Safety and Efficacy of Tixagevimab and Cilgavimab for Prophylaxis of Covid-19 in a Cohort of Immunosuppressed Rheumatic Patients Treated with Rituximab: A Real-Life Experience

Silvia Peretti , Francesco Bonomi , Elisa Fiorentini , Francesca Bartoli , Gemma Lepri , Silvia Bellando-Randone , Serena Guiducci *

Posted Date: 7 December 2023

doi: 10.20944/preprints202312.0525.v1

Keywords: SARS-CoV-2, COVID-19, Tixagevimab, Cilgavimab, Rituximab, immunosuppression

Article

Safety and Efficacy of Tixagevimab and Cilgavimab for Prophylaxis of Covid-19 in a Cohort of Immunosuppressed Rheumatic Patients Treated with Rituximab: A Real-Life Experience

Silvia Peretti [1], Francesco Bonomi [1], Elisa Fiorentini [1], Francesca Bartoli [1], Gemma Lepri [1], Silvia Bellando-Randone [1] and Serena Guiducci [1,*]

[1] 1 Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy; silvia.peretti@unifi.it (S.P); francesco.bonomi@unifi.it (F.B.); elisa.fiorentini@unifi.it (E.F); bartolifr@aou-careggi.toscana.it (F.B), gemma.lepri@unifi.it (G.L); silvia.bellandorandone@unifi.it (S.B.R.); serena.guiducci@unifi.it (S.G).

* Correspondence: serena.guiducci@unifi.it (S.G).

Abstract: (1) Background: Immunosuppressed patients, especially those receiving B-cells depleting therapies (BCDT), are at major risk to develop reduced vaccine seroconversion and contract severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. The aim of our study is to assess safety and efficacy of the pre-exposure prophylactic combination of Tixagevimab and Cilgavimab (TGM-CGM) in a cohort of rheumatic patients diagnosed with Autoimmune Rheumatic Diseases; (2) Methods: We performed a prospective study using the clinical medical charts of 25 patients treated with Rituximab and received a single injection of TGM/CGM. The cohort was followed for 6 months from the injection and compared to a control group of 25 immunosuppressed patients who did not receive TGM-CGM. We assessed the incidence and the severity of Covid-19 in both groups, as well as early and late adverse events; (3) Results: Despite the small sample, we noticed a downward trend in the incidence and severity of symptomatic infection in the group treated with TGM/CGM. In the experimental cohort, one patient was completely asymptomatic, four patients were oligosymptomatic infection, and just one had mild-moderate infection versus 4 oligosymptomatic and 5 mild-moderate infection in the control group. We observed also a reduction in time to nasopharyngeal swab negativization. No adverse events were reported in our data. We collected the dosage of anti-Receptor-Binding Domain (RBD) SARS-CoV2 spike protein for 21 patients, revealing adequate seroconversion in 12 patients out of 21; (4) Conclusions: Even though the study was conducted during the Omicron wave, notably known to be less responsive to monoclonal antibodies, we proved that TGM-CGM could be a risk-free additional tool to prevent SARS-Cov2 infection in rheumatic immunosuppressed patients.

Keywords: SARS-CoV-2; COVID-19; Tixagevimab; Cilgavimab; Rituximab; immunosuppression

1. Introduction

Since the beginning of pandemic in 2020, SARS-Cov2 has killed more than 6 million people worldwide, of which more than 190 thousand only in Italy [1].

To date, it is still controversial if people affected by autoimmune rheumatic diseases present an increased risk of contracting SARS-CoV2 and/or having more severe disease. Some studies showed equal incidence and severity of Coronavirus disease-2019 (COVID-19) in rheumatic patients compared with general population [2-5]. By contrast, other studies underlined that the use of conventional disease-modifying antirheumatic drugs (cDMARDs), of Tumor Necrosis Factor-Alpha (TNFa) antagonists and tocilizumab do not affect the course of COVID-19, whereas the use of B-cell-depleting therapies (BCDT) such as Rituximab (RTX) seems to be associated to more severe disease and worst outcome [6-11].

 doi:10.20944/preprints202312.0525.v1

Vaccination worldwide has been the primary and the most important strategy to stem the virus' spread as well as decrease the severity and the mortality of COVID-19 [12-13]. However, certain immunocompromised patients especially those receiving Rituximab, have shown reduced response to anti-SARS-CoV-2 vaccine, impairing the protective effect against the infection [14-19]. Hence, the need to find a new strategy to protect fragile patients.

In March 2022, the European Medicine Agency (EMA) approved a new drug as a pre-exposure passive prophylaxis against SARS-CoV2 for individuals who had a suboptimal vaccination response or for the unvaccinated [20]. TGM-CGM, also known as AZD7442, is composed by two fully human monoclonal antibodies tixagevimab and cilgavimab (TGM-CGM), capable of binding to different segments of the SARS-CoV-2 spike proteins, preventing the virus entrance in human cells [21]. The use of TGM/CGM has been supported by the PROVENT study where a reduction of 76.7% in the relative risk of symptomatic infection was observed [22].

