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Original article

The relationship between blood eosinophil count and disease activity in ankylosing spondylitis patients treated with TNF-α inhibitors

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ABSTRACT

Aim: Anti-tumor necrosis factor-alpha (Anti-TNF-α) therapy has achieved an important position, are widely used for ankylosing spondylitis (AS) patients. TNF-α inhibition improves clinical outcomes and has differential effects on haematopoiesis. Information about effects on eosinophils is limited. The aim of our study is to determine the relationship between blood eosinophil counts in AS patients treated with TNF-α inhibitors.

Methods: Seventy-five patients diagnosed with AS according to modified New York criteria were enrolled in this study. Disease activity was assessed by BASDAI, and erythrocyte sedimentation rate, C-reactive protein of patients were evaluated. All data were analyzed with Spearman's correlation and Friedman's Two-Way by using SPSS version 19.0 statistical software, and $p < 0.05$ was considered as statistically significant.

Results: Seventy-five AS (F/M: 27/48, the mean age of 41 ± 10 years) patients were evaluated. On the 3rd month of treatment, there was a correlation between BASDAI and CRP ($r = 0.32$, $p = 0.005$), but no correlation between BASDAI and ESR ($r = 0.21$, $p = 0.06$). Blood eosinophil count was not correlated with BASDAI, ESR and CRP on pre-, post-therapy ($p > 0.05$). It counts lower before anti-TNF-α therapy compare with post-treatment (130/mm^3, 140/mm^3 and 190/mm^3, respectively). There was no statistically significant difference between pre- and 3rd month ($p > 0.05$), while correlation was found between pre- and 6th month, and also 3rd month and 6th month ($p < 0.001$, $p = 0.002$, respectively) for blood eosinophil count.

Conclusion: To the best of our knowledge, our study is the first to evaluate blood eosinophil counts and disease activity with anti-TNF-α therapy. Blood eosinophil count may be affected by TNF-α inhibition in patients with AS.

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1. Introduction

Ankylosing spondylitis (AS) is an inflammatory rheumatic disorder and a prototype of spondyloarthritis, characterized by axial skeleton and sacroiliac joint involvement (McVeigh and Cairns, 2006). Genetic, environmental factors and immune-mediated mechanisms play role in the pathogenesis of AS. Proinflammatory cytokines (Tumor necrosis factor [TNF]-α, Interleukin [IL]-1, IL-6 etc.), T cells and macrophages were observed in the cartilage of AS patients. Also, TNF-α serum levels were significantly higher in AS patients (Gonzalez-Lopez et al., 2017; Liu et al., 2015). TNF-α expression in cartilage and serum provided grounds for TNF-α inhibitor treatment.

TNF-α inhibition improves clinical outcomes and has differential effects on haematopoiesis. Inflammation, therefore cytokines have important effects on hematopoietic system (Jacobsen et al., 1994). Increased platelet levels, erythrocyte sedimentation rate (ESR), normochromic normocytic anemia have been reported during active stages of AS (McVeigh and Cairns, 2006). Hematopoiesis would be improved with the remission of the inflammation by TNF-α inhibition. Anti-TNF-α therapy leads to some changes in hematological parameters such as such neutropenia and aplastic anemia (Montané et al., 2007; Kuruvilla et al., 2003). But, there were few studies about the relationship between the blood

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eosinophil counts and TNF-α. It is known that eosinophils are generally associated with allergic and parasitic disorders. Infectious or inflammatory processes markedly suppress eosinophil count. It is related to the bone marrow suppression and blocking the release of mature eosinophils from the bone marrow. Also, stress may lead to decreases in the number of eosinophils due to epinephrine and glucocorticoids (Temkin and Levi-Schaffer, 2001; Liao et al., 2016).

To the best of our knowledge, the association between blood eosinophil counts, disease activity, and TNF-inhibition has not been reported in AS patients. The purpose of this study was to investigate the possible role of TNF on eosinophil counts and determine the relationship of TNF-α inhibition and eosinophil counts on inflammatory markers and disease activity.

