



Case Report

First Case of Prolonged Pure Red Cell Aplasia Associated with the Administration of Dalbavancin

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Abstract

Introduction: Dalbavancin (DBV) is a semi-synthetic lipoglycopeptidic antibiotic drug, effective for the treatment of gram-positive bacteria Acute Bacterial Skin and Skin-Structure Infections (ABSSSIs), showing excellent effectiveness.

Case presentation: In this report, we describe the first case reported of severe and prolonged red blood cells aplasia following the administration of DBV in a 70-year-old Caucasian man with surgical wound bacterial infection. The patient required a prolonged hospitalisation, 27 transfusions, immune-modulating treatment and a multidisciplinary approach after a single-dose DBV infusion.

Discussion: Dalbavancin has showed an excellent profile of tolerability, with minor adverse events registered. To date, no case of prolonged aplastic anaemia has been previously reported. No deficient, haemorrhagic, malignant, myelodysplastic, genetic or haemolytic origin of the anaemia has been retained and it was lastly ascribed as secondary to DBV administration, with a possible and not defined immunological cause.

Conclusion: We suggest that an immune-allergic process is involved due to the time-correlation and the efficacy of the immunomodulatory treatment. More data from the surveillance are needed to better explain the responsible immunological reaction.

Keywords: Dalbavancin; Long-Acting; Serious Adverse Events; Pharmacology; Anaemia; Pure Red Cell Aplasia; TDM

Introduction

Dalbavancin (DBV) is a semi-synthetic lipoglycopeptidic antibiotic drug, effective for the treatment of infections caused

by gram positive bacteria [1]. DBV is highly lipophilic antibiotic with a half-life (t_{1/2}) of about 9 days [2]. In humans 93% of the DBV binds to plasma proteins (mainly albumin) guaranteeing a long lasting release and action. This long t_{1/2} allows the use in one single dose or dual once weekly doses for the treatment of Acute Bacterial Skin and Skin-Structure Infections (ABSSSIs) [3],

showing excellent effectiveness. Additionally, there is growing data showing its effectiveness in several off-label indications also due to its convenient Pharmacokinetic/Pharmacodynamic (PK/PD) profile. DBV is associated with an excellent tolerability profile being nausea, diarrhoea and headache the commonest ones [4]. Yet further studies are needed considering limited post-marketing experience with this antibiotic [5].

Case Presentation

We report the case of a 70-year-old Caucasian man that presented a surgical wound bacterial infection following prosthesis for a trimalleolar fracture. Past medical history included sigmoid diverticulosis with polyposis, arterial hypertension, hyperuricemia, sleep apnoea syndrome treated with nocturnal CPAP-therapy and COVID-19 disease with pneumonia during the first wave of SARS-CoV-2 pandemic. A not-well defined allergy to metals and mesalazine is reported. The patient had a severe trauma ten months before presenting to our Clinic, which required surgical stabilization of the tibia with screw and plates. After surgery, he never reached complete healing of the surgical wound with persistent diastasis of the flaps, serous drainage, rash and oedema extended to the entire distal third of the leg (Figure 1a). Surgical removal of the prosthesis was performed; methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated on intraoperative samples. The 3-week course of levofloxacin, empirically started after the surgery, was clinically ineffective with no improvement on the site of infection. The distal third of the leg remained swollen with tubular erythema, diastasis of the surgical flaps and a dense drainage. He was treated as an outpatient with teicoplanin (800 mg once daily, approximately 8.5 mg/Kg) for 2 weeks (during which a mild allergic reaction with rash and hives was reported) and subsequently with a single-dose of DBV (1500 mg). The infusion was well tolerated with no immediate side effect. The patient was followed with weekly clinical evaluations and blood tests, including therapeutic drug monitoring (TDM) for plasma DBV concentrations. A progressive improvement in the surgical site infection was observed. A validated liquid chromatography-tandem mass spectrometry method (UHPLC-MS/MS) analytical kit (Kit-System Antibiotics) was used to measure total dalbavancin in plasma samples. Five weeks after DBV administration the patient started experiencing weakness and asthenia; blood tests showed severe anaemia with haemoglobin (Hb) dropping from 14.1 to 5.8 gr/dL. The patient was therefore transferred from the Infectious Diseases Outpatient Clinic to the Intern Medicine Ward. The faecal occult blood test result positive on three different occasions. He underwent an esophagogastroduodenoscopy and colonoscopy, which showed diverticulitis and rectal vascular congestion but overall no site of active bleeding. Further tests revealed no evidence of vitamin or iron deficiency. Reticulocytes were greatly reduced (15000/uL, normal range 25000-75000/uL). The anaemia was initially then

