Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

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Scientific summary

Background

Bone and joint infection in adults causes considerable morbidity. Treatment costs are estimated at £20,000–40,000 per patient. The current standard of care in most UK centres includes a prolonged course (i.e. 4–6 weeks) of intravenous (IV) antibiotics during the early treatment phase, although there is no evidence that PO antibiotic therapy results in worse outcomes.

Objectives

The primary objective of the OVIVA (Oral Versus IntraVenous Antibiotics) trial was to determine whether or not oral (PO) antibiotic therapy is non-inferior to IV therapy when given for the first 6 weeks of treatment for bone and joint infection, as judged by the proportion of patients experiencing definite treatment failure during 1 year of follow-up.

Secondary objectives included assessment of:

1. serious adverse events (SAEs), including death (i.e. all cause) according to treatment allocation
2. IV catheter line complications (i.e. infection, thrombosis or other events requiring early removal of the line)
3. Clostridium difficile-associated diarrhoea
4. ‘probable’ and ‘possible’ treatment failure as composites with definitive treatment failure
5. early termination of the planned 6-week period of PO or IV antibiotics
6. resource allocation using (1) length of hospital stay, (2) outpatient visits and (3) antibiotic costs
7. quality of life, as evaluated by EuroQol-5 Dimensions questionnaire
8. Oxford Hip and Knee Scores (when infection involved the hip or knee)
9. patient adherence to treatment, as indicated by a Medication Event Monitoring System (MEMS) in a subset of participants.

Methods

The trial was a multicentre, open-label, parallel-group, randomised (1 : 1), non-inferiority study. The primary end point was definite treatment failure within 1 year. Eligible patients had anticipated life expectancy of > 1 year, had a bone and joint infection for which at least 6 weeks of antibiotic therapy was considered necessary and had received ≤ 7 days of IV antibiotic therapy following surgery (or from the start date of planned curative therapy if there was no planned surgical intervention). Exclusion criteria were recent Staphylococcus aureus bacteraemia, bacterial endocarditis or other infection mandating a prolonged course of IV antibiotic therapy. Data were collected manually from care records, direct patient contact and questionnaires prior to entry onto a centralised database (OpenClinica Enterprise version 3.4, 2014; Waltham, MA, USA). The occurrence of definitive treatment failure was adjudicated by a blinded end-point committee that reviewed relevant clinical records, redacted for indicators of treatment allocation and patient identifiers.

Data were analysed using Stata® (version 14SE, StataCorp LP, College Station, TX, USA). The non-inferiority margin was set at 7.5% [i.e. an absolute upper two-sided 90% confidence interval (CI) around the unadjusted difference between PO and IV therapy of ≤ 7.5% was considered non-inferior].
Results

A total of 1054 participants from 26 UK centres (including 228 from a single-site internal pilot study) were randomised. Participants were evenly matched between the two arms of the trial for age, clinical presentation, comorbidities, site and type of surgery, organism and histopathological diagnosis. Primary end-point data were available for 1015 (96%) participants.

Definitive treatment failures were observed in 74 out of 527 (14.04%) participants in the IV arm and 67 out of 527 (12.71%) participants in the PO arm. A total of 432 (81.97%) and 442 (83.87%) participants in the IV and PO arms, respectively, did not experience definitive treatment failures over the 1-year follow-up. Data on treatment failures were missing for 21 (3.98%) participants in the IV arm and 18 (3.42%) participants in the PO arm.

In an intention-to-treat analysis, using multiple imputation to include all randomised participants, the imputed risk difference (PO – IV) for definitive treatment failure was estimated to be –1.38% (90% CI –4.94% to 2.19%).

In a complete-case analysis, which included only those participants with primary end-point data at 1-year follow-up, 74 out of 506 (14.62%) and 67 out of 509 (13.16%) participants in the IV and PO arms of the trial, respectively, suffered a definitive treatment failure, representing a risk difference (PO – IV) of –1.46% (90% CI –5.03% to 2.11%).

A per-protocol analysis, which included 909 patients who followed their allocated treatment strategy for at least 4 weeks, showed definitive treatment failure in 69 out of 443 (15.58%) participants in the IV arm and 61 out of 466 (13.09%) in the PO arm of the trial, representing a risk difference of –2.49% (90% CI –6.31% to 1.34%).