2. Materials and methods

Seventy-five patients fulfilled the modified New York criteria were enrolled the study, retrospectively. All AS patients were refractory to conventional therapy for at least three months and treated with Anti-TNF-α therapy (adalimumab = 15, certolizumab pegol = 8, etanercept = 14, golimumab = 14, infliximab = 24). Disease activity was determined by Bath ankylosing spondylitis Disease Activity Index (BASDAI) score in AS patients (Garrett et al., 1994). Refractory patients were defined as BASDAI score > 4. Patients with the medical history of systemic diseases (dyslipidemia, diabetes mellitus, hypertension, hepatic-renal-vascular-cardiac disease, asthma, chronic obstructive pulmonary disease), infections, malignancies, smoking, treatment with corticosteroids, and modification on the treatment during the period of this study were excluded from the study. The study protocol was approved by the Ethics Board of our University.

The patients' demographic data, laboratory results, physical examination and disease activity of all patients (complete blood count, ESR, C-reactive protein (CRP), renal and hepatic function tests) of patients were extracted from patients' medical records. Whole blood cell count was measured by Coulter Gene-S instrument (Beckman Coulter, California, USA). Statistical Package for Social Sciences (SPSS) version 19.0 software was used for statistical analysis. Kolmogorov-Smirnov test was used to determine the distribution of normality. Descriptive data were displayed as mean ± standard deviation, median, minimum, maximum, and percentage values. Spearman's correlation and Friedman's Two-Way were used to comparing variables of patients and determine the correlation between BASDAI, ESH, CRP and blood eosinophil count. p-value of < 0.05 was considered as statistically significant.

3. Results

In this study, 75 AS patients were evaluated. Of 75 patients, 27 (36%) were female and 48 (64%) were male. The mean age of AS was 41 ± 10 years. Demographic features, disease activity score and laboratory findings of AS patients are shown in Table 1.

Table 1
Demographic features of patients with ankylosing spondylitis.

Clinical characteristics		Ankylosing spondylitis (n:75)
Age (year ± SD)		41 ± 10
Gender n (%)	Female	27 (36%)
	Male	48 (64%)
Biological agents (%)	Adalimumab	15 (20%)
	Certolizumab pegol	8 (10.7%)
	Etanercept	14 (18.7%)
	Golimumab	14 (18.7%)
	Infliximab	24 (32%)

Table 2
The distribution of ESR, CRP, BASDAI score and blood eosinophil count and their relationship with treatment.

	AS pre-treatment n = 75	AS post-treatment (3th month)	AS post-treatment (6th month)
ESR (mm/h)	35 [16–50.5]	29 [21–51]	23 [12–33]
CRP (mg/dL)	10.2 [4.3–21.6]	9 [4.4–13.6]	4.1 [1.5–8.1]
BASDAI score	5.4 [5.1–5.9]	3.2 [3–3.7]	2.8 [2.6–3.2]
Eosinophil count (/mm^3)	130 [90–210]	140 [100–200]	190 [110–240]

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI: Bath ankylosing spondylitis disease activity index, median and interquartile range [25th–75th percentile].

Table 3
Statistical analysis of changes in blood eosinophil count with each anti-TNF-α agent.

	p-value (0–3 month)	p-value (3–6 month)	p-value (0–6 month)
Adalimumab	1	0.07	0.03*
Certolizumab pegol	0.118		
Etanercept	1	0.42	0.002*
Golimumab	0.291		
Infliximab	<0.001*		

* p-value of <0.05 was considered as statistically significant.

BASDAI score, the levels of ESR and CRP were statistically significantly different between pre- and post-treatment. After the anti-TNF-α therapy, levels of ESR, CRP, and the mean BASDAI score decreased significantly. The median BASDAI score decreased significantly on the 3th month (5.4 [5.1–5.9] vs 3.2 [3–3.7]; $p \leq 0001$) and 6th month (5.4 [5.1–5.9] vs 2.8 [2.6–3.2]; $p \leq 0001$) of treatment compared to baseline. The initial BASDAI score was correlated with CRP ($r = 0.32$, $p = 0004$), while there was no correlation between ESR and BASDAI score ($r = 0.17$, $p = 0.1$). On the 3th month of anti-TNF-α therapy, there was a correlation between BASDAI and CRP ($r = 0.32$, $p = 0005$), but no correlation was found between BASDAI score and ESR ($r = 0.21$, $p = 0.06$). But, there was a correlation between BASDAI score and ESR on the 6th month of anti-TNF-α therapy ($r = 0.33$, $p = 0.03$).

