IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 9 Ser.9 (September. 2021), PP 17-23
www.iosrjournals.org

A Study on the Extra-Articular Manifestations of Rheumatoid Arthritis

Dr.R.Jegatheesh[1], Dr.G.Ponmozhi[2], Dr. S. Usha[3]
[3]*(Professor, Department of Medicine, Coimbatore Medical College, Tamilnadu, India)*
[1,2]*(Senior Resident, Department of Medicine, Coimbatore Medical College, Tamilnadu, India)*
The TamilnaduDr.MGR Medical University, Tamilnadu, India

Abstract: *Rheumatoid arthritis is a chronic systemic inflammatory disease of unknown etiology marked by symmetric peripheral polyarthritis.Hence it may result in a variety of extra-articular manifestations including fatigue, subcutaneous nodule, lung involvement, pericarditis, peripheral neuropathy,vasculitis and hematological abnormalities.In our study, the extra-articular manifestations develop in 80% of RA factorseropositivitypatients,with duration of illness was 15.6years.Anaemia of chronic disease was found to be the most common extra- articular manifestation.Among others,12% cardiac,18%ocular,24% dermatological,27%Pulmonary manifestation,6% overlap syndromes.Extra- articular manifestations contribute significantly to the morbidity and mortality of rheumatoid arthritis. So careful screening of all patients for extra-articular manifestations may help reduce the same.*

Keywords: *Rheumatoid arthritis,Extra-articular manifestations,diseaseduration,morbidity*

Date of Submission: 06-09-2021 Date of Acceptance: 20-09-2021

I. Introduction

Rheumatoid arthritis is a chronic inflammatory and progressive disease characterized by various extra-articular manifestations. The presence of extra- articular manifestations of RA is associated with more severe disease, high rheumatoid factor levels and is considered a risk factor for early death in patients with rheumatoid arthritis. The presence of extra-articular manifestations may vary in different geographic areas and different ethnic groups. Extra- articular organ involvement includes skin, eyes, heart, lung, vasculitis, hematology etc. The presence of extra-articular manifestations is a major predictor of mortality in RA patients.[1]

Our study focuses on the extra-articular manifestations in 100cases of rheumatoid arthritis attending outpatient department or admitted to ward at Coimbatore medical college hospital.

II. Epidemiology

RA occurs worldwide in virtually all ethnic groups, with a prevalence estimated between 0.5% and 1%. It is significantly more common in females than in males.Death often results from infection, heart disease, respiratory failure, renal failure, or gastrointestinal disease rather than from joint disease itself. Whether this is due to an inflammatory process or due to exposure to antirheumatic drugs or both is unclear.[2]

III. Objectives

To investigate and compare the frequency and type of extra-articular manifestations
To correlate the number of extra-articular manifestations with the duration of the study In a well defined community based cohort of patients with rheumatoid arthritis

IV. Methodology

Study design: Descriptive study
Study population: 100 patients of Rheumatoid Arthritis.
Study period: One year.
Inclusion criteria:
a.Patients diagnosed as Rheumatoid Arthritis fulfilling the American College of Rheumatism (ACR) and the EULAR criteria.
Exclusion criteria:
1) Patients presenting with polyarthritis but not satisfying the ACR and EULAR criteria.
2) With other causes of polyarthritis.
3) With other inflammatory diseases.

V. Observation And Results

In our study,Patients who have been already diagnosed with RA were retrospectively evaluated from the hospital records. All these patients were subjected to complete medical history and physical examination, complete blood count, urine analysis and blood biochemistry by using a well structured pro- forma.The diagnosis of extra-articular manifestations will be confirmed by peripheral smear, chest radiography, pulmonary function tests, CT chest, ophthalmic examination, ECG, Echocardiography and skin biopsy if skin manifestations are present. The overall frequency of extra-articular manifestations of RA in CMCH were studied.

Our study was conducted in Coimbatore medical college hospital from June 2017 to June 2018. A total of 100 patients were studied.Our study population revealed the ratio of male to female is 1:2.9.In age group wise,14% are below 30yrs,37% are between 31 to 45 yrs,39% are between 46 to 60yrs and above 60 yrs are 10%. In the study done by Turesson et al., the mean duration of disease was found to be 11.8years.this is comparable to our study with the mean duration of disease was 15.6years.

