



POST-NEW ORLEANS 2022

Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI

Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO

Paolo Corradini
Mauro Krampere
Fabrizio Pane
Adriano Venditti

Malattie emorragiche su base costituzionale

Mariasanta Napolitano





Dichiarazioni Mariasanta Napolitano

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario :Bayer, Novo Nordisk, Sobi, and Amgen
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board Kedrion, Amgen, Takeda, CSLBehring, Novo Nordisk, Novartis, Bayer, Sanofi Genzyme.
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**



Topics



Donne e deficit emorragici congeniti



Terapia genica dell'emofilia A e B



Terapie non sostitutive in emofilia



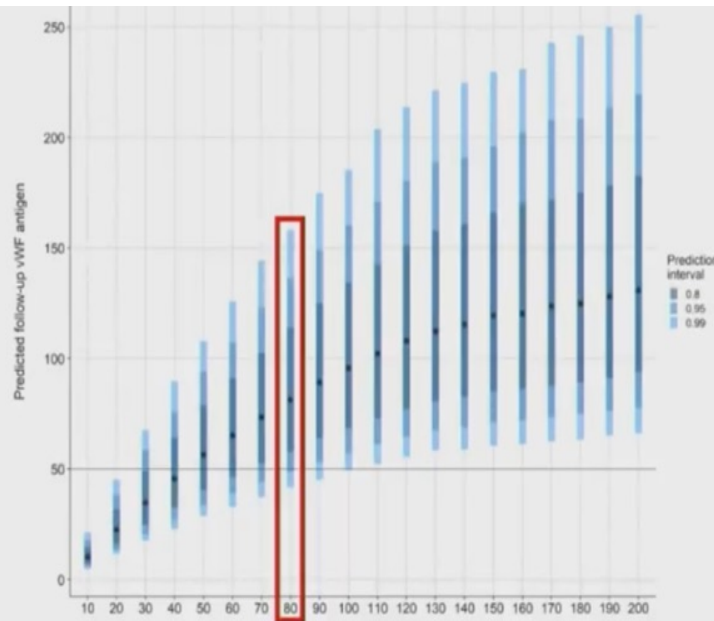
Deficit rari (FXI, VKORD1)



Repeat or Not Repeat, That Is the Question: Von Willebrand Testing in Adolescent Girls with Heavy Menstrual Bleeding

VWF Prediction Model

Initial VWF Antigen	Probability of normal ($\geq 50\%$) VWF value on repeat testing
50%	67.7%
60%	84.6%
70%	92.8%
80%	97.0%
90%	98.7%
$\geq 100\%$	$\geq 99.4\%$

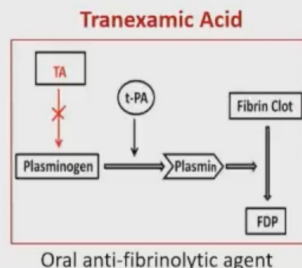
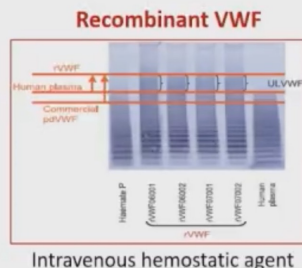


Clay Cohen ha mostrato che nelle adolescenti di età compresa tra 9 e 21 anni con flussi mestruali eccessivi, se il livello iniziale di vWF:Ag risulta superiore a 80%, non è necessario ripetere dosaggio vWF



Multicenter, Randomized Crossover Trial Comparing Recombinant Von Willebrand Factor and Tranexamic Acid for Heavy Menstrual Bleeding in Von Willebrand Disease

Intervention



Cycles 1, 2

Group 1: rVWF 40 IU/kg IV on day 1

Group 2: TA 1300 mg po tid on days 1-5

Cycles 3, 4

TA 1300 mg po tid on days 1-5

rVWF 40 IU/kg IV on day 1

Cost Analysis of TA vs. rVWF in HMB

I. Drug Costs

	Cost ¹	Unit Cost	Dose	Total Cost Per Patient
Recombinant VWF (N=17)			@40 IU/kg/60kg	Not including infusion cost
500 IU	\$287.83	\$0.576	2400 IU	\$1,381.58
1000 IU	\$453.74	\$0.454	2400 IU	\$1,088.98
Tranexamic Acid (N=19)			@30/5 days	Drug cost only
650 mg	\$14.87	\$0.496	30 tabs	\$14.87

