What we have learned from the Corona pandemic: Vaccination in immunocompromised patients

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September 23, 2022

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Disclosures

- Speaker honorarium: Amicus, Allmiral, Alexion, Merck, Roche, Biogen, Novartis, Sanofi Genzyme
- Consultant/advisory Boards: Amicus, Alexion, Roche, Merck, Sandoz, Teva
- Research Grants: Roche, Merck, Austrian Science Funds (FWF)

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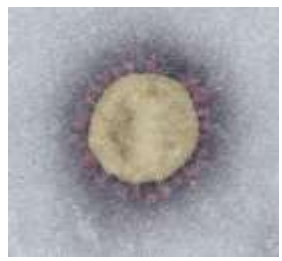
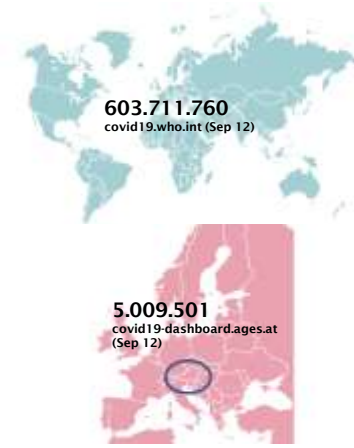
COVID-19 Pandemic



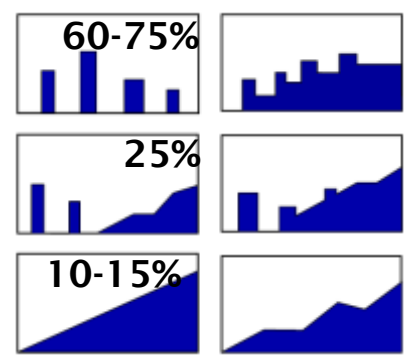


https://www.rki.de/DE/Content/Infekt/NRZ/EM/Aufnahmen/EM_Tab_covid.html, accessed 2022, May 11

3

Multiple Sclerosis

- Most frequent neurological disorders leading to disability in young adults
- Worldwide more than 2,5 mio patients, in Austria 15,000 130,000 in UK (7,000 new patients every year)
- Female:male 3-4:1
- Prognosis?
- Treatment: immunomodulatory/ immunosuppressive symptomatic



Reich et al. 2020
Salhofer-Polanyi et al. 2017
Weinhsenker 1989m
https://www.mssociety.org.uk

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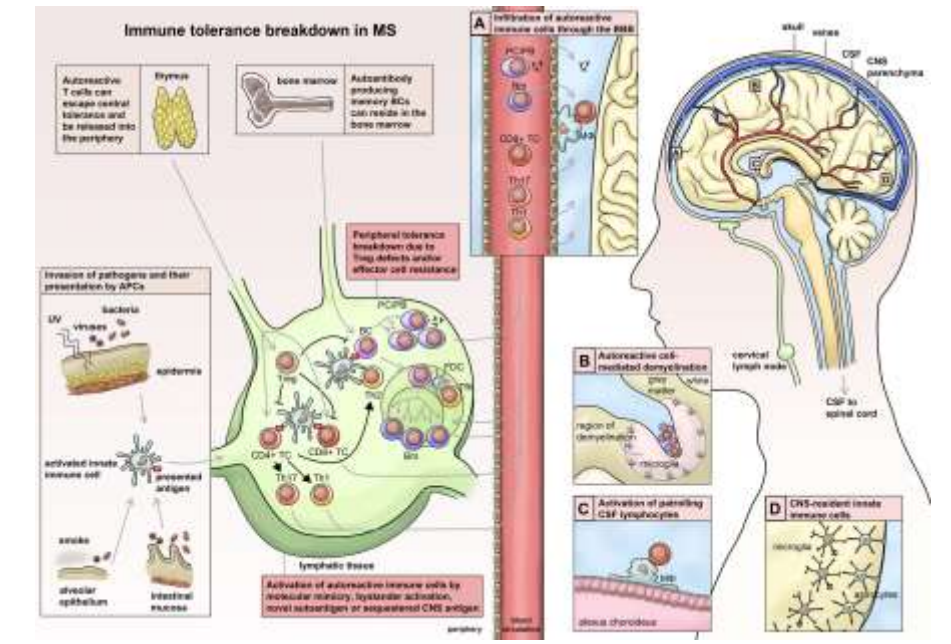

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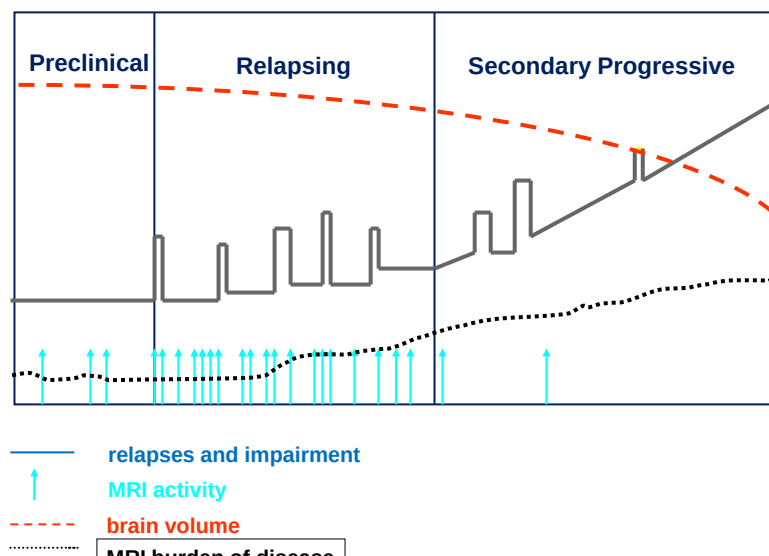
The Natural History of Multiple Sclerosis