In real-life experience, the efficacy of TGM-CGM has been demonstrated in patients immunocompromised for B-cell malignancies, cancer, neuroinflammatory diseases, hematopoietic stem cell or organ transplants but still little is known about autoimmune rheumatic diseases [23-26].

The aim of this case-control prospective study is to assess the efficacy of preventing SARS-CoV2 infection and the safety of the use of TGM-CGM in a cohort of immunosuppressed patients suffering from Connective Tissue Disease (CTD) or Rheumatoid Arthritis (RA) that received at least one infusion of Rituximab in 2022.

2. Materials and Methods

2.1. Inclusion criteria

We included outpatients aged > 18 years with any of the following diseases: Systemic sclerosis (SSc), Idiopathic Inflammatory myophaty (IIM), Sjogren Syndrome (SS), Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD) and Rheumatoid Arthritis (RA) according to the ACR/EULAR recommendations [27-32]. Moreover, patients should be able to understand and sign an informed consent and they should have received at least one intravenous infusion of RTX in the six months previous to TGM-CGM administration.

We excluded patients aged < 18 years, unable to understand informed consent, diagnosed with a different disease from the previously reported, those who never received RTX infusion or who concluded the RTX administration before than the last six months from the start of the observation.

2.2. Data management

We performed a prospective study using the clinical medical charts of patients followed in the Rheumatology Unit at the University of Florence.

The experimental group (EG) was composed of patients who received a single dose of TGM-CGM from September 2022 to December 2022. They were followed for six months from the day of administration. We chose this frame time since in Italy, the winter season is the most likely period to contract infection.

The Control Group (CG) was composed of patients who met the inclusion criteria but refused the proposed drug during the pre-established period. They were followed for six months from the start of the study.

The TGM-CGM administration consists of a subsequential intramuscular injection of 150 mg Tixagevimab and 150 mg Cilgavimab. Patients were monitored for two hours in the healthcare setting right after the administration, and they were contacted after the first 24 hours from the injection.

2.3. Endpoint of the study

The safety endpoint was the incidence of early and late adverse events.

Early adverse events were considered as allergic reaction, local erythema or hematoma in the site injection, headache or asthenia. Late adverse events were evaluated after three and after six

 doi:10.20944/preprints202312.0525.v1

months from the administration and we inquired especially for the incidence of thromboembolic events such as myocardial infarction, pulmonary embolism and deep vein thrombosis for any cause.

The efficacy endpoint was to assess the incidence of Covid-19 within three (T3) and six months (T6) from the TGM-CGM administration. The incidence of Covid-19 in the EG was compared with the incidence in the CG, followed for the same amount of time. Symptomatic patients underwent the nasopharyngeal antigenic test, while the asymptomatic patients performed a serological test dosing IgM anti SARS-COV2.

We assessed also severity of COVID-19, considering asymptomatic infection when no symptoms nor worsening of the underlying rheumatic disease was reported. Oligosymptomatic infection was defined by the presence of rhinitis, fever not higher than 37.5°C and time to swab negativization ≤ 10 days in the absence of dyspnea, hospitalization or any limitation in the daily activities. Mild-moderate infection was defined by fever >37.5°, dry cough, dyspnea, profuse asthenia, marked limitation in the daily activities and time to nasopharyngeal swab negativization more than 10 days, in the absence of need for hospitalization nor oxygen equipment. Severe infection was defined by the need for hospitalization and/or oxygen equipment.

For each patient clinical data were collected as well as information about the vaccination cycle. We also collected, when available, the dosage of anti-Receptor-Binding Domain (RBD) of SARS-CoV2 spike protein. We considered suboptimal response to vaccines when the anti-RBD IgG level was less than 506 since some studies suggest 80% efficacy of vaccines when the titer is above this cut-off [33].

2.4. Statistical analysis

Statistical analysis was performed using software R 3.5.2 GUI 1.70 El Capitan build. Continuous variables were represented by average and standard deviation, categorical variables were described by percentage and frequency distribution. Comparison of clinical and demographical characteristics between EG and CG was made by unpaired t test for continuous variables and Chi squared for categorical variables. The incidence of Covid infection at T3 and at T6 was compared between EG and CG by Fisher exact test. A logistic regression analysis was performed considering as outcome variable the presence of Covid infection at T3 and at T6 and as predictors variables concerning disease's and patients' characteristics. Significance level was fixed at 5%.

3. Results

Between September 2022 and December 2022, 50 patients were enrolled in the study. Of these, 25 accepted the administration of TGM-CGM, forming the experimental group; while the other 25 did not and they formed the control group.

Patients enrolled in the experimental group (F/M= 24/1) had a mean age of 57.96 (± 15.57) and a mean disease duration of 6.56 (± 6.12). Nine patients (36%) had IIM, 7 (28 %) SSc, 3 (12 %) SLE, 3 (12%) had RA, 2 (8%) had SS, and 1 (4%) had MCTD.

