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Original Article

Efficacy of the combination of BRII-196/BRII-198 in the treatment of COVID-19 vaccine breakthrough infections

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Abstract: Background: BRII-196 and BRII-198 are two recombinant human immunoglobulin (Ig) G1 monoclonal antibodies (mAbs) that non-competitively target distinct epitope regions within the receptor-binding domain (RBD) of the coronavirus spike glycoproteins. These antibodies are derived directly from human B cells of individuals who recovered from COVID-19. Objective: To analyze the efficacy of BRII-196/BRII-198 in the treatment of coronavirus disease 2019 (COVID-19) vaccine breakthrough infections. Methods: COVID-19 patients at high risk of progressing to severe and critical illness, with an initial SARS-CoV-2 immunoglobulin (Ig) G antibody level < 1.0 S/CO (detected within 24-48 hours post COVID-19 diagnosis), were treated with BRII-196/BRII-198 within three days of symptom onset. Treatment continued until the antibody level exceeded 1.0 S/CO. Patients whose absolute lymphocyte count (ALC) at first detection (within 24-48 h post-diagnosis) was < 0.8×10^9/L received thymalfasin therapy within three days of symptom onset, continuing until the ALC level surpassed 0.8×10^9/L. We determined the correlation of SARS-CoV-2 IgG antibody level and ALC with the condition of COVID-19 patients. Additionally, we analyzed the effects of BRII-196/BRII-198 on SARS-CoV-2 nucleic acid (NA) negative conversion, lymphocyte count recovery, and the change in SARS-CoV-2 IgG antibody level from the first positive NA test for SARS-CoV-2 to negative conversion in COVID-19 patients. Results: A total of 61 cases of breakthrough infections were observed, classified as 10 mild cases, 31 ordinary cases, and 20 severe cases. Among these, 20%, 48.4% and 75% of the patients with mild, ordinary, and severe COVID-19, respectively, had initial SARS-CoV-2 IgG antibody level < 1.0 S/CO. Additionally, 0%, 35% and 70% had initial ALC < 0.8×10^9/L, respectively. Fifteen ordinary and 15 severe COVID-19 patients were treated with BRII-196/BRII-198. In severely infected patients, BRII-196/BRII-198 treatment showed statistically significant differences in NA negative conversion time and changes in SARS-CoV-2 IgG antibody levels ($P < 0.05$). However, in patients classified with ordinary severity, BRII-196/BRII-198 treatment did not lead to notable differences in NA negative conversion time or changes in SARS-CoV-2 IgG antibody level ($P > 0.05$). BRII-196/BRII-198 therapy was not associated with lymphocyte count recovery time in patients with either ordinary and/or severe COVID-19 ($P > 0.05$). Conclusions: The initial levels of SARS-CoV-2 IgG antibody and lymphocytes in fully vaccinated patients with breakthrough infections are inversely correlated with the severity of the disease. Early treatment with BRII-196/BRII-198 can shorten NA negative conversion time in severe COVID-19 patients and increase in vivo neutralizing antibody levels post-conversion, providing lasting protection. However, BRII-196/BRII-198 does not influence lymphocyte count recovery in patients with either ordinary and/or severe COVID-19.

Keywords: COVID-19 vaccines, neutralization, BRII-196, BRII-198, immunoglobulin G

Introduction

Since the first reported cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 [1], coronavirus disease 2019 (COVID-19) has spread globally. While most SARS-CoV-2 infected patients experience mild or no symptoms, a significant number develop serious, life-threatening conditions. Neutralizing monoclonal antibodies (mAbs) are a promising option for preventing and treating known and emerging infectious diseases, including viral infections [2]. Clinical trials have demonstrated therapeutic and prophylactic benefits of monoclonal antibodies [3, 4]. Antibody drugs with high efficacy are crucial for short-term prevention of SARS-CoV-2 infection and treatment of COVID-19, playing a piv-

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otal role in epidemic management and control. To address the continuous mutation of SARS-CoV-2 and the widespread emergence of variants, cocktail therapies combining multiple antibodies have been developed [5].

