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

Recommendations for the Management of Infectious Risks in Routine MS Clinical Practice

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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Recommendations from an MS Expert's Perspective. What Needs to Be Done Before Starting Treatment and During Treatment?

Dr Ludwig Kappos
University Hospital Basel, CH
Plenary Session, April 21st 2021

DMTs in MS Treatment

From a global perspective, immunomodulating and immunosuppressive MS treatments have provided much more benefits than issues.

- **The impact of these compounds on associated infections was expected to be much higher**
- **Patients' risk stratification and risk mitigation strategies help in managing and reducing DMTs' side effects.**

Risk Stratification and Mitigation

Risk Stratification

Based on the assessed risk, mitigation strategies may be adopted:

- Alternative treatment
- Vaccination before treatment initiation
- Prophylaxis (HBV, TB risk)
- Frequent re-evaluation of risk factors
- Risk/benefit trade-off can shift over time and thus needs to be regularly repeated
- Alert patient to mitigated infection symptoms

Risk Mitigation

A comprehensive personalized risk assessment includes:

- Vaccination status
- Concomitant diseases, age
- Infection history
- WBC differential count
- Serology (e.g. for JCV and Natalizumab therapy)
- TBC test (to avoid reactivation)
- IgG levels

Risk/benefit trade-off is required to choose MS therapy

DMTs Associated Risk of Infection

Natalizumab

- Associated with the highest JC-Virus infection risk and thus PML development
- **PML-Risk Stratification:**
  - JCV serology, treatment duration, and previous immunosuppressive treatment
- **PML-Risk Mitigation:**
  - JCV-negative patients: annual MRI; regular check of JCV serology
  - JCV-positive patients: alternative treatment; high vigilance for PML symptoms; avoid prior immunosuppressants; frequent MRI monitoring
- Risk mitigation strategies adapted to patients' individual risk led to a reduced PML bincidence in MS patients
- A prolonged dosing interval approach may help in further mitigating risk without compromising efficacy

Dimethyl fumarate

- Main risk factor is a low lymphocyte count occurring within 6-12 months after treatment initiation
- Clinical observations and immunophenotyping data show that efficacy against the disease and the risk of increased immunosuppression are differently regulated

DMTs Associated Risk of Infection

Natalizumab

- Is associated with a higher risk of infection (but lower than initially expected!)
- Infectious risk mainly occurs with the first phase of treatment (1-2 months after initiation)
- Long-term data are lacking especially with repeated (>2) treatments

S1P modulators

- S1P-derived lymphopenia is not correlated with increased risk of infection
- The associated higher risk of Herpes infection is not due to lymphopenia

Anti-CD20 Monoclonals

- They are associated with a low risk of infection maybe because of the preservation of certain B cell subpopulations
- A tendency towards increased risk is observed starting from 5 years after treatment initiation (Ocrelizumab)
- Higher rates of serious infections are associated with IgG level below the Lower Limit of Normal (LLN)

Alemtuzumab

- Risk associated with the courses of treatment (three months after treatment)
- The risk is mitigated by prophylaxis against Herpes infections

Conclusions

- **DMTs are important therapeutic tools in MS treatment** even though often associated with increased risk of infection

- **Risk stratification and a regular risk/benefit trade-off should be performed for each MS patient**

- **Risk mitigation strategies allow for better prevention and control of clinical complications** due to treatment-associated infections.

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Recommendations for the Management of Infectious Risks in Routine MS Clinical Practice from an Infectious Disease Expert's Point of View

Dr Isabel Ruiz Camps
Hospital Universitario Vall d'Hebron, Barcelona, Spain
Plenary Session, April 21st 2021

Risk of Infections in MS Patients

- Regardless of their treatment, MS patients have a **higher risk of infections** compared to the general population
- Most of the infections are mild, but in **< 3% of cases can be severe**
- The **added risk of infections due to individual MS treatments** is **difficult to estimate** (different drug mechanisms and their effect on immunomodulation/immunosuppression)
- When investigating the **causality of an infection,** both the **host** and the **drug** should be considered.

Infections Associated with MS Treatments

- **Herpes Viruses** (Glatiramer Acetate, Natalizumab, Steroids, Alemtuzumab, Fingolimod, Cladribine, antiCD20)
- **CMV** replication (Alemtuzumab)
- **HBV/HCV** (antiCD20, Alemtuzumab, Fingolimod, Teriflunomide)
- **Reactivation of latent TB** (Steroids, Natalizumab, Teriflunomide, Alemtuzumab, Cladribine)
- **PML** (most of the drugs)
- **Fungal infections** (Alemtuzumab, Fingolimod, Natalizumab, antiCD20)
- **HPV** (Alemtuzumab, Fingolimod)
- **Toxoplasma** (Natalizumab, Fingolimod, Alemtuzumab)

MS Infection Prevention

DMTs are **long-lasting treatments,** therefore prevention should be done both **before treatment and during the treatment period**

Before Treatment	During Treatment
Complete clinical history review (comorbidities, childhood infectious diseases, travels, sexual behaviour, drug history)	Usual MS controls
Vaccination (influenza annually, pneumococcal infections, hepatitis, varicella, measles, Herpes, HPV)	Dietary/healthy life counselling
Screen for latent infections	Annual HPV screening (all females and males who have sex with males)
CBC, Ig (before Rituximab and Ocrelizumab)	Prophylaxis in some cases (avoid indiscriminate use of antibiotics)

Suspected Infection

- Accurate clinical history
- Laboratory and microbiological testing
- Targeted antibiotic selection (avoid broad spectrum) for the indicated length of treatment

Personalized approach whether to continue or to stop an MS treatment after an infection episode

Conclusions

- Infections in MS patients are **frequent**
- Most of the infections are **similar to those observed in the general population**
- Infections **depend on the host and on the drug**
- Preventive measures **before starting a treatment and during the treatment**
- **Timely infection diagnosis** to select the appropriate therapy (targeted antibiotic approach).