

Combined prednisolone and intravenous immunoglobulin treatment for acquired factor VIII inhibitors: a 2-year review

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Summary. Acquired inhibitors to factor VIII (FVIII) are rare, but life-threatening in up to 22% of cases. The optimal therapy for suppression of these inhibitors remains unclear. Prednisolone is the mainstay of therapy, producing responses in approximately 30% of cases. Intravenous immunoglobulin (IVIg) has a similar response rate, but a more rapid effect. We report the results of prednisolone 1 mg kg⁻¹ combined with IVIg 2 g kg⁻¹ in divided doses as first-line therapy in seven consecutive patients with acquired FVIII inhibitors. All patients were bleeding at the time of diagnosis with prolonged activated partial thromboplastin time.

There were four complete responses, one partial response, one nonresponse and one with an inadequate follow-up for assessment of response, giving an overall response rate of 71%. In all complete responders the inhibitor declined rapidly and was undetectable by day 21 from start of treatment. Therapy was well tolerated and responses have been maintained off treatment for 2–8 months. This is a safe, well-tolerated rapidly acting regimen with good response rates.

Keywords: acquired haemophilia, factor VIII inhibitor, factor VIII, immunosuppressive therapy.

Introduction

Acquired inhibitors to Factor VIII in nonhaemophilic patients are rare, but serious, having an incidence of 1–4 million⁻¹ year⁻¹ [1,2]. These inhibitors are autoantibodies, usually IgG and polyclonal in nature. The majority occur in older people, with a median age at presentation of 60–67 [1,3,4], although they may also occur during pregnancy and in the postpartum period. Fifty percent of cases have identifiable associated conditions, including pregnancy, malignancy and autoimmune disease. Serious bleeding occurs in up to 87% of cases and between 13 and 22% die due to uncontrolled haemorrhage, usually within a few weeks of presentation [4,5].

Treatment consists of immunosuppression, most commonly using steroid to suppress the inhibitor, and factor replacement to control haemorrhage if appropriate. Prednisolone 1 mg kg⁻¹ day⁻¹ suppresses around 30% of acquired inhibitors, and a response

will usually be seen within 3–6 weeks [4,6,7]. A response rate of 30% has also been reported for intravenous immunoglobulin (IVIg) alone. This is thought to be an anti-idiotypic effect with responses seen within 5 days [8]. Combination therapy with prednisolone and cyclophosphamide produces responses in 60–70% [7,9]. Other immunosuppressive regimens have varying success [10–12]. Likelihood of response to treatment cannot be predicted from clinical parameters, although in pregnancy-related inhibitors, spontaneous remission is likely.

The use of prednisolone and IVIg together is appealing, as the combination may produce a more rapid response than either agent alone, without the toxicity seen in more immunosuppressive regimens. There are few published reports of this combination but it is recommended as first-line therapy in some countries [13]. We report here on 2 years' experience of initial treatment of acquired FVIII inhibitors using a standard regimen of prednisolone 1 mg kg⁻¹ day⁻¹ and IVIg 2 g kg⁻¹ in divided doses.

Patient details & laboratory evaluation

Between June 1998 and June 2000 seven patients with newly diagnosed acquired inhibitors of FVIII

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were treated. There were four males and three females, with a median age of 77 years (65 years – 83 years). Four of the patients gave a history of minor bleeding over the preceding weeks to months. All patients had active bleeding and a prolonged activated partial thromboplastin time (APTT) at the time of presentation.

FVIII activity was measured with a one-stage APTT based system using FVIII-deficient plasma (Diagen, Oxon, UK). Where results were nonlinear, the FVIII level was taken from the 1 : 5 dilution. The FVIII inhibitor assay was carried out according to the Bethesda method [14] without the Nijmegen modification. IgG and IgM anticardiolipin antibodies (ACA) were measured by ELISA (Cambridge Life Sciences, Cambridge, UK) and functional lupus inhibitor studies were performed (dilute Russell Viper Venom Test (dRVVT); Diagen), with confirmatory testing by platelet neutralization.

Therapy

All patients received standardized treatment with prednisolone 1 mg kg⁻¹ day⁻¹ and IVIg 2 g kg⁻¹. The IVIg was initially divided into two daily doses (patients 2 and 5) but later given over 5 days to reduce the risk of developing acute renal impairment [15]. Prednisolone was given at 1 mg kg⁻¹ for 2 weeks then tapered. Blood products were administered based on clinical judgement of severity of bleeding.

