Infectious complications in MS: An audit of high efficacy therapies pre-treatment screening and risk mitigation

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Background

- No gold standard for infection screening / risk mitigation prior to initiating DMTs
- SPC recommendations based on clinical trial results and post marketing pharmacovigilance reports
- Clinical trials: Finite participant numbers, duration ≈ 24 months & exclude those with known risk factors
- Known class effects experienced in other disease areas often excluded

Real world practice

New product information wording – Extracts from PRAC recommendations on signals

Adopted at the 3-6 September 2018 PRAC

1. Alemtuzumab – Cytomegalovirus infection (EPITT no 19193)

Summary of product characteristics

4.4. Special warnings and precautions for use

Infections

[...]

Cytomegalovirus (CMV) infections including cases of CMV reactivation have been reported in LEMTRADA-treated patients. Most cases occurred within 2 months of alemtuzumab dosing. Before initiation of therapy, evaluation of immune serostatus could be considered according to local guidelines.

Primary cytomegalovirus infection in a patient with relapsing-remitting multiple sclerosis under treatment with alemtuzumab.

[Article in English, Spanish]

Eichau S[1], López Ruiz R[2], Castón Osorio JJ[3], Ramírez E[4], Domínguez-Mayoral A[1], Izquierdo G[1].

Author information

PMID: 29907474 DOI: 10.1016/j.nrl.2018.03.015

Active CMV infection in two patients with multiple sclerosis treated with alemtuzumab

Marinella Clerico, Stefania De Mercanti, Carlo Alberto Artusi, more... Show all authors

First Published February 1, 2017 | Case Report | Check for updates

Bacterial and CMV pneumonia in a patient treated with alemtuzumab for multiple sclerosis

Antonio Riccardo Buonomo[a,*], Francesco Saccà[b], Emanuela Zappulo[a], Federico De Zottis[a], Roberta Lanzillo[b], Ivan Gentile[a], Antonio Carotenuto[b], Guglielmo Borgia[a], Cinzia Valeria Russo[b]

PlumX Metrics

DOI: https://doi.org/10.1016/j.msard.2018.09.031 | Check for updates

Hepatic microabscesses during CMV reactivation in a multiple sclerosis patient after alemtuzumab treatment

Stefania Barone[a], Sara Scannapieco[a], Carlo Torti[b], Enrica Filippelli[a], Vincenzo Pisani[b], Alfredo Granata[a], Domenico Console[c], Giulio Demonte[a], Tiziana Tallarico[a], Serena Polidoro[a], Aldo Quattrone[a,d], Paola Valentino[a,*]

PlumX Metrics

DOI: https://doi.org/10.1016/j.msard.2017.12.009 | Check for updates

Recommendations from the literature

Drug	LTBI Screening	Acyclovir Prophylaxis[a]	PML Screening and Monitoring	HBV Risk	Other
Natalizumab	Consider[b]	Consider[c]	Yes; see Table 4	Universal screening; see Table 3	Universal screening for HCV and HIV
Alemtuzumab	Yes	Yes[d]	No	Universal screening; see Table 3	Universal screening for HCV and HIV
Ocrelizumab	No[e]	No[f]	No	Universal screening; see Table 3	Universal screening for HCV and HIV
Mitoxantrone	Consider[b]	No[f]	No	Universal screening; see Table 3	Universal screening for HCV and HIV
Fingolimod	Consider[b]	Consider[g]	No	Universal screening; see Table 3	Universal screening for HCV and HIV

Epstein et al. Open Forum Infectious Diseases, August 2018 -Infectious Complications of Multiple Sclerosis Therapies: Implications for Screening, Prophylaxis, and Management

Mikulska Clin Microbiol Infect. June 2018 - ESCMID Study Group for Infections in Compromised Hosts Consensus Document on the safety of targeted and biological therapies (CD19, CD20 and CD52).

Our standards

Standard set of tests: HBV screening (including core antibody) HCV Ab, VZV IgG, HIV Ab/ Ag, HSV IgG, CMV IgG and TB Elispot IGRA, based on:

- Known and predicted risks based on mechanisms of action.
- Acknowledge, high efficacy DMTs do not carry the same level of risk for the above infections
- Standardised tests make consistent infection screening more likely
- Screening for multiple infections regardless of planned treatment aids decision making when switching treatment

Our standards

Prior to starting long term immunosuppression with Ocrelizumab.

