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Research Paper

Risk of hepatitis B reactivation and cytomegalovirus related infections with Mogamulizumab: A retrospective study of international pharmacovigilance database

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ABSTRACT

Background: Mogamulizumab (Moga) is a C—C chemokine receptor-4 antibody approved in the United States for relapsed /refractory mycosis fungoides and Sézary syndrome. Few cases reported an increased risk of hepatitis B reactivation and cytomegalovirus (CMV) related infection post-Moga. However, literature is limited to mainly case reports and series, while no study has used the Food and Drug Administration adverse events reporting system (FARES) database to investigate the relationship.

Methods: Using United States Food and Drug Administration adverse events reporting system database, we collected all cases of hepatitis B reactivation and CMV related infection between January 1, 2011, and December 31, 2019, for Moga and other drugs. The reporting odds ratio (ROR) was calculated, which was considered significant when the lower limit of 95% confidence interval (CI) >1.

Findings: Three hundred and thirty-eight total adverse cases were reported for Moga during the study period, with 261 cases reported indication for use, including cutaneous T cell lymphoma (47.04%), and adult T cell leukemia/lymphoma (30.18%). Eight cases were reported for hepatitis B reactivation with Moga use, compared to 2290 cases with other medications. The ROR is 143.67 ($p<0.001$, 95% CI, 71.17−290.04). CMV related infection was noted in 17 cases using Moga, while 12,849 cases with others. The ROR is 55.89 ($p<0.001$, 95% CI, 34.31−91.06). In the Moga group, five deaths occurred in hepatitis B reactivation patients and nine deaths with CMV cases.

Interpretation: A signal has been identified between Moga exposure and hepatitis B reactivation as well as CMV related infection. A consideration in future studies should be placed on determining the relationship and investigating the need for pre-treatment screening, close monitoring, and utilization of prophylaxis in this population-based on pre-treatment risks.

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1. Introduction

Adult T cell leukemia/lymphoma (ATL), a rare and aggressive malignancy, can be classified into four clinical subtypes: acute, lymphoma, chronic, and smoldering types based on presenting features [1]. First-line treatment encompasses high-intensity chemotherapy combination with good response. However, for relapsed/refractory cases, the treatment options are limited [2]. Advanced stage cutaneous T cell lymphomas (CTCL) also pose significant treatment challenge to physicians [3]. Novel targeted medications have been studied actively in the past 20 years, with some of them showing a significant survival benefit in these conditions [4,5]. Mogamulizumab (Moga), a defucosylated humanized monoclonal antibody against C—C chemokine receptor 4 (CCR4) [6], has been approved for the treatment of CCR4-positive relapsed/refractory ATL in Japan in 2012 [7]. And, further approved for CCR4-positive relapsed/refractory CTCL in 2014 [7]. In the United States, the Food and Drug Administration (FDA) approved Moga for the treatment of relapsed/refractory mycosis fungoides and Sézary syndrome in 2018 [8]. The phase I and phase II clinical trials illustrated the efficacy of Moga in treating both ATL and CTCL with tolerable toxicities [6,9−11]. In one phase II clinical trial in ATL patients, overall response rate (ORR) was observed to be 50%, whereas – progression free survival (PFS) and overall survival

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Research in context

Evidence before this study

Before the study, we reviewed literature via PubMed, Scopus, and Google search for Moga and infectious events, including hepatitis B reactivation and CMV related infections. Only a few case reports and case series discussed the possible risk. We used FAERS to conduct disproportionality analysis for possible signal, and the last access date is July 29,2020. As a voluntary reporting database, FAERS allows for signal data mining, but with the limitations as mentioned above.

Added value of this study

Our study is the first study using a large scale database to investigate the relationship between Moga and hepatitis B reactivation and cytomegalovirus related infection. Through disproportionality analysis, a signal was determined between the use of Moga and the above infections.

Implications of all the available evidence

Our study result warrants further studies to determine the risk and discuss the need for pre-treatment screening, monitoring and even prophylaxis in particular high-risk population.

(OS) was 5.2 and 13.7 months respectively [6]. Another phase II clinical trial demonstrated an objective response of 35% and PFS of 3 months in CTCL post-Moga [10].