II. Other Costs

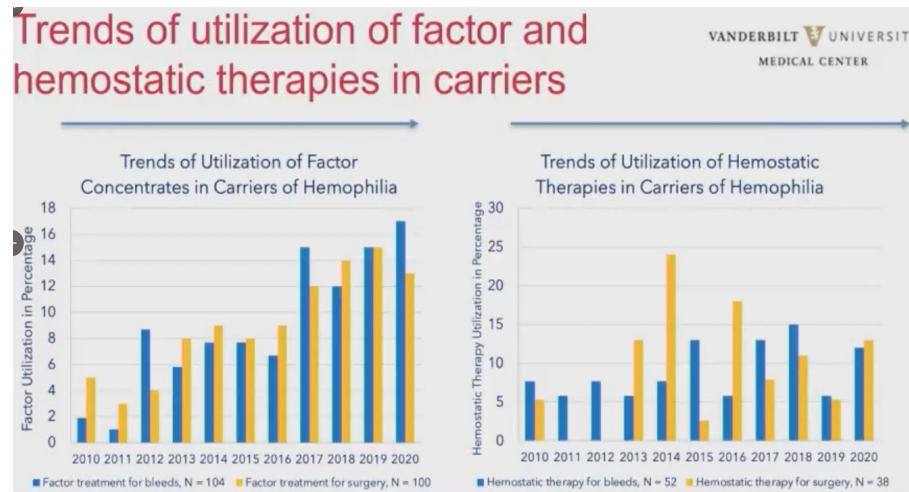
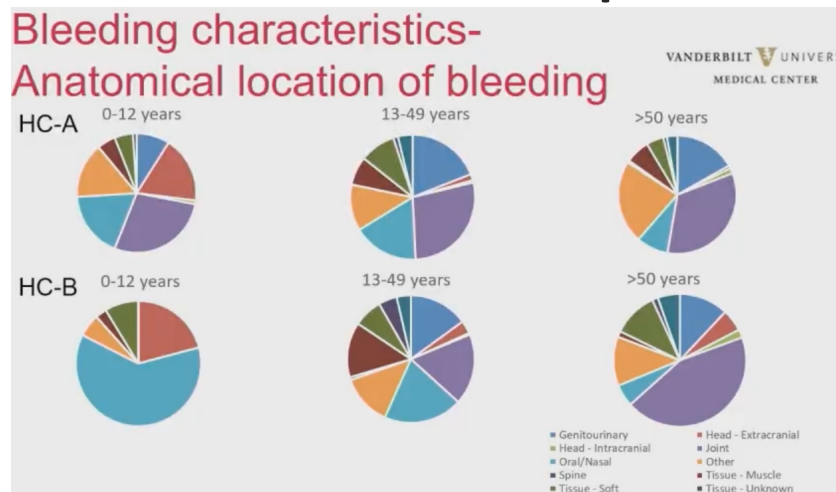
	Cost ²	Average Cost Per Patient ⁴
Emergency Dept. Visit		
Moderate-high (99284)	\$123.20	\$21.74
Lost Income		
Average hourly wage	\$32.11	\$256.88
Total private non-farm (Jun 22)		

Conclusion: TA is cost saving and more effective than rVWF in reducing HMB in VWD.

Margaret Ragni ha mostrato che in donne con vWD e HMB, VWF ricombinante risulta inferiore ad acido tranexamico (TA) nel ridurre PBAC score, nessuna differenza in qualità di vita è stata riportata.



Characterization of Bleeding and Laboratory Phenotype of Carriers of Hemophilia and Trends of Utilization of Factor Concentrates and Hemostatic Therapies: Analysis of the National Athndataset



Neeraja Swaminathan ha riportato i dati relativi a hemophilia carriers. La maggior parte degli eventi emorragici si verifica tra 13-49 anni. Incremento nell'uso di concentrati; Incremento dei livelli di Fattore nel tempo (intervallo non molto lungo); Scarsi i dati relativi a sanguinamenti mestruali.

