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Research Article
Pentoxifylline in Rheumatoid Arthritis Treatment as an Adjutant to the Synthetic Disease Modified Anti-rheumatic Drugs and Glucocorticoids

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Abstract

Background and Objective: Rheumatoid arthritis is a chronic inflammatory disease with relatively high prevalence and if uncontrolled can lead to high morbidity. Biological agents especially, anti-tumor necrosis factors have an important role in controlling disease activity in rheumatoid arthritis today, but in practice, high price makes many patients not able to use them. Usually, effective alternative drugs could be valuable. Pentoxifylline shows anti-tumor necrosis factors-alpha effects *in vitro* and *in vivo* and it could be a good candidate. This study evaluates the effect of adding pentoxifylline to the treatment of rheumatoid arthritis with synthetic disease modified anti-rheumatic drugs as an adjuvant therapy. **Methodology:** Pentoxifylline was added to the treatment regimen of 16 patients with rheumatoid arthritis who had active disease despite receiving synthetic disease modified anti-rheumatic drugs. Disease activity was compared before and few weeks after of pentoxifylline usage. **Results:** The patient and physician global assessment of disease activity and the number of tender joints were significantly improved after receiving pentoxifylline (p-value = 0.012, 0.03 and 0.02). Also, measures of disease activity score in 28 joints, simple disease activity index and clinical disease activity index were significantly improved (p-value = 0.03, 0.012 and 0.011). Changes in swollen joints counts, erythrocyte sedimentation rate, C-reactive protein, hemoglobin and platelet count were not significant. **Conclusion:** Pentoxifylline may play a role in the control of disease activity in rheumatoid arthritis.

Key words: Treatments, anti-tumor necrosis factor, synthetic, pentoxifylline, SDAI

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease with relatively high prevalence and without appropriate treatment it can lead to high morbidity[1].

Now-a-days, biological agents, especially anti-tumor necrosis factors (anti TNFs) have an important role in control of disease activity in RA and frequently used or recommended in early disease in patients who are resistant to the traditional disease modified anti-rheumatic drugs (DMARDs) or even as first line treatment in sever disease[1,2]. But in practice there is an important concern about anti TNFs, which many patients are not able to use because of its high price[3]. In some countries including Iran, biological agents are unavailable for treatment of some diseases, therefore, finding alternative drugs will be important.

One of the drugs that can be used in this regard is pentoxifylline (PTX). Many studies have showed that pentoxifylline has anti TNF-alpha effects *in vitro* and *in vivo*[4,5]. Furthermore, this agent have been used with some success in the treatment of rheumatoid arthritis and other disease such as psoriasis and pemphigus vulgaris[6-8]. This study evaluates the effect of adding pentoxifylline to the treatment of RA patients who are resistance to the synthetic DMARDs and glucocorticoids as an adjuvant therapy.

MATERIALS AND METHODS

The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within, which the study was undertaken and has therefore, been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki.

Methods: This is a prospective, before and after study in RA patients who referred to rheumatology clinics. Only patients with active disease based on Clinical Disease Activity Index (CDAI) score were included. The RA was defined based on ACR criteria 1987 or ACR/EULAR criteria 2010[9,10]. Patients with remitted disease, patients on biologic DMARDs or any change in the treatment regimen during the past two months were excluded. Seventeen patients were enrolled. They were informed about objectives of the study, drug benefits and complications and completed informed consent forms. The global disease severity was assessed with symptom score instrument which uses a 0-10 Visual Analogue Scale (VAS) by physician and the patients (0 "best condition" to 10 "the most severe condition". Twenty eight joints included in disease activity scores of RA (DAS28, SDAI and CDAI) were assessed and the number of tender and swallowed joints recorded by the physician. The ESR, Hb and platelet count also were measured. After primary assessment, patients received PTX 400 mg daily up to1200 mg daily if they tolerated. Second visit scheduled 8 weeks later and all of the above mentioned parameters of disease activity were assessed again. For dealing with inter-observation variability, assessing before and after clinical assessments was performed by an expert rheumatologist.

