Access And Rational Use of Plasma Protein Therapies (PPTs)

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Background to Plasma Protein Therapies (PPTs)

Although the first PPTs were anti-toxins, raised in horses against pathogens (diphtheria, tetanus) [1] 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 [2]. The Cohn scheme yielded albumin as a final product while producing, amongst others, therapeutically useful fractions of fibrinogen and immunoglobulins which could not be employed in widespread use because of safety issues. Following initial safety problems, albumin, gained widespread medical acceptance because of its dramatic effectiveness reported in victims of shock [3], and was the plasma industry's staple product until the 1970's. Its position as a safe and effective plasma expander went unchallenged up to the 1990's, when the introduction of cheaper synthetic colloids and a Cochrane Meta analysis [4] threw doubts on its use, which were subsequently dispelled through clinical trials [5].

While studies showed that careful plasma processing of Cohn's Fraction I could yield a product which was therapeutically useful in haemophilia A [6], it took Judith Pool's widespread adoption of cryoprecipitate from blood bank plasma [7] to result in the next milestone in the history of PPT's. Pool's technique was rapidly adapted for large scale fractionation without affecting the Cohn Method [8] and resulted in the first industrial scale production of haemophilia therapy. The capacity to treat effectively a previously life limiting disease made the manufacture of FVIII concentrate the driver for the plasma industry in the 1970's, usurping albumin's historical position. The revolution this produced in the life of haemophiliacs cannot be underestimated, and neither can be underappreciated the effects of viral transmission by the products, on patients and industry alike, a risk which was under recognised in the heady days of the 1970's.

While the industry hastened to in-

troduce enhanced safety measures, particularly viral inactivation which by the mid 1980's had made haemophilia products safe, an effect of this tragedy was the rapid development of recombinant FVIII concentrates, once the FVIII gene was cloned in 1984 [9]. Clinical trials, published in 1989 [10] rapidly led to widespread acceptance of this therapy to its current position as the dominant haemophilia treatment modality in the developed world. 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 [11]. 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 Rh Ig fraction is the most famous of these applications [12]. However, early clinical observations that intravenous administration of Ig solutions led to severe reactions meant that Ig administrations was limited to the intramuscular route, limiting dosage and patient comfort. Efforts to address this problem led to several imperfect intravenously administrable Ig products, in which measures to eliminate the entities causing reactions, principally aggregates of Ig, formed during fractionation, also damaged the Ig molecule, limiting its half-life invivo [13].

The efforts to overcome these difficulties were spurred on by clinical findings that large dose IVIg administration was helpful in ameliorating a number of autoimmune pathologies, such as immune thrombocytopenic purpura (ITP). Once well tolerated and molecularly intact IVIg could be produced, the efficacy of the product in a wide range of these pathologies continued to be demonstrated [14]. In addition, the capacity to deliver large doses intravenously allowed more effective treatment of immune deficient states [15]. These combined features led to IVIg becoming the predominant PPT, and the industry's driver, by the 1990s, a position it holds today.

Despite this, the three generations of staple PPTs- albumin, FVIII and IVIg- form part of every manufacturer's portfolio and are claimed to be crucial in maintaining the industry's viability [16]. 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 [17].

Current Access Issues for (PPTs)

Reimbursement Issues

PPTs 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 costs 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 PPT's.

As health budgets have come under increasing pressures, the funding, through reimbursement pathways from private and public payers, has come under scrutiny. This has led to PPT's 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 these 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 – Factor VIII and IgG.

Demand modelling shows that unrestricted access for the full spectrum of treatment currently considered optimal [18] 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 [19]. The use of prophylaxis rather than on-demand therapy, and variations in the dosage thereof, represents the demand model's highest and most sensitive contributions. Prophylaxis has been demonstrated to be highly efficacious in limiting joint damage relative to on-demand treatment, but in current CUA, the cost pr QALY is outside the range normally considered justifiable by payers [20]. It is notable that, besides preserving joint architecture and function [21] prophylaxis results in lower incidences of other serious morbidities [21] and has also been associated with lower FVIII inhibitor incidence in naive patients [22]. These kinds of inputs in a CUA model may be expected to affect the cost/QUALY. Such work is ongoing in the author's group.

Similarly, currently recommended dosages of IgG in treating immune deficiency [23] are still associated with an infection prevalence which can be further avoided with higher doses [24]. The potential demand for these therapies is still unspecified; eg trough levels for Ig treatment for avoiding pneumonia

[24] have not been delineated. Hence structuring reimbursement on the basis of current QALY costs has no guarantee of optimal patient care. Rather, care can be 'rationalised' through individualising and tailoring treatment regimens to individual patient characteristics. Universal guidelines for e.g. prophylaxis and Ig dosage need to accentuate the clinical findings that these interventions are not necessarily indicated for all patients [25].

