Anti tumor necrosis factor α (TNF-α) and risks of tuberculosis

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To the Editor,

The use of anti-TNF (tumor necrosis factor) has improved significantly the treatment of inflammatory conditions such as rheumatoid arthritis (RA)[1]. However the long term surveillance shows that these drugs can cause serious adverse events due to intracellular organism infections such as tuberculosis (TB)[1]. TB infections appear usually within the first months of exposition to the drug and are characterized by a high proportion of extra pulmonary involvement[1]. It is noteworthy that active disease in anti-TNF users appears to constitute reactivation of latent focus and is therefore a reflection of a previously acquired infection[2]. The use of monoclonal antibodies against TNF (infliximab and adalimumab) seems to carry higher risk than the soluble receptor (etanercept)[3]. As TB is common in our country, the Brazilian Guidelines for RA Treatment[4] suggests that each patient about to receive anti-TNFα should have chest XRs and PPD beforehand and prophylactic isoniazid should be given to those with skin test ≥5mm. However, very little is known about risks of TB infection in long time anti-TNF users. This analysis is difficult because RA itself increases risk of bacterial infections[1,2] and these patients also use other immunosuppressive drugs. To study this we analyzed 47 RA anti-TNFα users – 25/47 (53.2%) with infliximab, 11/47 (23.4%) with adalimumab, 11/47 (23.4%) with etanercept) with median time of use of 36 months (range 12-98) matched with 58 RA patients without biologic treatment. This study received local Ethics Committee approval. We excluded patients that had previous diagnosis of TB and those that began prophylaxis prior

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TABLE I. DATA ON SAMPLE PAIRING AND RESULTS OF PPD IN ANTI-TNF USERS AND CONTROLS

	With anti TNF N=47	Without anti TNF N=58	P
Mean age (years)	47.40±13.28	52.67±12.70	0.11(*)
Gender (Male/female)	11/36	7/51	0.19 (#)
Glucocorticoid users (number)	39/47 (82.9%)	40/58 (68.9%)	0.11(##)
Glucocorticoid dose§ (mg/day of prednisone or equivalent)	5 to 20 Median 10 (IQR=7.5-15)	5 to 20 Median 7.5 (IQR=5.0-15.0)	0.12(**)
Methotrexate users	34/47 (72.3%)	40/58 (68.9%)	0.70(##)
Leflunomide users	21/47 (44.6%)	16/58 (27.5%)	0.09(##)
Sulfassalazine users	8/47 (17.0%)	8/58 (13.7%)	0.64(##)
Antimalarial users	24/47 (51.0%)	26/58 (44.8%)	0.52(##)
Median interval between the two PPDs (in months)	12 to 72 (median=24; IQR 12-48)	12 to 72 (median=12; IQR 12-24)	0.10(**)
Conversion	3/47- (6.38%) 2-using etanercept 1-using infliximab	6/58 (10.3%)	0.72(##)

(*)unpaired t test; (**) Mann Whitey test; (#)- Fisher test ; (##) Chi squared test; §dose at the second PPD. IQR=interquartil range

to anti-TNF use. All patients had two PPD evaluations[5] and conversion was defined as increase of 6 mm between the two tests[4]. Sample pairing and results are on Table I.

Our results suggest that, after a median time of 2 years use (after the initial risk of reactivation has past) the possibility of TB infection in RA patients that use anti-TNF is equal to AR patients using non biological medications.

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AGENDA

XV MEDITERRANEAN CONGRESS OF RHEUMATOLOGY

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Local e Data: Lisboa, Portugal, 7 de Outubro de 2014

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Local e Data: Belo Horizonte, Brasil, 10 a 14 de Outubro de 2014

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Local e Data: Madeira, Portugal, 5 a 7 de Novembro de 2014

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Local e Data: Boston, EUA, 14 a 19 de Novembro de 2014

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Local e Data: Lisboa, Portugal, 27 a 28 de Novembro de 2014