

## Publications du Site Transfusionnel (depuis 2000)

**2009**

**STIELTJES N., TORCHET M.F., MISRAHI L., ROUSSEL-ROBERT V., LAMBERT T., GUEROIS C., BERTRAND M.A., BRIQUEL M.E., BOREL-DERLON A., DIRAT G.**

Epidemiological survey of haemophiliacs with inhibitors in France: orthopaedic status, quality of life and cost - the 'Statut Orthopedique des Patients Hemophiles' avec Inhibiteur study.

*Blood Coagulat. Fibrinol.*, 20 (1), 4-11, 2009

(Services cités : Transfusion Sanguine)

The physical condition of severe haemophilia and the impact of advances in replacement therapy have been much studied, but little work has been done on patients who developed inhibitors. The 'Statut Orthopedique des Patients Hemophiles avec Inhibiteur' study was conducted in France in order to assess the orthopaedic status and quality of life of such patients, and the cost of their medical management. Fifty haemophiliacs aged 12-63 years with a history of high-responder inhibitors were included. Clinical assessment showed that only 12% of the patients had a nil pain score and 2% a nil clinical score, as per Gilbert scale. The mean clinical score was significantly higher in patients over 35 years of age than in younger ones. However, younger patients appeared to have a more impaired orthopaedic status than young haemophiliacs without inhibitors of similar age in previous published cohorts. Surprisingly, older haemophiliacs tended to have the best mental quality of life, contrasting with their highly impaired orthopaedic condition and physical quality of life. The mean cost of clinical resources consumed during the year preceding enrolment was (sic)268 999, 99% of which was related to clotting factor. Marked between-patient differences in cost were noted. Our study suggests that the management of haemophiliacs with inhibitors should be improved in order to prevent haemophilic arthropathy to an extent similar to that of patients without inhibitors. Cost-benefit assessment of any therapeutic strategy should always be combined with quality-of-life evaluation. *Blood Coagul Fibrinolysis* 20:4-11 (C) 2009 Wolters Kluwer Health vertical bar Lippincott Williams & Wilkins.

**2008**

**NEGRIER C., ROTHSCHILD C., GOUEMAND J., BORG J.Y., CLAEYSSSENS S., ALESSI M.C., JAFFRY A.C., TEBOUL C., PADRAZZI B., WAEGEMANS T.**

Pharmacokinetics and pharmacodynamics of a new highly-secured fibrinogen concentrate.

*J. Thromb. Haemost.*, 6 (9), 1494-1499, 2008

(Services cités : Transfusion Sanguine)

Background: Inherited afibrinogenemia is a rare autosomal recessive disorder characterized by the absence or trace amounts of plasma fibrinogen inducing varying bleeding tendency. Little is known about the pharmacokinetics of plasma-derived fibrinogen concentrates used in the treatment of afibrinogenemic patients. Objective: This open, prospective, multicenter study assessed the pharmacokinetic and pharmacodynamic profiles of FIBRINOGENE T1 (FGT1, LFB, Les Ulis, France), a human fibrinogen concentrate treated with three specific biological safety steps. Patients/methods: Five adult patients with congenital afibrinogenemia received a single infusion of 0.06 g/kg of FGT1. Plasma samples drawn up to Day 14 were assayed for fibrinogen antigen and activity and for coagulation parameters in a central laboratory. Results: Fibrinogen antigen and activity were similar and highly correlated, with very low between-patient variability for PK parameters. Fibrinogen levels increased rapidly and significantly with a mean plasma concentration of 1.39 g/l achieved 1 hour after the end of the infusion leading to an

almost complete in vivo recovery (94%). The mean half-life was 3.4 days with a slow linear elimination and the distribution was mainly restricted to the vascular compartment. Coagulation parameters were normalised after the infusion and during to the following 6 -10 days. FGT1 was well tolerated overall. Conclusions: FGT1 behaves as the natural functional fibrinogen and its pharmacokinetic properties are in line with those expected from a fibrinogen concentrate. Our findings suggest that FGT1 can restore an efficient haemostasis in afibrinogenaemic patients, and predict a good clinical efficacy.

**2007**

**RICHARDS M., ALTISENT C., BATOROVA A., CHAMBOST H., DOLAN G., de MOERLOOSE P., FRAGA M., HERMANS C., KARAFOLIDOU A., KLAMROTH R., LASSILA R., ROTHSCHILD C.**

Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data.

