Comparison of 10 Year Cardiovascular Risk in Rheumatoid Arthritis Patients Verses Non-Rheumatoid Arthritis Patients

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Abstract

Objective: To compare 10 year cardiovascular risk in rheumatoid arthritis (RA) patients and control group using different cardiovascular risk scores and to assess the usefulness of these scores in rheumatoid arthritis

Methods: Case control study conducted at FFH and HFH from 1st September 2019 to 29th February 2020. Patients 40 to 80 years of age were selected. 196 patients all females were included, 98 patients diagnosed RA according to American College of Rheumatology (ACR) 2010 criteria (RA group). 98 patients which are non RA matched healthy controls (control group). Blood was taken for lipid profile, erythrocyte Sedimentation rate, creatinine levels, rheumatoid factor and anti-cyclic citrullinated peptides. Weight, height, Glomerular filtration rate were measured. Framingham risk score, Systemic Coronary risk evaluation, QRISK2, and American College of Cardiology/American Heart Association was calculated for both groups using online calculator.

Results: Mean age of RA patients was 52.87 ± 10.42. Most common comorbidity in RA patients was found to be hypertension 82(42%), 100(48.78%) were overweight with mean BMI of 25.35 ± 4.96. RA group have mean high FRS, QRISK2, ACC/AHA and SCORE i.e 14.84 ± 7.36, 17.89 ± 17.98, 10.00 ± 13.94 and 2.31 ± 2.40 than control group.QRISK2 scores identify more high risk patients than other scores

Conclusion: Large proportion of RA patients had high risk of cardiovascular disease as compared to healthy controls on the basis of FRS, QRISK2, ACC/AHA and SCORE. QRISK2 scores is better predictor of categorizing cardiovascular risk as high risk than other scores used in the study.

Keywords: Cardiovascular Risk • Rheumatoid Arthritis • QRISK2 • ACC/AHA • SCORE • Framingham Risk Score.

Introduction

Immune mediated joint diseases like rheumatoid arthritis (RA), systemic lupus erythromatosis (SLE), psoriatic arthritis (PsA) and other seronegative arthropathies have increased risk of myocardial infarction, cerebrovascular accidents and peripheral vascular disease [1]. The reason behind this increased cardiovascular risk is mainly due to release of cytokines and other chemotactic factors which are increased in these diseases like in RA there are increased levels of tumor necrosis factor α (TNFα), interleukin 6(IL-6)and interleukin 1(IL-1) [2,3]. Similarly in PsA, TNF α, Interleukin 17(IL-17) and Interleukin-23(IL-23) are increased. SLE has increased levels of B cell activating factor (BAFF). These cytokines cause joint inflammation as well they have adverse effect on cardiovascular system as a result they increase atherosclerosis and increase the risk of myocardial infarction and stroke in these already immunocompromised patients [4,5].

Apart from cytokines another factor which is responsible for increased cardiovascular risk in immune mediated joint diseases is use of a number of drugs like non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids which are cornerstone in the management most of these illnesses. NSAIDS long term increase the free radicals, and decrease prostaglandin synthesis which results in premature arthrosclerosis [6,7].

Rheumatoid arthritis is a systemic and autoimmune disease mainly involving the synovial joints of the body. Due to overall inflammatory milieu in a patient of RA, these pro inflammatory cytokines acts on blood vessels and heart which increases the chances of early arthrosclerosis resulting in dyslipidemias, hypertension, diabetes which are the risk factors for cardiovascular disease. Apart from joints there are number extra-articular manifestations like rheumatoid nodules, anemia, keratoconjuctivitis sicca, neuropathy, and felty syndrome common in these patients [8].

The management of diabetes hypertension, weight, dyslipidemia should be an important part of management of patients with immune related diseases especially in the high risk group it significantly decreased mortality in these patients [9].

RA has a worldwide prevalence of disease of 1% [8]. In Pakistan it has a prevalence of 1% according to a study conducted in Pakistan by Farooqi and colleagues in late 90's [10]. The true prevalence in our country is difficult to estimate due to lack of RA registry here.

A number of cardiovascular risk scores are used to determine the cardiovascular risk scores in RA patients like American college of cardiology /American heart association (ACC/AHA 2013), Systemic coronary risk evaluation (SCORE), QRISK2, QRISK3 score, Framingham risk score (FRS), Ryenolds risk score (RRS) and expanded risk score in rheumatoid arthritis (ERS-RA).The significance of one above the other is not known. These risk assessment tools are usually used in general population and their use in specific autoimmune diseases like RA, SLE and seronegative spondyloarthropathies is suspicious. And this is not clear which of them is most accurate in RA patients as compared to others [11,12].

