The treatment of COVID-19-related autoimmune haemolytic anaemia

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ABSTRACT

COVID-19-related autoimmune haemolytic anaemia (AIHA) has been reported since the onset of the pandemic. However, the precise aetiology is not fully understood and there is no consensus on the optimal treatment for COVID-19-related AIHA. To address this issue, we performed a literature review. Based on the available case reports, out of the 25 cases of COVID-19-related AIHA, 14 were diagnosed as warm AIHA and 11 as cold agglutinin disease (CAD). Thirteen out of the 14 warm AIHA cases were treated with steroids, while three were treated for CAD. Rituximab may be considered for use in steroid-refractory cases, with careful consideration of immunosuppression.

Keywords: COVID-19, autoimmune haemolytic anaemia (AIHA), treatment, steroid

INTRODUCTION

COVID-19-related autoimmune haemolytic anaemia (AIHA) has been reported since the onset of the pandemic. The most prevalent haematologic autoimmune disorder is immune thrombocytopenic purpura (ITP), followed by AIHA [1].

The pathogenesis of secondary AIHA caused by viral infection is thought to involve the activation of B cells through viral stimulation, leading to the production of autoantibodies. These autoantibodies bind to erythrocytes, resulting in phagocytosis by the activated macrophages. Angileri et al. proposed that molecular mimicry between the spike protein of the COVID-19 virus SARS-CoV-2 and erythrocyte membrane protein may be responsible for inducing COVID-19-related AIHA [2]. However, the precise aetiology of autoimmune disorders in COVID-19 is not fully understood. And there is no consensus on the optimal treatment for COVID-19-related AIHA. To address this issue, we performed a literature review.

Taherifard et al. [1] summarized 94 cases of COVID-19-related autoimmune disorders, including 22 cases of AIHA, and AbouYabis et al. [3] described 26 cases of COVID-19-related AIHA. However, neither paper was written with a focus on treatment.

MATERIAL AND METHODS

We reviewed the treatment of the previous 25 cases, excluding cases with Evans syndrome or those who developed AIHA long after COVID-19 infection, as shown in Table 1 [4–17].

Of the 25 AIHA cases, 11 were diagnosed as cold agglutinin disease (CAD) and 14 as warm AIHA. The median ages of patients with CAD and warm AIHA did not differ significantly; however, the male was dominant in patients with CAD. Patients with solid tumours develop CAD, whereas those with chronic lymphocytic leukaemia (CLL) develop warm AIHA. Previous autoimmune disorders were present in both groups. There was no significant difference in the date of onset after COVID-19 infection of haemolytic anaemia between the two groups. Steroids were the most commonly used treatment for warm AIHA (87%) compared to only 36% for CAD. The most used steroid dosage was prednisolone (1 mg/kg/day) in four cases, followed by steroid pulse therapy using methylprednisolone at doses of 500 or 1000 mg/day in three cases, and dexamethasone at a dosage of 40 mg/day in two cases. Dexamethasone treatment overlapped with treatment for COVID-19 pneumonia. Two patients received steroid pulse ther-

Table 1. Cases of COVID-19 related AIHA

Case	Age	Gender	Covid risk factor	COVID status	COVID Tx	Onset (days from COVID)	CA	Risk for haemolytic anaemia	AIHA Tx					Outcome	Reference
									Steroid	IVIG	RIT	T/F	Others		
1	62	F	Malignancy, HTN, LC	Severe	N/A	4	+	Lymphoma	+					N/A	4
2	69	F	Malignancy, obesity	Moderate	N/A	10	+	Lymphoma	+					N/A	4
3	61	M	Malignancy, HTN, CRF, DM, HL	Mild	N/A	11	+	Prostate ca				+		N/A	4
4	51	F	Malignancy	Moderate	HCQ	1	+	Breats ca	+					Recovery	5
5	62	M	Malignancy, HTN, smoking	Severe	N/A	16	+	Lung ca				+		Recovery	6
6	43	F	MS, obesity	Moderate	None	6	+	AID						Recovery	7
7	63	M	HTN	Moderate	None	1	+							Recovery	7
8	48	M	HTN, DM, CRF, obesity	Mild	None	1	+					+		Dead	8
9	70	M	N/A	Severe	HCQ/AZM	5	+							N/A	9
10	67	M	N/A	Severe	HCQ/AZM	10	+							Dead	9
11	54	M	None	Moderate	HCQ/TCZ	1	+		+				Plasma exchange	Recovery	10
12	61	M	DM	Severe	N/A	9	-		+		+			N/A	4
13	61	M	Malignancy, HTN, CRF	Moderate	N/A	13	-	CLL	+					N/A	4
14	89	F	HTN, CRF	Mild	N/A	7	-	MGUS	+					N/A	4
15	75	M	Malignancy, DM, COPD, HL cardiac disorder	Moderate	N/A	6	-	CLL			+	+		N/A	4
16	56	M	HTN	Moderate	FVP	4	-		+	+		+		Recovery	11
17	50	M	HTN	Mild	None	14	-							Recovery	12
18	33	F	Hypothyroidism	Moderate	TCZ	2	-	AID	+		+	+		Recovery	13
19	35	F	None	Moderate	N/A	1	-		+	+				Recovery	14
20	58	F	None	Moderate	N/A	1	-		+	+				Recovery	14
21	84	M	HL	Moderate	RDV/DEX	13	-		+			+		Recovery	15
22	33	F	None	Mild	N/A	1	-		+					Recovery	16
23	72	F	None	Severe	HCQ/TCZ/DEX	1	-		+			+		Recovery	10
24	76	F	Malignancy, HTN hypothyroidism	Moderate	HCQ/DEX	1	-	CLL, AID	+			+		Recovery	10
25	54	M	DM	Moderate	None	8	-		+					Recovery	17