*Haemophilia*, 13 (5), 473-479, 2007

(Services cités : Transfusion Sanguine)

A survey of 21 haemophilia doctors, throughout Europe, who care for a total of approximately 5000 patients with bleeding disorders addressing practice and opinions regarding prophylaxis in patients aged 16-24 years and adults aged over 50 years, is presented. The outcome of adolescent patients who reduced or stopped prophylaxis was recorded. Eighteen of 19 respondents would consider modification of established prophylaxis in the adolescent age group, principal considerations being avoidance of risks of further concentrate exposure, predicted poor compliance and treatment costs. The preferred age for modification was 16-20 years, but there was very little consensus on the particular prophylactic regime recommended. Approximately, half of a cohort of 218 patients with severe haemophilia successfully reduced or stopped prophylaxis when they reached adolescence. Only 26 of 92 (28%) of the patient cohort who stopped prophylaxis, required reintroduction of a prophylactic regime and 12 of 59 (20%) of those who reduced the intensity of prophylaxis had to reintroduce a more intensive regime. A majority of respondents would consider starting prophylaxis in those over 50 years. There was no consensus as to indications for this practice or the nature of the prophylaxis protocol. We conclude that there is an absence of consensus on the management of patients with severe haemophilia, as they pass through adolescence and young adulthood, and reach the age of 50. Aggregate outcome data suggest a significant proportion of patients in the 18-22 years age range may be able to reduce or stop prophylaxis. A substantial number of older patients are on prophylaxis.

**2006**

**GOUEMAND J., ROTHSCHILD C., DEMIGUEL V., VINCIGUERRAT C., LAMBERT T., CHAMBOST H., BOREL-DERLON A., CLAEYSSSENS S., LAURIAN Y., CALVEZ T.**  
Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A.

*Blood*, 107 (1), 46-51, 2006

(Services cités : Centre d'Hémobiologie François JOSSO)

Inhibitor development is the major treatment complication in children with severe hemophilia A. It is not clear whether the risk of inhibitors is higher with recombinant factor VIII or with plasma-derived factor VIII. We used multivariate analysis to compare 2 cohorts of previously untreated patients (PUPs) with severe hemophilia A: 62 patients treated with the same brand of high-purity

plasma-derived FVIII (pFVIII) containing von Willebrand factor (VWF) and 86 patients treated with full-length recombinant FVIII (rFVIII). In addition to the usual end points (all inhibitors, high inhibitors), we also examined a third end point (high inhibitors and/or immune tolerance induction). The risk of inhibitor development was higher in patients treated with rFVIII than in patients treated with pFVIII, regardless of other risk factors (F8 genotype; nonwhite origin; history of inhibitors in patients with a family history of hemophilia; age at first FVIII infusion). The adjusted relative risk (RRa) for inhibitor development with rFVIII versus pFVIII was 2.4 (all inhibitors), 2.6 (high inhibitors), and 3.2 (high inhibitors and/or immune tolerance induction), respectively, depending on the end point (above). The pathophysiology of this large effect must be understood in order to improve the characteristics of recombinant products and to reduce the incidence of inhibitors to FVIII.

**2005**

**BOULAT C., CLERO B.**

Evolution of indications and consumptions of fresh frozen plasma from 1997 to 2003 in a teaching Hospital.

*Transfus. Clin. Biol.*, 12 (3), 251-256, 2005

(Services cités : Centre d'Hémobiologie François JOSSO)

Objective. - Study the evolution for 7 years of the distribution of fresh frozen plasma consumptions (FFP) according to the therapeutic indications. Materials and methods. - Introduction in the software of the blood bank of a specific character during the distribution of all the homologous FFP allowing a selective sort of the consumptions of FFP according to their therapeutic indications. These "qualifying terms" are defined in function, not only of the French legal references (issued on 3 December 1991), - consumption coagulopathy - global or specific deficit in coagulation factor, but also according to the specificities of our health care institution (liver transplant - thrombotic microangiopathies - open heart surgery). Results. - During 7 years, the consumption of FFP trebled in our institution. The indications of the FFP are now mainly medical, its use in surgery dramatically decreased. The complications are not very frequent, most of them are slight allergic reactions. Conclusion. - New therapies, molecules coming from the research, recombinant proteins or coming from the plasma fractionation will certainly modify the indications of the fresh plasma frozen in the coming years. The supervision of our practices remains essential.

