

## Plasma-derived medicines: access and usage issues

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### Background to plasma-derived medicines

Although the first plasma-derived medicines were anti-toxins, raised in horses against pathogens (diphtheria, tetanus)<sup>1</sup>, the inception of plasma protein therapy occurred when Edwin Cohn developed his fractional ethanol precipitation scheme to isolate a stable albumin solution for the treatment of battle field injury and blood loss<sup>2</sup>. The Cohn scheme yielded albumin as a final product while producing, among others, therapeutically useful fractions of fibrinogen and immunoglobulins which could not be employed widely because of safety issues. Following initial safety problems, albumin gained widespread medical acceptance because of its dramatic effectiveness reported in victims of shock<sup>3</sup>, and was the plasma industry's staple product until the 1970s. Its position as a safe and effective plasma expander went unchallenged up to the 1990s, when the introduction of cheaper synthetic colloids and a Cochrane meta-analysis<sup>4</sup> threw doubts on its use, which were subsequently dispelled through clinical trials<sup>5</sup>.

While studies showed that careful plasma processing of Cohn's Fraction I could yield a product which was therapeutically useful in haemophilia A<sup>6</sup>, it took Judith Pool's widespread adoption of cryoprecipitate from blood bank plasma<sup>7</sup> to result in the next milestone in the history of plasma protein therapies. Pool's technique was rapidly adapted for large-scale fractionation without affecting the Cohn method<sup>8</sup> and resulted in the first industrial scale production of haemophilia therapy. The capacity to treat a previously life-limiting disease effectively made the manufacture of factor VIII (FVIII) concentrate the driver for the plasma industry in the 1970s, usurping albumin's historical position. The revolution this produced in the life of haemophiliacs cannot be underestimated, just as the effects, on patients and industry alike, of viral transmission by the products cannot be underappreciated, although

in the heady days of the 1970s this risk of this transmission was under recognised.

While industry hastened to introduce enhanced safety measures, particularly viral inactivation which by the mid 1980s had made haemophilia products safe, an effect of this tragedy was the rapid development of recombinant FVIII concentrates, once the F8 gene had been cloned in 1984<sup>9</sup>. The results of clinical trials, published in 1989<sup>10</sup>, rapidly led to widespread acceptance of this therapy to its current position as the dominant haemophilia treatment modality in many countries of the developed world, including the United States, the United Kingdom, Canada and Australia, and greatly increased the market and the availability of FVIII, allowing interventions such as prophylaxis and tolerisation. In some other, mostly European countries, plasma-derived FVIII has retained a strong presence, due, primarily, to the continuing debate regarding the different capacity of different FVIII products to result in inhibitors to FVIII<sup>11</sup>. This development would have had a profound effect on the economic, and indeed, the viability of the industry, but other developments in the field of immunotherapy obviated it.

Cohn's original method allowed the harvesting of immunoglobulin (Ig) fractions which could be concentrated into solutions and used to treat patients with Ig deficiencies<sup>12</sup>. In addition, Ig solutions from the plasma of donors immunised to specific antigens could be used for the treatment or prophylaxis of various diseases; the use of the Rh Ig fraction is the most famous of these applications<sup>13</sup>. However, early clinical observations that intravenous administration of Ig solutions led to severe reactions meant that Ig administration was limited to the intramuscular route, limiting dosage and patients' comfort. Efforts to address this problem led to several imperfect intravenously administrable Ig products, in which measures, such as enzymatic digestion of the entities

causing reactions, principally aggregates of Ig, formed during fractionation, also damaged the Ig molecule, limiting its half-life *in vivo*<sup>14</sup>.

The efforts to overcome these difficulties were spurred on by clinical findings that intravenous administration of large doses of Ig was helpful in ameliorating a number of autoimmune pathologies, such as immune thrombocytopenic purpura (ITP). Once well-tolerated and molecularly intact intravenous immunoglobulins (IVIg) were produced, the efficacy of the product in a wide range of these pathologies continued to be demonstrated<sup>15</sup>. In addition, the capacity to deliver large doses intravenously allowed more effective treatment of immune deficient states<sup>16</sup>. These combined features led to IVIg becoming the predominant plasma protein therapy, and the industry's driver, by the 1990s, a position it holds today. Table I lists the main approved indications for IVIg and their recommended dosages.

Despite this, the three generations of staple plasma-derived medicines-albumin, FVIII and IVIg- form part of every manufacturer's portfolio

**Table I -** Main indications for administration of intravenous immunoglobulin.

Indication	Dosage
Antibody-associated immune deficiencies	0.4 g/kg/4 weeks
Chronic inflammatory demyelinating polyneuropathy	2 g/kg in 2 to 5 divided doses
Multifocal motor neuropathy	2 g/kg in 2 to 5 divided doses
Guillain-Barré syndrome	2 g/kg in 2 to 5 divided doses
Idiopathic (autoimmune) thrombocytopenic purpura in adults	1 to 2 g/kg as single or divided dose
Kawasaki disease	2 g/kg in a single dose

Dosages and indications are from "Criteria for the clinical use of intravenous immunoglobulin in Australia". Australian National Blood Authority. Available at <http://www.nba.gov.au/ivig/index.html#ivig/pdf/criteria.pdf>. Accessed on 4 November 2011.

