



Why Does the Precautionary Principle Suffice for Blood Regulation?

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Accepted: 8 August 2021 / Published online: 7 September 2021
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Abstract

Traditional approaches to blood regulation emphasise the precautionary principle and pursue zero-risk for viral transmission; these traditional approaches have usually followed tragedy, such as the HIV and hepatitis C infections that followed the use of factor VIII concentrates. However, a much more haphazard haemovigilance system operates for general adverse events. Such imprecise assessment of hazards prevents sound benefit-risk assessment, and for blood products this is further confounded by the fact that their efficacy has attracted little systematic study. The ongoing COVID-19 pandemic has now prompted the proposal of a convalescent plasma (CP) blood product. Clearly, mere freedom from infectious agents will not suffice in assessing CP, and an objective measure of efficacy, so as to permit formal benefit-risk analysis, is essential. This is both a scientific and an ethical demand, as has been the case for other experimental COVID-19 treatments. With special reference to COVID-19 CP, the well-recognized adverse events of transfusion-associated lung injury (TRALI) and transfusion-associated circulatory overload (TACO) will be important. Furthermore, not only efficacy but also product quality attributes (e.g., antibody titre) will have to be defined. Both of these are outside the traditional regulatory philosophy for blood products and are needed to truly assess the benefit-risk of this putative therapeutic product.

1 Introduction

Orthodox medicinal products are licensed for ordinary clinical use after rigorous demonstration of product quality, efficacy and safety; this is the underpinning of medicinal product regulation worldwide. The evidence provided to regulatory agencies is usually obtained from product development and clinical research campaigns, which are themselves regulated. In broad terms, these research programmes establish a benefit-risk profile for each product and assist in finding the place of the new product in the pre-existing therapeutic landscape. There are procedures for expediting that process (recent examples include dexamethasone and remdesivir for COVID-19 indications), but even these rely on the same three fundamentals of demonstrating quality, efficacy and safety.

For some reason, blood components have hitherto been exempted from this regulatory *sine qua non*. There are many

Key Points

Hitherto, blood has been regulated on the basis of the precautionary principle, i.e., regulation has the intent of absolute minimisation of risk arising from hazards (real or imaginary). This approach leads to neither rational identification of hazard nor quantitation of risk, and, in the face of sometimes critical supply issues, accreting regulation is rarely reversed.

Regardless of current regulation, blood products are intended as therapeutic agents. With a few exceptions (e.g., treatments for haemophilia), the efficacy of blood products has rarely been studied.

With acute situations emerging (e.g., the potential for convalescent plasma to treat severe SARS-CoV-19 infection), the absence of rigorous efficacy testing prevents a risk-benefit approach to blood regulation. This can hamper further development of blood products, automatically preventing the optimal deployment of a finite resource, and insulting the humanity of the millions of donors who deserve a better return for their generosity.

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clinical scenarios and indications for these products. Whole blood and packed red cells are used for priming cardiopulmonary bypass pumps, and to support patients during surgery, after trauma, and following bone marrow insults (such as chemotherapy). Whole plasma has similar uses and is also fractionated for specific proteins such as Factor VIII and anti-sera.¹ Nonetheless, to date, very few randomised controlled trials (RCTs) have been completed with blood components (so as to demonstrate efficacy and quantitate tolerability), and of these, few report that statistically significant results (cf. placebo or some ethical comparator) are unachieved [1].

The COVID-19 pandemic has focussed attention not only on the speed of the orthodox regulatory process, but also its outcomes. Multiple vaccines have been developed, approved and dispensed: this was at high speed, but without departure from the regulatory fundamentals.

Convalescent plasma (CP), from donors who have recovered from COVID-19 is now becoming available. This has been hypothesised to have a place in the therapeutic landscape because its mode of action differs from vaccines, dexamethasone and remdesivir [2]. A further hypothetical advantage is the possibility that CP may contain polyclonal antibodies, and, thus, as a single therapy, be capable of attacking coronavirus with a variety of molecular pharmacologies and a corresponding reduction in the potential for development of viral resistance [3]. But while the current regulatory regime is probably adequate to cater for viral contamination of CP (as many other blood products/components), will it drive an appropriate risk-benefit assessment of this novel therapy?

