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turoctocog alfa pegol

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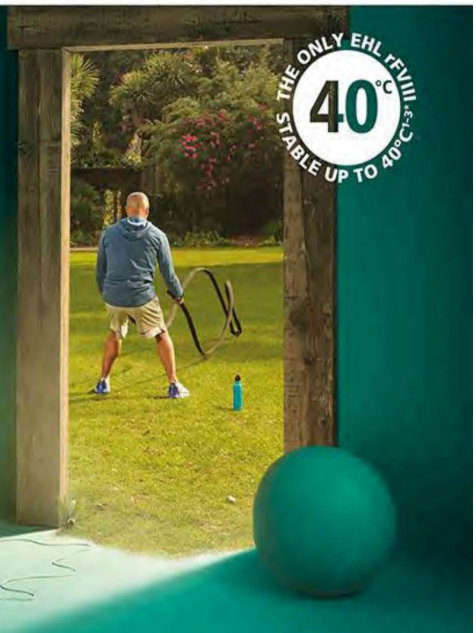

As an extended half-life recombinant FVIII, Esperoct®offers a simple way to reach higher trough FVIII activity levels compared to standard half-life treatments.**[1,4-10]

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In adults and adolescents† with severe haemophilia A, Esperoct® demonstrated:

A simple, fixed starting dose:[1,4]
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Higher trough FVIII activity levels vs. SHL treatments:[1,4-10]
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Median total ABR‡ of 1.18

*40°C storage for up to 3 months before reconstitution[1] **Esperoct® is licenced for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency)[1]

This advertisement is intended for Healthcare Professionals

Prescribing Information

Esperoct®▼

Esperoct 500 IU Esperoct 1000 IU Esperoct 1500 IU Esperoct 2000 IU Esperoct 3000 IU (powder and solvent for solution for injection) Turoctocog alfa pegol. Human factor VIII, produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line, and no additives of human or animal origin are used in the cell culture, purification, conjugation or formulation. **Indication:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency) **Posology and administration:** The dose, dosing interval and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. On demand treatment and treatment of bleeding episodes: Required dose IU = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL). *Mild haemorrhage*: early haemarthrosis, mild muscle bleeding or mild oral bleeding. Factor VIII level required (IU/dL or % of normal): 20-40. Frequency of doses: 12-24, until the bleeding is resolved. *Moderate haemorrhage:* More extensive haemarthrosis, muscle bleeding, haematoma. Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses: 12-24, until the bleeding is resolved. *Severe or life-threatening haemorrhages:* Factor VIII level required (IU/dL or % of normal) – 60-100. Frequency of doses: 8-24, until the threat is resolved. Perioperative management: *Minor surgery Including tooth extraction.* Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses (hours): within one hour before surgery; repeat after 24 hours if necessary. Duration of therapy: single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. *Major surgery.* Factor VIII level required (IU/dL or % of normal): 80-100 (pre- and post-operative). Frequency of doses (hours): Within one hour before surgery to achieve factor VIII activity within the target range. Repeat every 8 to 24 hours to maintain factor VIII activity within the target range. Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved. Consider continuing therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Prophylaxis: The recommended starting dose is 50 IU of Esperoct per kg body weight every 4 days. The maximum single dose is 75 IU/kg. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The dose in adolescents (12 years and above) is the same as for adults. In children below 12 years long-term safety has not been established. Method of administration: Intravenous injection (over approximately 2 minutes) after reconstitution of the powder with 4 mL supplied solvent (sodium chloride 9 mg/mL (0.9%) solution for injection). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, or to hamster protein. **Special warnings and precautions for use**: Hypersensitivity: Allergic-type hypersensitivity reactions are possible due to traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to immediately discontinue the use of the medicinal product and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. Patients treated with coagulation factor VIII products should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Cardiovascular events: In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk. Catheter-related complications: If a central venous access device (CVAD) is required, the risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. Paediatric population: Listed warnings and precautions apply both to adults and adolescents (12-18 years). Excipient-related considerations: Product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2.0 g sodium for an adult. **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects**: The Summary of Product Characteristics (SmPC) should be consulted for a full list of side effects. Common (≥ 1/100 to < 1/10): Rash, erythema, pruritus, injection site reactions. Uncommon (≥1/1,000 to <1/100): Factor VIII inhibition, hypersensitivity. **MA numbers and Basic NHS Price:** Esperoct 500 IU EU/1/19/1374/001 £425 Esperoct 1000 IU EU/1/19/1374/002 £850 Esperoct 1500 IU EU/1/19/1374/003 £1,275 Esperoct 2000 IU EU/1/19/1374/004 £1,700 Esperoct 3000 IU EU/1/19/1374/005 £2,550 **Legal category:** POM. **For full prescribing information please refer to the SmPC** which can be obtained from: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. **Marketing Authorisation Holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised:** March 2020