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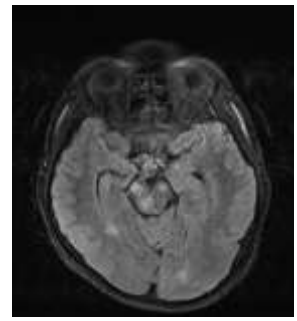
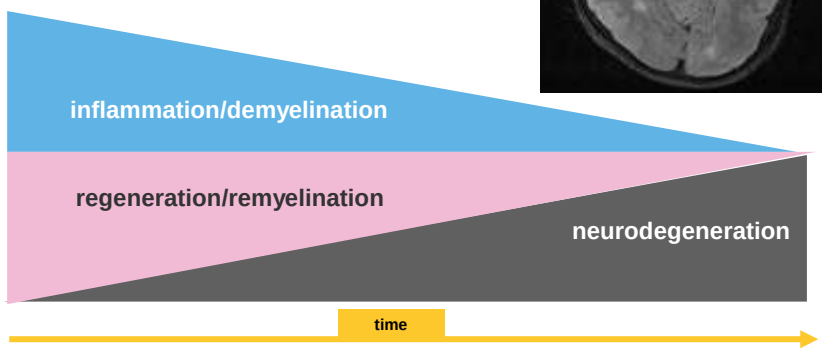
Multiple Sclerosis – pathology





Lancet 2002; 359: 1221-1231.

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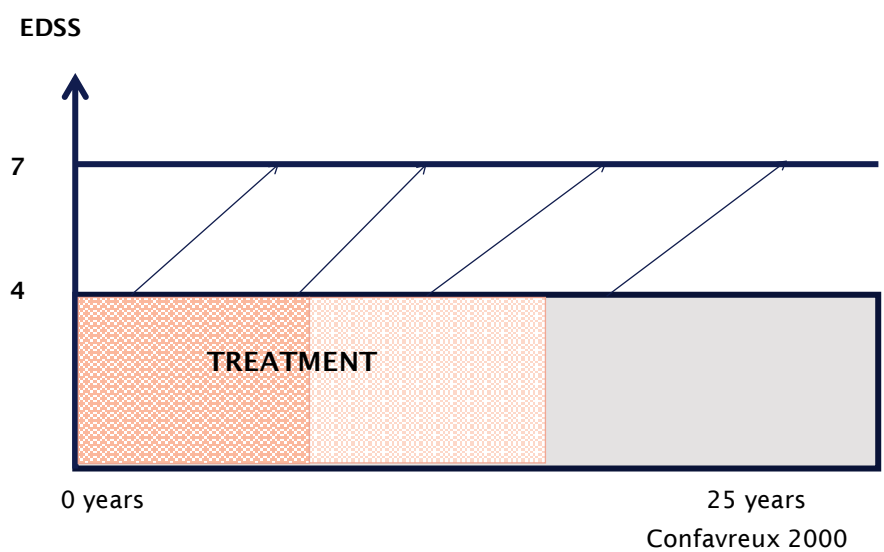
Window of opportunity



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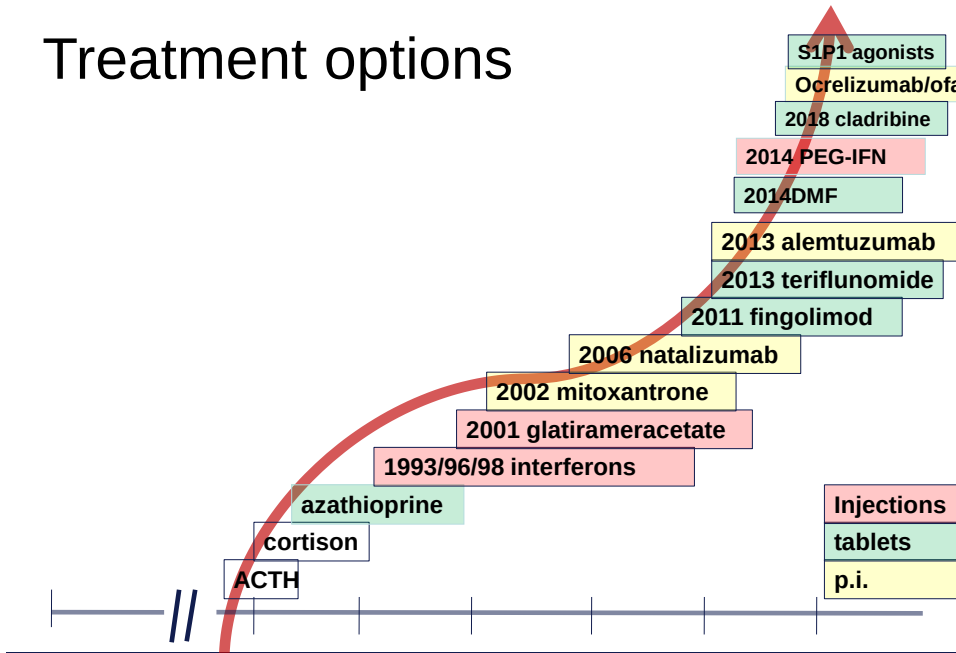
Treatment options



