Cost-effectiveness of intrapleural use of tissue plasminogen activator and DNase in pleural infection: evidence from the MIST2 randomised controlled trial

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The MIST2 trial showed that combined intrapleural use of t-PA and DNase was effective when compared with single agents or placebo in the treatment of pleural infection. This economic evaluation shows that t-PA–DNase is likely to be highly cost-effective. bit.ly/2vYZhWt

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ABSTRACT The MIST2 (Second Multicentre Intrapleural Sepsis Trial) trial showed that combined intrapleural use of tissue plasminogen activator (t-PA) and recombinant human DNase was effective when compared with single agents or placebo. However, the treatment costs are significant and overall cost-effectiveness of combined therapy remains unclear.

An economic evaluation of the MIST2 trial was performed to assess the cost-effectiveness of combined therapy. Costs included were those related to study medications, initial hospital stay and subsequent hospitalisations. Outcomes were measured in terms of life-years gained. All costs were reported in euro and in 2016 prices.

Mean annual costs were lowest in the t-PA–DNase group (EUR 10 605 for t-PA, EUR 17 856 for DNase, EUR 13 483 for placebo and EUR 7248 for t-PA–DNase; p=0.209). Mean 1-year life expectancy was 0.988 for t-PA, 0.923 for DNase, and 0.969 for both placebo and t-PA–DNase (p=0.296). Both DNase and placebo were less effective, in terms of life-years gained, and more costly than t-PA. When placebo was compared with t-PA–DNase, the incremental cost per life-year gained of placebo was EUR 1.6 billion, with a probability of 0.85 of t-PA–DNase being cost-effective.

This study demonstrates that combined t-PA–DNase is likely to be highly cost-effective. In light of this evidence, a definitive trial designed to facilitate a thorough economic evaluation is warranted to provide further evidence on the cost-effectiveness of this promising combined intervention.

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Clinical trial: The MIST2 trial on which this study is based was registered at the ISRCTN registry with identifier ISRCTN57454527. No individual patient data will be made available. The study protocol is available on request.

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Introduction

Pleural infection is a common and highly morbid condition. The incidence is increasing in both children and adults [1–5], and outcomes remain poor with up to 20% mortality at 1 year and failure of medical therapy in up to 30% of cases [6–10]. Median hospital stay is between 12 and 15 days [6, 7, 9, 10], and we have previously estimated this condition as costing EUR 4223 per patient [7]. Interventions to improve drainage, reduce infection and improve outcomes such as need for surgery and time in hospital are therefore priorities in care [8].

The MIST2 (Second Multicentre Intrapleural Sepsis Trial) trial was a double-blind, double-dummy, randomised placebo controlled trial assessing the combination of intrapleural tissue plasminogen activator (t-PA) and recombinant human DNase as an adjunct to drainage in patients with pleural infection. This study demonstrated significantly improved fluid drainage (measured radiologically) when compared with the single use of medications and placebo [7]. In secondary outcomes, MIST2 demonstrated t-PA–DNase therapy reduced the frequency of surgical referral (OR 0.17; p=0.03) and shortened length of stay in hospital.

Since publication of the MIST2 trial, there have been numerous case series of the use of t-PA–DNase as both "rescue therapy" and as an alternative to surgery in selected patients, totalling over 500 patients to date [11–20]. However, the costs of t-PA and DNase given twice daily for 3 days (as per the MIST2 protocol) are considerable (British National Formulary: www.bnf.org). It is not as yet clear if these increased medication costs are offset by reductions in surgical referral and shortened length of hospital stay.

This study was therefore conducted to specifically address whether use of t-PA–DNase therapy is cost-effective compared with individual use of DNase, t-PA and placebo, using the original data from the MIST2 trial.

Methods

Patients

Eligibility criteria were clinical evidence of infection and pleural fluid that was macroscopically purulent, positive on culture for bacterial infection, or positive for bacteria on Gram staining, or pleural fluid that had a pH <7.2 (measured by means of a blood gas analyser). Evidence of infection, which was assessed by the recruiting physician, included the presence of fever and elevated serum levels of inflammatory markers such as C-reactive protein or an elevated white cell count.

