GUIDELINES

Italian guidelines for the diagnosis and treatment of patients with haemophilia and inhibitors

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Summary. The Italian Association of Haemophilia Centres reviewed and finally approved in November 2004 the new Italian Guidelines for the diagnosis and treatment of patients with clotting factor inhibitors. The recommendations have been based on the identification of levels of clinical evidence derived from the systematic review carried out in 2003 by the School of Health and Related Research, the University of Sheffield, UK, and further integrated by clinical studies published from 2003 to 2004. The Italian guidelines consist of six major domains concerning inhibitor definition, epidemiology, risk factors, diagnosis, inhibitor eradication, management of bleeding episodes, in patients with congenital and acquired coagulation disorders, with 121 statements, 59 synthesis and 54 recommendations. We report here recommendations and open issues concerning the diagnosis and monitoring of inhibitors, inhibitor eradication and the management of bleeding in patients with haemophilia A and B.

Keywords: bleeding, bypassing agents, guidelines, haemophilia, immune tolerance induction, inhibitors

Introduction

The management of patients with haemophilia who have developed clotting factor inhibitors is the most challenging for the haemophilia physicians as it compromises the mainstay of treatment [1], namely the factor replacement and requires an enormous amount of human and economic resources [2]. This issue is made even more difficult by the almost complete absence of evidence-based guidelines, with the exception of the comprehensive UK Haemophilia Centre Doctors’ Organization guidelines [3–5]. The Italian Association of Haemophilia Centres (AICE) approved in November 2004, new Guidelines for the diagnosis and treatment of patients with clotting factor inhibitors. We report here a synthesis of these guidelines, in particular those addressing specific issues on diagnosis, inhibitor eradication, treatment of bleeding and prophylaxis.

Methods

In 2004, AICE decided to update the guidelines on the management of patients with inhibitors previously prepared in 1994 and 1999. The inspiring principle was to provide the physician and the patient with a tool in order to take appropriate decision in specific clinical circumstances. The methodology adopted was the identification of clinical evidence levels [6] (Table 1) based on the systematic review carried out by the School of Health and Related Research, the University of Sheffield, UK [4,7–9], and integrated by a supplementary computer search of Medline and Embase to include clinical studies published from 2003 to 2004.

A preliminary draft was distributed by e-mail to all the members of AICE who were solicited to make comments, corrections and integrations. Telematic discussion was carried out on those issues where full agreement was not preliminary achieved. This process was repeated by e-mail until a final consensus was achieved. Finally, the guidelines were formally approved in the general assembly of AICE, held in Palermo, November 18, 2004.
The final version consists of six major domains, i.e. inhibitor definition, epidemiology, risk factors, diagnosis, inhibitor eradication, management of bleeding episodes, with 121 statements, 59 synthesis and 54 recommendations.

**Diagnosis**

Because of the frequency of inhibitor occurrence, ‘every patient should be considered at risk of inhibitor development’ [7] (grade B recommendation based on level III evidence).

Diagnosis of inhibitors occurrence is recommended to be confirmed and measured by Bethesda assay [10] with Nijmegen modification [11] (grade B recommendation based on level IIa evidence), as endorsed by the Factor VIII (FVIII) and Factor IX (FIX) Scientific Subcommittee of the International Society of Thrombosis and Haemostasis [12], in order to increase the specificity and reliability. According to another recommendation of this Scientific Subcommittee, ‘historical peaks of anamnestic response of inhibitor levels up to 5 BU mL$^{-1}$ identify the so-called low responders, while peak inhibitor levels >5 BU mL$^{-1}$ identify the high responders [13] (grade C recommendation based on level IV evidence). Transient inhibitors are defined as inhibitors, usually at low levels, that disappear spontaneously with the continuation of the same replacement treatment within 6 months from the occurrence, with no anamnestic response after re-exposure to the deficient factor [14]. If possible, a pharmacokinetic analysis should be carried out in each patient on the occasion of the first treatment and periodically repeated (grade C recommendation based on level IV evidence): in presence of very low levels of inhibitors, pharmacokinetic parameters are very sensitive and hence of great help for clinical evaluation [15–17]. Recovery testing or trough level testing during prophylaxis is of help for an early detection of an inhibitor.

In haemophilia B, it is recommended to test each severely affected patient for large gene deletions that are more frequently associated with inhibitor development and with severe allergic or anaphylactic reactions [18–20]. In these patients FIX-containing products should be infused under medical control for at least 20 exposure days (grade C recommendation based on level IV evidence).

As the risk of inhibitor development in previously untreated patients (PUPs) is maximal during the first days of exposure (ED) to factor concentrates, an accurate monitoring should be carried out during the first 150 EDs [21,22]. Inhibitor presence should be looked by means of sensitive methods (recovery and half-life studies, activated partial thromboplastin time-based methods and/or the Bethesda assay) for every 3–5 EDs in the first 20–25 EDs, every 10 EDs in the following 20–30 EDs, then every 3 months for the first 150 EDs and every 6–12 months thereafter [23] (grade B recommendation based on level III evidence).

It is recommended that inhibitor testing would be repeated every 3–5 EDs for the first 20–30 EDs when patients are exposed to new products, not previously used by the patient [22], particularly when a novel product is administered (grade B recommendation based on level III evidence).

In particular, in occasion of major surgery it is recommended to measure the inhibitor or at least the recovery of factor infused, ideally to carry out a pharmacokinetic study [3] (grade C recommendation based on level IV evidence).

In patients with inhibitors, levels should be tested at least quarterly in order to promptly orientate the treatment in case of an emergency [1] (grade C recommendation based on level IV evidence). During immune tolerance induction (ITI) treatment, inhibitor levels should be tested monthly and at least 24 h after the last factor infusion. To confirm the loss of the inhibitor, the test should be carried out after a wash-out period of at least 3 days from the last infusion [3,24] (grade C recommendation based on level IV evidence).

**Inhibitor eradication**

Eradication of the inhibitor in patients with haemophilia represents the main goal of treatment because
it allows replacement therapy with clotting factor concentrates, i.e. the therapy with the most favourable cost–efficacy ratio. Every patient with high-responding inhibitors should undergo, as early as possible an ITI treatment [1,5,24–28] (grade B recommendation based on level IIb evidence). ITI is also recommended in low-responding patients when substitution therapy is not feasible and effective, as soon as it is possible to exclude a transient inhibitor (grade B recommendation based on level IIb evidence), i.e. when the inhibitor persists after at least 6 months of continuation of the same replacement therapy. ITI treatment is not indicated in those children with haemophilia B and inhibitors that have suffered from anaphylactic reactions after exposure to FIX [19–21] (grade C recommendation based on level IV evidence: in fact, the repeated exposure can cause a nephrotic syndrome in these children [29]).

Inhibitor eradication by ITI treatment can be achieved in about three-fourth of patients, as firstly demonstrated by Brackmann and Gormsen [30]. This is usually accomplished by repeated injections of high doses of clotting factors, up to 300 U kg\(^{-1}\) body weight a day [24] even though lower doses have been shown to be effective [31–33], over a time period ranging from 1 to more than 24 months.

Open issues of ITI treatment are the dose regimen, the product type, the time to start and the role of added immunomodulating treatments [34–40]. Several National and International Registries have indicated some favourable prognostic factors [26,34,41–44]: (i) an inhibitor level <10 BU mL\(^{-1}\) when ITI treatment is started; (ii) a historical peak of <200–500 BU mL\(^{-1}\); (iii) an early ITI treatment, within 2 years from the onset of the inhibitor and/or at an age below 6 years; (iv) a daily dose >100 IU kg\(^{-1}\). Therefore, the efficacy of high dose regimens (>100 IU kg\(^{-1}\) a day) seems to be supported by larger observational cohorts [34], but a controlled trial is still ongoing. Because of the urgent need of controlled clinical trials in order to gather evidences on dosage to be use first, AICE recommended that all eligible children should be enrolled in the ongoing International ITI Study (http://www.iritstudy.com), designed to compare high daily doses (200 IU kg\(^{-1}\)) with lower doses (50 IU kg\(^{-1}\)) three times a week [45] (grade C recommendation based on level IV evidence). This study does not indicate which product should be used, with the aim to carry on a post hoc analysis on the type of product. Common practice is to start with the same product that induced the inhibitory response: usually PUPs are treated with recombinant FVIII or FIX products and hence they undergo ITI treatment with recombinant products, while plasma-derived products are usually as rescue treatment after a previous ITI failure. There is some indication that plasma-derived products containing large amounts of von Willebrand factor play a role in ITI-resistant patients [46,47]. More evidences should be gathered in order to know the real impact of these observations, the right time to judge as failed an on-going ITI and hence the time to switch to a different product.

