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ACQUIRED HEMOPHILIA

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ABSTRACT

Acquired hemophilia is a very rare disease, characterized by the presence of an autoantibody (mainly IgG) to factor VIII, with a clinical presentation resembling hemophilia A. It is associated with various autoimmune or dermatologic diseases, pregnancy, cancer, or drug ingestion, but in almost 50% of patients, no underlying disorder is found. The treatment of acquired hemophilia is particularly complex, because response to therapy is unpredictable. If an acute hemorrhage occurs, despite the observance of preventive measures, two complementary strategies must be respected: to stop the bleeding, and to decrease the factor VIII inhibitor, using human or porcine factor VIII, DDAVP, prothrombin complex concentrates, intravenous immunoglobulin, immunosupression, or extracorporeal removal of the inhibitor. The autoantibody titer, the previous response at a given treatment, and the severity of the clinical presentation must be taken into account to make a choice between some of these different therapeutic options, which will be often associated.

Key words: autoimmunity, factor VIII inhibitor, hemophilia, acquired hemorrhagic syndrome, immunosuppressive therapy

Acquired hemophilia is caused by the spontaneous development of autoantibodies against factor VIII protein (FVIII).[1,2] It is an extremely rare event, occuring in approximately one in 5 million persons,[3] in contrast with the 10 to 20% of hemophiliacs who develop alloantibodies.[4]

The first major review concerning acquired anticoagulants was made in 1961,[5] but the most interesting informations about the evolution of acquired hemophilia were collected by Green and Lechner in 1981.[6]

A better understanding of the mechanisms of this disease has permitted to develop new approaches for treatment. But the appropriate therapeutic strategy for acquired hemophilia is really difficult to define, because of its rarity and the resulting difficulty in performing randomized trials.

Structure and function of factor VIII

The mature FVIII molecule, comprising 2332 aminoacids, circulates in plasma as two-chain heterodimers: a heavy chain containing residues 1-740 and a light chain containing residues 1649-2332, separated by a connecting region, the B domain, the function of which is unknown. The heavy chain contains a variable amount of this B region.[4] The FVIII protein can be divided into a series of repeated domains, A1-A2-B-A3-C1-C2. The entire molecule circulates as a complex with von Willebrand factor. FVIII is activated by thrombin or factor Xa cleavage at arginine residues 372 and 1689, with separation from von Willebrand factor. Inactivation is mediated by activated protein C cleavage at arginine residues 336 and 562.[4] The role of FVIII in coagulation is to accelerate the rate of cleavage of factor X by factor IXa.[4,7] In fact, the formation of a complex containing FVIII, factor IXa, phospholipid and calcium, is necessary to activate factor X.

Immunochemistry

Autoantibodies against FVIII are mainly IgG, with the IgG 4 subclass predominating and a preponderance of kappa light chains.[8] This may

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explain the absence of complement-mediated pathology, because IgG 4 do not fix complement.[3,7] IgA and IgM have been rarely observed.[9,10]

It is important to note that anti-FVIII antibodies may be detected from the plasma from about 17% of healthy individuals.[11] The biological significance of these "natural" antibodies is not yet understood. Although most hemophiliac antibodies completely inhibit exogenous FVIII in a dose-dependent, linear fashion caracteristic of type I reaction, a complex type II reaction pattern is more common with autoantibodies, which are not saturable and have decreased affinity for FVIII.[3] This explains why low levels of FVIII activity are almost always detectable despite the presence of these type II antibodies.

The localization of epitopes for FVIII antibodies has been performed by immunoblotting techniques.[12-16] These assays have shown that inhibitors bind predominantly to epitopes within the A2 (residues 379-538) and/or C2 (residues 2178-2332) domains.

