Long term follow-up of pediatric-onset Evans syndrome: broad immunopathological manifestations and high treatment burden

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Supplemental Table 1. Patient selection and definitions

Inclusion criteria
Evans syndrome (ES) is defined as the simultaneous (less than 1 month) or sequential association of immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA).
Patients are included in the cohort if they are less than 18 years old at first cytopenia diagnosis, regardless of the age at inclusion. Follow-up is calculated from first cytopenia diagnosis.
ITP, AIHA and ES definitions
ITP is defined according to the international working group criteria (Rodeghiero *et al., Blood* 2009).
AIHA is defined as Hb < 110 g/L with a positive direct antiglobulin test (DAT) and at least one of the following hemolysis criteria: reticulocyte count > 120 G/L, free bilirubin > 17 mmol/L, or haptoglobin < 10 mg/dL.
Autoimmune neutropenia (AIN) is defined as peripheral neutropenia < 1 G/L persisting for more than 6 months that is neither infection nor drug driven, regardless of the presence or absence of neutrophil autoantibodies. Patients with AIHA and autoimmune neutropenia (AIN) or with ITP and AIN are not classified as ES in the present analysis; patients with isolated DAT or anti-platelet antibodies, or compensated hemolysis without AIHA were only considered as having ES when cytopenia was present.
Exclusion criteria
Inherited red cell or platelet disease.
Autoimmune cytopenia secondary to human immunodeficiency virus infection.
Chemotherapy before ES.
Bone marrow or organ transplantation before ES.
Known PIDs before ES onset.
Systemic lupus erythematosus known before ES onset.
Patients living outside metropolitan France.
Immune thrombocytopenic purpura and autoimmune hemolytic anemia status
ITP and AIHA status were separately classified as follows: no remission (NR) = platelet count < 30 G/L or Hb < 70 g/L; partial remission (PR) = platelet count 30–100 G/L or Hb 70–110 g/L, with reticulocytes > 120 G/L; complete remission (CR) = platelet count > 100 G/L or Hb ≥ 110 g/L, with reticulocytes ≤ 120 G/L.
Cytopenia flare was defined as change of status from CR or PR to NR, whether the CR or PR has been reached spontaneously or after a first-line treatment.
Immunopathological manifestations
Lymphoproliferation: significant splenomegaly without hemolysis or significant persistent lymphadenopathy (> 1 cm), eventually requiring a biopsy.
Clinical IMs: lymphoproliferation or autoimmune / autoinflammatory organ disease : pulmonary (granulomatous-lymphocytic interstitial lung disease), liver and digestive tract

	problems (lymphoïd enteropathy, coeliac-like disease, inflammatory bowel disease, chronic gastritis, autoimmune or giant cell hepatitis, cirrhosis), neurologic (autoimmune or autoinflammatory or granulomatous or vascular manifestations), endocrinologic (autoimmune thyroiditis, Grave's disease or isolated specific autoantibodies), dermatologic (psoriasis, vitiligo, alopecia, vasculitis) and other autoimmune or autoinflammatory manifestations (ophthalmologic, cardiac, renal or hematological).
	Biological IMs*: hypogammaglobulinemia, systemic lupus erythematosus (SLE) biomarkers, or autoimmune lymphoproliferative syndrome (ALPS) first line biomarkers.
	Hypogammaglobulinemia: Immunoglobulin (Ig)G levels below the mean for the subject's age (at least 2 SD) on two separate samples, associated or not with IgA levels below the mean for the subject's age (at least 2 SD) or with defects in vaccine immunizations.
	SLE biomarkers*: antinuclear antibodies titer > 1/160; anti double-stranded DNA or Smith, hypocomplementemia, and lupus anticoagulant (all in two separate samples).
	ALPS biomarkers*: persistent hypergammaglobulinemia (at least 2 SD over the mean for age), or high counts of circulating TCRαβ CD4- CD8- double negative T lymphocytes.
Severe or recurrent infections	
	Bacteremia, pneumonia, bronchiectasis, recurrent pyogenes infections, severe herpes virus infections, or opportunistic infections.
Second-line treatments	
	All immunomodulatory or immunosuppressive treatments (including splenectomy), except steroids or intravenous immunoglobulins (considered as first-line treatments).
Loss to follow-up	
	A patient is classified "lost to follow-up" if no data are available for more than 2 years and no future appointments are scheduled.