Pai et al., Jonssonet al., Sahatciu-Mekaet al., Turesson et al., all have found high percentage of their cases to be rheumatoid factor positive. All have found rheumatoid factor positivity together with higher percentage of extra-articular manifestation. In our study 80% of RA patients were sero-positive for RA factor and 20% were seronegative, this is comparable to the above quoted study.

TABLE 1: AGE,SEX DISTRIBUTION,DURATION OF ILLNESS IN RHEUMATOID ARTHRITIS PATIENTS

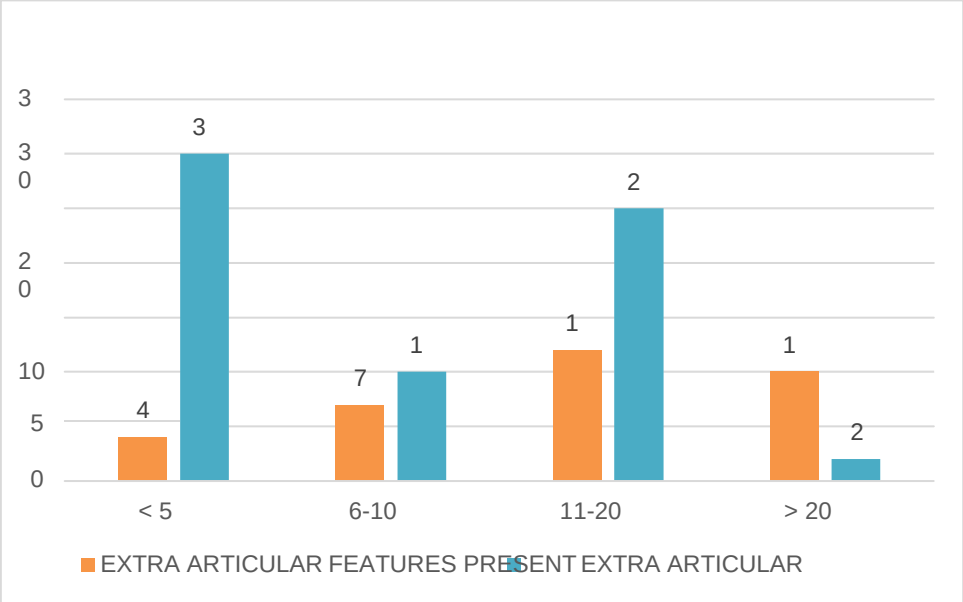
		NO OF PATIENTS
AGE	<30 YRS	14
	31-45 YRS	37
	46-60 YRS	39
	>60 YRS	10
SEX	MALE	21
	FEMALE	79
DURATION	0-5 YRS	34
	6-10 YRS	17
	11-20 YRS	37
	>20 YRS	12

In the study out of 100 patients, 33% of RA patient had extra-articular manifestations.Out of these,Hematological Manifestation being the more common in 42% of the diseased.

TABLE2: SYSTEM WISE EXTRA-ARTICULAR MANIFESTATIONS

SYSTEM	**NO.OF PATIENTS**	**PERCENTAGE %**
HAEMATOLOGY	14	42
CARDIOLOGY	4	12
DERMATOLOGY	8	24
PULMONOLOGY	9	27
OPHTHALMOLOGY	6	18
OTHERS	3	10
OVERLAPSYNDROMES	2	6

CHART1: DURATION OF DISEASE AND EA FEATURES



In my study the predominant extra-articular manifestation is hematological.
The most common is anaemia of chronic disease and is present in 42.85%.
In the study done by Sahatciu-Meka et al.,anaemia was the predominant manifestation with 97.8%of the patients having anaemia. this is higher comparable to our study. Various haematological manifestations observed in these patients were anaemia of chronic disease-42.85%, iron deficiency anaemia- 35.71%,megaloblastic anaemia-7%,neutropenia-7%,eosinophilia- 7%,thrombocytopenia-7%, thrombocytosis-7%
In our study, cardiac manifestations constitute 12% and the various manifestations seen are cardiac failure, pulmonary artery hypertension and pericardial effusion.

In the present study, ocular manifestations are found in 18%. ophthalmological manifestations observed in this study were dry eyes(83%) and episcleritis(17%).In the study done by Fleming A et al., episcleritis was observed in 9%of the cases scleritis was observed in 4% of cases. In the current study shows higher incidence of episcleritis than this study.