Statistical analysis: For statistical analysis, paired t-test was used to assess pre and post treatment values with normal distributed mean differences. Wilcoxon signed rank test was performed for non-normal values. The statistical significance level at $p<0.05$ was established.

RESULTS

Out of 17 patients, one patient was excluded from the study due to drug intolerance, which was restlessness but by using PTX her global assessment of disease severity became better (from 4/10-7/10). So the data of 16 patients were evaluated. The difference between mean of 5 variables scores (patient global assessment, doctor global assessment, disease activity score in 28 joints, simple disease activity index and clinical disease activity Index) before and after treatments were normally distributed (Table 1). All of these disease activity indicators improved after PTX. Paired t-test used to evaluate the significances of these changes. The PTX improved significantly patient global assessment (p-value = 0.012), doctor global assessment (p-value = 0.03), disease activity score in 28 joints (p-value = 0.03), simple disease activity index (p-value = 0.018) and clinical disease activity index (p-value = 0.011) (Table 2).

The differences between before and after values of other variables including tender and swollen joints, hemoglobin, ESR and platelet count were not distributed normally so it was applied Wilcoxon signed rank test for these variables (Table 3).

Table 1: Mean of 5 variables scores before and after treatment

Variable (before)	Mean	Variable (after)	Mean
pGA[1]	6.31	pGA	4.63
dGA[2]	5.06	dGA	4.00
DAS28[3]	4.32	DAS28	3.75
SDAI[4]	15.68	SDAI	12.00
CDAI[5]	21.44	CDAI	16.19

pGA: Patient global assessment, dGA: Doctor global assessment, DAS28: Disease activity score in 28 joints, SDAI: Simple disease activity index and CDAI: Clinical disease activity index

Table 2: Paired t-test of 5 variables scores before and after treatment

		95% Confidence interval of the difference			
Variable (before and after)	Mean±SD	Lower	Upper	t	Significance (2-tailed)
Pair 1 (pGA[1] before-pGA after)	1.688±2.36	0.431	2.944	2.862	0.012
Pair 2 (dGA[2] before-dGA after)	1.063±1.77	0.120	2.005	2.403	0.030
Pair 3 (DAS[3] before-DAS28 after)	0.556±0.93	0.062	1.049	2.400	0.030
Pair 4 (SDAI[4] before-SDAI after)	3.681±5.55	0.722	6.640	2.651	0.018
Pair 5 (CDAI[5] before-CDAI after)	5.250±7.28	1.820	1.371	15.00	0.011

pGA: Patient global assessment, dGA: Doctor global assessment, DAS28: Disease activity score in 28 joints, SDAI: Simple disease activity index and CDAI: Clinical disease activity index

Table 3: Wilcoxon signed rank test of other variables

	SJ[1] after-SJ before	TJ[2] after-TJ before	Hb[3] after-Hb before	Plt[4] after-Plt before	ESR[5] after-ESR before
Z	-1.268[a]	-2.318[a]	-0.220[b]	-0.085[b]	-0.105[b]
Asymptotic significance (2-tailed)	0.205	0.020	0.826	0.932	0.916

Z: The differences between before and after values, [a]Based on positive ranks, [b]Based on negative ranks. SJ: Swollen joint, TJ: Tender joint, Hb: Hemoglobin, Plt: Platelet count and EDR: Erythrocytes sedimentation rate

The patients tender and swollen joints decreased after taking PTX but this improvement were statistically significant only for tender joints (p-value = 0.02). The changes were not significant for swollen joints, hemoglobin, platelet count and ESR (Table 3).

DISCUSSION

This study was designed to evaluate the effects of PTX on active RA. All of the subjective indicators of disease activity improved significantly in this study (Table 2). Also all of the criteria of rheumatoid disease activity improved after adding PTX to the RA treatment (Table 2). But the objective findings such as number of swollen joints and ESR did not change.

