Ocrevus and Lymphopenia

This article responds to your request for information on Ocrevus® (ocrelizumab) and lymphopenia.This response was developed according to the principles of evidence-based medicine and summarizes data from the pivotal phase III trials of Ocrevus in multiple sclerosis.

In brief

- In the Ocrevus phase III trials in multiple sclerosis, an initial decrease in mean and median lymphocyte counts was observed in Ocrevus-treated patients, which remained stable thereafter. This was likely driven by the therapeutic effect of B cell depletion.
- The majority of cases of decreased lymphocyte counts were Grade 1 and 2 (mild lymphopenia).
- No association was observed between low lymphocyte levels and rates of serious infections.

Abbreviations

ALC=absolute lymphocyte count	MS=multiple sclerosis
CTCAE=common terminology criteria for adverse events	NK=natural killer
DMT=disease modifying therapy	PPMS=primary progressive multiple sclerosis
LLN=lower level of normal	RMS=relapsing multiple sclerosis

Definition and classification of lymphopenia

Lymphopenia is defined by abnormally low levels of lymphocytes in the blood. According to the CTCAE version 5.0, lymphopenia may be classified by the ALC per cubic millimetre (mm^3) of blood as follows:[1]

- Grade 1 (mild lymphopenia) — ALC<LLN to 800/mm^3
- Grade 2 (moderate lymphopenia) — ALC<800–500/mm^3
- Grade 3 (severe lymphopenia) — ALC<500–200/mm^3
- Grade 4 — ALC<200/mm^3

In the clinical trials of Ocrevus in MS, marked or clinically relevant lymphopenia was defined as lymphocyte counts <700 cells/mm^3 or a change from baseline values of at least 30%. The LLN was defined as ALC<910mm^3.[2,3]

Circulating lymphocytes make up only approximately 2% of the body's total lymphocyte population and therefore provides only limited information on the overall immune status of a patient.[4]

The relationship between disease modifying therapies and lymphopenia

In the MS population, exposure to almost all DMTs, except for natalizumab, has been associated with lymphopenia to varying degrees. Lymphopenia that is unrelated to DMT exposure may also occur in patients with MS.[4] There is also significant intra- and inter-individual variation in lymphocyte counts and the 'normal' range needs to be redefined for each DMT after initiating treatment.

Occurrence of lymphopenia in Ocrevus clinical trials

OPERA I and II trials in relapsing multiple sclerosis

Most of the marked laboratory abnormalities were single occurrences and were not sustained or replicated.[2] Decreases in lymphocytes <LLN was observed in 20.7% of patients treated with Ocrevus compared with 32.6% of patients treated with interferon beta-1a. Peripheral blood T cell counts were comparable between treatment groups at baseline. There was no impact of treatment with Ocrevus on NK lymphocyte counts across the controlled treatment period.

ORATORIO trial in primary progressive multiple sclerosis

Similar to the RMS population, most of the marked laboratory abnormalities were single occurrences and were not sustained or replicated.[3] A decrease in lymphocytes <LLN was observed in 26.3% of Ocrevus-treated patients compared to 11.7% of placebo-treated patients. Peripheral T cell counts were comparable between groups at baseline. There was no apparent impact of Ocrevus treatment on NK lymphocyte counts during the controlled treatment period. Mean values remained generally similar to the placebo group.

Across both trials[2,3]

- the majority of cases of decreased lymphocyte counts were Grade 1 and 2
- approximately 1% of Ocrevus-treated patients had Grade 3 lymphopenia, and
- there were no reports of Grade 4 lymphopenia.

Association between lymphopenia and the risk of infection in Ocrevus clinical trials

In the phase 3 clinical trial programme and open-label extension population (n = 2,092, exposure up to 7 years), no association was observed between low lymphocyte levels and rates of serious infections.[5]

Table 1. Lymphocyte levels and rates of serious infections

Lymphocyte level	Serious infections Rate per 100 PY (95% CI)
ALC<LLN	3.17 (1.96–4.84)
ALC≥LLN	2.23 (1.95–2.53)

LLN=ALC<910mm^3

Ocrevus prescribing recommendations

Roche recommends that physicians check the patient's immune status before dosing. Severely immunocompromised patients (e.g., with lymphopenia, neutropenia, hypogammaglobulinemia) should not be treated with Ocrevus.[6] In addition, administration of Ocrevus must be delayed in patients with an active infection until the infection is resolved.

There is no recommended threshold for lymphocyte levels to inform whether to suspend treatment with Ocrevus. This is because lymphocyte levels are known to fluctuate due to multiple factors. As decreases in lymphocyte levels may increase the risk of infection, it is up to the treating clinician to decide whether to continue treatment, taking into consideration other factors that might increase the chance of infection.

References

1. Common Terminology criteria for adverse events (CTCAE) 5.0. . November 27, 2017. Available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf . Accessed on July 14, 2023.

2. Hauser S, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017;376:221-234. https://www.ncbi.nlm.nih.gov/pubmed/28002679

3. Montalban X, Hauser S, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med 2017;376:209-220. https://www.ncbi.nlm.nih.gov/pubmed/28002688

4. Schweitzer F, Laurent S, Fink G, et al. Effects of disease-modifying therapy on peripheral leukocytes in patients with multiple sclerosis. J Neurol 2021;268:2379-2389. https://www.ncbi.nlm.nih.gov/pubmed/32036423

5. Hauser S, Kappos L, Montalban X, et al. Safety of Ocrelizumab in Patients With Relapsing and Primary Progressive Multiple Sclerosis. Neurology 2021;97:e1546-e1559. https://www.ncbi.nlm.nih.gov/pubmed/34475123

6. Roche Internal Regulatory Report (Accessed on 8 August 2023).