Introduction

Myalgias and arthralgias were the most frequent systemic adverse events related to quinupristin/dalfopristin treatment of vancomycin-resistant Enterococcus (VRE) infections in large, multicentre, prospective, non-comparative trials.\(^1,2\) Recently, three studies reported myalgias/arthralgias occurring at a rate of 33% and 50% in patients receiving quinupristin/dalfopristin.\(^3\,4,5\) These adverse events—associated with quinupristin/dalfopristin—have been shown to occur more frequently in patients with chronic liver disease or who have received a liver transplant.\(^5\)

The objective of this current study was to determine, through post-hoc analysis of a previously published study from our institution,\(^6\) whether myalgias/arthralgias occurring in cancer patients who received quinupristin/dalfopristin were associated with biliary tract dysfunction, as measured by alkaline phosphatase levels.

Materials and methods

Between February 1994 and November 1998, 56 cancer patients with proven VRE infections were entered in an open-label quinupristin/dalfopristin study published previously,\(^6\) whereby they were treated with a combination of quinupristin/dalfopristin 7.5 mg/kg every 8 h and minocycline 100 mg every 12 h. Written informed consent, approved by the Institutional Review Board of our institution, was signed by all subjects who participated in the study. Patients were followed prospectively during the treatment and up to 4 weeks after the cessation of quinupristin/dalfopristin therapy. Clinical information collected on all patients included gender, age, underlying cancer and its stage, prior transplant within a 1 year period, APACHE II score, whether the patient was intubated, site of the infection (bloodstream, urine, lung, wound, etc.), VRE stool colonization, gastrointestinal complications within 30 days prior to the infection and infectious complications associated with the...
infection (such as abscesses, pneumonias, hypotension or septic shock). In addition, the presence of a central venous catheter (CVC), neutropenia and the duration of neutropenia were determined for all patients. Myalgias/arthralgias were defined as any muscle aches or joint pain that occurred during the treatment with quinupristin/dalfopristin and could not be attributed to any other medication other than quinupristin/dalfopristin, with complete resolution of these symptoms upon discontinuation of quinupristin/dalfopristin therapy.

Medications that were given within 1 month prior to the initiation of quinupristin/dalfopristin with minocycline, or during the antimicrobial therapy with this combination, were determined for all patients that were included. This comprised total parenteral nutrition and other interventions, such as total body irradiation.

Liver function tests, including tests of bilirubin, alkaline phosphatase, alanine aminotransferase and albumin, were performed on all patients in the week before therapy, mid-term during therapy and within 1 week after completion of therapy.

Categorical variables were compared through the \( \chi^2 \) test or the Fisher exact test, and continuous variables were compared using the Student’s \( t \)-test or the Mann–Whitney test, as appropriate. All comparisons were based on two-tailed tests of significance at \( P \leq 0.05 \). Analyses were performed using a statistical computing package (SPSS version 11.0 for Windows; SPSS Inc., Chicago, IL, USA).

**Results**

As was previously reported in a study published earlier, most (68%) of the 56 patients included in the study responded to quinupristin/dalfopristin plus minocycline. Myalgias/arthralgias were the leading adverse events, occurring in 20 (36%) of the patients. Other adverse events included liver function abnormalities (7%) and leucopenia (5%).

As shown in Table 1, a post-hoc analysis was performed comparing patients who developed myalgias/arthralgias with those patients who did not develop these symptoms. The two groups were comparable in terms of gender, age, underlying disease, previous transplant within 1 year, APACHE II score, intubation status (Table 1) as well as site of infection and the presence of infectious complications (such as abscesses, hypotension, pneumonias and septic shock)—Table 1).

In another study, by Carver et al., reported myalgia/arthralgia as the only adverse events related to quinupristin/dalfopristin and minocycline combination or during treatment—for antibiotics, steroids, total parenteral nutrition, antacids, cyclosporin and other chemotherapeutic agents.

However, as shown in Table 2, patients who developed myalgias/arthralgias were different from those patients who did not develop these symptoms in that they had higher alkaline phosphatase levels mid-therapy (\( P = 0.05 \)), although not at pre-treatment or post-treatment. In addition, those patients who had more than five times normal alkaline phosphatase levels were more likely to develop myalgias/arthralgias (\( P = 0.04 \)). However, levels of bilirubin, transaminases, total protein and albumin were comparable between the two groups at pre-treatment, mid-treatment and post-treatment intervals. In addition, those patients who developed myalgias/arthralgias were more likely to have a relapsing haematological malignancy (\( P = 0.01 \)), to have received tacrolimus during the month prior to treatment (\( P = 0.04 \)) and to have received methotrexate during antimicrobial therapy with quinupristin/dalfopristin (\( P = 0.05 \)). Myalgias/arthralgias led to the termination of quinupristin/dalfopristin in two patients after 5 and 9 days of therapy, respectively.

