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一般的名称	①乾燥抗 HBs 人免疫グロブリン ②ポリエチレングリコール処理抗 HBs 人免疫グロブリン		研究報告の公表状況	FDA/CBER/20060808	公表国 アメリカ	
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研究報告の概要	使用上の注意記載状況・その他参考事項等
FDA/CBER 発行の 2002 年 1 月付" Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"の修正ガイダンス案である。勧告内容は以下の通り。 1980 年以降にフランス国内で血液又は血液成分の投与を受けたことのあるドナーは全て永久供血停止とする。但し、この勧告に基づけば供血停止とされるドナーであっても、もし当該ドナーが、非注射剤製造用にのみ血液成分の採取を認める CBER 認可プログラムに関与する場合は、供血を続けるよう推奨する。当該ドナー由来の製品には特別なラベルを付するよう推奨する。 このガイダンス案は、輸血用全血並びに血液成分、及び注射剤の製造に供される血液成分（回収血漿、原料白血球並びに原料血漿を含む）に適用される。	代表として静注用ヘブスブリンーIH の記載を示す。 2. 重要な基本的注意 (1)略 1)略 2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

報告企業の意見	今後の対応
FDA/CBER発行の2002年1月付" Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"の修正ガイダンス案である。 これまで血漿分画製剤によってvCJDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。	vCJD の疫学情報については、今後も注視することとする。

Guidance for Industry

Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"

DRAFT GUIDANCE

This guidance is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http:www.fda.gov/dockets/ecomments. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register.*

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448 or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact Dr. Sharyn Orton, Division of Blood Applications at 301-827-3524.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
August 2006

Contains Nonbinding Recommendations

Draft – Not for Implementation

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Guidance for Industry

Amendment (Donor Deferral for Transfusion in France Since 1980) to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products"

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance, which we are issuing as a level I guidance, is intended to amend the "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" (CJD/vCJD guidance), dated January 2002 (Ref. 1), by adding a donor deferral recommendation for donors who have received a transfusion of blood or blood components in France since 1980. After we review comments received on this draft guidance, we will amend the CJD/vCJD guidance by incorporating this donor deferral recommendation, update any outdated information, and reissue the revised CJD/vCJD guidance as a level II guidance document for immediate implementation.

This draft guidance applies to Whole Blood and blood components intended for transfusion, and blood components intended for use in further manufacturing into injectable products, including recovered plasma, Source Leukocytes and Source Plasma. Special provisions apply to donors of blood components intended solely for manufacturing of non-injectable products (see section III). Within this document, "donors" refers to donors of Whole Blood and blood components and "you" refers to blood collecting establishments.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Since the publication of the CJD/vCJD guidance, we have learned of additional information warranting revision to the guidance to address a possible increased risk of vCJD transmission from individuals who have been transfused in France since 1980. This revision is based on (1) the likelihood of exposure to the Bovine Spongiform Encephalopathy (BSE) agent in that country and (2) the recent documentation of three presumptive cases of transfusion-transmitted vCJD infection in the United Kingdom (U.K). As of August 1, 2005, 14 definite or probable cases of vCJD have been reported in France (Ref. 2).

Available data suggest that large amounts of U.K. beef exported to France during the peak years of the U.K. BSE epidemic constituted a substantial source of exposure in France to the BSE agent. An estimated 60% of U.K. bovine carcasses were exported to France (Ref. 3) accounting for approximately 6% of French consumption of beef products (Ref. 4). It is believed that the first recognized vCJD cases in France were infected by consuming imported U.K. beef because: 1) none of the individuals had lived in the U.K.; 2) the indigenous French BSE epidemic is relatively small and more recent than that in the U.K.; and 3) travels to the U.K. accounted for only 2% of the French total exposure to the BSE agent (Ref 3).

There have been a total of three presumptive cases of transfusion-transmitted vCJD, and all have been in the U.K. The first presumptive transfusion-transmitted case of vCJD by red blood cells was reported to the U.K. Parliament on December 17, 2003 (Ref. 5). A second presumptive case was reported in the U.K. in 2004 (Ref. 6). A third presumptive case was publicly announced by authorities in the U.K. in 2006 (Ref. 7).

On February 8, 2005, the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) discussed the available data and recommendations for deferral of U.S. donors transfused since 1980 in France and in other European countries. The TSEAC voted for deferral of blood donors who have received a transfusion of blood or blood components in France since 1980 but against deferral of Source Plasma donors with that same history. The TSEAC did not support deferral of blood donors or Source Plasma donors with history of transfusion in other European countries since 1980 (Ref. 8).

