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What's ahead in the treatment of hemophilia - Section 2

Monoclonal antibody-based therapies

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Take Home Messages

- FVIIIa mimicking bispecific antibodies and anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibodies are currently being developed as alternative therapeutics for patients with hemophilia.
- Pre-clinical and clinical studies have demonstrated promising prophylactic effects using subcutaneous injections irrespective of the presence of inhibitors.
- Thrombotic events should be carefully monitored during concomitant use of these antibodies with bypassing agents in the event of breakthrough bleeding.

Introduction

Although regular and early prophylaxis substantially improves the quality of life in patients with hemophilia by reducing bleeding and preventing joint damage, several issues remain to be resolved. In particular, the necessity for repeated intravenous injections and the maintenance of adequate trough levels during treatment present difficult challenges. In addition, the development and treatment of patients with inhibitor persist as serious complications. Immune tolerance induction (ITI) has been well demonstrated to be effective in patients with inhibitor, and this is now regarded as essential treatment under these circumstances. Unsuccessful ITI and hemophilia B patients with inhibitor continue to provide major difficulties in clinical management of these cases, however. Recent advances in antibody technology, and the development of various monoclonal antibody-based therapeutics for malignant diseases and rheumatoid arthritis, illustrate the modern concept of immuno-therapy. In hemophilia, a FVIIIa mimicking bispecific antibody and an anti-TFPI monoclonal antibody have been recently developed. Both of these antibodies are administered subcutaneously and appear to be effective irrespective of the presence of inhibitors.

FVIIIa mimicking bispecific antibody

Basic concept and preclinical study

A FVIIIa mimicking bispecific antibody has been developed on the concept that the cofactor function of FVIIIa is dependent on the location of FIXa and FX in a spatially suitable position to promote the FIXa- catalyzed FX activation. The monoclonal antibody was produced by initially immunizing animals (mice, rats and rabbits) with human FIXa and FX to prepare 200 different monoclonal antibodies. After cloning the variable region, approximately 40,000 bispecific antibodies were expressed in HEK cells and were screened for FVIIIa cofactor activity. The humanized lead chimeric antibody, hBS23, shortened the APTT in plasma from severe hemophilia A patients even in the presence of FVIII inhibitor. The *in vivo* hemostatic effect of hBS23 was confirmed in an antibody-induced monkey model of acquired hemophilia A.[1] The original hBS23 was improved by multiple optimization[2] and renamed ACE910 (emicizumab). The prophylactic efficiency of ACE910 was confirmed using weekly subcutaneous injections in the monkey model.[3] Although emicizumab mimicks FVIIIa, it is different from native FVIIIa in various functional aspects. Enzymatic kinetic studies of FIXa-catalyzed FX activation mediated by emicizumab revealed a kcat 1/44 that of FVIIIa. Moreover, the Kd values of emicizumab for FIX, FIXa, FX and FXa were 1.58, 1.52, 1.85 and 0.978, respectively.[4] Affinity with these molecules were much lower, therefore, than expected with standard antagonistic antibody therapeutics (<nM). This could lead to repeated attachment and detachment of the antibody, and a faster release of FXa downstream in the coagulation cascade. Another important difference appears to be the lack of inhibition by APC/PS or A1/A2 dissociation, resulting in an improved stability of the FVIIIa mimicking effect. Furthermore, emicizumab effect does not require stabilization by VWF. Further studies are required to fully characterize the FVIIIa related effects of emicizumab. Nevertheless, the current evidence demonstrates that emicizumab provides an interesting tool for understanding FVIIIa cofactor function in association with its application as a novel therapeutic.