Blood eosinophil counts did not correlate with BASDAI score, ESR and CRP before and after anti-TNF-α therapy ($p > 0.05$). Initial median blood eosinophil count of AS patients were 130/mm^3 (90–210/mm^3) and 140/mm^3 (100–200/mm^3) on the 3rd month and 190 (110–240) on the 6th month of anti-TNF-α therapy. It counts lower before anti-TNF-α therapy when compared to post-treatment. There was no statistically significant difference between pre- and on the 3rd month ($p > 0.05$), while statistically significant difference was found between pre- and on the 6th months, and also on the 3rd month and on the 6th month ($p < 0001$, $p = 0002$, respectively) of anti-TNF-α therapy for blood eosinophil counts (Table 2). The median eosinophil count was determined within normal ranges before and after (on the 3rd and 6th month) anti-TNF-α therapy. However, eosinophilia (770/mm^3) was observed in a patient receiving golimumab on the 3rd month, but it was within normal ranges on the 6th month of anti-TNF-α therapy. Statistical analysis of changes in blood eosinophil count with each anti-TNF-α agent is shown in Table 3.

4. Discussion

The aim of AS treatment is to control inflammatory process, prevent functions, and improve the quality of life. Physical therapy, non-steroidal anti-inflammatory drugs, slow-acting anti-rheumatic drugs (conditionally, in patients with peripheral arthritis), and systemic glucocorticoids (conditionally, in patients with

peripheral arthritis or during pregnancy) have used for effective control of AS (van der Heijde et al., 2017). Anti-TNF-α therapy has achieved an important position for the treatment of AS since 15 years. Anti-TNF-α therapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) are now widely used for active AS patients who fail to NSAIDs. All AS patients of this study were refractory to conventional therapy for at least 3 months. TNF-α inhibitors have improved clinical symptoms in AS patients with persistently high disease activity. In this study, BASDAI decreased with anti-TNF-α therapy on the 3rd and 6th month of treatment compared with baseline. Safety and side effect have been discussed with the increasing use of Anti-TNF-α agents such as infections, immunogenicity, injection site reaction, lupus-like reactions, and exacerbation of heart failure (Nanau and Neuman, 2014). Also, leukopenia, thrombocytopenia (Azevedo et al., 2012), neutropenia (Wenham et al., 2008), severe pancytopenia (Martínez Santana et al., 2012), and severe neutrophilia (de Oliveira et al., 2008) have been reported with anti-TNF-α therapy. In our study, no side effect was found with TNF-α inhibitors on the follow-up. However, eosinophilia was observed in a patient receiving golimumab on the 3rd month, but it was within normal ranges on the 6th month of anti-TNF-α therapy.

TNF-α is an important cytokine in the pathogenesis of AS. TNF-α is a homotrimer, biologically active protein, consisting of 2 forms (17-kDa-secreted, 26-kDa-cell-associated), and predominantly produced by activated macrophages and T lymphocytes. It is thought that membrane TNF-α is associated with signaling secondary to cellular contact. TNF-α should bind to the receptors to activate intracellular pathways for biological effects (Alexopoulou et al., 1997). TNF-α has higher affinity to TNF receptor 2 (TNFR2-p75-CD120b without death domain) than TNFR1 (p55-CD120a). While TNFR1 has dual signaling pathway including survival (due to TNFR-associated factor-2), and apoptotic or cellular death (due to Fas-associated death-domain-containing protein and TNFR1-associated death-domain-containing protein), TNFR2 is associated with homeostasis, regeneration and immune regulation (Palladino et al., 2003; Tartaglia et al., 1993). TNF-α is bifunctional on hematopoiesis like growth enhancer at low concentrations and inhibitor of bone marrow progenitors. The regulation of stem cells are complex, and it is difficult to predict. TNFR2 appears to be restricted to inhibitory effects on primitive hematopoietic progenitors (Kuruvilla et al., 2003; Jacobsen et al., 1994). So, TNF-α inhibition may lead to the recovery of the hematopoietic system (Jacobsen et al., 1994, Bes et al., 2013).

