Use of third-generation hepatitis C virus (HCV) enzyme immunoassay (EIA) to resolve second-generation HCV EIA-reactive and second-generation recombinant immunoblot assay-indeterminate blood samples: data to support current Food and Drug Administration guidance on HCV lookback

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On March 20, 1998, the Food and Drug Administration (FDA) issued a draft guidance document[1] on hepatitis C virus (HCV) lookback. In this document, the FDA recommended that, before lookback-related consignee notification proceeds, further testing should be performed for cases involving donors who were identified as reactive by multiantigen second-generation HCV enzyme immunoassay (HCV EIA 2.0) and who were either not tested by a supplemental HCV assay or who tested indeterminate by the currently licensed second-generation HCV recombinant immunoblot assay (RIBA 2.0). Two options for further testing of these cases were presented. Option 1 applied when a stored donation sample was available which could be tested using the investigational third-generation HCV RIBA (RIBA 3.0) under an investigational new drug (IND) exemption. If the RIBA 3.0 was positive, consignee notification must proceed; if it was negative or indeterminate, consignee notification was not required or recommended. Option 2 involved the recall of the HCV EIA-2.0-reactive, RIBA 2.0-indeterminate donor and testing of a fresh blood sample from the donor by use of a currently licensed multiantigen screening test (e.g., third-generation HCV EIA [HCV EIA-3.0]). If the screening test was nonreactive, no further action was needed; if it was repeatedly reactive (RR), either a licensed or investigational supplemental HCV assay should be performed to resolve the donor's status and determine whether lookback was warranted.

Because retention samples exist for the majority of relevant HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations (Stramer SS, oral communication, June 8,1998 and because donor recall is logistically difficult and often incomplete, further testing of the stored donation samples (Option 1 above) was clearly the preferred course of action for most blood centers. Unfortunately, investigational RIBA 3.0 kits were not available to support the testing stipulated above in the test volume required (e.g., the American Red Cross alone had over 10,000 HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations that would require RIBA 3.0 testing). The lack of availability of RIBA 3.0 presented a serious problem to blood centers attempting to complete lookback activity in as timely a fashion as possible to avoid regulatory and/or litigation problems. In response to this dilemma, several blood centers were considering triggering lookback on all HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, despite the knowledge that only 15 to 20 percent of these donations (or the donors) are predicted to test positive by RIBA 3.0, that less than 5 percent will test positive for HCV RNA, and prior donations by these donors have not been documented to be associated with recipient infection in lookback studies from Europe.[2,3]

Several sources of data suggested to us that the currently licensed HCV EIA 3.0 could serve as a test to triage these cases into those that do warrant potential triggering of lookback (i.e., HCV EIA 3.0-RR) and those that don't (i.e.,

ABBREVIATIONS: FDA = Food and Drug Administration; HCV = hepatitis C virus; HCV EIA 2.0 = second-generation HCV enzyme immunoassay; HCV EIA 3.0 = third-generation HCV EIA; IND = ivestigational new drug; PCR = polymerase chain reaction; RIBA 2.0 = second-generation recombinant immunoblot assay; RIBA 3.0 = third-generation RIBA; RR = repeatably reactive.

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HCV EIA 3.0-nonreactive). The premise for this recommendation is that the HCV EIA 3.0 has sensitivity superior to that of the HCV EIA 2.0, with respect both to earlier detection of HCV seroconversion[4,5] and to detection of additional HCV infections (albeit mostly remote or resolved infections) in large cross-sectional studies.[6,7] The HCV EIA 3.0 is also reported to be more specific than the HCV EIA 2.0.[8,9]

In considering this strategy, we initiated an analysis of data addressing critical issues: first, what proportion of HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations will be classified as reactive versus nonreactive by HCV EIA 3.0; and, second, what the correlations are between HCV EIA 3.0 reactivity and RIBA 3.0 reactivity and between HCV EIA 3.0 reactivity and HCV polymerase chain reaction (PCR) results (HCV RNA).

PREVIOUS STUDIES

Studies based on HCV EIA 2.0 screening

In the HCV EIA 3.0 product license application, data were reported from the screening of 30,025 volunteer donors.[7] Of 107 donations that tested as reactive by both HCV EIA 2.0 and 3.0, 97 (91%) were positive in RIBA 3.0, while 88 (82%) were positive in RIBA 2.0, a result that suggests a high positive-predictive value when HCV EIA 3.0 is applied to HCV EIA 2.0-reactive donations.

