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Use of eltrombopag in aplastic anemia in Europe

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Abstract

Eltrombopag (ELT), an oral thrombopoietin receptor agonist, has recently emerged as a promising new drug for the treatment of aplastic anemia (AA). How ELT is used outside of clinical trials in the real-world setting and results of this treatment are not known. We conducted therefore a retrospective survey on the use of ELT in AA among EBMT member centers. We analyzed the 134 patients reported in our survey together with 46 patients recently published by Lengline et al. The median follow-up from start of ELT treatment was 15.3 months, with 85.6% patients alive at last follow-up. Importantly, only 28.9% of our patients received ELT according to the FDA/EMA label as monotherapy in the relapsed/refractory setting, whereas 16.7% received ELT upfront. The overall response rate in our cohort was 62%, very similar to the results of the pivotal ELT trial. In multivariate analysis, combination therapy with ELT/cyclosporine/ATG and response to previous therapy were associated with response. Overall survival was favorable with a 1-year survival from ELT start of 87.4%. We identified age, AA severity before ELT start and response to ELT as variables significantly associated with OS. Two patients transformed to MDS; other adverse events were mostly benign. In sum, ELT is used widely in Europe to treat AA patients, mostly in the relapsed/refractory setting. Response to

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ELT is similar to the clinical trial data across different age groups, treatment lines, and treatment combinations and results in favorable survival.

Keywords Aplastic anemia · Eltrombopag · Growth factors · Immunosuppression

Introduction

Severe aplastic anemia (SAA) is a rare heterogenous disease mostly autoimmune, in which T cell attack on hematopoietic stem (HSCs) and progenitor cells results in progressive bone marrow failure [1]. In patients not selected for potentially curative allogeneic hematopoietic stem cell transplantation (allo-HSCT), the standard therapy consists of immunosuppression (IS) with horse anti-thymocyte globulin (ATG) and cyclosporine A (CYA) [2]. About 70% of patients do respond, but survival with good marrow function without relapse is in the order of only 30–40% [3]. Treatment options are unsatisfactory for patients refractory to or relapsing after first-line treatment and not eligible for allo-HSCT from a matched unrelated donor, with response rates to an additional course of ATG or anabolic steroids in the order of 30–60% [4–6]. In addition to the modest efficacy, repeated courses of immunosuppression (IS) may predispose to secondary malignancies [7]. Furthermore, the intensive immunosuppressive ATG-CYA combination cannot be applied in a proportion of AA patients due to advanced age or contraindications such as active infection [8].

Eltrombopag (ELT), a small molecule thrombopoietin (TPO) mimetic has been introduced in the AA therapy armamentarium recently. In contrast to previous failed attempts to stimulate the HSC compartment by diverse growth factors such as G-CSF, GM-CSF, or EPO [3, 9], ELT induced trilinear hematopoietic responses in refractory SAA patients [10]. Mechanistically, ELT binds to the TPO receptor c-MPL expressed on HSCs and leads to their proliferation and expansion [11, 12], although additional, immune modulatory effects might also be involved [13]. Results of a phase II trial examining ELT monotherapy in refractory SAA patients showing a 40% response rate [10, 14] led to the approval of ELT as monotherapy in relapsed-refractory SAA in the USA and Europe [15, 16]. Recently, increased response rate to ELT in combination with standard ATG-CYA immunosuppression as compared to historical controls has been reported by the NIH group [17] and the use of ELT in the first-line setting is currently being tested in several ongoing clinical trials. Less is known about the use of ELT outside clinical trials. So far, real-world data of two cohorts described robust response to ELT administered as monotherapy or part of various combination regimens [18–20]. Romiplostim is a peptide-analogue TPO agonist with a very different chemical structure and different

binding site on MPL, but similar efficacy as ELT in immune thrombocytopenia (ITP) [21]. Although romiplostim has been shown also to stimulate HSCs in animal models [11], its use in SAA remains anecdotal [19]. As in ITP switch from one TPO agonist to the other in refractory patients results in a high response rate [22], exploration of romiplostim for the treatment of SAA patients is clearly warranted.