Study design

MIST2 was a double-blind, double-dummy, factorial randomised trial conducted at 11 centres in the UK between December 2005 and November 2008 (ISRCTN registry identifier ISRCTN57454527) [7]. As per the study protocol, patients who did not receive any of the study medications and had pleural opacity at baseline that was <5% of the hemithorax area on chest radiography were excluded. A total of 210 adult patients were enrolled into the study and randomised: 55 received double placebo, 52 t-PA, 51 DNase, and 52 t-PA and DNase. Patients were then followed-up for a period of 12 months. The dose of DNase was 5 mg and the dose of t-PA was 10 mg. Intrapleural medications were each given twice daily for 3 days and each administration was followed by clamping of the drain to permit the study drug to remain in the pleural space for 1 h.

Assessments

The perspective adopted in the economic analysis was that of the hospital provider, with only the direct healthcare costs associated with initial hospitalisation, surgery and subsequent hospitalisation over the 12-month follow-up period included. All costs were reported in 2016 prices. British pounds were converted to euro (GBP 1=EUR 0.877; http://ec.europa.eu/Eurostat).

Initial hospitalisation length of stay was estimated using information from patients' trial records. This was defined as the time between the date of randomisation and discharge to home or to a nursing/residential care home. For patients who required thoracic surgery, duration of time in a surgical ward was estimated as the time between the date of surgery and the date of discharge from surgery. Unit costs were obtained from NHS Reference Costs [21]. A day in hospital was valued using the weighted daily average for Healthcare Resource Groups (HRGs) for "Lung Abscess and Empyema with Interventions", which was then multiplied to the patient's length of stay. For patients requiring thoracic surgery, a day in hospital was valued using the weighted daily averages of the three elective and three nonelective HRGs for "Major Thoracic Procedures, 19 years and over". Costs relating to admissions where patients underwent surgical procedures included both the cost of the hospital stay and of the procedures captured under that HRG.

Information on subsequent hospitalisations over the 12-month follow-up period was obtained from patients' trial records. For each hospitalisation, information on the date of admission and discharge and the reason for that admission was recorded. Reasons for admission were translated into International Statistical Classification of Diseases and Related Health Problems 10th Revision codes and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures version 4 codes, which in turn were converted into an HRG using the HRG4+ Reference Cost Grouper (NHS Information Centre). HRGs were then valued using NHS Reference Costs [21]. Unit costs are reported in table 1. Medication costs were obtained from the British National Formulary. Total medication costs for each patient were then estimated: for t-PA (alteplase) EUR 164×twice daily×3 days and for DNase (Pulmozyme) EUR 19×two doses of 2.5 mg×twice daily×3 days.

In the absence of prospectively collected health-related quality of life, which would have enabled the estimation of quality-adjusted life-years gained, we evaluated the impact of the interventions on life-years gained. Life-years gained were defined in this study as the number of days a patient survived during the year after they were randomised in the study divided by 365.25 days. Therefore, a value of 1 life-year gained was assigned for surviving patients.

Statistical analysis

A within-trial economic analysis was undertaken, with total healthcare costs and life-years gained per patient calculated for the 12 months of the trial period in each of the four groups. Given the timeframe of the analysis as 1 year, discounting of costs and benefits was not performed. All analyses were carried out on an intention-to-treat basis using Stata/MP version 13 (StataCorp, College Station, TX, USA). Length of stay in hospital, costs and life-years gained are reported as means with standard deviations, with differences across the four groups compared using ANOVA. Statistical significance was considered at $p<0.050$.

Treatment with chest tube drainage, antibiotics and saline flushes is current practice in the UK according to evidence-based guidelines (*i.e.* comparable to placebo in MIST2) [8]. As a result, we first compared each of the three trial interventions with placebo. To assess cost-effectiveness we estimated the incremental cost-effectiveness ratio (ICER), undertaken by dividing the mean cost difference between the placebo and the intervention by the difference in mean life-years gained.

In addition, an incremental analysis was conducted, rank ordering each intervention in terms of total costs. The mean cost difference between the second least costly intervention and the least costly intervention divided by the difference in mean life-years gained for these two interventions was used to estimate the ICER. Analysis was then repeated in increasing order of cost. 95% confidence intervals were derived for the mean cost and life-years gained differences between the groups using nonparametric bootstrap sampling with 1000 replications. To assess the probability that an intervention was cost-effective at different willingness to pay thresholds for an additional life-year gained, cost-effectiveness acceptability curves were used with 1000 bootstrap estimates of mean costs and life-years gained for each of the four interventions [22]. An intervention was deemed cost-effective if the additional cost per life-year gained was below GBP 30 000 (EUR 34 220) [23].