Of 33 RIBA 2.0-indeterminate donations detected by HCV EIA 2.0, 15 (45%) were reactive in HCV EIA 3.0, while 18 (55%) were nonreactive. None of the 18 HCV EIA 3.0-nonreactive donations demonstrated evidence of HCV infection in supplemental assays (RIBA 3.0 or PCR). By contrast, 8 (53%) of the 15 donations that were HCV EIA 3.0 reactive were positive in RIBA 3.0, although all were PCR negative. These data support the negative and positive predictive value, respectively, of HCV EIA 3.0 for resolving HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations.

Two published studies from Europe further support the proposed role of HCV EIA 3.0 in the resolution of HCV EIA 2.0-reactive specimens. First, a study by Dutch investigators[8] reported that the HCV EIA 3.0 (Ortho Diagnostics, Raritan, NJ) detected 100 percent of 398 HCV EIA 2.0-RR/PCR-positive specimens as well as 100 percent of 442 HCV EIA 2.0-RR/RIBA 2.0-positive samples evaluated. These data strongly support the sensitivity of HCV EIA 3.0 for HCV EIA 2.0-reactive donations determined to be infected on the basis of RIBA 3.0 and/or PCR analyses. In a second study by Uyttendaele et al.,[9] HCV EIA 3.0 reacted with 91 (45%) of 203 HCV EIA 2.0-RR blood donor sera, including 37 (50%) of 74 RIBA 2.0-indeterminate samples. Four (11%) of the 37 HCV EIA 3.0-reactive samples tested RIBA 3.0-positive. In contrast, none of the 37 HCV EIA 2.0-RR/RIBA 2.0-indeterminate sera that tested nonreactive by HCV EIA 3.0 tested positive by RIBA 3.0. Instead, 31 (84%) were negative and 6 (16%) remained indeterminate in RIBA 3.0.

Investigators at the Blood Center of Southeastern Wisconsin obtained similar results in a large study[10] evaluating the performance of the Ortho HCV EIA 3.0 on donor specimens that were RR on HCV EIA 2.0 tests from two manufacturers (Ortho; and Abbott Diagnostics, Abbott Park, IL). Of 301 HCV EIA 2.0-RR/RIBA 2.0-indeterminate specimens, 129 (43%) tested reactive in HCV EIA 3.0. Of the 129, 80 (62%) were identified as reactive by the Abbott HCV EIA 2.0 and 49 (38%) by the Ortho HCV EIA 2.0. RIBA 3.0 testing performed on 125 samples identified as Abbott HCV EIA 2.0-RR/RIBA 2-indeterminate were subsequently determined to be nonreactive in HCV EIA 3.0. None of the 125 HCV EIA 3.0-nonreactive sera tested RIBA 3.0-positive, which supports the negative predictive value of HCV EIA 3.0 for resolving such specimens.

Studies based on HCV EIA 3.0 screening

A recent study for the Retrovirus Epidemiology Donor Study investigated the performance of supplemental assays in testing HCV EIA 3.0-screened specimens. The results supported the positive predictive value of HCV EIA 3.0 in RIBA 2.0-indeterminate specimens. RIBA 2.0 and RIBA 3.0 were performed in parallel on 245 sequential HCV EIA 3.0-reactive donations identified immediately subsequent to licensure of the HCV EIA 3.0 (i.e., from June 1996 through June 1997).[11] Of 43 RIBA 2.0-indeterminate donations, 32 (74%) tested positive in RIBA 3.0; 5 (16%) of the 32 RIBA 2.0-indeterminate/RIBA 3.0-positive donations tested PCR-positive, whereas none of the RIBA 3.0-negative or -indeterminate donations did so. Thus, among HCV EIA 3.0-screened donation samples, an indeterminate RIBA 2.0 pattern was highly predictive of RIBA 3.0 positivity and moderately predictive of viremia. Consequently, in the absence of RIBA 3.0 availability, triggering lookback on HCV EIA 3.0-reactive/RIBA 2.0-indeterminate donations seemed reasonable, and this algorithm has been implemented for prospective lookback at a number of blood centers.

PRESENT STUDY

To further determine the performance of HCV EIA 3.0 and RIBA 3.0 on retrospective HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, a study was initiated at Blood Centers of the Pacific in collaboration with the Community Blood Center of Greater Kansas City and with testing support from Chiron Corporation (Emeryville, CA), Ortho Diagnostics, and Gen-Probe (San Diego, CA).

