Economic evaluation of tobramycin nebuliser solution in cystic fibrosis
Iles R, Leigh-Smith J, Drummond M, Prevost A, Vowler S

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Tobramycin nebuliser solution (300 mg/5 ml; TNS) was compared with usual therapy for the prophylaxis and treatment of chronic pulmonary Pseudomonas aeruginosa (P. aeruginosa) infection in cystic fibrosis (CF). TNS was administered twice daily, preferably at 12-hour intervals but not less than 6 hourly. Each cycle of treatment comprised 28 days of TNS therapy followed by 28 days without TNS.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult and paediatric patients aged 6 years or older, who had a confirmed diagnosis of CF.

Setting
The setting was the community and tertiary care. The economic study was carried out in the UK.

Dates to which data relate
The two years during which data were collected for the effectiveness analysis, resource use and prices were not reported. The price year was 2001.

Source of effectiveness data
The evidence for the effectiveness outcomes was derived from a single study.

Link between effectiveness and cost data
The costing was performed retrospectively using a sub-sample of the patients included in the effectiveness analysis.

Study sample
No power calculations were described. The effectiveness data were gathered from the medical records of patients with confirmed CF who attended the participating centres. Patients who met the study criteria (see 'Study Population' field) and consented to participate, and were treated with TNS during at least two cycles of 28 (+/- 4) days, were considered for the effectiveness analysis. Patients were excluded if they had not been treated in accordance with the manufacturer's summary of product characteristics, or if they received fewer than two cycles of TNS treatment. Seventy-one patients were included in the trial, of which 41 had been treated with TNS and 30 were recruited as matched controls. A sub-set
of 19 patients aged less than 18 years was identified for a sub-group analysis. The authors did not report the number of patients who refused to participate, or who were excluded. There was no evidence that the study sample was representative of the study population.

Study design
The study used two designs. A retrospective comparative study with historical controls was employed to carry out a between-group comparison analysis, while a within-group comparison study was undertaken to compare TNS patients before and after receiving TNS treatment. The sub-analysis of the younger patients was also a within-group analysis. The study was multi-centred, with data being collected from 8 sites. The follow-up period was 2 years for TNS patients (one year before and one year after TNS treatment was administered), and 1 year for patients who did not receive TNS treatment. The authors did not report any loss to follow-up. The patients were matched in terms of age, gender, lung function and chronic infection with P. aeruginosa, although the method used was not reported.

Analysis of effectiveness
All of the patients included in the study were accounted for in the analysis. The primary health outcomes assessed were lung function and body weight. These were reported as the change in the average value between the year before and after TNS treatment (for the within-group comparisons), and as the difference between the average change experienced by the TNS patients and by the control patients (which was defined as the net effect). Lung function was measured by percentage forced expiratory volume in one second (FEV1%), while body weight was measured by standard deviation (SD) scores. Some of the resources used were reported as a proxy of effectiveness outcomes in the study:

- the number of days in hospital,
- the number of days of intravenous (IV) administration,
- the number of clinic visits,
- the number of outpatient visits,
- IV courses,
- ward admissions, and
- intensive care unit (ICU) admissions.

The results from within-group comparisons were also reported for the sub-group of patients aged less than 18 years.

At the start of the trial, the TNS-treated group and the control group of 30 matched pairs were shown to be comparable in terms of FEV1%, age and gender, although they were not comparable in prior use of antibiotics and hospital admissions. The TNS group received more inhaled antibiotics and had more admissions in the year before TNS administration.