* The biological workup is made at the clinician's discretion, which is annually in most cases.

Supplemental Table 2. Immunopathological and other manifestations

	Number (%)	Median age (years) at onset (min–max)
Clinical IMs		
Lymphoproliferation	71 (47)	7.8 (0–41)
Superficial (palpable) adenopathies	61 (40.4)	8 (0–41)
Deep (abdominal or thoracic) adenopathies	16 (10.6)	10.9 (2.7–19.1)
Splenomegaly	49 (32.5)	7.6 (0–19)
Associated hepatomegaly	17 (11.3)	5.0 (0.3–19)
Pneumological	16 (10.6)	14.3 (4.6–27.7)
Granulomatous–lymphocytic interstitial lung disease	16 (10.6)	14.3 (4.6–27.7)
Gastrointestinal/hepatic	23 (15.2)	13 (0.7–25.9)
Coeliac disease	3 (2)	1 (0.7–14.9)

Autoimmune hepatitis	7 (4.6)	11.3 (1.6–14.7)
Lymphoid enteropathy	5 (3.3)	16.4 (6–25.9)
Chronic gastritis	5 (3.3)	16.5 (6.5–19.4)
Inflammatory bowel disease	2 (1.3)	14.4 (9.8–18.9)
Rosai–Dorfman	1 (0.7)	7.3
Primary sclerosing cholangitis	1 (0.7)	13 (13–13)
Neurological	13 (8.6)	16.3 (7.8–27.9)
Vasculitis	3 (2)	13.1 (12.1–17.8)
Lymphoproliferation	1 (0.7)	7.8
Myelitis	2 (1.3)	26.7 (25.4–27.9)
Infratentorial inflammatory lesions	2 (1.3)	18.2 (11.9–24.6)
Subtentorial inflammatory lesions	7 (4.6)	14.2 (7.8–27.9)
Sensitive ganglionopathy	1 (0.7)	16.3
Endocrinological	5 (3.3)	12.2 (3–41.1)
Type 1 diabetes	2 (1.3)	3.2 (3–3.3)
Grave's hyperthyroidism	2 (1.3)	29.1 (17.1–41.1)
Hashimoto thyroiditis	1 (0.7)	12.2
Dermatological	26 (17.2)	15.5 (0–27.3)
Vitiligo	4 (2.6)	3 (0–15.5)
Chronic urticaria	2 (1.3)	8.2 (0.8–15.6)
Psoriasis	3 (2)	21.1 (15.6–27.3)
Bullous pemphigoid	1 (0.7)	15.5
Eczema	4 (2.6)	10.9 (0–17.2)
Cutaneous lupus erythematosus involvement	8 (5.3)	17.2 (12.1–21.5)
Granuloma	2 (1.3)	7.8 (0–15.6)
Immunoglobulin A vasculitis	2 (1.3)	11.8 (5.7–17.9)
Sjögren's syndrome	1 (0.7)	15.5
Livedo reticularis	1 (0.7)	17.6
Rheumatological	12 (7.9)	15.1 (2.6–41.1)
Monoarthritis	3 (2)	13.7 (2.6–15.4)
Oligoarthritis	2 (1.3)	16.6 (16.3–16.9)
Polyarthritis	5 (3.3)	14.4 (5.9–41.1)
Polyarticular pain without arthritis	3 (2)	15 (13.7–19.3)
Cardiological	4 (2.6)	15.9 (12.7–20.9)
Pericarditis	3 (2)	15.2 (12.7–20.9)
Granulomatous aortitis	1 (0.7)	16.6
Ophthalmological	8 (5.3)	9.6 (6.1–15.6)
Keratitis	4 (2.6)	8.7 (6.1–9.7)
Uveitis	4 (2.6)	12 (7.9–15.6)
Ischemic optic neuropathy	1 (0.7)	12.1

