

# Determinants of Risk Infection During Therapy with Anti TNF-Alpha Blocking Agents in Rheumatoid Arthritis

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**Abstract:** The use of TNF-alpha antagonists (infliximab, etanercept, adalimumab) has changed the course of many rheumatic diseases including rheumatoid arthritis (RA). Since their approval, some questions regarding their safety including infections have been observed. The aim of the study was to evaluate the changes in cytokines levels and cells subsets in patients with RA during anti TNF blocking agents treatment and the possible effect on infections' development. We evaluated in 89 RA patients [39 treated with etanercept (ETN), 29 with adalimumab (ADA) and 21 with infliximab (IFN)] at baseline and after 6 months the following parameters: procalcitonin, ESR, CRP, cytokines as TNF, IL-6, IL-10, IL-8 and the TNF/IL-10 ratio, and peripheral mononuclear cells as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD3-/CD16+/56+, CD14+HLADR+, CD20+, CD19+/CD38+. Peripheral mononuclear cells were detected by flow cytometric system Cytomics FC500 and cytokines circulating levels by a quantitative sandwich enzyme immunoassay technique (Human IL-8 Instant ELISAE Bioscience, Human IL-6 Instant ELISA e Bioscience, Human IL-10 Instant ELISAE Bioscience and Human TNF-a Quantikine immunoassay RD system). A lower reduction of CD14+HLADR+ in ADA group 54.6±10.4% vs ETA 48.4±15.7% vs INF 40.7±16.5%, p<0.039 was found. No differences in all three groups on peripheral mononuclear cells CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD 20+, CD19+/CD38+, CD3-/CD16+/56+, and cytokine circulating levels were found. The number of infections at 6 months was: 10.3% in ADA group, 12.8% in ETN group and 19.04% in IFN group. A correlation was found between the reduction in CD14+HLADR+ cells and IFN treatment. Our data showed that the level of CD14+HLADR+ cells was reduced during therapy with IFN. ADA and ETN don't reduce lymphocyte populations and their subsets such as CD14+HLADR+ cells that play an important role host defence.

**Keywords:** Infections, TNF blocking agents, peripheral mononuclear cells.

## INTRODUCTION

Rheumatoid arthritis (RA) has terrible effects on a wide range of health outcomes, ranges from bone damage to musculoskeletal system. RA is associated with increased mortality and comorbidity related to different causes compared to the general population, including infections [1, 2]. Biologic therapies give the opportunity to target the precise immune and inflammatory pathway leads to improve the RA patients' outcomes and to reduce the associated comorbidity and mortality. The anti-TNF drugs were the first biologic agents to become available in management of RA patients who fail to respond to traditional non-biologic Disease-modifying antirheumatic drugs (DMARDs). However, TNF plays an important role in host defence [3, 4]; consequently the introduction of anti-TNF agents induce the

necessity to evaluate and understand the effect of this drugs on infections' risk. During bacterial infections as a sepsis different cytokines are secreted such as interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and high levels of these cytokines can induce an increased risk of mortality [5], but anti-cytokines treatment cannot improve the patients' survival [6]. Moreover, TNF release from macrophages play a crucial role in maintenance and formation of granuloma and in intracellular organisms the defence. Furthermore, TNF plays a role in leucocyte trafficking and Immune Complement (IC) clearance [7].

The aim of the study was to evaluate the changes in cytokines levels and cells subsets in patients with RA during anti TNF- $\alpha$  blocking agents treatment and the possible effect on infections' development.

## MATERIAL AND METHODS

We evaluated 89 RA patients of a single centre that started a therapy with tumor necrosis factor  $\alpha$  blocking agents in the period January 2008- December 2010, affected by RA according to the American College of Rheumatology

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(ACR) criteria 1998. We included 39 patients treated with etanercept (ETN), 29 with adalimumab (ADA) and 21 with infliximab (IFN) combined with corticosteroids (mean dosage  $5.1 \pm 2.1$  mg) and methotrexate (MTX) (mean dosage  $12.5$  mg/weekly, range  $20-7.5$  mg). The patients were evaluated at baseline and after 6 months for the following parameters: procalcitonin, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), cytokine such as tumour necrosis factor-alpha (TNF- $\alpha$ ), IL6, IL-10, IL-8 and the TNF/IL-10 ratio, and peripheral mononuclear cells as CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD3-/CD16+/56+, CD14+HLADR+, CD20+, CD19+/CD38+.

