CURRENT APPROACHES TO THE TREATMENT OF INHIBITOR PATIENTS IN THE U.K.

BACKGROUND

There are more than 100 designated haemophilia centres in the U.K. of which 10 are Reference Centres. In 1983, out of a total of 4716 patients with Haemophilia A registered at these centres, 273 were reported to have inhibitors.

Approximately 50% of the inhibitor patients are registered with the reference centres and the remainder are distributed between the other centres.

The intention of this report is to summarise the national trends in the treatment of haemophiliacs with inhibitors and then to address more specifically the current views and approaches of the directors of the major haemophilia centres to the treatment of their patients, with particular emphasis on their attitudes towards Hyate:C.

E.A.W. 2.11.84

The usage of FEIBA increased in 1982, but fell back in 1983 and has now been overtaken by Hyate:C.

Porcine FVIII is the only product to have shown a marked and consistent increase in usage, over the 3 years. (N.B. Hyate:C was first used clinically in June 1980).

Table 2 shows the sales of Hyate:C in the U.K. for 1981-84 broken down by centre. Discrepancies between sales and usage presumably reflect stock levels in some centres. It can be seen from Table 2 that the majority of sales are made to the reference centres.

2. THE REFERENCE CENTRES - CURRENT ATTITUDES TOWARDS USE OF HYATE:C

The optimal approach towards the use of Hyate:C is probably that described by Kernoff et al (see Table 3). It should be noted that this is a policy for initial management, rather than for long-term management. In practice the Royal Free use NHS FIX quite extensively - partly for financial reasons since the FIX is 'free'. However, the scheme shows the areas in which treatment with Hyate:C may be considered appropriate.

1) The Royal Free Hospital, London. Dr. Peter Kernoff & Dr. Ted Tuddenham

The Royal Free have 18 patients with FVIII inhibitors; of these about 11 are classified as 'low-titre low responder' patients and are generally managed successfully with human FVIII.

Of the remaining 7 patients, 2 were classified as 'high responders' to human FVIII, but were found to show little or no immune response to Hyate:C . One of these patients is treated prophylactically with Hyate:C on a home-care basis, whilst the other received Hyate:C for most of his bleeds, but NHS FIX for some minor ones (for financial reasons).

The other 5 high responder patients are treated with NHS FIX rountinely on a home-care basis. This has the advantages for the patient of the psychological benefit of being on home-treatment and also of not needing to attend the centre and thus being able to rest the bleed.

In addition, treatment with Factor IX allows the antibody level to subside so that, in the event of major bleeds or surgical procedures, the patient can be treated more effectively, usually with porcine FVIII. Four out of these 5 patients have at some time been treated with Hyate:C.

The Royal Free have never used Autoplex and have not used FEIBA for several years. They have considered using plasmapheresis in conjunction with porcine FVIII in high titre antibody patients but because the procedure is difficult and time consuming, they have not done so as yet.

11) Manchester Royal Infirmary - Dr. IrvineDelamore & Dr. Richard Wensley

MRI have 16 inhibitor patients of whom 14 are normally treated with either human FVIII or human FVIII and plasma exchange. Plasma exchange is normally effective for inhibitor titres of up to 50 Old Oxford units, and is used for major bleeds or surgery when the inhibitor titre is too high to be overcome by factor VIII alone.

In other circumstances an immune tolerance regimen is favoured whereby on presentation with a bleed the patient is given a minimum of 20,000 u FVIII over the first 5 days to produce the maximum anamnestic response and then 250 u is given every other day, until the inhibitor is suppressed. Manchester claim to have reduced the inhibitor titre in 13 out of 14 of the patients using this regimen.

Two other patients have high titre inhibitors. They were previously treated in the Autoplex trial, but would not be treated again with Autoplex. Hyate:C has beensent to them for antibody assays and if the results are favourable, these patients would probably be treated with Hyate:C in future.

Comments

MRI has a fairly idiosyncratic approach to the treatment of inhibitors. They consider the use of activated or non-activated FIX 'almost

unethical' in view of its low degree of efficacy. They have no fundamental objections to using porcine FVIII but don't feel that they are likely to have the need to use it very often. They are, however, very interested in using it in 'virgin' non-inhibitor patients, but see cost as being the main drawback in this area.

