treated with disease-modifying therapies (DMTs) need further elucidation.
Aim: To investigate COVID-19 BNT162b2 vaccine effect concerning antibody seroconversion, T cells-associated cytokines production and immunophenotype assessment in pwMS under three different DMTs: cladribine, fingolimod, ocrelizumab.
Methods: Enzyme immunoassay test was used for anti-spike IgG detection in 98 DMTs-treated pwMS completing first vaccination cycle. In a subset of patients (n=47), serum T cells-associated cytokines (GrB, IFN-γ and TNF-α) were quantified using an automatic ELISA (ELLA) and blood immunophenotype was assessed by flow cytometry. ANCOVA followed by post hoc tukey's test was used to compare anti-spike IgG response in the different DMTs, Student's paired t-test was used to evaluate differences between pre- and post-vaccination in pairwise samples and Pearson's correlation was applied to evaluate association between spike-specific IgG antibody titer and lymphocytes count.
Results: More pwMS treated with ocrelizumab (63%) lacked anti-spike IgG compared to patients treated with cladribine (14%) and fingolimod (20%) ($p<0.001$). When present, the anti-spike IgG titer in the ocrelizumab group was lower than in cladribine- ($p<0.001$) and in fingolimod-treated pwMS ($p=0.003$). No significant differences in lymphocytes count and T-cell associated cytokines were observed in cladribine- and in fingolimod-treated pwMS, while in pwMS on ocrelizumab a significant increase in GrB serum levels ($p=0.021$) and a trend of increased $CD4^+$ T cells count were observed after vaccination. Specifically considering non-seroconverted ocrelizumab-treated pwMS, a significant increase of GrB serum levels ($p=0.008$) and of $CD4^+$ T lymphocytes count ($p=0.040$) was foundafter vaccination and a negative correlation was observed between anti-spike IgG production and $CD4^+$T cells count (rho=-0.452, $p=0.014$).
Conclusion: Our data confirmed differences in spike-specific antibodies among different DMTs and provided evidence of T-cell immunity preservation and activations after BNT162b2 vaccination in ocrelizumab-treated pwMS, specifically in pwMS patients lacking anti-spike IgG, suggesting a protective T-cell response that might explain why the ongoing treatment with ocrelizumab is not associated with a higher risk of COVID-19 infection.

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Efficacy and persistence between dimethyl fumarate, fingolimod, and ocrelizumab after natalizumab cessation

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Introduction: Natalizumab therapy is often discontinued to mitigate the risk of progressive multifocal leukoencephalopathy. The optimal DMT following natalizumab cessation has yet to be determined.

Objectives: To compare the effectiveness and treatment persistence of three DMTs (ocrelizumab, fingolimod, and dimethyl fumarate [DMF)] after natalizumab cessation among patients with relapsing-remitting multiple sclerosis (RRMS).
Methods: Using data from MSBase registry, we included 1,386 subjects who had used natalizumab for ⩾6 months and switched to ocrelizumab, fingolimod, or DMF <3 months after natalizumab discontinuation. The primary outcomes were annualized relapse rate (ARR) and time to the first relapse. Secondary outcomes were confirmed disability progression, confirmed disability improvement, and treatment discontinuation. Disability outcomes were limited to comparison between fingolimod and ocrelizumab due to limited DMF numbers. We used negative binomial models to compare ARRs and Cox proportional-hazards models for other outcomes. We used inverse probability weighting based on propensity scores to balance informative covariates. Individual propensity scores were calculated using multinomial logistic regression.
Results: 425 patients switched from natalizumab to ocrelizumab, 823 to fingolimod, and 138 to DMF. The ARR for ocrelizumab was 0.06, fingolimod, 0.26, and DMF, 0.27.ARR ratio (95% confidence interval [CI]) of fingolimod/ocrelizumab was 4.33 (3.12-6.01) and of DMF/ocrelizumab 4.50 (2.89-7.03). Compared to ocrelizumab, the hazard ratio (HR) of time to first relapse was 4.02 (2.83-5.70) for fingolimod, 3.70 (2.35-5.84) for DMF; the HR for discontinuation was 2.57 (1.74-3.80) for fingolimod and 4.26 (2.65-6.84) for DMF. Fingolimod was associated with a 49% higher risk of confirmed disability progression than ocrelizumab. There was no difference in disability improvement rates between fingolimod and ocrelizumab.
Conclusion: Among the three DMTs that the RRMS patients switched from natalizumab to, ocrelizumab use was associated with the lowest ARR and discontinuation rates, and the longest time to first relapse.

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Long-term safety of teriflunomide in multiple sclerosis patients: results of prospective comparative studies in three European countries

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Background: Teriflunomide (TF) is a disease modifying therapy (DMT) indicated for the treatment of remitting-relapsing forms of multiple sclerosis (MS). This post authorisation safety study assessed risks of adverse events of special interest (AESI) associated with TF use.
Methods: The study was based on secondary use of individual data of patients from the Danish MS Registry (DMSR), the French National Health Data System (SNDS), the Belgian national database of health care claims (AIM-IMA) and the Belgian Treatments in MS Registry (BELTRIMS). Study cohorts included treatment-naive patients who started a DMT or switched to another DMT after the date of TF reimbursement. In each data source, hazard rates (HR) and (95% confidence intervals) of AESI were computed by comparing AESI occurrence in patients treated with TF to AESI occurrence in patients treated with a platform DMT other than TF. For non-cancerous AESI, HR were derived from Cox models with time-dependent exposure. For cancerous AESI, HR were derived from Cox model with ever/never exposure. HR were adjusted for gender, age, new or prevalent user status, major comorbidities, and (when available), the expanded disability status scale (EDSS).
Results: 81,620 patients (72% women) were included in the study, of whom 22,324 (27%) were treated with TF. After a median treatment duration with TF of 3.5 years, TF use compared to other platform DMT was not associated with a risk of all-cause mortality, severe infection, pneumoniae, herpes zoster reactivation, pancreatitis, peripheral neuropathy, cardiovascular condition, and cancerous conditions. Results were mostly consistent across data sources. No case of progressive multifocal leukoencephalopathy was identified among TF users. For opportunistic infections, HR for TF vs other platform DMT was 2.4 (1.2-4.8) in the SNDS, which was not bound to a particular type of opportunistic agent. For renal failure, HR was 2.0 (1.1-3.7) in the SNDS, but was not increased in other data sources. Among 187 French patients with history of renal failure and treated with TF prior to cohort entry, none had a renal failure after TF start. Because of few cases, results on interstitial lung disease, psoriasis and peripheral neuropathy were not informative.
Interpretation: This large study conducted in nationwide registers found no evidence that TF use would be associated with an increased risk of AESI. The conflicting results on renal failure are considered inconclusive.

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Safety of shorter ocrelizumab infusion confirmed over multiple administrations: results of the ENSEMBLE PLUS substudy

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