Ortho HCV EIA 2.0-RR/RIBA 2.0-indeterminate specimens

One hundred forty-three Ortho HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, identified from mid-1992 through June 1996, were tested by HCV EIA 3.0 and RIBA 3.0 and (for HCV RNA) by transcription-mediated amplifica-

TABLE 1. Comparison of HCV EIA 3.0, RIBA 3.0, and HCV RNA (TMA) results in Abbott and Ortho HCV EIA 2.0-RR/ RIBA 2.0-indeterminate specimens

		RIBA 3.0		
	Number	Positive	Indeterminate	Negative
Ortho HCV EIA 2.0-RR/				
RIBA 2.0-indeterminate	143			
HCV EIA 3.0-reactive	89 (62%)	19 (21%)	28 (32%)	42 (47%)
HCV RNA-positive	2	1 (5%)	1 (3.5%)	0
HCV EIA 3.0-nonreactive	54 (38%)	2* (4%)	18 (33%)	34 (63%)
HCV RNA-positive	0	0	0	0
Abbott HCV 2.0 RR/				
RIBA 2.0-Indeterminate	189			
HCV EIA 3.0-reactive	98 (52%)	28 (28%)	33 (34%)	37 (38%)
HCV RNA-positive	10	10 (36%)	0 (0%)	0 (0%)
HCV EIA 3.0-nonreactive	91 (48%)	0	29 (32%)	62 (68%)
HCV RNA-positive	0	0	0	0

* After repeat RIBA 3.0 testing, one specimen remained RIBA 3.0-positive (i.e., 2+ c100p/5-1-1p and 1+ NS5), while the second specimen was indeterminate (i.e., ±c33c and 2+ c22p).

tion (TMA).[12] As summarized in Table 1, 89 (62%) of 143 Ortho HCV EIA 2.0-RR samples tested HCV EIA 3.0-reactive: of these, 19 (21%) tested positive, 28 indeterminate, and 42 negative in RIBA 3.0. Two of the 89 HCV EIA 3.0-reactive samples tested HCV RNA-positive; 1 sample was RIBA 2.0 c22-indeterminate (1+) and RIBA 3.0-positive (1+ c100p and 1+ c22p), while the second sample was c33c-indeterminate in both RIBA 2.0 and RIBA 3.0. In comparison, 39 (76%) of 51 HCV EIA 2.0-RR/RIBA 2.0-positive samples tested in parallel were HCV RNA positive (Table 2). One of the two HCV EIA 3.0-reactive RR/HCV RNA-positive samples would not have triggered lookback, according to the current FDA recommendation, on the basis of an indeterminate RIBA 3.0 result.

Of the 54 HCV EIA 3.0-nonreactive samples, 2 tested positive, 18 indeterminate, and 34 negative in RIBA 3.0; all 54 samples were HCV RNA negative (Table 1). One of the two HCV EIA 3.0-nonreactive/RIBA 3.0-positive samples was borderline nonreactive in HCV EIA 3.0 (signal-to-cutoff ratio: 0.92). This sample's band pattern was 1+ for c33c and 2+ for c22p by initial RIBA 3.0 testing, but, upon retesting by RIBA 3.0, the c33c reactivity was less than that of the control band, and the sample was classified as indeterminate. The second sample was nonreactive in HCV EIA 3.0 (signal-to-cutoff ratio: 0.08), and it was positive (3+ c100 and 2+ NS5 bands) in RIBA 3.0. These results were confirmed on retesting. Both these samples tested HCV RNA negative.

TABLE 2. HCV RNA (TMA) results on Ortho and Abbott HCV EIA 2.0-RR/ RIBA 2.0-positive specimens

HCV EIA 2.0-RR/RIBA 2.0-positive specimens	Total number tested	HCV RNA-positve specimens Number (%)
Ortho HCV EIA 2.0	51	39 (76%)
Abbott HCV EIA 2.0	20	17 (85%)

Abbott HCV EIA 2.0-RR/RIBA 2.0-indeterminate specimens

One hundred eighty-nine Abbott HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations identified from 1992 through 1996 were evaluated by HCV EIA 3.0 and RIBA 3.0 and (for HCV RNA) by TMA. As illustrated in Table 1, 98 (52%) of the 189 Abbott HCV EIA 2.0-RR samples tested HCV EIA 3.0-reactive, of which 28 (28%) tested positive, 33 indeterminate, and 37 negative in RIBA 3.0. Of the 28 HCV EIA 3.0-reactive/ RIBA 3.0-positive samples, 10 (36%) tested HCV RNA-positive, whereas all 33 RIBA 3.0-indeterminate and 37 RIBA 3.0-negative samples were HCV RNA negative. In comparison, 17 (85%) of 20 HCV EIA 2.0-RR/RIBA 2.0-positive samples stored and tested in parallel were HCV RNA positive in TMA (Table 2). None of the 91 HCV EIA 3.0-nonreactive samples tested positive in RIBA 3.0 (29 were indeterminate and 62 were negative). All 91 HCV EIA 3.0-nonreactive samples tested HCV RNA-negative. Table 3 compiles the results from the previous studies and the current study.

