8th ECTRIMS Focused Workshop

Day 1

Session 2a

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

Infectious Risks in Specific Populations of MS Patients Planning to Start or Already Receiving Immunosuppressive or Immunomodulatory Treatments: What Should We Do?

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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Paediatric MS

Dr Yael Hacohen
UCL, London, UK
Session 2a, April 14th 2021

Some Considerations on Paediatric MS

- Paediatric MS is **rare**, particularly in pre-puberty
- Paediatric MS patients are usually changing several therapies, including immunosuppressive or immunomodulatory treatments
- High disease activity is sometimes observed in paediatric onset MS
- Longer disease corresponds to longer treatment period and more DMTs
- Not enough data yet to properly assess a causal relationship between the use of DMTs and risks of infection

Case Reports

Case 1

- 9-year-old girl affected by RRMS with 3 clinical events in 2016
- Commenced on Fingolimod 0.5 mg/day in 2018 (weight 32 kg*)
- Dose adapted to 0.5 mg alt day in 2020, but relapse

Which is the appropriate dosage to be used in children and what about the efficacy of using half adult dose/day Fingolimod for < 40 kg?

*Company's recommendation: 0.25 mg/day for weight < 40 kg

Case Reports

Case 2

- 12-year-old girl with AQP4-Ab NMOSD
- Very severe presentation and need for intensive care support
- Miraculous recovery after 6 months with steroids, PLEX x2 and Rituximab
- Persistent neutropenia for 2 years, so changed to Azathioprine and neutropenia resolved

What are the **haematologic and immunologic effects of Rituximab** in children?

Data from a multicentre, multinational study by Dale and colleagues (Neurology 2014) on children ≤ 5 years under Rituximab

show an increase of immune-mediated complications beyond B-cell depletion (i.e. hypogammaglobulinemia and lymphopenia)

Case Reports

Case 3

- 10-year-old boy with RRMS presented in 2010
- Initially on Betaferon, but continued to relapse
- Changed to Fingolimod, but had another relapse (2018)
- Changed to Ocrelizumab (2020)

What are the effects of changing **many DMTs** and of **long treatment period** (> 10 years)?

Data from a multicentre, multinational study by Dale and colleagues (Neurology 2014) on children ≤ 5 years under Rituximab

show an increase of immune-mediated complications beyond B-cell depletion (i.e. hypogammaglobulinemia and lymphopenia)

Case Reports

Case 4

- 15-year-old girl with limbic encephalitis
- Received steroids and Rituximab
- Complete recovery in 1 month and back to school
- After 3 months few TB cases at her school
- Put on preventive TB treatment for 6 months and remained asymptomatic

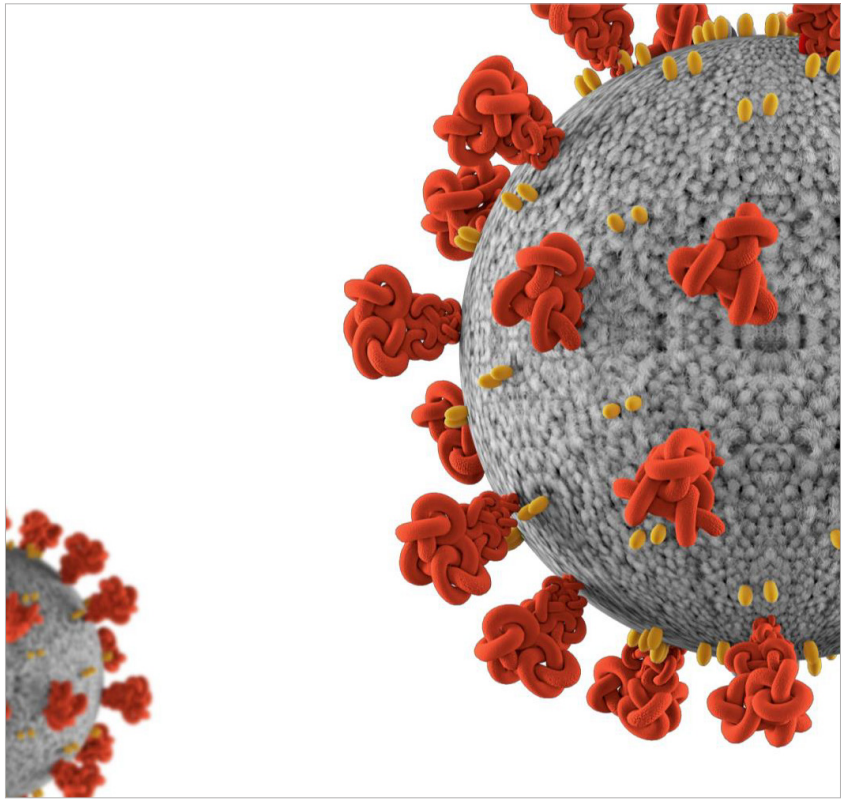
How to deal with **environmental risks** when children continue their normal life?