Nephrological	3 (2)	14.2 (10.6–16.4)
Tubulopathy	1 (0.7)	10.6
Granulomatous infiltration	2 (1.3)	15.3 (14.2–16.4)
Hematological, other	2 (1.3)	6.9 (2.9–10.9)
Myelofibrosis	1 (0.7)	10.9
Acquired thrombotic thrombocytopenic purpura	1 (0.7)	2.9
Biological IMs		
Hypogammaglobulinemia	54 (35.8)	10 (2.3–23)
Low IgG before anti-CD20	44 (29.1)	10.5 (2.3–22.4)
Low IgG persisting after anti-CD20	8 (5.3)	9.5 (5–23)
Low IgA	5 (3.3)	11 (6.5–15.8)
Immunoglobulin replacement therapy	24 (15.9)	9.4 (2.3–22.4)
SLE biomarkers	42 (27.8)	10.2 (0.3–19.5)
Antinuclear antibodies	38 (25.2)	9.8 (0.3–19.5)
Anti double-stranded DNA or anti Smith	6 (4)	14.7 (6–19.5)
Hypocomplementemia	10 (6.6)	12.6 (0.3–19.5)
Lupus anticoagulant	6 (4)	10.6 (0.8–16)
ALPS biomarkers	24 (15.9)	8.4 (2.8–26.7)
Hypergammaglobulinemia	14 (9.3)	7.8 (2.8–26.7)
Elevated Fas ligand	5 (3.3)	8 (4–10.8)
Defective Fas-mediated apoptosis	3 (2)	9.6 (4–13.5)
Increase IL-10 and/or vitamin B12	2 (1.3)	13.8 (13.5–14)
Elevated alpha beta double-negative T cells	10 (6.6)	9.2 (5.2–15)
Other manifestations		
Granuloma on pathology, any localization	9 (6)	16.57 (0–26.2)
Lymph node	3 (2)	14.6 (2.7–17.8)
Lung	3 (2)	10.1 (7.4–26.2)
Cutaneous	2 (1.3)	7.8 (0–15.6)
Another organ	4 (2.6)	15.4 (2.7–18)
Malignancies	4 (2.6)	20.5 (16.3–28.8)
Angioimmunoblastic T-cell lymphoma	1 (0.7)	28.8
Juvenile myelomonocytic leukemia	1 (0.7)	20
EBV-negative Hodgkin Lymphoma IVBb	1 (0.7)	16.3
Large granular lymphocytic leukemia	1 (0.7)	21

A given patient may have several manifestations within the same category.

Abbreviations: IMs, immunopathological manifestations; EBV, Epstein–Barr Virus; Ig, immunoglobulin; SLE, systemic lupus erythematosus; ALPS, autoimmune lymphoproliferative syndrome; IL, interleukin.

Supplemental Table 3. Second-line treatments received

Second-line treatment	Number of patients	Percentage of patients	At treatment start (years)	
			Median time after first cytopenia (min–max)	Median age (min–max)
Rituximab	79	52.3	5.6 (0.0–35.5)	14.1 (0.8–47.4)
Azathioprine	55	36.4	3.8 (0.0–27.8)	12.4 (0.5–39.8)
Splenectomy	36	23.8	6.7 (0.1–16.0)	11.1 (1.5–19.8)
Mycophenolate	29	19.2	6.1 (0.1–29.1)	11.5 (2.4–14.7)
Ciclosporin	28	18.5	4.0 (0.2–15.0)	10.8 (0.8–19.8)
Hydroxychloroquine	27	17.9	5.9 (0.0–17.5)	15.8 (5.6–39.8)
Mercaptopurine	12	7.9	4.8 (0.2–11.9)	13.9 (2.8–18.3)
Romiplostim	12	7.9	14.7 (0.5–38.1)	19.4 (5.3–50.0)
Vinblastine	11	7.3	5.5 (0.3–24.3)	13.8 (1.8–36.5)
Cyclophosphamide	10	6.6	3.2 (0.2–18.5)	11.6 (1.8–23.8)
Colchicine	8	5.3	4.3 (0.9–20.9)	15.3 (9.3–30.6)
Sirolimus	8	5.3	6.7 (3.2–11.4)	11.4 (8.0–19.8)
Vincristine	7	4.6	7.9 (0.1–16.6)	12.3 (0.5–20.8)
Eltrombopag	6	4.0	14.7 (6.1–35.4)	22.6 (9.0–47.3)
Abatacept	5	3.3	12.5 (7.5–20.5)	20.0 (9.7–26.5)
Dapsone	4	2.6	6.7 (1.6–11.2)	11.9 (4.3–19.0)
Anti-D immunoglobulin	3	2.0	0.2 (0.0–7.1)	2.9 (2.4–14.7)
Allogenic hematopoietic stem-cell transplantation	3	2.0	8.7 (1.2–14.2)	11.5 (2.5–18.2)
Danazol	2	1.3	6.7 (2.9–10.5)	12.7 (5.7–19.7)
Everolimus	1	0.7	11.7	14.3

