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ACQUIRED HAEMOPHILIA

NORDIC GUIDELINES FOR DIAGNOSIS AND TREATMENT

Working Group on Acquired Haemophilia of the Nordic Haemophilia Centres

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C O N T E N T S

1 ACQUIRED HAEMOPHILIA - SUMMARY

Acquired haemophilia (AH) is a severe bleeding disorder caused by inhibiting autoantibodies against a coagulation factor, most often factor (F) VIII, developing in a patient with no previous history of bleeding. It is a rare disorder with an incidence of about 1-2/one million and year. Mostly elderly persons are affected with the exception of the rare occurrence in females postpartum. The APTT is prolonged but other laboratory screening tests for haemostasis like platelet count and prothrombin time are normal. Patients with AH represent a demanding clinical challenge. The morbidity and mortality are quite high, and treatment involves the use of specific and expensive coagulation promoting products. The diagnosis requires identification of autoantibodies (inhibitors) with a specialised test. Consequently, both special laboratory facilities and clinical experience are required to deal with this group of patients. The physician on duty at a haemophilia centre should be consulted.

In recent years, valuable information was gathered in the meta-analysis of 234 evaluated patients from the literature presented by Delgado et al (1). Most important is the data from the surveillance study in the United Kingdom conducted by Dr Peter Collins (2), in which principally all patients were included, altogether 172, diagnosed in England and Wales with acquired haemophilia A (AHA) during a two-year-period starting in 2001. This large unbiased patient material provides lots of information regarding e.g. incidence, frequency of co-existing disorders, mortality and risk of bleeding as well as eradication therapy. The patients were treated in acute bleeds and with immunosuppressive drugs at the discretion of the local clinician according to UK national guidelines (3). Moreover, in a pan-European register, EACH/EACH2 (4), open Jan 1, 2003 to Dec 31, 2008 altogether 400 patients with AHA were included and the data is now under interpretation.

2 DIAGNOSIS

2.1 Incidence and co-morbidity

As mentioned above, AH is rare and mostly elderly people are affected. In the UK material the incidence was 1.5/million and year. The median age was 77 years (range 2-98 years). The incidence per million per year was increasing with age from 0.3 in 16-64 years old to 9 in 65-84 years old and 15 in those aged 85 and older.

There was a slight overweight for females, 57 %. Three females developed AHA postpartum at day 1, week 8 and month 7, respectively.

In about 65 % of the patients no other disorder could be disclosed. In the remaining 35 %, malignancies or autoimmune diseases were present at the time of diagnosis. Rarely, AH arise as idiosyncratic reactions to medication including antibiotics, psychiatric and immunomodulatory drugs (5).

The relative high number of co-existing autoimmune disorders in the patients or among his/her relatives may be striking. Therefore, recent findings suggesting polymorphisms in immune regulatory genes to be associated with the incidence of acquired haemophilia may be of importance. The concept as such, i.e. an association between polymorphisms in immune regulatory genes and antibody formation, has been described for several autoimmune antibody-mediated diseases. In addition, the polymorphic genetic profiles of these genes differ between ethnic groups and may partly explain the variation observed in different populations. Pavlova and co-workers identified an association between a specific polymorphism in coding regions of the CTLA-4 (Cytotoxic T-lymphocyte associated protein-4) gene and acquired haemophilia (6). However, there are several additional candidate genes and to really understand the importance of these findings confirmatory data in other cohorts are needed.

2.2 Symptoms and signs

Easy bruising with extensive enlargement, muscle haematomas and profuse bleeds after trauma and surgery are the most common symptoms in a patient who has never had any signs of bleeding tendency earlier. Extraordinary bleeds may also occur elsewhere as in the gastrointestinal tract, the retroperitoneal space and rarely into joints. Haematuria with intermittent clotting and occlusion of ureter(s) may decrease renal function. Massive bleeds may occur after intravenous venipuncture if special care is not taken. Severe bleeds may be life-threatening.