The incubation period for classical CJD may be as long as 38.5 years. Accumulating evidence suggests that the asymptomatic incubation periods of vCJD may be very long as well (sometimes exceeding 12 years from the time of exposure to the BSE agent), and blood collected as long as three years before otherwise healthy blood donors showed any sign of illness is presumed to have transmitted vCJD infection to recipients (Refs. 5 and 6). While the risk of dietary exposure to the BSE agent in France, as in the U.K. and other European countries, has almost certainly decreased in recent years thanks to successful efforts to control the BSE epidemic in cattle and to protect food from contamination with the BSE agent, an unknown but possibly significant number of blood donors might have already been infected in France during the peak years of the BSE outbreak in Europe. These considerations led FDA, consistent with the recommendations of the TSEAC, to conclude that it would be a prudent

preventive measure to indefinitely defer blood donors who have received transfusions of blood or blood components in France since 1980. Laboratory studies using model TSE agents have demonstrated that TSE infectivity may be reduced by certain plasma fractionation manufacturing steps (Ref. 9). While experimental studies are reassuring, not all products have been thoroughly studied. In addition, it remains uncertain whether the models accurately reflect the form of infectivity in blood, which has not been characterized. Therefore, as an added safeguard and prudent preventive measure, we also recommend that Source Plasma donors who have received a transfusion of blood or blood components in France since 1980 be indefinitely deferred. However, we believe that blood components collected solely for manufacturing into non-injectable products (e.g., materials used in in vitro diagnostic test kits) need not be deferred. We will continue to monitor the BSE epidemic and re-evaluate the necessity of deferring donors transfused in other European countries.

III. RECOMMENDATIONS

You should indefinitely defer all donors who have received a transfusion of blood or blood components in France since 1980.

NOTE: Donors who are otherwise deferred based upon this recommendation should continue to donate if they are participating in a CBER-approved program that allows collection of blood components solely for use in manufacturing of non-injectable products. We recommend special labeling for products obtained from such donors (see section VII.A of the CJD/vCJD guidance).

All other recommendations from the CJD/vCJD guidance remain unchanged.

IV. IMPLEMENTATION

We recommend that you implement this donor deferral recommendation within six months of the date that we finalize this draft guidance amendment. This draft guidance amendment will be finalized by reissuing the CJD/vCJD guidance inclusive of the amended language.

V. REFERENCES

1. FDA "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," January 2002; http://www.fda.gov/cber/gdlns/cjdvcjd.htm.
2. http://www.invs.sante.fr/publications/mcj/donnees_mcj.html
3. Chadeau-Hyam, M. and A. Alperovitch, "Risk of Variant Creutzfeldt-Jakob Disease in France," *International Journal of Epidemiology*, 34(1):46-52, 2005.
4. Supervie, V. and D. Costagliola, "The Unrecognised French BSE Epidemic," *Veterinary Research*, 35(3):349-62, 2004.
5. Llewelyn, C.A., P.E. Hewitt, R.S. Knight, et al., "Possible Transmission of Variant Creutzfeldt-Jakob disease by Blood Transfusion," *Lancet*, 363(9407):417-21, 2004.
6. Peden A.H., M.W. Head, D.L. Ritchie, et al., "Preclinical vCJD After Blood Transfusion in a PRNP Codon 129 Heterozygous Patient," *Lancet*, 364(9433):527-9, 2004.
7. http://www.eurosurveillance.org/ew/2006/060209.asp
8. http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4088t1.doc
9. Foster, P.R., A.G. Welch, C. McLean, et al., "Studies on the Removal of Abnormal Prion Protein by Processes Used in the Manufacture of Human Plasma Products," *Vox Sanguinis*, 78:86-95, 2000.

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別紙 3-3

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2006 年 2 月 28 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	Clinical implications of emerging pathogens in haemophilia: the variant Creutzfeldt-Jakob disease experience Golan, G. Haemophilia 12, (Suppl. 1), 16 - 20 (2006)	公表国 英国	
販売名（企業名）						

研究報告の概要	使用上の注意記載状況・その他参考事項等
本文献は英国の血友病の実地臨床における変異型クロイツフェルト・ヤコブ病(vCJD)の影響を報告している。1980年代，血漿由来製剤による治療で，血友病患者団体がHIVとC型肝炎ウイルス感染の危険に直面するという厳しい教訓を得た。このため，1997年に英国血友病センターの医師団は，血友病患者に対する最適な治療法は遺伝子組換え凝固因子であると述べた。1996年の，英国で最初のvCJD症例報告の直後に，輸血を介してvCJD感染の恐れがあるという懸念が生じた。1997年，vCJDは英国においてのみ確認され，多くの血友病患者が英国由来の血漿因子濃縮製剤の投与を受けていたため，遺伝子組換え凝固因子による治療を受けられない患者には，非ヨーロッパ諸国，好ましくは米国で処理が行われた血漿因子濃縮製剤を用いるべきである，という追加勧告がなされた。後に，1996-97年に英国で供血された血漿因子濃縮製剤のいくつかのバッチが実際にvCJDを引き起こす病原因子で汚染されていたことが明らかになった。この結果，2005年4月現在，A型及びB型血友病患者全員に遺伝子組換え凝固因子が投与されている。輸血を介してvCJDに感染した最初の患者が2003年12月に死亡後，ヒト間での感染リスクが減少するよう計画された法案により，1980年から2001年の間に英国で供血されたヒト血漿由来の治療を受けた全血友病患者の取扱いが決定した。例えば，これらの患者が中枢神経系に関わる手術を受けた際，使用された手術器具は全て廃棄されなければならない。したがって，筆者は血友病患者にはリスクの最も低い治療法のみを適用することを推奨している。	BYL-2006-0220-3