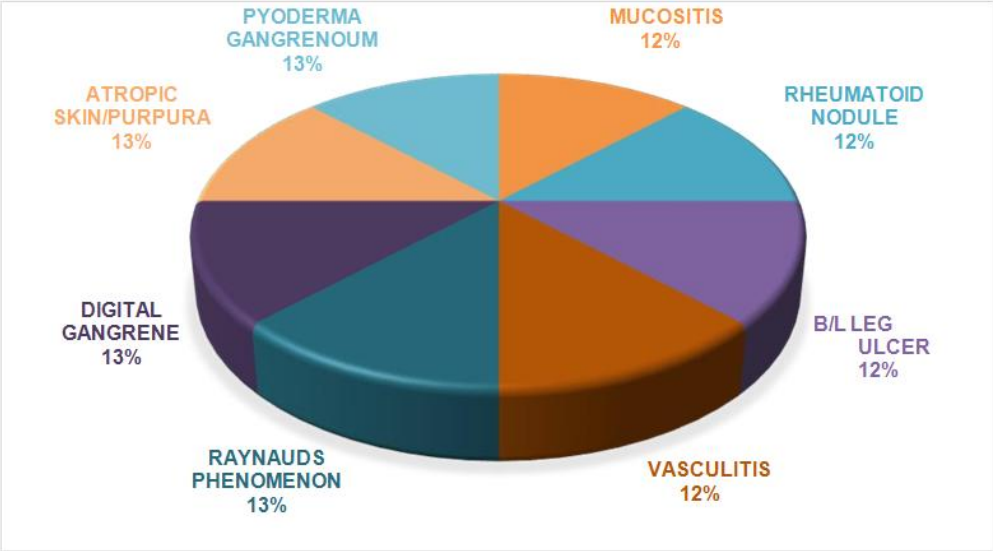
It was present in 8 patients out of 33 which is 24%.and various manifestations include methotrexate induced mucositis, rheumatoid nodule, bilateral leg ulcers, small vessel vascuitis, raynaud phenomenon, digital gangrene,atrophic skin with purpura and pyodermagangrenosum.In the study done by Sharma et al, vasculitis was present in 2%. In our study vasculitis was present in 12.5% which was higher than the study quoted.

In our study rheumatoid nodule was found in 12.5%. In the study done by Sahatciu-Meka et al., rheumatoid nodules were seen in 12% of the cases. This is comparable to our study.

In our study raynaud phenomenon was present in 12.5%. In the study done by M.Calguineri et al raynauds was present in 3% of patients which is lesser comparable to current study.

In the current study purpura was present in 12.5%. In the study done by Sahatciu-Meka et al., purpura was observed in 12% of the cases. This is comparable to current study.

CHART2: DERMATOLOGICAL MANIFESTATIONS IN EA RHEUMATOID ARTHRITIS



PULMONARY MANIFESTATIONS:

In the current study pulmonary manifestation was present in 27%.In the study done by SandipanBanik et al pulmonary involvement occur in 33%.this is comparable to the current study. In this study pulmonology manifestations were present in 9 patients out of 33 and it is the second most common extra-articular manifestations of RA.3 had interstitial lung disease 3 had recurrent infections. 1 had pleural effusion 1 had pulmonary fibrosis 1 had respiratory failure 1 had eosinophilic pneumonia. Those with duration of illness more than 20yrs 4 had pulmonological manifestations.

PERIPHERAL NEUROPATHY

In the current study peripheral neuropathy was present in 6%.In the study done by Turesson et al peripheral neuropathy is seen in 2.1% of cases. This is lower compared to current study. The other manifestations observed in this study include distal poly neuropathy which is present in 1patient and mononeuritis multiplex is present in 1 patient.

OTHERS

Drug induced UGI bleed is present in 1 patient.

