8th ECTRIMS Focused Workshop

Day 1

Session 3

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

Complex Situations in the Management of Infectious Risks: the Covid-19 Pandemic

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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

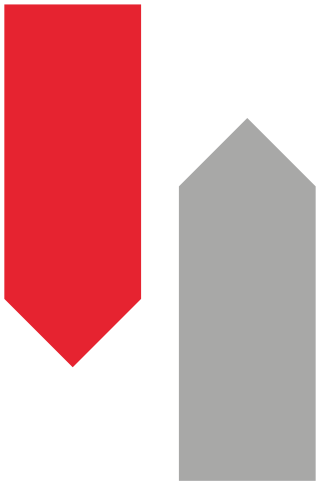
Prof. Heinz Wiendl
Department of Neurology, Münster University, Germany
Session 3, April 14th 2021

Concerns about B-cell Depletion Therapies in the Covid-19 Era

Facing the emergence of the pandemics, two opposite views regarding the impact of B-cell depletion therapies on Covid-19 infections and disease severity:

B-cell depletion therapies could provoke **humoral immunity reduction**

> better not to start or to continue, or delay such therapies

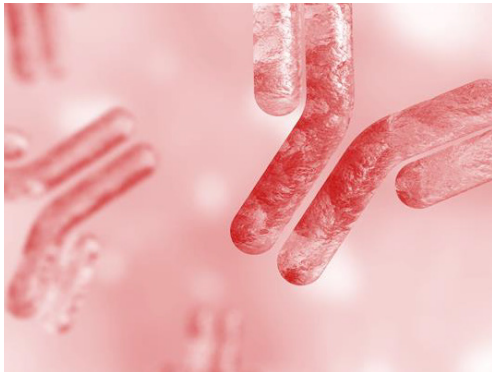


B-cell depletion therapies might have a **modest impact on humoral immunity** and the reduction of antibody production may be **beneficial to prevent secondary hyperinflammation in Covid-19**

> start, continue, or optimize treatment

What are the Arguments to Support these Opposite Positions?

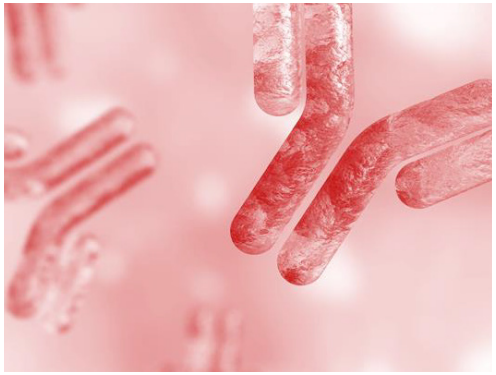
Impact of B-cell depletion on primary immune reactions



- CD8+ and innate responses are not impaired
- Data from the **VELOCE vaccination study with Ocrelizumab:** response to vaccination is attenuated or suppressed. The effect is more dramatic when exposed to a new antigen or to vaccines involving mainly the humoral response (ex pneumococcus) compared to those involving cellular responses (ex tetanus)
- Data from **rheumatoid arthritis patients treated with Rituximab:** all vaccines tested were attenuated for quite long after B-cell depletion therapy
- Data from **oncological patients treated with Rituximab:** impairment of secondary humoral immune response for quite a long period of time after treatment.

What are the Arguments to Support these Opposite Positions?

B-cell depletion with depleting agents distinct from CD20 antibodies?



- **Small retrospective study:** Cladribine seems not to affect the protective immunity against varicella zoster and seasonal influenza
- **Data from the MAGNIFY trial with Cladribine:** Drastic, quick and long-lasting decrease of B-cell subtypes (including memory B cells) after treatment, whilst T cells not much affected
- **Data from Israel vaccination experience:** Low antibody production against SarsCov-2 among patients with MS treated by Fingolimod and vaccinated against Covid-19.