**DAZET D.**

L'éducation des enfants et des parents, une démarche fondamentale.

*Rev. Infirm.*, (112), 28, 2005

(Services cités : Centre d'Hémobiologie François JOSSO)

**KREUZ W., GILL J.C., ROTHSCHILD C., MANCO-JOHNSON M.J., LUSHER J.M., KELLERMANN E., GORINA E., LARSON P.J.**

Full-length sucrose-formulated recombinant factor VIII for treatment of previously untreated or minimally treated young children with severe haemophilia A: results of an international clinical investigation.

*Thromb. Haemost.*, 93 (3), 457-467, 2005

(Services cités : Centre d'Hémobiologie François JOSSO)

The safety and efficacy of a full-length sucrose-formulated recombinant factor VIII product (rFVIII-FS; Kogenate FS; Kogenate Bayer) was evaluated in previously untreated (PUPs) and minimally treated (MTP) patients with severe haemophilia A (FVIII <2%). Patients (37 PUPs; 24 MTPs) aged 0.1-25.7 months were treated with rFVIII-FS for a cumulative of 9,141 exposure days (EDs), median 114 EDs (range 4-478), on prophylactic or on-demand therapy. Eighty-nine percent of all treated bleeding episodes were successfully treated with 1 (74%) or 2 (15%) infusions. Clinical response to first infusion for each bleeding episode was rated as 'excellent' in 58%, or 'good' in 33%, of all cases. Recombinant FVIII-FS was used in 27 surgical procedures, mainly catheter implantations, which were all conducted without bleeding complications. FVIII recovery mean values (approximately 2%/kg/IU) were as expected for any licensed FVIII concentrate. FVIII neutralizing antibody formation was 15% (9/60). Aside from inhibitor formation, three adverse events were rated as 'at least possibly drug-related' for a total drug-related adverse event rate of 0.14%. No viral seroconversions were observed. Overall, excellent safety and efficacy were demonstrated with rFVIII-FS for therapy of young children with severe haemophilia A.

**LASSILA R., ROTHSCHILD C., MOERLOOSE P., RICHARDS M., PEREZ R., GAJEK H.**

Recommendations for postmarketing surveillance studies in haemophilia and other bleeding disorders.

*Haemophilia*, 11 (4), 353-359, 2005

(Services cités : Centre d'Hémobiologie François JOSSO)

Summary. Prospective surveillance studies to monitor drug safety in the postapproval period are rarely employed systematically, although they are of greatest value for caregivers, drug users and regulatory authorities. Safety issues have affected not only conventional pharmaceuticals, but also especially coagulation factors in haemophilia treatment. The reputation of postmarketing surveillance (PMS) studies has been questionable, mainly due to their misuse to solicit prescriptions. Other weaknesses include inappropriate design, lack of standardized observation, limited follow-up periods, absence of rigour in identifying potential adverse drug effects, and infrequent publication. Although well-designed clinical trials represent the gold standard for generating sound clinical evidence, a number of aspects would make PMS studies valuable, if properly conducted. One of their main advantages is broader inclusion, and absence of an 'experimental' design. Lack of proper guidelines, and standardization may constitute a reason for the generally low quality of PMS studies. This paper proposes guidelines for haemophilia-specific PMS studies, in order to improve the acceptance of a basically valuable tool. In the absence of consistent regulatory guidance it will be especially important that the design and supervision of PMS studies involves physicians from the beginning. This will not only make such studies more scientifically relevant, but also help to implement them into daily clinical practice. Specifically in haemophilia, PMS studies may provide valuable data on clinical outcomes, or Quality of Life, which is of great importance when considering adequate standards of care in haemophilia patients.

**2004**

**HUGUET H.C., LASNE D., ROTHSCHILD C., SIALI R., JOZEFONVICZ J.**

Extracorporeal adsorption of anti-factor VIII allo-antibodies on randomly functionalized

polystyrene resins.