Data from a multicentre, multinational study by Dale and colleagues (Neurology 2014) on children ≤ 5 years under Rituximab

show an increase of immune-mediated complications beyond B-cell depletion (i.e. hypogammaglobulinemia and lymphopenia)

Impact of Covid-19 on Paediatric MS Patients

- **No direct complications** from Covid-19
- **Reduced compliance** to treatments during home schooling
- Recurrent observation that patients under immunotherapies **take longer to clear Covid-19** (measured by PCR) which interferes with their clinical management when coming to hospital for infusions, blood monitoring, or MRI



Conclusions

- Because of the rarity of paediatric MS, no data are available on the **long-term impact of treatments on risks of systemic illness, oncological diagnoses, and fertility**

- Nevertheless, **risks of infection should be considered** when using biologic therapies

- Gathering data from **international cohort studies,** as well as **Phase 4 clinical studies,** could help shed light on the efficacy and safety of DMTs in children.

2

Pregnant Women

Dr Ruth Dobson
QMUL, London, UK
Session 2a, April 14th 2021

Immune Changes During Pregnancy

- Knowledge about the immunology ofpregnancy is quite poor
- The immune system **adapts to the pregnancy** (“immunological clock”)
- **Increasing tolerance to the fetus** is required for successful pregnancy outcomes.

Most Relevant Maternal Infections During Pregnancy

Listeriosis
- 17% of infections during pregnancy
- Concerns more for the fetus than for the mother (transplacental transmission to the fetus)
- Generally associated with immunosuppression

Nonrespiratory viral infections
- More risks for the fetus than for the mother
- Congenital CMV well described

Urinary tract infection
- Most common during pregnancy and not uncommon in MS
- Associated with a range of adverse pregnancy outcomes

Varicella Zoster Virus (VZV)
- Congenital varicella syndrome
- Vaccination pre-therapy in seronegative women
- Vaccination contraindicated during pregnancy

Other Herpes viruses (HSV-1 & HSV-2)
- Primary infection is the concern
- Late HSV-2 maternal infection can lead to neonatal infection during childbirth
- Suppressive therapy during the last month of pregnancy

Impact of Maternal Infections During Pregnancy

- On the mother
- On the baby

Mild or self limiting infections may be associated with adverse outcomes in the baby (i.e. rubella, CMV, varicella,...)

Many of these infections are vaccine preventable or treatable and a number of them are incorporated into antenatal screening

Vaccination Strategies

- **Varicella** vaccination: routine prior to Fingolimod therapy
- **Rubella** vaccination: routine schedule during adolescence/adulthood and not necessarily checked pre-DMTs
- **Whooping cough** vaccination: routinely given during pregnancy, might have low efficacy in dose on DMTs
- Possibly a reduced response to **influenza** vaccination in women under DMTs, as well as during pregnancy

Covid-19, MS, and Pregnancy

- Infection rate and clinical syndrome **similar to non-pregnant women**
- **Early infection** seems associated with **increased risk of spontaneous abortion**
- Increasing evidence of **asymptomatic Covid-19 disease** during pregnancy (not high fatality rate)

Conclusions

- Very **little data to guide practice** on DMTs during pregnancy

- **Time of vaccination in people under DMTs** is key, as there is increasing evidence of attenuation of vaccine response in people receiving anti CD-20 therapy

- Important to **consider future pregnancy when initiating treatment,** particularly with respect to vaccine efficacy and long-term consequences.