Safety Signal from a North American MS Registry

- Cohort of 1600 MS patients in North America
- Looked at risk factors associated with SARS-CoV-2 infection
- **Rituximab, recent treatment with corticosteroids, and common risk factors** in the population like obesity or cardiovascular comorbidities were **associated with worst Covid-19 clinical severity.**

Would the same be true for Ocrelizumab?

Conclusions

- Rather **reassuring data for secondary immunization protocols** (tetanus, influenza, pneumococcus)
- **Less reassuring data on primary vaccination responses,** but little data is available for SarsCov2
- Unsuccessful class shifting is a reasonable hypothesis
- Potential **safety signal** from an MS registry on Covid-19 clinical severity.

RECOMMENDATIONS

- If possible, perform vaccination before starting a B-cell depletion therapy
- If B-cell therapy already ongoing, wait 3-4 months after the last depleting cycle and 4 weeks before the next depleting cycle

2

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

Dr Céline Louapre
Pitié Salpêtrière Hospital, Paris, France
Session 3, April 14th 2021

The COVISEP Registry

- **A retrospective, observational, multi-centre, cohort study** conducted in France, Switzerland, and Luxemburg
- Aim was to **assess the clinical outcomes of Covid-19 in MS patients** and to **identify the risk factors that could contribute to disease severity**
- Main outcome of the registry: **Covid-19 severity score,** ranging from 1 (not hospitalized, no limitations on activities) to 7 (death). Outcome for the analysis in two groups (severity score > =3 vs severity score <3)
- Data presented have been collected between March 2020 and April 2021.

Demographic and Clinical Characteristic of the Cohort

- **1284** MS patients enrolled, mostly with **RRMS**
- 21% of the patients not treated with DMTs
- **Comorbidities** collected including cardiovascular disease, pulmonary disease, diabetes, obesity, and smoking
- **Lymphopenic state** before Covid-19 onset available
- Covid-19 diagnosis mainly based on **PCR positive test**

Covid-19 Outcomes in MS Patients

- Mostly observed symptoms: **asthenia, cough, fever, headache, anosmia, dyspnea, digestive disorders, dizziness**
- **Fever and dyspnea** strongly associated with disease severity score ≥ 3
- Most of the patients had a disease severity score of 1 or 2, requiring no hospitalization
- Most of the severe cases were in the untreated group of patients

- 12.2% of patients hospitalized due to Covid-19
- 1.3% of patients died because of the disease

Covid-19 Risk Factors in MS Patients

- Hospitalized patients had **older age** and **higher EDSS**
- Multivariate analysis showed that **age, male sex, cardiac comorbidity, and EDSS ≥ 3** could contribute to develop a severe Covid-19 disease
- **Anti-CD20 and corticosteroids** contributed to the **worsening of Covid-19 clinical outcome** compared to DMTs other than anti-CD20

Conclusions

- Overall, **Covid-19 outcome was favourable in MS patients** (12.2% hospitalization rate and 1.3% death rate)

- **EDSS, age, cardiac comorbidity, anti-CD20, and corticosteroids** were the major contributors to severe form of Covid-19

- Preliminary results of patients under **anti-CD20** therapy show a **lower rate of positive serology** after Sars-CoV-2 infection.

3

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

Dr Steve Simpson-Yap
The University of Melbourne, Melbourne, Australia
Session 3, April 14th 2021

Covid-19 & MS Global Data Sharing Initiative

- Large **international cross-sectional study** (2340 participants pooled from different countries)

- **4 clinical outcomes:**
  - Hospitalization
  - Admission to ICU
  - Artificial ventilation
  - Death

- Aim was to **assess the impact of DMTs on Covid-19 risk and severity:**
  - What are the characteristics of Covid-19 severity, particularly DMT type?
  - What is the risk for more severe Covid-19 in patients treated with anti-CD20 DMTs versus other DMTs?
  - What is the risk for more severe Covid-19 in patients treated with anti-CD20 DMTs versus Natalizumab?

