医薬品
医薬部外品　　研究報告　調査報告書
化粧品

識別番号・報告回数			報告日	第一報入手日 2004 年 8 月 26 日	新医薬品等の区分 該当なし	厚生労働省処理欄
一般的名称	人ハプトグロビン		研究報告の公表状況	HHS, FDA, 80th Meeting of BLOOD PRODUCTS ADVISORY COMMITTEE/ July 23, 2004 Transcript, 6-28	公表国 アメリカ	
販売名 （企業名）	ハプトグロビン注－ヨシトミ(ベネシス)					

研究報告の概要

2004 年 7 月 23 日に米国で開催された血液製剤諮問委員会（BPAC）において CBER の Dr. Nakhasi は、" Update on West Nile Virus" と題するプレゼンテーションの中で以下のように述べた。
『WNV に関しての供血停止期間は症状の発現から少なくとも 28 日とガイダンスで勧告しているが、WNV のウイルス血症の持続期間について ARC の研究では 49 日と 39 日の事例があり、BSL の研究では 49 日の事例があった。WNV RNA は IgM と共存する可能性がある。我々は供血停止期間を現在の頭痛や発熱を含む WNV による症状発現後 28 日から 56 日に延長することを考えている（症状が 56 日以上になる場合は、症状が回復してから 14 日）。また、ドナーに復帰させるのは、症状が無くなってから 30 日後で WNV の IgM 又は個別 NAT が陰性になってからと考えている。勧告を出す前に、次の定例 AABB 作業委員会で討議する予定である。』

使用上の注意記載状況・その他参考事項等

2. 重要な基本的注意
(1) 本剤の原材料となる血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理(ナノフィルトレーション)を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
ARC、BSL による WNV 感染ドナーの研究結果に基づき、供血停止期間を現在の発症後 28 日から 56 日に延長することを考えているとの BPAC における CBER の Dr. Nakhasi の発言。 FDA は 2003 年 5 月の業界向けガイダンス改訂版において「FDA はすべての血漿分画製剤について現在行われているウイルス低減工程を再調査した。現在行われている方法は、WNV と分類上関連しているフラビウイルスを不活化することがバリデートされている。」と評価し、CPMP もまた 2003 年 7 月のポジションステートメントにおいて、血漿分画製剤の製造工程で WNV は不活化・除去されると評価している。 米国の弊社への原料血漿供給元では、2003 年 6 月より WNV の問診を開始している。また、WNV と類似した特徴を有している BVD をモデルウイルスとしたウイルスバリデーション試験成績から、万一原料血漿に WNV が混入したとしても、本剤の製造工程において十分に不活化・除去されると考えている。	本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLOOD PRODUCTS ADVISORY COMMITTEE

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service: Accordingly the Food and Drug Administration makes no representation as to its accuracy.

Friday, July 23, 2004

8:00 a.m.

Gaithersburg Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland 20877

PARTICIPANTS

Kenrad E. Nelson, M.D., Chair
Linda A. Smallwood, Ph.D., Executive Secretary
Pearline K. Muckelvene, Scientific Advisors
& Consultants Staff

MEMBERS:

James R. Allen, M.D., M.P.H.
Kenneth Davis, Jr., M.D.
Donna M. DiMichele, M.D.
Samuel H. Doppelt, M.D.
Jonathan C. Goldsmith, M.D.
Harvey G. Klein, M.D.
Suman Laal, Ph.D.
Katherine E. Knowles,
Acting Consumer Representative
D. Michael Strong,
Non-Voting Industry Representative

TEMPORARY VOTING MEMBERS:

Liana Harvath, Ph.D.
F. Blaine Hollinger, M.D.
Katharine E. Knowles
Matthew J. Kuehnert, M.D.
Susan F. Leitman, M.D.
Keith C. Quirolo, M.D.
George B. Schreiber, Sc.D.
Donna S. Whittaker, Ph.D.