Framingham risk score (FRS) is the oldest score used derived from the Framingham heart study and may be divided into Framingham risk score-lipids and Framingham risk score- body mass index (FRS-BMI) [13].

QRISK2 2017 and now QRISK3 is also available that includes more factors than QRISK2 to help physicians to identify those at risk of heart disease and stroke, such as chronic kidney disease, migraine, corticosteroids use, SLE, atypical antipsychotics, severe mental illness, erectile dysfunction, and a measure of systolic blood pressure variability [12,14]

Ryenolds risk score also includes C-reactive protein as compared to other traditional risk factors [15]. Others include expanded risk score in rheumatoid arthritis (ERS-RA) and Systemic Coronary Risk Evaluation (SCORE) which are somewhat specialized scores for rheumatoid arthritis even then there efficacy is not proven [12,16]

American College of Cardiology and American Heart association (ACC/AHA) score can also be used to assess cardiovascular risk in rheumatoid arthritis [17]. To date this is a debatable topic and needs further assessment and comparison with some sonological evidence of arthrosclerosis like carotid plaques on ultrasound Doppler or angiography to determine the correct assessment of high risk patients in this disease population [18].

Cardiovascular risk assessment in patients having autoimmune diseases like RA and SLE should be done as recommended by European League against Rheumatism (EULAR). The calculated risk score should be multiplied by 1.5 to adjust the increased risk associated with RA and SLE.1 The purpose of this study is calculating these risk scores in RA patients as well as in a control group and see their usefulness. This will help the clinicians to give due importance to cardiovascular risks in all RA patients and assess their 10 year cardiovascular risk using the score which is found to be most accurate. And address those having high cardiovascular risks in a timely manner. This quantification will help in earlier screening of high-risk patients for better intervention to manage these risk factors.

Local data on utilization of such risk scores is limited. So, this study was planned to calculate increased CVD risk in RA patients in comparison to matched healthy participants. This study will also help us to find out the most appropriate test for 10 year cardiovascular risk in RA patients among these four risk scores.

Materials and Methods

Patients and method

This is a cross sectional comparative study conducted at Fauji Foundation hospital Rawalpindi and HolyFamily hospital Rawalpindi. Patients between ages 40 to 80 were selected from outpatient department (OPD) of rheumatology at FFH Rawalpindi and HFH Rawalpindi. At total of 196 patients all females were included in the study. Written and informed consent were taken from each participant. Approval from Institutional Review Board and ethical committee was taken. Out of these 196, 98 patients were known to have RA according to American College of Rheumatology (ACR) 2010 criteria and labeled as RA group [19]. 98 patients who came to Rheumatology/ medical OPD which are age matched having no evidence of rheumatoid arthritis were included in the other group and labelled as non RA group or control group. Patients were included in the study if they do not have any history of myocardial infarction, stroke and peripheral vascular disease in the past and not taking statins or antiplatelet drugs. Personal profile questions and baseline data were noted in a proforma for both groups. Blood pressure was measured two times on two different days by using sphygmomanometer after 5 minutes of rest and their mean was taken and use of antihypertensive was noted. Diabetes Mellitus was labelled as self-reported diagnosis of diabetes or taking insulin or oral hypoglycemic drugs. After 12 hours of fasting, venous blood was taken for total cholesterol (TC), triglycerides (TG), low density lipoproteins (LDL), high density lipoproteins (HDL), erythrocyte sedimentation rate (ESR) and renal function tests .Blood samples were also drawn to note down patients antibody profile including both rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti CCP). Smoking status was also documented in the proforma. Disease activity status of each patient was calculated using Disease activity score 28 (DAS-28) by counting tender joints (TJ), swollen joints (SJ) and pain on a visual analogue scale (0-10) .Weight and height of patients were measured and body mass index (BMI) of each patient was calculated by using formula (weight in kg/ (height in meters2). Electrocardiogram (ECG) was done of all patients to document atrial fibrillation. Glomerular filtration rate (GFR) was measured using Cockcroft Gault equation and labeled as chronic kidney disease if patient has GFR less than 60ml/min. Framingham risk score, QRISK2, ACC/AHA was calculated of both groups using online calculator. Systemic coronary risk evaluation score (SCORE) was measured using high risk chart. The risk calculated by online calculators is multiplied by a factor 1.5 except QRISK2 as it already includes Rheumatoid arthritis in calculator. Data was entered and analysed using SPSS version 23.0. Mean and Standard deviation was calculated for numeric variables and frequencies with percentages were calculated for categorical data. Paired t-test is used to compare means of continuous data. Chi square test is used to compare the categorical data. The comparison of the mean FRS, QRISK2, ACC/AHA and SCORE of RA group and control group was done using ANOVA test and p-value ≤ 0.05 was considered significant.

