Inhibitor screening for patients with hemophilia in Turkey*

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ABSTRACT

Development of factor VIII inhibitors remains the most serious and life-threatening complication of hemophilia therapy. The aim of this study was to determine the prevalence of inhibitor development in Turkish patients with hemophilia. Totally 1226 patients were screened [HA: 1057, HB: 105, von Willebrand's disease (vWD): 64]. Ages ranged from 1 to 55 years (mean: 16.5 years). Sixty-two percent of patients (657/1057) were severe hemophilia. This study showed that inhibitor prevalence in Turkish hemophiliacs exposed to factor concentrates and fresh frozen plasma (FFP) is 11.2% for all HA and 15.8% for severe HA versus 1.9% for HB after eliminating transient inhibitors. Totally 122 patients were found inhibitor positive [high responder (HR) inhibitor= 60 and low responder (LR) inhibitor= 59 for HA/2 LR for HB/1 LR for vWD]. Thanks to this project, patients with inhibitor development can be treated with specific products such as recombinant factor VIIa or activated protrombin complex concentrates for their bleeding episodes or in their elective operations.

Key Words: Hemophilia, Inhibitor, Bethesda test, Inhibitor prevalence.

ÖZET

Türkiye'deki hemofili hastalarında inhibitör taraması

Hemofili A hastalarında inhibitör gelişmesi, hemofili tedavisinin en ciddi ve hayatı tehdit eden komplikasyonudur. Bu çalışmanın amacı; Türk hemofili hastalarında inhibitör gelişme prevalansının saptanmasıdır. Toplam 1226 hastada inhibitör taraması tamamlandı (1057 hemofili A, 105 hemofili B, 64 von Willebrand hastalığı). Yaş dağılımı 1-55 yıl (ortalama: 16.5) idi. Hemofili A hastalarının %62'si ağır hemofili A idi (657/1057). Çalış-

ma sonunda geçici inhibitör saptananlar çıkarıldıktan sonra hemofili hastalarında inhibitör gelişme sıklığı tüm hemofili A'da %11.2, ağır hemofili A'da %15.8 bulundu. Hemofili B hastalarında saptanan inhibitör gelişme oranı ise %1.9 idi. Toplam 122 hastada inhibitör saptandı (yüksek titrajlı: 60, düşük titrajlı: 59/hemofili A) (iki düşük titrajlı/hemofili B'de) (bir düşük titrajlı/von Willebrand hastalığında). Bu proje sayesinde Türkiye'deki inhibitörlü hemofili hastaları kendileri için gerekli olan hayati ilaçları (rekombinant faktör VIIa veya APCC konsantreleri) ciddi kanamalarında ve planlanmış operasyonlarında kullanabilmektedir.

Anahtar Kelimeler: Hemofili, İnhibitör, Bethesda testi, İnhibitör sıklığı.

INTRODUCTION

The development of antibodies against factor VIII is one of the major complications in the treatment of hemophilia. These antibodies react with FVIII to render it ineffective. Depending on the inhibitor titer, FVIII treatment may become completely ineffective. Hence, inhibitors may cause serious problems that can be life-threatening[1-3]. In order to prevent serious bleedings and potential complications, every hemophilia patient should be screened for inhibitor possibility. In severe hemophilia A (HA) patients, the prevalence of inhibitor development was reported as 6-27% whereas in hemophilia B (HB) the risk is very low (3-5%)[4-7]. Since only a few centers are able to perform the Bethesda test in our country, many hemophilia patients in Turkey were not screened prior to 2001. Since inhibitor diagnosis could not be done many patients used incorrect therapy. Hence, the cost of treatment was increased and the lives of the patients were placed at risk.

The primary aim of this prospective cohort study was to screen all patients with hemophilia in Turkey and determine the prevalence of inhibitor formation in Turkish patients with hemophilia. We also aimed to evaluate the incidence rate of inhibitor frequency for a two-year prospective period. With this project, we planned to support both patients and their responsible physicians who could not perform inhibitor testing.

MATERIALS and METHODS

According to the latest official data published in 2001 by The Turkish Hematology Association, 1059 HA and 252 HB patients are currently under treatment and actively followed in Turkey[8]. It was planned to perform a prospective global inhibitor screening program in most of these patients over a two-year period.

Ethics Commitee Approval and Good Clinical Practice (GCP) Rules:

• This project was approved by the Ethics Commitees of Istanbul University, Ankara University and Ege University Medical Faculties between July and September 2001.

• All participants and/or their parents were informed and gave their written consent before blood sampling.

• Ethics Committee approvals and the completion of standardization procedures among laboratories, and postage of formal letters of invitation to the centers were completed by the end of September 2001.

