8th ECTRIMS Focused Workshop

Week 1

Session 1

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

Current Data on Infections Associated with MS Disease-Modifying Treatments

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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1

Progressive Multifocal Leukoencephalopathy (PML) Risk, Prevention, and Management -2021

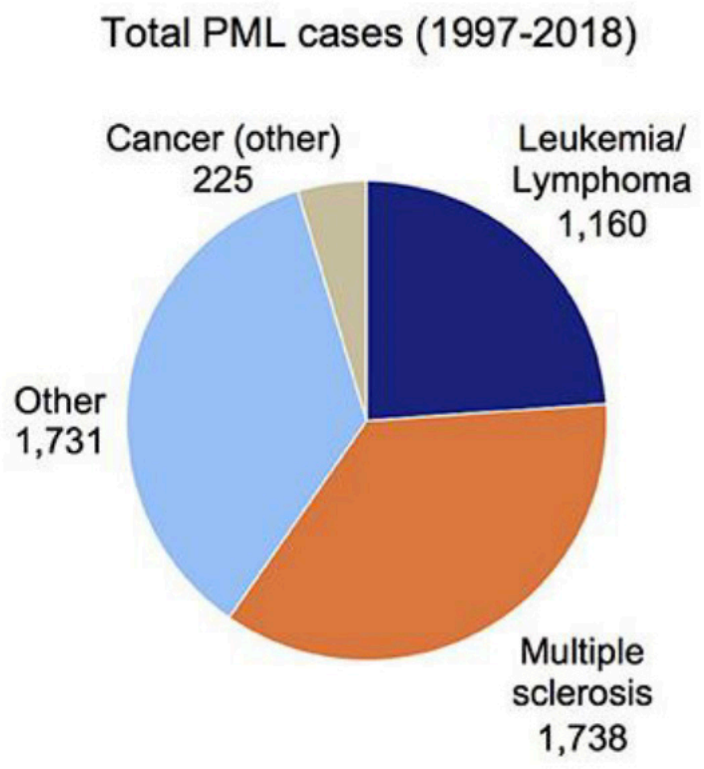
Dr. David B. Clifford
Washington University in St. Louis, USA
Session 1, April 14th 2021

PML & MS

- **Correct diagnosis** is crucial:
  - Identify progressing lesions
  - Identify JC virus in brain or CSF
  - Seek underlying cellular immunity

- PML develops only in people whose immune system has been significantly modulated — **1/3 of PML patients are suffering from MS**

- Such high prevalence might be at least partially triggered by the demargination of virus-carrying cells from the bone marrow driven by **Natalizumab**