**Table II -** Second tier plasma products - usage in different regions.

Product	Units	North America	South America	Europe	Asia and Pacific
Fibrin sealant	mL (x1000)	15	10	932	875
Prothrombin complex concentrate	International Biological Units (x10 <sup>6</sup> )	7	23.1	306	16.9
Alpha 1 anti-trypsin	Vials (x1000)	470	/	166	/
Anti-thrombin III	International Biological Units (x10 <sup>6</sup> )	15.0	0.8	289.9	349.6

Data extracted from The Worldwide Plasma Fractions Market 2008, The Market Research Bureau 2011.

and are claimed to be crucial in maintaining the industry's viability<sup>17</sup>. A number of less economically important but therapeutically crucial additional products have also evolved over the years, including therapies for other bleeding disorders, for congenital deficiencies of the plasma proteins and for treating injury<sup>18</sup>. Table II summarises some features of these "second tier" products. Significant regional variations are found in the usage of these products, resulting from differences in clinical practice, regulatory approval and availability in specific areas.

## Current access issues regarding plasma-derived medicines

### Reimbursement issues

Plasma-derived medicines are the products of expensive technologies using a complex raw material, human plasma, which has to be procured from large numbers of blood or plasma donors. The complex technologies, the price of the raw material and the multiple safety measures contribute to the cost of these products. With some notable exceptions, the target patient populations are small, suffer from rare disorders and the indications are often classifiable as orphan indications. Together, these factors contribute to the relatively high cost of plasma protein therapies.

As health budgets have been subjected to increasing pressures, the funding, through reimbursement pathways from private and public payers, has come under scrutiny. This has led to plasma protein therapies being drawn into the landscape of Health Technology Assessments (HTA), including the possible application of cost-utility analysis (CUA) in the allocation of reimbursement funds. Given the high cost of the therapies and the relatively nascent nature of many of the indications for their use, application of these tools of health economics can lead to restriction of the supply of products for patients in genuine need of them.

This can occur if appropriate attention to all the factors contributing to clinical efficacy and quality of life are not considered. These issues will be discussed in relation to two "staple" products, FVIII and IgG.

Demand modelling shows that unrestricted access to the full spectrum of treatment currently considered optimal<sup>19</sup> requires delivery of about 7 IU FVIII/capita of population. This level is currently reached by very few countries, but has already been exceeded in some<sup>20</sup>. The use of prophylaxis rather than on-demand therapy, and variations in the dosage thereof, represent the demand model's greatest and most sensitive contributions. Prophylaxis has been demonstrated to be highly efficacious in limiting joint damage in comparison to on-demand treatment, but in current CUA, the cost per QALY (Quality Adjusted Life Year) of prophylaxis is outside the range normally considered justifiable by payers<sup>21</sup>. It is notable that, besides preserving joint architecture and function<sup>22</sup>, prophylaxis results in lower incidences of other serious morbidities<sup>21</sup> and has also been associated with lower FVIII inhibitor incidence in naïve patients<sup>23</sup>. Were these findings to be confirmed in large clinical trials, their inclusion in a CUA model would be expected to affect the cost per QALY.

Similarly, currently recommended dosages of IgG in treating immune deficiency<sup>24</sup> are still associated with a prevalence of infection which could be further lowered with higher doses<sup>25</sup>. The potential demand for these therapies is still unspecified; e.g. trough levels for Ig treatment for avoiding pneumonia<sup>24</sup> have not been delineated. Likewise, different routes of administration could have different costs<sup>26</sup>. Hence structuring reimbursement on the basis of current QALY costs has no guarantee of optimal patients' care. Rather, care can be "rationalised" through individualising and tailoring treatment regimens to individual patients' characteristics. Universal guidelines for prophylaxis and Ig dosage, for example, may reflect the clinical findings that these interventions are not necessarily indicated for all patients<sup>27</sup>.

### **Access to the raw material**

Unlike the situation for most pharmaceuticals<sup>16</sup>, the costliest component of the manufacture of plasma protein therapies is the raw material, plasma.

In well-managed and economically unrestricted environments, there is seldom a problem in assuring product supply, as compensation of donors ensures a constant supply of raw material which, in countries subject to resourced regulatory agencies, is entirely safe. Restrictions to industry's capacity to access donors are, therefore, an impediment to access to plasma protein therapy. Driven by considerations which include WHO resolutions<sup>28</sup> and underpinned by economic factors, including the protection of domestic blood systems, some countries declare a policy of "self-sufficiency" in plasma-derived medicines. In practice, this policy is usually a policy of "non-importation", as a particular form of trade barrier, as there is little "sufficiency" in the availability of plasma products in these countries. In many cases, the self-sufficiency countries include those which supply the lowest amounts of essential therapies. Interestingly, this is not a function of economic status—rich countries such as Japan may have a low consumption of some products such as FVIII and Ig through restricting the use of non-domestic products, while some less economically developed countries, such as Hungary, show higher than expected levels of consumption<sup>29</sup> through allowing access. Global sufficiency of plasma protein therapies requires unrestricted collection of plasma according to regulatory and clinical requirements, free access of traded products across borders and usage practices based on clinical needs and evidence. A policy that results in restricting access to treatment for the population of vulnerable plasma protein recipients is ethically dubious at best.