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ABR, annualised bleed rate; EHL, extended half-life; FVIII, factor VIII; rFVIII, recombinant factor VIII; SHL, standard half-life

†Previously treated patients, 12 years and above[1]

‡Total ABR includes all bleeds: spontaneous, traumatic and joint bleeds[4]

References: 1. Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** Kogenate® Summary of Product Characteristics. **8.** NovoEight® Summary of Product Characteristics. **9.** Nuwiq® Summary of Product Characteristics. **10.** Refacto AF® Summary of Product Characteristics.

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The effect of monoclonal or ion-exchange purified factor VIII concentrate on HIV disease progression: a prospective cohort comparison

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Summary. The CD4 count has been reported to decline less rapidly in HIV-infected haemophiliacs treated with monoclonally purified factor VIII concentrates than in those using intermediate-purity concentrates. No survival advantage has been demonstrated for this effect, and it is unclear whether this effect occurs with all high-purity concentrates. Two cohorts of patients with severe haemophilia A and HIV treated with either ion-exchange-purified or monoclonally-purified concentrates were compared. The CD4 count, survival, AIDS-defining illnesses, CDC category and antiretroviral therapy were recorded at 6-monthly intervals for 3 years following the change from intermediate to high-purity factor VIII. 116 patients were recruited, 37 of whom were treated with an ion-exchange purified factor VIII concentrate at three centres, mean (SD) age 31·1 (12·2) years, and 79 were treated with monoclonally purified factor VIII concentrate at two centres, mean (SD) age 29·8 (11·2) years. At the start of the study the median CD4 count was (monoclonal *v* ion-exchange) 0·30 *v* $0{\cdot}16 \times 10^9$/l.

The CD4 count declined in both arms to a median of (monoclonal *v* ion-exchange) 0·16 *v* $0{\cdot}08 \times 10^9$/l at the final visit. Analysis of the $(\text{CD4 count})^{1/2}$ over time, using a random coefficients model, found that the mean (SE) rates of decline were not statistically significantly different in the two treatment groups (monoclonal *v* ion exchange: −0·050 (0·008) *v* −0·034 (0·011) $(\text{CD4 count})^{1/2}$ per year, $P = 0{\cdot}24$). No statistically significant difference in survival (log-rank test: $P = 0{\cdot}33$) was found. There was no difference in the proportion of individuals experiencing one or more AIDS-defining illnesses ($P = 0{\cdot}32$) or in the proportion progressing to CDC category IV ($P = 0{\cdot}28$) during the study. The CD4 count declined during the study at a rate similar to that previously reported in patients treated with intermediate-purity factor VIII concentrate, and there was no evidence of any difference between the two treatment groups.

Keywords: HIV-infected haemophiliacs, purified factor VIII concentrates, CD4.

Changing from intermediate-purity to high-purity monoclonally immunopurified factor VIII concentrates has been reported to slow or halt the rate of decline in CD4 count in HIV-seropositive haemophilic patients (Menitove *et al*, 1983; De Biasi *et al*, 1991; Goldsmith *et al*, 1991; Seremetis *et al*, 1993; Hilgartner *et al*, 1993; Berntorp, 1994; UKHCDO, 1992). Allotypically heterologous and denatured proteins in intermediate-purity concentrates are thought to stimulate the immune system, increasing the rate of HIV replication and leading to a more rapid decline in the CD4 count (Menitove *et al*, 1983). Doubt has been cast on these findings because the studies were small and because complete stabilization of CD4 counts (De Biasi *et al*, 1991; Goldsmith *et al*, 1991; Seremetis *et al*, 1993) is not generally observed in haemophilic patients or other risk-groups requiring no blood-product therapy (Berntorp, 1994). More recent studies have demonstrated a slowing of the rate of decline of the CD4 count rather than stabilization following the change to high-purity factor VIII (Hilgartner *et al*, 1993).