Access to raw material

(See accompanying paper "Sufficiency of Plasma for Fractionation" A Farrugia, this issue)

The plasma raw material is, unlike the situation for most pharmaceuticals [16], the costliest component for the manufacture of PPT's. In well-managed and economically unrestricted environments, this is seldom a problem in assuring product supply. The provision of plasma for Ig proves to be the driver in most current medical environments, and accessing plasma from apheresed donors who are compensated has proven to be an efficient way of getting sufficient raw material. Restrictions on the industry's capacity to access donors, as is practiced in several 'self-sufficiency' environments, are therefore, an impediment to access. The issue of 'self-sufficiency' is therefore relevant to this debate.

Self-Insufficiency versus Global Sufficiency

Driven by ideological considerations as articulated by WHO resolutions, and underpinned by economic considerations, which includes the protection of domestic fractionators, some countries declare a policy of 'self-sufficiency' in PPTs. In practice, this policy is actually 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. With virtually no exception, the self-sufficiency countries include those which supply the lowest amounts of essential therapies. Interestingly, this is not a function of economic status – a rich countries such as Japan may have a low consumption of e.g. FVIII and Ig through restricting the use of non-domestic products, while some less economically developed countries, such as Hungary show higher consumption levels than is expected [26] through allowing access. The proclamation of 'self-sufficiency' by countries whose clinical policies, when examined, reveal an absence of prophylaxis, unrealistically low prevalence of plasma protein disorders, minimal Ig dosages for PID etc, must be viewed for what it is – insufficiency of essential treatments. The reality is that global sufficiency of plasma protein therapies demands 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. To use the population of vulnerable plasma protein recipients as the practical victims of these restrictive policies is unethical.

Usage of PPT's – Evidence, tradition and dogma

The evidence based medicine (EBM) movement has started to engage the PPT landscape, and its outcomes are of relevance, particularly in the reimbursement agencies. Historically, this has been a late development relative to other medical interventions. Like anything derived from 'pure and eloquent' blood, the efficacy of PPT's, following initial studies not structured according to EMB tenets, has more often than not been assumed. Introducing processes for the clinical corroboration or refutation of these early observations is therefore a welcome development. Structuring haemophilia treatment and Ig use according to clinical guidelines based on the EBM 'hierarchy' [27] for example, has facilitated access in several countries [28] and, perhaps unintentionally, has been accompanied by substantially increased product usage.

These benefits of the application of EBM are threatened by overzealous and dogmatic interpretations of the definition of 'best quality' evidence as requiring randomized clinical trials (RCTs). Despite protestations to the contrary by the EBM advocates, the EBM hierarchy is too frequently reduced to the requirement for RCT's with other levels of evidence being considered inadequate. The epistemological problems around RCT's have been discussed [29], suffice it to say that claims to its superiority as a tool for assessing guidance are doubtful. In particular relevance to PPT's in small patient populations, EBM dogmatism dismissing, for example, well-conducted observational studies, excludes from consideration the majority of clinical experience with rare disorders.

A recent example of this type of thinking from the Cochrane Colloboration dismisses the efficacy of alpha 1 anti-trypsin augmentation in patients with alpha 1 anti-trypsin deficiency through limiting a meta-analysis to two small RCT's performed by the same clinical group in one location [30]. Ignoring the considerable body of evidence, in this instance, through other forms of evidence [31] indicates the unwillingness of many Cochrane reviewers to consider all levels of evidence. Coupled with frequent comments on the cost of treatments, (see eg comments in [30], the perception arises that many of these reviewers are committed to cost-minimisation to a greater extent than generating evidence.

Conversely, claims that PPT's do not require corroborative evidence of

historically visible efficacy are equally disputable. Alternative methodologies to the standard frequentist approach include the use of Bayesian analysis, interim analysis , sequential designs and N of 1 trials [32] can and should be used to provide evidence for efficacy in PPTs. Some examples of this use in small populations of patients with rare plasma protein disorders are available [33]. It behoves industry and treaters to make genuine efforts to use these methodologies, which are slowly gaining acceptance by regulatory authorities [34].

Conclusions

Although every societal grouping claims its issues are unique, there are several distinctive features which differentiate PPT's from mainstream treatments produced for large patient populations. There is no reason for these differences to provide 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.

References

1. Good, R.A. & Lorenz, E. (1994) Historic aspects of intravenous immunoglobulin therapy. Cancer, 68 (Suppl.), 1415±1421.

2. Cohn, E.J., Strong, L.E., Hughes, W.L., Mulford, D.J., Ashworth, J.N., Melin, M. & Taylor, H.L. (1946) Preparation and properties of serum and plasma proteins. IV. A system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. Journal of the American Chemistry Society, 68, 459±475.

3. Kendrick DB. The blood program in World War II. On http://history.amedd.army.mil/booksdocs/wwii/blood/chapter12.htm

4. Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. BMJ 317:235-240, 1998

5. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247-2256, 2004

6. NILSSON IM, BLOMBACK M, JORPES E, BLOMBACK B, JOHANSSON SA Von Willebrand's disease and its correction with human plasma fraction 1-0. Acta Med Scand. 1957 Nov 29;159(3):179-88.