BRII-196/BRII-198, the first approved neutralizing antibody (NAb) combination therapy in China with independent intellectual property rights, is also the only antibody drug that has been evaluated globally for the treatment of SARS-CoV-2 mutant (mainly Delta variant) infections, delivering some of the most compelling efficacy data to date. BRII-196 and BRII-198, two recombinant human IgG1 mAbs, were originally derived from the B cells of patients who recovered from COVID-19 [6]. Their non-competitive binding to distinct epitope regions of the receptor-binding domain (RBD) in the coronavirus spike glycoprotein enables them to retain neutralizing activity against the original SARS-CoV-2 strain and major SARS-CoV-2 variants, including 1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.617.2 (Delta), and AY.4.2 (Delta Plus), et al. [7-9]. Additionally, BRII-196 and BRII-198 incorporate a triple amino acid substitution (M252Y/S254T/T256E [YTE]) in the fragment-crystallizable (Fc) region, effectively prolonging their half-life [10]. This study aims to analyze the efficacy of BRII-196/BRII-198 in treating Delta-variant SARS-CoV-2 breakthrough infections among patients fully vaccinated with COVID-19 inactivated vaccines.

Materials and methods

Participants

Inclusion criteria for COVID-19 patients for the retrospective analysis were as follows: (1) Delta variant infection traced to a tourism communication chain in Gansu Province, China, at the end of October 2021; (2) Patients had received 2 doses of National Food and Drug Administration (FDA)-approved inactivated COVID-19 vaccines prior to SARS-CoV-2 infection; (3) Age 18 years or older; (4) SARS-CoV-2 nucleic acid (NA) positivity within 2 days, confirmed by nose or throat swab using RT-PCR; (5) Onset of COVID-19 related symptoms within 3 days; (6) Completion of initial SARS-CoV-2 IgG antibody testing, routine blood work, biochemistry, blood oxygen saturation or blood gas analysis, and chest CT scan within 24 to 48 hours after confirming SARS-CoV-2 NA positivity; (7) Classification of COVID-19 according to the Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition) [11]. Exclusion criteria: (1) Pregnancy; (2) Those suffering from autoimmune diseases; (3) Use of immunosuppressants or hormonal drugs in the past 3 months; (4) Cancer patients that needed radiotherapy or chemotherapy; (5) Those with incomplete patient information. This retrospective study was approved by the Ethic Committee of Pulmonary Hospital of Lanzhou.

Methods

All patients received prone ventilation for over 12 hours daily and antiviral treatment with a traditional Chinese medicine decoction aimed at ventilating the lungs, dispelling pathogens, and strengthening qi and yin [12]. Biochemical indices such as creatine kinase isoenzyme (CK-MB), lactic dehydrogenase (LDH), C-reactive protein (CRP), and white blood cell count (WBC) were regularly tested in all patients. Patients with severe infections received varying forms of oxygen therapy and respiratory support based on their condition. For ordinary and severe COVID-19 patients with SARS-CoV-2 IgG antibody level < 1.0 S/CO at initial detection and at high risk of progressing to severe or critical illness were treated with a NAb cocktail within 3 days of symptom onset.

Furthermore, BRII-196/BRII-198 (not marketed until 2022 and unavailable during the initial COVID-19 outbreak in Gansu Province in October 2021) was administered. The State FDA approved the marketing application for the combination of these two antibodies on December 8, amidst the ongoing epidemic. Given the outbreak's origin in elderly tour groups, patients were older, with many underlying conditions and high-risk factors for the development of severe and critical COVID-19. The drugs were directly donated by the government through Tengsheng Huachuang Pharmaceutical Technology (Beijing) Co., Ltd., following a request from Professor Qiu Haibo, an expert from the National COVID-19 Rescue Team. Therefore, the medication bottles lacked manufacturer details, batch numbers, or specifications. Instead, BRII-196 and BRII-198 were labeled as No.1 and No.2, respectively, each containing 500 mg. Related information can be found in the announcement or article about the