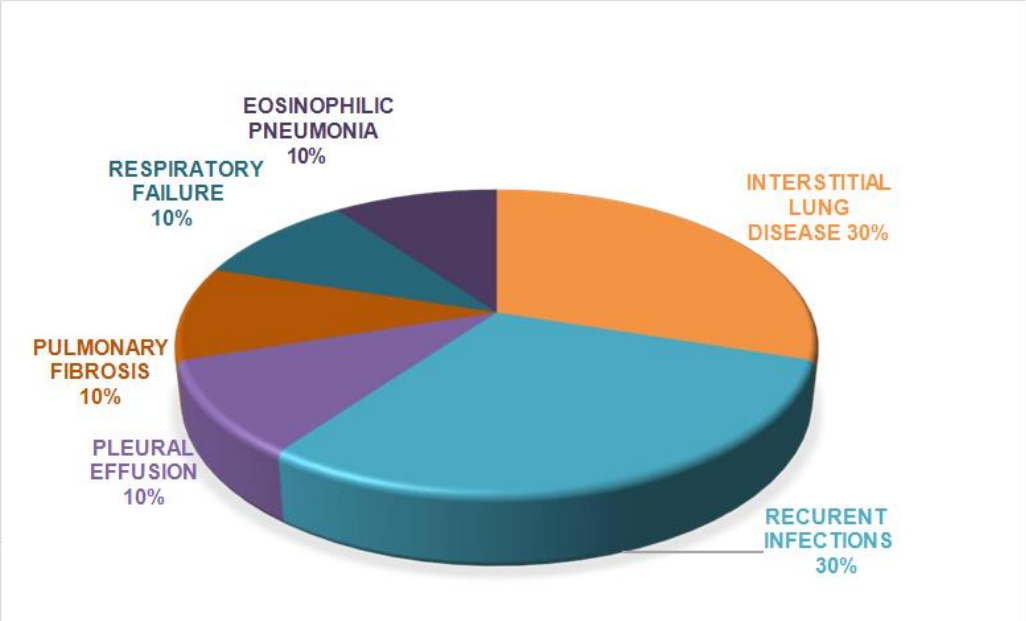
OVERLAP SYNDROMES

ANA was done for these patients and SLE overlap was found in 1 patient.

She was 40yrs female with 6-10 yrs of disease with seropositivity of RF. Scleroderma overlap was present in 1 patient. She was 47yrs old female with 6- 10yrs of disease with seronegative for RA factor. The overall presence of majority of extra-articular manifestation is lesser in the present study as compared to other studies. This could be attributed to the following reasons:

1) The incidence of extra-articular manifestations is much lower in Indian patients as evidenced by the Kaushal et al study.
2) The duration of disease was much lower in this study as compared to other studies.
3) The number of cases in the present study is much lower compared to the other studies.

CHART3: VARIOUS PULMONARY MANIFESTATIONS IN EXTRA ARTICULAR RA



TABLE

Extra articular Manifestations		RHEUMATOID FACTOR		Significance(p value)
		Present	Absent	
Cardiac	Yes	4	0	Non significant(0.367)
	No	76	20	
Pulmonary	Yes	6	3	Non significant(0.295)
	No	74	17	
Hematology	Yes	12	2	Non significant(0.564)
	No	68	18	
Dermatology	Yes	7	1	Non significant(0.580)
	No	74	19	
Ophthalmology	Yes	5	1	Non significant(0.833)
	No	75	19	
Others	Yes	2	1	Non significant(0.580)
	No	78	19	
Overlapsyndromes	Yes			
	No			

VI. Discussion

Rheumatoid arthritis (RA) is a chronic, destructive, inflammatory arthropathy manifested by articular and extra-articular features. RA has profound effects on patient function and morbidity and exacts a substantial economic burden on the affected persons. Although the pathology of the synovial inflammation and cartilage destruction that occurs in patients with RA has been described for decades, many important developments in the understanding of genetic influences and immune pathophysiologic mechanisms have recently been defined.Basic research delineating the molecular mechanisms of synovial inflammation has driven the development of innovative therapies for patients with RA. Hopefully, new genomic and proteomic information will allow further stratification and identification of subsets of RA patients who respond better, longer, and with fewer adverse reactions to targeted therapies(1)

The pathology of RA involves a complex interaction of three different scientific domains:

1) a complex genetic predisposition to the disease plus some environmental stimulus;
2) a self-perpetuating, self amplifying, intra-synovial immune response; and at the final stage,
3) Tissue injury mediated by pro-inflammatory cells, inflammatory effector molecules, and derivative

enzymes.
In individuals with RA, this process is orthotropic and produces a characteristic pathologic lesion in the synovium as well as the hallmark erosion of bone and destruction of cartilage at the joint margin.

