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ORIGINAL ARTICLE

Immunosuppressive treatment for acquired haemophilia: current practice and future directions in Germany, Austria and Switzerland

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Abstract Acquired haemophilia is an autoimmune disorder characterised by autoantibody formation against coagulation factor VIII. Immunosuppressive treatments including steroids, cytotoxic drugs, rituximab or combinations thereof have been used to eradicate autoantibodies. Very few prospective studies exist evaluating the use of these treatments. Here, we performed a survey among 73 physicians from 57 haemophilia treatment centres in order to describe current practice patterns and critical issues for future research in acquired haemophilia. The results demonstrate a high diversity of first- and second-line treatments. Factors influencing treatment decision were underlying disorder,

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severity of bleeding and inhibitor titre. Frequently used first-line treatments were steroids plus cyclophosphamide (44%) and steroids alone (11%). Second-line treatment was most often rituximab (30%), with or without steroids and/or cyclophosphamide. Most participants indicated to change from first- to second-line treatment after 4 weeks in case of failure to obtain partial remission (31%), continued bleeding (40%) or continued severe bleeding requiring bypass treatment (59%). Immunoadsorption was preferred for first- and second-line treatment by 10% and 9% of participants, respectively. These results highlight critical issues in the field. Open questions and directions for future research are discussed.

Keywords Acquired haemophilia · Autoimmunity · Immunosuppressive agents · Glucocorticoids · Cyclophosphamide · Rituximab

Introduction

Acquired haemophilia is a rare autoimmune disorder characterised by the formation of neutralising antibodies, so-called inhibitors, to coagulation factor VIII (FVIII). Anti-FVIII antibody formation is sometimes transient but usually requires immunosuppressive treatment to achieve remission [1, 2]. A meta-analysis of published cases suggested that steroids, as compared to no immunosuppressive treatment, increased the probability of remission [3]. Cyclophosphamide, with or without steroids, were shown to further shorten the time to remission as compared to steroids alone [3]. A combination of cyclophosphamide and steroids appears to be the most widely used initial treatment for acquired haemophilia today. Notably, a recent prospective non-randomised cohort study did not document a higher probability of remission or shorter time to remission with cyclophosphamide or other cytotoxic drugs as an adjunct to steroids [4].

Time to remission appears to be an important variable as patients remain at a high risk of bleeding until they achieve remission. On the other hand, cytotoxic drugs may exert serious side effects including cytopenias and infection. Therefore, immunosuppressive treatment deserves to be studied in order to optimise both time to remission and the risk of serious adverse events.

We performed a survey among members of the Thrombosis and Haemostasis Society (*Gesellschaft für Thrombose-und Hämostaseforschung* (GTH)) in order to describe the current practice of immunosuppressive treatment for acquired haemophilia in Germany, Austria and Switzerland. These results help to define some critical issues for future research and will also be useful to evaluate the feasibility of studies in that area.

Materials and methods

Five hundred twenty-two unselected members of the GTH were asked by email to participate in a survey if they had personal experience in the treatment of acquired haemophilia. Eighty-one (16%) responded to the request, 73 (84%) of whom completed the full questionnaire ("the participants").

In addition to questions relating to professional and institutional background, we asked 30 questions addressing the management of acquired haemophilia and preferences for future research in the area. The questions were (1) multiple choice questions with one or multiple answers where appropriate, (2) numerical questions, and (3) rating scales. Free comments could be added where appropriate.

Throughout the survey, we defined as complete remission (CR) a normal FVIII activity and a negative Bethesda inhibitor assay; as partial remission (PR) a FVIII activity >30 IU/dl, an inhibitor titre <5 Bethesda units/ml and the absence of bleeding that required haemostyptic therapy. Simple descriptive statistics were used to present the data. Concerning the number of patients treated per year, data were aggregated if more than one participant per institution took part in the survey or if it was known to the authors that two or more institutions collaborated closely and could be assumed to refer to the same patients.

Results

Participants and institutions

Eighty-one members of the GTH participated in the survey, 73 of whom completed the questionnaire indicating they had personal experience in the treatment of acquired haemophilia (the "participants"). The participants were from 57 different institutions and were mainly affiliated with hospitals including most of the Haemophilia Treatment Centres (Table 1).

Table 1 Participants

	Number (%)
Total	73
Country	
Germany	56 (77%)
Switzerland	12 (16%)
Austria	5 (7%)
Affiliation	
Hospital	61 (84%)
Private practice	11 (15%)
Other	1 (1%)

Acquired haemophilia is an exceptionally rare disorder. Participants reported personal treatment experience in one to four cases (44% of participants), five to ten cases (24%), 11 to 20 cases (18%) or more than 20 cases (13%). Between 2004 and 2006, the median number of cases treated in the participants' institutions was 1.8 per year (range 0–10). The total number of patients ranged between 103 and 106 per year. Assuming the reported incidence of 1.48 cases per million per year [4], 143 patients were to be expected in the geographic area per year. The number of cases reported by the participants in the European Acquired Haemophilia (EACH) registry [5] at the time of the survey ranged between 12 and 20 per year, corresponding to an average of 16% of the total number of cases reported per year.