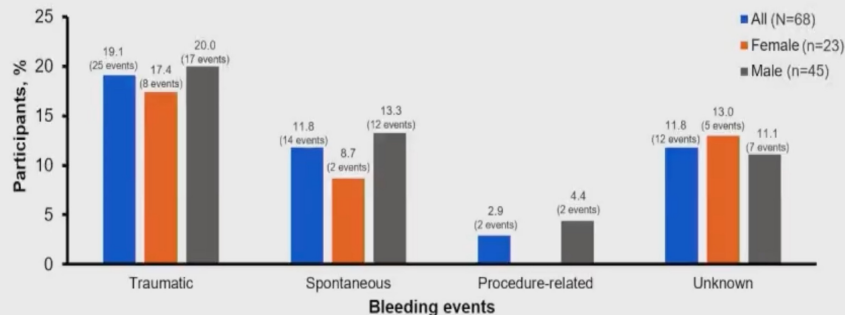


Characteristics and Bleeding Behavior of Females with Mild Hemophilia A

A: Longitudinal Study from Picnichealth Hemophilia A Database

Bleeding patterns in females and males with mild HA

- Overall, **60.9%** of females with mild HA and **60.0%** of males with mild HA **had no bleeding events** in the 1 year prior to enrollment
- The **small number** of recorded events **does not allow** for meaningful conclusions about the differences in bleeding phenotypes between females and males with mild HA



Conclusions



This real-world cohort study, with one of the largest female populations with mild HA to date, observed differences in disease characteristics between females and males with mild HA, but statistical analysis was limited by low participant numbers



Females with mild HA had a higher median age at diagnosis and higher baseline FVIII levels compared with males with mild HA



The proportion of females with mild HA treated with FVIII prophylaxis was lower than the males with mild HA; however, this conclusion is limited by the small sample size and relatively high proportion of participants with an unknown regimen



As this database relies on patient participation, there was a potential selection bias towards those with more symptomatic disease, and some data were incomplete



Future studies will analyze ongoing prospective data, collect more granular data on bleeding phenotype, and compare cohorts stratified by baseline FVIII levels

Angela Weyand ha comparato maschi affetti da emofilia lieve e donne affette da emofilia.
Tassi di sanguinamento sovrapponibili tra maschi e femmine



Comparative Study > Haemophilia. 2020 Jan;26(1):117-121. doi: 10.1111/hae.13891.

Epub 2019 Dec 9.

Can we compare haemophilia carriers with clotting factor deficiency to male patients with mild haemophilia?

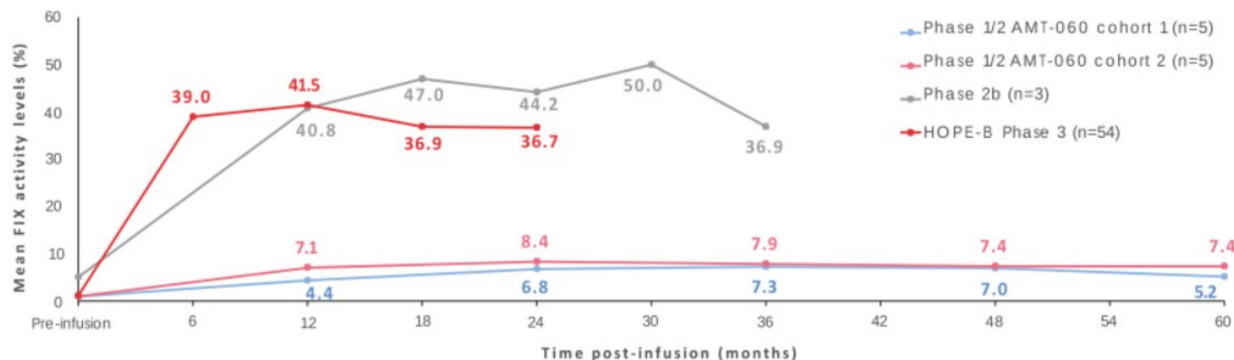
Simona Raso ^{1 2}, Catherine Lambert ², Ana Boban ^{2 3}, Mariasanta Napolitano ⁴, Sergio Siragusa ⁴,
Cedric Hermans ²



Adults with Severe or Moderately Severe Hemophilia B Receiving Etranacogene Dezaparvovec in the HOPE-B Phase 3 Clinical Trial Continue to Experience a Stable Increase in Mean Factor IX Activity Levels and Durable Hemostatic Protection after 24 Months' Follow-up

Wolfgang Miesbach ha presentato i dati a due anni relativi alla fase 3 di HOPE-B trial (AMT061). I livelli di FIX sono stabili con una media pari a 36.7% a 2 anni vs 39.0% a 6 mesi.

Figure 2. Mean FIX activity levels over time in the clinical trials of AMT-060 and etranacogene dezaparvovec^a



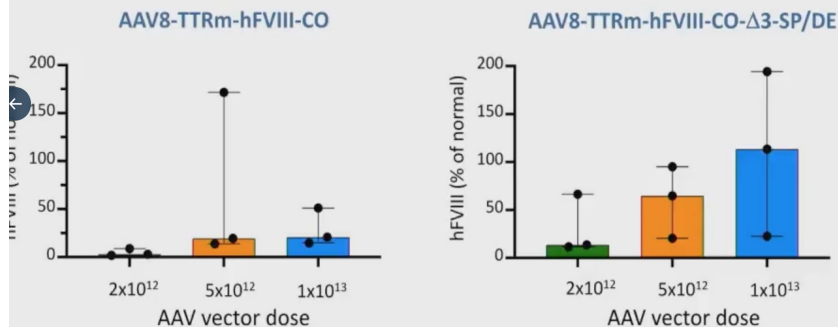
^a Phase 1/2 AMT-060 and Phase 2b had no lead-in period; Phase 3 HOPE-B had a ≥ 6 month lead-in period where participants received FIX prophylaxis. For Phase 2b, baseline FIX expression was 0-2%, but no washout of infused FIX was required prior to day 1; n=3 for all timepoints except pre-infusion (n=1), 18 months (n=2), and 36 months (n=2). For HOPE-B Phase 3, n=54 at pre-infusion, n=51 at 6 months, and n=50 at 12, 18 and 24 months. FIX, factor IX.



Second Generation Adeno-Associated Viral Vector Using a Novel Factor VIII Variant with Improved Secretion Achieves Higher Factor VIII Expression in Non-Human Primates

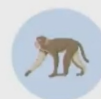
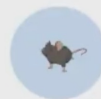
AAV delivery of hFVIII-BDD variant and hFVIII-BDD in NHP

Peak hFVIII antigen levels



Conclusions

- Δ3-SP/DE has increased expression that is 3-5-fold higher than wild type hFVIII following gene transfer.



- The hFVIII-Δ3-SP/DE variant has enhanced secretion compared to wild type hFVIII which overcomes a key barrier in AAV gene therapy for hemophilia A.
- Provides a novel strategy for reducing the AAV vector dose and improving the safety profile of AAV-FVIII.

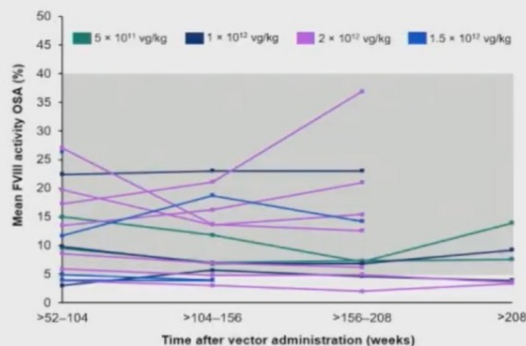
Denise Sabatino ha presentato dati relativi a vettore AAV di seconda generazione per terapia genica di emofilia A, disponibili ad oggi solo studi animali



Long-Term Durable FVIII Expression with Improvements in Bleeding Rates Following AAV-Mediated FVIII Gene Transfer for Hemophilia A: Multiyear Follow-up on the Phase I/II Trial of SPK-8011

Stacy Croteau ha illustrato i dati aggiornati dello studio con SPK8011 su terapia genica di FVIII. In contrasto con tutti gli altri programmi relativi a terapia genica di emofilia A, i livelli di FVIII sono stabili

Durable FVIII activity observed up to 5 years post SPK-8011



Majority of participants maintain FVIII:C expression within mild hemophilia range

Dose cohort	Participant	FVIII:C (OSA) Mean % (n)			
		>52-104 weeks	>104-156 weeks	>156-208 weeks	>208 weeks
5 × 10 ¹¹ vg/kg	1	15.0 (4)	11.8 (4)	7.1 (5)	13.9 (3)
	2	9.5 (4)	7.0 (3)	7.3 (2)	7.6 (4)
	3	3.0 (1)	5.7 (3)	4.6 (3)	3.9 (1)
1 × 10 ¹² vg/kg	4	9.8 (4)	6.8 (3)	6.8 (2)	9.2 (2)
	6	22.4 (3)	23.0 (4)	23.0 (3)	*
	7	27.0 (5)	13.7 (1)	12.6 (2)	†
2 × 10 ¹² vg/kg	8	3.9 (3)	3.0 (4)	2.0 (1)	3.4 (1)
	9	8.6 (4)	6.9 (3)	6.2 (3)	
	10	13.5 (4)	16.2 (4)	21.0 (3)	
	11	19.7 (4)	13.6 (4)	15.4 (3)	
	13	5.9 (4)	4.8 (5)	4.9 (1)	3.6 (1)
	14	17.3 (6)	21.1 (2)	36.9 (2)	
	15	11.7 (3)	18.7 (5)	14.2 (2)	
1.5 × 10 ¹² vg/kg	16	4.0 (15)	3.9 (4)		
	17	4.9 (11)	4.0 (3)		
	18	26.3 (4)			