3

The Role of Comorbidities and Advanced Age on the Risk of Infections

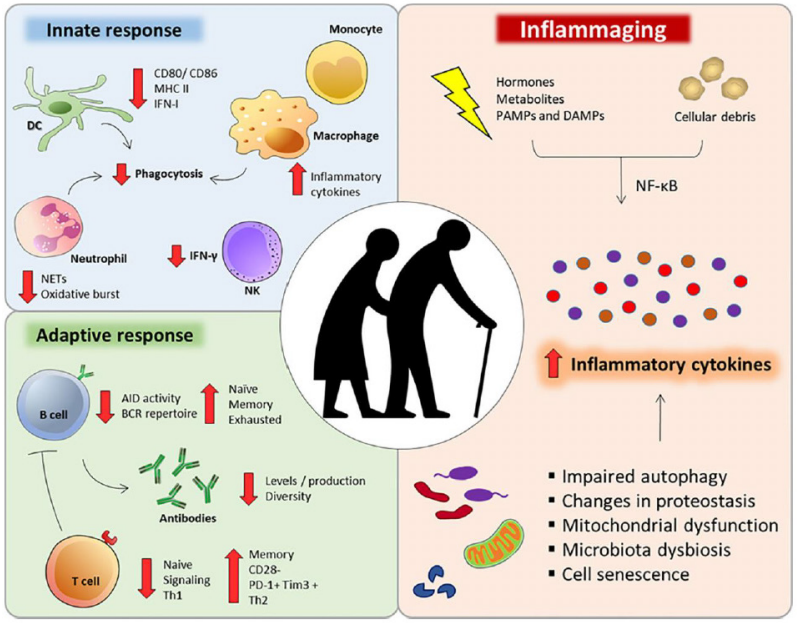
Dr Kathryn Fitzgerald
John Hopkins School of Medicine, Baltimore, US
Session 2a, April 14th 2021

Effects of Aging on the Immune System

- Age is associated with **distinctive changes in the immune system,** known as **immunosenescence** (i.e. CD8+ and CD4+ changes, decrease in B cell precursors, changes in innate immunity)

- A component of immunosenescence is **inflammaging,** a low-grade inflammatory state associated with age.

In MS patients a general loss of immune capacity associated with age is observed



Pietrobon et al., Front. Immunol., 2015

DMTs Use and Risk of Infections

- Higher risk of infections in aged MS patients can be related to the use of DMTs that may accelerate immunosenescence
- Older people with MS are at higher risk of DMT-induced lymphopenia
- Additional changes in immune cell number and function due to DMTs can be detrimental to the already compromised capacity of the aged population.

Infections Associated with DMTs Use

- **Progressive Multifocal Leukoencephalopathy (PML)**
  - Low lymphocyte count and function in the CNS increase the risk of PML
  - Initiation of Natalizumab at older age is associated with earlier onset of PML
  - PML risk associated with other DMTs often due to lymphopenia and modified by age

- **Cryptococcal infection & Varicella Zoster Virus (VZV) reactivation**
  - Higher risk in people ≥ 50 years treated with Fingolimod (as well as higher risk of PML)

Aging induces similar effects to the immune system as many MS DMTs

Summary table of aging and some MS DMTs effects on the immune system

		Aging	Natalizumab	Fingolimod	DMF	Anti-CD20	Teriflunomide	Alemtuzumab
Peripheral	CD19+ B cells	▼	▲	▼▼	▼▼	▼▼▼	▼▼	▼▼▼
	CD3+ B cells	▼	▲	▼▼	▼▼	▼	▼	▼▼▼
	CD4+ T cells	▼	–	▼▼	▼	– / ▼	▼	▼▼▼
	CD8+ T cells	▼	– /▲	▼	▼▼	–	▼	▼▼▼
	CD4+/CD8+	▼	– / ▼	▼	▲	– / ▼	▲	▼
CNS	CD19+ B cells		▼▼			▼▼▼		
	CD3+ T cells		▼▼			▼▼		
	CD4+ T cells		▼▼					
	CD8+ T cells			▼				
	CD4+/ CD8+			▼				

Adapted from Mills et al. MSJ 2018

Infection Risk Modification by Comorbidity

- **Limited data** to establish a relationship between comorbidity and risk of infections associated with DMTs use (clinical studies do not often report comorbidity burden and do not enroll older participants with comorbidities)

- **Data from other autoimmune populations:** comorbidities increase the risk of infections overall and among patients treated with biologic drugs (i.e. Rituximab)

- **Dual contribution of age and comorbidity** (both decreasing immune capacity) can shift the risk-benefit profile of MS people under DMTs