Mechanism of inactivation of FVIII is only understood with inhibitors having light chain specificity, which are the most frequent.[16] They are acting by preventing the binding of FVIII to phospholipid.[17] The other mechanisms suggested concern interference of autoantibodies either with thrombin cleavage of FVIII, or with FVIII's interactions with activated factor IX or X.[16]

A last important point to develop concerns the heterogeneity of the immune response to FVIII. Fulcher et al.[14] showed that a FVIII inhibitor patient can potentially produce antibody to multiple areas on the FVIII molecule, whereas Scandella et al.[18] demonstrated that almost 75% of plasmas examined for inhibitors (allo- and mainly auto-antibodies) contained at least two different anti-FVIII antibodies. These findings have important implications for the development of specific therapeutic products, either rFVIII without antigenic determinant, or specific inhibitor-neutralizing fragments of FVIII.

Clinical presentation

The majority of patients with acquired hemophilia are over 50 years of age, with a small peak at age 21-30 consisting mainly of post-partum patients,[6] and approximately an equal number of males and females.

Hemorrhagic events are somewhat different from hemophilia A, since there are more soft tissues ecchymoses and mucosal bleeding with fewer hemarthroses (19). Death from hemorrhage occurs in 12 to 40% of cases, often within months of inhibitors detection.[10]

Associated disorders

The survey by Green and Lechner[6] provides the best information concerning underlying disorders in acquired hemophilia. About 18% of FVIII inhibitors are associated with autoimmune disease (mainly rheumatoid arthritis and systemic lupus), 7.3% with pregnancy or the immediate post-partum period, 6.7% with malignancy, 5.6% with drug ingestion (most commonly penicillin and its derivatives, phenytoin, chloramphenicol), 4.5% with dermatologic disorders (psoriasis, pemphigus), and 11.8% with various diseases. However, in 46.1% of the patients, no underlying disorder was identified.

Laboratory diagnosis

The presence of an autoantibody against FVIII must be suspected if there is an unexplained prolongation of the activated partial thromboplastin time with normal prothrombin time and normal thrombin time.[3,10] The same results can be found with inhibitors against any of the intrinsic clotting factors and the lupus anticoagulant.[10] The specificity of the inhibitor for FVIII is confirmed by incubating patient's plasma with an equal volume of normal plasma. The activated partial thromboplastin time is not corrected, and only FVIII decreases over time in the incubation period.

It is very important for therapeutic strategies to obtain a quantitative assay for FVIII inhibitor. The Bethesda method is the most often performed. A Bethesda unit (BU) is the amount of patient plasma that destroys half the FVIII in an equal mixture of normal and patient plasma incubated 2 hours at 37°C.[20] A low titer is defined as less than 10 BU, intermediate as 10 to 20 BU, and high as more than 20 BU.[21]

Management

A. Generalities

Despite the study by Lottenberg et al.[22] who concluded that there is no mandate for any therapeutic regimen, even immunosupression, the survey by Green and Lechner[6] clearly indicates that any immunosuppressive therapy they described gives a better outcome than no treatment, and that inhibitors disappear infrequently in untreated patients. Those with low levels inhibitors presenting either no underlying disease, either post-partum inhibitor have most likely spontaneous remissions,[6,10] which probably occurs through idiotypic suppression of autoantibodies.[23]

Prevention of hemorrhagic event is more important than for classic hemophiliac patients, because it may be refractory to any treatment. Thus, intramuscular injections, aspirin, invasive diagnostic techniques, cosmetic surgery, and activities predisposing to injury must be avoided, whereas all surgery should be postponed, except if its benefit justifies the hemorrhagic risk.[21,24]

Treatment of acute hemorrhage depends on two complementary strategies: to stop the bleeding, and to try to obtain a rapid decrease of the FVIII inhibitor.[25]

B. To stop the bleeding

Human FVIII. Patients with FVIII autoantibodies have usually no anamnestic response to infusions of FVIII. Human FVIII may be used when inhibitor titer is low, preferably less than 5-10 BU, because a saturation of the inhibitor is then possible.[21,25] Different protocols of infusion have been reviewed by Macik[21] and Weiller et al.[26] Any patient may become a high responder (as defined as an increase of the antibody titer to greater than 10 BU after FVIII infusion) during any FVIII administration (21).

