



XLIX
CONGRESSO
NAZIONALE
AIEOP

Emofilia e ITP

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Bologna, 02/10/2024



La sottoscritta Paola Giordano

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

- ☐ *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*
- ☒ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*
- Roche
 - Sobi



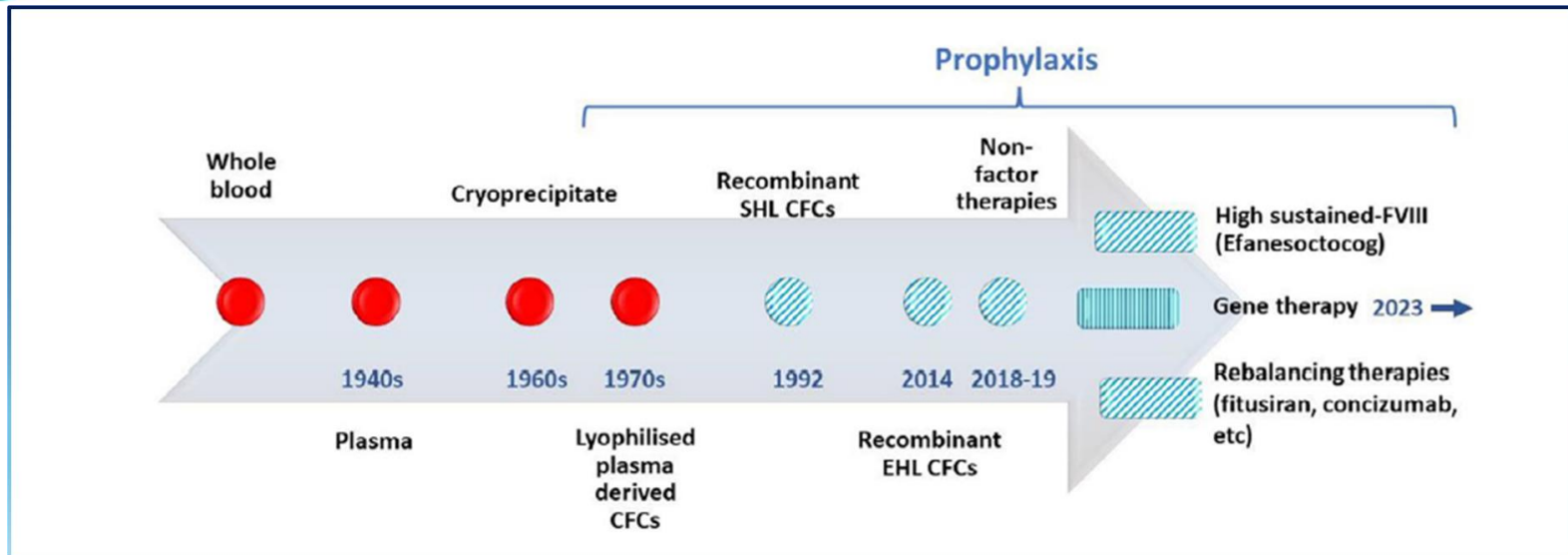
EMOFILIA A E B

L'emofilia è una malattia rara, congenita ed ereditaria X-linked, caratterizzata da un deficit del fattore VIII (FVIII) della coagulazione, nel caso dell'emofilia A, o del fattore IX (FIX), nel caso dell'emofilia B

Il deficit di fattore dipende da mutazioni nei geni *F8* o *F9*, che codificano rispettivamente per il FVIII ed il FIX

La prevalenza stimata alla nascita è di 24.6 casi su 100 000 maschi per tutti i gradi di severità dell'emofilia A (9.5 casi per la forma severa) e di 5.0 casi su 100 000 maschi per tutti i gradi di severità dell'emofilia B (1.5 casi per la forma severa)

Si stima che l'emofilia A rappresenti l'80%-85% di tutti i casi di emofilia mentre si stima che l'emofilia B rappresenti il 15-20% di tutti i casi di emofilia





DOI: 10.1111/hae.14046

Check for updates

SUPPLEMENT ARTICLE

Haemophilia  WILEY

WFH Guidelines for the Management of Hemophilia, 3rd edition

Alok Srivastava¹ | Elena Santagostino² | Alison Dougall³ | Steve Kitchen⁴ | Megan Sutherland⁵ | Steven W. Pipe⁶ | Manuel Carcao⁷ | Johnny Mahlangu⁸ | Margaret V. Ragni⁹ | Jerzy Windyga¹⁰ | Adolfo Llinás¹¹ | Nicholas J. Goddard¹² | Richa Mohan¹³ | Pradeep M. Poonnoose¹⁴ | Brian M. Feldman¹⁵ | Sandra Zelman Lewis¹⁶ | H. Marijke van den Berg¹⁷ | Glenn F. Pierce¹⁸ | on behalf of the WFH Guidelines for the Management of Hemophilia panelists and co-authors*

Haemophilia. 2020 Aug;26 Suppl 6:1-158. doi: 10.1111/hae.14046.

Prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability. Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical and social activities (at home, school, work, and in the community), similar to the non-hemophilic population.



In passato il livello minimo efficace (trough level) del fattore sostitutivo ritenuto adeguato in profilassi era dell'1%

Successivamente si è ritenuto più opportuno elevare il livello a valori ~3-5% con i concentrati ad emivita prolungata utili a preservare le articolazioni...

Meglio sarebbe adattare il regime terapeutico caso per caso sulla base delle esigenze personali

(Raccomandazione 3 delle linee guida WFH)
Haematologica. 2020 Aug;105(8):2038-2043



Table 1 Definitions of continuous prophylaxis (see reference [1])

	No. large joint bleeds*	Age to start (year)	Clinical arthropathy, osteochondral disease
Primary	≤1	≤3	absent
Secondary	≥2	any	absent
Tertiary	≥2	any	present

All refer to continuous prophylaxis intended for 52 weeks per year, and taken for at least 45 weeks of the year under consideration

*large joints = knees, ankles, elbows, hips, shoulders

Table 2 Primary prophylaxis regimens

	Dosing
High/full-dose (Malmö/Swedish) [2]	25–40 IU kg ⁻¹ 3 times a week or every other days starting at age 1–2 years, irrespective of bleeding history
Intermediate-dose (Dutch) [8]	15–25 IU kg ⁻¹ 2–3 times per week, usually started after ≥1 hemarthrosis
Escalating-dose (Canadian) [9]	50 IU kg ⁻¹ once a week, with dose increased to 30 IU kg ⁻¹ twice a week, then 25 IU kg ⁻¹ every other day, in response to bleeding frequency

The objective of prophylaxis has been to convert a person with severe hemophilia (baseline FVIII/FIX level <1 IU/dL [1%]) to a bleeding phenotype typical of moderate or mild hemophilia by maintaining factor levels above 1 IU/dL (1%) at all times.

However, there has been increasing recognition and evidence that factor trough levels of 1-3 IU/dL (1%-3%) are insufficient to totally prevent bleeds in all people with hemophilia and allow occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan.

When baseline FVIII:C levels are above 15 IU/dL (15%), spontaneous bleeding is uncommon



TECNICHE DI PRODUZIONE DEI CONCENTRATI RICOMBINANTI AD EMIVITA PROLUNGATA

➤ Fusione col frammento Fc dell'IgG1

Blood. 2012;119(13):3024-3030

➤ Fusione con l'albumina

Thromb Res 2013;131 (Suppl. 2):s2-s6

➤ Coniugazione chimica con polyethylene glycol (PEG)

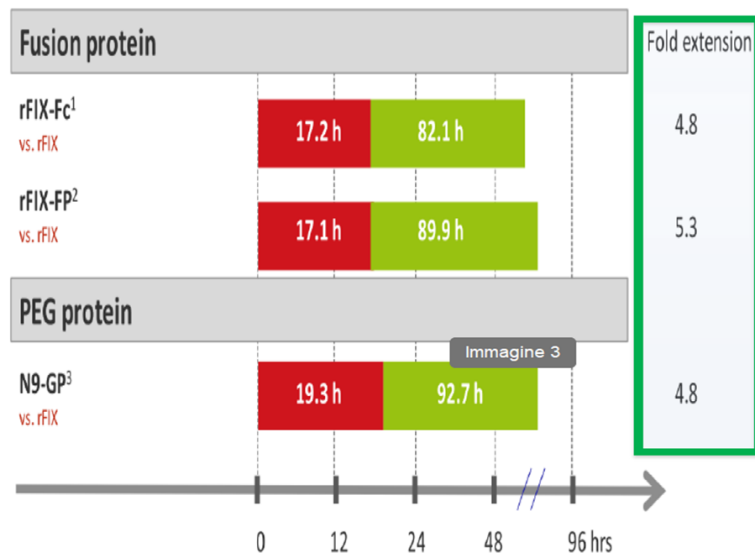
Expert Opin Emerg Drugs. 2015;20(4):531-536.

Proteine ad emivita prolungata

La pegilazione lega la molecola ai recettori di clearance prolungando l'emivita



EHL FVIII AND FIX PRODUCTS: HALF-LIFE EXTENSION





CONCENTRATI DI FVIII RICOMBINANTE AD EMIVITA PROLUNGATA

FVIII	Anno di licenza	linea cellulare/molecola	Emivita plasmatica (ore)	Emivita prolungata (incremento)
Efmoroctocog alfa Fc-fusion Per tutte le età	2014	HEK/Dominio B eliminato	19	1.5-1.7 volte
Rurioctocog alfa pegol Età ≥12 anni	2015	CHO/lunghezza integra	14.3	1.3-1.5 volte
Damoctocog alfa pegol Età ≥12 anni	2018	BHK/lunghezza integra	19	1.6 volte
Turoctocog alfa pegol Età ≥12 anni	2019	CHO/Dominio B troncato	18.4	1.6 volte



IL POLIPEPTIDE XTEN

XTEN è un polipeptide “non strutturato”, ingegnerizzato (caratterizzato dall’assenza di aminoacidi idrofobi), che al contrario della PEGilazione conferisce alla molecola con cui si lega una maggiore riduzione della clearance, una bio-degradabilità e una minore immunogenicità, facile produzione...