2.3 Laboratory screening methods

- APTT is prolonged
- Prothrombin time assays (including the INR) are normal
- Template bleeding time is often normal, but may be prolonged
- Platelet and leukocyte counts are generally normal. The erythrocyte count and the haemoglobin value may be low due to bleeds

2.4 Specialised laboratory methods

The diagnosis should be confirmed at a specialised coagulation laboratory.

Blood sampling
Blood samples are drawn in 5 mL vacutainer tubes containing 0.5 mL 3.2-3.8 % (0.11-0.13 M) trisodium citrate. The tubes must be filled and immediately turned 5-10 times for even mixing of blood and citrate. The tubes should be centrifuged within 30 minutes after blood sampling at 2000 g during 20 minutes. The plasma is removed from the blood cells and frozen immediately at -20°C if testing is not performed immediately.

Transport of blood samples
Blood samples must be transported on dry ice. The coagulation laboratory should be notified about the transport.

Testing at the coagulation laboratory

Mixing test (can also be performed at non-specialised laboratories):

- Patient plasma is mixed with an equal volume of pooled normal plasma and incubated for 1-2 h at 37°C. In normal conditions, the APTT will lengthen slightly if incubated 1-2 h at 37°C, because of a spontaneous decay of the labile FVIII. However, the APTT will be more lengthened in the presence of an inhibitor. This can be examined if a control sample (normal plasma) is incubated and analysed in parallel with the patient plasma. An APTT that is 10-15 seconds longer than the control is indicative of an inhibitory activity. The APTT can also be prolonged by an inhibitor to clotting factors other than FVIII or by a lupus anticoagulant. In contrast to the time-dependent FVIII-inhibitor, the lupus anticoagulant type of antibodies does often yield a prolonged APTT both at time 0 and after 1-2 h.

Specific methods

- Determination of FVIII:C or, occasionally, other coagulation factors such as FIX. Autoantibodies to other factors are extremely rare.
- Antibodies to FVIII (or other coagulation factors): most often the inhibitor titre is expressed in Bethesda units (BU). One Bethesda Unit is defined as the quantity of antibody, which reduces the FVIII activity by half in normal plasma when patient plasma is mixed with an equal volume of normal plasma for 2 h at 37°C. Test procedure: normal pooled plasma is mixed with an equal volume of patient plasma in serial dilutions and incubated for 2 h at 37°C. The normal plasma is stabilised with imidazole buffer in order to prevent pH-dependent inactivation of FVIII (the Nijmegen modification of the Bethesda assay for FVIII inhibitors (7)). A control sample based on a mixture of normal plasma and FVIII deficient plasma is run to calculate the residual activity in the patient plasma. The factor activity is measured using a clotting or chromogenic method.

  Assays for antibodies to FVIII (or other coagulation factors) can also be performed in plasma transported at room temperature.

  It should be noted that there is no international inhibitor standard available for the determination of the inhibitor titre.

2.5 Characteristics of the autoantibodies

Autoantibodies against FVIII are composed predominantly of IgG, most often of the IgG4 subclass, and have a preponderance of kappa light chains. The main antigenic epitopes of the FVIII molecule are the A2 and C2 domains. Bound inhibitors block the binding of FVIII to phospholipids, von Willebrand factor and cofactors of the FVIII molecule.

The autoantibodies follow a type II inactivation pattern, which means that there is incomplete neutralisation of FVIII activity. Therefore, low levels of residual FVIII activity may be detectable in patient plasma despite the concomitant presence high titres of the FVIII inhibitor. The complex type II kinetics makes it difficult to evaluate the clinical importance of the titre level or the factor level.

This is in contrast to alloantibodies seen in patients with congenital haemophilia which follow type I kinetics characterised by complete inactivation in a linear relationship between antibody titre and residual FVIII activity.

3 TREATMENT OF ACUTE BLEEDS

3.1 Principles - summary

Transfusions of packed red blood cells are administered according to normal routine procedures.

Infusion of coagulation factor concentrates or by-passing concentrates are the main haemostatic agents in moderate and severe bleeds. In life threatening bleeds when these drugs may be ineffective plasmapheresis or protein A-adsorption may be considered.

