Safety profile of ocrelizumab for the treatment of multiple sclerosis: a systematic review

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INTRODUCTION

- Ocrelizumab has been approved for the treatment of relapsing and primary progressive multiple sclerosis (MS).
- This review aims to provide a comprehensive summary of reported adverse event for ocrelizumab, using a systematic approach.

METHODS

- We searched **four biomedical databases** (Medline, Embase, Web of Science and Toxicology Data Network-TOXLINE) from inception **to 08-July-2020**, using search terms 'multiple sclerosis, clinically isolated syndrome and ocrelizumab'.
- We also searched clinical trial registries, drug company websites and ocrelizumab product monograph.
- We included **clinical trials, observational studies and case studies** reporting any **adverse events** for **individuals with a diagnosis of MS or clinically isolated syndrome**, regardless of age and sex.
- Searches and data extraction were conducted independently by two authors with any disagreements resolved with the third author.

RESULTS

Studies included in the review

2236 records

- identified (as of 08-July-2020).

78 records

- included which accounted for :
- **4 randomized controlled trials (RCTs)**
- **4 open-label trials**
- **29 observational studies**
- **27 case reports**

Overview of adverse events by study

Adverse event	Study design (type of comparator)	Ocrelizumab group	Comparator group	Pooled frequency ocrelizumab (%)
Serious adverse events	RCT (vs beta-interferon)	58 / 825	73 / 826	**218 / 3128 (7.0)**
	RCT (vs placebo)	102 / 486	56 / 239	
	RCT (high or low dose vs placebo)	4 / 110	2 / 54	
	RCT (conventional vs shorter infusion)	3 / 291 3 / 289		
	OLT (no comparator)	34 / 680		
	OBS (no compactor)	14 / 447		
Adverse events leading to discontinuation	RCT (vs beta-interferon)	29 / 825	51 / 826	**171 / 6577 (2.6)**
	RCT (vs placebo)	20 / 486	8 / 239	
	RCT (high or low dose vs placebo)	3 / 110	0 / 54	
	RCT (pooled frequency from ocrelizumab treated RCTs/ OLTs)	141 / 4611		
	RCT (conventional vs shorter infusion)	1 / 291 0 / 289		
	OLT (no comparator)	7 / 680		
	OBS (vs rituximab)	11 / 161	8 / 311	
	OBS (no comparator)	18 / 1225		
Any adverse events	RCT (vs beta-interferon)	688 / 825	689 / 826	**2756 / 4498 (61.3)**
	RCT (vs placebo)	462 / 486	216 / 239	
	RCT (high or low dose vs placebo)	70 / 110	38 / 54	
	RCT (conventional vs shorter infusion)	125 / 291 120 / 289		
	OLT (no comparator)	701 / 833		
	OBS (no compactor)	590 / 1664		

Key: RCT, randomized controlled trial; OLT, open-label trial; OBS, observational studies.

Summary of adverse events by symptom, body site or laboratory parameter

Adverse event	Pooled frequency ocrelizumab (%)
Infections and infestations	
Serious infections	236 / 3244 (7.3)
Infections	1342 / 3424 (39.2)
Nasopharyngitis	248 / 1574 (15.8)
Upper respiratory tract infections	319 / 2268 (14.1)
Skin infections	68 / 486 (14.0)
Urinary tract infections	338 / 2485 (13.6)
Lower respiratory tract infections	115 / 1311 (8.8)
Influenza	95 / 1311 (7.2)
Herpesvirus-related infection	72 / 1311 (5.5)
Sinusitis	70 / 1464 (4.8)
Bronchitis	76 / 1646 (4.6)
Gastroenteritis	51 / 1521 (3.4)
Oral herpes	39 / 1421 (2.7)
Viral infection	33 / 1311 (2.5)
Rhinitis	29 / 1311 (2.2)
Herpes zoster	31 / 1754 (1.8)
Other infections (type unspecified)	40 / 335 (11.9)
Progressive multifocal leukoencephalopathy (PML)[a]	9 cases
Serious potential opportunistic infections	6 cases
Meningitis	2 case reports
Enterovirus-associated fulminant hepatitis B	1 case report
Infective endocarditis	1 case report
Viral encephalitis	1 case report

[a]8 cases had prior exposure to another DMD, while 1 case had no prior DMD exposure.