Patients of the control group (F:M= 24/1) had a mean age of 58.6 (± 9.13) and a mean disease of 8.36 (±7.33) years. Three (12%) had IIM, 11 (44%) had SSc, 3 (12%) SLE, 2 (12 %) RA, 5 (20%) had SS and 1 (4%) MCTD. Clinical data are represented in Table 1.

Table 1. Clinical data of the enrolled patients.

	TGM-CGM GROUP	CONTROL GROUP
Sex		
Male (%)	1 (4%)	1 (4%)
Female (%)	24 (96 %)	24 (96%)
Age mean (± SD)	57.96 (± 15.57)	58.6 (± 9.13)
Disease duration mean (± SD)	6.56 (± 6.12)	8.36 (± 7.33)
Disease		
IIM	9/25 (36%)	3/25 (12%)

 doi:10.20944/preprints202312.0525.v1

SSc	7/25 (28%)	11/25 (44%)
SLE	3/25 (12%)	3/25 (12%)
RA	3/25 (12%)	2/25 (8%)
SS	2/25 (8%)	5/25 (20%)
MCTD	1/25 (4%)	1/25 (4%)
Comorbidities		
Arterial hypertention	10/25 (40%)	9/25 (36%)
Dyslipidemia	6/25 (24%)	4/25 (16%)
Diabetes mellitus	2/25 (8%)	3/25 (12%)
BMI 25-30	8/25 (32%)	8/25 (32%)
BMI >30	4/25 (16%)	3/25 (12%)
COPD	1/25 (4%)	2/25 (8%)
ILD	7/25 (28%)	14/25 (56%)
Active Smoker	1/25 (4%)	3/25 (12%)
Ex Smoker	4/25 (16%)	2/25 (8%)
Concomitant therapies		
Hydroxychloroquine	8/25 (32%)	5/25 (20%)
Methotrexate	5/25 (20%)	5/25 (20%)
Mycophenolate mofetil	1/25 (4%)	1/25 (4%)
IVIG	7/25 (28%)	3/25 (12%)
Prednisone ≤ 5mg/day	4/25 (16%)	9/25 (36%)
Prednisone >5mg/day	4/25 (16%)	3/25 (12%)
Vaccination		
No vaccine	0/25 (0%)	2/25 (8%)
2 doses	1/25 (4%)	8/25 (32%)
3 doses	16/25 (74%)	12/25 (48%)
4 doses	8/25 (32%)	3/25 (12%)
Rituximab, n° of cycles		
<5	18/25 (%)	15/25 (%)
5-10	4/25 (16%)	8/25 (32%)
>10	3/25 (12%)	2/25 (%)

* **Table 1: Anamnestic and clinical data of enrolled patients.** IIM: Idiopathic Inflammatory myophaty; SSc: Systemic Sclerosis; SLE: Systemic Lupus Erythematosus, RA: Rheumatoid Arthritis, SS Sjogren Syndrome; MCTD: Mixed Connective Tissue Disease; BMI: Body Mass Index, COPD: chronic obstructive pulmonary disease, ILD: Interstitial Lung Disease, IVIG: Intravenous Immunoglobulin.

Three patients in the EG developed infection within three months from the received injection, while other three were infected from three to six months after the injection. None of them required hospitalization nor oxygen equipment. One was completely asymptomatic, 4 developed oligosymptomatic infections and 1 had a mild-moderate infection with time to nasal swab negativization of 12 days. All of them was vaccinated with at least two doses and the majority received three doses. Mean time to nasal swab negativization was 6.83 days (± 4.26). Two patients were treated with nirmatrelvir while the other 4 required just symptomatic therapy with paracetamol.

In the CG, 8 patients contracted Covid-19 in the first three months of the observation, while one was detected in the last three months. None of them required hospitalization nor oxygen requirement. Five experienced a mild-moderate course of infection, with fever >38°, dry cough and marked limitation in the daily activities whereas one had oligosymptomatic infection. Mean time to swab negativization was 12.55 days (± 3.94). Six patients required the use of nirmatrelvir while three

 doi:10.20944/preprints202312.0525.v1

just used symptomatic therapy with paracetamol. In the CG two patients were unvaccinated due to contraindication, whereas the other 23 received at least 2 doses of vaccines.

For 21 patients, the dosage of anti-Receptor-Binding Domain (RBD) SARS-CoV2 spike protein was available.

Two of them did not reach any antibody protection (anti-RBD IgG =0) at the end of vaccination cycle, while 7 had a suboptimal protection with a titer <506 BAU/mL (33).

Concerning safety of TGM-CGM injection, only one patient reported headache and asthenia in the first 24 hours from the injection, no other early events were registered. No serious adverse events were recorded within six months, particularly we focused on myocardial infarction, pulmonary embolism or deep vein thrombosis. None of the above conditions was observed. Results obtained from our study are summarized in Table 2.

Table 2. Results obtained from the study.

