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Recommendations and metaanalyses

Serological response to SARS-CoV-2 vaccination in patients with inflammatory rheumatic disease treated with disease modifying anti-rheumatic drugs: A cohort study and a meta-analysis

suppl. Informations

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ABSTRACT

Introduction: Vaccination is considered as a cornerstone of the management of COVID-19 pandemic. However, while vaccines provide a robust protection in immunocompetent individuals, the immunogenicity in patients with inflammatory rheumatic diseases (IRD) is not well established.
Methods: A monocentric observational study evaluated the immunogenicity of a two-dose regimen vaccine in adult patients with IRD ($n = 123$) treated with targeted or biological therapies. Serum IgG antibody levels against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins were measured after the second vaccination. In addition, a search for observational studies performed in IRD under biologic or targeted therapies up to September 31, 2021 (PROSPERO registration number: CRD42021259410) was undertaken in publication databases, preprint servers, and grey literature sources. Studies that reported sample size, study date, location, and seroprevalence estimate were included. A meta-analysis was conducted to identify demographic differences in the prevalence of SARS-CoV-2 antibodies.
Results: Of 123 patients (median age 66 IQR 57–75), 69.9% have seroconverted after vaccination. Seroconverted patients were older than non-seroconverted ones in our cohort. Rituximab was associated with a significantly low antibody response. Besides, we identified 20 seroprevalence studies in addition to our cohort including 4423 participants in 11 countries. Meta-analysis confirmed a negative impact of rituximab on seroconversion rate and suggested a less substantial effect of abatacept, leflunomide and methotrexate.
Conclusion: Rituximab impairs serological response to SARS-CoV-2 vaccines in patients with IRD. This work suggests also a negative impact of abatacept, methotrexate or leflunomide especially when associated to biological therapy.

1. Introduction

Patients treated with immunosuppressive therapies have an increased risk of infections. International guidelines recommend the update of vaccinal calendar before starting an immunosuppressive treatment [1]. Previous works regarding pneumococcal or influenza vaccination have shown a decreased immunogenicity of vaccines in patients treated with immunosuppressive agents

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[2–5]. A recent review by Friedman MA et al. has highlighted the negative impact of conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) such Methotrexate and biological treatments such rituximab or abatacept on immunogenicity of different vaccines [6]. Efficacy and safety of COVID-19 vaccines have been assessed in large clinical trials [7–10] but inflammatory rheumatic diseases (IRD) patients have been largely excluded from these clinical trials, because of a theoretical risk of disease flare, induced inflammatory diseases [11] and a potential impaired immune response to vaccine due to the use of immunosuppressive agents. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection does not occur necessarily more frequently than in healthy subjects [12], it has been shown to be more severe in patients treated with rituximab, mycophenolate mofetil or high-dose glucocorticoids [13–18]. Despite limited data on efficacy and safety of SARS-CoV-2 vaccines, patients with inflammatory diseases treated with immunosuppressive agents have been prioritized to receive SARS-CoV-2 vaccination according American College of Rheumatology (ACR) guidelines [19].

Several studies report the serological response to SARS-CoV-2 vaccines in IRD patients [20–39]. We aimed to synthesize immunogenicity data to identify high-risk groups and inform public health decision making.

2. Methods

2.1. Cohort study design and patients

Adult patients with IRD were recruited from May 2021 to September 2021 from rheumatology and internal medicine departments of our Lyon Sud University Hospital (France). Patients who underwent a serological assessment of response to SARS-CoV-2 vaccine after a full vaccination scheme were retrospectively included in this study. Patients with a history of symptomatic RT-PCR-confirmed COVID-19 were excluded from the study. Medical history and medication use were recorded. Data regarding disease, disease activity and laboratory tests were retrieved from patients' medical records, within up to 3 months before vaccination. All eligible patients were informed. The inclusion criteria were established diagnosis of IRD, age ≥18 years, treatment with targeted or biologic therapy, injection of two doses of SARS-Cov-2 vaccines (BNT162b2 mRNA [Pfizer-BioNTech], mRNA-1273 [NIH-Moderna]), ChAdOx1 nCoV-19 [Oxford–*AstraZeneca*]), serological assessment performed using commercially available assay dosing IgG (or total) anti-Spike antibodies. The cut-off value as indicated in the technical sheet of each assay was used to define responders and non-responders. Serology results were standardized in BAU/mL according to the WHO guidelines [40].

Baseline characteristics were assessed by descriptive statistics. Categorical variables were compared using the chi-squared statistic. Continuous variables were compared using the non-parametric Wilcoxon test. To identify factors associated with SARS-CoV2 seroconversion, univariate logistic regression was conducted, followed by a multivariate logistic regression including variables with *P*-value < 0.1. Odds ratio (OR) are presented with their 95% confidence interval (95% CI). A *P*-value lower than 0.05 was considered statistically significant. All analyses were performed using R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

The study protocol was approved by local etic committee (Hospices Civils de Lyon Scientific and ethic committee, Number 21_572, September 6, 2021).

2.2. Meta-analysis

The protocol of the present study was registered before in the International prospective register of systematic reviews (PROSPERO), available in: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021259410, registration number: CRD42021259410. Reporting method was consistent with current recommendations of Meta-analysis of observational studies in epidemiology group (MOOSE) [41].

2.2.1. Literature Search strategy

We consulted the MEDLINE database for papers published in English up to September 31, 2021 using the search string in PubMed describe in Material S1 [See the supplementary material associated with this article online].

