

Bob Stewart
from Helene

0008. FMM-REPLY
ROY

HELENA ✓
KATHARINE ✓
BILLY ✓
PUM ✓

for info
(from Jim
Smith)

. f
serum

Thank

GRO-C



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**FACTOR VIII CONCENTRATES
AND TREATMENT OF HEMOPHILIA:
STATE OF THE ART IN 1990**
**CONCENTRATI DI FATTORE VIII
E TRATTAMENTO DELL'EMOFILIA:
STATO DELL'ARTE NEL 1990**

January 18-19, 1990

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Con il patrocinio di
Ministero della Sanità
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Fondazione Nazionale Emofilia

Istituto Superiore di Sanità
Viale Regina Elena, 299 - Roma

Delegate: J.K. Smith

Factor VIII Concentrates and Treatment of Haemophilia:
State of the Art in 1990

I said before the meeting that it looked like another benefit match for the League of Purity, but it turned out to be much more open minded, in the enquiring and somewhat conservative spirit of the FDA/BLI meeting last year in Bethesda. It here was any Baxter or Armour money going into this meeting, they should sue.

Effectiveness and virus safety of factor VIII concentrates

Aledort reviewed the history of replacement therapy's hopes and bitter disappointments, culminating in the AIDS tragedy and the precipitous rise in costs of concentrates. It must be realised throughout this report that, in the US, there had been a stark choice between extortionate, "monoclonally-purified" (MP), probably virus-safe concentrates, and IP concentrates known to transmit NANBH; pasteurised IP and HP concentrates have not made much quantitative impact until recently, have been even more expensive than MP and have been reserved for vWD.

Morgenthaler gave a very sober account of virus inactivation methods, cautioning against optimistic claims about physical clearance - he claimed that immunoabsorbents remove only about two logs of some viruses. There were indications that HIV-2 might need longer than HIV-1. He thought multi-layer 105 nm filtration was interesting, and mentioned some alternative chemical treatments such as copper/phenanthroline, and fatty acids. Essentially photochemical methods include UV/psoralen, low-intensity pulsed 308 nm radiation, and 630 nm radiation with DHE. The window for gamma irradiation was judged to be too narrow, at least for concentrates. He went out of his way to be generous about 80° dry heating, for the first time in public by a fractionator who does not use our methods.

(In conversation he said that SRK were starting to use the Baxter package for VIII and will probably use immunoaffinity columns for factor IX, but he did not wish to defend or explain these decisions taken by others.)

Verani for the "Italian NIBSC" gave a long list of viruses which, probably to possibly, could infect man through murine monoclonals. She made the interesting point that validation e.g. by spiking could only attempt to mimic the important variables in virus inactivation and demonstrate reproducibility; the absolute value of indicative experiments could only be verified by clinical trial of the real thing over a long period. Predictably, she was lumbered with accusations that European control authorities were being hysterical about hypothetical risks to keep out good, clean, US apple pies. Why, if the FDA said OK, it must be OK. No-one was unkind enough to remind us explicitly of the hysterical circumstances in which FDA approval was given to MP concentrates and to SD inactivation.

Mannucci had some new slides. Of 125 seroconversions to HIV-1 reported to CDC since 1985, 22 met their criteria for probable transmission:

- 5 from 60° 30h only
- 10 from 60° 30h, + others
- 1 60° 24h only
- 1 60° 72h only
- 1 60° 20h in heptane only
- 1 60° 20h in heptane, + 68° 72h
- 3 more complicated exposures

In prospective studies, mainly in Europe (to get seronegatives), more than 100 million iu had been used in 1489 patients without seroconversions, making an incidence of <1 per 4000 patient years.

He has grasped that the plasma base is increasingly free of HB and HIV and that this has implications for the interpretation of recent clinical trials. I am not sure whether he wants to grasp the implications of surrogate or anti-HIV screening for NANBH trials.

