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322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Chinese Severe Hemophilia a Children with High-Titer Inhibitors Obtain More Benefit from Intermediate-Dose Immune Tolerance Induction: The Interim Result of Lome Part a

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Background
We previously showed that low-dose immune tolerance induction (LD-ITI) strategy [incorporating immunosuppressants (IS) partially] for severe hemophilia A (SHA) patients with high-titer inhibitors (HTI) had relatively equivalent success rate with lower cost compared to those on high-dose ITI from international (I)-ITI randomized clinical trial (RCT). However, it is lack of RCT to compare the efficacy, safety, and cost of LD-ITI strategy to higher-dose ITI [intermediate-dose (MD)-ITI] strategy in China. Currently, the domestic recombinant FVIII (rFVIII) sponsored by the SinoCelltech Ltd., provides an opportunity to conduct the LOME study: a multicenter controlled randomized clinical trial of LOw- versus InterMEdiate-dose immune tolerance induction with recombinant factor VIII in China, to answer this question.

Objectives
Conduct the RCT to compare the efficacy, safety and cost of LD- to MD-ITI strategy using rFVIII (Omfiloctocog alfa, SCT800) for SHA children with HTI in China.

Methods
A perspective, multicenter RCT, enrolled SHA children ≤8year-old at enrollment, with peak historical inhibitor-titer 5 - 200 Bethesda Unit (BU)/mL, 1:1 randomized in LD- (Omfiloctocog alfa, rFVIII 50 IU/kg once-every-day) or MD- (Omfiloctocog alfa, rFVIII 100IU/kg/day) ITI group.
IS was added (the initial regimen) in patients who met the criteria as follows: (i) the inhibitor titer during ITI increased to ≥200 BU/mL; (ii) the peak titer did not appear within 3 months after ITI-start; (iii) inadequate reduction (<20%) in titer over 6 months. Success: negative inhibitor titer twice consecutively at least 4 weeks apart and FVIII recovery ≥66% of expected within 24 months of treatment. Partial success: negative inhibitor titer twice consecutively at least 4 weeks apart, but with persistently abnormal FVIII recovery.
Average consumption cost (per kg body weight) was calculated based on the median number of treatment doses consumed to achieve success. This included the cost of rFVIII and rituximab for ITI, PCC and rFVIIa for treatment of breakthrough bleeding, and IVIG for infection prevention in IS patients. The rituximab and IVIG were calculated based on the actual IS-using rate in 2 groups. Additionally, PCC and rFVIIa were calculated based on the actual using-rate in all breakthrough bleedings.
Trial registration number: ChiCTR2200056603. This was the interim analysis. The first participant was enrolled on March 2022.

Results
Total 31 patients (16 in MD-, 15 in LD-ITI group) from 3 hemophilia centers with median followed-up 9 months since ITI-start (Table 1). A total 26 (83.9%) patients underwent peripherally inserted central catheter (PICC) (14 in MD-, 12 in LD-ITI group).
A total 10 (32.3%, 2 in MD-, and 8 in LD-ITI group) patients received IS at median 2.9 months since ITI-start. Among them, 6 patients added IS because of inhibitor titer ≥200BU/mL during ITI, and the rest for delayed-occurred peak-titer or unsatisfactory decrease of titer.
The MD- and LD-ITI group achieved similar success rate (75% vs. 40%). None success patients relapsed over a median follow-up period of 5.1 months since achieving success. The Kaplan-Meier curves demonstrated that patients in MD-ITI group had significantly shorter time to success (median, 2.9 months vs. 9.0 months), and partial success (2.4 months vs. 5.7 months). (Figure 1A and Figure 1B)
Patients in MD-ITI group had lower mean bleeding rate (bleedings/month) (0.38 vs. 1.40) and joint bleeding rate (0.11 vs. 0.83) before achieving partial success, compared with those in LD-ITI group (Figure 1C and Figure 1D). But during the phase from achieving partial success to achieving success, the 2 groups had similar bleeding rate (0.09 vs. 0.11) and joint bleeding rate (0.07 vs. 0.16).