Data cut-off: Oct 4 2022

*Participant terminated study participation due to site closure; †Sample >208 weeks unable to be processed. Analysis includes participants with >52 weeks of follow up (n=16); data for two participants (#5 & #12), who lost complete transgene FVIII expression following presumed capsid immune response, are censored. Grey shaded area in figure indicates the mild range of hemophilia A. FVIII assessments obtained within 5 days of administration of a FVIII infusion were excluded. FVIII:C, FVIII coagulant activity; OSA, one-stage assay



Non-factor therapies

Contact activation (intrinsic) pathway

Damaged surface

XII

XIIa

Emicizumab Mim8

Tissue factor (extrinsic) pathway

Trauma

TFPI

Concizumab
Marstacimab
MG1113

Via di somministrazione sottocute, intervalli prolungati

Fitusiran

Serpin PC

Active Protein C

Protein S

Protein C + Thrombomodulin

Fibrinogen (I)

Fibrin (Ia)

XIIIa

XIII

Cross-linked
fibrin clot

V



Subcutaneous Concizumab Prophylaxis in Patients with Hemophilia A or B with Inhibitors: Efficacy and Safety Results By Hemophilia Subtype from the Phase 3 Explorer7 Trial

Melissa Frei-Jones ha riportato i dati relativi a profilassi quotidiana con concizumab in pazienti affetti da emofilia A e B con inibitore. La molecola è risultata efficace, nessun evento tromboembolico registrato

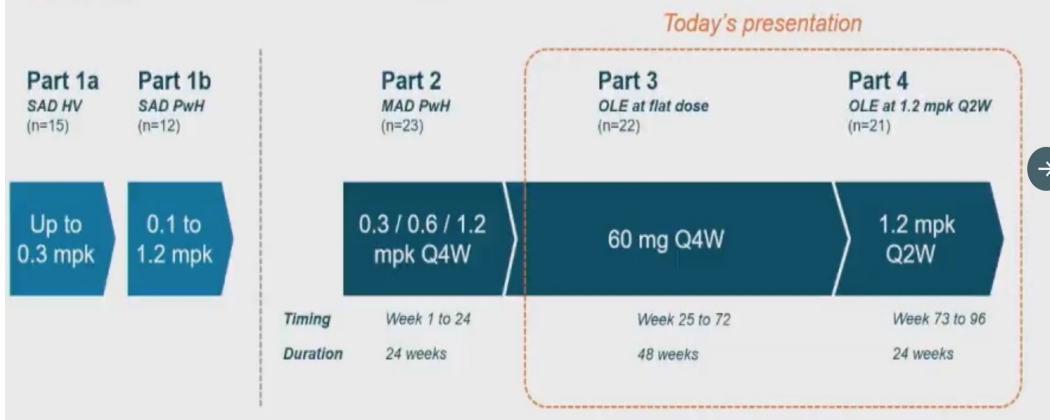
Overall median ABR on concizumab prophylaxis was 0.0 in both the HAwI and HBwI subgroups (arms 1 to 4)

Spontaneous and traumatic bleeding episodes by hemophilia subtype (HAwI and HBwI) for concizumab prophylaxis in explorer7 arms 1-4		
Median ABR (P25-P75)	HAwI Concizumab PPX (n=76)	HBwI Concizumab PPX (n=51)
Treated spontaneous and traumatic bleeding episodes	0.0 (0.0-3.7)	0.0 (0.0-3.3)
Treated spontaneous bleeding episodes	0.0 (0.0-1.4)	0.0 (0.0-2.2)
Treated spontaneous and traumatic joint bleeding episodes	0.0 (0.0-2.0)	0.0 (0.0-2.6)
Treated spontaneous and traumatic target joint bleeding episodes	0.0 (0.0-0.0)	0.0 (0.0-0.0)
All treated and untreated spontaneous and	2.2 (0.0-4.5)	2.2 (0.0-5.7)