attributed to an unknown intestinal disease and he was discharged after the transfusion of five red blood cell concentrates (RBC-T) with the contextual rise of the haemoglobin up to 9.2 gr/dL. A week later, a subsequent reduction of the haemoglobin (Hb at 7 gr/dL) was observed, this time associated with low level of folate and B12 vitamin, reduced reticulocyte count, high erythropoietin and negative faecal occult blood tests. A first bone marrow biopsy was performed that showed pure erythroid aplasia with no sign of myelodysplasia (Figure 2) and negative Parvovirus B19 and HHV 6-8 DNA. Anaemia did not respond to folate and vitamin B12 supplementation and required six RBC-T. Lymphadenopathy or splenomegaly were excluded with a full set of radiological images. Antibiotic-induced haemolytic anaemia was excluded with serial blood test, which showed preserved hepatic function, with bilirubin and LDH in range and no haptoglobin consumption, although the detection of anti-DBV antibodies in the patient's plasma was not performed. Moreover, we observed aplasia of the red blood cell in the BOM and a reduction in the circulating reticulocytes. A possible allergic aetiology for the anaemia were hypothesised, as a reaction to some dalbavancin excipients, but none of the findings were conclusive. During hospitalisation the patient deteriorated with pneumonia and the concomitant finding of *Klebsiella pneumoniae*. Piperacillin/tazobactam (10 days) and daptomycin (8 days) were administered with clinical and laboratory improvement. A Positron Emission Tomography/Computed Tomography showed the persistence of the known ABSSSI in the ankle and a lung consolidation but no sign of lymphoproliferative disease or thymoma. The anaemia responded only to transfusions and not to the deficiencies corrections. Two further bone marrow biopsies were performed: in both, the morphological and immunohistochemical analysis showed the complete absence of erythroid series. No signs of lymphocytic dysplasia were observed. He received two RBC-T weekly for five weeks managing to keep a median haemoglobin level around 7.8 gr/dL. During follow up visits, increasing level of blood ferritin required a chelation therapy with deferasirox (360 mg/die) which was stopped after one week because of suspected allergic reaction presenting with itchy skin rash with urticaria. Empiric treatment for autoimmune/allergic disease was started with cycles of four-days steroid-therapy with dexamethasone (16 mg per day) with a consequent increase in Hb (11.2 gr/dL), reticulocytes count and ratio resulting in a reduction of the RBC-T transfusion needed over time. Improvement lasted two weeks after the discontinuation of dexamethasone with Hb falling again to 6.7 gr/dL: further six RBC-T were administered in the following weeks. Considering the previous response to steroid treatment, the possible diagnosis of Pure Red Cell Aplasia (PRCA) was made. The patient started immunosuppressant therapy with cyclosporin (100 mg twice a day) with stable levels of haemoglobin and no more transfusions needed. Cyclosporine therapy is currently ongoing and well

tolerated, except for the finding of hypertension treated with benefit with alpha-blocker. Plasma monitoring of the drug has been performed throughout the period of cyclosporine treatment, with good stability of plasma levels (Figure 3). The wound progressively healed by secondary intention with reduction of the erythema and no drainage nor oedema (Figure 1b). Dalbavancin concentration showed a peak after infusion (304 mg/L) with a fast decrease after five weeks (5 mg/L) followed by a slow terminal elimination (7.7 mg/L one month later and 0.55 mg/L 18 weeks after infusion) (Figure 3). Twenty-four weeks after infusion we found no DBV in plasma and in bone marrow blood (with the method lacking validation on the latter) confirming the complete elimination of the parental compound and the lack of compartmental accumulation.