### **Usage of plasma protein therapies: evidence versus tradition**

Blood-derived therapies have been sheltered, historically, from many of the requirements which other medicines have for the provision of evidence of efficacy. This is still predominantly the situation for fresh blood components, which, while subject to scrutiny for safety and quality through the application of standards and good manufacturing practices, are not required to show efficacy in most regulatory frameworks. This state of affairs may change in the face of accruing evidence that many of the traditional assumptions regarding issues of efficacy, dosage, etc. for red cells, platelets and plasma are

questionable<sup>30-32</sup>. In contrast, the suppliers of plasma-derived medicines have had to satisfy therapeutic claims since the absorption of these products into mainstream medicinal regulation such as found in North America and the European Union.

In addition, the application of the tenets of the evidence-based medicine (EBM) movement has started to engage the landscape of plasma-derived medicines, in ways which influence access to treatments over and above the need to satisfy regulatory requirements. Structuring haemophilia treatment and Ig use according to clinical guidelines based on the EBM "hierarchy"<sup>33</sup> for example, has facilitated access in several countries<sup>34</sup> and, somewhat unexpectedly, has been accompanied by substantially increased product usage in some countries. These benefits of the application of EBM are offset, potentially, by the strict interpretation of the definition of "best quality" evidence as requiring randomised clinical trials. The epistemological problems concerning randomised clinical trials have been discussed<sup>35</sup> and lead to questions regarding claims to superiority of such trials as the sole tool for generating evidence. With particular relevance to plasma-derived medicines in small populations of patients, well-conducted observational studies are important if consideration of the majority of clinical experience with rare disorders is to be drawn upon. As a recent example, the dismissal of the efficacy of alpha 1 anti-trypsin augmentation in patients with alpha 1 anti-trypsin deficiency through limiting a meta-analysis to two small randomised clinical trials performed by the same clinical group in one location compels critical scrutiny of the Cochrane Review which performed this analysis<sup>36</sup>. Other forms of evidence, more suited to small populations of patients, indicate the value of this treatment<sup>37</sup>. Occasional comments on the cost of treatments (for example, those in<sup>36</sup>) within these assessments result in the perception of a commitment to cost-minimisation rather than to generating evidence.

Conversely, claims that plasma protein therapies do not require corroborative evidence of historically visible efficacy are equally disputable. Alternative methodologies to the standard frequentist approach, including Bayesian analysis, interim analysis, sequential designs and N of 1 trials<sup>38</sup>, can and should be used to provide evidence for efficacy in

plasma-derived medicines. Some examples of the use of such methodologies in small populations of patients with rare plasma protein disorders are available<sup>39</sup>. It behoves industry and care-deliverers to make genuine efforts to use these methodologies, which are slowly gaining acceptance by regulatory authorities<sup>40</sup>.

## Conclusions

Although every societal grouping claims its issues are unique, there are several distinctive features which differentiate plasma protein therapies from mainstream treatments produced for large populations of patients. There is no reason for these differences to constitute insurmountable problems to the provision and use of these therapies, as long as the need for adaption of standard reimbursement and evidence processes is accepted. Recognising the clear benefits to chronically diseased patients needing these treatment should be foremost in the minds of the relevant decision-makers. Finally, it must be recognised that the pressures on access in the developed countries, substantial as they are in the current financial climate, still fade into insignificance when compared to those in the less developed world. The World Federation of Hemophilia estimates that 70% of people with haemophilia worldwide are still unable to access any treatment, primarily because of economic factors. A similar situation exists for the other chronic deficiencies such as primary immune deficiency. Efforts are underway to develop pathways for access to plasma products for these countries, such as the World Health Organisation's "Achilles Project"<sup>41</sup>, which seeks to improve the quality of recovered plasma and channel it to contract fractionation agencies, which have been shown to be very effective in a number of countries<sup>42</sup>. These efforts need to be made in synergy with the development of clinical blood services geared to the specific needs of these countries, and the need for plasma products must not impede the availability of, for example, whole blood for transfusion, which is a needed modality for the treatment of acute bleeding in many countries. Planning at national and regional levels, involving all the players delivering care, is fundamental to ensure access to all the needed haemotherapies by all the patients requiring them.

**Keywords:** plasma, medicines, access, evidence.

## Conflict of interest disclosure

The authors provide consultancy and contractual services to the manufacturers of biotherapeutics such as plasma-derived products which are the subject of this paper.

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