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Immunoadsorption for the Treatment of Acquired Hemophilia: New Observational Data, Systematic Review, and Meta-Analysis

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ABSTRACT

The treatment of patients with acquired hemophilia is challenging due to life-threatening hemorrhages, delayed response, and adverse effects to immunosuppressive agents. Even though immunoadsorption (IA) rapidly removes autoantibodies against factor VIII, this intervention's effectiveness is still a matter of debate. We aimed to study important outcomes of IA as adjunctive treatment in patients with acquired hemophilia. We performed comprehensive literature searches in MEDLINE and EMBASE databases. Clinical and laboratory data of all patients treated in our institution were additionally included. Literature searching yielded 498 records, of which 10 studies describing 106 patients were finally included. The number of patients varied from 1 to 65, and patients' ages ranged between 14 and 89. Treatment criteria in most patients were (1) failed response to immunosuppressive treatment alone, and/or (2) uncontrollable bleeding episodes, and/or (3) high inhibitor titer. Methodological quality was moderate. The number of IA sessions varied from 1 to 24. Within our institution, 12 patients have been treated since 2002; median age was 76 years (range 34-86); median titer of factor VIII inhibitor was 20 Bethesda units (range 3-214). Pooled estimates, modeling a random-effect binominal distribution incorporating the Freeman-Tukey double arcsine transformation, were 86% in case of factor VIII recovery (95% confidence interval 76%-94%), 95% for reduction of factor VIII inhibitor (83%, 100%), and 7% in case of death (0%, 18%). Our data suggest that IA might be a beneficial adjunctive treatment in patients with high-risk acquired hemophilia, but future studies shall confirm this observation.

Introduction

Treatment of patients with acquired hemophilia is challenging. Often, patients present with large ecchymosis, extensive muscle hemorrhages, gastrointestinal bleeding, or even intracerebral hemorrhage [1-3]. The mortality is high because of bleeding complications and treatment complications such as infection [4,5]. The pathogenesis of acquired hemophilia is heterogeneous. The most common associated conditions are malignancy [6,7], autoimmune disorder [8-11], drug-induced [12,13], or postpartum status [14,15]. On multivariate analysis, factors that predict improved overall survival are the achievement of complete remission, age below 65 years, and postpartum status. The largest patient cohort has been described by the EACH2 registry of 501 patients [16]. The cohort comprised 266 men (53.1%) and 235 women (46.9%). The median age at diagnosis was 73.9 years, demonstrating a preponderance of older patients but the data revealed also a second small population of younger female patients ($n = 42$; 8.4%) with a median age of 33.9 years who presented with peripartum acquired hemophilia (8 antepartum and 34 postpartum). Whereas the whole EACH2 cohort showed upon treatment a CR of 73% and a preliminary survival rate of 68% at final follow up, 36 of 42 women were in CR (86%), and 40 of 40 (100%) alive at final follow up [17]. This excellent survival reflects the younger age and better overall health of the female subgroup and has been described by other retrospective studies and reviews.

Physicians are confronted with a variety of drugs to stop the bleeding and eradicate the inhibitor against factor VIII (FVIII) [5,18-20]. However, results from randomized controlled trials to

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inform physicians regarding treatment decisions are not available. Stopping the bleeding is the first treatment objective, which is pursued using recombinant activated factor VII (rFVIIa), porcine VIII, activated prothrombin complex concentrate, or even high-dose human FVIII [4,5,18,20,21]. To prevent additional bleeding, some patients have been treated with emicizumab, a bispecific FVIIIa mimetic antibody, with interesting responses [22]. Even though it is not yet approved for acquired hemophilia and clinical trials are missing, it has possible hemostatic prophylactic effectivity with weekly or bi-weekly subcutaneous injection-application, can be done in an outpatient setting, and is bridging the time until immunosuppression is effective. To eradicate inhibitors against FVIII, a combined immunosuppressive treatment can be applied. Often, a combination of corticosteroids and cyclophosphamide is given [18,23]. However, response to treatment might take several weeks or even months and the treatment is not successful in a relevant number of patients [16,24-26]. Other immunosuppressive regimens include azathioprine, mycophenolate mofetil, and bortezomib [27,28]. Because of the low rate of adverse events, Rituximab has recently gained increasing acceptance in combination with steroids, used in the first line or the second line after no response to cyclophosphamide and steroid treatment, but these regimes have not yet been studied in controlled trials [17,29-31].

immunoadsorption (IA) is suggested to rapidly eradicate autoantibodies against FVIII by removing circulating immunoglobulins [32]. Patient plasma is separated from whole blood using a plasma separation device and it is passed through columns containing absorbent ligands [33-35]. Several adsorbent ligands are used: (1) re-usable columns comprised of *Staphylococcus aureus* protein A and bound to sepharose matrix (protein A sepharose) [36-38], (2) re-usable columns with antihuman IgG sheep bound to sepharose matrix (Therasorb-Ig) [36-38], (3) disposable tryptophan-based columns (Immusorba TR-350) [39-41], and (4) a synthetic peptide GAM bound to sepharose matrix (Globaffin) [42,43]. With most columns, IgG immunoglobulins are selectively removed [36] and the inhibitor titers of the autoantibodies are lowered significantly within few sessions [44]. However, publications describing the clinical effectiveness of this approach are scarce and scattered in the literature. Comparable to other rare diseases, no randomized controlled trials have been conducted. Thus, no conclusion or recommendation as to whether or not IA should be implemented in treatment regimens for acquired hemophilia has been made to date [4,18,23,36,45-47].

Aim

The aim of the present investigation was to systematically search and retrieve available clinical and laboratory data from studies describing the use of IA for the treatment of acquired hemophilia, to report on patients treated on our own institution in this way, and to summarize all data using meta-analytic methods.

Methods

Study Design and Setting

In a retrospective cohort study, we systematically searched and retrieved data from all patients with acquired hemophilia treated at our institution between 2002 and May 2019. Inselspital Bern is the only tertiary hospital in the Greater Bern Area covering more than 1.5 million inhabitants. Due to the retrospective design and absence of general informed consent of patients attending the hospital before 2016, not all patients had provided informed consent – the local ethics committee waived this need. The local ethics committee approved the protocol (Ethikkommission Bern #2019-00478) and we conducted the study in accordance with the Declaration of Helsinki.

Inclusion Criteria and Identification of Patients

Patients were identified from the patient documentation within the apheresis unit. Inclusion criteria were an established diagnosis of acquired hemophilia with a FVIII activity below 5 IU/dL and an inhibitor titer >1 BU/mL. Predefined clinical data including year of diagnosis, age at admission, sex, bleeding presentation, concomitant disorders, aPTT, FVIII activity and inhibitor titer were retrieved in duplicate (MP, MN) from electronic patient documentation. In addition, FVIII recovery, reduction of the inhibitor titer, bleeding events and deaths were recorded at predefined follow-up time points: 30 days, 3 months and 12 months. A specifically designed data extraction form was used, and the accuracy was checked by a second investigator (MN). Discrepancies were resolved by discussion.

