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REVIEW

TRANSFUSION

Use of convalescent plasma in COVID-19 patients with immunosuppression

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Abstract

In the absence of effective countermeasures, human convalescent plasma has been widely used to treat severe acute respiratory syndrome coronavirus 2, the causative agent of novel coronavirus disease 19 (COVID-19), including among patients with innate or acquired immunosuppression. However, the association between COVID-19-associated mortality in patients with immunosuppression and therapeutic use of convalescent plasma is unknown. We review 75 reports, including one large matched-control registry study of 143 COVID-19 patients with hematological malignancies, and 51 case reports and 23 case series representing 238 COVID-19 patients with immunosuppression. We review clinical features and treatment protocols of COVID-19 patients with immunosuppression

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after treatment with human convalescent plasma. We also discuss the time course and clinical features of recovery. The available data from case reports and case series provide evidence suggesting a mortality benefit and rapid clinical improvement in patients with several forms of immunosuppression following COVID-19 convalescent plasma transfusion. The utility of convalescent plasma or other forms of antibody therapy in immune-deficient and immune-suppressed patients with COVID-19 warrants further investigation.

KEYWORDS

FFP transfusion, transplantation—solid organ, transfusion practices (oncology–hematology)

1 | INTRODUCTION

Convalescent plasma is a passive antibody therapy that has been used to prevent or treat infectious diseases for more than a century.[1,2] In the absence of effective countermeasures, human convalescent plasma has been widely used to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of novel coronavirus disease 19 (COVID-19). Convalescent plasma has received full or conditional regulatory authorization in the United States and many other countries for therapeutic use in adults and children hospitalized with suspected or laboratory-confirmed SARS-CoV-2 positive COVID-19.[3,4] The evidence supporting the use of convalescent plasma to treat patients with COVID-19 is not definitive.[5–15] There is evidence that supports the therapeutic use of convalescent plasma among patients with COVID-19 who are treated earlier in the disease course using plasma with sufficient antibody levels.[18,19] In contrast, however, several large clinical trials that transfused severely ill patients later in the disease course have suggested there is no mortality benefit conferred from COVID-19 convalescent plasma.[16,17]

Although there are many studies evaluating the clinical efficacy of convalescent plasma in otherwise immunocompetent patients, there is a paucity of studies evaluating the use of convalescent plasma in COVID-19 patients with immunosuppression or immunodeficiency. Patients with immunosuppression or immunodeficiency have been disproportionately affected by the COVID-19 pandemic,[20] and often present with persistent SARS-CoV-2 infection and may shed viable SARS-CoV-2 for months.[21] In this context, we summarize the growing number of contemporary case reports and case series of the clinical experiences of COVID-19 patients with primary and secondary immunosuppression who were treated with specific neutralizing antibodies via COVID-19 convalescent plasma transfusion. Importantly, evaluation of the clinical responses to convalescent plasma transfusion in immunosuppressed patients who cannot generate innate immune responses may provide an optimal opportunity to assess the effect of convalescent plasma per se.

2 | METHODS

We included investigations of the impact of human convalescent plasma therapy on COVID-19 patient mortality in patients with primary or secondary immunosuppression, which included case series, case reports, and media reports in lay press. References for this review were identified through searches of the online PubMed and MEDLINE databases for articles published from January 1, 2020 to April 10, 2021. Keywords used in the search included: (convalescent plasma or convalescent serum) AND COVID-19 (and Medical Subject Headings terms; MeSH terms). During review of abstracts, additional keywords used to search for relevant articles included: immunosuppressed, immunocompromised, immunodeficient, cancer, transplant, malignancy, and agammaglobulinemia. Relevant articles and data were also identified through non-systematic searches in Google Scholar and medRXiv. Articles resulting from these searches and relevant references cited in those articles were examined.

To be considered eligible for inclusion, studies must have: (1) included hospitalized patients with primary or secondary immunosuppression and a confirmed diagnosis of COVID-19, (2) used convalescent plasma as a COVID-19 treatment, and (3) reported patient mortality. Using an a posteriori approach, studies were further restricted to include only the following: (1) hypogammaglobulinemia or x-linked agammaglobulinemia, (2) common variable immune deficiency, (3) hematological malignancy, or (4) solid organ transplants. Although our search yielded articles describing use of COVID-19 convalescent plasma in the context of other potentially relevant conditions (myasthenia gravis,[22] trisomy 21,[23]

