Hospitalization rates among patients with community-acquired pneumonia treated with telithromycin vs clarithromycin: results from two randomized, double-blind, clinical trials


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
The use of oral treatment with telithromycin for patients with community-acquired pneumonia (CAP) was compared with oral treatment with clarithromycin. Patients received telithromycin 800 mg once daily for a period of 5, 7 or 10 days, or clarithromycin 500 mg given twice daily for 10 days.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult (18 years and older) patients with a suspected diagnosis of acute CAP who were eligible for oral therapy. Patients with severe CAP requiring either immediate admission to an intensive care unit or parental antibacterial treatment were excluded, as were patients with infections attributable to sources other than community-acquired bacterial pathogens. Also excluded were patients who had received more than 24 hours' treatment with other antibacterials within 7 days prior to enrolment and patients who had a documented infection with a pathogen resistant to the study medication prior to enrolment.

Setting
The setting was secondary care. Two clinical studies were carried out, one in four countries and one in nine countries. The countries reported by the authors were Argentina, USA, Brazil, Germany, South Africa and Canada.

Dates to which data relate
The effectiveness data and health care resource use data were derived from two clinical studies published in 2004. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from two published studies.

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

Study sample
The study sample was taken from two clinical studies. It consisted of adults (18 years and older), both outpatients (study
I) and outpatients and inpatients (study II), with a suspected diagnosis of acute CAP for whom oral therapy was eligible. The diagnosis of CAP was based on the production of purulent sputum and new onset of defined clinical signs and symptoms, as well as chest X-ray findings. The severity of CAP was defined according to the Fine scale, which ranges from Class I (lowest risk of mortality) to Class V (highest risk).

A total of 1,074 patients were enrolled in the two studies. Of these, 1,023 patients were finally randomised and received at least one dose of the study medication. More specifically, 18.7% (n=193) to 5 days' telithromycin, 19% (n=195) to 7 days' telithromycin, 21.9% (n=224) to 10 days' telithromycin and 40.2% (n=411) to 10 days' clarithromycin. Nine hundred and seventy-five patients received at least one dose of medication (n = 187, 191, 204 and 393, respectively).

Study design
Both studies were randomised, double-blind, multinational Phase III clinical studies. They were multi-centre studies conducted in several countries. Study 1 involved 54 clinical centres in 4 countries, whereas study 2 involved 77 clinical centres in 9 countries. In both studies, the investigators were blinded to the treatment regimen. The method of randomisation was not reported in the current paper. The data were collected for one month following randomisation. No information on loss to follow-up was given. More detailed information is given in the original studies (see 'Other Publications of Related Interest' below for bibliographic details).

Analysis of effectiveness
The analysis of effectiveness was performed post-therapy/test of cure (TOC) days 17 to 24 in the clinical evaluable per-protocol (PPc) population and in the modified intent to treat (mITT) population. The PPc population comprised all patients with a confirmed diagnosis of CAP who received at least one dose of study medication, with major protocol violators excluded; major protocol violators were not excluded from the mITT population. In addition, the data from the two studies were pooled to present effectiveness results. The primary health outcome was the clinical cure rate, which was defined as an improvement with no subsequent antibacterial therapy required, or return to pre-infection state. No statistically significant differences in demographic or baseline clinical characteristics were found across the treatment groups.

Effectiveness results
Study I (PPc); the clinical cure rate was 88.3% (143 of 162) with 10-day telithromycin and 88.5% (138 of 156) with 10-day clarithromycin. The difference was -0.2% (95% confidence interval, CI: -7.8 - 7.5)

Study I (mITT): the clinical cure rate was 78.9% (161 of 204) with 10-day telithromycin and 80.75% (171 of 212) with 10-day clarithromycin. The difference was -1.7% (95% CI: -9.9 - 6.5).

Study II (PPc): the clinical cure rate was 89.3% (142 of 159) with 5-day telithromycin, 88.8% (143 of 161) with 7-day telithromycin, and 91.8% (134 of 146) with 10-day clarithromycin. The differences were -2.5% (95% CI: -9.7 - 4.7) and -3.0% (95% CI: -10.2 - 4.3) for 5- and 7-day telithromycin, respectively.

Study II (mITT): the clinical cure rate was 82.4% (154 of 187) with 5-day telithromycin, 82.2% (157 of 191) with 7-day telithromycin, and 81.2% (147 of 181) with 10-day clarithromycin. The differences were 1.1% (95% CI: -7.3 - 9.6) and 1.0% (95% CI: -7.4 - 9.4) for 5- and 7-day telithromycin, respectively.

The pooled clinical cure rates (ITT) were 77.1% (472 of 612) for telithromycin and 77.3% (318 of 411) for clarithromycin.

The tolerability profiles for both medicines were similar.

Clinical conclusions
The clinical cure rates for 5-, 7- and 10-day telithromycin were statistically equivalent to those for 10-day clarithromycin in both PPc and mITT populations.
Measure of benefits used in the economic analysis
No measure of benefit was used for the economic analysis. The effectiveness data were considered to be equivalent so only the costs were considered in the economic analysis.