報告企業の意見	今後の対応
弊社の第 VIII 因子製剤は遺伝子組換え製剤である。本剤の培養培地にはヒト血漿由来成分が使用されているが，弊社の血漿分画製剤の製造工程は，4log を上回るプリオンを除去することが確認されている。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

Haemophilia (2006), **12**, (Suppl. 1), 16–20

Clinical implications of emerging pathogens in haemophilia: the variant Creutzfeldt–Jakob disease experience

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Summary. The impact of variant Creutzfeldt–Jakob disease (vCJD) on the clinical practice of haemophilia in the UK is coloured by the haemophilia community's experience of hepatitis C virus and human immunodeficiency virus (HIV) transmission via plasma-derived therapies in the 1980s, when the delay in recognizing and acting on the potential risks cost many patients their lives and left others to manage another chronic disease. This crisis prompted organisations such as the United Kingdom Haemophilia Centre Doctors' Organisation to advocate for the introduction of haemophilia therapies that would not be susceptible to contamination with blood-borne pathogens. After the identification of vCJD in 1996, a number of public health measures were taken in response to a government-sponsored vCJD risk assessment, and following reports of transfusion-transmission of vCJD, additional guidelines have been developed to prevent person-to-person transmission, some of which may impact the quality and availability of medical and surgical care. Variant CJD has had a significant negative effect on the UK haemophilia community, shaking patient confidence in the therapies they have received over the last 21 years, affecting the quality of care and creating the risk of stigmatizing the community as it was in the 1980s. As with HIV and vCJD, emerging blood-borne infectious agents will likely affect blood and blood-derived therapies well before we become aware of its presence. As a result, only therapies with the lowest level of risk should be used for care of patients with haemophilia.

Keywords: haemophilia, pathogen, variant Creutzfeldt–Jakob disease

Introduction

This article will review the impact of variant Creutzfeldt–Jakob disease (vCJD) on the clinical practice of haemophilia in the UK, with particular attention to how haemophilia treater and patient organizations have responded to this concern. The haemophilia community's response to vCJD is best understood in the context of the significant morbidity and mortality caused by the transfusion-transmitted hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections contracted in the 1980s. Given the delayed recognition of the risk that HIV and HCV posed to patients with haemophilia, the subsequent lack of rapid response and the many missed opportunities to protect patients from contaminated plasma-derived therapies, it is understandable that many patients with haemophilia and their caregivers are now very alert to the potential implications of emerging pathogens such as vCJD. This is especially true for those patients who still rely on plasma-derived therapies and transfusions.

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UKHCDO therapeutic guidelines

The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) was established in 1968 by doctors treating patients with bleeding disorders who sought to improve care, conduct research into the disorders and facilitate healthcare planning. The UKHCDO and the patient organization the Haemophilia Society had, for many years, argued for the introduction of recombinant therapies. This view was reflected in the UKHCDO haemophilia treatment guidelines, published in 1997, which stated that recombinant factor concentrates were the treatment of choice for patients with haemophilia [1]. The guidelines further stated that recombinant factor concentrates were the safest with respect to reducing the risk of transfusion-transmitted infection. At the

time the UKHCDO guidelines were released, the general consensus among haemophilia treaters was that the plasma therapies used in the UK had a relatively low risk for transmission of hepatitis or HIV, but because they could transmit other infectious agents, such as parvovirus B19 and hepatitis A, [2,3] they might in theory be the route of infection for new or altered agents.

The UKHCDO guidelines were accepted by most treaters but not by the majority of healthcare commissioners. In particular, the future risk of infection by emerging pathogens through plasma therapy was not accepted. Approximately 6 months later, the potential threat of vCJD to the haemophilia community emerged.

Shortly after vCJD was first described in the UK in 1996, concerns were raised that it could be transmitted through blood transfusion and blood therapies [4]. As a result, the UKHCDO convened a meeting with experts on prion diseases, including members of the National CJD Surveillance Unit and the Spongiform Encephalopathy Advisory Committee (SEAC), both of which were formed in 1990. The National CJD Surveillance Unit is sponsored by the Department of Health (DOH) and the Scottish Executive Health Department; SEAC is sponsored jointly by the Department for Environment, Food and Rural Affairs, the DOH and the Food Standards Agency (FSA). The purpose of the meeting was to determine, by means of a thorough review of all available evidence, if there were any measures available to effectively reduce the risk to patients with haemophilia of contracting vCJD and other prion-based diseases.