The histopathology of RA synovium has been well described. The synovial lining, the interstitium, and the microvasculature are all involved. Early in the process, the synovial lining, which includes both Type A (macrophage-like) and Type B (mesenchymal or fibroblast-like) cells, becomes proliferative. The synovial lining increases in cell number and mass. Likewise, a diffuse and nodular inflammatory cell infiltrate is observed in the interstitium. It includes CD4+ and CD8+ lymphocytes, dendritic cells, and other antigen presenting cells. In some patients, the histologic appearance is quite dramatic, showing focal aggregation of both T- and B-cells, as well as the presence of germinal centers similar to that which is seen in lymphoid tissues. (2)

The synovium of the rheumatoid joint, although not malignant, often times behaves as a local invasive "tumor." The microvasculature initially reveals endothelial cell activation. As the process matures, plasma cells and multinucleated giant cells appear, and the vascular supply becomes exuberant. Finally, the growing synovium appears as granulation tissue as it advances to the hyaline cartilage at the margin of the joint.(2) A local effect of degradative enzymes and activated osteoclasts produces the classic erosion at the bone and cartilage margin. These enzymes may also affect structures that are more distant, including the tendons, ligaments, and other musculoskeletal structures. Erosions are produced by bone and matrix protein resorbing osteoclasts, which may be induced and activated by cytokines released into the inflammatory milieu.(2)
In the study done by Sahatciu-Meka et al.,anaemia was the predominant manifestation with 97.8%of the patients having anaemia.this is higher comparable to the present study. various haematological manifestations observed in these patients were anaemia of chronic disease-42.85%,iron deficiency anaemia-35.71%,megaloblasticanaemia-7%,neutropenia-7%,eosinophilia-7%,thrombocytopenia- 7%,thrombocytosis-7%
In the study done by Maioneet al.,cardiac manifestations were seen in 43% of the patients which is higher compared to the current study.
In thestudy done by Fleming A et al.,episcleritiswas observed in 9%of the cases scleritis wasobserved in 4% of cases.In the current study shows higher incidence of episcleritis than this study.
In thestudy done by Sharma et al,vasculitiswas present in 2%. In our study vasculitis waspresent in 12.5% which was higher than the study quoted.
In our study rheumatoid nodulewas found in 12.5%. In the study done by Sahatciu-Meka et al.,rheumatoid nodules were seen in 12% of the cases.This is comparable to our study.
In our study raynaud phenomenon was present in 12.5%.In the study done by M.Calguineri et al raynauds was present in 3% of patients which is lesser comparable to current study.
In the current study purpura was present in 12.5%. In the study done by Sahatciu-Meka et al.,purpura was observed in 12% of the cases. This is comparable to current study.
In the study done bySandipanBanik et al pulmonary involvement occur in 33%.this is comparable to the current study.

VII. Conclusion

In Our Study,Extra-articular manifestations were found in 33 cases of rheumatoid arthritis and the highest number of patients with EAM were found in the age group of 46-60years. Male to female ratio was 1:2.9. The mean duration of disease was found to be 15.6years with maximum number of cases having disease duration between 11 and 20years.

Anaemia of chronic disease was found to be the most common extra-articular manifestation found in our study. The other extra-articular manifestations noted were cardiac manifestations – 12%; ocular manifestations-18%; dermatological manifestation-24%.Pulmonary manifestation-27%; other-10%;overlap syndromes - 6%.

Rheumatoid factor was positive in 80% of patients in our study

Conflict of interest:
The authors declare that there is no conflict of interest

References

[1]. Weyand CM, Hicock KC, Conn DL, Goronzy JJ. The influence of HLA-DRB1 geneson disease severity in rheumatoid arthritis. Ann Intern Med.1992; 117:801-886.
[2]. Arend W, Dayer J. Inhibition of the production and effects of Interleukin-1 and tumor necrosis factor in rheumatoid arthritis. Arthritis Rheum. 1995: 38:2,151- 160.
[3]. Mojcik C, Shevach E. Adhesion molecules. Arthritis Rheum. 1997;40:6,991- 1004.
[4]. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis: an approach to understanding the molecular genetics of

susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987;30:1205-1213.
[5]. Wolfe F, Mitchell D, Sibley J, et al. The mortality of rheumatoid arthritis. Arthritis Rheum. 1994;37:4, 481-494.
[6]. Yelin E, Wanke L. An assessment of the annual and long-term direct costs of rheumatoid arthritis. The impact of poor function and functional decline. Arthritis Rheum. 1999;42:6,1209-1218
[7]. Gabrial S, Crowson C, O'Fallon W. The epidemiology of rheumatoid arthritis in Rochester, Min-nesota. Arthritis Rheum. 1999;42:3,415-420.
[8]. Kaipiainen-Seppä T, Aho K. Incidence of chronic inflammatory jointdiseases in Finland in 1995. J Rheumatol. 2000;27:94-100.
[9]. TuessonC,Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. Rheumatology. 1999;38:668-674.
[10]. McQueen FM. Magnetic resonance imaging in early inflammatory arthritis: what is its role? Rheumatology. 2000;39:700-706.
[11]. Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst. 1993;85:307-11.
[12]. Boden SD. Rheumatoid arthritis of the cervical spine. Surgical decision making based on predictors of paralysis and recovery. Spine. 1994; 19:2275- 80.
[13]. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib long-term arthritis safety study. JAMA. 2000;284:1247-1255.
[14]. Furst DE. Are there differences among nonsteroidal anti-inflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylatednonsteroidal anti-inflammatory drugs. Arthritis Rheum. 1994;37:1-9.
[15]. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatoid Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995;333:142-146.
[16]. Baxter JD. Minimizing the side effects of glucocorticoid therapy. Adv Intern Med. 1990;35:173-193.
[17]. Tugwell P, Pincus T, Yocum D, Stein M, Gluck O, Kraag G, et al. Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. The Methotrexate-Cyclosporine Combination Study Group. N Engl J Med. 1995;333:137-141.
[18]. Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma- Frankfort C. The effectiveness of early treatment with second-line antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996;124:699-707.
[19]. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996;334:1287-1291.
[20]. Fries JF, Williams CA, Ramey D, Bloch DA. The relative toxicity of disease- modifying antirheumatic drugs. Arthritis Rheum. 1993;36:297-306.
[21]. Kamel OW, van de Rijn M, Weis LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermato-myositis. N Engl J Med. 1993;328:1317-1321.
[22]. Kremer JM. The mechanism of action of methotrexate in rheumatoid arthritis: the search continues. J Rheumatol. 1994;21:1-5.
[23]. Walker AM, Funch D, Dreyer NA, Toman KG, Kremer JM, Alarcon GS. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum. 1993;36:329-335.
[24]. Maini R, Breedveld F, Kalden J, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41:9, 1552-1563.
[25]. Moreland L, Schiff M, Baumgartner S, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Ann Intern Med.1999;130:478-486.
[26]. Barnett M, Kremer J, St Clair E, et al. Treatment of rheumatoid arthritis with oral type II collagen. Results of a multicenter, double-blind, placebo- controlled trial. Arthritis Rheum. 1998;41:2,290-297.
[27]. Snowden J, Kearney P, Kearney A, et al. Long-term outcome of autoimmune disease following allogenic bone marrow transplantation. Arthritis Rheum. 1998;41:3,453-459.
[28]. McKown K, Carbone L, Kaplan S, et al. Lack of efficacy of oral bovine type II collagen added to existing therapy in rheumatoid arthritis. Arthritis Rheum. 99:42;6,1204-1208.
[29]. O'Dell J, Paulsen G, Haire C, et al. Treatment of early seropositive rheumatoid arthritis with minocycline. Arthritis Rheum. 1999;42:8, 1691- 1695.
[30]. Felson D, LaValley M, Baldassare A, et al. The prosorba column for treatment of refractory rheumatoid arthritis. A randomized, double-blind, sham- controlled trial. Arthritis Rheum. 1999;42:10,2153-2159.
[31]. Conn D, Arnold W, Hollister J. Alternative treat-ments and rheumatic diseases. Arthritis Foundation. 1999;48:7:12,1-2.
[32]. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic out-comes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt Study). Arthritis Rheum. 2005;52:3381-3390.
[33]. Genovese MC, Becker J-C, Schiff M, et al. Abata-cept for rheumatoid arthritis refractory to tumor necrosis factor inhibition. N Engl J Med. 2005;353:1114- 1123.

Dr.R.Jegatheesh, et. al. "A Study on the Extra-Articular Manifestations of Rheumatoid Arthritis.'' *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS),* 20(09), 2021, pp. 17-23.