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Mean Platelet Volume in Patients with Rheumatoid Arthritis: the Effect of anti-TNF-alpha Therapy

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Abstract

A number of mediators are involved in the inflammatory processes that affect joints and vascular wall of patients with rheumatoid arthritis (RA). Tumour necrosis factor alpha (TNF α) is one such mediator, and it is widely regarded as an important target for anti-rheumatic treatment. Most recent studies show that anti-TNF α medication suppresses inflammation and reduces overall activity of RA.

The aim of the current study was to investigate changes of mean platelet volume (MPV) in response to the 3-month anti-TNF α therapy in RA.

Twenty one RA patients without established cardiovascular disease were recruited for anti-TNF α therapy and underwent thorough clinical and laboratory evaluation at baseline, 2 weeks and 12 weeks. Anti-TNF α therapy resulted in a significant ($p=0.01$) increase in MPV over the duration of the study (7.7 ± 0.9 , 7.8 ± 1.1 , and 8.4 ± 1.1 fL at baseline, 2, and 12 weeks, respectively). The results of the study expand perspectives of the use of MPV in conditions associated with high-grade inflammation, particularly RA, for monitoring anti-inflammatory treatment. More prospective studies with large numbers of patients are warranted to ascertain associations of high and low values of MPV with diverse markers of inflammation and vascular pathology.

Keywords:

Rheumatoid arthritis; Mean platelet volume; Inflammation; Anti-TNF-alpha therapy.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by tenderness, swelling, and stiffness of the joints, with progressive destruction of cartilage and bone. Rheumatoid inflammation may lead to systemic manifestations, including accelerated atherosclerotic disease, which is the main cause of increased cardiovascular disease (CVD)-related morbidity and mortality in RA [1-3]. This may be due to a combination of reasons, including established CVD risk factors such as hypertension [4], dyslipidaemia [5], obesity [6], and physical inactivity [7], as well as due to the effects of systemic inflammation on the endothelium and generation of a prothrombotic state [8]. Amongst several pro-inflammatory agents involved in the initiation and propagation of pathological processes in the joints and vascular wall, tumour necrosis factor alpha (TNF α) is one of the most important targets of therapy. TNF α strongly associates with a variety of other mediators of systemic rheumatoid inflammation such as interleukins (IL) -1 and -6 and C-reactive protein (CRP) [9]. Agents blocking TNF α may reduce CVD in RA by dampening inflammation and improving endothelial function [10]. This may be more so in patients who previously failed to respond to disease-modifying anti-rheumatic drugs (DMARDs), who present with poorly controlled inflammation and high rheumatoid activity. There are, however, conflicting data about the effect of this group of biological agents in RA patients with advanced CVD and moderate to severe heart failure, which are even considered as a contraindication for anti-TNF α therapy [11]. In this regard, better understanding of biological effects of anti-TNF α on inflammatory, metabolic, and prothrombotic markers implicated in CVD may be useful for individualising the use of this promising group of drugs in RA.

Circulating platelets are an abundant source of prothrombotic agents closely related to inflammatory markers, and play a crucial role in the initiation and propagation of vascular disease [12]. Therefore, it would seem useful to study the effects of blocking TNF-alpha on various parameters of platelet function in RA, which still remain largely unknown. A recent study demonstrated significant decrease of circulating markers of coagulation such as prothrombin fragment F1+2 and D-dimer; the latter was associated with suppression of TNF α and IL-6 production [13]. Short-term effects of Infliximab infusions on platelet count were investigated in a few small studies, which yielded conflicting results, i.e. no effect or decreased platelet counts [14, 15].

Mean platelet volume (MPV) is one of the most widely used surrogate markers of platelet function and has been shown to reflect inflammatory burden and disease activity in RA [16, 17]. Despite this, changes in MPV have not been studied in the context of anti-TNF α therapy in RA. The aim of the present study was to investigate short-term effects of anti-TNF α on MPV in patients with RA.

METHODS

The study was approved by the local research ethics committee and the Research and Development Directorate of the Dudley Group of Hospitals NHS Foundation Trust, UK, and all participants provided

written informed consent. Twenty one consecutive patients fulfilling 1987 ACR criteria for RA [18], without known established CVD, requiring clinically indicated anti-TNF α therapy and eligible according to guidelines of the National Institute for Health and Clinical Excellence (NICE) [19], were recruited from rheumatology outpatient clinics.