	TGM-CGM GROUP	CONTROL GROUP	p-value
Infection			
≤ 3mont	3/25 (12%)	8/25 (32%)	0.171
>3 months	3/25 (12%)	1/25 (4%)	0.609
Severity			
Asymptomatic	1/6	0/9	
Oligosymptomatic	5/6	4/9	
Mild-moderate infectio	0/6	5/9	
Severe infection	0/6	0/9	
Time to swab negativization	6.83 ± 4.26	12.55 ± 3.94	
Use of antiviral	2/6	6/9	
Early adverse Events			
Injection site pain	0/25		
Injection site erythema	0/25		
Injection site haematoma	0/25		
Diffuse skin rash	0/25		
Anaphylactic reaction	0/25		
Headache	1/25		
Asthenia	1/25		
Late adverse events	0/25	0/25	
Myocardial infarction	0/25	0/25	
Venous Thromboembolic events	0/25	0/25	
Arterial thromboembolic event	0/25	0/25	
Pulmonary embolism			

* The table shows the incidence and the severity of SARS-CoV2 infection in the analyzed populations, as well as early and late adverse events.

4. Discussion

To our knowledge, this is the first case-control study with the aim of assessing the effectiveness and safety of TGM-CGM in a cohort of immunosuppressed rheumatic patients treated with BCTD.

Our study proved a downward trend in the incidence of symptomatic infection (20% in EG versus 36% in the CG) and a reduction in disease severity. Indeed, just one (16%) of the infected patients in the EG experienced mild-moderate infection, 4 (66 %) had oligosymptomatic Covid and 1 (16%) had completely asymptomatic infection versus 55%, 44% and 0% respectively in the CG. Moreover, just two patients of the infected patients in the EG required additional treatment with nirmatrelvir compared to the 6 in the control group.

 doi:10.20944/preprints202312.0525.v1

Contrarily to the PROVENT study that observed a sharp decrease in relative risk of 76.7%, extended to 82.8 % at 6 months follow-up, our results did not reach statistical significance for different reasons [22]. First, the PROVENT study enrolled a small percentage of immunosuppressed people (just 5%), while our patients were affected by systemic autoimmune diseases requiring several cycles of immunosuppression. Second, PROVENT study was conducted at the beginning of the pandemic when the most frequent circulating virus variants were alpha, Beta and Delta [22]; whereas our study was performed during the Omicron variant predominance [34]. Indeed, some studies proved that CGM-CGM is less effective in neutralizing Omicron subvariants BA.1 and BA.2 [35-37].

Beyond the PROVENT study, we found several articles showing the efficacy of TGM-CGM in decreasing the incidence of symptomatic Covid, hospitalization and ICU admission in immunosuppressed patients diagnosed with B cells malignancy or solid organ transplantation [23,24,38-44]. Anyway, still few data are available about real-world experience in rheumatologic patients.

In March 2023, Ocon et al. performed a study involving 43 patients treated with rituximab and affected by one of the following diseases: rheumatoid arthritis, ANCA vasculitis, immune-mediated myositis, Sjogren syndrome or systemic lupus erythematosus. During the mean follow up of 100±33 days after the received TGM-CGM injection, just one individual contracted symptomatic SARS-CoV2 infection, while the other 97.8% did not. Although the follow-up lasted just three months, instead of six months, as it is the estimated time of TGM-CGM protection.

Another study observed that among the 412 enrolled patients diagnosed with immune-mediated inflammatory diseases (both rheumatological, immunological and neurological), just 12 contracted the infection from January to May 2022. Overall, 11 had a mild course and just one required hospitalization and oxygen equipment [45].

Conversely, a higher incidence of covid was reported in a study conducted on 21 patients affected by ANCA-associated vasculitis on rituximab. Indeed, in this cohort of patients, 4 out of 21 experienced the symptomatic infection [46]. Despite the encouraging results for the pre-exposure prophylaxis in fragile patients, all the aforementioned studies have the limitation of lacking a comparator group.

A case-control study with a larger population has been performed involving patients with neuroinflammatory diseases who received immunosuppression with CBDT (rituximab, ocrelizumab, ofatumamb) or sphingosine-1-phosphate modulators (S1P). The rate of COVID-19 was significantly lower in the 31 patients who received TGM-CGM, compared to the control group (6.5% vs 34.1%) (26). Similarly to our results, all the breakthrough infection in the TGM-CGM group were mild, whereas in the control group a higher amount of moderate infection was observed. Another study analyzed the incidence of covid-19 before and after the prophylactic injection of TCG-CGM. The Authors observed a slight reduction of symptomatic infection after TGM-CGM (7.9% vs 8.1%) with a reduced need of hospitalization after the injection (5.9% vs 24.8%). However, data are scarcely comparable since different variants of virus were spread during the course of the study. BA.1 variant was predominant during the pre- TGM-CGM treatment, while BA.5 was predominant in post TGM-CGM treatment.

Concerning safety, some studies, including the PROVENT study, reported higher number of serious thrombotic events (myocardial infarction, deep vein thrombosis or pulmonary embolism) when compared with placebo group [22,47]. These events seemed to be more likely in patients with increased cardiovascular risk.