Systematic Review: Study Identification, Eligibility, and Data Extraction

A search strategy for MEDLINE and EMBASE was developed using the Ovid interface and refined using keywords from references found in a pilot search and after manual review of reference lists (Supplementary Material). No restrictions with regard to language or publication date were applied. The last search run was performed on October 29, 2019 and obtained records were screened by 2 investigators in parallel (MN, MP). The titles and abstracts of all hits were assessed for eligibility. The following inclusion criteria were applied: (1) acquired hemophilia patients with FVIII levels below 20%, and an inhibitor titer ≥1, (2) patients that have had at least 1 session of IA in addition to standard treatment, (3) laboratory outcomes reported (FVIII recovery and/or course of inhibitor titer), and (4) reporting of clinical outcomes (bleeding events and/or mortality). Studies were excluded if (1) only patients with hereditary hemophilia were described, (2) plasma exchange was conducted, (3) no clinical outcomes were reported, or (4) no laboratory outcomes were presented. The most complete publication was selected where multiple publications describing the same cohort were found. Full-text articles were assessed by 2 investigators. Studies selected for inclusion were reviewed in duplicate and the following data were extracted: author, year of publication, number of patients, age range, sex, aPTT, FVIII, inhibitor titer, cotreatment and observation period. The treatment protocols, including the absorbing agent, the number of IA sessions and the cotreatment(s) were extracted, as well as FVIII-recovery, reduction of the inhibitor titer, remission status and death. The systematic review protocol used here was submitted to the PROSPERO international prospective register of systematic reviews and the results have been reported according to the PRISMA guideline.

Assessment of Methodological Quality

For assessment of methodological quality, we used the Newcastle-Ottawa Scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS is an established tool to assess the methodological quality of nonrandomized studies including case-control and cohort studies [48]. The following items were assessed: (1) representative patients, (2) control group selected, (3) patients treated, (4) end points absent at the start of treatment, (5) control group comparable, (6) determination of end points, (7) interval of follow-up, and (8) complete follow-up.

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Table 1
Characteristics of patients receiving an IA treatment for acquired hemophilia at our institution, Inselspital, Bern University Hospital.

Patient number	Year of diagnosis	Age *Years*	Sex	Type of bleeding	Concomitant disorders	aPTT *Seconds*	FVIII activity *IU/dL*	Inhibitor titer *BU/mL*
1	2002	77	Female	GI bleeding	Osteoporosis, COPD	52	<1	3
2	2002	75	Female	GI bleeding	Sjogren syndrome	55	<1	18
3	2003	53	Male	Extensive bruising	Chronic hepatitis C	57	<1	16
4	2004	34	Female	Extensive bruising	nr	130	3	>200
5	2006	80	Male	Extensive bruising	CHD, hypertension, renal impairment	65	<1	13
6	2010	70	Female	Extensive bruising, GI bleeding	Sepsis, diabetes type 2	68	3.5	15
7	2012	77	Male	Bleeding after tooth extraction	Granulomatosis with polyangiitis, atrial fibrillation, renal impairment	108	<1	32
8	2013	81	Male	Extensive bruising	Renal impairment, diabetes type 2, CHD	60	2	22
9	2013	64	Male	Extensive bruising	Chronic venous insufficiency	77	<1	214
10	2016	86	Male	Extensive bruising	CHD, renal impairment	84	<1	47
11	2018	73	Male	Extensive bruising	CHD, COPD, renal impairment	119	<1	7
12	2019	77	Male	Extensive bruising, GI bleeding, compartment syndrome	Multiple myeloma, hypertension, atrial fibrillation, renal impairment	119	<1	102

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal tract.

Definition of Outcomes

FVIII recovery or complete remission, respectively, was defined as a stable FVIII recovery of higher than 70 IU/dL. Partial remission was defined as a FVIII recovery of more than 30 IU/dL [49]. Reduction of inhibitor titer was defined as a titer below 10 BU/mL and/or a decline of more than 70% [50]. Mortality was defined as overall mortality or the proportion of patients who died within the given observation period.

Statistical Analysis

For descriptive purposes, numbers and/or proportions and median and/or range were used as appropriate. Pooled proportions of patients with FVIII recovery (complete response), reduction of inhibitor titer and deaths were calculated in relevant subgroups using the binominal distribution and Freeman-Tukey double arcsine transformation [51,52]. Heterogeneity was tested using the I^2 statistics, which describes the proportion of total variation due to between-study heterogeneity. Sensitivity analyses were conducted in retrospective studies and in studies using different absorbing agents (Protein A sepharose vs Ig-Therasorb vs Immuno-sorba TR-350). The Stata 14.1 statistics software package (StataCorp. 2015. Stata Statistical Software: Release 14.2. College Station, TX, USA: StataCorp LP) was used for statistical analyses.

Results

Characteristics, Treatment, and Outcomes

Within our institution, 12 patients with acquired hemophilia have been treated since 2002; detailed patient characteristics are shown in Table 1. The median age was 76 years (range 34-86) and 4 patients were female. The bleeding phenotype was extensive bruising and/ or muscle hematomas in 9 patients, gastrointestinal bleeding in 2 patients and extensive bleeding after tooth extraction in 1 patient. At admission, median aPTT was 72.5 seconds (range 52-130), FVIII activity was below 1 IU/dL in 9 patients, and median FVIII inhibitor was 20 BU/mL (range 3-214). Treatment criteria for IA was either (1) failed response to immunosuppressive therapy alone, (2) severe bleeding episodes that could not be controlled, or (3) high inhibitor titer. Clinical and laboratory outcomes are reported in Table 2. Observation period varied from 22 days to 4 years and the number of IA sessions varied from 2 to 9. In each session, we treated 2 to 2.5 times the patients' plasma volume. Cyclophosphamide was used in addition to steroids (prednisolone in 10 patients and methylprednisolone in 2 patients) as immunosuppressive treatment in all patients. Other factor concentrates (recombinant factor VIIa, activated prothrombin complex concentrate, (human) FVIII concentrate), and intravenous immunoglobulin G were used in some patients. At day 30, the median FVIII was 34 IU/dL (range <0.01-241) and the median inhibitor titer was 1.1 BU/mL (range 0-326.5). At 3 months, the median FVIII was 80 IU/dL (range 32-360) and the median inhibitor titer was 0.15 BU/mL (range 0-2). After 1-year, median FVIII was 147 IU/dL (range 132-162), and the median inhibitor titer was 0 (for only 2 available patients). Bleeding could be stopped in 9 patients and 3 patients did not respond to the treatment.

Selection of Studies and Methodological Quality

Our literature search yielded 498 records (Figure 1). After removal of duplicates, the title and abstract were screened in 444 records. We selected 52 publications for full-text review of which 42 were excluded because IA was not applied, because of double publication, or missing data. Adding our own data, we included eleven studies comprising 118 patients (Table 3). The overall quality of primary studies according to the adapted NOS was rated as moderate. The most important limitations were that (1) no control group was available, and (2) data were collected retrospectively in all but 1 case [53]. Thus, items 2 and 5 from the adapted NOS were rated as "unfavorable" in all studies; the ratings of the other items of NOS are shown in Figure 2. The study populations were regarded as "very representative" because all patients were treated in 3 of 11 studies, and "somewhat representative" in all other studies. The items "Were patients really treated" and "Were end points absent at the time of inclusion" were rated as "Yes" in all studies. For all end points, data were available, but no blinded assessment was done. Follow up was carried out ≥3 months in 9 of 11 studies, and the frequency of patients lost to follow-up was below 20% in all studies. The individual ratings for all studies are shown in the Supplementary Table S1.

Systematic Review

Reports of 106 patients with acquired hemophilia treated with IA were identified; the observation period varied between 43 days [37] and 14 years [53]. Details are reported in detail below, patient characteristics are summarized in Table 3, treatment details and outcomes are given in Table 4.

In a retrospective analysis, Gjoerstrup et al report about 3 non-pregnant patients (43, 62, and 75 years of age; 1 female) with ac-

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Table 2
Treatment details and outcomes of patients treated at our institution, Inselspital, Bern University Hospital.

