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COVID-19 convalescent plasma: current status, lessons from the past and future perspectives

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ABSTRACT

When the COVID-19 pandemic hit, blood transfusion services worldwide started collection of convalescent plasma as early as possible, as exemplified by the response in Norway. There were challenges related to donor selection, donor safety, testing for relevant antibodies and indications for and dosing of the convalescent plasma. As more knowledge became available, the product quality was more standardised. Multiple case reports, observational studies and some randomized studies were published during the pandemic, as well as laboratory studies reporting different approaches to antibody testing. The results were conflicting and the importance of convalescent plasma was disputed.

Even though there has been strong international collaboration with involvement of many key organisations, we may better prepare for the next pandemic. An even stronger, more formalised collaboration between these organisations could provide more clear evidence of the importance of convalescent plasma, based on the principles of passive immunisation.

1. Introduction

When the COVID-19 pandemic struck, no efficient medications nor vaccines were available. The SARS-CoV-2 virus belongs to the coronavirus family and earlier reports indicated that convalescent plasma could be useful in treatment of patients with corona virus infections as SARS and MERS [1,2]. Hence, transfusion of plasma from individuals who had recovered from the infection presented as a treatment option.

Due to the criticality of the situation, and in accordance with recommendations from leading institutions as EU, US FDA and WHO, compassionate use was encouraged, although the authorities, the blood establishments and the clinical users recommended randomised studies. However, as large multicentre drug studies were started e.g., from WHO, the room for randomized studies involving convalescent plasma was limited. Thus, the available information on effects of convalescent plasma was dependent on multiple smaller studies that were conducted worldwide, reporting varying results. As an exemption, a large, randomized study on convalescent plasma was conducted in the United Kingdom (RECOVERY) – a study that compared several treatment options [3].

2. Use of convalescent plasma in Norway

The actions taken in Norway were probably illustrative for the measures implemented by the transfusion services in many countries. Supported by the national health authorities, the blood banks started to collect convalescent plasma from blood donors who had recovered from COVID-19. The deferral time after the infection followed European guidelines, which varied throughout the period the collection activity lasted.

Initially, two clinical studies were planned in Norway. A randomised controlled study on the effects of convalescent plasma was approved by the ethical committee and had sufficient funding but became impossible as most of the eligible patients were already recruited in drug studies. An interventional study in nursing homes became impossible due to lack of financial support. Therefore, a monitoring study was the only option: The patients who received convalescent plasma and consented to participate, were monitored by clinical and laboratory parameters.

In the early phase, there were uncertainties concerning the quality of the plasma as the different laboratories used different antibody tests. Following recommendations from the Norwegian microbiologists involved in the project, the testing regimen gradually became

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standardised. There was a limited capacity for testing for neutralising antibodies and it was a significant improvement when the Immunology laboratory at Oslo University Hospital developed a pseudo-neutralisation test based on ACE-1 inhibition [4]. Plasma from nearly all donations were tested by this method, some in retrospect.

Norway was mildly affected by the pandemic. This, in combination with reluctance from many clinicians to use convalescent plasma since hard evidence of effects was lacking, the number of transfusions was low. The majority of transfusions was given to immunocompromised patients without own immune response. A comprehensive report on plasma donations will be published in the Journal of the Norwegian Medical Association [5].

3. Effects of convalescent plasma

The literature concerning use of convalescent plasma during the COVID-19 pandemic is overwhelming. Publication types include [often small] randomised studies conducted in different patient groups, studies related to patient age, to time between infection and initiation of treatment, observational studies and case reports [6]. In addition, there is also a multitude of laboratory papers describing different assays to detect immune responses in the patients and how these tests can be used to evaluate the quality of convalescent plasma [7].

Due to this enormous flow of information, it is difficult to create a timeline to describe the status of convalescent plasma treatment. In the initial phase of the COVID-19 pandemic, many reports indicated positive effects achieved by transfusion of convalescent plasma [8,9]. However, also reports indicating no effects of the plasma transfusions appeared in the scientific journals. The perception that convalescent plasma had no place in the treatment of COVID-19 was supported by the first publication from the RECOVERY study [3], and reinforced by an editorial in British Medical Journal [10] based on a smaller, randomized study from Argentina [11]. However, some studies showed positive effects in defined patient groups – patients who were immunosuppressed and high-risk patients who received early plasma treatment [12]. Other papers contradicted these results [13].