Porcine FVIII. Porcine FVIII should be considered as a first line therapy for hemorrhagic events, especially in patients with high titers inhibitors.[10,21,25,27-33] This is explained by the reduced cross-reactivity with human inhibitors, significantly lower than with alloantibodies.[28,31] Anamnestic responses are infrequent, and only 20 % of patients develop specific antiporcine antibodies.[30,33] There is no correlation between pretreatment human inhibitor level and clinical response. However, response is inversely correlated with antiporcine inhibitor titer. Moreover, a higher antihuman titer is usually associated with a proportionally increased antiporcine titer.[21]

Side effects, which are considerably lower since a new highly purified porcine FVIII (HYATE:C®, Porton Speywood Ltd, Wrexham, UK) has been obtained, consist in chills, fever, headache, and uncommon anaphylactic responses. Thrombocytopenia is less frequent than earlier, because of the decrease of residual von Willebrand factor in the concentrate. Another advantage of porcine FVIII is the presumed absent risk of blood-borne pathogenic viruses. Once again, Macik[21] has reviewed different schedules of administration.

Fresh Frozen Plasma (FFP). FFP is not very useful because its small content of F VIII is rapidely inactivated by circulating antibodies.[24]

DDAVP. In patients with low titer inhibitor, DDAVP (1-deamino 8 D-arginine vasopressin), a synthetic vasopressin derivative, may provoke the release of endogenous FVIII/VWF from storage sites (probably endothelial cells) to obtain an adequate hemostasis.[34-36] After the infusion of 0.3 to 0.4 mg/kg, FVIII level should be over 0.3. However, tachyphylaxis frequently occurs, and long term use of DDAVP is of uncertain value.[10]

Prothrombin complex concentrates. Prothrombin complex concentrates (PCC), containing vitamin K-dependent clotting factors, can be separated in two categories: *standard* PCC which demonstrate clotting activity only in presence of thromboplastin, and *activated* PCC (APCC), inducing spontaneous clotting activity in plasma.[37,38] The latter contains activated clotting factors, because there is an assumption that a factor VIII *bypassing activity* depends on the presence of an activated factor.[39]

The two APCC products available, Autoplex T® (Baxter-Hyland) and FEIBA® (Immuno), are

the most currently used. However, there is no study which clearly establishes that they are more efficient than standard PCC. Furthermore, the most important clinical trials concern mainly hemophiliacs.[40,41] But a strong consensus exists in recent medical litterature to recognize potential efficacy of APCC, especially in patients with high titers FVIII inhibitors in whom FVIII infusions are ineffective.[10,21,42] Effectiveness is unpredictable, and multiple doses are often required, at a dosage of 50-100 u/kg.

Anamnestic responses are infrequent,[43] but the use of APCC must be cautious, because of the possibility of blood-borne viruses transmission, especially hepatitis,[37,40] disseminated intravascular coagulation,[44] and the occurence of thromboembolism, which appears mainly in hemophilia B patients.[37,45] To avoid these complications, it is important to use APCC as seldom as possible, and to consider another therapeutic modality if 2 or 3 doses are not effective within the first few days of treatment.[10]

FVIIa. Plasma-derived FVIIa concentrates or human recombinant FVIIa have been used to treat hemorrhage in hemophiliacs with inhibitor, but as far as we know, there is no report of such a use in acquired hemophilia.

C. To decrease FVIII inhibitor

IVIg. Sultan et al.[46] have first described the anti-idiotypic suppression of spontaneous FVIII inhibitors by high dose intravenous immunoglobulin (IVIg). Many case reports have since confirmed this successful approach.[47,49] Different studies have demonstrated that the interaction between IVIg and autoantibodies depends on the presence of anti-idiotype antibodies against these inhibitors.[23,50-55]

The best source of anti-idiotypic activity against FVIII autoantibodies are aged donors, multiparous women,[56] and theoretically patients convalescing from acquired hemophilia, but they do not qualify as blood donors.[57]

