Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia

Etienne Lengline,[1] Bernard Drenou,[2] Pierre Peterlin,[3] Olivier Tournilhac,[4] Julie Abraham,[5] Ana Berceanu,[6] Brigitte Dupriez,[7] Gaelle Guillerm,[8] Emmanuel Raffoux,[1] Flore Sicre de Fontbrune,[1] Lionel Ades,[1] Marie Balsat,[9] Driss Chaoui,[10] Paul Coppo,[11] Selim Corm,[12] Thierry Leblanc,[1,13] Natacha Maillard,[14] Louis Terriou,[15] Gerard Socié[1,16]* and Regis Peffault de Latour[1]*

[1]Department of Hematology, CRNMR Aplasie Médullaire, Saint-Louis University Hospital – AP-HP, Paris; [2]Department of Hematology, Hôpital Emile Muller - CH de Mulhouse; [3]Department of Hematology, Nantes University Hospital; [4]Service d'Hematologie Clinique et de Therapie Cellulaire, CHU, Universite d'Auvergne, Clermont-Ferrand; [5]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU de Limoges; [6]Department of Hematology, Besançon University Hospital; [7]Department of Hematology, Centre hospitalier de Lens; [8]Department of Hematology and Oncology, CH Augustin Morvan, Brest; [9]Department of Hematology 1G, Centre Hospitalier Lyon Sud, Pierre Benite; [10]Department of Hematology, CH Victor Dupouy, Argenteuil; [11]Department of Hematology, French Reference Center for Thrombotic Microangiopathies, Saint Antoine University Hospital, Paris; [12]Department of Hematology, Hôpital Privé Médipole de Savoie, Challes les Eaux; [13]Department of Pediatric Hematology, Robert-Debré University Hospital, Paris; [14]Bone Marrow Transplant Unit Clinical Hematology, Hopital La Miletrie, Poitiers University Hospital; [15]Department of Internal Medicine, Clinical Immunology, Hôpital Huriez Lille University Hospital and [16]University Paris Denis Diderot & INSERM UMR 1160, France

**GS and RPL contributed equally to this work.*

 doi:10.3324/haematol.2017.176339

Received: July 12, 2017.

Accepted: November 15, 2017.

Pre-published: November 23, 2017.

Correspondence: etienne.lengline@aphp.fr

Supplementary Materials:

1. **Supplementary methods**
2. **Supplementary Table 1**
3. **Copy of the translated survey**

Supplementary methods

French aplastic anemia reference center

The French aplastic anemia reference center (national rare disease network) gives all French physicians the chance to review diagnosis patterns and treatment choices for AA patients, as decided by a board of specialist biologists and hematology physicians convened on a monthly basis.

Procedures:

Flow-FISH telomere length was measured only in the subset of patients (n=7) treated in the national reference center, and was not assessed routinely during follow-up.

In France, paroxysmal nocturnal hemoglobinuria (PNH) clone assessment has been standardized through the efforts of HPNAFC, a group of French flow cytometry experts for PNH. All patients included in our survey were therefore tested by different centers all using the same six-color combination (CD24, CD14, CD33, CD15, CD45, and fluorescent aerolysin). PNH clone size detection was considered positive above 0.1% (test sensitivity in all centers).
Anti-thymocyte globulin was given to hospitalized patients, whereas ELT was administered on an outpatient basis.

Antimicrobial prophylaxis was administered in accordance with local policy. Blood product transfusions were provided in accordance with national guidelines.

Toxicities were graded using the CTCAE V4 scoring system.

Data collection

Case files were forwarded anonymously by local centers to the national reference center. Baseline biological and clinical characteristics, pre- and post-ELT treatment characteristics, as well as transfusion and follow-up data were extracted from the local files to perform this analysis.

Supplementary Table 1: details of all karyotype analysis performed in patients included in this study before and after ELT therapy.

