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NHS
Blood and Transplant

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75 Cranmer Terrace
Tooting
London
SW17 0RB

Tel: 020 8258 8300
Fax: 020 8258 8453
www.nhsbt.nhs.uk

Mr Nick Fish
Scheme Administrator
The Skipton Fund
PO Box 50107
London
SW1H OYF

Dear Nick,

Thank you for forwarding to us the letter from Professor Graham Foster (dated 7th October 2009) regarding hepatitis C and intramuscular gamma-globulin.

Professor Foster is quite correct to say that there have been published reports of hepatitis C infection in recipients of immunoglobulin. He has not, however, made a distinction between intravenous and intramuscular immunoglobulin. While there have been no documented reports of hepatitis C transmission through intramuscular immunoglobulin, there have been several reports linking hepatitis C transmission to the use of intravenous immunoglobulin. An internet search will reveal numerous reports linking hepatitis C transmission and immunoglobulin, but many of the abstracts available on the web fail to specify which type of immunoglobulin was involved. Nevertheless, reference back to the relevant papers makes it clear that all such reports related to intravenous immunoglobulin.

Intramuscular immunoglobulins have a long and excellent safety record. Although transmission of hepatitis B virus through intramuscular immunoglobulin occurred in the 1970s, transmission of viruses has not been documented since then in association with these products. This is despite the fact that prior to HCV screening of blood and plasma donations more than one half of the intramuscular preparations of immunoglobulins contained detectable HCV RNA. Intramuscular immunoglobulin preparations are prepared according to the Cohn fractionation process, which separates the fraction containing antibodies that neutralize various infectious agents. The resulting preparations are highly concentrated. Other manufacturing procedures do not ensure the same safety. Over the last fifty years, many millions of individuals worldwide have received intramuscular immunoglobulins [including intramuscular anti-Rh(D)] without contracting infections. Intramuscular immunoglobulin prepared according to the Cohn process has been declared safe by the Centres for Disease Control and by the World Health Organization. The safety of intramuscular immunoglobulin preparations has been attributed to several factors relevant to the manufacturing process, including partitioning and inactivation of viruses.

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In contrast, intravenous immunoglobulin undergoes different manufacturing processes in order to enable it to be administered by the intravenous route. Between 1983 and 1994 at least eight outbreaks of non-A, non-B (HCV) infections occurred in subjects who received intravenous immunoglobulin. In 1994 an outbreak of HCV infection was associated with intravenous immunoglobulin (Gammagard) produced by Baxter Healthcare Corporation. Cases were reported in Europe and the United States. At the time, the Gammagard product was produced without any of the additional HCV inactivation processes that later came into use.

There have been two reports of HCV transmission associated with the use of **intravenous** anti-Rh(D) immunoglobulins, which were produced in East Germany and the Republic of Ireland. Both these products were produced by the Anion-exchange chromatography method as opposed to the Cohn cold ethanol fractionation method employed for most other intravenous immunoglobulin products. The outbreak in East Germany occurred in the late 1970s and was attributed to a single donor. Similarly, the outbreak in Ireland, involving anti-Rh(D) produced for intravenous use, was linked to a single infected plasma donor.

To illustrate the difference between the risk from intravenous and intramuscular immunoglobulins, an unfortunate experience by BPL can be used. BPL manufactured an intravenous immunoglobulin in the early 1980s and arranged a comparative study against the then standard intramuscular immunoglobulin treatment for patients with immunodeficiency. Twelve patients were allocated to receive intravenous immunoglobulin preparation, and another twelve received the intramuscular preparation. All twelve of those who received the intravenous immunoglobulin had previously received weekly intramuscular immunoglobulin therapy. Nevertheless, all twelve developed non-A, non-B hepatitis soon after starting intravenous immunoglobulin treatment, whereas none of those receiving the intramuscular product produced from the same plasma developed hepatitis. This study was reported in The Lancet. The study added further support to the differences in risks from intramuscular and intravenous immunoglobulins and led to the suspension of intravenous immunoglobulin production at BPL for many years, until a safe product could be developed.

All anti-Rh(D) immunoglobulin used in the UK for prophylactic treatment of women before and after childbirth in the prevention of Rh alloimmunisation was traditionally provided from the NHS through the intramuscular immunoglobulin products produced by BPL and the Protein Fractionation Centre (Scotland). Until the late 1990s the starting material for all these products was UK derived plasma. Intravenous anti-Rh(D) immunoglobulin was used rarely, on a named patient basis, for Rh(D) negative women who had either received an inadvertent transfusion of Rh(D) positive blood, or who had suffered a large transplacental haemorrhage at the time of childbirth. The product used in the 1980s was imported from Ireland by the National Blood Service (now NHS Blood and Transplant) and issued on a named patient basis to hospitals for these very specific uses. When the association

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of the Irish intravenous anti-Rh(D) product with hepatitis C transmission was recognised, the Irish Blood Transfusion Service Board carried out a lookback on all issued batches of their intravenous anti-Rh(D) product, and NHSBT traced all recipients who had received the product on a named patient basis. It is therefore exceedingly unlikely that any women who had received anti-Rh(D) intravenous immunoglobulin in the UK before 1991 remain untraced, and all other women who received anti-Rh(D) immunoglobulin would have received the UK produced intramuscular products, which are recognised to be safe from viral transmission.

This information has been provided in the past to the Skipton Fund Appeal Panel. We are aware that the Appeal Panel has taken this information into account in coming to its view that hepatitis C transmission through the use of intramuscular immunoglobulin is improbable.

We are aware of other situations in the past, where it has been apparent that women have been given incomplete or inaccurate information about the risks of anti-Rh(D) intramuscular immunoglobulin administered to them within the UK. This in its turn has led to unrealistic expectations.

As Professor Foster says, in view of the above it is highly unlikely that an individual patient would be able to prove that infection occurred through the use of anti-Rh(D) immunoglobulin. Perhaps Professor Foster would be willing to consider how the information in our letter could be promulgated to other Hepatologists who are similarly advising patients on their possible source of hepatitis C infection, in order to avoid further dilemmas for patients.

Yours sincerely,

GRO-C

Dr Patricia Hewitt
Consultant Specialist in Transfusion
NHS Blood and Transplant
[and Skipton Fund Appeals Panel Member]
Tel: 020 312 8307
Fax: 020 312 8491
e-mail: GRO-C

GRO-C

Dr Clive Dash
Medical Director
Bio Products Laboratory
Direct Tel: GRO-C
e-mail: GRO-C

Enc. References listing

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