The first level of selection was performed by two independent reviewers (MA and BL) by reading the title and abstract. The second level of selection was also performed by two independent reviewers (MA and BC) by reading the full text. Inclusion criteria were:

- patients with IRD, treated with conventional synthetic DMARDs, biological or targeted therapies used in daily rheumatologic practice (methotrexate (MTX), leflunomide (LEF), hydroxychloroquine (HCQ), sulfasalazine (SLZ), corticosteroids (CS), TNF inhibitors, IL-6 inhibitors, IL-17 inhibitors, IL-1 receptor antagonist, abatacept, rituximab, belimumab). For example, patients with inflammatory bowel diseases were included if, they were treated with TNF inhibitors but not vedolizumab;
- patients who received two doses of vaccines ((BNT162b2 mRNA [Pfizer-BioNTech], mRNA-1273 [NIH-Moderna]), ChAdOx1 nCoV-19 [Oxford–*AstraZeneca*], CoronaVac [Sinovac Life Science Co.]), or only one dose for Ad26.COV2.S [Jonhson and Jonhson];
- cohort study with at least five patients;
- reported serological data according to the treatments received.

Exclusion criteria were:

- insufficient data regarding treatment group or disease included in the study;
- history of a symptomatic SARS-CoV-2 infection (confirmed by RT-PCR) prior to vaccination;
- publication in another language than english.

2.2.2. Data extraction and quality assessment

Study data were independently extracted by two authors (MA and FC): first author's last name, title of the article, year, month and journal of publication, country where the study was conducted (or countries in the case of multicentre studies), population size, age, gender, biologic or targeted drugs. We also extracted data of potential confounders, including co-prescription of immunosuppressant drugs. Differences were resolved by consensus. Quality of included studies was evaluated by one investigator (MA) using the Newcastle-Ottawa quality assessment scale (NOS scale) that explores three board areas: selection, comparability, and ascertainment of the exposure or outcome of interest in cohort studies [42]. Studies with a score≥5 stars were considered high quality, while studies with a score < 5 stars were rated as low quality.

2.2.3. Statistical analysis

The proportion of patients with positive SARS-CoV-2 serology and its 95% confidence interval (95%CI) were estimated using arcsine transformation for all treatments and each of them. Heterogeneity between study-specific estimates was assessed using inconsistency index I^2 [43], and random-effects models were a priori chosen because of expected heterogeneity. The risk of publication bias was determined by funnel plot aspect. All analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) with package 'meta' and 'metafor'.

Table 1
Characteristics of seroconverted and non-seroconverted populations.

	Overall *N* = 123	Responders *N* = 86/123 (69.9%)	Non responders *N* = 37/123 (30.1%)
Age, median (IQR)	66 [57–75]	64 [56–73]	74 [59–79][a]
Female, *n* (%)	94 (76.4)	65	29[b]
Vaccine			
BNT162b2 mRNA [Pfizer-BioNTech], *n* (%)	105 (85.4)	72	33
mRNA-1273 [NIH-Moderna], *n* (%)	9 (7.3)	8	1
Unspecifised mRNA, *n* (%)	6 (4.9)	3	3
ChAdOx1 nCoV-19 [Oxford–*AstraZeneca*], *n* (%)	3 (2.44)	3	0
Days between 2 doses, median (IQR)	30 [27–32]	30 [28–33]	28 [28–32][b]
Delay between second dose and serology, median (IQR)	47 [30–57]	42 [28–63]	57 [34–86][b]
Diseases			
RA, *n* (%)	92 (74.8)	59/92	33/92
SpA, *n* (%)	17 (13.8)	15/17	2/17
PsA, *n* (%)	7 (5.7)	6/7	1/7
Others, *n* (%)	7 (5.7)	6/7	1/7
Disease duration, median (IQR)	17 [9–26]	15 [8–24]	19 [12–26][b]
Treatments			
Rituximab, *n* (%)	43 (35.9)	14/43(32.5)	29/43(67.4)
D1/D15, *n* (%)	−20 (16.3)	−3/20 (15)	−17/20 (85)
D1 only, *n* (%)	−23 (18.7)	−11/23 (47.8)	−12/23 (52.2)
Abatacept, *n* (%)	6 (4.9)	5/6 (83.3)	1/6 (6.7)
Belimumab, *n* (%)	1 (0.8)	1/1 (100)	0/1 (0)
TNF inhibitors *n* (%)	39 (31.7)	34/39 (87.2)	5/39 (12.8)
Monotherapy	− 13 (10.6)	− 12/13 (92.3)	− 1/13 (7.7)
+ MTX	− 26 (21.1)	− 22/26 (84.6)	− 4/26 (15.4)
Tocilizumab, *n* (%)	27 (21.9)	26/27 (96.3)	1/27 (3.7)
Monotherapy	− 14/27 (51.9)	− 14/14 (100)	− 0/14 (0)
+ MTX	− 13/27 (48.1)	− 12/13 (92.3)	− 1/13 (7.7)
Ixekizumab, *n* (%)	2 (1.6)	2/2 (100)	0/2 (0)
JAK inhibitors, *n* (%)	5 (4.1)	4/5 (80)	1/5 (20)

IQR: Interquartile range; RA: rheumatoid arthritis; SpA: Spondylarthritis; PsA: Psoriatic arthritis; D1: Day 1; D15: Day 15; MTX: Methotrexate,
[a] $P < 0.05$
[b] P non significant (comparisons were made between responders and non responders)

Table 2
Factors associated with seroconversion: univariate and multivariate analysis.

	Univariate analysis		Multivariate analysis	
Characteristics	OR[a]	95% CI[a]	OR[a]	95% CI[a]
Female sex	1.17	0.48, 3.09[b]		
Age	0.98	0.95, 1.01[b]		
Disease				
Other	—	—		
RA	0.30	0.02, 1.85[b]		
SpA	1.25	0.05, 15.7[b]		
PsA	1.00	0.03, 29.5[b]		
Treatments				
Biologic				
TNF inhibitors	—	—	—	—
Other	0.88	0.16, 6.73[b]	1.04	0.07, 27.8[b]
Rituximab	0.07	0.02, 0.21[d]	0.07	0.00, 0.67[c]
IL-6R inhibitor	3.82	0.57, 75.6[b]	1.94	0.14, 47.2[b]
csDMARDs				
None.Other	—	—		
MTX.LEF	0.59	0.26, 1.30[b]		
Corticosteroids dose	0.92	0.82, 1.03[b]		
Days between second dose and serologyRituximab group	0.99	0.98, 1.00[c]	0.96	0.92, 1.00[b]
Number of CD19+ cells	1.01	0.99, 1.05[b]		
Number of CD20+ cells	1.01	0.99, 1.05[b]		
Days between 2 doses of vaccine	1.06	1.00, 1.14[b]	0.99	0.98, 1.19[b]
Duration of disease	0.98	0.95, 1.02[b]		

MTX: Methotrexate; LEF: Leflunomide.
[a] OR: Odds Ratio, CI: Confidence Interval.
[b] *P* not significant.
[c] $P < 0.05$.
[d] $P < 0.01$.

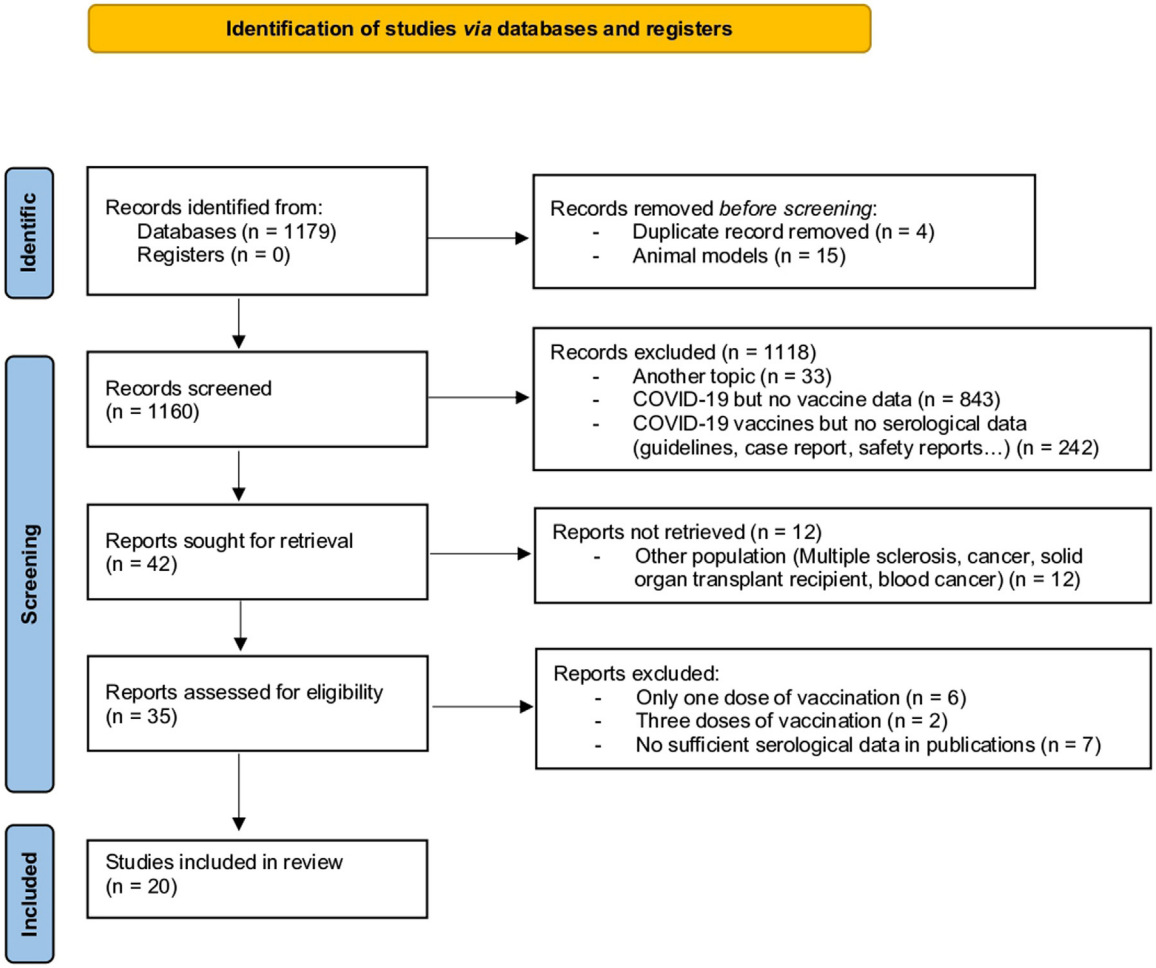

Fig. 1. Flow chart.

3. Results

3.1. Cohort

Overall, 123 patients (76.4% of female) were included with a median age of 66 (interquartile range (IQR) 57-75) years. Among them, 92 patients (74.8%) had rheumatoid arthritis (RA), 17 (13.8%) spondyloarthritis (SpA) and 7 (5.7%) psoriatic arthritis (PsA). The mean disease duration was 18.6 (±10.96) years. None of the patients reported previous infection by SARS-CoV-2. All of them received at least 2 doses of vaccines and 19 patients (15.4%) received 3 doses. While SARS-CoV-2 mRNA based vaccines were the most frequently used (in 120 patients (97.6%)), 3 patients (2.3%) received SARS-CoV-2 adenovirus based vaccines. Serological assessment was performed after a median of 47 IQR(30–57) days following the second vaccine injection.

The overall response rate was 69.9% (86/123). Characteristics of seroconverted and non-seroconverted patients are shown in Table 1. There were no significant differences between the two groups in terms of sex, disease duration, interval between the 2 doses of vaccine or the delay between the second dose and the serological assessment. Of note, non-seroconverted patients were statistically older than seroconverted ones (median age 74 IQR(59–79) vs 64 IQR(56–73), $P < 0.05$).

In our cohort, seroconversion was obtained in 34/39 (87.2%) patients treated by TNF inhibitors and 26/27 (96.3%) patients treated with IL-6R inhibitors. Among patients treated with abatacept, 5/6 (83.3%) had seroconverted and 4/5 (80%) patients treated with JAK inhibitors had a positive serology. Rituximab was associated with a significant reduction of the response rate with only 14/43 patients (32.6%) who had seroconverted compared to 72/80 (90%) in patients treated with other biological or targeted therapies. In multivariate analysis (after adjustment on age and delay between second dose and serology), rituximab was associated with an OR 0.06 IC95% [0.00–0.50] ($P < 0.05$) of seroconversion compared to TNF inhibitors (Table 2).

Considering the subgroup of patients treated with rituximab, we found that the delay between last infusion and first vaccination dose was significantly longer in responders than in non-responders (respectively median time 174 (IQR 161–240) days in responders vs 121 (IQR 73–188) days in non-responders).

We next analysed the influence of the rituximab regimen (i.e 1G on day 1 (D1) and 15 (D15) every 6 months or 1G only on day 1 every 6 months or more): in the group D1 only, 48% of patients have seroconverted, whereas 15% in the group D1/D15 (univariate analysis OR 0.19, 95% CI 0.04–0.77, remaining significant when adjusting on the delay between the last infusion of rituximab and the first dose of vaccine: OR 0.14, 95% CI 0.018–0.74).

The mean number of CD19+ cells (when available, $n = 14$) was higher in patients with a positive serology compared to patients with a negative serology (72/μL vs 30/μL, P not significant). Of note, 11 of our patients treated with rituximab have received a third dose of vaccination and only one seroconverted after the third dose.

Finally, we found in our cohort that the mean antibody titer ($n = 106$) was also significantly lower in patients treated with

Table 3
Characteristics of the studies included in the meta-analysis.

Source	Participants				Vaccine					Serology	
First author	Pathology details	Total of participants, *n*	Female, *n*	Age, mean or median	mRNA-1273 [NIH-Moderna] n	BNT162b2 mRNA [Pfizer-BioNTech] n	ChAdOx1 nCoV-19 [Oxford–AstraZeneca] *n*	CoronaVac [Sinovac Life Science Co.] *n*	Ad26.COV2.S [Jonhson and Jonhson] *n*	Method	Threshold of positivity (AU/mL)
Ammitzboll C. et al.	73 RA 61 SLE	134	90	65.7	–	134	–	–	–	Vitros	1
Auroux M. et al.	92 RA 17 SpA 7 PsA 7 others	123	94	65.3	9	105	3	–	–	Siemens	1
Braun-Moscovici Y. et al.	96 RA 30 PsA 21 SpA 87 CTD 19 vasculitis 11 others	264	201	57.6	–	264	–	–	–	Abbott Architect	50
Furer V. et al.	263 RA 165 PsA 68 SpA 101 SLE 19 myositis 93 vasculitis	686	475	59	–	686	–	–	–	Diasorin	15
Geisen U.M. et al.	8 RA 3 SpA 6 PsA/Pso 2 SLE 7 others	26	17	50.5	NA	NA	NA	NA	NA	Euroimmun	NA
Haberman R.H. et al.	22 RA 24 PsA 5 others	51	36	56.01	–	51	–	–	–	Euroimmun	5.7
Kappelman M.D. et al.	171 IBD	171	128	47.4	81	90	–	–	–	Labcorp	1
Kennedy N.A. et al.	20 IBD	20	NA	NA	–	20	–	–	–	Roche	15
Medeiros-Ribeiro A. et al.	IRD	859	660	51	–	–	–	859	–	NA	69
Mrak D. et al.	33 RA 22 CTD 17 vasculitis 2 others	74	57	61.7	13	61	-	-	–	Roche	1
Rubbert-Roth A. et al.	51 RA	51	29	64.6	9	44	–	–	–	Roche	15
Ruddy J.A. et al.	180 RA 87 SLE 24 myositis 105 CTD 8 vasculitis	404	385	44	204	198	–	–	–	Roche	0.79
Simon D. et al.	27 SpA 8 Pso 25 RA 16 others	84	55	53.1	-	84	–	–	–	Euroimmun	NA
Simon D. et al.	3 RA 1 myositis 4 others	8	5	53.5	-	8	–	–	–	Euroimmun	0,8

Table 3 (*Continued*)

Source	Participants				Vaccine					Serology	
First author	Pathology details	Total of partici-pants, *n*	Female, *n*	Age, mean or median	mRNA-1273 [NIH-Moderna] n	BNT162b2 mRNA [Pfizer-BioNTech] n	ChAdOx1 nCoV-19 [Oxford–AstraZeneca] *n*	CoronaVac [Sinovac Life Science Co.] *n*	Ad26.COV2.S [Jonhson and Jonhson] *n*	Method	Threshold of positivity (AU/mL)
Spiera R. et al.	23 RA 10 SLE 6 PsA 19 CTD 20 vasculatis 11 others	89	68	61.3	38	51	–	–	–	Roche	NA
Veenstra J. et al.	IRD	8	7	55.9	NA	NA	NA	NA	NA	NA	25
Boekel L et al.	NA	106	NA	63	NA	NA	NA	NA	NA	In-house	4
Chiang TP et al.	461 IA 283 CTD 216 SLE 54 myositis 22 vasculitis	1039	875	NA	994	–	–	45	Roche	NA	-
Moor MB. Et al.	6 RA 6 SLE 21 vasculitis 15 CTD 48 others	96	51	67	38	58	–	–	–	Euroimmun	1.1
Picchianti-Diamanti A et al.	35 RA	35	27	59	–	35	–	–	–	Abbott Architect	1.4
Seror R et al.	98 RA 15 PsA	113	81	61.8	NA	NA	NA	NA	NA	NA	NA

Number of seroconversion/Number of patients treated

Biologics							csDMARDs					
Rituximab, *n*	Abatacept, *n*	Belimumab, *n*	TNF-inhibitors, *n*	IL-6R inhibitors, *n*	IL-17 inhibitors *n*	JAK inhibitors, *n*	MTX, *n*	HCQ, *n*	LEF, *n*	SLZ, *n*	GC, *n*	GC mean dose (mg/day)
4/17	3/6	3/3	31/36	6/8	-	6/8	32/46	34/38	6/8	–	27/37	NA
14/43	5/6	1/1	34/39	26/27	2/2	4/5	40/59	1/1	6/11	–	17/28	6,54
24/46	5/8	9/11	63/63	35/35	4/5	9/9	68/78	–	–	–	76/92	5,6
36/87	10/16	7/9	167/172	37/37	47/48	41/45	148/176	120/133	25/28	-	86/130	6,7
–	–	1/1	13/13	1/1	2/2	–	–	3/3	2/2	1/1	7/7	NA
–	–	–	??/31	–	–	–	18/25	–	–	–	–	NA
–	–	–	122/132	–	38/39	–	–	–	–	–	–	NA
–	–	–	17/20	–	-	–	–	–	–	–	–	-
8/19	20/49	17/30	86/131	33/45	26/28	15/18	131/219	182/254	84/121	61/71	188/330	5
29/74	–	–	–	–	–	–	10/24	3/7	2/4	1/1	8/22	NA
–	4/5	–	17/18	–	–	8/12	24/28	–	–	–	16/17	5
5/19	24/24	53/56	98/98	6/7	14/14	15/15	92/94	160/170	19/19	14/15	96/117	21
–	–	–	11/11	–	–	–	–	3/3	–	1/1	10/10	NA
0/8	–	–	-	–	–	–	–	–	–	–	–	NA
10/30	1/1	1/2	9/9	1/2	2/2	6/6	12/13	17/19	2/3	1/1	12/17	NA
–	–	–	1/1	–	1/1	0/1	1/1	1/1	–	–	1/2	NA
3/7	–	–	22/23	–	–	–	25/27	–	–	–	4/5	NA
–	–	–	–	–	–	–	–	–	–	–	–	–
47/96	–	–	–	–	–	–	–	–	–	–	–	–
–	12/13	–	7/7	8/8	–	–	5/5	–	–	–	–	–
–	–	–	–	–	–	100/113	–	–	–	–	–	–

MTX: Methotrexate; GC: Glucocorticoids; HCQ: Hydroxychloroquine; LEF: Leflunomide; SLZ: Sulfasalazine; RA: rheumatoid arthritis; SLE: Systemic lupus erythematosus; SpA: Spondylarthritis; Psa: Psoriatic arthritis; CTD: connective tissue disease; IBD: inflammatory bowel disease; IRD: inflammatory rheumatic disease; csDMARDs: conventionnal synthetic disease modifying anti-rheumatic drugs.