C O N T E N T S

PROCEEDINGS

DR. SMALLWOOD: May I ask all advisory committee members to, please, take your seats? Welcome to the second day of the Blood Products Advisory Committee meeting. Yesterday I read the conflict of interest statement that applies to this meeting, however, we have a new process now and we will read a conflict of interest statement for each day.

So, if you will indulge me, I will read that at this point. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting yesterday, and is part of the public record for the Blood Products Advisory Committee meeting on July 23, 2004. This announcement addresses conflicts of interest for topic V.

Drs. Liana Harvath, Blaine Hollinger, Matthew Kuehnert, Susan Leitman, Keith Quirolo, George Schreiber, Donna Whittaker and Ms. Katherine Knowles have been appointed as temporary voting members for this meeting

Dr. Michael Strong is participating in this meeting as the non-voting industry representative, acting on behalf of regulated industry. The Food and Drug Administration has prepared general matters waivers for the special government employees participating in this meeting who required a waiver under Title XVIII, United States Code 208.

In addition, there are regulated industry and other outside organization speakers making presentations. These speakers have financial interests associated with their employers and with other regulated firms. They were not screened for these conflicts of interest. I would just like to remind everyone participating to, please, make known, if you have not already done so, any affiliation you may have and your status with that affiliation prior to speaking.

Our committee chairman, Dr. Kenrad Nelson has joined us this morning, and we also have Dr. Blaine Hollinger who will also be part of the committee this morning.

I just wanted to announce to those who

were not here yesterday that the next date, which is tentative however pretty much firm, for the next Blood Products Advisory Committee meeting will be October 21st and 22nd, 2004.

At this time I will turn over the proceedings of the meeting to the chairman, Dr. Kenrad Nelson.

Update on West Nile Virus

DR. NELSON: Thank you, Dr. Smallwood. I will try to keep awake after the 24-hour airplane ride. I came in last night but I feel really pretty good and I am very interested in the topic today so I think that will help.

The first topic is an update on West Nile virus by Hira Nakhasi.

DR. NAKHASI: Good morning. I just want to give you an update, as Dr. Kenrad Nelson mentioned, on the West Nile epidemic and donor testing which is happening now, in 2004. First I will try to wrap up last year's things and then come up to 2004.

Next slide, please. The topics which I

will update you on are, as I said, last year's epidemiology and the investigational West Nile testing outcome of that, and some of the transfusion-transmitted cases, and then the trigger for the ID-NAT testing. Then I will update you on the West Nile donor and product management recommendations with the recent revelations we have got. Then I will update you on the 2004 epidemic and investigational West Nile testing, and also our efforts in-house on the panel development and other scientific issues--you know, the variation among the strains of viruses infectivity of these studies.

Next slide, please. If you summarize in one slide the last year's epidemic, it really basically sums up that we had approximately 1000 [sic] cases or, to be precise, 9862 cases, human cases, and 264 deaths. And, the proportion of the West Nile meningitis/encephalitis was 29 percent, whereas, the fever was 69 percent in the human cases.

Forty-six states, including Washington,

D.C., were endemic, and donor testing started, as all of you know, in July of 2003, using two investigational NAT testing. In some cases, a small proportion started in the middle of June. Despite this testing, I think these two investigational NAT testing--these are minipool and the two tests were the Gen-Probe test and the Roche test, and Roche tested, as you know, in pools of 6 and the Gen-Probe test involves a pool of 16.

Despite testing, there were some transfusion-transmitted cases and CDC had investigated a total of 23 cases. They were confirmed by NAT and IgM reactivity and also by follow-up of both the donor and the recipient. Out of the 23, 6 were confirmed cases. Only 4/6, you may recall, had very low viremia, around 0.1 pfu/ml. Eleven cases did not confirm; 3 were inconclusive because of the follow-up situation; and 3 were open investigations.

Next slide, please. As I said, since it started on July 1 of last year, screening using minipool NAT and IND, all geographic regions of the

U.S. were screening at that time. With that, what happened 1000 units of West Nile infected blood donors were interdicted after screening approximately 8 million donations. So, I think it was a very, very vast improvement over the year before when there was no testing. The last positive donation was reported in the middle of December in 2003.

