ACVSB 4/3

Report on the Meeting in Rome to Discuss Chiron Testing

Attached is the report prepared by Dr Gunson on the meeting which took place in Rome on 14-15 September.

U.K. ADVISORY COMMITTEE ON TRANSFUSION TRANSMITTED DISEASES

ANTI-HCV TESTS

1. **BACKGROUND**

Much of the information on which the conclusions and recommendations given in this paper were derived from presentations at the first International Meeting on the Hepatitis C virus, Rome, 14th-15th September 1989.

Using DNA technology, the Chiron Corporation have cloned part of the genome of non A, non B virus (NANBH). By inserting this DNA sequence into a plasmid they have produced a polypeptide which has been used as an antigen to develop a test for the antibody to the agent responsible for NANBH. It has been claimed that a positive result with this test is an indicator of infection with the NANB virus and it has been recommended that the test should be applied to all blood donations.

2. **PURPOSE OF THE MEETING**

2.1 Representatives from Europe, USA, and Scandinavia met in Rome and the data presented comprised preliminary investigations of the use of the antibody test (now called the anti-HCV test and marketed by Ortho Diagnostics) in patients suffering from clinically diagnosed NANBH and in blood donors.

2.2 Several questions required an answer.

2.21 Does the anti HCV test detect the presence of a virus which causes NANBH?

2.22 Does a positive anti-HCV test indicate infection to a virus which causes NANBH?

2.23 Will the routine use of the anti-HCV test to test blood donors reduce the incidence of transfusion transmitted NANBH?

2.24 Will a positive result in the anti-HCV test indicate that a blood donor will transmit NANBH?

2.25 Does a negative result in the anti-HCV test indicate that a blood donor will not transmit NANBH?

2.26 What policy should be followed when blood donors are found anti-HCV positive?

2.27 What is the status of the non-specific tests for NANBH (ALT and anti-HBc) now that the anti-HCV test is available?

3. COMMENTS ON TESTS ON PATIENTS DEFINED AS SUFFERING FROM CLINICAL NANBH

3.1 Studies carried out by retrospective testing on stored samples on groups of patients suffering from NANBH, showed that the first abnormality found was usually a raised level of serum alanine aminotransferase levels. Positive anti-HCV tests were found in 60-80% of patients with a seroconversion between 10 and 52 weeks (mean 21/22 weeks). Seropositives with these frequencies were found with both transfusion transmitted NANBH and sporadic, or community acquired NANBH. A significant number of patients with carcinoma of the liver were also anti-HCV positive. In general, 70-80% of patients suffering from treated (or severe) haemophilia were anti-HCV positive.

3.2 Table 1 gives the percentages of anti-HCV positives reported by Centres following studies on patients suffering from various illnesses and intravenous drug use.

3.3 Persistence of anti-HCV was found commonly with chronic NANBH, but the test may become negative; in one case reported the negative result occurred after 9 years. Several presentations also included the tracing of blood donations which had been given to patients suffering from transfusion transmitted NANBH. Generally, in 80% of cases an anti-HCV positive donor was found.

3.4 Although the majority of studies had very few patients due to the short time that the test has been available, they showed consistent results. It seems that anti-HCV seropositivity indicates that a patient is suffering from NANBH and that the test is detecting a viral marker associated with NANBH. If a second agent causes NANBH it was considered that this could only account for 10-20% of cases.

3.5 Those patients with clinical NANBH with negative anti-HCV test may be due to low levels of circulating virus. This probably accounts for the increased seropositivity in patients who are suffering from chronic hepatitis, but no titres were presented to support this.

4. ANTI-HCV TESTS ON BLOOD DONORS

4.1 Several countries have tested blood donations for anti-HCV and the results are summarised in Table 2. In many countries the numbers tested are small, but there is consistency in the number of seropositives, usually between 0.5 and 1.0 per cent. The exception is Italy, well known for high prevalence of NANBH where considerably higher seropositivity was found in parts of that country.

4.2 The results in the USA are worthy of comment since it has always been considered, as a result of previous studies, that the transfusion transmission of NANBH is higher than in Europe. The results of donor testing in four sites in the USA (not specified) reveal seropositivity comparable with that found in Northern European Countries.

