and a first or early infection with P aeruginosa were eligible. Early infection was defined as a new detection of P aeruginosa in a respiratory culture after negative cultures for at least 1 year if at least four documented negative cultures were available or up to 2 years with four documented negative cultures in this time period in the absence of anti-pseudomonal treatment. Patients were excluded if they had a history of aminoglycoside hypersensitivity or adverse reaction to inhaled aminoglycosides; signs or symptoms of acute pulmonary disease (eg, pneumonia, pneumothorax); a history of hearing loss; had received any investigational drug within 50 days, loop diuretics within 7 days before enrolment, or macrolide antibiotics as a maintenance therapy for ≥12 days during the 28 days before visit 1 (screening/baseline).

All patients received TIS twice daily for 28 days administered via PARI LC PLUS jet nebuliser and a suitable compressor (pressure and flow operating...
parameters of 110–217 kPa and 4–6 L/min, respectively). Randomisation occurred at day 28. Patients were excluded from randomisation if antibody titres assessed with a sensitive radio-immunoassay were >1000 or serum creatinine levels exceeded the upper normal limit for age. Eligible patients at day 28 were randomised 1:1 to either stop study drug or to receive an additional 28 days of treatment (Figure 1; 56-day group). Randomisation occurred at day 28. Patients were excluded from randomisation if antibody titres assessed with a sensitive radio-immunoassay was >1000. Serum tobramycin and serum creatinine levels were analysed using the Cochran–Mantel–Haenszel test. Spirometry variables, AEs and other safety variables were analysed using descriptive statistics.

RESULTS

Baseline demographic and clinical characteristics
A total of 123 patients were recruited into the study. Of these, 88 were randomised (45 in the 28-day TIS group and 43 in the 56-day TIS group; figure 2) and 65 were included in the efficacy evaluable population (34 and 31 in the 28-day and 56-day TIS groups, respectively). Thirty-five patients were not randomised, 31 because of high P aeruginosa antibody titres and four for other reasons (figure 2). The baseline demographic and clinical characteristics were similar between the two treatment groups (table 1). The mean (SD) age at diagnosis was 12.4 (4.4) years and the proportion of patients free of P aeruginosa at screening and microbiological assessments at 1 month after their last dose of TIS, with the following exceptions: no eradication at 1 month after their last dose of TIS, protocol deviation or use of prohibited medications. For other efficacy analyses the safety population was used, which included all patients who received at least one dose of study medication.

For the primary outcome, time to recurrence of P aeruginosa was estimated by the Kaplan–Meier method using t = 0 at 1 month following the end of treatment in each group. A log rank test was used to detect differences between treatment groups and the relative risk of recurrence and 95% CIs were estimated using a Cox proportional hazard model. Comparisons between the treatment groups for the other efficacy variables were analysed using the Cochran–Mantel–Haenszel test. Spirometry variables, AEs and other safety variables were analysed with descriptive statistics.

Efficacy
The proportion of patients free of P aeruginosa at day 28 and 1 month after the end of treatment was comparable in both groups (figure 3). The proportion of patients free of P aeruginosa at 1 month after the end of treatment was similar in sputum producers and non-sputum producers (figure 4). Patients' age, baseline lung function and baseline infection status did not influence the findings (data not shown).

Sixty-five patients (34 and 31 in the 28-day and 56-day TIS groups, respectively) could be included in the evaluation of the primary outcome (time to recurrence of P aeruginosa). The median time to recurrence was 26.12 and 25.82 months following TIS for 28 and 56 days, respectively, and differences between groups were not significant (p = 0.593; HR 0.81, 95% CI 0.37 to 1.75; figure 5). Similar results were observed for deep throat swab and sputum samples (figures E1 and E2 in the online supplement). At the time of each patient’s final study visit, 66% of patients remained free of P aeruginosa in the 28-day TIS group (n = 41) and 69% remained free of P aeruginosa in the 56-day TIS group (n = 56).

Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at

Figure 1 Trial design. TIS, tobramycin inhalation solution 300 mg/5 ml.
recurrence. For the remaining patients (n=9), paired samples were of a different genotype. There were no consistent trends in the emergence of non-
*Pseudomonas aeruginosa* organisms (table 2). Two patients (5.5%) in the 56-day TIS group were hospitalised on one occasion, each for a pulmonary exacerbation during the study (ie, until recurrence of *P. aeruginosa*) although neither was receiving treat-

Table 1 Baseline demographic and clinical characteristics (all enrolled population)

<table>
<thead>
<tr>
<th>Age group, n (%)</th>
<th>28-day TIS (n=45)</th>
<th>56-day TIS (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months&lt;6 years</td>
<td>19 (42)</td>
<td>18 (42)</td>
</tr>
<tr>
<td>6&lt;18 years</td>
<td>20 (44)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>$\geq$18 years</td>
<td>6 (13)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (42)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Male</td>
<td>26 (58)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>30.0 (19.8)</td>
<td>27.4 (17.3)</td>
</tr>
<tr>
<td>Mean (SD) height (cm)</td>
<td>124.8 (34.3)</td>
<td>121.9 (31.7)</td>
</tr>
<tr>
<td>Previously vaccinated against Pa, n (%)</td>
<td>2 (4)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Cystic fibrosis genotype, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F508/F508</td>
<td>17 (38)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>F508/other</td>
<td>19 (42)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Other/other</td>
<td>5 (11)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Unknown/not available</td>
<td>4 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Infection with Pa, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>28 (62)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Early, after 1 year negative culture</td>
<td>8 (18)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Early, after 2 years negative culture</td>
<td>8 (18)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pulmonary function tests, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF25–75 % predicted</td>
<td>61.5 (28.8)</td>
<td>63.4 (26.9)</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>91.1 (15.3)</td>
<td>99.2 (20.2)</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>80.2 (18.9)</td>
<td>87.0 (19.2)</td>
</tr>
</tbody>
</table>

Figure 2 Patient disposition. TIS, tobramycin inhalation solution 300 mg/5 ml. Inappropriate enrolment includes having positive antibody titres for any of the three *Pseudomonas aeruginosa* exoenzymes, abnormal creatinine levels, an abnormal audiology test or negative for *P aeruginosa* at baseline.

Figure 3 Kaplan–Meier plot of time to recurrence of any strain of *Pseudomonas aeruginosa* in patients with cystic fibrosis treated with tobramycin inhalation solution twice daily (efficacy evaluable population).

Safety

Treatment-emergent AEs (TEAEs) occurring up to month 3 were reported by 32 (73%), 25 (58%) and 7 (20%) patients in the 28-day TIS, 56-day TIS and the non-randomised groups, respectively (table 4). TEAEs occurring after month 3 were reported by 21 (60%) and 19 (53%) patients in the 28-day and 56-day TIS groups, respectively (table 4). Overall, cough was the most commonly reported TEAE. AEs up to month 3 that were considered possibly or probably related to treatment were reported by 14 patients in each TIS group, with the majority of patients receiving treatment at the time of the exacerbation. One patient was hospitalised for 1 day for bronchitis and the other patient was hospitalised for *P aeruginosa* exacerbation. This patient was treated with intravenous cefazidime and tobramycin for 14 days.

No major short- or long-term changes in spirometric parameters were observed during the study period (table 3). Treatment with TIS for 28 and 56 days did not influence weight, height or body mass index of patients in any of the age groups (data not shown).
None of the 65 patients (55% of the safety population) with audiometry measurements exhibited ototoxicity, defined as a bilateral increase of \( \geq 15 \text{ dB} \) in hearing threshold at two consecutive frequencies between 2 and 8 kHz. There were, however, minor increases measured sporadically in two patients in the 56-day group which were reported as an AE of ‘deafness’ or hearing loss, one mild and one moderate-to-severe in severity. Both events were reported as probably related to study medication, but no action was taken and both patients’ hearing returned to normal.