Results

The mean age in RA group was 52.87 ± 10.42 years and in control group was 53.22 ± 10.18 year. P value was not statistically significant (p -value 0.821).The mean values of TC, TG, LDL, HDL were 196.77 ± 31.54 vs 189.91 ± 29.16, 167.20 ± 67.15 vs 162.04 ± 53.58, 118.92 ± 28.79 vs 114.91 ± 30.75, and 41.48 ± 7.00 vs 41.19 ± 7.33 in RA group and control group respectively. P value was not significant for all four lipid profile parameters. The mean values of weight were (26.59 ± 4.96 vs. 24.33 ± 4.81 kgs) in RA group and control group respectively. There was statistically significant difference in weight of RA group and control group (P value 0.001). Systolic Blood Pressure (SBP) (131.73 ± 18.99 vs. 125.76 ± 15.84) and Diastolic Blood Pressure (DBP) (79.69 ± 9.38 vs. 77.90 ± 8.37) were significantly higher in RA patient's group in comparison to normal healthy controls. The p value was statistically significant for SBP. (P value 0.022) (Tables 1-3)

Table 1. Distribution of Demographic characteristics and lipid profile of RA Group and healthy controls.

	Group	RA group N=98	Control group N=98	P value
		Mean	Mean	
1.	Age (years)	52.87±10.42	53.22±10.18	0.821
2.	Duration of disease(years)	9.89 ±7.09	-	
3.	Triglyceride levels TG (mg/dL)	167.20±67.15	162.04±53.58	0.565
4.	Mean LDL (mg/dL)	118.92±28.79	114.91±30.75	0.346
5.	Mean HDL (mg/dL)	41.48±7.00	41.19±7.33	0.782
6.	Mean total cholesterol TC(mg/dL)	196.77±31.54	189.91±29.16	0.118
7.	Weight(kgs)	26.59±4.96	24.33±4.81	0.001
8.	Mean SBP (mmHg)	131.73±18.99	125.76±15.84	0.022
9.	Mean DBP (mmHg)	79.69±9.38	77.90±8.37	0.157

* Difference is statistically significant at 5% level of significance ** Difference is highly significant at 1% level of significance.

Table 2. Comparison of risk factors for cardiovascular disease between RA and Non RA groups.

Group	RA group N=98	Control group N=98	P value
Seropositive	69(69.7%)	Nil	
Seronegative	29(29.3%)		
Hypertension			
Yes	44(44.9%)	36(36.4%)	0.036
No	54(55.1%)	62(62.6%)	
Diabetes mellitus			
Yes	21(21.2%)	16(16.3%)	0.537
No	77(77.8%)	82(83.7%)	
Smoker			
Yes	14(14.2%)	11(11.2%)	0.511
No	84(84.8%)	87(88.8%)	
Osteoporosis			
Yes	11(11.2%)	11(11.2%)	0.25
No	87(88.8%)	87(88.8%)	
Disease activity(DAS28)			

Remission(<2.6)	48(48.5%)	nil	
Mild(2.6-3.1)	11(11.1%)		
Moderate(3.2-5.1)	29(29.3%)		
High (>5.1)	10(10.1%)		
LDL			
Normal	31(31.3%)	34(34.7%)	0.792
Near normal	39(39.4%)	43(43.9%)	
Borderline high	19(19.2%)	16(16.3%)	
High	7(7.1%)	3(3.1%)	
Very high	7(7.1%)	2(2%)	
HDL			
Less than 40	58(58.4%)	60(61.2%)	0.445
Optimal	36(36.4%)	34(34.7%)	
More than 60	4(4%)	4(4.1%)	
Triglycerides			
Normal <150	12(12.2%)	6(6.1%)	0.625
Borderline high 150-199	38(38.8%)	39(39.8%)	0.625
High 200-499	24(24.5%)	32(32.7%)	
Very high >500	24(24.5%)	21(21.4%)	
BMI			
Underweight	1(1%)	7(7.1%)	0.981
Normal weight	37(37.4%)	55(56.1%)	
Overweight	41(41.8%)	24(24.5%)	
Obese	19(19.2%)	12(12.2%)	

Table 3. Comparison of Framingham risk Score between RA cases and normal controls.