The previous studies on NANBH in the US were carried out on samples collected in the late 1970's and early 1980's. The changing pattern of donors following self-exclusion for HIV risk categories may have led to a change in the US donor population.

4.3 The tests carried out in the US have been on voluntary blood donors. No data is available on professional donors used by pharmaceutical companies.

4.4 It cannot be assumed that all anti-HCV positive donors will transmit NANBH. A study in Spain showed that not all recipients of an anti-HCV positive unit of blood developed NANBH and the predictive value was approximately 60%, which is much higher than that for non-specific tests (circa 30%).

5. RELATIONSHIP OF ANTI-HCV TESTS WITH NON-SPECIFIC TESTS FOR NANBH

5.1 Several studies included the correlation of ALT and/or anti-HBc with anti-HCV positives. In Tables 3a and 3b detailed results are given for the U.K. In Table 3a the number and percentage of raised ALT values and anti-HBc positive donor samples found in a multicentre trial (Bristol, Manchester and North London RTCs) in England and a Scottish study are presented. The results of testing donor samples with raised ALT values or anti-HBc positive from these Centres for anti-HCV are given in Table 3b. In Table 4 a summary of similar tests for anti-HCV in samples with raised ALT and anti-HBc positives found in Centres in several countries, is presented.

5.2 It can be seen from these Tables that there is some association between a raised ALT and anti-HBc positive and the seropositivity for anti-HCV in that a higher percentage of anti-HCV positives is found in samples selected for abnormal non specific markers It is also apparent that the majority of anti-HCV positives do not have non-specific markers.

5.3 A detailed evaluation of the HCV antibody test system has been carried out by the Scottish National Blood Transfusion Service and the results are given in Appendix II. This study comprises tests on randomly selected blood donors, correlation between raised ALT and anti-HCV and a technical evaluation of two batches of test kits. In this study it was estimated that use of the test would have prevented only 21% of

transfusion transmitted NANBH, a lower figure than reported elsewhere. This difference may partly be explained by the limited clinical data associated with retrospective studies and/or assay differences. On the other hand, it may prove to be real.

6. CONCLUSIONS

The answers to the questions posed in paragraph 2.2 could be answered fully, partially or not at all from the data presented.

6.1 It seems certain that the anti-HCV test detects a viral marker associated with NANBH. With recovery, the test may become negative, but with chronic disease and complications such as carcinoma of the liver, a high percentage of patients remain anti-HCV positive.

6.2 From donor/recipient studies it seems that anti-HCV positivity means that the blood of the person may be infectious for NANBH, although not in all instances.

6.3 Evidence presented suggested that routine anti-HCV tests on blood donations would reduce the incidence of transfusion transmitted NANBH. The clinical impact of this will, of course, depend on the incidence of transfusion transmitted NANBH in a particular country.

6.4 Anti-HCV positivity in a blood donor may not necessarily mean that the seropositive donor transmits NANBH. An unknown proportion also may be false positives.

6.5 A confirmatory test is not yet available. The Chiron Corporation have issued a statement concerning confirmatory tests, as follows.

> "The question of a confirmatory test for anti-HCV has been an issue for several months. The circular argument of a confirmatory approach utilizing the same antigen as the screening test has been brought to everybody's attention.
>
> Nevertheless, Ortho and Chiron are pursuing feasibility studies of a RIBA (Recombinant Immunoblot Assay) for HCV. The current evaluations are centered around three antigens: HCV antigen produced in yeast, HCV antigen produced in E coli, and SOD produced in yeast. SOD (superoxide dismutase) is used as a fusion protein to facilitate an easier expression of the CHV antigen and can lead to some very rare cases of nonspecific reactivity.
>
> Ortho and Chiron will provide information about the value of such an approach for the clarification of HCV positive samples as soon as available."

6.6 The finding that in acute NANBH the anti-HCV test may become negative after a period of time has not yet been correlated with loss of infectivity. If routine screening of blood donations is commenced, a proportion of the anti-HCV negatives will be those who have been seropositive and have converted to seronegative. Some donors who are found initially seropositive may be seronegative on a future occasion.