Not all patients respond to IVIg, because the specificity of the anti-idiotypes appears to be restricted to particular idiotypes.[57] Usual dose is 0.4 g/kg/day for 5 days,[58,59] and a decrease in inhibitor titer must be observed within 48 hours following the first infusion.[57,58] Apparently, inhibition of anti-FVIII activity in vitro does not always correlate with the efficacy of IVIg *in vivo*.[60]

Immunosuppressive therapies. Green and Lechner[6] have first established the favourable effect of immunosuppressive agents in acquired hemophilia. The elimination of the cell clone responsible for the synthesis of FVIII inhibitors is the goal of this kind of treatment.[61]

The first drugs used were corticosteroids, with a favourable response rate varying from 54 to 69%.[6,62] Since there is apparently no superiority of other immunosuppressive agents as compared with corticosteroids, the latter should be the choice for initial treatment.[6,63] Furthermore, corticosteroids are relatively benign if given over a short time, at a dose of 1 to 2 mg prednisone/kg/day. If patients do not respond, Green[63] recommends oral administration of cyclophosphamide at a divided daily dose of 2 mg/kg, which is easier to use and less toxic than intravenous pulse therapy. A randomized trial is currently in progress to determine whether prednisone alone, cyclophosphamide alone, or the combination of these agents is the most efficacious. It is also suggested that patients who do not respond to this latter association may benefit from concomitant infusion of FVIII.[63-65]

Lian et al.[66] have tried a combined FVIII-CVP (cyclophosphamide, vincristine and prednisone) therapy which was very effective, since inhibitor was eradicated in 11 patients on 12. The only patient who did not respond has an inhibitor titer as high as 3000 BU/ml. It confirms the observation that patients with inhibitors at high titers are less responsive to immunosuppression.[61] Finally, some case reports[67,68] show a favourable effect of cyclosporine.

It is noteworthy that Allain et al.[69] have proposed to consider the return of the VIII:Ag/VIII:C ratio to unity as an objective criteria to interrupt the immunosupressive treatment. A proposition of schedule of immunosuppressive therapy is given in Table 1.

Table 1. Different steps of the immunosuppressive treatment of acquired hemophilia.

Prednisone 1-2 mg/kg/day
Cyclophosphamide 2 mg/kg/day*
Concomitant infusion of FVIII with cyclophosphamide
Use of a combined FVIII-CVP

** The benefit of the association with prednisone is unknown.*

Table 2. Schedule of plasmapheresis for extracorporeal removal of FVIII inhibitors.

Continuous plasma exchange at a rate of 25 ml/min (duration 3-4 h)
Remove 100-160% of the initial plasma volume
Replace plasma removed by freh frozen plasma, 4% albumin, fluid gelatin and lactated Ringer's solution
Repeat this treatment every day for 3-4 consecutive days in an emergency situation

Extracorporeal removal of inhibitors. Plasmapheresis is to be considered in patients with high titers inhibitors presenting severe bleeding.[70-73] There are some different techniques in these reports. A complete schedule of plasmapheresis is proposed by Sultan and Algiman (Table 2).[74] This therapy should be combined with FVIII infusions, given during or immediately after plasma exchange, whereas immunosupressive therapy may not be necessary.[71]

The greater limitation of this technique is its lack of selectivity, causing removal of many plasma proteins. To avoid this disadvantage, extracorporeal immunoadsorption has been developed, but mainly in hemophiliacs. Négrier et al.[75] used columns containing protein A, a component of staphylococcus aureus, which binds selectively to IgG (except IgG 3). Since there is no need of albumin or plasma substitution, and protein A columns may serve several times, selective immunoadsorption seems to be a promising procedure.

Future approaches. Hoyer[76] has described various theoretical future modalities. Two attractive techniques would be either the production of rFVIII molecules without antigenic determinant, either the use of FVIII domains for extracorporeal removal of inhibitors. However, studies by Fulcher[14] and Scandella[18] must be taken into account for the development of these procedures. Other strategies, based on the induction of immune self-tolerance to FVIII, are also evoked.

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