Cost-effectiveness of gatifloxacin vs ceftriaxone with a macrolide for the treatment of community-acquired pneumonia

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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
Two antibiotic strategies for treating community-acquired pneumonia (CAP) requiring hospitalisation were examined. The strategies were sequential intravenous (IV) to oral gatifloxacin, and IV ceftriaxone with or without erythromycin to oral clarithromycin. IV gatifloxacin was administered at a dose of 400 mg every day. The dose of IV ceftriaxone was 1 or 2 g every 24 hours (dosage at the discretion of the prescribing physician). The dose of IV erythromycin was 500 mg or 1 g four times a day.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients hospitalised with clinical, laboratory and radiological evidence of CAP. Patients were excluded if they had received an antibiotic in the last 7 days, had a need for concomitant systemic antibiotics, or were hypersensitive to any of the study medications. They were also excluded if the investigator believed that more than 14 days of therapy would be required, or if they were expected to survive less than 72 hours. Renal insufficiency and clinically significant hepatic disease were further criteria for exclusion.

Setting
The setting was secondary care and tertiary care. The economic study was conducted in the USA.

Dates to which data relate
The clinical trial, published in 1999 (see Other Publications of Related Interest), provided data on both the costs and effectiveness. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
Prospective resource utilisation data were collected from the same study sample as that used in the effectiveness analysis.

Study sample
Power calculations to determine the sample size were not reported in the present paper. All clinically evaluable patients enrolled in the trial were eligible for the pharmacoeconomic analysis. The included patients had a diagnosis of CAP and were enrolled less than 24 hours after hospitalisation. The sample was appropriate for the study question of evaluating patients hospitalised with mostly severe CAP. A total of 283 patients were enrolled, 141 in the gatifloxacin group and 142 in the ceftriaxone group. However, 205 patients were considered clinically evaluable, 99 in the gatifloxacin group and 106 receiving ceftriaxone. Further details can be obtained from the original clinical trial (see Other Publications of Related Interest).

**Study design**

This was a multi-centre, double-blind, randomised controlled trial (RCT) that was carried out in 45 North American sites. Randomisation was conducted on the basis of a 1:1 allocation to each antibiotic regimen. The tool used to allocate the patients to the study groups was not reported. The method used for concealment was not described.

**Analysis of effectiveness**

The analysis was conducted on clinically (and economically) evaluable patients. The primary outcome used was treatment success or failure according to the clinical investigator assessment at the post-therapy test-of-cure visit. The two groups were similar in patient demographics and prognostic factors. For example, the mean age was 66 to 67 years, and 71 to 75% of the patients had severe CAP.

**Effectiveness results**

The clinical success rates were 97% with gatifloxacin and 91% with ceftriaxone, (95% confidence interval, CI: 2.5 - 17.6%; p non significant).

In patients with severe CAP, the success rates were 96% with gatifloxacin versus 90% with ceftriaxone, (p not reported). In those with mild to moderate CAP, the success rates were 100% (gatifloxacin) and 92% (ceftriaxone), respectively, (p not reported).

Among microbiologically evaluable patients (49%), the cure rates were 97% with gatifloxacin and 91% with ceftriaxone.

Gastrointestinal adverse events were more common in the ceftriaxone group than in the gatifloxacin group. The adverse effects reported were diarrhoea (13% versus 6%), dyspepsia (6% versus 3%) and vomiting (6% versus 2%).

Drug-related discontinuations were similar in the two groups.

**Clinical conclusions**

The use of gatifloxacin monotherapy (IV to oral regimen) for treating CAP patients requiring hospitalisation gave similar results to a regimen of IV ceftriaxone with or without erythromycin with a switch to oral clarithromycin. Although the results tended to slightly favour the gatifloxacin group, statistically significant results were not achieved, probably due to the limited size of the trial sample.

**Modelling**

A decision tree was used to categorise the patients as treatment successes or failures. It was also used to perform a sensitivity analysis to test the robustness of the study results.

**Measure of benefits used in the economic analysis**

The measure of benefit used in the economic analysis was treatment success. This was derived from the effectiveness analysis.
Direct costs
Discounting was, appropriately, not carried out since this was a short-term study. The quantities and the costs were analysed separately from the institution perspective. The quantities evaluated, derived from the actual data, were the antibiotic-related length of stay (LOS), adverse event LOS and subsequent antibiotic treatment for treatment failures. The antibiotic-related LOS was from the start of antibiotic treatment to discontinuation or discharge. The cost of treating adverse events was extracted from the case report forms, as was that of concomitant medication.

The costs were analysed at three levels. Level 1 related to the pharmacy perspective, considering acquisition price only). Level 2 considered the costs directly related to antibiotic use and infection treatment, exclusive of the hospital per diem cost (e.g. preparation, dispensing, administration, drug monitoring, treatment of adverse events and treatment failures). Level 3 incorporated hospital per diem and other hospital costs (the antibiotic-related LOS was used to quantify this component). The costs were derived from published sources and indexed to 1999 to 2000. The per diem cost was estimated through a sub-group of similar patients extracted from a national database of CAP patients and was derived through a regression using the natural logarithm of the total charges as the dependent variable. This provided a total charge estimate for two patient strata (mild to moderate and severe CAP) and for intensive care unit (ICU) and non-ICU LOS. These were then converted to costs using published cost-to-charge ratios. The costs of outpatient visits and subsequent out of hospital treatment were not included.

Statistical analysis of costs
The costs were treated stochastically. The Kruskal Wallis non-parametric test was used to compare the LOS, antibiotic-related LOS, ICU LOS, and the mean patient costs between groups. A multivariate logistic regression analysis of predictors of ICU admission was also performed. The variables included age, CAP severity, the presence of co-morbidities, the presence of hypoxemia, bilateral or multilobar involvement, and microbiological evaluability.