At the time, in 1997, vCJD had only been identified in Great Britain. Limited research indicated that this was a new disease with a long incubation period [5]. Relatively little epidemiological data were available, but evidence from some animal studies indicated that there existed the possibility of transfusion-transmitted vCJD infections. Further, it was surmised that many vCJD-infected, yet asymptomatic, individuals were continuing to donate blood that would be used in the processing of factor VIII and factor IX therapies. At that time, many patients with haemophilia in the UK were treated with UK-sourced plasma factor concentrates.

Based on the 1997 meeting of the UKHCDO, SEAC and the National CJD Surveillance Unit, several recommendations emerged [4]:

1 Healthcare providers should reduce the risk of vCJD transmission by using plasma factor concentrates sourced in other countries.

2 Recombinant factor concentrates should remain the treatment of choice for patients with haemophilia.

3 Plasma-derived concentrates processed with non-European plasma, preferably from the US, should be provided for those patients for whom recombinant factor concentrates were not made available.

As a consequence of these recommendations, the two main UK fractionators of plasma, Bio Products Laboratory and the Scottish National Blood Transfusion Service, were obligated to stop processing factor concentrate therapies. In the meantime, the UK imported plasma from the US for processing factor VIII and factor IX. This ban on utilization of UK-derived plasma resulted in long delays in resuming the processing of factors and interrupted the supply of other niche therapies such as factor VII and factor XI.

Patients and providers respond

Prior to 1997, many patients with haemophilia and their physicians held the view that UK-sourced plasma therapies were safer than any alternative and there had been a relatively slow uptake of recombinant therapies. With the introduction of these policies recommending the use of non-UK-sourced plasma, however, patient confidence was undermined and the pressure increased on government and healthcare commissioners to make recombinant therapies more widely available.

Against a background of increasing concern about the possible risk of vCJD, England's Department of Health agreed that recombinant therapies should be made available to all children with haemophilia [6]. In other health departments, in Scotland, Wales and Northern Ireland, they took the recommendations one step further and introduced recombinant therapies for all patients. But in England, the most populous country in the UK, adults continued to be prescribed and use plasma therapies, although derived from plasma imported from the USA.

Variant CJD: a potential new threat to factor concentrate safety

In 2000, Bio Products Laboratory notified the UKHCDO about the identification of batches of factor concentrates that had been prepared in 1996 and 1997 and used before 1998. It was determined that these concentrates were prepared from plasma pools that included plasma from a donor who had

subsequently developed vCJD. Since then there have been further notifications of batches of factor concentrates prepared from plasma from donors who were later diagnosed with vCJD. Table 1 enumerates all the batches of therapies distributed and subsequently identified as being potentially infected with vCJD, as of September 2004 [7]. These therapies were produced by either Bio Products Laboratory or Protein Fractionation Centre and, in most circumstances, many patients were treated with these therapies before notification had been given.

At the time there was no clear evidence that vCJD could be transmitted by blood products. There was no test to identify potentially asymptomatic but infected donors, and there was no treatment to offer patients for reassurance or for further assessment. Because vCJD has a long incubation period, clinical examination was of little or no use. With these facts in mind, healthcare providers and policy makers were faced with the decision of what, or even if, to tell their patients.

Response to possible risk of transfusion-transmitted vCJD

In 2004, the decision was made to inform all patients about the possible risk of transfusion transmitted vCJD, irrespective of whether they had received concentrates or not from the implicated batches. Patients were given three choices: they could come into their healthcare providers' offices and discuss the information in person; they could choose to be fully informed by letter; or they could refuse to be informed in any way. Many patients chose the third option. Patients who chose to be educated about the potential risks were given information disclosing that they might be infected with vCJD. Given that the majority of patients were not able to have access to recombinant therapies, this situation caused considerable concern.

For the UKHCDO, responding to the potential infection of haemophilia patients created a huge administrative burden. There was an urgent need to review all records, to contact all patients possibly infected and to give each of them the option to review all information then known about vCJD. Added to the administrative burden were government-mandated timelines as to when the patients needed to be informed.

The threat of vCJD among members of the haemophilia community increased the political pressure for more widespread use of recombinant coagulation factor concentrates in the UK. And as a result, as of April 2005, all patients with haemophilia A and B have been offered recombinant factor concentrates.

Table 1. Batches of 'implicated' UK plasma therapies [7].

Factor VIII	16*
Factor IX	8*
Antithrombin	1
Immunoglobulin G	11
Albumin 4.5%	28
Albumin 20%	21
Factor VIII with albumin excipient	76
Intramuscular immunoglobulin	12

*Indicates widely distributed throughout the UK.

Risk of vCJD from implicated plasma-derived concentrates

One of the questions that remain unanswered today is what risk do the recipients of plasma concentrates exposed to vCJD pose to others? This issue came to the forefront in December 2003 when the Health Secretary informed the UK Parliament of the first death probably related to transfusion-transmitted vCJD. This case was later confirmed as being related to vCJD [8,9].

