Intravenous or oral antibiotic treatment in adults and children with cystic fibrosis and *Pseudomonas aeruginosa* infection: the TORPEDO-CF RCT

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Scientific summary

The TORPEDO-CF RCT

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Scientific summary

Background

Cystic fibrosis is the most common life-limiting recessively inherited condition in white populations. It is a multisystem disorder in which the airways frequently become blocked with mucus, often associated with respiratory infections. These infections may lead to progressive respiratory failure and ultimately to death from breathing failure. *Pseudomonas aeruginosa* is a common infection in the lungs of patients with cystic fibrosis.

However, there is uncertainty about the best method to eradicate *P. aeruginosa* from the lower respiratory tract and several different strategies are used, including oral quinolones such as ciprofloxacin, and intravenous and nebulised antibiotics.

The Trial of Optimal TheRapy for Pseudomonas EraDicatiOn in Cystic Fibrosis (TORPEDO-CF) was conducted to assess the effectiveness and safety of two eradication regimens in children, young people and adults with cystic fibrosis.

Methods

Study design

This was a Phase IV, multicentre, parallel-group, randomised controlled trial that compared the effects of intravenous therapy with oral therapy in participants with cystic fibrosis.

Participants were randomised in a ratio of 1 : 1 to receive up to 3 months of treatment, and, once treatment had stopped, they were then followed up for a minimum of 15 months.

The trial also included an economic evaluation to estimate the incremental cost per quality-adjusted life-year for intravenous therapy compared with oral therapy.

Eligibility criteria

Eligible participants had a confirmed diagnosis of cystic fibrosis and a positive isolation of *P. aeruginosa*, were aged > 28 days, were either *Pseudomonas* naive (i.e. never previously had *P. aeruginosa* isolated from samples) or *Pseudomonas* free (i.e. infection free for at least 1 year), and were able to start allocated treatment within 21 days from the date of the positive microbiology report. Participants were excluded if the *P. aeruginosa* was resistant to one or more of the trial antibiotics, if they had a known hypersensitivity or other contraindication to any of the trial antibiotics, if they were already receiving *P. aeruginosa* suppressive therapy (such as an inhaled antibiotics), if they had received any *P. aeruginosa* eradication therapy within the previous 9 months, or if they were pregnant or breastfeeding. Participants could be randomised into TORPEDO-CF only once and could not be randomised within 4 weeks of taking part in another intervention trial.

Recruitment

Randomisation and blinding

Participants were randomised in a 1 : 1 ratio; randomisation sequences were computer-generated, stratified by centre. Owing to the nature of both therapies, blinding was not possible during the course of the trial.

Outcome measures

Primary outcome

The primary outcome of the trial was defined as successful eradication of *P. aeruginosa* infection 3 months after allocated treatment had started, with the participant remaining infection free through to 15 months after the start of allocated treatment.

Secondary outcomes

The secondary outcomes of the trial were:

- time to reoccurrence of original *P. aeruginosa* infection
- reinfection with a different genotype of *P. aeruginosa*
- lung function (forced expiratory volume in 1 second, forced vital capacity and forced expiratory flow at 25–75% of forced vital capacity)
- oxygen saturation
- growth and nutritional status – height, weight and body mass index
- number of pulmonary exacerbations
- admission to hospital
- number of days spent as an inpatient in hospital during treatment phase, and between 3 and 15 months after randomisation
- quality of life (as measured using the Cystic Fibrosis Questionnaire)
- utility (as measured using the EuroQol-5 Dimensions)
- adverse events
- other sputum/cough microbiology (meticillin-resistant *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Aspergillus* spp., *Candida* spp. infection)
- cost per patient (from an NHS perspective)
- incremental cost-effectiveness ratio (cost per successfully treated patient, cost per quality-adjusted life-year)
- carer burden (absenteeism from education or work)
- participant burden (absenteeism from education or work).

The protocol wording for the outcome 'number of days spent as an inpatient in hospital during treatment phase and between 3 and 15 months after randomisation' is 'Number of days spent as inpatient in hospital over the three-month period after allocated treatment has finished treatment, and between three months and 15 months after eradication treatment has finished (other than 14 days spent on initial intravenous treatment)'. It has been changed in the list of secondary outcomes to aid clarity.

Sample size

The total target number of participants was 286 (143 in each treatment group).

Statistical methods

Primary and secondary outcome data were analysed following the intention-to-treat principle. Safety analyses included participants' data if they had received at least one dose of the randomised treatment.

The statistical analysis plan was developed prior to the final analyses being conducted.

The number and percentage of participants who were classified as a success or a failure for the primary outcome were presented for each treatment arm. The difference between the groups was tested using the chi-squared test, and the relative risk and associated 95% confidence intervals were presented.

The secondary outcomes were analysed using the following methods: binary outcomes were analysed using the chi-squared test, longitudinal data were analysed using mixed models, time-to-event data were analysed using log-rank tests, and continuous data were analysed using a Mann–Whitney *U*-test, as appropriate.

