

## Prion reduction filters

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In today's *Lancet*, Luisa Gregori and colleagues<sup>1</sup> show that an affinity-resin column is capable of removing infectivity associated with endogenous prions from leucofiltered whole blood in a scrapie-infected hamster model. This builds on previous work by this group<sup>2,3</sup> and others<sup>4,5</sup> showing that prion reduction via filtration could reduce the risk of transmitting variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion. What is the current level of risk and how effective are these devices likely to be?

So far, 200 clinical cases of vCJD have been recorded, 164 in the UK. Some cases have also been found in France (n=21); Ireland (n=4); the USA (n=3); the Netherlands (n=2); and Canada, Japan, Saudi Arabia, Portugal, Spain, and Italy (all n=1).<sup>6</sup> The overall incidence of clinical disease is falling in the UK, with current estimates of around 70 (95% CI 10–190) further clinical cases.<sup>7</sup> However, a retrospective study of UK tonsil and appendix samples revealed that three of 12 674 samples were positive for abnormal prion protein on western blot analysis,<sup>8</sup> although the specificity and sensitivity of the assay in this context are uncertain. Mathematical modelling based on this suggests a minimum likelihood estimate of 3000 infected people (520–6810) in the UK, mainly aged 10–30 years.<sup>7</sup> If correct, about 93% (70–97%) of these infected individuals could develop long-term subclinical infection, possibly associated with heterozygosity or valine homozygosity at codon 129 of the *PRNP* prion gene.<sup>9,10</sup> This possibility is consistent with research in animals<sup>11,12</sup> and long-term studies on iatrogenic CJD and kuru.<sup>13,14</sup>

Observed transmission of vCJD prions by non-leucocyte-depleted red-cell concentrate<sup>15,16</sup> underlines the concern that secondary transmission from infected individuals via blood or tissue products could extend the outbreak of this disease, especially if compounded with other potential routes of transmission, such as surgery or interventional medical procedures. Several key uncertainties undermine our ability to judge the magnitude of this risk accurately: the prevalence of subclinical disease in various donor populations, the concentration and distribution of infectivity in the peripheral blood and tissues of infected individuals, and the overall transmissibility of the disease via blood transfusion. Similarly, the effectiveness of current risk reduction measures, including enhanced

donor deferral criteria and removal of white cells from blood components (universal leucodepletion), remains unclear.<sup>2,17</sup>

Specific prion reduction filters for red-cell concentrates offer the possibility of a further substantial reduction in infectivity and in the overall risk of transmission. However, concerns exist about how best to assess the efficacy of these technologies, since current assays are not sufficiently sensitive to detect infectivity in the blood of patients with clinical vCJD. Prion reduction filters have therefore had to be developed by spiking blood with infected brain homogenates and using animal models of endogenous infectivity, the applicability of which to infected human blood is uncertain. Potential negative effects also exist, including additional blood loss in the dead space of the filter and potential alterations to red-cell antigenicity or membrane properties.

The UK and Irish Blood Services have produced quality, efficacy, and operational specifications for such filters and are considering an assessment programme that will include independent investigation of efficacy and clinical safety studies.



Leucodepleted red-cell concentrate

Until these technologies can be clinically and operationally assessed, the best protection against the uncertain risk of transfusion-associated prion disease remains in ensuring that blood products are used only if needed and that the uncertainties surrounding potential risks are communicated effectively to patients and to the public at large.

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## Haemoglobin concentrations in chronic kidney disease



In June, 1989, the US Food and Drug Administration (FDA) licensed epoetin alfa, a recombinant human erythropoietin, for the treatment of anaemia associated with chronic renal failure. Since then, epoetin has substantially raised mean monthly haemoglobin concentrations in hundreds of thousands of patients—some who require dialysis and some who do not—diminishing the need for blood transfusions and improving quality of life. Epoetin products are among the most clinically successful recombinant molecules, and they have also generated billions of dollars for drug companies and dialysis facilities. Medicare spending on their use in end-stage renal disease reached US\$1.8 billion in 2004—an increase of 17% from 2003.<sup>1</sup>

Between 1991 and 2005, the mean administered dose of epoetin increased about four-fold in dialysis patients in the USA; the mean monthly haemoglobin increased from about 95 g/L to about 120 g/L (figure 1).<sup>1</sup> Persistent haemoglobin concentrations below 100 g/L were common in the 1990s. Now, they are rare, unless

there are specific reasons, such as chronic infections or occult bleeding (figure 2).<sup>1</sup>

There are, however, longstanding safety concerns about haemoglobin values above 120 g/L.<sup>2,3</sup> Patients with chronic kidney disease have a high prevalence of cardiovascular illness, a frequent cause of death. It has been thought, but not proven by evidence, that a normal haemoglobin level might decrease cardiovascular illness and death. Unfortunately, erythropoietic therapies may increase the risk of cardiovascular events, and the higher risk might be associated with higher haemoglobin levels or rapid increases in those values.<sup>4</sup> The reasons are uncertain, but could be related directly to the haemoglobin concentrations, to the higher epoetin dose required to maintain them, or both. Prescribing information for both darbepoetin alfa, a longer-acting agent, and epoetin alfa states that the dose should be managed to avoid haemoglobin exceeding 120 g/L.<sup>4–6</sup> In June, 2005, however, 50% of US patients undergoing dialysis had a mean monthly

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