# ROLE OF MONOCLONAL ANTIBODIES IN RHEUMATOID ARTHRITIS

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**Abstract**

Rheumatoid Arthritis is an autoimmune mediated condition which affects the joints but with critical extra articular manifestations, including a significantly increased cardiovascular risk. Patients suffering from rheumatoid arthritis can develop deforming and disabling alterations of the affected joints. In majority of patients with established rheumatoid arthritis anticitrullinated protein antibodies can be found. Antibody therapies inhibiting Tumour necrosis factor-alpha patients with active rheumatoid arthritis have set a new standard in terms of rapid and sustained improvements in symptoms and signs of disease, improvements in 'quality of life' and protection of joints from structural damage.

**Key words:** Rheumatoid Arthritis, Anticitrullinated antibodies, Tumour necrosis factor-alpha.

## Introduction

Rheumatoid Arthritis (RA), a chronic disease affecting 0.5%-1% adults, is characterized by persistent synovitis, systemic inflammation, and immunological abnormalities. Uncontrolled active RA causes joint damage, disability, diminished quality of life, and cardiovascular and other comorbidities.[1] Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients. The onset of disease is not similar in all patients but varies in regard to type, number, and the pattern of joint involvement. The course of disease may be also different according to the presence or absence of several variables including genetic background, frequency of swollen joints, autoantibody in the serum and the severity of inflammatory process[2]. RA is typically divided into two subtypes designated 'seropositive' and 'seronegative' disease, with seropositivity being defined as the presence of serum elevations of the autoantibodies Rheumatoid Factor (RF) and the more recently described antibodies to citrullinated protein/peptide antigens (ACPAs)[3]. The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation. It can also afflict young children even before the age of 16 years, referred to as Juvenile RA (JRA), which is similar to RA except that rheumatoid factor is not found.[4]

## Aetiology[5]

The current hypothesis consists of the following principles:

1. RA is not a disease of recent origin, and was both present and problematic hundreds, possibly thousands of years ago, potentially with a geographic distribution distinct from its current profile.
2. RA occurs as a response to an environmental stimulus or stimuli experienced by genetically susceptible individuals.
3. The identities and origins of these stimuli or inciting events are still incompletely known, although tantalizing clues have emerged.
4. Distinct environmental triggers may be important in subsets of patients with RA. For example, smoking may be a more important risk factor in RA patients who carry an MHC allele that encodes the shared-epitope and who have autoantibodies to citrulline-containing proteins. Thus, the historical analysis of RA needs to incorporate the likely possibility that what we currently define as RA is more than one disease.

## Risk Factors

Several factors have strongly suggested that genetics are a major influence on the development of RA. These factors include the general increased prevalence of RA within families, leading to estimations of familial risk contribution to seropositive RA of ~40–50% of seropositive RA, with strongest risks seen in first-degree relatives (FDRs)[6]

**Environmental risk factors[3]**

Female sex

Exposure to tobacco smoke

Occupational dust (silica)

Air pollution

High sodium, red meat and iron consumption

Obesity

Low vitamin D intake

Microbiota and mucosal inflammation may influence the early immunologic changes that leading to classifiable RA[7]

**Epidemiology**

Rheumatoid arthritis (RA) affects about 0.92% adult population in India. There are about 20-40 new cases per Lakh population each year and the disease occur more frequently in female. The onset can be after delivery although the disease remains silent during pregnancy. Stress and environmental triggers can precipitate onset of the disease. About 5% of first-degree relatives are at risk of developing RA. [8]. In the West, the prevalence of RA is believed to be 1–2% and 1% worldwide [9].

**Clinical Manifestations[10]**

**Symptoms**

Joint pain and stiffness for more than 6 weeks duration.

More than one joint is affected.

Small joints (wrists, certain joints in the hands and feet) are typically affected first.

The same joints on both sides of the body are affected.

May experience fatigue, weakness, low grade fever, loss of appetite.

Muscle pain and fatigue may also be present.

**Signs**

Tenderness with warmth and swelling over affected joints usually involving hands and feet.

Fig 1:swelling of hands in rheumatoid arthritis patient.

Distribution of joint involvement is frequently symmetrical.

Rheumatoid nodules may also be present.