What are the Characteristics of Covid-19 Severity?

- **Older age, progressiveMS, and higher disability** are associated with worse outcomes
- **Rituximab positively associated with hospitalization, ICU admission, and ventilation, but not death**
- **Ocrelizumab positive trend for hospitalization and ICU admission**
- Untreated patients show a similar trend to Ocrelizumab users

What is the Risk of More Severe Covid-19 in Patients Treated with Anti-CD20 DMTs versus Other DMTs?

- 251 patients under Rituximab, 463 under Ocrelizumab, and 1082 under other DMTs
- **Rituximab** compared to other DMTs is associated with **higher frequencies of hospitalization, ICU admission, and ventilation**
- **Ocrelizumab** is only **associated with hospitalization and ICU admission**
- Neither of them is associated with death (only positive trend was for Rituximab)

Same clinical outcomes observed for anti-CD20 DMTs versus Natalizumab

Conclusions

- Both **anti-CD20 DMTs** are **positively associated with Covid-19 severity**
- **Rituximab effect is consistently stronger** than Ocrelizumab, which is not associated with artificial ventilation
- Overall, in line with results from the French and Italian registries, **Covid-19 may need to be considered in treatment decisions for MS patients**

4

Challenges with Covid-19 Vaccines

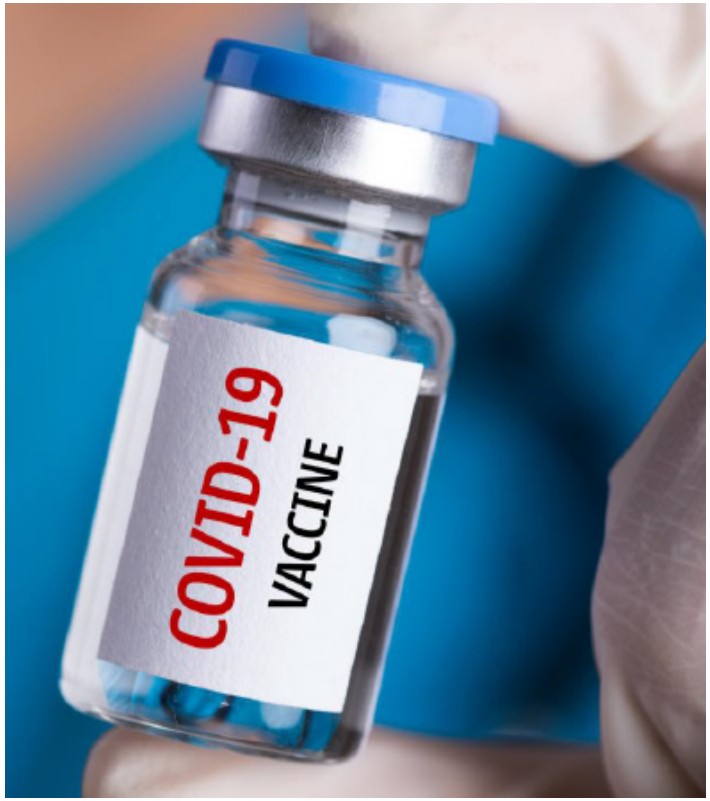
Dr Steve Simpson-Yap
The University of Melbourne, Melbourne, Australia
Session 3, April 14th 2021

Are Covid-19 Vaccines Safe and Effective in MS Patients?

- **Statement from the National MS Society (NMSS)** in 2021:
  - Covid-19 RNA vaccines are **safe** in MS patients, therefore **vaccination is highly recommended**
  - There could be some **timing implication** related to specific DMTs
  - For all the approved/available Covid-19 vaccines **efficacy and safety have been clearly demonstrated**

- Like any other vaccine, Covid-19 vaccines can produce **immune-mediated side effects,** mainly mild ones, but on some occasions severe

- DMTs may **protect against some of the vaccine-related immune-mediated adverse events**



Do Certain DMTs Influence Covid-19 Vaccine Efficacy and Safety?