Though promising treatment response, adverse events (AE) are also documented. Among them, infusion reactions and skin rashes are most commonly reported, including Steven-Johnson syndrome [9–11]. With post-marketing utilization of this novel medication, some studies and case reports have shown an increased risk of hepatitis B reactivation, and cytomegalovirus (CMV) related infection [11–14]. However, studies are limited to case reports and series, while no study used large population-based database. Therefore, by a query of Food and Drug Administration adverse events reporting system (FAERS), we aim to investigate the possible relationship between hepatitis B reactivation and CMV related infection and Moga use.

2. Methods

The FAERS database is a voluntary drug and product reporting system that contains data submitted by health care professionals, manufacturers, and consumers [15,16]. AE was coded according to the Medical Dictionary for Regulatory Activities (MedDRA) [17]. This spontaneous reporting system, containing both reports from the United States (US) and other countries, has received more than 17 million reports since 1968. FARES, functioning as one of the FDA's post-marketing surveillance tools receives AE, and medical error report continuously and globally. It is a robust method for signal mining. Our study inquired data from FAERS public dashboard between January 1, 2011, and December 31, 2019. AE data for patients who received Moga during the period above were obtained using "Mogamulizumab" and "Mogamulizumab Kpkc." We then queried the hepatitis B reactivation and CMV related infection in this population using "Hepatitis B Reactivation", and "Cytomegalovirus Viraemia", "Cytomegalovirus Infection", "Cytomegalovirus Chorioretinitis", "Cytomegalovirus Enteritis", "Cytomegalovirus Enterocolitis", "Pneumonia Cytomegaloviral", "Cytomegalovirus Colitis", "Cytomegalovirus Duodenitis", "Cytomegalovirus Gastritis", "Cytomegalovirus Gastrointestinal Infection", "Cytomegalovirus Gastrointestinal Ulcer", "Cytomegalovirus Gastroenteritis", "Cytomegalovirus Hepatitis", "Cytomegalovirus Mononucleosis", "Cytomegalovirus Mucocutaneous Ulcer", "Cytomegalovirus myocarditis", "Cytomegalovirus Myelomeningoradiculitis", "Cytomegalovirus Nephritis", "Cytomegalovirus Syndrome", "Cytomegalovirus Oesophagitis", "Cytomegalovirus Pancreatitis", "Cytomegalovirus Test Positive", "Cytomegalovirus Urinary Tract Infection", "Encephalitis Cytomegalovirus" and "Disseminated Cytomegalovirus Infection". Then all hepatitis B reactivation and CMV related infection reported in other drugs and biological products were compared to those related to Moga use. The same comparisons were made with rituximab using "Rituximab" and "Rituximab-Abbs," as well as alemtuzumab using "Alemtuzumab". Cases were compiled into Microsoft Excel 2016. Variables including suspect product names, the reason for use, reactions, outcomes, sex, event date, patient age, reporter type, concomitant product names, the country where events occurred were collected and analyzed. The reporting odds ratio (ROR) was calculated by SPSS 26 for disproportionality signal analysis (Table 1). The lower limit of two-sided 95% confidence interval (CI) of ROR >1 is considered significant [18,19].

Our study adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). The GATHER checklist is attached.No institutional review board or ethics review laws required in our study.

Role of the funding source
No funding in our study.

3. Result

There were in total 13,574,208 reports between January 1, 2011, and December 31, 2019. Among them, 338 (0.00249%) individual cases were related to Moga. Indication for use was reported in only 261 cases, with 159 (47.04%) for CTCL and 102 (30.18%) for ATL. Country of AE origin was reported in 334 cases (98.82%), where 133 (39.35%) were from Asia, 150 (44.37%) from the United States, and 51 (15.09%) from Europe. In the Moga exposure group, five deaths occurred in patients with hepatitis B reactivation, and nine deaths in CMV related infection cases. (Table 2)

Eight cases were reported for hepatitis B reactivation with Moga use, compared to 2290 cases by using other medications (Table 3). The ROR is 143.67 ($p<0.001$, 95% CI, 71.17–290.04). Two (25%) males and two (25%) females were reported with hepatitis B reactivation, while the gender of rest four (50%) cases was not reported. Only in one case out of eight with hepatitis B reactivation, Moga was suspected without concomitant drug use. Other drugs used concomitantly including cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), pirarubicin, and carboplatin were also suspected for causing AE. Hepatitis B reactivation was the only reported AE in all eight cases without concomitant AE.