Although it was expected that relative preservation of the CD4 count might eventually lead to a survival advantage, no significant reduction in mortality has yet been demonstrated.

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However, previous studies had a very low mortality, probably because follow-up was limited to 2–3 years and patients with CD4 counts $< 0{\cdot}3 \times 10^9$/l were not admitted to these studies (De Biasi *et al*, 1991; Goldsmith *et al*, 1991; Seremetis *et al*, 1993; Hilgartner *et al*, 1993; Mannucci *et al*, 1992). It is possible that a study with longer follow-up and no lower limit for CD4 count at entry might be able to demonstrate a survival advantage in changing to a high-purity factor VIII.

The United Kingdom Haemophilia Centre Directors decided to recommend that HIV seropositive patients with haemophilia should be treated with high-purity concentrates, although the product-type was not stipulated (UKHCDO, 1992, 1997). Although these recommendations assumed that all high-purity concentrates were similar in this respect, there was no positive evidence that monoclonal and ion-exchange purified concentrates had the same beneficial effect on immune function (UKHCDO, 1992). Indeed, the only prospective controlled trial comparing the effects of intermediate-purity and ion-exchange purified high-purity concentrates failed to demonstrate a statistically significant difference in the rate of decline of the CD4 count in the two treatment arms (Mannucci *et al*, 1992). This study had only 33 subjects and a follow-up time of 2 years and may therefore have lacked the power to demonstrate a difference between the two products. Several studies have shown ion-exchange purified and intermediate-purity concentrates to have similar inhibitory effects on immune function *in vitro* whereas monoclonal products have little or no inhibitory activity in such systems (Wadhwa *et al*, 1992, 1994; Hay & McEvoy, 1992). There are marked differences in the immunoglobulin, fibronectin, TGF-beta and protease content of the two types of concentrate, and so it would not be surprising if their chronic effects on immune function were dissimilar (Wadhwa *et al*, 1994; Morfini *et al*, 1989). This has yet to be established in a large clinical trial.

The two U.K. domestic plasma fractionators decided to manufacture different types of high-purity factor VIII concentrates. Bioproducts Ltd, Elstree, decided to manufacture monoclonally immunopurified factor VIII under license from Baxter for supply in England and Wales. The Scottish National Blood Transfusion Service decided to manufacture ion exchange purified factor VIII under license from CRTS, France, for supply in Scotland and Northern Ireland. This offered us an opportunity to compare the effects of these two products on immune function, survival, HIV disease progression and use of anti-retroviral drugs in a prospective 3-year cohort study.

METHODS

Subjects and methods. Two cohorts of patients with severe haemophilia A and HIV infection, receiving intermediate-purity factor VIII, were recruited and their treatment changed to either monoclonally immunopurified or ion-exchange purified concentrate. Patients from the Royal Liverpool Hospital and the Royal Free Hospital, London, were treated with monoclonally purified factor VIII (Monoclate, Centeon, Kankakee, U.S.A., Replenate, Bioproducts Laboratory, Elstree, U.K.). Patients from the Royal Infirmary of Edinburgh, Glasgow Royal Infirmary and the Royal Victoria Hospital, Belfast, were treated with ion-exchange purified factor VIII concentrate (Liberate, Scottish National Blood Transfusion Service (SNBTS), Edinburgh).

There was no lower limit for the CD4 count at entry and there were no medical exclusions. To avoid the introduction of bias, all patients from these centres fulfilling these entry criteria were followed for 3 years, from the time that therapy was changed from intermediate-purity to high-purity factor VIII concentrate, or until death or loss to follow-up. The CD4 count, survival, AIDS-defining illnesses, CDC category, use of anti-retroviral drugs and factor VIII usage were monitored every 6 months. The CD4 count was measured locally by flow cytometry. Each laboratory participates in the national quality control scheme for CD4 count and is a consistently good performer. The CDC classification criteria did not change during the study. The CD4 count, survival, HIV disease progression and use of anti-retroviral drugs during the study were identified in the protocol as the principal end-points for this study. HIV disease progression was measured by both the occurrence of AIDS-defining illnesses and the progression from CDC category II or III to CDC category IV during the study.