Peripheral mononuclear cells were detected by flow cytometric system Cytomics FC500 (Beckman Coulter, Fullerton, CA, USA). We used the monoclonal antibodies CYTO-STAT tetra CHROME CD45FITC/CD4RD1, CD8ECD/CD3PC5, CD45FITC/CD56RD1/CD19ECD/CD3PC5, CD19PE/CD38PC5/CD20FITC, CD14FITC/HLADRPC5 and the absolute count and the percentage of lymphocytes were detected. Cytokine circulating levels were evaluated by a quantitative sandwich enzyme immunoassay technique (Human IL-8 Instant ELISAe Bioscience, Human IL-6 Instant ELISAe Bioscience, Human IL-10 Instant ELISAe Bioscience and Human TNFa Quantikine Immunoassay RD System).

The study was approved by the Ethics Committees and written informed consent was obtained from patients before inclusion in the study.

#### Statistical Analysis

Statistical analysis was performed using SPSS statistical package (SPSS Inc., Chicago, IL, USA; version 14.0, 2006). Quantitative variables were expressed as mean values and standard deviation. The associations between the quantitative variables were studied by means of correlation analysis, and those between the qualitative variables by means of contingency tables. Statistical significance was tested by ANOVA for parametric analysis and non parametric using the Kruskal-Wallis test. A two-tailed P value of  $<0.05$  was considered statistically significant.

## RESULTS

The clinical characteristics of the patients included in the study are reported in Table 1.

No difference in baseline values among the three treated group on mononuclear cells and cytokines was detected (Tables 1 and 2) We evaluated at baseline the normal range of peripheral mononuclear cells in donors health age matched. A lower reduction of CD14+HLADR+ in ADA group  $54.6 \pm 10.4\%$  vs ETA  $48.4 \pm 15.7\%$  vs INF  $40.7 \pm 16.5\%$ ,  $p < 0.039$  was found after twenty-four weeks of treatment with anti-TNF agents. No differences in all three groups on peripheral mononuclear cells CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD20+, CD19+/CD38+, CD3-/CD16+/56+ and cytokine circulating levels was found after treatment with anti-TNFa agents (Tables 2 and 3). The number of infections at 6 months was: 10.3% in ADA group (2 in respiratory tract, 1 in urinary tract), 12.8% in ETN group (3 in respiratory tract, 2 in urinary tract) and 19.04% (3 in respiratory tract, 1 herpes zoster) in IFN group. No hospitalization was observed in the three groups.

No correlation between the number of infections in the group of INF and ETN and ADA was found.

## DISCUSSION

In this paper we have evaluated the role of the integrity of immune system and the variations under therapy with three different TNF $\alpha$  blocking agents in RA patients during the first six months of treatment. RA patients have been recognised to be at increased risk of infection for several decades [8]. Given the involvement of CD14+ in disease, including sepsis and chronic heart failure, the discovery of signal transduction pathways activated exclusively *via* CD14+ is an important step towards the development of potential treatments involving interference with CD14+ functions [9].

In human monocytes/macrophages pre-incubated with TNF-R1-expressing human endothelial cells, reverse signalling through transmembrane TNF-a mediated LPS resistance as indicated by the down-regulation of LPS-induced soluble TNF-a and IL-6 as well as IL-1 and -10 [10]. Pre-treatment with soluble TNF-R1 for inducing reverse

**Table 1. The Clinical Characteristic of the Patients Included in the Study**

	Etanercept Group (39 pts)	Adalimumab Group (29 pts)	Infliximab Group (21 pts)
Age mean years	$59.6 \pm 9.8$	$58.7 \pm 10.6$	$60.1 \pm 9.3$
Disease mean	$8.4 \pm 3.2$	$8.2 \pm 4.2$	$8.5 \pm 4.1$
Female/Male	33/6	25/4	19/2
Corticosteroid dose mg	$5.2 \pm 2.1$	$4.8 \pm 2.2$	$4.9 \pm 2.2$
Methotrexate dose mg/w	$11.5 \pm 3.6$	$12.6 \pm 2.5$	$12.7 \pm 2.3$
RF positive	67%	68%	66%
Anti CC-P positive	83%	81%	80%
DAS28	$4.8 \pm 1.4$	$4.7 \pm 1.6$	$4.6 \pm 1.5$
ESR mm/h	$49.3 \pm 12.5$	$51.2 \pm 9.6$	$51.6 \pm 9.9$
CRP mg/dl	$3.2 \pm 1.4$	$3.3 \pm 1.6$	$3.1 \pm 1.8$