Patients were predominantly female (n=13 [61.9%]; age 56.5 \pm 13.4 years). They underwent thorough clinical and laboratory evaluation, including complete medical history, seropositivity test for rheumatoid factor (RF), current disease activity score (DAS28) [20], and recording of drug treatment at baseline, 2 weeks, and 12 weeks after commencing anti-TNF α agents. All patients, except for one, were RF positive. Patients were treated with one of the 3 licensed in the UK anti-TNF α agents: 14 patients received Adalimumab 40mg subcutaneously every other week; 6 patients received Etanercept 50mg subcutaneously once weekly; and 1 patient received Infliximab 3mg/kg infusions at baseline, 2, 4, and then every 8 weeks. DMARD therapy (as monotherapy or in most cases combination therapy) remained stable throughout the study and was as follows: 14 patients were on Methotrexate (7.5-20 mg weekly with folic acid supplementation at 5mg once weekly), 7 patients on Sulfasalazine, 3 on Hydroxychloroquine, 5 on Glucocorticosteroids (oral Prednisolone 2.5-7.5 mg daily), 4 on Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and 4 on Statins.

Blood samples were collected between 8-11 a.m. after an overnight fast. Venepuncture was performed using 23G needle and blood samples were first collected in vacutainers (Becton Dickinson, UK) for CRP and ESR measurements, and then in EDTA-containing tubes for haematology tests. Haematological analyses were performed according to the previously published recommendations to avoid swelling of platelets stored in EDTA-containing test tubes [21]. MPV was analyzed by the Advia[®]120 automated blood cell counter. The size of platelets was quantified by flow cytometry on a cell-by-cell basis by measuring the intensity of scattered light at angular range of 2 $^{\circ}$ -3 $^{\circ}$. MPV measurements were obtained from the platelet volume histograms. The estimated coefficient of variation of MPV was 1.1-2.2%.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 15 (SPSS, Chicago, IL, USA). Continuous variables were tested for normality by the Kolmogorov–Smirnov test. Normally distributed data are presented as means and standard deviations (SDs). The effects of treatment on variables were tested by one-way repeated measures ANOVA with Bonferroni post-hoc test. A two-tailed P value below 0.05 was considered statistically significant.

The sample size of 21 patients was sufficient to reach power of 80% or greater for alpha=0.05 for the model of the effect of treatment on all recorded variables.

RESULTS

Results are summarised in Table 1. Anti-TNF α therapy resulted in statistically significant decrease of levels of inflammatory markers (ESR and CRP) and rheumatoid activity (DAS28). The decrease was more pronounced in the first two weeks of treatment. In fact, significant difference was noted in levels of ESR and fibrinogen at baseline and 2 weeks of anti-TNF α therapy (24.0 \pm 19.0 vs 13.8 \pm 11.0 mm/h, P=0.003). Also, DAS28 significantly decreased from its baseline level of 4.225 \pm 0.99 to 2.807 \pm 1.45 over the same period (P=0.001). Platelet count decreased as a result of the 3-month treatment (P=0.025) with a significant difference achieved at 2 weeks. Interestingly, MPV demonstrated gradual increase up to the end of the study (up to 8.4 \pm 1.1 fL). The overall effect of the treatment on MPV was significant (P=0.01).

Table 1. Description of laboratory findings over the 3-month study period

	Baseline	2 weeks	P ₁₋₂	3 months	P ₂₋₃	P ₁₋₃	Df _M , Df _R	F- ratio	P
ESR, mm/hour	24.0 \pm 19.0	13.8 \pm 11.0	0.003	19.0 \pm 20.6	NS	NS	1.54, 30.7	3.8*	0.044
CRP, mg/L	13.1 \pm 18.2	4.4 \pm 3.3	NS	6.2 \pm 4.1	NS	NS	1.1, 21.3	5.1*	0.032
DAS28	4.225 \pm 0.99	2.807 \pm 1.45	0.001	2.673 \pm 1.47	NS	<0.001	2, 38	19.6	<0.001
Platelets, x10 ⁹ /L	316.4 \pm 81.3	286.9 \pm 61.7	0.015	291.9 \pm 72.1	NS	NS	1.5, 30.9	4.6*	0.025
MPV, fL	7.7 \pm 0.9	7.8 \pm 1.1	NS	8.4 \pm 1.1	NS	0.016	2, 40	5.1	0.01

P₁₋₂ – statistical significance of differences between baseline and 2 weeks measurements, P₂₋₃ – 2 weeks and 3 months, P₁₋₃ – baseline and 3 months, P – statistical significance of the model.