The Department of Health established the CJD Incidents Panel, an expert committee sub group of the Advisory Committee on Dangerous Pathogens Working Group on Transmissible Spongiform Encephalopathies, in 2000 in order to help the medical community handle cases such as this. The mandate of this committee is to review the available literature, establish a formal risk assessment of infectivity of blood and blood therapies and formulate guidelines for response by the medical community. The CJD Incidents Panel advises hospitals, trusts and public health teams throughout the UK on how to manage incidents involving possible transmission of CJD between patients.

Based on a risk assessment commissioned by the DOH in 2003, the CJD Incidents Panel attempted to identify patients who had received at least one dose of a plasma therapy, which the committee judged to increase the risk of vCJD exposure by more than 1% over background. Therapies that were considered the highest risk were factor VIII, factor IX and antithrombin. The administration of just one vial, or 500 units, was considered enough to put patients in a high-risk category. Medium risk therapies included intravenous immunoglobulin G and albumin 4.5% administered in large doses. Low-risk therapies were defined as albumin 20%, intramuscular immunoglobulin and factor VIII with excipient albumin administered in extremely large doses [10].

In refining the risk assessment, the question emerged: which of the 'at risk' patients need be treated with precaution: those with known exposure to contaminated or potentially contaminated batches of plasma concentrates, or any patient treated with plasma-derived concentrate in the period from 1980 to 2001? Because the possibility existed that, over time, additional donors might be identified as having vCJD, it was decided to treat all haemophilia patients who had used therapies from UK-derived plasma in this 21-year-period with measures designed to reduce the risk of human-to-human transmission [11].

Measures to prevent human-to-human vCJD transmission

Following the 2001 release of a DOH-sponsored summary of the risks of vCJD transmission via surgical implements [12], the Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee published a set of guidelines in 2003 for the precautionary management of potentially-infected patients, both healthy and deceased, in order to minimise the risks of transmission to other patients and healthcare staff [13]. These guidelines were a significantly expanded version of recommendations that were released in 1998 but kept under review until a number of uncertainties were better understood, including the routes of infection, threshold infectious dose, potential for inactivating the agent and the quantity of people who might be incubating the disease.

The detailed guidelines recommend measures for laboratory containment and control, infection control of CJD and related disorders in a healthcare setting, decontamination and waste disposal and quarantining of surgical instruments, among others. For example, when patients who used UK-sourced plasma-based therapies in the years 1980–2001 undergo any surgery involving high-risk tissues, such as the central nervous system or the lymphatic system, the surgical instruments used must be subsequently destroyed [14].

Some general precautions included using single-use instruments wherever possible; performing all procedures in a controlled environment, such as an operating theatre; performing the procedure after all others; involving the minimum number of healthcare personnel; and using liquid-repellent operating gowns over plastic aprons, as well as goggles or full-face visors [15].

More controversially, the guidelines stipulated that if these patients have an endoscopic procedure of the gastrointestinal tract or the olfactory mucosa, the instruments used in those procedures also must be quarantined, i.e. not used again or destroyed [15]. The quarantine or destruction of surgical instruments has, of course, financial consequences: the quarantine of an endoscope is estimated to cost approximately £30 000 per instrument per year. Endoscopy services are in high demand, and quarantining an endoscope, or destroying it after every use, is not a reasonable or cost-effective policy for any healthcare institution. In the risk-assessment guidelines, it was suggested that capsule wireless endoscopes be used instead, but expertise in capsule endoscopy is limited, so the issue has yet to be fully resolved.

Potential stigmatization

One of the negative outcomes of the distribution of the guidelines of the CJD Incidents Panel was that persons with haemophilia became identified as presenting a risk of infection to others. In some medical centres, reluctance to performing invasive procedures became an issue in all but serious cases.

Despite assertions that these precautions should not compromise care for patients with haemophilia, the potential exists that these patients will be stigmatized again, as they were early in the HIV crisis, and that their normal medical and surgical care may be interrupted.

Scope of the problem

Cases of vCJD have also been reported outside the UK. In France, for example, 14 cases of vCJD have been reported, with three identified in persons who donated blood over a 10-year-period. Again, most of the donations have been used to make factor VIII, von Willebrand factor, and other plasma therapies. In response, the French have recalled all plasma-derived therapies, where possible, and all patients have been informed.

To further complicate matters, it is known that the French fractionators have exported concentrates to other countries, such as Belgium. And in the UK, Bio Products Laboratory also exported factor concentrate to other countries. At this point in time, there are no clear guidelines on how to manage potential risk in these situations.

Another concern involves haemophilia patients who visited the UK: unknown numbers of visitors were treated with UK-sourced factor concentrates during the crucial 21-year-period. Because records on the treatment of visitors to the UK are not readily

available, it is very difficult to identify or advise those patients.