	AT BASELINE				BEFORE ELT THERAPY					AFTER ELT THERAPY						
Cohort	Sex	age	Karyotype analysis	FISH cen(7)	days between analysis and ELT start	Blast cells (%)	Dysplastic changes	Karyotype analysis	FISH cen(7)	Bone marrow after ELT start	days between ELT start and analysis	Blast cells (%)	Dysplastic changes	Karyotype analysis	FISH cen(7)	ELT exposition time (d)
A	M	74	45,X,-Y	NA	140	4	yes	45,X,-Y	NA	no						615
A	F	79	46,XX,inv2(p12;q14)	NA	126	0	no	XX,inv2(p12;q1	NA	no						96
A	F	49	Failure	NA	56	0	no	Normal	NA	no						516
A	F	84	NA	NA	65	0	no	NA	NA	no						407
A	M	73	Normal	NA	493	0	no	Normal	NA	no						200
A	M	26	Normal	normal	1533	1	no	Normal	NA	no						161
A	F	77	Normal	NA	208	0	no	Normal	NA	no						105
A	M	75	Normal	normal	357	0	no	Normal	Normal	no						126
A	F	80	Normal	NA	40	0	no	Normal	NA	no						98
A	F	67	Normal	NA	960	2	yes	Normal	NA	no						225
A	F	68	Normal	NA	633	0	no	Normal	NA	yes	396	1	0	Normal	NA	112
B	M	71	45,X,-Y	NA	95	3	yes	NA	NA	no						132
B	M	74	46,XY,+8	NA	85	0	no	Normal	NA	yes	800	0	0	46,XY,+8	Normal	138
B	M	19	Failure	NA	78	0	no	Failure	NA	no						106
B	F	13	Failure	normal	17	7	no	Normal	Normal	yes	542	0	0	Normal	Normal	178
B	F	40	Failure	normal	59	0	no	Normal	Normal	no						88
B	M	72	Failure	NA	114	0	no	Failure	NA	no						858
B	F	69	Failure	NA	322	0	no	Failure	NA	no						126
B	F	55	NA	NA	0	0	no	Normal	NA	no						392
B	M	54	NA	NA	322	0	no	NA	NA	no						639
B	M	69	NA	NA	0	0	no	NA	NA	no						335
B	M	53	NA	NA	442	0	no	Normal	NA	no						140
B	F	50	NA	NA	20	2	no	Failure	Normal	no						245
B	M	30	NA	NA	170	1	no	Normal	Normal	no						140
B	F	59	NA	NA	43	0	no	Normal	NA	no						112
B	M	34	NA	NA	0	1	no	Failure	NA	no						156
B	F	61	Normal	NA	202	0	no	Normal	NA	no						231
B	M	24	Normal	normal	365	0	no	Normal	Normal	no						365
B	M	31	Normal	NA	74	1	no	Normal	NA	no						115
B	M	68	Normal	NA	200	0	no	Normal	NA	yes	42	0	0	Normal	NA	181
B	M	63	Normal	NA	18	6	yes	45,XY,-7	abnormal	no						541
B	M	69	Normal	NA	0	0	no	Normal	NA	yes	496	1	1	Normal	NA	159
B	F	48	Normal	NA	0	1	no	Normal	NA	yes	91	1	0	Normal	NA	204
B	M	33	Normal	NA	79	0	no	Normal	NA	no						231
B	M	68	Normal	NA	50	0	no	Normal	NA	no						117
B	F	53	Normal	NA	342	3	no	Normal	NA	yes	198	3	0	Normal	NA	198
B	F	63	Normal	NA	14	0	no	45,XX,-7	abnormal	yes	189	0	0	NA	NA	159
B	M	19	Normal	normal	24	0	no	Normal	NA	no						122
B	M	22	Normal	NA	84	1	no	Normal	Normal	yes	930	0	0	Normal	Normal	186
B	F	77	Normal	normal	7	1	no	Normal	Normal	no						1196
B	F	62	Normal	NA	340	0	no	Normal	NA	no						251
B	F	41	Normal	NA	254	2	no	Normal	NA	yes	763	0	0	Normal	NA	800
B	M	69	Normal	NA	160	0	no	Normal	NA	no						295
B	M	71	Normal	NA	737	0	no	Normal	NA	yes	650	0	0	Normal	NA	650
B	F	55	Normal	NA	235	0	no	Normal	NA	yes	62	0	0	Normal	NA	62
B	M	38	Normal	NA						no						545