Framingham Risk Score	RA group N=98	Control group N=98	P-value
Mean ± SD/Median	14.84 ± 7.36/ 15	11.25 ± 4.30/ 11	0.107
Mild risk (less than 10%)	27(27.3%)	47(48%)	0.224
Moderate risk (11 to 20%)	46(46.5%)	50(51%)	
Severe risk (>20%)	25(25.3%)	1(1%)	

Table 4. Comparison of QRISK2 score between RA cases and normal controls.

QRISK2 Score	RA group N=98	Control group N=98	P-value
Mean ± SD/Median	17.89 ± 17.98/12.23	15.62 ± 13.33/ 10	0.107
Mild risk (less than 10%)	40(40.8%)	53(54.1%)	0.224
Moderate risk (11 to 20%)	31(31.6%)	20(20.4%)	
Severe risk (>20%)	27(27.6%)	25(25.5%)	

Table 5. Comparison of ACC/AHA Score between RA cases and normal controls.

ACC/AHA Score	RA group n=98	Control group n=98	P value
Mean ± SD/median	10.00±13.94/5.47	5.89±7.50/3	0.013
Low risk(less than 5%)	44(44.9%)	60(61.2%)	0.175
Borderline risk (5 to 7.4%)	17(17.3%)	15(15.3%)	
Intermediate risk (7.5 to 19.9 %)	22(22.4%)	20(20.4%)	
High risk (more than 20%)	15(15.3%)	3(3.1%)	

Table 6. Comparison of SCORE between RA cases and normal controls.

Systemic coronary risk evaluation	RA group n=98	Control group n=98	P value
Mean ± SD/median	2.31 ± 2.40/2.31	1.72 ± 1.78/1	0.065
Low risk(less than 1%)	26(26.5%)	20(20.4%)	0.832
Borderline risk (less than 5%)	63(64.3%)	69(70.4%)	
Intermediate risk (6 to 10 %)	7(7.1%)	8(8.2%)	
High risk (more than 10%)	2(2%)	1(1%)	

The comparison of comorbidities between the two groups showed that hypertension is present in increased number of patients in RA group as compared to non- RA group with significant P value. (P value 0.036). There are increased cases of diabetes, smoking and overweight patients in RA group as compared to control group but it was not statistically significant.

The results of our study showed that there was significant (p-value<0.05) difference in mean value of ACC/AHA Score of RA group and normal healthy controls. The average value of QRISK2 and ACC/AHA was noted significantly greater in RA patients as compared to normal healthy controls with mean value of 17.89 ± 17.98 vs 10.00 ± 13.94 and 15.62 ± 13.33 vs 5.89 ± 7.50 showing a highly significant increase in RA patients with p value of 0.107 and 0.013 respectively (Tables 4-6).

In the study FRS assessed 25.3% patients having high cardiovascular risk, QRISK2 27.6%, ACC/AHA 15.3% in high risk as compared to control group. While SCORE detect only 9.1% having high risk score as compared to non-RA patients.

Discussion

Rheumatoid arthritis is a chronic and multisystem autoimmune disorder which mainly affect the female population. With passage of time in patients with RA many other severe complications like cardiovascular disease increases significantly. After a period of 10 years, most common cause of death among RA patients is cardiovascular disease1. There is an increase of 50 to 70 % increase cardiovascular risk [20]. Many epidemiological studies have identified some non-conventional/disease specific factors along with classical conventional risk factors, which stimulate the enhanced chances of atherosclerosis in inflammatory diseases like RA.

The results of this present study showed that almost all the patients in cases group were females and that's why in control group all female participants were enrolled in control group. Many studies in literature also support this highly predominance of females in RA disease [21]. The rate of morbidity and mortality significantly increases in patient with RA as compared to general population. The main causes for such increase are infections and cardiovascular disease [8]. The main origin of cardiovascular disease and other cardiac related manifestations is accelerated atherosclerosis, which increases the significance of its proper management. As seen by the results it is found that mean age between the RA group and control group was similar. Mean weight, SBP, DBP, TG, HDL, LDL, and TC levels are lower in the control group as compared to the RA group. This is due to altered lipid synthesis in RA patients as compared to those who do not have RA.