2 Convalescent Plasma: *a priori* Evidence

Case series, retrospective analyses and single-arm trials of CP for the treatment of hospitalised patients with COVID-19 have been considered encouraging [4–6]. Indeed, an Emergency Use Authorisation (EUA) by the U.S. Food and Drug Administration (FDA) was issued on 23 August 2020 for the use of CP for hospitalised patients and this is still in place. Under the BioShield Act 2004 (ss.564, 564A and 564B; the ‘Act’), the FDA Commissioner is empowered to issue an EUA, which authorises the prescription of unapproved medicinal products, or allows a previously licensed product to be used for an unapproved indication; this can be without data from rigorous RCTs. Technically, the product remains unlicensed and the EUA can never create a new Standard of

Care (SOC); results from RCTs will eventually have to be available before a full product license can be obtained [7]. For example, remdesivir use began under an EUA, although it has now received an orthodox New Drug Approval based on comprehensive clinical research and robust demonstration of quality, safety and efficacy [8]. In contrast, the value of RCTs was demonstrated by the failure of hydroxychloroquine (HCQ) to progress any further than an EUA; its lack of efficacy was compounded, tragically, by safety issues (long QT syndrome) [9].² However, the EUA process has enabled prompt accessibility of numerous therapeutic interventions, such as CP, while maintaining regulatory oversight.

Convalescent plasma, and its components, have much prior, positive clinical experience (e.g., anti-diphtheria toxin as long ago as the 1920s). The database at <http://www.clinicaltrials.gov> contains over 200 clinical trials that have been or are being conducted with COVID-19. Why, then, is it so difficult to establish CP as a fully approved treatment option (and possibly a new SOC) for COVID-19 infection?

3 Regulating Convalescent Plasma for a COVID-19 Indication

Currently, most aspects of CP are regulated like fresh frozen plasma (FFP). These are blood components and are regulated as a blood transfusion. Thus, CP is considered neither an investigational, nor an approved medicinal product in most countries. In the USA, blood products are regulated by the Centre for Biologics Evaluation and Research (CBER) within FDA (per the regulations at 21 CFR 601, 630 and 640).³ This suite of regulations provides standards for transfusion and manufacture of blood products according to a five-layer approach: (1) donor screening and suitability standards, (2) donor deferral, (3) blood testing, (4) quarantining blood and blood components, and (5) monitoring establishments for deficiencies [10]. Meanwhile, in the EU, blood collection systems and blood components for transfusion are governed in a decentralised manner by individual, national competent authorities (European Commission Directives 2002/98/EC, 2004/33/EC, 2005/61/EC, and 2005/62/EC). The amending Directive 2016/2014 sets out quality, safety, distribution and reporting standards that member states should apply for blood and its components [11–15]. Overall, regulatory requirements are similar elsewhere in the world (e.g., as published by the WHO) [16].

² The likelihood of political influence dictating the initial EUA for HCQ is beyond the scope of this article.

³ The Center for Drug Evaluation and Research regulates investigational medicinal products under 21 CFR 312, New Drugs under 21 CFR 314, and Biological Licence Applications (*sic*) under 21 CFR 601.2.

¹ While some of these compounds are discussed below, fractionated plasma is treated like medicinal products in most countries, and whole plasma is regarded as a starting material.

In practice, most of this blood regulation has resulted from clinical disaster. Obvious examples are the infection and deaths of many thousands of individuals who received transfusions contaminated with human immunodeficiency virus (HIV) and/or hepatitis C virus (HCV); these viruses were transmitted not only in whole blood or packed red cells, but also in fractionated, and often pooled source products such as factor VIII concentrate for patients with haemophilia [17]. The reactive regulatory systems created after these incidents were designed to prevent recurrence, and indeed these viral threats seem to have been broadly eliminated from blood supply systems, at least in the developed world. Importantly, these precautions are in place even where there is no hazard and are a good example of the undiluted precautionary principle [18].

Crucially, clinical disasters also drive public opinion and political action. Unquestionably, the blood supply system is universally perceived as an important public good, and any appearance of failure to protect it causes widespread disillusion. In the case of factor VIII concentrate, that disillusion found its outlet in a host of analyses, much litigation, and public enquiries about blood-borne HIV and HCV transmissions. These responses have focussed not only on the events themselves, but also on the (in-)action and decision-making by governments. In Canada, the Krever inquiry opened in 1993, and its report in 1997 meticulously described the events leading up to the transfusion tragedy and made recommendations on how it could be prevented in the future; in a nutshell, this inquiry reinforced the precautionary principle by stipulating that an important tenet in the philosophy of public health must be to always mitigate risk before awaiting scientific certainty [19]. In the UK, a similar inquiry was opened in February 2018 (more than 15 years after the tragic events themselves, and only after longstanding public pressure); it has still not reported [20].