For treatment start assessments only, each separate course has been included for a given patient.

Supplemental Table 4. Severe or recurrent infections

Infection type	Number (%)	Infection type	Number (%)
Herpes zoster	17 (11.3)	Oral or genital herpes simplex infection	4 (2.6)
Sinusitis/otitis media	15 (9.9)	Aphthous stomatitis	4 (2.6)
Pneumopathy	12 (8.0)	Cellulitis	3 (2.0)
Bronchopathy	11 (7.3)	Nontuberculous mycobacteria	2 (1.3)
Bacteremia*	8 (5.3)	Meningitis***	2 (1.3)
Impetigo/furuncle/cutaneous abscesses	7 (4.6)	Chronic blood EBV replication	2 (1.3)
Other	7 (4.6)	Cutaneous warts	2 (1.3)
Gastrointestinal infections**	5 (3.1)	Molluscum contagiosum	2 (1.3)

Other (once each): cerebral toxoplasmosis, pityriasis versicolor, oral abscess, anogenital warts, bacterial arthritis, CMV disseminated infection, parotitis.

* Microorganisms identified: *Staphylococcus aureus, Pasteurella, Streptococcus pneumococcus, Pseudomonas aeruginosa*

** Microorganisms identified: *Campylobacter, Salmonella*

*** Microorganisms identified: *HSV, Streptococcus pneumococcus*

The onset times of recurrent infections could not be determined. Therefore, age data were not collected.

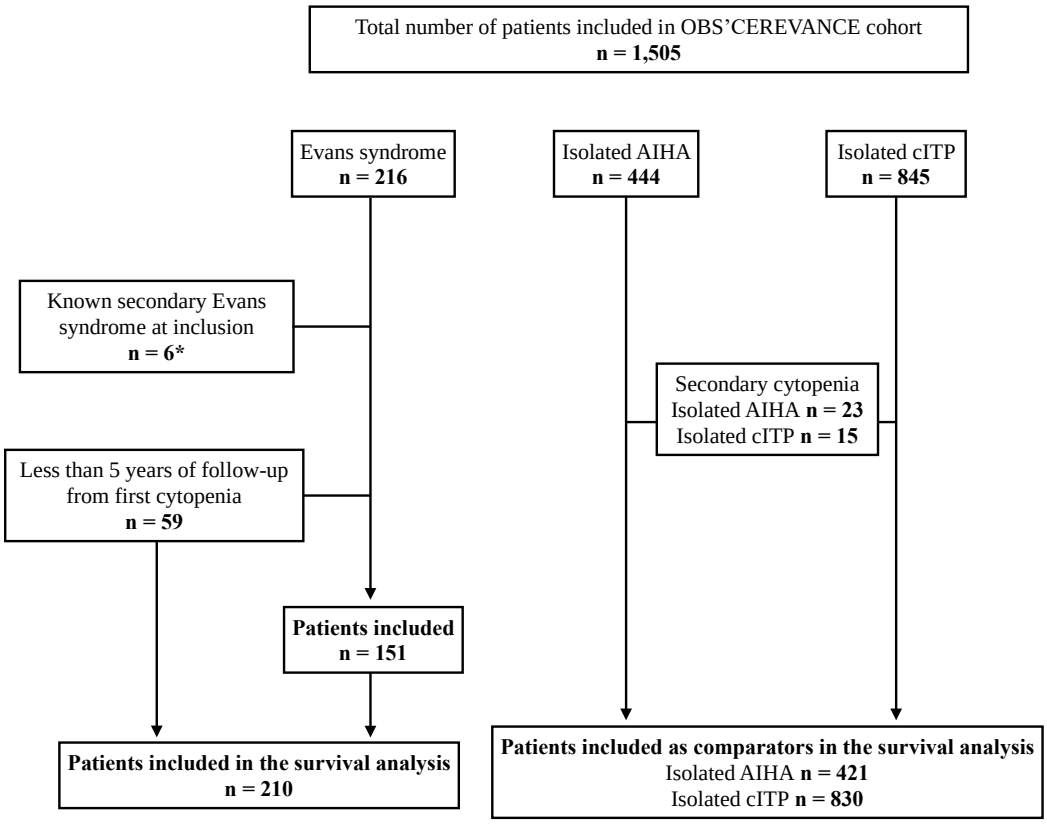
Abbreviations: HSV, herpes simplex virus; EBV, Epstein–Barr virus; CMV, cytomegalovirus.