Nach Limmroth 2010; Kliniken der Stadt Köln GmbH

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Immunology of COVID-19 and disease-modifying therapies: The good, the bad and the unknown

Tobias Zrzavy | Isabella Wimmer | Paulus S. Rommer | Thomas Berger DOI: 10.1111/ene.14978

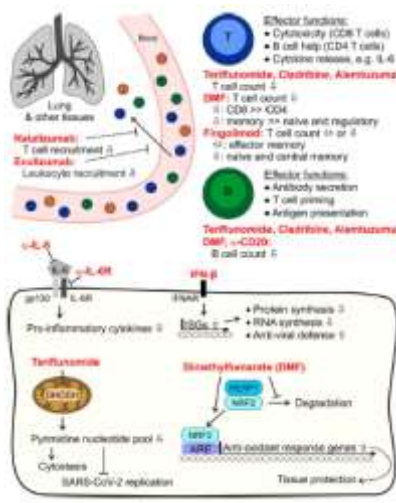

TABLE 1 Disease-modifying therapies and impact on COVID-19

Drug	Mode of action	Risk of viral infection	Impact on COVID-19 disease severity	Other considerations
Interferon	Lymphocyte activation/migration ↓	None	Potentially beneficial	
Glatiramer acetate	Th2→Th2 shift; Treg↑	None	Unlikely	
Siponimod	Lymphocyte egress ↓	Probably	Potentially beneficial/deleterious	Lymphocyte count
Teriflunomide	Lymphocyte proliferation ↓	None/low	Potentially beneficial	Lymphocyte count
Dimethylfumarate	Antioxidative response ↑, Th1→Th2 shift, macrophage activation ↓	Probably	Potentially beneficial	Lymphocyte count
Cladribine	Lymphocyte replication ↓	Probably	Potentially beneficial/deleterious	Lymphocyte count, effects lasting for years
Natalizumab	Blockade of α4-integrin	Unlikely	Unlikely	Potential severe neuroinvasion
Alemtuzumab	CD52+ depletion	Increased risk	Potentially deleterious	Effects lasting for years
Anti-CD20 mAb	CD20+ cell depletion	Probably	Potentially beneficial/deleterious	Effects lasting for months
Complement inhibition	Blockade of C5 cleavage	Uncertain	Potentially beneficial/deleterious	
Anti-IL-6 and Anti-IL-6R mAb	Inhibition of IL-6	Probably	Potentially beneficial	

Abbreviations: IL, interleukin; IL-6R, interleukin-6 receptor; mAb, monoclonal antibody; Siponimod, sphingosine-1-P; sphingosine-1-phosphate receptor modulator; TH, T helper cell.

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ORIGINAL ARTICLE

Multiple sclerosis and COVID-19: How many are at risk?

Gabriel Bsteh | Christina Bitschnau | Harald Hegen | Michael Auer | Franziska Di Pauli | Paulus Rommer | Florian Deisenhammer | Thomas Berger

TABLE 1 Modified COVID-19 mortality risk score [Colour table can be viewed at wileyonlinelibrary.com]

Factor	Score
Diabetes and age <40 years	5
Age ≥65 years	3
Chronic kidney disease	3
Severe physical disability (EDSS >6)	2
Chronic obstructive pulmonary disease	1
Cardiovascular disease	1
Current malignancy	1
Obesity (BMI ≥30)	1
Diabetes	1
Smoking	1
Age >40 years	−6
Risk category	Score interval
Low risk	≤0
Mild risk	1–3
Moderate risk	4–7
High risk	8–11
Very high risk	≥12

Note: Modified according to Belle-Chavolla et al [13].
Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale.
Color shades correspond to the level of risk.

Risk category	Patients at risk	Proportion under DMT	Proportion under immunosuppressive treatment
Low risk (score ≤0)	1224 (63.4)	863 (70.5)	69 (5.6)
Mild risk (score 1–3)	501 (26.0)	291 (58.1)	15 (2.9)
Moderate risk (score 4–7)	170 (8.8)	30 (17.7)	7 (4.1)
High risk (score 8–11)	13 (0.7)	1 (8.3)	0 (0)
Very high risk (score ≥12)	3 (0.2)	0 (0)	0 (0)

Note: Immunosuppressive treatment, alemtuzumab, cladribine, mitoxantrone, ocrelizumab or rituximab.
Abbreviation: DMT, disease-modifying therapy.
Color shades correspond to the level of risk.

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Austrian Registry on COVID 19 severity and mortality

Table 2. Characteristics of the AUT-MuSC-19 cohort.

	n = 126
Female[a]	90 (71.4)
Age (years)[b,c]	43.2 (13.4; 21–79)
BMI[c]	24.1 (17.4–41.0)
Smokers[a]	17 (3.5)
Ethnicity[a]	
Caucasian[a]	123 (97.6)
Other[a]	3 (2.4)
No of comorbidities associated with increased COVID-19 morbidity[c,*]	0 (0–5)
Disease duration (years)[b]	12.0 (9.3)
Disease course[a]	
RRMS[a]	98 (77.8)
SPMS[a]	19 (15.1)
PPMS[a]	9 (7.1)
EDSS[c]	2.0 (0–8.5)
On DMT[a]	90 (71.4)
IM-DMT	48 (38.1)
Interferon-beta[a]	6 (4.8)
Glatiramer acetate[a]	11 (8.7)
Dimethyl fumarate[a]	19 (15.1)
Teriflunomide[a]	2 (1.6)
Natalizumab[a]	10 (7.9)
IS-DMT	41 (32.5)
Fingolimod[a]	16 (12.7)
Ocrelizumab/Rituximab[a]	12 (9.5)
Alemtuzumab[a]	2 (1.6)
Cladribine	2 (1.6)
Azathioprin[a]	1 (0.8)
Lymphopenia at last lab before SARS-CoV2 infection[a,*]	19 (18.4)
Grade 3 or lower[a]	7 (6.8)