A series of one-way sensitivity analyses was then performed. As there were a large number of different reasons why patients were readmitted into hospital, with each of these reasons varying substantially in

TABLE 1 Unit costs

	Unit cost EUR	Source
Study medications, per dose		
Alteplase 10 mg	164	British National Formulary
Pulmozyme 2.5 mg	19	British National Formulary
Initial hospital stays, per day		
Initial stay, nonsurgery	502	NHS Reference Costs
Initial stay, surgery	955	NHS Reference Costs
Subsequent admissions		
Hospital stay[#]	756[#]	NHS Reference Costs

Individual hospitalisation costs were applied in the main analysis. Based on the British National Formulary (www.bnf.org) and NHS Reference Costs [21]. [#]: weighted average for the 37 different reasons patients were readmitted during study follow-up.

cost, rather than applying cause-specific unit costs, we applied the weighted average unit cost reported in table 1. As costs of trial medications are likely to vary considerably both over time (*e.g.* introduction of generic versions) and across countries, we varied the costs of medications by reducing their cost by 50% and increasing their cost by 100%.

Results

A total of 210 adult patients were enrolled into the study and randomised: 55 received double placebo, 52 t-PA, 51 DNase, and 52 t-PA and DNase. However, there was missing length of stay and subsequent resource use in 32 patients (seven receiving double placebo, eight t-PA, 10 DNase, and seven t-PA and DNase). As a result, this analysis is based on the 178 patients having complete resource use: 48 receiving double placebo; 44 t-PA, 41 DNase, and 45 t-PA and DNase.

Resource use, costs and life-years gained

There were no significant differences across the four groups in terms of initial hospital stays and total number of days in hospital over the 12-month period (p=0.265 and p=0.273, respectively). However, although not statistically significant, the mean number of days in hospital was lower for the t-PA–DNase group, in terms of initial hospital stays (both surgical and nonsurgical) and hospital readmissions (table 2).

Except for trial medications, patients randomised to t-PA–DNase had the lowest levels of hospital care costs (table 3). Over the 12-month follow-up period, and after including the costs of medications, patients randomised to t-PA–DNase had total costs of EUR 7248±4922 compared with EUR 10 605±15 413 for t-PA, EUR 17 856±34 861 for DNase and EUR 13 483±28 798 for placebo. Although differences in total costs between the four patient groups were not statistically significant (p=0.209), patients in the t-PA–DNase group incurred significantly lower costs than patients randomised to DNase (p=0.041). Patients randomised to t-PA had the highest number of life-years gained (0.988±0.081 life-years gained), whereas patients randomised to DNase had the lowest number of life-years gained (0.923±0.228 life-years gained). However, differences in 1-year life expectancy were not statistically significant across patient groups (p=0.296).

Cost-effectiveness: placebo versus trial interventions

Given that placebo is currently standard UK practice in the form of saline flushes, we individually compared placebo with each of the three interventions in the trial (table 3). Placebo was found to be dominant over DNase (*i.e.* it was both more effective and less costly), whereas it was dominated by t-PA (*i.e.* placebo was less effective and more costly). When placebo was compared with t-PA–DNase the additional cost per life-year gained was EUR 1.6 billion. In this comparison, the probability that t-PA–DNase was cost-effective at a GBP 30 000 (EUR 34 220) cost per life-year gained threshold was 0.96.

Results of the sensitivity analysis showed that varying trial medication costs (reduction of 50% and increase of 100%) had no impact on cost-effectiveness. Using the overall mean-weighted unit cost to value subsequent days in hospital, rather than cause-specific unit costs, did not impact cost-effectiveness (supplementary material).

When we compared all the interventions in an incremental analysis, we found that DNase and placebo were less effective, in terms of life-years gained, and more costly than t-PA. As a result, for the incremental cost-effectiveness analysis t-PA was compared with t-PA–DNase, the least costly intervention (table 4).