Supplemental Table 5. Characteristics of patients who died

Sex	Year of death	Delay after first cytopenia (years)	Age at death (years)	IM	Second-line treatments		Cause of death
					Nb	Sequence	
M	2006	0.1	1.7	No	1	VBL	Cerebral hemorrhage
F	2002	1.8	3.8	Yes	7	CsA, RTX, SPX, AZT, VCR, CPX, HSCT	Sepsis
F	2018	0.9	3.9	Yes	1	CD20	Fulminant hepatitis
M	2001	1.6	5.0	Yes	3	CsA, AZT, CD20	Sepsis
M	1996	3.0	8.3	Yes	4	AZA, VCR, DAP, SPX	Cerebral hemorrhage
F	2017	5.2	10.7	Yes	1	AZT	HLH and cerebral vasculitis
M	2001	1.3	11.6	Yes	2	CD20, CsA	Pancreatitis
M	2010	10.3	11.9	Yes	3	CsA, AZT, CD20	Gastrointestinal hemorrhage
M	1995	8.1	12.7	Yes	3	CsA, SPX, VBL	Cerebral hemorrhage
M	1995	8.8	15.5	Yes	2	SPX, CsA	Sepsis
F	2007	12.9	17.8	Yes	1	CD20	Sepsis
M	2010	16.4	18.2	Yes	4	AZT, SPX, MMF, CD20	Sepsis
F	2014	8.9	18.4	Yes	4	AZT, CD20, CsA, 6MP	EBV-related lymphoproliferation
F	2002	14.6	18.5	Yes	7	SPX, CPX, HCQ, AZT, CD20, CsA, HSCT	Post-HSCT CMV infection
F	2016	12.4	19.3	Yes	4	CD20, AZT, CPX, MMF	Fulminant pneumococcal infection
F	2017	6.0	19.4	Yes	0		Unknown
M	2013	15.1	20.0	Yes	3	CD20, SPX, 6MP	JMML
F	2013	5.1	21.1	Yes	4	CD20, HCQ, SPX, CPX	Vasculitis, SLE
F	2012	12.9	24.5	Yes	3	SPX, CD20, AZT	Probably sepsis
M	2011	24.2	28.1	Yes	5	SPX, CsA, AZT, HCQ, MMF	Sepsis
M	2017	24.3	28.9	Yes	1	DAP	Probably sepsis
M	2015	18.3	31.5	Yes	6	MMF, CsA, HCQ, CD20, SPX, TPO-RA	Probably sepsis

Patients are ordered by age at death. Among the 22 patients with available data, 16 were being followed by pediatric teams, and six patients (aged 20–31.5 years) were being followed by adult teams.