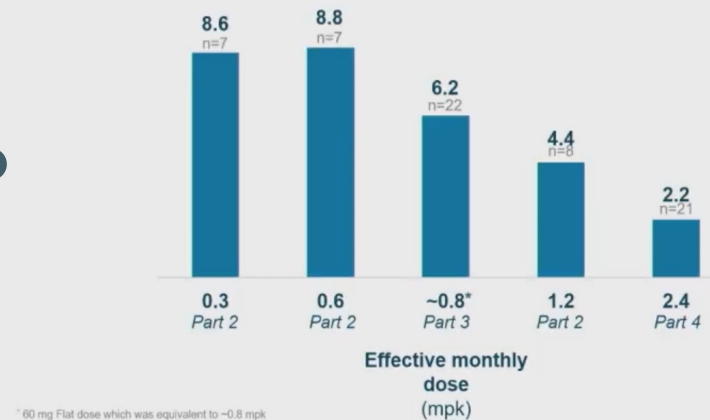


Serpinpc in Persons with Severe Hemophilia (PwH): Updated Results from a Multi-Center, Multi-Part, First-in-Human Study

AP-0101 study design: adaptive first-in-human study to investigate the safety, tolerability, efficacy and PK of SerpinPC



AP-0101: All bleed median ABR by dose level

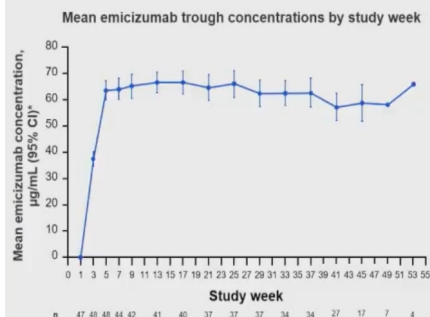


Trevor Baglin ha riportato i risultati relativi alla somministrazione di SerpinPC (inibitore di proteina C attivata) in emofilia. ABR ridotto da 34 a 2.2, 100% dei pazienti con target joints ad inizio studio.



Emicizumab Prophylaxis for the Treatment of Infants with Severe Hemophilia A without Factor VIII Inhibitors: Results from the Interim Analysis of the HAVEN 7 Study

Effective emicizumab trough concentrations were achieved and sustained in infants



Emicizumab trough concentrations by study week

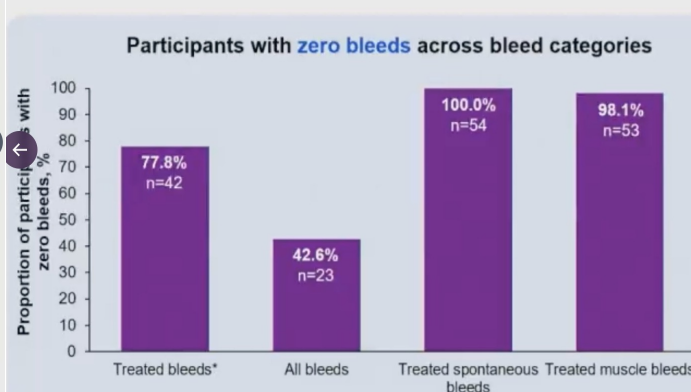
- Following loading doses, mean (95% CI) trough concentrations were **63.2 (59.5–66.8) µg/mL**
- Steady-state trough concentrations of **~60–65 µg/mL** were above that reported in previous HAVEN studies and maintained throughout the study period

Emicizumab trough concentrations by age

- Mean steady-state trough concentrations **increased slightly with age** until approximately 6 months of age when they reached approximately 65 µg/mL
- Mean FIX and FX concentrations were **not impacted by emicizumab treatment**
- aPTT was **normalized by Week 3*** in most participants

*Confidence intervals are displayed only for study weeks in which ≥ 10 assessments are available. *This was the first time point when samples were obtained for testing aPTT due to limitations on taking blood samples in infants. aPTT, activated partial thromboplastin time; CI, confidence interval; F, factor

Emicizumab demonstrated consistent efficacy across bleeding endpoints



Median (min, max) age at IA: 16 (1, 26) months (N=54)

Steven Pipe ha illustrato i dati dello studio HAVEN7 Emicizumab nei lattanti di età <12 mesi, 54 partecipanti, buoni i livelli medi di emicizumab, buona efficacia, sicuro