Table 1. General information of patients

Clinical features	Patients with SARS-CoV-2 Delta variant vaccine-breakthrough infections (n=61)
Sex	
Male	26
Female	35
Age (years)	57 (42, 69)
Classification	
Mild	10
Ordinary	31
Severe	20
Time interval between two vaccinations	114 (68, 129)
Biochemical indexes	
CK-MB (U/L)	29.0 (11.0, 38.5)
LDH (U/L)	182.1 (156.0, 207.5)
CRP (mg/L)	14.49 (2.93, 18.17)
WBC (× 10^9/L)	5.38 (4.05, 6.30)

Note: CK-MB, creatine kinase tsoenzym; LDH, lactic dehydrogenase; CRP, C-reactive protein; WBC, white blood cell count.

drug released by Zhang Linqi's team of Tsinghua University [13]. For administration, each antibody was diluted in 100 ml of 0.9% sodium chloride injection and injected sequentially at a rate not exceeding 4 ml/min, with 100 ml of 0.9% sodium chloride used to flush the tube between administrations. BRII-196/BRII-198 was administered once daily, with fasting blood samples collected the following morning to monitor SARS-CoV-2 IgG antibody levels. Treatment was discontinued once the antibody level exceeded 1.0 S/CO or continued until this threshold was reached.

Based upon results from blood analyses, patients with an absolute lymphocyte count (ALC) < 0.8 × 10^9/L within 3 days of onset were subcutaneously injected with 1.6 mg of thymalfasin (Shenzhen Hybio Pharmaceutical Co., Ltd., Batch Number: 2063230104, specification: 1.6 mg/piece) daily. Fasting blood samples were drawn the next morning for routine examination. Thymalfasin administration was ceased when ALC level rose above 0.8 × 10^9/L. Recorded data included the time of ALC recovery to 0.8 × 10^9/L or higher, the time required for SARS-CoV-2 NA to hit an inflection and begin to decrease, and the variance in SARS-CoV-2 IgG antibody levels between initial positivity and subsequent recovery.

Statistical analyses

Data were processed and analyzed using the SPSS 23.0 software. Measurement data following a normal distribution were described as mean ± standard deviation ($\bar{x}$ ± s), and independent samples t-tests were used for between-group comparisons. Non-normally distributed measurement data were presented as medians, with the Mann-Whitney rank-sum test used for inter-group comparisons. Pearson correlation and binary logistic regression analyses were employed to analyze the effect of NAbs on lymphocyte count recovery time and the influence of combined NAbs and thymalfasin therapy on this recovery time, respectively. All tests were two-tailed with a significance level of α=0.05.

Results

General information

A total of 61 cases of eligible SARS-CoV-2 Delta variant vaccine-breakthrough infections, fully vaccinated with the inactivated COVID-19 vaccine, were included in this study. The patient demographics, encompassing 10 mild cases, 31 ordinary cases, and 20 severe cases, are presented in **Table 1**. Biochemical index results at admission are detailed in **Table 2**, revealing abnormal levels of indicators in all patients. Among the mild, ordinary, and severe COVID-19 patients, 2 (20%), 15 (48.4%), and 15 (75%) respectively had a SARS-CoV-2 IgG antibody level < 1.0 S/CO at initial detection upon COVID-19 diagnosis. These patients met the discontinuation criteria after receiving combined treatment with BRII-196/BRII-198 in dosages of 0 mg, 1000-3000 mg, and 1000-5000 mg, respectively. Additionally, 0 cases (0%) of mild, 11 cases (35%) of ordinary, and 14 cases (70%) of severe COVID-19 had an absolute lymphocyte count (ALC) < 0.8 × 10^9/L at first detection post-diagnosis. The discontinuation criteria were met after treatment with 0 mg, 1.6-6.4

Table 2. Basic information of treatment for patients with different disease severity

