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REPORT ON 1ST INTERNATIONAL MEETING ON THE HEPATITIS C VIRUS

Rome - 14th/15th September 1989

1. BACKGROUND

Using DNA technology, the Chiron Corporation, a division of Johnson and Johnson, have cloned part of the genome of non A, non B virus (NANB). Using a polypeptide which has been used as an antigen a test for the antibody to NANB has been developed. 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 and the presentations comprised preliminary investigations of the use of the antibody test (now called the anti-HCV test) in patients suffering from clinically diagnosed NANBH and in blood donors.

2.2 From my own point of view, several questions required an answer and some of the presentations addressed these, viz:

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 OF PATIENTS DEFINED AS SUFFERING FROM CLINICAL NANBH

3.1 Anti-HCV tests carried out on groups of patients suffering from NANBH, mostly carried out on retrospective testing showed that the first abnormality found was a raised level of serum alanine aminotransferase levels. Positive anti-HCV tests were found in 60-80% 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% patients suffering from treated (or severe) haemophilia were anti-HCV positive.

3.2 Persistence of anti-HCV was found commonly with chronic NANBH, but the test may become negative after acute NANBH and 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.

3.3 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 indeed is detecting the presence of a virus which causes NANBH. If a second agent causes NANBH it was considered that this could only account for 10-20% of cases.

3.4 Those patients with clinical NANBH with negative anti-HCV test may be due to low levels of circulating virus, which is not a good immunogen. This probably accounts for the increased seropositivity in patients who are suffering from chronic hepatitis, but no titres were presented.

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 1. In many the numbers tested, to-date, are small, but there is a 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 the south 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 results comparable with those in Northern European Countries.

The 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 difference in the US donor population. One factor which may have been contributory is that in one study 76% seropositives have been found in tests on intravenous drug users.

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

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. The results are summarised in Table 2.

5.2 It can be seen that there is a correlation between a raised ALT and anti-HBc positive and the seropositivity for anti-HCV. However, it is also apparent that the majority of anti-HCV positives do not have non-specific markers. One conclusion that can be drawn from this is that the non-specific markers exclude many more donors than is necessary, a factor which has been recognised for some time.

5.3 The above conclusion assumes that all anti-HCV positives will transmit NANBH. This is not so. 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%).

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 anti-HCV does detect virus which causes NANBH. With acute disease and 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 seroepidemiological studies it seems that anti-HCV positivity means that the blood of the person may be infective for NANBH.

6.3 Evidence presented suggested strongly that routine anti-HCV tests on blood donations would reduce by 80% the incidence of transfusion transmitted NANBH. The clinical effect of this will, of course, depend on the incidence of transfusion transmitted NANBH.

6.4 Anti-HCV positivity in a blood donor may not necessarily mean that the seropositive donor may transmit NANBH. In a population where seropositives are of low frequency an unknown proportion may be false positives, e.g. an antibody to yeast.

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."

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

6.6 Although there is a correlation of anti-HCV seropositivity with abnormal non-specific tests (raised ALT and anti-HCV 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; this is more in most countries than will be excluded for anti-HCV positivity.

Several speakers from the USA stated that ALT and anti-HBc tests on blood donations would continue. The reasons given were that the ALT rise occurred earlier than anti-HCV positivity and that this test may detect a second virus causing NANBH post-transfusion. The first of these premises can be questioned. The statement may be true for patients at risk, but is unlikely to be so for a stable population of blood donors. The second can be questioned also, in at least the majority of instances.

6.7 The present anti-HCV test is of limited range and sensitivity and has been compared with using a test such as the detection of the e antigen for diagnosis of a carrier for HBV disease.

7. RECOMMENDATIONS

7.1 It will be difficult not to introduce routine screening of blood donations for anti-HCV since there is, even from the early studies, the possibility that the incidence of tranfusion transmitted NANBH will be significantly reduced. Although this disease is usually mild with recovery, some patients may develop cirrhosis of the liver.

7.2 A confirmatory test for seropositive blood donors is urgently needed. The one proposed by the Chiron Corporation has limitations, but will at least be able to resolve false results due to cross-reaction with yeast antibodies and superoxide dismutase.

7.3 The test is not yet licensed by the FDA and routine testing will not routinely commence in the USA until licensed by FDA, which is expected in the first half of 1990. It could be argued that the routine use of the test for blood donations in the UK should not commence before such a licensing procedure is effected.

7.4 The time taken to complete the current test is three hours; this is a long time when the urgent release of platelets is required. All tests to date have been performed on library samples and routine introduction is urgently required.

7.5 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 handling the seropositive donors has been defined.

7.6 The routine introduction of non-specific tests should be deferred, unless this is necessary for the licensed production of blood products in the U.K.

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

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NATIONAL DIRECTORATE

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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	0.8
ITALY -	Turin	420	16	3.8
	Naples	411	19	4.6
	Milan	427	6	1.4
	Fenara	318	7	2.2
	Padora	505	5	1.0
NETHERLANDS		5117	37	0.72
YUGOSLAVIA		718	4	0.56
SWITZERLAND		884	3	0.34
UK -	Manchester	2910	22	0.75
	Bristol	2950	12	0.40
	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 1

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COMPARISON OF NON-SPECIFIC TESTS WITH ANTI-HCV TESTS

COUNTRY	No. Tested		% anti-HCV+
ITALY -			
Padora	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	8870	raised ALT -	
		Manchester	2.0
		Bristol	0.87
		N. London	3.28
		anti-HBc pos. -	
		Manchester	0
		Bristol	0
		N. London	3.7
		raised ALT + anti-HBc pos.	33 (only 3 donors)

TABLE 2

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 the number of positives and loss of donors is higher than the national average and in these RTCs the above staffing levels may have to be exceeded.