First-line immunosuppressive treatment

Forty-five per cent of the participants considered every first diagnosis of acquired haemophilia as an indication to start immunosuppressive treatment. Others considered only patients with bleeding symptoms (32%) or clinically severe bleeding symptoms (16%) for immunosuppressive treatment.

For first-line treatment, 38% of the participants used a standard protocol for most of their patients, whereas 55% indicated to choose treatment individually for each patient. The most important factors influencing their decision were underlying disorder (important or very important, 55%), severity of bleeding symptoms (52%), inhibitor titre (41%) and concomitant medication (41%).

We next asked the participants for their usually preferred first-line treatment schedule (Table 2). Steroids plus cyclophosphamide (44%, either daily or as pulse therapy) and steroids alone (11%) were the most frequently used treatments. Rituximab-based treatments were considered infrequently. Twenty-three per cent of participants indicated they did not prefer any of these treatment schemes but rather used more individualized treatments.

Second-line immunosuppressive treatment

Participants were asked when they would consider a failure of first-line treatment and therefore start second-line treatment (Fig. 1). Most participants indicated to do so after 4 weeks of first-line therapy in case of bleeding that required bypassing agents (59%), any bleeding (40%) or failure to obtain PR (31%). In contrast, failure to obtain CR was infrequently considered a reason to start second-line treatment.

Participants preferring steroids alone for first-line treatment, as compared to participants preferring steroids plus cyclophosphamide, were more likely to change to second-line treatment after 4 weeks in case of ongoing bleeding (80% vs. 43%) or failure to obtain CR (33% vs. 0%) or PR (43% vs. 32%).

Preferred treatment schedules for second-line treatment are given in Table 2. Compared to first-line treatment, rituximab-containing regimens were considered more frequently (30%, either alone or in combination with steroids and/or cyclophosphamide). Almost half of the participants indicated to choose second-line treatment individually for each patient.

Contraindications to immunosuppressive treatment

Participants were asked to indicate absolute contraindications for different immunosuppressive drugs in patients with acquired haemophilia and a severe bleeding tendency (Table 3). For steroids, uncontrolled infection and a personal history of steroid-induced psychiatric disorders were specified by more than 20% of participants. However, 33% of participants stated that, in the context of acquired haemophilia, steroids have no absolute contraindication. For cyclophosphamide, pregnancy or breast feeding, uncontrolled infection, and leukopenia or thrombocytopenia were specified by more than 20% of the participants. For rituximab, pregnancy or breast feeding, uncontrolled

Table 2 Immunosuppressive treatment of acquired haemophilia

	First-line N (%)	Second-line N (%)
Response rate	71 (97)	64 (88)
No preferred protocol (individual treatment)	16 (23)	29 (45)
Steroids alone	8 (11)	0 (0)
Steroids, cyclophosphamide (p.o., daily)	21 (30)	4 (6)
Steroids, cyclophosphamide (i.v. pulse therapy)	10 (14)	1 (2)
Rituximab alone	1 (1)	9 (14)
Rituximab, steroids	1 (1)	2 (3)
Rituximab, steroids, cyclophosphamide	1 (1)	8 (13)
Immunoadsorption	7 (10)	6 (9)
Other protocols	6 (8)	5 (8)

Participants were asked to indicate the treatment protocol most often used in their clinical practice