	Patients with SARS-CoV-2 Delta variant vaccine-breakthrough infections (n=61)		
	Mild (n=10)	Ordinary (n=31)	Severe (n=20)
SARS-CoV-2 IgG antibody level < 1.0 S/CO at first detection	2	15	15
Absolute lymphocyte count < 0.8 × 10^9/L at first detection	0	11	14
Thymalfasin + BRII-196/BRII-198	-	8	10

Table 3. Pre-treatment index levels of patients with ordinary and severe COVID-19

	Absolute lymphocyte count at first detection (× 10^9/L)	SARS-CoV-2 IgG antibody (S/CO) level before treatment
Ordinary (n=15)	0.8667±0.3658	1.5147±2.1780
Severe (n=15)	0.8333±0.3754	0.4007±0.3169
t	0.2468	1.9603
P	0.8068	0.0599

mg, and 3.2-8.0 mg of thymalfasin, respectively. Eight patients with ordinary COVID-19 and 10 patients with severe COVID-19 underwent treatment with both thymalfasin and BRII-196/BRII-198. It was observed that the severity of SARS-CoV-2 breakthrough infections in fully vaccinated patients was inversely correlated with lymphocyte (correlation coefficient =-0.513) and NAb counts (correlation coefficient =-0.200) in the body. Patients with mild COVID-19 were not treated with BRII-196/BRII-198 and were thus excluded from the statistical analysis of this study, as indicated in **Table 3**.

The ALC at initial detection upon SARS-CoV-2 diagnosis in 15 ordinary and 15 severe COVID-19 patients before BRII-196/BRII-198 treatment were (0.8667±0.36580) × 10^9/L and (0.8333±0.37544) × 10^9/L, respectively. The SARS-CoV-2 IgG antibody levels were (1.5147±2.17799) S/CO and (0.4007±0.31692) S/CO, respectively, with neither showing statistical significance (P=0.8068 and *P*=0.0599) (**Table 3**).

Effect of thymalfasin on SARS-CoV-2 NA negative conversion time and SARS-CoV-2 IgG antibody level

Eleven ordinary and thirteen severe COVID-19 patients with an ALC < 0.8 × 10^9/L at initial detection post-diagnosis were treated with thymalfasin. The remaining 27 cases, either ordinary or severe COVID-19 with an ALC > 0.8 × 10^9/L at first detection, did not receive thymalfasin. No significant differences were found between the thymalfasin-treated and non-thymalfasin-treated groups in terms of SARS-CoV-2 NA negative conversion time (*P*=0.693) and the SARS-CoV-2 IgG antibody level detected when SARS-CoV-2 NA turned negative (*P*=0.563), as shown in **Table 4**.

Effect of BRII-196/BRII-198 on NA negative conversion time and SARS-CoV-2 IgG antibody level variance between the first positive SARS-CoV-2 NA test and the negative conversion

All patients underwent testing for SARS-CoV-2 NA negative conversion. Among the patients, 30 patients had ordinary and severe COVID-19 and their SARS-CoV-2 IgG antibody level was less than 1.0 S/CO at first detection when they were diagnosed. They were also at high risk of developing to severe and critical illness. Compared with the 21 patients with either ordinary or severe COVID-19 who were not treated with BRII-196/BRII-198, the 30 patients receiving BRII-196/BRII-198 therapy showed significant differences in SARS-CoV-2 NA negative conversion time (*P*=0.037), but no statistical difference in SARS-CoV-2 IgG antibody levels between the first positive SARS-CoV-2 NA test and the negative conversion (*P*=0.118). Among patients with ordinary illness, the 15 BRII-196/BRII-198-treated patients exhibited no marked difference in NA negative conversion time (*P*=0.399) and SARS-CoV-2 IgG antibody level variance between the first positive SARS-CoV-2 NA test and the first NA negative conversion (*P*=0.979) when juxtaposed with 16 untreated patients. In contrast, among the severe COVID-19 patients, the 15 treated with BRII-196/BRII-198 showed significant differences not only in NA negative conversion time (*P*=0.005) but also in the variance of SARS-CoV-2 IgG antibody