Mean FRS, QRISK2, ACC/AHA, FRS and ACC/AHA score is less in control group as compared to RA group, this can be explained as overall cardiovascular risk is less in general population as compared to RA. This is also seen in a study done in Pakistan in Lahore at Sheikh Zayed hospital that shows same increase FRS and QRISK2 score in RA group as compared to our population. Results of SBP, DBP and lipid profiles are quite similar like our study [22].

Cardiovascular risk was also found to be increased in RA in another study conducted at Fauji Foundation hospital Rawalpindi [23].

In a study conducted on Mexican population in 2017showed that median FRS was 8.47 in RA group while in our study it was 15. QRISK2 median in that study was 5.55 which is quite lower than our population which is [12,23]. ACC/AHA is 5.47 in our study as compared to 3.6 in the Mexican population [11]. The difference and increase cardiovascular risk in RA population in our study was due to ethnicity difference or environmental factors may play a role. This needs to be investigated further.

In another study conducted by Salaffi F and colleagues showed that ACC/AHA identifies 39.3% high risk patients, 29.8% in QRISK2 group, 28.6% in FRS and 19% in SCORE. FRS and ACC/AHA high risk patients number were similar to our study but QRISK2 and SCORE are low and high respectively as compared to our study [12].

When comparison of different scores was done between RA and non RA group for it was found that QRISK2 gives the gives the most accurate mean when compared to control group. In another study comparing FRS with QRISK2 score done in Pakistan shows that QRISK 2 score is more specific for RA as compared to FRS. Our study also shows that QRISK2 score can identify more high risk patients than other scores used in our study. QRISK2 identify 27.6% as having high risk of cardiovascular disease and ACC/AHA score shows 15.3% patients having high risk. While FRS showed 25.3% patients having high cardiovascular risk and SCORE shows only 9.1% have high risk. These scores underestimate the risk in RA patients [24,25].

The risk of cardiovascular events increases considerably in patients of RA due to atherosclerosis. This increase in risk cannot be explained completely on the basis of traditional cardiac risk factors. It was an established belief that lipids accumulate in arterial wall to form plaque. But recent researches have clearly revealed that main cause of atherosclerotic plaque is inflammation. Preventive strategies for modifiable cardiac risk factors can help in lowering the chance of cardiovascular events by reducing the possibility of atherosclerosis among RA patients. Plaque formation due to inflammation is a main reason for atherosclerosis and treatment to neutralize the immunologic responses that results in plague formation can considerably reduce the chance of cardiovascular disease among RA patients.

It highlights importance to create a high awareness of this risk among RA patients, and the attainment of target cholesterol and blood pressure levels in these high-risk patients. Further attention should be paid to optimal CVD risk categorization and management in RA patients.

Conclusion

A considerably large proportion of RA patients had high risk of cardiovascular disease as compared to normal healthy controls on the basis of FRS, QRISK2, ACC/AHA and SCORE. QRISK2 scores is better predictor of categorizing cardiovascular risk as high risk than other scores used in the study.

Limitations of the study

The study should be done at a large scale with large sample size to see the accurate cardiovascular risk, it should be multicentered study and male patients were not included in the study they should be included.

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Authors contributions

Muhammad Salman Mushtaq: Conceived and designed study, did statistical analysis, Drafting, writing and editing of manuscript.

Muhammad Arif and Babar Salim: Did supervision, critical review, statistical analysis and final approval of manuscript.

Omer Daraz, Saba Samreen, Haris Gul: Data Collection, statistical analysis, data interpretation and its presentation.