A total 6 (23.1%) patients occurred PICC-related complications (5 in MD-, 1 in LD-ITI group) with mean follow-up period of 270 days. All complications including infection (1 person-time), thrombosis (1 person-time), rashes (3 person-time), accidental detachment (3 person-time).
Similar per kg treatment cost from ITI-start to ITI success was found in 2 groups (US$ 2905.18 vs. US$ 2838.23).

Conclusions

Similar success rate was found in LD-ITI (rFVIII) strategy and MD-ITI (rFVIII) strategy for SHA children with HTI. On the premise of similar cost, shorter time to success, less bleedings were observed in MD-ITI strategy. PICC implantation is a safe option to conduct ITI.

Disclosures No relevant conflicts of interest to declare.

Table 1 Patient baseline demographics and clinical characteristics.

Characteristic	Total Cohort N = 31	LD-ITI N = 15	MD-ITI N = 16	*p*
	Median (range) N (%)	Median (range) N (%)	Median (range) N (%)	
Ages				
Age at initial bleeding, m	8.0 (0 - 55.0)	6.0 (0 - 46.0)	13.0 (5.0 - 55.0)	0.984
Age at initial FVIII exposure, m	14.0 (0.1 - 64.0)	14.0 (3.0 – 64.0)	16 (8.0 – 55.0)	0.495
Age at inhibitor-diagnosis, y	2.3 (0.6 - 6.9)	2.2 (0.7 - 6.9)	2.6 (1 - 5.4)	0.892
Age at ITI, y	2.7 (0.7 - 6.9)	3.3 (0.8 - 6.9)	3.1 (1 - 5.4)	0.379
Genetic background				
Family history of hemophilia	8 (25.8)	4 (26.7)	4 (25)	0.375
Family history of inhibitor	2 (6.5)	1 (6.7)	1 (6.3)	0.146
F8 genotype* (n = 30)				
High-risk	5 (16.7)	4 (28.6)	1 (6.2)	0.819
Medium-risk	21 (70.0)	8 (57.1)	13 (81.3)	
Low-risk	4 (13.3)	2 (14.3)	2 (12.5)	
Inhibitor characteristics				
Titer at inhibitor-diagnosis, BU/mL	12.7 (0.6 - 198)	18.5 (0.6 - 198)	11.8 (1.8 - 51.2)	0.711
Exposure day, d	21 (1 - 200)	19 (5 - 100)	20.5 (4 - 200)	0.707
Peak historical inhibitor titer, BU/mL	24.0 (5.7 - 198)	43.3 (5.7 - 198)	17.6 (5.7 - 198)	0.520
Peak historical inhibitor titer ≥100 BU/mL	5 (19.4)	3 (20.0)	3 (18.8)	0.105
Immediate pre-ITI titer, BU/mL	15.1 (1.7 - 198)	16.8 (1.7 - 168.8)	14.5 (2 - 200)	0.892
Immediate pre-ITI titer ≥10BU/mL	24 (77.4)	12 (80.0)	12 (75.0)	0.500
Characteristics of ITI				
Time from inhibitor-diagnosis to ITI-start, m	0.8 (0.1 - 50.8)	0.7 (0.2 - 50.8)	1.7 (0.1 - 16.6)	0.732
Breakthrough bleeds before ITI				
Bleeds/m	1.2 (0.8 - 2.5)	1.2 (0.9 - 2.5)	1.3 (0.8 - 1.7)	0.498
Joint bleeds/m	0.4 (0 - 1.0)	0.4 (0.2 - 1.0)	0.4 (0 - 0.9)	0.752
Quality of life				
CHO-KLAT (n = 13)				
Parents' main sheet	65.7 (56.0 - 80.0)	65.2 (56.0 - 79.0)	64.9 (56.0 - 80.0)	0.930
Parents' SEC sheet	68.8 (59 - 83)	67.7 (62.0 - 83.0)	69.0 (59.0 - 82.0)	0.991
Joint status evaluation				
HJHS (n = 13)	3.7 (1.0 - 6.0)	3.5 (1.0 - 6.0)	3.8 (2.0 - 4.0)	0.560
HEAD-US	4.5 (0 - 6.0)	4.0 (0 - 6.0)	4.5 (0 - 6.0)	0.471