AID — autoimmune disease; AZM — azithromycin; CA — cold agglutinin; CLL — chronic lymphocytic leukaemia; COPD — chronic obstructive pulmonary disease; CRF — chronic renal failure; DEX — dexamethasone; DM — diabetes mellitus; F — female; FVP — favipiravir; HCQ — hydroxychloroquine; HL — hyperlipidaemia; HTN — hypertension; IVIG — intravenous immunoglobulin; LC — liver cirrhosis; M — male; MGUS — monoclonal gammopathy of undetermined significance; MS — multiple sclerosis; N/A — not available; RDV — remdesivir; RIT — rituximab; TCZ — tocilizumab; T/F — transfusion

apy reduced to methylprednisolone at doses of 120 or 20 mg/day, whereas the dosage in the remaining cases was unknown. Among the three patients with CAD treated with steroids, one showed a good response to steroids, whereas two showed a partial response. Of the 13 patients with AIHA who were treated with steroids, one patient experienced treatment failure, one patient showed a partial response, and the remaining patients showed a good response. For patients with an inadequate response to steroid therapy, rituximab was administered, which resulted in recovery. The CAD group had two deaths (18%), whereas no deaths were observed in the warm AIHA group. Two deaths occurred in patients with CAD, and both involved blood clots. Blood clots are known to occur in COVID-19 patients, and the likelihood of blood clot formation may increase in CAD. It is possible that both factors contributed to the development of blood clots in these cases. There was no exacerbation of COVID-19 owing to steroid administration.

RESULTS

Based on the available case reports, treatment decisions for COVID-19-related AIHA are typically influenced by the original AIHA therapy received. Steroids are commonly used as first-line treatment for warm AIHA but are generally considered less effective in CAD and are used in only 36% of cases. However, in cases of COVID-19, steroids are recommended only for patients with pneumonia requiring oxygenation and are not recommended for mild cases owing to their immunosuppressive effects [18]. To date, there have been no reports of exacerbation of COVID-19 infection itself using steroids for AIHA, and it seems safe to administer steroids while the patient is being treated for COVID-19.

In three cases, intravenous immunoglobulin (IVIG) was also administered; however, this treatment appeared to have been chosen in accordance with ITP. The literature suggests that the IVIG dose required for AIHA is three to five times higher than that used for ITP, and the effect is transient. Therefore, IVIG is not considered a standard therapy for AIHA [19].

Rituximab is considered an effective treatment for steroid-refractory AIHA and was administered in three cases. Although rituximab has been demonstrated to be effective in treating warm AIHA in non-COVID-19 patients, there are concerns regarding its potential immunosuppressive effects in COVID-19-related AIHA. Nevertheless, rituximab has been proven effective in treating both CAD and warm AIHA and could be considered in cases where steroids have proven ineffective. Reports have shown the efficacy of plasma exchange for CAD; however, it has not been established as a treatment for AIHA in general [20]. The use of plasma exchange as a treatment for COVID-19-related AIHA remains unclear.

CONCLUSIONS

This report summarizes cases of COVID-19-related AIHA with a focus on the available treatment options. The lack of consensus regarding treatment is a significant concern in clinical practice. Although there are concerns about exacerbating COVID-19 infection itself by administering steroids, there have been no reports of such exacerbations to date. Hence, we conclude that steroid administration should be chosen in the treatment of COVID-19-related AIHA although the amount of it is up to the physician's discretion. Nevertheless, additional cases must be collected to establish a safer and more effective treatment approach for COVID-19-related AIHA.

Article information and declarations

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