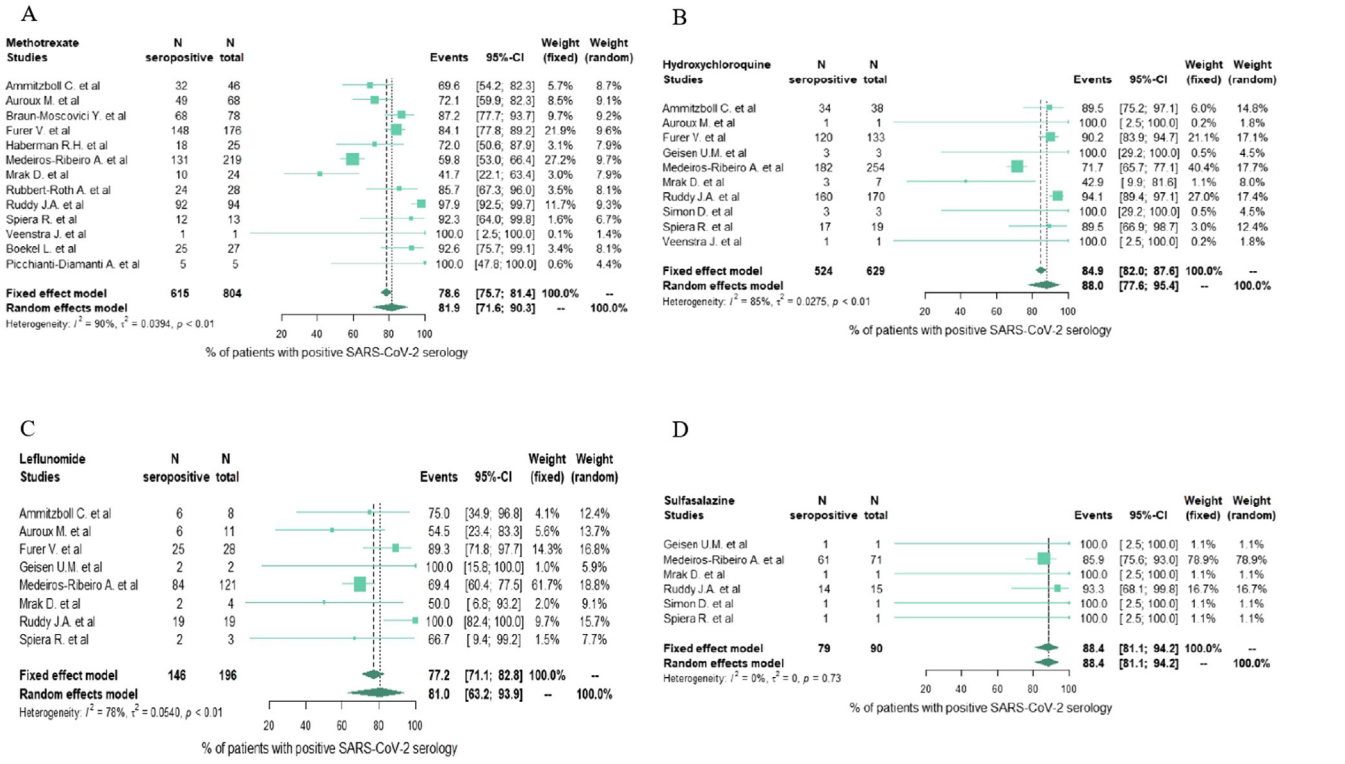

Fig. 2. Forrest plot of seroconversion rate regarding each treatment group of csDMARDs.

biologic in combination with methotrexate compared to biologic monotherapy (767 BAU/mL vs 359 BAU/mL, Wilcoxon test $P < 0.05$).

3.2. Meta-analysis

A total of 1179 publications were identified. Thirty-five records were assessed for eligibility and finally 20 articles coming from 11 different countries were included in the meta-analysis in addition to our cohort (Fig. 1). The characteristics of these studies are shown in Table 3. Most of these studies (19/21) used a mRNA vaccine (BNT162b2 mRNA [Pfizer-BioNTech], mRNA-1273 [NIH-Moderna]), one study used ChAdOx1 nCoV-19 [Oxford–*AstraZeneca*], and one study used CoronaVac [Sinovac Life Science Co.]. All studies have measured anti-spike protein IgG antibodies using different laboratory techniques. Antibody titers were measured between 2 and 16 weeks after the second dose of vaccine. Visual inspection of the funnel plot did not indicate publication bias (Material S2). NOS criteria are presented in Material S3. The overall serological response rate to two doses of vaccine ($n = 4423$ patients) was 84.8% (IC95%78.9–89.8) with a high degree of heterogeneity ($I^2 = 96\%$).

Regarding csDMARDS, hydroxychloroquine and sulfasalazine were associated with the highest seroconversion rate (respectively 88.0% [IC95%77.6-95.4; $I^2 = 85\%$] for hydroxychloroquine and 88.4% [IC95% 81.1-94.2; $I^2 = 0\%$] for sulfasalazine) (Fig. 2). Methotrexate (either use in monotherapy or in combination with other treatments) was associated with a low response rate of 81.9 [IC95% 71.6-90.3; $I^2 = 90\%$].

Among patients treated with targeted or biological therapies (Fig. 3), rituximab was associated with the lowest serological response, with only 36.3% [IC95% 28.6–44.4; $I^2 = 62\%$] of seroconversion rate. Abatacept (which targets CTLA-4 involved in the co-stimulation between B cells and T cells) was associated with a serological response rate of 77.7% [IC95%53.2–94.8; $I^2 = 86\%$]. Belimumab was associated with a good seroconversion rate of 84.3% [IC95%65.5–96.6; $I^2 = 70\%$] (Material S4). Anti-cytokine treatments were associated with a good seroconversion rate respectively 95.9% [IC95%89.7–99.4; $I^2 = 90\%$] for TNF inhibitors, 93.9% [IC95%81.5–99.7; $I^2 = 80\%$] for IL-6 inhibitors, 97.3% [IC95%93.9–99.3; $I^2 = 0\%$] for IL-17 inhibitors, 97.0% [IC95%76.5–100.0; $I^2 = 30\%$] for IL-1 receptor antagonist ($n = 15$ patients, Material S4) and 89.8% [IC95%80.3–96.5; $I^2 = 65\%$] for JAK inhibitors.

4. Discussion

The impact of DMARDs on the immune response to vaccine is clearly variable. The main factor implicated in impaired response to SARS-CoV-2 mRNA vaccine in patients with IRD was the immunotherapeutic agents rather than the underlying disease itself. An overall seroconversion rate of 84.8% was found in our meta-analysis. As a comparator, the seroconversion rate in healthy individuals enrolled in control groups of studies included in our meta-analysis was analysed. We found that 730/733 (99.5%) had seroconverted (excluding control group of Meideros-Ribeiro et al. [27] which received Coronavac and not mRNA based vaccine).

In our cohort, rituximab was clearly associated with deeply reduced immune response, consistently with our meta-analysis.