Study design and statistics. Initial consideration was given to comparing the two products using a randomized trial. This would have introduced an undesirable delay in patients starting to use high-purity factor VIII while the study was set up, as well as a problem with the continuing attrition of the limited number of patients. It was also believed that an insufficient number of patients with severe haemophilia A and HIV would agree to be randomized. For these reasons a prospective cohort design was adopted rather than a randomized trial.

The number of patients in the monoclonal group was determined by the availability of patients with severe haemophilia A and HIV at the two participating centres in England, and the number in the ion-exchange group was determined by the availability of eligible patients living in Scotland and Northern Ireland. As a result, the numbers of patients in the monoclonal and ion-exchange groups are approximately in the ratio of 2:1, but this leads to only a relatively small loss in the efficiency compared to an equal number in both cohorts. As the distribution of the rate of decline in CD4 count was unknown, no prior power calculations could be made. A post-hoc power calculation is reported in the results.

The two treatment groups were compared at the start of their treatment with high-purity factor VIII with regard to age using the two-sample *t*-test, with regard to the proportion of patients in CDC category IV using Fisher's exact test and with regard to CD4 count using the Wilcoxon rank-sum test. The monoclonal and ion-exchange factor VIII groups were compared with regard to the intensity of factor VIII treatment during the study using the Wilcoxon rank-sum test.

The primary analysis of the CD4 counts over time required a square root transformation of the CD4 counts prior to their analysis, due to the asymmetric distribution of CD4 counts. The relationship between the $(\text{CD4 count})^{1/2}$ and time since

Table I. Comparison of the two treatment groups at the start of treatment with high-purity factor VIII.

Treatment arm	Monoclonal ($n=79$)	Ion-exchange ($n=37$)
Mean (SD) age (years)	29·8 (11·2)	31·1 (12·2)
CDC category		
II	53 (67%)	22 (59%)
III	0 (0%)	1 (3%)
IV	62 (33%)	14 (38%)
Median (range)		
CD4 count $\times 10^9$/l	0·30 (0·10–1·20)	0·16 (0·0–0·78)

entry to the study was examined using a random coefficients model with intercept, time, treatment group, and treatment group by time interaction terms as fixed effects and intercept and time as random coefficients. The Kaplan-Meier method was used to produce survival curves by the type of factor VIII concentrate used and also by age groups, CD4 count groups and CDC classification at the beginning of the study. The survival curves were compared using the log-rank test. A Cox proportional hazards model was used to compare survival in the two treatment groups adjusting for the effect of the following covariates: age, $(\text{CD4 count})^{1/2}$ and CDC category at the beginning of the study. The proportion of patients experiencing one or more AIDS-defining illnesses, the proportion progressing from CDC category II or III to CDC category IV and the proportion using one or more anti-retroviral drugs during the study were compared using Fisher's exact test. A logistic regression model was also used to compare the probability of anti-retroviral drug use in the two treatment groups adjusting for the effects of age, $(\text{CD4 count})^{1/2}$ and CDC category at the start of the study. All the statistical tests performed were two-tailed.

RESULTS

116 patients with severe haemophilia A entered the study, 79 using monoclonal and 37 ion-exchange-purified factor VIII. Recruitment was completed in 1992–93. Post-hoc, the study had an 80% power to detect a difference of 0·029 between the two groups in the mean rate of change in $(\text{CD4 count})^{1/2}$ per year as significant at the 5% level, using the estimate of 0·053 from the random coefficients model for the standard deviation of the rate of change in $(\text{CD4 count})^{1/2}$ per year.

