Eltrombopag in the management of aplastic anaemia: real-world experience in a non-trial setting

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ABSTRACT

Objective: The thrombopoietin mimetic eltrombopag has been used in clinical trials for the frontline and salvage treatment of aplastic anaemia (AA). Eltrombopag was investigated in AA patients on a non-trial all-comer basis.

Methods: Consecutive newly diagnosed and relapsed/refractory AA patients were treated with eltrombopag.

Results: In a 4.5-year period, 20 consecutive AA patients (newly diagnosed, \(N=10\); relapsed/refractory, \(N=10\)) at a median age of 47 (22–84) years were treated with eltrombopag. For newly diagnosed patients, the frontline use of eltrombopag (concomitant medications: anti-thymocyte globulin, ATG, and ciclosporin, \(N=4\); ciclosporin, \(N=5\); nil, \(N=1\)) at a median maximum dose of 150 (50–300) mg/day led to an overall response rate (ORR) of 90% (trilineage: 60%; neutrophil: 20%; platelet: 10%). After a median follow-up of 47 (14–179) weeks, responses were maintained in all cases. In relapsed/refractory patients, eltrombopag at a median maximum dose of 150 (50–300) mg/day led to an ORR of 50% (trilineage: 40%; neutrophil: 10%), with responses maintained after a median follow-up of 115 (53–253) weeks.

Adverse effects included reversible skin pigmentation (observed in all patients taking eltrombopag at \(\geq 150\) mg/day), dyspepsia, and liver function derangement.

Conclusion: In a routine haematological practice, the use of eltrombopag in AA patients was feasible, safe, and associated with very favourable responses.

KEYWORDS

Aplastic anaemia; newly diagnosed; relapsed; refractory; eltrombopag; anti-thymocyte globulin; ciclosporin

Introduction

Acquired aplastic anaemia (AA) is due putatively to immune targeting of haematopoietic stem cells, leading to bone marrow failure [1]. Immunosuppression is the current standard for patients aged >40 [1] to >50 [2] years, whereas allogeneic haematopoietic stem cell transplantation (HSCT) is recommended for patients younger than these age limits, if donors are available.

Immunosuppression with anti-thymocyte globulin (ATG) and ciclosporin results in an overall response rate (ORR) of about 70% (complete response, CR: 10%; partial response, PR: 60%) [3]. Although horse ATG was regarded to result in a better outcome than rabbit ATG [4], not all studies could confirm this observation [1]. In Asian AA patients, horse ATG and rabbit ATG resulted apparently in similar ORRs and survivals [5,6]. The low CR rate of immunosuppression with ATG suggests that other strategies are needed to improve outcome.

Eltrombopag is an oral thrombopoietin receptor agonist. Because the thrombopoietin receptor is expressed on both megakaryocytes and haematopoietic stem cells, treatment with eltrombopag may stimulate megakaryocytopenia as well as erythropoiesis and myelopoiesis [7]. Consequently, eltrombopag had been tested in severe AA. Preliminary results showed that haematopoiesis was improved in these patients [8]. In an expanded cohort of 43 patients, eltrombopag as a single agent (ceiling dose: 150 mg/day) gave an ORR of 40% (CR: 16%) [9]. In a recent study of newly diagnosed AA patients, eltrombopag (150 mg/day) was used with horse ATG and ciclosporin. In three different cohorts of patients who received eltrombopag from day 14 to 6 months, day 14 to 3 months, and day 1 to 6 months; the respective ORRs at 6 months were 80%, 87%, and 94%; and the respective CR rates were 33%, 26%, and 58% [10]. These findings show that eltrombopag has significant activities in stimulating trilineage haematopoiesis.

Data of eltrombopag in AA have so far been limited to clinical trials, and its efficacy in routine practice remains undefined. We described previously high ORR and CR rates in a cohort of AA patients receiving eltrombopag at higher doses (up to 300 mg/day) [11]. In this study, we report the outcome of an expanded cohort of AA patients treated with eltrombopag.

Materials and methods

Patients

From November 2012 to June 2017, consecutive AA (newly diagnosed and relapsed/refractory) patients
who received treatment with eltrombopag were analysed. Although therapeutic decisions were made by the attending physicians, practically every AA patient was offered eltrombopag [1]. Inclusion criteria for eltrombopag treatment were confirmed diagnosis of AA, and need for therapy (dependency on red cell or platelet transfusion, ≥ regular granulocyte colony stimulating factor, G-CSF). Exclusion criteria for eltrombopag treatment included proven paroxysmal nocturnal haemoglobinuria phenotype clinically and on flow cytometry, and clonal karyotypic aberrations on presentation [7,8]. All patients were treated with informed consent in the same centre. To be eligible for the analysis in this study, eltrombopag must have been administered for at least 12 weeks (the first time-point of assessment of response).

