Acquired factor VIII inhibitors

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Acquired hemophilia A is a rare bleeding diathesis caused by autoantibodies directed against clotting factor VIII and associated with an increased morbidity and mortality. This autoimmune disorder most commonly occurs in the elderly. Although it may be associated with several underlying pathologies, up to 50% of reported cases remain idiopathic. In contrast with congenital hemophilia, which is commonly characterized by hemarthroses, hemorrhages in patients with acquired hemophilia involve most frequently soft tissues. The 2 treatment priorities are to arrest the acute bleeding and to eradicate the factor VIII autoantibody. Acute bleeding episodes in patients with low-titer inhibitors can be treated using human factor VIII concentrates, whereas factor VIII bypassing agents, such as activated prothrombin complex concentrates or recombinant activated factor VII, are effective for the treatment of those with high-titer inhibitors. An analysis of the literature shows that the most effective first-line treatment for the eradication of factor VIII autoantibodies is the combination of steroids and cyclophosphamide. However, there is increasing evidence on the effectiveness of other treatment approaches, such as immune tolerance regimens and rituximab. If confirmed by large controlled studies, these innovative therapies might become a valid option for long-term eradication of factor VIII inhibitors. (Blood. 2008;112:250-255)

Introduction

Acquired inhibitors against factor VIII (FVIII), also termed acquired hemophilia A, occur rarely in the nonhemophilic population, with an incidence of approximately 1 to 4 per million/year.5-9 Although uncommon, these autoantibodies are associated with a high rate of morbidity and mortality as severe bleeds occur in up to 90% of affected patients and the mortality rate is high, ranging from 8% to 22%.10-12 For these reasons, patients with acquired hemophilia A represent a demanding clinical challenge.

The incidence of acquired hemophilia A increases with age, being a very uncommon condition in children.13 Indeed, the incidence in children younger than 16 years has been estimated to be 0.045 per million/year compared with 14.7 per million/year in the elderly aged older than 85 years.9 However, it is also likely that the incidence of this autoimmune disorder is significantly underestimated, especially in elderly patients. The age distribution of autoantibodies is typically bimodal with a small peak between 20 and 30 years, due to postpartum inhibitors and a major peak in patients aged 68 to 80 years. The incidence in men and women is similar except in the age range 20 to 40 years, when the effect of pregnancy results in a preponderance in women.6 In approximately 50% of cases, FVIII autoantibodies occur in patients lacking any relevant concomitant disease, while the remaining cases may be associated with postpartum period, autoimmune diseases, underlying hematologic or solid cancers, infections, or use of medications (Table 1).14-29

The bleeding pattern of acquired hemophilia A is rather different from that of congenital hemophilia A. Thus, most patients with FVIII autoantibodies have hemorrhages into the skin, muscles or soft tissues, and mucous membranes (eg, epistaxis, gastrointestinal and urologic bleeds, retroperitoneal hematomas, postpartum bleeding), whereas hemarthroses, a typical feature of congenital factor VIII deficiency, are uncommon.5-10 The hemorrhages are often serious or life threatening and the disease may manifest more dramatically by excessive bleeding following trauma or surgery or by cerebral hemorrhage.5

The diagnosis of acquired hemophilia A in a patient with no previous personal or family history of bleeding is typically based on (1) the initial detection of an isolated prolongation of activated partial thromboplastin time (APTT), which cannot be corrected by incubating for 2 hours at 37°C equal volumes of patient plasma and normal plasma (mixing study), and (2) subsequent identification of a reduced FVIII level with evidence of FVIII inhibitor activity (titrated using the Bethesda assay or its Nijmegen modification).1

The epidemiology, pathogenesis, clinical associations, and diagnosis of acquired hemophilia A have been extensively reviewed elsewhere,1-7 so in this review we will focus on the current treatment of this autoimmune hemorrhagic disorder.