Df_M - Degrees of the freedom for the effect of the model. Df_R - Degrees of the freedom for the residuals of the model.

*Greenhouse-Geisser corrected estimates of sphericity

DISCUSSION

Suppression of local and systemic inflammation is the main goal of the management of RA, which can delay the destruction of joints and progression of inflammation-related co-morbidities. With the advent of biological agents blocking TNF α , suppression of inflammation and control of disease activity, at least during several months, have substantially optimised. These agents administered alone or in combination with DMARDs appeared useful in suppressing pro-inflammatory cytokines and acute-phase reactants [22]. Based on the evidence, indicating a decrease of inflammatory markers, such as CRP and adhesion molecules, and

enhancement of endothelial function, the effects of anti-TNF α agents were regarded as not only anti-rheumatoid but also as potentially anti-atherogenic [23].

Despite advances in clinical practice achieved with the advent of this group of biological agents, opportunities have been offered to further explore involvement of diverse inflammatory biomarkers in the pathophysiology of RA.

The aim of this study was to investigate changes of one of the markers of platelet function, MPV, in response to anti-TNF α treatment. To the best of our knowledge, this issue has not been previously addressed. Our preliminary results indicate that the 3-month treatment with anti-TNF α , has a significant effect on MPV. Interestingly, over the 3-month period, patients experienced dramatic decrease of disease activity (DAS28), ESR, and CRP. There was also slight but statistically significant decreasing effect on platelet count ($P < 0.025$), which reflects observed earlier inverse relationship between changes of platelet count and size [24]. It seems likely that RA patients with high disease activity tend to have smaller size of platelets than those at recovery. The latter reiterates the results of a study [17], which found low size of platelets in RA patients at active stage, compared to the same parameter after a 2-month conventional anti-rheumatic treatment (7.1 ± 0.93 vs 7.72 ± 0.98 fL; $P < 0.001$). There is, however, another small longitudinal study [16], which demonstrated opposite direction of changes of MPV, measured at baseline and after 2 years of DMARDs therapy (8.7 ± 1.0 and 7.9 ± 1.3 fL, respectively; $P < 0.001$). The observed discrepancies, most probably, reflect time-dependent changes of MPV, and its dual pathophysiological role in RA (i.e., involvement in inflammation and thrombogenesis) [25]. Over a relatively short period of time, in conditions associated with high activity of inflammatory markers, such as active stage of RA, MPV values might indicate intensity of the inflammatory process. Overproduction of pro-inflammatory cytokines and acute-phase reactants can suppress size of platelets by interfering with megakaryopoiesis with subsequent release of small size platelets from the bone marrow [25]. Another possible explanation of the decreased size of circulating platelets in active RA relates to the intensive consumption of large platelets at sites of inflammation (vascular wall and synovial membranes). It is known that large platelets are more active in releasing a variety of pro-inflammatory and thrombotic agents than smaller size platelets, and their demand is increased during acute stage of inflammation.

In the current study, size of platelets was shown to gradually increase with significant difference reached at the end of the 3-month treatment. The latter may suggest that modulation of megakaryopoiesis in a new environment and release of critical mass of large platelets into the circulation requires period of time longer than 2 weeks. It should be noted that among several variables of platelet function produced by automated blood cell counters only MPV is well studied in a number of prospective studies in different populations of patients. Though mechanisms of MPV changes have not been fully explored, it is largely regarded as a useful surrogate marker of platelet activation, and a large platelet size of was shown to independently predict vascular events in patients with coronary artery disease and cerebrovascular disease [26, 27]. High values of MPV have been found in a number of clinical conditions associated with an increased risk of thrombotic

events (e.g., diabetes, hypertension, metabolic syndrome) [28-30], and, also, was found to be useful in monitoring results of cardiovascular drug therapy [31]. The results of our study further expand perspectives of use of MPV in conditions associated with high-grade inflammation for monitoring treatment, and, once again, emphasise the dual role of this marker, largely influenced by the intensity of inflammation. Prospective studies with large numbers of patients are warranted to ascertain associations of high and low values of MPV with diverse markers of inflammation and vascular pathology.

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