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Report

Re-Evaluation of HCV Ab Detection Kits Approved for Marketing in Japan

Committee for Evaluation of In Vitro Diagnostic Devices,
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INTRODUCTION

As of 2001, the Japanese Ministry of Health and Welfare (Ministry of Health, Labour and Welfare at present; MHLW) has approved approximately 30 diagnostic kits for detection of antibodies against various epitopes of HCV (Hepatitis C virus) in clinical settings. All of them are commercially available in Japan. In order to provide medical personnel with up-to-date information on each kit's characteristics, such as its sensitivity and specificity, in order to enable them to choose appropriate HCV Ab (antibody) detection kits, National Institute of Infectious Diseases (NIID), according to the guidance of the MHLW, has re-evaluated the diagnostic kits provided by manufacturers/distributors. The present reports are the results of the re-evaluation of HCV Ab detection kits.

METHODS

HCV Ab detection kits evaluated in this study (Table 1)

In this study, we categorized HCV Ab detection kits into the following four groups according to principle/procedure used; (A) IRMA (Immunoradiometric assay), (B) Immunochromatography, (C) Agglutination/aggregation (including Passive Hemagglutination Test, Particle Agglutination Test, Latex Photometric Immunoassay, and Particle Agglutination Mediated Immunoassay, designated as PHA, PA, LPIA, and PAMIA, respectively), (D) EIA (Enzyme Immunoassay), (E) CLEIA/CLIA (Chemiluminescent [enzyme] immunoassay), (F) EV-FIA (Evanescent wave fluoro immunoassay), and (G) RIBA (Immunoblot). These kits were also categorized into four groups according to another criterion, i.e., the HCV antigens utilized for detection of anti-HCV Ab, namely, Core Ab detection kit, 1st generation kit (NS3-NS4 protein), 2nd generation kit (NS3-NS4 protein + Core protein), and 3rd generation kit (NS3-NS4 protein + Core protein + NS5 protein). Listed in Table 1 are the product names, manufactures/distributors, and assay objects.

Test Procedure

Test samples utilized in the present re-evaluation tests were as follows:

① Negative samples: Eighteen HCV Ab-negative sera, which have been utilized at NIID for in-house qualification tests, and one HCV Ab-negative sample (Accurun 1 multi-marker negative control serum) purchased from Boston Biomedica Inc. ([BBI], West Bridgewater, Mass., USA).

② HCV Ab low titer panel: PHV-105 (15 samples) purchased from BBI.

③ HCV Ab mixed titer panel: Twenty HCV Ab-positive sera kept at NIID.

④ HCV Ab seroconversion panels (genotype 1b): PHV-906 (7 samples) and PHV-907 (7 samples) purchased from BBI. Sample numbers 1 to 7 indicate the order of bleedings during the course of infection.

The above 68 samples were analyzed independently twice using each test kit, and the results are shown in Table 2. The results of the 1st generation kit, the Core-Ab detection kits (3 kits), and the RIBA3 kit were included in the present report as references, although they are not intended for diagnostic purposes. In the result chart, "generation" and "principle/procedure" of the kits were indicated so that one can compare the results obtained by using different kits within the same category. The results obtained from the RIBA3 kit were also included in the charts, which would be useful for interpretation of the antigen specificities detected by each kit. The RIBA3 results are expressed as intensities of bands (levels 1 to 4) detected on the test strips. "+/−" represents a visible band with an intensity of less than level 1. Empty boxes indicate that no visible band was detected. Interpretation of the RIBA3 results is as follows: REACTIVE = level 1 or greater reactivity to any two HCV recombinant antigens, INDETERMINATE = Bands of level 1 or greater reactivity are present but the pattern does not meet the criteria for REACTIVE, and NONREACTIVE = No bands of level 1 or greater reactivity are present.