APLASIE MEDULLAIRE centre de référence

CRF Retrospective study of AA management with TPO agonist in France:

Patient ID (N/P): ❑M /❑F D.O.B.: __/__/__

CENTRE: Ref. Physician: Tel: e-mail:

AA Diagnosis: ❑ Idiopathic, ❑ PNH, ❑ Inherited, ❑ Toxic, ❑ post-hepatitis, ❑ Other:

Diag date (marrow biopsy): _____ CBC *(at diag)*: Neutro: I_I_I_I_I /mm3 Ly: I_I_I_I_I /mm3 Hb:I_I_I_I gr/dL VGM: I_I_I_I μ^3 Reticulo: I_I_I_I G/L Platelets: I_I_I_I G/L

According to CAMITA:

Hepatitis at diag:❑Yes / ❑No / ❑Unknown

Moderate:❑ Severe:❑ Very severe:❑

Fanconi anemia: Not searched: ❑ Done: ❑ normal: ❑ Explain: (test/date/result)

Telomere length: Not done: ❑ Done: ❑ Date: __/__/__ Result:

Donor availability **Familial geno-id:** Yes:❑ / No: ❑ **Unrelated:** Yes:❑ / No **Not searched:** ❑

Explain:

At AA DIAGNOSIS

BM aspiration diag: Date: __/__/__ Cellularity: Dysplasia: Y / N

Karyotype BM diag: Not done: ❑ Done: ❑ Mitoses analysed (no.): I_I_I ; Result:

FISH 7 5 8: Not done: ❑ Done: ❑❑❑ FISH normal: ❑ Abnormal: ❑ Precise:

PNH Clone diag: Not done: ❑ Done: ❑ Date: Size: I_I_I % (Neutro) I_I_I % (Mono)

Liver test diag: Transaminase I_I_IxN Bilirubin: I_I_I xN

BIOLOGICAL PARAMETERS BEFORE Eltrombopag

(Closest to the date of Eltrombopag start)

CBC before ELT: Date: __/__/__ WBC: I_I_I_I_I Neutro: I_I_I_I_I Ly I_I_I_I_I Retic I_I_I_I_I G/L Hb I_I_I gr/dL Pq I_I_I G/L

BM aspiration diag: Date: __/__/__ Cellularity: Dysplasia: Y / N

Karyotype BM diag: Not done: ❑ Done: ❑ Mitoses analysed (no.): I_I_I ; Result:

FISH 7 5 8: Not done: ❑ Done: ❑❑❑ FISH normal: ❑ Abnormal: ❑ Precise:

PNH Clone diag: Not done: ❑ Done: ❑ date: Size: I_I_I % (Neutro) I_I_I % (Mono)

Liver test diag: Transaminase I_I_IxN Bilirubin: I_I_I xN

Transfusions: RBC pack: Nb /month: I_I **Platelets Unit:** Nb /month: I_I

BIOLOGIE AFTER Eltrombopag

(Closest to the Last eltrombopag administration)

CBC before ELT: Date: __/__/__ WBC: I_I_I_I_I Neutro: I_I_I_I_I Ly I_I_I_I_I Retic I_I_I_I_I G/L Hb I_I_I gr/dL Pq I_I_I G/L

BM aspiration diag: date: __/__/__ Cellularity: Dysplasia: Y / N

Karyotype BM diag: Not done: ❑ Done: ❑ Mitoses analysed (no.): I_I_I ; Result:

FISH 7 5 8: Not done: ❑ Done: ❑❑❑ FISH normal: ❑ Abnormal: ❑ Precise:

PNH Clone diag: Not done: ❑ Done: ❑ date: Size: I_I_I % (Neutro) I_I_I % (Mono)

Liver test diag: Transaminase I_I_IxN maximum Bilirubin: I_I_I xN maximum ➔ Date:

Transfusions: RBC pack: Nb /month: I_I **Platelets Unit:** Nb /month: I_I

PREVIOUS TREATMENTS

ATG course #1: Type: Date: Date of evaluation: Result: ❑ CR ❑ PR ❑ Refractory

Concomitant medications: ❑CSA ❑Steroids ❑GCSF ❑Androgen ❑Epo ❑ Others tx:_____

ATG course #2: Type: Date: Date of evaluation: Result: ❑ CR ❑ PR ❑ Refractory

Concomitant medications: ❑CSA ❑Steroids ❑GCSF ❑Androgen ❑Epo ❑ Others tx:_____

ATG course #3: Type: Date: Date of evaluation: Result: ❑ CR ❑ PR ❑ Refractory

Concomitant medications: ❑CSA ❑Steroids ❑GCSF ❑Androgen ❑Epo ❑ Others tx:_____

ATG course #4: Type: Date: Date of evaluation: Result: ❑ CR ❑ PR ❑ Refractory

Concomitant medications: ❑CSA ❑Steroids ❑GCSF ❑Androgen ❑Epo ❑ Others tx:_____

---

* For all dates: dd/mm/yyyy.

Number of ATG courses: I_I_I please indicate: AA: ❑ Primary refractory / ❑ Relapse

START DATE Eltrombopag **(M0)**: __/__/__

ELT Interruption Nb I_I_I / Cumulative no. of days with interrupted ELT I_I_I

END DATE Eltrombopag: __/__/__

Purpose of ELT stop: qToxicity / qFailure / qRobust response (NIH criteria)

Maximal Dosage: ____ mg/d Date of max dosage: __/__/__

Transfusion Dependence **before** ELT: RBC pack: ❑YES/❑NO Platelets Unit: ❑YES/❑NO
Transfusion Dependence **after (or during)** ELT: RBC pack: ❑YES/❑NO Platelets Unit: ❑YES/❑NO

Hematological / transfusion parameters during ELT Treatment:

M1 Date: WBC:I_I_I_I Neutro: I_I_I_I Pt I_I_I_I Retic I_I_I_I G/L Hb I_I_I gr/dL **RBC pack:** nb /mo: I_I **Pt:** Unit /mo: I_I

M3 Date: WBC:I_I_I_I Neutro: I_I_I_I Pt I_I_I_I Retic I_I_I_I G/L Hb I_I_I gr/dL **RBC pack:** nb /mo: I_I **Pt:** Unit /mo: I_I

M6 Date: WBC:I_I_I_I Neutro: I_I_I_I Pt I_I_I_I Retic I_I_I_I G/L Hb I_I_I gr/dL **RBC pack:** nb /mo: I_I **Pt:** Unit /mo: I_I

M12 Date: WBC:I_I_I_I Neutro: I_I_I_I Pt I_I_I_I Retic I_I_I_I G/L Hb I_I_I gr/dL **RBC pack:** nb /mo: I_I **Pt:** Unit /mo: I_I

Last FU Date: WBC:I_I_I_I Neutro: I_I_I_I Pt I_I_I_I Retic I_I_I_I G/L Hb I_I_I gr/dL **RBC pack:** nb /mo: I_I **Pt:** Unit /mo: I_I

Concomitant medications: ❑CSA ❑steroids ❑GCSF ❑Androgen ❑Epo ❑ Others tx:_____

Date(s) of concomitant medications

Adverse event during ELT treatment period:

- **Infection:** ❑YES/❑NO / Grade (CTCAE V4) I_I
- **Liver transaminase elevation:** ❑YES/❑NO / Grade (CTCAE V4) I_I
- **Bleeding:** ❑YES/❑NO / Grade (CTCAE V4) I_I
- **Other toxicity:** ❑YES/❑NO / Grade (CTCAE V4) I_I Explain: _____

BM biopsy after ELT: Not done: ❑ Done: ❑ Date: Cellularity:

BM Fibrosis: ❑YES/❑NO / Grade (CTCAE V4) I_I

Allo-HSCT: ❑YES/❑NO

Date HSCT: ❑Matched sibling / ❑Matched Unrelated 10/10 / ❑Mismatch / ❑Cord blood/ ❑Haplo

Last Follow-up: Status LFU: ❑ Alive ❑ Dead

* For all dates: dd/mm/yyyy.