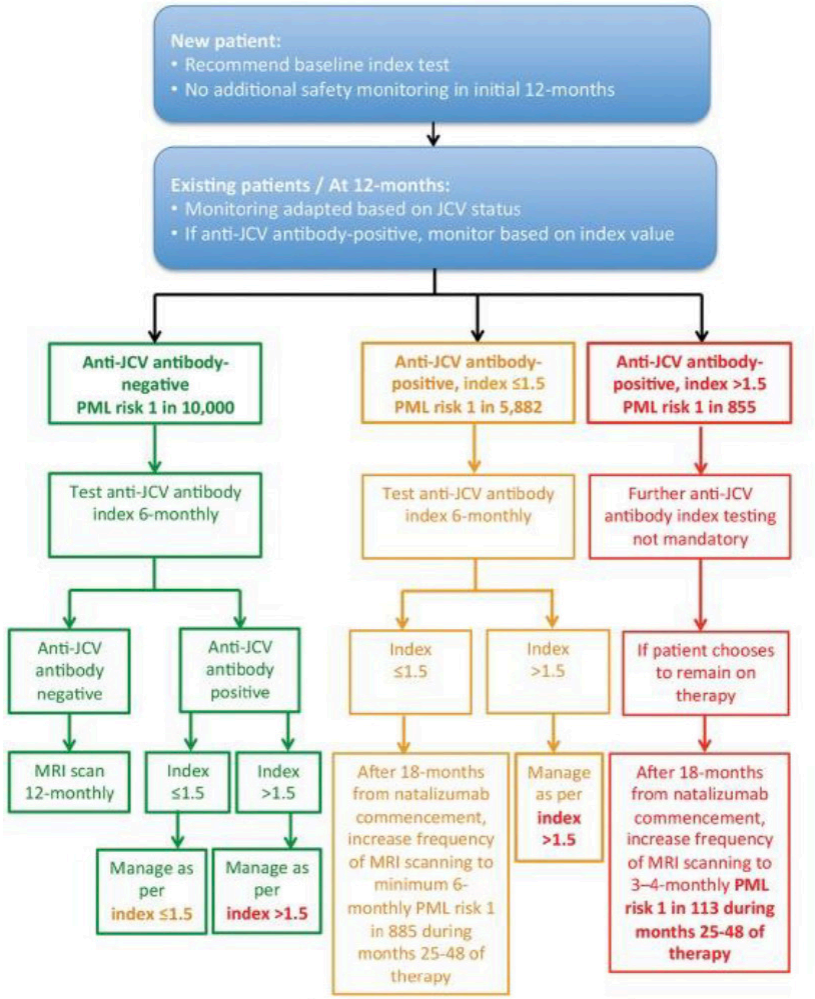


Eis *et al., Front. Neurol.* 2020

Patient Risk Stratification

- **PML Risk in MS patients** depends on:
  1. JC antibody positivity and anti-JCV antibody index score
  2. Duration of exposure to Natalizumab
  3. Exposure to prior immunosuppressive therapy

- A proper **risk management approach** relies on:
  - Anti-JCV antibody monitoring
  - Adequate MRI surveillance to catch PML as early as possible
  - The availability of an alternative therapy



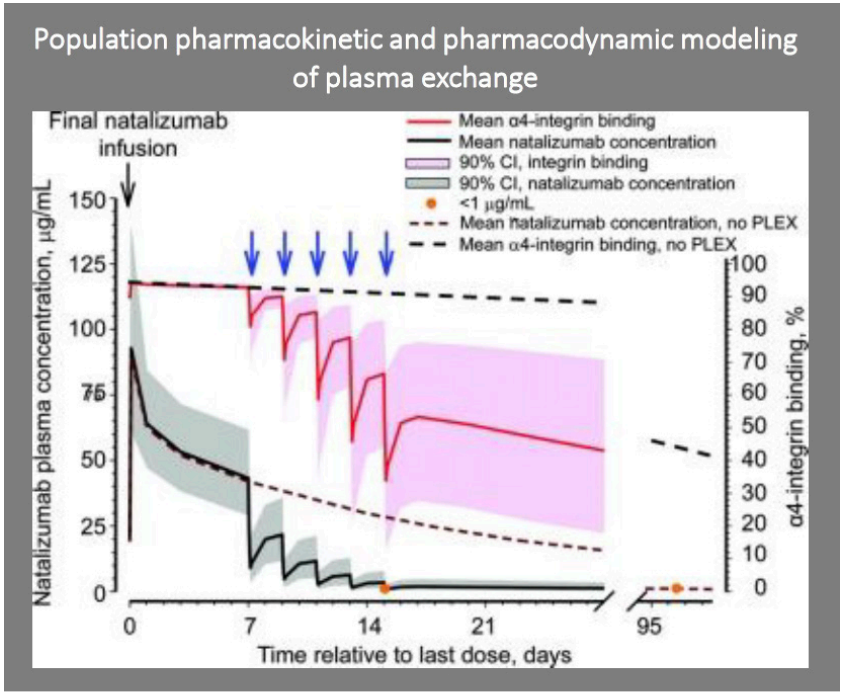
McGuigan *et al., J Neurol Neurosurg Psychiatry* 2016

Changing PML Risk in MS Patients

- The **introduction of new DMTs** has contributed to bend the curve of the increasing incidence of PML in MS patients
- **Stretching out the interval dosing of natalizumab** appears to be a promising risk modifying behaviour (trial still in progress)
- **Risk estimates of alternative drugs should be considered**
- The **choice of a new MS drug** after switch from Natalizumab should be based on:
  - Efficacy for MS
  - Tolerability
  - Patient risk profile