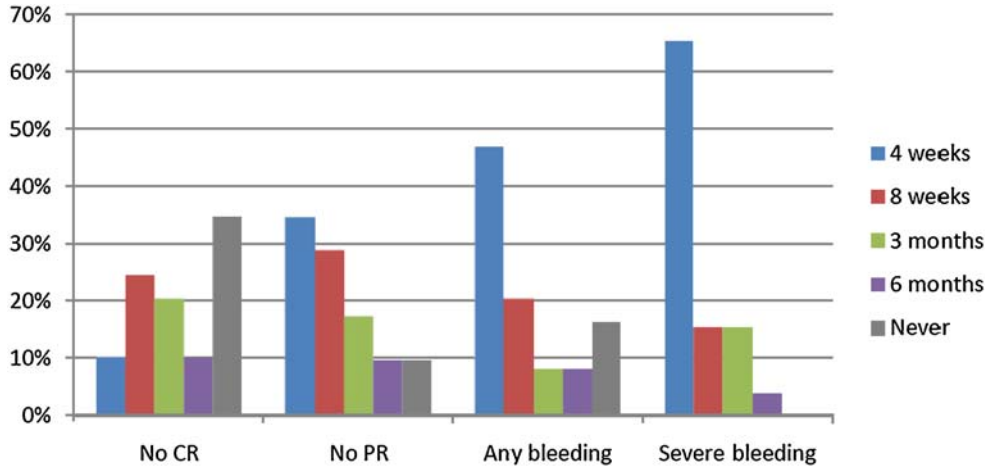

Fig. 1 Reasons for treatment escalation. Participants were asked to estimate why and when they would consider failure of first-line immunosuppressive treatment and therefore start second-line treatment. Complete remission (*CR*) was defined as normal FVIII activity and no detectable FVIII inhibitor. Partial remission (*PR*) was defined as FVIII >30%, FVIII inhibitor <5 Bethesda units/ml and absence of bleeding that required haemostyptic treatment. Severe bleeding was defined as bleeding requiring treatment with bypassing agents

infection and polymerase chain reaction (PCR)-detectable viraemia of human immunodeficiency virus or hepatitis C virus were considered absolute contraindications by more than 20% of participants.

Immunoadsorption

Immunoadsorption, either alone or as part of the modified Bonn–Malmö protocol [6], was the preferred mode of treatment for 10% and 9% of participants for first- and second-line treatment, respectively (Table 1). These participants were from five different centres. When asked for indications for immunoadsorption, most participants identified life-threatening bleeding (70%), urgent surgery (56%) and very high doses of bypassing agents needed to obtain haemostasis (54%). Failure of first- and second-line immunosuppressive treatment (47%) and high inhibitor titre before starting treatment (28%) were also frequently considered as indications. Fifty-one per cent of participants indicated that immunoadsorption could be performed in their own institution if needed. Most participants would combine immunoadsorption with steroids (86%), cyclophosphamide (72%), intravenous immunoglobulin (61%) and FVIII concentrate (44%).

Direction for future clinical research

Despite of an obvious need for clinical research in this area, there are major obstacles in the design of clinical trials. In general, randomised controlled trials were regarded feasible

Table 3 Contraindications to immunosuppressive treatments

	Participants (in per cent)		
	Steroids	Cyclophosphamide	Rituximab
Present, uncontrolled infection	40	48	40
Risk of infection due to co-morbidity	6	6	14
PCR-detectable HIV or HCV viraemia	19	18	23
Cytopenia	–	33	–
Renal insufficiency	–	18	–
Diabetes mellitus	8	–	–
Severe congestive heart failure	3	–	–
Hypertension	6	–	–
History of SIPD	23	–	–
Pregnancy or breast feeding	11	51	41
Reproductive age	–	16	–
None	33	10	16

Participants were asked which of the given conditions they would consider absolute contraindications in the context of acquired haemophilia with severe bleeding tendency
HCV hepatitis C virus, *HIV* human immunodeficiency virus, *SIPD* steroid-induced psychiatric disorder

by 60% of the participants, whereas 32% considered such trials unfeasible. The most frequently identified obstacles were the rarity of the disease as well as legal and administrative requirements (Table 4). Preferred designs for investigator-driven studies were prospective cohort studies with treatment stratification according to patient characteristics (75%), prospective cohort studies evaluating uniform treatment protocols (44%) and randomised open-label trials (40%). Registries of patients undergoing individual treatments at the discretion of the local physician were preferred by few participants (7%).

Immunosuppressive drugs most attractive for future research were rituximab (91%) and mycophenolate mofetil (57%). Other candidates such as ciclosporin A (36%), tacrolimus (25%), azathioprin (23%) or methotrexate (9%) received less attention.

Intensification of the currently used first-line treatments appears to be an interesting option for future research. A majority of participants agreed that a more intense first-line treatment may potentially achieve faster remission (68%), result in less cumulative drug exposure and reduction of side effects (61%) and could reduce the need for bypassing agents (59%).

Discussion

This survey sheds light on several interesting aspects of the current practice of immunosuppressive treatment for acquired haemophilia. Treatment experience, even among expert physicians, is limited to few cases, underscoring the need for collaborative studies in the field. Registries such as the EACH registry were successful providing large cohorts of patients [7]. However, our survey indicates that, at least for our countries, the fraction of patients reported in the registry was rather small, raising concerns of selection bias.