*Thromb. Haemost.*, 91 (2), 259-266, 2004

(Services cités : Centre d'Hémobiologie François JOSSO, Laboratoire d'Hématologie)

The occurrence of anti-factor VIII (FVIII) allo-antibodies is a severe complication of the treatment of haemophilia A patients, leading to the inhibition of transfused FVIII activity. The effective elimination of these inhibitory antibodies plays a decisive role in the management of affected patients. To achieve this, immunoabsorption devices employing synthetic adsorbers, which selectively eliminate inhibitors, are of interest in the treatment strategy of haemophilia A patients with inhibitors. Adsorbers consisting of polystyrene-based beads substituted with sulphonate and L-tyrosyl methylester groups, which mimic part of epitope of FVIII molecule recognized by inhibitors, exhibit selective binding capacities towards anti-FVIII antibodies. The adsorption of FVIII inhibitors was investigated by simulating an extracorporeal circulation of haemophilic plasma over these functionalized resins. These innovative adsorbers are able to remove around 25% of anti-FVIII antibodies in 15 minutes depending on the plasma tested. Furthermore, they do not modify the amount of essential plasmatic proteins or residual immunoglobulins G. Experiments which were carried out using different plasmas with various inhibitor titres demonstrate a good reproducibility regarding the adsorption capacity of the synthetic resin. The characteristics of adsorption are similar on either native or regenerated resins. Both the purely synthetic nature of the resin and its easy processability demonstrate the real advantages over currently available protocols. This synthetic adsorber is a major technological advance in selective removal of FVIII inhibitory antibodies.

**2003**

**MAUNOURY C., ACAR P., de MONTALEMBERT M., SIDI D.**

Myocardial perfusion in children with sickle cell disease.

*Amer. J. Cardiol.*, 91 (3), 374-376, 2003

(Services cités : Centre d'Hémobiologie François JOSSO, Cardiologie Pédiatrique, Biophysique & Médecine Nucléaire)

**ROUSSEL-ROBERT V., TORCHET M.F., LEGRAND F., ROTHSCHILD C., STIELTJES N.**

Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four hemophilia A previously treated patients.

*J. Thromb. Haemost.*, 1 (11), 2450-2451, 2003

(Services cités : Centre d'Hémobiologie François JOSSO)

**ROUSSEL-ROBERT V., TORCHET M.F., LEGRAND F., ROTHSCHILD C., STIELTJES N.**

Factor VIII inhibitors development following introduction of B-domain-deleted recombinant factor VIII in four hemophilia A previously treated patients.

*J. Thromb. Haemost.*, 1 (11), 2445-2446, 2003

(Services cités : Centre d'Hémobiologie François JOSSO)

2002

**CARON C., DELAHOUSSE B., DROULLE C., POUZOL P., DUBANCHET A., ROTHSCHILD C.**

A blinded in vitro study with Refacto(R) mock plasma samples: similar FVIII results between the chromogenic assay and a one-stage assay when using a higher cephalin dilution.

*Haemophilia*, 8 (5), 639-643, 2002

(Services cités : Centre d'Hémobiologie François JOSSO, Laboratoire d'Hématologie)

Assay of factor VIII (FVIII) in patient samples is routinely carried out using the one-stage assay rather than the chromogenic substrate assay. The introduction of new FVIII preparations for the treatment of haemophilia A, including immunopurified FVIII and particularly, recombinant FVIII (rFVIII) concentrates, has led to discrepancies between the results obtained with the two assays. In patients treated with rFVIII concentrates, FVIII levels measured with the one-stage assay can be 20-50% lower than those measured with the chromogenic assay. In this study, the one-stage assay was performed with cephalin dilutions higher than those recommended by the manufacturer. B-domain-deleted recombinant FVIII, Refacto(R), was diluted to eight different concentrations, ranging from 1-100 IU dL<sup>-1</sup>, in FVIII-deficient plasma and the FVIII activity of the eight solutions was determined by the chromogenic method in a central laboratory. Aliquots were then assayed by the one-stage method in the four participating laboratories, using different dilutions of CK-Prest(R). When CK-Prest(R) was reconstituted according to the manufacturer's recommendations (dilution 1 : 1), the difference between the one-stage and chromogenic methods was close to 30%. CK-Prest(R) cephalin dilutions of 1 : 5 and 1 : 8 gave very similar results with the two methods, without increasing the interlaboratory coefficient of variation. These findings confirm the influence of phospholipids on the one-stage assay, particularly the importance of using a phospholipid concentration close to the physiological value in platelets. This modified one-stage method may therefore offer an alternative to the use of a concentrate-specific standard.