Indirect Costs
The indirect costs were not considered in the present study.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were performed to investigate the robustness of the estimated cost-effectiveness results. The parameters included in one-way sensitivity analyses were drug acquisition price, hospital per diem and probability of success. The ranges were derived from authors’ assumptions and an observed range of per diem costs.

Estimated benefits used in the economic analysis
The clinical success rates were 97% for gatifloxacin and 91% for ceftriaxone, (95% CI: -2.5 - 17.6%, p non significant), as observed in the effectiveness analysis.

Cost results
There was a trend towards a longer LOS and antibiotic-related LOS in the ceftriaxone group. This was driven by four clinical failures that needed readmission. The geometric mean for antibiotic-related LOS was 4.1 days in the gatifloxacin group versus 4.9 days in the ceftriaxone group. The geometric mean LOS was 4.2 days (gatifloxacin) versus 4.9 days (ceftriaxone). The multivariate regression analysis showed that none of the potential predictors had a significant impact on the LOS.

The total costs are expressed in geometric means (followed by the coefficient of variation). For the gatifloxacin versus ceftriaxone-macrolide groups, the total costs were:
at level 1, $73 (43) versus $124 (52), (p<0.0005);

at level 2, $101 (43) versus $195 (60), (p<0.0005); and

at level 3, $5,109 (67) versus $6,164 (57), (p=0.0114).

Synthesis of costs and benefits
The mean cost per expected cure derived from a decision tree (cost-effectiveness ratio) was $5,236:1 for gatifloxacin compared with $7,047:1 for ceftriaxone. There was a difference of $1,811 per successful outcome in favour of gatifloxacin.

Varying the drug acquisition costs (+/- 25%) or hospital per diem costs (from $885 to $1,970) did not affect the overall results.

Changing the probability of success (45 to 95%) did not significantly affect the gatifloxacin costs, as a treatment success had a similar cost to a failure. However, it affected the cost-effectiveness of ceftriaxone, as the treatment failures were much more costly. Within this range gatifloxacin was always the most cost-effective treatment.

When cost data from patients treated in the ICU were removed, gatifloxacin remained the dominant regimen (mean level 3 cost of $5,038 versus $5,739; p=0.049).

Authors' conclusions
Gatifloxacin monotherapy for patients with community-acquired pneumonia (CAP) requiring hospitalisation is clinically effective and provides an economic advantage compared with the regimen of ceftriaxone with or without intravenous (IV) erythromycin and with a switch to oral clarithromycin.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was justified. The authors referred to guidelines by several organisations, such as the IDSA. The comparator would appear to represent current practice in the authors' setting.

Validity of estimate of measure of effectiveness
The effectiveness data were obtained from a double-blind RCT. This trial was appropriate for the study question, although underpowered to detect the observed differences. The study sample was representative of the hospitalised CAP population. The patient groups were broadly comparable and the differences observed could have been due to small imbalances, such as a few more severe cases of CAP in the ceftriaxone group. There were also more admissions to the ICU in the ceftriaxone group, 11 versus 3. Nine and three of these, respectively, were admitted on the enrolment day and should thus be viewed as an effect of randomisation and not of the treatment group. The exclusion of this group did not change the main results. The analysis was conducted on clinically evaluable patients. It was unclear whether the analysis was conducted on an intention to treat basis.

Validity of estimate of measure of benefit
The measure of benefit chosen (success rate) was useful to compare the two treatments, but it cannot be used to evaluate their relative cost-effectiveness in comparison with other technologies. The use of a more generalisable measure would have been helpful.

Validity of estimate of costs
The categories of costs relevant to the hospital perspective were included. As such, ambulatory costs were excluded but they would probably not have been very influential. The costs and the quantities were reported separately. Resource use data were taken from the parent RCT and a statistical analysis of the quantities was performed. This increases the
validity of the results. The unit costs were from published sources and some were derived through a statistical analysis of a primary cost database. A sensitivity analysis of the unit costs was conducted, adding robustness to the conclusions. The charges were converted to costs using appropriate sources. The price year was also reported, thus facilitating reflation exercises in other settings.

**Other issues**
The authors made appropriate comparisons with other studies. Generalisability to other settings was addressed through the RCT, which had a few exclusion criteria, and the sensitivity analysis conducted. Therefore, the external validity of the analysis was high. Although the analysis was mainly conducted on severe CAP patients, it applies primarily to patients not treated in the ICU. Treatment failures were important drivers of the economic analysis, but the number was too small to derive a statistical inference. The clinical trial on which the cost-effectiveness analysis was based was not powered to detect a statistical difference in the clinical outcomes, but it did show a beneficial trend of gatifloxacin.

**Implications of the study**
There is evidence that gatifloxacin monotherapy is a safe and effective alternative for CAP. The study offers further evidence that fluoroquinolone monotherapy, in this case gatifloxacin, represents a cost-effective alternative to the standard regimen of IV ceftriaxone with or without an IV macrolide.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
11348951

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adolescent; Adult; Aged; Aged, 80 and over; Anti-Bacterial Agents /economics /therapeutic use; Anti-Infective Agents /economics /therapeutic use; Ceftriaxone /economics /therapeutic use; Cephalosporins /economics /therapeutic use; Community-Acquired Infections /drug therapy /economics; Cost-Benefit Analysis; Decision Trees; Double-Blind Method; Female; Fluoroquinolones; Humans; Macrolides; Male; Middle Aged; Pneumonia, Bacterial /drug therapy /economics; Prospective Studies

**AccessionNumber**
22001001119

**Date bibliographic record published**
31/07/2004

**Date abstract record published**
31/07/2004