TABLE 2 Number of days in hospital over the 12-month follow-up period

	t-PA	DNase	Placebo	t-PA–DNase
Subjects	44	41	48	45
Initial hospital stay				
Number of days, nonsurgical	14.48±20.21	22.59±58.74	23.65±54.90	11.43±9.31
Number of days, surgical	2.05±9.30	5.66±18.07	1.17±4.36	0.24±1.15
Number of days, total	16.52±22.79	28.24±61.41	24.81±56.11	11.78±9.43
Subsequent hospital stays				
Patients with one or more subsequent admissions	3 (7)	1 (2)	4 (8)	1 (2)
Number of days	0.75±2.96	0.75±4.83	1.38±6.54	0.16±1.04
Total hospital stays				
Number of days	17.27±24.79	29.00±62.01	26.19±56.66	11.93±9.57

Data are presented as n, mean±SD or n (%). t-PA: tissue plasminogen activator.

TABLE 3 Mean costs and outcomes over the 12-month follow-up period

	t-PA	DNase	Placebo	t-PA–DNase
Subjects	44	41	48	45
Costs EUR				
Trial medications	986	227	0	1213
Initial hospital stay, nonsurgical	7155±9991	11 164±27 892	11 687±27 133	5701±4604
Initial hospital stay, surgical	1953±8874	5401±17 247	1113±4159	234±1098
Subsequent admissions	511±2026	1065±6820	682±2865	102±682
Total costs	10 605±15 413	17 856±34 861	13 483±28 798	7248±4922
Life-years gained	0.988±0.081	0.923±0.228	0.969±0.147	0.969±0.153
Cost-effectiveness of placebo *versus* trial interventions				
ICER	t-PA dominant	Placebo dominant	NA	EUR 1.6 billion
Probability placebo cost-effective	0.24	0.81	NA	0.04

Data are presented as n or mean±SD. t-PA: tissue plasminogen activator; ICER: incremental cost-effectiveness ratio; NA: not applicable.

When compared with t-PA–DNase, the incremental cost per life-year gained was EUR 178 166. This is much higher than the currently recommended willingness to pay thresholds recommended by the National Institute for Health and Care Excellence [23]. At a threshold of GBP 30 000 (EUR 34 220) per life-year gained, the probability that t-PA–DNase was cost-effective was 0.86, whereas for t-PA this was 0.12. Placebo and DNase had a probability of less than 0.05 of being cost-effective. As shown in figure 1, at any willingness to pay threshold for an additional life-year gained ranging between GBP 0 and GBP 100 000 (EUR 114 000) the probability of t-PA–DNase being cost-effective remained above 0.50. For placebo and DNase the probability of being cost-effective never exceeded 0.10.

Discussion

Using costs collected alongside a randomised clinical trial evaluating intrapleural therapy for empyema over a 1-year period, we found that administration of t-PA–DNase given twice daily for 3 days was most cost-effective compared with t-PA alone, DNase alone or placebo. Despite the added medication costs associated with t-PA and DNase, overall costs were lower in the combined treatment group than with individual therapies alone, highlighting the benefit seen in the original clinical trial in terms of reduced length of stay in hospital and surgical interventions.

This finding is clinically important with potential impact on current treatment. Although the MIST2 regimen is currently used only in patients who are failing medical therapy for pleural infection, and may not have a surgical option in most hospitals, these data suggest that it may be cost-effective to treat patients with pleural infections with a combination of t-PA and DNase early in treatment. The MIST2 trial recruited all patients with pleural infection and began treatment as soon as possible on admission; therefore, this study provides some economic rationale as to the use of the MIST2 regimen in all such cases. Our results suggest that using t-PA–DNase in preference to standard care (saline flushes, which is equivalent to placebo) in patients with pleural infection might save EUR 5700 per patient treated.

There are limitations to this analysis. First, the economic evaluation was conducted retrospectively and not concurrently alongside the clinical trial. The number of patients in each trial group was small, with the trial not being designed to detect differences in healthcare costs between the groups. Relevant healthcare resource use categories such as use of accident and emergency services, critical care, and outpatient and primary care were not evaluated. Furthermore, the timeframe of our analysis is <1 year and therefore cost-effectiveness of t-PA–DNase beyond this period is uncertain. However, given the acute nature of

TABLE 4 Cost-effectiveness of treatments for pleural infection at 12 months

	Incremental costs EUR (95% CI)	Incremental life-years (95% CI)	Incremental cost-effectiveness ratio	Probability of intervention being cost-effective[#]
t-PA–DNase				0.86
t-PA	3357 (−335–8114)	0.019 (−0.025–0.062)	EUR 178 166	0.12
Placebo	2878 (−4280–10 874)	−0.019 (−0.061–0.020)	t-PA both more effective and less costly	0.03
DNase	4373 (−6700–15 940)	−0.045 (−0.116–0.016)	t-PA both more effective and less costly	0.001

t-PA: tissue plasminogen activator. #: assuming a cost-effectiveness threshold of GBP 30 000 (EUR 34 220) per life-year gained.

