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M E M O

From: Dr. J.K. Smith

To: Dr. R.S. Lane
Dr. T.J. Snape

11th April, 1985.

Heated factor IX concentrate, 9D

This memo is intended to clarify our ever-changing perspectives on the options for issuing heated factor IX; to serve as a basis for discussion at BPL on 8th May; and to start a Working Party at PFL to ensure that there will be no avoidable delay in clinical trial of the heated product.

1. Previous BPL/PFL policy

There was no evidence until early this year that there should be any concern about in vitro tests for safety of heated factor IX. However, the lack of correlation between in vitro test results, animal testing and clinical evidence of thromboembolism led us to insist on dog infusions (DIC model) before releasing any modified factor IX concentrate. These infusions started in February but only one or two dogs can be handled each week, three or more dogs are needed for each experimental point, and several kinds of control and calibrating infusions are necessary. These are on course.

2. Evidence since November 1984

2.1 Under the conditions used to heat 8Y, namely 80° for three days, no significant loss of potency of factor IX, II or X is observed and NAPTT is not adversely affected. However, it was later confirmed, using a test required by B.Ph. and Eu.Ph. but not thought to have physiological significance, that heating results in an increase in the free thrombin content from $<10^{-3}$ u/ml to 10^{-1}-10^{-2} u/ml (i.e. FDA time reduced from >6h to 1-3h). The effect is apparent even down to approximately 70° for 24h.

2.2 PFC have confirmed, using specific inhibitors, that the coagulant activity is thrombin.

2.3 Dogs are known to tolerate infusions of 150 u/kg of thrombin (equivalent to perhaps 10-100 u/ml thrombin in a factor IX concentrate i.e. 100-1000 times higher than in a concentrate with a 1h FDA time), but will show transient DIC. There is no previous experience of infusing concentrates containing thrombin at 10^{-1}-10^{-2} u/ml without activated IX and X (NAPTT >150 seconds). Interpretation of any difference between infusions of heated and unheated 9D may therefore be difficult; only a null effect will be comforting.

2.4 Even if heated 9D appears to cause no further potential thromboembolic effect than the unheated 9D, the short FDA time will be an embarrassment. We would have to take the line that we have a new generation of concentrate which does not meet an earlier over-specification, but which offers the best balance of safety in several respects.

2.5 Recognising the above potential embarrassment, Dr. Feldman has

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carried out experiments to "protect" 9D from thrombin generation during heating. First quantitative results suggest that

(a) Addition of 25 u pasteurised AT III concentrate per litre of 9D before drying improves the FDA time of unheated 9D from 2.5 to >6h, and of heated 9D from 1.5-4h.

(b) Addition of 300 u/L increases the FDA time of heated 9D to >6h.

(c) Addition of AT III after heating is less effective (and of course difficult to use).

(d) NAPTT is increased by 20-30 seconds.

(e) Heparin alone is not effective and heparin added to AT III does not significantly improve the effect of AT III - there is ample time for progressive antithrombin to do its work.

3. What heated concentrate should we aim to issue first?

3.1 Availability. Heated 9D minus AT III is already locked into the dog infusion programme and there is enough of the dog-trial batches to support a Stage 1 trial of immediate safety and efficacy in people. Supplies of heated product (if we accept limited QC on batches fit for release unheated) could be available within two weeks of a decision to issue.

9D plus AT III has to be generated from unfinished eluate, freeze-dried, heated and QC-ed with sterility test before infusion. We can accept retrospective (or short-incubation) sterility data for dog infusions in the interest of speed. Heated 9D plus AT III cannot be available for trial human infusion before the first week in June.

3.2 Dog infusions. Heated 9D minus AT III is likely to have been tested in at least some dogs by the end of April but if there are changes after heating, further experiments may be necessary to clarify their significance. I cannot guess whether there will be significant differences. I suggest that we will not issue this product if there is anything at all suspicious and that we focus on whether we would issue it with a short FDA time even if the dogs showed no significant problem.

Heated 9D plus AT III cannot be ready for dog infusions before mid-May and I would need to negotiate its earliest possible infusion after that. Mid-June might be a sensible target date for evaluation and release to clinical trial. I would not recommend issuing this product without dog infusions, simply having "fixed" an awkward problem of in vitro testing.

3.3 Further confirmation of benefits of AT III addition

3.3.1 Closer standardisation of dose-response to AT III: experiments on 9D 3183 with 25-250 u/L of AT 2211. Results expected 15th-16th April.

3.3.2 Multi-batch survey: 12 batches of 9D, various provenances and characteristics, to be treated with 50 and 250 u/L of AT 2211 and pre- and post-heating FDA etc. compared with untreated controls. Results expected 15th-19th April.

3.3.3 Production experience: very small eluate 9D 1889 to be finished

with and without AT 2211 addition, heated and subjected to full QC except sterility.

3.3.4 Trial batches for dogs and people: three batches 2337-9 to be finished 17th-19th April with a definitive concentration of AT III, heated and expected to be through QC by late May - possibly earlier, without full sterility test, for dog experiments.

These experiments are expected to add in vitro respectability to any decision to accelerate the use of AT III, which would still be preceded by dog infusions and Stage 1 trials of safety and efficacy in patients before general release.

3.4 Miscellaneous points

3.4.1 9D already finished cannot readily be converted to 9D plus AT III. How much stock do we have and therefore stand to lose?

3.4.2 It may be embarrassing to apply for a second licence for 9D plus AT III shortly after receiving one for 9D minus AT III.

3.4.3 We should be prepared for the possibility that the addition of AT III will show no significant improvement in dog responses.

3.4.4 Do we know how commercial heated factor IX concentrates currently on offer compare with ours e.g. in FDA time or in animal models?

4. Some feasible policies

4.1 Issue 9D heated minus AT III on favourable assessment of dog infusions.

4.2 Decline to issue 9D heated minus AT III, even with good dog results, on grounds of in vitro FDA test and imminence of a better product.

4.3 Issue heated 9D (plus or minus AT III) to selected patients, at high risk from HTLV III but low risk of thromboembolism, on a named-patient basis with adequate warning, until 9D plus AT III is tested.

4.4 Seek product licence for 9D plus AT III without extensive production or in vivo experience.

4.5 Wait for 9D plus AT III to fulfil the original criteria for trial and issue.

5. Interim policy at PFL

While policy is being determined, PFL will aim at the most rapid possible provision of finished 9D plus AT III for dog infusions and clinical trial (and potentially the most pressing treatment of little-exposed patients) but cannot greatly affect national supplies for severe haemophilia B. We will not interfere with the planned dog infusions this month of one batch of 9D minus AT III, but our second trial product would be 9D plus AT III.

cc. Mr. D.R. Evans, Mr. M.E. Haddon, Dr. P.A. Feldman, Mr. G.E. Mallory, Mr. E.D. Wesley, Mr. P.J. Prince, Dr. M.J. Harvey.