Consistent with findings of Furer et al. [22], Chung et al. [44] or Verhoeven et al. [45], the delay between the last infusion of rituximab and the first injection of vaccine seems to have a critical impact on antibody response: a short delay between last rituximab infusion and first vaccination dose was shown to be associated with an impaired serological response to SARS-COV-2 vaccination. We found in our cohort a smaller delay between last infusion and first dose of vaccination in non-responders than in responders (respectively median time 174 (IQR 161-240) days in responders vs 121 (IQR 73–188) days in non-responders). Our work also suggests an impact of the rituximab dose on seroconversion rate, with more

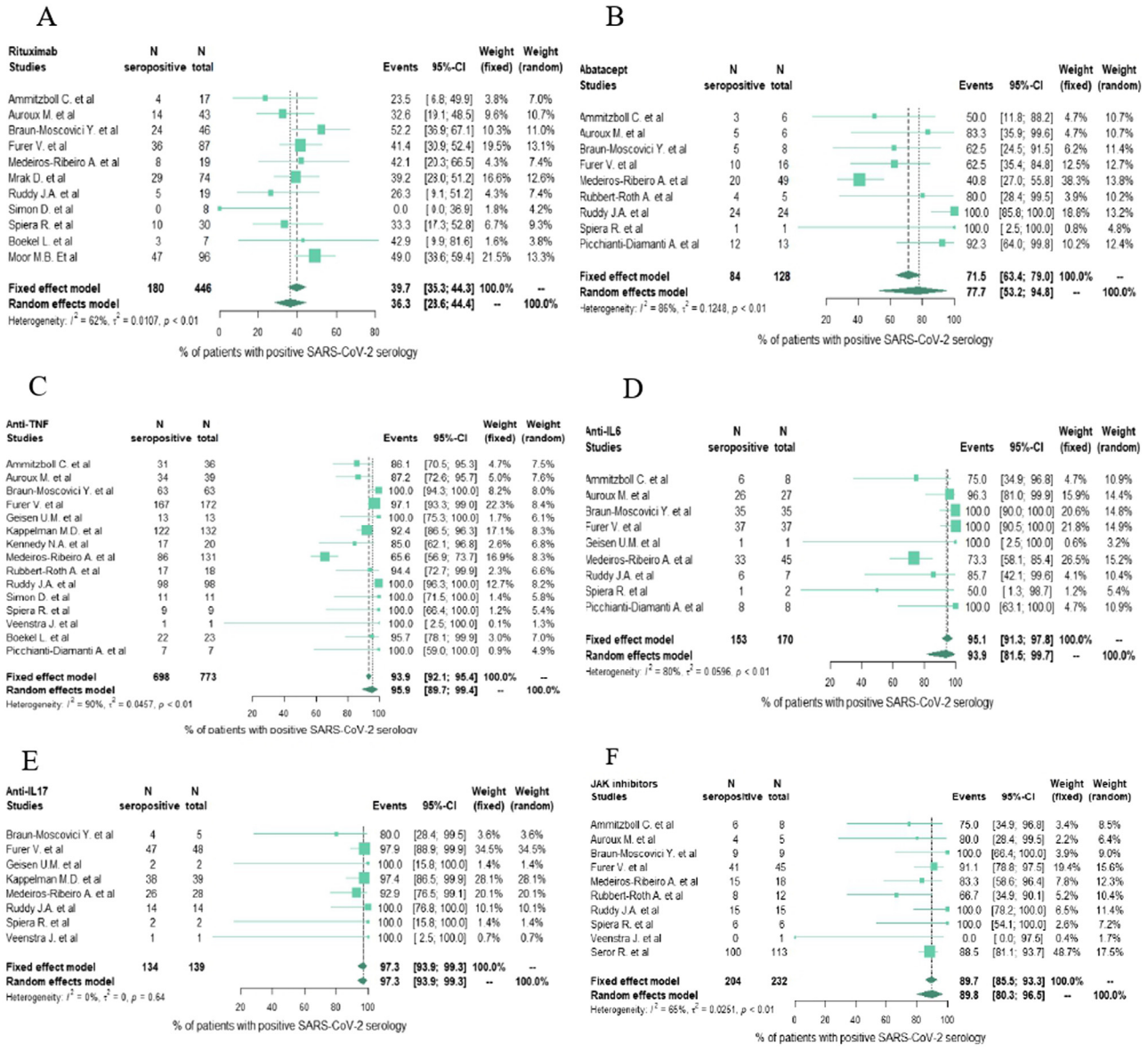

Fig. 3. Forest plots of seroconversion rate regarding each treatment group.

responders when patients are treated with 1G each cycle compared to 1G on day 1 and day 15.

In our cohort, we have shown that the number of CD19+ cells was lower (unless the statistical significance was not obtained due to small effectives) in patients without seroconversion in the rituximab subgroup. This is consistent with previous findings of Mrak et al. [28] and more recently by Stefanski et al. [46]. We know that rituximab treatment is associated with a long immunosuppression duration, at least 6 to 9 months [47]. Therefore, the ACR guidelines [19] recommend to vaccine patients 2 to 4 weeks before the next rituximab infusion (i.e at least 5 months after the last injection). It might be interesting to measure the number of CD19+/CD20+ cells and vaccinate patients only when they are detectable if the disease is controlled at that time.

Few studies have investigated the effect of the rituximab dose. In our cohort, we demonstrated that the proportion of serological response in patients receiving rituximab 1 g on day 1 and day 15 every 6 months was lower than in patients receiving 1 g only at day 1.