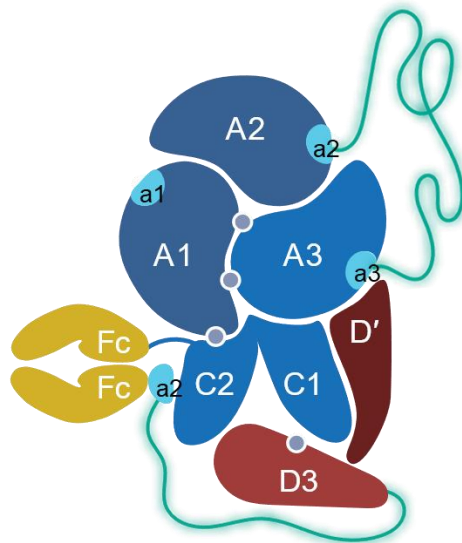
Efanesoctocog alfa

rF.VIII -FvW-XTEN



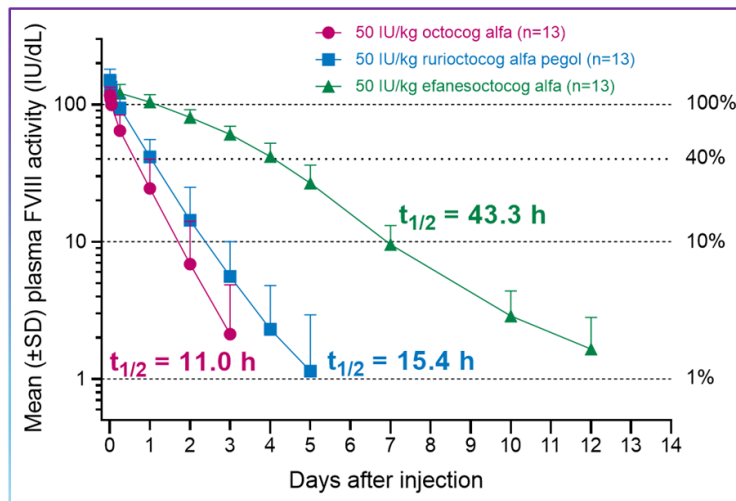
Efanesoctocog alfa

rFVIIIFC – FVW-XTEN



In a Phase 1 sequential PK study, efanesoctocog alfa had a 3–4-fold longer half-life than standard half-life and extended half-life rFVIII product comparators³

Single-Dose Efanesoctocog Alfa Resulted in a 3–4-Fold Longer Half-Life than the Other FVIII Products



PK parameters ^a	Efanesoctocog alfa versus:	Fold increase	90% CI
$t_{1/2}$ hours	Octocog alfa (SHL) Rurioctocog alfa pegol (EHL)	3.9 2.8	3.5 to 4.5 2.5 to 3.2
AUC_{inf} IU × h/dL	Octocog alfa (SHL) Rurioctocog alfa pegol (EHL)	6.0 3.6	5.3 to 6.8 3.2 to 4.1

Baseline-corrected FVIII activity was determined by the 1-stage aPTT-based clotting assay

aPTT, activated partial thromboplastin time; AUC_{inf} , area under the activity time curve extrapolated to infinity; CI, confidence interval; EHL, extended half-life; FVIII, factor VIII; h, hour; PK, pharmacokinetic;

SD, standard deviation; SHL, standard half-life; $t_{1/2}$, elimination half-life.

^aPK sampling was performed over a period of 3, 5, and 14 days after the administration of octocog alfa, rurioctocog alfa pegol, and efanesoctocog alfa, respectively. Lissitchkov T, et al. *Res Pract Thromb Haemost*. 2023;7(4):100176.



XTEND-1 phase 3 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A

Annette von Drygalski, M.D., Pharm.D., R.M.S.K., Pratima Chowdary, M.D.,
Roshni Kulkarni, M.D., Sophie Susen, M.D., Ph.D., Barbara A. Konkle, M.D.,
Johannes Oldenburg, M.D., Davide Matino, M.D., Robert Klamroth, M.D., Ph.D.,
Angela C. Weyand, M.D., Victor Jimenez-Yuste, M.D., Ph.D., Keiji Nogami, M.D.,
Stacey Poloskey, M.D., Bent Winding, M.D., Annemieke Willemze, M.D., Ph.D.,
and Karin Knobe, M.D., Ph.D., for the XTEND-1 Trial Group*

N Engl J Med 2023; 388:310-318

A **Phase 3** open-label, multicenter study of the safety, efficacy, and PK of efanesoctocog alfa in previously treated adult and adolescent (≥ 12 years of age) patients with severe hemophilia A



RISULTATI ESSENZIALI

I risultati della fase 3 dello studio XTEND-1 hanno dimostrato che la profilassi con efanesoctocog alfa una volta la settimana è stata ben tollerata e superiore rispetto alla profilassi precedente nel proteggere dai sanguinamenti con un miglioramento della stato articolare



La profilassi con efanesoctocog alfa ha dimostrato una elevata attività dei livelli di FVIII normali o prossimi alla normalità (>40%) nella maggior parte della settimana, con una media di 15% dopo 7 giorni post-dose.



La profilassi con efanesoctocog alfa una volta la settimana ha dimostrato superiorità nella protezione dell'emorragie se comparato con la profilassi adottata precedentemente.



I pazienti in profilassi con efanesoctocog alfa hanno dimostrato un miglioramento clinicamente rilevante delle articolazioni, della salute fisica e del dolore.



Gli eventi avversi non sono stati differenti da quelli riscontrati comunemente nei soggetti adulti/adolescenti con emofilia A grave



XTEND-Kids: Open-Label, Multicentre, Phase 3 Study of Efanesoctocog Alfa in Previously Treated Children (<12 Years of Age)

Criteri di elegibilità



- bambini (<12 anni) con emofilia A grave (FVIII < 1 IU/dL)
- Trattamento precedente con FVIII ricombinante e/o plasma-derivato, o crioprecipitato
 - ≥ 150 Eds pts di 6 / < 12 anni
 - ≥ 50 EDs pts < 6 anni

Screening

Profilassi una volta la settimana con Efanesoctocog alfa 50 IU/kg IV (N=74)

Week -8

Baseline

Week 52

End point primario



Sviluppo dell'inibitore

Endpoint secondari



ABR per tipo e sede



Gestione perioperatoria



PK



Trattamento dei sanguinamenti



Sicurezza e tollerabilità

ABR, annualized bleed rate; ED, exposure days; FVIII, factor VIII; IV, intravenous; pts, patients.

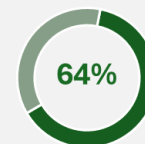
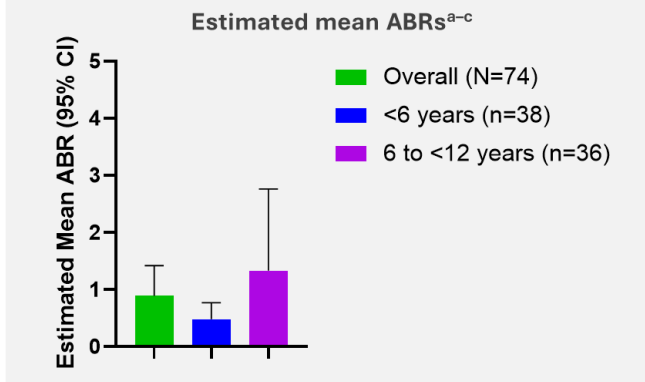
^aOr a documented genotype known to produce severe haemophilia A. ^bDefined as an inhibitor result of ≥ 0.6 BU/mL and confirmed by a second test result from a separate sample drawn 2–4 weeks following the date of the original sample.

Malec L, et al. Oral presentation LB 01.1, ISTH 2023.

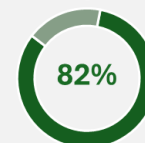


Efanesoctocog Alfa Prophylaxis Demonstrated Effective Protection Against Bleeds

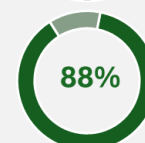
Overall (N=74)	
Median ABR (IQR)	0.00 (0.00–1.02)
Estimated mean ABR (95% CI) ^{a,b}	0.89 (0.56–1.42)



of patients **had zero bleeding episodes** (47/74)^a



of patients **had zero joint bleeds** (61/74)^a



of patients **had zero spontaneous bleeds** (65/74)^a

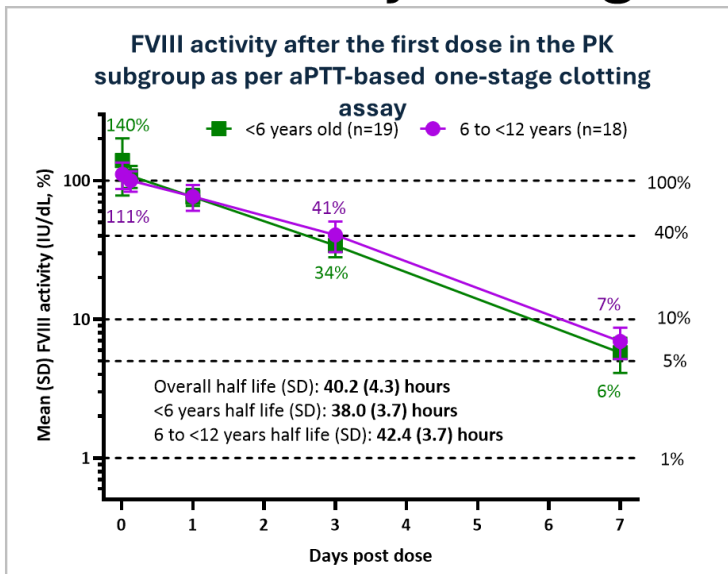
ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range; PK, pharmacokinetic.

^aBased on treated bleeds. ^bEstimated using a negative binomial model with the total number of treated bleeds during the efficacy period as the response variable and log-transformed efficacy period duration in years as an offset variable. The efficacy period reflects the sum of all intervals of time during which patients are treated with efanesoctocog alfa, excluding periods of PK evaluation, surgery/rehabilitation (minor and major), and large injection intervals >28 days. ^cOverall ABR: 0.89; <6 years: 0.48; 6 to <12 years: 1.33.

Malec L, et al. Oral presentation LB 01.1, ISTH 2023.



The Efanesoctocog Alfa PK Profile Allows for Once-Weekly Dosing in Children



Mean (SD) values after the first dose, PK subgroup ^{a,b}	<6 years (n=19)	6 to <12 years (n=18)
$t_{1/2}$, hours	38.0 (3.72)	42.4 (3.70)
CL, mL/h/kg	0.742 (0.121)	0.681 (0.139)
IR, IU/dL per IU/kg	2.81 (1.10)	2.24 (0.437)
C_{max} , IU/dL	143 (57.8)	113 (22.7)

Mean FVIII levels remained above the following levels post-dose at Week 26 (steady state):^c

- >40 IU/dL for ~3 days
- >15 IU/dL for ~5 days
- >10 IU/dL for ~7 days

aPTT, activated partial thromboplastin time; CL, clearance; C_{max} , peak serum concentration; FVIII, factor VIII; IR, incremental recovery; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life.

^aThe PK subgroup included at least the first 12 participants enrolled in each of the two age groups wherein samples were collected at baseline, after the first dose, and up to 7 days post-dose.

^bAs measured by aPTT-based one-stage clotting assay. ^cData from a population PK model.

Malec L, et al. Oral presentation LB 01.1, ISTH 2023.



CONCLUSIONI (X-tend-Kids study)

Nessun sviluppo di inibitore anti-FVIII e anti-farmaco

La profilassi con efanesoctocog alfa ha garantito un efficace livello di FVIII >40 IU/dL per ~3 days.