PML Management in MS Patients

- **No effective JC viral therapy** is available
- **Immune reconstitution** is essential:
  - IRIS treated with **steroids** if seriously symptomatic
  - **Plasma exchange** – controversial but helpful for early fight against PML
  - **New therapies** under development to augment the immune system (not necessary in an MS context):
    - PD-1 inhibitors
    - IL-15 superagonists
    - Allogeneic T cell transfer



Khatri *et al., Neurology* 2009

Conclusions

- **Practice prevention:**
  - Risk monitoring tools
  - Switch from high to low risk drugs
  - Follow the developments of the extended interval dosing approach
- **Do not give up on patients developing PML:**
  - They can have a good outcome
  - Early detection is crucial

2

Infections Associated with S1P Modulators

Dr. Matthias Mehling
University Hospital Basel, CH
Session 1, April 14th 2021

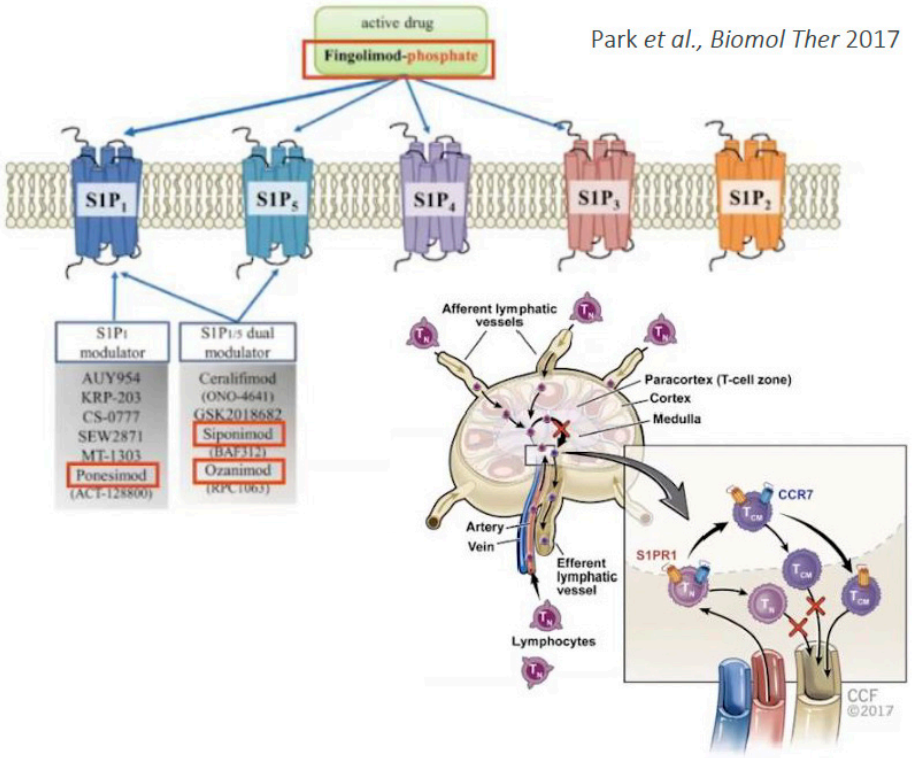
Context

S1P Modulators

- Some are already approved, some are still under development
- As of today, S1P modulators used in therapy primarily target S1P1:
  - They prevent the egress of lymphocytes from lymph nodes to the peripheral blood
  - They lead to lymphopenia: naïve T cells and central memory T cells are affected

Serious infection risk for MS patients

- 15% of untreated patients develop serious infections over 6 years
- The risk increases for treated patients (Rituximab, Fingolimod, Natalizumab, Interferon beta/GA)



Park *et al., Biomol Ther* 2017

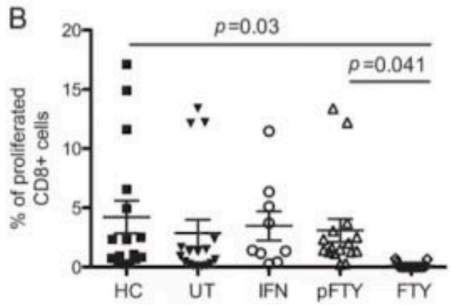
Chaudry *et al., Neurotherap* 2017

S1P Modulators-Associated Infectious Risk

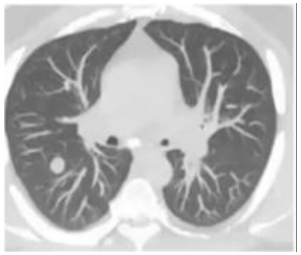
Infection Type	Fingolimod	Siponimod	Ponesimod	Ozanimod
Respiratory Tract Infections	X	X	X	X
JC-virus (PML)	X			
Cryptococcal infection	X	X		
Cutaneous leprosy	X			
Fungal infection		X		
Herpes Virus (HSV)	X	X	X	X

