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Short communication

SARS-CoV-2 variants in immunocompromised COVID-19 patients: The underlying causes and the way forward

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1. Introduction

Since the first case of coronavirus disease 2019 (COVID-19) in November 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has undergone continuous evolution as a result of various mutations. These mutations have resulted in the production of variants of concern such as B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617.2 (delta), B.1.1.529 (omicron) variants that have resulted in recurrent waves of COVID-19 pandemic. All these variants have one thing in common; all of them have multiple mutations as compared to the wild type of SARS-CoV-2. It has emerged that COVID-19 patients who are immunocompromised may be a source of these variants [1]. There is evidence that B.1.1.7 (alpha) variant which was first detected in the United Kingdom may have evolved from an immunocompromised host [1,2]. Most recently, there is concern that B.1.1.529 (omicron) variant may also have originated from an immunocompromised host [3].

2. COVID-19 convalescent plasma in the management of immunocompromised patients

It is now known that COVID-19 patients with immunodeficiency have a defective viral clearance and are at an increased risk of developing a chronic prolonged phase of infection [4]. Immunocompromised patients are unable to mount an immune response against the SARS-CoV-2 and therefore are ideal candidates for the administration of passive antibody therapy against SARS-CoV-2 [5]. Numerous case reports/-series have analyzed the safety and clinical efficacy of COVID-19 convalescent plasma (CCP) in immunocompromised COVID-19 patients and are available in the literature [6–17]. Notably, in many of these reports, CCP therapy was initiated late in the course of COVID-19, still, it resulted in rapid symptomatic improvement in the patients [6,8–10,13–16]. CCP appears to be particularly effective in patients with B- cell lymphoproliferative disorders. In February 2021, the FDA revised the emergency use authorization for CCP use and limited the use of high titre convalescent plasma in the early stages of COVID-19 only with the exception of immunocompromised patients, in which case CCP could be administered at any stage of COVID-19 [15].

3. COVID-19 convalescent plasma therapy and SARS-CoV-2 variants

It is argued that CCP therapy in immunocompromised COVID-19 patients can lead to the generation of SARS-CoV-2 variants due to multiple mutations during the prolonged phase of infection [18]. We did a literature search and found 9 case reports/series which analyzed the evolution and subsequent mutations in SARS-CoV-2 in chronically infected immunocompromised patients [4,19–26]. The findings of these studies are summarised (Table 1). Out of these, CCP was used in the management of the patients in five studies, monoclonal antibodies (mAbs) in two studies and neither of these in two studies. Notably, multiple mutations were seen in all cases irrespective of the use of CCP in the management of these patients [21–23,26]. However, Chen et al. [19]. And Kemp et al. [20] observed that the mutations occurred after the initiation of CCP therapy in the patients. Khatamzas et al. observed an increased frequency of mutation in the SARS-CoV-2 after initiation of the CCP therapy in the patient [25]. The multi-mutations after CCP therapy in these patients especially in the spike protein region can be explained by immunological selective pressure as a result of antispike treatment [20]. This might also explain the reason for mutations in spike protein. However, the appearance of mutations in the absence of CCP therapy suggests that the immunocompromised host is acting as an ideal niche for SARS-CoV-2 to undergo chronic adaptive evolution [22]. Therefore, from the current evidence it appears that although CCP might accelerate the generation of SARS-CoV-2 mutants, it is the defective immune response of the immunocompromised patients which remains the underlying cause for the generation of SARS-CoV-2 mutants.

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Table 1
Summary of the studies reporting SARS-CoV-2 variants in immunocompromised COVID-19 patients.