RESULTS AND DISCUSSION

Results of each of the 25 kits, including three core Ab-detection kits (Nos. 1, 2, and 3), one 1st generation kit (No. 4), and one RIBA3 kit (No. 25), are shown in Table 2. As a whole, there are no noticeable differences in sensitivities as well as specificities between the 2nd and 3rd generation kits. In other words, we could not obtain any evidence indicating that the 3rd generation kits are more sensitive than the 2nd generation kits. These results support the previous suggestion that the inclusion of the NS5 antigen in the 3rd generation kits does not improve the specificities/sensitivities of the kits (Vernelen, K. et al. [1994]: Lancet, 343, 853; Goffin, E. et al. [1994]: Lancet, 343, 853-854). There are substantial differences in the sensitivities among kits within the same generation. It is likely that variation of some HCV antigens, other than the NS5 in the 3rd generation kits, might be responsible for such differences. For example, when the seroconversion panel PHV-906 was tested, the kit No.13 judged all the samples negative, although the same samples were judged positive by the kits No.10 and No.11, which belong to the same category as the kit No.13 (Table 2). On the other hand, when the PHV-907 panel was tested, the kit No. 13 seemed to be more sensitive than the kits No. 10 and No.11 (Table 2). These

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Table 1.

(A) Core-Ab detection kit

No.	Name	Manufacturer/Distributor	Method	Detection of HCV Ab in
1	Ortho HCV Core-Ab IRMA test	Mitsubishi Kagaku Medical, Inc.	IRMA	serum/plasma
2	SMITEST (HCV Core Ab) ELISA	MEDICAL & BIOLOGICAL LABORATORIES CO., LTD.	EIA	serum/plasma
3	Lumipulse II Ortho HCV Core-Ab	FUJIREBIO INC.	CLEIA/CLIA	serum/plasma

(B) 1st generation kit

No.	Name	Manufacturer/Distributor	Method	Detection of HCV Ab in
4	Ortho HCV IRMA test	Mitsubishi Kagaku Medical, Inc.	IRMA	serum/plasma

(C) 2nd generation kit

No.	Name	Manufacturer/Distributor	Method	Detection of HCV Ab in
5	ABBOTT HCV PHA 2nd Generation	DAINABOT CO., LTD.	PHA	serum/plasma
6	SERODIA-HCV	FUJIREBIO INC.	PA	serum/plasma
7	Ortho HCV Ab PA test II Auto	FUJIREBIO INC.	PA	serum/plasma
8	Lumispot "Eiken" HCV-Ab	EIKEN CHEMICAL CO., LTD.	CLEIA/CLIA	serum/plasma
9	ABBOTT HCV EIA 2nd Generation	DAINABOT CO., LTD.	EIA	serum/plasma
10	IMx Abbott HCV	DAINABOT CO., LTD.	EIA	serum/plasma
11	AxSYM Abbott HCV	DAINABOT CO., LTD.	EIA	serum/plasma
12	Imucheck · F-HCV C50 Ab Kokusai	International Reagents Corporation	EIA	serum/plasma
13	DETECT-HCV	AZWELL Inc.	EIA	serum/plasma
14	ARCHITECT · Anti-HCV	DAINABOT CO., LTD.	CLEIA/CLIA	serum/plasma

(D) 3rd generation kit

No.	Name	Manufacturer/Distributor	Method	Detection of HCV Ab in
15	Quick CHASER HCV Ab	MIZUHO MEDY	Immunochromato.	serum/plasma
16	RANREAM HCV II EX	SYSMEX CORPORATION	PAMIA	serum
17	Ortho HCV Ab LPIA test	Mitsubishi Kagaku Medical, Inc.	LPIA	serum/plasma
18	Ortho HCV Ab IRMA test III	Mitsubishi Kagaku Medical, Inc.	IRMA	serum/plasma
19	Ortho HCV 3.0 ELISA TEST SYSTEM with Enhanced SAVe	Ortho Clinical Diagnostics K.K.	EIA	serum/plasma
20	ABBOTT EIA 3.0	DAINABOT CO., LTD.	EIA	serum/plasma
21	Cobas Core Anti-HCV EIA	Roche Diagnostics K.K.	EIA	serum/plasma
22	EVATEST HCV Ab	NISSUI PHARMACEUTICAL	EV-FIA	serum/plasma
23	ABBOTT PRISM HCV	DAINABOT CO., LTD.	CLEIA/CLIA	serum/plasma
24	Lumipulse II Ortho HCV	FUJIREBIO INC.	CLEIA/CLIA	serum
25	CHIRON RIBA 3.0 Strip Immunoblot Assay (SIA)	Ortho Clinical Diagnostics K.K.	RIBA (Immunoblot)	serum/plasma