A substantial proportion of participants advocate for individually tailored therapy during first- and second-line treatment. The severity of bleeding, along with other factors such as inhibitor titre, appears to influence the decision to start immunosuppressive treatment as well as the choice of regimen. It should be noted that the bleeding phenotype at first diagnosis does not predict severe or fatal bleeding in the future [4]. Therefore, immunosuppressive treatment aiming to obtain CR should be administered to every patient regardless of the severity of bleeding. Likewise, data do not support the view that severity of bleeding is related to the probability of achieving remission or to the time to achieve remission. It may not be justified to give more aggressive immunosuppressive treatment to patients with more severe bleeding. More aggressive treatment in heavily bleeding patients may in fact potentiate the risk of serious complications in this critically ill patient population. On the other hand, patients with less severe bleeding in the beginning, who received less aggressive or no immunosuppressive treatment, may need a long time to achieve remission and, until then, may not be protected from new, potentially severe bleeding. In conclusion, bleeding severity and other factors sometimes considered in the choice of treatment require rigorous study before they can be recommended as predictors for treatment success.

The evaluation of immunosuppressive treatments is difficult due to the time lapse between start of treatment and success. Cohort studies demonstrated the time to achieve remission being notoriously variable. In the collection by Sperr et al., 44 patients receiving steroids and cyclophosphamide achieved remission after a median of 6.3 weeks with a range of 2 to 86 weeks; 28 patients receiving rituximab achieved remission after a median of 8.3 weeks with a range of 2 to 76 weeks [8]. In a given patient, it is virtually impossible to predict the time to remission. Vice versa, failure of a treatment in a given patient cannot be certain, even after weeks of unsuccessful treatment. Our survey indicates that failure of first-line treatment is often considered after 4 weeks of treatment. However, only 30% to 40% of patients can be expected to be in remission at this time.

Table 4 Barriers for research

	Participants (in per cent)		
	Not significant	Significant, but solvable	Significant and unsolvable
Rarity of the disorder	4	52	45
Administrative and legal requirements	18	79	0
Limited staff at sites	18	75	2
Ethical considerations	32	50	13
Restrictions to freedom of therapy	23	61	11
Cost	13	66	5

Participants were asked how they think of the following potential barriers for performing controlled clinical trials in acquired haemophilia (percentages missing to 100 were missing responses)

Notably, physicians who preferred a milder first-line treatment (steroids only) were more likely to start a second-line treatment early, i.e. after 4 weeks. This strategy may prevent over-treatment in those patients who respond within 2 to 4 weeks of treatment; however, it may also prolong the time to remission in those patients who do not respond quickly. The optimal intensity of first-line treatment and the time point for treatment intensification remains an open issue that requires adequately designed studies.

This survey was the first approach to describe treatment patterns and physicians' opinions in acquired haemophilia. The number of cases treated by the participating physicians between 2004 and 2006 was a substantial proportion (about three fourths) of all patients with acquired haemophilia in the geographic area. Therefore, the survey can be considered representative. However, several limitations need to be considered. The survey was limited to three countries, and results may not be valid for other countries. The personal treatment experience of most participants was limited to a few cases. Such experience may not be representative of the entire clinical spectrum of the disease and potentially bias some opinions stated in the survey. Other forms of bias typical for surveys of this kind may also be a concern, especially response bias and recall bias.

In summary, this survey points towards some of the many open issues in the field. Future studies aiming to characterise prognostic factors or comparing the currently used treatments are eagerly awaited. The rarity of the disease and other major difficulties for clinical studies in the field demand the cooperation of Haemophilia Treatment Centres.

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References

1. Collins PW (2007) Treatment of acquired hemophilia A. J Thromb Haemost 5:893–900 doi:10.1111/j.1538-7836.2007.02433.x
2. Franchini M, Lippi G (2008) How I treat acquired factor VIII inhibitors. Blood 112(2):250–255 doi:10.1182/blood-2008-03-143586
3. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A (2003) Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol 121:21–35 doi:10.1046/j.1365-2141.2003.04162.x
4. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, Keeling DM, Liesner R, Brown SA, Hay CR (2007) Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 109:1870–1877 doi:10.1182/blood-2006-06-029850
5. Watling M (2004) The European acquired haemophilia registry. Blood Coagul Fibrinolysis 15(Suppl. 1):29 doi:10.1097/00001721-200405001-00006
6. Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, Vetter H, Brackmann HH (2005) Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept. Blood 105:2287–2293 doi:10.1182/blood-2004-05-1811
7. Baudo F, Levesque H, Huth-Kühne A, Knoebl P, Marco P, Nemes L, Peerlinck K, Tengborn L (2008) The European Acquired Hemophilia Registry (EACH2): a preliminary data analysis. Haemophilia 14(Suppl. 2):1
8. Sperr WR, Lechner K, Pabinger I (2007) Rituximab for the treatment of acquired antibodies to factor VIII. Haematologica 92:66–71 doi:10.3324/haematol.10553