Abbreviations: IM, immunopathological manifestation; Nb, number; DAP, dapsone; AZT, azathioprine; CD20, rituximab; CPX, cyclophosphamide; MMF, mycophenolate; CsA, ciclosporine; HCQ, hydroxychloroquine; TPO-RA, thrombopoietin receptor agonist; VBL, vinblastine; SLE, systemic erythematosus lupus; SPX, splenectomy; HSCT, hematopoietic stem-cell transplantation; HLH, hemophagocytic lymphohistiocytosis; EBV, Epstein–Barr virus; CMV, cytomegalovirus. JMML: Juvenile myelomonocytic leukemia

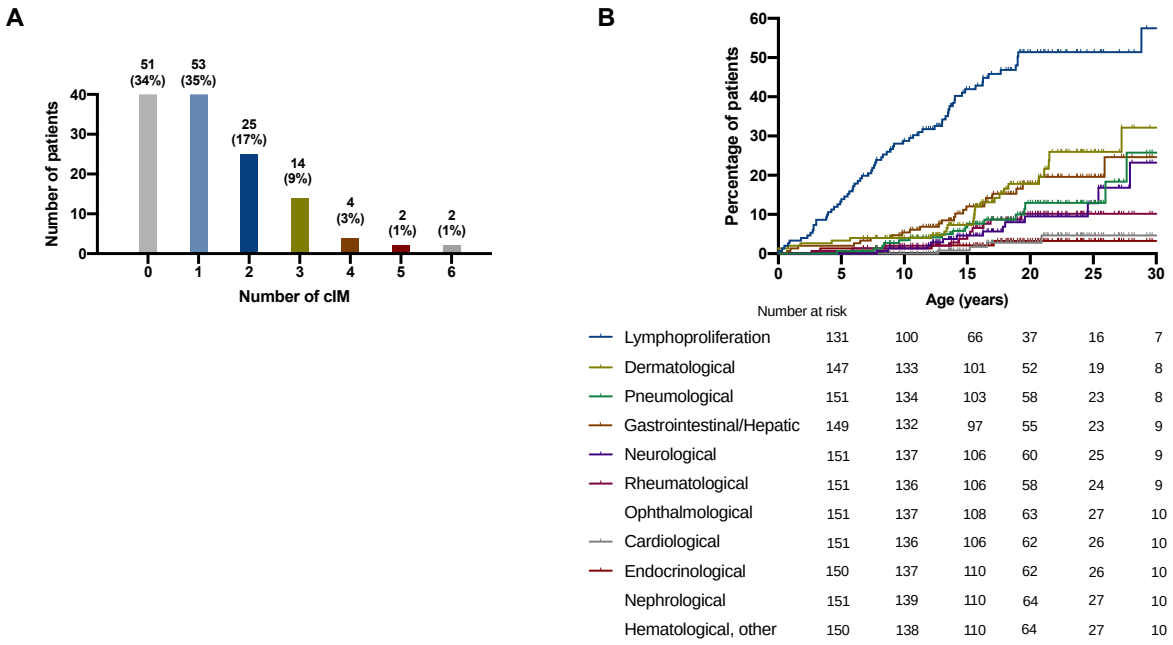


*post allogeneic hematopoietic stem cell transplantation (n = 3), autoimmune lymphoproliferative syndrome (n = 2), 22q11 microdeletion (n = 1).