Hemorrhagic and Thrombotic Adverse Events Associated with Emicizumab and Extended Half-Life FVIII Replacement Drugs in Patients with Hemophilia a: Data from the Eudravigilance Database

Results

ADR reported in 2021

Total	EMICIZUMAB 406	EHL products 376	ROR (95%CI)
Hemorrhagic	232 (57%)	275 (73%)	0,49 (0,36-0,66)
Thrombotic	24 (6%)	9 (2,4%)	2,56 (1,18-5,59)

Flora Peyvandi ha riportato il profilo di eventi avversi secondari a esposizione ad emicizumab vs FVIII EHL per eventi trombotici e emorragici dal database Eudravigilance

Thrombotic ADR

EMICIZUMAB

1 DIC*
1 microangiopathy*
8 venous thrombosis**
14 arterial thrombosis ***
(5 MI, 3 stroke, 2 peripheral artery occlusion, 1 TIA, 1 renal infarct, 1 mesenteric artery occlusion)

EHL products

1 DIC
3 venous thrombosis**
5 arterial thrombosis (5 MI)

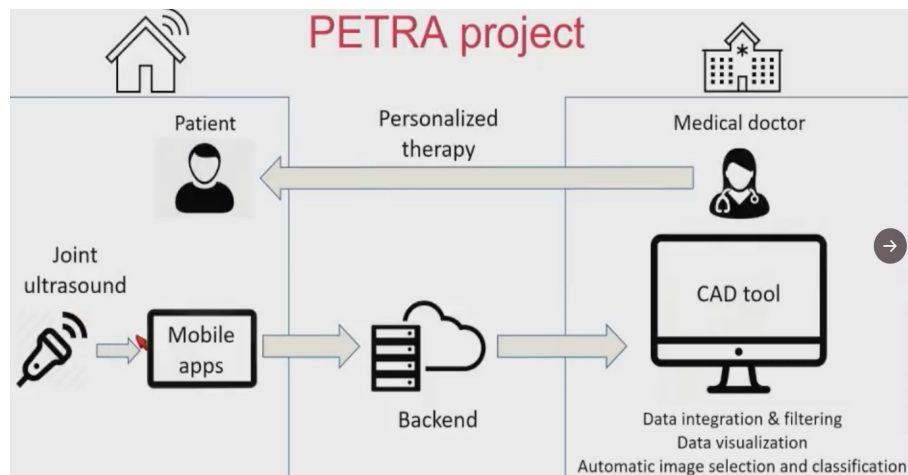
9 (27%) thrombotic ADR during concomitant treatment with bypassing agent
→ All but one were reported with FVIIa

Conclusion

- A lower reporting frequency of hemorrhagic ADR and a higher reporting frequency of thrombotic ADR for emicizumab compared to EHL FVIII products was present
- About one-third of thrombotic ADR were reported with concomitant use of emicizumab and FVIIa
- Benefit risk profile requires a detailed evaluation of both bleeding and thrombotic risk
- An accurate pharmacosurveillance is required for a long term safety evaluation



A Computer-Aided Diagnosis Tool for the Detection of Hemarthrosis By Remote Joint Ultrasound in Patients with Hemophilia



Conclusions

The accuracy of an AI-based algorithm for the automatic detection of joint capsule distension was good, performance may require further improvement

Standardisation of the definitions of ultrasound joint health is necessary to tackle early hemarthrosis and delay the progression of hemophilic arthropathy

A telemedicine system to early detect hemarthrosis in patients with hemophilia will allow early personalized management of patients with hemophilia

E' possibile per i pazienti affetti da emofilia adoperare a domicilio US per diagnosticare emartro con l'aiuto di un algoritmo basato su intelligenza artificiale.

Roberta Gualtierotti ha presentato il progetto PETRA



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Poster presentations



Enhancing the Genetic Diversity of FXI Deficiency: Structural Variants and New Cross Reactive Positive Variants

Maria Eugenia de la Morena-Barrio, PhD, Universidad de Murcia

Identificazione di deficit genetici responsabili di carenza di FXI per valutarne i diversi siti interessati e l'impatto clinico

91 famiglie di razza Caucasica con deficit di FXI (FXI:C<70%) identificate tramite allungamento di aPTT, studiate tramite gene sequencing in NGS

Identificate 31 varianti di FXI, tre di esse sono nuove varianti strutturali nucleotidiche, includono due parziali duplicazioni, una a carico di esoni 8-9 e esone 14; una delezione di 7 MB (142 basi).