BMI: body mass index. DMT: disease modifying treatment. EDSS: Expanded Disability Status Scale. IM-DMT: Immunomodulating DMT = dimethyl fumarate, glatiramer acetate, interferon beta preparations, natalizumab, and teriflunomide. IS-DMT: Immunosuppressive DMT = alemtuzumab, cladribine, fingolimod, ocrelizumab or [illegible] MS. RRMS: relapsing-remitting MS. SPMS: secondary

PLOS ONE | https://doi.org/10.1371/journal.pone.0250316 July 27, 2021

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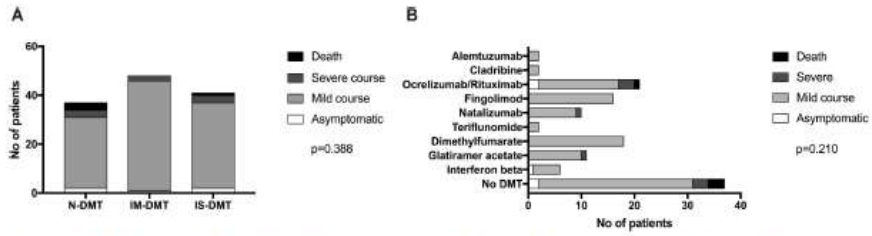

Fig 1. COVID-19 outcome according to DMT classes (A) and single substances (B). DMT: disease modifying treatment. IM-DMT: Immunomodulating DMT = dimethyl fumarate, glatiramer acetate, interferon beta preparations, natalizumab, and teriflunomide. IS-DMT: Immunosuppressive DMT = alemtuzumab, cladribine, fingolimod, ocrelizumab or rituximab. p-values calculated by chi-square test. N-DMT: no DMT.

Table 3. COVID-19 severity and mortality according to a-priori risk and DMT class.

Risk category		At risk	Severe COVID-19	p-value	Fatal COVID-19	p-value
Low risk (Score ≤0) N = 75	N-DMT	17	0	0.455[1]	0 (0)	NA
	IM-DMT	31	1		0 (0)	
	IS-DMT	27	2		0 (0)	
Mild risk (Score 1–3) N = 39	N-DMT	11	0	0.315[1]	0 (0)	NA
	IM-DMT	16	0		0 (0)	
	IS-DMT	12	1		0 (0)	
Moderate/high risk (Score ≥4) N = 12	N-DMT	9	6	0.687[1]	3	0.677[1]
	IM-DMT	1	1		0	
	IS-DMT	2	1		1	

DMT: disease modifying treatment. IM-DMT: Immunomodulating DMT = dimethyl fumarate, glatiramer acetate, interferon beta preparations, natalizumab, and teriflunomide. IS-DMT: Immunosuppressive DMT = alemtuzumab, cladribine, fingolimod, ocrelizumab or rituximab.
[1]calculated by chi-square test. N-DMT: no DMT.

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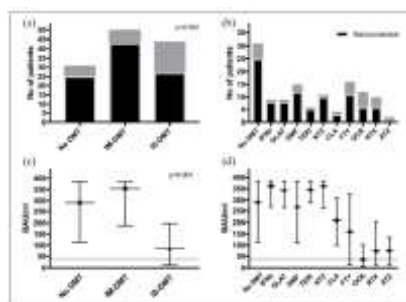
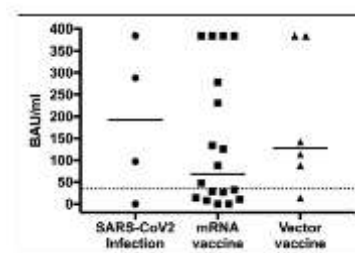
Treatment and SARS-CoV2 Antibodies





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Vaccination in Multiple Sclerosis: Friend or Foe?

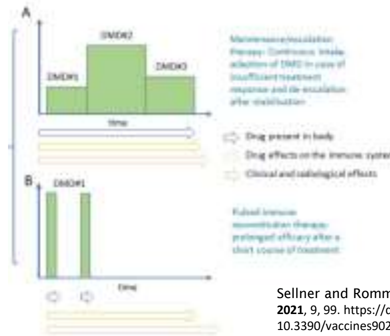
Tobias Zrzavy[1], Herwig Kollaritsch[2], Paulus S. Rommer[1,3], Nina Boxberger[4], Micha Loebermann[4], Isabella Wimmer[1], Alexander Winkelmann[5] and Uwe K. Zettl[5]*

published: 07 August 2019
doi: 10.3389/fimmu.2019.01883

Vaccination and multiple sclerosis in the era of the COVID-19 pandemic

Tobias Monschein,[1] Hans-Peter Hartung,[1,2] Tobias Zrzavy,[1] Michael Barnett,[3] Nina Boxberger,[4] Thomas Berger,[1] Jeremy Chataway,[5] Amit Bar-Or,[6] Paulus Stefan Rommer,[1,4] Uwe K. Zettl[4]

