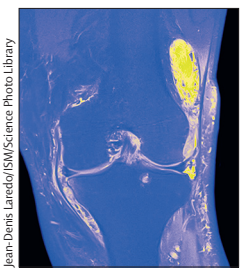
A pragmatic trial in bone and joint infection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Antimicrobial therapy is generally the treatment of choice for acute osteomyelitis and joint infections. Both reviews[1] and guidelines, such as those from the Infectious Diseases Society of America,[2] recommend, as a general principle, that antibiotics be given intravenously for 4–6 weeks.

The pharmacokinetic rationale behind this treatment schedule is that it overcomes the variability in the bioavailability of oral antibiotics, as well as ensuring a high systemic exposure, thus achieving sufficient drug concentrations in bone or joint spaces, compartments that are difficult to reach.[3] Although this rationale appears logical, clinical data for this approach are either inconclusive or reliant on old studies.[4,5]

In January, 2019, the results of Li and colleagues' OVIVA trial were published.[6] This was an open-label, randomised, controlled parallel group study to compare intravenous and oral antibiotic therapy in complex orthopaedic infections. 1054 adults with native osteomyelitis, native joint infection, prosthetic joint infection, or orthopaedic fixation device infection were enrolled at 26 centres in the UK and randomly assigned to receive intravenous or oral antibiotics for 6 weeks. The antibiotic choice was at the investigator's discretion. Treatment failure, defined by clinical, microbiological, or histological criteria occurred in 74 (15%) of 506 participants in the intravenous group and 67 (13%) of 509 participants in the oral group. On the basis of a difference in risk of definitive treatment failure (oral group *vs* intravenous group) of –1·4 percentage points (95% CI –5·6 to 2·9) the authors concluded that oral treatment was not inferior to intravenous therapy. Additionally, tolerability of oral therapy was greater, mainly due to the absence of local infusion related adverse events.

Because these conclusions might have a substantial effect on treatment guidelines and clinical practice, they should be scrutinised in the context of the study design. The authors designed a pragmatic open-label trial, which they justified with ethical concerns. However, the absence of blinding is the biggest source of potential bias in the trial, and double dummy designs comparing different administration routes have been shown to be feasible for infectious diseases.[7,8] Theoretically, blinding might not be mandatory in the case of strict protocol adherence and hard outcomes. However, during the first 7 days, about 80% of patients randomly assigned to receive oral treatment received intravenous antibiotics; at other times during the study this figure was 10%.

Moreover, the primary outcome, treatment failure, was strongly affected by investigators' subjective visual inspection of the infection site (clinical findings were relevant in 83 [59%] of 141 outcomes). Masked central assessment after photographic documentation would have removed this potential bias,[9] whereas the committee review of investigators' judgment done in this study hardly increased objectiveness.

Failure was observed in a proportion of patients three-times larger than expected (15% [74 of 506] *vs* 5%) for intravenous treatment. All intravenous drugs, except carbapenems, performed poorly, which suggests under-dosing of glycopeptides and other intravenously used drugs, but information regarding dosing was not provided. Equally problematic is the fact that 487 (52%) of 945 patients in the oral group were provided with rifampicin versus 142 (15%) of 917 in the intravenous group; thus, a comparison of oral combination therapy and intravenous monotherapy seems to have been made. Although rifampicin might have increased efficacy in the oral group, this antibiotic is one of the most potent inducers of cytochrome P450 isoenzymes. Given that the majority of patients will be older and thus polypharmacy is more likely, there may have been a large number of potential drug interactions.[10] The potential need for change or dose adaptation of various concomitant medications including oral anticoagulants, immunosuppressive therapy, and digitoxin was not specifically addressed.

In conclusion, although assessment of differences in clinical effectiveness is clearly needed, the shortcomings in trial design mean that we do not learn substantially from this kind of pragmatic strategy. Better tools to combine the advantages of real-world evidence and objective determination of pharmacological effect are needed for trials in infectious diseases. Meanwhile, widespread use of oral therapy for bone and joint infection appears premature.

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I declare no competing interests.

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