Conclusion

The phenomenon of emerging vCJD is yet another warning against the complacent assumption that plasma-derived therapies can be made completely safe. Variant CJD has had a significant negative effect on the haemophilia community in the UK, shaking patient confidence in the therapies they have received over the last 21 years, affecting the quality of current and future medical and surgical care and creating the risk of stigmatizing the community as it was in the 1980s, at the beginning of the HIV crisis.

Our awareness of vCJD is not even a decade old. Much about the disease is still unknown, including the best means for preclinical detection and effective inactivation. But given its long incubation period, it's possible that the impact of vCJD on patients with haemophilia may be significant.

As described elsewhere in this supplement, the barriers to the emergence of pathogenic agents, both air- and blood-borne, continue to diminish. And as with HIV and vCJD, the next emerging blood-borne infectious agent will likely affect blood and blood-derived therapies well before we become aware of its presence. It is because of these reasons that only the therapies with the lowest level of risk should be used for care of patients with haemophilia.

References

1 United Kingdom Haemophilia Centre Doctors' Organisation. Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders. *Haemophilia* 1997; 3: 63–77.

2 Soucie JM, Siwak EB, Hooper WC, Evatt BL, Hollinger FB and the Universal Data Collection Project Working Group. Human parvovirus B19 in young male patients with hemophilia A: associations with treatment product exposure and joint range-of-motion limitation. *Transfusion* 2004; 44: 1179–85.

3 Schneider B, Becker M, Hans-Hermann B, Eis-Hubinger AM. Contamination of coagulation factor concentrates with human parvovirus B19 genotype 1 and 2. *Thromb Haemost* 2004; 92: 838–45.

4 Ludlam CA, on behalf of the executive Committee of the UKHCDO. New-variant Creutzfeldt–Jakob disease and treatment of haemophilia. *Lancet* 1997; 350: 1704.

5 Will RG. Variant Creutzfeldt–Jakob disease. *Acta Neurobiol Exp* 2002; 62: 167–73.

6 National Health Service. *Provision of Recombinant Factor VIII for New Patients and Children Under the Age of 16.* Health Service Circular. HSC 1998/033. 17 March 1998. Published online at http://www.dh.gov.uk/assetRoot/04/01/16/95/04011695.pdf. Accessed September 2005.

7 Health Protection Agency. *vCJD and Plasma Products – Tables of vCJD Implicated Batch Numbers: To Those Responsible for Tracing vCJD Implicated Plasma Product Batches in the UK.* 7 September 2004. Published online at http://www.wfh.org/2/docs/Safety_Supply/Recall_BPL_Sept2004.pdf. Accessed September 2005.

8 Llewellyn CA, Hewitt PE, Knight RSG *et al.* Possible transmission of variant Creutzfeldt–Jakob disease by blood transfusion. *Lancet* 2004; 363: 417–21.

9 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; 364: 527–9.

10 Det Norske Veritas for Department of Health. *Risk Assessment of Exposure to vCJD Infectivity in Blood and Blood Products.* February 2003, 1–30. Published online at http://www.dnv.co.uk/Binaries/vCJD_Update_Report_tcm23-74414.pdf. Accessed September 2005.

11 Health Protection Agency. *vCJD and Plasma Products – Clinical Information.* 7 September 2004. Published online at http://www.hpa.org.uk/infections/topics_az/cjd/Clinical.pdf. Accessed September 2005.

12 Department of Health, Economics and Operational Research Division (EOR4). *Risk Assessment for Transmission of vCJD via Surgical Instruments: a Modelling Approach and Numerical Scenarios.* February 2001. Skipton House, London. Published online at http://www.dh.gov.uk/assetRoot/04/07/53/88/04075388.pdf. Accessed September 2005.

13 Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee. Foreword. In: *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection,* 2003. Available at http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/. Accessed September 2005.

14 Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee. Annex E: Quarantining of surgical instruments. In: *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection,* 2003. Published online at http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/tseguidance_annexe.pdf. Accessed September 2005.

15 Advisory Committee on Dangerous Pathogens and the Spongiform Encephalopathy Advisory Committee. Part 4: Infection control of CJD and related disorders in the healthcare setting. In: *Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection,* 2003. Published online at http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/tseguidancepart4.pdf. Accessed September 2005.

