Highlights from the 8th ECTRIMS Focused Workshop

"The Risk of Infections for MS Disease Modifying Treatments (DMTs)"

Progressive Multifocal Leukoencephalopathy (PML). Risk, Prevention, and Management

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PML is a demyelinating disease of the CNS caused by the JC virus (JCV) that affects patients with compromised immune systems. Almost one third of PML cases is represented by MS patients. Such a high percentage, which is equal to HIV patients, may be explained by the mechanism of action of Natalizumab, which drives the migration of virus-carrying cells from the bone marrow and the up-regulation of transcription factors supporting JC virus growth. Prevention and infectious risk assessment are crucial in MS patients: anti-JC antibody positivity and index, as well as duration of exposure to Natalizumab or prior exposure to immunosuppressive therapy are the main criteria to consider. Proper risk management relies on the monitoring of anti-JCV antibodies and the MRI surveillance of progressing lesions. The choice of the MS therapy has also a strong impact on PML risk: drugs others than Natalizumab with sufficient efficacy, tolerability and lower PML risk estimates might be an option. Alternatively, stretching out the dosing interval of Natalizumab appears as a further promising strategy. Without an effective JC therapy, immune reconstitution is required to deal with PML: steroid treatment may be helpful in case of severe symptoms; the controversial plasma exchange therapy allows the immune system to recover and act fast against the infection. Prevention, risk monitoring and early detection of the infection remain crucial to minimize CNS injury and help to improve disease outcomes.

Infection Associated with S1P Modulators

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Patients with MS are exposed to an infectious risk which is increased to different extents by MS treatments. S1P modulators currently used in MS therapy primarily target S1P1 to prevent the egress of lymphocytes from lymph nodes to the peripheral blood. The resulting lymphopenia mainly affects naïve T cells and central memory T cells, while the proportion of effective memory T cells remains unchanged or even increases. S1P modulators have been associated with specific infectious risks: respiratory tract infections and herpes virus infections are possible complications of Fingolimod, Siponimod, Ponesimod and Ozanimod treatment. Both Varicella Zoster (VZV) primary infection and reactivation have been detected in Fingolimod-treated patients who showed a reduced number of VZV-specific T cells in blood and signs of subclinical reactivation of the virus in the saliva. These data suggest that VZV-screening should be performed before starting the administration of S1P modulators. Siponimod-treated cases have developed cryptococcal and fungal infections, while Fingolimod treatment has been associated with cryptococcal infections, cutaneous leprosy and PML risk.

Infections Associated with CD52 Lymphodepleting Therapy

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CD52 is expressed on T and B lymphocytes which are thought to mediate MS inflammation and it is therefore a crucial target of lymphodepleting therapies. The altered balance of the immune system resulting from the repopulation of depleted cells drives the consequent reduced MS disease activity. Alemtuzumab is a humanized monoclonal antibody depleting circulating CD52+ T and B lymphocytes. Upon its administration, the full recovery of the B cell population requires from three to six months, while at least one year is necessary for T cells to reach a level equal to the lower limit of normal (LLN). Furthermore, Alemtuzumab leads to an increase in the percentage of CD4+ Treg subtype and does not affect innate immune cells. With regards to adverse events, alemtuzumab-treated patients show an increased incidence of mild-to-moderate infections compared with IFNb-treated patients. Most common infections affect the upper respiratory tract and a high incidence rate has also been observed for herpetic infections. Serious infections are uncommon, but they may be life-threatening. Long-term data show that the risk of infections does not increase over time or as a consequence of multiple Alemtuzumab treatment courses. Risk mitigation strategies adapted to the type of infection, such as vaccination, prophylaxis, screening or infection treatment, should be implemented before the initiation of Alemtuzumab therapy.