Direct costs
The direct costs were for inpatient hospitalisation and additional health care resources (i.e. non protocol-driven resource use at the end of the therapy, post-therapy and late post-therapy). The latter consisted of outpatient visits (general practitioner, pulmonary specialists, infectious disease specialists, other health care professionals, hospital emergency departments), community nurse contacts, additional ambulatory and inpatient tests and procedures, hospitalisations relating to CAP, and concomitant antibacterial agents related to the treatment of a respiratory tract infection. Protocol-driven costs were not included.

Hospitalisations and the number of days hospitalised were recorded on Serious Adverse Events forms and Health Care resource Utilization Case Report forms. In addition, CAP-related hospitalisations were distinguished on the basis of clinical symptoms assessed by investigators (blinded to treatment group) at the time of the patient's admission. The hospitalisation costs and quantities were reported and analysed separately. The cost of a hospitalisation day was derived from the average daily rate for short-term hospitalisation published by the American Hospital Association. The price year was 2002. Discounting was not performed, which was appropriate since the costs were incurred within one year.

Statistical analysis of costs
The costs were treated stochastically. Analyses of variance (ANOVAs) were used to compare the costs and quantities for each treatment group and to create 95% CIs. In addition, chi-squared analyses were performed to confirm the p-values generated by the ANOVAs.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sub-group analyses were carried out on patients aged 65 years or older and patients with more severe CAP (Fine score > II).

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

Cost results
The hospitalisation cost per 100 patients was $14,753 for telithromycin patients (all groups) and $43,623 for clarithromycin patients. This resulted in a saving of $30,231 (95% CI: -56,621 - -3,840) per 100 patients. The hospitalisation costs of telithromycin patients treated for 7 and 10 days were significantly lower than those of clarithromycin patients and resulted in savings of $32,289 per 100 patients.

Some significant differences in resource use were reported. The absolute all-cause hospitalisation rate was 24 among patients treated with telithromycin versus 27 among clarithromycin patients. This resulted in 3.9 versus 6.6 admissions per 100 patients receiving telithromycin and clarithromycin, respectively, (p=0.090).

CAP-related hospitalisation rates were 1.3 and 3.6 per 100 patients receiving telithromycin and clarithromycin,
respectively, which resulted in a significant difference in favour of telithromycin, (p=0.025).

In addition, the number of CAP-related days of hospitalisation was significantly lower for telithromycin recipients (11.4 versus 33.8; p<=0.050).

These significant differences were also found in the sub-group analyses.

No significant differences in other (additional) health care resource use were found between the alternative treatment groups.

**Synthesis of costs and benefits**
Not applicable.

**Authors’ conclusions**
Treatment with telithromycin was associated with significantly fewer hospitalisations associated with community-acquired pneumonia (CAP) and CAP-related hospital days than treatment with clarithromycin. No statistical difference was found between the efficacy data of the alternative treatments.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was clear. Clarithromycin was the commonly used first-line recommended therapy for adults with CAP and is likely to represent current practice. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from two randomised, double-blind, controlled clinical trials. The data from the two studies were presented separately and were shown to be comparable. Given the study designs, the internal validity of the results is likely to be high. In addition, the varied location of the clinical centres makes the effectiveness results more transferable.

**Validity of estimate of measure of benefit**
The authors did not derive a measure of health benefit. The analysis was based upon the therapeutic equivalence of the treatment alternatives and, as such, only the costs were considered in the economic analysis.

**Validity of estimate of costs**
Assuming that a health care perspective was chosen, all the categories of costs relevant to this perspective were included in the analysis. The costs of hospitalisation were reported separately from the quantities, thus enhancing the reproducibility of the study. The resource use quantities were gathered prospectively but were taken from the studies that were included. Differences in resource use between the alternative patient groups were analysed appropriately. A statistical analysis of the quantities was performed. The unit cost of hospital stay was taken from the American Hospital Association. The price year was stated.

**Other issues**
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to other settings was addressed. The results were not presented selectively and the conclusions would appear to reflect the scope of the analysis. Sub-group analyses were performed and these confirmed the findings among all patients included. Further limitations of the study were discussed. For example, the transferability of the cost results to other countries and the use of CAP-related hospitalisations, which may have been a more subjective approach. Finally, the authors reported that the reasons for the lower rate of hospitalisation among patients treated with
telithromycin were unclear, while the clinical efficacy of telithromycin and clarithromycin was similar.

**Implications of the study**
The findings of this study suggested that telithromycin, 800 mg once daily for 7 to 10 days, is a potentially useful therapeutic option for the treatment of patients with mild to moderate CAP and could have significant cost-saving implications.

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**Other publications of related interest**


Tellier G, Chang JR, Asche VC, Lavin B, Stewart J, Sullivan DS. Comparison of hospitalisation rates in patients with community acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. Current Medical Research and Opinion 2004;20:739-47.

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Aged, 80 and over; Anti-Bacterial Agents /therapeutic use; Clarithromycin /therapeutic use; Community-Acquired Infections /drug therapy; Double-Blind Method; Female; Hospitalization /statistics & numerical data /trends; Humans; Ketolides /therapeutic use; Macrolides /therapeutic use; Male; Middle Aged; Pneumonia, Bacterial /drug therapy

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