The characteristics of the patients in each treatment group at the beginning of the study are summarized in Table I. There was no significant difference between the two treatment groups in age ($P=0·58$) and CDC classification ($P=0·68$) at the study outset. The ion-exchange group had significantly lower CD4 counts than the monoclonal group at the beginning of the study ($P=0·002$). This difference was principally accounted for by the comparatively low CD4 counts of patients from a single centre, Edinburgh.

The median (range) factor VIII use during the course of the study was 94 038 IU (7000–464 000 IU) in the monoclonal group and 81 866 IU (26 000–346 000 IU) in the ion-exchange group. The small difference between the two groups in the intensity of factor VIII replacement therapy during the study was not statistically significant ($P=0·92$).

The CD4 count declined in both arms to a median of (monoclonal *v* ion-exchange) 0·16 *v* 0·08 $\times 10^9$/l at the final visit. The median change in CD4 count during the study was $-0·08 \times 10^9$/l in the monoclonal group and $-0·03 \times 10^9$/l in the ion-exchange group. The analysis of the $(\text{CD4 count})^{1/2}$ over time using a random coefficients model found the mean (SE) rates of decline were similar in the two treatment groups (monoclonal *v* ion-exchange: −0·050 (0·008) *v* −0·034 (0·011) $(\text{CD4 count})^{1/2}$ per year, $P=0·24$).

Twenty-five patients died (15 monoclonal, 10 ion-exchange), and three were lost to follow-up during the study (one monoclonal, two ion exchange). The remaining 88 patients completed 3 years of follow-up. The median follow-up or survival time for all 116 patients was 35·4

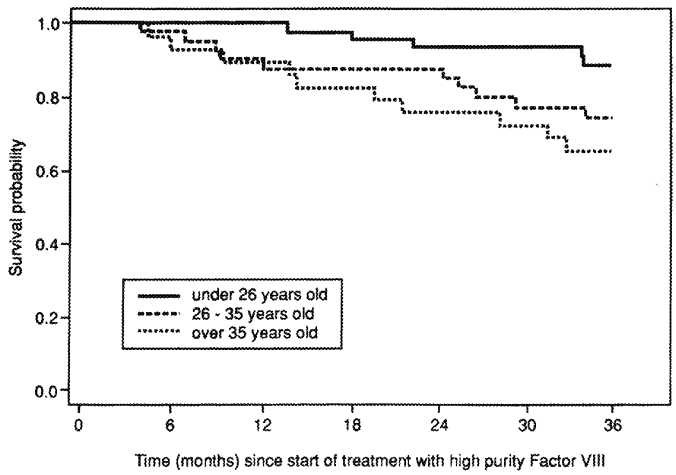

Fig 1. Kaplan-Meier plot showing survival according to age at start of treatment with high-purity factor VIII.

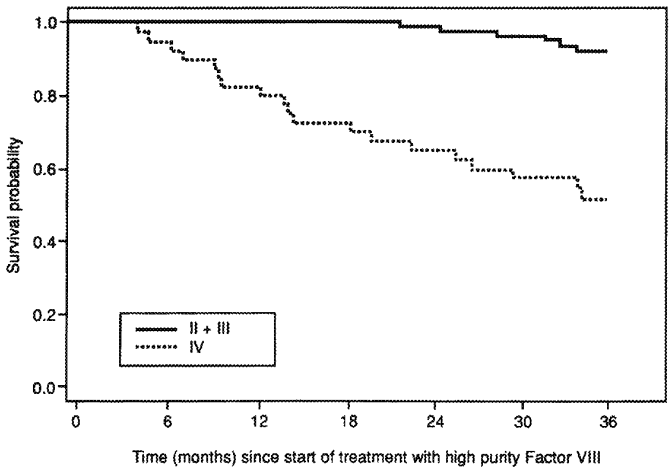

Fig 2. Kaplan-Meier plot showing survival according to CDC classification at start of treatment with high-purity factor VIII.