6.7 Although there is an association of anti-HCV seropositivity with abnormal non-specific tests (raised ALT and anti-HBc positives) it is apparent that the majority of anti-HCV positives do not possess non-specific markers. It has been known for some time that the non-specific markers exclude far more donors than necessary to prevent transmission of NANBH. This is more in most countries than will be excluded for anti-HCV positivity. This is exemplified for the U.K. in Tables 3a and 3b.

Information received indicated that in the USA (and possibly in some European countries) ALT and anti-HBc testing would not be withdrawn when anti-HCV screening commenced. The reasons given were that the ALT rise may occur earlier than anti-HCV positivity and thus the ALT was perceived as a back-up to detect at least part of the "window period". A second reason was that the ALT may detect a second virus causing post-transfusion NANBH which may not be detected using the anti-HCV test.

7. RECOMMENDATIONS

7.1 Routine screening of blood donations for anti-HCV should be introduced when practical, since there is, even from the early international studies, the probability that the incidence of transfusion transmitted NANBH will be reduced.

The Committee is asked to approve the routine testing of blood donations for anti-HCV in principle and request the National Directors in England and Scotland to arrange for the simultaneous introduction of the tests at an appropriate time when a policy for counselling and management of the seropositive donors has been defined.

7.2 A confirmatory test for seropositive blood donors is urgently needed. The one proposed by the Chiron Corporation has limitations. Every effort must be made to ensure that a confirmatory test is available in the U.K. at the time routine donor screening is introduced.

It should be noted that significant additional manpower and other resources will be required in reference laboratories.

7.3 The Ortho/Chiron anti-HCV screening test is not yet licensed by the FDA and routine testing will not commence in the USA until such a license is obtained. This is expected in the first half of 1990. The routine use of the test for blood donations in the U.K. should not commence before an FDA licensing procedure is effected.

7.4 All U.K. tests to date have been performed on library (frozen/thawed) samples. The quality of the performance of the anti-HCV test using such samples may be in doubt. Pilot studies involving the routine prospective use of the test in RTCs should be established as soon as possible. This will not only allow an evaluation of the test on freshly collected blood samples, but also an assessment of how the test can be integrated into working practices. An application for £25,000 has been made to DH to carry out such studies in three RTCs.

7.5 The routine introduction of non-specific tests should be deferred, unless this is necessary for the acquisition of product licences in the U.K. for fractionated plasma products. It is the intention of the Committee to keep this topic under close review.

7.6 An estimate of the financial consequences of introducing routine anti-HCV tests on blood donations in England and Wales is given in Appendix I.

Separate data for Scotland will be submitted to SHHD in due course.

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CHAIRMAN

10.10.89.

TABLE 1

Data from abstracts submitted to 1st International Meeting on Hepatitis C: Rome, September 1989

PREVALENCE OF ANTI HCV % REPORTED, BY CENTRE, IN;

Centre	Haemophiliacs	Homosexuals	IV Drug Users	Acute (<90dd) Hepatitis NANB	Post acute (>90dd) NANB Hepatitis	PINANB Chronic Hepatitis	'Crytogenic' Chronic Hepatitis	Non HBV associated Hepatocellular Carcinoma
Turin						87	71	37
Milan	82					70	68	65
Bari						92	74	
Padua				28	48	92	83	60
Palermo						90	69	
Naples						67	{76	
							{69	62
Rome							79	
Brescia		23	75					
Genoa								
Bern								
Copenhagen	82							
Amsterdam	77							
(Surinam)								
Vienna			80	10	45			
Berlin/Munich						75	75	
Frankfurt	70	33	32			74		
Munich	80					79	72	
N Germany								
S Germany								
Barcelona						88	{78	
							{82	
Lyon					45	45	74	43
Paris	66							
Budapest								
UK		{HIV +26	81	29				
		{HIV - 4						
USA		3	57		70	80		