Effectiveness results
The results from the between-group analysis showed that the mean FEV1% in both groups decreased with a net effect of +0.27 (95% confidence interval, CI: -2.86 - +3.40) in favour of TNS patients. The mean body weight in both groups increased with a net effect of +0.09 (95% CI: -0.18 - +0.32) for TNS patients. There was a reduction in the mean total number of days in hospital in both groups, but the results were affected by an outlier in the control group (net effect +2.4, 95% CI: -10.6 - +33.3). Both groups showed a reduction in the number of clinic attendances (net effect -1.46, 95% CI: -5.86 - +1.79) and ward admissions (net effect -0.34, 95% CI: -1.31 - +0.58). The TNS group had a decreased number of outpatient visits (net effect -0.42, 95% CI: -1.33 - +0.07) and IV courses (net effect -1.27, 95% CI: -2.28 - -0.34), but increases were observed for the control groups. The TNS group had a slight increase in ICU admission, whereas there was a decrease in the control group (net effect +0.08, 95% CI: -0.27 - +0.53). None of these differences were statistically significant. There was a reduction of 24.1 days of IV antibiotic treatment in the TNS group, with no...
change in the controls, and this was statistically significant (net effect -23.3, 95% CI: -37.6 - -11.4; p<0.001).

The within-group analysis showed that lung function declined, with a difference between the mean FEV1% scores in the year before and after TNS treatment of -1.26 (95% CI: -3.34 - +0.83). The mean weight SD scores increased by +0.07 (95% CI: -0.08 - +0.23). Reductions were observed in the number of days in hospital (mean -7.8, 95% CI: -13.0 - -3.2) the number of days of IV administration (mean -16.4, 95% CI: -27.4 - -7.9), the number of clinics attended (mean -1.95, 95% CI: -5.43 - -0.29), the number of IV courses (mean -0.98, 95% CI: -1.71 - -0.45), and the number of ward admissions (mean -0.83, 95% CI: -1.52 - -0.32). There was no change in the number of outpatient visits (mean 0, 95% CI: -0.66 - +0.85), but there was an increase in the number of ICU admissions (mean +0.05, 95% CI: -0.20 - +0.59).

In the sub-analysis of the younger patients, the mean FEV1% scores increased by +0.19 (95% CI: -3.44 - +3.82) and the mean weight SD scores increased by +0.07 (95% CI: -0.08 - +0.23).

Reductions were also observed in all other clinical outcomes:
the number of days in hospital (mean -10.7, 95% CI: -16.7 - -5.8),
the number of days of IV administration (mean -20.2, 95% CI: -39.3 - -8.8),
the number of clinics attended (mean -3.53, 95% CI: -10.74 - -0.63),
the number of out patient visits (mean -1.00, 95% CI: -2.11 - -0.11),
the number of IV courses (mean -1.63, 95% CI: -2.95 - -0.89),
the number of ward admissions (mean -0.82, 95% CI: -1.74 - -0.26), and
the number of ICU admissions (mean -0.05, 95% CI: -0.53 - +0.05).

Clinical conclusions
There was a greater reduction in lung volume function for patients in the control group over the study period, although this was not significant. A reduction in lung volume was also observed in the TNS group after TNS treatment, in comparison with the period before treatment, although the change was not significant. No significant differences in weight changes were found in either between-group or within-group comparisons. A larger clinical benefit was observed in the sub-set of younger patients.

Measure of benefits used in the economic analysis
The authors did not derive a summary measure of benefit. In effect, a cost-consequences analysis was performed.

Direct costs
Although the perspective used for the economic analysis was not reported, health service costs appear to have been analysed. These included the costs of TNS, drugs (antibiotics and other drugs) and hospitalisation (both ward and ICU), as well as costs related to other health care interventions (such as intercurrent illnesses and surgical procedures). The costs and the mean resource quantities used were reported separately. The resource quantities were obtained from medical records, while the unit costs were extracted from National Health Service (NHS) reference data.

The cost analysis was only undertaken on the 41 patients who received the intervention and on the sub-set of 19 patients aged less than 18 years. The time horizon used for the estimation of costs was 1 year for each of the treatment strategies considered (TNS versus previous treatment). Hence, discounting was correctly not applied. The average costs per patient were reported. The date of the price data was 2001. The authors stated that they made some adjustments so as to estimate one-year costs for those patients with a shorter follow-up. They scaled up the costs on a pro-rata basis.
Statistical analysis of costs
The data were treated as stochastic. Uncertainty in the resource use and cost measures was addressed using the non-parametric Bootstrap Bca method to establish 95% CIs.