Despite this testing, as you see, the majority of cases were interdicted, more than 75 percent, but there was a small percentage which went through because, as you know, this was done in minipool NAT.

Next slide, please. This slide is Mike Busch's slide where he showed why we were missing some of these cases, and we knew that minipool NAT sensitivity was such. The areas, you know, where the wrap-up takes place when--you know, he calls it stage I, II, III, IV and V, and in stage I and II they are ID-NAT positive but minipool NAT negative, IgM negative. So, it could be plus/minus. So, during that stage they become IgM positive but they

become minipool negative and they are still ID-NAT positive. So, this region and this region were the ones where they went through. But, you know, these were IgM negative and these were IgM positive so the question is what is the infection of these types of samples.

Next slide, please. So there was a potential for transmission of West Nile through minipool NAT negative blood of low viremia in some patients. Therefore, what happened at that time is that limited prospective ID-NAT testing started in high incidence areas. If you remember last year, Colorado, Kansas and certain other areas, and Nebraska were hot spots and ID-NAT was triggered at that time, and the trigger was based on if the preceding the rate of 1/200 minipool NAT positive rate of 1/250, then they would start testing with ID-NAT testing. Also, what happened at that time is that there was voluntary withdrawal of the frozen transfusables in the high incidence areas before the ID-NAT was initiated by some blood establishments.

Next slide, please. There was also another initiative started at that time. The initiative was to go back to do the retrospective study on the minipool NAT negative samples and test them by ID-NAT to find out how many we missed. It would also let us know what was the low level of viremic high incidence samples in high incidence areas where minipool NAT did not pick them up.

The other purpose of the study was also to identify samples which are like minipool NAT low titer, minipool NAT negative but ID-NAT positive for infectivity studies. I told you that we do not know whether those samples are still infectious at low levels, and what is the level of infectivity. So, these samples would be tested in various animal models including non-human primates. Also, the purpose of these samples is to really find out the relative clinical sensitivity of various West Nile investigational testing. I will report in a minute what is happening with the infectivity state.

Next slide, please. Based on the observation that we had minipool testing and we

missed some of the samples because the viremia was low, and also in the ID-NAT testing in the high incidence areas--based on those studies and based on the logistics issues, the question was what should be the trigger for ID-NAT, and also logistic issues such the availability of adequate resources, recruitment, reagents and trained technologists.

So, the discussion about the trigger for ID-NAT was held in collaboration with the AABB task force. By the way, we are very indebted to the AABB task force for the biweekly meetings almost throughout the year, and weekly meetings with the task force during the epidemic to update us and jointly discuss the strategies for how to go forward with the testing performance, as well as the epidemic.

So, based on that discussion, which was held in February, the recommendations were the following for the ID-NAT trigger: It was discussed that we should monitor reactive rates by zones daily, enrolled 7 days when the epidemic was starting, which was usually, you know, around the

beginning of July and early June even and this year even May some cases were found. The trigger was that if you have 2-4 cases in any geographic area--that is the blood collection, and the frequency of 1/1000. This was based on the fact that every 1/4 would be missed by minipool NAT and require ID-NAT. This was the study done by ARC and BSL and they found out that that would be the trigger. And, you go back to minipool NAT only when you see ID-NAT reactivity and you don't find zero cases in a consecutive 3-4 day period or the rate is less than 1/1000. So, that was the trigger because, you know, we wanted to be prepared this year because last year it was on an ad hoc basis to start ID-NAT testing in those hot areas. So, we wanted to be prepared this year if these areas become hot so that we get the logistics present there so we can start without interruption of the ID-NAT testing.

Next slide, please. Now we come to 2004, where are we now? As of July 20, which is a couple of days back--as you see, every week the numbers

keep changing. Last week there were 108. This week it is 182 human cases out of which there were 4 deaths. There are 2 from Arizona, 1 from Texas and 1 from Iowa. Out of total infections, 74 percent of cases are neuroinvasive West Nile illness and 26 percent cases are West Nile fever. At the moment there are 35 states endemic for West Nile. This slide has been kindly provided by Jen Brown, from CDC, and other slides which I will mention later.