CMV related infections were noted in 17 cases using Moga. CMV infection presented as CMV viremia or infection in seven (41.18%) cases, and CMV end-organ disease, including CMV pneumonia in seven (41.18%) cases, CMV enteritis or enterocolitis in two (11.76%) cases, and CMV chorioretinitis in one (5.88%) case, compared with 12,849 cases of CMV related infection using other medications (Tables 4 and 5). The ROR is 55.89 ($p<0.001$, 95% CI, 34.31–91.06).

Table 1
Reporting odds ratio of drug of interest.

	Drug of interest	Other medications	sum
AE of interest	A	B	$A+B$
Other AE	C	D	$C+D$
	$A+C$	$B+D$	$A+B+C+D$

AE: Adverse Events
$\mathrm{ROR}=\frac{A/C}{B/D}=A\frac{XD}{BXC}$
$95\%\ \mathrm{CI}=e^{\ln(ROR)\pm 1.96\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}}$

Table 2
Characteristics of Patients with Hepatitis B Reactivation and CMV Related Infections Post Moga.

	Total (proportion%)	Hepatitis B reactivation	CMV related infections
Areas			
Asia	133 (39.35%)	6 (75.00%)	17 (100%)
US	150 (44.38%)	0 (0%)	0 (0%)
Europe	51 (15.09%)	1 (12.50%)	0 (0%)
Unspecified	4 (1.18%)	1 (12.50%)	0 (0%)
Indication			
ATL	102 (30.18%)	7 (87.50%)	14 (82.35%)
CTCL	159 (47.04%)	1 (12.50%)	3 (17.65%)
Unknown/others	77 (22.78%)	0 (0%)	0 (0%)
Gender			
Male	61 (18.05%)	2 (25.00%)	6 (35.29%)
Female	63 (18.64%)	2 (25.00%)	2 (11.76%)
Unknown	214 (63.31%)	4 (50.00%)	9 (52.94%)
Median age (years) (interquartile range)	66(59.50−72)	68.5 (65−72)	63 (63−64.25)
Concomitant medications			
No	206 (60.95%)	1 (12.50%)	5 (29.41%)
Yes	132 (39.05%)	7 (87.50%)	12 (70.59%)
Other reactions			
No		8 (100%)	7 (41.18%)
1 other reaction		0 (0%)	4 (23.53%)
2 or more reactions		0 (0%)	6 (35.29%)
Outcome			
Died	78 (23.08%)	5 (62.50%)	9 (52.94%)
Hospitalized	95 (28.11%)	1 (12.50%)	5 (29.41%)
Others	165 (48.82%)	2 (25.00%)	3 (17.65%)
Reporter			
Health care professional	295 (87.28%)	8 (100%)	17 (100%)
Consumer	41 (12.13%)	0 (0%)	0 (0%)
Unspecified	2 (0.59%)	0 (0%)	0 (0%)

Moga=Mogamulizumab; CMV=Cytomegalovirus.

Table 3
Hepatitis B Reactivation in Moga and Other Medications, 2011−2019.

	Moga	All other medications	Sum	ROR (95%CI)	*P* value
Hepatitis B reactivation	8	2290	2298	143.67 (71.17−290.04)	0.000
All other events	330	13,571,580	13,571,910		
Sum	338	13,573,870	13,574,208		

Moga=Mogamulizumab, ROR=Reporting Odds Ratio; CI=Confidence Interval.