III) University Hospital of Wales, Cardiff. Prof Arthur Bloom

Cardiff have 13 inhibitor patients, 8 of whom are treated with human FVIII routinely. (3 of these rarely bleed and so are rarely treated at all).

Five patients are 'high responders'. For minor to moderate bleeds they are treated with NHS FIX followed by FEIBA if the former is ineffective. The rationale is to keep the inhibitor titre as low as possible. If FEIBA fails, either human or porcine FVIII is given depending on the relative inhibitor titres. For severe bleeds, porcine or human FVIII would be considered much sooner.

The main restraint in using porcine FVIII more readily in these patients is cost.

Three patients in Cardiff have been treated with Hyate:C as part of the European clinical trial.

IV) St. Thomas' Hospital, London. Dr. Geoff Savidge

St. Thomas' have 18 inhibitor patients of whom 14 are treated with human FVIII, for most bleeds. The remaining 4 are very high responders (antibody levels going up to 1,000 - 2,000 B.U.) and these have been treated with FIX or Autoplex for minor bleeds and human FVIII or Autoplex for major bleeds.

Dr. Savidge has been reluctant to use porcine FVIII in the past,but claims to have been reassured by recent publications and by the approval of our UK Product Licence.

St. Thomas' have a very aggressive approach towards surgery in haemophilia and carry out a large number of joint-replacement operations. Porcine FVIII is an obvious choice for surgery in inhibitor patients and Dr. Savidge intends to use it if the need arises. He is obtaining some equipment from Sweden to enable him to carry out extracorporeal adsorption of antibody to immobulised Protein A (described by Nilsson et al in Blood in '81) and hopes to have the system operating by mid 1985. This will enable him to carry out surgery on the high-titre inhibitor patients in which case he will use porcine FVIII as one of forms of replacement therapy.

Dr. Savidge considers that the most important restriction on wider usage of porcine FVIII is cost - particularly relative to human FVIII.

V) The Churchill Hospital, Oxford - Dr. Charles Rizza

Oxford is by far the largest haemophilia centre in the country, having 34 inhibitor patients registered. Of these, only 24 ever present for treatment, the remainder preferring to manage bleeds conservatively at home.

The policy for treatment in Oxford is to give Human FVIII on an episodic basis, irrespective of the patients inhibitor titre. Dr. Rizza maintains that, not only is the FVIII haemostatically effective despite the fact that recovery in the plasma cannot be measured, but over a period of time the inhibitor level will diminish in at least some of the patients. (Rizza et al Brit. J. Haem 52 13 1982)

In an emergency if human FVIII appears to be ineffective, he uses porcine FVIII. He would like to have a stock available in the hospital, but

could only do so on a 'sale or return' basis, because their usage is so infrequent. He would also consider using NHS FIX if human FVIII failed, but has not done so yet.

He has never used either Autoplex or FEIBA.

His only reservation about the use of porcine FVIII is cost.

VI) Royal Victoria Infirmary, Newcastle upon Tyne, Dr. Peter Jones

Newcastle have 11 inhibitor patients, 8 of whom are treated with human FVIII and 3 with NHS FIX (2 on prophylactic home treatment.)

Dr. Jones considers porcine FVIII the first choice if either of the other forms of treatment fails and is relatively unconcerned about price. considering that in an emergency the cost can be justified.

His greatest concern about using porcine FVIII for a prolonged period is the development of 'resistance' to the product. The publication of the French experience with long term prophylaxis may help to allaythis concern to some extent.

He would like us to consider the possibility of modifying the porcine FVIII molecule (as was done with insulin) to prevent resistance occuring - he then feels that there would be a very much wider application for the product.

Dr. Jones currently holds a stock for clinical trial purposes, but in future would like to have a small stock on a 'sale or return' basis.

VII) Edinburgh Royal Infirmary. Dr. Chris Ludlam

There are 10 inhibitor patients registered in Edinburgh, but because of the former centre director's policy of conservative treatment, many rarely present for treatment of bleeds. However, when they are treated the policy is to use human FVIII for low titre antibodies, FIX for minor bleeds with high-titre antibodies and if the antibody cross-reactivity is favourable, porcine FVIII for major bleeds in high titre

patients, or FEIBA if Hyate:C is not appropriate.