The total number of presumptive West Nile viremic donors reported to the CDC ArboNet--that is why I highlighted this, is 23. There are more cases than that but, as you know, there is a delay in reporting to the ArboNet from the health departments. So, using minipool NAT as well as ID-NAT in select areas, starting on May 4. Out of these 23 presumptive West Nile viremic donors, 21 are from Arizona. The majority are from the Maricopa county near Phoenix, in Arizona; 1 from New Mexico and 1 from Iowa. But this is the tip of the iceberg.

Next slide, please. This slide, again, is provided by Jen. You can see the distribution of the West Nile, both the animal, avian and mosquito infection, which is in this color, and the blue color shows you the human cases. You can see it is very high in Arizona and California. I am telling Mike Strong that it is creeping up in Washington soon. So, he has been telling me we don't see anything and I said, well, wait and watch! As you remember, in 1999, how this started and how it is spreading and, you know, it just keeps on going. I hope it will end up in the ocean sometime.

Next slide, please. This is just to give you how early the human cases can be detected. As you see from the slide, the earliest one was in April. So, you know, there is an expansion of this epidemic, it looks like. We were told in the textbooks it is mostly in August and September or late July but you can see it as early as April now, and last year we saw it as late as December, in the middle of December. So, you know, it is almost a year-round activity now.

Next slide, please. Thanks to all the blood establishments and testing establishments, I got these data from several folks and I will acknowledge them as I speak. The total number, according to my calculations but this may not be right, is 61 presumptive viremic donors reported, starting in May, 2004. As I said, some of them are reported to ArboNet and some of them are not. So, it is not in addition to that; it is inclusive of the ArboNet reports. ARC has told me--Sue Stramer gave the data from June 16 to July 20, 7 hard cases. Again, this is also in the Arizona area. But she says no region has their ID-NAT trigger.

Mike Strong gave me this data from Roche. There are 2 positive confirmed by ID-NAT--around 300,000 donations screened.

BSL, Sally Caglioti and Mike Busch told me that there are 23 confirmed, out of which 16 came from minipool NAT and 7 came from ID-NAT, confirmed positives. There are 14 pending and he was saying that some of them are ID-NAT and would have been missed by minipool NAT. Also, some of them are low

viremic and also there are some which are IgM positive. The denominator is around 400,000.

Gen-Probe, Leanne Kiviharju, gave the data. These are non-ARC data but I am not sure--I sent an email to Leanne--whether this is also non-BSL but I am not sure; maybe we can find out from here, but 21 confirmed positive and 7 are pending. I am glad that you guys sent me several slides. I was basically trying to summarize what the presumptive donors are and, you know, I really appreciate your sending extra slides.

The Department of Defense, Ron Hagey sent me the data which has 8 confirmed out of 62,774 since January of 2004.

So, you know, this is the majority of the screening going on at this time and there may be a few cases which have not been reported yet, but this is where we stand as of today.

Next slide, please. I just wanted to sort of briefly remind you that FDA is still continuing to work closely with the test kit manufacturers and we would like to facilitate implementation of these

tests and expediter test licensure. I just want to remind you that we issued two guidances in October, 2002 and May, 2003. There are 3 INDs for West Nile minipool-NAT. One is from Roche, one from Gen-Probe and one from ARC. This is public information. FDA is continuing to work with the AABB task force. I think that has been a wonderful, wonderful collaboration with the AABB task force and the people on the task force are really helpful in doing this project together, and with the CDC, NIH help, and to monitor the epidemic and monitor the testing.

