Eltrombopag fails to improve severe thrombocytopenia in late-stage dyskeratosis congenita and diamond-blackfan-anaemia

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Dear Sirs,

Thrombopoietin receptor agonists (TPO-RAs) have been successfully used for the treatment of acquired immune thrombocytopenia (ITP). More recently it was shown that TPO-RA are able to improve thrombocytopenia in in MYH9-related disorders (1–3) and in some cases of severe aplastic anemia (SAA) (4). There is little experience using TPO-RA for the treatment of thrombocytopenia related to congenital bone marrow failure syndromes.

The small molecule, orally bioavailable thrombopoietin receptor agonist eltrombopag is approved for the treatment of chronic ITP. By interacting selectively with the thrombopoietin receptor, eltrombopag is able to activate intracellular signal transduction pathways and ultimately leads to increased proliferation and differentiation of human bone marrow progenitor cells (5).

Here we describe our experience with eltrombopag in patients with diamond-blackfan-anaemia (DBA) or dyskeratosis congenita (DC). Both diseases belong to the group of inherited bone marrow failure syndromes and may present with thrombocytopenia (6, 7).

The first patient was a 31-year-old female who was diagnosed with DBA in early childhood with continuous red blood cell transfusion support since birth. Diagnosis of DBA was based solely on clinical criteria, with typical physical and laboratory features present. Apart from transfusion-dependent anaemia, progressive thrombocytopenia developed in 2006. Leukocyte count remained normal. A bone marrow biopsy in February 2011 revealed secondary bone marrow failure with cellular hypoplasia, a normal karyotype and no definite signs of myelodysplastic syndrome (MDS). Megakaryocytes were significantly reduced in the bone marrow, but only slightly dysplastic (9%). When platelets fell below 20 x 10⁹/l, the patient developed petechial bleeding and recurrent haematomas (grade 1 bleeding according to WHO classification). Evtrombopag was initiated at a daily dose of 25 mg. Dosing was later increased to 75 mg. No response was observed and treatment was discontinued after six months. All patients had provided informed consent to off-label use of eltrombopag. No adverse events due to eltrombopag were observed in any of the three patients.

In contrast to significant improvements of thrombocytopenia following eltrombopag treatment in MYH9-related disease (1–3), we failed to achieve the same results in DBA and DC. The hallmark of DBA is anaemia with thrombocytopenia sometimes developing in the course of disease (5). In DC, bone marrow failure typically begins with thrombocytopenia or anaemia, followed by pancytopenia (7). In both cases, haematopoietic failure is often associated with severe bone marrow hypoplasia (7), as seen in our patients. While it is known that DBA is caused by defects of ribosome synthesis and function, the exact mechanisms leading to secondary marrow hypoplasia and concomitant thrombocytopenia remain obscure.

Two other patients, a 21-year-old male and his 17-year-old sister both suffered from DC, as shown by a heterozygous C116T-mutation of the TERC gene (8). In both cases pancytopenia with leading thrombocytopenia developed around the age of 10. At the time of first presentation to our department in February 2011 both siblings required intermittent platelet transfusions. Bone marrow biopsies revealed severe bone marrow hypoplasia without evidence of MDS or myelofibrosis (Fig. 1). Conventional cytogenetic analysis did not reveal any aberrations. Both patients started eltrombopag at a daily dose of 50 mg with subsequent increase to 75 mg. When starting eltrombopag their blood counts showed pancytopenia with marked thrombocytopenia (platelet counts in both DC patients at the beginning of therapy: 7 x 10⁹/l). However, no platelet or erythroid response was observed and treatment was discontinued after six months. All patients had provided informed consent to off-label use of eltrombopag. No adverse events due to eltrombopag were observed in any of the three patients.

Figure 1: Bone marrow biopsies from the two siblings with DC (A = sibling 1, B = sibling 2). Bone marrow is profoundly hypocellular with a decrease in all haematopoietic elements including megakaryocytes; the marrow space is mostly composed of fat cells and lymphocytes.
topenia are poorly understood (6). In DC haematopoietic failure is considered as a result of replicative exhaustion of the bone marrow reserve due to accelerated telomere shortening (8).

In contrast to these bone marrow failure syndromes, thrombocytopenia in MYH9-related disease probably derives from complex defects of platelet release (1, 9–11). Here, bone marrow is normocellular and shows normal or elevated numbers of megakaryocytes (12).

In DC and DBA the remaining megakaryocytes could be dysfunctional and unable to respond to external growth stimulation, which might explain the inefficacy of eltrombopag in our patients. This hypothesis is supported by the fact that treatment with haematopoietic growth factors has been largely unsuccessful in DBA and revealed conflicting results in DC (7). Interestingly, we observed excessive endogenous levels of TPO in all patients before start of treatment (DBA patient: TPO 1,484 ng/l; DC patient #1: TPO 1,514 ng/l; DC patient #2: TPO 1,976 ng/l; reference range 0–228 ng/l).

Of note, preliminary data from a phase II study by Olnes et al. (4) indicates that eltrombopag is able to improve platelet counts in a substantial number of patients with acquired SAA, who are refractory to immunosuppressive therapy.

Although our findings need to be confirmed in a larger patient cohort, they suggest that the efficacy of TPO-RA depends on the underlying pathophysiology of the disorder causing thrombocytopenia.

Conflicts of interest
U. Platzbecker has received lecture fees from GlaxoSmithKline. None of the other authors declares any conflicts of interest.

References