



## **Effect of Exposure to Tobacco Smoke on Response to Anti-Tumor Necrosis Factor-Alpha Treatment in Patients with Rheumatoid Arthritis**

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### **Dear Editor-in-chief**

Rheumatoid Arthritis (RA) patients who are active smokers have high levels of Tumor Necrosis Factor (TNF) and a relatively higher ratio of TNF binding to soluble TNF receptor. Passive smoking may also impact the response of TNF treatment in patients with RA (1). The objective of this study was to assess the effect of tobacco smoke exposure, both through active and passive smoking, on response to anti-TNF- $\alpha$  agents at 12-month assessment.

In this study, patients with a diagnosis of RA under treatment with infliximab, etanercept and adalimumab therapy were retrospectively evaluated. Rheumatoid Factor (RF) positive patients undergoing a methotrexate (MTX) based anti-TNF treatments were enrolled. Patients were questioned whether they were active smokers or were passively exposed to tobacco smoke through a close contact. Outcome at 12 months was categorized according to the Disease Activity Score-28 (DAS28) scores using two approaches. First; non-responder (an improvement of  $< 0.6$  or have a final DAS28 score  $> 5.1$ ), moderate response and good response (an improvement of at least 1.2 units and achieves an absolute score of  $< 3.2$ ). Moderate responders were those that fall in between. Second; patients achieved remission at 12

months with DAS28  $< 2.6$ . Functional disability was determined using the Health Assessment Questionnaire (HAQ) (2).

Statistical analyses were performed using the SPSS, Chicago, IL, USA version 11.5. Yates' chi-squared and Fisher's exact tests were used to assess the differences within groups. Univariate analysis of variance test was used to determine the change within anti-TNF $\alpha$  groups in both DAS-28 and HAQ levels. A  $P$ -value  $< 0.05$  was considered as indicative of statistical significance. The files of 81 RA patients were examined but only 39 patients could be included in the study. The demographic characteristics of the patients are presented in Table 1. The anti-TNF agents used by patients were infliximab (28%), etanercept (41%) and adalimumab (31%). The distribution of DAS-28 levels were statistically similar in patients with and without cigarette smoking ( $P = 0.987$ ). Similar results were observed between the groups with and without exposure to smoking ( $P = 0.454$ ).

Among active smokers, 50% were determined as good responders and 20% as non-responders at the end of the 12 months. Among non-smokers, 76% were good responders, and only 3% were non-responders. Similar results were observed

when comparing patients with and without exposure to smoking (with exposure; good response: 60%, non-response: 9%, and without exposure; good response: 82%, non-response: 6%). The effect of smoking on DAS-28 and HAQ levels at the end of the 12 months is demonstrated in Table 2.

**Table 1:** Demographic features

Age (yr)	(mean $\pm$ SD) / n (%)
	50.1 $\pm$ 13.7
Sex	
Female	29 (74.4)
Male	10 (25.6)
Education (year)	5.9 $\pm$ 3.2
Disease duration (year)	16.9 $\pm$ 9.6
Smoker	10 (25)
Non-smoker	29 (75)
Exposure	23 (59)
Non-exposure	16 (41)

Smoking was a negative prognostic factor for both MTX and anti-TNF treatment response (3). Moreover, a correlation between smoking and

disease activity at start of anti-TNF treatment could not be demonstrated (4). The prevalence and effect on disease activity of having had second-hand exposure to tobacco smoke was analyzed in RA patients who had never smoked (5). No differences were found between patients who had never smoked and who had been exposed or had not been exposed second-hand to tobacco smoke. Similarly, in this study, patients with RA who had been exposed or had not been exposed to tobacco smoke showed a statistically significant decrease in the level of DAS-28 as well as the HAQ scores compared to baseline and end of the 12 month. In contrast to previous reports, no association between cigarette smoking or tobacco smoke exposure and poor response to anti-TNF treatment was found (6).

In summary, findings show that no difference was detected between active smokers, exposed to tobacco smoke, and non-smokers in terms of response to anti-TNF treatment in RA. Prospective controlled studies that include exposed to tobacco smoke are required to better define the response to anti-TNF- $\alpha$  agents.

**Table 2:** Effect of smoking on DAS-28 and HAQ levels

	Smoker (mean $\pm$ SD)	P	Non-smoker (mean $\pm$ SD)	P	P
DAS-28 0.month	6.1 $\pm$ 0.6		6.4 $\pm$ 0.9		
		0.01		0.00	0.41
DAS-28 12.month	4.2 $\pm$ 1.6		4.1 $\pm$ 1.4		
HAQ 0.month	1.6 $\pm$ 0.4		1.7 $\pm$ 0.6		
		0.01		0.00	0.86
HAQ 12.month	1 $\pm$ 0.9		1.1 $\pm$ 0.7		

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The authors declare that there is no conflict of interest.

## References

1. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM (2010). Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. *J Clin Rheumatol*, 16: 15-8.
2. Kucukdeveci AA, Sahin H, Ataman S, Grifiths B, Tennant A (2004). Issues in cross-cultural validity: example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. *Arthritis Rheum*, 51: 14-9.
3. Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, Ask-

- ling J, Alfredsson L, Klareskog L (2011). Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and TNF inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum*, 63: 26-36.
4. Soderlin MK, Petersson IF, Geborek P (2012). The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. *Scand J Rheumatol*, 41: 1-9.
  5. Söderlin MK, Andersson M, Bergman S (2013). Second-hand exposure to tobacco smoke and its effect on disease activity in Swedish rheumatoid arthritis patients. *Clin Exp Rheumatol*, 31: 122-4.
  6. Mathey DL, Brownfield A, Dawes PT (2009). Relationship between packyear history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. *J Rheumatol*. 36: 1180-1187.

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