**ROTHSCHILD C., SCHARRER I., BRACKMANN H.H., STIELTJES N., VICARIOT M., TORCHET M.F., EFFENBERGER W.**

European data of a clinical trial with a sucrose formulated recombinant factor VIII in previously treated haemophilia A patients.

*Haemophilia*, 8 Suppl 2 10-14, 2002

(Services cités : Centre d'Hémobiologie François JOSSO)

To increase the safety of antihemophilic treatment, the production process of full-length recombinant factor VIII (FVIII) KOGENATE(R) Bayer (Kogenate(R)FS) has been modified. Human albumin is no longer added as stabilizer during purification and in final formulation. Instead, the new KOGENATE(R) Bayer production process uses sucrose as a stabilizer in the formulation and adds solvent/detergent virus inactivation step. An European clinical trial was carried out in Germany and France in previously treated patients with severe haemophilia A who had more than 100 exposure days to exogenous FVIII. Pharmacokinetic data was analysed according to one-stage and chromogenic assays. Efficacy and safety during home therapy and in surgical procedures were evaluated; inhibitor formation was carefully monitored. Safety and efficacy were evaluated in 33 European patients for 24 months. Patients received more than 13 million IU KOGENATE(R) Bayer. Over 75% of patients accrued more than 100 exposure days with the new product. Of 875 bleeding episodes, 90.7% were treated with 1 or 2 infusions and 75.8% of responses to treatment were rated as 'excellent' or 'good'. Prophylactic treatment was the

most common mode of therapy (60.7% of infusions). The product was well-tolerated and FVIII recovery studies were consistent throughout the study period. Only 0.26% of adverse events were reported to be drug related. No evidence of de novo inhibitor formation was observed. Overall, KOGENATE(R) Bayer was efficacious, safe and well-tolerated for the treatment of haemophilia A in multitransfused patients.

2001

**CALVEZ T., BIOU M., COSTAGLIOLA D., JULLIEN A.M., LAURIAN Y., ROSSI F., ROTHSCHILD C., SIE P.**

The french haemophilia cohort: rationale and organization of a long-term national pharmacosurveillance system.

*Haemophilia*, 7 (1), 82-88, 2001

(Services cités : Centre d'Hémobiologie François JOSSO)

Medicinal products of biological origin still carry a specific iatrogenic risk, mainly because of their starting material, mode of preparation and variability. Careful postmarketing surveillance systems are therefore necessary. To assess the long-term safety of haemophilia treatment with plasma-derived and recombinant clotting factor products, a cohort study was set up in France in 1994. Participants were patients with haemophilia A and B, with or without previous clotting factor therapy. Clinical events, treatments, biological data and adverse events were recorded on standard forms. Blood samples were separated into serum, plasma and peripheral blood mononuclear cells, frozen, and banked in a central laboratory. The same data and samples were collected at yearly follow-up visits. As of December 1999, 1234 haemophiliacs were enrolled in 39 haemophilia centres. At enrolment, 50.2% of patients were under 15 years of age, and the cumulative number of days of exposure to the product was below 50 in 35.1% of cases. The median duration of follow-up was 26.9 months, with a total of 2729 patient-years (135 947 days of exposure and 211 million units of factor VIII or IX). To date, only 17 patients were lost to follow-up. The initial results show good compliance with this health-watch policy among patients and clinicians specializing in haemophilia. The regular follow-up data and centralized sample bank will serve to investigate rapidly any suspected outbreaks as soon as reliable biological tests become available in the future.

**CHRETIENNOT-BARA C., GUET A., BALZAMO E., NOSEDA G., TORCHET M.F., ROTHSCHILD C., BLAKIME C., SCHMIT J.P.**

Spinal hematoma in the hemophiliac child: diagnostic problems.

