Comparison of hospitalization rates in patients with community-acquired pneumonia treated with 10 days of telithromycin or clarithromycin


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 treatments for adults with community-acquired pneumonia (CAP) were assessed. The treatments were oral telithromycin (800 mg once daily) and clarithromycin (500 mg twice daily) for 10 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adults with a suspected diagnosis of CAP. Patients were excluded if they had severe CAP, infections attributable to sources other than community-acquired bacterial pathogens, or risk factors for drug-resistant S. pneumonia. They were also excluded if they had received more than 24 hours of treatment with other antibacterials within the 7 days prior to enrolment, had documented infection with a pathogen resistant to the study medication prior to enrolment, had a history of alcohol abuse, or were immunocompromised.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence and costing data were collected between May 1998 and September 1999. The price year seems to have been 1999.

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

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
It was not reported whether sample size calculations were performed in the planning phase of the study to assure a certain power. Instead, the authors retrospectively stated that the study was powered to investigate clinical efficacy but not other patient outcomes. The study sample was selected by including adults (aged at least 18 years) outpatients with a suspected diagnosis of CAP. A total of 493 patients were enrolled. Of these, 448 were randomised into two groups and
received at least one dose of medication. There were 224 patients in each of the two groups. The patients in the telithromycin group had a mean age of 44.1 years and 50% were male. The patients in the clarithromycin group had a mean age of 46.0 years and 49.1% were male. The authors did not report any withdrawals, nor did they give the reasons why some patients were not finally randomised to the study groups. There was no evidence that the study sample was representative of the study population.

Study design
The analysis was based on a multi-centred, randomised, double-blind, parallel-group Phase III clinical trial. The patients were randomised in equal numbers to the two study groups, although the method of randomisation was not reported. The study investigators were blinded to the treatment assessment. The study was based at 54 centres across four countries, that is, Argentina (7), Canada (10), Chile (2) and the USA (35). The patients were followed for 1 month and were evaluated at pre-therapy/entry (day 1), on-therapy (days 3 - 5), end of therapy (days 11 - 13), post-therapy/test of cure (TOC) (days 17 - 24), and late post-therapy (days 31 - 36). The authors did not report whether any patients were lost to follow-up.

Analysis of effectiveness
The analysis was reported to have been conducted on an intention to treat basis. An additional analysis, which considered only patients who had a clinical and radiologic confirmation of the diagnosis of CAP (i.e. 416 patients: 204 telithromycin-treated patients and 212 clarithromycin-treated patients), was also performed. The primary effectiveness outcome was the clinical cure rate (i.e. the percentage of patients who improved with no subsequent antibacterial therapy requirements, or who returned to the pre-infection state). The secondary efficacy variables were bacteriological efficacy rates at the post-therapy/TOC visit and at the late post-therapy visit, and safety and tolerability profiles (e.g. electrocardiogram recordings and emergence of adverse events). The authors reported that there were no statistical differences across the treatment groups in terms of demographics (i.e. gender, age, body mass index and smoking status) or baseline infection characteristics (as measured by the Fine score severity classification for assessing pneumonia severity).

Effectiveness results
The clinical cure rate was 88.3% (143 out of 162) for telithromycin and 88.5% (138 out of 156) for clarithromycin (difference -0.2%, 95% confidence interval, CI: -7.8 - 7.5). These results were also supported when only patients with clinical and radiologic confirmation of the diagnosis of CAP were considered for the analysis. The authors reported that bacteriological outcomes and tolerability profiles were similar for the two treatment regimes, although the figures or statistical results for these outcomes were not reported.

Clinical conclusions
The clinical efficacy of telithromycin and clarithromycin (in terms of cure rates, bacteriological outcomes and tolerability profiles) was shown to be statistically equivalent.

Measure of benefits used in the economic analysis
The authors did not estimate a summary measure of benefits. Instead, they reported that since no significant clinical differences were observed, a cost-minimisation analysis would be carried out.

Direct costs
A perspective for the cost analysis was not reported. The authors reported that the resource use data were collected from patients over the period of the trial using case report forms. These forms included information about protocol-derived and non protocol-derived health care resources, concomitant medications and serious adverse events. Protocol-derived health care resources covered X-rays, electrocardiograms, visits, examinations and tests. Non protocol-derived health care resources covered hospital emergency visits, additional contact with a general practitioner, pulmonary specialist, infectious disease specialist, community nurses and other health care professionals, and additional
ambulatory and inpatient tests or procedures.