Treatment of acquired FVIII inhibitors

The appropriate pharmacological treatment of patients with acquired hemophilia depends essentially on the natural history of any concomitant pathology and the clinical presentation of coagulopathy.10,32 The fundamental aspects of therapeutic strategy in patients with acquired hemophilia A are the treatment of acute bleeding episodes and the long-term eradication of the autoantibody (Table 2). On the other hand, the cure of the possible associated disease is also important as, in some cases, it will lead to the disappearance of the inhibitor.36

Finally, we must outline that the next sections report our own approach to the treatment of this syndrome, all primarily based on our personal experience and subjective interpretation of the available literature data, which is sparse on adequately powered, prospective, randomized, and controlled trials.
**Table 1. Conditions associated with acquired hemophilia A**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td></td>
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<tr>
<td>Autoimmune disorders</td>
<td>Systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis,</td>
</tr>
<tr>
<td></td>
<td>Sjögren syndrome, autoimmune hemolytic anemia, Goodpasture syndrome,</td>
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<tr>
<td></td>
<td>myasthenia gravis, Graves disease, autoimmune hypothyroidism</td>
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<tr>
<td>Solid cancers</td>
<td>Prostate, lung, colon, pancreas, stomach, cholecodochus, head, neck,</td>
</tr>
<tr>
<td></td>
<td>cervix, breast, melanoma, kidney</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>Chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma,</td>
</tr>
<tr>
<td></td>
<td>Waldenström macroglobulinemia, myelodysplastic syndrome, myelofibrosis,</td>
</tr>
<tr>
<td></td>
<td>erythroleukemia</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Dermatologic disorders</td>
<td>Psoriasis, pemphigus</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>Asthma, chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
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<tr>
<td>Acute hepatitis B and C infection</td>
<td>Penicillin and its derivatives, sulfa antibiotics, phenytoin,</td>
</tr>
<tr>
<td></td>
<td>chloramphenicol, methylidopa, depot thioxanthene, interferon-α,</td>
</tr>
<tr>
<td></td>
<td>fludarabine, levodopa, clopidogrel</td>
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</table>

**Treatment of acute hemorrhages**

Two options are currently available for hemostatic control of acute bleeding: the use of bypassing agents and strategies aimed to raise the level of circulating FVIII. The choice of the most appropriate therapeutic strategy will depend on the site and severity of the bleeding and the inhibitor titer. Of note, any potential additional risk situation for bleeding, such as intramuscular injections, invasive procedures, or the use of antplatelet agents, should also be avoided.

**Bypassing agents**

Bypassing agents are currently the most used first-line treatment, and both the recombinant activated factor VII (rFVIIa) and the activated prothrombin complex concentrate (aPCC) factor 8 inhibitor bypassing activity (FEIBA) have been proven effective in the treatment of acquired hemophilia A. As regards the latter, a large retrospective study conducted by Goudemand and the French FEIBA Study Group reviewed the use of FEIBA for the treatment of 55 bleeding events in 17 patients with acquired hemophilia. At a median dosage of 68 U/kg (range, 35-80 U/kg) administered every 8 to 24 hours for a median of 3.5 days (range, 1-17 days), FEIBA was found to provide an excellent or good hemostatic efficacy in 89% of the bleeding episodes. Sallah retrospectively analyzed the efficacy of FEIBA in 34 patients with acquired hemophilia, the majority of whom received a dose of 75 U/kg every 8 to 12 hours. A complete response was achieved in 76% of severe and 100% of moderate bleeding episodes, for an overall complete response rate of 86%. Holme et al reported the Norwegian experience with FEIBA in acquired hemophilia. The hemostatic efficacy of this bypassing agent, administered at a dosage of 70 U/kg every 8 hours, was judged to be excellent in all 8 severe bleeds treated. Thus, based on the literature, the recommended dose of aPCC ranges between 50 and 100 IU/kg administered every 8 to 12 hours.