Indirect Costs
The indirect costs were not reported.

Currency
UK pounds sterling (§).

Sensitivity analysis
No sensitivity analysis was undertaken.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean total cost per patient was 28,394 in the year in which TNS was administered and 22,102 in the year preceding TNS treatment. This represented a mean difference of 6,292 (95% CI: +3,138 - +9,193).

For the sub-group of younger patients, the mean total cost per patient was 28,080 in the year in which TNS was administered and 24,250 in the year preceding TNS treatment. This represented a mean difference of 3,830 (95% CI: -1,165 - +6,805).

The cost of adverse effects was not specifically addressed.

Synthesis of costs and benefits
Not applicable because, in effect, a cost-consequences analysis was performed.

Authors' conclusions
The use of tobramycin nebuliser solution (TNS) for the treatment of patients moderately severely affected with cystic fibrosis (CF) led to reductions in hospital attendance and intravenous (IV) antibiotic administration, which would be expected to improve the patients' quality of life and reduce interference to schooling and work. The higher cost of TNS treatment was partially offset by other savings. The clinical benefit observed was larger for the sub-group of younger patients.

CRD COMMENTARY - Selection of comparators
The comparator was "usual therapy", which represented current practice in the authors' setting. The usual therapy was not described, and this will make it difficult to determine if the comparator represents current practice in other settings.

Validity of estimate of measure of effectiveness
The study designs used in the effectiveness analysis are associated with some limitations, given the study question. The authors specifically chose to undertake an observational study, rather than a randomised controlled trial, because they wanted to investigate actual clinical practice.

For the between-group analysis, the authors used a retrospective comparative study with historical matched controls.
from the same clinic, but it was unclear how the patients were selected to be treated with TNS, and if those patients differed in a systematic way from those who did not receive the drug. The authors noted that it is likely that the frequency of pulmonary exacerbations, rather than the level of FEV1%, influenced prescribing of TNS, and that bias would underestimate the effect of TNS. There is some uncertainty surrounding the results of the between-group analysis since the patient groups were not comparable at analysis. There were significant differences between the intervention and control groups at baseline in terms of prior use of antibiotics and the number of hospital admissions.

The within-group study design is associated with problems of confounding. The lack of a control group makes it difficult to establish how much of the effect seen in the patients was due to the intervention, and how much was caused by other factors, including participation in the study. The results from the between-group analysis showed that the matched controls also experienced improvement in their outcomes, which weakens the validity of the results from the within-group analysis.

The study sample may have been representative of the study population since patients from eight sites were included in the effectiveness analysis. No power calculations were reported. Uncertainty in the effectiveness measures was examined by using bootstrapping to create 95% CIs.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**
The authors did not explicitly state the perspective adopted in the study, so it is not possible to determine whether all the relevant categories of cost were included in the analysis. The authors noted that some costs were omitted from the analysis, such as the cost of oxygen, laboratory tests, imaging and community care, patient and family expenses and productivity losses. They concluded that had these costs been included they would have supported the cost case for TNS. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study to other settings. The resource use results from the study were subjected to bootstrapping, and 95% CIs were reported. The costs were taken from NHS reference data, and uncertainty in the cost data was allowed for by using bootstrapping to create 95% CIs. The costs were incurred during a 2-year period and discounting was, correctly, not applied. Costs, rather than charges, were reported. The price year was reported, which will aid any future reflation exercises.

**Other issues**
The authors compared their findings with those from other studies. In general, their findings were in agreement with those from other studies. The authors did not directly address the issue of the generalisability of the results to other settings, although they did compare their results with those from the USA. The authors do not appear to have presented their results selectively. The study enrolled patients with varying disease severity and across the age spectrum, and this was reflected in the authors' conclusions. The authors did not report any limitations to their study.

**Implications of the study**
The authors suggested the policy for TNS should be reviewed. There is a tendency in the NHS to reserve TNS for more severely affected patients who tend to be older. The current study and others carried out in the USA suggest that younger patients have a greater clinical benefit from TNS therapy.

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