Patient number	Observation period *Months*	IA-sessions[a]	Absorbing agent	Co-treatment	FVIII recovery[b] *IU/dL*	Reduction of inhibitor titer[c] *BU/mL*	Clinical outcome
1	1	2	Protein-A-Sepharose	- Cyclophosphamide 75 mg/d - IVIG 0.5 g/kg/d - rFVIIa 6 mg - Prednisolone 75 mg/d	34 (30d)	nr	Bleeding stopped
2	1	4	Protein-A-Sepharose	- Cyclophosphamide 50 mg/d - Prednisolone 100 mg/d - IVIG 0.5 g/kg/d	2 (30d)	17.6 (30d)	Nonresponse
3	3	5	Protein-A-Sepharose	- IVIG 0.5 g/kg/d - FVIII concentrate - Prednisolone 50 mg - Cyclophosphamide 100 mg/d	34 (30d) 360 (3m)	nr	Bleeding stopped
4	3	6	Protein-A-Sepharose	- Prednisolone 75 mg/d - Cyclophosphamide - rFVIIa 4.8 mg	25 (30d) 62 (3m)	0 (3m)	Bleeding stopped
5	1	3	Protein-A-Sepharose	- Cyclophosphamide 100 mg/d - Methylprednisolone 125 mg/d - Tranexamic acid 500 mg 3x/d	241 (30d)	0 (30d)	Bleeding stopped
6	0.8	5	Protein-A-Sepharose	- Prednisolone 80 mg/d - rFVIIa 90 µg/kg - Cyclophosphamide 100 mg/d	No recovery	No reduction	No response
7	2	7	Protein-A-Sepharose	- Cyclophosphamide 100 mg/d - IVIG 0.5 g/kg/d - Rituximab 375 mg/kg - rFVIIa 90 µg/kg - Prednisolone 75 mg/d	326.5 (30d)	<1 (30d)	No response; death
8	12	6	Protein-A-Sepharose	- Prednisolone 75 mg/d - Cyclophosphamide 100 mg/d - rFVIIa 90 µg/kg	11 (30d) 80 (3m) 132 (12m)	2.1 (30d) 0.3 (3m) 0 (12m)	Bleeding stopped[$]
9	48	4	Protein-A-Sepharose	- Cyclophosphamide 100 mg/d - IVIG 0.5 g/kg/d - Prednisolone 75 mg/d	194 (30d) 43 (3m) 162(12m)	0.2 (30d) 0.5 (3m) 0 (12m)	Bleeding stopped
10	6	5	Protein-A-Sepharose	- Prednisolone 100 mg/d - Cyclophosphamide 100 mg/d - rFVIIa 90 µg/kg	123 (30d) 32 (3m)	1.2 (30d) 2 (3m)	Bleeding stopped; relapse 3 months after diagnosis; death 6 months after diagnosis
11	3	9	Protein-A-Sepharose	- Methylprednisolone 125 mg - aPCC 3700 U - rFVIIa 90 µg/kg - Cyclophosphamide 100 mg/d - Prednisolone 75 mg/d	141 (30d) 150 (3m)	0 (30d) 0 (3m)	Bleeding stopped
12	5	7	Globaffin	- Prednisolone 1 mg/kg/d - Cyclophosphamide 150 mg/d	48 (30d) 199 (3m)	1 (30d) 0 (3m)	Bleeding stopped

aFVII, activated factor VII; aPCC, activated prothrombin complex concentrate; IVIG, intravenous immunoglobulin G; nr, not reported.
[a] Number of IA sessions.
[b] the factor VIII activity is given at 30 days (30d), 3 months (3m), and 12 months (12m) as available.
[c] the inhibitor titer in Bethesda units is given at 30 days (30d), 3 months (3m), and 12 months (12m) as available; $, death 1 year after diagnosis independent from acquired hemophilia.

Table 3
IA treatment of acquired hemophilia: Patient characteristics in primary studies.

#	Author, year	No. of patients	Design	Age *Years; median (range)*	Sex *Numbers male/ female*	Observation period *Years; median or range*	aPTT *Seconds; median (range)*	FVIII activity[a] *IU/dL; median (range)*	Inhibitor titer[a] *BU/mL; median (range)*
[54]	Gjörstrup, 1991	3	Retrospective	62 (43-75)	2/1	nr	nr	nr	63 (36-155)
[50]	Watt,1992	9	Retrospective	58 (24-76)	6/3	3	nr	5 (<5-8)	600 (8-1587)
[55]	Jansen, 2001	7	Retrospective	70 (24-77)	5/2	2.1	90 (70-200)	<1 (<1-15)	114 (18-540)
[37]	Guillet, 2001	2	Retrospective	29/62	1/1	0.1-1	95-56	4 (<1-7)	15 (22-8)
[56]	Mansouri Taleghani, 2001	4	Retrospective	59 (27-67)	2/2	0.7 (0.25-1)	Nr	nr	100 (3-138)
[57]	Rivard, 2003	5	Retrospective	59 (28-80)	2/3	3	114 (150-122)	1 (<1-15)	100 (12-144)
[39]	Brzoska, 2007	9	Retrospective	70 (50-78)	6/3	2	Nr	2	37 (3.61-1085)
[41]	Seibert, 2011	1	Retrospective	73	0/1	nr	89	1	1500
[53]	Zeitler, 2013	65	Prospective	67 (28-89)	27/38	1-14	67 (28-89)	<1	228 (8-3600)
[63]	Bilgin, 2013	1	Retrospective	78	1/0	0.5	157	4	10
Current	Esteves Pereira, 2021	12	Retrospective	76 (range 34-86)	8/4	0.4 (0.1-4)	73 (52, 130)	<1 (<1-3)	20 (3-214)

nr, not reported.
Cohort studies, case series, and case reports were included.
[a] before treatment.

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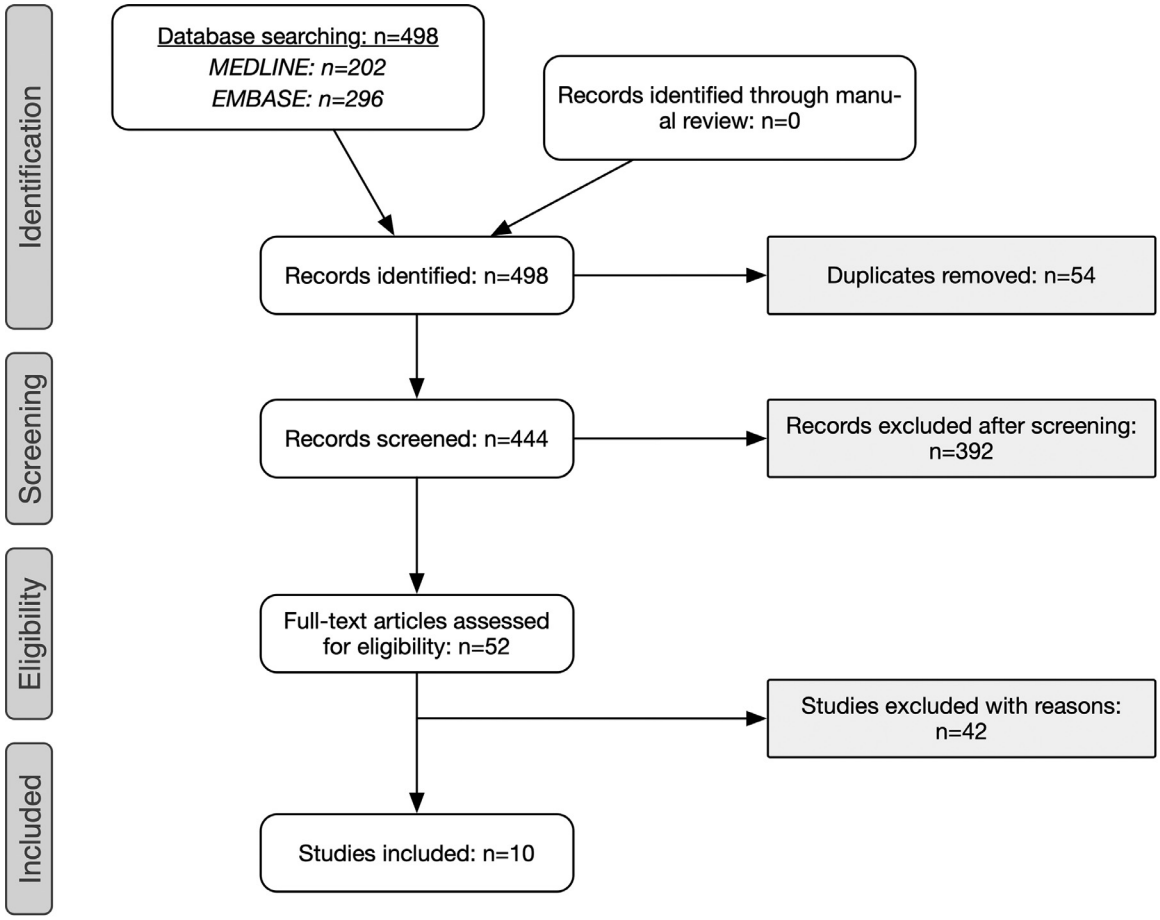

Fig. 1. Selection process of primary studies.