• There was no expense for the participating patients and no fee was paid to investigators and technicians.

• The study procedures, including the transfer of blood samples and essential laboratory reagents, were covered by the official sponsor of this study, Novo Nordisk (Denmark). The budget of project was also approved by the Ethics Committees.

Design of the Investigation:

• This project was a multi-center designed screening study.

• This project was limited to establishing the frequency of inhibitor development in various types of hemophilia and von Willebrand's

disease (vWD). The treatment of patients determined to have inhibitor was under the control and responsibility of the physicians.

• An observation period of two years was applied in all patients in this prospective cohort study fto determine the incidence rate (September 2001 to November 2003).

• No drug treatment was given in the study as it was a phase-4 study.

Reference Centers

• Three centers (Izmir, Ankara and Istanbul) were selected as reference centers from among coagulation laboratories where members of The Hemophilia Committee of the Turkish Hematology Association actively work.

• The scientific responsibility for the tests was assumed by the performing laboratory.

Patients

• Severe HA patients were tested twice a year at six-month intervals and non-severe HA and HB patients were tested once per year.

• There was no age limit. The age range was from 1 to 59 years (mean: 16.5 years). Every patient with the diagnosis of HA or HB or vWD type-3 could be included. Sixty-two percent of patients had severe type of disease in HA (657/1057).

• It was planned to perform inhibitor tests in at least 300 patients in each laboratory in the centers located in Ankara, Istanbul and Izmir, thereby reaching at least 900 patients at the end of the two-year period.

Criteria for Inclusion

• All patients using blood products (fresh frozen plasma-FFP or factor VIII/IX concentrates) for treatment among the patients with a diagnosis of HA, HB and vWD would be tested with the aim of inhibitor screening.

• Severity of hemophilia was defined as FVIII:C < 2%.

• All hemophilia patients who would undergo operation would be screened primarily for inhibitor.

• Patients whose bleeding can not be stopped by administration of factor treatment by the following physician and for whom there is clinical suspicion of inhibitor will be tested at the request of the physician.

Criteria for Exclusion

• Hemophilia patients who used any blood products were excluded.

Methods of the Inhibitor tests

• Inhibitor tests were performed using Bethesda method[9].

• The cut-off level for inhibitor positivity was defined as > 0.6 BU/mL anything below this level was determined as “negative”.

• Low Responder (LR) inhibitors were defined as < 5 BU/mL.

• High Responder (HR) inhibitors were defined as > 5 BU/mL.

• The Nijmegen modification of Bethesda test[10] was used for confirmation of lower values (0.6-2.0 BU/mL).

• Factor VIII:C and IX:C activities were determined by an one stage assay with STA-Compact Analyzer (Diagnostica Stago, Asnieres-sur-siene, France).

Collecting of Blood Samples and Transportation

• Plasma samples collected from Istanbul and the Marmara region were taken by the transfer company in charge and tested in Istanbul University Cerrahpaşa Medical Faculty Hematology Laboratory under the responsibility of Prof. Dr. Gülten Aktuğlu (Table 1).

• Blood samples collected from Izmir, Aegean region and Mediterranean region were tested in the Ege University Medical Faculty Pediatric Hematology Laboratory under the responsibility of Prof. Dr. Kaan Kavaklı (Table 1). This region spans from Çanakkale to

Table 1. Patient groups accordind to reference centers

	All Turkey	Izmir	Ankara	Istanbul
Hemophilia A	1057	375	303	379
(severe)	(657)	(281)	(212)	(164)
Hemophilia B	105	45	10	50
von Willebrand disease	64	53	2	9
All patients	1226	473	315	438

Antalya, from Balıkesir to Eskişehir and from Muğla to Denizli.

• Blood samples collected from Ankara, inner Anatolia, Black Sea region, Adana and all East and Southeast regions were forwarded to the center in Ankara (Table 1). The reference center was Ankara University Medical Faculty Pediatric Hematology Laboratory under the responsibility of Prof. Dr. Sabri Kemahli.

Communication of the Results and Publication Policy

• Results were sent to participating centers each month. Positive results were reported by telephone and e-mail to the responsible physician as soon as possible. The overall results obtained at the end of the study were listed and sent to participating centers. The official results are now available to any interested individuals and may be considered as an official scientific database that can be used by all Turkish hematologists.

RESULTS

The project began in 2001 and was completed at the end of the 2003. In the 24 months from the beginning of the study period, totally 1226 patients were screened in the three reference centers (HA: 1057, HB: 105, vWD: 64)(Table 1). However, prospective follow-up of patients could be carried out in only half of the patients and consecutive inhibitor tests were performed in this group. For this reason, our project was defined as "prevalence" study rather than "incidence" study.