Figure 1: Clinical evolution of the surgical wound.

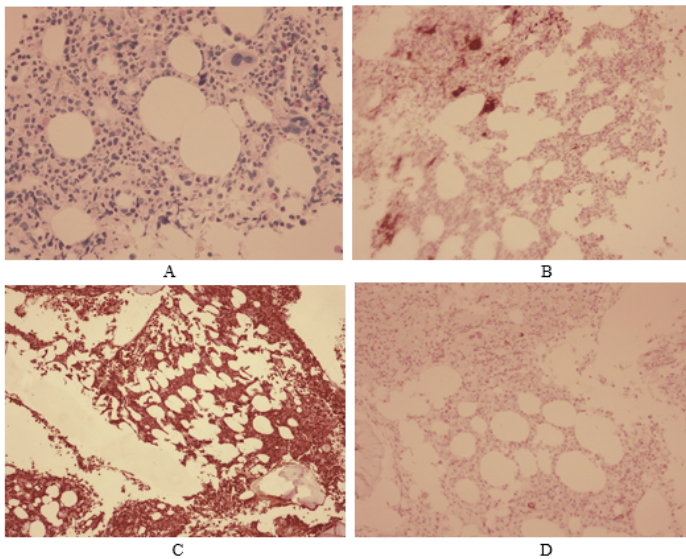


Figure 2: Bone marrow biopsy showing pure erythroid aplasia with no sign of myelodysplasia. 2a: Haematoxylin eosin staining-topographical distribution of medullary haematic series. 2b: CD61+ immunohistochemical staining- well represented cellularity of megakaryocytic series. 2c: MPO staining- Myeloid series were normally represented. 2d: CD71+ immunohistochemical staining-almost complete loss of erythroid series.

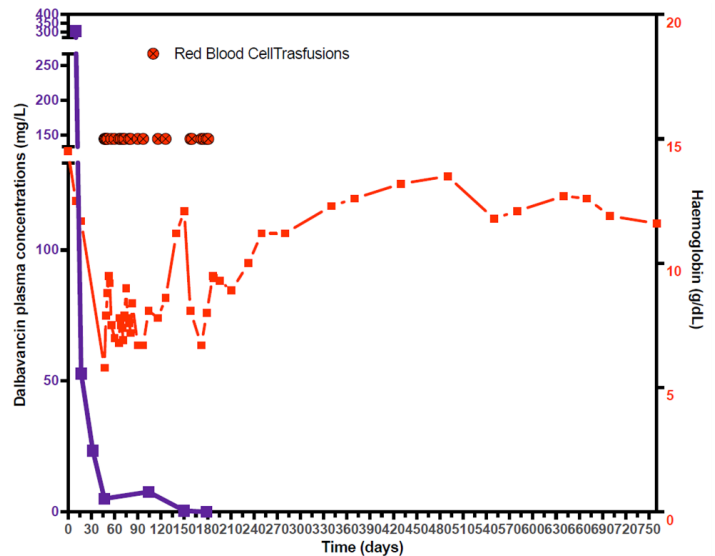


Figure 3: Haemoglobin levels (red) in relation to DBV concentration (blue) and red blood cell transfusions (X).

