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Eltrombopag in aplastic anaemia

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Abstract

The treatment of aplastic anemia is currently with immunosuppressive therapy (IST) with antithymocyte globulin and cyclosporine, to which two thirds of patients respond. However, a significant proportion of these responders relapse and many have persistent cytopenias. The management of these patients is challenging. Modifications to this standard approach using alternative immunosuppressive agents or adding hematopoietic cytokines such as G-CSF and erythropoietin have not improved outcome. A recent trial has shown that eltrombopag, a thrombopoeitin mimetic, is efficacious in the treatment of patients with severe aplastic anemia (SAA) refractory to IST. There is evidence that this drug works by directly stimulating marrow stem and progenitor cells thereby promoting hematopoietic recovery in patients with bone marrow failure. Several trials are ongoing in our institution using this very promising drug in combination therapy in the upfront treatment of SAA, in IST refractory SAA and in moderate disease.

INTRODUCTION

Aplastic anemia is a rare haematological disorder characterized by pancytopenia and a hypocellular marrow. Patients are usually symptomatic on presentation but some are detected incidentally when unexpected cytopenias are found on a routine blood count. The diagnosis of severe aplastic anemia is made in the setting of a hypocellular bone marrow when 2 of 3 blood counts are met: absolute neutrophil count < 500/μL, absolute reticulocyte count < 60 000/μL, and platelet count < 20 000/μL and myelodysplastic syndrome is outruled[1]. The principle mechanism leading to bone marrow failure in most cases is immune-mediated destruction of hematopoietic stem and progenitor cells[2]. There is evidence that effector T-cells such as activated cytotoxic T-cells are elevated in the bone marrow of patients with aplastic anemia.[3–5] The effects exerted by cytotoxic T-lymphocytes are mediated in part due to Fas ligand-induced apoptosis of hematopoietic progenitor cells.

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T cell receptor gene rearrangement studies have demonstrated clonal expansion of these cells in aplastic bone marrows.[6] Immune-mediated marrow destruction with many similarities to the pathophysiology of human aplastic anemia can be modeled in the mouse.[7] The result of this immune attack is profound hematopoietic stem cell (HSC) depletion.[8]

The clinical consequences are anemia, usually with a requirement for frequent red blood cell transfusions, life-threatening bleeding from thrombocytopenia, and infection as a result of neutropenia. Bacterial and fungal infections are most common and are a significant cause of morbidity and mortality.

Treatment should be instituted as soon as the diagnosis is established. Definitive and potentially curative therapy with allogeneic bone marrow transplantation is generally only available for younger patients with histocompatible donors[9]. Survival rates with allogeneic hematopoietic stem cell transplantation from a histocompatible sibling are excellent and have been reported to be as high as 90% from single institution studies, and approximately 70% in registry data.[10,11] Graft-versus-host disease, however, continues to be a major toxicity and affects long-term quality of life.[12] Initial treatment with immunosuppressive therapy (IST) in patients without transplant options ameliorates disease in about two thirds of cases. Horse ATG and cyclosporine is now considered the standard of care for newly diagnosed patients[13]. Response is associated with a favourable long term outlook. However, of these responders, 30–40% relapse[13,14]. Retreatment of relapse with IST, usually only reinstitution of cyclosporine but occasionally repeating lymphocyte depletion with rabbit antithymocyte globulin or alemtuzumab, can be successful; patients who relapse are maintained on cyclosporine for years, often with clear dependence of blood counts on drug dose. A significant minority of patients do not respond to initial immunosuppression, and cytopenias persist in these “refractory” cases, with long-term transfusion dependence. It is unknown whether cytopenias in individual refractory patients represent a failure of immunosuppression to completely ablate autoreactive immune cells (30–40% of patients who fail treatment with horse ATG respond to alternative IST), or a persistent stem cell deficiency in the absence of active immune cell attack. The management of persistently refractory patients in challenging. Eltrombopag has recently been shown to be efficacious in the setting of refractory severe aplastic anemia (SAA) with trilineage responses in some patients and many achieving transfusion independence[15,16].

THROMBOPOIETIN AND HEMATOPOIESIS

Thrombopoietin (TPO) is a glycoprotein class 1 hematopoietic cytokine, produced primarily in the liver[17]. It binds to the receptor c-mpl and is the primary regulator of megakaryopoiesis. After 3 decades of failed attempts to purify TPO, the discovery of the proto-oncogene Mpl aided cloning of TPO in 1994 and its many functional properties became evident thereafter through *in vitro* studies[18].