**DISCUSSION**

The ELITE trial shows that treatment with TIS for 28 days is effective for treating early \( P. \text{aeruginosa} \) infection, and extending TIS treatment to 56 days does not provide notable additional improvements. Over 90% of randomised patients in the 28-day and 56-day TIS groups had negative cultures for \( P. \text{aeruginosa} \) 1 month after the end of treatment, and the majority of these patients remained free from infection for up to 27 months. The results were similar in sputum and non-sputum producers and were unaffected by the patient’s baseline characteristics (age, lung function and first versus recurrent infection).

Antibiotics, either alone or in combination, have been shown to be effective in the treatment of early \( P. \text{aeruginosa} \) infection. However, to date there have been no reports of comparative studies assessing different treatment regimens and only a few controlled studies have been performed. In an open controlled trial, inhaled colistin and oral ciprofloxacin twice daily for 3 weeks was shown to delay chronic \( P. \text{aeruginosa} \) infection in patients with CF. Extension of the treatment period to 3 months has been shown to provide additional benefit. This treatment regimen has been adopted by other centres and effectively reduced the rate of chronic \( P. \text{aeruginosa} \) infection as well as treatment cost.

In previous studies, including a placebo-controlled trial of antibiotic monotherapy, early treatment with inhaled tobramycin 80 mg twice daily for 12 months was shown to have a success rate similar to that seen with combination therapy. A further study showed that TIS 300 mg twice daily for 28 days resulted in negative bronchoalveolar lavage cultures at the end of treatment in all eight patients receiving tobramycin, whereas \( P. \text{aeruginosa} \) density was unchanged with placebo. This was supported by a subsequent study showing that TIS monotherapy for 28 and 56 days eradicated lower airway \( P. \text{aeruginosa} \) for up to 3 months. It should be noted that patients with a history of \( P. \text{aeruginosa} \) infection within the last 12 months were included in these studies. In contrast, the ELITE study, similar to other European studies on this topic, focused on patients with first or early infection. Treatment success rates in this trial compare favourably with previous studies. The ELITE trial also demonstrated long-term efficacy and further supports the use of inhaled tobramycin alone as a successful treatment strategy for early \( P. \text{aeruginosa} \) infection.

Inhaled antibiotics may not reach all areas of the lung due to mucus plugs obstructing the airways, and the addition of systemic therapy may increase the chances of eradication. Deposition of antibiotics is less homogeneous in patients with more advanced disease, and this population may benefit from a combined treatment approach. In the ELITE trial, efficacy was similar in patients with normal versus reduced lung function (FEV\(_1\)) at baseline, and age did not influence the treatment effect. The overall success rate of treatment was high and compares favourably with results for other regimens.
Head-to-head comparisons of inhaled antibiotics alone versus a combination of inhaled antibiotics with oral ciprofloxacin have not been reported. However, the Early Pseudomonas Infection Control study is currently ongoing and will compare different treatment strategies, including the combination of TIS with oral ciprofloxacin versus TIS alone.\textsuperscript{19}

Accurate diagnosis of lower airway infection is challenging in younger children and patients with milder disease as they often do not expectorate sputum. In such cases, throat or cough swabs are used. Studies comparing bronchoalveolar lavage with throat swabs have shown a good negative but low positive predictive value of these swabs.\textsuperscript{10} This suggests that throat swabs are most useful in excluding lower airway infection in CF. Treatment decisions based solely on throat swabs may lead to overtreatment as the low positive predictive may overestimate the proportion of patients with \textit{P. aeruginosa} in their lower respiratory tract. The presence of \textit{P. aeruginosa} in the upper airway may, however, convey a risk for subsequent lower airway infection. Although this sequence of events is under debate, placebo-controlled studies have shown that the majority of untreated patients with a positive throat swab for \textit{P. aeruginosa} will develop chronic infection.\textsuperscript{20} This therefore favours aggressive treatment strategies where any respiratory culture is positive for \textit{P. aeruginosa}. In the ELITE trial, approximately 50% of the patients were sputum producers and it is reassuring that the efficacy was similar in both sputum-producing and non-sputum-producing patients.