Adverse event	Pooled frequency ocrelizumab (%)
General disorders and administration site conditions	
Serious infusion-related reaction	6 / 1452 (0.4)
Infusion-related reaction (IRR)	1391 / 5301 (26.2)
Rash (IRR)	127 / 1439 (8.8)
Pruritus (IRR)	144 / 1649 (8.7)
Throat irritation (IRR)	127 / 1891 (6.7)
Fatigue/ tiredness	159 / 2358 (6.7)
Flushing (IRR)	93 / 1439 (6.5)
Edema peripheral	29 / 486 (6.0)
Headache (IRR)	107 / 2270 (4.7)
Influenza-like illness/ flu-like symptoms	46 / 1063 (4.3)
Oropharyngeal pain (IRR)	39 / 1311 (3.0)
Urticaria/ allergic rash (IRR)	40 / 1352 (3.0)
Pyrexia (IRR)	40 / 1439 (2.8)
Nausea (IRR)	31 / 1690 (1.8)
Tachycardia (IRR)	30 / 1649 (1.8)
Dizziness (IRR)	24 / 1439 (1.7)
General disorders and administration site conditions (type unspecified)	46 / 493 (9.3)
Psychiatric disorders	
Depression including suicide	117 / 1311 (8.9)
Insomnia	74 / 1311 (5.6)
Atypical psychiatric presentation	2 case reports
Pregnancy, puerperium and perinatal conditions	
Birth defects	6 / 48 (12.5)
Structural malformations	3 / 48 (6.3)
Still birth	1 / 267 *Numerator refers to the number of pregnancies, not number of women*
Preterm birth	5 / 267 *Numerator refers to the number of pregnancies, not number of women*

Adverse event	Pooled frequency ocrelizumab (%)
Neoplasms	
Malignancies	72 / 5528 (1.3)
Breast cancer	95 *Estimated denominator from the drug manufacturer*
Investigations	
'*Decreased lymphocytes*' below the LLN[b]	299 / 1311 (22.8)
Lymphopenia (<500/mm3)	44 / 1712 (2.6)
'*Decreased neutrophils*' level[b]	184 / 1311 (14.0)
Abnormal alanine aminotransferase[c]	76 / 1311 (5.8)
Abnormal gamma-glutamyl transferase[c]	69 / 1311 (5.3)
Abnormal aspartate aminotransferase[c]	32 / 1311 (2.4)
Investigations (type unspecified)	25 / 493 (5.1)
Late-onset neutropenia	3 case reports
Early-onset/ rapid onset neutropenia	2 case reports
Nervous system disorders	
Headache	177 / 1590 (11.1)
Nervous system disorder (type unspecified)	114 / 646 (17.6)
Seizure	2 / 235 and 3 case reports
Musculoskeletal and connective tissue disorders	
Back pain	115 / 1311 (8.8)
Pain in extremity	76 / 1311 (5.8)
Musculoskeletal and connective tissue disorders (type unspecified)	35 / 493 (7.1)
Other serious adverse events	
Death	26 / 4946 (0.5)
Cholecystitis/ cholelithiasis	7 / 1311 (0.5)
Pancreatitis	4 / 1311 (0.3)
Possible case of serum sickness	1 case report
Colitis	1 case report
Reactivation of rheumatic cardiopathy	1 case report
Drug reaction with eosinophilia and systemic symptoms (DRESS)	1 case report

Key: LLN, lower limit of normal.
[b]No definition of 'decreased' was provided, so it was unclear what was decreased relative to what. Of note, none of these findings appeared in peer-reviewed scientific publications.
[c]'Abnormal' was defined by authors as 'clinically important abnormalities' but the level of abnormalities was not specified.

CONCLUSION

- This systematic review collated all reported adverse events for over 7000 patients treated with ocrelizumab for MS from a diverse range of sources, including completed and ongoing clinical trials, post-marketing surveillance and case reports.
- Adverse events affected 2756/4498 (61.3%) of ocrelizumab-exposed patients.
- **Infections** were the most commonly reported adverse events, **affecting 4 in every 10 patients** treated with ocrelizumab, followed by **infusion-related reactions**, **affecting nearly 1 in 3**.
- The **longer-term safety** of ocrelizumab, including **malignancy and serious infections remain unknown**.

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- **Dr Luzon** was a former employee of Merck and is a current employee of Xenon Pharmaceuticals, although was a full-time student at the University of British Columbia when this study was conducted.
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