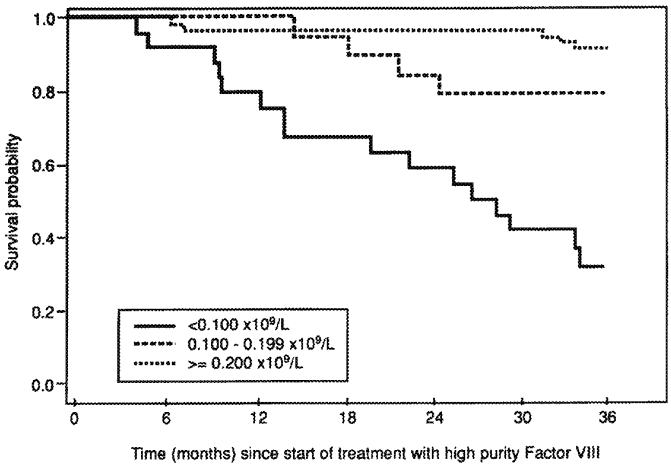

Fig 3. Kaplan-Meier plot showing survival according to CD4 count at start of treatment with high-purity factor VIII.

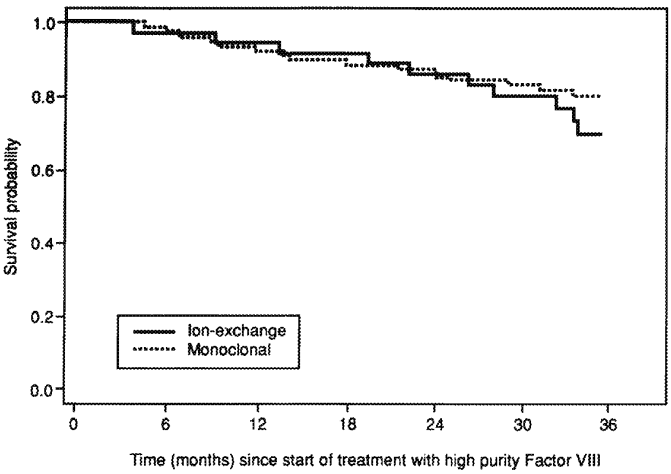

Fig 4. Kaplan-Meier plot showing survival according to type of high-purity factor VIII concentrate used.

months, range 4·3–36 months. Survival was related significantly to age (Fig 1, $P=0·040$), CDC category (Fig 2, $P<0·001$) and CD4 count (Fig 3, $P<0·001$) at the start of treatment. Unadjusted survival was slightly better in the monoclonal group than the ion-exchange group with 3-year survival rates of 81% and 70% respectively (Fig 4, $P=0·33$). Survival in the two treatment groups was also compared adjusting for the starting CD4 count, CDC category and age. There was still no statistically significant difference in survival between the two groups, although, after correcting for the effects of these other variables, survival was slightly greater in the ion-exchange group (hazard ratio 1·49, 95% CI 0·63–3·51, $P=0·36$).

There was no statistically significant difference between the two treatment arms in the proportion experiencing one or more AIDS-defining illnesses (monoclonal *v* ion-exchange 38% *v* 49%, $P=0·32$) or in the proportion progressing from CDC category II or III to CDC category IV (monoclonal *v* ion-exchange 23% *v* 35%, $P=0·28$). 30 patients suffered 62 AIDS-related illnesses/infections in the monoclonal group compared with 18 patients suffering 33 AIDS-related illnesses and infections in the ion-exchange group.

Significantly more of the patients in the ion-exchange group used one or more anti-retroviral drugs during the study (monoclonal *v* ion-exchange: 44% *v* 73%, $P=0·005$). Anti-retroviral drug use in the two groups was also compared adjusting for the CD4 count, CDC category and age at the start of the study. After correcting for the effects of these variables, the difference in the use of anti-retroviral drugs was not quite statistically significant (odds ratio: 0·38, 95% CI 0·14–1·03, $P=0·056$).

DISCUSSION

This study was a relatively large prospective comparison of the effect of two different factor VIII concentrate types on immune function. Furthermore, only three patients were lost to follow-up, thus avoiding a significant potential source of bias which may have affected several earlier studies (Goldsmith *et al*, 1991; Seremetis *et al*, 1993; Hilgartner *et al*, 1993). As we needed to analyse CD4 counts after a transformation, the post-hoc power described in the results is not readily interpreted. However, the power of the study may be illustrated by supposing that subjects in each group were starting from a level of $0·30\times10^9$/l. In that case we would have 80% power to detect differences between levels of $0·21\times10^9$/l and $0·14\times10^9$/l in the two treatment groups after 3 years at the 5% significant level.

