IS A PRO-ACTIVE TDM-BASED APPROACH FOR PERSONALIZING LINEZOLID THERAPY USEFUL IN REDUCING THE RISK OF THROMBOCYTOPENIA IN ADULT PATIENTS REQUIRING LONG-LASTING TREATMENT?

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Introduction: Therapeutic drug monitoring (TDM) has proved to be a helpful tool for dose personalization of most antimicrobials, including linezolid. Linezolid at the standard dose of 600 mg every 12h is licensed for ≤ 28days of treatment, in order to minimize the risk of drug-induced toxicity that may occur in 18-56.7% of cases. However, it is increasingly used especially in the long-term treatment of chronic infections. The aim of this study was to evaluate if a pro-active TDM approach of dose adjustment of linezolid may be beneficial in reducing the risk of thrombocytopenia in adult patients receiving treatment > 28days.

Methods: This is a single-center prospective interventional study conducted at the Azienda Sanitaria Universitaria Integrata of Udine, Italy, between June 2015and December 2017. Patients > 18years of age and who were expected to receive linezolid for > 10 days were included. Each patient underwent TDM of linezolid trough concentration (C_{min}) and platelet count assessment once-weekly from baseline until the end of treatment. Desired range (DR) of linezolid was defined as C_{min} 2-8mg/L. Thrombocytopenia was defined as platelet count < 112.5x 10^3cells/μL at any time during therapy. Three predicted scenario of drug exposure were identified: linezolid exposure always in DR (group A), overexposure but subsequent attainment of DR (group B), overexposure but non-attainment of DR (group C). The study was approved by the Ethics Committee of the FVG Region and informed written consent was collected from all the patients.

Results: Sixty-one patients (47males) of median (IQR) age and weight of 62(43-73) years and 75(66-85) kg, respectively, were enrolled. The main reason for linezolid therapy were bone and joint infections [osteomyelitis (19.7%, 12/61), prosthetic joint infections (18.1%, 11/61) and spondylodiscitis (13.1%, 8/61)]. Microbiological isolates were identified in 59% (36/61) of patients. Twenty-nine out of sixty-one patients were included in group B, 4/61patients in group C and 28/61patients in group A. No difference in any demographic and clinical characteristic among groups was observed. Linezolid dose was reduced in all the patients of group B (1and ≥2dose reductions in 22/29[75.9%] and 7/29[24.1%] patients, respectively), in 2/4(50%) of the patients in group C, and in 7/28(25%) of the patients in group A. Overall, thrombocytopenia occurred in 14.75% (9/61) of patients, with an incidence rate of 10.34% (3/29), 75% (3/4) and 10.71% (3/28) for groups B, C and A, respectively (p=0.61) After post-hoc Bonferroni analysis, a significant difference was observed between group B and C (p=0.014) and between group A and C (p=0.015). Multivariate logistic regression analysis of the clinical variables potentially associated with the occurrence of thrombocytopenia (age, gender, weight, creatinine clearance, mean linezolid daily dose, length of therapy and DR attainment) showed that DR attainment reduced significantly the risk (OR: 0.035, 95%CI: 0.003-0.421). No significant differences in median platelet count during therapy (225vs. 232× 10^3cells/μL, p=0.48) and in the occurrence of thrombocytopenia (22.7% vs. 10.26%, p=0.26) were observed when comparing patients with duration of therapy < 28days (n=22) vs. ≥ 28days (n=39)

Conclusion: A proactive TDM-based approach to dose adjustment of linezolid may be helpful in significantly lowering the risk of thrombocytopenia even when treatments > 28days are needed.