S1P Modulators-Associated Infectious Risk: Fingolimod

- **Varicella Zoster primary infections and reactivation**
  - Treated patients show a reduced number of VZV-specific T cells in blood
  - Signs of subclinical reactivation of the virus in the saliva
- **JC-Virus: Progressive Multifocal Leukoencephalopathy (PML)**
  - Incidence: 0.12 per 1000 patients (Novartis safety database)
  - Associated with treatment duration
  - Increased risk for older patients
- **Cryptococcal infections**
  - Primary cutaneous, pulmonary, and disseminated cryptococcosis; cryptococcal meningoencephalitis
- **Cutaneous leprosy**
  - 1 case only
  - Differential diagnosis with basal cell carcinoma to be considered
- **SARS-CoV-2 infection**
  - No increased risk for severe infection has been observed



VZV-specific T cells in blood
Ricklin et al., Neurology 2013



Pulmonary cryptococcosis
Samudralwar et al., Int J MS Care 2019

Conclusions

- **There are multiple infectious complications associated with S1P modulators:**
  - Respiratory tract infections
  - Herpes virus infections
  - JC-Virus infections
  - Cryptococcal infections
- **Consider VZV-screening before starting SP1 treatment**
- **There is a certain risk of developing PML which has to be checked at the lowest thresholds**

3

Infections Associated with CD52 Lymphodepleting Therapies

Dr. Krzystof Selmaj
University of WM, Olsztyn, and Center of Neurology, Lodz, PL
Session 1, April 14th 2021

Alemtuzumab

- **Humanized Ab depleting circulating T and B lymphocytes which express CD52:**
  - B cell recovery completes in 3 to 6 months
  - T cell recovery requires at least one year to reach the lower limit of normal (LLN)
  - The percentage of the CD4+ Treg subtype increases
  - Innate immune cells are not affected
- **Adverse events** (CARE-MS I and II studies):
  - Infections are 1/3 more common compared with IFNb, but they are mild-to-moderate and respond to conventional therapy
  - Upper respiratory tract infections are the most common
  - Herpes viral infections have a high incidence rate (4 to 8 fold higher than IFNb); acyclovir prophylaxis is effective
  - Acalculous cholecystitis (8 cases in trials and post-marketing), potentially life-threatening condition

Alemtuzumab Related Infections

- **Long-term data**
  - No cumulative effect of time with regards to the risk of infections (Caveat: possible selection bias)
    - Incidence of infection is lower in years 3-6 compared with years 0-2 after treatment onset
    - Multiple Alemtuzumab treatment courses do not impact on infection risk
    - No correlation has been observed between lymphocyte count and infection risk
- **Post-marketing data**
  - Most common infections:
    - Herpetic infections
    - Listeria monocytogenes
    - CMV Tuberculosis
    - PML
- **Alemtuzumab and SARS-CoV-2 infection:** 5 cases with mild course reported (new analysis upcoming by Sanofi)
- **5 fatal cases** of probable Alemtuzumab-related infections have been reported

Risk Mitigation Strategies

Pre-alemtuzumab initiation strategies	Herpetic infections	Listeria	Tuberculosis	HPV	Hepatitis B and C
Prophylaxis	X	X		X	
Vaccination	X				
Nutritional Recommendations		X			
Screening			X	X	X
Treatment			X		

Conclusions

- Infection risk increased; it peaks after the first course of alemtuzumab and then declines over time
- Most Alemtuzumab related infections are mild-to-moderate and respond to conventional therapy
- Serious infections are uncommon, but some might be lifethreatening
- Risk mitigation strategies should be considered prior to Alemtuzumab treatment initiation

