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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Iron mobilization in a real life cohort of aplastic anemia patients treated with eltrombopag

To the Editor:

Aplastic anemia (AA) is a rare hematologic disease characterized by immune mediated bone marrow failure with consequent life-threatening cytopenias. Most AA patients are heavily transfusion-dependent of both platelets and red blood cells, and iron overload may become an issue. There is increasing evidence that excess iron may hamper the function of several organs (liver, heart, kidney, and endocrine system), but also have a negative effect on normal hematopoiesis. This is harmful in various diseases, including hemoglobinopaties, myelodysplastic syndromes, and myelofibrosis, but may be particularly detrimental in AA, where residual normal hematopoiesis is even poorer. The thrombopoietin (TPO) analogue eltrombopag (EPAG) has been shown to improve hematopoiesis in 40% to 45% of patients with both relapsed/refractory and newly diagnosed AA.[1,2] The trilineage response observed is linked to a direct effect on hematopoietic stem cells expressing TPO-receptor. In addition to bone marrow stimulation, recent reports demonstrated iron-mobilizing activity of the EPAG in vitro.[3] Furthermore, data from two trials of severe and moderate AA cases showed harmonic oscillation of serum ferritin, concomitant to EPAG initiation and discontinuation, indicating an iron mobilization effect also in vivo.[4] Here we report iron status dynamics in a real life series of 10 AA patients treated with EPAG and prospectively followed at our Institution (from August 2000 until May 2019). Furthermore, we describe an emblematic case, where EPAG combined to iron chelation seemed to modify outcome.

Figure 1A shows hematologic parameters and iron status at baseline and at various time points during EPAG treatment. At the time of drug initiation, six cases presented severe AA according to Camitta criteria, and transfusion dependence (TD) was recorded in 60% of patients. Three patients were therapy naïve and received EPAG (150 mg/day since day +14) together with frontline immunosuppression; seven cases were relapsed/refractory, previously treated with anti-thymocyte globulin (ATG) and cyclosporine (2), cyclosporine alone (2), and steroids only (2). Median age was 43 years (23-91), and male to female ratio 1:1. Median time from diagnosis to EPAG start was 5.36 months (1-137).

Hb, neutrophils, and platelets values significantly ameliorated from baseline to month +3, and during follow up. Mean increase from baseline was 0.7 ± 1.6 g/dL for Hb, 0.3 ± 0.48 × 10^9/L for neutrophils, and 27 ± 38 × 10^9/L for platelets. Of note, transfusion requirement was progressively lost, and overall response rate progressively ameliorated from 56% at month +3 to 100% at month +6 and thereafter, although complete response was observed in two patients only.

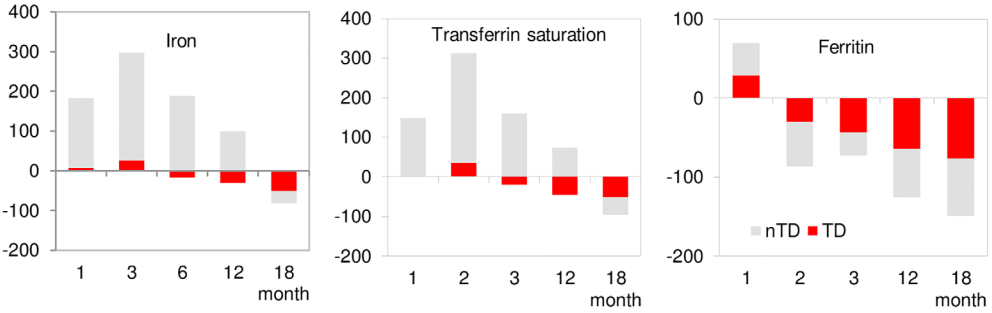
Ferritin values increased from baseline to month +1 (P = .04), and iron and transferrin saturation were persistently augmented at month +1, +3, and +6 vs baseline (P = .01, P = .03, P = .04, respectively). Iron chelation was performed in two cases starting from month +6, possibly accounting for the decrease of all iron parameters observed at month +12. To exclude the confounding effect of iron chelation and transfusions, we separately analyzed TD and non-TD cases excluding the two chelated ones (Figure 1A). Both groups showed the same trend with initial increase of serum iron and transferrin saturation, followed by a progressive decrease. Notably, ferritin levels showed an earlier reduction from month +3 onwards, with a delta decline greater than 100% (Figure 1B). These trends are consistent with an effect of EPAG on iron mobilization in both TD and non-TD cases.