La profilassi con efanesoctocog alfa una volta la settimana ha dimostrato efficacia nel prevenire e trattare gli eventi emorragici

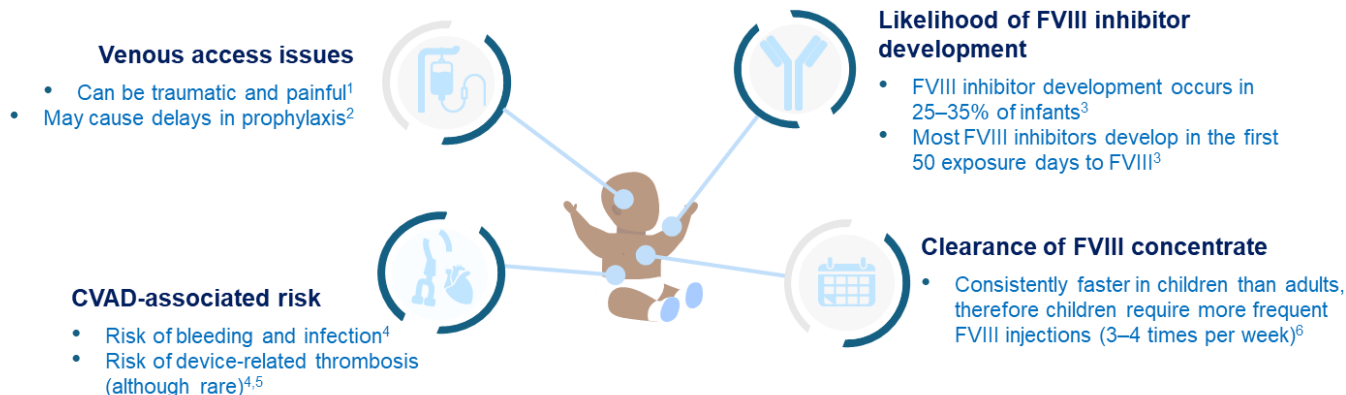
Gli eventi avversi non erano diversi da quelli comunemente riscontrati all'inizio del trattamento nei bambini con emofilia A

Nella fase 3 dell'XTEND-Kids study, 50 IU/kg di efanesoctocog alfa in profiassi una volta la settimana è stato ben tollerato e ha garantito una elevata efficacia nel proteggere dai sanguinamenti e nel trattamento in bambini di età <12 anni con emofilia A grave, con risultati sovrapponibili a quelli ottenuti nello studio XTEND-1 negli adulti/adolescenti



PROFILASSI IN EMOFILIA A

Challenges and complications of FVIII prophylaxis in infants with HA



Prophylaxis with FVIII replacement in infants is challenging due to the high treatment burden associated with frequent intravenous infusions and the risk of inhibitor development⁷

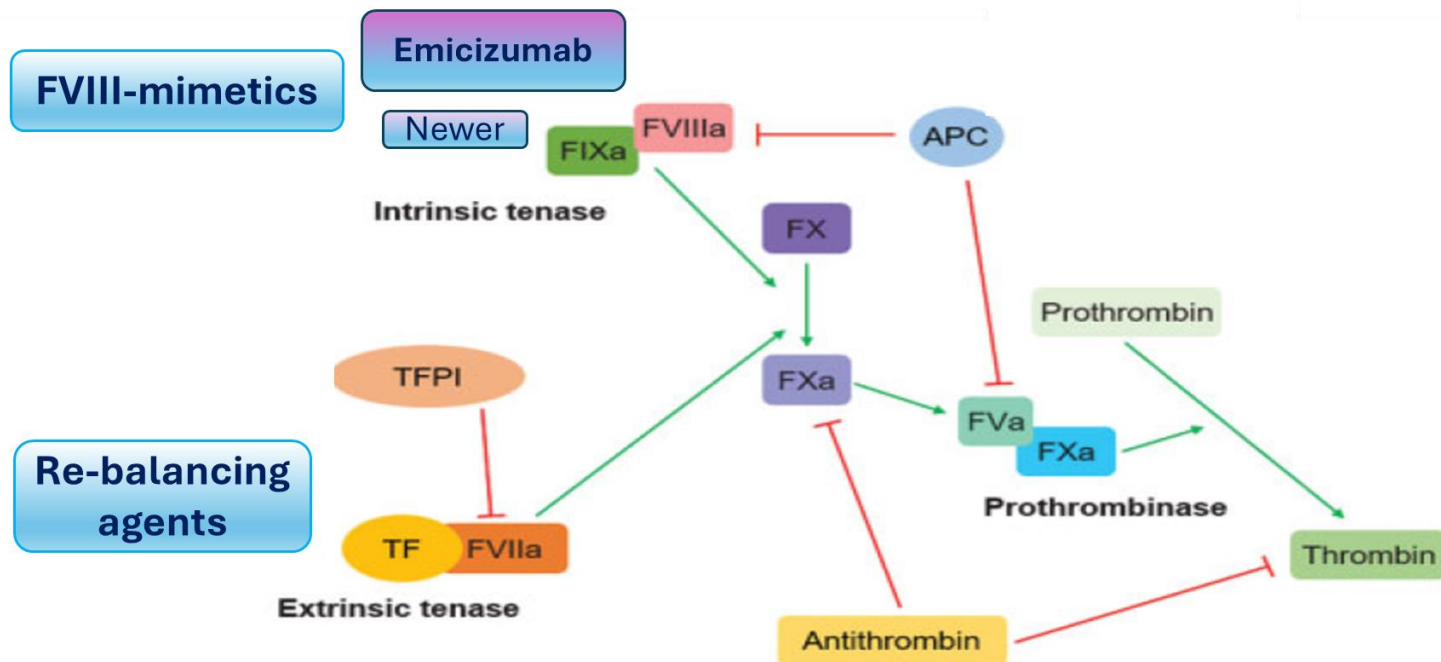


Nonfactor Therapies: New Approaches to Prophylactic Treatment of Haemophilia

Pratima Chowdary¹

Hamostaseologie 2021;41:247–256.

NON-REPLACEMENT



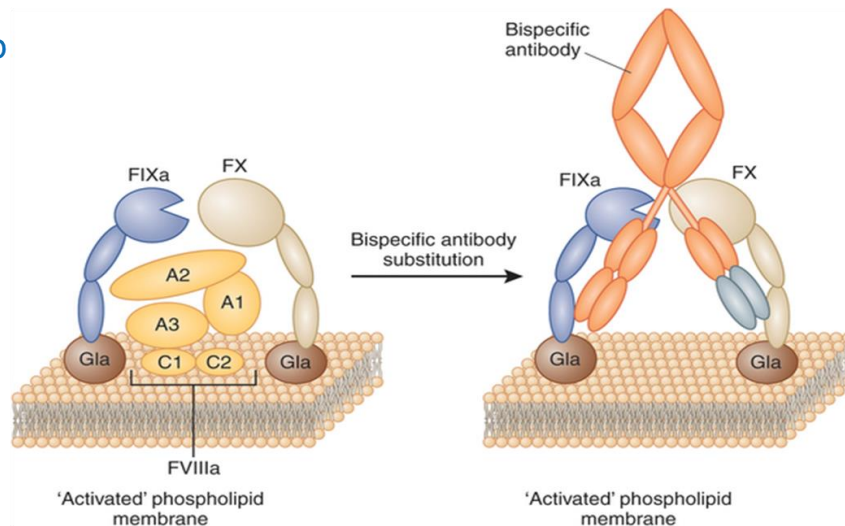


Emicizumab (HA with/without inhibitors)

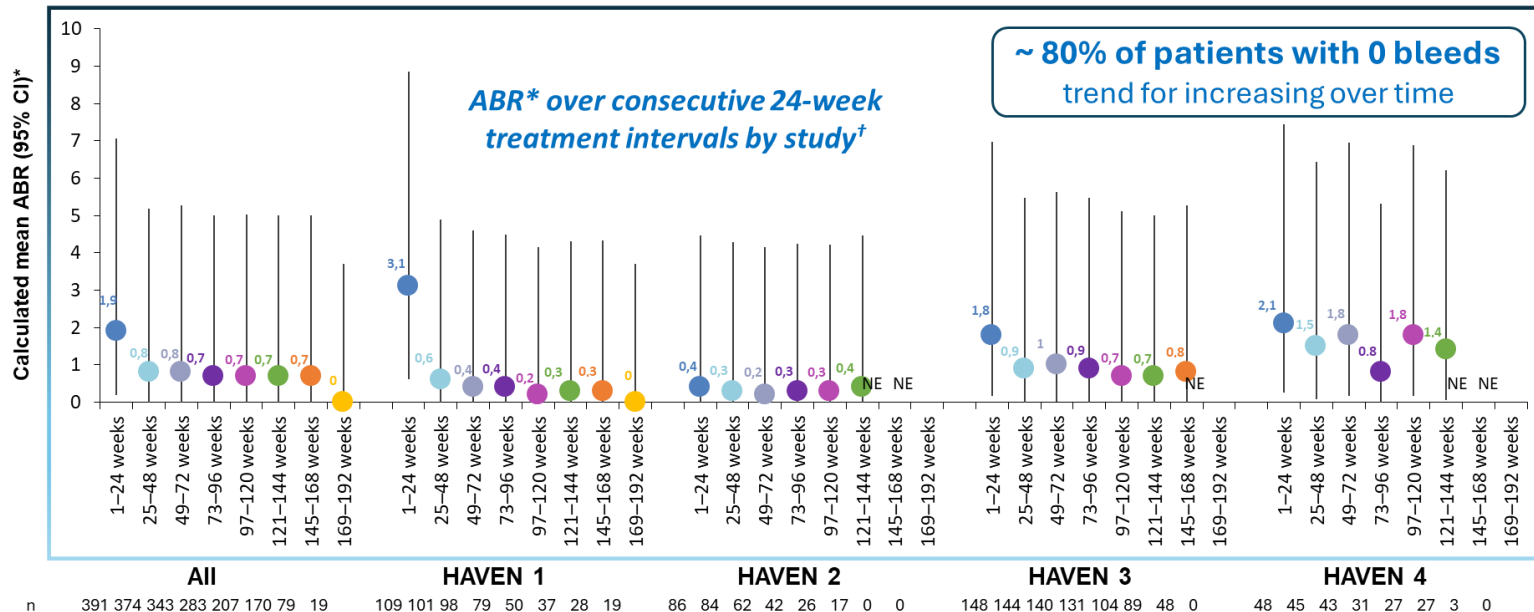
- Primo farmaco s.c. nel trattamento dell'emofilia
- Lunga emivita (4-5 settimane)
- Dose di carico (1,5 mg/Kg wk x 4 wks)
- Mantenimento ogni 1 (1,5 mg/Kg), 2 (3 mg/Kg), o 4 (6 mg/Kg) settimane
- Non variazioni in base ad età e comorbilità

Anticorpo umanizzato bispecifico disegnato per mimare l'azione del FVIIIa legando FIXa e FX

Non neutralizzato dagli inibitori anti-FVIII



HAVEN 1-4: mean ABR consistent and reduced over time



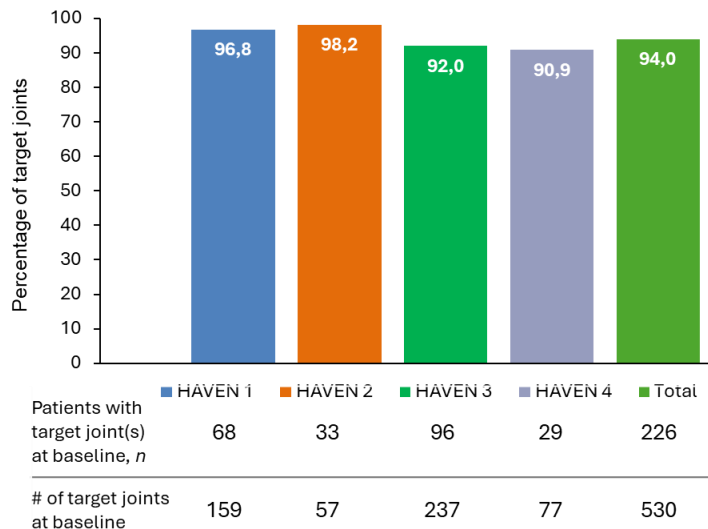
- There was a trend for decreasing ABR in each study over time¹
- With longer follow-up, the adult inhibitor/non-inhibitor ABRs decreased to be closer to the rates of paediatric patients, who tend to have lower ABR due to less damaged joints¹

*Based on the calculated annualised bleed rate for bleeds treated with coagulation factors. [†]Only data for time intervals with ≥10 participants are reported.
ABR, annualised bleed rate; CI, confidence interval; NE, not estimable



HAVEN 1–4: target joint resolution

Target joints with zero spontaneous or traumatic bleeds



- ≤2 spontaneous bleeds in 524 of 530 (98.9%) baseline target joints

Callaghan et al, Blood 2021

*Target joints were defined as major joints (e.g. hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeding events occurred over a 24-week period.