The cost is especially relevant in Scotland, because both FVIII and FIX are 'free' - Scotland being self-sufficient in production of FVIII — and therefore the relative cost of any other form of treatment is perceived to be much higher. Dr. Ludlam feels he would use the material more readily if it were less expensive.

VIII) Glasgow Royal Infirmary - Dr. Charles Forbes & Dr. Gordon Lowe

Glasgow have 6 inhibitor patients, 4 of whom are regularly managed with human FVIII.

Their policy with the 2 high responder patients has been to treat with FEIBA and/or NHS FIX but they say their policy is changing as a result of favourable reports on Hyate:C in the journals and at meetings and they would now consider Hyate:C to be the first line of treatment for high-titre patients, if the antibody crossreactivity was favourable. They have at least one suitable patient whom they intend to treat with Hyate:C next time he requires therapy.

IX) The Hallamshire Hospital, Sheffield. Dr. Eric Preston

The Hallamshire have 6 inhibitor patients. 3 are treated routinely with human FVIII; one has been on home-treatment with porcine FVIII since 1981, one is treated with Autoplex and FEIBA and one is a previously mild haemophiliac newly diagnosed as having inhibitors, who will probably be treated with Hyate:C.

Dr. Preston admitted to having had reservations about using Hyate:C (despite having had a patient on home treatment for 3 years!) because in 1982 another of his patients was treated with Hyate:C , had a massive anamnestic response and subsequently died of haemorrhage. However, he now recognises that his subsequent reluctance to use Hyate:C was mainly an emotional reaction.

He has promised to look at T-cell subsets and for HTLV III antibody in the patient who has been on Hyate:C alone for 3 years.

X) Royal Victoria Hospital, Belfast. Dr. Elizabeth Mayne

Belfast was our largest customer in 1983, and so clearly have no reservations about using Hyate:C. I have not yet visited the centre to obtain up to date information, but will do so later in the month. However, I did not think it necessary to hold up this report until the information was available as it can be supplied at a later date.

3. OTHER MAJOR HAEMOPHILIA CENTRES - CURRENT ATTITUDES TOWARDS HYATE:C

I) Birmingham - Dr. Frank Hill

Dr. Hill has responsibility for the patients at both the Childrens Hospital and the Queen Elizabeth Hospital and has about 12 inhibitor patients at the former and 8 at the latter. This means that Birmingham have more patients than most of the reference centres. (They were invited to be a reference centre, but declined).

Dr. Hill treats all the patients with human FVIII in a similar way to Oxford. If that fails he uses FIX or FEIBA, but would use porcine FVIII if the crossreactiviity were favourable. He has FEIBA available in the in the pharmacy on a 'sale or return' basis and says he would be more inclined to use Hyate:C if that were similarly available.

He is extremely cost-conscious and would not use Hyate:C unless he thought there was a definite financial advantage in doing so.

II) Lord Mayor Treloar College, Alton - Dr. Tony Aronstam

This is a residential school for handicapped boys of whom a significant proportion are haemophiliacs. Seven of the boys have FVIII inhibitors; 4 are low-responders and are treated solely with human FVIII. The other 3 are high responders; one is treated with high-dose,high-purity human FVIII and the other 2 are treated mainly with NHS FIX and with Autoplex or FEIBA on occasions. Porcine FVIII is also used on occasions.

11) The London Hospital, Whitechapel. Dr. Brian Colvin

Dr. Colvin has 6 inhibitor patients, 3 of whom are low responders, 2 are high responders and one has spontaneously acquired antibodies. His policy is to give human FVIII to all the patients for all bleeds, and if that fails, to use porcine FVIII He has treated 2 patients with Hyate:C to date. (One congenital, one acquired).

The above 3 centres are probably the largest of the non-reference centres. Table 4 summarises the numbers of inhibitor patients at reference and non-reference centres. This list is not comprehensive. A considerable number of other small centres must also be treating inhibitor patients.