- Main **concern about vaccine efficacy** for patients under DMTs:
  - INFβ, GA, Teriflunomide and Natalizumab: no or slight effect on vaccine efficacy
  - Same for the Fumarates (if no lymphopenia)
  - S1P modulators: possible attenuation of the immune response to vaccine, but eventually partially protective. Treatment interruption is not recommended
  - Ocrelizumab and Ofatumumab: probable attenuation of the immune response to vaccine, but eventually partially protective
  - Alemtuzumab and Cladribine: similar attenuation and partially protective mechanism
- As long as the vaccine **is not a live vaccine,** all the others should be safe under any DMTs. Nevertheless, additional safety data on viral vector-based vaccines in immunosuppressed patients are necessary

Timing of Vaccine Administration Matters While Under DMTs?

Ofatumumab (monthly infusions):

- Timing is more complicated
- For best vaccine efficacy complete vaccination 4 weeks before starting treatment when possible
- During treatment, better to vaccinate 1 month after the last injection and delay the next injection to 1 month after the last vaccine dose, if possible (dose skipping)
- Easier to use a single dose vaccine (i.e. Johnson & Johnson)

Fumarates:

- eventually consider treatment interruption prior to vaccine in lymphopenic patients, but more data needs to be gathered

Alemtuzumab and Cladribine:

- For best vaccine efficacy complete vaccination 4-6 weeks before starting treatment when possible
- To maximize vaccine efficacy administer 6 months after dosing

Ocrelizumab (6-monthly infusion):

- For best vaccine efficacy complete vaccination 4 weeks before starting treatment when possible
- To maximize efficacy during treatment, best to administer vaccine between months 3 and 5 after dosing and complete 1 month before next dosing

Conclusions

- **MS patients should get vaccinated** as Covid-19 vaccines are expected to be safe and effective

- The **effectiveness** of the vaccine **might be reduced by certain DMTs,** but they could also provide a partial immune protection

- **Live-attenuated vaccines should be avoided** for MS patients under DMTs

- **Co-ordinating timing of vaccination to timing of DMTs dosing** can maximize the benefit.

4

Covid-19 Pandemic and Future Pandemics?

Prof. Jean-Laurent Casanova
The Rockefeller University, NY, US
Session 3, April 14th 2021

Clinical Variability in the Course of SARS-CoV-2 Infection

- **Huge inter-individual clinical variability** observed in the course of SARS-CoV-2 infection

- Epidemiological **«risk factors» of life-threatening Covid-19** infections:
  - Age – the older the worst
  - Sex
  - Comorbidities – the latter two having a smaller impact than age

- Still huge inter-individual clinical variability in each demographic category…

…so, what are the causes of lethal Covid-19 infection?

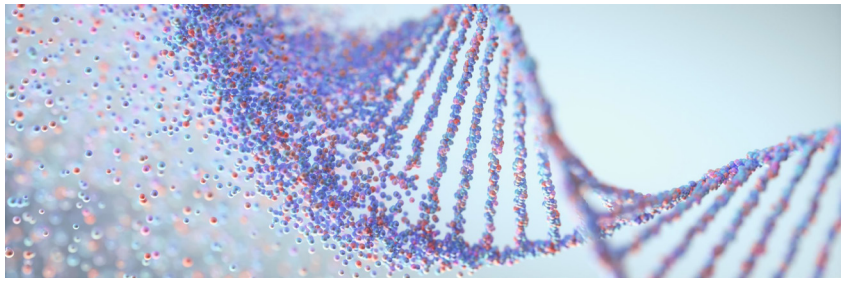
Unravel the Genetic Cause of Lethal Covid-19 Infection

- Hypothesis: some of the individuals developing Covid-19 life-threatening infection might harbor **single-gene inborn errors of immunity**

- **COVID Human Genetic Effort (3500 subjects sequenced by Nov 1 2020):**
  - > 1000 hospitals worldwide
  - > 50 sequencing hubs
  - Genomes and exomes from patients with severe Covid-19 pneumonia and patients with silent infections considered as controls

Specific hypothesis when analyzing the sequencing data:

Could Covid-19 severe pneumonia be allelic to critical *influenza* pneumonia?



