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Correspondence

QJM

Outpatient parenteral antibiotic therapy for Lyme borreliosis: a 'real world' view

Sir,

White *et al.* describe their 'real world' experience with outpatient parenteral antibiotic therapy (OPAT) administered to patients with suspected Lyme borreliosis presumably caused by the spirochete *Borrelia burgdorferi*.[1] The authors focus on the risk of OPAT and the low overall response rate in their heterogeneous group of patients, thereby generating good news and bad news. The good news is that the treatment risk for their patients was similar to the risk considered to be acceptable in OPAT studies of other diseases,[2,3] and 86% of patients tolerated OPAT without serious adverse events. The bad news is that by blending their treatment results the authors failed to recognize a significant outcome in the subset of patients with proven Lyme borreliosis.

The study subjects were classified according to Lyme serology results, and those with positive serology were further classified according to whether treatment guidelines recommended intravenous antibiotic therapy or not (Figure 1 in the article). Of the 47 patients for whom antibiotic therapy was considered appropriate, 34 received short-course treatment with intravenous antibiotics for 3 weeks or less, whereas 13 received prolonged therapy with intravenous antibiotics or combined intravenous and oral antibiotics for more than 3 weeks. The median follow-up was 4 weeks after intravenous antibiotic therapy was discontinued.

Using an intent-to-treat analysis, 26/34 patients (76%) in the short-course treatment group failed to achieve acceptable improvement in symptoms or signs. In contrast, 8/13 patients (62%) in the prolonged treatment group achieved 'definite improvement' in symptoms or signs. Despite the small sample size, the proportion of subjects with definite improvement was significantly higher in patients treated with prolonged therapy compared to patients treated with short-course therapy with an odds ratio of 4.99 (Fisher Exact Test 95% CI: 1.09–25.8, $P = 0.02$). The findings are robust even if the two patients without treatment outcome data are removed from the analysis ($P < 0.05$). Thus, the study demonstrated a significant benefit of prolonged vs. short-course antibiotic therapy in carefully chosen patients with 'debilitating symptoms' of Lyme borreliosis.

Although the authors claim that no previous studies have examined the risks and benefits of OPAT in patients with Lyme borreliosis, this statement is incorrect. A number of studies have reported the risks of short-course intravenous antibiotic therapy in these patients (reviewed in Stricker *et al.*[3]), and a recent study found that the risk of prolonged OPAT was low when strict practice guidelines were adhered to.[3] In terms of benefit, a more recent study demonstrated significant improvement in cognitive function with 6–12 months of intravenous ceftriaxone therapy in patients with chronic neuroborreliosis.[4] The report by White *et al.* supports this clinical observation. Although the authors state that there is 'excellent evidence' against the use of prolonged antibiotic therapy in patients with chronic symptoms of Lyme disease, this evidence has recently been challenged,[5,6] and persistent infection with the Lyme spirochete has been documented in animal models of Lyme borreliosis and in humans with persistent symptoms of tickborne disease.[7,8] Taken together, this evidence supports the need for further studies of prolonged antibiotic therapy in 'real world' patients with Lyme borreliosis.

Conflict of interest statement. R.B.S. serves without compensation on the medical advisory panel of QMedRx Inc. He has no financial ties to the company. A.K.D. and L.J. have no conflicts to declare.

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Letter of response to Stricker *et al.*

Sir,

We appreciate Dr Stricker *et al.*'s interest in our article describing the use of outpatient parenteral antibiotic therapy in the treatment of Lyme disease.[1] They highlight the finding that, of the 47 patients for whom intravenous antibiotic therapy was recommended, the 13 that received prolonged antibiotics appeared to do better than those who received the currently recommended duration of therapy (14–28 days) and then provide a statistical analysis to demonstrate that this difference was statistically significant. Of these 13 patients, 7 received 2–4 weeks of parenteral ceftriaxone followed by a median of 3 weeks of oral doxycycline (range 1–6 weeks), 5 obtaining a definite improvement in symptoms; 3 received prolonged parenteral therapy (each receiving a 6-week course of ceftriaxone), 2 with a definite improvement in symptoms. Three actually had to stop intravenous antibiotics early due to side effects from the treatment and so went on to receive a subsequent course of prolonged (2–5 weeks) oral antibiotics. Our study was not designed or powered to determine the outcome of different lengths of antibiotic treatment in groups of patients with different disease presentations. Subgroup analysis carried out in this fashion is fraught with errors in interpretation. We feel strongly that it is not possible to infer a result of statistical significance from a small heterogenous subgroup of patients from an observational cohort study.

Dr Stricker *et al.*[2] also follow this analysis by stating that our findings support that of a recently published study from his group which they state demonstrated a significant improvement in cognitive function with 6–12 months of intravenous ceftriaxone in patients with chronic neuroborreliosis. First, in keeping with our comment above we do not feel our article provides evidence to either support or discourage prolonged antibiotics in this group of patients. Second, we would urge caution in accepting Stricker *et al.*'s study findings as evidence to support prolonged antibiotic therapy; there was no control group used, patients were not randomized in their treatment duration and their measure of treatment success was based on a change in patient-assessed symptom severity, focussing on four subjective symptoms (myalgia, arthralgia, fatigue and 'cognition' or 'brain fog'). In addition, the authors have not considered or described adverse treatment events associated with prolonged antimicrobial therapy and indeed the reasons for some of the cohort receiving different treatment durations.

In our opinion, therefore, neither our observational study nor that of Dr Stricker *et al.*[2] provides robust evidence to support more prolonged therapy in this group of patients. If there are concerns that the four randomized controlled trials[3–5] whose conclusions discourage the use of prolonged antibiotic therapy are not robust, then the onus is on these clinicians to develop a larger, well-designed randomized controlled trial with robust outcome measures to provide clarity on this issue.

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