All end-point analyses, as well as sensitivity analyses to investigate the potential impact of missing data, were consistent in showing that the non-inferiority criteria were met.

Time to event modelling showed no difference in the time to definitive treatment failure between the arms.

Prespecified subgroup analyses according to recruiting centre, pathogen and surgical management (e.g. retention or removal of metalware) showed no significant difference in rate of definitive failure between the two arms of the trial.

With the exception of line complications [49/523 (9.37%) in the IV arm vs. 5/523 (0.96%) in the PO arm], there was no significant difference between the two arms of the trial in the incidence of SAEs, including death.

Participants randomised to IV therapy were hospitalised for longer than those randomised to PO therapy, with a median (interquartile range) inpatient stay of 14 (11–21) days and 11 (8–20) days, respectively. Patients randomised to IV therapy had an unadjusted excess treatment cost of £2727 (95% CI £1437 to £3980) through to 1 year of follow-up.

Implications

1. Clinical outcome. The OVIVA trial demonstrates no clinical advantage of using prolonged IV therapy compared with PO therapy in the early treatment of bone and joint infections requiring ≥ 6 weeks of antibiotic therapy. The findings directly challenge a widely held view that the management of bone and joint infection mandates a prolonged course of IV antibiotic therapy. This dogma was most notably published as a specialist opinion in 1970, and since then it had been perpetuated through several
iterations of guidelines, protocols and textbooks. A number of smaller studies investigating the effectiveness of PO antibiotic therapy in osteomyelitis, including a meta-analysis involving 180 patients, have suggested similar results but none was large enough to influence management. We believe that the findings of the OVIVA study provide sufficiently robust evidence to inform a widespread change in clinical practice.

2. Safety. Use of PO antibiotic therapy mitigates the risks associated with long-term IV access. In our trial, around 10% of participants randomised to IV therapy developed complications directly related to the use of IV lines.

3. Cost. In addition to the clinical findings, the results demonstrate that PO antibiotic therapy provides a significant cost benefit and cost-effectiveness advantage over IV therapy, without additional risk of adverse events. Assuming a total of 9000 bone and joint infections in adults are managed in UK secondary care per year, routine use of PO as opposed to IV therapy could save the NHS around £25M per year.

4. Patient pathway. Compared with IV therapy, PO antibiotics allow for earlier discharge from hospital. This is of considerable advantage to patients and the NHS. It provides patient satisfaction, contributes to the cost savings, optimises inpatient flow and limits the risks of health-care associated infections. Although not formally assessed during the study, our experience suggests that use of PO therapy is widely perceived as more convenient for patients. Most patients on prolonged IV therapy require regular attendance of health-care providers and often are restricted in their social and professional activities by the IV access device.

5. Antibiotic stewardship. The current availability of a wide range of effective PO antibiotics allows clinicians to select the most appropriate, narrow-spectrum agent. This directly supports a national objective of protecting the most valuable IV antibiotic agents against emergence of resistance by minimising the use of unnecessarily broad-spectrum IV antibiotics.

Conclusion

Oral antibiotics are a safe, effective and convenient alternative to IV therapy in the early management of serious bone and joint infection. Translation of these findings into routine clinical practice is likely to benefit patients and provides an opportunity for substantial cost savings to the NHS.

Future research

1. Duration of therapy. To further support patient safety, cost improvement and antimicrobial stewardship, additional work to define the optimal total duration of antibiotic therapy in bone and joint infection is necessary. Currently, there is considerable variation between centres and between clinicians, which suggests that there may be significant redundancy in antibiotic use. This almost certainly contributes to the risk of emerging resistance to antimicrobials, an issue that is high on the agenda of the Department of Health and Social Care and the medical community globally.

2. Antibiotic choice and dose. Effective antibiotic therapy requires the presence of therapeutic drug levels at the site of the infected tissue. This depends on both bioavailability and tissue penetration. Optimising antibiotic choice will require a programme of work that may include techniques such as microdialysis of tissue fluid at the site of deep surgical infection.

Trial registration

This trial is registered as ISRCTN91566927.
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