For those with incomplete immunisation records:

- MMR IgG and VZV IgG serology,
- Vaccines: DTP, MenACWY, Pneumococcal 23 valent, Hib, influenza and Men B

Audit

- Baseline infection screening prior to starting Alemtuzumab, Cladribine, fingolimod, Natalizumab and Ocrelizumab
- Determine compliance with local standards (+ risk mitigation)
- Jan 2015 to Nov 2018 VS Dec 2018 to April 2019
- Exclusions: Treatment initiated during clinical trials, treatment initiated by another MS centre and incomplete electronic records (from local district general hospital or out of area).
- Total of 83 records were reviewed

Outcomes

Jan 2015 to Nov 2018 (n=65)

Tests were based on SPC recommendations	
HBV screening	62%
HCV Ab	62%
VZV IgG	94%,
HIV Ab/ Ag	69%
HSV IgG	0%
CMV IgG	0.2%
TB Elispot IGRA	49%

Dec 2018 to April 2019 (n=18)

Post implementation of new standards	
HBV screening	100%
HCV Ab	100%
VZV IgG	100%
HIV Ab/ Ag	100%
HSV IgG	100%
CMV IgG	100%
TB Elispot IGRA	88%

Outcomes

- Measles IgG, Mumps IgG and Rubella IgG screening on 2 as immunisation records unavailable.
- Latent TB x 2 (pre-alemtuzumab / natalizumab) treated with isoniazid
- HSV positive x 6
- CMV IgG positive x 4
- Multiple +ve viral screening tests (n=1) antibody/Immunoglobulin acquired from prior IVIg infusion?
- Vaccine status check lists were not available to audit from clinical electronic records.

What next?

Ocrelizumab Screening Checklist PowerPlan (Initiated Pending) 18/Jan/2019 12:56		
Previous DMT (If Yes record name and date of last dose in outcome Note)	✓ 18/Jan/2019 12:56	
Previous DMT is Natalizumab	✓ 18/Jan/2019 12:57	
Predisposition to cancer, especially breast cancer	✓ 18/Jan/2019 12:57	
Patient information leaflet given	✓ 18/Jan/2019 12:57	
Written consent obtained from patient	✓ 18/Jan/2019 12:57	
Contraception (Women of child bearing age): discussed and agreed	✗ 18/Jan/2019 12:57	
Hepatitis C & Hepatitis B screen (surface and core antibodies) results reviewed?	✓ 18/Jan/2019 12:57	
HSV Ig results reviewed. If positive inform patient of risk of disease reactivation	✓ 18/Jan/2019 12:57	
CMV Ig results reviewed. If positive inform patient of risk of disease reactivation	✓ 18/Jan/2019 12:57	
TB Elispot results reviewed	✓ 18/Jan/2019 12:57	
Chest X-ray reviewed	✓ 18/Jan/2019 12:57	
HIV test results reviewed	✓ 18/Jan/2019 12:57	
VZV serology results reviewed. If negative vaccine to be given at least 6 weeks before treatment		
Collect pre-infusion sample for: CD19 (EDTA tube), CD4+, CD8+, CD19+ titres	✓ 18/Jan/2019 12:57	
IgG, IgA and IgM results reviewed. If IgG < 6g/L discuss with MS consultant +- immunologist	✗ 18/Jan/2019 12:57	
Vaccine status checked. Live vaccines must be given at least 6 weeks before treatment	✓ 18/Jan/2019 12:58	
Pneumococcal vaccine given	✓ 18/Jan/2019 12:58	
Haemophilus influenza type B vaccine given	✓ 18/Jan/2019 12:58	
FBC: lymphopenia and/or neutropenia excluded	✓ 18/Jan/2019 12:58	

What next?

- Collaboration with other specialties to better manage risk e.g. infectious diseases
- Develop toolkit for managing infection risks associated with MS DMTs
- Consensus statement on managing infection risks associated with MS DMTs

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