Table 4
IA treatment of acquired hemophilia: Treatment details and results.

#	Author, year	Nr. of IA *median (range)*	Absorbing agent	Co-treatment	FVIII recovery *Number of patients out of all patients*	Reduction of inhibitor titer *Number of patients out of all patients*	Death *Number of patients out of all patients*
[54]	Gjörstrup, 1991	2 (2-4)	Protein A Sepharose	FVIII-concentrates, steroids, cyclophosphamide	2/3	2/3	0/3
[50]	Watt, 1992	3,5 (2-6)	Protein A Sepharose	Various drugs	5/7	7/7	0/9
[55]	Jansen, 2001	7 (4-19)	Therasorb-Ig	aPCC, steroids, cyclophosphamide	6/7	6/7	0/7
[37]	Guillet, 2001	3.5 (3-4)	Protein A Sepharose	rFVIIa, steroids, cyclophosphamide	1/2	2/2	1/2
[56]	Mansouri Taleghani, 2001	3 (1-4)	Protein A Sepharose	nr	4/4	4/4	0/4
[57]	Rivard, 2003	5 (4-5)	Protein A Sepharose	hFVIII, hFIX, hFXIII, rFVIIa, pFVIII, steroids, cyclophosphamide	4/5	4/5	1/5
[39]	Brzoska, 2007	11 (4-20)	Immusorba TR-350	rFVIIa, steroids, cyclophosphamide	7/9	8/9	2/9
[41]	Seibert, 2011	24	Immusorba TR-350	Fresh frozen plasma, IVIG, rFVIIa, tranexamic acid, steroids, cyclophosphamide	0/1	0/1	nr
[53]	Zeitler, 2013	16	Therasorb-Ig	Steroids, cyclophosphamide, azathioprine, vincristine, rituximab	54/65	63/65	6/65
[63]	Bilgin, 2013	5	nr	rFVIIa, steroids, cyclophosphamide	1/1	1/1	1/1
Current	Esteves Pereira, 2021	5 (2-7)	Protein A Sepharose	Steroids, cyclophosphamide, hFVIII, rFVIIa, tranexamic acid, IVIG, rituximab	8/10	6/8	2/8

aPCC, activated prothrombin complex concentrate; hFVIII, human factor VIII; IVIG, intravenous IgG; nr, not reported; PCC, prothrombin complex concentrate; pFVIII, porcine factor VIII; rFVIIa, recombinant activated factor VII.

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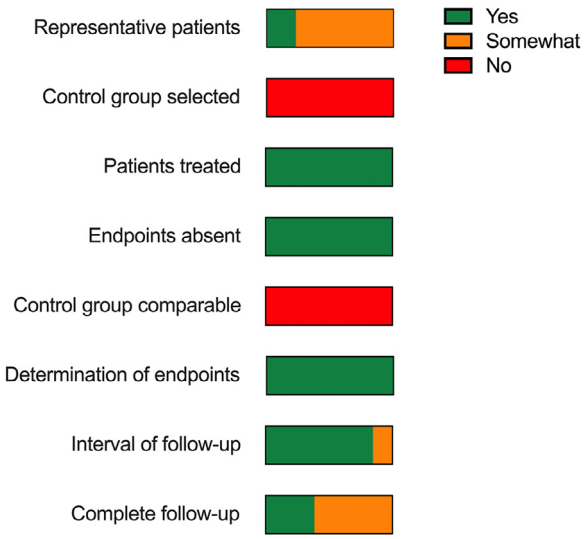

Fig. 2. Methodological quality of observational studies according to an adapted Newcastle-Ottawa Scale. The proportions of studies are shown; the individual items are (1) Are reported patients representative for all treated patients?, (2) Selection of the control group, (3) Were patients really treated?, (4) Were end points absent at the time of inclusion?, (5) Are exposed and unexposed patients comparable?, (6) Determination of end points, (7) Follow-up time long enough?, (8) Complete follow-up.

quired hemophilia [54]. The treatment indication was acute bleeding, and all patients had high inhibitor titers (36, 850, and 1500 BU/mL). Two to 4 cycles of IA using Immunosorba protein A sepharose were applied in addition to steroids, cyclophosphamide, intravenous immunoglobulins, and FVIII concentrate. Recovery of FVIII and a marked reduction of the inhibitor titer was observed in 2 of 3 patients; no deaths occurred. No side effects were reported, and the observation period was not mentioned.

Watt et al summarized data of 9 nonpregnant patients with acquired hemophilia (median age 58 years, range 14-76; 3 females), which were included in an application of an Investigational Device Exemption (IDE) to the Food and Drug Administration (FDA) [50]. The median FVIII activity was 5 IU/dL (range <5-8), and the median inhibitor titer was 600 BU/mL (range 8-1587); the treatment indication was severe bleeding. Two to 6 IA cycles using protein A sepharose were used, and various additional treatments were applied. Even though the inhibitor's titer was markedly reduced in 7 of 7 patients (not recorded in 2 patients), FVIII recovery was achieved only in 5 of 7. The bleeding stopped in all but 1 patient. No deaths were reported, but the observation period was 4 weeks only. Adverse events were assessed carefully, and grade I events reported: nausea and vomiting in 11% of the procedures, paresthesia due to chelation of ionized Ca2+ in 10%, and mild hypotension in 6%.

In another retrospective analysis, Jansen et al report about 7 patients with acquired hemophilia (median age 58, range 24-76; 2 female), including 1 patient with a pregnancy-associated disease, and 1 patient with pre-existing rheumatoid disease [55]. The treatment indication was severe bleeding in 4 cases and high inhibitor titer in all other cases (median titer 114 BU/mL, range 18-540; median FVIII activity <1 IU/dL, range <1-15). In addition to steroids and cyclophosphamide, patients received FVIII, activated factor VII, activated prothrombin complex concentrate, or fresh frozen plasma. Four to 19 cycles of IA using Therasorb®-Ig were applied. Recovery of FVIII and marked reduction of the inhibitor titer was recorded in 6/7 patients. Remission was not achieved in an elderly male patient (76 years) with a high inhibitor titer (540 BU/ml). No deaths were reported over an observation period of several months (not specified); mild side effects, including nausea and flushing, was reported in 6% of the cycles.

Guillet et al retrospectively describes 2 patients [37]: A 29-year-old male patient with underlying autoimmune disease who experienced massive abdominal hemorrhage with shock following a liver biopsy (FVIII <0.01 IU/mL, inhibitor titer 80 BU/mL), and a 62-year-old female patient with rheumatoid arthritis and massive retroperitoneal hemorrhage (FVIII = 0.03 IU/mL, inhibitor titer 15 BU/mL). Indication for IA was a treatment-refractory situation in both cases. Three or 4 IA cycles using protein A Sepharose were applied in addition to porcine FVIII, activated prothrombin complex concentrate, and steroids (case 1) or steroids, cyclophosphamide, and rFVIIa (case 2), respectively. Even though a marked reduction in the inhibitor titer was observed in both patients, complete FVIII recovery was observed in 1 patient only (observation period 1 year). One patient died due to septic shock.