4

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

Dr. Krzystof Selmaj
University of WM, Olsztyn, and Center of Neurology, Lodz, PL
Session 1, April 14th 2021

DMTs – Introduction

Cladribine

- Chlorinated deoxyadenosine
- In lymphocytes, accumulation of activated cladribine leads to apoptosis
- Rapid and profound decrease in B lymphocytes – recovery in 6 months
- Less important but persistent decrease of CD4+ T lymphocytes

Dimethyl fumarate (DMF)

- Targets the intracellular Nrf2 pathway with its anti-inflammatory and cytoprotective proteins

Teriflunomide

- Inhibits the dihydro-orotate dehydrogenase
- Interferes with the pyrimidine metabolism in blasting lymphocytes only

Cladribine Treatment and Infections

- **CLARITY Placebo-controlled trial:**
  - Only Herpes Zoster showed an increase in cladribine-treated patients compared with placebo, which was correlated with Grade >3 lymphopenia

- **Long-term data** (Phase III trials and registered data):
  - No increase in severe infections
  - Increase in opportunistic infections, in particular Herpes Zoster
  - Herpes infection was increased especially in year 2 after the treatment
  - No PML cases were reported

Dimethyl Fumarate Treatment and Infections

- **DEFINE and CONFIRM placebo-controlled studies:**
  - No increase in infections in DMF-treated versus placebo patients
  - The 9 years follow-up ENDORSE study showed an increase of serious and opportunistic infections in presence of severe prolonged lymphopenia
- **PML:**
  - 9 reported cases including prior natalizumab or mitoxantrone treatment, lymphopenia is a risk factor
  - Hypothesized mechanism: a decrease of JCV-specific CD8+ T cells allows JC Virus reactivation leading to PML
- **Post-marketing data**
  - 11 cases of CNS opportunistic infections reported

Teriflunomide Treatment and Infections

- **TEMSO and TOWER placebo-controlled trials:**
  - No increase in any respiratory or urinary tract or serious infections
  - One case of opportunistic infection (reactivation of intestinal tuberculosis)
- **Pooled analysis of CTs and extension studies:**
  - In periods with no or Grade 1 lymphopenia there was no increased incidence in all infections/ serious infections
  - No PML cases reported

MS Treatment and Covid-19

- **Data from 2340 cases showed:**
  - No increased risk of hospitalization and ICU admissions for cladribine and teriflunomide treated patients (DMF as a reference)
  - Increased risk of hospitalization and ICU admission for CD20-treated patients

- **ECTRIMS survey on MS care and management to 360 neurologists:**
  - No modifications required for DMF and teriflunomide treated patients, except for a small group of patients with severe lymphopenia
  - Suspension/switch/delay of treatment was generally recommended to cladribine-treated patients

Conclusions

- **Cladribine** is associated with increased occurrence of herpes zoster infection, especially in periods of severe lymphopenia
- **Dimethyl fumarate** is not correlated with increased incidence of infections except for period of prolonged severe lymphopenia (as for PML)
- **Teriflunomide therapy** is not associated with a higher risk of infections
- Only anti-CD20 treatments are likely to affect the severity of Covid-19.

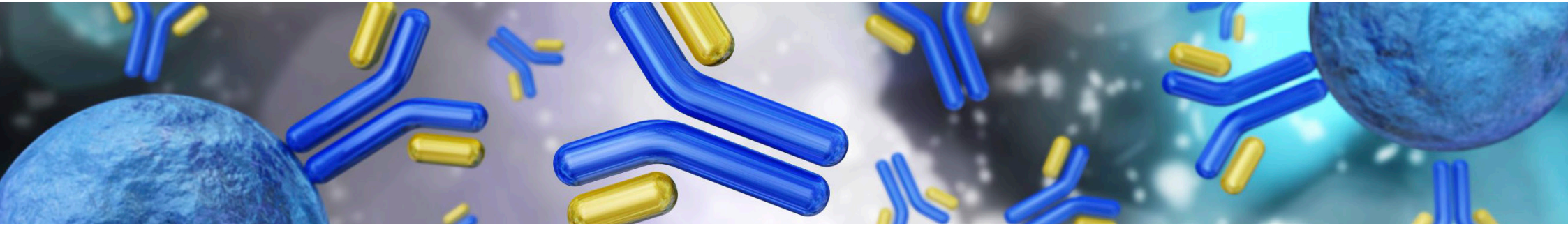
5

Infections Using Anti-CD20 Therapies

Prof. Fredrik Piehl
Karolinska University Hospital, Stockholm, SE
Session 1, April 14th 2021