Although the first results on ELT in SAA are promising, its optimal use, the necessity for concomitant IS, as well as predictors of response or incidence of relapse remain unknown, particularly for patients not representative of the clinical trial population or treated outside of the FDA/EMA label. Similarly, some safety concerns about clonal evolution and transformation to myelodysplastic syndromes in patients on ELT remain [14]. Analysis of a large cohort of SAA patients treated with ELT outside clinical trials is likely to give valuable insight into these open questions. Therefore, the EBMT SAA working party conducted a Europe-wide survey on the use of TPO agonists to treat AA in member centers. Here we report the results of the largest cohort of ELT treated AA patients so far.

Methods

Data collection

The EBMT SAA working party invited 441 EBMT centers to participate in this survey, 103 (23%) centers answered, 92 (21%) accepted to participate. Fifty centers (11%) with potentially eligible patients received the survey form (supplementary material) based on the EBMT minimal-essential data (MED) B+C forms used to record SAA patients in the EBMT registry. Patients with AA (moderate, severe, very severe) or PNH with AA phenotype treated with TPO agonists (ELT or romiplostim) either as first-line treatment or as rescue treatment outside clinical study protocols could be included in the survey. We considered ELT as first-line treatment if it was started within 60 days from beginning of the first therapy. Rescue treatment includes patients refractory or with insufficient response to one or several initial line(s) of therapy. Relapse includes patients who lost their response to any previous therapy, including those failing initial IS therapy for relapse.

Complete response (CR) was defined as recovery of blood counts (hemoglobin > 100 g/l, neutrophil count > 1.5×10^6 /ml, platelet count > 100×10^6 /ml). Partial response (PR) was defined as transfusion independence with any degree of improvement of blood counts. Minimal response was defined as some improvement in one or more lineage but not fulfilling the criteria of PR. No response refers to patients not fulfilling any of the above criteria.

We received data on 137 patients from 31 EBMT centers. In addition, we obtained individual patient level data from the French Reference Center for Aplastic Anemia on ELT-treated SAA patients published recently [20]. As the two cohorts had very similar inclusion/exclusion criteria, the two cohorts were merged in a single database (total 183 patients from 46 centers, median number of patients per center 2, range 1–21).

Data analysis

Due to low numbers ($n = 3$), patients treated with romiplostim were not considered further. Analyses were conducted on all ELT treated patients ($n = 180$).

Descriptive statistics are presented as percent of all patients with available data. Categorical data were compared using the Chi-square test, continuous variables were analyzed using the Kruskal-Wallis non-parametric test. Survival is presented using the Kaplan-Meier estimator. Comparisons among groups were by the log-rank test, multivariate models were created using the Cox regression model including response to ELT as a time-dependent covariate. Response to ELT was analyzed as cumulative incidence with death as a competing event. Univariate comparisons were done using the Gray test and multivariate models were built according to Fine and Gray [23] using EZR software [24]. A p value of < 0.05 was considered significant.

Results

Use of ELT for AA in Europe

Treatment episodes started from 11/2011 to 10/2017. The median follow-up from start of ELT treatment was 15.3 months (95% CI 13–17.6 months), with 85.6% patients alive at last follow-up. All patients were treated with ELT, in a median and maximum dose of 150 mg/day, 11 patients (6.4%) received a higher dose up to 450 mg. ELT dose was not different in patients with or without a response. ELT was ongoing in 50% of patients alive at last follow-up.