Six (35.29%) were males, and two (11.76%) were females, whereas, in nine (52.94%) cases, gender was not specified. In five (29.41%) cases, Moga was the only drug reported to be related to CMV related infection. In comparison, 12 (70.59%) cases have concomitant drug use, including lenalidomide, sulfamethoxazole\trimethoprim, prednisolone, bexarotene, sobuzoxane, etoposide, CHOP, carboplatin, cytarabine, and methotrexate. In patients with only Moga use, one (20.00%) of five died; comparing to eight (66.67%) out of 12 patients died in group receiving Moga and concomitant drugs, though no significant statistical difference of death was noticed between the two groups ($p = 0.079$). Seven (41.18%) cases had only CMV related infection, while four (23.53%) and six (35.29%) cases reportedly had 1 and 2 or more concomitant other reactions, respectively. The most common concomitant AE are skin rash or erythema in five patients (29.41%), neutropenia in four (23.53%), anemia in two (11.76%), thrombocytopenia in two (11.76%), hypoalbuminemia in two (11.76%), interstitial lung disease in two (11.76%). Heart failure, lymphopenia, infusion-related reaction, transaminitis, cystitis, sepsis, herpes zoster infection, fungal infection, systemic candida, mycotic endophthalmitis, disseminated intravascular coagulation (DIC), hypertriglyceridemia, hypothyroidism, hyperglycemia and weight gain each has been reported once (5.88%)(Table 6).

Table 4
CMV Related Infection Post Moga.

Type of CMV infection	Number of patients	death
CMV viremia or infection	7	3
CMV end organ disease	10	6
CMV pneumonia	7	6
CMV enteritis or enterocolitis	2	0
CMV chorioretinitis	1	0

CMV=Cytomegalovirus.

Table 5
CMV Related infection in Moga and other medications, 2011−2019.

	Moga	All other medications	Sum	ROR (95%CI)	*P* value
CMV related infection	17	12,849	12,866	55.89 (34.31- 91.06)	0.000
All other events	321	13,561,021	13,561,342		
Sum	338	13,573,870	13,574,208		

Moga=Mogamulizumab, ROR=Reporting Odds Ratio; CI=Confidence Interval.

Table 6
Other adverse events in patients with CMV related infections post Moga.

Adverse Events	Number of patient(s)
Skin rash or erythema	5
Neutropenia	4
Anemia	2
Thrombocytopenia	2
Hypoalbuminaemia	2
Interstitial lung disease	2
Heart failure	1
Lymphopenia	1
Infusion related reaction	1
Transaminitis	1
Cystitis	1
Sepsis	1
Herpes zoster infection	1
Fungal infection	1
Systemic candida	1
Mycotic endophthalmitis	1
DIC	1
Hypertriglyceridaemia	1
Hypothyroidism	1
Hyperglycemia	1
Weight gain	1

Moga=Mogamulizumab;.

In comparison, a total of 69,096 AE reported by rituximab and 9662 AE cases by alemtuzumab from 2011 to 2019. For rituximab, 568 cases reported hepatitis B reactivation, with ROR 64.70 ($p<0.05$, 95% CI, 58.83−71.15). While 1088 patients developed CMV infection. The ROR is 18.33 ($p<0.05$, 95% CI, 17.22−19.51). In cases of alemtuzumab, seven reports about hepatitis B reactivation, with ROR of 4.29 ($p<0.05$, 95%CI, 2.04−9.02); and 578 cases had CMV related infection with a ROR of 70.17 ($p<0.05$, 95%CI, 64.40−76.47). (Table 7)

4. Discussion

ATL, caused by human T-cell lymphotropic virus type 1 (HTLV-1), is an aggressive peripheral T cell lymphoma with poor prognosis[1]. Moga has shown to be an effective and safe medication as monotherapy or in combination with chemotherapy in relapsed/refractory ATL. Moga aims at CCR-4 chemokine receptor, which is expressed on most ATL cells [21]. By binding to CCR-4, Moga enhances antibody-dependent cellular cytotoxicity (ADCC) effect and depletes targeted cells [21]. Moga was later proved to be effective in treating CTCL, which is a heterogeneous group of extranodal non-Hodgkin's lymphomas. The major types in CTCL are mycosis fungoides (MF), Sézary syndrome (SS), and primary cutaneous peripheral T cell lymphomas not otherwise specified (PCTCL - NOS). Besides advancement in the treatment of ATL and CTCL, some clinical trials evaluating the effectiveness of Moga for other diseases, including solid tumors and HTLV-1 associated myelopathy, have completed [23]. Doi et al. evaluated Moga in combination with nivolumab in treating advanced or metastatic solid tumors, and 12% ORR was observed in six tumor subtypes with the highest one seen in hepatocellular carcinoma cohort (27%; 95% CI, 8−55) [24]. In a phase 1−2a clinical trial in HTLV-1 associated myelopathy, Moga has shown to decrease the HTLV-1 infected cells and level of inflammatory markers [25].