B-cells and Anti-CD20 Therapies

- **B cells immunological functions:**
  - Cytokine production
  - T cells activation
  - Antibody production
- **Anti-CD20 therapies:**
  - Eliminate most B cells between the pre-B and the plasma blast stage
  - Hinder the humoral response to vaccination, as proven by tetanus and pneumococci vaccines administered 3 months after Ocrelizumab



Anti-CD20 Therapy Associated Infections

- **Non-MS conditions, mainly haematological and rheumatic:**
  - Increased rate of severe infections
  - Rare opportunistic infections
  - HBV reactivation in haematological conditions
  - Rare PML
  - Low risk of tuberculosis and herpes reactivation
  - Low IgG levels- associated infections risk dependent on baseline characteristics
  - Infrequent dosing likely lowering the risk
  - Very low IgG levels association with serious infections
  - Most serious infections associated with normal IgG levels
- **In MS settings:**
  - Small impact on infection rate over the medium term

Anti-CD20 Therapy Associated Infections

- **Real world data - Swedish nationwide registry linkage study**
  - Rituximab-associated serious infections were significantly higher than IFNb-treated patients
  - 70% increased risk for Rituximab treated compared with IFNb treated patients
  - Increased use of antibiotics following Natalizumab and Rituximab therapy
  - Increased use of herpes antivirals following Fingolimod and Natalizumab therapy
  - No deaths reported due to infection
- **Covid-19:**
  - Anti-CD20 associated with increased risk of hospitalization but not mortality rate
  - Specific IgG and/or T cell response occurred even with lymphopenia

Risk Mitigation Strategies

- **Before CD20 therapy:**
  - HBV screening
  - IgG levels and lymphocytes check
  - Vaccination boost
- **During CD20 therapy:**
  - IgG levels check before each infusion
  - Optimization of vaccination timing to improve immune response
- **In case of infections:**
  - Possibility of interval dosing extension
  - IVIG substitution if low IgG levels

Conclusions

- Reduce Ig levels

- Are associated with:
  - Increased occurrence of severe infections
  - Limited risk of TB or herpes reactivation
  - Possible reactivation of viral hepatitis
  - Very low risk of PML