SUMMARY

In considering a proposed role for HCV EIA 3.0 in resolving the lookback status of HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, two critical questions must be considered.

The first of these questions is: What is the probability that a nonreactive HCV EIA 3.0 result in such samples will result in misclassification of an infected donation as negative, precluding lookback that would have been triggered had RIBA 3.0 been performed as recommended by the draft guidance document?

In the studies reviewed above, a total of 325 HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations tested HCV EIA 3.0-nonreactive and were further tested by RIBA 3.0 and, in most cases, for

TABLE 3. Compiled results on 644 HCV EIA 2.0-RR/RIBA 2.0-indeterminate blood donor specimens

Institution	Number	HCV EIA 3.0-RR	RIBA 3.0-positive	HCV PCR-positive	HCV EIA 3.0-nonreactive	RIBA 3.0-positive	HCV PCR-positive
Ortho-Clinical Diagnostics PLA*	33	15 (45%)	8 (53%)	0	18 (55%)	0	0
European studies†	74	37 (50%)	4 (11%)	NA	37 (50%)	0	NA
Blood Center of SE Wisconsin‡	205	80 (39%)	NA§	NA	125 (61%)	0	NA
Present study	332	187 (56%)	47 (25%)	11(23%)	145 (44%)	2 (1.4%)¶	0
Total	644	319 (50%)	59/294 (20%)	11/55 (20%)	325 (50%)	2/325 (0.6%)¶	0/2

* Data from Product Licensing Application (Lee S, written communication, January 1998).
† Uyttendaele et al.[9]
‡ Destree et al.[10]
§ Data not available.
¶ Two HCV EIA 3.0-nonreactive specimens were initially RIBA 3.0 positive. After additional RIBA 3.0 testing, the interpretation of one specimen remained positive, while the interpretation of the second specimen was indeterminate.

HCV RNA by PCR or TMA (Table 3). Two (0.6%) of these samples tested RIBA 3.0-positive; one of these was indeterminate on repeat RIBA 3.0 testing and both were negative for HCV RNA. We believe this low rate of RIBA 3.0 positivity and the absence of HCV RNA positivity support a recommendation that further testing and lookback are not warranted on HCV EIA 3.0-nonreactive donations.

The second question is: What is the probability that a reactive HCV EIA 3.0 result on such samples will be corroborated by a positive RIBA 3.0 result that would justify lookback?

Before performing the present study on HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, we predicted that the rate of RIBA 3.0 positivity among HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations that were further tested and found to be HCV EIA 3.0-reactive would be similar to the 75-percent rate observed among HCV EIA 3.0-reactive/RIBA 2.0-indeterminate donations.[11] If this were confirmed, we felt it would be reasonable to trigger lookback on the basis of the reactive HCV EIA 3.0 results, as is currently being done for prospectively identified HCV EIA 3.0-RR/RIBA 2.0-indeterminate donors. In the pilot study, we found that only about 30 percent of HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations that tested HCV EIA 3.0-reactive were RIBA 3.0 positive. A likely explanation for this discrepancy is that, during the several years of testing donors with an HCV EIA 2.0, donors with "false-positive" reactivity, characterized by concordant HCV EIA 2.0 and HCV EIA 3.0 reactivity and indeterminate RIBA 2.0 results, were identified and deferred (i.e., removed from the donor base). Consequently, the likelihood (predictive value) that a donation with an RR HCV EIA 3.0 and indeterminate RIBA 2.0 will test RIBA 3.0-positive is greater among current HCV EIA 3.0-RR donors than during the initial period of HCV EIA 2.0 screening. In light of this relatively low rate of RIBA 3.0 positivity among HCV EIA 3.0-reactive samples identified among retrospective HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations, we do not believe that triggering lookback on the basis of positive HCV EIA 3.0 results alone is justified. Further testing of these samples by RIBA 3.0 is strongly recommended.

