Hemophilia Treatment: Factors to Consider

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TOPA

1

Disclosures

- There are no relevant financial interests to disclose for myself or my spouse/partner from within the last 12 months.

TOPA

2

Objectives

- Discuss standard half life and extended half life factor treatment options for patients with hemophilia
- Describe emicizumab-kxwh role in therapy for Hemophilia A

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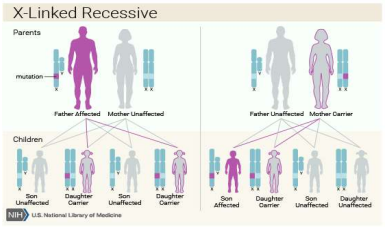
3

Hemophilia

Hemophilia A
- Factor VIII (FVIII) Deficiency
- 80% of cases

Hemophilia B
- Factor IX (FIX) Deficiency
- 20% of cases



MedlinePlus, National Library of Medicine.

4

Complications and Classification

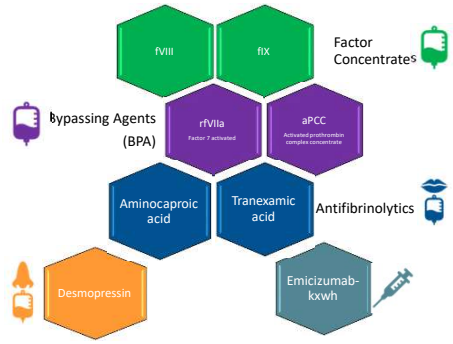
Severity	Mild	Moderate	Severe
Baseline Factor Level (% of normal)	6-30%	1-5%	<1 %
Bleeding	Major Trauma	Minor Trauma	No Trauma

- Life threatening bleeds
- Joint damage and Immobility
- Inhibitors (factor antibodies)
- Viral Transmission

Srivastava A. *Hemophilia.* 2020.

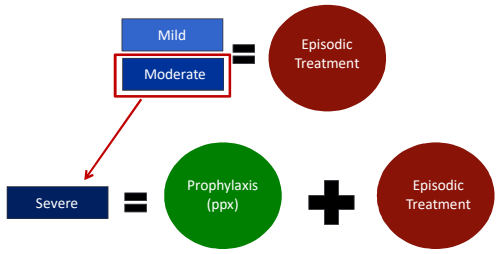
5

Treatment Options



6

Treatment Approaches



7

Prophylactic Therapy

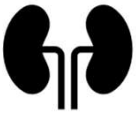
- Primary Prophylaxis
  - Initiation of preventative therapy before onset of joint disease, second clinically relevant bleed, and 3 years of age
- Secondary Prophylaxis
  - Initiation of preventative therapy after two or more joint bleeds but before disease and typically > 3 years of age
- Tertiary Prophylaxis
  - Initiation of preventative therapy after onset joint disease

Manco-Johnson,et al. *NEJM.* 2007; Strisava A. *Hemophilia.* 2020

8

Recombinant Factor Concentrates

- First Generation
  - Animal and/or human proteins in final formulation
- Second Generation
  - Animal and/or human proteins in culture medium but not final formulation
- Third Generation ⭐
  - No animal and/or human proteins in medium or final formulation



MASAC #263. *NHF.* 2020

9

Factor Concentrates

- Standard Half-Life (SHL)
  - FVIII: ~12hr
  - FIX: ~18-24hr
- Extended Half-Life (EHL)
  - FVIII: 1.4-1.6x half-life SHL
  - FIX: 3-5x half-life SHL
    - Recovery and extravascular distribution differ from SHL FIX and between EHL FIX concentrates

FVIII/FIX Pegylated

FVIII/FIX Fc fragment IgG

FIX Albumin

MASAC #263. *NHF.* 2020; Srivastava A. *Hemophilia.* 2020.

10

Third Generation FVIII Concentrates

Extended Half Life

- Efmoroctocog alfa (Eloctate®)
- Damoctocog alfa pegol (Jivi®)
- Ruiroctocog alfa pegol (Adynovate®)
- Turoctocog alfa pegol (Esperoct®)

- Octocog alfa (Advate®; Kovaltry®)
- Simoctocog alfa (Nuwiq®)
- Turoctocog alfa (NovoEight®)
- Moroctocog alfa (Xyntha®)
- Lonoctocog alfa (Afstyla®)

Standard Half Life

11

Third Generation FIX Concentrates

Extended Half Life

Eftrenonacog alfa (Alprolix®)

Albutrepenonacog alfa (Idelvion®)

Nonacog beta pegol (Rebinyn®)

Nonacog alfa (Benefix®)