**Health Effects of RA[11]**

**Eyes:** Dryness, pain, inflammation, redness, sensitivity to light and trouble seeing properly.

**Mouth:** Dryness and gum inflammation, irritation or infection.

**Skin:** Rheumatoid nodules – small lumps under the skin over bony areas.

**Lungs:** Inflammation and scarring that can lead to shortness of breath and lung disease.

**Blood vessels:** Inflammation of blood vessels that can lead to damage in the nerves, skin and other organs

**Blood:** Lower than normal number of red blood cells.

**Heart:** Inflammation can damage the heart muscle and the surrounding areas.

**Diagnosis:**

Identification of RA at initial presentation and treatment at earlier stage can affect disease course, prevent the development of joint erosions or retard progression of erosive disease[12]. Abnormal values of the laboratory tests are the most typical features of RA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) provide the best information about the acute phase response. The level of CRP was shown to be significantly correlated with the severity of disease as well as radiographic changes[13]. Anti-CCP exerts additional diagnostic ability in recognizing seronegative RA. Arthrocynthesis and synovial fluid analysis can be also helpful for diagnosing inflammatory arthritis as well as in discriminating inflammatory from non-inflammatory arthritis[14]. Synovitis is the early findings of RA and is strong predictor of bone erosion. Soft tissue swelling and mild juxtaarticular osteoporosis may be the initial radiographic features of hand joints in early – RA. Imaging tests like sonography and MRI are more sensitive and seem promising but can be used in a limited centre's[15].

**Treatment:**

**First Line management –** NSAIDs and Corticosteroids

**Second Line management –** Disease Modifying Anti Rheumatic Drugs (DMARDs)

**Newer Medications –** Leflunomide, TNF inhibitors (Monoclonal Antibodies)[4]

**Table 1: First Line Management**[10,16]

| Class | Drug | Dose |
|---|---|---|
| Carboxylic acids | Aspirin | 2.6 – 5.2g QID |
| | Diclofenac | 150 - 200mg TID/QID |
| | Etodolac | 0.2 – 1.2gm BID/QID<br>Max- 20mg/kg |
| | Indomethacin | 50 – 200mg BID/QID |
| | Ketorolac | 10 mg TID/QID<br>Max- 40mg/day |
| | Sulindac | 300 – 400mg BID |
| | Tolmetin | 0.6 – 1.8gm BID/QID |
| | Flubiprofen | 200 – 300mg BID/QID |
| | Ketoprofen | 50mg TID/QID |
| | Oxaprozin | 0.6 – 1.8gm TID<br>Max – 26mg/kg |
| | Ibuprofen | 1.2 – 3.2gm TID/QID |
| | Naproxen | 0.5 – 1g BID |
| | Fenoprofen | 0.9 – 3gm QID |
| | Meclofenamate | 200 – 400mg TID/QID |
| Enolic Acids | Phenyl butazone | 100mg OD |
| | Piroxicam | 10 – 20mg OD |
| | Meloxicam | 7.5 – 15mg OD |
| | Nabumetone | 1 – 2gm OD/BID |
| Cox2 Selective Inhibitors | Celecoxib | 200 – 400mg OD/BID |

**Table 2: Modern Pharmacological therapies for RA**[17]

| Classification | Drug | Dose | Side Effects |
|---|---|---|---|
| Conventional synthetic DMARDs | Methotrexate | 7.5 mg PO as a single weekly dose, (OR)<br><br>2.5 mg PO q12 hr for 3 sequential doses per week | Increased liver enzymes, pulmonary damage |
| | Leflunomide/ Teriflunomide | 10 mg/20mg once daily | Hypertension, diarrhoea and nausea, hepatotoxicity. |
| | Sulfasalazine | 2-3 g/day PO divided TID after meals; may start 0.5-1 g day | Gastrointestinal, central nervous system, and hematologic adverse effect. |
| | Chloroquine /Hydroxychloroquine | 200 mg to 400 mg daily, administered as a single daily dose or in two divided doses. | Gastrointestinal tract, skin, central nervous system adverse effect and retinal toxicity |
| Biological DMARDs antibody based therapies | | | |
| TNF-α targeted therapy | Infliximab | 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks | Infection (pneumonia and atypical tuberculosis) injection-site reaction. |
| | Adalimumab | 40 mg subcutaneously (SC) every 2 weeks | Hypertension |
| | Etanercept<br>Golimumab<br><br>Certolizumab pegol | 50 mg twice weekly<br>50 mg administered by subcutaneous injection once a month.<br>200 mg SC q 2 Weeks OR 400 mg SC q 4 Weeks | Severe /anaphylactoid transfusion reaction |
| B-cell targeted therapy | Rituximab | 2-1000 mg intravenous infusions separated by 2 weeks. | Infection, hypertension, hypogammaglobulinemia, viral reactivation, vaccination responses |
| | Ofatumumab | doses of 300 mg, 700 mg, and 1000 mg administered as IV 2 infusions 2 weeks | Late-onset neutropenia |
| | Belimumab | 10 mg/kg/Iv at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. | Severe/anaphylactoid transfusion reaction. |
| | Atacicept | atacicept was administered subcutaneously twice a week for initial 4 weeks, followed by once a week for subsequent 21 weeks. | |
| | Tabalumab | loading dose of 240 milligram(mg)given as two subcutaneous (SC) injections each of 120 mg followed by 120 mg SC injection every two weeks for 12 weeks. | |
| T-cell targeted therapy | Abatacept | 125 mg SC qWeek | Infection, malignancy. |
| | Belatacept | 15 mg/day (10-20 mg/day) by the first 6weeksand remained at ~10 mg/day(5-10mg/day) for the first 6 months post-transplant | |
| Interleukin targeted therapy | Tocilizumab | 4 mg/kg IV over 60 min q4Weeks initially;may increase to 8 mg/kg q4Weeks | Infections (most notably skin and soft tissue), increases in serum cholesterol, transient decreases in neutrophil count and abnormal liver function. |
| | Anakinra | 1-2 mg/kg SC qDay (initially);may increase by 0.5-1 mg/kg | Injection site reactions, infections, neutropenia, malignancy. |
| | Canakinumab | 150 mg SC q4wk | |