J Neurol Neurosurg Psychiatry 2021;92:1033–1043. doi:10.1136/jnnp-2021-326839



Sellner and Rommer, Vaccines **2021**, 9, 99. https://doi.org/10.3390/vaccines9020099

DMT	Live vaccines	Non-live vaccine	Gene-based vaccine mRNA	Gene-based vaccine Vector	Timing of vaccine after DMT is stopped*	Timing of vaccine after DMT†	Timing of DMT after vaccine‡	Immune response§
HDMP	Contraindicated	Yes	Yes	Yes¶	≥1 month	Therapy stopped**	≥2–4 weeks‡	May be reduced
Interferon	Strict indication	Yes	Yes	Yes¶	Anytime	Anytime	≥2–4 weeks‡	Similar
Glatiramer acetate	Strict indication	Yes	Yes	Yes¶	Anytime	Anytime	≥2–4 weeks‡	Similar
Dimethyl fumarate	Strict indication	Yes	Yes	Yes¶	Not specified	Anytime	≥2–4 weeks‡	Similar
Teriflunomide	Contraindicated	Yes	Yes	Yes¶	≥6 months††	Anytime	≥2–4 weeks‡	Slightly reduced
S1P modulators‡‡	Contraindicated	Yes	Yes	Yes¶	≥2 months	Anytime	≥2–4 weeks‡	Reduced
Natalizumab	Contraindicated	Yes	Yes	Yes¶	≥3 months	Anytime	≥2–4 weeks‡	Similar
B cell-depleting agents§§	Contraindicated	Yes	Yes	Yes¶	Specified¶¶	≥3–6 months***	≥2–4 weeks‡	Reduced
Alemtuzumab	Contraindicated	Yes	Yes	Yes¶	Not specified178,≤201	≥3–6 months***	≥2–4 weeks‡	Reduced
Cladribine	Contraindicated	Yes	Yes	Yes¶	Specified†††	Specified‡‡‡	≥2–4 weeks‡	Similar
Mitoxantrone	Contraindicated	Yes	Yes	Yes¶	≥3 months	Not specified	≥2–4 weeks‡	May be reduced

*Recommended timing of vaccination for live/attenuated vaccines after stopping DMT, with timing meant to avoid the risk of infection from the vaccine itself in immunocompromised individuals.

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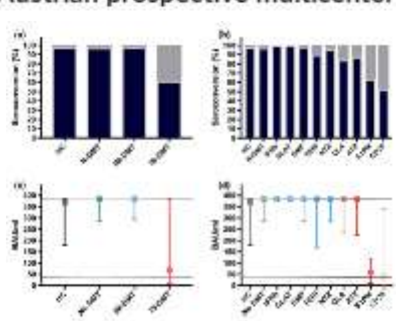
Received: 6 December 2021 | Accepted: 20 January 2022
DOI: 10.1111/ene.15265

european journal of neurology

SHORT COMMUNICATION

Comparing humoral immune response to SARS-CoV2 vaccines in people with multiple sclerosis and healthy controls: An Austrian prospective multicenter cohort study



	Seropositivity		
Wald-test	OR	95% CI	p-value
Age (per 5 years)	0.99	0.96–1.02	0.271
DMT			
N-DMT	0.90	0.15–5.5	0.908
M-DMT	0.83	0.18–3.8	0.812
S-DMT	0.04	0.01–0.13	<0.001
Lymphocyte count (per 0.1 G/L)	1.14	0.90–1.59	0.234
	R squared 0.573; p < 0.001		
Subgroup analyses			
S1PM subgroup			
S1PMs	0.05	0.01–0.33	<0.001
Lymphocyte count (per 0.1 G/L)	1.31	1.00–1.77	0.035
CD20 mAb subgroup			
CD20 mAbs	0.03	0.01–0.14	<0.001
Complete B-cell depletion	0.52	0.34–0.93	0.036
Time since last DMT intake (per month)	1.34	0.56–4.10	0.729
Subgroup ATZ/CLA			
ATZ/CLA	0.10	0.03–0.39	0.049
Lymphocyte count (per 0.1 G/L)	1.24	0.72–2.02	0.600
Time since last DMT intake (per month)	1.30	1.06–1.98	0.026

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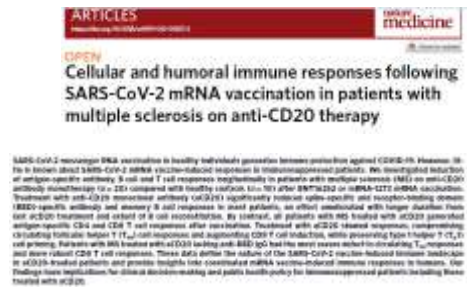
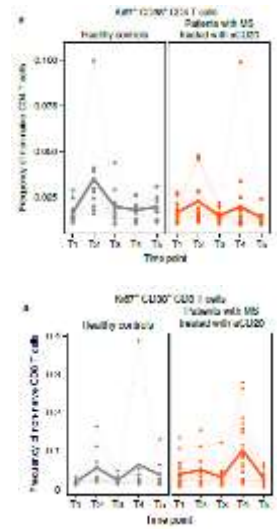
How's about CD20?