Meaningful **improvement of HRQoL** in up to 65% of patients, by week 13 of treatment and maintained throughout the follow-up (*Haem-A-QoL, physical health and total scores*)

Proportion of patients in HAVEN 3 and 4 with **0 missed school/work days** (previous 4 wks) increased to >90%

Skinner et al, Haemophilia 2021

Increasing proportion of patients over time with **no joint pain or reduced frequency of pain**, in all age groups (HRQoL questionnaires, pain-related domains)

Hermans et al, EAHAD 2023



HAVEN 1–4: safety

	Total (N = 399)*
Total number of participants with ≥ 1 AE, n (%)	381 (95.5)
Total number of patients, n (%)	
AE with fatal outcome	1 (0.3)
Serious AE	93 (23.3)
AE leading to withdrawal from treatment	5 (1.3)
Grade ≥ 3 AE	87 (21.8)
Local injection-site reaction [†]	111 (27.8)
Adverse events of special interest	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	1 (0.3) [‡]
TMA event related to concomitant aPCC and emicizumab	3 (0.8)
TE related to concomitant aPCC and emicizumab	2 (0.5)
Other TE	2 (0.5)

*The safety population only included those patients who received emicizumab. One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analyses. [†]All ISRs, regardless of relatedness to treatment. The majority of ISRs (104/111; 93.7%) were mild in severity. [‡]Assessed using the Sampson Criteria and including all participants that experienced indicative symptoms. One participant experienced symptoms of abdominal pain and cough that were identified as a potential systemic hypersensitivity/anaphylactic/anaphylactoid reaction using the protocol-defined search criteria; however, medical review of the case confirmed that this was not indicative of a systemic hypersensitivity, anaphylactic or anaphylactoid reaction.
ADA, antidrug antibody; AE, adverse event; aPCC, activated prothrombin complex concentrate; ISR, injection-site reaction;
SAE, serious adverse event; TE, thromboembolic event; TMA, thrombotic microangiopathy

- No TMA events were observed beyond those reported in the HAVEN 1 primary analysis²
 - Two additional TEs that occurred in cases without concurrent aPCC were **deemed unrelated to emicizumab**¹
- 144 SAEs were reported in 93 participants¹
- The most common treatment-related AEs were **Injection Site Reactions**^{†1}
- **Anti-Drug Antibodies** with neutralising potential were observed in $<1\%$ (3/398) of participants^{1,3}






Received: 9 January 2024 | Revised: 20 March 2024 | Accepted: 31 March 2024

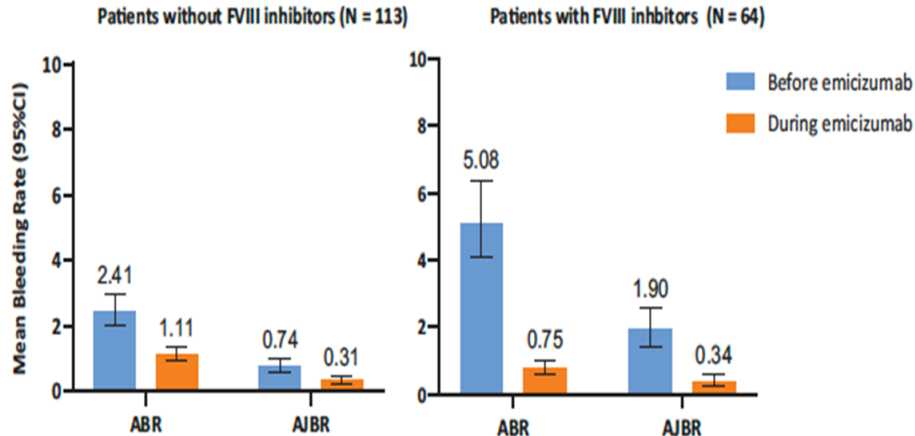
DOI: 10.1111/hae.15015

ORIGINAL ARTICLE

Haemophilia  WILEY

Bleeding control improves after switching to emicizumab: Real-world experience of 177 children in the PedNet registry

Konrad van der Zwet¹  | Marloes de Kovel²  | Jayashree Motwani³ | Chris van Geet⁴ | Beatrice Nolan⁵ | Heidi Glosli⁶ | Carmen Escuriola Ettingshausen⁷ | Christoph Königs⁸ | Gili Kenet^{9,10}  | Kathelijn Fischer¹  | the PedNet Investigators



168 (95%) severe
113 (64%) without inhibitor (22 tolerized)
Emicizumab start: median 8.6 yrs (IQR 4.8-13.1)
Follow-up pre-emi: median 1.68 yrs (IQR 1.2-1.9)
on emi: median 1.32 yrs (IQR 0.94-2.11)

- **No life-threatening bleed (vs. 6 pre)**
Non inh: - 97.6% FVIII consumption
- 73% injections
Inh: - 94.8% rFVIIa - 97.6% FVIII cons.
- 86% injections

- **No thromboembolic event or thrombotic microangiopathy**
- **No inhibitor recurrence in tolerized patients**
- **1 (0.6%) neutralizing ADA**
- **4 (2.2%) injection site reactions**



HAVEN 7: early prophylaxis in newborns and infants. Primary analysis

	Participants (N = 55)
Age at informed consent, mo	
Mean (SD)	5.0 (3.9)
Median (range)	4.0 (9 days to 11 months 30 days)
Age group, n (%)	
0-<3 mo	25 (45.5)
3-12 mo	30 (54.5)
Historical bleeding episodes prior to first emicizumab dose	
Participants with ≥1 bleed, n (%)	36 (65.5)
Total number of bleeds, n	77

Cause/type of bleed	n (%)
Spontaneous	25 (32.5)
Joint	8 (32.0)
Traumatic	18 (24.7)
Joint	0 (0.0)
Procedural/surgery	33 (42.9)
Joint	0 (0.0)

	Participants (N = 55)
Median (range) follow-up,* wk	101.9 (52.6-119.7)
Model-based ABR (95% CI)	
All bleeds	2.0 (1.49-2.66)
Treated bleeds	0.4 (0.30-0.63)
Treated spontaneous bleeds	0.0†
Treated joint bleeds	0.0 (0.01-0.09)
Calculated median ABR (IQR)	
All bleeds	1.0 (0.53-2.93)
Treated bleeds	0.0 (0.00-0.81)
Treated spontaneous bleeds	0.0 (0.00-0.00)
Treated joint bleeds	0.0 (0.00-0.00)
Participants with 0 bleeds, n (%)	
Zero treated or untreated bleeds	9 (16.4)
Zero treated bleeds	30 (54.5)
Zero treated spontaneous bleeds	55 (100.0)
Zero treated joint bleeds	52 (94.5)

Total n of bleeds, n	207
Cause/type of bleed	n (%)
Spontaneous	18 (8.7)
Joint	0 (0.0)
Traumatic	182 (87.9)
Joint	4 (2.2)
Procedural/surgery	7 (3.4)
Joint	0 (0.0)
Total n of treated bleeds, n	42
Cause/type of bleed	n (%)
Traumatic	42 (100)
Joint	3 (7.1)
Muscle	5 (11.9)
Other.	34 (81.0)

Adverse Events (AE), n (n, % participants)	
Total n	314 (50, 92.6)
Fatal outcome	0 (0, 0)
Leading to tr. withdrawal	0 (0, 0)
Leading to dose withdrawal	0 (0, 0)
Treatment-related	23 (9,16.7)
<i>all injection site reactions</i>	
Severe AE (SAE)	12 (8, 14.8)
AE of special interest (AESI)	0 (0, 0)
Syst. Hypersens/Anaphylaxis	0 (0, 0)
Thromboembolic event	0 (0, 0)
Thrombotic microangiopathy	0 (0, 0)



EXTENDING NON-REPLACEMENT TREATMENT TO NON-SEVERE HA: HAVEN 6 TRIAL

<https://clinicaltrials.gov/ct2/show/NCT04158648>

Key inclusion criteria

- Moderate or mild HA*
- Without FVIII inhibitors
- Prophylaxis warranted as assessed by the Investigator
- All ages

N = 73

(52 moderate; 21 mild)

Emicizumab
3 mg/kg QW
N = 72[†]

Loading dose
(4 weeks)

Emicizumab
1.5 mg/kg QW or
3 mg/kg Q2W or
6 mg/kg Q4W

Maintenance dose
(participant choice)

Efficacy end-points: ABRs for treated bleeds, all bleeds, and joint/target joint/spontaneous bleeds

Safety end-points: AEs, SAEs, AESI (including TEs and TMAs), drug discontinuation due to AEs

Baseline assessment	Participants (N = 72)
Current treatment regimen, n (%)	
Prophylactic	37 (51.4)
Episodic	35 (48.6)
Number of bleeds in the past 24 weeks[†]	
Mean (SD)	4.7 (13.2)
Median (range)	2.0 (0–96)
Model-based ABR prior to study [†] , mean (95% CI)	10.1 (6.93–14.76)
Median ABR prior to study [†] , (IQR)	4.3 (0.00–9.78)
Participants with target joints, n (%)	24 (33.3)
Number of target joints at baseline	
Mean (SD)	0.6 (1.2)
Median (range)	0 (0–8)

Median (range) follow-up:
55.6 (8.7–88.9) weeks



HAVEN 6: EFFICACY

Efficacy assessment	Participants (N = 72)				
	Treated bleeds	Treated joint bleeds	Treated spontaneous bleeds*	Treated target joint bleeds	All bleeds
Calculated median ABR (IQR) [†]	0.0 (0.00–0.98)	0.0 (0.00–0.00)	0.0 (0.00–0.00)	0.0 (0.00–0.00)	1.0 (0.00–3.11)
Model-based ABR (95% CI)	0.9 (0.55–1.52)	0.2 (0.09–0.57)	0.2 (0.11–0.33)	0.1 (0.03–0.40)	2.3 (1.67–3.12)
Calculated mean ABR (95% CI) [†]	0.9 (0.02–5.48)	0.2 (0.00–4.15)	0.3 (0.00–4.23)	0.1 (0.00–3.92)	2.3 (0.35–7.75)
Calculated ABR range [†]	0.00–7.05	0.00–3.63	0.00–6.09	0.00–3.21	0.00–21.04
Participants with zero bleeds, n (%)	48 (66.7)	64 (88.9)	59 (81.9)	68 (94.4)	24 (33.3)



The majority of treated bleeds (78.9%) were traumatic (spontaneous, 21.1%)
 >84% of participants had zero treated bleeds in any 12-week interval up to one year¹
 All median bleed rates were **zero** except for all bleeds¹
 95.2% of participants with target joints at baseline **resolved target joints**

* [†]Calculated by: (number of bleeds/total number of days during the efficacy period)×365.25.
 ABR, annualised bleed rate; CI, confidence interval; IQR, interquartile range.

