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Matching-adjusted indirect comparisons of diroximel fumarate, ponesimod, and teriflunomide for relapsing multiple sclerosis

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Introduction: Diroximel fumarate (DRF), ponesimod (PON), and teriflunomide (TERI) are oral disease-modifying therapies (DMTs) approved for treatment of relapsing multiple sclerosis. No randomized trials have directly compared DRF vs. PON or TERI.
Objectives: Using matching-adjusted indirect comparisons, we compared efficacy of DRF vs. PON and DRF vs. TERI for annualized relapse rate (ARR), 12-week confirmed disability progression (CDP), 24-week CDP, absence of gadolinium-enhancing (Gd+) T1 lesions, and absence of new/enlarging T2 lesions.
Methods: We used individual patient data from EVOLVE-MS-1, a 2-year, open-label, single-arm, phase 3 trial of DRF (n=1,057), and aggregated data from OPTIMUM, a 2-year, double-blind, phase 3 trial comparing the efficacy of PON (n=567) and TERI (n=566). To account for cross-trial differences, data from EVOLVE-MS-1 were weighted to match average baseline characteristics in OPTIMUM. Results are reported with PON or TERI as the reference (negative rate/risk differences for ARR and CDP indicate favourable outcomes for DRF; positive risk differences for absence of Gd+ T1 lesions and absence of new/enlarging T2 lesions favour DRF).
Results: After weighting, all groups were balanced on baseline variables. DRF and PON had similar efficacy for ARR (rate difference for DRF vs. PON: -0.02; 95% confidence interval [CI]: -0.08, 0.04), 12-week CDP (risk difference: -2.4%; 95% CI: -6.3%, 1.3%), and 24-week CDP (risk difference: -1.7%; 95% CI: -5.1%, 1.7%). DRF had higher proportions of patients without Gd+ T1 lesions (risk difference: 11%; 95% CI: 5.9%, 16%) and new/enlarging T2 lesions (risk difference: 35%; 95% CI: 28%, 41%) compared with PON. In the comparison of DRF and TERI, the rate difference for ARR (DRF vs. TERI) was -0.08 (95% CI: -0.15, -0.01), risk difference for 12-week CDP was -4.0% (95% CI: -8.0%, -0.11%), risk difference for 24-week CDP was -3.2% (95% CI: -6.7%, 0.13%), risk difference for the absence of Gd+ T1 lesions was 25% (95% CI: 19%, 30%), and risk difference for the absence of new/enlarging T2 lesions was 45% (95% CI: 39%, 52%).
Conclusions: DRF and PON had similar efficacy for ARR and 12- and 24-week CDP. However, DRF was associated with a higher proportion of subjects who did not have Gd+ T1 lesions and new/enlarging T2 lesions at the end of follow-up. DRF had greater efficacy than TERI for all clinical and radiological outcomes, except for 24-week CDP, in which there was similar efficacy.

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Disclosure
TJ, CS, KS, JBL, and IB are all employees of and hold stock/stock options in Biogen.

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Effect of SARS-CoV-2 vaccination on natural killer cell responses in multiple sclerosis

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Introduction: Anti-SARS-CoV2 vaccination induces specific T- and B-cell responses in healthy subjects (HS). In MS patients treated with anti-CD20 drugs, the antibody response is reduced or absent, whereas specific T-cell responses are maintained. It is not known whether and how vaccination affects innate responses mediated by natural killer (NK) cells in HS and in MS patients treated with anti-CD20 drugs.
Objective: To evaluate whether and how NK cells contribute to the immune response following anti-SARS-CoV2 vaccination in HS and in ocrelizumab-treated MS patients
Aims: The aims of this work were: 1) to evaluate the effects of anti-SARS CoV2 vaccination on the phenotype of NK cells from HS and from ocrelizumab-treated MS patients and 2) to evaluate how peptides from the SARS-CoV2 spike protein affect NK cell responses before and after anti-SARS-CoV2 vaccination.
Methods: We enrolled 21 MS patients treated with ocrelizumab and 20 HS. Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood and stored under liquid nitrogen. Thawed PBMCs were cultured overnight in presence/absence of SARS-CoV2 peptides or peptides from the cytomegalovirus (CMV), with/without activating cytokines. Phenotype of NK cells through a 13-marker flow cytometry panel and intracellular production of IFN-γ were evaluated after culture.
Results: Findings: 1) Vaccination increased the proportion of $CD56^{dim}$ NK cells in HS and MS patients. $CD56^{pos}CD16^{neg}$ NK cells, more abundant in MS patients before vaccination, decreased thereafter. Lower pre-vaccination activation capability of NK cells from MS patients compared to HS in response to stimulus with cytokines was reverted by vaccination. 2) Before vaccination, peptides from the SARS-CoV2 protein downregulated the production of IFN- γ from NK cells of HS, but not ocrelizumab-treated MS patients, who had significantly lower baseline IFN-γ NK cells 3) After vaccination, peptides from the SARS-CoV2 protein did not affect the production of IFN- γ from NK cells of HS.
Conclusions: The results of this work demonstrate anti-SARS-CoV2 vaccination increases the proportion of effector $CD56^{dim}$

NK cells in HS and ocrelizumab-treated patients. Spike peptides inhibit the function of NK cells from HS before, but not after vaccination. Such phenomenon may contribute to the pathogenicity of SARS-CoV2 in unvaccinated subjects.

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P710
Mesenchymal stem cells for multiple sclerosis: effect of treatment on peripheral immune cells

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Introduction: Autologous, bone marrow-derived mesenchymal stem/stromal cells (MSC) have shown promising results in the treatment of the animal model of multiple sclerosis (MS) due to their immunomodulatory and neuroprotective features. Based on these data, an international, multicenter, randomized, double blind, cross-over, phase I/II, clinical trial, Mesenchymal Stem Cells for Multiple Sclerosis (MESEMS), was conducted.
Objectives: To evaluate the effect of treatment with autologous MSC on peripheral immune cells in MS.
Aims: To assess the changes in phenotype of peripheral immune cells in patients treated with MSC compared to placebo and to correlate such changes to MRI and clinical activity.
Methods: 38 patients with MS from three centers participating to the MESEMS clinical trial were enrolled. From blood samples drawn throughout the study, peripheral mononuclear blood cells were isolated at each center and frozen; cells were shipped to the coordinating center for flow cytometric staining and analysis. T-, B- and NK immune cell subsets were evaluated with a standardized flow cytometry panel. Anova for repeated measures was employed to evaluate differences in the immune cell trend in the first 24 weeks of treatment and paired t-test was employed to evaluate the change in immune cell subsets in the first 4 weeks after treatment with MSC towards placebo.
Results: 27/38 patients had immunological evaluations at all time points and were included in the present analysis. Treatment with MSC led to significant changes in the phenotype of circulating immune cells at 4 weeks: in detail, treatment with MSC led to increased frequency of transitional B cells (i.e. B regulatory cells), and CD4+ T regulatory cells; moreover, patients treated with MSC had higher CD4+T regulatory effector/naïve ratio. We did not find significant changes in the trend of T-B- and NK cell subsets throughout the first 24 weeks. Increase in CD4+ Tregs in the first 4-treatments weeks was observed in patients with no relapses in the following 20 weeks, compared to decrease of CD4+ Tregs in patients with relapses. Decrease of naïve CD4+ Tregs in the first 4 weeks of treatment was associated with higher MRI activity in the following weeks.
Conclusions: Treatment with MSC led to increased proportion of regulatory subsets among T and B lymphocytes. Clinical/MRI response to MSC treatment was associated to short-term increase in CD4+T regulatory cells.

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