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Does remdesivir favor long-term SARS-CoV-2 infection and mutations in immunocompromised patients?

Dear Editor,

We read with great interest the report by Tarhini et al. [1] on three cases of prolonged SARS-CoV-2 shedding of more than 90 days in immunocompromised patients (low CD4 count, HIV infection, heart transplant and rheumatoid arthritis on immunosuppressive treatment) Paris, France. Patient 3, in this report was positive by PCR on day 84, with seven mutations in the viral genome that were not observed in samples obtained at day 73. The authors propose that superinfection with a second viral strain may explain this picture.

We have had more than two thousand people hospitalized for COVID-19 in our institute. Among them, 212 were severely immunocompromised. A total of 190/241 patients were comparable with those reported by Tarhini et al. [1] (Table 1): 98 with chronic inflammatory

disease on immunosuppressive therapy, 60 with active solid cancer, 22 with organ transplant and 10 with HIV infection. Half of these patients (100/190, 52.6%) were treated with a combination of hydroxychloroquine and azithromycin. We and others were able to show that it shortened viral carriage [2]. A total of 74/190 (41.6%) received one of these two drugs. None of them had viral persistence lasting more than 90 days. In contrast, among 22 patients who had active lymphoma, two had viral persistence greater than 90 days.

We were therefore surprised by the frequency of viral persistence in the Tarhini et al. [1] study compared to our study, in which it was exceptional and involved only two lymphoma patients, including the only patient in our entire cohort of more than 2000 hospitalized patients who received remdesivir and convalescent plasma therapy (in an intensive care unit outside our institute).

Treatment data are missing in this work [1], and it would be interesting if the authors could report this, enabling us to know in particular if these patients received remdesivir and anti-SARS-CoV-2 antibodies.

Indeed, in the literature there are now at least six publications [3-8] (Table 1) reporting persistent infections associated with mutations of the virus in immunocompromised patients (with inflammatory diseases treated with immunosuppressive agents, or lymphoma) having received remdesivir. Five of them had also received convalescent plasma, and four out of five presented, among the many mutations observed, a mutation in the viral genome encoding for the spike protein at position 501, which is known for the emergence of the UK variant, and now Brazilian and South African variants present the same mutation.

These observations suggest that remdesivir is not virucidal, that it promotes mutations, including in the spike protein (possibly promoted by transfused antibodies in the immunocompromised host). We hypothesized that the third patient in Tarhini et al. [1] work

received remdesivir and consequently exhibited mutations, including in the spike. The origin of the mutants, including the currently spreading 501Y spike mutant, may have been promoted by remdesivir.

In summary, we believe that it is mandatory in experimental therapy to perform genome sequencing of viruses when treatment failed. This allows to identify the emergence of SARS-CoV-2 variants.

Acknowledgements

We thank Léa Delorme for her kind technical help.

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Table 1. Long-term SARS-CoV-2 shedding in immunocompromised patients

Type of immunosuppression	Total cases	COVID-19 (N) Treatment	Viral shedding >17 days	Viral shedding ≥90 days otherwise specified	Reference
Low CD4 count HIV infection	10	HCQ[a] + AZ[b] (3)	0	0	This paper
		AZ (6)	0	0	
		HCQ (0)	0	0	
		No HCQ, no AZ (1)	0	0	
	Not available	Not available	1	1	[1]
Organ transplant	22	HCQ + AZ (9)	3	0	This paper
		AZ (10)			
		HCQ (3)	2	0	
		No HCQ, no AZ (0)			
			0	0	
			0	0	
	Not available	Not available	1	1	[1]
Active neoplasia (except lymphoma)	60	HCQ + AZ (36)	0	0	This paper
		AZ (22)	2	0	
		HCQ (0)	0	0	
		No HCQ, no AZ (2)	0	0	
Inflammatory diseases treated with immunosuppressive agents, including corticosteroids	98	HCQ + AZ (52)	3	0	This paper
		AZ (36)	2	0	
		HCQ (2)	0	0	
		No HCQ, no AZ (8)	2	0	
	Not available	Not available	1	1	[1]
	Not available	Remdesivir + anti-Spike antibody cocktail (1)	1	1	[3]
Lymphoma	22	HCQ + AZ (15)[c]	2	1	This paper
		AZ (6)	1	0	
		HCQ (0)	0	0	
		HCQ + AZ + Remdesivir + convalescent plasma (1)[d]	1	1	
		No HCQ, no AZ (0)	0	0	
	Not available	Remdesivir + convalescent plasma (1)	1	0[e]	[4]

Not available	Remdesivir + convalescent plasma (1)	1	1	[5]
Not available	Remdesivir + convalescent plasma (1)	1	0	[6]
Not available	Remdesivir + convalescent plasma (1)	1	1	[7]
Not available	Remdesivir + convalescent plasma (1)	1	1	[8]

[a]hydroxychloroquine; [b]azithromycin; [c]1/30 patients had at least a 104-day carriage (ongoing follow-up); [d]this patient had a 112-day SARS CoV-2 carriage before death; [e]this patient had a 71-day SARS CoV-2 carriage before death.