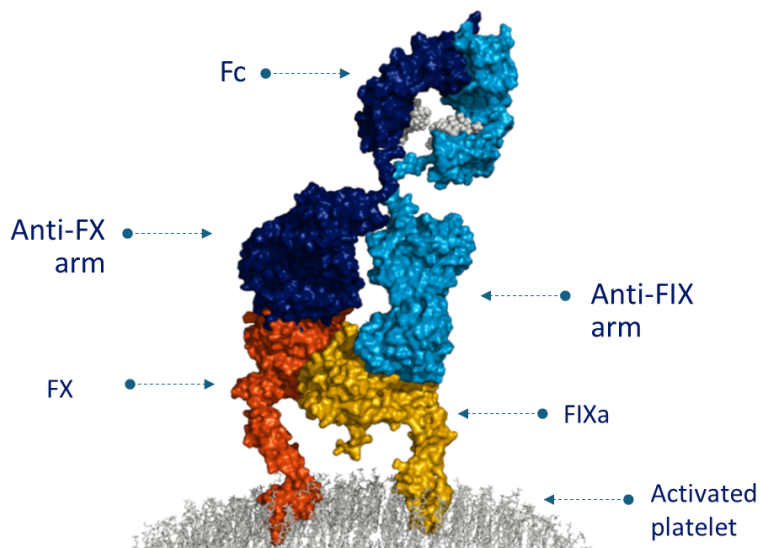


HAVEN 6: SAFETY AND PROS

- **Safety:** no death or thrombotic microangiopathy; one unrelated thrombosed haemorrhoids; no related SAE; 17% headache and injection-site reactions
- **HRQoL assessment** (CATCH score) showed a **trend to improvement** from baseline for **both adolescent and adult populations** in the treatment burden domain (the other domains remaining stable)
- 95.2% of patients and 85.7% of caregivers responding to the Emi-pref questionnaire preferred emicizumab to their previous treatment

01.02.2023
EMA approval in moderate hemophilia A
with severe bleeding phenotype

NEW MIMETICS: THE MIM8 MOLECULE



**Membrane localization; weak binding in the circulation
to avoid systemic activation of coagulation**



Novel, next-generation FVIII mimetic



For subcutaneous prophylactic
treatment of haemophilia A with and
without inhibitors



Fully human IgG4 bispecific antibody

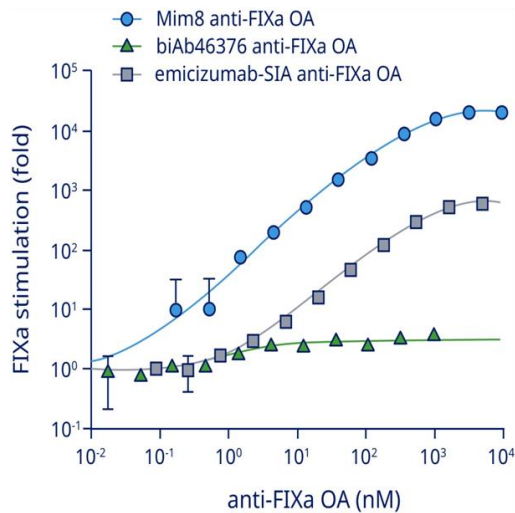


Unique binding epitopes to FIXa and FX

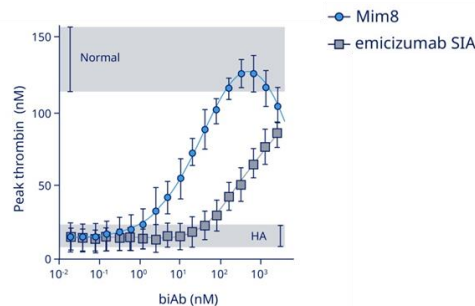
- Strong stimulation of FIXa proteolytic activity
- Facilitated delivery of FX to FIXa and exchange of FIXa for FX



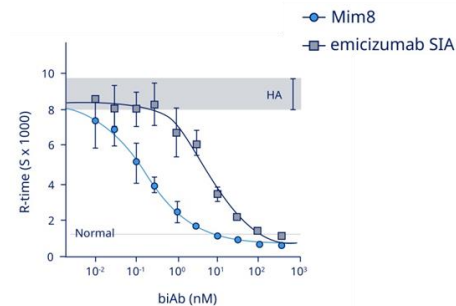
MORE EFFICIENT FIXa ACTIVITY STIMULATION AND THROMBIN GENERATION THAN THOSE OF EMICIZUMAB



TGT: TF-triggered



TEG: clot time

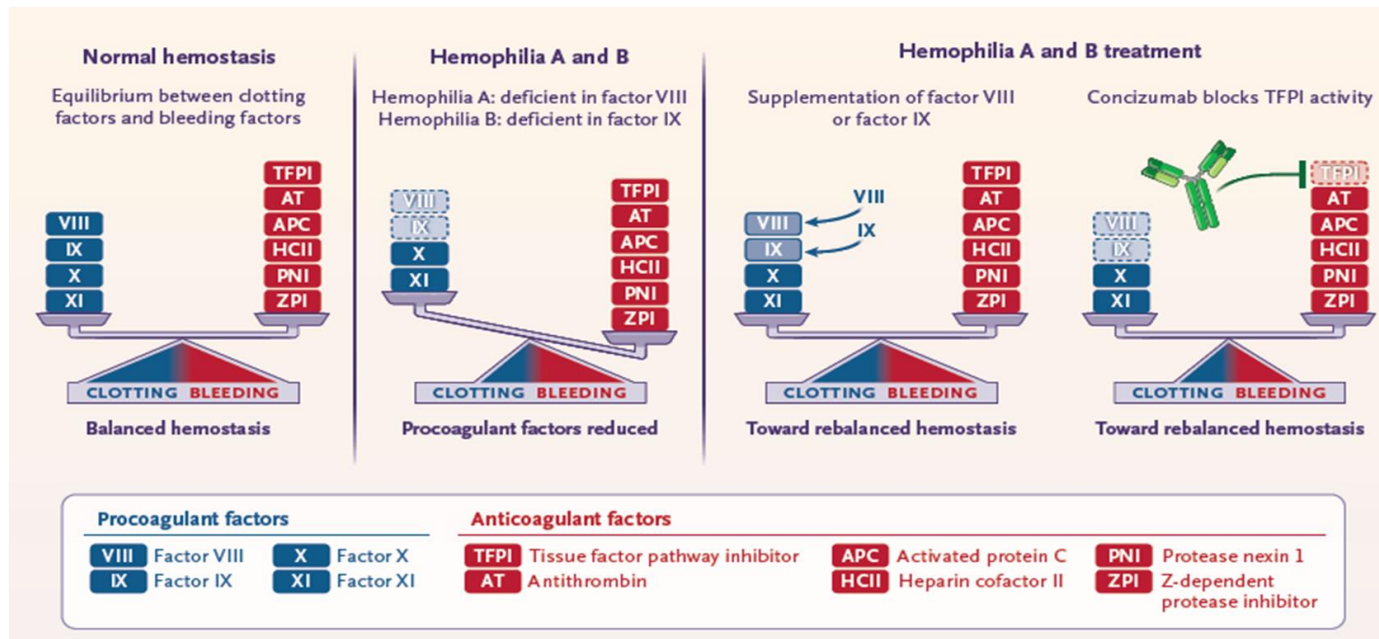


Mim8 normalized thrombin generation while emicizumab failed to do so in this setting, even at the highest concentration



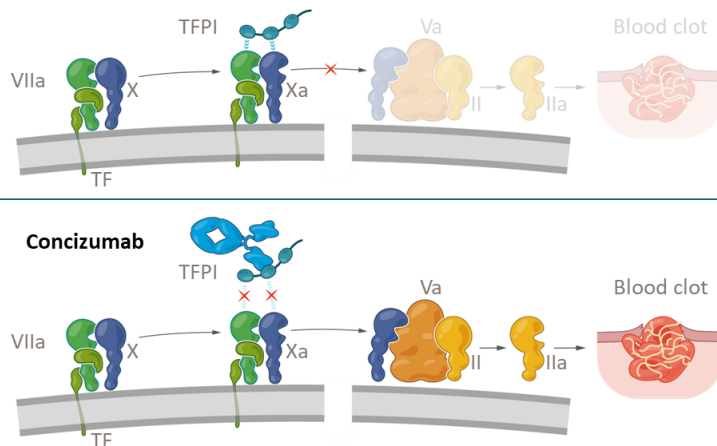
Potency of Mim8 based on R-time was improved by **18-fold**, relative to emicizumab SIA

REBALANCING THERAPIES



CONCIZUMAB: anti-TFPI

High-affinity, humanised,
monoclonal IgG₄ antibody against TFPI



Blocks inhibition of TF/FVIIa/FXa by TFPI

Extends the initiation phase of coagulation

Restores thrombin (FIIa) generation despite FVIII or FIX deficiency

No interference with other major inhibitors of the coagulation pathway

Concizumab restores haemostatic potential by limiting the initial regulator
TFPI
allowing the coagulation cascade to continue

Daily s.c.
administration

HA & HB
with and without
inhibitors



MONOCLONAL ANTIBODIES TO TFPI

Concizumab:

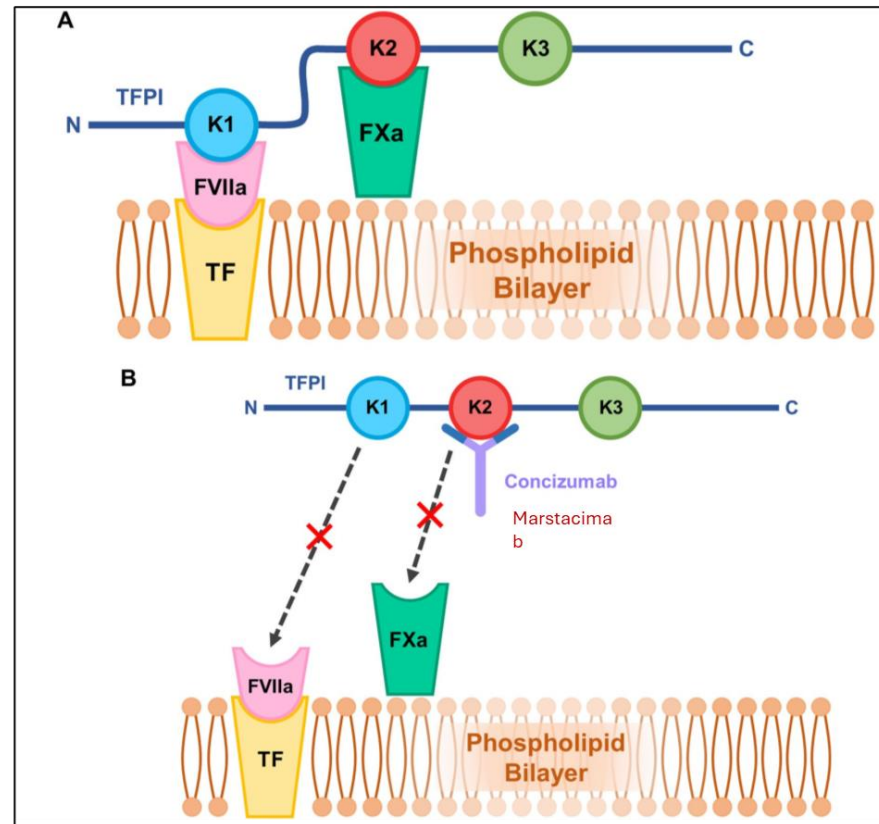
High-affinity, humanised, monoclonal IgG₄ antibody against TFPI