**Table 2. The Values of Cytokines at Baseline and After 6 Months of Anti-TNF $\alpha$  Treatment**

Cytokines Value	ADA Group Week 0	ETN Group Week 0	IFN Group Week 0	ADA Group Week 24	ETN Group Week 24	IFN Group Week 24	P Value
TNF $\alpha$ pg/ml	33.1 $\pm$ 12.3	33.1 $\pm$ 12.3	34.4 $\pm$ 12.6	86.7 $\pm$ 70.3	171.4 $\pm$ 69.4	182.5 $\pm$ 47.4	NS
IL-6 pg/ml	6.7 $\pm$ 3.5	7.6 $\pm$ 2.9	7.1 $\pm$ 3.1	8.8 $\pm$ 2.7	4.7 $\pm$ 3.5	6.4 $\pm$ 4.3	NS
IL-10 pg/ml	3.2 $\pm$ 1.5	3.6 $\pm$ 2.1	2.5 $\pm$ 1.6	3.9 $\pm$ 2.8	2.5 $\pm$ 2.3	5.5 $\pm$ 5.1	NS
IL-8 pg/ml	4.8 $\pm$ 2.1	3.7 $\pm$ 2.1	4.1 $\pm$ 1.9	3.03 $\pm$ 2.1	5.8 $\pm$ 4.1	4.7 $\pm$ 2.9	NS
TNF $\alpha$ /IL10 ratio	78.9 $\pm$ 11.7	54.1 $\pm$ 12.7	54.2 $\pm$ 13.9	78.9 $\pm$ 11.7	54.1 $\pm$ 12.7	54.2 $\pm$ 13.9	NS

**Table 3. The Values of Lymphocytes at Baseline and After 6 Months of Anti-TNF $\alpha$  Treatment**

Cells	ADA Group Week 0	ETN Group Week 0	IFN Group Week 0	Normal Value in Donors Age Matched	P Value	ADA Group Week 24	ETN Group Week 24	IFN Group Week 24	P Value
CD3+	1734 $\pm$ 657	1725 $\pm$ 688	1724 $\pm$ 637	1100-1700	NS	1838 $\pm$ 632	1653 $\pm$ 736	1645 $\pm$ 624	NS
CD3+/CD4+	1734 $\pm$ 657	1134 $\pm$ 317	1158 $\pm$ 366	650-1400	NS	1250 $\pm$ 496	1065 $\pm$ 562	1067 $\pm$ 446	NS
CD3+/CD8+	470 $\pm$ 210	445 $\pm$ 218	480 $\pm$ 205	320-900	NS	520 $\pm$ 230	489 $\pm$ 223	534 $\pm$ 321	NS
CD19+	268 $\pm$ 89	245 $\pm$ 92	259 $\pm$ 91	200-400	NS	273 $\pm$ 143	261 $\pm$ 202	255 $\pm$ 174	NS
CD20+	198 $\pm$ 156	191 $\pm$ 146	188 $\pm$ 126	150-400	NS	193 $\pm$ 179	164 $\pm$ 85	99 $\pm$ 17	NS
CD19+/CD38+	234 $\pm$ 143	223 $\pm$ 133	214 $\pm$ 163	150-400	NS	240 $\pm$ 155	109 $\pm$ 74	79 $\pm$ 15	NS
CD16+/56+	211 $\pm$ 72	217 $\pm$ 68	213 $\pm$ 67	200-400	NS	219 $\pm$ 87	211 $\pm$ 54	210 $\pm$ 45	NS
CD14+HLADR+%	57 $\pm$ 12	55 $\pm$ 14	59 $\pm$ 12	50-90	NS	54.6 $\pm$ 10.4	48.4 $\pm$ 15.7	40.7 $\pm$ 16.5	<0.039
CD14+HLADR+	345 $\pm$ 213	335 $\pm$ 223	349 $\pm$ 209	300-400	NS	326 $\pm$ 214	311 $\pm$ 230	246 $\pm$ 78	<0.05

signalling through transmembrane TNF- $\alpha$  sensitized human monocyte cell line U937 cells to soluble TNF- $\alpha$ -induced activation, whereas stimulation of transmembrane TNF- $\alpha$  after soluble TNF- $\alpha$ -induced activation of U937 cells reduced mRNA stability of IL-1 $\beta$  and IL-8 [11]. In contrast to these findings that transmembrane TNF- $\alpha$  may inhibit sustained activation of monocytes, transmembrane TNF- $\alpha$  played a positive role in the activation of monocytes. Ligation of transmembrane TNF- $\alpha$  on monocytes by TNF-R2 on T cells or soluble TNF-R2: Ig receptor construct (etanercept) induced TNF- $\alpha$  production due to outside-to-inside signalling through transmembrane TNF- $\alpha$  [12].

The effects of three TNF $\alpha$  blocking agents are different on immune system [13]. Infliximab binds to both monomer and trimer forms of soluble TNF- $\alpha$ , whereas etanercept binds only to the trimer form [14]. Infliximab formed stable complexes with soluble TNF- $\alpha$ , while etanercept formed relatively unstable complexes. Each infliximab molecule is capable of binding to two TNF- $\alpha$  molecules, and up to three infliximab molecules can bind to each TNF- $\alpha$  homotrimer. In contrast, etanercept is supposed to form 1 : 1 complex with the TNF- $\alpha$  trimer [15].