医薬品
医薬部外品　研究報告　調査報告書
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一般的名称			研究報告の公表状況	Implications of emerging pathogens in the management of haemophilia Haemophilia 12, (Suppl. 1), 26 -28 (2006)	公表国 米国	
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研究報告の概要

英国保健当局と医療関係者間の以下2点に関する議論の要旨である。
i) 現在の血友病患者が直面している新規の，血液媒介病原体による潜在的感染の危険性
ii) 過去25年間にこの分野で判明した教訓
2番目の議論に関して，英国の血友病患者にとってエイズまたは変異型クロイツフェルトヤコブ病(vCJD)の危険性が大きな脅威であった。これまで，血液凝固第VIII因子，又は第IX因子療法を受けている患者のvCJD症例報告はなかった。しかし，正式にこの可能性を否定するには，恐らく以前より時間がかかるであろう。また，白血球除去や血漿分画といった技術改善は感染症のリスクを減少させる際に僅かに効力を示すのみであった。
最近では，遺伝子組換え製剤による治療は完全にウイルス感染リスクをなくすわけではない，ということが明らかになっている。特に，現在の不活性化法に耐性のあるパルボウイルスB19のような非エンベロープウイルスとなるとなおさらである。西ナイルウイルスのような血液を介して感染する新規病原体は予想以上に早く出現する，と医師はみている。そのため彼らは最高水準の安全管理を推奨し，新規病原体のスクリーニングテストが可能となれば即時，血友病患者に対して積極的に行い，適切な手段と規制を実施することを提案している。

報告企業の意見	今後の対応
弊社の第 VIII 因子製剤は遺伝子組換え製剤であるが，本剤の培養培地にはヒト血漿由来成分が使用されている。しかしながら，弊社製剤中に残存しうる血漿由来成分は，プール血漿において NAT を実施するとともに，その製造工程でウイルス不活化・除去工程を実施し安全性を確保している。	現時点で新たな安全対策上の措置を講じる必要は無いと考える。引き続き関連情報の収集に努める。

使用上の注意記載状況・その他参考事項等

BYL-2006-0220-4

26

Haemophilia (2006), 12, (Suppl. 1), 26–28

DISCUSSION SESSION

Implications of Emerging Pathogens in the Management of Haemophilia

Discussion Session

1. Is there any evidence that haemophilia patients in the UK have been infected with variant Creutzfeldt–Jakob disease (vCJD) via therapies made from contaminated blood donations? Phrased differently, are there good data to support the decision in the UK to phase out the use of recombinant factor VIII (rFVIII) therapies processed with plasma additives, and are the surgical precautions in treating haemophilia patients necessary?

DOLAN: Initial discussions surrounding these issues were definitely controversial, and we in the medical community were not sure how far we needed to go in trying to protect patients. But the recommendations and surgical measures were devised after very detailed consultation with experts who knew far more about prion disease than we did.

Certain decisions, such as ceasing use of UK plasma-derived therapies, were difficult for both patients and their providers. But the subsequent events, in particular the later evidence that there have been at least two probable cases of transfusion-transmitted variant CJD, seem to justify that early stance by not just the UK but other countries as well.

2. Do you think that the fact that vCJD has not been identified in any patient receiving plasma derivatives worldwide since 1980 suggests that the risk of vCJD is minimal or non-existent from these therapies?

IRONSIDE: First of all, let's be quite clear about why 1980 has become a benchmark. The date 1980 was chosen simply because that was thought to be the earliest date at which human exposure to bovine spongiform encephalopathy (BSE) in the UK was likely to have occurred. Overall, human exposure to BSE probably would be very low in the early 1980s and highest in the late 1980s and early 1990s. It is also important to remember that we are dealing with a primary disease transmission with an incubation period of approximately 15 years on average. So, we may have to wait a few more years before we can be certain about the absolute risk of contracting vCJD.

I would be very cautious about relaxing policies and guidelines at present because, as we all understand, there are other emerging infectious agents – identified and unidentified – that are cause for concern in addition to the vCJD-causing prion.

3. Do you know of any vCJD transmissions by plasma-derived FVIII/FIX therapies?

IRONSIDE: At present, no. There is no evidence that vCJD has occurred or infection has been transmitted by these therapies. Although, as I stated earlier, this may be due to the fact that we are dealing with an agent that has a long incubation period. The level of infectivity in plasma therapies may be lower or variable. But it is too soon to exclude that possibility.

The United Kingdom Haemophilia Centre Doctors' Organisation, along with several patient groups, is engaged in enhanced surveillance of the haemophilia population. We are looking for evidence of vCJD – even of subclinical infection – in patients who died or who have a lymphoid tissue biopsy for whatever reason.

4. What is the likely impact of the UK experience with vCJD in the United States and what might those treatment implications be?

DOLAN: Reported cases of BSE in the United States are very few. And if the number of cases remains at this low level, or even disappears altogether, then perhaps US practitioners and policy makers won't be obligated to take the more sweeping measures that we did in the UK. However, as a general concept, we must all remember that emerging pathogens can affect transfusion therapy. So, based on the UK experience, if healthcare providers have an opportunity to minimize risk to patients, then it is a prudent course of direction that should be considered seriously and likely taken.

5. Are there data that leukodepletion of blood will decrease the risk of transmitting vCJD? If not, what is the rationale?

IRONSIDE: This is a very interesting question because the UK has been using leukodepletion as one of its main strategies for risk reduction in terms of blood transfusion. The data from experimental

studies do indicate that although leukodepletion will reduce infectivity, it will not remove it entirely.