Figure 1C shows hematologic and iron parameters of a typical case: a 91-year-old female referred in June 2017 because of worsening pancytopenia (Hb 8.5 g/dL, platelets 21 × 10^9/L, and neutrophils 1.57 × 10^9/L). Past medical history was positive for arterial hypertension, atrial fibrillation, and hypothyroidism, and renal function was moderately impaired (creatinine clearance 50 mL/min). Bone marrow showed severe hypocellularity (5%), without dysplastic features,

(A)

	baseline	month+1	month+3	month+6	month+12	Month+18
HI and response	N=10	N=10	N=10	N=10	N=9	N=8
Hb g/dL	8,9 (7,6-16,6)	9 (6,2-16)	11,3 (6,2-16,4)	10,3 (8,5-15,1)	11 (8,8-16,1)	11 (6,5-16)
ANC x10^9/L	1,2 (0,48-1,88)	1,7 (0,57-2,47)	2,23 (0,59-3,28)	1,57 (0,43-2,35)	1,99 (0,6-2,87)	2,2 (0,4-4,56)
PLTs x10^9/L	25,5 (14-53)	18 (11-83)	40 (10-148)	49,5 (12-136)	75 (31-89)	83 (38-132)
ORR N(%)	/	/	6 (60)	10 (100)	9 (100)	8 (100)
PR N(%)	/	/	5 (50)	9 (90)	7 (78)	6 (75)
CR N(%)	/	/	1 (10)	1 (10)	2 (22)	2 (25)
Iron status			Trasfusion dependent			
Iron, µg/dL	252 (211-311)	322 (272-475)	472 (259-1543)	260 (157-513)	231 (177-522)	197 (113-1571)
Transferrin, mg/dL	187 (167-215)	194 (160-206)	174 (147-217)	170 (140-211)	223 (142-241)	189 (180-243)
Ferritin, µg/L	2267 (821-3232)	3295 (1558-4141)	3194 (1091-10866)	2414 (885-6595)	1544 (632-2661)	573 (465-2118)
Transferrin saturation, %	97 (81-106)	125 (100-168)	209 (84-593)	107 (56-258)	95 (51-165)	74 (43-455)
Chelation N(%)	0(0)	0(0)	0 (0)	2 (22)	2 (22)	2 (22)
			Trasfusion independent			
Iron, µg/dL	120 (113-171)	470 (158-578)	423 (348-693)	398 (176-1343)	150 (76-743)	100 (73-188)
Transferrin, mg/dL	233 (138-241)	227 (153-232)	231 (176-310)	244 (173-376)	172 (179-393)	306 (170-359)
Ferritin, µg/L	133 (24-1022)	261 (195-1448)	90 (19-713)	48 (23-686)	50 (9-561)	32 (73-283)
Transferrin saturation, %	35 (34-87)	175 (49-216)	139 (128-156)	140 (50-230)	48 (18-180)	32 (14-50)

(B)



(C)

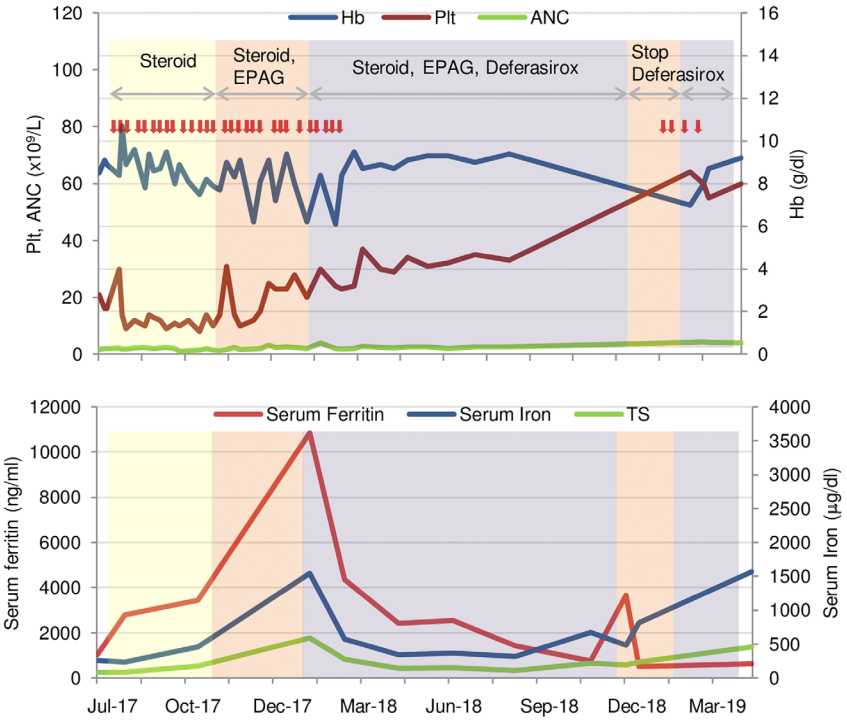


FIGURE 1 A, Hematologic parameters and iron status at baseline and at various time points during EPAG treatment. Values are given as median (range) or as number (percentage). B, Delta percentage increase or reduction of iron parameters over time in transfusion dependent (TD) and independent (nTD) cases. C, Hematologic and iron parameters of a typical patient. Red arrows indicate red blood transfusions. ANC, absolute neutrophil counts; CR, complete response; PLT, platelets; PR, partial response; ORR, overall response rate; TS, transferrin saturation