ANTI-HCV TESTING OF BLOOD DONORS

COUNTRY		No Tested	Repeatable anti-HCV+	%
AUSTRIA		617	4	0.65
BELGIUM		2000	11	0.55
DENMARK		600	2	0.3
FED.REP. GERMANY		3123	13	0.24-0.74
FINLAND	(1)	428	1	0.2
	(2)	571	3	0.7
FRANCE		25,137	17	0.52-0.78
ITALY -	Turin	420	16	3.8
	Naples	273	4	1.5
	Milan	427	6	1.4
	Ferrara	318	7	2.2
	Padova	505	5	1.0
NETHERLANDS		5117	37	0.72
YUGOSLAVIA		718	4	0.56
SWITZERLAND		884	3	0.34
UK -	Bristol	3032	11	0.36
	Manchester	3642	25	0.69
	N. London	3010	25	0.83
USA -	1	2000	12	0.6
	2	1999	20	1.0
	3	1999	8	0.4
	4	4000	15	0.4

TABLE 2

CENTRE	NO. TESTED FOR ALT AND/OR ANTI-HBc	NO. WITH RAISED ALT(%)	NO ANTI-HBc POSITIVE (%)
Bristol	3,015	137 (4.54)	17 (0.56)
Manchester	3,164 3,690	63 (1.99)	22 (0.59)
N. London	3,036	93 (3.06)	26 (0.86)
Scotland	10,799	313 (2.90)	-
Total (1) (2)	20,014 9,741	606 (3.03)	65 (0.67)

Table 3(a) The number (and percentages) of random blood donor samples found to have an elevated serum alanine aminotransferase (ALT) level and anti-HBc positivity from three English RTCs and from Scotland.

CENTRE	NO. ANTI-HCV TESTED	NO. POS. (%)	NO. RAISED ALT	NO. ANTI-HCV POS. (%)	NO. ANTI-HBc POS.	NO. ANTI-HCV POS. (%)
Bristol	3,032	11(0.36)	114	1(0.87)	16	0
Manchester	3,642	25(0.69)	49	1(2.04)	24	0
N. London	3,010	25(0.83)	93	3(3.23)	22	1(4.5)
Scotland	2,745	13(0.47)	167	4(2.40)	-	-
Total	11,615	72(0.62)	423	9(2.12)	62	1(1.6)

Note: Elevated ALT and anti-HBc positive was found in only two donors in the three English RTCs; one was anti-HCV positive (N. London) and one was anti-HCV negative (Manchester).

Table 3(b) The number (and percentages) of random blood donor samples found anti-HCV positive and comparable data with donor samples having a raised ALT and anti-HBc positivity from three English RTCs and from Scotland.

COMPARISON OF NON-SPECIFIC TESTS WITH ANTI-HCV TESTS

COUNTRY	No. Tested		% anti-HCV+
FRANCE	206	abnormal ALT	5.34
	932	anti-HBc pos.	2.36
ITALY -			
Padova	505	anti-HBc	0.6
		anti-ABC + anti-HBS	5.9
		normal ALT	0.8
		abnormal ALT	7.7
Turin	420	normal ALT	2.0
		abnormal ALT	6.0
Naples	411	anti-HBc neg.	1.5
		anti-HBc pos.	7.9
Milan	427	abnormal ALT anti-HBc pos.	10.0
SWITZERLAND	1080	normal ALT	0.34
		abnormal ALT	4.1
USA	9998 cumulative results	raised ALT	12.7
		anti-HBc pos.	7.3
		raised ALT + anti-HBC pos.	9.1
		normal ALT + anti-HBc neg.	70.9
UK (ENGLAND)	8870	raised ALT -	
		Manchester	2.04
		Bristol	0.87
		N. London	3.23
		anti-HBc pos. -	
		Manchester	0
		Bristol	0
		N. London	4.5
		normal ALT and anti HBc neg.	90.06
SCOTLAND	167	raised ALT	2.4

TABLE 4

APPENDIX I

ESTIMATED ANNUAL COSTS OF ROUTINE ANTI-HCV TESTS ON BLOOD DONATIONS IN ENGLAND AND WALES

	£
Approx. 2.3 million tests at £1.70 + VAT	4,500,000
Staffing costs; £20,000 per RTC	320,000
Counselling and follow-up of donors: 0.5 wte clinical assistant 1 secretary	300,000
Replacement of lost donors, say	500,000
	5,620,000

It is difficult to estimate costs in detail and the above may be an under-estimate since there will be some RTCs where additional equipment will be required and the number of positives and loss of donations is higher than the national average. In these RTCs the loss of donations which will have to be replaced could exceed the average and this will result in additional staff and donor replacement tests.