Genetic Cause of Lethal Covid-19 Infection

- 23 patients **(3% of the study population)** presented **inborn errors at 8 loci within the type I interferons pathway**
- **4/23** patients showed **autosomal recessive inheritance** of these variants (interestingly all were young people with no previous history of serious infections)
- **Impaired innate and intrinsic immune responses against SarsCov2** were demonstrated *in vitro* in presence of the mutated phenotypes
- Future project plan is to study > 500 genes upstream/ downstream within the type I interferons pathway

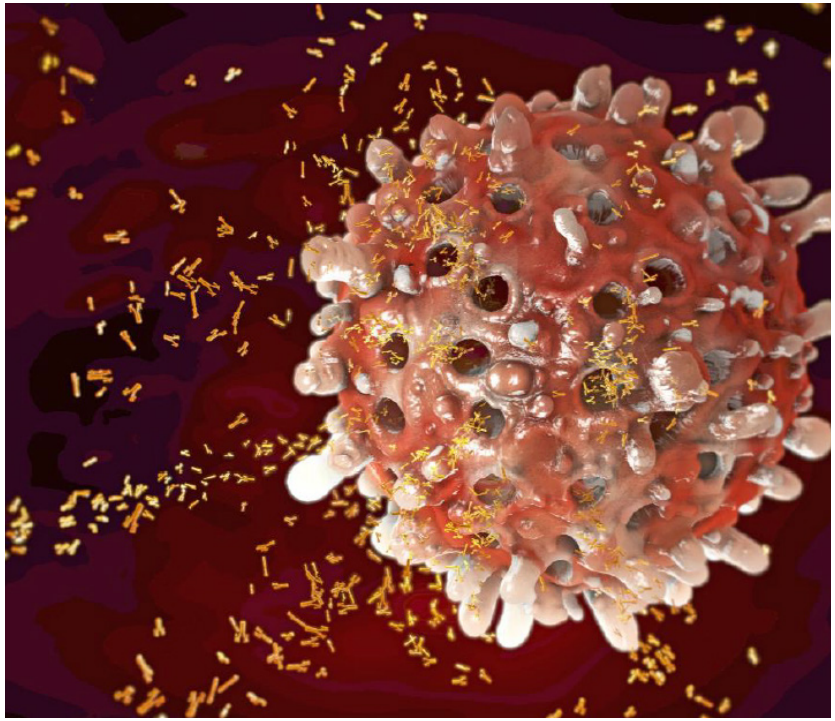
Zhang at al. Science 2020

Immunological Cause of Lethal Covid-19 Infection

- Hypothesis: some other individuals developing Covid-19 life-threatening infection might carry **pre-existing auto-immune neutralizing antibodies against type I interferons mimicking inborn errors**

- **Results of the immunological testing on a cohort of the study population (N=987):**
  - **10%** of the patients tested **positive for anti-type I interferons autoantibodies**
  - - 94% are **men**
  - - 50% are aged **> 65 years**

- The autoantibodies were shown *in vitro* and *in vivo* to be able to **neutralize interferons-mediated defense against SARS-CoV-2.**



Conclusions

- **Type I interferons immunity** is essential for host defense against SARS-CoV-2 infection

- **Two distinct mechanisms disrupting type I interferons immunity** can partially explain the cause of some lethal Covid-19 infection:
  - **Inborn genetic errors** at type I interferons loci (accounting for **3%** of the patients)
  - **Neutralizing autoantibodies** against type I interferons (in **10%** of the patients)