Infections Associated with Other Lymphodepleting Therapies: Cladribine, Dimethyl fumarate and Teriflunomide

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Cladribine, dimethyl fumarate and teriflunomide are three different DMTs currently used in MS therapy. Cladribine is a chlorinated deoxyadenosine whose activated form accumulates in lymphocytes and leads to cellular apoptosis. It has a strong impact on B lymphocytes with a 6-month recovery time and a less profound but persistent effect on CD4+ T cells. Cladribine-treated patients show an increased incidence of Herpes Zoster infection compared with placebo which correlates with severe lymphopenia. Similarly, prolonged periods of severe lymphopenia are associated with an increased occurrence of serious and opportunistic infections in patients treated with dimethyl fumarate, a drug which targets the anti-inflammatory and cytoprotective proteins of the intracellular Nrf2 pathway. Nine cases of PML have also been reported following dimethyl fumarate treatment, associated with prolonged lymphopenia, as well as eleven cases of other CNS opportunistic infections. In contrast to cladribine and dimethyl fumarate, teriflunomide, which interferes with the pyrimidine metabolism in blasting lymphocytes, has not been associated with increased occurrence of infections despite being an immunosuppressive drug. With regards to Covid- 19, neither cladribine- nor teriflunomide-treated patients showed an increased risk of hospitalization or admission to intensive care units (dimethyl fumarate was used as a reference), which has only been observed with anti-CD20 agents. However, the majority of the neurologists taking part in a recent ECTRIMS survey recommended the suspension, switch or delay of treatment to patients treated with cladribine.

Infections Using Anti-CD20 Therapies

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B cells are CD20+ cells and play key immunological functions, including cytokine and antibody production and T cell activation. Anti-CD20 drugs, such as Rituximab, exert a profound effect on the B cell repertoire by eliminating most B cells between the early stages of development up to the plasma cell stage. In haematological and rheumatic conditions, such therapies have been associated with increased rates of severe infection, reactivation of hepatitis B, opportunistic infections and rare cases of PML. Infrequent dosing of anti-CD20 drugs is likely to lower the risk of treatment-associated infections. Clinical studies on selected MS patient populations showed a small impact on infection rate over the medium term. However, a large nationwide registry linkage study performed in Sweden showed that Rituximab was associated with a higher rate of serious infections compared to IFNb treatment, and that multiple DMTs increased the chance of antibiotic use and the need for herpes antivirals. A higher risk of hospitalization but not of mortality following SARS-CoV-2 infection has also been shown in anti-CD20-treated MS patients. To reduce infection risk, prior to the initiation of the anti-CD20 therapy, it is recommended that patients are screened for HBV, they complete the required vaccinations (to ensure an effective humoral immune response to the vaccine), and their levels of both IgG and lymphocytes are checked. Should infections occur during anti-CD20 therapy, extending dose intervals and IVIG substitution may be considered.

Infections Associated with New NMOSD Treatments: Anti-CD19 (Inebilizumab), Eculizumab and Satralizumab

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New monoclonal antibodies have been recently developed for NMSOD treatment. Inebilizumab targets CD19 which is expressed on a broad swath of B cells, including plasmablasts, the main producers of the pathogenic AQP4 IgG. Satralizumab is instead an antagonist of the IL6 receptor, a key survival factor of plasmablasts. Eculizumab antagonizes the complement molecule C5, which is recruited following complement activation triggered by the AQP4 IgG binding to AQP4 on astrocytes. Randomized, controlled trials of the three agents have proven their efficacy in relapse reduction, with a more pronounced effect on AQP4 IgG positive patients. Although only one out of four studies showed a significant reduction in disability, all of them indicated that the new treatments were very safe. Rates of infections in Eculizumab and Satralizumab-treated patients were no different to those seen with placebo and overall, a very low rate of infections occurred in the 6-months Inebilizumab trial. However, considering data with the same drugs used for different diseases and other agents with the same molecular targets on B cells, excess risk of serious infections over the long-term cannot yet be excluded. Preventive vaccination and specific bacterial and viral testing are therefore indicated before treatment initiation. Assessment of baseline IgG/M/A levels and their monitoring during therapy is also recommended especially with Inebilizumab treatment, so that should treatment-related hypogammaglobulinemia occur, IVIG treatment can be considered.