The first large experience on the use of rFVIIa in patients with acquired hemophilia comes from Hay et al, who published a multicenter retrospective analysis of 38 patients treated for 74 bleeding episodes with rFVIIa. The average starting dose was 90 μg/kg (range, 45-181 μg/kg) every 2 to 6 hours, while a median of 28 doses (range, 1-541 doses) were given per episode, over a median 3.9 days (range, 0-43 days). The authors reported a good response in 100% of patients when rFVIIa was used as a first-line treatment, and a good response in 75% of patients when it was used as salvage therapy. Recently, Sumner et al collected the available data on the use of rFVIIa in acquired hemophilia patients from

**Table 2. Treatment options for acquired hemophilia A**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing and clinical recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of acute bleeding</td>
<td></td>
</tr>
<tr>
<td>Bypassing agents</td>
<td></td>
</tr>
<tr>
<td>aPCC</td>
<td>50-100 IU/kg iv every 8-12 hours until clinical response</td>
</tr>
<tr>
<td>rFVIIa</td>
<td>90-120 μg/kg iv every 2-3 hours until clinical response</td>
</tr>
<tr>
<td>Treatments to raise circulating FVIII</td>
<td></td>
</tr>
<tr>
<td>levels</td>
<td></td>
</tr>
<tr>
<td>Porcine FVIII concentrates</td>
<td>Not currently available for routine clinical use</td>
</tr>
<tr>
<td>Human FVIII concentrates</td>
<td>Patients with inhibitor titer &lt; 5 BU: 20 IU/kg iv for each BU of inhibitor plus 40 IU/Kg iv</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Patients with inhibitor titer &lt; 5BU and minor bleeding episodes: 0.3 μg/kg iv/sc</td>
</tr>
<tr>
<td>Inhibitor eradication</td>
<td></td>
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<tr>
<td>Immunosuppressive agents</td>
<td></td>
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<tr>
<td>Prednisone plus cyclophosphamide</td>
<td>Prednisone (1 mg/kg per day) plus cyclophosphamide (1-2 mg/kg per day) po for at least 5 weeks</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>200-300 mg/day alone or in association with prednisone as second-line therapy</td>
</tr>
<tr>
<td>High-dose intravenous immunoglobulin</td>
<td>0.4 g/kg per day for 5 days or 1.0 g/kg per day for 2 days in association with other treatments (steroids, immunoadsorption, IT regimens)</td>
</tr>
<tr>
<td>Immunoabsorption</td>
<td>Rapid but transitory removal of the inhibitor; in association with FVIII concentrates or IT</td>
</tr>
<tr>
<td>Immune tolerance</td>
<td>FVIII concentrates in combination with various eradication therapies (DiMichele, Green; and Nemes and Pittlik)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² weekly for 4 weeks as second-line therapy in association with steroids</td>
</tr>
</tbody>
</table>

aPCC indicates activated prothrombin complex concentrates; rFVIIa, recombinant activated factor VII; iv, intravenously; sc, subcutaneously; IT, immune tolerance; and po, by mouth.
compassionate use programs, the Hemophilia and Thrombosis Research Society (HTRS) Registry, and from the published literature. A total of 139 patients were treated with rFVIIa for 204 bleeding episodes. The overall efficacy rate (complete or partial) of rFVIIa was 88% (161/182 evaluable bleeding episodes). rFVIIa as a first-line treatment was effective overall in 95% of bleeding episodes compared with 80% when it was used as salvage therapy after failure of other hemostatic agents. Interestingly, to overcome the short half-life of rFVIIa (approximately 2.5 hours), some pharmaceutical industries are developing rFVIIa molecules with an extended half-life obtained with pegylated formulations or with the fusion of FVIIa to human albumin.53,44

Although there are no comparative studies on the efficacy and risk of adverse events of aPCC and rFVIIa for the management of acute bleeds in acquired hemophilia patients, personally we prefer the latter due to its viral safety (ie, recombinant product) and its excellent safety and efficacy profile.45 We recommend a intravenous bolus dose of 90 to 120 μg/kg repeated every 2 to 3 hours depending on the clinical response. Although continuous infusion of rFVIIa is an interesting alternative to bolus injection, and has been explored in order to simplify the method of administration and to reduce the costs,46,47 it is not yet well standardized and officially registered.