We didn't investigate the cellular response to mRNA vaccination in our population. Sahin et al. have previously reported the induction of poly-specific T-cell after mRNA vaccination [8]. Data are scarce in patients treated with immunosuppressive agents. Interestingly, Mahil et al. have found that T-cell reactivity against SARS-Cov-2 (measured by the induction of IFN gamma, IL-1 or IL-12 production) was present in patients without serological response to a single dose of BNT162b2 vaccine treated with TNF inhibitors, methotrexate or anti-IL23 [48]. Bonelli et al. have recently published similar results in 4 patients treated with rituximab and no serological response to 2 doses of BNT161b2 vaccine [49]. Whether this T-cell response without serological conversion (especially in rituximab treated patients) is effective to prevent COVID-19 infection, or at least serious infection, is unknown to date.

Finally, the persistence of these antibodies and the effective protection they confer during time is largely unknown in immunosuppressed patients. Especially for patients treated with rituximab, data regarding the evolution of antibody titer after the treatment

restart are scarce. Data from prospective studies currently conducted would improve our knowledge.

Regarding other biological or targeted therapies, abatacept seems to be associated with a decreased response, consistent with the mechanism of this drug action that targets CTLA-4 involved in the B-T cells co-stimulation. We observed a higher serological response, greater than 80% with anti-cytokine therapies such TNF/IL-6/IL-17 inhibitors or IL-1 receptor antagonist.

To improve serological response in immunosuppressed patients, recent data have shown a positive impact of a third booster dose of vaccination. In our cohort, 19 patients treated with rituximab received a third dose of vaccine but only one of them had seroconverted. In a small case serie published by Felten R et al. [50], the administration of a third dose results in higher antibody titers in patients who had seroconverted after the second dose (7/10 patients), more efficient neutralizing activity of these antibody in 5/10 patients and seroconversion of 1/3 who didn't show positive serology after 2 doses. Similarly, Simon D et al. [51] have shown that seroconversion finally occurs after a third dose of vaccination in 26/33 non-rituximab-treated patients and 6/33 in rituximab-treated patients.

Methotrexate has been shown to negatively affect response to influenza and pneumococcal vaccine [4,52,53]. Regarding SARS-COV-2 vaccination, results are conflicting. Ammitzboll et al. found a lower response rate in patients treated with MTX in combination with a biologic treatment compared to biologic monotherapy [20]. Furer et al. found that MTX monotherapy was associated with a lower seroconversion rate compared to healthy controls but in a smaller magnitude than observed with rituximab [22]. In addition, in the study of Braun-Moscovici et al., antibody titers were lower when MTX was used [21]. In our cohort, methotrexate when combined with biological or targeted agents was associated with a significant decreased antibody titer. In meta-analysis, seroconversion rate reflects what could be seen in a global population of immunosuppressed patients. It was impossible for the majority of studies to know if MTX was taken alone or in combination with biologic or targeted therapies. Prospective studies are needed to better understand the impact of MTX on serological response but there are some evidence for a negative impact. It would also be interesting to look at the correlation between MTX dose and antibody responses. Based on previous findings concerning influenza vaccine, some authors have suggested to stop for few weeks MTX to improve serological response [19]. This approach needs to take in consideration the risk of disease flare in our patients.

Regarding the type of vaccine, ACR guidelines [19] recommend only mRNA-based vaccines for immunosuppressed patients. This is consistent with results from the inactivated vaccine CoronaVac showing a significantly decreased response rate in immunosuppressed patients compared to seroconversion rate observed in cohort vaccinated with mRNA-based vaccines [27]. In our meta-analysis, this study contributed in part to the heterogeneity we observed, but the results we have presented remained similar when this study was excluded from the analyses.

This meta-analysis confirmed the negative impact of rituximab on seroconversion rate and suggested a negative impact of abatacept, methotrexate and leflunomide. A strength of our study is that we choose to investigate the impact of treatment in real-life conditions. We were very selective regarding the pathologies included and the treatment studied. In comparison to other meta-analysis that have been published so far in other diseases [54], we also selected only studies reporting seroconversion rate after a complete vaccinal schema of 2 doses and therefore analysed data on more than 4500 patients. On the other hand, we also know that studies included in this meta-analysis are mainly retrospective and non-exhaustive. Moreover, the populations are sometimes heterogeneous in terms of age or co-morbidities.

In conclusion, we found that patients treated with immunosuppressive agents have a decreased serological response to mRNA vaccines especially when treated with rituximab and probably with abatacept, leflunomide or methotrexate. In this population, a third dose of vaccination is highly recommended. Prospective works are in progress to evaluate the effectiveness of this protection in immunosuppressed patients and the persistence of it during time, this will be of peculiar interest.

Disclosure of interest

MA has received consulting fees from Bristol-Myers Squibb outside from this work.

FC has received consulting fees from Abbvie, Bristol-Myers Squibb, Janssen, Lilly, MSD, Novartis, Pfizer, Sanofi and has received research support from Abbvie, Biogen, Celgene, Novartis, Pfizer, Roche-Chugai, UCB outside from this work.

EM has received consulting fees from Abbvie, Amgen, Biogen, BMS, Fresenius, Galapagos, Janssen, Lilly, Medac, MSD, Novartis, Pfizer, Roche-Chugai, Sandoz UCB, outside from this work.

ID reports grants from the French Ministry of health and from the Non Profit Organization "Vaincre la mucoviscidose", travel reimbursement from Zambon, outside from this work and was part of board membership of Vertex without personal fees, outside from this work.

BL, BC, AM, CBC, JCL, SM have no conflict of interest to declare.

Contributors

All authors contributed to manuscript preparation.

Online Supplement. Supplementary data

Supplementary data (Material S1-S4) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2022.105380.

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