4 Discussion

However, the precautionary principle has limitations, and inquiries that merely reinforce that principle might be missing the point. First, it is deceptive: elimination of all hazards is actually impossible, and there is no definition of how much residual risk, no matter how small, can be tolerated; the engineering professions use the acronym ALARA (as low as reasonably achievable), but this is not applied in the transfusion community. The consequent accreting regulation, for example, donor deferral policies for men having sex with men (MSM), then remain in place long after the hazard has disappeared. Conversely, the tenet of pursuing the lowest achievable risk level does not seem to be consistently pursued. For example, first-time donors can carry a 2- to 3-fold higher risk of transfusion-transmitted infection (TTI)

than repeat donors (albeit the absolute risk is very small for both groups of donors). Yet, only a few countries, such as the Netherlands, require a candidate donor, i.e., a person who wishes to begin donating blood (for transfusion purposes) to undergo viral pre-screening before returning to the blood bank for his/her first donation [21, 22].

Second, most regulations are easily implemented but hard to repeal. For example, the deferral policy for donors suspected of suffering from chronic fatigue syndrome (CFS) have not been reversed, even though the alleged aetiology (transmission of xenotropic murine leukaemia virus-related virus [XMRV] infection by transfusion) has been soundly refuted [23]. If deferral of patients with CFS is in the interest of donor health, then that is clinical beneficence; but it is nothing to do with a hypothetical pathogenic virus that has been confirmed to originate from laboratory contamination events.

Third, an unrealistic zero-risk attitude can cause a disproportionate deployment of immense but finite resources, thus creating lost opportunity costs elsewhere. While the precautionary principle has helped to significantly reduce blood viral contamination, this has often been at enormous cost, well beyond any customary health economic threshold. For example, the cost of HIV p24 antigen testing, and nucleic acid testing for Zika virus infection, have been among the least cost-effective interventions in medicine [24, 25]. For these reasons, HIV p24 antigen has now been replaced by more sensitive HIV NAT testing; meanwhile, Zika NAT testing was first relaxed to testing on the pool (rather than donation) level, and more recently discontinued. The implementation of both assays remained disputed amongst stakeholders, as did their haphazard replacement and discontinuation [26–29].

It is to be remembered that blood safety is not just freedom from viral hazard. While transfusion of blood and blood components is mostly well tolerated nowadays, there are, nonetheless, other types of transfusion-associated adverse events. For these, the precautionary principle, as currently implemented, provides no risk mitigation.

Other adverse event types obviously include not only immune responses, but also transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI). Without systematic evidence, it is thought that TACO can sometimes be mitigated with prophylactic administration of spironolactone, furosemide and/or potassium. For TRALI, HLA antibody testing and use of male-only plasma has been suggested (because one suggested aetiology is monocyte-activating HLA antibody production after an initial immunisation during multiparous pregnancy). TACO and TRALI are uncommon, but nonetheless still have considerable case fatality rates [30, 31]. Moreover, while TACO and TRALI have been known for decades, it is only recently that attempts have been made to standardise disease

definitions, let alone guidelines for treatment. Therefore, it is very likely that the incidence of these adverse reaction types is currently underestimated. [32, 33] For both of these adverse reactions, diagnosis remains highly dependent on clinical suspicion and recognition and there is no predictive laboratory testing. In the case of CP for COVID-19 infection, there is a further complexity in that due to their respiratory signs and symptoms, both TACO and TRALI can be mistaken for worsening COVID-19 pneumonitis, especially in ventilated and sedated patients, where the clinical presentations can be multifaceted and complicated. Similarly, disseminated intravascular coagulopathies can be encountered in the ITU environment with and without plasma transfusions. All these conditions present with hypoxia, pulmonary oedema and (eventually) acute respiratory distress syndrome. At best, a differential diagnosis might depend upon chronology: an abrupt decline in the patient's condition shortly after a transfusion might favour TRALI over the complications of COVID-19 infection [34].

The product surveillance systems for blood products ('haemovigilance') are rudimentary and another weakness in blood product regulation. Common, severe and serious adverse events are not fully captured or characterised. Where they exist at all, most haemovigilance systems are operated within the geographical limits of the local blood transfusion service [35]. Some harmonisation efforts have been made, for example, the European Union has issued Directive 2005/61/EC, which attempts to render the reporting of serious adverse events mandatory [36]. However, although there is nothing unlawful in the different ways that member states gather adverse event reports following transfusion of blood components, there is often no compulsion for clinicians to report, and it is suspected that under-reporting is preferred by socialised transfusion services for fear of lawsuits [37]. For these reasons, while the precautionary principle may be good enough to reduce transfusion-associated viral transmission, it is quite inadequate for other adverse event types. Blood products do not benefit from Good Pharmacovigilance Practice. Where the safety profile of blood components remains poorly defined, there cannot possibly be any accurate benefit-risk assessment as a prerequisite for product approval. As things stand, 'haemovigilance' is in its infancy.