Treatments to raise FVIII levels

Regarding possible therapeutic strategies aimed to raise the levels of circulating FVIII, plasma-derived porcine FVIII, which has been successfully used in the past to achieve hemostatic levels in situations where human FVIII was ineffective, is not currently available for routine clinical use.48,49 However, a recombinant B domain–deleted porcine factor VIII (OBI-1) has recently been tested in a phase 2 open-label study in congenital hemophilia A patients with inhibitors.50 Given the promising results of this study, OBI-1 could also be tested in trials on patients with acquired FVIII inhibitors.

Human FVIII concentrates usually represent an inadequate hemostatic therapy unless the inhibitor titer is low (ie, less than 5 Bethesda units [BU]). Patients with low-titer inhibitors can be treated with plasma-derived or recombinant human FVIII concentrates, which should be administered at doses sufficient to overwhelm the inhibitor and thus achieve hemostatic levels of factor VIII.32 While a number of formulas have been proposed for calculating the optimal dose of FVIII to administer, the inaccuracy inherent in the laboratory measurement of inhibitor titers in acquired hemophilia makes these very approximate tools, and thus regular monitoring of plasma FVIII levels and clinical response are required. Accordingly, we recommend an intravenous bolus dose of 20 IU/kg for each BU of the inhibitor plus an additional 40 IU/kg, the monitoring of FVIII activity (FVIII:C) levels 10 minutes after the initial dose, and the subsequent administration of an additional bolus dose if the incremental recovery is not adequate.

Some hemophilia centers use human FVIII concentrates in association with immunoadsorption to reach hemostatic FVIII levels despite high initial anti-FVIII inhibitor titers. Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) alone or in association with human FVIII concentrates may also be effective in patients with a low titer of inhibitor for the treatment of minor bleeding episodes.51 We have documented a positive experience on the use of DDAVP alone, at a dose of 0.3 μg/kg per day given subcutaneously for 3 to 5 days, in a series of patients with low inhibitor titer for the treatment of non–life-threatening hemorrhages (hematomas, mucosal hemorrhages, hemarthroses) or for hemostatic coverage of invasive procedures.52,53

Inhibitor eradication

The elimination of the FVIII autoantibody may be achieved through various therapeutic options, which have been variably combined, including immunosuppressive agents (steroids, cytotoxic drugs such as cyclophosphamide, azathioprine and vincristine, cyclosporine, and rituximab [“Immunosuppressive agents”]), high-dose intravenous immunoglobulin (IVIG), immunoadsorption, and immune tolerance.6,32

Immunosuppressive agents

While a number of studies have been published on the immunosuppressive therapy of patients with acquired hemophilia, the great majority of them are case reports or small single center retrospective surveys. In the only randomized prospective trial available on this subject in the literature,54 31 patients were initially treated with prednisone alone at a dose of 1 mg/kg per day for 3 weeks. If the autoantibody was still detectable, the patients were then randomized to receive for an additional 6 weeks prednisone alone, prednisone with oral cyclophosphamide (2 mg/kg per day), or cyclophosphamide alone. Approximately one-third of the patients responded to the initial prednisone course, while approximately 50% of the steroid-resistant patients responded to cyclophosphamide-containing regimens. In a case series published by Shaffer and Phillips,55 the association of oral cyclophosphamide and prednisone was successful in achieving a complete remission (CR) in all of the 9 consecutive acquired hemophilia patients enrolled. A nonrandomized study conducted by the United Kingdom Hemophilia Center Doctors’ Organization (UKHDCO)9 did not find a significant difference among the groups treated with steroid alone or with a combination of steroids and cytotoxic agents (76% vs 78%). In their meta-analysis, combining data from 20 reports, Delgado et al1 concluded that cyclophosphamide use was superior to that of prednisone in terms of inhibitor eradication but not in terms of overall survival. The combined data available from uncontrolled cohort studies recently reviewed by Collins, suggested a benefit for combined steroids and cytotoxic agents.32 Other combinations, such as prednisone with azathioprine or prednisone with cyclophosphamide and vincristine, were also proven effective.56,57 Thus, on the basis of the available literature and our personal experience, we usually prefer to start inhibitor-eradicating therapy with prednisone (1 mg/kg per day) and cyclophosphamide (1-2 mg/kg per day) for at least 5 weeks. However, we must emphasize that immunosuppressive therapy should be strictly tailored to the patients’ characteristics (ie, age, sex, and general health status) to minimize the treatment-related adverse effects.58 Indeed, an analysis of the data from the European Acquired Hemophilia Registry (EACH) showed that infections related to immunosuppressive therapy were the first cause of death in patients with acquired hemophilia (F. Baudo, unpublished data, June 2008). Similarly, in the meta-analysis conducted by Delgado et al1 that included 249 patients, a substantial proportion of patients receiving cyclophosphamide, especially elderly, died as a result of complications related to this agent, mainly neutropenia-related infections. Thus, cyclophosphamide and other alkylating agents should be used cautiously in elderly patients, due to the increasing rate of side effects. Indeed, we usually reduce the dose and duration of
cyclophosphamide treatment (ie, 50 mg/day for 3–4 weeks) in these patients. Furthermore, these cytotoxic agents should be avoided in women of reproductive age, as they may cause infertility. As a consequence, we usually start first-line eradication therapy.