3.2 Treatment with specific products

3.2.1 Replacement therapy with FVIII (or FIX) concentrates

FVIII concentrates may be useful in patients with FVIII autoantibodies. It may be advantageous in some cases to use a FVIII concentrate that also contains von Willebrand factor (VWF). FIX concentrates may be useful in patients with FIX autoantibodies, which only occur rarely.

The success of treatment with FVIII/IX concentrates is dependant on, above all, the inhibitor titre but also the severity and localisation of the bleeding as well as the previous experience of administration of concentrate to the patient (see 3.6.2). For a newly diagnosed patient with a moderate or severe bleeding, a high bolus dose of 100-200 IU FVIII/kg BW may be used. Very high doses of FIX concentrate should be avoided, as a risk of developing thrombosis cannot be entirely excluded especially in elderly patients, as seen with the previously used prothrombin complex concentrates. FVIII/IX concentrates are generally not effective in patients with high antibody titres, >5-10 BU.

FVIII and FIX concentrates may be administered intermittently or as continuous infusion.

Monitoring of effect: clinical effect and factor levels in plasma. Factor levels should be determined at least once daily initially in order to evaluate the continued treatment. A level of 0.30 kIU/L or more should be aimed at. There is, however, no definite correlation between plasma levels and the clinical response, as the antibodies follow type II kinetics, therefore the clinical condition must be carefully evaluated on a daily basis.

Available plasma-derived human FVIII concentrates (varies between countries; the concentrates mentioned below are those licensed in Sweden)
Haemate® (contains both FVIII and VWF)
Immunate® (contains both FVIII and VWF)

Octanate® (contains both FVIII and VWF)

Available recombinant human FVIII concentrates (contains only FVIII) (varies between countries)
Advate®
Helixate NexGen®
Kogenate® Bayer
Recombinate®
ReFacto®

Available plasma-derived human FIX concentrates (varies between countries)
Immunine®
Mononine®
Nanotiv®

Available recombinant human FIX concentrate
BeneFIX®

3.2.2 By-pass therapy with Feiba®

Feiba® is an activated prothrombin complex concentrate (APCC), a plasma-derived, virus-inactivated product, containing small amounts of activated factors II, VII, IX and X. It is a "bypassing agent" as the activated clotting factors bypasses the inhibited step in the coagulation cascade.

Sallah (8) presented a retrospective analysis from a 10-year-survey with treatment in three tertiary medical centres with Feiba® in patients with AHA. The material comprised of 34 patients with 55 bleeding episodes. The majority received Feiba® at a dose of 75 U/kg every 8-12 h and response was assessed at 24, 48 and 72 h after the first administration. The mean number of doses was 10 in severe bleedings and 6 in moderate bleedings. Complete response was achieved in 76 % of the severe and in 100 % in the moderate bleeding episodes with a total complete response of 86 %. Feiba® was very well tolerated and only minor side effects were noticed. Holme et al (9) presented 5 patients with AH successfully treated with Feiba® in 8 severe bleeding events.

Dosage: Feiba® 50-100 U/kg BW infused slowly 2-3 times/day. The maximal daily dose is 200 U/kg BW.

Experiences with ROTEM thromboelastography may be useful in tailoring the treatment for the individual patient as shown by Johansen et al. (10).

Systemic use of tranexamic acid is not recommended when Feiba® is administered because of the risk of thrombosis. At least 6 h must pass after a dose of tranexamic acid before Feiba® is given. Tranexamic acid may be used locally.

Relative contraindications: advanced arteriosclerosis, signs of abnormal proteolysis as in ongoing massive infection.

Monitoring of the effect: only clinical monitoring is possible.

Side effects: thromboembolic complications, allergic reactions.

If no signs of clinical improvement are seen in the patient and switching to NovoSeven® is planned, at least 6 h should pass before NovoSeven® is given.

3.2.3 By-pass therapy with NovoSeven®

NovoSeven® is recombinant activated FVII.

The dosage of NovoSeven® has not been definitely defined. A dose of 60-120 microgram/kg BW every 2-3 hours until haemostasis is achieved, is generally recommended to patients with congenital haemophilia with inhibitors. Higher doses up to 200-300 microgram/kg BW is evaluated in various patient groups, but should only be administered by experienced specialists, and there is no documentation on its efficacy and risk profile in acquired haemophilia.

Sumner et al (11) reviewed 139 patients with AH who were treated with NovoSeven® at 124 non-surgical and 57 surgical situations. Mean age of the patients were around 60 years, range 2-92 years. The dose regimens and length of treatment were similar for both non-surgical and surgical treatment with administration either as bolus injection (46-150 microgram/kg at 2-24 h intervals) or continuous infusion (8-50 microgram/kg/h), most treatment less than < 7 days. The overall clinical response was evaluated as excellent or effective in 74.7 %, partially effective in 13.7 % and ineffective in 11.5 %. Ten thrombotic events occurred in 9 patients (6.5 %): 7 cerebral ischaemia/infarction, 2 cardiac arrest/AMI, and 1 DVT/PE.

ROTEM thrombelastography may be useful in tailoring the treatment for the individual patient as shown by Johansen et al (10).

Generally, tranexamic acid is added during treatment with NovoSeven®.

Relative contraindications: advanced arteriosclerosis, signs of abnormal proteolysis as in ongoing massive infection.

Monitoring of the effect: only clinical monitoring is possible.

Side effects: thromboembolic complications, allergic reactions.

If no signs of clinical improvement are seen in the patient and switching to Feiba® is planned, at least 3 h should pass before Feiba® is given. Systemic use of tranexamic acid during treatment with Feiba® is not recommended.

3.3 Desmopressin (Octostim®, Minirin®)

Desmopressin is a synthetic analogue of vasopressin. It stimulates the endogenous release of FVIII, VWF and t-PA (tissue plasminogen activator).

If the inhibitor titre is low and residual FVIII measurable, desmopressin may raise the circulating FVIII activity sufficiently to treat a minor non life-threatening bleeding. Desmopressin has no place in the management of patients with a very low FVIII level (12).

Dosage: 0.3 microgram/kg i.v. or s.c., or 300 microgram by nasal spray. The dose may be repeated once or twice with 8, 12 or 24 h intervals. A higher dose does not improve the effect. A lower dose does not reduce the antidiuretic side effects. If repeated doses are given, sodium levels should be monitored and fluids should be restricted. When used for home treatment, dosing once or twice daily more than three consecutive days should be avoided. In some individuals dosing for more than three-four consecutive days may cause tachyphylaxis, with insufficient FVIII response.

Desmopressin should be combined with tranexamic acid if no contraindications or side effects of this drug are present.

Relative contraindication: symptomatic ischaemic heart disease

Monitoring of effect: clinical effect and FVIII levels in plasma.

Side effects: water retention, hyponatremia, headache, facial flush convulsions.

3.4 Plasmapheresis and immunoadsorption

Plasmapheresis or immunoadsorption followed by FVIII/IX concentrate may be the ultimate choice if the other alternatives of treatment have failed (13). A FVIII/IX concentrate should be given immediately after plasmapheretic reduction, as inhibiting antibodies from the extravascular space are continuously leaking into the circulation and neutralise the effect of the factor concentrate.

Immunoadsorption may also be a component in eradication of the antibodies, see also MBMP 5.9.

3.5 Tranexamic acid (Cyklokapron®, Tranon®)

Tranexamic acid is an efficient inhibitor of fibrinolysis. It may be useful in prevention of bleeds in AH but is rather to be considered as a concomitant medication with the exception of ongoing treatment with Feiba®.

Dosage: 10 mg/kg BW i.v. 3-4 times daily. The oral dose is 20-25 mg/kg BW 3-4 times daily.

Tranexamic acid should be avoided when the patient is treated with Feiba®. Also it should not be used in (proximal) haematuria.

Side effects: nausea, diarrhoea, blood clots in urinary tract in patients with proximal haematuria.

3.6 Some practical advice concerning treatment of bleeds

Few patients are diagnosed en passant without bleeding symptoms, but the predominant part shows some type of bleedings. Alternative treatments are available, but none of them are evidence-based. The treating physician has to select treatment according to her/his previous experience, availability of drugs and the clinical situation.