ARTICLES

nature medicine

OPEN

Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy



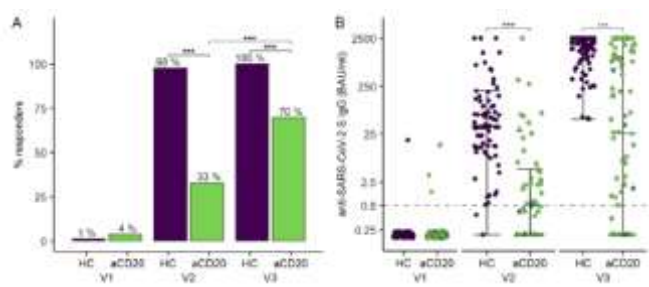
- 20 MS patients on CD20 and 10 healthy controls (5 Timepoints)
- ALL patients antigen-specific CD4 and CD8 responses (no major differences)
- Lacking RBD-IgG in most compromised T_{FH} responses and most robust CD8 T cells

How's about CD20?

ANN NEUROL 2022;91:342–352

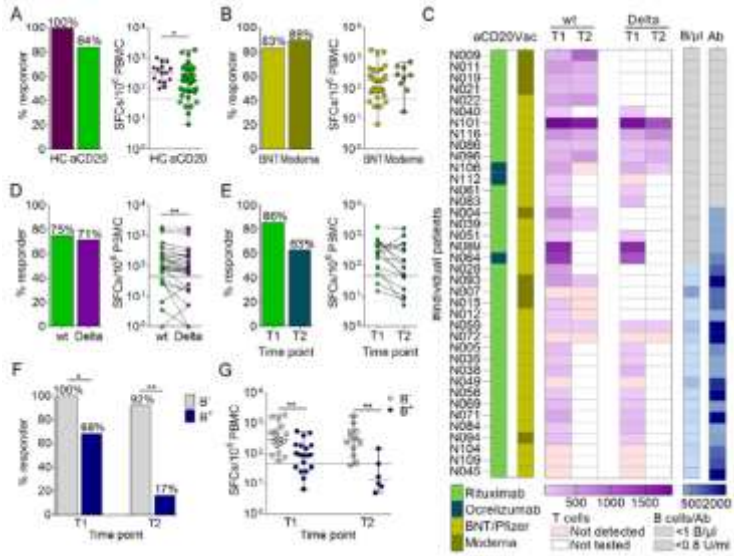
B Cell Depletion and SARS-CoV-2 Vaccine Responses in Neuroimmunologic Patients

Barbara Kornek, MD,[1] Fritz Leutmezer, MD,[1] Paulus S. Rommer, MD,[1]



ANN NEUROL 2022;91:342–352

How‘s about CD20?



A) T cells response
B) Vaccine types
C) B cells
D) Wt/Delta strain
E) Timepoint
F) B cells

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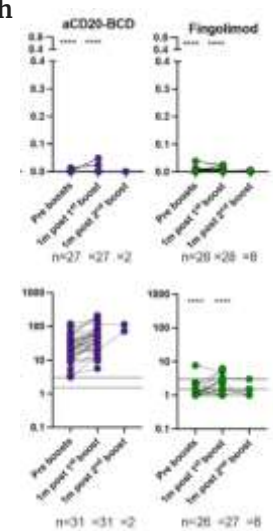
… and in S1P?

SARS-CoV-2 mRNA vaccinations fail to elicit humoral and cellular immune responses in patients with multiple sclerosis receiving fingolimod

J Neurol Neurosurg Psychiatry. 2022 Sep;93(9):960-971.

- humoral immune response reduced in CD20 and S1P
- cellular response (CD4) in CD20
- Booster: no effects in S1P



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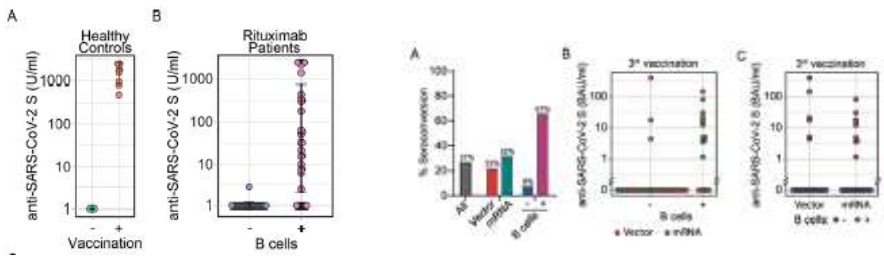
… and from rheumatology …

CD20 two vaccinations Third vaccination



Mrak D, *et al. Ann Rheum Dis* 2021;**80**:1345–1350. doi:10.1136/annrheumdis-2021-220781 Boyarsky M, *et al. Ann Rheum Dis* 2022;**81**:687–694. doi:10.1136/annrheumdis-2021-221558

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… and from rheumatology …

Key messages

What is already known about this subject?
- B cell-depleting therapy with rituximab (RTX) can lead to severe or prolonged disease courses after SARS-CoV-2 infection.
- B cell-depleting therapy with RTX affects humoral immune responses after vaccination. It is still unclear whether patients without measurable peripheral B cells after RTX treatment can develop antibodies against SARS-CoV-2 after vaccination and whether T cell-mediated immune response is affected.

What does this study add?
- This study describes that patients who received RTX treatment and have no measurable peripheral B cells do not develop antibodies after SARS-CoV-2 vaccination. Patients with repopulated B cells can mount antibody responses after COVID-19 vaccination.
- T cell-mediated immune response after COVID-19 vaccination was detected in the majority of patients after RTX treatment irrespective of the presence or absence of B cells and a humoral immune response.