Sjögrens syndrome,[24] hemodialysis,[25] and rheumatoid arthritis[26,27]), there were very few represented patient cases, thus, our a posteriori restriction provided more robust evidence on fewer cohorts of patients. Two reviewers (J.W.S and S.A.K.) independently screened the titles and abstracts of all studies identified by the search to determine eligibility. Studies that were deemed potentially eligible had their full text reviewed (J.W.S and S.A.K.) to determine if they met the criteria for inclusion in the review. Disagreement was resolved by consensus. Three reviewers (J.W.S, S.A.K., and S.K.F.) extracted study and patient characteristics as well as clinical information, and extracted data were independently reviewed (K.A.S.). All procedures accessed public information and did not require ethical review as determined by the Mayo Clinic Institutional Review Board in accordance with the Code of Federal Regulations, 45 CFR 46.102, and the Declaration of Helsinki.

Disease severity of COVID-19 was delineated using a six-level ordinal scale, with higher scores indicating more progressed clinical course of COVID-19 at the time of convalescent plasma transfusion.[28] Scores on the ordinal scale were define as follows: a score of 1 indicated not hospitalized; 2, hospitalized and not receiving supplemental oxygen; 3, hospitalized and receiving supplemental oxygen; 4, hospitalized and receiving oxygen supplementation administered by a high-flow nasal cannula or noninvasive ventilation; 5, hospitalized and receiving extracorporeal membrane oxygenation or invasive mechanical ventilation; and 6, death.

In all studies but one large matched-control study,[29] there were no appropriate and comparable control groups. Thus, no analytical statistics analyses were performed, and no novel measures of probability are reported. Descriptive statistics are presented as frequencies and percentages based on numerical values reported in primary literature. These descriptive statistics should not be used to infer definitive treatment effects.

2.1 | Aggregate results

The literature search yielded 831 reports, of which 75 reports met the eligibility criteria and were included in the systematic review (Figure 1). This review includes one large matched-control registry study of 143 patients with hematological malignancies, and 51 case reports and 23 case series representing 238 COVID-19 patients with primary immunosuppression due to Agammaglobulinemia (X-linked or autosomal) or Common Variable Immunodeficiency, and secondary immunosuppression related to hematological malignancies and solid organ transplants who were transfused with convalescent plasma. A summary overview of patient characteristics,

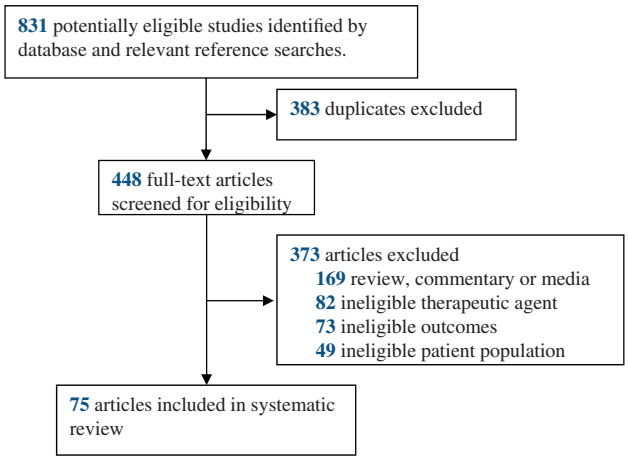

FIGURE 1 Flow chart of the study selection [Color figure can be viewed at wileyonlinelibrary.com]

COVID-19 therapies used (including convalescent plasma), and clinical symptomology of these patients is available as Tables S1–S3. Mortality among these hospitalized COVID-19 patients with immunosuppression who were treated with convalescent plasma was 16% (60 of 381 patients) with ~60% of patients demonstrating rapid clinical improvement within 5 days of convalescent plasma therapy, see Table 1.

3 | PRIMARY IMMUNODEFICIENCY

3.1 | Agammaglobulinemia

Patients with Agammaglobulinemia do not produce endogenous antibodies and require regular intravenous infusions or subcutaneous injections of immunoglobulins to avoid serial infections from common pathogens.[30] However, immunoglobulin replacement therapy cannot protect immunosuppressed patients against pathogens for which antibodies are uncommon or absent in the immunoglobulin donor pool, such as the SARS-CoV-2 virus.[30] We identified 15 patients from six case reports[31–36] and three case series.[37–39] The COVID-19 patients with agammaglobulinemia were predominantly male and primarily young to middle-aged (range, 3–40 years). These patients also had a wide range of disease severity (range, 2–5) assessed using a six-level ordinal scale to assess the clinical course of COVID-19.[28] Overall, the observed mortality rate was 7% (1 of 15 patients) and rapid improvement in supplemental oxygen was observed in three of six patients (50%) that reported on these metrics. In a case series, three male patients with X-linked Agammaglobulinemia (aged 10, 24 and 40 years) with prolonged COVID-19 who required oxygen support were treated with