Next slide, please. Both ARC and BSL did a study, which is unpublished observation. We had a small discussion at the task force on what they found out in some of the viremic donors when they followed up. They wanted to find out what is the rate of the disappearance of RNA when they convert IgM and IgG. As you remember, in the last years before the testing started the literature was that it can go as long as 28 days of viremia. But from their studies, and I don't want to go into detail

here because these are unpublished and, you know, I don't want to divulge information--the gist of that was that what they found out in both cases is that the viremia may last up to 49 days in one case and 39 days in the ARC study, and in the BSL 49 days, and West Nile RNA may go coexist with IgM. Therefore, this sort of started us thinking. In the guidance document we put 28-day donor deferral and so we may have to rethink the deferral for that.

Next slide, please. We have not discussed it with the AABB task force but we will be discussing with the task force that, you know, the integration of West Nile testing information. We are thinking about maybe 56-day deferral for West Nile diagnosis of symptoms, including headache and fever, or 14 days after symptom resolution if it is more than 56 days. Potential reinstatement of donor deferral for West Nile symptoms only following 30 days without symptoms, and negative by West Nile IgM or ID-NAT. Again, this is current thinking. We have nothing in the works yet but we

have internal discussions, and we will discuss it at our next regular AABB task force before we come up with a recommendation. Dr. Alan Williams is spearheading this initiative.

Next slide, please. With regard to our activities in-house, as I mentioned last year also, we are still working on the panel development. The purpose is to monitor sensitivity of assays to detect viral nucleic acid antibodies, and also trying to isolate and characterize West Nile strains from human samples during 2003 and 2002 epidemics. The purpose of this study, which is done by Dr. Maria Rios in our group--and all these studies actually really are done by Dr. Maria Rios' group--is the genetic variation of viral strains; detection by currently available West Nile assays. The purpose is to really see if there is any genetic variation and also infectivity studies using animal models. Currently, the samples have been identified which could be used for infectivity studies. However, there are logistic issues about the animals, baboons, which are being worked out

with the Southeast Medical Center. I guess the task force is working on that. Hopefully, we will get some information by fall and we will be set to do those studies.

Next slide, please. Briefly, they have two isolates, NY99 in 2002, which have been characterized by genetic sequencing which I can show you in a minute. The viral infectivity is determined by in vitro studies using cell lines and primary human blood cell cultures. Final panel specifications are being established through the collaborative studies, and the range of concentration ranges between 1000-5 copies/ml.

Next slide, please. Just a piece of information here that Maria was kind enough to provide to me. You know, she did the comparison of the human 2002 strain and the NY99 flamingo isolate and then passed through the Vero cells. She found there were 20 nucleotide mutations and one insertion. The mutations are distributed all across the region which result in 5 amino acid substitutions. She is characterizing more isolates

and she already has 6 from 2002, 11 from 2003 and 6 from 2004. So, the purpose is to really compare and to see what the differences are and how those differences impact on our tests.

Next slide please. The outcome of the panel testing--six laboratories participated in that. She tells me there were no false-positive results reported. More variability in detection was found towards the lower end of the viral concentration, i.e., 80 percent of the time detected 100 copies/ml member but all laboratories detected 100 percent of the time the panel members of 500-1000 copies/ml. Further testing is going to define the consensus copy number.

Next slide, please. This is the important slide. I would like to thank all the people who really helped to make this talk possible. Jennifer Brown, whom I have always been bugging to provide the slides. Thank you, Jennifer. Dr. Sue Stramer, Dr. Mike Busch and Sally Caglioti, Dr. Mike Strong, Leanne Kiviharju, Roland, Maria and all these people--whoever I send an email they are kind

enough to respond quickly. Also my colleagues at the FDA, Maria Rios, Alan Williams, Dr. Epstein, Martin Ruta, Indira Hewlett--always helping in this whole project and, last but not the least, the AABB task force. I am really, really grateful to them for providing all the information and helpful discussion. Thank you very much.

DR. NELSON: Thank you. Any questions or comments? Yes?

DR. GOLDSMITH: Do you have additional data on the level of viremia in these samples that you have been studying? What is the maximum level of viremia?

DR. NAKHASI: Which samples are you talking about?

DR. GOLDSMITH: The ones that you recovered from the viremic donors.

DR. NAKHASI: From the viremic donors, I don't know. Maria, do you know what the levels are?

