blood advances

COUNTERPOINT Emicizumab should be prescribed independent of immune tolerance induction

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Background and introduction

The development of neutralizing alloantibodies to factor VIII (FVIII), commonly called "inhibitors," is a major complication of hemophilia A (HA) replacement therapy, occurring in 20% to 30% of patients with severe HA.[1-3] In these patients, FVIII replacement becomes inefficient and bleeding events are treated or prevented using bypassing agents (BPAs), which include activated prothrombin complex concentrates (aPCCs) and recombinant factor VIIa (rFVIIa).[4,5] BPAs are effective in restoring hemostasis but are often not able to completely normalize thrombin generation, in contrast to FVIII replacement.[6] In addition, they have been associated with rare thrombotic adverse events (AEs).[7,8] Thus, patients with persistent FVIII inhibitors present increased disease-related morbidity and should be offered immune tolerance induction (ITI). ITI consists of daily infusions of large doses of FVIII given until FVIII inhibitors disappear and FVIII pharmacokinetic parameters normalize.[9] Considering suboptimal success rate of such regimens (in the range of 60%-80%),[10] inconvenience of repetitive venous access, compliance issues, and cost, there is a major unmet need for therapeutic agents that are associated with effective bleeding control and improved quality of life.

Recently, both the US Food and Drug Administration and the European Medicines Agency approved a non–factor replacement therapy, emicizumab, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in HA adult and pediatric patients with FVIII inhibitors. The purpose of this paper is to bring arguments, based on results obtained from recent studies, that would support the use of prophylaxis with emicizumab independently of ITI.

Emicizumab pharmacologic profile confers effective prophylaxis in HA patients with or without FVIII inhibitors

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody that bridges activated factor IX (FIXa) and FX to partially restore the function of missing FVIII, which is required for effective hemostasis.[11] Advantageously, emicizumab is not affected by existing FVIII inhibitors, irrespective of FVIII-inhibitor titer.[12] Indeed, in ex vivo FVIII-neutralized plasma obtained from healthy volunteers, emicizumab shortened activated partial thromboplastin time and increased the peak height of thrombin generation in a dose-dependent manner.[13]

Overall, the pharmacokinetic profile and the route of administration of emicizumab make it particularly attractive for prophylactic use. Single subcutaneous injection of emicizumab of 0.1, 0.3, and 1 mg/kg body weight in healthy subjects provides a linear pharmacokinetic profile and a half-life of ~4 to 5 weeks,[13] which support the rationale for an infrequent dosing regimen. In HA patients with or without FVIII inhibitors receiving once-weekly 0.3, 1, and 3 mg/kg body weight administration of emicizumab, plasma emicizumab concentrations increased in a dose-proportional manner and reached steady state ~12 weeks after treatment initiation, where a loading dose was administered.[14,15] These studies suggested that the trough levels of plasma emicizumab concentrations and the resulting hemostatic effect is predictable. Based on these observations and pharmacologic modeling,[16] a novel dosing regimen was investigated in the phase 3 HAVEN 1 trial (www.clinicaltrials.gov #NCT02622321), which was conducted in 109 HA adult patients with FVIII inhibitors.[17] Mean steady-state plasma emicizumab concentrations reached >50 μg/mL after 4 weeks of a weekly loading dose of 3 mg/kg body weight and were sustained throughout the trial with a once-weekly maintenance dose of 1.5 mg/kg body weight. The trough plasma emicizumab concentrations were expected to correspond to at least 10 to 15 IU/dL of equivalent FVIII activity (FVIII:C), which represents a level of FVIII:C associated with a low risk of joint bleeding.[18] Therefore, we can speculate that emicizumab represents an interesting therapeutic

approach in patients who have developed FVIII inhibitors because it has been shown that the lower the bleeding rate, the lower the long-term complications of hemophilia (eg, hemophilic arthropathy)[19,20] and the higher the health-related quality of life.[21]

Emicizumab prophylaxis reduces the bleeding rate more efficiently than BPA treatment

It is obvious that emicizumab prophylaxis should be considered for HA patients with high-titer FVIII inhibitors who will not receive ITI or for those who failed ITI attempts. It has indeed been demonstrated that prophylaxis using emicizumab significantly reduced the bleeding rate in HA patients with FVIII inhibitors[14,15,17] compared with a prior treatment strategy. In the phase 3 HAVEN 1 trial, once-weekly administration of emicizumab resulted in an 87% ($P < .001$) reduction of the annualized bleeding rate compared with the group with no prophylaxis who received episodic treatment with BPAs.[17] Additionally, a direct intraindividual comparison between previous prophylaxis with BPAs and emicizumab prophylaxis was assessed during a prospective noninterventional study (www.clinicaltrials.gov #NCT02476942). Emicizumab prophylaxis resulted in a 79% ($P < .001$) lower bleeding rate than that observed with previous BPA prophylaxis. Among adult patients (>12 years of age) receiving emicizumab prophylaxis, a total of 63% experienced no bleeds during the trial.[17] Such efficacy was confirmed in pediatric patients, who are the most prone to develop FVIII inhibitors and receive ITI.[22] In the phase 3 HAVEN 2 trial (www.clinicaltrials.gov #NCT02795767) enrolling 60 HA children (2-12 years of age) with FVIII inhibitors, 94.7% of patients who received once-weekly emicizumab had no treated bleeds. Intraindividual comparison analysis showed that emicizumab prophylaxis resulted in a 99% reduction in treated bleeds compared with previous treatment with BPAs.[23] The markedly better efficacy of emicizumab prophylaxis over BPA treatment in preventing bleeding episodes is a major argument for the use of this drug in patients who have developed FVIII inhibitors.

