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NOTE OF CLINICAL TRIAL REVIEW MEETING HELD ON MONDAY 1 DECEMBER 1986

Present: Dr R Perry (Chairman)
Dr R Crawford
Dr B Cuthbertson
Dr P L Yap
Dr J D Cash
Miss I McKinney (Minutes)

1. INTRODUCTION

Dr Perry indicated that the meeting had been set up as an annual event with the intention of reviewing the status, results and future of clinical trials sponsored by SNBTS in respect of PFC products. The membership of the group would be flexible, reflecting the type of trial in progress or planned and the SNBTS consultant co-ordinating the trial. However, the core membership would be Drs Perry, Cuthbertson and Cash, the latter acting specifically in his capacity as ex officio medical advisor to PFC.

It was subsequently agreed that the group would, in due course, address regulatory aspects of clinical trials and in compliance with procedures for initiating and co-ordinating trials.

2. INTRAVENOUS IGG (N) IN HYPOGAMMAGLOBULINAEMIA

2.1 The present IV IgG product is sucrose stabilised and accordingly is a variation on the product for which a product licence has been granted. Dr Cuthbertson advised that the new product had now been fully evaluated by Dr Yap and the variation application would be submitted before Christmas. The variation would also include minor modifications to the product leaflet. It was noted that the licence was conditional on continuing patient follow-up and generation of virus inactivation data.

It was agreed that the product was in a post-marketing surveillance period and therefore it was appropriate that Dr Yap should continue to monitor and follow-up all hypogammaglobulinaemia patients receiving the product on the understanding that such continued follow-up could be reduced to a core group of 6-12 patients. Dr Yap indicated that he had established a patient serum library for future (and as yet unidentified) studies particularly with respect to viral safety.

Dr Yap et al will be submitting a paper to the Scottish Medical Journal in due course concerning clinical experience to date of the PFC product.

The need for on-going patient surveillance (co-ordinated by Dr Yap) would be reviewed in one year's time.

It was agreed that the SNBTS would continue to support the treatment of a small cohort of hypogamma patients in England since they formed an important component of the post-marketing surveillance exercise.

Dr Yap confirmed that while there had been patient deaths within the hypogamma cohort under study, these were related to malignant disease or other factors unrelated to IV IgG. The unresponsiveness of sinusitis to IV IgG therapy remains an important area for future clinical studies.

2.2 Role of IV IgG in Treatment of HIV Positive Patients

Dr Yap reported that 2 infants in the Edinburgh area and both born of HIV positive mothers had been treated with IV IgG. There is preliminary evidence that the first infant has responded to treatment, the course of treatment for the second infant has only just commenced.

Dr Yap further reported that he was planning, subject to funding (SHHD), a double blind placebo controlled trial of IV IgG for the prophylaxis of AIDS or ARC in infants born to HIV positive mothers. Ethical approval for this trial has already been received and would be conducted as a collaborative study with the Infectious Diseases Unit and the University of Edinburgh.

Dr Perry undertook to find out if a Doctors and Dentists Exemption Certificate was required for this study.

3. INTRAVENOUS IGG FOR THE TREATMENT OF ITP

Dr Perry confirmed that the PFC product was not licenced for this application and at the present time all product issues were on a named patient basis, co-ordinated by Dr Crawford for the purpose of follow-up and on-going evaluation of product safety.

Dr Crawford presented extensive data on the use of the PFC product for ITP and other diseases. The data included adverse reactions, virological safety data. To date 84 patients had been followed-up. It was noted that anecdotal reports of hair loss following high dose treatment with IV IgG had not been unequivocally related to IV IgG therapy. It was agreed that the substantive report submitted by Dr Crawford would serve as an excellent basis for licence variation to permit the use of PFC IV IgG for ITP and it was therefore agreed that:

(a) Drs Perry, Cuthbertson and Crawford should review the document with a view to its submission in support of a licence variation.

(b) The variation should, at this time, only relate to ITP.

(c) Dr Crawford should arrange to provide graphical or tabulated data for such measurements as platelet counts for each patient as part of the clinical submission.

(d) Drs Crawford, Yap and Cuthbertson should redraft the product insert leaflet to reflect the use of IV IgG for ITP. It was noted that the Sandoglobulin and Gammaimmune leaflets would serve as useful models for this purpose.