The different conclusions reflected in the papers are also mirrored in review papers and meta-analyses. Some authors claim that there are positive effects of convalescent plasma whereas others disagree [14–16].

4. The lessons from the past

As the status concerning use of convalescent plasma is dubious, it may be wise to go back to the sources: The great work performed in Germany by von Behring, Kitasato and Ehrlich from the 1880-ties and onwards. Their extensive experiments on passive immunisation really progressed the knowledge on and the practical implications of immunological principles. They conducted many still important experiments and they were awarded two Nobel prizes in medicine. The original papers are not easily accessed today but review papers provide excellent information on their work and include references to major publications [17–19].

From their work, at least three principles for therapy are prominent:

1. The treatment should start early.
2. The more severe clinical situation, the higher antibody dose.
3. There must be a minimal dose of antibodies.

In an emergency situation, as was the case with the rapid development of the COVID-19 pandemic, it is impossible to comply with all these recommendations initially, as the clinically effective antibodies are not defined – and the patient groups needing treatment may also not be defined.

5. Convalescent plasma: International COVID-19 pandemic response – and future perspectives

In the response to the COVID-19 pandemic, there were impressive responses nationally and internationally – from blood transfusion establishments and general health authorities. EBA, EU, ISBT, AABB, FDA and WHO responded quickly and international collaboration concerning collection of data started immediately [20,21].

Although these efforts were executed, we should always look for possible improvements [6]. Based on the works from the pioneers on passive immunisation, maybe a standing committee of international experts could act as a reference group if large-scale use of convalescent plasma would be appropriate during the next pandemic. This committee could ensure even more standardised approaches to key issues.

Is there indication for convalescent plasma? We know that effects of passive immunisation is dependent on the infectious agent. Also, the indications for plasma treatment must be adjusted as other options become available, as vaccination regimen, availability of monoclonal antibodies and other effective drugs.

If there is indication for convalescent plasma therapy, optimal donor selection is necessary. Who should donate blood, what is the deferral time after infection and the donation interval? To be able to answer these questions, optimal donor testing is required. Therefore, not only initial guidelines are needed, the information must be continuously updated as new information becomes available. A relevant example is if the use of laborious tests for neutralising antibodies can be substituted by less resource demanding tests without compromising the relevance of the results. As vaccination regimen are developed, the immune response from vaccinated donors may be more beneficial than from recovered donors. The number of convalescent plasma units transfused initially varied. Maybe it will be appropriate to transfuse larger volumes of convalescent plasma in the early phase when the effective antibodies are less defined than in a later stage when this is known. The indications for therapy should be adjusted based on available information. An international committee providing up-to-date information would be helpful for guidance on these critical issues.

A major concern during the current pandemic has been the few large randomised clinical studies. To conduct good clinical studies, the dose of the actual drug intervention, the indications, the inclusion and exclusion criteria must be well defined. In the first phase, it will be impossible to fulfil these criteria. If an international expert group agrees when sufficient information is provided, a multicentre study may be launched. As the number of patients can be large, results from interim evaluations may provide further guidance.

There are also security and safety issues related to convalescent plasma as several harmful effects may occur. These include the common transfusion reactions, including HLA-, HNA- and HPA-antibodies. Several reports indicate that the risk of such reactions are not increased compared to regular transfusion reactions [22,23]. If multiple units of convalescent plasma were pooled, this could improve efficacy of the product and it would lead to standardisation [24]. Ideally, such products should be validated in animal studies before clinical use. When available, monoclonal antibodies will be another alternative to single donor convalescent plasma [25].

Clinical studies are expensive to perform. The experiences from the COVID-19 pandemic show that many national and international authorities provide extensive support to pandemic-related research. A joint proposal for financial support should therefore be ready rapidly, as proved by the EBA applications during the present pandemic. It is also important to notice the WHO approach: To support studies comparing effects of different drugs. Convalescent plasma as one arm in a WHO study could be an ideal approach to evaluate the effects of convalescent plasma.

6. Conclusions

Convalescent plasma has been widely used during the COVID-19 pandemic as the product was made widely available by blood establishments worldwide early in the pandemic. However, the clinical effects of convalescent plasma are still uncertain and many scientists and clinicians deem the treatment as inappropriate. Despite extensive international collaboration, there were no general agreement on indications and dosing of convalescent plasma. In case of future demand for convalescent plasma, even stronger, more formalised cooperation may provide more clear evidence of the importance of convalescent plasma, based on the principles of passive immunisation.

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