TPO’s role in hematopoiesis was elucidated initially in cell culture experiments. The c-mpl receptor was shown to be expressed and functional on primitive hematopoietic stem and progenitor cells[19] and these cells could proliferate in the presence of TPO when other cytokines were added[20,21]. The generation of transgenic mice lacking the TPO or c-mpl

gene allowed direct *in vivo* investigation of the function of TPO. In transplantation studies, "knockout" mice had decreased HSC expansion compared to wild type controls[22] and reduced numbers of hematopoietic progenitors[12]. In humans, loss of function mutations in *c-MPL* result in congenital amegakaryocytic thrombocytopenia, with affected children presenting initially with isolated thrombocytopenia and progressive pancytopenia due to a reduction in bone marrow HSCs[23]. Recently, a mutation in the gene encoding TPO (*THPO*) was demonstrated in a family with autosomal recessive aplastic anemia[24].

RATIONALE FOR THROMBOPOIETIN STIMULATION IN APLASTIC ANEMIA

The control of TPO levels and TPO production is complex and involves sensing of c-mpl receptor occupancy, with TPO levels inversely proportional to megakaryocyte mass rather than peripheral platelet counts. TPO levels are high in bone marrow failure syndromes such as myelodysplastic syndromes and SAA and low to normal in chronic ITP[25–27].

Hematopoietic cytokines such as erythropoietin and granulocyte stimulating growth factor (G-CSF) have historically had a very limited role in the treatment of patients with SAA[28,29]. A large, randomized study comparing standard IST with anti-thymocyte globulin and cyclosporine versus the same IST with the addition of G-CSF showed no difference in hematological response[30]. Erythropoietin (Epo) levels in SAA are also very high, and not surprisingly, the addition of Epo to IST, often in addition to G-CSF, has also not shown benefit in terms of increasing response in red cell or other lineages[31]. As noted above, TPO levels are increased in SAA patients. Why then should treatment with TPO receptor agonists be beneficial? Other hematopoietic growth factors act only on more committed myeloid or erythroid progenitors, which are largely lacking in SAA since the defect is at a much early hematopoietic stem cell stage [8]. TPO acts on HSCs as well as megakaryocytes, and thus despite the high endogenous levels of TPO in SAA, studying the clinical activity of TPO mimetics in refractory bone marrow failure syndromes was an attractive concept.

Eltrombopag is a synthetic, non-peptide TPO mimetic, which can be administered orally. It was originally developed for the treatment of chronic immune thrombocytopenic purpura[32]. Eltrombopag selectively binds to c-mpl at the transmembrane and juxtamembrane domains of the thrombopoietin receptor, at sites distinct from the binding site of TPO. Eltrombopag therefore does not compete for binding with the native molecule[17].

Unfortunately, in vivo animal studies investigating the impact and potential mechanism of action of eltrombopag are not possible, since eltrombopag binds only to the human or chimpanzee TPO receptors. The NOD/SCID mouse xenotransplant model was utilized in one report to show that eltrombopag could selectively in vivo expand engrafting human cord blood hematopoietic stem/progenitor cells [33].

TPO is primarily synthesized by the liver, but also by bone marrow stromal cells, and eltrombopag may influence the microenvironment directly in a paracrine fashion. As previous mentioned, high serum levels of TPO are seen in aplastic anemia. The concentration of TPO in the bone marrow niche may be more important for stimulating stem cells and eltrombopag, with small molecule kinetics, may be capable of entering the niche more effectively than TPO. Alternatively, eltrombopag and endogenous TPO may be

capable of inducing alternative signal transduction cascades given the potential for dual stimulation of the TPO receptor by both eltrombopag and endogenous TPO. TPO clearly has a pleiotropic role in regulating hematopoiesis beyond megakaryopoiesis and platelet production. Recent in vitro studies also implicate roles for TPO in DNA repair, and some of the effects of eltrombopag may be independent of TPO receptor stimulation[34,35].