| | | | |
|---|---|---|---|
| | Rilonacept | subcutaneous injections of 160 mg on the same day at two different sites | |
| | Secukinumab | 150 mg subcutaneously at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter | Infections, nasopharyngitis, candidiasis, neutropenia, safety data of mental health is limited |
| | Ixekizumab | 160 mg SC (ie, as two 80-mg injections) once, THEN 80 mg SC q4wk | |
| Growth and differentiation factors | Denosumab | 60 mg subcutaneously once every 6 months | Low Ca2+ and phosphate in the blood, muscle cramps, cellulitis, and numbness |
| | Mavrilimumab | 100 mg every other week | Safety file needs further research |
| Small molecules JAK pathway | Tofacitinib | 5 mg or 10mg twice daily | Zoster infection (advice is to vaccinate beforehand) and other potential side-effects should be monitored carefully through further study. |
| | Baricitinib | 2 mg PO qDay | |
| | Filgotinib | 25 mg po twice daily | |

**Table 3: Biological agents used in treatment of RA**[18]

| Drug | Usual dose | Route |
|---|---|---|
| Adalimumab | 40mg q 2 weeks | SC |
| Certolizumab pegol | 400mg at week 0,2 & 4 then 200mg every 2 weeks thereafter | SC |
| Etanercept | 25mg BID or 50mg weekly | SC |
| Golimumab | 50mg Monthly | SC |
| Infliximab | 3mg/kg at week 0,2 & 6 then every 8 weeks thereafter | IV |
| Abatacept | 750mg at week 0,2 &4 then every 4 weeks thereafter | IV |
| Anakinra | 100mg daily | SC |
| Tocilizumab | 8mg/kg q 4 weeks | IV |

**Role of biologics in treating RA:** Monoclonal antibodies can be broadly divided into 3 categories[18]

1. Inhibits cytokines
2. Bind to adhesion molecules
3. Target Major Histocompatibility Complexes and T cells

**Targeting Cytokine in RA[19]:** Tumour necrosis factor-a is a potent pro-inflammatory cytokine that has been implicated in the pathogenesis of RA. It promotes inflammation by stimulating the release of other cytokines such as IL-1, IL-6 and granulocyte macrophage colony stimulating factor. Treatment with anti tumour necrosis factor-a mAb suppresses inflammation. Two anti-tumour necrosis factor-a mAbs, cA2 (Centocor) and CDP571 (Celltech Therapeutics Ltd, also known as Bay103356, Bayer Corp.), have been used in RA. The side effects of anti Tumor necrosis factor-a mAb include skin rashes, infections and, surprisingly, the development of autoantibodies including anti-dsDNA and anti-cardiolipin antibodies.

**Anti-adhesion molecules[20]:** The migration of leucocytes into the synovial joint is an important mechanism which perpetuates synovitis. Circulation of leucocytes into different tissues is regulated by adhesion molecules expressed on the surface of leucocytes and endothelial cells. Some of these adhesion molecules also play crucial role in thymic selection, T-cell activation, and cytotoxicity. During an inflammatory process, leucocytes roll on the surface of endothelial cells; a process mediated by the adhesion molecules sialyl-Lewis-X and E-selectin Subsequently, firm attachment of these leucocytes to the endothelial cells is mediated by ICAM-1 and leucocyte function associated antigen-1(LFA-1). ICAM-1 is a 90 kDa cell surface glycoprotein expressed by endothelial cells, monocytes and antigen-presenting cells. The interruption of ICAM-1 and LFA-1 interaction should theoretically inhibit leucocyte migration into the synovial joint, and thereby suppresses inflammation in RA.

**Anti T cell Therapy[21]:** T cells regulate the disease process in RA on multiple levels and represent a logical choice for anti-inflammatory therapy. In the inflamed joint they promote neoangiogenesis and lymphoid organogenesis, and stimulate synoviocyte

proliferation and development of bone-eroding osteoclasts. The design of T-cell-targeted therapies for RA needs to take into account the uniqueness of T-cell generation, turnover and differentiation in affected patients.