results may indicate that the kit No.13 is more sensitive in detecting anti-Core Ab but less sensitive in detecting the NS3/NS4 antigens than the kits No. 10 and No.11. It is suggested that kits within the same category differ in their ability for detecting HCV-related Ab, depending on the qualitative as well as quantitative differences in their utilization of HCV antigens as epitopes. This kind of difference is quite apparent when the seroconversion panel PHV-906, whose donor did not elicit the anti-Core Ab, was tested. The results indicate that there are substantial differences in capabilities of detecting the NS region antigens among various kits.

CONCLUSION

Since the HCV Ab detection kits available in Japan have in general been developed rather recently, they appear to be indistinguishable from each other with respect to their quality, whereas several kits, such as No.15 (immunochromatography), seem to have room for improvement. As already mentioned in the report regarding the re-evaluation of HBsAg detection kits, diagnosis of HCV infection should not rely solely upon the results obtained by a single HCV detection kit. Serological confirmatory tests such as the RIBA3 and/or tests for detection of HCV virus RNA should be utilized to obtain the final judgment.

Legends to Table 2.

Numbers 1 through 25 at the top of the charts indicate the serial numbers of the kits tested, and correspond to the numbers appearing in Table 1.
Symbols:
□: Negative.
■: Positive in duplicate assays.
▨: Positive in one assay and negative in the other.
▨: +/- in one assay and negative in the other.
▨: Indeterminate.
▨: Not done.
Principle/procedure of the kits are indicated as alphabets:
a: IRMA (Immunoradiometric assay)
b: Immunochromatography
c: Agglutination/aggregation (PHA / PA / LPIA / PAMIA)
d: EIA (Enzyme immunoassay)
e: CLEIA/CLIA (Chemiluminescent [enzyme] immunoassay)
f: EV-FIA (Evanescent wave fluoro immunoassay)

Table 2.

Applic.	monitoring				diagnosis																				confirmatory				
Gener.	Core			1	2nd										3rd										RIBA3 (3rd)				
Method	a	d	e	a	c	c	c	e	d	d	d	d	d	e	b	c	c	a	d	d	d	f	e	e					
Kit No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	NS4	NS3	C	NS5
Neg-1																													
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18																													
19																													
Low-1																										2	3	1/2	1
2																									+/-	+/-	+/-	4	+/-
3																										+/-	1	1	+/-
4																										1	4	+/-	+/-
5																										+/-	1	1	+/-
6																										2/3	1/2	2/3	+/-
7																									+/-		1/2		+/-
8																									+/-		3		+/-
9																									+/-	+/-	+/-	1	
10																													
11																									+/-		+/-	3	
12																										4	2		
13															+/-										+/-	+/-	1	+/-	
14						+/-																			+/-		2		
15															+/-											+/-	1	2	
Mix-1																										4	4	4	3
2																										4	4	4	4
3																										4	4	4	4
4																							X			4	4	4	4
5																										4	4	4	3
6																										4	4	4	4
7																										1/2	4	4	4
8																										4	4	4	4
9																										3	2/3	4	4
10																										3	4	4	
11																										3	4	4	
12																										4	4	4	4
13																										4	4	4	
14																										4	4	4	4
15																										4	4	4	
16																										3	4	4	3
17																										2/3	4	4	+/-
18																										4	4	4	4
19																										4	4	4	4
20																										4	4	4	4
SC 906-1															+/-										+/-	+/-	3		
2															+/-											1	3		
3																										2	3		
4																										3	4		
5																										3	4		
6																										4	4		
7																										4	4		
SC 907-1																													
2																													
3																													
4						/																			+/-			1	
5															+/-										+/-		+/-	3	
6															+/-										+/-		+/-	3	
7																										4	3/4	4	2

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APPENDIX

The members of the committee are as follows:

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