In another retrospective study, Mansouri et al reports about 4 patients followed for an observation period of 2 to 5 years [56]: a 27-year-old female with pregnancy-associated IA (76 BU/mL), a 63-year-old female (123 BU/mL), a 54-year-old male (138 BU/mL), and a 67-year-old male (3 BU/mL). Treatment indication was severe bleeding and high inhibitor titer (3 patients). Further patient characteristics were not given. One to 4 IA cycles using protein A Sepharose were applied in addition to steroids and cyclophosphamide. Recovery of FVIII and reduction of inhibitor titer were observed, no side effects or death occurred.

Rivard et al retrospectively report on 1 female patient with pregnancy-associated acquired hemophilia (28-year-old), a 67-year-old male patient with concomitant bladder cancer, an 80-year-old female with cardiopulmonary comorbidities, a 59-year-old male, and a 59-year-old female [57]. Treatment indication was high inhibitor titer (median 100 BU/mL, range 12-144), persistent bleeding despite treatment, or serious comorbidities (patient 2). FVIII was 1 (<1-15) IU/dL. Four to 5 IA cycles using protein A Sepharose were applied in addition to steroids, cyclophosphamide, and various factor concentrates (Table 2). Recovery of FVIII and marked reduction of inhibitor titer was observed in 4 of 5 patients. In the 80-year-old female patient, no remission was achieved, and bleeding was ongoing. The patient died after all treatment was stopped intentionally. A hematoma related to the central line was reported as a side effect; the median observation period was 3 years.

Brozska et al conducted a retrospective analysis in 9 nonpregnant patients followed for a median of 2 years [39]. The median age was 70 years (range 50-78), 3 patients were female. Various comorbidities were reported (cancer, polyarthritis, pulmonary disease, diabetes, and bullous pemphigoid. The median FVIII activity was 2 IU/dL, median inhibitor titer 37 BU/mL (range 3.61-1085). Treatment indication was persistent bleeding, and high inhibitor titer in some cases remained however unclear in other cases. Four to twenty cycles of IA using Immusorba TR-350 (median 11) were applied in addition to rFVIIa, steroids, and cyclophosphamide. FVIII recovery was observed in 7 patients, and the reduction of the inhibitor titer in 8 patients; 2 patients died because of persistent bleeding or pneumonia, respectively. No side effects were reported.

The case of a 73-year-old female patient with cerebral bleeding due to acquired hemophilia was reported by Seibert et al [41]. The FVIII activity was 1 IU/dL, inhibitor titer 1500 BU/mL. Treatment was initiated on day 17 because of persistent bleeding despite steroids, cyclophosphamide, tranexamic acid, rituximab, and mycophenolic acid. After 14 IA cycles using Immusorba TR-350, bleedings stopped, FVIII increased to 5% and the inhibitor titer was 23 BU/mL. Further follow-up was not conducted.

Zeitler et al prospectively developed a treatment protocol and treated 65 patients with acquired hemophilia, details of which were reported in various publications [49,53,58-62]. Most data were retrieved from the most complete article [53], but other pub-

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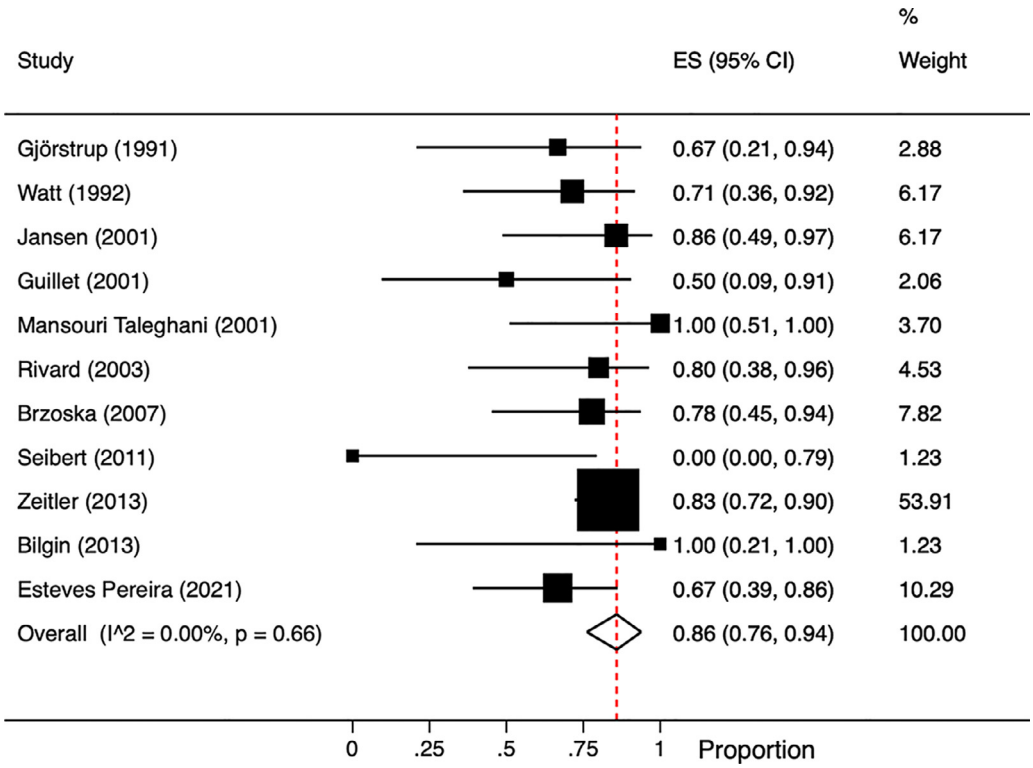

Fig. 3. Factor VIII recovery in patients with acquired hemophilia treated with IA (complete remission). The proportions of patients are shown (denoted as estimate, ES). A pooled estimate was calculated using a random-effects binominal distribution incorporating the Freeman-Tukey double arcsine transformation; 95% confidence intervals were computed using the score statistic.

lications were also used. The median age was 67 years (28-89), 58% of the patients were female. Pregnancy-associated acquired hemophilia was present in 6 patients, 8 patients suffered from autoimmune disorders, and 5 patients had cancer. Treatment indication was a high inhibitor titer (>5 BU/mL), the median inhibitor titer was 228 BU/mL (range 8-3600), and median FVIII was below 1 IU/dL. The protocol consists of 16 IA cycles using Therasorb-Ig in addition to prednisolone and cyclophosphamide; azathioprine, vincristine, rituximab was given in some cases. FVIII recovery was observed in 54 cases (83%; partial recovery in 5 more patients), reduction of the inhibitor titer in 63 patients. Six patients died in an observation period between 1 and 14 years, the cause of which was assigned to cancer or infection. Serious side effects were not reported.

Bilgin et al reported a 78-year-old male patient with chronic obstructive pulmonary disease who presented with multiple ecchymoses and hematomas [63]. FVIII was <1 IU/dL, and the inhibitor titer was 44 BU/mL. Indication for IA was failed treatment with rFVIIa, steroids, and cyclophosphamide, and ongoing bleeding. FVIII recovery and the reduction of inhibitor titer were achieved after 5 IA cycles; the columns were not reported. Even though bleeding stopped rapidly, FVIII recovered, and inhibitor titer was 0 BU/mL, the patient died after 6 months due to pulmonary disease.