Finally, cyclophosphamide, at a dose of 200 to 300 mg/day alone or in combination with steroids, has been used successfully as a salvage therapy.59,60

**High-dose intravenous immunoglobulin**

Intravenous immunoglobulins (IVIGs) are derived from the pooled plasmas of thousands of blood donors and contain anti-idiotypic antibodies directed against FVIII inhibitors.5 The first report on the successful use of high-dose IVIGs in patients with acquired hemophilia comes from Sultan et al.61 In a subsequent prospective multicenter study evaluating the efficacy of high-dose IVIGs in acquired FVIII inhibitors, a rather low response rate of between 25% and 37% was observed, with complete remissions occurring almost exclusively with low-titer inhibitors.62 A study of 6 patients treated concomitantly with steroids and IVIGs reported a CR rate of 66%.63 However, a literature review of acquired hemophilia patients treated with IVIGs with no concomitant immunosuppressive treatment was disappointing, as only a 12% CR rate was observed.64 Finally, a recent study comparing patients who either did or did not receive IVIGs showed no benefit for those taking IVIGs.9 Thus, the current clinical results indicate that high-dose IVIGs are not useful as a first choice for the suppression of FVIII autoantibodies, but may play a role as adjunctive therapy to other inhibitor-eradicating treatments (steroids, immunoadsorption, immune tolerance regimens). The usual administered dose is 2 g/kg for 2 consecutive days or 0.4 g/kg for 5 consecutive days. As IVIGs are well tolerated and with few toxic effects, they are particularly suitable as an adjunct therapeutic option for elderly patients with acquired FVIII inhibitors.52

**Immunoadsorption**

Exchange plasmapheresis has been used for many years for a temporary, rapid, extracorporeal removal of the autoantibody, especially in cases of severe bleeding associated with high-titer inhibitors.65 The introduction of immunoadsorption techniques, including sepharose-bound staphylococcal protein A and sepharose-bound polyclonal sheep antihuman antibodies, has increased the volume of plasma processed and the efficacy of the procedure.66,67 The transitory drop of the inhibitor titer permits replacement therapy with human FVIII concentrates, which must then be administered immediately after the treatment cycle to achieve hemostasis.68 Immunoadsorption has also been used in the setting of immune tolerance protocols (see “Immune tolerance”). The main limits of this technique are that it is costly and technically demanding. For this reason, it is performed only in specialized centers.