Aplastic anemia (Kuruvilla et al., 2003), leukopenia, thrombocytopenia (Azevedo et al., 2012), neutropenia (Wenham et al., 2008), severe pancytopenia (Martínez Santana et al., 2012), and severe neutrophilia (de Oliveira et al., 2008) have been reported with adalimumab, etanercept, and infliximab. Although neutrophil autoantibodies (de Oliveira et al., 2008), inhibition of neutrophil chemotaxis or stem cell differentiation are suspected as the cause of neutropenia (Wenham et al., 2008; Martínez Santana et al., 2012), the mechanism is unclear. Also, other abnormalities about granulocytic series such as eosinophilia have been reported. According to the eHealthMe database (eHealthMe), 0.06% of patients who have side effects due to adalimumab have eosinophilia with the female predominance (Tsukahara et al., 1999). The rate of reported side effect is 0.03% for etanercept, 0.07% for infliximab, and 0.04% for golimumab. No report has been found about certolizumab (Guidelli et al., 2014; eHealthMe). In our study, eosinophilia was observed in a patient on the 3rd month of golimumab. But, eosinophil count was within normal ranges before and on the 6th month of anti-TNF-α therapy. The patient had no medical history of atopy. The parasite screen was negative and total IgE levels and hematological profile (except for eosinophilia) were within normal ranges.

Peripheral blood eosinophil count is a valuable biomarker for allergic diseases, parasitic infections, asthma, hypereosinophilic syndrome and sepsis. The formation and migration of eosinophil are suppressed due to inflammation in bone marrow (Liao et al., 2016). Both of Nuclear Factor-κB (NF-κB) and TNF-α have an important role in the regulation of cellular death (Tsukahara et al., 1999; McDonald and Cassatella, 1997). TNF-α induces cytoplasmic IkBα (inhibitor subunit of NF-kB) degradation in eosinophils. In a study, it was reported that TNF-α-induced apoptosis is up-regulated by gliotoxin in eosinophils (Fujihara et al., 2002). Eosinophils express TNFR1 and TNFR2, and their activation is thought to promote eosinophil apoptosis. Otherwise, TNF-α has been reported to be associated with eosinophil survival through the granulocyte-macrophage colony-stimulating factor and p38 kinase pathway (Tsukahara et al., 1999; Ward et al., 1999). Also, the level of eosinophil cationic protein that is a specific protein of eosinophil decrease with sulfasalazine treatment (Feltelius et al., 1987).

In a patient with rheumatoid arthritis (RA), perivascular and interstitial eosinophilic infiltrates were observed in the histologic dermal specimen of developing skin reactions with etanercept (Martínez Santana et al., 2012). The etiopathogenesis is not known whether with etanercept or component of the vehicle. Transient blood eosinophilia with adalimumab was reported (Vester et al., 2012). It was mentioned that type I and type III hypersensitivity reactions might be related to adalimumab-associated eosinophilic cellulitis. Also, case series were of eosinophilia reported during psoriasis treatment with adalimumab (Chiriac et al., 2016). Eosinophilia, elevated immunoglobulin E, and development of asthma has been reported in RA patients with the treatment of adalimumab. The clinical outcomes were thought to be as a result of activated Th2 pathway due to suppression of Th1 (shifting Th1 to Th2 phenotype) by TNF-α inhibition. There was reported 3 cases with eosinophilia during psoriasis treatment with TNF-α inhibitors in the literature (Malisiewicz et al., 2011). The first case had relative eosinophilia and history of allergic rhinitis before adalimumab. On the 3.25 months of treatment, the patients' eosinophil count was 1.550/μg/L with normal IgE and no evidence for paracytic and hematological disorders. In the second patient, eosinophilia was developed on the 8.5th month of adalimumab. And, eosinophilia was developed in another atopic patient with adalimumab and etanercept therapy. Eosinophil counts returned to normal ranges with the discontinuation of the suspected drug in all patients. In another patient diagnosed with rheumatoid arthritis, peripheral eosinophilia and eosinophilic infiltrates were detected in the biopsy of patients' papulovesicular lesion after infliximab treatment. Eosinophilia was observed in the same patient due to switching infliximab to etanercept.

The specificity and sensitivity of CRP and ESR used to assess the disease activity is low in patients with spondyloarthropathies (Seng et al., 2018). An easy, practical, and objective biomarker has always been a research topic. Therefore, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), mean platelet volume (MPV) (Seng et al., 2018), pentraxin-3 (Nisihara et al., 2018), and intercellular adhesion molecules (Liu et al., 2016) have been investigated as disease activity markers in patients with spondyloarthritis. Significant correlations between disease activity and ICAM-2, but not ICAM-1 levels reported in a study (Liu et al., 2016). However, there was no significant correlation between disease activity and NLR, PLR, MPV (Seng et al., 2018), pentraxin-3 (Nisihara et al., 2018). In our study, there was a decrease in the BASDAI score and increase in the number of eosinophil count with anti-TNF-α therapy. However, no correlation of eosinophil count with BASDAI was observed. Therefore, eosinophil count cannot be used as a biomarker that reflects disease activity.