DR. RIOS: Between 10 5 and 106 is the high level of viremia that we have found. Are you

asking for the range of viremia or the high level of viremia?

DR. GOLDSMITH: I was just curious about the high but it is fine to give the range.

DR. RIOS: It varies. It varies. The assays, in general, that use lower volumes do not detect them. Assays that have higher volume and high throughput detect, but do not give accurate quantitation, to 10 6 copies/ml.

DR. NELSON: One of your slides had 23 positives with 16 by minipool and 7 by ID. Were those 7 not detectable by minipool or was it just that ID screening was triggered and they weren't tested by minipool?

DR. NAKHASI: I think they came for the ID-NAT testing. Is that true? Yes. You know, in BSL they had already started ID-NAT testing in Maricopa County. The trigger had started earlier.

DR. NELSON: So, they were negative by minipool?

DR. STRONG: No, the trigger was activated and they started doing ID screening so they haven't

gone back yet, I think, to see if those would have been picked up by minipool.

DR. BUSCH: Actually, 7/12 that were picked up in the region that had been converted to ID-NAT, 7 of them had been fully worked up and 5 of those 7 are negative at 1:16 dilutions so they would have been missed by minipool. Of those 5, 1 of them is antibody negative and 4 have IgM and IgG.

DR. NELSON: Has anybody looked at the characteristics of the donors that have low levels? Are there host factors that might influence whether somebody has high level or low level? I know one feature may be antibody but in those that are antibody negative, I wonder if there are any donor characteristics that influence the level of viremia.

DR. BUSCH: Sue has looked at that I think more formally and there wasn't any correlation. These are representative donors of the donor pool in terms of the viremics, non-viremics and low viremics. I think it is just by chance. This

phase of early viremia is completely asymptomatic.

DR. RIOS: It may have some inherited characteristics that limit the viral replication. The reason why we think that is because we have performed some in vitro studies with human primary macrophages and there is a great variability not only in the day of the viral peak, but some individuals can have a very steady and low titer that doesn't progress to peak. So, that indicates that some inheritance variability may interfere with replication.

DR. NELSON: That is interesting. Other questions?

DR. LAAL: Unless I misunderstood, I noticed that in 2003 we had a majority of your isolates from people who had fever, and about one-quarter were from neuroinvasive cases. In 2004 it is reversed.

DR. NAKHASI: Yes, that is an important point. I discussed it with the CDC folks and they said, you know, don't pay attention to that because the fever cases were--you know, this year they are

paying more attention so some of the fever cases were not real fever cases. You are right, you saw the switch.

DR. LAAL: But then in the isolates that you are picking up now for the genetic studies, are you carefully making sure that you look at both types?

DR. NAKHASI: Maybe Maria can say; I don't know.

DR. RIOS: The isolates that have been studied so far don't come from patients. Actually, that is the effort we are going to move towards now. They are identified through the blood screening. So, in order to evaluate if there is any isolate that may not be picked up by the blood screening we need to acquire samples from cases that are non-blood donors to investigate this possibility.

DR. NELSON: Yes, Mike?

DR. STRONG: Just a quick comment on the donors. In the studies that were done last year, many of the donors that were interviewed, in fact,

were symptomatic either shortly before or shortly after their donations but the screening questions just didn't pick them up.

IV. Hepatitis B Virus Nucleic Acid Testing (NAT) for Donors of Whole Blood

DR. NELSON: Thanks. The next topic is hepatitis B virus nucleic acid testing for donors of whole blood. Dr. Gerardo Kaplan will introduce this and give us background.

A. Introduction and Background

DR. KAPLAN: Good morning.

[Slide]

I am Gerardo Kaplan, Chief of the Lab of Hepatitis and Related Virus Emerging Agents. I am with the Office of Blood, and I will introduce for you the hepatitis B virus n nucleic acid testing for donors of whole blood.

[Slide]

The general agenda for this meeting is that after the introduction and background, Dr. Blaine Hollinger will give us an update on the serology of hepatitis G. This will be followed by