Table 4. Treatment of thymalfasin-treated and non-thymalfasin-treated groups

	SARS-CoV-2 nucleic acid negative conversion time (days)	SARS-CoV-2 IgG antibody level when SARS-CoV-2 nucleic acid turned negative
Thymalfasin-treated group (n=24)	18.42±5.06	64.52±53.38
Non-thymalfasin-treated group (n=27)	19.07±6.43	73.26±51.69
t	0.398	0.583
P	0.693	0.563

Table 5. Comparison of therapeutic effects between patients with BRII-196/BRII-198 treatment and those without

		SARS-CoV-2 nucleic acid negative conversion (days)	SARS-CoV-2 IgG antibody level when SARS-CoV-2 nucleic acid turned negative
BRII-196/BRII-198-treated group (n=30)		17.37±5.05	78.73±48.40
Non-BRII-196/BRII-198-treated group (n=21)		20.76±6.27	55.46±55.40
t		2.139	1.592
P		0.037	0.118
Ordinary	BRII-196/BRII-198-treated group (n=15)	17.93±6.03	60.17±55.65
	Non-BRII-196/BRII-198-treated group (n=16)	17.93±6.03	59.64±57.17
t		0.856	0.026
P		0.399	0.979
Severe	BRII-196/BRII-198-treated group (n=15)	16.80±3.97	97.28±31.90
	Non-BRII-196/BRII-198-treated group (n=5)	23.60±4.67	42.10±52.85
		3.185	2.843
		0.005	0.011

levels between the first positive NA test and negative conversion (P=0.011), compared to 5 untreated patients. Detailed data can be found in **Table 5**. Furthermore, logistic analysis indicated that the severity of the disease and the use of BRII-196/BRII-198 were influencing factors for the SARS-CoV-2 IgG antibody level at the time of SARS-CoV-2 nucleic acid negative conversion (**Table 6**).

Effect of BRII-196/BRII-198 on lymphocyte count recovery time in patients with COVID-19

The correlation coefficient between BRII-196/BRII-198 therapy and lymphocyte count recovery time in patients with ordinary and severe COVID-19 was 0.355 (P=0.054). For ordinary COVID-19 patients, the correlation coefficient was 0.028 (P=0.921), while for severe COVID-19 patients, the correlation coefficient was 0.396 (P=0.144 in the 18 COVID-19 cases treated with both BRII-196/BRII-198 and thymalfasin), the correlation coefficient for BRII-196/BRII-198 treatment and lymphocyte count recovery time was 0.396 (P=0.102). The correlation coefficient between thymalfasin treatment and lymphocyte count recovery time was 1 ($P < 0.0001$). This indicates that there is no significant correlation between BRII-196/BRII-198 therapy and lymphocyte count recovery time in patients with ordinary and/or severe COVID-19. However, there is a complete positive correlation between thymalfasin therapy and lymphocyte count recovery time in patients with both ordinary and severe COVID-19, as shown in **Table 7**.

Discussion

Clinical trials and real-world data indicate that a significant proportion of patients develop breakthrough infections regardless of the COVID-19 vaccine type received [14]. Various COVID-19 vaccines induce protective NAbs, which alleviate clinical symptoms in COVID-19 patients. Antibody cocktail therapies targeting different epitopes of the spike protein (S) of the novel coronavirus have proven more effective

Table 6. Logistic analysis of the influence factor of IgG level when SARS-CoV-2 nucleic acid turned negative

Variate		β	SE	Wald	P	HR	95%
Constant		-1.838	1.684	1.192	0.275	0.159	1.084-14.868
Age	Continuous	-0.032	0.022	2.055	0.152	0.969	0.928-1.012
Severity	Ordinary =0, Mild =1, Serve =2	1.610	0.605	7.087	0.008	5.003	1.529-16.370
IgG at first detection	Continuous	0.024	0.016	2.199	0.138	1.024	0.992-1.057
Absolute lymphocyte count at first detection	Continuous	0.551	0.731	0.568	0.451	1.736	0.414-7.275
BRII-196/BRII-198 treatment	No =0, Yes =1	1.390	0.668	4.331	0.037	4.015	1.084-14.868