He gave preliminary results of clinical trial of the new HP Hemate. 21/29 analysable, three with elevations (but we all know that these blips don't mean anything) and all negative for anti-HCV. So that's all right.

He confirmed his view that at least three of four apparent transmissions of HB by Immuno's VIII in Italy were real. One of these became anti-HCV positive at eight weeks and is thought to have had a double infection. Embarrassingly, three of the 28 "virgins" in the study now proved to have been HCV positive before entry, "possibly due to unreported treatment with single donor products".

The audience was interested in ALT and anti-HCV patterns in untreated control groups, but went unrewarded. In Vienna, the Turkish population had a high incidence of juvenile cases of NANBH.

Morfini repeated his recent Thrombosis Research paper on what is in factor VIII concentrates and why MP products are obviously "not going to cause immune modulation". Except that there is murine IgG in both MPs (not in rVIII). More interestingly, all concentrates, including MPs, were positive for B19 DNA by PCR.

Impact of factor VIII concentrates on the immune system

Martha Eibl summarised published work on the in vitro effect of factor VIII concentrates on Sc receptors on monocytes. Polymeric IgG depresses FCR I, II and III. Monomeric IgG binds but does not suppress, unless it is bound to another surface. Immune complexes are very potent suppressors of rosette formation. FCR I is involved in co-suppression of the complement receptor.

All factor VIII concentrates suppress FCR by about 30-40% in a pattern similar to that seen with aggregated IgG. Suppression is independent of virus inactivation treatment or the concentration of IgG. Effector function is also suppressed in proportion to receptor function and release of oxygen radicals. Because of the link with complement receptors, bacterial killing is suppressed. The suppressor in factor VIII concentrate is of high MW, and MP concentrates have approximately the same effect as conventional concentrates. This is attributed to ng/ml concentrations of murine IgG. She thought that these in vitro observations might well translate to "serious effects" on the haemophiliac's immune system, but did not predict specific observable consequences.

Barrowcliffe summarised published work on suppression of IL-2 released by Jurkat cells by factor VIII concentrates. Neither MP concentrate had appreciable effect, but all others had some effect (8Y has the least effect after MP). Suppression was not proportional to specific activity or FPLC pattern, and he is now less inclined to blame "wet heating". Only the early part of the IL-2 secretion process was affected. The inhibitor was not binding to the cells. He now thought that the effect was probably not due to total protein, albumin, IgG, fibrinogen, fibronectin, IIa, lipoprotein or polymeric IgG but might involve factor XIII, immune complexes, calcium binding or receptor down-regulation. There seemed to be no connection between the agents causing this effect and Eibl's. Concentrates vary greatly in the diminution of suppression after dialysis, and some of the audience thought this might hold the key to the entire picture - I have offered to help him find out.

Brettler was more subdued than usual, and not quite so selective in her statistics. She conceded that Gjerset's and Tsoukas' 1989 reports showed no difference in CD4, CD8 and IgG changes between HIV-negative patients on MP and on IP concentrates. A recent study by Green suggests differences, but this was contradicted by another from Mills - I have not seen these papers. She gave the familiar story on HIV-positive patients and admitted that she had to use special pleading to show differences in CD4 loss between patients on MP and IP concentrates. It is noticeable that the IP group started with much lower CD4, and it seems likely that they were further down the slope. It should be easy to test this influence and allow for it, so I suppose the answer is inconvenient.

In discussion, there were more rumours about MP and rVIII using up their statistical ration of inhibitor incidence rather early. Eibl made the remarkable suggestion that she would be in no hurry to remove immune complexes from VIII concentrates, since

they might just be suppressing an otherwise natural progression to inhibitor formation in all treated haemophiliacs.

It would be ironic if Levine and Brettler's claims for MPs in HIV-positive patients (roundly condemned by Kernoff as a cynical promise of treatment for these desperate people) might be having some marginal effect because of its contamination with murine IgG.