Meta-Analysis

The pooled proportion of patients with VIII recovery as defined above (complete remission) was 86% (95% confidence interval [CI] 76%, 94%), the I^2 statistics was 0%. The forest plot is shown in Figure 3. The pooled proportion of patients with a reduction of the inhibitor titer was 95% (95%CI 83%-100%), the I^2 statistics was 32% (Figure 4). The pooled mortality was 7% (95%CI 0%-18%; I^2 =24%; Figure 5). Sensitivity analyses did not reveal any significant differences in retrospective studies or in studies using different absorbing agents (Protein A Sepharose vs Therasorb-Ig vs Immusorba TR-350).

Discussion

The number of studies investigating IA for the treatment of acquired hemophilia is limited and most of them are retrospective case series. Additionally, observation period varied between few days and several years. Many patients were treated because of a high inhibitor titer, severe bleeding events, or a failed response to routine treatment with steroids and cyclophosphamide. Recovery of FVIII and reduction of the inhibitor titer was achieved in the majority of patients, while the mortality was limited. Factors associated with study design, patient population, or treatment details affecting clinical outcomes were not apparent.

This is the first systematic review summarizing available literature on IA for the treatment of acquired hemophilia and pooling available data. The results extracted from our analysis are better than in most previous studies conducted without IA. A complete remission frequency of 73% has been reported in the European EACH2 registry [16]. In a study conducted in Germany, Austria, and Switzerland (GTH-AH), a complete remission was observed in 61% of the patients [26]. In a UK-based surveillance study, complete remission occurred in 71% of the patients [25]. In the French SACHA study, complete remission was reported in 61% of the patients [24]. Our results are favorable also with regard to mortality (26% in EACH2, 33% in GTH-AH, 43% in the UK study, and 33% in SACHA). And it is noteworthy that patients treated with IA are at a high-risk for bleeding or in a treatment-refractory situation.

The strength of our investigation is that we conducted a comprehensive literature search using a well-designed search strategy and covering 2 major databases (MEDLINE, EMBASE). In addition, we applied strict inclusion criteria and 2 investigators searched the literature and retrieved the data in parallel. Our study has limita-

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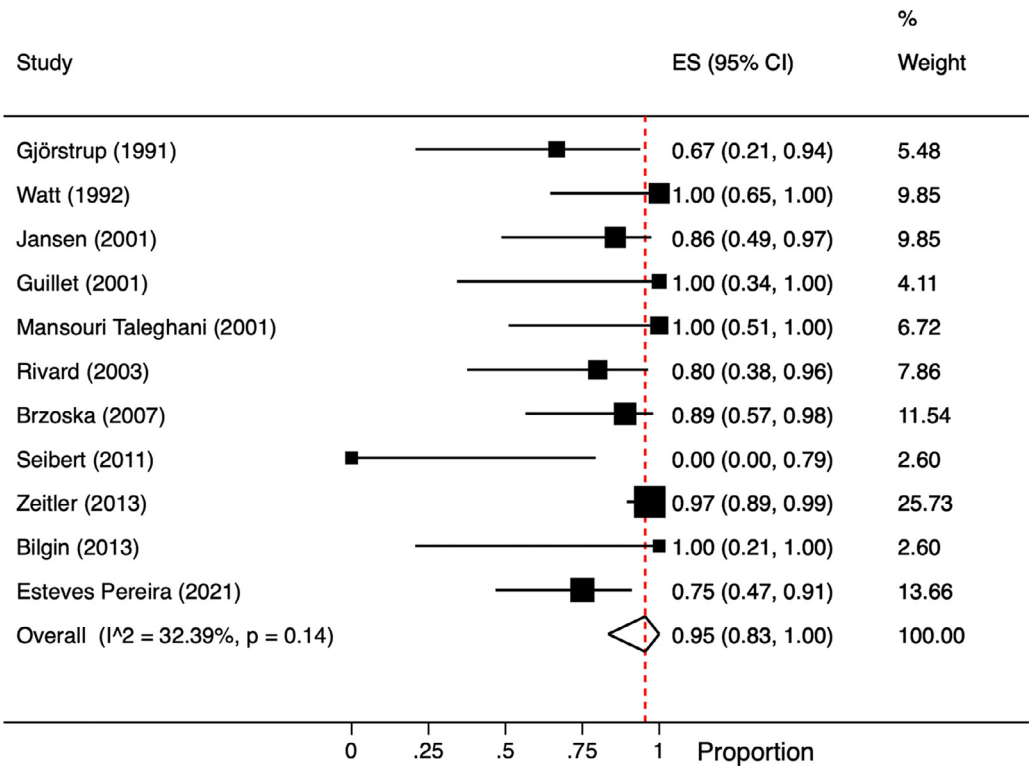

Fig. 4. Reduction of inhibitor titer in patients with acquired hemophilia treated with IA. The proportions patients are shown (denoted as estimate, ES). Pooled estimate was calculated using a random-effects binominal distribution incorporating the Freeman-Tukey double arcsine transformation; 95% confidence intervals were computed using the score statistic.

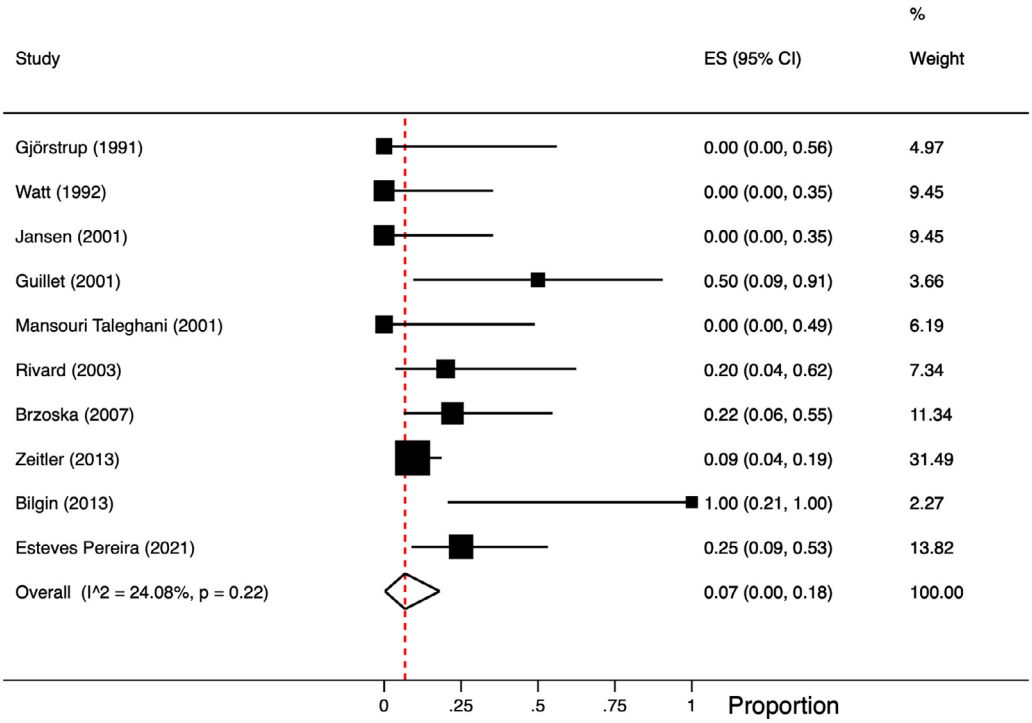

Fig. 5. Mortality of patients with acquired hemophilia treated with IA. The proportions of patients are shown (denoted as estimate, ES). A pooled estimate was calculated using a random-effects binominal distribution incorporating the Freeman-Tukey double arcsine transformation; 95% confidence intervals were computed using the score statistic.