5. Conclusion

The present study has demonstrated that eosinophil count was increased on the 3rd and 6th month in AS patients treated with anti-TNF-α agents. Blood eosinophil count may be affected by TNF-α inhibition in patients with AS. To the best of our knowledge, our study is the first to evaluate blood eosinophil counts, disease activity with anti-TNF-α therapy. The limitation of our study is the long-term results of this study are not known. Nevertheless, comprehensive prospective studies with large number of patients are needed to confirm relationship between disease activity.

Conflict of interest

All authors declare that no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The registration number of clinic trial is TPF 16786.

References

Alexopoulou, L., Pasparakis, M., Kollias, G., 1997. A murine transmembrane tumor necrosis factor (TNF) transgene induces arthritis by cooperative p55/p75 TNF receptor signaling. Eur. J. Immunol. 27 (10), 2588–2592.

Azevedo, V.F., Silva, M.B., Marinello, D.K., Santos, F.D., Silva, G.B., 2012. Leukopenia and thrombocytopenia induced by etanercept: two case reports and literature review. Rev. Bras. Reumatol. 52 (1), 110–112.

Bes, C., Yazici, A., Soy, M., 2013. Monoclonal anti-TNF antibodies can elevate hemoglobin level in patients with ankylosing spondylitis. Rheumatol. Int. 33 (6), 1415–1418.

Chiriac, A., Brzezinski, P., Stolnicu, S., Podoleanu, C., Moldovan, C., Molnar, C., et al., 2016. Eosinophilia–a rare possible adverse reaction during anti-tumor necrosis factor-alpha therapy for psoriasis. J. Dermatolog. Treat. 27 (2), 110–113.

de Oliveira, J.P., Levy, A., Morel, P., Guibal, F., 2008. Severe neutrophilia induced by infliximab for psoriasis. Br. J. Dermatol. 158 (1), 200–201.

eHealthMe. Available from: http:// www.ehealthme.com.

Feltelius, N., Hällgren, R., Venge, P., 1987. Raised circulating levels of the eosinophil cationic protein in ankylosing spondylitis: relation with the inflammatory activity and the influence of sulphasalazine treatment. Ann. Rheum. Dis. 46 (5), 403–407.

Fujihara, S., Ward, C., Dransfield, I., Hay, R.T., Uings, I.J., Hayes, B., et al., 2002. Inhibition of nuclear factor-kappaB activation un-masks the ability of TNF-alpha to induce human eosinophil apoptosis. Eur. J. Immunol. 32 (2), 457–466.

Garrett, S., Jenkinson, T., Kennedy, L.G., Whitelock, H., Gaisford, P., Calin, A., 1994. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J. Rheumatol. 21 (12), 2286–2291.

Gonzalez-Lopez, L., Fajardo-Robledo, N.S., Miriam Saldaña-Cruz, A., Moreno-Sandoval, I.V., Bonilla-Lara, D., Zavaleta-Muñiz, S., et al., 2017. Association of adipokines, interleukin-6, and tumor necrosis factor-α concentrations with clinical characteristics and presence of spinal syndesmophytes in patients with ankylosing spondylitis: a cross-sectional study. J. Int. Med. Res. 45 (3), 1024–1035.

Guidelli, G.M., Tenti, S., Fioravanti, A., 2014. Severe eosinophilia during anti-tumor necrosis factor-alpha therapy for psoriatic arthritis. Indian J. Dermatol. Venereol. Leprol. 80 (2), 187–189.

Jacobsen, S.E., Jacobsen, F.W., Fahlman, C., Rusten, L.S., 1994. TNF-alpha, the great imitator: role of p55 and p75 TNF receptors in hematopoiesis. Stem Cells 1, 111–126.

Kuruvilla, J., Leitch, H.A., Vickars, L.M., Galbraith, P.F., Li, C.H., Al-Saab, S., et al., 2003. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. Eur. J. Haematol. 71 (5), 396–398.