TABLE 1 Summary of hospital course and disposition of coronavirus disease 19 (COVID-19) patients with immunosuppression after transfusion of convalescent plasma

Condition	No. patients	COVID-19 disease severity scale[a]	Illness onset to treatment (days)[a]	Mortality (*n*, %)[a]	Rapid improvement in supplemental oxygen (≤5 days) (*n*, %)[a]	Discharge (days)[a]
Primary immunosuppression						
Agammaglobulinemia	15	3 (2–5)	27 (12–69)	1, 7%	3 of 6, 50%	10 (1–50)
Common variable immune deficiency	7	3 (2–5)	20 (11–28)	1, 14%	2 of 2, 100%	10 (7–13)
Secondary immunosuppression						
Hematological malignancies	150	3 (2–5)	26 (2–103)	30, 20%	37 of 55, 67%	27 (1–148)
Solid organ transplants	66	3 (2–5)	9 (2–31)	9, 14%	25 of 37, 68%	18 (2–58)

Note: Data are presented as mean (range), count (*n*), or mean (%).

[a]Data were not reported for all patients, please see Tables S1–S3 for additional information. WHO Disease Severity Scale: 1 (not hospitalized), 2 (hospitalized, no supplemental oxygen), 3 (hospitalized, non-high flow supplemental oxygen), 4 (hospitalized, high flow supplemental oxygen), 5 (hospitalized, intubated or extracorporeal membrane oxygenation), 6 (deceased).

broad-spectrum antibiotics with limited or no clinical improvement.[37] Each patient then received convalescent plasma, resulting in rapid clinical improvement in all three patients and hospital discharge within 72 hours for the two adult patients.[37]

3.2 | Common variable immunodeficiency

Common variable immunodeficiency represents a heterogeneous collection of immunodeficiencies commonly characterized by intrinsic B-cell defects and suppressed antibody production.[40] Patients with common variable immunodeficiency often present with inflammatory and autoimmune disorders, which are suspected to elevate patient risk for progression to severe COVID-19.[38,40] We identified seven patients with common variable immunodeficiency from three case reports[39,41,42] and one case series.[38] Among these seven patients, ~50% were female, ~50% were receiving mechanical ventilation or extracorporeal membrane oxygenation, and one mortality was observed. In the case series, four patients with antibody-deficient common variable immunodeficiency diagnosed with severe or life-threatening COVID-19 were transfused with convalescent plasma for COVID-19 therapy.[38] Three of these patients survived following convalescent plasma transfusion, including two patients whose clinical symptomatology required mechanical ventilation or extracorporeal membrane oxygenation. In two case studies of a young male (37 years) and young female (25 years) who had life-threatening COVID-19 which required mechanical ventilation or extracorporeal membrane oxygenation, both patients demonstrated rapid clinical improvement resulting in successful weaning from invasive ventilation within 48 h.[41,42]

These data from patients with primary immunodeficiencies suggest that COVID-19 convalescent plasma could be a valuable therapeutic approach, but further studies should be performed to determine the therapeutic outcomes of convalescent plasma transfusion in patients with abnormal capacity to produce antibody responses.

4 | SECONDARY IMMUNODEFICIENCY

4.1 | Hematological malignancy

Hematological malignancies are associated with deficits in both humoral and cellular immunity which may contribute to increased risk of progression to severe COVID-19.[29] Many treatments of hematologic malignancies, such as the cornerstone of treatment (anti-CD-20 monoclonal antibodies), may lead to prolonged B-cell depletion and impaired immune responses.[43,44] From 32 case reports[45–76] and 11 case series,[27,44,77–85] we identified 150 COVID-19 patients with hematological malignancies treated with convalescent plasma. Among these 150 patients, the mortality rate was 20% (30 of 150 patients), 37 patients demonstrated rapid clinical improvement after convalescent plasma transfusion, and the average time between convalescent plasma transfusion and hospital discharge was 27 days. In a case series, 17 patients with B-cell lymphopenia and protracted COVID-19 received convalescent plasma with high neutralizing antibody titers.[44] Although patients received plasma late in the

disease course (7–83 days after symptom onset), 16 patients demonstrated improvement of clinical symptoms and reduction in SARS-CoV-2 RNAemia within 7–14 days. One patient, who required mechanical ventilation, died.[44] Similarly, in a separate cohort of 14 patients with hematological malignancies,[78] most patients exhibited improvement in clinical symptomatology, including reduced oxygen requirements, after treatment with convalescent plasma. Notably, a patient with protracted COVID-19, evidenced by three separate COVID-19-related hospitalizations over a 100+ day period, and with lymphoma-associated B-cell immunodeficiency demonstrated rapid reductions in fever, oxygen requirements, and lung infiltrates (via chest computed tomography) forthwith after two separate convalescent plasma transfusions separated by ~90 days.[46]