Our data did not confirm the aforementioned warning, showing a great safety profile both in early and late adverse events. Indeed, none of the EG experienced serious cardiovascular adverse events and just one patient complained transient headache and fatigue the day after injection. Our results were in line with those underlined by a real-world observational study in which the authors compared 8627 people receiving TGM-CGM with 295347 controls without proving an increased risk of cardiovascular major events in the 90 days after the injection [48]. Conversely this study demonstrated a reduced risk in myocardial infarction after 30 and 90 days from the received injection. Moreover, a lower 30% mortality rate was observed in the TGM-CGM group compared with placebo

arm [49]. The two protective effects could be explained by the decrease of sars-cov2 infection and severity.

In addition, we collected the dosage of the anti-RBD SARS-CoV2 spike protein that were available in 21 patients. Interestingly, seven people out of 21 (33.3%) showed a suboptimal vaccine response with a titer lower than 506 BAU/mL and just 2 people (9.5%) had the autoantibody titer close to 0. The other 12 patients (57.2%) presented a great immunological response. This result was unexpected since many studies in literature revealed that patients treated with Rituximab did not develop neutralizing autoantibodies even after a complete vaccination cycle [50]. We speculated that our patients developed a sufficient rate of anti-spike autoantibodies because vaccinations were administrated at the end of the sixth month from the previous Rituximab infusion and at least two weeks before the following dose. In effect, it is well known that humor response to vaccination is dependent on timing of the received RTX infusion [51].

Our study presents some limitations that should be considered. First, being a monocentric study involving patients with rare diseases, we obtained just a small sample size whose results did not reach statistical significance. Moreover, TGM-CGM was designed when the alpha and Beta variants were dominating, but we administered it during the Omicron variant that is notably less sensitive to CGM-CGM. Last, the retrospective nature of our research impaired the homogenous collection of data. However, despite there are limitations, our study has the strength of being the first case-control real-life experience on rheumatic autoimmune diseases. Due to the descriptive nature of the study and the very small sample for each single disease included, these observations need to be confirmed in future real-world studies able to adjust observations for confounders.

5. Conclusions

Assessing the efficacy of pre-exposure prophylactic monoclonal autoantibodies for COVID-19 is still challenging since it is difficult to distinguish its efficacy from that of vaccination and since virus seems to vary very quickly. Anyway, TGM-CGM has been proved to be a safe additional tool to prevent serious outcome in high risk population, especially in patients treated with BCTD.

Author Contributions: S.P (Silvia Peretti): conceptualization; data curation; investigation; methodology, writing original draft; F.B (Francesco Bonomi): data curation, visualization and writing; E.F (Elisa Fiorentini): data curation; visualization, review and editing, F.B (Francesca Bartoli): investigation, methodology, review and editing, G.L (Gemma Lepri): visualization, review and editing; S.B.R (Silvia Bellando-Randone): supervision; investigation; methodology; review and editing; S.G (Serena Guiducci): conceptualization; supervision; investigation; methodology; review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Azienda Ospedaliera Universitaria Careggi.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. WHO Coronavirus (COVID-19) Dashboard [Internet]. Available at https://covid19.who.int
2. Favalli, E.G.; Monti, S.; Ingegnoli, F.; Balduzzi, S.; Caporali, R.; Montecucco, C. Incidence of COVID-19 in Patients With Rheumatic Diseases Treated With Targeted Immunosuppressive Drugs: What Can We Learn From Observational Data? *Arthritis Rheumatol Hoboken NJ* **2020,** 72(10):1600–6
3. Sarzi-Puttini, P.; Marotto, D.; Caporali, R.; Montecucco, C.M.; Favalli, E.G.; Franceschini, F.; Fredi, M.; Balduzzi, S.; Bazzani, C.; Bongiovanni, S.; et al. Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: A multicentre retrospective study. *J Autoimmun*. **2021**, 116:102545.