In addition to historical peak level of FVIII inhibitors, it was suggested that ITI results may also be influenced by the pre-ITI FVIII-inhibitor titer.[24] For the caregivers who decide to initiate ITI when the FVIII inhibitor titer falls below 10 BU/mL, the interval to reach this titer could represent a period of up to 6 months.[25] During this period, avoiding FVIII antigen exposure and treating or preventing bleeding with rFVIIa are usually recommended.[24] However, the prophylactic regimen proposed in a subset of patients having a severe bleeding tendency frequently requires daily infusions of rFVIIa, owing to its short half-life of ~3 hours.[24,26] In this context, emicizumab prophylaxis may also be of particular interest, as it does not contain FVIII, is more effective than rFVIIa, and lessens the burden of regular IV infusions.

Emicizumab prophylaxis provides a good safety profile

Potential drawbacks to the use of emicizumab, independent of ITI, include the risk of thrombosis. For patients who received once-weekly administration of emicizumab with no concurrent use of BPAs, no case of thromboembolic event was identified. The most common AEs occurring in >10% of patients taking emicizumab were mild injection-site reactions and headache.[13,15,17,23] No emicizumab-related serious AEs were reported during the phase 1 studies[13-15] or during the phase 3 HAVEN 2 trial in pediatric patients.[23] However, 3 cases of thrombotic microangiopathy and 2 cases of thrombosis occurred in 5 HA adult patients during the treatment of breakthrough bleeds with cumulative doses of aPCC > 100 U/kg per day for >1 day, while no such cases were seen in association with rFVIIa.[17] The combination of aPCC administration, an FIXa-containing concentrate,[27] and emicizumab prophylaxis was concluded to be at increased risk of thrombosis.[11,28] Since the manufacturer has provided recommendations for the use and dosing of BPAs during emicizumab prophylaxis, no new potentially emicizumab-related serious thrombotic AEs have been recorded.[29]

Emicizumab prophylaxis could be pursued during ITI

Despite controlling ~70% to 80% of bleeding episodes associated with high-titer FVIII inhibitors, including perioperative periods,[30-32] the hemostatic efficacy of BPAs remains somewhat unpredictable[33,34] and does not reach the hemostatic efficacy observed with FVIII replacement in patients without FVIII inhibitors.[33,35] Prophylaxis regimens using either rFVIIa or aPCC showed a maximum of 62% reduction of bleeding events in patients with FVIII inhibitors.[36,37] The bleeding-related burden of orthopedic complications, including pain and joint damage, is more severe in HA patients with FVIII inhibitors than in age-related HA patients without FVIII inhibitors.[38] Thus, eradication of FVIII inhibitors with ITI remains the standard of care. Two different ITI regimens have been used: low dose and high dose. Although both ITI regimens had comparable success rates in a randomized clinical trial, patients receiving the low-dose regimen (50 IU/kg three times a week) took a longer time to achieve FVIII-inhibitor eradication and had a higher bleeding rate than patients in the high-dose group (200 IU/kg per day).[39] These results suggested that reduction of recurrent hemorrhages and subsequent avoidance of inflammatory environment might shorten ITI duration.[24] Therefore, prophylaxis using BPAs is recommended for patients who still experience frequent bleeding while on the ITI regimen.[24] By providing higher efficacy in preventing bleeding episodes compared with BPA prophylaxis, subcutaneous emicizumab prophylaxis may represent a therapeutic intervention favoring low-dose regimen, with subsequent reduction of the need for central venous access devices and their related complications, such as infection and thrombosis.[40] Whether low-dose ITI combined with emicizumab prophylaxis would be more cost efficient than high-dose ITI remains to be determined.

Safety concerns, including the potential risk of thrombosis following the administration of emicizumab and FVIII concentrates, may arise. Both emicizumab and FVIIIa bring FIXa and FX in close proximity, but emicizumab has a much lower affinity for FIXa and FX compared with FVIIIa.[41] Therefore, it is unlikely that the administration of emicizumab and FVIII concentrates provides additive enhancement of FXa generation when the FVIII-inhibitor titer decreases. We can speculate that the formation of the FIXa-emicizumab-FX tenase complex would progressively translate to the formation of the FIXa-FVIIIa-FX tenase complex for the generation of FXa (and subsequent thrombin generation). In addition, HA patients have a normal regulation of the coagulation process, including FVIIIa inactivation. It has recently been shown that emicizumab-mediated FXa generation is downregulated by direct inactivation of FVa through the activated protein C pathway.[42] Supporting these assumptions, no thrombotic events were identified in HA patients without FVIII inhibitors receiving emicizumab prophylaxis in combination with repetitive FVIII infusions for the treatment of breakthrough bleeds or during surgery.[15] This may bring another argument for continuing emicizumab prophylaxis irrespective of the level of FVIII recovery detected in patients undergoing ITI.

One of the questions that remains unanswered is whether prophylaxis with emicizumab should be stopped when tolerance is achieved or whether it should be maintained in association with on-demand FVIII infusions in case of breakthrough bleeds or surgery.

Conclusion

Clinical data have clearly shown that emicizumab is safe and effective for preventing bleeding in HA patients with FVIII inhibitors. Considering that reduction of bleeding frequency provides better long-term clinical outcomes and improved quality of life, we believe that emicizumab should be prescribed independent of ITI in these patients. Further clinical data are needed regarding the potential use of emicizumab in the context of ITI.

Authorship

Contribution: S.L.Q. and C.N. wrote the manuscript.

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