This study has revealed that inhibitor prevalence in Turkish hemophiliacs exposed to plasma-derived factor concentrates and FFP was 14% for overall HA, %22.6 for severe HA, and 5.7% for HB. However after eliminating transient inhibitors; the rates were 11.2%, 15.8 and, 1.9, respectively (Table 2). At the end of the project, 119 HA (HR inhibitor: 60, LR inhibitor: 59), 2 HB (1 HR and 1 LR) and 1 wWD (1 LR)(totally 122) patients were found to be inhibitor-positive (Table 2). Inhibitor titers ranged from 0.6 BU/mL to 2240 BU/mL (Table 3). Distribution of inhibitor prevalence ratios among the three reference centers is shown in Table 4.

DISCUSSION

Development of antibodies against factor VIII and IX proteins is one of the most serious adverse effects that can occur after administration of blood products in hemophilia patients. This situation called the development of "inhibitor" may cause life-threatening problems because such patients do not respond to treatment with factor concentrates during bleeding and bleeding cannot be stopped[1-3]. In the operations performed in patients with inhibitor life-threatening bleedings are possible. As previously mentioned, inhibitor tests could be performed in only a limited number of patients in our country prior to the organization of this project[11,12].

The epidemiology of inhibitors is generally evaluated with prevalence, and incidence studies. "Prevalence" is defined as the percentage of patients with hemophilia who ha-

Table 2. Inhibitor prevalences in Turkish hemophiliacs

Type	n	All inhibitor patients (including transients)	Inhibitors patients (excluding transients)
Hemophilia A	1057	149	119
		(14%)	(11.2%)
Severe hemophilia A	(657)	(149)	(104)
		(22.6%)	(15.8%)
Hemophilia B	105	6	2
		(5.7%)	(1.9%)
von Willebrand	64	1	1
		(1.5%)	(1.5%)
	1226	**156**	**122**

Table 3. Inhibitor titers in inhibitor-positive patients with hemophilia

Low responders (LR)	72
High responders (HR)	83
Total patients	155
	(HA= 149/HB= 6)
Transient inhibitors	34
Persistent inhibitor	121
	(HA= 119/HB= 2)
	(HR= 60 pts, LR= 59 pts for HA)

HA: Hemophilia A, HB:Hemophilia B.

ve inhibitors at any given time. They are cross-sectional or retrospective surveys. "Incidence" is defined as the occurrence of inhibitors over a particular period of time. They are prospectiive cohort studies. Thus prevalence data may underestimate the risk of acquiring an inhibitor in patients on treatment with factor concentrates. It is obvious that the cumulative incidence of inhibitor development must be higher than the prevalence[6]. As a conclusion, incidence studies are more valuable than prevalence data. Our present data was, in fact, planned as an incidence study with a two-year prospective period for all patients. However, after two years we were only able to prospectively evaluate half of the patients. Due to only one testing for half of the patients we re-evaluauted our data as "prevalence" rather than "incidence" data in spite of two-year observation period. Based on data reported worldwide, there is a large difference in reported incidence rates of inhibitors in severe HA patients treated with FVIII concentrates, ranging from 0 to 52%[1,2,4-6,13]. The reason for this wide spectrum in the frequency of inhibitor development is influenced by several variables which can be patient-, therapy- or assay-related[7]. However, reported prevalence rates for inhibitors are widely variable ranging from 6% to 27%. Based on the related literature we reviewed, there were a few published

Table 4. Distribution of inhibitor prevalence rates among the three reference centers

	Izmir	Ankara	Istanbul	All Turkey
Hemophilia-A	13.8%	10.5%	9.2%	11.2%
Severe HA	18.5%	15.1%	12.2%	15.8%
Hemophilia-B	2.2%	0%	2%	1.9%

studies about inhibitor screening in more than 1000 patients with hemophilia (Table 5). As shown in the literature, prevalence studies tend to produce lower figures than in incidence studies as would be expected.

At present, recombinant factor concentrates are not yet available in the Turkish market. Hence, in our study, all patients with hemophilia used only plasma-derived factor concentrates and/or FFP. Formerly, some authors pointed out that recombinant factor concentrates have a greater risk for inhibitor development more than plasma-derived products. However, in prospective previously untreated patients (PUP) studies, there was no statistically difference between recombinant and plasma-derived products. Lusher et al.[17] reported 24.8% and high titer inhibitor rate of 18% in Kogenate study. Bray et al.[18] also reported in the Recombinate study a cumulative incidence of 38.4% and a high titer inhibitor rate of 11.3%. These multi-center studies showed that most of the inhibitors were transient in patients who used recombinant factors. PUP studies reflect the higher figures versus the prevalence data due to the aforementioned reasons.