Table 7. Effects of different treatments on lymphocyte count recovery

	Effect of BRII-196/BRII-198 therapy on lymphocyte count recovery in COVID-19 patients			Effect of BRII-196/BRII-198 + thymalfasin on lymphocyte count recovery in COVID-19 patients	
	Ordinary (n=15)	Severe (n=15)	Ordinary + severe (n=30)	Thymalfasin	BRII-196/BRII-198
Correlation coefficient	0.028	0.396	0.355	1	0.396
P-value	0.921	0.144	0.054	0	0.102

than monotherapy [15]. NAbs can rapidly reduce the viral load in COVID-19 patients, particularly in those with an uninitiated immune response or high baseline viral load, with the most substantial benefit observed in patients receiving exogenously supplied NAbs prior to initiating an immune response [4]. The extended half-life of BRII-196 and BRII-198 translates into stable drug concentrations during the therapeutic window and supports their use as an alternative for pre-exposure prophylaxis, addressing a significant global unmet need [16]. For example, it is estimated that 2.7% of the population is immunocompromised and not adequately protected by the COVID-19 vaccine [17]. As an indicator of humoral immunity against SARS-CoV-2, the neutralizing activity of antibody production is highly predictive of immunoprotection against symptomatic SARS-CoV-2 infection [18].

Clinical trials [4, 15] have demonstrated the efficacy of multiple NAb drugs in mild, non-hospitalized COVID-19 patients but not in severe, hospitalized patients. An evaluation of the efficacy of the BRII-196/BRII-198 antibody combination in emergency inpatients aged ≥ 18 years with moderate to severe symptoms lasting up to 12 days (those admitted for COVID-19 but without organ failure or major extrapulmonary manifestations) revealed that BRII-196/BRII-198 was effective in inhibiting SARS-CoV-2 replication. However, it did not show superiority over placebo in improving clinical outcomes in hospitalized adults with COVID-19 [19]. In this study, BRII-196/BRII-198 therapy shortened the NA negative conversion time in severe but not ordinary COVID-19 patients. Research indicates that the higher the severity of COVID-19, the greater the viral load [20]. Thus, the findings of this study suggest that NAb therapy can effectively accelerate NA negative conversion in severe patients when the early endogenous immune response has not been activated. This is contrary to the previously reported ineffectiveness of BRII-196/BRII-198 [19]. This discrepancy may be attributed to two factors: First, the classification criteria for COVID-19 severity differ. The 'severe' category in the prior study [19] corresponds to the 'ordinary' category in China, aligning with the finding that BRII-196/BRII-198 treatment does not affect the NA negative conversion time in ordinary COVID-19 patients in this study; Second, the subjects were emergency inpatients with symptoms lasting up to 12 days, whose endogenous immune response had already been elicited and was in varying stages, with cytokine storms initiated. However, the clinical symptoms of patients in this study appeared within 3 days, and the inflammatory response had either not started or was in the early stage, leading to contrasting results with the ineffectiveness evaluation [20]. Therefore, the results of this study recommend applying NAbs in the early stage of the disease. In severe COVID-19 patients, particu-

larly in the early stages of infection when the endogenous immune response is not yet activated, NAb treatment can effectively shorten the time for SARS-CoV-2 NA to hit an inflection.