Liao, W., Long, H., Chang, C.C., Lu, Q., 2016. The eosinophil in health and disease: from bench to bedside and back. Clin. Rev. Allergy Immunol. 50 (2), 125–139.

Liu, K.G., He, Q.H., Tan, J.W., Liao, G.J., 2015. Expression of TNF-α, VEGF, and MMP-3 mRNAs in synovial tissues and their roles in fibroblast-mediated osteogenesis in ankylosing spondylitis. Genet. Mol. Res. 14 (2), 6852–6858.

Liu, R., Yue, Z., Peng, X., Wang, X., Feng, Z., Wan, L. 2016. Association Between Intercellular Adhesion Molecule-1, -2, -3 Plasma Levels and Disease Activity of Ankylosing Spondylitis in the Chinese Han Population. Spine (Phila Pa 1976). 41:618–624.

Malisiewicz, B., Murer, C., Pachlopnik Schmid, J., French, L.E., Schmid-Grendelmeier, P., Navarini, A.A., 2011. Eosinophilia during psoriasis treatment with TNF antagonists. Dermatology 223 (4), 311–315.

Martínez Santana, V., Izquierdo Navarro, M., Calleja Hernández, M.Á., Sánchez Sánchez, T., Sainz Gil, M., 2012. Severe pancytopenia following etanercept administration in rheumatoid arthritis. Int. J. Rheum. Dis. 15 (4), 78–79.

McDonald, P.P., Cassatella, M.A., 1997. Activation of transcription factor NF-kappa B by phagocytic stimuli in human neutrophils. FEBS Lett. 412 (3), 583–586.

McVeigh, C.M., Cairns, A.P., 2006. Diagnosis and management of ankylosing spondylitis. BMJ 333 (7568), 581–585.

Montané, E., Sallés, M., Barriocanal, A., Riera, E., Costa, J., Tena, X., 2007. Antitumor necrosis factor-induced neutropenia: a case report with double positive rechallenges. Clin. Rheumatol. 26 (9), 1527–1529.

Nanau, R.M., Neuman, M.G., 2014. Safety of anti-tumor necrosis factor therapies in arthritis patients. J. Pharm. Pharm. Sci. 17 (3), 324–361.

Nisihara, R., Skare, T.L., Zeni, J.O., Rasera, H., Lidani, K., Messias-Reason, I., 2018. Plasma levels of pentraxin 3 in patients with spondyloarthritis. Biomarkers 23 (1), 14–17.

Palladino, M.A., Bahjat, F.R., Theodorakis, E.A., Moldawer, L.L., 2003. Anti-TNF-alpha therapies: the next generation. Nat. Rev. Drug Discov. 2 (9), 736–746.

Seng, J.J.B., Kwan, Y.H., Low, L.L., Thumboo, J., Fong, W.S.W. 2018. Role of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) in assessing disease control in Asian patients with axial spondyloarthritis. Biomarkers.

Tartaglia, L.A., Pennica, D., Goeddel, D.V., 1993. Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor. J. Biol. Chem. 268 (25), 18542–18548.

Temkin, V., Levi-Schaffer, F., 2001. Mechanism of tumour necrosis factor alpha mediated eosinophil survival. Cytokine 15 (1), 20–26.

Tsukahara, K., Nakao, A., Hiraguri, M., Miike, S., Mamura, M., Saito, Y., et al., 1999. Tumor necrosis factor-alpha mediates antiapoptotic signals partially via p38 MAP kinase activation in human eosinophils. Int. Arch. Allergy Immunol. 120, 54–59.

van der Heijde, D., Ramiro, S., Landewé, R., Baraliakos, X., Van den Bosch, F., Sepriano, A., et al., 2017. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann. Rheum. Dis. 76 (6), 978–991.

Vester, K., Rüger, R.D., Harth, W., Simon, J.C., 2012. Transient blood eosinophilia during treatment with Adalimumab. J. Eur. Acad. Dermatol. Venereol. 26 (7), 924–925.

Ward, C., Chilvers, E.R., Lawson, M.F., Pryde, J.G., Fujihara, S., Farrow, S.N., et al., 1999. NF-kappaB activation is a critical regulator of human granulocyte apoptosis in vitro. J. Biol. Chem. 274 (7), 4309–4318.

Wenham, C., Gadsby, K., Deighton, C., 2008. Three significant cases of neutropenia with etanercept. Rheumatology (Oxford) 47 (3), 376–377.