Benefit-risk assessment of blood products is hampered not only by poor risk assessment (rudimentary haemovigilance), but also by inadequate measurements of benefit (i.e., product efficacy). Not being regulated in the same way as orthodox drugs, there has been little motivation to conduct RCTs in transfusion medicine. Clinical decision making, i.e., whether or not to transfuse, seems to be driven by unrecorded experience, and traditions in training, that are not evidence based. Part of this is doubtless because of the difficulty of study design; products such as whole blood and packed red cells are administered in very diverse clinical

situations, and clinical experience might not be generalisable. For example, extrapolating findings from intensive care unit (ICU) patients to the routine intra-operative setting would seem unjustified [38]. Furthermore, ethically and scientifically acceptable comparator groups are hard to determine (e.g., withholding transfusion by randomisation, or matching a saline infusion for volume when, unlike plasma, it distributes into the total body water) [39]. An important exception is that pathogen reduction in blood and plasma has been extensively studied under well-controlled conditions, albeit using *in vitro* endpoints that are often sufficient [40]. It is also encouraging that various specialist societies are taking an interest in establishing criteria for red cell storage and transfusion based upon haemoglobin concentration and platelet counts (even when these cannot be established by RCTs), thus emphasising the importance of rigorous product quality criteria.

In the special case of CP for COVID-19, it is rational to require product quality criteria beyond those that apply to fresh frozen plasma: there is no point in infusing CP unless the administered antibody titre exceeds that already present in the infected patient [41]. Several approaches for ensuring quantity and quality of antibodies exist. Currently, the EUA in the USA mandates that a minimum neutralising antibody titre in CP is quantified by FDA-approved assay systems [7]. Individual donations with a minimum antibody titre can be pre-selected and pooled. If still inadequate then this CP pool can be further concentrated as an industrial process, so as to obtain antibodies in their purest form as immunoglobulin concentrates. Standardisation of antibody titre assays and identification of threshold levels, and, given the serious condition of the patient, it is the testing and product qualification in a timely manner that becomes the next challenge.

All these approaches come with advantages and challenges. Testing of individual donations could be technologically straightforward (it is only adding one more screening assay to the test panel) but can also be costly. A decentralised approach at the blood establishment level will require antibody assay standardisation and reference standards. CP pools would allow for standardisation of material on a batch scale and potentially pathogen inactivation, so as to prevent donations with lower antibody titres from diluting the pool. Process steps for purification of antibodies would enable isolation of the desired compound and therefore better definition of material and longer shelf life, but such manufacturing processes are likely to require large volumes of CP as raw material. However, this would have the benefit that prior to industrial processing, the source plasma would be regarded as a biological starting material, and, thereafter, the product would be classified as a medicinal product and regulated like any other biological drug. The highly concentrated, polyclonal material would then be subjected to orthodox regulation, including proper pharmacovigilance.

5 Conclusions

Currently, blood regulation focusses on eliminating viral hazard. No benefit-risk assessment (comparable to that needed for medicinal product approval) is stipulated by the applicable regulatory guidance documents. Moreover, risk-benefit assessment is impossible because there are no proper pharmacovigilance systems (including no general agreement on adverse event terminology) and no robust development of evidence of efficacy. Blood components such as FFP are currently used based on consensus recommendations, which are not harmonised.

For COVID-19 CP, there is now a clear opportunity. Reassurance by the EUA for COVID-19 CP is encouraging but must remain uncertain, given the precedent of hydroxychloroquine. Numerous clinical trials are being conducted, with some *a priori* potential to measure a favourable treatment effect. Currently, some of these clinical trials have not been positive, while others do show evidence of CP effectiveness [42, 43]. In an environment where COVID-19 is evolving (and this is to be expected, especially when dealing with an RNA virus), enthusiasm for CP having a potential therapeutic role, is still accumulating [44]. Therefore, attempts are being made to develop robust evidence for efficacy of CP, and this is a positive development in the area of blood product research.

In order for COVID-19 CP to become a viable treatment option and obtain its place as SOC, it should be developed within the ambit of conventional clinical research, and within the regulation of orthodox, approved medicinal products. The shortcomings of the existing, haphazard systems for blood transfusion regulation are crucially illustrated by considering the possibility of COVID-19 CP, if not in patients with severe pneumonia [45].

Declarations

Funding Neither Dr Seifner nor Dr Fox received any funding for this article.

Conflict of interest Drs. Seifner and Fox have no conflicts of interest that are relevant to this article.

Availability of data and material Not applicable.

Code availability Not applicable.

Authors contributions This article derives from a dissertation presented by Dr. Seifner in partial fulfilment of requirements for an M.Sc. degree at King's College London, and Dr. Tony Lockett is kindly acknowledged. Both authors meet the ICMJE criteria for authorship. Both authors drafted and critically revised the manuscript.

Ethics approval This article required no acquisition of human data.

Consent to participate Not applicable.

Consent for publication Not applicable.

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