Criteria for assessing response to therapy were those defined by Spero *et al.* A complete response (CR) was defined as disappearance of the inhibitor, improvement of the FVIII activity to greater than 50 IU dL⁻¹ and cessation of bleeding. A partial response (PR) involved a decrease of inhibitor titre of greater than 75%, improvement in the FVIII activity to less than 50 IU dL and/or improvement in haemorrhagic signs. No response (NR) was a failure to improve or worsening of laboratory and/or clinical findings after at least 14 days of treatment [6].

Results

Table 1 summarizes the main clinical and laboratory details and outcomes of the seven patients. One patient with recurrent squamous cell carcinoma died within 3 months of diagnosis of the inhibitor. Response to treatment in this patient could not be assessed as he was discharged to terminal care after 12 days, at which time there was no improvement in FVIII activity. All other patients are surviving with

Table 1. Details of presentation and outcome after treatment with prednisolone and IVIg in acquired Factor VIII inhibitor patients.

| Patient number | Sex | Age (years) | Underlying disease | Symptom | FVIII at diagnosis (IU dL ⁻¹) | Inhibitor at diagnosis (BU) | ACA IgG (0–9 U mL ⁻¹) | ACA IgM (0–5 U mL ⁻¹) | Response to initial therapy | Duration of CR without therapy |
|----------------|-----|-------------|---------------------|--------------------------------|---|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------|--------------------------------|
| 1 | F | 66 | None | Tracheal compression | 7 | 54 | 5.6 | 20 | No | - |
| 2 | F | 83 | DM, HT, hypothyroid | Soft tissue haematoma | 7 | 38 | 15.6 | 1.7 | Yes | 7 months |
| 3 | F | 65 | TCC bladder, HT | Haematuria | 21 | 1 | 1 | 1 | Yes | 8 months |
| 4 | M | 79 | IHD | Melaena | 6 | 77 | 12 | >120 | Yes | 2 months |
| 5 | M | 83 | IHD | Soft tissue haematoma | 6 | 4.2 | 3.4 | 2.5 | Yes | 6 months |
| 6 | M | 77 | DM, AF, DU | Iliopsoas haematoma/haematuria | 8 | 32 | 3.9 | 1.2 | Partial | - |
| 7 | M | 65 | SCC neck | Soft tissue haematoma | 10 | 4 | <1 | <1 | No | Died SCC |

DM, diabetes mellitus; HT, hypertension; TCC, transitional cell carcinoma; IHD, ischaemic heart disease; AF, atrial fibrillation; DU, duodenal ulcer; SCC, squamous cell carcinoma.

no evidence of bleeding, with a median follow-up time of 10.5 months (3–24 months).

FVIII activity at diagnosis was $< 10 \text{ IU dL}^{-1}$ in all but one case (patient 3, 21 IU dL^{-1}). Inhibitor levels at diagnosis ranged from 1 to 77 Bethesda units (BU), with four being above 10 BU. Three patients (patients 1, 2 & 4) had raised anticardiolipin antibodies (ACA) at diagnosis, two had raised IgM levels (20 and $> 120 \text{ U mL}^{-1}$; normal $0\text{--}5 \text{ U mL}^{-1}$) and two had raised IgG (12 and 15.6 U mL^{-1} ; normal $0\text{--}9 \text{ U mL}^{-1}$). Patient 7 was positive for lupus anticoagulant. In all other patients this test was normal.

Response to IVIg and prednisolone

Serial FVIII activities and inhibitor levels for all patients are shown in Fig. 1. Four patients attained CR, with a rapid reduction of inhibitor titres, all being undetectable by day 21 (median 5.5 days). Transfusion-independent FVIII activity of $> 20 \text{ IU dL}^{-1}$ was reached at a median of 14 days (range 5–35 days), and $> 50 \text{ IU dL}^{-1}$ at a median of 31 days (8–150 days). One patient (patient 6)

attained a PR; the inhibitor level became undetectable and the FVIII activity rose to $> 20 \text{ IU dL}^{-1}$ by day 28, but the FVIII failed to normalize despite the subsequent addition of cyclophosphamide. There was one nonresponder (patient 1) who presented with life-threatening tracheal compression requiring tracheostomy because of a spontaneous haematoma and an inhibitor level of 54 BU, subsequently rising to 205 BU. Only after 9 months and additional cyclophosphamide did the inhibitor titre become undetectable. FVIII activity remained poor, ranging between 8 IU dL^{-1} and 40 IU dL^{-1} 18 months after diagnosis.

Six of the seven patients were noted to have significant bleeding at the time of diagnosis. Five were treated with FVIII concentrate and four with prothrombin complex concentrate (three were given both).

One patient (patient 2) relapsed 2 months after diagnosis as the prednisolone dose was tapered, but responded to increased prednisolone and the addition of cyclophosphamide. Of the four patients who attained CR (including the second remission in patient 2), normal FVIII activity has been maintained without treatment for 2–8 months.