ELTROMBOPAG IN REFRACTORY APLASTIC ANEMIA

Recently, we published the results of a non-randomized, phase 2 study from the National Institutes of Health using eltrombopag in SAA[16]. 43 patients with SAA refractory to at least one course of IST initiated at least 6 months previously and with platelet counts less than $30x10^3$/ul were enrolled. Subjects were treated using a dose escalation schedule starting at 50 mg and increasing every 2 weeks by 25 mg to a maximum of 150 mg. The primary endpoint was hematological response at 3–4 months. If patients responded, they were offered entry to the extension phase of the study, and they could remain on drug indefinitely or until a decision was made to discontinue. The patients enrolled were heavily pre-treated, having received a median of 2 prior courses of IST. Almost all were both red cell and platelet transfusion dependent, and 6 patients met criteria for very severe aplastic anemia defined as SAA and a neutrophil count of <200/ul. Seventeen of 43 patients (40%) had a hematological response to eltrombopag. Several multilineage responses were seen (Figure 1) at response assessment. The majority of patients who remained on eltrombopag showed continued improvement of blood counts, and several of the unilineage responders improved other lineages. Seven patients eventually showed trilineage responses. Only baseline reticulocyte count was a pretreatment predictor for response, perhaps reflecting residual HSC numbers, as has previously been demonstrated in IST[36]. Eltrombopag was well tolerated with no dose limiting toxicities, apart from infrequent reversible transaminitis, similar to the larger safety and efficacy studies in ITP[37]. All patients had bone marrow biopsies at baseline and while on drug and none showed an increase in reticulin staining, which was a concern in a recent study of ITP[38]. An increase in bone marrow cellularity was seen in several responders (figure 2).

CAN ELTROMBOPAG BE DISCONTINUED IN REFRACTORY SAA WITHOUT RISK OF RELAPSE?

One patient in the National Institutes of Health study had eltrombopag withdrawn at 10 weeks because of a cataract misdiagnosis. Despite stopping study drug, he went on to have a trilineage response and remains transfusion independent. The protocol was subsequently amended to allow discontinuation of drug when blood counts in all three lineages reached acceptable levels and transfusions were no longer necessary. Six patients had drug withdrawn and all continue to maintain stable counts with normocellular bone marrow biopsies at a median of 24 months off drug (Figure 2). It is possible to conclude that when a critical mass of HSCs is generated, functional hematopoiesis can sustain blood counts in the near normal range without need for continued or continual exposure to eltrombopag. Whether the primitive progenitor cells stimulated by this agent have more favorable repopulating capabilities is unknown, but is an area currently under investigation. While the

follow up time is relatively short, we believe there is evidence that transient exposure to eltrombopag may be sufficient, at least in a subset of patients, for hematopoietic recovery.

CLONAL EVOLUTION

Clonal evolution was a concern in this study. Eight of 43 patients developed new cytogenetic abnormalities. Most were non-responders at response assessment but 2 had previously responded. All patients who clonally progressed had eltrombopag withdrawn. Since publication one patient who was a non-responder and developed trisomy 21 at 3 months went on to develop monosomy 7 at 6 months with disappearance of the previous cytogenetic abnormality. However, on follow up marrow examination, there was normal karyotype; at least in this case, abnormal clones appeared transiently and disappeared with discontinuation of drug. In this particular patient, the platelet count further increased after study drug had been discontinued. Only two of the eight patients with newly detected cytogenetic abnormalities had dysplastic changes on the marrow examined at the time the abnormal cytogenetic clone was detected. No patient has developed AML, although 5 patients went on to have allogeneic stem cell transplant. The commonest chromosomal changes were chromosome 7 abnormalities, which developed in 5 of the 8 evolvers. This clonal transformation is associated with a poor outcome[1], but all patients who developed chromosome 7 changes in the current series were successfully transplanted. Two eltrombopag responders evolved at 9 and 13 months with 13q deletion, which is considered a good prognostic cytogenetic change in patients with MDS transformed from SAA[39,40]. One of these patients has maintained his response off drug.

Dormant clones, undetectable to conventional cytogenetic analysis at baseline, may have been stimulated by eltrombopag. We performed CGH-SNP arrays on pretreatment marrow samples to investigate whether clones were detectable by alternative methods sensitive to rearrangement and loss of smaller amounts of chromatin, with negative results. Another hypothesis is that growth factor stimulation caused destabilization of the genome by driving proliferation of HSCs, leading to accelerated telomere attrition and subsequent emergence of clonal hematopoiesis. Patients with SAA have a baseline risk of developing clonal marrow dysfunction: 15% will show clonal progression by 10 years from diagnosis[41]. Concern for higher rates of transformation to AML in the treatment arm of a phase 3 study using the other available TPO receptor agonist Romiplostim in MDS caused this trial to be terminated early. However, subsequent follow up of these data (published in abstract form) found no difference in rates of progression between placebo and treatment arms[42]. Refractoriness to therapy is a particular risk factor for progression but true rates for evolution in this group are unknown[43]. While direct comparison with historical series is difficult, the association of clonal evolution with eltrombopag is possible and the drug should currently be used in aplastic anemia in the setting of a clinical research trial or with very close monitoring for transformation in refractory disease.