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tions, however, and we cannot fully exclude that this might have influenced our results. First, the methodological quality was moderate only and no control group was included in any study. As with other rare diseases, no randomized controlled trials are available studying the treatment of acquired hemophilia. This makes it impossible to accurately assess the actual "added value" over the rest of the treatment. However, the FVIII recovery rate was high despite the patients being treated being at high risk for bleeding and in a treatment-refractory situation. Secondly, we cannot fully exclude a publication bias resulting from unsuccessful treatments that were not published. However, most authors mention that the patient cohort is complete with regard to all patients treated. Thirdly, pooled estimates of proportions might be imprecise and even biased if studies have either 0 or 1 or in case of extreme differences in the number of participants in case Freeman-Tukey double arcsine transformation is used [64]. However, we believe that the risk is low in our study because (1) the differences in study size are much smaller than in the analysis mentioned above, and (2) the magnitude of the effect sizes is comparable among studies if case reports are excluded. Fourthly, we were not able to conduct a proper sensitivity analysis because primary studies did not provide data on different cut-offs. Even though we cannot fully conclude that this might have introduced any bias, we did not have identified apparent sources of variability. Fifthly, the observation periods varied remarkably, even within studies, and we cannot entirely exclude that this might have introduced any bias. However, there are currently no studies available with a better methodology.

Even though firm evidence is still lacking and the actual "added value" of IA cannot be adequately assessed, we believe that IA might be a beneficial adjunctive treatment modality in some patients with acquired hemophilia. It was associated with a complete remission in the majority of patients, most of whom are at high risk of bleeding. Few side effects were reported; most of them were mild only (nausea and vomiting; paresthesia; and mild hypotension). However, a central venous catheter is often used, exposing the patient to a risk of bleeding and infection. Thus, we believe that adjunctive IA is justified in selected high-risk patients with acquired hemophilia. The question arises whether IA might improve clinical outcomes in the long-term. Even though rates of platelet recovery, reduction of inhibitor titer, and death are at least comparable to large registries of unselected patients [16], outcomes cannot be compared directly because of different observation periods. This issue must be clarified in future studies directly comparing different treatment strategies. Although IA is, per se, an expensive procedure, the often-necessary regular treatment of this patient group with FVIII bypassing agents is very much higher and may even be already be justified, if this period can be shortened by 1 or 2 days. Indeed, some authors have previously argued that the expenditure associated with IA is counterbalanced by a reduced need for coagulation factors such as rFVIIa or pFVIII [34,55]. IA is only available in a limited number of specialized centers in Switzerland. The procedure takes about 6 to 8 hours and has to be done in combination with a regular apheresis machine for plasma separation. An IA with a nonreusable column is reimbursed with ca. 1500 CHF per adsorption round. Using an IA with a reusable column, the reimbursement is ca. 3000 CHF per adsorption round. At our institution, IA is considered on a case-by-case base rather than a strict cut-off level. Strong arguments are (1) live-threatening bleeding complications, (2) inhibitor titers $\geq$20 BU/mL, or (c) failed immunosuppressive treatment with corticosteroids and cyclophosphamide using an established dose regimen [3].

In conclusion, our data suggest that IA might be a beneficial adjunctive treatment modality in high-risk patients with acquired hemophilia. Future register data would be expected to add important information to the current state of knowledge.

Conflicts of Interest

The authors have no conflict of interest to disclose in relation to the submitted review.

Author Contributions

MN designed the study, collected the data, conducted the analysis, interpreted the results and wrote the manuscript. MEP collected the data, wrote the manuscript and contributed to analysis and interpretation. BMT implemented IA at our institution and contributed to study design and interpretation of results. MM contributed to the analysis plan, analysis and interpretation. CB, JAKH, and MD provided data and contributed to the interpretation of results. All authors contributed to the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tmrv.2021.01.001.

References

[1] Knobl P. Prevention and management of bleeding episodes in patients with acquired hemophilia A. Drugs 2018;78:1861–72.
[2] Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol 2017;92:695–705.
[3] Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica 2020;105:1791–801.
[4] Giangrande P. Acquired hemophilia. In: Montréal: World Federation of Hemophilia (WFH); 2012. p. 1–7.
[5] Shetty S, Bhave M, Ghosh K. Acquired hemophilia A: diagnosis, aetiology, clinical spectrum and treatment options. Autoimmun Rev 2011;10:311–16.
[6] Hauser I, Lechner K. Solid tumors and factor VIII antibodies. Thromb Haemost 1999;82:1005–7.
[7] Sallah S, Wan JY. Inhibitors against factor VIII in patients with cancer. Analysis of 41 patients. Cancer 2001;91:1067–74.
[8] Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. Thromb Haemost 1981;45:200–3.
[9] Green D, Schuette PT, Wallace WH. Factor VIII antibodies in rheumatoid arthritis. Effect of cyclophosphamide. Arch Intern Med 1980;140:1232–5.
[10] Soriano RM, Matthews JM, Guerado-Parra E. Acquired haemophilia and rheumatoid arthritis. Br J Rheumatol 1987;26:381–3.
[11] Ballard HS, Nyamuswa G. Life-threatening haemorrhage in a patient with rheumatoid arthritis and a lupus anticoagulant coexisting with acquired autoantibodies against factor VIII. Br J Rheumatol 1993;32:515–17.
[12] Franchini M, Gandini G, Di Paolantonio T, Mariani G. Acquired hemophilia A: a concise review. Am J Hematol 2005;80:55–63.
[13] Sborov DW, Rodgers GM. Acquired hemophilia A: a current review of autoantibody disease. Clin Adv Hematol Oncol 2012;10:19–27.
[14] Hauser I, Schneider B, Lechner K. Post-partum factor VIII inhibitors. A review of the literature with special reference to the value of steroid and immunosuppressive treatment. Thromb Haemost 1995;73:1–5.
[15] Michiels JJ. Acquired hemophilia A in women postpartum: clinical manifestations, diagnosis, and treatment. Clin Appl Thromb Hemost 2000;6:82–6.
[16] Knoebl P, Marco P, Baudo F, Collins P, Huth-Kuhne A, Nemes L, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 2012;10:622–31.
[17] Tengborn L, Baudo F, Huth-Kuhne A, Knoebl P, Levesque H, Marco P, et al. Pregnancy-associated acquired haemophilia A: results from the European Acquired Haemophilia (EACH2) registry. BJOG 2012;119:1529–37.
[18] Baudo F, Collins P, Huth-Kuhne A, Levesque H, Marco P, Nemes L, et al. EACH2 registry contributors. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. Blood 2012;120:39–46.
[19] Bouvry P, Recloux P. Acquired hemophilia. Haematologica 1994;79:550–6.
[20] Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol 2003;121:21–35.
[21] Amano K, Seita I, Higasa S, Sawada A, Kuwahara M, Shima M. Treatment of acute bleeding in acquired haemophilia A with recombinant activated factor VII: analysis of 10-year Japanese postmarketing surveillance data. Haemophilia 2017;23:50–8.
[22] Knoebl P, Thaler J, Jilma P, Quehenberger P, Gleixner KV, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood 2020. doi:10.1182/blood.2020006315.
[23] Sborov DW, Rodgers GM. How I manage patients with acquired haemophilia A. Br J Haematol 2013;161:157–65.