**Discussion**

Our data show that myalgias/arthralgias related to quinupristin/ dalfopristin treatment occur frequently in at least one-third of the cancer patients treated with this agent. This is consistent with the previously reported studies. Winstin et al., reported myalgia/arthralgia as the only adverse events related to quinupristin/dalfopristin in 33% of hospitalized patients (63% of whom were liver transplant recipients) who were treated with the drug. Olsen et al. reported on 32 hospitalized patients who received quinupristin/dalfopristin treatment at a dose of 7.5 mg/kg every 8 h. Myalgias/arthralgias occurred in at least 47% of the treated patients. In another study, by Carver et al.,
which included patients with chronic liver disease, liver transplantation, bone marrow transplantation and haematological malignancy, quinupristin/dalfopristin treatment was associated with myalgias/arthritis in 50% of the treated patients.

A subject of controversy has been whether myalgias/arthritis—as the leading adverse event associated with quinupristin/dalfopristin treatment—are associated with hepatic dysfunction. Olsen et al. showed no significant relationship between increases in hepatic transaminases or total bilirubin levels and myalgias/arthritis associated with quinupristin/dalfopristin treatment. Nevertheless, more recently, Carver et al. through multivariate analysis, demonstrated that myalgias/arthritis secondary to quinupristin/dalfopristin treatment were associated with chronic liver disease, prior liver transplantation, elevated bilirubin level at baseline and the use of hepatotoxic drugs such as ciclosporin. In a multivariate analysis of a large patient population consisting of 1099 patients who were treated with quinupristin/dalfopristin, hepatic disease (particularly gallbladder disease) was found to be an independent risk factor associated with myalgias/arthritis.

Data from this current study reconcile the findings from the previous literature and point to the fact that myalgias/arthritis could be related to biliary dysfunction rather than any hepatic disease. According to our data, there was no correlation between increased bilirubin or transaminase levels and myalgias/arthritis. However, there was a significant association between increased alkaline phosphatase levels at mid-therapy and the occurrence of myalgias/arthritis. Alkaline phosphatase is a crude measure of biliary dysfunction. Quinupristin/dalfopristin is predominantly (>80%) excreted through the biliary tract. Biliary tract dysfunction, as measured by increased alkaline phosphatase levels, could have led to decreased excretion of this drug, predisposing to a higher frequency of myalgias/arthritis, which started mostly on the third day of therapy. Hence, on the one hand, we have demonstrated, like Olsen et al., that there is no relationship between increased transaminases or total bilirubin levels and myalgias/arthritis. On the other hand, our data are consistent with the findings of Talbot & Zhu, whereby patients with hepatobiliary disease (particularly those patients with gallbladder disease, implying a biliary dysfunction) were more prone to develop myalgias/arthritis.

Other variables, such as methotrexate and tacrolimus treatment or relapse of leukaemia, were also significantly associated with the occurrence of myalgias/arthritis. All of these factors are known to be associated with hepatobiliary dysfunction. Methotrexate and tacrolimus are known to cause hepatotoxicity and cholestatic jaundice. Therefore, cancer patients who received methotrexate and tacrolimus could have developed biliary dysfunction and intra-hepatic cholestasis, and hence, they may have become predisposed to develop myalgias/arthritis upon receiving quinupristin/dalfopristin. Similarly, patients with a relapse of leukaemia or lymphoma are at higher risk of developing hepatic infiltration with a tumour leading to intra-hepatic cholestasis, which could have predisposed them to myalgias/arthritis.

All of the patients in this current study who survived the infection had the myalgias and arthralgias resolved upon the discontinuation of quinupristin/dalfopristin. Winston et al. showed that myalgias/arthritis were dose-related and occurred only in patients who received 7.5 mg/kg every 8 h, but not in most patients who received 5 mg/kg every 8 h. However, there are several limitations in this current study that keep us from suggesting dose adjustment or definitively concluding that biliary dysfunction predisposes to myalgias/arthritis. The first is the small number of patients. Secondly, this was not a prospective, randomized study that involved dose adjustment. Thirdly, the difference in alkaline phosphatase levels between patients who developed myalgias/arthritis and those who did not, occurred at the point of mid-term therapy with quinupristin/dalfopristin. This could be because this antibiotic may have induced changes in alkaline phosphatase in some high-risk patients, which could have contributed to myalgias/arthritis. Finally, as a test, alkaline phosphatase is not specific for biliary dysfunction and could originate from bone.

Myalgias/arthritis remain a major limitation to the use of quinupristin/dalfopristin; however, this drug has been shown to be effective in the treatment of resistant Gram-positive infections. Data from our study show that myalgias/arthritis in patients receiving quinupristin/dalfopristin are associated with increased alkaline phosphatase (which could be suggestive of biliary dysfunction) or other factors (such as tacrolimus, methotrexate or leukaemia/lymphoma relapse) that would predispose to intra-hepatic cholestasis.

In patients with biliary dysfunction receiving quinupristin/dalfopristin, the impact of dose adjustment on the prevention of
myalgias/arthralgias should be studied in a prospective, randomized manner.

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References