Conclusions

- Aging is associated with **quantitative and functional changes to the immune system**
- Age is associated with an **increased risk of infections and lymphopenia for some DMTs**
- **Limited data** are available on **comorbidity** and risk of infections associated with DMTs use
- More research is needed to evaluate comorbidity and safety of DMTs, as well as the concomitant effects of aging and comorbidity

8th ECTRIMS Focused Workshop

Day 1

Session 2b

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

Populations of MS in High Infection Burden Regions:
Infections and Specific Infections Reported.
Risk Mitigation Strategies

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1

Infectious Risks in Specific Populations: Latin America

Dr María Zuluaga Rodas
Instituto Neurológico de Colombia, Medellín, Colombia
Session 2b, April 14th 2021

MS Prevalence in Latin America

- **MS prevalence in Latin America is low** due to (probable protective) genetic and environmental factors (i.e. genetic mixture of ancestries, higher sun exposure, higher levels of vitamin D, ...)
- **Prevalence has increased** in recent years, as well as female/male ratio, in line with worldwide observations
- **Minor latitudinal differences** in the frequency of MS exists between different Latin American countries

No precise prevalence data are available due to lack of official government statistics and heterogeneous sources of data

MS Treatments in Latin America

Information is scarce regarding DMT use and the risk of infections in Latin America

- Similar to international recommendations
- Availability of DMTs may vary from country to country
- Global access to DMTs is a limiting factor
- Post-marketing studies with some DMTs have demonstrated similar efficacy and safety compared to results of international clinical trials

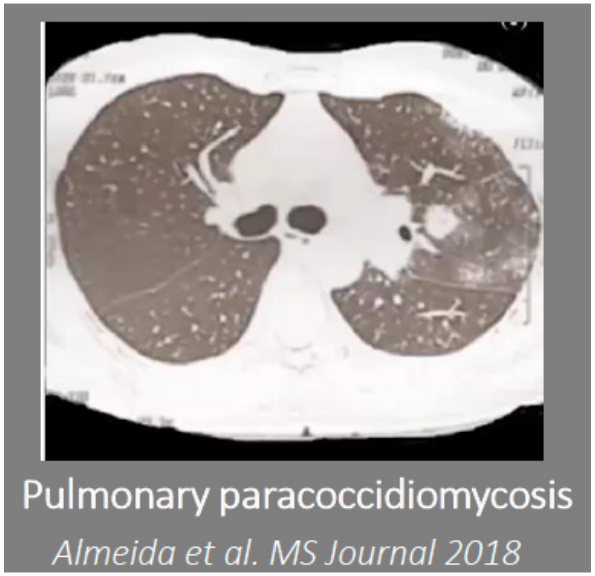
Evidence on Safety of DMTs in the Latin American Population

Natalizumab

- Data from 16 MS centers in Brazil: mostly mild infections, but a few serious uncommon AEs (i.e. recurrent fungal skin infections and severe respiratory tract infection with fatal outcome)
- Opportunistic infections reported in a few cases (i.e. pulmonary paracoccidioidomycosis from an endemic fungus in Latin America)

Fingolimod

- Clinical trials enrolling Hispanic patients: similar results in terms of frequency of infections to non-Latin American patients
- Open label post-marketing study with Hispanic patients: 23% rate of infection, predominantly mild
- Post-marketing study in Argentina: similar rate of infection as seen in other post-marketing studies and safety profile similar to results seen in clinical trials



Pulmonary paracoccidiomycosis

Almeida et al. MS Journal 2018

Infectious complications reported for every used DMT in the local experience

Latent Tubercolosis

- Prevalence of latent TB in Latin America is 17% (very common)
- The probability of re-activation of latent TB and increase of other opportunistic infections due to the use of DMTs with immunosuppressive properties are a concern in some areas of the world

Consensus recommendations for MS patients starting DMTs:

- Latent TB screening recommended for all patients in high-risk regions
- Initiation of DMTs 4 to 8 weeks after treatment initiation for latent TB
- Negative latent TB patients at screening in high-risk regions should be checked annually and treated if become positive

Conclusions

- **More evidence** needs to be gathered **on the frequency and risk of infectious complications** in Latin American MS patients

- Data from **post-marketing studies and real-world evidence** available in the Latin American population **do not differ from results of international clinical trials**

- Nevertheless, it is necessary to be **cautious of infectious complications** in Latin American MS patients (i.e. latent tuberculosis)

2

Infectious Risks in Specific Populations: India/Asia

Dr Lekha Pandit
Centre for Advanced Neurological Research, Nitte University, India
Session 2b, April 14th 2021

MS Management in India

- Because of its low prevalence, MS is considered as an orphan disease in India
- In local low-income settings “off label” treatments like immunosuppressants are the preferential treatment choice instead of less affordable DMTs
- Experience of a hospital-based MS registry (Mangalore Demyelinating Disease Registry): subsidized treatments and patient friendly initiatives ensure compliance and regular follow-up of patients.