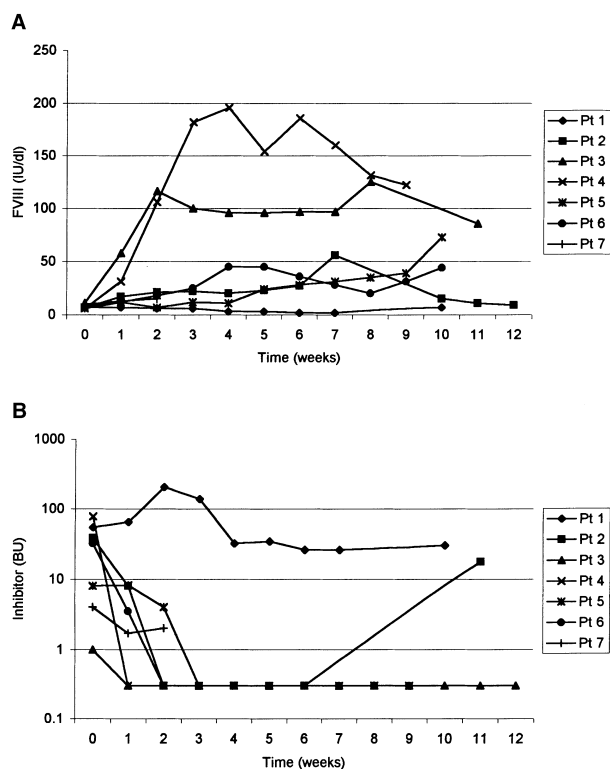


Fig. 1. (A,B). FVIII activity and inhibitor levels for all patients over the first 12 weeks from diagnosis. Inhibitor levels are shown on a logarithmic scale. Inhibitor levels below the level of detection are arbitrarily shown as 0.3 BU.

Discussion

Over a period of 2 years, our institution has treated seven patients with acquired inhibitors to FVIII. An eighth case was treated locally. Thus, the annual incidence in this area (covering approx 2.5 million) is 1.8 million^{-1} , a figure in keeping with other estimates [1]. Although several patients had pre-existing illnesses such as diabetes and ischaemic heart disease, these may simply reflect the age of the population. Two patients had malignancy related to the formation of their inhibitor. Thus underlying pathology was established in only 29% of cases, which is less than the often quoted 50%, but similar to that found by others [12].

Although there is good evidence that some inhibitors remit spontaneously, this occurs in less than one-third of patients [1], partially treated patients remain at risk of haemorrhage-related death [6]. Therefore, effective suppression of inhibitor with normalization of FVIII levels is the goal of treatment. Treatment regimens must be suitable for the patients, who are typically elderly, often with multiple co-existing diseases. Prednisolone is well tolerated and IVIg-related renal impairment can be avoided by dividing the dose over 5 days.

The overall response rate for IVIg and prednisolone as primary therapy in this series is 5/7 (71%).

This is better than for prednisolone or IVIg alone (each around 30%) [6,8], but is similar to that reported for cyclophosphamide plus prednisolone [4,7]. Lian *et al.* used combination chemotherapy (cyclophosphamide, vincristine, prednisolone) with FVIII concentrate infusion successfully in 11/12 patients, who required between one and three courses to achieve prolonged remissions [11]. However, this impressive result was at the cost of significant neutropenic side-effects, and we feel this regimen is too toxic as a first-line therapy.

There was a rapid drop in inhibitor level in the responding patients, becoming undetectable by day 21 in all CRs, and by day 28 in the one PR. FVIII activity was slightly slower to reach normal (median 31 days). It is difficult to make accurate comparisons of time to response for alternative therapeutic regimens, although response times in our cohort are certainly shorter than some [10–12,16], particularly for suppression of the inhibitor [7]. This may be important in the prevention of early haemorrhagic deaths.

Response to treatment was not related to patient age or gender, nor to the presence or absence of underlying malignancy. Inhibitor level at diagnosis did not act as a guide to response, as suggested by some investigators [9], and in fact the case with the highest initial inhibitor level achieved CR.

We have found that the combination of prednisolone 1 mg kg⁻¹ day⁻¹ with IVIg 2 g kg⁻¹ in divided doses, in conjunction with active factor replacement for bleeding, is a successful approach to the suppression of acquired inhibitors. However, it is not possible to assess effectiveness of this regimen in the treatment of pregnancy or auto-immune associated acquired inhibitors as neither group was represented in our patient cohort. This treatment protocol is easy to administer, well-tolerated, and can be started with little delay at the time of diagnosis. The regimen produces a good response rate, and the speed of response, particularly the reduction in inhibitor level, is rapid, perhaps helping to prevent early haemorrhagic deaths.

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