4. Del Papa, N.; Sambataro, G.; Minniti, A.; Maglione, W.; Pignataro, F.; Caminati, A.; Harari, S.; Sambataro, D.; Vitali, C.; Caporali, R.F. Impact of COVID-19 outbreak in an Italian cohort of patients with systemic sclerosis. *Ther Adv Musculoskelet Dis.* **2020**, 12:1759720X20953356.
5. Murray, K.; Quinn, S.; Turk, M.; O'Rourke, A.; Molloy, E.; O'Neill, L.; Mongey, A.B.; Fearon, U.; Veale, D.J. COVID-19 and rheumatic musculoskeletal disease patients: infection rates, attitudes and medication adherence in an Irish population. *Rheumatol Oxf Engl.* 1 febbraio **2021**, 60(2):902–6.
6. Bakasis, A.D.; Mavragani, C.P.; Boki, K.A.; Tzioufas, A.G.; Vlachoyiannopoulos, P.G.; Stergiou, I.E.; Skopouli, F.N.; Moutsopoulos, H.M. COVID-19 infection among autoimmune rheumatic disease patients: Data from an observational study and literature review. *J Autoimmun*. **2021**, 123:102687.
7. Furlan, A.; Forner, G.; Cipriani, L.; Vian, E.; Rigoli, R.; Gherlinzoni, F.; Scotton, P. COVID-19 in B Cell-Depleted Patients After Rituximab: A Diagnostic and Therapeutic Challenge. *Front Immunol.* **2021**, 12:763412.
8. Sharmeen, S., Elghawy, A.; Zarlasht, F.; Yao, Q. COVID-19 in rheumatic disease patients on immunosuppressive agents. *Semin Arthritis Rheum.* **2020**, 50(4):680–6.
9. Pang, R.; Zhao, J.; Gan, Z.; Hu, Z.; Xue, X.; Wu Y, Qiao, Q.; Zhong, A.; Xia, X.; Liao, H.; et al. Evolution of COVID-19 in patients with autoimmune rheumatic diseases. *Aging.* **2020** 12(23):23427–35.
10. Pakhchanian, H.; Khan, H.; Raiker, R.; Ahmed, S.; Kavadichanda, C.; Abbasi, M.; Kardeş, S.; Agarwal, V.; Aggarwal, R.; Gupta, L. COVID-19 outcomes in patients with Dermatomyositis: A registry-based cohort analysis. *Semin Arthritis Rheum.* **2022** 56:152034.
11. Goldman, J.D.; Robinson, P.C.; Uldrick, T.S.; Ljungman, P. COVID-19 in immunocompromised populations: implications for prognosis and repurposing of immunotherapies. *J Immunother Cancer.* **2021**, 9(6):e002630.
12. Lauring, A.S.; Tenforde, M.W.; Chappell, J.D.; Gaglani, M.; Ginde, A.A.; McNeal, T.; Ghamande, S.; Douin, D.J.; Talbot, H.K.; Casey, J.D.; et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ*. **2022**, 376:e069761.
13. Baden, L.R.; El Sahly, H.M.; Essink, B.; Kotloff, K.; Frey, S.; Novak, R.; Diemert, D.; Spector, S.A.; Rouphael, N.; Creech, C.B.; et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. **2021**, 384(5):403–16.
14. Kearns, P.; Siebert, S.; Willicombe, M.; Gaskell, C.; Kirkham, A.; Pirrie, S.; Bowden, S.; Magwaro, S.; Hughes, A.; Lim, Z.; et al. Examining the Immunological Effects of COVID-19 Vaccination in Patients with Conditions Potentially Leading to Diminished Immune Response Capacity – The OCTAVE Trial [Internet]. Rochester, NY; **2021**, Available at: https://papers.ssrn.com/abstract=3910058
15. Prendecki, M.; Clarke, C.; Edwards, H.; McIntyre, S.; Mortimer, P.; Gleeson, S.; Martin, P.; Thomson, T.; Randell, P.; Shah, A.; et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. *Ann Rheum Dis.* **2021**, 80(10):1322–9.
16. Magliulo, D.; Wade, S.D.; Kyttaris, V.C. Immunogenicity of SARS-CoV-2 vaccination in rituximab-treated patients: Effect of timing and immunologic parameters. *Clin Immunol Orlando Fla.* **2022**, 234:108897.
17. Ferri, C.; Ursini, F.; Gragnani, L.; Raimondo, V.; Giuggioli, D.; Foti, R.; Caminiti, M.; Olivo, D.; Cuomo, G.; Visentini, M.; et al. Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. *J Autoimmun* **2021**, 125:102744.
18. Bitoun, S.; Avouac, J.; Henry, J.; Ghossan, R.; Al Tabaa, O.; Belkhir, R.; Nocturne, G.; Mariaggi, A.A.; Rozenberg, F.; Vauloup-Fellous, C.; et al. Very low rate of humoral response after a third COVID-19 vaccine dose in patients with autoimmune diseases treated with rituximab and non-responders to two doses. *RMD Open* **2022**, 8(1):e002308.
19. Zen, M.; Fuzzi, E.; Astorri, D.; Saccon, F.; Padoan, R.; Ienna, L.; Cozzi, G.; Depascale, R.; Zanatta, E.; Gasparotto, M.; et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. *J Autoimmun*. **2020**, 112:102502.
20. EMA. European Medicines Agency. 2022 EMA recommends authorisation of COVID-19 medicine Evusheld. Available at: https://www.ema.europa.eu/en/news/ema-recommends-authorisation-covid-19-medicine-evusheld
21. Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19. *JAMA* (2022) 327(4):384–5.
22. Levin, M.J.; Ustianowski, A.; De Wit, S.; Launay, O.; Avila, M.; Templeton, A.; Yuan, Y.; Seegobin, S.; Ellery, A.; Levinson, D.J.; et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. *N Engl J Med* **2022**, 386(23):2188–200.
23. Jondreville, L.; D'Aveni, M.; Labussière-Wallet, H.; Le Bourgeois, A.; Villate, A.; Berceanu, A.; Bezsera, S.M.; Thiebaut, A.; Boissard-Simonet, M.; Legrand, M.; et al. Pre-exposure prophylaxis with tixagevimab/cilgavimab (AZD7442) prevents severe SARS-CoV-2 infection in recipients of allogeneic hematopoietic stem cell transplantation during the Omicron wave: a multicentric retrospective study of SFGM-TC. *J Hematol Oncol* **2022**, 15(1):169.