All the reports were in agreement that infliximab and adalimumab induced CDC (cytotoxicity dependent complement) much more potently than etanercept. In contrast, certolizumab pegol did not have any CDC activity [15], which reflects its absence of the Fc portion of IgG1. It is thus difficult for etanercept to make a membrane attack complex of complement proteins (C5b-C9) for CDC at least *in vitro*.

When activated human peripheral blood mononuclear cells were studied as target cells, none of these three anti-TNF agents induced CDC [16]. Infliximab, adalimumab and etanercept showed similar antibody dependent cell-mediated cytotoxicity (ADCC) activity using mTNF-transfected Jurkat T cells as target [17], while infliximab and adalimumab showed much more potent ADCC than etanercept in NS0 cells [15]. The discrepancy in etanercept-induced ADCC is not clear, but may be explained by the different experimental conditions, such as difference in the species of target cell, in the expression level of transmembrane TNF- $\alpha$ . Both mAbs and etanercept weakly bound to Fc $\gamma$  receptors in the absence of soluble TNF- $\alpha$ , but in the presence of soluble TNF- $\alpha$ , there was a marked increase in binding only by mAbs infliximab and adalimumab [18]. As for infliximab, induction of both CDC and ADCC has been reported by others [19].

Outside-to-inside signalling (reverse signalling) is a novel function of anti-TNF agents for the inhibition of TNF- $\alpha$ -producing cells, which is mediated by mechanisms independent of CDC and ADCC [17-20]. Infliximab and adalimumab, but not etanercept, induced apoptosis and cell cycle G0/G1 arrest upon binding to transmembrane TNF- $\alpha$ -expressing Jurkat T cells. Cross-linking of etanercept bound to the cell-surface transmembrane TNF- $\alpha$  resulted in increased apoptosis [20], which indicates that multimer formation with mAbs and transmembrane TNF- $\alpha$  may be essential for the initiation of the subsequent intracellular signals. IL-10 production was induced by infliximab, but not by etanercept, in transmembrane TNF- $\alpha$ -expressing

Jurkat T cells [20]. We didn't evaluate in our study a subgroup of patients with RA without therapy with anti-TNF, but previous study has shown that RA patients have a nearly 2 -fold increased risk for infection compared with the age and sex matched control subjects for accelerated immunosenescence particularly of T cells [21]. Our data showed that no differences in all three groups on peripheral mononuclear cells CD3+, CD3+/CD4+, CD3+/CD8+, CD19+, CD20+, CD19+/CD38+, CD3-/CD16+/56+ and cytokine circulating levels were found after treatment with anti-TNF agents but the levels of CD14+HLADR+ markers of monocytes were reduced during therapy with IFN in the first six months and this could be a parameter of possible correlation with more infection that we have in this subgroup of patients with RA. Our data reveal that Adalimumab and Etanercept don't reduce lymphocyte population and subsets such as CD14+HLADR+ cells that have an important role against infections. Expression of class II major histocompatibility complex (MHC) on monocytes is a prerequisite for effective antigen presentation and processing, an important component of the immune response to infection [22]. It has been reported that the level of monocyte class II expression may identify patients who go on to develop infective complications following trauma [23]. Membrane CD14 (mCD14), a 55-kD glycoprotein on the cell membrane of monocytes and polymorphonuclear cells, plays a key role in transmitting LPS signals intracellularly and ultimately activating tumor necrosis factor (TNF)- $\alpha$  production [24]. A animal model study showed that a monocyte mCD14 and HLA-DR expression decreased might contribute to endotoxin tolerance and a rapid reduction on LPS responsiveness [25]. The high reduction in patients in treatment with INF could be explained by the major effects of this monoclonal antibody on ADC and CDC. Moreover, it has been suggested that monoclonal antibodies carry a higher risk than ETN because of their different effects on different cells including this subset of monocytes [26].

A review of observational research designs has revealed a higher risk of infections in the first few months of anti-TNF treatment [27], followed by a progressive reduction and our finding confirm this data suggesting that these cells can play a role.

In the literature the data on infections induced by anti-TNF agents were extrapolated by the Registers that involve a large amount of the patients [28,29]. A recent paper on a large cohort of 16.506 patients treated with anti-TNF showed 7,1% of serious infections most of which were pneumonia, skin and soft tissue infections [30].

Moreover, this is a pilot study focused on researching of some biomarkers associated with the infection risk that can help in clinical practice to prevent this complications.

Further studies are required to confirm these data and to define precise biomarkers for assessing and managing infections in RA patients treated with anti-TNF agents involving a large cohort of patients.

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None declared.

#### CONFLICT OF INTEREST

None declared.

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