fibrosis or blasts, consistent with the diagnosis of severe AA. Soon after referral the patient became transfusion dependent (both red blood cells and platelets). A short course of steroids was ineffective and immunosuppression with ATG and cyclosporine was not considered because of comorbidities. Hence, EPAG (150 mg/day) was introduced in November 2017 without hematological response after 3 months. Of note, ferritin levels disproportionally increased (10 866 µg/L) after the introduction of EPAG and, as expected, dropped after chelation was initiated (deferasirox 360 mg daily, reduced dose because of renal insufficiency). In the subsequent months, transfusion-requirement

progressively decreased and disappeared, and iron chelation was stopped after 1 year. One month later, Hb values dropped to 6.5 g/dL, the patient was transfused and deferasirox was re-started obtaining a new partial response (Hb 9.5 g/dL) that is still ongoing. In this prospective series, an early and rapid increase of serum iron, transferrin saturation, and ferritin was observed after EPAG initiation, in both TD and non-TD patients. This effect could be explained by EPAG ability to mobilize iron from hepatocytes, cardiomyocytes, and pancreatic cells, reported in preclinical models.[3] This was followed by a decrease of reactive oxygen species and restoration of normal tissue functioning.[3] In our patients, the initial increase of iron parameters was followed by a progressive reduction of all markers (particularly ferritin) on continuing EPAG, suggesting a progressive clearance of mobilized iron. These data are in line with the iron depletion observed in children with immune thrombocytopenia after 3 to 9 months of EPAG therapy, with 8/12 cases showing decreased ferritin, and three developing anemia.[5] Interestingly, a synergism of EPAG in combination with chelators was recently reported: EPAG is able to transfer iron to deferasirox (shuttling) with subsequent elimination ex vivo and in vitro.[3] This was also demonstrated in bone tissue from thalassemia patients, with subsequent remodulation of osteoclasts activity.[6] Moreover, hematologic response after chelation has been reported in several cases of myelodysplastic and myeloproliferative neoplasms (10%-45% of cases). The synergism between EPAG and deferasirox is further highlighted by our case report of TD elderly patient, who showed hematologic improvement after combined therapy. Altogether, our findings confirm previous reports and indicate that the iron mobilizing effect of EPAG combined with chelation may be of clinical utility in AA patients.

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Italian survey on clinical practice in myeloproliferative neoplasms. A GIMEMA Myeloproliferative Neoplasms Working Party initiative

To the Editor:

Classic myeloproliferative neoplasms (MPNs) are clonal disorders including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), primary MF (PMF) or post PV and post ET-MF. Important changes took place recently in the management of these neoplasms. The aim of this study, conducted as a web-based questionnaire, was to analyze the behavior of Italian hematologists directly involved in MPN patients, in particular how they face with guidelines and recommendations in a real-life setting. The GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) Myeloproliferative Neoplasms Working Party e-mailed to 950 hematologists, belonging to 100 Italian hematology institutions, an anonymous online questionnaire (see Supporting Information) of 64 multiple-choice questions to survey aspects of diagnosis, risk stratification, management, and therapeutic options.

One hundred-eighty hematologists (18.9%) declared to be routinely involved in MPN patients' management, and successfully completed the survey. Most practiced in University Hospital (61.7%), 35% in General Hospital and 3.3% in Private Hospital/practice setting. As many as 61.7% of respondents referred clinical experience in the field of MPNs since more than 10 years, 23.3% of 6 to 10 years, the remaining 13% for less than 5 years.

For the diagnosis of PV, 95.6% of physicians routinely prescribe *JAK2*V617F genotyping, 74.6% erythropoietin levels, 47.5% bone marrow (BM) aspirate and biopsy. The proportion of patients with recent diagnosis of PV lacking a *JAK2* genotype was less than 5% for 42.2% of respondents, while 45% declared that 100% of their patients labeled as PV had a positive *JAK2*V617F or exon 12 mutation tests. For diagnosis of ET, BM biopsy is performed routinely by 87.7% of respondents. In