

# Could Anti-Erythropoietin Receptor Antibodies Be the Future Management of Beta Thalassemia Intermedia?

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## To the Editor

Thalassemia syndromes are the most common hereditary genetic diseases of mankind. They result from an imbalance between the number of alpha-and beta-globin chains. When the amount of beta-globin chains are absent or reduced, the disease is called beta thalassemia. However, the pathology is entirely related to the relative excess of alpha-globin chains. These highly unstable chains precipitate within erythroid precursors in the bone marrow causing direct membrane damage and premature cell death by apoptosis. This central hemolysis is termed as 'ineffective erythropoiesis' and is the main determinant of anemia in beta thalassemia [1]. Peripheral hemolysis of mature red blood cells is caused by this mechanism but has a trivial contribution to anemia in these patients. Instead, it has been linked to pulmonary hypertension with secondary heart failure and thromboembolic phenomena [2]. Beta thalassemia has two main clinicopathologic forms: heterozygous and homozygous. In its homozygotic form, beta thalassemia overwhelms patients with a vicious cycle of ineffective erythropoiesis and iron overload. However, this form is clearly divided into two phenotypes on the basis of transfusion dependence; thalassemia major ( $\beta$ -TM) which represents the major domain and thalassemia intermedia ( $\beta$ -TI). The latter is one of three thalassemia syndromes that constitute the entity of non-transfusion-dependent thalassemias (NTDT).  $\beta$ -TI has a characteristic molecular structure owing to certain genetic modifiers that skew the imbalance between the number of alpha-and beta-globin chains, thus alleviating the degree of anemia. These genetic modifiers include co-inheritance of abnormal alpha- or gamma-chain genes or inheritance of a mild or silent beta-chain mutation [3].  $\beta$ -TI is clinically important in certain geographic areas and is legion in the Sultanate of Oman for two main reasons: exceptional occurrence of Hb Dhofar and prevalence of alpha thalassemia trait in the native population [4]. Hb Dhofar is a variant hemoglobin unique to the Sultanate of Oman that clinically behaves as  $\beta$ -TI phenotype [5]. As  $\beta$ -TI is NTDT, the compensatory mechanisms in response to

the chronic anemic state results in erythropoietin production become unchecked [6]. Erythropoietin drives the proliferation of erythroid precursors in the bone marrow and extramedullary sites. Erythroid marrow hypertrophy can reach up to 25 - 30 times the normal marrow cavity volume and leads to the characteristic skeletal deformities, osteoporosis and pathological fractures of long bones [7]. More interestingly is the extramedullary expansion. This results from the arrest at differentiation of erythroid precursors in response to sustained erythropoietin surge leading to sustained proliferation of the erythropoietic tissue that sweep past the bone marrow to invade and colonize all body sites but predominantly homing the spleen and liver. This is termed 'extramedullary hematopoiesis' (EMH) which can result in devastating complications as these masses can grow up in tumor-like forms. The most debilitating complication is the spinal cord compression secondary to paraspinal masses [8]. Intrathoracic masses have been also reported in patients with EMH [9]. Splenomegaly can exacerbate anemia and increases transfusion requirements in  $\beta$ -TI patients [10]. On the other hand, by virtue of their indigenous transfusion dependence, the ineffective erythropoiesis - erythropoietin drive axis is suppressed leading to the rare occurrence of excessive medullary or EMH in patients with  $\beta$ -TM [11]. This means that ineffective erythropoiesis is unique to  $\beta$ -TI. This was clearly demonstrated in OPTIMAL CARE study where EMH ranked the second most frequent complication encountered in  $\beta$ -TI patients. The study included 584  $\beta$ -TI patients, the largest cohort of patients published so far. Notably, osteoporosis ranked the most frequent complication. Interestingly, both osteoporosis and EMH are induced by ineffective erythropoiesis. However, the study value was limited to highlighting the complications of the disease rather than evaluating the potential benefits of current therapeutic options. The study concluded desperately that no clear guidelines exist for managing  $\beta$ -TI patients [12]. Traditionally, treatment options for EMH are splenectomy [3], radiotherapy [13], transfusion therapy [14], hydroxyurea [15] or even surgery [16]. In the era of modern molecular biology, emerging alternative therapies for  $\beta$  thalassemia are being sought. Two important upcoming agents are transferrin injections and JAK-2 inhibitors. Research into transferrin injections is still a murine model where long-term administration of transferrin injections to Hbbth1/th1 mice increased Hb production, decreased serum erythropoietin levels and reversed splenomegaly [17]. However, the most convincing theory is the role of Janus kinase-2 (JAK2) inhibitors in preventing the complications of EMH associated with  $\beta$  thalassemia. The principle is that persistent phosphorylation of JAK2 as a consequence

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of high erythropoietin levels induces erythroid hyperplasia and massive EMH [18]. By virtue of its role in erythropoietin-EMH pathway, JAK2 inhibitor ruxolitinib was utilized in and approved for treatment of myeloproliferative disorders (polycythemia vera/myelofibrosis) [19]. Preliminary studies in murine models of  $\beta$  thalassemia have shown that JAK2 inhibitors can affect ineffective erythropoiesis and decrease spleen size. However, there are many drawbacks from using this drug in beta thalassemia patients. JAK2-related neoplasms are induced by a mutated form of JAK2 that makes the erythroid precursors hypersensitive to erythropoietin rather than induced by high levels of erythropoietin itself. This means that EMH in  $\beta$  thalassemia is related to quantitative rather than qualitative error of the erythropoietin cascade. Another difference is that progression of EMH occurs more rapidly in myeloproliferative disorders than in beta thalassemia [20]. More importantly, ruxolitinib can cause serious side effects and is still not licensed for use in children [21].

In summary, whereas in  $\beta$ -TM iron overload is the prevailing clinical problem, ineffective erythropoiesis dominates the scene in  $\beta$ -TI. Ineffective erythropoiesis induces perpetual erythropoietin overproduction colliding with failed erythropoietic differentiation that eventually culminates in imperishable hematopoiesis in medullary and extramedullary sites. Resulting complications can be dreadful in parallel to shortcoming research in this area. Although that  $\beta$ -TI patients are privileged by their independence on regular blood transfusions, the complications secondary to erythropoietin storm counterbalance or even supersede the benefits of omitting transfusions. This leads to the conclusion that erythropoietin storm is the main pathologic feature of  $\beta$ -TI patients. Despite the occurrence of anti-erythropoietin antibodies in humans treated with recombinant erythropoietin molecules [22, 23], no one has ever thought that such antibodies can be utilized in treating the erythropoietin storm in  $\beta$ -TI patients. Theoretically, these antibodies can prevent or even reverse the unopposed excessive medullary and EMH by binding to and neutralizing erythropoietin and thus trimming its effect on the erythropoietic tissue. By targeting erythropoietin, this model can serve as a paradigmatic example for treatment of diseases originating from erythropoietin-dependent erythroid progenitor proliferation and circumvent the need for undesired aggressive treatment. Erythropoietin-dependent erythroid progenitor proliferation is either secondary to chronic anemic states like  $\beta$ -TI and hereditary spherocytosis [24] or myeloproliferative disorders. Nowadays recombinant antibody technology is extremely advanced demanding for an urgent research to take the theory of anti-erythropoietin receptor antibodies from the bench to the bedside.

### Competing Interests

None.

### Funding

None.

### Abbreviations

NTDT: non-transfusion-dependent thalassemias;  $\beta$ -TI: beta thalassemia intermedia; EMH: extramedullary hematopoiesis; JAK2: Janus kinase-2

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