3.6.1 Local treatment

- Immobilisation of a limb may help to relieve pain and stabilise the clot
- Ice bags - do not forget a towel to avoid freeze lesions on the skin!
- Fibrin glue, spongostan and similar products can be used locally, e.g. after tooth extractions
- Tranexamic acid can be administered locally
- A solution of lidocainhydroklorid + nafazolin (α-adrenergic vasoconstrictor) may be used in mucous membrane bleed.
- Careful examination!

3.6.2 Systemic treatment

3.6.2.1 Mild bleeds

Mild bleeds: muscle and extensive superficial bleeds without any substantial effect on skin and function

- Tranexamic acid
  Orally 25 mg/kg BW 3 or 4 times daily
  Intravenously 10 mg/kg BW 3-4 times daily

- Desmopressin (if acquired haemophilia A) (see 3.3):
  Intranasally one puff in each nostril if more than 30 kg BW, one puff only if less than 30 kg BW or s.c. or i.v. 0.3 microgram/kg BW. Desmopressin may be repeated once or twice with 8, 12 or 24 h interval or according to previous measurement of factor VIII and clinical outcome. Monitor fluid balance and S-Na if repeated doses are given.

3.6.2.2 Moderate/severe bleeds in a patient with unknown response to factor concentrate

Bleeds, such as massive muscle haematomas with or without compression of nerves or arterial circulation, more extensive superficial bleeds, gastrointestinal bleeds, cerebral bleeds:

Factor VIII (or IX) concentrate
Give one or two doses (100-200 IU/kg BW i.v.). Evaluate the clinical effect and measure the increase of FVIII (or IX). If the treatment is efficacious, continue with the factor concentrate. The dose should be adjusted according to symptoms and factor levels (usually 30-50 IU/kg BW) once or several times daily.

If there is no clinical effect of replacement therapy with a FVIII (or IX) concentrate and no increase of the factor VIII (or IX) level, by-pass therapy with Feiba® or NovoSeven® should be used.

- Feiba®
  Give 1-3 i.v. injections of Feiba® with 8-12 h interval, 50-100 U/kg BW, at maximum 200 U/kg BW daily. The effect is evaluated after 8-12 h.

- NovoSeven®
  Give 60-120 microgram/kg BW with 2-3 h intervals. The effect is evaluated after 6 h.

  Switching between Feiba® and NovoSeven® may increase the risk of thromboembolic complications, especially when switching from Feiba® to NovoSeven®, because of the long half-life of activated factors in Feiba®, see 3.2.2.

- Tranexamic acid
  Orally 20-25 mg/kg BW or i.v. 10 mg/kg BW 3 or 4 times daily as supplementary drug. Tranexamic acid is continued for at least one week. Systemic use of tranexamic acid should be avoided when the patient is treated with Feiba®.

If no effect of Feiba® or NovoSeven® is achieved a combination of the two may be considered (14).

Porcine FVIII concentrate will again be available as a potential treatment alternative in AHA.

4 PROPHYLAXIS IN CONNECTION WITH SURGERY

Surgery or other invasive procedures should be avoided in patients with AH because of the risk of uncontrollable bleeds. If surgery is inevitably necessary it should be undertaken with rigorous precautions. The surgeon must be familiar with operations on haemophilia patients and various strategies must be available for the coagulation expert as well as unconventional solutions. If time is available a test dose of FVIII/IX concentrate may give valuable information before the surgical procedure. Administration of a factor concentrate (FVIII/IX, Feiba®, NovoSeven®) is usually sufficient for relieving the alarming symptoms in the compartment syndrome or ileus, making surgery unnecessary.

Administration of FVIII/IX concentrate, intermittently or as a continuous infusion, would be the most efficient treatment if the levels of FVIII/IX are

increased after injection. In addition, assessment of the factor levels can be done in order to facilitate the monitoring of the dosage.

Alternative treatment can be given with the activated products Feiba® and NovoSeven®. Several case reports indicate that these drugs are efficient in surgery.

For dosage recommendations, please refer to the sections about treatment of acute bleeds.