Phase 1 studies in healthy individuals and hemophilia A patients

Phase 1 studies in healthy subjects were conducted using single subcutaneous injections. The half-disappearance time ranged from 28.3 to34.4 days. One subject developed a neutralizing anti-ACE910 antibody (ADA). The APTT was prolonged, but there were no clinical symptoms.[5] In this study, the prophylactic effects of the antibody were also assessed in a total of 18 hemophilia A patients, including 6 patients with FVIII inhibitor. Emicizumab was administered by weekly subcutaneous injection

for 12 weeks in the three doses, 0.3, 1 and 3 mg/kg. In all dose cohorts, ABR was remarkably reduced. The reduction rate of the median ABR was 86.5, 100 and 100%, respectively. There were no serious adverse events (AE) nor clinically relevant coagulation abnormalities.[6] 16 out of the 18 patients continued into extended 12-week studies with a median follow up time of 32.6 (32.2-33.3), 27.0 (8.2-28.5), and 21.5 months (11.1-22.6) respectively for three different cohorts. A significant decrease in the ABR remained evident in all three cohorts, with a reduction of 96, 99 and 100%, respectively. Four patients required dose up-titration because of suboptimal bleeding control, and the additional therapy in these patients led to a further reduction in ABR.[7]

Phase 3 international clinical trials

Phase 3 studies were initiated on November 17, 2015 (Table 1). In HAVEN 1, 109 patients with inhibitor (>12 y.o.) were enrolled. Emicizumab was administered weekly, at 1.5 mg/kg after initial loading dosing at 3.0 mg for 4 weeks.[8,9] The participants receiving episodic treatment with bypassing agents (BPA) were randomly assigned in a 2:1 ratio to emicizumab prophylaxis (group A) or no prophylaxis (group B). The median ABR in group A and B were 2.9 and 23.3, respectively. The reduction rate was 87% (p<0.0001), and 62.9% of patients experienced zero bleeds in the emicizumab-treated group compared to 6% (1 patient) in group B. 49 participants treated with BPA prophylaxis, were assigned to group C in which intra-individual comparisons were assessed. The median ABR prior to and after emicizumab prophylaxis was 15.7 and 3.3, respectively. In 70% of the participants, the bleeding rate was zero. Three participants developed thrombotic microangiopathy (TMA) and two developed thrombophlebitis (TE). All cases had received multiple infusions of activated prothrombin complex concentrates (APCC). No participants developed ADA in this HAVEN 1 study. In November 2017, the FDA and CHMP approved emicizumab prophylaxis for hemophilia A patients with inhibitor in November 2017 and January 2018, respectively. In HAVEN2, 18 children (<12 y.o.) were enrolled. Median ABR 24 weeks before emicizumab prophylaxis was 6, and the reduction in all types of bleeding was remarkable. The mean number of the treated bleeds was 0.4.[10] There were no significant differences in pharmokinetics (PK) from HAVEN1. No TMA/TE were reported. In HAVEN3 emicizumab was administered to non-inhibitor patients at either 1.5 mg/kg weekly or 3 mg/kg every two weeks. In HAVEN 4, 41 participants were enrolled in an expanded cohort at an initial weekly dose of 3mg/kg followed by a maintenance dose of 6 mg/kg every 4 weeks for over 24 weeks. The PK data were similar to those of previous studies. The number of the treated bleeds was zero and 85.7% of the patients experienced no bleeds. No serious AE (including TMA/TE) were

Table 1. Current status of clinical trials of bispecific antibody and anti-TFPI antibodies.