Discussion

In this report, we describe the first case reported of severe and prolonged anaemia following the administration of DBV. Dalbavancin has showed an excellent profile of tolerability up to date, with minor adverse events registered, which makes it a suitable antibiotic for outpatient therapy, both for ABSSSIs and, potentially, other under-study indications. Little is known about its PK/PD profile and the majority of data on that topic come from modelling. DBV MIC for *Staphylococcus aureus* is 0.250 mg/L, with 99.9% of organisms inhibited at a concentration of 0.12 mg/l [6]; during follow-up DBV concentration stayed far above this MIC for more than 20 weeks, suggesting a long therapeutic window. DBV levels lasted almost six months in serum, persistently overtaking pathogen's MIC by several fold and leading to complete wound healing. It remains unclear why DBV plasma levels were slightly higher (instead of following the slow decline usually observed) after four months. A possible explanation for the prolonged detectable levels of DBV could be attributed to the high plasma binding protein characteristics of DBV, but more data are needed from population pharmacokinetics to better assess the overall resulting picture. The case we presented has been strictly followed up due to the severity and unexpectedness of the anaemia developed following DBV administration. The patient required 27 transfusions, immune-modulating treatment and a multidisciplinary approach [7]. A safety report was also sent to AIFA (Agenzia Italiana del Farmaco) and EMA (European Medicines Agency). We monitored the drugs level in plasma in parallel with hematologic parameters and worked in accordance with Haematologists and Immunologists to assess the possible

origin of such persistent anaemia. To date, no case of such serious adverse event associated to DBV administration has been reported. No deficient, haemorrhagic, malignant, myelodysplastic or genetic origin of the anaemia has been discovered. Despite the lack of a clearly identified immunological aetiology, we suggested a connection between the anaemia and the DBV injection as a potential cause. Several antibiotics have been shown to be associated with severe cases of anaemia, usually on an immunological basis [8]. Antibiotic-induced haemolytic anaemia, although rare (with an estimated incidence of 1 per million per year) [9] has been widely reported in literature, usually associated with piperacillin and cephalosporins [10], but almost all the beta-lactams [11] and also vancomycin [12] has been related to this dangerous side effect. However, in our case, no sign of intravascular haemolysis was found in blood tests with preserved levels of LDH, indirect bilirubin and haptoglobin and no schistocyte on peripheral blood smear. Moreover, a complete aplasia of the red blood cell was observed at the bone marrow biopsy, associated with a concomitant reduction of the reticulocyte. History of unclear allergy to metals and several drugs was further explored with the drug manufacturer and with allergy specialists but no clear bulking agent or excipient has been advocated as causative. Of note, the patient received both teicoplanin and daptomycin, which highly resemble DBV in their composition, without any serious reaction. We were not able to prove a direct causality between the use of DBV and the onset of the anaemia but it was possible to observe a temporal correlation between the two events. In consideration of the timing of the beginning of the symptoms, the decreased requirement for transfusion as DBV concentration become undetectable in serum, the absence of sign of haemolysis and the response to immunosuppressant medication we came to the conclusion that the prolonged red blood cell aplasia could be explained as an allergic reaction associated to the DBV infusion.

Conclusions

We described, of our knowledge, the first case recorded of severe pure red blood cell aplasia associated to the infusion of dalbavancin. We suggest that an immune-allergic process is involved due to the time-correlation and the efficacy of the immunomodulatory treatment. We are aware that the data provided are not enough to better evaluate and assess the underlying mechanism that lead to the RBC aplasia: more data from the surveillance may reveal similar adverse events and possibly help explaining the responsible immunological reaction.

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Conflicts of interest: The authors declare that they have no conflict of interest to disclose.

Ethical approval: All procedures performed in studies involving

human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Patient signed a written informed consent for TDM measurement and anonymous use of personal data.

Informed consent: Informed consent was obtained from the participant included in the study.

Author's contributions: Gaviraghi A and Stroffolini G contributed equally to the paper. All authors contributed to the study conception and design. Material preparation, data collection and description were performed by Alberto Gaviraghi, Giacomo Stroffolini, Federico Itri and Giovanni Di Perri. The first draft of the manuscript was written by Alberto Gaviraghi and Giacomo Stroffolini all authors commented on previous

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