Economic analysis

An economic analysis was conducted that assessed the incremental cost per successful eradication of *P. aeruginosa* infection 3 months after allocated treatment had started, and remaining infection free through to 15 months after the start of allocated treatment, in the oral therapy arm compared with the intravenous therapy arm. The time horizon for the analysis was 15 months post randomisation, and an NHS and Personal Social Services perspective was used for the collection and incorporation of resource use. All costs were calculated in Great British pounds using the price year 2016/17. Where possible, unit costs were sourced from national databases. To account for missingness in the data, multiple imputation was used ($m = 25$). Regression analysis for incremental costs and outcomes was adjusted for baseline utility and age, with the correlation between costs and patient outcomes controlled using bootstrap sampling with replacement ($n = 2000$).

The secondary analysis calculated quality-adjusted life-years by applying preference weights to recorded EuroQol-5 Dimensions, three-level version, scores from patients or carers (on behalf of patients). Using a cost-effectiveness threshold (λ) of £20,000 per quality-adjusted life-year, the incremental net benefit of treating patients with oral therapy compared with intravenous therapy was calculated. Sensitivity analyses explored key drivers of cost-effectiveness identified a priori, including the use of the specialised cystic fibrosis reimbursement tariff for patients, societal costs and using different functional forms for the cost regression-based models.

Results

Participants who were randomised to the intravenous antibiotic therapy group had a reduced likelihood of successful eradication of *P. aeruginosa* 3 months after the start of treatment and remaining infection free through to 15 months after the start of allocated treatment (relative risk 0.84, 95% confidence interval 0.65 to 1.09; $p = 0.184$). The results from the sensitivity analysis were robust to changes that were made. These results did not change the original conclusion.

Owing to the small number of participants with samples available for variable number tandem repeat typing at both time points, the analysis of the outcome 'time to reoccurrence of the original *P. aeruginosa* infection' should be interpreted with caution. This also applies to the results of the analysis of the outcome 'infection with a different and distinct genotype of *P. aeruginosa*'.

The results of the analysis of the secondary outcomes did not show an effect over time on percentage predicted forced expiratory volume in 1 second, percentage predicted forced expiratory flow at 25–75% of forced vital capacity, or oxygen saturation. Forced vital capacity was significantly better in the intravenous antibiotic group than in the oral group (mean difference 3.14, 95% confidence interval 0.15 to 6.14; $p = 0.040$); however, this finding should be interpreted with caution as there was no adjustment for multiple testing. Similarly, body mass index (adults) was significantly lower in the intravenous group than in the oral group (mean difference −0.73, 95% confidence interval −1.39 to −0.08; $p = 0.029$) but this was based on a small number of adults with available data (13 in total). There was no evidence of an effect at 15 months on oxygen saturation or on height for age *z*-score, weight for age *z*-score or body mass index *z*-scores in children.

During 15 months' follow-up, 52 out of 146 (35.6%) participants in the oral antibiotic group and 38 out of 137 (27.7%) participants in the intravenous antibiotic group experienced a pulmonary exacerbation.

The difference was not statistically significant. Significantly fewer participants in the intravenous group [intravenous 40/129 (31%) vs. oral 61/136 (44.9%)] were hospitalised in the 12 months following eradication treatment (relative risk 0.69, 95% confidence interval 0.50 to 0.95; $p = 0.020$). During the same 12-month period, the median hospital stay for participants in both groups was 0 days (interquartile range 0–13 days for the oral group and 0–3 days for the intravenous group; $p = 0.005$). There were no statistically significant differences between study groups for the number of participants who had cough or sputum samples containing meticillin-resistant *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Aspergillus* spp. or *Candida* spp.

There were no statistically significantly differences between the two treatment groups at 15 months across any of the domains in each of the quality-of-life questionnaires.

The median number of days of absenteeism from education or work for carers and participants was not statistically significantly different between the two treatment groups.

There were no significant safety concerns in either of the groups.

Oral therapy led to lower overall costs than intravenous therapy, and had similar or greater clinical effectiveness. For a threshold of £20,000 per quality-adjusted life-year, oral therapy generated £6770.80 (95% confidence interval £5027.40 to £7906.20) benefit per patient compared with intravenous therapy.

Conclusions

Intravenous therapy did not significantly improve the eradication rate of *P. aeruginosa* when compared with oral therapy; the clinically important difference that was set at the beginning of the trial was not contained in the 95% confidence interval, indicating that intravenous therapy is not clinically beneficial when compared with oral therapy in the treatment of *P. aeruginosa*. The health economic analysis also showed that oral therapy was more cost-effective than intravenous therapy, indicating that when the findings of this trial are implemented in routine clinical practice, most patients will receive oral treatment as an outpatient and many admissions will be avoided. This will reduce treatment burden and will reduce health-care costs.

Recommendations for future research

Future research studies should combine long-term follow-up with regimens to reduce reoccurrence after eradication.

Trial registration

This trial is registered as ISRCTN02734162 and EudraCT 2009-012575-10.

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This report

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