24. Ocon, A.J.; Ocon, K.E.; Battaglia, J.; Low, S.K.; Neupane, N.; Saeed, H.; Jamshed, S.; Mustafa, S.S. Real-World Effectiveness of Tixagevimab and Cilgavimab (Evusheld) in Patients With Hematological Malignancies. *J Hematol* **2022**, 11(6):210–5.
25. Nguyen, Y.; Flahault, A.; Chavarot, N.; Melenotte, C.; Cheminant, M.; Deschamps, P.; Carlier, N.; Lafont, E.; Thomas, M.; Flamarion, E.; et al. Pre-exposure prophylaxis with tixagevimab and cilgavimab (Evusheld) for COVID-19 among 1112 severely immunocompromised patients. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis.* **2022**, 28(12):1654.e1-1654.e4.
26. Jakimovski, D.; Eckert, S.P.; Mirmosayyeb, O.; Thapa, S.; Pennington, P.; Hojnacki, D.; Weinstock-Guttman, B. Tixagevimab and Cilgavimab (EvusheldTM) Prophylaxis Prevents Breakthrough COVID-19 Infections in Immunosuppressed Population: 6-Month Prospective Study. *Vaccines* **2023**, 11(2):350.
27. Kay, J.; Upchurch, K.S. ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatol Oxf Engl.* **2012**, 51 Suppl 6:vi5-9.
28. Van den Hoogen, F.; Khanna, D.; Fransen, J.; Johnson, S.R.; Baron, M.; Tyndall, A.; Matucci-Cerinic, M.; Naden, R.P.; Medsger, T.A. Jr; Carreira, P.E.; et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* **2013**, 72(11):1747–55.
29. Shiboski, C.H.; Shiboski, S.C.; Seror, R.; Criswell, L.A.; Labetoulle, M.; Lietman, T.M.; Rasmussen, A.; Scofield, H.; Vitali, C.; Bowman, S.J.; et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol Hoboken NJ* **2017**, 69(1):35–45.
30. Hoffmann-Vold, A.M.; Gunnarsson, R.; Garen, T.; Midtvedt, Ø.; Molberg, Ø. Performance of the 2013 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Systemic Sclerosis (SSc) in large, well-defined cohorts of SSc and mixed connective tissue disease. *J Rheumatol* **2015**, 42(1):60–3.
31. Lundberg, I.E.; Tjärnlund, A.; Bottai, M.; Werth, V.P.; Pilkington, C.; Visser, M.; Alfredsson, L.; Amato, A.A.; Barohn, R.J.; Liang, M.H., et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis* **2017**, 76(12):1955–64.
32. Aringer, M.; Costenbader, K.; Daikh, D.; Brinks, R.; Mosca, M.; Ramsey-Goldman, R.; Smolen, J.S.; Wofsy, D.; Boumpas, D.T.; Kamen, D.L.; et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* **2019**, 78(9):1151–9.
33. Feng, S.; Phillips, D.J.; White, T.; Sayal, H.; Aley, P.K.; Bibi, S.; Dold, C.; Fuskova, M.; Gilbert, S.C.; Hirsch, I.; et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* **2021**, 27(11):2032–40.
34. Tracking SARS-CoV-2 variants [Internet]. Available at: https://www.who.int/activities/tracking-SARS-CoV-2-variants
35. Tao, K.; Tzou, P.L.; Kosakovsky Pond, S.L.; Ioannidis, J.P.A.; Shafer, R.W. Susceptibility of SARS-CoV-2 Omicron Variants to Therapeutic Monoclonal Antibodies: Systematic Review and Meta-analysis. *Microbiol Spectr.* **2022**, 10(4):e0092622.
36. Zhou, H.; Dcosta, B.M.; Landau, N.R.; Tada, T. Resistance of SARS-CoV-2 Omicron BA.1 and BA.2 Variants to Vaccine-Elicited Sera and Therapeutic Monoclonal Antibodies. *Viruses* **2022**, 14(6):1334.
37. Convertino, I.; Ferraro, S.; Cappello, E.; Valdiserra, G.; Bonaso, M.; Tuccori, M. Tixagevimab + cilgavimab against SARS-CoV-2: the preclinical and clinical development and real-world evidence. *Expert Opinion on Drug Discovery* **2023**, 18:3, 231-245.
38. Cochran, W.; Salto-Alejandre, S.; Barker, L.; Langlee, J.; Freed, K.; Carter, D.; Bannon, J.; Goddard, D.; Mostafa, H.; Werbel, W.; et al. COVID-19 Outcomes in Solid Organ Transplant Recipients Who Received Tixagevimab-cilgavimab Prophylaxis and/or Bebtelovimab Treatment in a Nurse-driven Monoclonal Antibody Program During the Omicron Surge. *Transplantation* **2023**, 107(2):e60–1.
39. Davis, J.A.; Granger, K.; Roubal, K.; Smith, D.; Gaffney, K.J.; McGann, M.; Cendagorta, A.; Thurlapati, A.; Herbst, A.; Hendrickson, L.; et al. Efficacy of tixagevimab-cilgavimab in preventing SARS-CoV-2 for patients with B-cell malignancies. *Blood* **2023**, 141(2):200–3.
40. Otiniano, A.; van de Wyngaert, Z.; Brissot, E.; Dulery, R.; Gozlan, J.; Daguenel, A.; Abi Aad, Y.; Ricard, L.; Stocker, N.; Banet, A.; et al. Tixagevimab/cilgavimab for Omicron SARS-CoV-2 infection in patients with haematologic diseases. *Bone Marrow Transplant* **2023**, 58(3):340–2.
41. Suribhatla, R.; Starkey, T.; Ionescu, M.C.; Pagliuca, A.; Richter, A.; Lee, L.Y.W. Systematic review and meta-analysis of the clinical effectiveness of tixagevimab/cilgavimab for prophylaxis of COVID-19 in immunocompromised patients. *Br J Haematol* **2023**, 201(5):813–23.
42. Najjar-Debbiny, R.; Gronich, N.; Weber, G.; Stein, N.; Saliba, W. Effectiveness of Evusheld in Immunocompromised Patients: Propensity Score-Matched Analysis. *Clin Infect Dis Off Publ Infect Dis Soc Am* **2023**, 76(6):1067–73.