*Archives Pédiatrie*, 8 (8), 828-833, 2001

(Services cités : Centre d'Hémobiologie François JOSSO, Radiologie Pédiatrique, Département de Pédiatrie)

Spinal epidural hematoma is an uncommon complication in hemophilia. Case reports.-The cases of an extensive epidural hematoma in two boys with severe hemophilia are reported. Conclusion.- Acute onset of severe neck pain or backache leads to the diagnosis of epidural hematoma in children with hemophilia, even in the absence of neurologic symptoms. Early diagnosis is important and relies on magnetic resonance imaging. Replacement therapy is mandatory and must be prescribed before neuroradiologic imaging. Generally, children have a good neurologic outcome. (C) 2001 Editions scientifiques et médicales Elsevier SAS. [References: 11]

2000

**ABSHIRE T.C., BRACKMANN H.H., SCHARRER I., HOOTS K., GAZENGEL C., POWELL J.S., GORINA E., KELLERMANN E., VOSBURGH E.**

Sucrose formulated recombinant human antihemophilic factor viii is safe and efficacious for treatment of hemophilia a in home therapy - results of a multicenter, international, clinical investigation.

*Thromb. Haemost.*, 83 (6), 811-816, 2000

(Services cités : Centre d'Hémobiologie François JOSSO)

To add an increased level of safety to antihemophilic factor replacement therapy, a full-length, recombinant Factor VIII (rFVIII) product has been developed without human-derived plasma proteins during purification and formulation and using an additional solvent/detergent viral inactivation step. This first clinical trial of a sucrose-formulated full-length rFVIII (rFVIII-FS) was conducted in previously treated patients (greater than or equal to 100 prior exposure-days) with severe (<2% FVIII) hemophilia A in North America (NA) and Europe (EU).

Pharmacokinetic profiles for rFVIII-FS were compared with those of currently licensed rFVIII product (Kogenate((R))) in 35 patients. Safety and efficacy during home therapy were evaluated in 71 patients. The new formulation displayed a pharmacokinetic profile similar to that of rFVIII. Patients on home therapy received a cumulative total of 11,867 exposure days, 12,546 infusions, and 22,443,694 IU of rFVIII-FS. Of 2585 bleeds, 93.5% were treated with 1-2 infusions and 80.5% of responses were rated as excellent or good. No evidence of de novo inhibitor formation was observed. Only 0.27% of infusions were associated with any drug-related adverse event. Except for an episode of intermittent chest pain with palpitations which ceased after treatment with analgesics, associated adverse events were mild or moderate. Overall, rFVIII-FS provided excellent hemostatic control, was well-tolerated, and caused no significant adverse effects, thus demonstrating safety and efficacy for treatment of bleeds in patients with hemophilia A.

[References: 27]

**BARDAKJIAN J., BENKERROU M., BERNAUDIN F., BRIARD M.L., DUCROCQ R., LAMBILLIOTTE A., LENA-RUSSO D., de MONTALEMBERT M., THURET I., BEGUE P., ELION J., GALACTEROS F.**

Neonatal screening of sickle cell disease in metropolitan france.

*Archives Pédiatrie*, 7 (12), 1261-1263, 2000

(Services cités : Centre d'Hémobiologie François JOSSO)

**BOUCHAIR N., MANIGNE P., KANFER A., RAPHALEN P., de MONTALEMBERT M., HAGEGE I., VERSCHUUR A., MAIER REDELSPERGER M., GIROT R.**

Influence of multiple phlebotomies on sickle cell crises.

*Arch. Pédiatrie*, 7 (3), 249-255, 2000

(Services cités : Centre d'Hémobiologie François JOSSO)

Objectives. - Sickle cell disease patients suffering from frequent painful crises were submitted to phlebotomies in order to reduce hospitalization days due to pain, through hemoglobin (Hb) level reduction and iron deficiency in patients with an hemoglobin level equal to or above 9.5 g/dL.

Patients. - Seven sickle cell disease patients (four SC, three SS), aged four to 24 years, were submitted to sequential phlebotomies during periods from 18 months to four years. Methods. - The number of hospitalization days for crises was considered. The volumes and frequencies of