A minority of patients ($n = 30$, 16.7%) received ELT upfront, i.e., within 60 days following initiation of first-line treatment, whereas most patients were treated with ELT as a rescue treatment either for refractory disease or relapse (Fig. 1a). ELT was applied both as monotherapy and in combination with IS with CYA ± ATG (Fig. 1b). Based on this information, different

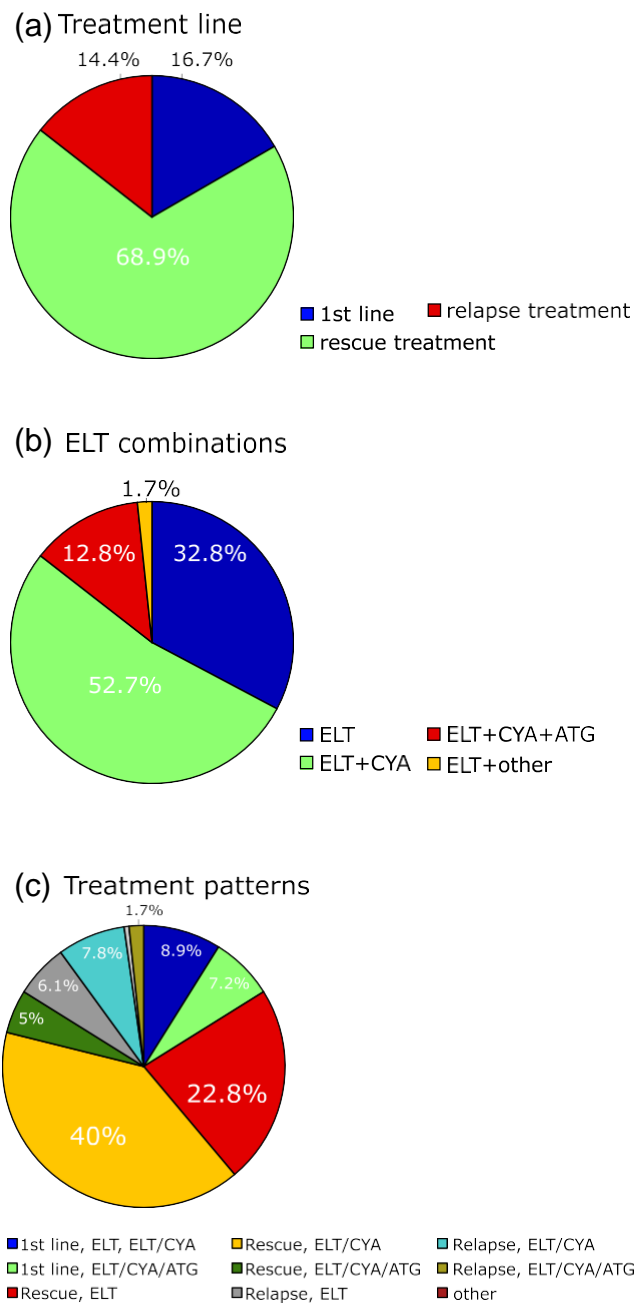


Fig. 1 Patterns of ELT use. a Treatment line, b combination regimens, and c treatment groups

associations with ELT are represented in our study population (Fig. 1c). Importantly, 71.1% of patients received ELT outside the FDA/EMA label, either in the first-line setting or as part of a combination therapy (irrespective of the therapy line). There was a significant ($p < 0.001$) association between treatment line and ELT combination, as the proportion of patients treated with ELT alone increased from first-line treatment to relapse, whereas ELT-CYA-ATG was used predominantly in the first-line setting (Table 1). Overall, 23 (12.8%) patients received ELT in combination with CYA-ATG (within 60 days of 1st ATG day), starting at day 14 (median) from the first ATG dose.

Table 1 ELT treatment combinations according to treatment line

$p < 0.001$	Treatment line		
	First-line $n = 30$	Rescue treatment $n = 124$	Relapse treatment $n = 26$
ELT	23.3%	33.1%	42.3%
ELT+CyA	30%	58.1%	53.8%
ELT+CyA/ATG	43.3%	7.3%	3.8%
ELT+other	3%	1.6%	0%
	100%	100%	100%

p value from chi-square test

Baseline characteristics

Baseline characteristics of the whole cohort are shown in Table 2. Most patients were dependent on RBC and PLT transfusions (93.3% and 90%, respectively) preceding ELT therapy. Interestingly, the choice of the ELT treatment combination (monotherapy vs. combination therapy) can be at least partly explained by differences in age or AA severity, as patients treated with ELT monotherapy were older and were more likely to present with moderate AA at diagnosis compared to patients treated with combination therapy ($p = < .001$ and $p = 0.069$, respectively, supplementary Table 1).