Dr Cash suggested that further discussion on the role of IV IgG and Anti-D

in the treatment of ITP would be useful and he agreed to contact Dr Adrian Newlands with a view to setting up a discussion/seminar on this issue. Dr Cuthbertson noted that some recipients of IV IgG in Dr Crawford's report had subsequently died and asked if these should be reported as adverse reactions (yellow card) to DHSS. Dr Crawford indicated that such notifications were the responsibility of the prescribing clinician and from his investigations he had satisfactorily concluded (with the agreement of the clinicians involved) that these deaths were unassociated with the course of IV IgG. The group endorsed these conclusions.

4. INTRAVENOUS IGG (MEASLES)

Dr Crawford referred to a report on a study concerning IM high dose IgG (25,000 IU) vs IV IgG (125,000 IU) and confirmed that the study was proceeding satisfactorily. However, it was now clear that the rate of enrolment into the study was such that the study would last 3 years. No morbidity has been seen as yet in either the control (IM) group or IV group.

It was agreed that Dr Crawford would attempt to obtain data on Measles morbidity in children with malignant disease from other areas of the UK who are receiving no propnylaxis since it is possible that the trial has coincided with a low level of National Measles incidents.

5. INTRAVENOUS IGG (CMV) - (RENAL TRIAL)

Drs Yap and Cuthbertson reported that this trial had now been concluded. A total of 33 patients had been enrolled into the trial and Dr Yap will be analysing the available data from the trial in the New Year. It was noted that the trial was unlikely to provide useful information on the therapeutic role of CMV in renal transplantation. However, it was noted that there probably now existed a large amount of data from "uncontrolled" administration of CMV IgG and Dr Yap would attempt to collate this information.

6. INTRAVENOUS IGG (CMV) - (BMT PROPHYLACTIC TRIAL)

This trial was initiated in August 1985 is on going. So far 33 patients have been recruited of which 20 have reached the 6 month stage in the protocol. However, it was noted that the uptake rate is slower than anticipated. It was hoped therefore that an expansion of participating centres could be achieved.

Plasma and product supplies are adequate to support the trial and it was noted that PFC was fractionating plasma from BPL to meet the English demand for ad hoc issues outwith the trial (Hammersmith).

Dr Jane Apperley is co-ordinating the trial until June 1987. Thereafter alternative arrangements will be necessary to ensure proper trial co-ordination and surveillance.

7. IGG (IM) ANTI-HEPATITIS A

Dr Yap reported that Sheila Polakoff had indicated that there had been no outbreaks of Hepatitis A and she had not therefore been able to carry out this study. The material had been administered to a few people however but

there had been no follow-up.

Dr Cuthbertson advised that this material expired in April 1987 and it was therefore agreed that the material should be returned to PFC pending a decision on how best to utilise this outdated material.

It was agreed that this product would no longer be evaluated in a clinical trial.

8. SPPS BURNS SOLUTION

Dr Cash reported that he had written to Dr Anne Sutherland but to date had not received a response. To date there has been no report on the multi-centred trial of this product.

Dr Cash agreed to contact Dr Settle (Wakefield) to establish if there was any merit in further pursuing this study.

9. FVIII (Z9) HEAT TREATED 75° C/72 HRS

Dr Perry reported that this product was now available for half-life and recovery studies in Edinburgh, Glasgow and Northern Ireland prior to its introduction into routine use. Dr Boulton is co-ordinating this study, the results of which will be used for application for licence variation.

10. LEAFLETS AND GUIDANCE NOTES

The Leaflet Working Party (LWP) have proposed that there are occasions on which it is necessary and useful to provide information leaflets and guidance notes for products entering clinical trials (eg CMV IgG) and non-licenced products.

It was agreed that this was an important and appropriate part of the LWP remit and that such guidance notes should be drafted and discussed by Directors as appropriate. RTD's could then use such guidance notes at their discretion within their own regions.

11. PROPOSALS FOR FUTURE CLINICAL TRIALS

11.1 Intravenous Rubella IgG

Whilst there may be a need for such a product (proposed by Dr Crawford) to achieve high and efficacious levels of circulatory antibody, it was generally agreed that the studies necessary to evaluate such a product in either male, non-immune volunteers or otherwise healthy pregnant mothers was likely to be unethical at the present time. Dr Crawford also confirmed that the prophylactic failure rate using the existing IM product was very low.

It was agreed that the group would review the need and possibility of such a product and associated studies at the next meeting.

11.2 Heat Treated IV IgG

Dr Yap confirmed that ethical approval had been given for such a