Marstacimab

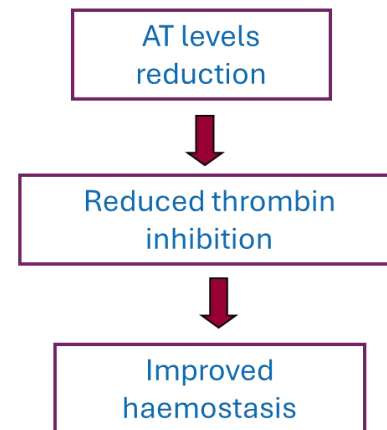
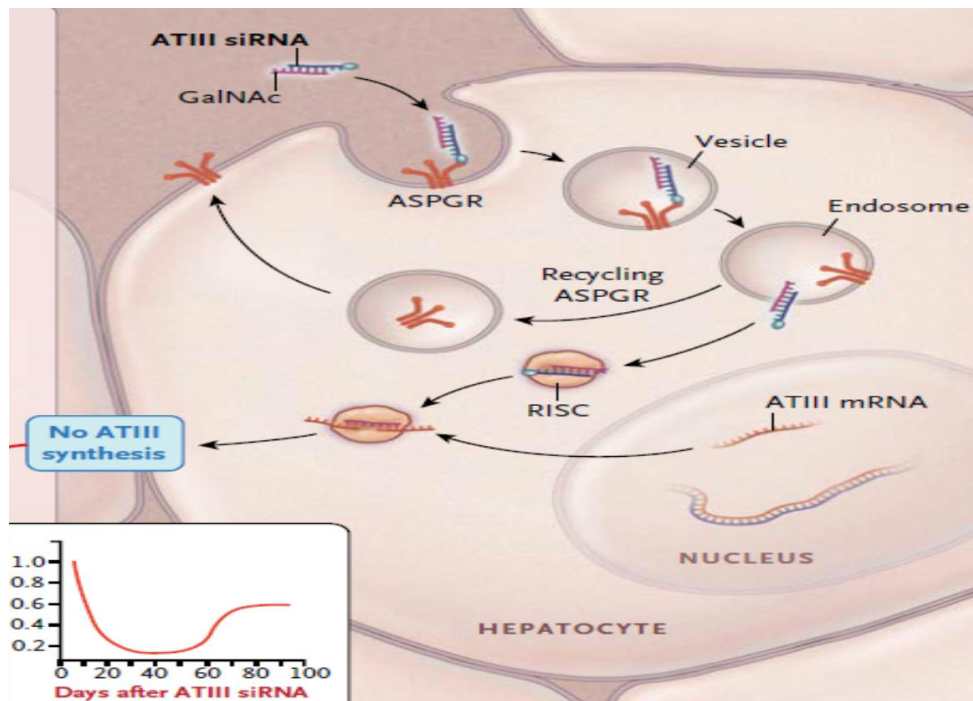
High-affinity, human, monoclonal IgG₁ antibody against TFPI

Target and inhibit TFPI (K2 domain)

Indication for both haemophilia A and B with and without inhibitor



Fitusiran: an RNAi therapy targeting Antithrombin (HA & HB with/without inhibitors)



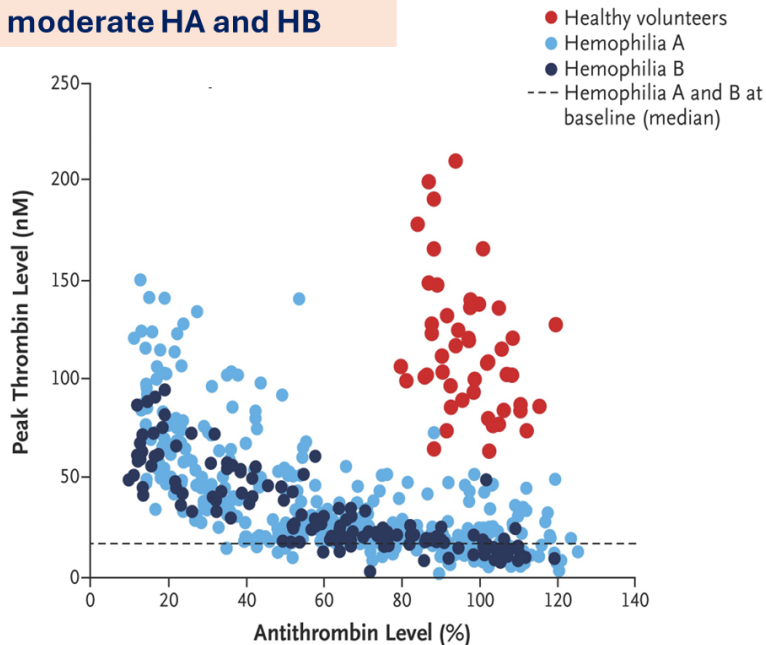
and durability of effect
on AT levels



Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy

N Engl J Med 2017;377:819-28.

Fitusiran monthly dosing in patients with severe and moderate HA and HB



	Peak Thrombin Generation, nM (Mean ± SD)	% Increase in Peak Thrombin Generation (Mean ± SD)
AT Lowering <25%	18 ± 9	20 ± 72%
AT Lowering 25-50%	26 ± 12	48 ± 61%
AT Lowering 50-75%	47 ± 29	218 ± 272%
AT Lowering >75%	62 ± 27**	285 ± 165%**

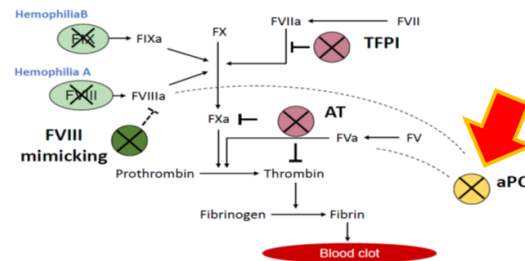
**p < 0.001, compared with AT lowering less than 25%

Relationship between antithrombin levels and thrombin generation



SerpinPC: inhibition of activated Protein C

- AP-0101, phase 1-2 trial; extension part 5
- Safety, tolerability and PK of s.c. administrations (different dosing, every 2 or 4 weeks; part 5: 1.2 mg/Kg **every 2 wks**)
- 23 HA&HB patients previously treated on demand
- 1 patient discontinued treatment due to **injection site reactions**
- 2 **anti-drug antibodies** remaining on treatment
- 88% reduction of all-bleeds ABR and 94% of spontaneous ABR
- No treatment-related AE, no thromboembolic events, no dose-dependent or sustained D-dimer increase





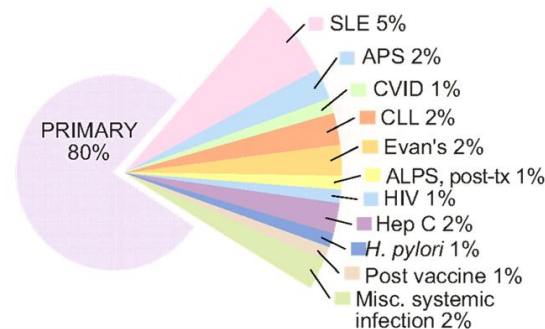
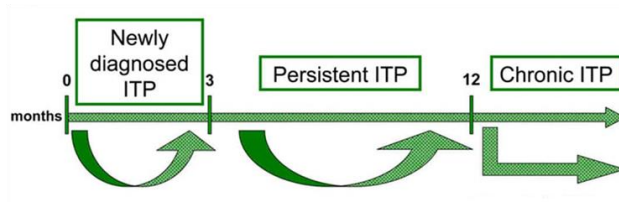
Trombocitopenia immune: definizione

ITP primaria

Disordine autoimmune caratterizzato da piastrinopenia isolata (conta piastrinica del sangue periferico $< 100 \times 10^9/l$) in assenza di altre cause o disordini che possano essere associati alla piastrinopenia. La diagnosi di ITP primaria viene fatta per esclusione. Al momento non ci sono parametri clinici o di laboratorio affidabili per poterla diagnosticare in modo accurato. Il principale problema clinico dell'ITP primaria risiede nell'aumentato rischio di sanguinamento, anche se i sintomi emorragici possono non essere sempre presenti.

ITP secondaria

Tutte le forme di piastrinopenia immune, ad esclusione dell'ITP primaria*





> Blood Transfus. 2023 Jul 27. doi: 10.2450/BloodTransfus.501. Online ahead of print.

Recommendations for the management of acute immune thrombocytopenia in children. A Consensus Conference from the Italian Association of Pediatric Hematology and Oncology

Giovanna Russo¹, Emilia Parodi², Piero Farruggia³, Lucia D Notarangelo⁴, Silverio Perrotta⁵, Maddalena Casale⁵, Simone Cesaro⁶, Giovanni Del Borrello⁷, Giovanni C Del Vecchio⁸, Fiorina Giona⁹, Chiara Gorio¹⁰, Saverio Ladogana¹¹, Giuseppe Lassandro⁸, Antonio Marzollo¹², Karolina Maslak¹, Maurizio Miano¹³, Margherita Nardi¹⁴, Giuseppe Palumbo¹⁵, Francesca Rossi⁵, Marco Spinelli¹⁶, Alessandra Tolva¹⁷, Paola Saracco¹⁸, Ugo Ramenghi¹⁸, Paola Giordano⁸

Affiliations + expand

PMID: 37677093 DOI: 10.2450/BloodTransfus.501

Free article

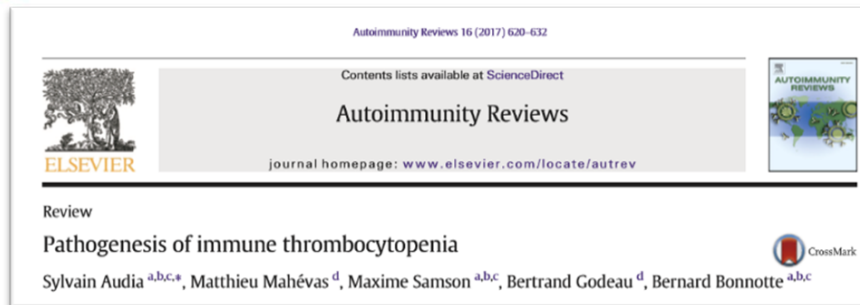
Abstract

Background: Immune thrombocytopenia (ITP) is an acquired immune-mediated bleeding disorder characterized by isolated thrombocytopenia. Its estimated yearly incidence in the pediatric population is 1.9-6.4/100,000. ITP in children is usually a self-limiting and benign disorder. The clinical management of children with ITP often remains controversial, as robust randomized trials on the management of this disorder are lacking. Treatments vary widely in clinical practice and existing guidelines from hematology societies on clinical management offer indications based largely on expert opinion rather than strong evidence.

Materials and methods: The Coagulative Disorder Working Group of the Italian Association of Pediatric Hematology and Oncology (AIEOP) developed this document to collect shared expert opinions on the management of newly diagnosed ITP, updating previous guidelines and providing recommendations to pediatricians. Each statement has been given a score expressing the strength of evidence, appropriateness and agreement among participants.