Response

The reported overall response rate in our cohort was 62%, with 17.9% CR, 26.8% PR, and 17.3% minimal response. In patients responding, best response was achieved in median after 224 days (95% confidence interval 136.5–311.5 days) (Fig. 2), although responses were reported at considerably later time points (range 8–1335 days). Time to first response was likely shorter, as response depth likely increases over time, but this information was not assessed in the survey. Twenty-four patients (21.6% of responding) stopped ELT after

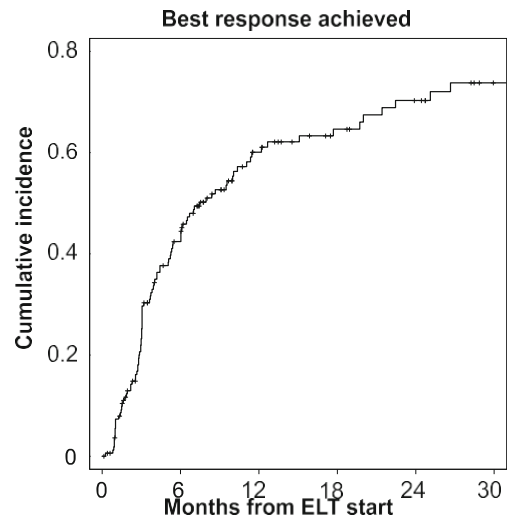


Fig. 2 Time to best response

having achieved a stable response, four (16.7%) relapsed in median 83 days (range 53–980) following response and in median 246 days (range 164–988 days) after start of ELT.

Overall, relapse occurred in 15 patients (14.7% of patients responding), in median 181 days (95% CI 162.7–199.3 days) after start of ELT. The median duration of response was not reached.

The response rate did not differ between treatment combinations ($p = 0.774$), treatment line ($p = 0.33$) or according to treatment groups shown in Fig. 1c ($p = 0.699$). We analyzed thus our cohort as a whole and sought to identify factors predicting response in a time-to-event manner.

In univariate models, we could not identify any baseline characteristic associated with response in the whole cohort, although severity of AA at diagnosis and at the time of ELT start, as well as first-line treatment were significantly associated with death without a response (Tables 3 and 4, Fig. S1). In the multivariate model, combination therapy was a predictor ($p = 0.04$) of response, with a hazard ratio for response of 2.95 (95% CI 1.28–6.83, $p = 0.01$) for the ELT/CYA/ATG

Table 2 Baseline characteristics

Sex		Age at start ELT, years, median (IQR)	48.4 (23.3–67)
Male	56.1%	Severity of AA at start ELT	
Female	43.9%	Moderate	16.8%
Age at diagnosis, years, median (IQR)	43.4 (20–65.5)	Severe	64.7%
Severity of AA at diagnosis		Very severe	17.9%
Moderate	13.5%	Number of previous treatment lines, median (IQR)	1 (1–2)
Severe	55.6%	Days from diagnosis to ELT start, median (IQR)	348.5 (195–1212)
Very severe	30.4%	Days from last treatment to ELT start, median (IQR)	140 (53–429)
PNH clone	18.9%	Days from last ATG to ELT start, median (IQR)	14 (7–20.5)