FUTURE DIRECTIONS

Clinical trials are ongoing in the NIH in other settings of bone marrow failure. We are conducting a pilot, non-randomized phase II trial at our institution using eltrombopag in

addition to horse ATG and cyclosporine for treatment naïve SAA. The aim is to augment the quality of the hematologic response to immunosuppression by stimulating stem cells during recovery. This may prevent both short-term complications, namely infections and bleeding, but could also prevent clonal evolution. Robust hematologic responses with IST are associated with better long-term survival and a decreased risk of clonal evolution[1]. A larger, more heterogeneous stem cell reserve may ensure less proliferative stress on an individual clone, thereby limiting oncogenesis. To date, the overall response rate appears higher and time to transfusion independence is shortened. However, these are early results and it is unclear whether the risk of clonal evolution will be decreased with the use of eltrombopag in the upfront setting, but the risk of relapse (likely mediated by residual pathophysiologic T cells) is unlikely to be altered. Larger randomized trials comparing the use of IST with and without eltrombopag are ultimately required to determine eltrombopag's influence on clonal evolution. Ongoing and future trials aim to abbreviate exposure and institute urgent treatment at diagnosis. These trials will be critical for informing safe prescribing practices given the existing temptation for physicians to use the drug off-label. The well-tolerated combination of eltrombopag and cyclosporine is also evident from these trials and may prove efficacious as therapy for SAA in developing countries where ATG is unavailable or simply not feasible.

Based on the initial results achieved in refractory SAA[15] we initiated a new trial in refractory aplastic anemia, using a fixed dose of 150mg of eltrombopag and assessing patients after six months of therapy. The treatment period was extended because of indications that some subjects in the initial study had signs of response at the 3–4 month response assessment but were unable to continue therapy because they could not be deemed responders by protocol definition. We are, also, treating patients with moderate aplastic anemia (MAA) and unilineage cytopenic syndromes with higher doses of eltrombopag with a maximum of 300 mg allowed in this study. The treatment period in this single arm trial is 16 weeks. Most patients have not previously been treated with IST suggesting that this group may not have a strong immunological cause for their disease. Lower rates of response to IST have been suggested in patients with moderate compared to SAA[44]. We have observed robust hematological responses in this cohort and have seen no instances of clonal evolution despite higher doses being utilized. A simple and safe oral treatment for these patients with currently no licensed drugs available makes this a very exciting therapeutic approach.

Eltrombopag represents an important new strategy to treat aplastic anemia. To date, suppression of the aberrant immune cells was the only available approach. The addition of alternative immunosuppressive agents to ATG and cyclosporine did not improve response rates in large randomized trials[9]. Based on the results of our study there is strong evidence that eltrombopag stimulates HSCs and can reconstitute hematopoiesis in patients with aplastic marrows. Ongoing research into the use of this agent in other acquired bone marrow failure syndromes such as MDS are underway in our institute and others and is described elsewhere in this journal. Recent reports of the successful use of eltrombopag in inherited thrombocytopenia derived from MYH9 mutations have been published[45]. One patient on our MAA study with a congenital red cell aplasia responded to eltrombopag, suggesting that there may be some utility in the treatment of other inherited disorders of hematopoiesis. A

phase 3 randomized study in upfront SAA is planned which will elucidate the risk of clonal evolution in patients who are IST naïve.

IST refractory SAA is a very challenging disease to treat. GlaxoSmithKline, the manufacturers of eltrombopag have recently made a submission to the Federal Food and Drug Agency for a licensed indication in refractory SAA and received breakthrough therapy designation allowing for an expedited review process.