One of the first trials of PTX in RA treatment was study, Huizinga *et al.*[11]. They used combination of PTX and thalidomide in an open study of rheumatoid arthritis patients to assess the effect on TNF production, the antiarthritic effects and toxicity of this combination, in which 12 patients with active rheumatoid arthritis were treated with 1200 mg pentoxifylline and 100 mg thalidomide daily for 12 weeks. The results showed a lowering in the TNF production capacity during treatment. Of the nine patients who completed the study, five fulfilled the ACR-20% response criteria after 12 weeks of treatment. Adverse events such as xerostomia, drowsiness and constipation occurred in almost all patients, which led to discontinuation in three. It was concluded that although pentoxifylline/thalidomide reduced the production capacity of TNF, the benefit/side effects ratio was poor due to multiple adverse effects, while clinical observation suggests limited efficacy. In this study, side effects of PTX was minor and only one patient stopped it because of nausea and dizziness.

Another interesting study is a case report of a 64 year-old man with seronegative RA who had 23 swollen joints, 32 painful joints and ESR 135 mm h^{-1} [12]. All these parameters were dramatically improved 3 weeks after administration of PTX 300 mg day^{-1} and prednisolone 5 mg day^{-1}. Discontinuation of PTX in this patient resulted in rapid exacerbation of RA and when PTX was restarted the patient showed complete recovery from arthritis with normalization of ESR within 3 months and was maintained a complete remission for another 1 year. This case further supports a potential antirheumatic effect of PTX on some patients with RA.

Pentoxifylline was given to the patients (in a prospective trial in 21 patients with active rheumatoid arthritis) a daily dosage of 1,200 mg for at least one month. After one month, a significant decrease in the pain severity score was noted, but all other clinical and laboratory efficacy parameters were unchanged. This is comparable with these results which showed swollen joints and ESR did not improve with PTX[7]. The pain in RA may be an only indicator of inflammation especially in mild inflammation. Thus, improvement of pain may be the sign of the efficacy of the treatment to reduce inflammation and disease activity. The dose-response relationship of the anti-inflammatory activity of PTX in experimental animal models of chronic inflammation in 2012 has been evaluated and they have found that PTX in a dose dependent pattern attenuates formaldehyde-induced chronic inflammation and cotton-pellet induced granuloma in rats and potentiates the anti-inflammatory activity of dexamethasone and methotrexate[13]. Only 5 of this cases tolerated 1200 mg PTX daily, on the other hand the sample size of present study was not suitable for subgroup analysis, so to do larger study was need to be able to evaluate effects of PTX in larger doses it

should consider that. The pain in RA patients is influenced by some other factors such as emotional factors and neuroendocrine system[14,15].

There are few placebo-controlled studies in PTX therapy for RA. It has been reported that in a double-blind, randomized and placebo-controlled study in which a total of 53 patients randomized to receive pentoxifylline or placebo. Pentoxifylline treatment reduced pain, swelling and joint tenderness. Also a statistically significant decrease in erythrocyte sedimentation rate and C-reactive protein was observed with pentoxifylline compared with placebo[8]. In this study, PTX effects as single treatment of RA was compared with placebo, though the improvements in disease activity can be more easily attributed to PTX therapy. Because of importance of early treatment of RA with DMARDs now it cannot ethically conduct such a placebo controlled trial and only can test adding PTX/placebo to standard treatment of RA.

Another recent study published in American Journal of Pharmacological Sciences, 2013, in which 40 patients who were using etanercept were randomly allocated to receive each day either pentoxifylline 400 mg tablet twice daily or placebo also twice daily and were evaluated at baseline and at week 8 for clinical and hematological parameters. Tumor Necrosis Factor (TNF), high sensitive C-reactive protein (hsCRP), duration of morning stiffness and cardiovascular risk were significantly more reduced in pentoxifylline group than placebo group after 8 weeks. Non-significant changes were observed in clinical parameter like swelling joints counts, tender joints counts, evaluator global assessment, DAS28-ESR, SDAI-CRP and hematological parameters like hemoglobin amount, erythrocyte sedimentation rate and white blood cells count between groups[16].

CONCLUSION

This study was a before-after investigation and we do not have any placebo control group, therefore, the more effects on the subjective variables may be due to a placebo effect of PTX. To evaluate the accurate answer to above hypothesis we need to do larger placebo/control trials.

As a result, PTX may consider as an adjutant treatment to decrease pain in RA discomfort.

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