Products	Studies	Subjects	Dose	Interval	Initiation	Number of pts
Emicizumab	Phase 3					
	HAVEN1	≧ 12 years, HA, inhibitor	1.5 mg/kg *	1/W (SC)	Nov, 2015	109
	HAVEN2	<12 years, HA, inhibitor	1.5 mg/kg * 3.0 mg/kg* 6.0 mg/kg*	1/W(SC) 1/2W(SC) 1/4W(SC)	Jun, 2016 Oct 2017	88
	HAVEN3	≧ 12 years, HA, non inhibitor	1.5 mg/kg * 3.0 mg/kg *	1/W(SC) 1/2W	Sep, 2016	152
	HAVEN4	≧ 12 years, HA, inhibitor, HA, non inhibitor	6.0 mg/kg *	1/4W(SC)	Jan, 2017	48
	JO39881 (in Japan)	<12 years, HA, Non inhibitor	3.0 mg/kg * 6.0mg/kg *	1/2W(SC) 1/4W(SC)	Sep, 2017	13
Concizumab	Phase 2					
	Explore 4	≧ 18 years, HA, HB, inhibitor	0.15mg/kg (~0.25mg/kg)	Daily, (SC)	Aug 2017	26
	Explore 5	≧ 18 years, HA , non inhibitor	0.15mg/kg (~0.25mg/kg)	Daily, (SC)	Aug 2017	33
BAY1093884	Phase 1					
		18-65 years H A, HB Inhibitor Non inhibitor	0.3mg/kg 150mg	Single (SC, IV) 1/W(SC)	Oct, 2015	32

* For the 1st 4 weeks, 3 mg/kg of emicizumab were injected weekly.

observed.[11] According to the information from Genentech to the patients group, five adults with hemophilia A with inhibitors taking emicizumab have passed away since 2016. One of the patients was enrolled in the HAVEN 1; one was in the U.S. expanded access program and three were compassionate use. In each of these cases, physician assessed that cause of death was not related to emicizumab.

Anti-TFPI monoclonal antibodies

TFPI regulates the initiation phase of coagulation by inhibiting TF-FVIIa and activated FX (FXa). Management of TF/FVIIa induced-FXa generation by moderating TFPI offers an alternative approach for hemophilia treatment. Concizumab is humanized recombinant monoclonal antibody with high affinity (K_D=25pM) for the Kunitz-2 domain, the binding site for FXa. The antibody directly inhibits binding of Kunitz-2 domain to FXa at an early stage, followed by indirect inhibition of the Kunitz-1 domain binding to FVIIa. Concizumab exhibits a dose-dependent procoagulant effect illustrated by an increase in endogenous thrombin potential (ETP) in assays of thrombin generation and fibrin clot formation *in vitro*.[12] In a phase 1 trial, concizumab was administered to healthy volunteers (n=28) and patients with hemophilia A and B (n=24) by single subcutaneous and intravenous injections. The antibody demonstrated a dose-dependent and non-linear PK profile due to target-mediated drug disposition compatible with other antagonistic antibodies. No serious AEs were detected in either healthy volunteers or hemophilia patients, and there were no significant abnormal coagulation consequences. In the Explore 3 trial, three doses (0.25, 0.5, 0.8 mg/kg) were administered by subcutaneous injections every 4th day in eight patients. No serious AE or thrombotic events were recorded, although increased levels of D-dimer and prothrombin fragment 1+2 were observed. There was a significant relationship between concizumab concentration and peak thrombin generation, and levels within the normal range of thrombin generation were achieved at over 100 ng/ml antibody. Bleeding incidence correlated with antibody concentration, and bleeding frequency appeared to be least at an antibody concentration above 100 ng/mL. A phase 2 clinical study has recently commenced. Dosing has been planned to maintain circulating antibody concentrations over 100 ng/mL but at much lower daily subcutaneous doses. A new phase 1 study has been recently initiated using an alternative anti-TFPI antibody, BAY 1093884,[13] inhibiting TFPI function by binding to Kunitz 1 and 2 domains (Table 1).

Future perspectives

These modern immuno-therapeutic agents offer considerable potential for hemophilia treatment. The risk of thrombosis-related complications remains to be fully determined, however, and laboratory techniques to reliably assess patient responses require standardization. Treatment for life-threatening bleeding or major surgery using these therapeutics is also at an early stage. Nevertheless, the improvements in ABR and QOL seen in the current clinical trials appear to be remarkably and warrant further long-term studies on physical and mental well-being in these clinically demanding patients.

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