CONCLUSION AND IMPACT

On the basis of this analysis, we recommended that the FDA approve the use of HCV EIA 3.0 to further resolve the lookback status of HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations. Approximately one-half of such donations are predicted to test reactive in HCV EIA 3.0 and one-half nonreactive. For donations that test nonreactive in HCV EIA 3.0, lookback should not be triggered, given the very low probability of RIBA 3.0 or HCV RNA positivity of these donations. If HCV EIA 3.0 is RR, the blood collection organization should determine if the donor has a donation history that would trigger lookback. Donation samples from these HCV EIA 3.0-RR repeat donors should be tested by RIBA 3.0 as soon as that test is available (either under IND testing by Chiron or subsequent to licensure). By use of the strategy of limiting the number of samples needing RIBA 3.0 testing to those that test HCV EIA 3.0-RR and are from repeat donors, the number of samples requiring RIBA 3.0 will be reduced to about 20 percent of the level currently slated for RIBA 3.0 resolution testing. At Blood Center A (Blood Centers of the Pacific) 82 (24%) of 341 HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations were HCV EIA 3.0-RR and were from repeat donors who would trigger lookback, while 61 (17%) of 364 HCV EIA 2.0-RR/RIBA 2.0-indeterminate donations at Blood Center B (Community Blood Center of Greater Kansas City) were HCV EIA 3.0-RR and were from repeat donors who would trigger lookback. If we extrapolate to the national level, we estimate that this strategy would reduce the number of RIBA 2.0-indeterminate donations requiring RIBA 3.0 testing from about 20,000 to about 3,000 to 4,000.

The recommendation we propose was reviewed and endorsed by the FDA and has been incorporated into the revised guidance document issued on September 23, 1998.[13] Figure 1 demonstrates the full impact of the application of this approach on targeted HCV lookback at the two blood centers that participated in this study. The use of HCV EIA 3.0 on HCV EIA 2.0-RR/RIBA 2.0-indeterminate donors reduced the number of repeat donations or donors triggering lookback from 157 to 82 (52% of earlier total) at Center

A and from 124 to 61 (49%) at Center B; the number of components that would require consignee notification was reduced from 832 to 356 (43%) and from 792 to 372 (47%), respectively. The use of RIBA 3.0 on the HCV EIA 3.0-RR specimens further reduced the number of donations requiring lookback to 24 (15%) and 6 (5%) and the number of components requiring consignee notification to 133 (16%) and 17 (2%), respectively.

Our experience demonstrates the utility of HCV EIA 3.0 for resolving the status of HCV EIA 2.0-RR/RIBA 2.0-indeterminate specimens. Our findings further highlight the importance of incorporating RIBA 3.0 into supplemental HCV testing algorithms. During the review process for this manuscript, the FDA licensed the RIBA 3.0. This should allow other blood centers to fully apply the resolution algorithm we propose and should permit the appropriate use of RIBA 3.0 for the resolution of donations prospectively identified as RR by HCV EIA 3.0 screening.

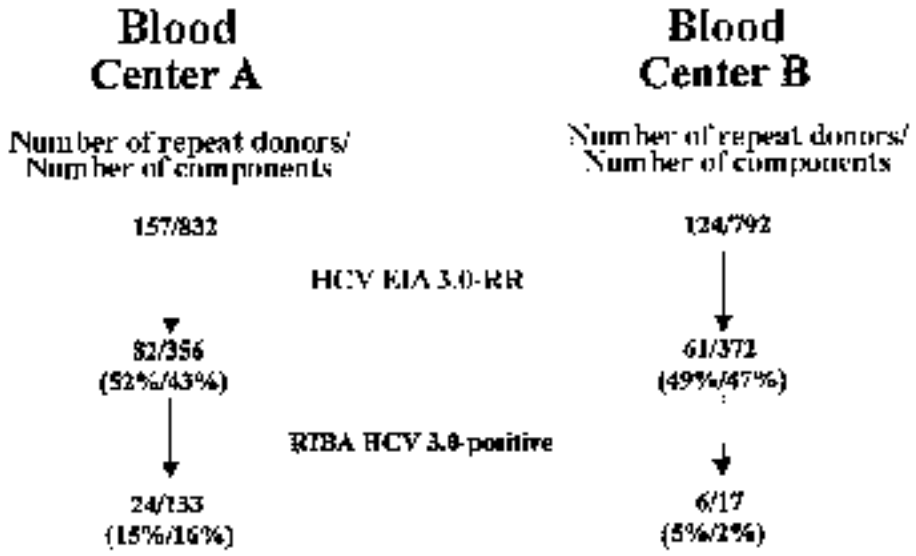

Fig. 1. Impact of using HCV EIA 3.0 and RIBA 3.0 on targeted lookback. Blood Center A, Blood Centers of the Pacific (all specimens were originally tested by Ortho HCV EIA 2.0); Blood Center B, Community Blood Center of Greater Kansas City (Ortho HCV EIA 2.0 performed until Abbott HCV EIA 2.0 was licensed).

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