**Newly diagnosed patients**

For immunosuppression, the choice of horse or rabbit ATG was determined by the attending physician. Because there was no special preference in our unit, horse and rabbit ATG were used roughly in a 1:1 ratio. Ciclosporin (75–100 mg twice daily) was used in combination with ATG. Patients not receiving ATG were treated with ciclosporin (90–125 mg twice daily). Eltrombopag was started at the same time as commencement of immunosuppression.

**Relapsed or refractory patients**

In relapsed/refractory patients, the time-point in the clinical course at which eltrombopag was started and the dose employed were according to the discretion of the attending physicians. In some patients, continuation of ciclosporin was allowed.

**Eltrombopag treatment**

Eltrombopag was started at 50 mg/day and dose-escalated until maximum response was achieved. On reaching an eltrombopag-induced response, immunosuppression including ciclosporin was gradually reduced and then stopped. After cessation of immunosuppression, the dose of eltrombopag was then tapered, but there was no pre-determined time-point at which eltrombopag was stopped.

**Safety and response**

Safety and response were determined at 12 and 16 weeks. Adverse events were graded according the Common Terminology Criteria for Adverse Events [12]. Response criteria have previously been described [8] Briefly, platelet response was defined as an increase in platelet count by at least $20 \times 10^9$/L above baseline without transfusion. Erythroid response was defined as an increase in haemoglobin by 1.5 g/dL above baseline without transfusion, in cases where the pre-treatment haemoglobin was < 9 g/dL, or reduction in transfusion requirement of ≥ 4 units in 8 weeks as compared with the preceding 8 weeks. Neutrophil response was defined as an increase in neutrophils by $\geq 0.5 \times 10^9$/L above baseline without the use of G-CSF.

**Allogeneic HSCT**

Search for an HLA-matched donor (sibling or voluntary unrelated) was conducted for eligible (age ≤ 60 years) newly diagnosed or relapsed/refractory patients. Because of the time required for the search and subsequent work up of suitable donors, necessity of allogeneic HSCT was effectively considered according to the outcome of the initial eltrombopag and immunosuppression therapy.

**Results**

**Patients**

Within the 4.5-year study period, 22 consecutive patients with an original diagnosis of AA were treated with eltrombopag. Two cases were excluded from the analysis, with one patient deciding to discontinue eltrombopag after four weeks, and the other patient later diagnosed to instead T-cell large granular lymphocytic leukaemia. Eleven men and nine women at a median age of 47 (22–84) years were analysed. Fourteen patients had severe AA. Ten patients have briefly been described before [11], and their long-term follow-up data were updated.

**Newly diagnosed patients**

Ten patients received eltrombopag as the initial therapy (Table 1). In four patients (cases 2, 3, 5, 6), concomitant ATG (horse, $N = 2$; rabbit, $N = 1$; rabbit then horse ATG, $N = 1$) and ciclosporin were administered. In five patients, concomitant ciclosporin was administered. ATG was not used because of advanced age (case 4), patient’s choice (case 8, 9, 10), and original mis-diagnosis as immune thrombocytopenia (case 7, which led to the previous administration of four doses of the anti-CD20 antibody obinutuzumab). In one patient (case 1), eltrombopag was the only drug used. This patient had severe rheumatoid arthritis treated with adalimumab and poorly controlled type I diabetes mellitus with neuropathy; so that further immunosuppression with ATG and ciclosporin was considered hazardous. The maximum dose of eltrombopag ranged from 50 to 300 mg/day (median: 150 mg/day).
Response of newly diagnosed patients to eltrombopag

At 12 weeks, the ORR was 90% (trilineage response: 40%; platelet response: 30%; neutrophil response: 20%), which was unchanged at 16 weeks. On continuation of treatment, two patients (cases 1, 2) achieved trilineage response, so that trilineage response was finally achieved in 6 of 10 (60%) patients. Of these patients, eltrombopag was successfully tapered off in two patients (cases 2 and 3), and maintained at lower doses in three patients (50 mg/day, \( N = 2 \); 75 mg/day, \( N = 1 \)). One patient elected to receive an allogeneic HSCT from a matched sibling while he was in trilineage response. One patient (case 6) did not respond despite two cycles of ATG therapy, and eltrombopag was tapered off. After a median follow-up of 47 (14–179) weeks, responses were still maintained in all nine responding patients.

Relapsed or refractory patients

Ten patients received eltrombopag as salvage therapy (Table 2). Eight patients had failed previous treatment with ATG and ciclosporin. One patient (case R1) did not receive ATG because of advanced age, and was on ciclosporin before eltrombopag treatment. Another patient (case R3) had previous splenectomy and extensive osteonecrosis because of prolonged corticosteroid therapy, and was considered unsuitable for ATG therapy. The maximum dose of eltrombopag ranged from 50 to 300 mg/day (median: 150 mg/day).