Supplemental Figure 1. Selection of patients within the OBS'CEREVANCE database

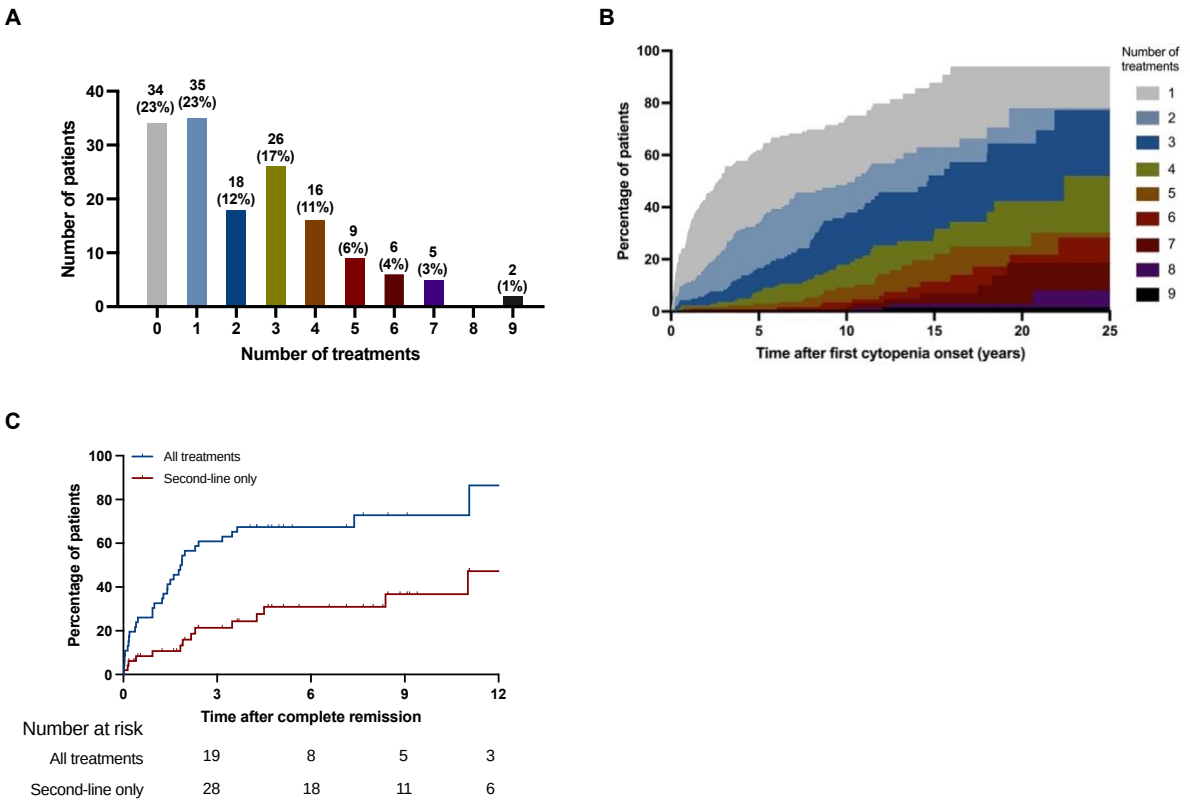
The numbers shown are those recorded on the day of data extraction (21 June 2019). Among the 151 patients with Evans syndrome with more than 5 years of follow-up, 115 were alive and actively followed by a pediatric hematologist (*n* = 73), an adult internist (*n* = 37), an adult hematologist (*n* = 4), or an adult gastroenterologist (*n* = 1).

Abbreviations: AIHA, autoimmune hemolytic anemia; cITP, chronic immune thrombocytopenic purpura.



Supplemental Figure 2. Clinical immunopathological manifestations (cIMs)

(A) Number of cIMs across the cohort. (B) Cumulative incidence of each cIM and numbers at risk.



Supplemental Figure 3. Second-line treatments

(A) Number and percentage of second-line treatments in the 151 patients with Evans syndrome (ES). Among these patients, 34 (23%) had none, 35 (23%) had one, and 82 (54%) had two or more second-line treatments. The median number of treatments received (2 [0–9]) was higher for ES than for cITP (1 [0–14]; $p < 0.0001$) but not AIHA (2 [0–7]; $p = 0.7$) alone. (B) Cumulative number of second-line treatments after first cytopenia onset. Half of the patients had received at least one, two, and three different treatments at 2.7, 10.5, and 14.7 years after first cytopenia diagnosis, respectively. (C) Cumulative incidence of treatments received after complete hematological remission, including the 61 patients with > 1 year of follow-up after complete remission from cytopenia. Second-line treatments are shown in red. All treatments (i.e., second-line, steroid, and therapeutic intravenous immunoglobulin treatments) are shown in blue.

Appendix

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