Tumor necrosis factor-a has been validated as a good target for treatment of RA. It was recently confirmed that anti-TNF therapy protects joints from structural damage as indicated by a change in the rate of deterioration of the hands and feet in radiographs, which is assessed by a scoring system that calculates cartilage and bone loss separately[22]. One year of combined therapy with methotrexate and infliximab, at doses of either 3 or 10 mg/kg, prevented the progressive joint damage characteristic of rheumatoid inflammation.

**Conclusion**

Antibody therapies inhibiting Tumor necrosis factor in patients with active RA have set a new standard in terms of rapid and sustained improvements in symptoms and signs of disease, improvements in 'quality of life' and protection of joints from structural damage. They may be used to treat disease flares and in combination with conventional DMARDs to achieve better disease control.Clinical Pharmacist has the potential to improve the patient's clinical, humanistic and economic outcomes in rheumatoid arthritis by providing pharmaceutical care. Pharmacist can resolve drug related problems and managing drug therapy, management of modifiable risk factors such as weight, recommending dietary and lifestyle changes. Providing patient counseling, disease education and medication advice and reducing the out-of-pocket costs can improve overall well being and quality of life of the patients.

**REFERENCES**


1. Toshio Tanaka,Yoshihiro Hishitani, and Atsushi Ogata Monoclonal antibodies in rheumatoid arthritis: comparative effectiveness of tocilizumab with tumor necrosis factor inhibitors Biologics: Target and therapy 2014; 8: 141–153
2. Behzad Heidari, MD Rheumatoid Arthritis: Early diagnosis and treatment outcomes Caspian J Intern Med. 2011 Winter; 2(1): 161–170.
3. Kevin D. Deane, M. Kristen Demoruelle, Lindsay B. Kelmenson, Kristine A. Kuhn, Jill M. Norris, andV. Michael Holers Genetic and environmental risk factors for rheumatoid arthritis Best Pract Res Clin Rheumatol. 2017 Feb; 31(1): 3–18. doi: 10.1016/j.berh.2017.08.003
4. Bullock J. Rizvi S.A.A. Saleh A.M. Ahmed S.S. Do D.P. Ansari R.A. Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment Med Princ Pract 2018;27:501–507 https://doi.org/10.1159/000493390
5. Pouya Entezami, BS, David A. Fox, MD, Philip J. Clapham, BS, and Kevin C. Chung, MD, MS Historical Perspective on the Etiology of Rheumatoid Arthritis Hand Clin. 2011 Feb; 27(1): 1–10.doi: 10.1016/j.hcl.2010.09.006
6. Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. Nat Rev Rheumatol. 2016;12(6):335–43.
7. Yeoh N, Burton JP, Suppiah P, Reid G, Stebbings S. The role of the microbiome in rheumatic diseases. Curr Rheumatol Rep. 2013;15(3):314.
8. Rhematoid arthritis, Arthritis india Fight arthritis with knowledge and courage http://www.arthritis-india.com/rheumatoid-arthritis.html
9. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum. 2006 Dec;36(3):182–8
10. Joseph T Dipiro, Robert L Talbert, Cary C Yee, Barbara G Wells, L Michael Posey Pharmacotherapy A Pathophysiologic approach 7th edition PgNo -1539
11. Rheumatoid arthritis, Arthritis foundation
12. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007;146:406–15.
13. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998;27:S18–24.
14. Quinn MA, Gough AK, Green MJ, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology (Oxford) 2006;45:478–80.
15. Wakefield RJ, Gibbon WW, Conaghan PG, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000;43:2762–70.
16. Leslie J Crofford Use of NSAIDs in treating patients with arthritis Arthritis Res Ther. 2013; 15(Suppl 3): S2
17. Qiang Guo, Yuxiang Wang, Dan Xu, Johannes Nossent, Nathan J. Pavlos, and Jiake Xu Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies Bone Res. 2018; 6: 15.
18. E. H. S. Choy, g. H. Kingsley and g. S. Panayi monoclonal antibody therapy in rheumatoid arthritis British Journal of Rheumatology 1998;37:484–490

19. Brennan FM, Maini RN, Feldmann M. TNF alpha—a pivotal role in rheumatoid arthritis? Br J Rheumatol 1992;31:293–8.

20. Pitzalis C, Kingsley G, Panayi G. Adhesion molecules in rheumatoid arthritis: role in the pathogenesis and prospects for therapy. Ann Rheum Dis 1994;53:287–8

**21.** Weyand CM, Goronzy JJ. T-cell-targeted therapies in rheumatoid arthritis. Nat Clin Pract Rheumatol. 2006 Apr;2(4):201-10.

22. Peter C Taylor Antibody therapy for rheumatoid arthritis ELSEVIER current opinion in pharmacology 2003; , 3:323–328.