During ITI treatment a few authors have suggested the concomitant use of immunosuppressive agents [37] and of high-dose intravenous immunoglobulins after extra corporeal immunoadsorption of inhibitory antibodies (Malmö protocol) [48–51]. Some concerns were raised about the potential risks of immunosuppressive agents in children. In addition, extracorporeal immune absorption can be problematic in small children, because of poor venous access and low exchange volume. Accordingly, the Malmö protocol is recommended only in patients resistant to ITI or at very high risk to fail (grade C recommendation based on level IV evidence). Immunosuppressive agents alone and/or high doses of intravenous immunoglobulins are not indicated [52–56] (grade B recommendation based on level III evidence).

Very recently, the anti-CD20 monoclonal antibody, rituximab, as it has been successfully used to manage autoimmune diseases, has been used so as to eradicate inhibitors mainly in patients with acquired haemophilia [57]. Some authors have shown some responsive cases of congenital haemophilia with reduction of inhibitor levels [58], and have suggested its potential role as a second-line management of inhibitors particularly in conjunction with conventional ITI. It is premature to provide recommendations about its use that should be at the present time limited to investigational purposes.

The ITI treatment should continue until the complete loss of inhibitors is achieved and when pharmacokinetic parameters normalize, but it should stop in the absence of an even partial response, i.e. 20% decrease of previous levels within 6 months [3] (grade C recommendation based on level IV evidence).

**Treatment of bleeding and prophylaxis**

The main criteria of choice for the treatment of bleeding events in haemophilia patients with inhibitors are inhibitor characteristics (level and anamnestic response) and site and severity of the bleeding episode [1,3,5,21,24,25,57–68] (grade B recommendation based on level III evidence) (Fig. 1).

In low-responders high doses of coagulation factor concentrate can overcome the presence of inhibitors
and allow the attainment of haemostatic levels of the factor infused [1,63,67,69,70] (grade B recommendation based on level III evidence). The recommended bolus dosage corresponds to the sum of the neutralizing dose with the incremental dose, where the neutralizing dose is obtained by multiplying the inhibitor level for the plasma volume. The subsequent doses are represented by the incremental dose administered every 6–12 h or by continuous intravenous infusion [71–73]. The same approach can also be considered in high-responders who have a temporarily low inhibitor level, but only for the treatment of life-or limb-threatening bleeds or on the occasion of major surgery, because an anamnestic response may develop [60,69,74] (grade B recommendation based on level III evidence).

Treatment with bypassing agents, such as activated prothrombin complex concentrates (APCCs) (grade A recommendation based on level Ib evidence) and activated recombinant FVII (rFVIIa) (grade B recommendation based on level III evidence), are recommended in high-responders with high inhibitor levels [75], or with temporarily low inhibitor levels and non-life-/limb-threatening bleeds, in order to avoid an anamnestic response [21] (grade C recommendation based on level IV evidence) and for the same reasons in patients waiting to start ITI treatment [76,77] (grade C recommendation based on level IV evidence). In particular situations like major surgery in high responders with high inhibitor levels or in case of failure with bypassing agents, extracorporeal immunoadsorption can decrease inhibitors to levels that can allow the replacement treatment with FVIII or FIX [78–84].