Eterogeneità genetica confermata in deficit di FXI in Caucasici.



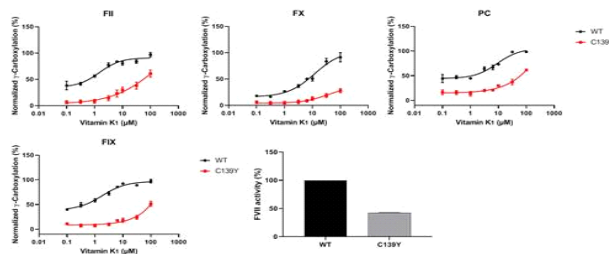
Novel Gamma-Glutamyl Carboxylase Mutation Causing Hemorrhagic and Non-Hemorrhagic VKCFD1 Phenotypes

Gianna M. Guzzardo, MD, Children's Hospital of Michigan

	Sibling 1 Pre Treatment	Sibling 1 Post Treatment
Factor II Activity	12%	40%
Factor VII Activity	2.7%	71%
Factor IX Activity	3.8%	68.6%
Factor X Activity	7.4%	53%
Protein C Activity	3.8%	38%
Protein S Activity	2.5%	15%
	Sibling 2 Pre Treatment	Sibling 2 Post Treatment
Factor II Activity	18%	39%
Factor VII Activity	27%	65%
Factor IX Activity	16.1%	62.7%
Factor X Activity	16%	45%
Protein C Activity	13%	25%
Protein S Activity	<8%	10%

Table 1: Vitamin K dependent coagulation factor activity levels pre and post Vitamin K supplementation after supplementation initially with 5mg vitamin K for both patients. Vitamin K dosing was subsequently increased to 10mg daily once patients reached 40kg.

Vitamin K dependent clotting factors



Vitamin K dependent proteins with function in bone metabolism

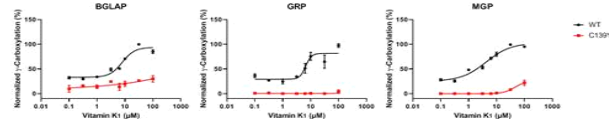


Figure 1: In vitro characterization of GGKX:p.C139Y

Clotting factors: Reduced activities for C139Y for all VKD clotting factors, which will never reach levels as for wild type, but sufficient increasing amounts via vitamin K supplementation as seen in the patients in this report

VKD bone proteins: Almost zero levels of carboxylated proteins BGLAP, GRP and MGP, which also do not increase by vitamin K supplementation, which explains the severity of the non-hemorrhagic phenotype of the siblings. Here it would be nice to see if the levels are really not increasing for the patients when supplemented with vitamin K via the ELISA from their blood samples.

Abbreviations: BGLAP: Bone Gla protein, ELISA: enzyme-linked immunoassay, GGKX: gamma-glutamyl carboxylase, GRP: Gla-rich protein, MGP: Matrix Gla protein, VKD: vitamin K dependent

Identificata in una famiglia araba una nuova mutazione nel gene GGKX,c.[416G>A];[416G>A] p.(Cys139Tyr) esone 4, responsabile di VKCFD1 in probando di 17 mesi.

Mutazione associata a easy bruising ed alterazioni scheletriche (alterazioni dentarie, ridotta distanza tra le falangi) Vitamina kappa, efficace nell' incrementare, ma non normalizzare, i livelli di fattori della coagulazione



An Antibody Targeting Human FV Promotes Thrombin Generation and Reduces Bleeding in a Hemophilic Mouse Model

Sean Quinn, PhD, Children's Hospital of Philadelphia

Agire sulle proprietà funzionali di FV/FVa potrebbe rappresentare un approccio per la gestione di emofilia A e B. Valutata la capacità di anticorpi monoclonali che agiscono su FVa con FXa, sulla superficie di cellule attivate e amplificano la cinetica di TF.

Valutato se tutte le forme di anticorpi monoclonali che agiscono su FV fossero efficaci nel promuovere la generazione di trombina (TG) in vivo e in vitro in modello murino

Identificato un anticorpo procoagulante (GB5) ad alta affinità con t(h)FV, FVa.

GB5 è un anticorpo monoclonale procoagulante che si lega ad alta affinità a FV e influenza le reazioni che portano alla sua attivazione e inattivazione, FVa ha il massimo impatto su TG.

Grazie!