* *F8* genotype risk-stratification was based on the review article by Garagiola et al. Gene mutation types with high risk of inhibitor development were large deletions or insertions in multiple exons and nonsense mutations in the light chain; gene mutation types with medium risk were large deletions or insertions in single-exon, nonsense mutations in the heavy chain, and intron 22 and 1 inversions; and gene mutation types with low-risk were small deletions or insertions, splice-site mutations, and missense mutations.

Range = minimum-maximum; ITI, immune tolerance induction; MD-ITI, intermediate-dose ITI group (recombinant FVIII 100 IU/kg/day); LD-ITI, low-dose ITI group (recombinant FVIII 50 IU/kg once every other day); y, years age; m, months; d, days; BU, Bethesda Units/mL; CHO-KLAT, the Canadian Hemophilia Outcomes-Kids Life Assessment Tool; HJHS, Hemophilia Joint Health Score; HEAD-US, Hemophilia Early Arthropathy Detection ultrasound.

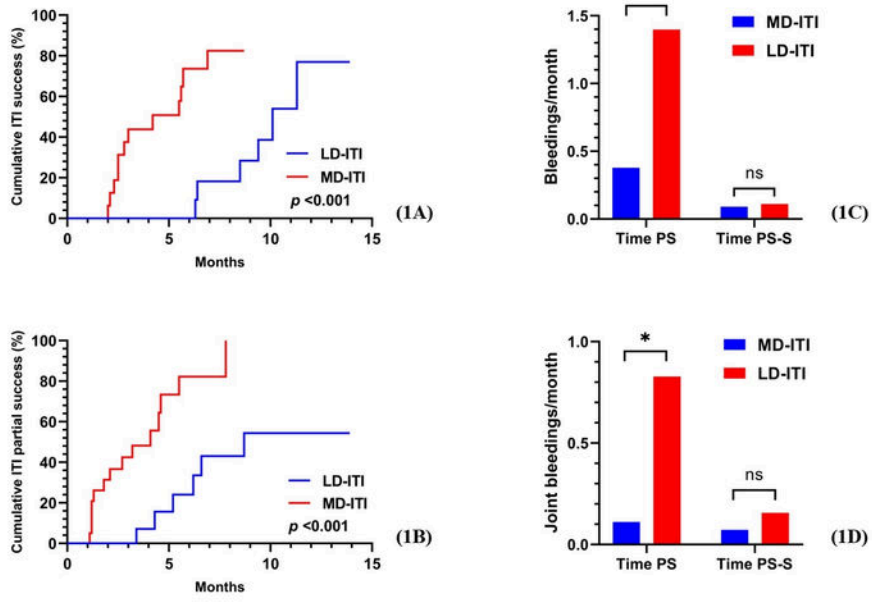

Figure 1 Time to success by treatment group **(1A)**, time to partial success by treatment group **(1B)**, bleedings/month by treatment group **(1C)**, joint bleedings/month by treatment group **(1D)**.

Kaplan-Meier plots show both the time to success and partial success were significant shorter in MD-ITI group, compared to LD-ITI group. Additionally, patients in MD-ITI group had significantly lower bleeding rate (bleedings/month) and joint bleeding rate (joint bleedings/month) before achieving partial success compared to LD-ITI group.

ITI, immune tolerance induction; MD, intermediate-dose ITI group (recombinant FVIII 100 IU/kg/day); LD, low-dose ITI group (recombinant FVIII 50 IU/kg once every other day); Time PS, the phase from ITI-start to achieving partial success; Time PS-S, the phase from achieving partial success to obtaining success.

*, p <0.05; ns, non-significant.

Figure 1

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