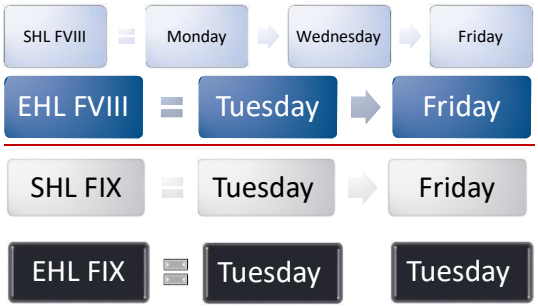
Trenonacog alfa (Ixinity®)

Nonacog gamma (Rixubis®)

Standard Half Life

12

Factor Concentrate Prophylaxis



13

Dosing for Prophylaxis

Conventional/ Fixed Dosing

- Standard dosing approaching that utilizes SHL
  - High dose
    - Achieves lowest annual joint bleeding rate (AJBR)
    - Essentially ensures patients always have measurable factor
  - Intermediate dose
    - Reduces AJBR ~90%
  - Low dose
    - Reduces AJBR ~80%

Tailored Approach

- Pharmacokinetic Approach
  - Typically targets maintaining factor trough >1-5%
  - Limited sampling strategy with Bayesian analysis
  - Extended sampling strategy ~11 samples
- Clinical Factors Approach
  - Bleeding phenotype
  - Physical activity

Srivastava A. *Hemophilia.* 2020.

14

Pharmacokinetic Modeling

- Pharmaceutical Manufacturers
  - myPKFiT®
  - Hemotik®
- PK Platforms
  - ADAPT®
  - WinNonlin®
- WAPPS-Hemo©
  - Endorsed by World Federation of Hemophilia
  - Bayesian approach
  - FREE
  - Worldwide product with wide variety of factor concentrates (SHL and EHL)
  - www.wapps-hemo.org

15

RL is a 14yo male with severe hemophilia A. He has previously refused factor prophylaxis, but recent developed multiple joint bleeds. The family and patient would like to begin a prophylactic factor concentrate regimen that allows for the least amount of infusions. What regimen do you recommend?

A. Efmoroctocog alfa (Eloctate®) 50 units/kg IV twice weekly with follow-up pharmacokinetic studies

B. Albutrepenonacog alfa (Idelvion®) 50 units/kg IV once weekly, with follow-up pharmacokinetic studies

C. Fixed dose Octocog alfa (Advate®) 25 units/kg twice weekly

D. Fixed dose Eftrenonacog alfa (Alprolix®) 50 units/kg IV once monthly

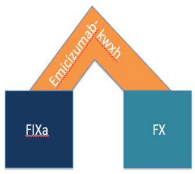
16

Alternative to Infusions?

17

Emicizumab-kxwh

- FDA approved for prophylaxis in adults and pediatric patients with Hemophilia A
- Subcutaneous injection
  - Loading dose 3 mg/kg weekly x 4 weeks
  - Maintenance dose:
    - 1.5 mg/kg weekly
    - 3 mg/kg every 2 weeks
    - 6 mg/kg every 4 weeks
- Most common side effect injection site reaction, headache, arthralgia
- Boxed warning for thromboembolism/thrombotic microangiopathy (TMA) when used in combination with aPCCs



Knight T. *Thera Adv in Hem.* 2018

18

Emicizumab Significantly Reduces Annual Bleeding Rate for Inhibitor Patients

	Study Population	Primary Objective	Outcome
HAVEN 1	Inhibitor Patients 12y+ Treated with bypassing agent (BPA) for episodic therapy or ppx + episodic therapy N=109	Difference annual bleeding rate (ABR) A: Emicizumab ppx B: Episodic treatment with BPA C: Previous ppx pts changed to emicizumab	ABR- 89% decrease between group A and B (p<0.001) A: 2.9 [1.7-5.0] B: 23.3 [12.3-43.9] C: Lowered ABR by 79% (p <0.001) than previous BPA for ppx therapy TMA (N=3) and thrombosis (N=1)treated with aPCC + emicizumab

Emicizumab dosing 3 mg/kg subQ weekly x 4 weeks, then 1.5 mg/kg subQ weekly

Oldenburg J, et al. *NEJM*, 2017.

19

Emicizumab Significantly Reduces ABR for *Pediatric* Inhibitor Patients

	Study	End Points	Outcome
HAVEN 2	Inhibitor Patients Age 1-15y Receiving BPA for episodic/ppx treatment N=88 (85 <12y)	ABR and bleeding reduction compared to prior BPA treatment; health QOL A: Emicizumab ppx once weekly B: Emicizumab ppx every 2 weeks C: Emicizumab ppx every 4 weeks	Intraindividual comparison to BPA showed 99% reduction [97.4-99.4] in ABR (n=15) A: ABR 0.3 [0.17-0.5], 77% ABR=0 B: ABR 0.2 [0.03-1.72] C: ABR 2.2 [0.69-6.81] AE: 2 patients developed antibodies, 1 lost efficacy