**Immune tolerance**

Immune tolerance (IT) protocols,31 like those successfully used for the treatment of alloantibody inhibitors in patients with congenital hemophilia, have also been proposed for the eradication of FVIII autoantibodies. The rationale for the use of IT in acquired hemophilia is that the stimulation of the immune system by exogenous FVIII infused increases the susceptibility of the inhibitor-producing B-cell clones to the effect of cytotoxic agents. In the case report published by Green54 in 1971, high doses of FVIII and intravenous cyclophosphamide were given simultaneously to successfully treat a patient with an acquired FVIII inhibitor unresponsive to combined immunosuppressive treatment. In a later report, Lian et al.69 treated 12 patients with cyclophosphamide, vincristine, and prednisone obtaining CR in all but 1 patient. The Budapest protocol,30 consisting of 3 weeks of treatment with a combination of human FVIII concentrates (30 IU/kg per day for the first week, 20 IU/kg per day for the second week, and 15 IU/kg per day for the third week), intravenous cyclophosphamide (200 mg/day for a total dose of 2-3 g), and intravenous methylprednisolone (100 mg/day for the first week, tapering the dose gradually over the next 2 weeks), resulted in a eradication of autoantibody in more than 90% of treated cases. Similarly, the modified Bonn-Malmö protocol,60 including a combination of oral cyclophosphamide (1-2 mg/kg per day), prednisolone (1 mg/kg per day), large-volume immunoadsorption (2.5-3.0 times the plasma volume on days 1-5 weekly), high-dose IVIGs (0.3 g/kg on days 5-7 weekly), and FVIII concentrates (100 IU/kg per day), obtained a rapid (median, 14 days) and complete remission in 88% of patients. Although undoubtedly of interest, positive results of immune tolerance protocols so far reported are only preliminary and need to be validated by further large controlled studies before they can be considered as a first-line treatment for patients with acquired hemophilia A.

**Novel eradicating therapies: rituximab**

Rituximab is a monoclonal antibody (against the pan B-cell antigen CD20) that induces a rapid in vivo depletion of normal B lymphocytes.30 Although this agent was originally developed for the use in patients with B-cell non-Hodgkin lymphomas, its use has been successfully extended to many autoimmune disorders.72 Indeed, biotherapy with rituximab has been also used to treat cohorts of patients with acquired hemophilia.73 Wiestner et al.73 described 3 patients with high-titer FVIII autoantibodies who experienced rapid and durable responses following treatment with rituximab alone or in association immunosuppressive therapy. The largest published study reported on 10 patients and documented CR in 8 of them, whereas the 2 nonresponders responded to subsequent intravenous cyclophosphamide. Three relapsed patients, with inhibitor titers higher than 100 BU, obtained a new sustained remission after rechallenge with the same cycle of rituximab. Since then, a number of case reports have described patients with acquired hemophilia refractory to first-line immunosuppressive treatments who responded to rituximab.74 Aggarwal et al.66 treated 4 patients with autoimmune hemophilia and high-titer inhibitors with rituximab and observed durable complete response in 2 of them. The other 2 patients initially responded, but relapsed at 3.5 and 8.5 months. However, both responded to second courses of rituximab and prednisone. Thus, based on their own positive experience, the authors proposed a treatment algorithm with the use of rituximab in association with immunosuppressive agents as first-line treatment in patients with high-titer FVIII autoantibodies. We have recently reviewed the literature data and collected 65 patients with acquired hemophilia A treated with this agent.75 In the majority of the cases, the dosing regimen of rituximab was 375 mg/m2 weekly for 4 weeks, with the cycle repeated if the patient relapsed. Although a response was observed in more than 90% of cases, we advise caution in the overinterpretation of these data as they are derived from case reports or small trials. Furthermore, most patients received concomitant immunosuppressive therapy, thus making the...
evaluation of the real effectiveness of this agent very difficult. For these reasons, in the absence of large prospective studies assessing the safety and efficacy of rituximab in acquired hemophilia, we prefer to use this agent, in association with steroids, as a second-line treatment.

Conclusions

Acquired hemophilia A is a rare disease associated with severe bleeding complications. Therefore, its prompt recognition is mandatory to initiate an early treatment. In the last few years, 2 agents (i.e., rFVIIa and rituximab) have significantly improved the therapeutic armamentarium for the management of this acquired hemorrhagic disorder. Indeed, while rFVIIa has proven an effective and safe tool for the treatment of acute bleeding related to FVIII autoantibodies, rituximab is a promising alternative option for the eradication of the autoantibody and restoration of normal hemostasis.

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Authorship

Contribution: M.F. and G.L. retrieved data and wrote the paper.

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