Table 3 Univariate analysis of response with death as a competing event

Univariate analysis (Gray test) for competing events							
Event:	n=	Response			Death		
		1-year incidence	95% CI	p value	1-year incidence	95% CI	p value
All patients							
Combination				0.15			0.163
Monotherapy	50	0.47	0.31–0.61		0.12	0.04–0.24	
ELT + Cya	91	0.61	0.5–0.71		0.05	0.02–0.11	
ELT + CyA/ATG	23	0.66	0.4–0.83		0.15	0.03–0.36	
Treatment line							
First-line	26	0.48	0.26–0.67	0.43	0.26	0.1–0.47	< 0.001
Rescue treatment	116	0.59	0.49–0.68		0.05	0.02–0.11	
Relapse treatment	25	0.56	0.32–0.73		0.05	0.003–0.22	
Sex							
Male	93	0.55	0.43–0.64	0.29	0.08	0.03–0.15	0.77
Female	74	0.6	0.47–0.71		0.09	0.04–0.17	
AA severity at diagnosis				0.5			< 0.001
Moderate	23	0.59	0.35–0.77		0.04	0.003–0.19	
Severe	88	0.57	0.46–0.68		0.03	0.01–0.08	
Very severe	47	0.55	0.37–0.69		0.21	0.1–0.36	
AA severity at ELT start							
Moderate	28	0.66	0.44–0.81	0.42	0		< 0.001
Severe	106	0.58	0.47–0.67		0.03	0.01–0.1	
Very severe	27	0.4	0.21–0.59		0.38	0.16–0.6	
Etiology							
AA	137	0.58	0.48–0.66	0.9	0.09	0.05–0.15	0.5
PNH	30	0.56	0.34–0.72		0.04	0.002–0.17	
Patients with previous treatment							
ATG-exposed				0.91			0.84
No	41	0.58	0.39–0.74		0.03	0.002–0.12	
Yes	100	0.59	0.48–0.68		0.06	0.02–0.12	
Response to previous therapy				0.02			0.34
No	98	0.533	0.42–0.63		0.06	0.02–0.13	
Yes	34	0.722	0.53–0.85		0.031	0.002–0.14	

group compared to ELT monotherapy (Tables 3 and 4). In the subgroup of patients with previous therapy, response to previous therapy was a predictor of response to subsequent ELT treatment (HR 1.689, 95% CI 1.04–2.75, $p=0.04$), whereas previous exposure to ATG, interval from diagnosis or interval from last treatment were not significantly associated with response (Tables 3 and 4).

Survival

The median survival was not reached, the 1-year survival from start of ELT was 87.4% (95% CI 81.9–92.9%) (Fig. 3a). Of the 26 patients who died during follow-up, seven (26.9%) had undergone allo-HSCT and in six of these, deaths were

classified as HSCT-related. In univariate and multivariate analysis, age at ELT start, and AA severity before ELT start were significantly associated with OS. Response to ELT included as a time-dependent covariate was similarly correlated with a lower incidence of death (Tables 5 and 6, Fig. 3b).

Safety

Adverse events were reported in 51 patients, although severe (grade III–IV) AEs were rare (17 patients, 30.4% of all AEs). The most frequent AE was hepatic toxicity, a well-known side effect of ELT (Table 7). Skin reactions were rare. Importantly, ELT was stopped only in four patients due to AEs.

Table 4 Multivariate analysis of response with death as a competing event

Multivariate analysis for response or death as competing events (Fine and Gray)			
	HR for response	95% CI	<i>p</i> value
All patients (<i>n</i> = 155 evaluable)			
Combination			Overall (Wald test):0.04
Monotherapy	1 (reference)		
ELT+CYA	1.36	0.77–2.4	0.29
ELT+CYA/ATG	2.95	1.28–6.83	0.01
Treatment line			Overall (Wald test): 0.16
First-line	1 (reference)		
Rescue treatment	1.96	0.91–4.2	
Relapse treatment	2.51	0.94–6.7	
Sex			
Male	1 (reference)		
Female	1.08	0.69–1.67	
AA severity at diagnosis			Overall (Wald test):0.72
Moderate	1 (reference)		
Severe	1.46	0.59–3.61	
Very severe	1.47	0.51–4.2	
AA severity at ELT start			Overall (Wald test): 0.52
Moderate	1 (reference)		
Severe	0.67	0.3–1.49	
Very severe	0.54	0.1842–1.59	
Etiology			
AA	1 (reference)		
PNH	0.78	0.41–1.45	
Age at ELT start	1.01	1.0–1.02	
Patients with previous treatment (<i>n</i> = 123 evaluable)			
ATG-exposed			
No	1 (reference)		
Yes	0.853	0.46–1.57	0.61
Response to previous therapy			
No	1 (reference)		
Yes	1.689	1.04–2.75	0.035
Time from diagnosis to ELT start	0.9998	0.9995–1	0.28
Time from last treatment to ELT start	1	0.9999–1	0.16