Response of relapsed or refractory patients to eltrombopag

At 12 weeks, the ORR was 40% (trilineage response: 20%; platelet response: 10%; neutrophil response: 10%). The ORR was unchanged at 16 weeks, although a patient with platelet response (case R5) achieved platelet + neutrophil response. On continuation of treatment, this patient achieved trilineage response. Furthermore, one patient (case R6) who did not show response at 12 weeks and 16 weeks also achieved trilineage response ultimately. At a median follow-up of 115 (53–253) weeks, trilineage and neutrophil responses were achieved and maintained in four and one patients, respectively, giving an ORR of 50%. Responding patients were still maintained on smaller doses of eltrombopag that ranged from 50 to 75 mg/day (median: 75 mg/day).

Safety profile

Skin hyperpigmentation (grade 2) was the most common adverse event (AE), which was dose-dependent and observed in every patient who took...
 eltrombopag at ≥150 mg/day [7]. The pigmentation was fully reversible on cessation of eltrombopag treatment. Dyspepsia requiring either histamine-H2 antagonists or proton pump inhibitors occurred in nine patients (45%) (grade 2, N = 7; grade 3, N = 2). Liver function derangement (grade 3) led to drug cessation in one patient (case R9). Another patient (case R7) received multiple trials of eltrombopag, which was stopped each time because of intolerable dyspepsia (grade 3). He developed acute myeloid leukaemia 62 weeks after cessation of the last dose of eltrombopag [11]. Monosomy 7 was found on karyotypic analysis. Retrospective fluorescence in situ hybridization did not show the presence of the monosomy 7 clone on presentation. However, the monosomy 7 clone was first observed after the first course of eltrombopag.

**Discussion**

This is to date the only published study of AA patients treated with eltrombopag on a non-trial all-comer basis. This real-life clinical experience showed interesting features. In newly diagnosed patients, the frontline use of eltrombopag led to an ORR of 90% and a trilineage response rate of 60%. In a previous prospective study of AA patients, eltrombopag was used in three dosing schedules: day 14–6 months, day 14–3 months, and day 1–6 months; together with ciclosporin and ATG [10]. The ORRs were 80%, 87%, and 94%, and the complete response rates were 33%, 36%, and 58%, respectively. The results showed that early and longer exposure to eltrombopag gave superior results. Our findings together with these published results [10] suggested that the early addition of eltrombopag to AA treatment would be beneficial. Hence, both the timing of treatment initiation and the total duration of exposure to eltrombopag have impacts on treatment response.

In frontline treatment with eltrombopag, three different approaches were used in our series: in combination with ATG and ciclosporin, in combination with ciclosporin, and alone. Several observations arise from our cohort. Trilineage response was achieved in all three groups of patients. In the ATG + ciclosporin group, three of four patients achieved trilineage response. Interestingly, in the ciclosporin group, all five patients responded, with two achieving trilineage response. One patient who received eltrombopag alone also achieved trilineage response. These observations showed that in newly diagnosed AA patients, eltrombopag induced very high response rates of up to 90%. Even including the two patients who were not evaluated because of treatment discontinuation or incorrect diagnosis, on an intention-to-treat basis, the response rate was still very high at 75%. Furthermore, although ATG is widely considered to be the

**Table 2. Response of relapsed/refractory AA patients to salvage treatment with eltrombopag.**

| Case | Sex/Age | Ethnicity | Before Tx | Previous Rx | Eltrombopag Response | Best response | Hb | WBC | ANC | Plat | Start | Max | Current | Time | FU | Outcome* |
|------|---------|-----------|-----------|------------|----------------------|---------------|----|-----|-----|------|-------|-----|---------|------|----|----------|
| R1   | M/68    | Chinese   | 8.8       | CsA        | Tri Tri Tri          | 8.8           | 3.8| 0.9  | 14   | 14   | 309 wk | 75 mg| 75 mg   | 121 wk| Tri| Stoppted, no response |
| R2   | F/69    | Chinese   | 8.6       | ATG (x2) + CsA | nil nil nil | 8.6 | 1.7  | 0.2  | 17   | 120 wk | 150 mg| 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R3   | F/53    | Chinese   | 12        | ATG (x2) + CsA | nil nil nil | 12 | 2.7  | 0.9  | 47   | 514 wk | 50 mg | 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R4   | F/40    | Chinese   | 9.6       | ATG (x2) + CsA | nil nil nil | 9.6 | 1.4  | 0.9  | 47   | 894 wk | 15 mg | 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R5   | F/57    | Portuguese| 7.5       | Alemtuzumab | nil nil nil | 7.5 | 3.4  | 1.5  | 47   | 120 wk | 200 mg| 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R6   | M/35    | Chinese   | 8.5       | CsA        | nil nil nil | 8.5 | 0.6  | 0.2  | 14   | 88 wk   | 150 mg| 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R7   | M/35    | Chinese   | 10.3      | ATG + CsA  | nil nil nil | 10.3 | 0.9  | 0.9  | 17   | 1196 wk | 150 mg| 75 mg   | 121 wk| Nil| Stoppted due to AE |
| R8   | M/64    | Chinese   | 5.5       | ATG + CsA  | nil nil nil | 5.5 | 2.3  | 0.8  | 14   | 676 wk | 125 mg| 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R9   | F/50    | Chinese   | 6.8       | ATG + CsA  | nil nil nil | 6.8 | 1.6  | 0.9  | 15   | 408 wk | 75 mg | 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R10  | M/21    | Chinese   | 6.8       | ATG + CsA  | nil nil nil | 6.8 | 1.6  | 0.9  | 15   | 408 wk | 75 mg | 50 mg   | 121 wk| Nil| Stoppted due to AE |
| R11  | F/21    | Chinese   | 6.8       | ATG + CsA  | nil nil nil | 6.8 | 1.6  | 0.9  | 15   | 408 wk | 75 mg | 50 mg   | 121 wk| Nil| Stoppted due to AE |