At the time of writing, there is one large matched-control study using registry data from the COVID-19 and Cancer Consortium (CCC19) international consortium.[29] The 30-day mortality was evaluated in hospitalized adults with hematologic malignancy and COVID-19, comparing 143 patients transfused with convalescent plasma and 823 matched controls who received standard care treatment. Death within 30 days occurred in 13.3% (19 of 143 patients) in the patients transfused with convalescent plasma and 24.8% (204 of 823 patients) in the matched control group. Among these patients with hematologic malignancy, convalescent plasma treatment was associated with a lower risk of death after adjustment for potential confounding factors (hazard ratio, 0.60; 95% confidence interval [CI], 0.37–0.97) or after propensity-score matching (hazard ratio, 0.52; 95% CI, 0.29–0.92). Although these data are consistent with a mortality benefit associated with administration of COVID-19 convalescent plasma in the context of hematological malignancy, this observational study should not be inferred for causality.

4.2 | Solid organ transplant

Recipients of solid organ transplants are known to be vulnerable to viral infections secondary to a weakened T-cell mediated immune response.[86] From 10 case reports[87–96] and 10 case series,[25,97–105] we identified 66 COVID-19 patients who received a solid organ transplant and who were treated with convalescent plasma. Of these 66 patients, mortality was observed in nine patients (14%), 4 patients remain hospitalized at the end of the observation period, and 25 patients demonstrated rapid improvement in clinical symptomatology. In a case series, 13 hospitalized patients with COVID-19 who were solid organ transplant recipients were transfused with two units of convalescent plasma and received concomitant therapies, primarily broad spectrum antibiotics and hydroxychloroquine.[97] Nine patients were discharged home without readmission, of which eight had de-escalating oxygen support within 7 days of plasma transfusion. One patient had a prolonged hospital admission and three patients died. Of the three patients who expired, two patients received plasma more than 2 weeks after symptom onset—a timeframe which may be associated with a reduced mortality benefit of COVID-19 convalescent plasma.[106] These data are consistent with a recent systematic review of clinical outcomes of COVID-19 among solid organ transplant recipients.[86]

5 | CONCLUSIONS

The available data from case reports and case series provide evidence suggesting a mortality benefit and rapid clinical improvement in patients with several forms of immunosuppression following COVID-19 convalescent plasma transfusion. In contrast to ongoing studies of convalescent plasma efficacy in clinical trials where the majority of patients are otherwise immunocompetent and thus mount their own protective antibody responses,[5] convalescent plasma use in immunosuppressed patients represents a situation where exogenous antibody is given in the setting of an immune deficit. However, there is some hesitancy about using convalescent plasma due to concern that it could select for the emergence of SARS-CoV-2 variants, given reports that new SARS-CoV-2 variants were found in a COVID-19 patient with immunosuppression treated with plasma.[67] As described elsewhere,[107] it is highly unlikely that convalescent plasma is the source of SARS-CoV-2 variants currently circulating, rather these variants were more likely selected by natural immune responses in infected patients and convalescent plasma may be one of few potential therapeutics for emerging SARS-CoV-2 variants.

The case series and case reports summarized here provide evidence suggesting a mortality benefit and rapid clinical improvement in patients with several forms of immunosuppression following COVID-19 convalescent plasma transfusion. These findings were an important component of the scientific evidence considered by the US Food and Drug Administration suggesting a longer potential therapeutic window for COVID-19 convalescent plasma among immunosuppressed or immunodeficient patients than is evident in immunocompetent patients. Although these summary findings are encouraging for the use of therapeutic convalescent plasma in COVID-19 patients with immunosuppression, well-controlled, published data in these populations remain lacking, including

only one large matched treatment-control study[29] and no randomized controlled trials. As such, the data should not be used to infer definitive treatment effects. The utility of convalescent plasma or other forms of antibody therapy in immunosuppressed or immunodeficient patients with COVID-19 warrants further investigation.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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