Highlights from the 8th ECTRIMS Focused Workshop

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

Covid-19 and Immunological Response: Focusing on B Cells and Risk of Reinfection

Prof. Heinz Wiendl, Department of Neurology, University of Münster, Münster, Germany

The Covid-19 pandemic has raised concerns regarding the use of B-cell depletion therapies to treat MS patients and their impact on Covid-19 infections and disease course. Two extreme positions emerged, one supporting the initiation or continuation of depletion therapies as they would have only a modest effect on humoral immunity, while the other recommending not to start or to continue, or to delay, such therapies because they could drastically reduce humoral immunity, therefore increasing the risk of infections and of a more severe course of Covid-19, as well as of recurrent infections. Some evidence is provided by the recent literature in the field: B-cell depletion therapies seem to not alter the immune response for secondary immunization protocols (i.e. tetanus, influenza, and pneumococcus), but to induce a reduction or suppression of primary vaccination responses to neoantigens. Data from a North American registry of MS patients alerted to the possible relationship between B-cell depleting therapies and worst Covid-19 clinical severity. Nowadays the recommendation from several health authorities is to perform vaccination before therapy' initiation, if possible, or, if B-cell depletion therapy is already ongoing, to wait at least 3-4 months after the end of the last depleting cycle and 4 weeks before the next depleting cycle.

Covid-19 Incidence and Severity in MS Treated Patients (France)

Dr Céline Louapre, Pitié Salpêtrière Hospital, Paris, France

The COVISEP registry is the result of a retrospective, observational, multi-centre study conducted in several hospitals in France, Switzerland, and Luxembourg with the aim of studying the impact of Sars-CoV-2 infection on MS patients and the contribution of potential risk factors to disease severity, including the use of DMTs with known immunosuppressive properties. More than 1280 patients have been enrolled in the study, most of them having RRMS. Comorbidities were collected, as well as the lymphogenic state before Covid-19 onset. In MS patients, fever and dyspnea were strongly associated with Covid-19 severity score ≥ 3 (requiring hospitalization). Overall, Covid-19 outcome was favourable in patients with MS from this cohort: only 12% of the patients were hospitalized due to Covid-19 and 1.3% died from the disease. Most of the patients had a low severity score, requiring no hospitalization. The risk factors associated with the most severe cases of Covid-19 were older age, cardiac comorbidity, and higher EDSS, the latter being the strongest predictor of severity. Anti-CD20 and corticosteroids also showed a worsening effect on the clinical outcome compared to other DMTs than anti-CD20.

Covid-19 Incidence and Severity in MS Treated Patients (International)

Dr Steve Simpson-Yap, The University of Melbourne, Melbourne, Australia

An international cross-sectional study was conducted to address concerns about the impact of DMTs on Covid-19 risk and severity. Data collected from the consortium aimed at answering some research questions: what the characteristics of Covid-19 severity are, with a particular focus on DMT type, and if patients treated with anti-CD20 therapies would have a higher risk for more severe Covid-19 with respect to other DMTs and to Natalizumab alone. Four clinical outcomes (hospitalization, admission to ICU, artificial ventilation, and death) were evaluated in the 2340 enrolled MS patients. Anti-CD20 therapies, Rituximab and Ocrelizumab, accounted for 11% and 21% of the patients, respectively. Older age, progressive MS, and higher disability were associated with worse clinical Covid-19 outcomes. Both anti-CD20 therapies were positively associated with Covid-19 severity and had a higher risk if compared to other DMTs and to Natalizumab. Rituximab effect was consistently stronger than Ocrelizumab, which was not associated with artificial ventilation. Neither of the treatments was associated with death, despite Rituximab showing a positive trend. Results, in line with previously reported data from the French and Italian registries, suggest that Covid-19 may need to be considered in treatment decisions for patients with MS.

Challenges with Covid-19 Vaccines

Prof. Hesham Abboud, University Hospitals Cleveland Medical Center, Cleveland, United States

First collected evidence-based data on MS patients suggest Covid-19 vaccination are safe and effective. Inactivated and protein-based vaccines (i.e. Sinopharm and Novavax) have shown their efficacy and safety in MS patients under DMTs, and the same applies to RNA/DNA vaccines (i.e. Pfizer, Moderna, Inovio). Immune-mediated adverse events due to Covid-19 vaccination reported to date are minimal, and of less risk than possible immune consequences due to Covid-19 infection. DMTs could partially protect against vaccine-related immune adverse events. Some DMTs, including S1P modulators, B-cell depletors, and non-selective lymphocyte depletors, might attenuate the efficacy of the vaccine. Coordinating timing of vaccination to timing of DMT administration could be challenging, but it can help maximize the benefit of vaccination. Of course, vaccine choice and timing should consider not only MS disease activity and treatment, but also patient preference, local vaccine availability and regulations. Overall, the benefits of vaccination seem to outweigh the risks in MS patients, but more evidence-based data are required to make specific recommendations regarding Covid-19 vaccination in MS patients under DMTs.

Covid-19 Pandemic and Future Pandemics?

Prof. Jean-Laurent Casanova, The Rockefeller University, New York, United States

The COVID Human Genetic Effort aims to identify the causes of life-threatening Covid-19 infections, considering the huge inter-individual clinical variability observed in the course of SARS-CoV-2 infection. For this purpose, the genome or exome of 3500 Covid-19 infected individuals worldwide (patients with life-threatening pneumonia and patients with silent infection considered as controls) was sequenced. The hypothesis behind the genetic study was that some of the individuals developing life-threatening infections could harbor single-gene inborn errors of immunity and that severe Covid-19 pneumonia could be allelic to critical influenza pneumonia. Inborn errors at 8 loci of type I interferons pathway were identified in 23 patients (3% of the sequenced individuals). Impaired innate and intrinsic immunity against SARS-CoV-2 infection was confirmed in vitro for some of the identified variants. An immunologic study was carried out in a subset of the study population to assess the hypothesis that some patients with life-threatening infections could carry pre-existing autoimmune neutralizing antibodies against type I interferons that could mimic inborn errors of immunity. Ten percent (10%) of tested patients were positive for anti-type I interferons auto-antibodies. Interestingly, 94% of these patients are men and 50% are older than 65 years. The autoantibodies were confirmed in vitro to neutralize interferons response against SARS-CoV-2. Taken together these results show that type I interferons immunity is essential in defense against SARS-CoV-2 infection.