Results: Clear-cut definitions of the clinical phases of the disease and clinical response are stated. Recommendations are given regarding the classification of bleeding symptoms, evaluation of bleeding risk, diagnosis, and prognostic factors. Specific recommendations for treatment include indications for first-line (intravenous immunoglobulins, steroids) and second-line (combined therapy, thrombopoietin receptor agonists, immunosuppressive drugs, rituximab) therapeutic agents, as well as hemorrhagic emergency and supportive treatment, including emergency splenectomy. The optimal follow-up schedule, the relation between ITP and vaccines and health-related quality-of-life issues are also discussed.

Discussion: The panel achieved broad consensus on issues related to how to treat children with newly diagnosed ITP, providing a comprehensive review of all relevant clinical aspects.



- Risposta anomala cellule T, cellule follicolari **T helper**, che stimola la proliferazione e la differenziazione delle **cellule B autoreattive**.
- Produzione di **anticorpi anti-piastrine** che facilitano la **fagocitosi piastrinica** da parte dei macrofagi, essenzialmente nella milza.
- I **macrofagi** contribuiscono al perpetuarsi della risposta autoimmune
- Le **cellule T CD8 +** partecipano anche alla trombocitopenia aumentando l'apoptosi piastrinica.
- Produzione inappropriata da parte del **midollo osseo** a causa di una **risposta immunitaria contro i megacariociti**.
- Livello di **trombopoietina** circolante, il principale fattore di crescita dei megacariociti, è basso.

Fisiopatologia

www.thelancet.com Vol 76 Month February, 2022

Recent advances in the mechanisms and treatment of immune thrombocytopenia

Drew Provan,^{a*} and John W. Semple^{b,c,d**}

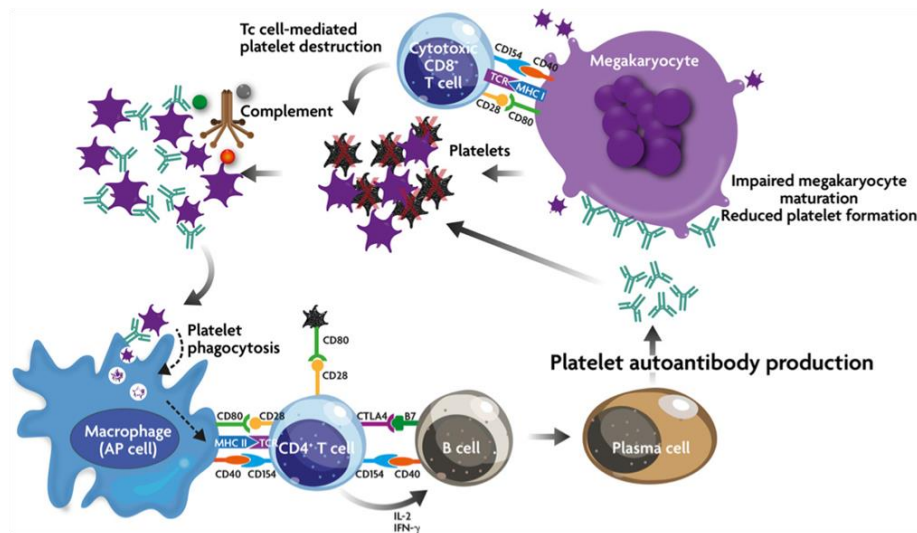




Table V - Differences between previous and current AIEOP recommendations and international guidelines

	AIEOP 2000 recommendations	AIEOP current recommendations	ASH current guidelines
Definitions: phase of the disease	Acute ITP <6 months Chronic >6 months	According to IWG: <ul style="list-style-type: none"> newly diagnosed (<3 months), persistent (3-12 months), chronic (>12 months) 	According to IWG: <ul style="list-style-type: none"> newly diagnosed (<3 months), persistent (3-12 months), chronic (>12 months)
Definitions: response to treatment	Not provided	According to IWG: <ul style="list-style-type: none"> complete response: PLT $>100 \times 10^9/L$ partial response: PLT $30-100 \times 10^9/L$ (at least doubling of baseline count) no response: PLT $<30 \times 10^9/L$ Refractory to "specific treatment indicated": persistent active bleeding, persistent low PLT count, despite first-line or rescue therapy	According to IWG: <ul style="list-style-type: none"> complete response: PLT $>100 \times 10^9/L$ partial response: PLT $30-100 \times 10^9/L$ (at least doubling of baseline count) no response: PLT $<30 \times 10^9/L$ Refractory: failure to splenectomy
Indications for treatment	Platelet count bleeding signs	Bleeding signs special needs	Bleeding signs special needs
First line - treatments	Steroids or IVIg	IVIg	Steroids
Second-line treatments	Not considered	Combined therapy TPO agonists immunosuppressive drugs rituximab	TPO agonists immunosuppressive drugs rituximab
Bone marrow biopsy at diagnosis	Mandatory prior to steroid administration	Suggested prior to steroid administration	Not recommended
Assessment of HRQoL issues	No	Yes	Yes

AIEOP: Italian Association of Pediatric Hematology and Oncology; ASH: American Society of Hematology; ITP: immune thrombocytopenia; IWG: International Working Group; PLT: platelets; IVIg: intravenous immunoglobulin; TPO: thrombopoietin; HRQoL: health-related quality of life.



ELTROMBOPAG



Eltrombopag was approved as a treatment for children aged ≥ 1 year with chronic ITP and refractory to other treatments

Eltrombopag was approved as a treatment for children aged ≥ 1 year with ITP > 6 months and refractory to other treatments



> Front Med (Lausanne). 2020 Feb 28;7:66. doi: 10.3389/fmed.2020.00066. eCollection 2020.

Use of Eltrombopag in Children With Chronic Immune Thrombocytopenia (ITP): A Real Life Retrospective Multicenter Experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP)

Paola Giordano ¹, Giuseppe Lassandro ¹, Angelica Barone ², Simone Cesaro ³, Ilaria Fotzi ⁴, Fiorina Giona ⁵, Saverio Ladogana ⁶, Maurizio Miano ⁷, Antonio Marzollo ⁸, Margherita Nardi ⁹, Lucia Dora Notarangelo ¹⁰, Andrea Pession ¹¹, Antonio Ruggiero ¹², Giovanna Russo ¹³, Paola Saracco ¹⁴, Marco Spinelli ¹⁵, Alessandra Tolva ¹⁶, Assunta Tornesello ¹⁷, Valentina Palladino ¹, Giovanni Carlo Del Vecchio ¹

Background: The thrombopoietin receptor agonist eltrombopag has been shown to be safe and effective for children with chronic immune thrombocytopenia (ITP). The aim of the present study was to characterize eltrombopag use in current clinical practice. **Material and Methods:** This is a retrospective multicenter study conducted in 17 centers affiliated to the Italian Association of Pediatric Hematology and Oncology (AIEOP). The primary objective of the study was to determine the prevalence of eltrombopag use in Italian children affected by chronic ITP, after EMA authorization for pediatric age. The secondary objective was to assess efficacy in the first 6 months and safety during the whole period of eltrombopag treatment in current clinical practice. A total of 386 children with chronic ITP were retrospectively enrolled and eligible for analysis. Among these patients, 71 received eltrombopag. **Results:** The prevalence of eltrombopag use was 19% (95% CI 0.15-0.23). Thirty-one patients (44%) were male and 40 patients (56%) were female. The median age at the first dose of eltrombopag was 12 years (3-17 years). The median duration of eltrombopag treatment was 11 months (1-32 months) and the median starting dose was 50 mg/day (12, 5-75 mg/day). Thirty-two patients (45%) required one or more concomitant ITP medications during the first 6 months of treatment with eltrombopag. Thirty-nine patients (55%) never required concomitant medications. Median platelet counts and proportion of patients achieving the target platelet count of at least $30 \times 10^9/L$ and $100 \times 10^9/L$ significantly increased during the first 6 months of treatment ($p < 0.0001$). Additionally, eltrombopag has been proved effective in the absence of concomitant therapies. The most common Adverse Events were headache (7%) and thrombocytosis (6%). **Conclusion:** Our study highlighted the crucial role of eltrombopag as second line treatment in children with chronic ITP.



> Front Med (Lausanne). 2023 Jul 14;10:1214308. doi: 10.3389/fmed.2023.1214308. eCollection 2023.

Long term use of eltrombopag in children with chronic immune thrombocytopenia: extended real life retrospective multicenter experience of the Italian Association of Pediatric Hematology and Oncology

Paola Giordano¹, Giuseppe Lassandro¹, Angelica Barone², Simone Cesaro³, Ilaria Fotzi⁴, Fiorina Giona⁵, Chiara Gorio⁶, Angela Maggio⁷, Maurizio Miano⁸, Antonio Marzollo⁹, Margherita Nardi¹⁰, Andrea Pession¹¹, Antonio Ruggiero¹², Giovanna Russo¹³, Paola Saracco¹⁴, Marco Spinelli¹⁵, Alessandra Tolva¹⁶, Assunta Tornesello¹⁷, Valentina Palladino¹, Giovanni Carlo Del Vecchio¹

Affiliations + expand

PMID: 37521342 PMID: PMC10375288 DOI: 10.3389/fmed.2023.1214308

Abstract

Background: The present multicenter retrospective study on eltrombopag administration in Italian children with chronic ITP aims to extend follow-up of our previous study.

Materials and methods: This retrospective multicenter study was conducted in 17 centers affiliated to the Italian Association of Pediatric Hematology and Oncology (AIEOP). Patients were classified into three subgroups: group 1 included patients who discontinued treatment due to a stable platelet count; group 2 included patients who discontinued treatment due to ineffectiveness; group 3 included patients who did not permanently discontinue treatment.

Results: 56 patients were eligible for analysis. The median duration of eltrombopag treatment was 40 months (7-71 months). Twenty patients (36%) discontinued permanently eltrombopag. The reasons of permanent discontinuation were adverse effects ($n = 1$), inefficacy ($n = 10$), stable platelet count ($n = 9$). All patients of group 1 maintained a durable response without additional treatments after eltrombopag discontinuation. We found that patients of group 2 were on treatment for less time (median treatment time: 13.5 months, min: 6.0 - max: 56.0) than patients of group 1 (median treatment time: 34 months, min: 16.0 - max: 62.0) ($p < 0.05$). Patients of group 2 mostly did not achieve a stable platelet count in the first 6 months of treatment and underwent concomitant therapies during follow-up respect of group 1 and group 3 ($p < 0.01$).

Conclusion: Our study found that the benefits of eltrombopag treatment, in terms of platelet count improvement and use of additional therapies, are identifiable from the first 6 months of treatment.



> Ann Hematol. 2024 Aug;103(8):2721-2727. doi: 10.1007/s00277-024-05857-y. Epub 2024 Jun 25.