Emicizumab dosing 3 mg/kg subQ weekly x 4 weeks, then (A) 1.5 mg/kg subQ weekly; (B)3 mg/kg subq every 2 weeks; (C) 6 mg/kg every 4 weeks

Young G. et al, *Blood*. 2019

20

Emicizumab Significantly Reduces ABR for Non-Inhibitor Patients

	Study	Primary Objective	Outcome
HAVEN 3	Non-inhibitor Patients 12y+ Receiving ppx or episodic fVIII N=152	Difference ABR, treated bleeds between groups A: Once weekly dosing B: q2week dosing C: No ppx D: previous on ppx with fVIII, once weekly	96% and 97% (p<0.001) reduction ABR treated bleeds for A and B compared to C A: 1.5 [0.9-2.5] B: 1.3 [0.8-2.3] C: 38.2 [22.9-63.8] D: 68% lower ABR (p<0.001) No major AE related to emicizumab

Emicizumab 3mg/kg subQ once week x 4 weeks; 1.5mg/kg weekly or 3mg/kg every other week

Mahlangu J. et al. *NEJM*. 2018.

21

Emicizumab Treatment Plan

Severe HemA = Prophylaxis = Emicizumab + Episodic treatment

- Episodic Treatment Options:
  - rFVIIa (inhibitor patients)
  - SHL or EHL rFVIII
  - Antifibrinolytics in addition to factor concentrates
  - Avoid aPCC due to risk of thrombosis and TMA

22

Coagulation Labs for Emicizumab Patients

- Emicizumab interferes with the following test
  - Activated Clotting Time (ACT)
  - Activated partial thomboplastin time (aPTT)
  - aPTT based clotting factor assays
    - Bethesda units
    - Intrinsic pathway clotting based assays
- Unaffected Assays
  - Bovine chromogenic Bethesda assay
  - One stage PT based single factor assays
  - Chromogenic based single factor assays
    - For fVIII, must be bovine based

23

RC is a 5yoM (25kg) with high titer inhibitor. He has a target joint of right elbow and family would like to switch from bypassing agent prophylaxis to emicizumab. They desire a regimen that minimizes injections but provides best prevention of bleeds. What do you recommend?

- Emicizumab 3 mg/kg weekly x 4 weeks, 3 mg/kg every 2 weeks; rfVIIa (Novoseven RT®) 90 mcg/kg prn bleeding episodes
- Emicizumab 3 mg/kg every 2 weeks; rfVIIa (Sevenfact®) 90 mcg/kg prn bleeding episode
- Emicizumab 3 mg/kg weekly x 4 weeks, 1.5 mg/kg every week; aPCC (FEIBA®) 50 units/kg q8h prn bleeding episode
- Emicizumab 3 mg/kg weekly x 4 weeks, 3 mg/kg every 2 weeks; Efmoroctocog alfa (Eloctate®) 50 units/kg prn severe bleeding episode

24

On the Horizon

- Non-factor therapies:
  - Concizumab
  - Fiturisan
  - Anti-TFPI monoclonal antibody
- Gene Therapy

Mannucci. *Haematologica*.2020

25

Hemophilia Treatment

- National and international guidelines do not give preference to emicizumab vs factor concentrates for the prophylactic treatment of Hemophilia A
- When utilizing factor concentrate for prophylaxis patients should be targeted to a trough of >1%
- Emicizumab is only approved for prophylaxis and patients must be provided with an episodic treatment option
- Patient's lifestyle and preference should be considered when choosing a treatment plan

26

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27

References

- National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD): The Library; 2020 Aug 17. [Illustration] X-Linked Recessive; [cited 2020 Sep 24]; Available from: https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns
- Franchini M and Mannucci PM. The History of Hemophilia. Semin Thromb Hemost. 2014; 40:571-76.
- Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. NEJM. 2007. 357(6):535-544.
- Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines to for the Management of Hemophilia, 3rd Edition. Hemophilia. 2020 Aug3.
- MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. National Hemophilia Foundation. 2020: 263. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/MASAC-Recommendations-Concerning-Products-Licensed-for-the-Treatment-of-Hemophilia-and-Other-Bleeding-Disorders
- WAPPS-Hemo, McMaster University. 2020. www.wapps-hemo.org.
- Knight T. and Callaghan MU. The Role of Emicizumab, a Bispecific Factor Ixa and Factor X-directed antibody, for the Prevention of Bleeding Episodes in Patients with Hemophilia A. Therapeutic Advances in Hematology. 2018; 9(10):319-334.
- Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in Hemophilia A with Inhibitors. NEJM. 2017; 377(9):809-18.
- Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019; 134(24):2127-38.
- Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. NEJM 2018: 379(9):811-22.
- Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A(HAVEN 4): a multicentre, open-label, non randomised phase 3 study. Lancet Haematol. 2019; 6(6):e295-305.
- Mannucci PM. Hemophilia therapy:the future has begun. Haematologica. 2020; 105(3):545-53.

28