How might this impact on clinical practice or future developments?
- RTX treatment should not preclude COVID-19 vaccination, since a robust T cell response can be mounted even in the absence of circulating B cells.
- Delaying RTX treatment may be justified in patients with stable disease until peripheral B cells repopulate to allow development of a humoral response to vaccination.

Key messages

What is already known about this subject?
- A third COVID-19 vaccination has been recommended by the US Food and Drug Administration for certain immunocompromised individuals.
- First clinical trial data have now reported on efficacy of a third vaccination in patients under immunosuppressive therapy.
- No clinical trial data exist which compare efficacy and safety of a heterologous versus homologous vaccination strategy in non-seroconverted patients under rituximab therapy.

What does this study add?
- The results from our study support efficacy and safety of an additional heterologous or homologous booster vaccination in immunosuppressed patients.
- Cellular and humoral immune response can be induced in B cell depleted patients undergoing rituximab treatment.

How might this impact on clinical practice or future developments?
- Based on these data, COVID-19 booster vaccination is recommended for non-seroconverted rituximab-treated patients.

Mrak D, *et al. Ann Rheum Dis* 2021;**80**:1345–1350. doi:10.1136/annrheumdis-2021-220781 Boyarsky M, *et al. Ann Rheum Dis* 2022;**81**:687–694. doi:10.1136/annrheumdis-2021-221558

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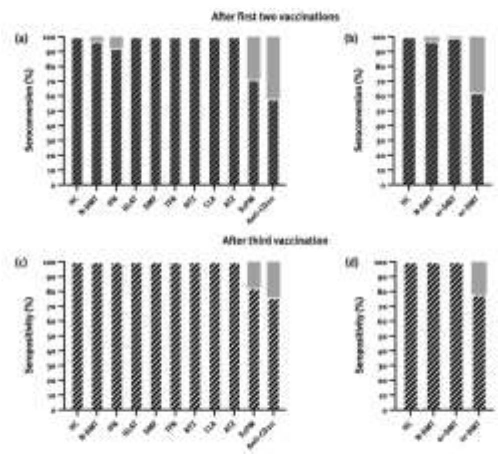
And in MS …

Humoral immune response to SARS-CoV-2 third vaccination in patients with multiple sclerosis and healthy controls: A prospective multicenter study



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Received: 1 April 2022 | Accepted: 30 June 2022
DOI: 10.1111/ene.15488

european journal of neurology

ORIGINAL ARTICLE

Impact of vaccination on COVID-19 outcome in multiple sclerosis

Abstract

Background and purpose: COVID-19 continues to challenge neurologists in counseling persons with multiple sclerosis (pwMS) regarding disease-modifying treatment (DMT) and vaccination. The objective here was to characterize predictors of COVID-19 outcome in pwMS.

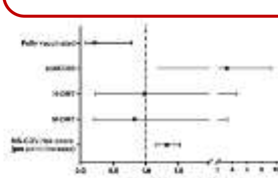
Methods: We included pwMS with polymerase chain reaction-confirmed COVID-19 diagnosis from a nationwide population-based registry. COVID-19 outcome was classified as either mild or severe. Impact of DMT, specifically anti-CD20 monoclonal antibodies (anti-CD20), and vaccination on COVID-19 outcome was determined by multivariate models adjusted for a priori risk (determined by a cumulative risk score comprising age, disability, and comorbidities).

Results: Of 317 pwMS with COVID-19 (mean age = 41.8 years [SD = 12.4], 71.9% female, median Expanded Disability Status Scale = 1.5 [range = 0–8.5], 77% on DMT [16% on anti-CD20]), 92.7% had a mild course and 7.3% a severe course, with 2.2% dying from COVID-19. Ninety-seven pwMS (30.6%) were fully vaccinated. After a median 3 months from vaccination to SARS-CoV-2 infection (range = 1–9), severe COVID-19 occurred in 2.1% of fully vaccinated pwMS compared to 9.5% in unvaccinated pwMS ($p = 0.018$). A priori risk robustly predicted COVID-19 severity ($R^2 = 0.605$, $p < 0.001$). Adjusting for a priori risk, anti-CD20 treatment was associated with increased COVID-19 severity (odds ratio [OR] = 3.3, $R^2 = 0.113$, $p = 0.003$), but exposure to any other DMT was not. Fully vaccinated pwMS showed a significantly decreased risk for severe COVID-19 (OR = 0.21, $R^2 = 0.144$, $p < 0.001$).

Conclusions: In a population-based MS cohort, COVID-19 course is primarily predicted by a priori risk (depending on age, disability, and comorbidities) explaining about 60% of variance. Anti-CD20 treatment is associated with a moderately increased risk, whereas reassuringly vaccination provides protection from severe COVID-19.

TABLE 2 Multivariate regression model of risk for severe COVID-19

	OR	95% CI	p	Change in R^2
MS-COV-risk score, per point increase	1.32	1.16–1.50	<0.001	0.605
DMT				
No DMT	Reference			0.113
M-DMT	0.82	0.20–3.33	0.782	
H-DMT	0.97	0.21–4.65	0.969	
Anti-CD20	3.29	1.17–9.34	0.003	
Fully vaccinated	0.21	0.07–0.78	<0.001	0.144



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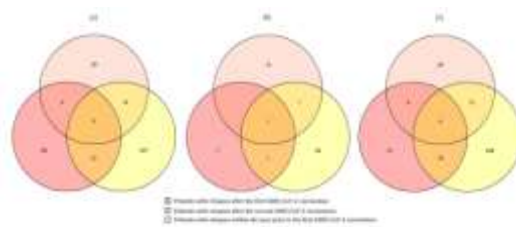
SARS-CoV-2 vaccination in patients with multiple sclerosis in Germany and the United Kingdom: Gender-specific results from a longitudinal observational study