This was the second international gathering which could not come up with any evidence that haemophiliacs were suffering from clinically meaningful immune modulation. The Birmingham TB case was aired, and effectively deflated by Kernoff. Ludlam's suggestion of greater susceptibility to HIV in proportion to CD4/CD8 is counterblanced by masses of neutral evidence in the US.

Brettler said that there was a current European study on MP versus IP in seronegative haemophiliacs, but she did not seem to be aware of Hill's cohort on 8Y, or the apparent genetic association between elevated CD8 and IgG in untreated haemophiliacs. I think MP products are beginning to suffer a reaction proportional to their original overselling on the grounds of unique virus safety and purity (before albumin addition).

How would you choose a factor VIII concentrate today - panel and discussion

Aledort said he would give an MP concentrate to any PUPs, because it was currently their turn for clinical trial, and they were usually free of charge. For all other patients not in a study, he would use the cheapest concentrate he could get, given that all were HIV safe. He did not think that "re-infection" of old lags with NANBH was a hazard.

Brettler had a familiar gut feeling that the MP products "should be" better, and would prefer them in all circumstances.

Cash thought that, in principle, high specific activity meant good clinical practice and (curiously) good manufacturing practice, but emphatically not at the expense of yield or unresolved potential new hazards such as mice and soapsuds. He reminded the audience that some European countries preferred to work within their own plasma resource, and that this had consequences for "choice".

Kasper uses a lot of IP concentrate (or would like to) for prophylaxis and induction of immune tolerance in inhibitor patients. She had seen no change in CD4 in these patients, or any adverse effect on immune function one year after heavy treatment for trauma or surgery. She reviewed hypothetical advantages of purity, but saw the recent literature as providing no indication of the superiority of MP over IP concentrates. She thought that any difference in the incidence of inhibitors would turn out to be small, either way. The main consideration was secure virus inactivation. Her policy was to give pasteurised, SD or MP concentrate where the patient had not yet been infected with NANBH, because they were virus-safe, not on the grounds of purity. All other patients would get the cheapest concentrate available. Occasionally, she would give cryo from a parent. In vWD, she preferred Hemate to cryo. She kept reminding the US participants that they had no licenced virus-safe PCC, factor IX or activated PCC, to name but a few. She estimated that a severe haemophiliac would need about \$3m worth of care in a full life.

Kernoff listed the concentrates to which he had access in the UK, and expressed confidence only in Monoclate, 8Y and Hemate (of which very little is available). What features of MP concentrates justified 72c/iu, rather than 40c/iu, for 8Y? He saw the actuarial progression of haemophiliacs to AIDS as identical to that of gays or PT cases, and had found no change in CD4 in 126 RFH patients on IP concentrate after five years. He had no qualms about using IP for any category of patient. He liked flying Concorde, but thought that the Jumbo was a more effective machine. Apart from Cash, he was the only one to mention the case for a national plasma economy which respects the blood donor.

Mariani had looked at HIV-positive and negative patients on IP concentrate (25 iu/mg) for six months, and HP (100 iu/mg) for 6-12 months. He had found no change in HIV status, total lymphocytes or CD4 counts.

Roberts did his thing. Not content with Concorde, he would like us to go for Space. An interesting throwaway was that inhibitor patients on activated PCC soon have difficulty with venous access - I have not heard that about patients on cold factor IX.

In a discussion which reflected a lot of cautious re-evaluations from the platform, Wunderle tried to explain to the advocates of purity that they would never get factor VIII alone in a vial. There would always be vehicles, excipients, preservatives of one kind or another, adventitious or deliberate, the only question being which had a higher risk/benefit than others.

I was greatly encouraged that some sobriety was returning to this debate, and that IP concentrates had lost no ground in 1989. If BPL has marketing energy to spare, this would be a good time to go on the offensive for our product, perhaps with a reasoned Q & A brochure.

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