Notes: Tx: treatment with eltrombopag; Hb: haemoglobin (g/dl); WBC: white cell count (× 10^9/L); ANC: absolute neutrophil count; Plat: platelet count (× 10^9/L); Rx: therapy; FU: follow-up duration; and A: outcome at the latest follow-up.
standard first-line treatment, it is apparently not mandatory for eltrombopag to be effective.

In relapsed and refractory patients, eltrombopag was used alone, although continuation of previous ciclosporin therapy was allowed in some patients. Trilineage response was obtained in four cases, which was remarkable given that these patients had failed multiple courses of ATG and ciclosporin. However, because a fixed time of stopping treatment is not mandated, responding patients are still on treatment, so it remains unclear if the response can be maintained once eltrombopag is tapered off.

These results are comparable with those reported in phase 1/2 clinical studies [8–10]. However, we have used eltrombopag at doses higher than those reported in these trials. Compared with other populations, eltrombopag clearance is 33–52% lower in Asian patients [12,13]. Therefore, it is generally recommended, in the setting of immune thrombocytopenic purpura, that the starting dose of eltrombopag in Asian patients should be about 50% of that of other populations [7]. In previous phase 1/2 studies of eltrombopag in predominantly non-Asian AA patients, the ceiling dose of eltrombopag has been set at 150 mg/day [8–10], which would be equivalent approximately to 75 mg/day in Asian patients. In our patients, however, we have used eltrombopag in doses of up to 300 mg/day, with a median dose of 150 mg/day; which could be equivalent to a maximum of 450 and 225 mg/day, respectively, in non-Asian patients [13,14]. It remains uncertain if such high doses were actually required to obtain responses in our patients. However, serious toxicities were not observed, suggesting that eltrombopag could be used in doses higher than those previously reported [8–10].

The short-term outcome of 10 patients in this series had previously been discussed [11]. Their extended follow-up for an additional 40 weeks (median follow-up in the current report: 115 weeks, in the previous report: 75 weeks [11]) showed that the responses initially reported were durable, with one patient maintaining trilineage response after cessation of eltrombopag treatment. Other limitations of this study are due primarily to patients being treated in actual practice and not in clinical trials. Follow-up marrow examination is not mandated, so that improvement in marrow cellularity cannot be confirmed. Also, clonal evolution and the possible appearance of new karyotypic aberrations cannot be defined in the absence of marrow samples. This is an important issue, as somatic gene mutations and clonal haematopoiesis are common in AA [15]. In this regard, the long-term safety of higher doses of eltrombopag must be assessed. Our study was not a clinical trial, and so we took the precaution of excluding patients who had clonal karyotypic aberrations on initial presentation; on the basis that it might not be easy to differentiate AA from hypoplastic myelodysplastic syndrome. We have not set a pre-determined time for cessation of treatment. Furthermore, some patients were on concomitant eltrombopag and ciclosporin. Ciclosporin was unlikely to be the key effective medication in relapsed/refractory patients, as they had previously failed ciclosporin treatment. However, in newly diagnosed patients, trilineage responses were obtained with eltrombopag and ciclosporin. Hence, whether a synergism between eltrombopag and ciclosporin is needed for response warrants examination.

In conclusion, we have shown that, outside clinical trials in everyday practice, eltrombopag usage is feasible, safe and associated with favourable responses in newly diagnosed and relapsed/refractory AA patients. The long-term safety of this approach remains to be defined.

Disclosure statement

No potential conflict of interest was reported by the authors.

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