SUCESSFUL LOW-DOSE IMMUNE TOLERANCE INDUCTION REGIMEN USING MULTIPLE PLASMA-DERIVED FACTOR VIII CONCENTRATES.

Marina Pereira Colella, Silmara Aparecida Lima Montalvão, Andrea Luisa de Almeida Sambo, Erich Vinicius De Paula, Margareth Castro Ozelo

Hemophilia Unit "Cláudio L. P. Correa" – INCT do Sangue
Hemocentro UNICAMP, University of Campinas – Campinas, SP, Brazil

INTRODUCTION

There are several immune tolerance induction (ITI) treatments in use worldwide, but the high costs involved limits the ITI access in many countries. In Brazil, until recently, ITI protocols were not feasible for many patients due to product access.

METHODS

We report the partial results of a low dose regimen using multiple plasma-derived factor VIII (pdFVIII) concentrates carried out in the Hemophilia Unit of Hemocentro Unicamp, in Brazil.

A total of seven patients, all with severe haemophilia A, started their ITI treatment in the period of November/2007 to June/2012. The patients' characteristics are shown in Table 1. All patients received pdFVIII concentrates, containing various concentrations of von Willebrand factor. The pdFVIII concentrate used by each patient changed three to four times during the course of the ITI, according to the product availability at each time point. Previously to the inhibitor development these patients received several pdFVIII concentrates similar to the products used during the ITI period.

Table 1 – Patients' clinical and laboratory characteristics

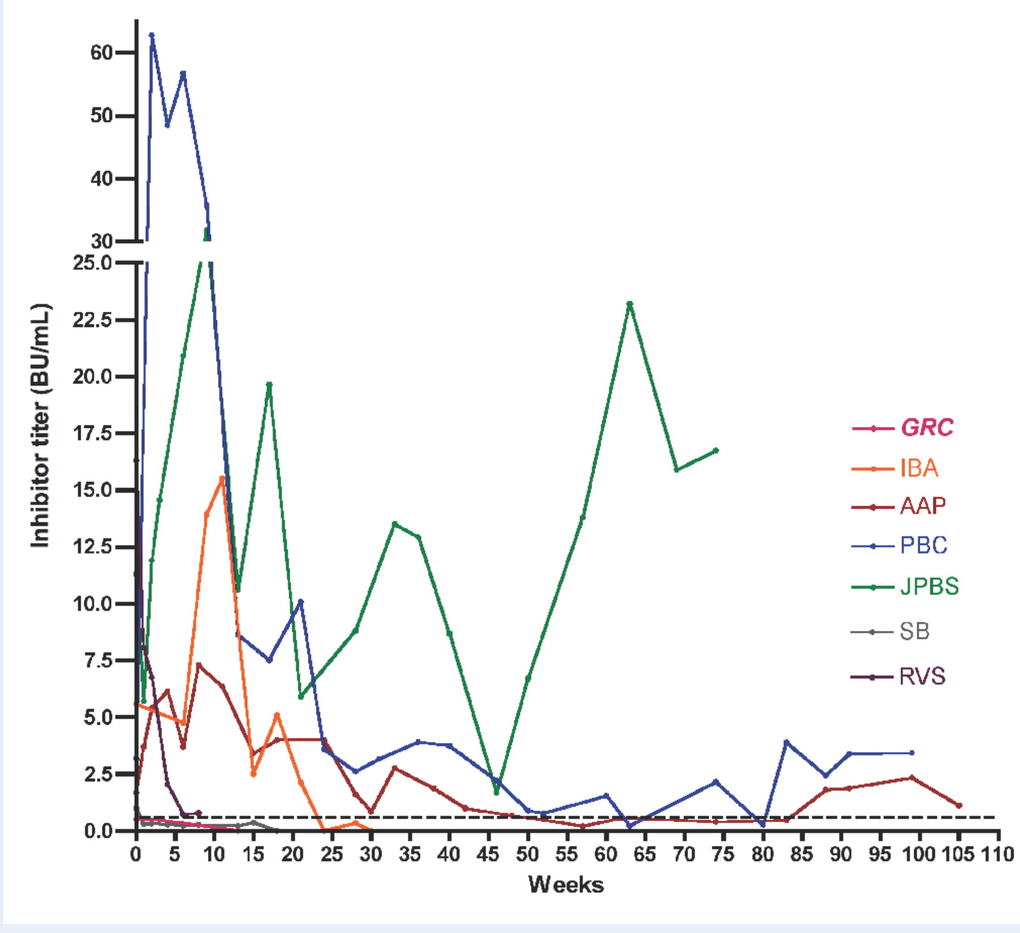
Patients ID	GRC	IBA	AAP	PBC	JPBS	SB	RVS
Age (y) at first inhibitor[1]	5	1.7	1.2	2.2	3.9	29	2
Age (y) at ITI start	11.5	7.7	4.6	5.7	13.2	35	2
Duration of the inhibitor (months)	78	71	41	43	111	72	1.5
F8 Mutation	Inv22	Inv22	NA	Inv22	Inv22	Small deletion	Inv22
Inhibitor historical peak (BU/mL)	70	79	54	150	56	13.5	16.3
Pre-ITI inhibitor titer (BU/mL)	0.5	5.6	1.7	3.7	11	0.9	16.3
pdFVIII dose (IU/Kg 3x/week)	25	25	25-35	25-50	50	25	35
N° of pdFVIII concentrates	NA	NA	4	4	2	2	1
Treatment period (weeks)	Completed	Completed	102	108	75	Completed	10
Response	Success[3]	Success[3]	Partial[4]	Partial[4]		Success[3]	Partial[4]
Time to response (weeks)[2]	4	23	Ongoing treatment	Ongoing treatment	Ongoing treatment	2	Ongoing treatment

[1]Age (in years) at the first detection of the inhibitor.
[2]Time (in weeks) until undetectable inhibitor level.
[3]Complete success defined as: undetectable inhibitor level, FVIII recovery ≥66% and FVIII half-life ≥6hours.
[4]Partial success defined as: inhibitor titer < 5.0 BU/mL and clinical response to FVIII concentrates.
Abreviations: ITI - immune tolerance induction; pdFVIII - plasma-derived factor VIII concentrate; Inv22 - *F*8 intron 22 inversion; NA - not available.

RESULTS

Three patients have completed the ITI treatment with complete success (undetectable inhibitor level, FVIII recovery ≥66% and FVIII half-life ≥ 6hours). The ITI course is ongoing in four patients, and three have achieved a partial response (inhibitor titers < 5BU/mL and clinical responses to FVIII infusions). The mean time to reach an undetectable inhibitor level in these three patients was 9.6 weeks (2 - 23 weeks). None of the patients needed a central venous catheter.

Figure 1 – Evaluation of patients' inhibitor titer



CONCLUSIONS

We believe these results are very encouraging due to the high success rate using a low-dose ITI regimen. We also highlight that the use of several pdFVIII concentrates did not interfere with the successful results.

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