4. COMMENTS ON THE FUTURE POTENTIAL FOR HYATE:C

a) All of the reference centre directors were of the opinion that Hyate:C is of value in treating high-responder inhibitor patients, and that if the inhibitor crossreactivity is favourable, it should be the treatment of choice for severe bleeds or surgery. No-one expressed any serious worries about adverse reactions, although potential immunogenicity (i.e. provocation of an anamnestic response) was thought by most to be an important consideration in treating minor bleeds.

b) Most centres thought that cost was the most significant factor in deciding which product to use for a mild bleed, and efficacy and cost when deciding for a severe bleed. The cost of using porcine FVIII relative to using high dose human FVIII was frequently mentioned (porcine being approximately 4 times the price of human) as was the cost relative to FEIBA. (which is currently 20p/unit)

c) Several centres would like to have Hyate:C in stock on a 'sale or return' basis and feel that in that case they would be more likely

to use it in an emergency. FEIBA is currently available on this basis. Three centres use the product sufficiently regularly for this to be unnecessary and four currently hold stocks for clinical trial purposes, but it might be advantageous to make this arrangement available to the other major centres. (A stock of 10,000 units should normally be sufficient).

d) It is clear that all the reference centre directors are well acquainted with Hyate;C and have used it or intend to use it to some extent. It seems likely that there will be a small, but steady increase in this sector of the market as familiarity with and confidence in the product grows.

However, the reference centres account for only 50% of the potential market for Hyate:C. The product has never been actively promoted in the smaller centres (partly because of the restrictions on promotion of an unlicenced product) and although most of the centre directors are aware that the product exists, there must be a considerable potential for increased sales in this area. Exploration of this potential may be made easier because it is rumoured that the reference centre directors intend to work more closely with the centres within their regions in the future, and hope to have a greater influence on treatment policies.

TABLE 1

THE USAGE OF CONCENTRATES IN THE TREATMENT OF HAEMOPHILIACS WITH INHIBITORS IN THE UNITED KINGDOM

YEAR	1981	1982	1983
Total No. of haemophiliacs with inhibitors		266	273
Number treated with concentrate	131	144	128
Number treated without concentrate	7	10	2
Total usage of concentrate per annum in units			
Cryoprecipitate	133,000	87,000	100,000
NHS FV111	1,345,000	763,000	1,299,000
Commerical FV111	4,186,000	5,001,000	4,158,000
Total FV111 Usage	5,664,000	5,851,000	5,557,000
Porcine FV111	924,000	1,183,000	1,513,000
Feiba	1,119,000	1,563,000	1,058,000
Autoplex	336,000	501,000	417,000
NHS F1X	377,000	1,388,000	1,217,000
Usage per annum per patient treated			
Cryoprecipitate	1,015	604	781
NHS FV111	10,267	5,298	10,148
Commercial FV111	31,954	34,729	32,484
Total FV111 Usage	43,236	40,631	43,413
Porcine FV111	7,053	8,215	11,820
Feiba	8,541	10,854	8,265
Autoplex	2,564	3,479	3,257
NHS F1X	2,877	9,638	9,508