43. Al-Obaidi, M.M.; Gungor, A.B.; Kurtin, S.E.; Mathias, A.E.; Tanriover, B.; Zangeneh, T.T. The Prevention of COVID-19 in High-Risk Patients Using Tixagevimab-Cilgavimab (Evusheld): Real-World Experience at a Large Academic Center. *Am J Med* **2023**, 136(1):96–9.
44. Kertes, J.; Shapiro Ben David, S.; Engel-Zohar, N.; Rosen, K.; Hemo, B.; Kantor, A.; Adler, L.; Shamir Stein, N.; Mizrahi Reuveni, M.; Shahar, A. Association Between AZD7442 (Tixagevimab-Cilgavimab) Administration and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection, Hospitalization, and Mortality. *Clin Infect Dis Off Publ Infect Dis Soc Am* (2023) 76(3):e126–32.
45. Calabrese, C.; Kirchner, E.; Villa-Forte, A.; Hajj-Ali, R.A.; Moss, B.P.; Fernandez, J.P.; Calabrese, L. Early experience with tixagevimab/cilgavimab pre-exposure prophylaxis in patients with immune-mediated inflammatory disease undergoing B cell depleting therapy and those with inborn errors of humoral immunity. *RMD Open* **2022**, 8(2):e002557.
46. Aqeel, F.; Geetha, D. Tixagevimab and Cilgavimab (Evusheld) in Rituximab-treated Antineutrophil Cytoplasmic Antibody Vasculitis Patients. *Kidney Int Rep* **2022**, 7(11):2537–8.
47. Montastruc, F.; Lafaurie, M.; Flumian, C.; de Canecaude, C. Increased reporting of venous and arterial thromboembolic events reported with tixagevimab-cilgavimab for coronavirus disease 2019. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* **2023**, 29(4):543.e1-543.e3.
48. Birabaharan, M.; Hill, E.; Begur, M.; Kaelber, D.C.; Martin, T.C.S.; Mehta, S.R. Cardiovascular Outcomes After Tixagevimab and Cilgavimab use for Pre-Exposure Prophylaxis Against Coronavirus Disease 2019: A Population-Based Propensity-matched Cohort Study. *Clin Infect Dis Off Publ Infect Dis Soc Am* **2023**, 76(8):1500–3.
49. ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. *Lancet Respir Med* **2022**, 10(10):972–84.
50. Bitoun, S.; Henry, J.; Desjardins, D.; Vauloup-Fellous, C.; Dib, N.; Belkhir, R.; Mouna, L.; Joly, C.; Bitu, M.; Ly, B.; et al. Rituximab Impairs B Cell Response But Not T Cell Response to COVID-19 Vaccine in Autoimmune Diseases. *Arthritis Rheumatol Hoboken NJ* **2022**, 74(6):927–33.
51. Van der Togt, C.J.T.; Ten Cate, D.F.; den Broeder, N.; Rahamat-Langendoen, J.; van den Bemt, B.J.F.; den Broeder, A.A. Humoral response to coronavirus disease-19 vaccines is dependent on dosage and timing of rituximab in patients with rheumatoid arthritis. *Rheumatol Oxf Engl* **2022**, 61(SI2):SI175–9.