Cytogenetic abnormalities were assessed at diagnosis and showed a normal karyotype in 123 patients (91.1%) and an abnormal karyotype in 12 cases (8.9%) including 3 cases of trisomy 8, 2 cases of monosomy 7, and 1 case of inv. (3;3q26). Cytogenetic information was not available for the remaining cases (*n* = 45, 25% of the whole cohort). Cytogenetic evolution during the course of the treatment was not assessed in the survey. Only two cases of transformation into myelodysplastic syndrome (MDS) were described, diagnosed 2 and 5.5 months after ELT start. One of these two patients with a subsequent MDS transformation had a monosomy X at AA diagnosis, the other had no cytogenetic

information available. No other secondary malignancies apart from two cases of squamous cell carcinoma of the skin occurred.

Discussion

Whereas IS addresses the autoimmune destruction of HSCs, allo-HSCT has been so far the only treatment modality correcting also the resulting stem cell defect in AA patients. The efficacy of ELT as monotherapy, presumably acting preferentially at the stem cell level, created much excitement in the field. The next logical step, combining ELT with IS has been

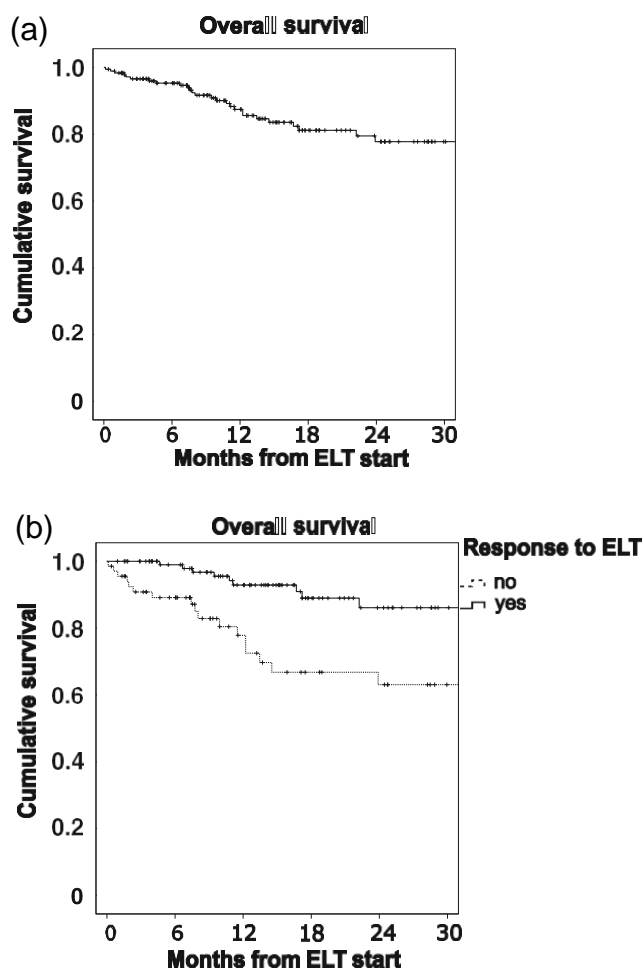


Fig. 3 Overall survival. a Whole cohort, b according to response to ELT, please refer also to the multivariate analysis of survival considering response to ELT as a time-dependent covariate

explored in phase II trials [17, 25] and is being examined in several ongoing phase III trials. Until the role of ELT in the first-line setting is clearly defined, ELT will be used mostly in patients relapsed or refractory to IS or allo-HSCT.