Since Moga approval, accumulating evidence indicates increased infection risk, including hepatitis B reactivation, CMV, bacteremia, herpes zoster, and mycobacterium infection [6,11-14,20,26,27]. To our knowledge, no previous study using an extensive population-based database has investigated the relationship between these two infections and Moga use. Our study result identified the signal between Moga use and a possible increased risk of developing hepatitis B reactivation and CMV related infection.

In order to investigate the relationship between Moga exposure and the above AEs, we applied disproportionality analysis using ROR. In the process of signal detection, disproportionately high AE rates in a drug of interest comparing to background frequency may indicate a signal [18,19]. ROR is one of the methods for disproportionality analysis. In our study, it means the odds of reporting hepatitis B reactivation and CMV related infection with Moga use is 143.67 times and 55.89 times of reporting the AE with other medications use, respectively. This disproportionately high frequencies also referred to as "unexpectedness", representing possibly important signal between Moga use and the increased infectious risks [18].

Hepatitis B reactivation risk has known to increase in patients receiving rituximab, a CD20 antibody, for B cell lymphoma [34]. In the setting of immunosuppressive conditions, hepatitis B reactivation may attribute to complications from acute hepatitis to fatal fulminant hepatitis [35]. However, antiviral treatment after hepatitis onset may not be sufficient to control the infection [35]. There are some reports of hepatitis B reactivation in ATL patients with Moga use, including pre-treatment HbsAg negative patients [12,13,26,27]. Similarly, CMV related infection and end-organ failure contribute to increased morbidity and mortality in patients receiving hematopoietic stem cell transplant (HSCT) [30]. CMV infection has also been reported in patients undergoing chemotherapy for lymphoma [32], and is a well-known infectious complication related to alemtuzumab and rituximab use [33,34]. Recent studies, including clinical trials, have also shown more CMV related infection in patients receiving Moga, especially in combination with chemotherapy [11,13]. Our study compared reported hepatitis B reactivation and CMV related infection in patients using rituximab and alemtuzumab to Moga during the same period. Surprisingly, ROR with Moga is higher in both infections than rituximab and alemtuzumab. Admittedly, being in the market for longer time, clinical practitioners are more familiar with infectious AE of rituximab and alemtuzumab's. This knowledge results in less voluntary reporting and can lower the contribution of reported infectious AE to all AE. Increased ROR is a signal that Moga use may increase both infection risk.

The mechanism for observed increased risk with Moga use is not well established. Host cells with CCR-4 receptors, like Th2 cells, some CD4+ memory cells, and Tregs [21,22], are all targeted by Moga. With the combined effect of lymphopenia, cellular and innate immune cells depletion, and the immunosuppressive nature of T-cell

Table 7
Comparison of Hepatitis B Reactivation and CMV Infection in Moga,Rituximab and Alemtuzumab,2011−2019.

		Moga	Rituximab	Alemtuzumab
Hepatitis B Reactivation	Number of events	8	568	7
	ROR (95%CI)	143.67 (71.17−290.042)	64.70 (58.83−71.15)	4.29 (2.04−9.02)
CMV related infection	Number of events	17	1088	578
	ROR (95%CI)	55.89 (34.31- 91.06)	18.33 (17.22−19.51)	70.17 (64.40−76.47)
Total reports		338	69,096	9662

Moga=Mogamulizumab; ROR=Reporting Odds Ratio; CI=Confidence Interval.

malignancy itself, infectious AE, including hepatitis B reactivation and CMV related infection, are expected. Also, immunologic exacerbation to infection may play a role in end-organ failure under the hypothesis of Treg cell impairment [29].