phlebotomies were adjusted according to the patients ages, the hemoglobin concentrations and the serum ferritin levels. Results. - One hundred and forty-four hospitalization days were recorded in the seven patients in the year preceding the treatment During the study period, the annual numbers of hospitalization days were respectively 20, five, six and one. Mean hemoglobin concentration was 10.7 g/dL before phlebotomies and 8.8 to 9.2 g/dL during the four years of treatment Mean corpuscular volume, mean corpuscular hemoglobin concentration and serum ferritin were also reduced. The volume of phlebotomies was 116 to 39 mL/kg/year according to the patients Comments and conclusion. - The striking decrease of the number of hospitalization days for ail the patients suggests a closed relationship between therapy and clinical improvement. The mechanism of this effect is probably multifactorial: a) the concentration of Hb level is known to influence the blood Viscosity and its decrease always improved rheology in sickle cell disease patients; 6) the mean corpuscular hemoglobin concentration is a critical factor concerning the HbS molecule polymerization in sickle cell disease, and its slight reduction may have an important biological effect We observed these two biological modifications in our patients and suggest that they mediate the clinical effects The iron deficiency induced by phlebotomies has no evident deleterious consequence either on height and weight in the children or on intellectual performance in any patients. (C) 2000 Editions scientifiques et medicales Elsevier SAS. [References: 23]

**NEONATO M.G., GUILLOUD BATAILLE M., BEAUVAIS P., BEGUE P., BELLOY M., BENKERROU M., DUCROCQ R., MAIER REDELSPERGER M., de MONTALEMBERT M., QUINET B., ELION J., FEINGOLD J., GIROT R.**

Acute clinical events in 299 homozygous sickle cell patients living in france.

*Eur. J. Haematol.*, 65 (3), 155-164, 2000

(Services cités : Centre d'Hémobiologie François JOSSO)

A subset of 299 patients with homozygous sickle cell anaemia. enrolled in the cohort of the French Study Group on sickle cell disease (SCD), was investigated in this study. The majority of patients were children (mean age 10.1 +/- 5.8 yr) of first generation immigrants from Western and Central Africa, the others originated from the French West Indies (20.2%). We report the frequency of the main clinical events (mean follow-up 4.2 +/- 2.2 yr). The prevalence of meningitis-septicaemia and osteomyelitis was, respectively, 11.4% and 12% acute chest syndrome was observed in 134 patients (44.8%). Twenty patients (6.7%) developed stroke with peak prevalence at 10-15 yr of age. One hundred and seventy-two patients (58%) suffered from one or more painful sickle cell crises, while the others (42.5%) never suffered from pain. The overall frequency of acute anaemic episodes was 50.5%, (acute aplastic anaemia 46% acute splenic sequestration 26%). A group of 27 patients were asymptomatic (follow-up >3 yr). Epistatic mechanisms influencing SCD were studied. Coinherited alpha-thalassemia strongly reduced the risk of stroke ( $p < 0.001$ ) and increased that of painful crises ( $p < 0.02$ ). There was a low prevalence of Senegal and Bantu (CAR) beta(s)-chromosomes in patients with meningitis ( $p < 0.04$ ) and osteomyelitis ( $p < 0.03$ ). Prevalence of Senegal beta(s)-chromosomes was lower in the asymptomatic group of 27 patients ( $p < 0.02$ ). The patients come from a population of unmixed immigrants in whom the beta-globin gene haplotype strongly reflects the geographic origin and identifies subgroups with a homogenous genetic background. Thus the observed effects might result more from differences in as yet unidentified determinants in the genetic background than from the direct linkage with differences in the beta-globin gene locus.

[References: 42]

**ROTHSCHILD C., GILL J., SCHARRER I., BRAY G.**

Transient inhibitors in the recombinant study.

*Thromb. Haemost.*, 84 (1), 145-146, 2000

(Services cités : Centre d'Hémodiologie François JOSSO)

**SCHARRER I., BRACKMANN H.H., SULTAN Y., ABSHIRE T., GAZENGEL C.,  
RAGNI M., GORINA E., VOSBURGH E., KELLERMANN E.**

Efficacy of a sucrose-formulated recombinant factor viii used for 22 surgical procedures in patients with severe haemophilia A.

*Haemophilia*, 6 (6), 614-618, 2000

(Services cités : Centre d'Hémodiologie François JOSSO)

A sucrose-formulated recombinant FVIII (rFVIII-SF) was investigated under clinical trial conditions during surgical procedures in previously treated patients (PTPs). Fifteen PTPs with severe haemophilia A (FVIII less than or equal to 1%) underwent 22 surgical procedures. The procedures performed cover a spectrum from minor to major surgery. Haemostatic outcome was assessed by the investigators to be excellent in 16 procedures and good in the remaining six procedures. It is concluded that rFVIII-SF is efficacious and safe in severe haemophilia A patients undergoing minor or major surgery. [References: 15]