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O0803 Infective risk in patients with multiple sclerosis treated with agents targeting CD20/CD52 surface antigens

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Background: Monoclonal antibodies directed against CD20/52 antigens are increasingly used in patients with multiple sclerosis (MS). However, several life-threatening opportunistic infections have been reported in post-marketing case series. The aim of this study was to investigate the incidence and predictive factors of infective complications in patients receiving anti-CD20 (ocrelizumab [OCR] and rituximab[RTX]) or anti-CD52 (alemtuzumab, ALM) drugs for MS treatment.

Materials/methods: A monocentric, retrospective study was led in patients with MS who started treatment with ALM, OCR and RTX (off-label use) from 1st November 2015 to 1st June 2018. Demographic, laboratory and clinical data were collected at baseline and in case of infection. Infective events were defined as new infections, both microbiologically and/or clinically documented, that persisted for over 24 hours. CMV reactivation was defined as detectable viraemia (>85 cp/ml), regardless from signs of CMV disease. During treatment, the development of immune impairment(IMI) -defined as new onset of lymphocytopenia[<800 cells/µl], and/or hypogammaglobulinemia[IgG <7 g/dl] and/or neutropenia[<1000 cells/µl])- was evaluated.

Results: A total of 163 patients were enrolled: 82 (41%) received ALM, 38 (23%) OCR and 58 RTX (36%). Median follow-up time was 226 days [IQR: 93-422]. During treatment, 41% of patients experienced lymphocytopenia, 6% hypogammaglobulinemia and 1% neutropenia. IMI's incidence was lower in patients receiving anti-CD20 agents (22% vs 87% in the ALM group, p<0.001). Eighty-six infectious adverse events were reported in 67 patients (41%) (Figure 1). Bacterial infections were significantly more common during anti-CD20 treatments, while viral infections prevailed with anti-CD52-regimens (p<0,001 for both). CMV reactivation rates were significantly higher in ALM-group (55%, 37/67 vs 7.5%, 5/66 patients, p <0.001) and most events occurred during the first month of treatment. The overall annualized infection rate amounted to 6.9/1000 patient-yrs, with higher figures in patients on anti-CD52 (21.8 vs 8.3/1000 patient-yrs, p=0.001). ALM administration, prior exposure to more than two MS drugs and development of IMI during treatment were significant predictive factors for infections at multivariate analysis (HR: 2,8, p=0,012; HR: 1,7, p=0,05 and HR: 3, p=0,004, respectively).

Conclusions: Due to the significant infective risk, MS patients treated with anti-CD20/CD52 agents should be assessed for tailored preventive interventions and follow-up strategies.

Figure 1 Infective adverse events in patients receiving different MAbs.

	Total (n=86) *n (%)*	Anti CD20 (n=28) *n (%)*	Anti CD52 (n=58) *n (%)*	p-Value
Recurrent infective events	9 (11)	4 (14)	5 (9)	NS
Etiology				
Bacterial	31 (36)	19 (68)	12 (21)	<0,001
Viral	49 (57)	7 (25)	42 (72)	<0,001
Fungal	5 (6)	2 (7)	3 (5)	NS
Severity				
Mild-moderate	67 (78)	20 (71)	47 (81)	NS
Severe	19 (22)	8 (29)	11 (19)	-
Type of infection				
UTI	23 (27)	13 (46)	10 (17)	0,004
RTI	8 (9)	6 (21)	2 (3)	0,013
CMV reactivation	42 (49)	5 (18)	37 (64)	<0,001
HSV or VZV reactivation	4 (5)	1 (4)	3 (5)	NS
Median time of onset (days) [IQR]	30 [23-94]	48 [10-103]	30 [28-92]	NS
First month onset	46 (54)	12 (43)	34 (59)	-
2-6 months onset	30 (35)	12 (43)	18 (31)	-
7-12 months onset	10 (12)	4 (14)	6 (10)	-
Immune-status				
Baseline				
Median lymphocytic count [IQR]	1125 [80-2070]	1580 [1053-2143]	610 [68-1838]	0,07
Lymphocytopenia (<800 cells/µl))	37 (43)	4 (14)	33 (57)	<0,001
C4+ T cells count < 200 cells/µl	18/78 (23)	4/26 (15.4)	14/52 (27)	NS
At infective event				
Median lymphocytic count [IQR]	670 [250-1350]	1205 [588-1580]	550 [220-910]	0,07
Lymphocytopenia (<800 cells/µl))	50 (58)	9 (32)	41 (71)	0,001
C4+ T cells count < 200 cells/µl	50/62 (81)	10/13 (77)	40/49 (82)	NS

Abbreviations: *UTI: urinary tract infections; RTI: respiratory tract infections, DMT: disease modifying therapies, CMV: cytomegalovirus; VZV: varicella zoster virus; HSV: herpes simplex virus; Data are expressed as number (percentage) or median [IQR, interquartile range].*

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