Name of the study	Age and clinical diagnosis	CCP regimen	Outcome	Mutation (s)
Chen et al. [19]	50 y; post kidney transplant	High titre CCP on day 1 of the admission	The patient became SARS-CoV-2 negative on day 45 of admission However, the patient died on day 94	5 different mutations in S protein on 21st day nasopharyngeal sample suggesting in host viral evolution
Kemp et al. [20]	70 y, B cell lymphoma	CCP therapy on day 57	The patient died on day 102	Mutations in spike protein after day 65
Bazykin et al. [21]	47 y, non-Hodgkin diffuse B cell lymphoma	CCP not used in management	The patient recovered after 120 days	140 deletions in spike – N terminal domain protein region
Borges et al. [22]	61 y, non-Hodgkin diffuse B cell lymphoma	CCP not used in the management	The patient was SARS-CoV-2 negative after 196 days	A total of 18 mutations had accumulated by day 164 Total 17 mutations in spike protein
Troung et al. [23]	3 y, ALL	CCP not used in the management	SARS-CoV-2 negative after 46 days	Multiple mutations in spike protein
	21 y, ALL	1 st CCP on day 103. Thereafter weekly CCP till day 144 and every alternate week after that	Patient was still SARS-CoV-2 positive on day 250 at the time of publication of the manuscript	Multiple mutations in spike protein both before and after CCP
	2 y, ALL	CCP not used in the management	Patient was SARS-CoV-2 negative on day 196	Multiple mutations in spike protein
Avanzato et al. [4]	71 y, CLL	2 course of CCP, 1st on day 70 2nd on day 95	SARS-CoV-2 negative after 105 days	Multiple mutations in spike protein; the majority of mutations had already occurred before the initiation of CCP
Choi et al. [24]	45 y, APS	Monoclonal antibodies given on day 143	The patient died on day 152	Multiple mutations in spike protein, majority of mutations had already occurred before initiation of monoclonal antibody therapy
Khatamzas et al. [25]	70 y, B-cell depleted lymphoma	CCP initiated on approximately day 40 of diagnosis	The patient died after 5 months of diagnosis	Multiple mutations in spike protein, the frequency of mutations increased after administration of CCP
Pommeret et al. [26]	5 patients with B-cell malignancies	Monoclonal antibodies given within 5 days of their first symptom	4 patients recovered after 38 to 63 days of diagnosis; 1 patient died after 56 days of diagnosis	Mutation in spike protein detected in 4 out of 5 patients after administration of monoclonal antibodies

APS: antiphospholipid syndrome; ALL: acute lymphoblastic leukemia; CLL: chronic lymphoblastic leukemia; CCP: COVID-19 convalescent plasma; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

4. Role of monoclonal antibodies in immunocompromised COVID-19 patients

More recently, neutralizing mAbs target the spike protein have also become available [27]. These mAbs contain a fixed amount of high titre neutralizing antibodies, whereas, in the case of CCP, the titre is variable from one unit to another. Therefore, as compared to CCP, neutralizing mAbs have the advantage that their dose can be standardised [28]. However, mAbs administered late in the course of infection in an immunocompromised patient can also favour evolution of SARS-CoV-2 through immunological selection pressure [26]. We could only find three published articles on the use of mAbs in the management of immunocompromised COVID-19 patients [24,26,28]. In the case report by Choi et al., mAb therapy was administered in the patient on day 143 of diagnosis; however, the patient died on day 152 of diagnosis [24]. Pulvirenti et al. reported eight cases of primary immune deficiency treated with mAbs early in the course of the disease (within 2 to 15 days of diagnosis). In fact, seven out of eight patients became asymptomatic within 3 to5 days of mAb administration. Notably, the viral persistence was significantly shorter in patients who underwent mAb therapy as compared to those who underwent standard care (22 days vs. 37.5 days) [28]. More data on the efficacy of monoclonal antibodies in the management of COVID-19 should become available in the near future. Clinical trial accessing the role of monoclonal antibodies as a prophylaxis against COVID-19 in immunocompromised patients is also ongoing [29].

5. Conclusions

Both CCP and mAbs are effective tools in the management of immunocompromised COVID-19 patients. However, the evidence that CCP can accelerate the generation of SARS-CoV-2 variants is a major public health issue. SARS-CoV-2 variants are the major hurdle in the eradication of the COVID-19 pandemic [30]. Therefore, whether mAbs treatment can be used as a substitute to CCP in immunocompromised individuals needs to be assessed on an urgent basis. A three parallel arm multicentric randomised controlled trial which involves the use of CCP in immunocompromised patients in one arm; use of mAbs in the second arm and use of standard care of treatment in the third arm; can probably answer whether CCP is associated with an accelerated development of SARS-CoV-2 variants or whether the immunocompromised host itself is acting as an ideal niche for SARS-CoV-2 to undergo evolution and further mutations. Indeed, if the generation of SARS-CoV-2 variants is blocked, then there could be a potential end to this COVID-19 pandemic.

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Disclosure of interest

The authors declare that they have no competing interest.

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