Because leukodepletion does not remove all infectivity, there have been a number of other approaches that utilize additional filters that might bind more specifically to any free prion protein in the plasma and thus, further reduce the risk.

6. Please describe the results of experiments in which blood was spiked with vCJD concentrate to determine whether prions could be removed.

IRONSIDE: Results of a spiking experiment were published using blood containing a range of prions, including both sporadic and variant CJD prions. The study looked at the effect of plasma fractionation in removing the prions. And indeed, fractionation did seem to have a positive effect.

However, there are a number of concerns about these spiking experiments because they involve inoculating brain homogenate into blood and using that as the spike. Essentially, it is infected brain tissue, which is very unphysiological. Therefore, it is unlikely to replicate the form of infectivity found in blood-endogenous infection, where it is probably free in plasma and not aggregated as it would be in brain. So, while the spiking experiments do provide some reassuring information, a number of questions persist as to just how valid the spiking method is.

7. What about the results of the study in which 11% of patients who received recombinant therapy only were seropositive for parvovirus B19 antibodies soon after start of treatment? Aren't recombinant therapies totally free of any virus transmission risk?

TAPPER: As has been stated, the non-lipid-encased viruses are obviously much more difficult to inactivate. So if you ask, do the current technologies inactivate all pathogens, the answer is clearly no, they do not.

Parvovirus is one of the classic markers for these types of viruses. In children, parvovirus is relatively benign, but older people tend to get sick from it. Parvovirus can be viewed as a marker for pathogens that are either difficult to inactivate or that simply have not been fully described as yet. There are many viruses that fall into this latter category. For example, where did severe acute respiratory syndrome come from? Where did the coronavirus come from? It is clearly a novel virus that probably made a cross-species jump. You could say very much the same thing about human immunodeficiency virus when it was first described in industrialized countries in the 1980s, but clearly, phylogenetically, it had been present in Africa for at least 50 years prior to that time.

Factors such as the vastly increased ability of populations to travel, the issues surrounding land encroachment and the disruptions of the natural barriers between humans and humans and between humans and animals are clearly going to continue. And within that context, you can anticipate that new pathogens will continue to emerge, at least some of which, like West Nile virus, will be transmissible via blood.

PIPE: The medical community is not particularly concerned with parvovirus, but we're looking at it as a marker because it is one of the non-lipid-enveloped viruses for which we can actually screen. At this point in time, the theoretical concern would involve early seroconversions among patients who have depended solely on recombinant therapies. We would need to ask: is there the potential for another infectious agent – which either has or has not emerged yet, or that we don't have a test for – to become a threat to these patients?

What it comes down to is an issue of vigilance, and I think it is encouraging to see that when testing is available, such as prion screening, we are actively looking for patients who have the protein. Another encouraging example involves West Nile virus. It was only a very short period of time from its appearance to actually having an effective screening tool; this rapid response illustrates that the scientific world can respond quickly to address these kinds of issues.

8. What is the justification of continuing to use a therapy that is processed with bovine plasma protein?

PIPE: In a single clinic, I might talk to a patient with von Willebrand disease and a patient with another rare coagulation deficiency, both of whom would rely on plasma derivatives. With these patients I discuss the continued vigilance and screening that have resulted in the safety of these therapies thus far. I think it is important to inform them that there are ongoing concerns with respect to emerging pathogens, but also that as we learn more about potentially infective agents, we establish policies that will go a long way toward preventing another crisis in which emerging pathogens contaminate blood-derived therapies.

Alternatively, I will have a conversation with a family member or patient with either haemophilia A or haemophilia B and discuss with them the availability of newer therapies that are not processed with human or animal protein additives. The conversation with the patient with von Willebrand disease is very different than the one with the haemophilia patient: one is a conversation of reassurance, and the other a conversation of striving to be proactive, to help these

patients and their caregivers consider new therapies that may reduce the risk of infection with disease-causing agents.

Our history with haemophilia patients is interesting. In 1992, we switched all of our paediatric patients on FVIII to recombinant therapies. Then, in 1998 when recombinant FIX was available, we switched all of our patients from plasma-derived FIX to recombinant. That therapy had reduced recovery time in paediatric patients, and as a result, many patients had to use up to twice the amount of factor units that they would have had they remained on plasma-derived therapies. There is also the increased cost associated with the therapy.

The decision to switch patients to recombinant therapies was not based on any evidence of a known infectious agent being transmitted by plasma derivatives. Yet if you look at the data from the US Centers for Disease Control and Prevention on the adoption of recombinant therapies in paediatric patients, and indeed for adult patients around the US, it is quite remarkable how enthusiastically patients and clinicians have embraced recombinant technology.

For some patients, unfortunately, choice is not an option. There are patients in some areas of the US who do not even have access to recombinants. So, for these patients we must rely on the 20 years of safety that we have enjoyed with plasma derivatives. This relative safety should not lull us into a mode of complacency where we ignore emerging pathogens such as vCJD.