Our study showed that 10 (58.82%) out of 17 patients with CMV related infection developed CMV end-organ diseases. Nine CMV related infection patients died, of whom six deaths (66.67%) occurred in patients with CMV end-organ disease. This ratio is higher than other reports: Tay et al. studied CMV infection and end-organ disease in Asian patients with lymphoma receiving chemotherapy, and 12 (25.00%) of 48 patients with CMV infection developed CMV end-organ disease [31]. The higher number of deaths in CMV end-organ disease in our study could be related to the under-reporting of CMV viremia patients in FAERS.

Furthermore, 10 (58.82%) of them have other AE reported in addition to CMV related infection. This is different from reports for hepatitis B reactivation, where all eight patients have no other AE documented. Seven (87.50%) of the eight patients with hepatitis B reactivation have concomitant chemotherapy use, some including steroids. Further studies are warranted to assess the impact of Moga alone and with chemotherapy on the increased risk of hepatitis B reactivation and CMV infection.

Many studies have evaluated the efficiency of preventive measures on patients with positive HBsAg [35,36]. For previously resolved hepatitis B (HBsAg negative), high-risk patients, including anti-HBc positive subjects to be treated with rituximab or those undergoing stem cell transplantation, antiviral prophylaxis is recommended [37]. Pre-emptive therapy by monitoring hepatitis B deoxyribonucleic aicd (DNA) has been recommended for moderate-risk patients in some guidelines [37]. In one study, a monthly hepatitis B DNA monitoring has shown to be useful in early detection of hepatitis B reactivation of previously resolved hepatitis B infection in patients receiving rituximab and steroid containing chemotherapy [38]. Pre-emptive screening of CMV for patients using alemtuzumab has been described in some guidelines [28]. Our result demonstrated a potential higher risk of infection with Moga use, and pre-emptive screening and risk analysis should be considered in clinical practice.

Our study has some limitations. First, we used FAERS, a voluntary reporting system database without strict research protocol, randomization, and control, for signal mining. The relationship between a specific drug and AE of interest is hard to be determined based only on the database, and causation relationship not necessarily exist even if significant disproportionality analysis result. Also, there is a possibility of duplicate reports when the consumer, and the sponsor submits the same case, and the data may change due to the correction for duplication. Though this change may not be significant in the long term, and FAERS provided quarterly extract files for all previous data. Besides, missing and incomplete information, including dosage, pre-treatment infection condition, patient baseline characteristics, and follow up data, may create bias when analyzing these data. For instance, pre-treatment hepatitis B serostatus is not available from the FAERS, which can lead to selection bias when discussing the risk of hepatitis B reactivation post-Moga exposure.

Second, even though more AE reports have been noticed than previous studies [9–14], the total number of reported hepatitis B reactivation and CMV related infections in this study is still low, given the limited period and nature of spontaneous reporting database.

Using FARES, we identified a positive signal between Moga exposure and hepatitis B reactivation as well as CMV related infection. A consideration in future studies should be placed on confirming the relationship and investigating need for pre-treatment screening, close monitoring, and utilization of prophylaxis in this population-based on pre-treatment risks.

Declaration of Competing Interest

Dr. Abhishek Kumar declared the following interest: Stocks in Abbvie Inc, Acadia Pharmaceuticals, ADMA Biologics, Agneus Inc, Aikido Pharma Inc, Albireo Pharma Inc, Amgen Inc, Aveo Pharma, Astrazeneca PLC, Bristol Meyer Squibb, Biopath Holdings, Beyond-Spring Inc, Blueprint Medicine, Cara Therapeutics, Chembio Diagnostics, contrafect Corp, Cardiff Oncology, CRISPR Therapeutics, CVS Health Corporation, Precision Biosciences, Editas Medicine Inc, Five Prime Therapeutics, Globus Medical Inc, IDEXX Laboratories, Immunomedics Inc, IOvance Biosciences, Johnson & Johnson, Eli Lilly and Co, Novavax Inc, Northwest Biotherapeutics, Pfizer, Poseida Therapeutics, PTC Therapeutics, Spectrum Therapeutics, Surgalign Holdings, Viking therapeutics, and, Vertex Pharmaceuticals. The other authors declared no conflicts of interest.

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Data sharing statement: All data can be freely accessed by FAERS website. By “search by product” and “search by reaction term”, and case listing, data can be exported for analysis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100601.

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