Similar to other studies, the ELITE trial used a microbiological and not a clinical outcome as the primary endpoint. Chronic \textit{P. aeruginosa} infection is associated with a more rapid decline in lung function, and eradication of the pathogen may reverse this process. Limited data suggest that, compared with patients without infection, those with \textit{P. aeruginosa} infection have reduced lung function even after successful eradication of the pathogen.\textsuperscript{21} In the ELITE trial, lung function remained stable throughout the study but, given the overall slow rate of decline in \textit{P. aeruginosa} in patients with \textit{P. aeruginosa} infection, the difference, if any, between the treatment groups and, moreover, the recurrence rate observed was lower than initial assumptions based on findings from previous studies. A post hoc sample size calculation based on the study results showed that 1560 patients would have to enter a trial to show a potential difference in treatment efficacy with 80% power, which makes it likely that even a considerably larger sample size may only be able to show a small and probably clinically insignificant difference, if any, between the treatment regimens.

Treatment with TIS was well tolerated. Only a few serious AEs or discontinuations due to AEs were reported and most appeared to be related to CF rather than the study drug. The study supports previous data that inhaled antibiotic therapy has a high safety margin and is unlikely to cause nephrotoxicity and otoxicity that is seen after parenteral administration of aminoglycosides.\textsuperscript{22} The two events of hearing loss reported, given their transient nature and spontaneous recovery, are of uncertain clinical significance. Importantly, no accumulation of tobramycin was observed even in young children and the lack of an age dependency in serum levels indicates that the same dose could be used from infancy to adulthood. Data for infants <6 months of age are still sparse, but the overall frequency of developing \textit{P. aeruginosa} infection in these young infants is relatively low.

Airway infection in patients with CF can be caused by multiple organisms and treatment of \textit{P. aeruginosa} could promote airway infection with other organisms. The ELITE trial used regular monthly monitoring of respiratory cultures in the first year to capture the emergence of any non-\textit{P. aeruginosa} pathogens. No obvious trends in emerging pathogens were observed, which supports the safety of this treatment approach.

Currently, there are no consistent guidelines for defining early, intermittent and chronic \textit{P. aeruginosa} infection, which mainly relies on detection of the pathogen alone or in combination with antibody testing. The ELITE trial used strict microbiological criteria along with antibody detection to exclude patients with longstanding \textit{P. aeruginosa} infection. Treatment efficacy appeared to be relatively high in patients excluded on the basis of positive antibodies, but long-term follow-up of these patients was not assessed in this trial. The patient selection process was intended to mimic clinical practice where \textit{P. aeruginosa} infection is usually first detected during a routine clinic visit. Further studies are required to determine whether or not this treatment regimen will be efficacious in patients with newly acquired \textit{P. aeruginosa} associated with clinical signs and symptoms of a pulmonary exacerbation.

In conclusion, TIS treatment for 28 and 56 days in patients aged ≥6 months is both effective and well tolerated in the treatment of early \textit{P. aeruginosa} infection with CF.
this study compare favourably with others using longer treatment regimens or combinations with oral ciprofloxacin. Head-to-head comparisons will clarify whether adding either oral ciprofloxacin or intravenous antibiotic therapy can further increase treatment success in patients with CF with early *P. aeruginosa* infection.

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Competing interests PK and GA work for Novartis, the sponsor of this trial. PK was involved in the collection, analysis and interpretation of data. Pharma AG, Basel, Switzerland, subsequently assumed sponsor’s responsibility and Chiron was involved in the initiation and design of the study. Novartis Helsinki and Good Clinical Practice according to the International Conference on Harmonisation guidelines. Each patient and/or their parent or legal guardian gave written informed consent.

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REFERENCES


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