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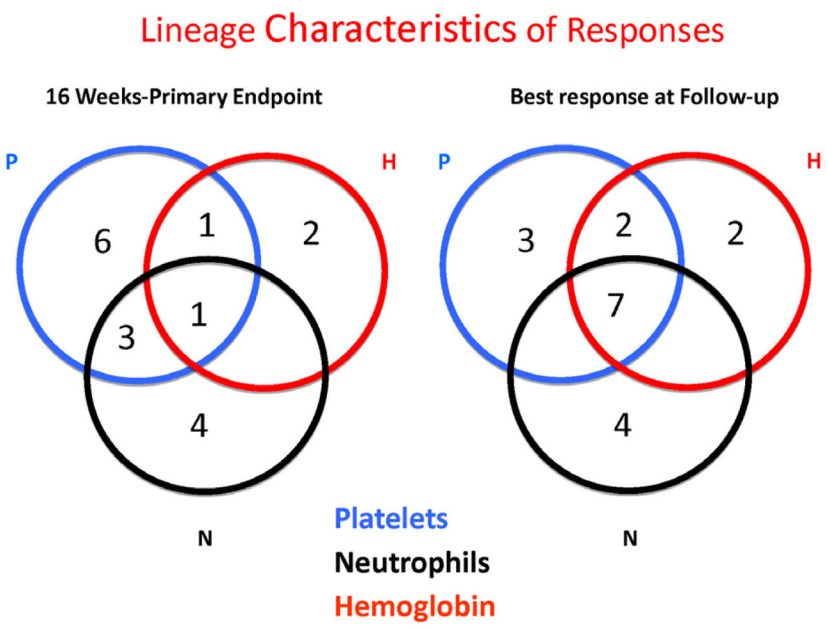

Figure 1.

Responses to eltrombopag by lineage in patients with SAA refractory to IST. These Venn diagrams show the numbers of patients with uni- and multilineage responses at response assessment (A) and best response at follow-up (B). Reprinted with permission[16].

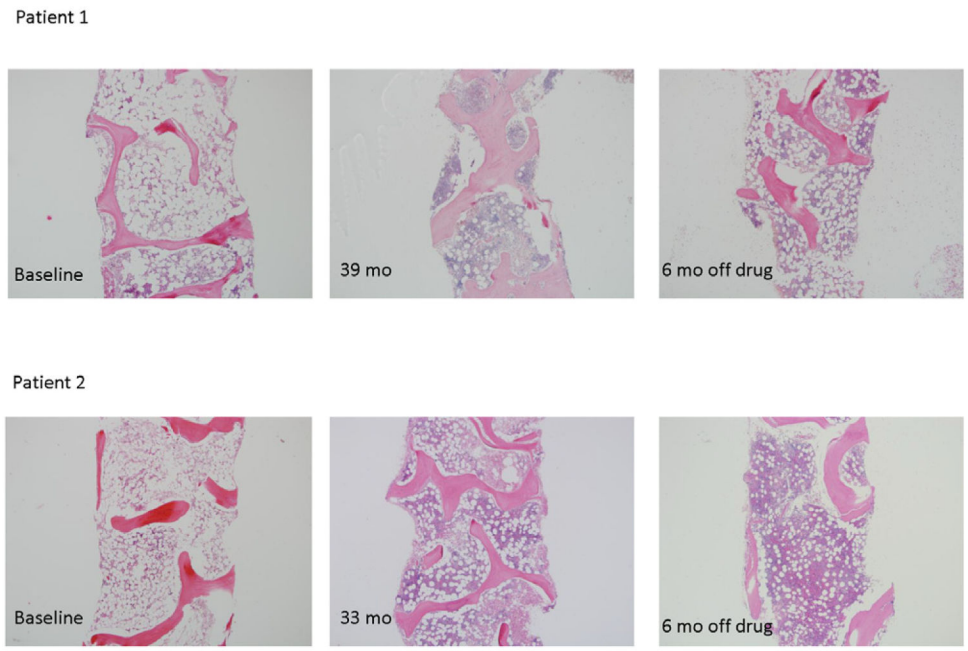

Figure 2.

Bone marrow cellularity in two patients responding to eltrombopag. The left panels show cellularity in these robust responders at baseline. The middle panels show cellularity just prior to discontinuing eltrombopag. The right panels demonstrate that, for Patients 1 and 2, the marrows remain cellular. The images were taken on an Olympus BX41 microscope with an Olympus DP72 camera, using a 4× UPlanFL N Olympus objective (original magnification ×40). Reprinted with permission[16].