The Lancet Regional Health - Europe
2022;22: 100502
Published online xxx

- Vaccination reactions in Germany and UK
- x^1 and (x^2)
  Germany: 2,346 (1,835)
  UK: 3,796 (683)
  Germany: Tozinameran (Biontech): 77%
  UK: AZD1222 (AstraZeneca): 61%
- Fatigue, headache and pain (females>males)
- Germany: 61% and 63%, UK 49% and 30%
- MS deterioration in 19% (Germany)
  patient reported relapses in 141 patients (x^1 = 3.6%, x^2 = 3.3%)
  year before: 14.8%



Has the pandemic changed treatment strategy in multiple sclerosis?

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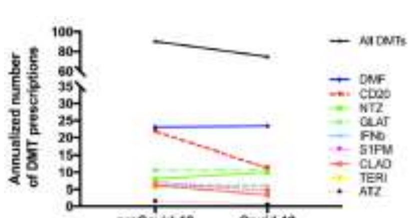

A B S T R A C T

Background: Social distancing measures during the Covid-19 pandemic reduced access to health care and concerns were raised over the safety of immunosuppressive disease modifying treatments (DMT) for multiple sclerosis (MS).
Objective: To investigate changes in DMT prescription before and during the pandemic in a large and well-characterized real-world cohort of MS patients.
Methods: From the Vienna MS database (VMSD) we extracted MS patients who were initiated on a new DMT (both treatment-naïve and switching) between January 1st 2017 and December 31st 2021. Two time periods were defined: 1) the preCovid-19 era (January 1st 2017 to March 15th 2020, i.e. the day of the first lockdown in Austria) and the Covid-19 era (March 16th 2020 to December 31st 2021). Average annualized DMT prescription rates were descriptively compared between the two periods.
Results: The average annualized number of prescriptions in the preCovid-19 era was 90.3/year and dropped to 74.8/year (-17.2%) in the Covid-19 era, driven by a marked reduction to 41.7/year (-54%) in the first nine months of the Covid-19 era, partly offset by a rise to 101 in 2021. Use of alemtuzumab (-64%), antiCD20 (-49%), cladribine (-40%), and S1PM (-30%) was reduced, while natalizumab increased by 24%. Lower efficacy treatments remained stable.
Conclusions: The pandemic coincides with a drop in DMT prescription, most markedly for immunosuppressive high-efficacy treatments, strongly suggesting the pandemic as the causal factor. If and how much this affects long-term outcome is yet to be determined.

Conclusion

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Conclusion

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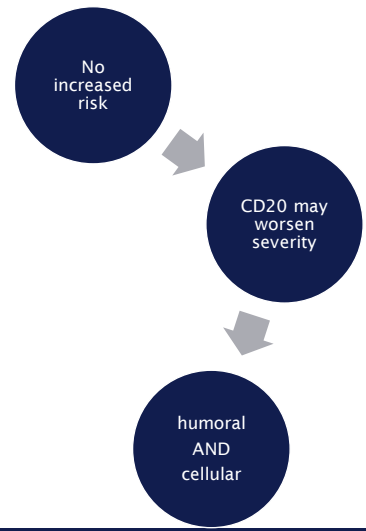
Conclusion



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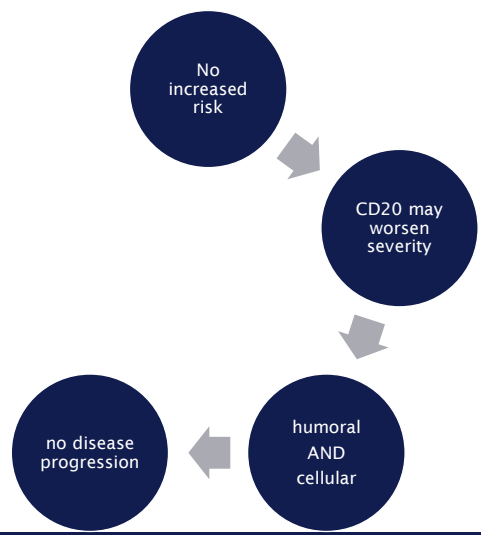
Conclusion



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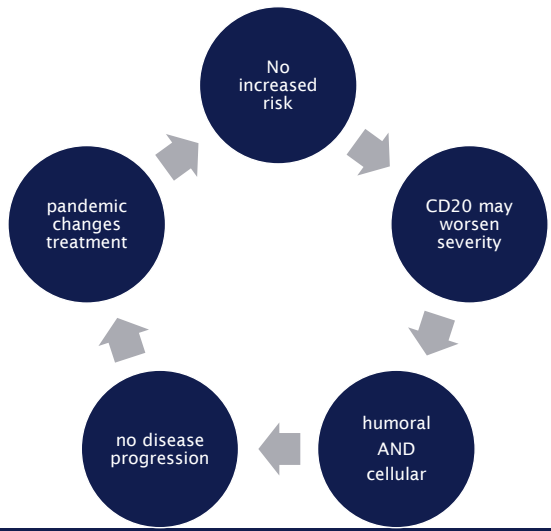
Conclusion



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Gerhard S. https://upload.wikimedia.org/wikipedia/commons/f/f8/Zicklacke.JPG

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Vaccination – Safety in MS