No data from controlled study are yet available so as to compare the efficacy and safety of APCC and rFVIIa [85]. APCCs are not indicated in patients waiting to start ITI treatment, as the small amount of
FVIII can induce an anamnestic response albeit rarely [86], and in FIX inhibitor patients known to have anaphylactic reactions (grade C recommendation based on level IV evidence).

Activated prothrombin complex concentrates are recommended at doses of 50–100 IU kg\(^{-1}\) every 8–24 h, never exceeding 200 IU kg\(^{-1}\) per day, in order to prevent adverse events [87] (Grade B recommendation based on level III evidence). The optimal dosage of rFVIIa is still an open issue [21]: doses range from 90 to 120 μg kg\(^{-1}\), even though lower and higher doses, up to three times the standard dose, have been used and reported as efficacious. Issues related to the use of rFVIIa are the short half-life that requires frequent and repeated infusions particularly for surgery and the extremely high cost of a course of treatment. Continuous infusion of rFVIIa 16.5–50.0 μg kg\(^{-1}\) [88–96], after administration of a bolus dose, has been shown to be effective with a 30% cost reduction [81,85,86], but no precise guidelines are available for its use by continuous infusion, a regimen that is not licensed at the moment.

No sufficient evidence is available about the safety of switching from one bypassing agent to another when the former has failed, but thrombogenic events have been reported in this situation [97,98]. On the contrary, a potential synergism of APCCs and rFVIIa has been reported with their sequential use at 6-h intervals, without adverse events or laboratory signs of disseminated intravascular coagulation [99,100]. On the whole, an interval of at least 3–6 h should be allowed after a rFVIIa injection before using APCCs, and a longer interval (6–12 h) should be allowed after an infusion of APCCs, monitoring the occurrence of any systemic activation of coagulation before and after this switch (grade C recommendation based on level IV evidence).

Bypassing agents have also been employed for secondary prophylaxis in patients with frequently recurrent bleeding episodes, but risk-efficacy and cost–benefit evaluations are still missing as well as the optimal dose and administration schedule [101–104].

Antifibrinolytic agents are frequently used in association with bypassing products even though their added efficacy has been shown only together with rFVIIa [88]. Their use is generally safe, with the exception of the association with APCC, because of a higher risk of thrombogenicity [23], and in case of haematuria, in which clot formation in the urinary tract is frequently the cause of pain and urinary tract obstruction [105–107] (grade C recommendation based on level IV evidence). Mouthwashes with antifibrinolytic agents have been shown to be safe and effective for mouth bleeds, also in association with APCCs, therefore their use as mouth washes is particularly recommended for oral cavity bleeding [108,109] (grade B recommendation based on level III evidence).

Conclusions

Many issues remain open in the treatment of patients with haemophilia and inhibitors and many recommendations are based on low levels of evidence. In synthesis, the AICE guidelines have pointed out that the main goal of treatment of patients with haemophilia and inhibitors is to eradicate the inhibitor by inducing immune tolerance, which should be tried in all high responders. High-dose FVIII/FIX replacement therapy is recommended in low responders. All the currently available bypassing agents used in inhibitor patients are effective but they have limitations such their unpredictable haemostatic effect, lack of laboratory assays to monitor haemostatic efficacy and the risk of thrombosis, which is more frequent when APCCs are infused in association with antifibrinolytic agents. However, the latter are recommended as mouthwashes for oral bleedings, being safe and cost effective.

Many dilemmas are still unresolved: which dosage and which product should be used for ITI treatment, which bypassing agent should be chosen in the different clinical situations, which dosage of rFVIIa should be employed, whether or not continuous infusion is equivalent to bolus doses, whether or not prophylaxis with bypassing agents is feasible and effective in inhibitor patients. The answers to these issues can only be provided by clinical trials, possibly controlled and randomized, which should also take into account costs and health-related quality of life. Accurate national and international registries of treatments of haemophilic patients with inhibitors are warranted to provide a better estimation of frequency of adverse events of the different therapeutic options.

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