F.o.C. — NHS FV111

6-8 p./unit — Commerical FV111

10-14 p./unit — Heat treated FVIII

↑ alpha Hbs free

Immuno 20p. — Feiba

Travenol 40p.? — Autoplex

f.o.c. — NHS F1X

high titre patient usage prob. not Hyate:C

minor bleeds, 50% efficacy but f.o.c. but AIDS

20 K/patient

Heat treated FIX commercial for Christmas disease ~13p./unit

TABLE 2

SALES OF HYATE:C IN THE U.K. 1981-84

	CUSTOMER	UNITS SOLD			
		1981	1982	1983	1984(to date)
4	* Royal Free, London	425,935	1,097,615	399,885	992,835
4	* Royal Victoria Belfast	28,200	117,210	799,795	865,870
4	* Royal Hallamshire, Sheffield	59,950	10,350	61,550	11,800 26p.
3	* Royal Victoria, Newcastle	174,290		34,160	187,550 for
2	* Churchill Hospital, Oxford	42,300		391,105	63,000 25p.
2	* Manchester Royal Infirmary			45,405	990
1	* Glasgow Royal Infirmary			10,920	
3	* U.H.W. Cardiff	17,310		99,830	21,780 for
2	* St. Thomas' London	45,300	30,000		
1	* Edinburgh Royal Infirmary				112,380 for
4	The London Hospital	36,290	64,000	7,410	20,400 30p.
4	Treloar College, Alton	11,400	16,820	10,200	10,080 30p.
1	Foresterhill, Aberdeen			8,120	
3	St. James' Hospital, Leeds	73,610		20,400	77,260 For
1	Queens Medical Centre,Nottingham			6,600	
1	Sick Childrens Hosp. London		5,220		
1	Queen Alexandras,Portsmouth		5,220		
1	Ninewells, Dundee		23,400		
1	Kings College Hosp. London	1,200	10,200		
1	Manchester Childrens Hosp.	1,120			
1	Middlesex Hospital,London	20,280			
1	St. George's Hosp. London	9,000			
1	Sheffield Childrens Hospital	11,700			15,000 30p.
23	Total Units Sold	957,885	1,380,035	1,854,980	2,300,945
		(15)	(10)	(13)	(10)

92

Out of 100

* Reference Centres

5 x (4)
3 x (3)
3 x (2)
12 x (1)

TABLE 3

POLICY FOR INITIAL MANAGEMENT OF PATIENTS WITH INHIBITORS AT THE ROYAL FREE HOSPITAL (Kernoff et al 1984)

Pre-treatment inhibitor level to human FVIII (Bethesda unit)	First choice therapeutic product and dose
<5	Mild/moderate episodes: human FVIII 20-50 u/Kg Severe episodes: Hyate:C 20 - 50 u/Kg
5 - 50	Hyate:c 50- 100 u/Kg
>50	Activated or nonactivated factor IX or Hyate:C if the antibody level against Hyate:C is < 13 old Oxford units.

TABLE 4

DISTRIBUTION OF PATIENTS WITH FVIII INHIBITORS IN THE U.K.

Centre	Total No. of inhibitors	Low responders	High responders
1. Royal Victoria Hospital, Belfast	10	8	5
2. U.H.W. Cardiff	13	6	4
3. Royal Infirmary, Edinburgh	10	6	4
4. Royal Infirmary, Glasgow	6	4	2
5. Royal Free. London	18	11	7
6 St. Thomas', London	18	14	4
7. Royal Victoria, Newcastle	11	8	3
8. Royal Infirmary, Manchester	16	14	2
9. Churchill Hospital, Oxford	34	34	-
10.Hallamshire Hospital, Sheffield	6	3	3
Total	142	102	66
11. Foresterhill, Aberdeen	2	1	1
12. Treloar College, Alton	7	4	3
13. Childrens Hospital & Q.E. B'Ham	20	20	-
14. Addenbrookes, Cambridge	4	4	-
15. Essex County Hosp. Colchester	2	-	2
16. Royal Infirmary, Derby	2	2	-
17. St. James' Hosp. London	5	-	-
18. The London Hosp. London	6	4	2
19. Kings College Hosp. London	2	1	1
20. Sick Childrens Hosp. London	5	5	-
21. The Middlesex. London	4	2	2
22. Lewisham Hospital	2	-	-
23 Royal Infirmary, Leicester	2	1	1
24. Royal Hospital, Liverpool	3	3	-

DISTRIBUTION OF PATIENTS WITH FVIII INHIBITORS IN THE U.K.

Centre	Total No. of inhibitors	Low responders	High responders
25. Childrens Hosp. Manchester	3	-	-
26. Royal Infirmary, Huddersfield	2	2	-
27. Queens Med. Centre Nottingham	2	2	-

Feiba 20p/unit (Immuno)

Autoplex ?60p/unit (Baxter Travenol – Hyland)

Total factor VIII in UK 1983 — NHS = 29.5m units

→ commercial = 35.8m

Cryoprecipitate = 3.0m

~ 8.0p per unit

Armour high purity ~ 15p/unit

Treactivity 30% of human VIII ∴ only 1/3

6 mths — discount starts.

Cost per unit?

Mottram Manufacturing report
Not accepted

HYATE:C

Haemophilia is present in 1:10,000 of the male population. Of these 10% - 15% are patients who develop inhibitor, 30% of patients have a low inhibitor titre and can be treated with human FVIII. 20% of inhibitor patients have a high inhibitor titre and demonstrate cross reactivity with porcine FVIII. Therefore 50% of inhibitor patients are suitable for Hyate:C therapy, and for them it is the treatment of choice.