MS Treatments in India

First line

for women of childbearing potential

- Interferon Beta (Imported, Biosimilar)
- Glatiramer Acetate (Imported, Biosimilar)
- Azathioprine (Generic -> unaffordable*)

*Cost of healthcare "out of pocket": immunosuppressants more affordable than DMTs

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First line

if no issues of childbearing potential

- Dimethyl Fumarate (Imported, Generic)
- Azathioprine (Generic -> unaffordable*)

*Cost of healthcare "out of pocket": immunosuppressants more affordable than DMTs

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Second line

- Rituximab (Biosimilar, affordable)
- Fingolimod (Generic)

MS Screening Protocol Before Treatment Initiation

Before Treatment

- Medical history of past **TB infections** or family history of TB infections
- Investigation of recent **weight loss, fever, or productive cough**
- Review of **vaccinations**
- **Serology** (HBV, HCV, HIV)
- Baseline **haemogram** including lymphocyte count and **urinalysis**
- **Chest Xray**
- **USG abdomen** (including post void residual volume)
- **CIC training** for urinary infection

During Treatment

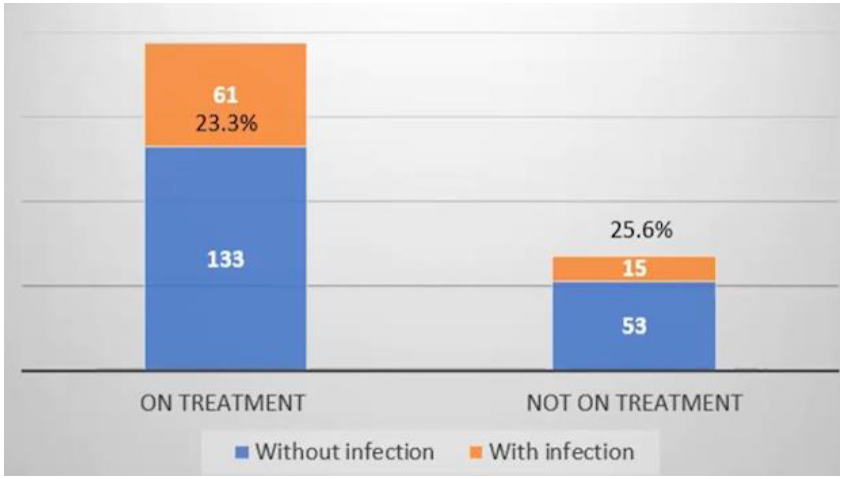
- 3 monthly remote monitoring / visits

Local Experience of a Small MS Patients' Cohort

- 262 MS patients followed-up for an average of 2 years (114 on immunosuppressants, 80 on DMTs, and 68 untreated)

- **Very similar percentage of patients who developed infections in the treated group (23.3%) vs non-treated group (25.6%)**

- **Most of the infections were mild and manageable** (mainly urinary tract infections, respiratory tract infections and a few cases of latent TB and varicella zoster).



Risk of infections seems to not be related to the type of therapy (DMTs vs immunosuppressants)

MS Treatment Management in the Covid-19 Era

- General guidance to **continue medication,** and, if possible, the **3-monthly monitoring of blood counts** and **CD19/20 counts** before planning the following Rituximab infusion

- All **relapses and infections monitored remotely** by general physicians

- 3 MS patients in the local registry developed Covid-19, but all recovered well and the ones under immunosuppressants who developed mild Covid-19 could continue their treatment

Conclusions

- In a small local cohort of Indian MS patients, **infections did not increase in treated patients** and were all **manageable** and **often mild,** probably because patients were monitored closely and most of the therapies were not lymphocyte suppressants

- In a resource poor setting, **making patients aware of the risk of infection and its prevention** together with **close patients' monitoring** is key for successful MS disease management.