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[24] Borg JY, Guillet B, Cam-Duchez VL, Goudemand J, Levesque H, Group SS. Outcome of acquired haemophilia in France: the prospective SACHA (Surveillance des Auto antiCorps au cours de l'Hemophilie Acquise) registry. Haemophilia 2013;19:564–70.
[25] Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood 2007;109:1870–7.
[26] Tiede A, Klamroth R, Scharf RE, Trappe RU, Holstein K, Huth-Kuhne A, et al. Prognostic factors for remission of and survival in acquired hemophilia A (AHA): results from the GTH-AH 01/2010 study. Blood 2015;125:1091–7.
[27] Tiede A, Huth-Kuhne A, Oldenburg J, Grossmann R, Geisen U, Krause M, et al. Immunosuppressive treatment for acquired haemophilia: current practice and future directions in Germany, Austria and Switzerland. Ann Hematol 2009;88:365–70.
[28] Baudo F, Caimi T, de Cataldo F. Diagnosis and treatment of acquired haemophilia. Haemophilia 2010;16:102–6.
[29] Boles JC, Key NS, Kasthuri R, Ma AD. Single-center experience with rituximab as first-line immunosuppression for acquired hemophilia. J Thromb Haemost 2011;9:1429–31.
[30] Franchini M, Mannucci PM. Inhibitor eradication with rituximab in haemophilia: where do we stand? Br J Haematol 2014;165:600–8.
[31] Zeng Y, Zhou R, Duan X, Long D, Yang S. Interventions for treating acute bleeding episodes in people with acquired hemophilia A. Cochrane Database Syst Rev 2014;8:CD010761 doi:10.1002/14651858.CD010761.pub2. PMID: 25165992.
[32] von Depka Prondzinski M. [Acquired haemophilia due to autoantibodies against factor VIII]. Hamostaseologie 2003;23:28–35.
[33] Freedman J, Garvey MB. Immunoadsorption of factor VIII inhibitors. Curr Opin Hematol 2004;11:327–33.
[34] Freedman J, Rand ML, Russell O, Davis C, Cheatley PL, Blanchette V, et al. Immunoadsorption may provide a cost-effective approach to management of patients with inhibitors to FVIII. Transfusion 2003;43:1508–13.
[35] Knobl P, Derfler K. Extracorporeal immunoadsorption for the treatment of haemophilic patients with inhibitors to factor VIII or IX. Vox Sang 1999;77(Suppl 1):57–64.
[36] Franchini M, Sassi M, Dell'Anna P, Manzato F, Salvagno GL, Montagnana M, et al. Extracorporeal immunoadsorption for the treatment of coagulation inhibitors. Semin Thromb Hemost 2009;35:76–80.
[37] Guillet B, Kriaa F, Huysse MG, Proulle V, George C, Tchernia G, et al. Protein A sepharose immunoadsorption: immunological and haemostatic effects in two cases of acquired haemophilia. Br J Haematol 2001;114:837–44.
[38] Nilsson IM, Jonsson S, Sundqvist SB, Ahlberg A, Bergentz SE. A procedure for removing high titer antibodies by extracorporeal protein-A-sepharose adsorption in hemophilia: substitution therapy and surgery in a patient with hemophilia B and antibodies. Blood 1981;58:38–44.
[39] Brzoska M, Krause M, Geiger H, Betz C. Immunoadsorption with single-use columns for the management of bleeding in acquired hemophilia A: a series of nine cases. J Clin Apher 2007;22:233–40.
[40] Koessler J, Kobsar A, Kuhn S, Koessler A, Yilmaz P, Weinig E, et al. The effect of immunoadsorption with the Immusorba TR-350 column on coagulation compared to plasma exchange. Vox Sang 2015;108:46–51.
[41] Seibert FS, Zidek W, Westhoff TH. Refractory acquired hemophilia: successful treatment by immunoadsorption with single-use columns. Ther Apher Dial 2011;15:336–7.
[42] Eming R, Rech J, Barth S, Kalden JR, Schuler G, Harrer T, et al. Prolonged clinical remission of patients with severe pemphigus upon rapid removal of desmoglein-reactive autoantibodies by immunoadsorption. Dermatology 2006;212:177–87.
[43] Hamilton P, Kanigicherla D, Hanumapura P, Walz L, Kramer D, Fischer M, et al. Peptide GAM immunoadsorption therapy in primary membranous nephropathy (PRISM): Phase II trial investigating the safety and feasibility of peptide GAM immunoadsorption in anti-PLA2 R positive primary membranous nephropathy. J Clin Apher 2018;33:283–90.
[44] Freiburghaus C, Berntorp E, Ekman M, Gunnarsson M, Kjellberg BM, Nilsson IM. Immunoadsorption for removal of inhibitors: update on treatments in Malmo-Lund between 1980 and 1995. Haemophilia 1998;4:16–20.
[45] Collins PW. Therapeutic challenges in acquired factor VIII deficiency. Hematology Am Soc Hematol Educ Program 2012;2012:369–74.
[46] Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost 2013;110:1114–20.
[47] Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica 2009;94:566–75.
[48] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[49] Zeitler H, Ulrich-Merzenich G, Panek D, Goldmann G, Vidovic N, Brackmann HH, et al. Extracorporeal treatment for the acute und long-term outcome of patients with life-threatening acquired hemophilia. Transfus Med Hemother 2012;39:264–70.
[50] Watt RM, Bunitsky K, Faulkner EB, Hart CM, Horan J, Ramstack JM, et al. Treatment of congenital and acquired hemophilia patients by extracorporeal removal of antibodies to coagulation factors: a review of US clinical studies 1987-1990. Hemophilia Study Group. Transfus Sci 1992;13:233–53.
[51] Freeman MF, Tukey JW. Transformations related to the angular and the square root. Ann Math Stat 1950;21:607–11.
[52] Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta–analysis of binomial data. Arch Public Health 2014;72:39.
[53] Zeitler H, Goldmann G, Marquardt N, Ulrich-Merzenich G. Long term outcome of patients with acquired haemophilia–a monocentre interim analysis of 82 patients. Atheroscler Suppl 2013;14:223–8.
[54] Gjorstrup P, Berntorp E, Larsson L, Nilsson IM. Kinetic aspects of the removal of IgG and inhibitors in hemophiliacs using protein A immunoadsorption. Vox Sang 1991;61:244–50.
[55] Jansen M, Schmaldienst S, Banyai S, Quehenberger P, Pabinger I, Derfler K, et al. Treatment of coagulation inhibitors with extracorporeal immunoadsorption (Ig-Therasorb). Br J Haematol 2001;112:91–7.
[56] Mansouri Taleghani B, Grossmann R. Treatment of patients with factor VIII autoantibodies by staphylococcal protein A-based immunoadsorption and immunosuppression. Br J Haematol 2001;114:956–8.
[57] Rivard GE, St Louis J, Lacroix S, Champagne M, Rock G. Immunoadsorption for coagulation factor inhibitors: a retrospective critical appraisal of 10 consecutive cases from a single institution. Haemophilia 2003;9:711–16.
[58] Zeitler H, Ulrich-Merzenich G, Goldmann G, Vidovic N, Brackmann HH, Oldenburg J. The relevance of the bleeding severity in the treatment of acquired haemophilia - an update of a single-centre experience with 67 patients. Haemophilia 2010;16:95–101.
[59] Zeitler H, Ulrich-Merzenich G, Hess L, Konsek E, Unkrig C, Walger P, et al. Treatment of acquired hemophilia by the Bonn-Malmo Protocol: documentation of an in vivo immunomodulating concept. Blood 2005;105:2287–93.
[60] Zeitler H, Ulrich-Merzenich G, Marquardt N, Oldenburg J, Goldmann G. Immunoadsorption for pregnancy-associated severe acquired hemophilia. Ther Apher Dial 2014;18:103–10.
[61] Zeitler H, Ulrich-Merzenich G, Panek D, Goldmann G, Vidovic N, Brackmann HH, et al. Immunoadsorption in the treatment of acquired haemophilia. Atheroscler Suppl 2009;10:122–5.
[62] Zeitler H, Ulrich-Merzenich G, Walger P, Dusing R, Vetter H, Brackmann HH. The modified Bonn Malmo protocol (MBMP) in the treatment of acquired haemophilia A. Dtsch Med Wochenschr 2006;131:141–7.
[63] Ugur Bilgin A, Ozcan M, Ayyildiz E, Ilhan O. The treatment of acquired hemophilia with combination therapy of immunosuppressives and immunoadsorption. Turk J Haematol 2014;31:194–6.
[64] Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rucker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta–analysis of single proportions. Res Synth Methods 2019;10:476–83.

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