Some of the resource quantities were reported separately from the unit costs (e.g. probabilities of using non-protocol resources, and the number of hospitalisations and length of stay for CAP-related hospitalisations). The resource use described in the cost analysis would appear to correspond to the health service perspective. However, the costs finally reported were hospitalisation costs per 100 patients. The authors reported that only those costs considered to be related to CAP were included in the analyses. The unit costs were obtained from a publication by the American Hospital Association. Discounting was not required because of the very short time horizon. The price year seems to have been 1999.

**Statistical analysis of costs**

An analysis of variance was used to compare continuous variables, Fisher's exact test was used to compare categorical variables, and 95% CIs were reported for the costs. Statistical significance was defined at a level of 5%.

**Indirect Costs**

Indirect costs assessing the cost impact of treatment on the individual or wider society were not reported. It was stated they were beyond the scope of the study.

**Currency**

US dollars ($).

**Sensitivity analysis**

There was no report of sensitivity analyses being carried out.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

The hospitalisation cost per 100 patients was $11,321 for telithromycin and $31,503 for clarithromycin (difference -$20,182, 95% CI: -49,531 - 9,168). This difference did not achieve statistical significance.

**Synthesis of costs and benefits**

Not relevant.

**Authors' conclusions**

Compared with clarithromycin, treatment with telithromycin was associated with a trend towards fewer hospitalisations and days required in hospital. The projected community-acquired pneumonia (CAP)-related hospitalisation costs were "numerically reduced" for telithromycin recipients, while clinical efficacy was statistically equivalent for both treatments.

**CRD COMMENTARY - Selection of comparators**

The authors compared telithromycin with clarithromycin. Telithromycin was chosen as it was reported to be the first in a new class of antibacterials to be approved for clinical use. Clarithromycin was chosen as the comparator because it was reported to be a commonly recommended first-line treatment, whose usefulness may have been compromised by the increased global prevalence of antibacterial resistance among S. pneumoniae. You should decide whether these are widely used health technologies for the treatment of adult patients with CAP in your own setting.
Validity of estimate of measure of effectiveness
The authors designed a double-blind, parallel-group Phase III clinical trial to compare the technologies. Although the authors did not report any evidence of it, the study sample is very likely to have been representative of the study population since patients from 54 centres located in four different countries were included in the clinical study. The study sample appears to have been appropriate for the clinical question. In addition, the patients groups were compared at baseline and there was no evidence of confounding factors. The results were presented as point estimates as well as CIs. However, not all of the relevant results were reported. The authors might have considered using a large population power to detect clinical differences rather than clinical equivalence. Although the authors reported that an intention to treat analysis was performed, the patients finally considered for the estimation of effectiveness outcomes (i.e. cure rates) did not correspond to those of the intention to treat population. Therefore, the effectiveness conclusions of this study might be subject to bias.

Validity of estimate of measure of benefit
Since the results from the effectiveness analysis showed the therapeutic equivalence of treatment alternatives, a cost-minimisation analysis was performed. Therefore, no summary measure of benefit was used in the economic analysis. The reader is consequently referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
A perspective for the cost analysis was not reported and it could not be inferred. This is because the authors appear to have collected resource use from a health service perspective, but the estimated costs were those related to hospitalisation. Consequently, it is not possible to assess whether all the relevant costs were included. The authors clearly stated that the indirect costs were beyond the scope of the study.

As the cost-differences did not achieve statistical significance, omissions of relevant costs might have altered the principle conclusions drawn. The authors also highlighted the potential for the miscategorisation of CAP-related hospitalisations, which could have introduced bias into the cost estimation. Examining the cost implications for individual countries might have revealed statistically significant differences in some countries and not others, owing to the differing structures in the countries. This might have been a useful result for readers who are interested in their own specific country, or who are interested in generalising the results.

Some, but not all of the resource quantities were reported separately. This may improve the readers' ability to understand the key cost-drivers and could facilitate reflation exercises in other settings with some limitations. Discounting was not performed, but it was not required as the time horizon was shorter than 2 years. The price year appears have been 1999.

Other issues
The authors drew comparisons with findings of other authors, highlighting, in particular, three studies with consistent findings in terms of health care resource use. However, two of these studies considered study populations that were different to the one considered in the clinical analysis of this study. The authors presented useful arguments suggesting the rationale for how clinically equivalent therapies can have potentially differing cost implications. The authors also reported that, although this was a multinational study, the economic analysis was performed from a US managed care perspective and the costing element may not, therefore, be applicable to other countries.

A number of limitations of the study were presented. For example, the trial was powered to detect clinical equivalence and not difference. The authors acknowledged such limitations and suggested that the results obtained here should be considered “observational”.

Implications of the study
The authors did not make any recommendations for policy or practice following their study. Further work in the form
of adding "support to the findings of these preliminary analyses" was suggested.

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