Furthermore, thymalfasin, an immunomodulator, demonstrated no effect on NA negative conversion time in ordinary and severe COVID-19 patients, nor on SARS-CoV-2 IgG antibody levels when SARS-CoV-2 NA begin to decrease in this study. However, BRII-196/BRII-198 treatment resulted in a statistically significant difference in SARS-CoV-2 IgG antibody levels between the first positive SARS-CoV-2 NA test and the first NA negative conversion in severe COVID-19 patients. The State FDA acknowledges the value of SARS-CoV-2 antibody testing in determining whether an immune response has been produced, reflecting to some extent the immune status of vaccinated individuals. In this study, SARS-CoV-2 IgG antibody testing was conducted within 24 to 48 hours post-diagnosis to assess patients' immune status post-vaccination. The results indicated that 20%, 48.4%, and 75% of mild, ordinary, and severe COVID-19 patients, respectively, had SARS-CoV-2 IgG antibody levels < 1.0 S/CO. This suggests that the NAb level in individuals with breakthrough infections who were fully vaccinated with inactivated COVID-19 vaccines could predict the severity of the disease, consistent with other research findings [17]. NAbs are known to decrease gradually in vivo after two doses of inactivated vaccines, but an antibody response can be rapidly elicited [21]. Upon invasion by SARS-CoV-2 in a fully vaccinated individual, the body's plasma cells produce virus-specific antibodies, including NAbs, typically in the middle to late stages of infection. Exogenous administration of NAbs in the early stage of infection can quickly neutralize and clear the virus from the patient's body, preventing further viral invasion. In this study, there was no difference in initial SARS-CoV-2 IgG antibody levels between ordinary and severe COVID-19 patients treated with BRII-196/BRII-198, but there was a difference in IgG antibody level variance (from first positive NA testing to NA negative conversion). This indicates that patients treated with NAbs maintained high SARS-CoV-2 IgG antibody levels upon NA inflection, suggesting that NAbs persist in the body during the recovery period and provide lasting protection.

This study found no correlation between neutralizing antibody (NAb) therapy and lymphocyte count recovery time in patients with either ordinary or severe COVID-19. However, it did reveal a clear positive association between thymalfasin therapy and lymphocyte count recovery time in patients, addressing the common issue of lymphocytopenia following SARS-CoV-2 infection. Diao et al. [22] indicated that the number of T lymphocytes is negatively correlated with disease severity, emphasizing the need for urgent intervention in cases where T lymphocytes fall below 0.8×10^9/L. In our study, the total lymphocyte count in mild COVID-19 patients was greater than 0.8×10^9/L, whereas 35% of ordinary and 70% of severe COVID-19 patients had counts below this threshold, supporting Diao et al.'s findings. We applied a NAb therapy to ordinary and severe COVID-19 patients in the early stage of the disease to maximize the neutralization of the virus, reduce the viral load, limit damage to various organs, and minimize the formation of cytokine storms. It is widely recognized that cytokine storms are a major factor in the progression of COVID-19 from mild to severe or critical stages, contributing to organ injury, functional failure, and mortality in severe and critical patients. Our research indicates that the longest lymphocyte count recovery time in COVID-19 patients, regardless of severity, is 5 days, while the progression of COVID-19 is more likely after 1 week [23]. Therefore, for patients with lymphocytopenia, early administration of NAbs before lymphocyte depletion can inhibit further disease progression and reduce or prevent the formation of cytokine storms, maximizing the therapeutic benefit of exogenous Nabs treatment.

However, this study has a few limitations. First, the relatively small sample size limits meaningful subgroup analyses by age or gender. Second, the assessment of neutralization activity was confined to live Delta variants, which are not currently the predominant global variant. Given that our findings demonstrate durable humoral immunoprotection from the long-acting monoclonal antibodies BRII-196 and BRII-198 compared to some vaccines, further studies are needed to validate their efficacy against other existing and emerging variants, including omicron BA 4/5.

Conclusion

In patients experiencing breakthrough infections after full vaccination with inactivated COVID-19 vaccines, there is an inverse correlation between lymphocyte count and neutralizing antibody (NAb) level and the severity of the disease. Early exogenous administration of BRII-196/BRII-198, ideally in the initial stage of SARS-CoV-2 infection and prior to the initiation of endogenous immune response, can expedite the conversion to SARS-CoV-2 NA negative in severe COVID-19 patients. This treatment also increases the level of NAbs in patients' bodies post-NA negative conversion, providing more enduring protection. Due to the going mutation of SARS-CoV-2, the efficacy of the original NAb combination may diminish or even become ineffective over time. To address immune escape resulting from viral mutations, future research may focus on the development of NAbs targeting highly conserved regions of SARS-CoV-2.

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Disclosure of conflict of interest

None.

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