



NATIONAL HEMOPHILIA FOUNDATION

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MASAC Document #220

MASAC RECOMMENDATION REGARDING PROPHYLAXIS WITH BYPASSING AGENTS IN PATIENTS WITH HEMOPHILIA AND HIGH TITER INHIBITORS

The following recommendation was approved by the Medical and Scientific Advisory Council (MASAC) on October 5, 2013, and adopted by the NHF Board of Directors on October 6, 2013.

Prophylaxis (regular administration of Factor VIII or Factor IX concentrate to prevent bleeds) is considered optimal therapy for patients with severe hemophilia. Patients with hemophilia who develop inhibitory antibodies (inhibitors) to factor VIII (FVIII) or factor IX (FIX) may no longer respond to FVIII or FIX concentrates. Immune tolerance Induction (ITI) may help restore clinical response to clotting factor in some of these patients. However, in hemophilia patients with high titer inhibitors who are on ITI, have not yet begun ITI, or have failed ITI, retrospective and prospective evidence is accumulating that secondary prophylaxis with bypassing agents [activated prothrombin complex concentrate (FEIBA NF) and recombinant FVIIa (NovoSeven)] reduces joint and other bleeding episodes.

Three randomized clinical trials in the USA and abroad [1-3] using these bypassing agents showed significant reduction in bleeding episodes in joints and other tissues as well as prevention of development of new target joints. Other benefits were an improvement in quality of life and reduced hospitalizations and days missed from school /work [1, 3]. There were no thromboembolic events. One subject developed an allergic response to FEIBA and one to FEIBA NF [2, 3].

The doses used in the 3 clinical trials were as follows:

Hemophilia A and B: rFVIIa (NovoSeven) prophylaxis, 90 μ g/kg or 270 μ g/kg once daily. Note that there was no statistically significant difference in bleeding episodes between the 2 doses.

Hemophilia A: Factor Eight Inhibitor Bypassing Activity (FEIBA) prophylaxis, 85 \pm 15 units/kg on 3 non-consecutive days a week.

Hemophilia A and B: Factor Eight Inhibitor Bypassing Activity (FEIBA NF) prophylaxis, 85 \pm 15 units/kg every other day.

All of these doses were shown to be effective and safe and likely to show long term benefits for preserving joint function, improving quality of life, and preventing premature death from life-threatening bleeds such as spontaneous intracranial hemorrhage.

In light of these studies, MASAC recommends that prophylaxis with bypassing agents should be considered in patients with inhibitors. There are no clear-cut guidelines as to when to stop prophylaxis. Joint bleeds with subsequent joint destruction are a lifelong problem for these individuals. Therefore, they may continue to benefit from prophylaxis throughout their life. MASAC encourages further surveillance and research on this topic.

References:

1. Antunes SV, Tangada S, Stasyshyn O, Mamonov V, Phillips J, Guzman-Becerra N, Grigorian A, Ewenstein B, Wong WY. Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors. *Haemophilia* 2013 Aug 1. doi: 10.1111/hae.12246. [Epub ahead of print] PubMed PMID: 23910578.
2. Leissinger C, Gringeri A, Antmen B, Berntorp E, Biasoli C, Carpenter S, Cortesi P, Jo H, Kavakli K, Lassila R, Morfini M, Négrier C, Rocino A, Schramm W, Serban M, Uscatescu MV, Windyga J, Zulfikar B, Mantovani L. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. 2011 Nov 3; 365(18): 1684-92.
3. Konkle BA, Ebbesen LS, Erhardtsen E, Bianco RP, Lissitchkov T, Rusen L, Serban MA. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost*. 2007 Sep; 5(9): 1904-13.