Eight years ago, Gürsel et al.[19] presented at the National Hemophilia Meeting in Turkey a rate of 47% in an inhibitor prevalence study performed in the Ankara region. These patients with inhibitor had no clinical problem as they patients had low titer inhibitors below than 2 BU/mL. In another study performed by Kavakli et al.[12] a prevalence rate of 21% was reported in the severe HA group which consisted of severe patients in total. This study is the first international publication by Turkish hematologists about inhibitor frequency among Turkish hemophiliacs. In this report there was no inhibitor positivity in 10 patients who used only FFP. All inhibitor patients had used factor concentrates (intermediate purity and pasteurized factor concentrates) with a median exposure of 52 days. Oren et al.[20] in her prevalance study also reported higher rates than observed in previous studies (41%) in 17 severe Turkish patients. Prior to the launch of our project, inhibitor prevalence for Turkish hemophiliacs seemed to be about 20-40%. Because inhibitor testing was previously rarely performed preoperatively, many hemophilia patients experienced very serious bleeding episodes in procedures such as circumcisions, dental extractions and other surgical interventions. Incorrect therapies caused unnecessary financial costs from national health budgets due to prescription of megadose factor concetrates over lonf periods which often resulted in no response in patients with inhibitors[3,12]. Thus it is of great importance to perform routine inhibitor assay in all of our patients in Turkey. Upon completion of this project, we have determined 11.2% for overall HA, 15.8% for severe HA, and 1.9% for HB after eliminating the transient inhibitors. The results of our study showed that inhibitor prevalence in a cohort of Turkish patients with hemophilia exposed to factor concentrates and to FFP was similar to that reported in the literature[1,2,6,7]. However, this figure is lower than in some reports from Western countries[4,5]. The reason why relatively lower inhibitor development rate in Turkish patients may be related to unsufficient factor concentrate use. Imported factor concentrates have been available in Turkey only for the last 10 years. Various social and insurance problems prevented most of the patients from using concentrates until the last five years[11,12]. As

Table 5. Inhibitor screening studies and prevalence rates from literature

Authors	Country	Reference	Prevalence (study groups)
Sultan et al.	France	14	12.8% (1565 severe HA)
Rizza et al.	England	15	12.7% (1546 severe HA)
Ghosh et al.	India	16	10.0% (292 severe HA)

HA: Hemophilia A, HB:Hemophilia B.

long as consumption and exposure days continue to increase, we assumed that the inhibitor development ratio will also increase in Turkish patients. Even though FFP has a relatively lower rate of inhibitor ratio, it is not recommended because of hazardous effects[21].

With respect to HB patients, our prevalence rate was found similar to that of Western countries[1,2]. The reported frequencies of inhibitor development among HB patients are generally low approximately 2-4%[4-7]. However, in a report from Sweden, a higher inhibitor development ratio of 34% was reported in HB patients. These patients had a relatively higher rate of deletion in their FIX genes. Our rate was 1.9% and similar to many other reports. With respect to genotype, our severe HB patients had no deletion and generally different point mutations[22].

Inhibitor development risk is variable in some races and societies. Hispanics and African Americans have greater risk than caucasians[23]. In our project, all Turkish patients were caucasians and inhibitor frequency was found similar to that observed in western countries.

The Bethesda inhibitor test technique was used in this project and it has been accepted as the gold standard test for inhibitor investigation. However some investigators have reported that the ELISA test can also be performed for inhibitor screening. Lindgren et al.[24] and Ghosh et al.[16] reported succesful results with ELISA testing. In fact, the ELISA test may be useful in mass screening because it is a simple and well-standardized method. It is also known as a relatively easy and less expensive test. However the Bethesda test can show anti-factor activity and neutralization of factor activity while the ELISA test can show only presence of antibodies to factor VIII.

There is no doubt that, the most accurate estimates of the true risk of inhibitor development come from prospective studies of newly diagnosed hemophiliacs who are tested regularly for the presence of inhibitors. In the present study even though it was a prevalence data, we evaluated more than 1000 Turkish patients who previously could not be tested. With this study, inhibitor frequency in Turkish hemophiliacs was determined as in Western countries. After realization of this project, more than 1000 patients have been screened and more than 100 patients were diagnosed with inhibitor positivity. Thus patients in Turkey with inhibitor are currently able to treated with specific products such as recombinant factor VIIa (NovoSeven®) or activated protrombin complex concentrates (APCCs)(FEIBA®) for therapy of their bleeding episodes or for use in their elective operations.

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