The long-term efficacy of eltrombopag in children with immune thrombocytopenia

Li- Yang ^{# 1}, Bao-Hua Sang ^{# 1}, Chun-Hui Yang ¹, Zu-Gang Xiao ¹, Chun-Lian Fang ¹, Yu Lv ¹, Na Li ¹, Qing Yang ¹, Shu-Min Chai ¹, Xin Tian ¹, Xian-Wen Zhang ², Ti-Long Huang ³

Affiliations + expand

PMID: 38916741 DOI: 10.1007/s00277-024-05857-y

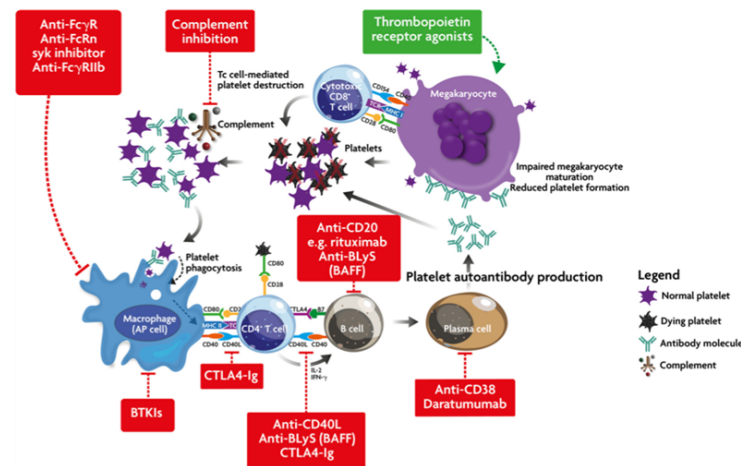
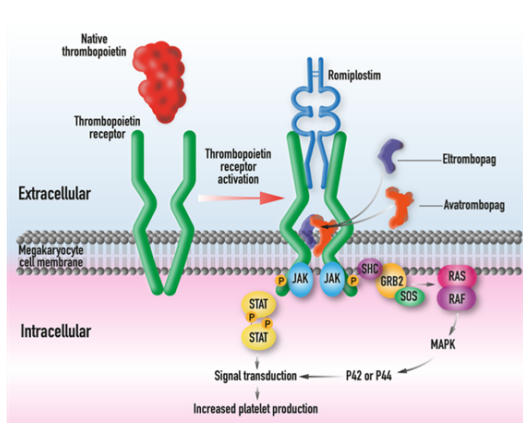
Abstract

Immune thrombocytopenia (ITP) is the most common autoimmune disorder characterized by decreased platelet counts and impaired platelet production. Eltrombopag has been demonstrated to be safe and effective for children with ITP. It is reported eltrombopag can achieve a sustained response off treatment. However, data on its overall efficacy and safety profile are scarce in children. This study aimed to investigate the long-term efficacy of eltrombopag in children with ITP. Treatment overall response (OR), complete response (CR), response (R), durable response (DR), no response (NR), treatment free remission (TFR), and relapse rate, were assessed in 103 children with ITP during eltrombopag therapy. The OR rate, CR rate, R rate, DR rate, NR rate, TFR rate, and relapse rate were 67.0%, 55.3%, 11.7%, 56.3%, 33.0%, 60%, 36.2%, respectively. Importantly, we discovered that newly diagnosed ITP patients showed a higher DR rate, TFR rate and lower relapse rate compared to persistent and chronic ITP patients. Furthermore, the CR rate, DR rate, and TFR rate of 5 patients under six months were 100%. None of them suffered relapse. The most common adverse event (AEs) was hepatotoxicity (7.77%). Our study highlighted the critical role of eltrombopag as the second-line treatment in children with ITP who were intolerant to first-line therapy.

Futuro

Recent advances in the mechanisms and treatment of immune thrombocytopenia

Drew Provan¹, John W Semple²



Legend
 ☆ Normal platelet
 ☆ Dying platelet
 ☆ Antibody molecule
 ☆ Complement

Drug	Description	Mechanism of action
Romiplostim ⁶⁸⁻⁷¹	Peptibody TPO-RA	Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production
Eltrombopag ^{72,73}	Small molecule TPO-RA	Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production
Avatrombopag ⁷⁴	Small molecule TPO-RA	Stimulates the JAK-STAT pathway. Megakaryocyte proliferation, maturation and platelet production
Fostamatinib ^{81,82}	syk inhibitor	Decreases antibody-dependent phagocytosis of platelets
Efgartigimod ⁸⁴	Anti-FcRn	Decreases the half-life of IgG, reduces plasma IgG both normal and pathogenic
Roazanolizumab ⁹⁰	Anti-FcRn	Decreases the half-life of IgG, reduces plasma IgG both normal and pathogenic
Rilzabrutinib ^{86,92}	BTKI	Inhibits Fcγ signal transduction, decreases platelet phagocytosis and autoantibody production
Sutimlimab ⁹³	Anti-C1s	Decreases complement-dependent cytotoxicity thereby reducing platelet destruction



SPLEEN TYROSINE KINASE (SYK)

- La tirosin chinasi della milza (SYK) è espressa principalmente nelle cellule ematopoietiche.
- SYK si lega ai recettori immunitari (B-cell receptors (BCR), Fc receptors (FcR), C-type lectin receptors (CLR) e ai motivi ITAM (Immunoreceptor Tyrosine-based Activation Motif)
- L'attivazione di SYK media diversi processi biologici, tra cui la produzione e la secrezione di citochine, la fagocitosi delle cellule rivestite di autoanticorpi, la maturazione degli osteoclasti e la regolazione dell'aggregazione piastrinica.



INIBITORI DI SYK

Drug	Formulation	Diseases Studied
Fostamatinib	Oral	<p>ITP: Approved</p> <p>RA: Phase 3 [NCT01197534, NCT01197521, NCT01197755, EudraCT 2010-020744-35, EudraCT 2010-020743-12]</p> <p>WAIHA: Phase 3 [NCT03764618, EudraCT 2018-004774-97]</p> <p>CLL: Phase 2 [NCT00446095, EudraCT 2009-009034-32]</p> <p>COVID-19: Phase 3 [NCT04629703, NCT04924660, EudraCT 2020-001750-22]</p> <p>Other diseases</p>
Entospletinib	Oral	<p>B-cell lymphoma: Phase 2 [NCT02568683, NCT03225924, EudraCT 2016-003103-56, EudraCT 2015-002731-17]</p> <p>Hematologic malignancies (leukemia, lymphoma): Phase 2 [NCT01796470, NCT01799889, NCT03010358]</p> <p>AML: Phase 3 [EudraCT 2021-000761-33]</p> <p>CLL: Phase 2 [EudraCT 2016-002768-15]</p>
HMPL-523	Oral	<p>B-cell lymphoma: Phase 1 [NCT03779113, NCT02857998]</p> <p>ITP: Phase 3 [NCT05029635]</p>
GSK2646264	Cream	<p>Urticaria: Phase 1 [NCT02424799]</p> <p>CLE: Phase 1 [NCT02927457]</p>
Lanraplenib	Oral	<p>Sjögren's syndrome: Phase 2 [NCT03100942]</p> <p>CLE: Phase 2 [NCT03134222]</p> <p>LMN: Phase 2 [NCT03285711]</p> <p>AML: Phase 2 [NCT05028751]</p>
Cevidopenib	Oral	<p>RA: Phase 2 [EudraCT 2018-003330-32]</p> <p>ITP: Phase 2 [EudraCT 2018-003329-26]</p>



SICUREZZA DEL FOSTAMATINIB NELL'ITP

- Fostamatinib è stato, in genere, ben tollerato nei pazienti con ITP
- Gli eventi avversi più comuni includevano disturbi gastrointestinali (come diarrea), ipertensione e transaminasi elevate. La maggior parte era di gravità lieve o moderata ed era gestibile con un trattamento appropriato o modifica/interruzione della dose;
- pochi pazienti hanno richiesto l'interruzione permanente di fostamatinib



TRATTAMENTI IN FASE DI SVILUPPO CLINICO


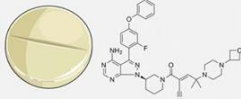



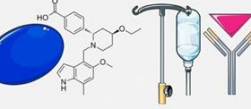
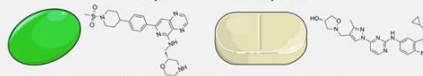
<p>Efgartigimod <i>Neonatal Fc Receptor Antagonist</i></p>  <p>Status: Completed Phase 3 ADVANCE IV Study (Intravenous): Positive ADVANCE SC Study (Subcutaneous): Negative</p>	<p>Rilzabrutinib <i>Bruton's Tyrosine Kinase Inhibitor</i></p>  <p>Status: Completed Phase 3 (Adults) LUNA 3 Study (Adult Portion): Positive LUNA 3 Study (Pediatric Portion): Ongoing</p>	<p>Ianalumab <i>BAFF Receptor Antagonist</i></p>  <p>Status: Ongoing Phase 2 and Phase 3 VAYHIT1 (1st Line + Steroids): Ongoing VAYHIT2 (2nd Line + Eltrombopag): Ongoing VAYHIT3 (Later line): Ongoing</p>
<p>Povetacicept <i>BAFF and APRIL Antagonist</i></p>  <p>Status: Ongoing Phase 2 RUBY-4 Study (Basket Trial): Ongoing</p>	<p>Anti-CD38 Antibodies <i>Mezagitamab, Daratumumab, CM313</i></p>  <p>Status: Completed and Ongoing Phase 2 TAK-079-1004 (Mezagitamab, SC): Positive DART Study (Daratumumab, SC): Ongoing 2022-CM313-ITP (CM313, IV): Positive</p>	<p>Complement Inhibitors <i>Iptacopan, Sutimlimab</i></p>  <p>Status: Completed Phase 1 and Phase 2 CLNP023L12201 (Iptacopan): Completed Phase 1 Study of Sutimlimab: Positive</p>
<p>Novel SYK Inhibitors <i>Sovleplenib and Cevidoplenib</i></p>  <p>Status: Completed Phase 2 and Phase 3 2018-523-00CH1 Study (Sovleplenib Phase 2): Positive ESLIM-1 (Sovleplenib Phase 3): Positive OSCO-P2101 Study (Cevidoplenib Phase 2): Positive</p>		<p>Conclusions:</p> <ul style="list-style-type: none"> Many agents in development target pathophysiologic mechanisms not previously targeted by agents in current use These agents represent promising options for patients with disease refractory to current therapies and may allow for more personalized treatment in the future New approaches to ITP clinical trials are in motion, including treatment with novel agents in combination with established agents early in disease to modify the disease course



TABLE 1 Summary of primary agents not currently approved for immune thrombocytopenia (ITP) currently in clinical trials discussed in this review.

Agent	Structure and mechanism of action	Mode of administration	Stage of development in ITP
Efgartigimod	Modified Fc fragment blocking the neonatal Fc receptor	Intravenous or subcutaneous	Completed phase 3
Rilzabrutinib	Small molecule Bruton's tyrosine kinase inhibitor	Oral	Completed phase 3
Ianalumab	Monoclonal antibody directed against BAFF-R	Intravenous	Ongoing phase 2 and phase 3
Povetacicept	Fc fusion protein that clears BAFF and APRIL	Subcutaneous	Ongoing phase 2
Daratumumab	Anti-CD38 monoclonal antibody	Subcutaneous	Ongoing phase 2
Mezagitamab	Anti-CD38 monoclonal antibody	Subcutaneous	Completed phase 2
CM313	Anti-CD38 monoclonal antibody	Intravenous	Completed phase 2
Sovlepenib	Small molecule spleen tyrosine kinase inhibitor	Oral	Completed phase 3
Cevidoplenib	Small molecule spleen tyrosine kinase inhibitor	Oral	Completed phase 2
Sutimlimab	Anti-complement C1s monoclonal antibody	Intravenous	Completed phase 1
Iptacopan	Small molecule complement factor B inhibitor	Oral	Ongoing phase 2

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BAFF-R, B-cell activating factor receptor.