5 ERADICATION THERAPY

5.1 GENERAL ASPECTS

Although spontaneous remission occurs immunosuppressive therapy (IST) is recommended to eradicate the inhibitors as soon as possible to reduce the length of time the patient is at risk for severe bleeding. The inhibitor level at presentation is not useful for predicting the severity of bleeding events. Most centres have advocated corticosteroids, cytotoxic drugs, or a combination of the two, originally studied by Green & Lechner (15).

In the UK surveillance study the patients were treated, as previously mentioned, at the discretion of the local clinician according to the national guidelines (3). The analysis showed that 40 patients were treated with steroids, almost invariably prednisolone 1 mg/kg and 48 were treated with prednisolone in combination with a cytotoxic agent usually oral cyclophosphamide 1-2 mg/kg. The groups were comparable regarding age, sex, and underlying disorder. Complete remission (CR) was defined as normal FVIII, no detectable inhibitor, and immunosuppression stopped or reduced to doses used before AH developed. CR was achieved in 76 and 78 %, respectively, after 49 days (95 % CI, 31-62) compared to 39 days (95 % CI, 34-57), P=0.51, i.e. not statistically significant. Neither was there any difference in mortality between the two groups. Relapse was found in 20 % in the 90 patients with available data. This occurred 1 week to 14 months after stopping IST stressing the recommendation of a long-term follow-up.

The UK guidelines state that in the absence of a response to the first line immunosuppressive agents within 6 weeks a second-line therapy with rituximab, ciclosporin A or other multiple-modality regimens may be considered (12).

Interim analysis of data from 176 analysable patients included in the EACH2 registry showed a higher proportion of patients achieved CR when steroids were combined with cyclophosphamide (82 versus 62 %). Moreover, fewer patients relapsed when steroids were combined with cyclophosphamide than with steroids alone (13 versus 19 %) (16).

5.2 Corticosteroids

Dosage: 1 mg prednisolon/kg BW p.o. once daily for 6 weeks, thereafter tapering the dose rapidly.

Monitoring of effect: see 5.5.

Side effects: oedemas, hypertension, Cushing symptoms, atrophy of skin and muscles, osteoporosis, electrolytic changes, diabetes mellitus, mental disturbances.

5.3 Cyclophosphamide

Dosage: 1.5-2 mg/kg BW p.o. once daily at maximum 3-4 months, alternatively 10 mg/kg BW i.v. on 2 consecutive days, followed by 1.5-2 mg/kg BW p.o. for 8 days.

Another alternative is a pulsative treatment with cyclophosphamide in combination with vincristin 1.4 mg/m^2 i.v. every 4^{th} week.

Monitoring of effect: see 5.5.

Side effects: leukopenia, thrombocytopenia, anemia, nausea, vomiting, alopecia, exanthema.

Cyclophosphamide should not be given to fertile women or young men since it may cause infertility.

Monitoring of side effects: haemoglobin, leukocytes and platelets are checked 3 times the first week if i.v. doses are given, otherwise once a week the first month, thereafter once a month.

5.4 Azathioprin

Dosage: 2 mg/kg BW once daily for 6 weeks.
Thereafter the dose is tapered slowly depending on the antibody titre and the factor level. Azathioprin is stopped if remission has occurred.

Monitoring of effect: see 5.5.

Side effects: leukopenia, thrombocytopenia and less often anemia, nausea, vomiting, alopecia, exanthema, liver dysfunction, susceptibility to infections.

Monitoring of side effects: haemoglobin, leukocytes, platelets and liver enzymes are checked once a week initially, thereafter once a month.

5.5 Ciclosporin

Dosage: the initial oral dose is 5 mg/kg BW and day divided in two doses; if renal insufficiency is present the dose has to be reduced.

Monitoring of effect of 5.2-5.5: clinical effect, FVIII inhibitor titre and FVIII levels (if AHA).

Side effects: renal dysfunction, liver dysfunction, tiredness, headache, abdominal pain, hypertension, nausea, vomiting, hyperlipidemia, electrolyte changes, muscle cramp.

Monitoring of side effects: creatinine, liver enzymes and electrolytes, blood levels of ciclosporin are recommended.

5.6 Human immunoglobulin for intravenous use (ivIG)

Use of ivIG has been successful in a few patients but the recent UK study (2) has shown no additive effect.