Table 5 Univariate analysis of survival

Univariate analysis for OS (log-rank test)	
Variable	<i>p</i> value
Sex	0.62
AA severity at diagnosis	0.17
Age at start ELT	0.01
PNH	0.11
AA severity at ELT start	< 0.001
ELT combination	0.55
Treatment line	0.1
Prev. ATG exposure	0.92
Best response to previous treatment	0.65

Table 6 Multivariate analysis of survival

Multivariate analysis for OS				
Variable	<i>p</i> value	HR for death	0.95 CI	
Age at start ELT	0.01	1.026	1.005	1.046
AA severity at ELT start	0			
Moderate				
Severe	0.49	1.7	0.4	7.9
Very severe	0.001	13.2	2.7	64
ELT combination	0.56			
ELT				
ELT+CYA				
ELT+CYA/ATG				
Response to ELT	0.01			
Yes (compared to none)		0.11	0	0.7

In line with this, only a small minority in our cohort was treated upfront with an ELT containing regimen. Although the reasons for ELT application in the first-line setting were not evident, age and comorbidities precluding use of standard ATG/CYA therapy leading to ELT use as part of a low intensity therapy on one hand and high-risk AA resulting in ELT in combination with ATG/CYA on the other are likely explanations. Supporting this hypothesis, the median age of patients treated with ELT alone or with CYA in the first-line setting was 55.5 years, compared to 23 years ($p < 0.001$) in patients treated with ELT/CYA/ATG. Severity of AA at diagnosis was similar. Since this is likely a selection of patients and is not representative of the entire patient population, the role of ELT in the first-line setting could not be clarified in our cohort. The response rate of 46.7% in patients with low intensity ELT treatment in the first-line setting is certainly meaningful, but not above the range expected, e.g., with CYA alone [26].

In our cohort, relapsed/refractory patients were treated with ELT mostly in combination with CYA \pm ATG, unlike in the pivotal trial using ELT as a monotherapy [14]. Although failure of IS argues against retreatment with another course of IS

Table 7 Adverse events

Adverse events			
	Grades I–II	Grades III–IV	Any grade
Bleeding	10.3%	18.8%	12.7%
Infection	5.1%	31.3%	12.7%
Hepatic toxicity	64.1%	25.0%	52.7%
Skin	0.0%	12.5%	3.6%
Other	20.5%	18.8%	18.2%
<i>n</i> = (events)	39	17	56

The number and percentage of AEs corresponds to the events reported

with ATG from a different source, alemtuzumab or an alternative calcineurin inhibitor, this strategy results in a response rate up to 50–80% [6, 27]. A detailed analysis of therapies preceding ELT was beyond the scope of our survey; we were therefore unable to discern whether patients benefitted from continuation of IS after insufficient response or retreatment with CYA /– ATG in relapse. Interestingly, a response to previous IS was a predictor of response to ELT only in patients treated with ELT in combination with IS, but not with ELT monotherapy. This might support independent predictive factors for response between IS and ELT, although differences in the number of patients in the two groups provides an alternative explanation. For CYA/ATG, several biological predictors of response, such as absolute reticulocyte count reflecting stem cell reserve or lymphocyte count and presence of a PNH clone reflecting the level of the immune attack have been defined [28, 29]. Such variables were not systematically queried in our survey, but clinical parameters might provide an approximation of these predictors. Age and time from diagnosis to ELT treatment, as proxy for stem cell reserve, were not negatively correlated with response. Similarly, presence of a PNH clone or treatment of relapse following IS, arguing for a predominant autoimmune etiology, did not affect response rates. Finally, severity of AA at ELT start could also not predict response, although it did correlate with death without response in competing risk analysis. It is unlikely, that merely increasing the size of such retrospective cohorts can discern predictors of response. Additional mechanistic studies in pre-clinical models as well as correlative analyses in uniformly treated patients in clinical trials will answer these urgent questions. Compared to the response used in current clinical trials, our more traditional response criteria did not assess trilineage response. Since almost all patients were RBC transfusion dependent, PR or CR to ELT essentially implies an erythroid response and rules out an isolated increase of platelets upon ELT treatment. In our multivariate analysis, combination therapy compared to ELT monotherapy was associated with a better response; this difference was driven mainly by the better response in the ATG combination group. Multivariate analyses can control for some confounding factors; these results must be interpreted cautiously in light of the very different patient characteristics.