The two treatment groups were similar in age and CDC status at the outset of the study and in intensity of factor VIII replacement during the study. They were also infected with HIV at about the same time, in most cases between 1981 and 1984, and so had been HIV-seropositive for between 10 and 12 years at the beginning of the study.

Changing from intermediate to high-purity concentrates did not prevent HIV disease progression and there was an appreciable mortality from AIDS in both treatment arms. The principal determinants of survival in this group were the starting CD4 count, CDC category and age, as previously described (Eyster *et al*, 1987; Darby *et al*, 1989; Lee *et al*, 1989). The influence of age on mortality was far less marked than has previously been reported, partly because many older patients died before the start of the study. Age may also be a weaker determinant of survival amongst long-survivors than amongst patients more recently infected.

When the influence on survival of these important covariates was estimated, and survival corrected for differences in age, CDC category and CD4 count at the beginning of the study, there was no evidence of any difference in survival between the two treatment arms. However, the power of this study to detect a difference in the effect of the two treatments on survival is limited. Similarly, there was no evidence of any difference between the groups in the proportion progressing to CDC category IV or the proportion experiencing one or more AIDS-defining illnesses during the study.

The lower median CD4 count observed in the ion-exchange group at the beginning of the study was largely accounted for by comparatively low counts from a single centre: Edinburgh. Most of the HIV seropositive patients attending this centre had been infected from a single donor whose donation infected a single batch of SNBTS concentrate which infected 18 patients in 1984 (Ludlam *et al*, 1985). Half of these patients were reported to be either dead or symptomatic from their HIV within 4 years of seroconversion, which suggests that they may have been infected with an unusually virulent strain of HIV (Steel *et al*, 1988).

The CD4 count declined in both treatment arms, but the difference between the two treatment arms in the rate of decline of the CD4 count failed to achieve statistical significance. The annual rate of decline of the CD4 count observed during our study was similar to the $0·06–0·08\times10^9$/l/year previously reported in patients treated with intermediate-purity factor VIII concentrate (De Biasi *et al*, 1991; Seremetis *et al*, 1993; Mannucci *et al*, 1992; Eyster *et al*, 1987; Lee *et al*, 1989; Sabin *et al*, 1994). This implies that changing to high-purity factor VIII concentrate may have no lasting beneficial effect on immune function in patients with haemophilia and HIV. Alternatively, the effect may be greatest in patients with higher CD4 counts or may be transient, features common to all single anti-retroviral treatments (Volberding *et al*, 1990; Fischl *et al*, 1990; Concorde Coordinating Committee, 1994). Support for this hypothesis comes from the report of Sabin *et al* (1994) who showed a reduction in the rate of decline of the CD4 count during the first 17 months after changing to monoclonal factor VIII. These patients, who constituted two-thirds of the monoclonal treatment arm of the present study, have failed to maintain this benefit over 3 years of follow-up. However, our data may not be directly comparable with that from earlier studies, since study design and patient selection criteria varied. Also our patients differed from those reported earlier as they were long-term survivors.

A significantly higher proportion of patients in the ion-exchange group used one or more reverse-transcriptase inhibitor agent during the study. This was partly a reflection of the lower starting CD4 count amongst the patients in this treatment arm. Interestingly, this difference in the use of

anti-retroviral therapy was not reflected in differences in mortality or HIV-disease progression in the two groups, and was comparable with the report from the Concorde study which showed no difference between patients randomized to receive 2 or 4 years treatment with zidovudine (Concorde Coordinating Committee, 1994). In many cases the patients had been treated with the same anti-retroviral agent for several years and are likely to have become resistant to this therapy before or during the study period (Concorde Coordinating Committee, 1994). It is unlikely, therefore, that the difference in the proportions of each group treated with anti-retroviral drugs will have significantly influenced the other outcomes in the study.

We were thus unable to find any evidence of a difference between the effect of monoclonal or ion-exchange-purified concentrates on CD4 cell decline, clinical HIV disease progression and survival.

ACKNOWLEDGMENTS

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