5.7 Rituximab (Mabthera®)

Mabthera® is a recombinant monoclonal antibody that binds in a specific manner to the transmembrane antigen CD20 localised on the pre-B and mature B lymphocytes. Mabthera® reduces the number of B-lymphocytes through a cytotoxic effect. The treatment schedule used in lymphoma treatment may be applied: a dose of 375 mg/m^2 body surface given slowly as i.v. infusion once a week for four weeks.

Mabthera® may be given in combination with cytotoxic drugs.
Monitoring of effect: clinical effect, FVIII-inhibitor titre and FVIII levels (if AHA).

Side effects: Asthenia, pain in bowel, back, chest, muscles or joints, lymphadenopathia, thrombocytopenia, neutropenia, anemia, hypertension, bradycardia, tachycardia, arythmia, postural hypotension, neurological symptoms, diarrhoea, activation of herpes simplex or herpes zoster, respiratory symptoms, hyperglycemia, hypocalcemia, coagulation disturbance. However, all these side effects have mainly been described in patients with a large tumour burden. In patients with acquired haemophilia, the side effects have generally been rare or absent.

Monitoring of side effects: close surveillance of blood pressure, pulse and vital signs during infusion. Measurement of blood counts, glucose and electrolytes.

The experience in acquired haemophilia is so far limited.

5.8 Factor VIII concentrate

Nemes (17) has been successful using a model for induction of tolerance in AHA with a combination of FVIII concentrate and cyclophosphamide 200 mg/day up to a total of 2-3 g and prednisolone 100 mg/day gradually tapering off. The following dosage of FVIII concentrate is given:

30 IU/kg/day in the first week,
20 IU/kg/day in the second week and
15 IU/kg/day in the third week.

A complete remission was obtained in 24 of 26 patients, typically in 4 weeks.

5.9 Modified Bonn/Malmö protocol (MBMP)

The aims of MBMP include suppression of bleeding, permanent elimination of inhibitors, and development of immune tolerance. Zeitler et al (18) presented 35 patients with high titre AHA and severe bleeding. Treatment cycles (days 1-7) were repeated until clinical and laboratory response were achieved. They underwent 1) large-volume adsorption 2.5 to 3 times the total plasma volume on days 1-5, 2) ivIG 0.3 g/kg on days 5-7, 3) prednisolone 1 mg/kg and cyclophosphamide 1-2 mg/kg daily until remission, and 4) FVIII concentrate infusion in a dosage of 100 up to 200 IU/kg every 6 h which was reduced when satisfactory response was achieved. With this regimen inhibitors were undetectable rapidly within 2-4 days, FVIII concentrate was stopped with a median of 12 days and the total treatment process was completed within 12-17 days. Such a massive treatment is considered to be indicated when other modalities have failed.

5.10 Relapse

The relapse rate after first CR was about 20 % in the UK surveillance study (2). Most of these patients achieved a second CR although some needed a long-term maintenance immunosuppression. Relapse of pregnancy-related AHA appears to be extremely rare but may occur.

6 CONCLUDING REMARKS

Acquired haemophilia is a rare clinical condition with high mortality and morbidity. Long-term morbidity due to bleeding and immunosuppression may be severe, and cost of recurrent treatment with expensive therapies may be considerable. No standard treatment protocol has been defined, neither for treatment of acute bleeds, nor for immunosuppression. Therapy therefore often needs to be tailored to the individual. Since some haemostatic treatment options are very expensive, the most potent haemostatic agent may not always be considered to be the first treatment of choice, especially considering the age and general health status of the patient.

In acute bleeds treatment with FVIII concentrates is generally efficient in AHA patients if the inhibitor titre is low, otherwise the by-passing agents Feiba® and NovoSeven® are the drugs of choice with apparently similar efficacy. IST should be started as soon as the diagnosis is established. Prednisolone 1 mg/kg BW, possibly in combination with cyclophosphamide 1-2 mg/kg BW, is recommended as the first-line choice. If there are no signs of response within 6 weeks a second-line therapy should be considered.

The treatment of the patients with AH should always be in close collaboration with the coagulation specialists.

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