Although the use of a second-line therapy such as ELT likely identifies patients with a less than average prognosis, the overall survival in our cohort was favorable. A considerable proportion of patients died due to allo-HSCT-related causes and not from progression of AA. Whereas traditionally AA patients have been treated in allo-HSCT centers, ELT might be also applied nowadays in less-specialized centers not included in our survey and thus introducing bias particularly in this regard. The association between response and survival is inherently biased particularly in retrospective studies. Despite this limitation, response to ELT considered as a

time-dependent variable in the multivariate Cox model was significantly associated with better survival, underscoring the importance of response.

Retrospective analyses likely underreport low-grade AEs, but the large number of patients is useful to detect rare, severe AEs of novel drugs. AEs in our survey were consistent with the favorable safety profile in AA trials and ITP patients, with common hepatic toxicity and a few cases of skin reactions. Although cytogenetic evolution was not systematically assessed in our survey, the low rate of MDS diagnosis (incidence of ~ 1 in 120 years of follow-up) is a reassuring signal, particularly since 6.7% of all patients had a cytogenetic abnormality before ELT treatment.

Additional limitations of our study include those associated with retrospective cohorts such as selection bias, recall bias, incomplete data, and limited follow-up. Conversely, the cohort represents real-world data from different countries across Europe. This is particularly important in a rare disease such as SAA with very different treatment trajectories often underrepresented in clinical trials. Along the same lines, the majority of the patients in our cohort received ELT outside of the EMA/FDA label and our data clearly supports this clinical practice.

Our survey is in line with previous, considerably smaller cohorts of AA patients treated with ELT. Gill et al. [19] reported initially a cohort of ten refractory AA patients from Hong Kong treated with ELT alone or in combination with CYA. The study was recently updated with a longer follow-up and inclusion of additional patients [18]. Interestingly, the response rate of ten patients in the expansion cohort receiving ELT in the first-line setting was 90% compared to 50% in refractory patients. The higher response was not explained by the use of ATG in the first-line patients, as all first-line patients treated with ELT/CYA without ATG responded. We could not confirm the higher response rate in patients treated upfront with ELT.

Similar results were observed in a group of 46, mostly relapsed or refractory patients from France [20]. Transfusion independence was achieved in 36% and 49% in ATG naïve and ATG pretreated patients, respectively. These 46 patients are notably contained in our analysis. In our whole cohort, 47.6% achieved at least a PR and thus transfusion independence. In contrast to the French cohort, there was no difference in time to response in patients with a response in the first-line vs. rescue/relapse setting.

In summary, ELT is already widely used in Europe among EBMT centers mostly as treatment for insufficient response to previous therapies or as relapse treatment. In contrast to the available clinical trial data, ELT is applied mostly in combination with CYA. The response rate was consistent across all treatment situations and was similar across combinations. The results of ongoing clinical trials with ELT in the first-line setting, as well as mechanistic studies investigating synergism between ELT and IS are eagerly awaited.

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Compliance with ethical standards

All procedures performed were in accordance with the ethical standards of the applicable institutional and national research committees, with the 1964 Helsinki declaration and its later amendments as well as comparable ethical standards. All patients provided informed consent to inclusion of their data in the EBMT SAA registry.

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