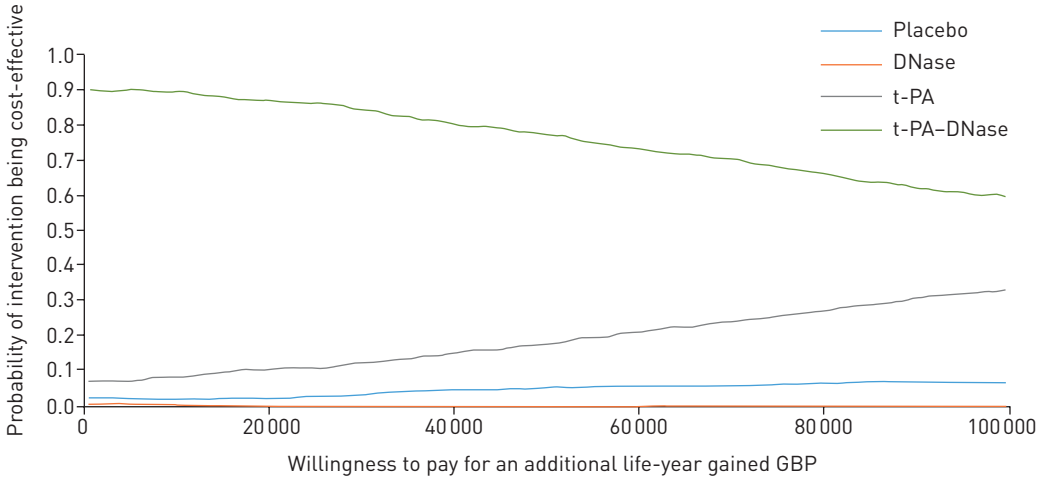

FIGURE 1 Cost-effectiveness acceptability curve. t-PA: tissue plasminogen activator.

empyema and its general treatment, it is reasonable to expect that all relevant hospitalisations and costs would have been captured in the 1-year follow-up period. Prospective follow-up data from randomised and observational studies suggest that the majority of outcomes occur within 3 months and all within 12 months in pleural infection [6, 7, 9, 10].

Quality of life *via* patient questionnaires was not assessed in this trial and therefore the health outcome expressed in our analysis was life-years gained. Ideally, in order to assist decision makers in choosing among different healthcare interventions, costs per quality-adjusted life-years are typically recommended [6]. However, given that combined treatment not only reduced hospitalisation stays over the 1-year follow-up period but also reduced surgical interventions, it is likely that quality of life would also be higher in the combined treatment group, hence improving the cost-effectiveness of the intervention.

Finally, the MIST2 trial was conducted in the UK, using British unit costs to value hospital resource use and medications. Therefore, the results presented will be most generalisable to UK settings. However, we do believe that our measures of resource use, showing the potential for combined t-PA–DNase treatment to considerably reduce overall hospital resource use, are likely to be applicable to other jurisdictions.

Previous evidence from the MIST2 trial showed that combination treatment with t-PA and DNase was effective in improving fluid drainage in patients with pleural infection [1]. This study now highlights that combined treatment is also likely to be highly cost-effective. In light of this evidence, a definitive trial designed to facilitate a thorough economic evaluation is therefore warranted to provide further evidence about the cost-effectiveness of this promising combined intervention in order to assist decision makers.

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Conflict of interest: R. Luengo-Fernandez has nothing to disclose. E. Penz reports personal fees (participation in advisory boards) from AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim, outside the submitted work. M. Dobson has nothing to disclose. I. Psallidas works as a Medical Science Director in AstraZeneca in a different scientific area not relevant to the article. A.J. Nunn reports an unrestricted educational grant from Roche UK, during the conduct of the study. N.A. Maskell has nothing to disclose. N.M. Rahman reports an unrestricted educational grant from Roche UK, during the conduct of the study.

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