References

1. Alam, J., et al. "Rheumatoid arthritis: recent advances on its etiology, role of cytokines and pharmacotherapy". *Biomedicine & Pharmacotherapy* 92 (2017): 615-633.
2. Brzustewicz, E., & Bryl, E. "The role of cytokines in the pathogenesis of rheumatoid arthritis-Practical and potential application of cytokines as biomarkers and targets of personalized therapy". *Cytokine* 76.2 (2015): 527-536.
3. Moelants, E.A., et al. "Regulation of TNFα with a focus on rheumatoid arthritis". *Immunology and cell biology*. 91.6 (2013): 393-401.
4. Shen, A., et al. "Total flavonoids of Bidens bipinnata L. ameliorate experimental adjuvant-induced arthritis through induction of synovial apoptosis". *BMC complementary and alternative medicine*. 15.1 (2015): 437.
5. Atzeni, F., et al. "Different effects of biological drugs in rheumatoid arthritis". *Autoimmunity reviews*. 12.5 (2013): 575-579.
6. Mendes, M.T., et al. "Basic aminopeptidase activity is an emerging biomarker in collagen-induced rheumatoid arthritis". *Regulatory peptides*. 167.3 (2011): 215-221.
7. Mendes, M.T., & Silveira, P.F. "Leukotriene-A4-Hydrolase and Basic Aminopeptidase Activities Are Related with Collagen-Induced Arthritis in a Compartment-Dependent Manner". *Open Journal of Rheumatology and Autoimmune Diseases*. 3.4 (2013): 255.
8. Caporali, R., et al. "Oral low-dose glucocorticoids should be included in any recommendation for the use of non-biologic and biologic disease-modifying antirheumatic drugs in the treatment of rheumatoid arthritis". *Neuroimmunomodulation*. 22.2 (2015): 104-111.
9. Curtis, J.R., et al. "The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents". *Annals of the rheumatic diseases*. 70.8 (2011): 1401-1406.
10. Grozdanova, A., et al. "Biosimilar medical products–licensing, pharmacovigilance and interchangeability". prilozi. 37.1 (2016): 27-36.

11. Grzelewska-Rzymowska, I., & Gorski, P. "Rupatadine: a novel second-generation antihistamine. Postepy Dermatologii i Alergologii. 28.6 (2011): 489.

12. Alexandre-Moreira, M.S., et al. "LASSBio-468: a new achiral thalidomide analogue which modulates TNF-α and NO production and inhibits endotoxic shock and arthritis in an animal model". *International immunopharmacology*. 5.3(2005): 485-494.

13. https://app.uff.br/riuff/handle/1/9743

14. Nyman, U., et al. "Amelioration of collagen IIinduced arthritis in rats by the type IV phosphodiesterase inhibitor Rolipram". *Clinical & Experimental Immunology*. 108.8 (1997): 415-419.

15. Thabet, R.H., et al. "Immune modulation and amelioration of joint edema by a PDE-inhibitor and its solvent". *American Journal of Research Communication*. 4.3 (2016): 28-42.

16. Bublikov, D., et al. "AB0384 The Effects of Pentoxifylline on Rheumatoid Arthritis Activity According To The DAS28 CRP Disease Activity Score". *BMJ Publishing Group Ltd* 75.2 (2016).

17. Francischi, J.N., et al. "Anti-inflammatory and analgesic effects of the phosphodiesterase 4 inhibitor rolipram in a rat model of arthritis". *European journal of pharmacology*. 399.3 (2000): 243-249.

18. Ishii, O., et al. "Remission induction after pentoxifylline treatment in a patient with rheumatoid arthritis. Ryumachi". *Rheumatism*. 37.6 (1997): 810-815.

19. GutiérrezRodríguez, O. "Thalidomide a promising new treatment for rheumatoid arthritis". *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*. 27.10 (1984): 1118-1121.

20. Gutierrez-Rodriguez, O, et al. "Treatment of refractory rheumatoid arthritis--the thalidomide experience". *The Journal of rheumatology*. 16.2 (1989): 158-163.

21. Mohammed, S.I., et al. "Pentoxifylline as adjuvant therapy to etanercept in patients with moderately to highly active rheumatoid arthritis". *Am J Pharm Sci*. 1(2013): 61-66.

22. Usha, P., et al. "Clinical Efficacy and Tolerability Evaluation of Pentoxifylline in Rheumatoid Arthritis". *Clinical drug investigation*. 22.5 (2002): 329-339.

23. Scoville, C. "Pilot study using the combination of methotrexate and thalidomide in the treatment of rheumatoid arthritis". *Clinical and experimental Rheumatology*. 19.3 (2001): 360.

24. Scoville, C.D., & Reading, J.C. "Open trial of thalidomide in the treatment of rheumatoid arthritis". *Journal of clinical rheumatology*. 5.5 (1999): 261-267.

25. Chen, J., et al. "Paeoniflorin inhibits proliferation of fibroblast-like synoviocytes through suppressing G-protein-coupled receptor kinase 2". *Planta medica*. 78.7 (2012): 665-671.

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