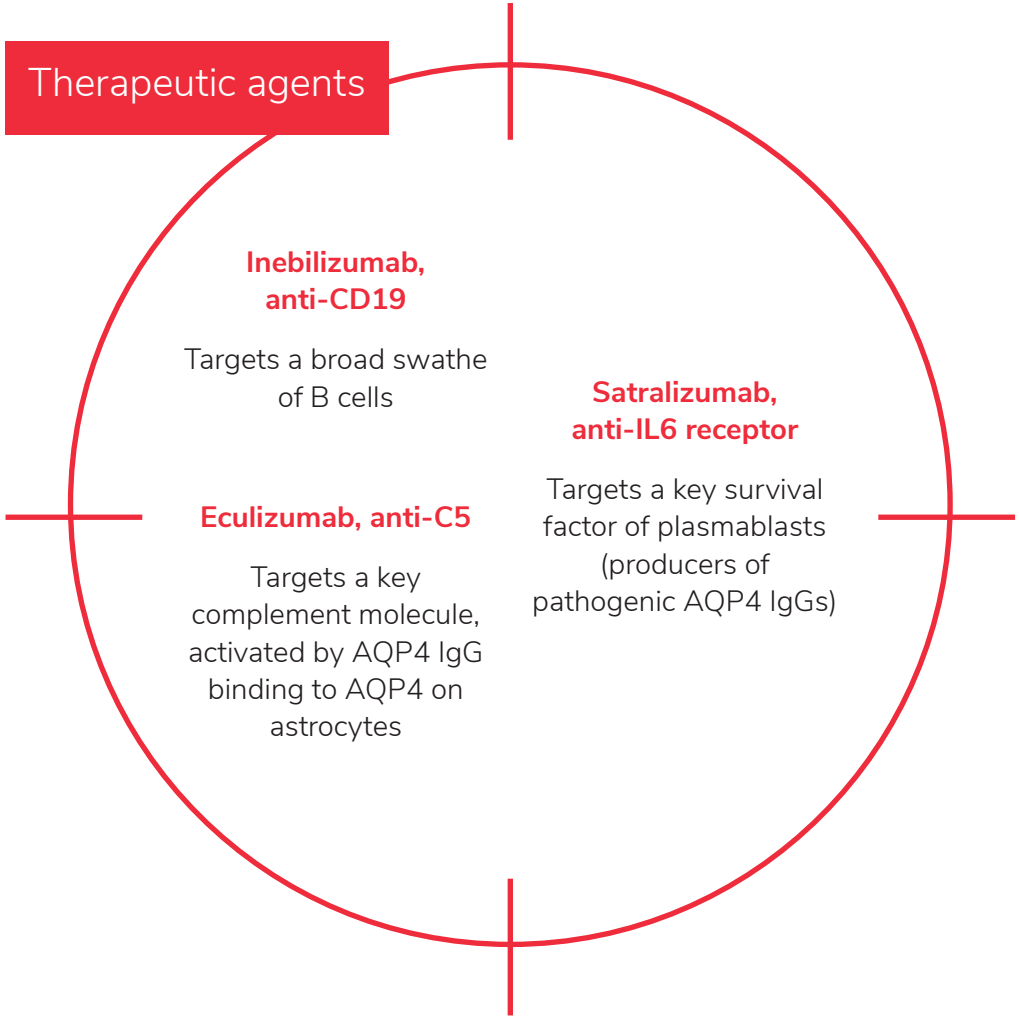
6

Infections Using New NMOSD Treatments: Anti-CD 19 (Inebilizumab); Eculizumab and Satralizumab

Prof. Brian Weinshenker
Mayo Clinic, Rochester, US
Session 1, April 14th 2021

New NMOSD Targeted Therapies

Therapeutic agents



Related clinical trials for NMOSD treatment

- Four clinical studies have been performed
- Two studies are placebo-controlled, two allowed concomitant immunosuppression
- All studies showed a significant relapse reduction which was more pronounced in AQP4 IgG+ patients
- One study showed a significant reduction of disability
- In all studies treatment appeared very safe

Safety: Clinical Evidence

- **Inebilizumab**
  - 6-month trial
  - Overall low rate of infections
- **Satralizumab**
  - Rate of infection observed is similar to that seen in the placebo group
  - Lower rate of serious infections than the placebo group with concomitant immunosuppression
- **Eculizumab**
  - NMOSD trial
    - Lower infection rate compared with placebo
    - No cases of meningococcal or opportunistic infections, one Neisseria gonorrhoeae case
  - Haemolytic Uraemic Syndrome Registry, 1300 patients, over 5 years
    - No overall increase of serious infections
    - Significantly more common serious infection in paediatric patients

Risk Management

- **Prophylaxis**
  - Vaccinations: S. pneumonia, Hemophilus b, TET, influenza, meningococcus
  - Monthly IVIG when IgG < 1.5 g/L
- **Clinical testing before the treatment**
  - PPD/Quantiferon Tb, Hep B (Inebilizumab and Satralizumab)
  - Baseline quantitative IgG/M/A (Inebilizumab)
- **Monitoring during Inebilizumab treatment**
  - Quantitative IgG/M/A
    - Experience with Rituximab in NMOSD patients showed hypogammaglobulinemia occurrence
    - If low IgG levels, replacement with IVIG is reasonable

Conclusions

- **Three new NMOSD targeted therapies:**
  - Inebilizumab, Satralizumab, Eculizumab
  - Highly efficacious
  - Very good safety profiles
  - Possible excess risks of serious infections over the long term cannot be excluded
  - Prophylaxis and IgG level monitoring contribute to risk management
- As the disability in NOMSD is associated mainly with relapses, the postpone of infusion of specific DMTs is strongly not recommended