DENOSUMAB, WITH AND WITHOUT BIOLOGIC THERAPY AND THE RISK OF INFECTION IN PATIENTS WITH RHEUMATOID ARTHRITIS

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INTRODUCTION: The use of biologic agents (BA) in the treatment of rheumatoid arthritis (RA) have increased the risk of all types of infections, non-opportunistic as well as opportunistic. The introduction of denosumab, a monoclonal antibody targeting the RANK ligand, has been associated with a possible increased risk of infection . As denosumab has a different therapeutic objective, specifically prevention of bone loss, it may be used in conjunction with other biologic agents raising the risk of infections in patient with RA.

OBJECTIVES: To evaluate the risk of infection in patients with RA treated with denosumab alone or concomitantly with a biologic agent (BA).

METHODS: Patients with RA followed at the Institut de Rhumatologie de Montréal and who were prescribed denosumab were followed prospectively between February 2005 and July 2014. Baseline demographics, co-morbidities, co-medication and infectious events were recorded in the RHUMADATA® database. Patients were divided in 2 groups, the first received denosumab concomitantly with a biologic agent and the second group took only denosumab without ever taking a BA. The rate of infection was evaluated one year prior to the initiation of the denosumab and compared to the rate of infection during the exposure to denosumab in both groups. The data were analyzed using the SAS statistical software (Version 9.3).

	Denosumab use group		
	Concomitant use of denosumab and a BA[1]	Denosumab alone	Total
N	20	43	63
Age (years)	68.7 (11.9)	71.1 (10.3)	70.3 (10.8)
Women, n (%)	19 (95.0%)	39 (90.7%)	58 (92.1%)
Cigarette smoking, n (%)	4 (20.0%)	7 (16.3%)	11 (17.5%)
Disease duration (years)	18.7 (9.2)	18.6 (15.2)	18.6 (13.5)
Comorbidity			
Diabetes, n (%)	2 (10.0%)	2 (4.7%)	4 (6.3%)
COPD, n (%)	0 (0.0%)	3 (7.0%)	3 (4.8%)
Cancer, n (%)	2 (10.0%)	10 (23.3%)	12 (19.0%)
Prednisone, n (%)	9 (45.0%)	12 (27.9%)	21 (33.3%)
Prednisone dose, (mg)	5.5 (2.0)	7.3 (5.0)	6.5 (4.0)
DMARDs			
Methotrexate, n (%)	9 (45.0%)	28 (65.1%)	37 (58.7%)
Hydroxychloroquine, n (%)	4 (20.0%)	15 (34.9%)	19 (30.2%)
Number of infections			
One year pre denosumab use	7	8	15
During denosumab use	9	17	26
One year pre biologic use	2	0	2
During biologic use	7	0	7
During concomitant use	5	0	5
Denosumab treatment duration (patient-years)	38.01	67.93	105.94
Biologic treatment duration (patient-years)	111.92	18.84	130.76
Concomitant treatment duration (patient-years)	31.83	0	31.83

[1] Data are presented as means and, in parentheses, standard deviations and as frequencies and percentages.

	Denosumab use group		
	Concomitant use of denosumab and a BA	Use of denosumab alone	Total
Infection rates (per 100 patient-year)[1]			
One year pre denosumab use	35.00 (8.29-61.71)	18.60 (8.03-36.60)	23.81 (13.33-39.27)
During denosumab use	23.68 (10.83-44.95)	25.03 (14.58-40.07)	24.54 (16.03-35.96)
One year pre biologic use	10.00 (12.11-36.12)	0 (0-0)	NA
During biologic use	6.25 (2.52-12.89)	0 (0-0)	NA
During concomitant use	15.71 (5.10-36.60)	NA	NA
Infections, n(%)			
Bronchitis	1 (5.0%)	1 (2.3%)	2 (3.2%)
Upper respiratory tract infection	10 (50.0%)	6 (14.0%)	16 (25.4%)
Gastro intestinal	2 (10.0%)	1 (2.3%)	3 (4.8%)
Urinary tract infection	1 (5.0%)	2 (4.7%)	3 (4.8%)
Herpes	1 (5.0%)	0 (0.0%)	1 (1.6%)
Otitis	1 (5.0%)	0 (0.0%)	1 (1.6%)
Warts	1 (5.0%)	0 (0.0%)	1 (1.6%)
Phlebitis	1 (5.0%)	0 (0.0%)	1 (1.6%)
Cutaneous	0 (0.0%)	1 (2.3%)	1 (1.6%)
Unknown	1 (5.0%)	9 (20.9%)	10 (15.9%)

[1] Observed infection rates and, in parentheses, their 95% confidence interval. NA=Not applicable.

RESULTS: A total of 63 patients were ever prescribed denosumab, 20 concomitantly with a BA and 43 without a BA. Patients were on average 70.3 years of age, 92% were women, and had a mean (SD) RA disease duration of 18.6(13.5) years. Exposure to denosumab was on average 1.9 years for Group 1 and 1.6 years for Group 2. No differences were noted for co-morbidities or co-medication between the 2 groups. For Group 1, the rates of infections per 100 pt.-years were respectively 35.0 in the year preceding the start of denosumab and 15.7 during the concomitant use with a BA (p=0.16). For Group 2 the rates were respectively 18.6 prior to denosumab use and 25.0 during denosumab use (p=0.49).

CONCLUSIONS In this cohort of RA patients whose baseline characteristics were similar, the risk of any infection was not increased by denosumab given alone or in combination with a biologic agent.

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