It is normal for a patient to experience at least one major bleed per year. Therapy will demand a dose of 30,000 - 100,000 units. In addition Hyate:C will be used for elective surgery. Allowing for competition from Autoplex and FIEBA then Hyate:C consumption could be 50,000 units per patient per year.

The theoretical market is therefore:

								Millions of units
U.K.	Population	55 M	Hyate:C	Patients	185	Consumption		9
France	"	54 M	"	"	180	"		9
Italy	"	57 M	"	"	190	"		10
Benelux	"	24 M	"	"	85	"		4
Scandinavia	"	17 M	"	"	60	"		3
Germany	"	60 M	"	"	190	"		10
Spain	"	37 M	"	"	120	"		6
U.S.A.	"	250 M	"	"	850	"		42
Other including E. Europe and Japan								30
			Total Theoretical Market					123

In projecting the possible world wide use of Hyate:C, allowance has been made for registration, clinical trials and introduction.

Units 000's	1983	1984	1985	1986	1987	1988
U.K.	1,800	3,000	4,000	4,000	4,000	4,000
France	750	1,700	2,500	3,000	3,000	3,000
Italy	650	2,000	2,500	3,000	3,000	3,000
Germany	100	1,000	2,000	3,000	3,000	3,000
Scandinavia	-	-	500	750	1,000	1,000
Benelux			500	750	1,000	1,000
U.S.A.	900	-	1,500	3,000	3,500	5,000
Spain	-	-	-	250	1,000	1,500
E.Europe			500	750	1,000	1,000
Other	200	1,000	1,150	1,500	1,500	1,500
Total	4,400	8,700	15,150	20,000	22,000	24,000

1983 Sales include clinical trial usage.

In the U.K. projected maximum use of Hyate:C is less than 50% of the theoretical market on a specified group of inhibitor patients. In European markets, where there is experience of the product maximum use is projected at less than 1/3rd of theoretical. In other countries use is projected between 5% and 25% of theoretical.

PRICING

U.K.

Prices of therapeutic products for haemophilia treatment in the U.K. are low. This results from the influence of free FVIII from Blood Products Laboratory, Elstree. High titre inhibitors are mainly treated with Hyate:C or, FEIBA currently priced at 30p per unit prior to the issue of a product licence, and Autoplex free for clinical trials prior to the issue of a product licence.

Intermediate level inhibitor patients are treated conservatively or with Hyate:C.

Low inhibitor level patients are treated with human at no cost or up to 15 pence per unit or Hyate:C. After a product licence has been granted the U.K. list price of Hyate:C will be set at 40 pence per unit.

The Target average selling price allowing for current contracts and quantity discounts will be 25 pence per unit in 1984.

(22.5 pence to be budgetted) and 30 pence target in 1985

(25 pence to be budgetted) increasing to 35 pence

in 1986-88 (30 pence to be budgetted).

U.S.A.

Our negotiations with Cutter have been based on the premise that they will require a 50% margin for distribution after importation, packaging and Quality Assurance expenses. The target selling price from Cutter to hospitals will be 65 US cents. Providing the value of Sterling does not exceed £1 = US $ 1.45 then Speywood will obtain an F.O.B. in excess of £0.20. We will attempt to negotiate a 20 pence per unit floor price, and this value will be used in our budgets.

EUROPE

Our target for Europe will be a local price in each territory equivalent to 40 pence per unit and the provision of a 25% commission to the distributor. This arrangement appears possible in France and Germany. Social security funding for drugs is however, under severe pressure in other European Countries and a 30 pence F.O.B. may not be possible.

Contractural committments in Italy will limit the price to 22.5 pence for 1984, and prior to INAM listing purchases have to be financed by hospital discretionary funds.

In view of the speculative nature of European pricing a 20 pence per unit forecast is included in the budget 1984-88.

CONCLUSION

The Sales forecast for Hyate:C may look conservative but this is necessary in view of the possible delays that could occur due to

The time taken to appoint Distributors

The delays that may occur in obtaining product registration

The difficulties that could be experienced in obtaining price approval.