7. Pool JG, Shannon AE Production of high-potency concentrates of antihemophilic globulin in a closed-bag system.N Engl J Med. 1965 Dec 30;273(27):1443-7

8. Hershgold EJ, Pool JG, Pappenhagen AR. The potent antihemophilic globulin concentrate derived from a cold insoluble fraction of human plasma: characterization and further data on preparation and clinical trial. J Lab Clin Med. 1966 Jan;67(1):23-32

9. Gitschier J, Wood WI, Goralka TM, Wion KL, Chen EY, Eaton DH, Vehar GA, Capon DJ, Lawn RM. Characterization of the human factor VIII gene. Nature 1984; 312: 326–30.

10. White GC II, McMillan CW, Kingdon HS, Shoemaker CB. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia . N Engl J Med

1989; 320:166–70.
11. Good RA, Varco RL. A clinical and experimental study of agammaglobulinemia. Lancet 1955;75(6):245–71.
12. Pollack W, Gorman JG, Freda VJ, et al. Results of clinical trials of RhoGAM in women. Transfusion 1968;8(3):151–3.
13. Eibl MM. History of Immunoglobulin Replacement. Immunol Allergy Clin N Am 28 (2008) 737–764
14. Hartung HP, Mouthon L, Ahmed R, Jordan S, Laupland KB, Jolles S.
Clinical applications of intravenous immunoglobulins (IVIg)–beyond immunodeficiencies and neurology. Clin Exp Immunol. 2009 Dec;158 Suppl 1:23-33.
15. Roifman CM, Lederman HM, Lavi S, et al. Benefit of intravenous IgG replacement in ypogammaglobulinemic patients with chronic sinopulmonary disease. Am J Med 1985;79:171–4.
16. Burnouf, T., Plasma proteins: Unique biopharmaceuticals - Unique economics, Pharmaceutical Policy & Law 7, 209-218, 2005-2006
17. Farrugia A, Robert P. Plasma protein therapies: current and future perspectives. Best Pract Res Clin Haematol. 2006;19(1):243-58.
18. Stonebraker JS, Amand RE, Bauman MV, Nagle AJ, Larson PJ. Modelling haemophilia epidemiology and treatment modalities to estimate the unconstrained factor VIII demand. Haemophilia. 2004 Jan;10(1):18-26.
19. Stonebraker JS, Brooker M, Amand RE, Farrugia A, Srivastava A. A study of reported factor VIII use around the world. Haemophilia. 2010 Jan;16(1):33-46
20. Miners AH, Sabin CA, Tolley KH, Lee CA. Cost-utility analysis of primary prophylaxis versus treatment on-demand for individuals with severe haemophilia. Pharmacoeconomics. 2002;20(11):759-74.
21. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L, Valentino LA, Hoots WK, Buchanan GR, DiMichele D, Recht M, Brown D, Leissinger C, Bleak S, Cohen A, Mathew P, Matsunaga A, Medeiros D, Nugent D, Thomas GA, Thompson AA, McRedmond K, Soucie JM, Austin H, Evatt BL. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007 Aug 9;357(6):535-44.
22. Morado M, Villar A, Jimenez, Yuste V, et al. Prophylactic treatment effects on inhibitor risk: experience in one centre. Haemophilia 2005; 11: 79–83
23. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effects of two differentdosages of intravenous immunoglobulin on the incidence of recurrent infectionsin patients with primary hypogammaglobulinemia: a randomized, double-blind, multi center crossover trial. Ann Intern Med 2001;135:165–74.
24. Orange JS, Grossman WJ, Navickis RJ, Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol. 2010 Oct;137(1):21-30.
25. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S, Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol. 2010 Jun;125(6):1354-1360.
26. Stonebraker JS, Amand RE, Nagle AJ. A country-by-country comparison of FVIII concentrate consumption and economic capacity for the global haemophilia community. Haemophilia. 2003 May;9(3):245-50.
27. Evidence-based medicine. A new approach to teaching the practice of medicine. Evidence-Based Medicine Working Group. JAMA 1992;268(17):2420-5.
28. Criteria for the Clinical Use of Intravenous

Immunoglobulin (IVIg) in Australia. On http://www.nba.gov.au/ivig/pdf/criteria.pdf
29. Senn SJ. Falsificationism and clinical trials. Stat Med. 1991 Nov;10(11):1679-92.
30. Gøtzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. 2010 Jul 7;(7):CD007851.
31. Chapman KR, Stockley RA, Dawkins C, Wilkes MM, Navickis RJ. Augmentation therapy for alpha1 antitrypsin deficiency: a meta-analysis.COPD. 2009 Jun;6(3):177-84.
32. Farrugia A. Trialing plasma protein therapies for rare disorders: Thinking outside the box. Pharmaceuticals Policy and Law 11 (2009) 345–352
33. Goodman SN, Sladky JT. A Bayesian approach to randomized controlled trials in children utilizing information from adults: the case of Guillain-Barre. Clin Trials August 2005 2: 305-310
34. European Medicines Agency 2006. GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS. On http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf