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The Role of Biologics in The Treatment of Rheumatoid Arthritis: A Review

Kishan Bookya[1*],Bairam Balaji[1], R. Kathyayani[2],Teelavath Mangilal[3].

[1*]*Department of Pathology, ACSR Govt medical College, Nellore, Andhra Pradesh, India.*
[1]*Department of General Medicine,KMC(MGMH),Warangal,Telangana,India.*
[2]*Department of Biochemistry, KMC(MGMH),Warangal,Telangana,India.*
[3]*Department of Pharmacy,UCT,Osmania University,Hyderabad,Telangana,India.*
Email:teelavath@gmail.com.

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Abstract
Rheumatoid arthritis (RA) is a chronic inflammatory disease, occurs due to the inflammation of the synovial fluid in the multiple joints. An inflamed synovial membrane releases cytokines, which damages the joint component such as cartilage, it leads to joint destruction. The conventional drugs used for treating RA are known as DMARDs (disease modifying antirheumatic drugs.The traditional DMARDs have limited use due to its side effects and/or the limited efficacy for treating RA. The actual cause of RA remains unknown. In recent times, an advancement in molecular technology facilitates to identify the cell surface markers, distinct targeted cells, and cell products which contribute to the immune mediated responses associated with RA. In the last decade, several novel biological have been introduced for the treatment of RA: anakinra (IL-1 receptor antagonist), infliximab, adalimumab and etanercept (anti TNF agents), rituximab (anti-CD20 agent), abatacept (selective T-cell modulator), and tocilizumab (anti-interleukin 6). In the present review, we made a brief discussion about the roles of these agents and their clinical efficacies in the treatment of RA.

Keywords: *Rheumatoid arthritis, DMARDs, anti-CD20 agent,selective T-cell modulator, tocilizumab.*

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory disease affects synovial membrane between the joints and causes systemic manifestations.The etiology of RA has been described that there is a perpetuation of autoimmune responses by the multiple endogenous and/ or exogenous antigenic triggers in the synovial compartment show the symptoms and signs of RA. Currently, several drug therapies are available to control the pain, slowing down the joint dysfunction such as nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics are helpful for the controlling of pain and disease modifying antirheumatic drugs (DMARDs) include methotrexate (MTX), sulfasalazine and the antimalarial drugs can prevent joint dysfunction and anatomical deformities caused by RA. The considerable change has been seen in the treatment of RA in the recent past by introducing of biologics such as infliximab, adalimumab, rituximab, anakinra, etanercept and abatacept. MTX is mostly preferred traditional DMARD agent for the treatment of RA. But, usually physicians do not prescribeMTX to the patients and limiting its use due to its toxicity. Thus, the chronic disease patients undergone standard therapy with an aggressive usage of oral agents and biologics and often these agents are prescribed in combination with MTX. In which, biologics can selectively block the cytokine effects. For instance, anakinra selectively blocks a natural proinflammatory cytokine known as interleukin 1 (IL-1). Tumor necrosis factor (TNF) inhibitors include infliximab, adalimumab and etanercept useful for blocking the interaction between cell surface receptors with TNF- α. Abatacept selectively blocking interactions of T-lymphocyte with CD28. Rituximab specifically binds to CD20, which results the depletion of B cells. All these mechanisms of biological agents can reduce various immunological and inflammatory responses.The present review summarizes the mechanisms of biologics and discusses their safety and efficacy on the basis of major clinical trials.

Biologic agents
Tumor necrosis factor (TNF) is a proinflammatory cytokine responsible for immune response. TNF alpha, IL-1 and IL-6 are of major importance in target therapy for rheumatoid arthritis (1). Five TNF inhibitors such as infliximab, golimumab, etanercept, adalimumab and certolizumab are approved for the treatment of rheumatoid arthritis. These agents showdifferent pharmacokinetic and

pharmacodynamic properties with each other. Since last decade, the use of biologics with different mechanism of actions have been significantly improved and used in the clinical practices. For instance, Tocilizumab is a IL-6 inhibitor, Rituximab mainly targets CD20 present on the B-cell surface and used in the treatment of lymphoma.

IL-1 blocking agent (Anakinra)

Several experimental animal models and clinical studies prove that the pivotal role of interleukin-1 (IL-1) cytokine causing synovial inflammation and destruction of articular tissue [1,2]. IL-1 inhibitor is a natural anti-inflammatory protein present at synovial tissue and also acts as a specific inhibitor to block IL-1 binding receptor[1,2]**.** Anakinra has a recombinant human segment of IL-1 receptor antagonist used in the treatment of active RA. It is prescribed alone or in combination with MTX, given subcutaneously at a dose of 100mg[3-5]**.**Clinically, Anakinra has been shown a significant improvement in signs, symptoms and/or laboratory parameters within 4months and also shown the slow rate of radiographic progression[5,6,7]**.** The usage of anakinra should be reevaluated if significant improvement is not seen within 16 weeks.Anakinra causes the severity of infections with increased doses in patients and it shows higher incidence in patients than DMARDs[7]**.**The rate of infection caused by anakinra was increased when it was administered in combination with etanercept than with monotherpy. Moreover, no increased efficiency has been observed with combinational therapy. Therefore, anakinra should not be administered in combination with etanercept[8]**.**

TNF blockers (Infliximab)

Theclinical trial studies support the activity of infliximab has been sufficient for the treatment of RA in patients[9-12]**.** Several Anti-TNF trials studied the treatment of RA with concomitant therapy[13,14] and rheumatoid arthritis of early onset study reveals that infliximab has been used for the treatment of rheumatoid arthritis in early-RA patients[15,16]**.**Infliximab in combination with MTX has been shown significant improvement of relief in symptoms in patients with RA.The Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (*ATTRACT*) Studies were conducted on 428 patients received infliximab 3mg/kg or 10 mg/kg in combination with MTX or placebo alone randomly at every 4 weeks or 8 weeks. The efficacy evaluation of infliximab was performed at week 30 on the basis of ACR 20 response and evaluation at week 54 for joint damage in synovial tissue[14]**.**The final results supported combinational therapy of infliximab with MTX had shown rapid improvement in relieving symptoms of RA based on ACR 20 responses achieved in 50% of patients received combinational drug compared with 17% of patients received placebo alone. An infusion-related reactions appear as side effects such as headache, hypotension, urticaria and nausea. The radiological studies proved that the significant progression in relieving symptoms shown by the placebo was more than with infliximab[14]**.**The *ATTRACT* study confirmed that receiving infliximab and MTX or MTX placebo alone has been safe during a second year extension[17]**.**However, the high rate of serious infections, particularly pneumonia caused with the continued usage of infliximab.

Interleukin-6 blocking agent (Tocilizumab)

Interleukin-6 (IL-6) is a mediator and pluripotent cytokine for the hepatic acute-phase response and used for the activation of T cells, macrophages, B cells and osteoclasts. An excessive production of IL-6 is responsible for abnormal laboratory findings and systemic inflammatory responses in patients with rheumatoid arthritis. The observations of elevated IL-6 levels in synovial fluid and serum of RA patients form a correlation between clinical and laboratory indices, and serum IL-6 levels of RA[18,19]**.** Tocilizumab is a humanized monoclonal antibody mainly acts asan IL-6 receptor antagonist and specifically inhibits the formation of IL-6 cytokine.

Rituximab as a targeted B cell therapy

Rituximab (Rituxan) is a part human and chimeric monoclonal antibody shows higher specificity to CD20, and genetically engineered by fusion of antihuman CD20 B-cell hybridoma with human IgG k-constant region. The fragment antigen binding (Fab fragment) of rituximab targetedly binds to CD20. As a result, the Fc fragments of immune effector cause cell lysis[20]**.** Cell fractionation or cell lysis is mainly mediated by antibody-dependent cell mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC)[21]**.** Rituximab was approved by FDA and used in the treatment of non Hodgkin's lymphoma (NHL)[22]**.** But, Rituximab depletes the CD20+ B-cell count which lasts upto six months. Subsequently, B cell count become normal level within 9-12months[23]**.** Rituximab administered by i.v. Infusion, 4 times within 22days, and also 300mg (day 2), 600mg (day 8, 15, and 22). Cyclophosphamide also given with a dose of 750mg by infusion on day 4th and 17th, patients necessarily be given Prednisolone at 30-60 mg/day for upto 22 days. The safety and efficacy results of these drugs were regularly followed up till 76th week. A significant improvement has been observed in all patients at synovial membrane region and achieved an ACR50 within six months, finally three patients have achieved an ACR70 response.Thereafter, the patients became successful

in maintaining their improvements up to six months. No major AEs reported during the treatment. On the other hand, these positive results help to interpret the significance of rituximab in treating RA is surprised by the associated use of high-dose steroids and cyclophosphamide. De Vita et al. Studied the treatment of five patients previously treated with anti-TNF therapy with rituximab (375 mg/mm) within four weeks[24].A distinct clinical improvement has been observed with ACR50 and ACR70 in two patients, respectively. In addition, an ACR20 reported in two additional patients. These studies showed the efficacy and safety of rituximab in the absence of high-dose steroids and cyclophosphamide. In another study, rituximab was given to 22 patients with or without high dose Prednisolone and/or cyclophosphamide at a dose range of 300 to 1400 mg/mm[25]. A clinically significant response of rituximab was achieved alone , or in combination with steroids and/or cyclophosphamide at a dose must be greater than 600 mg/mm. These reports confirm that the combination therapy using high-dose steroids and cyclophosphamide is unlikely responsible to achieve a high level dose response to treat RA.

All these studies prove that rituximab can be more efficacious in selective B cell depletion for the treatment of RA. A randomized, controlled and double-blinded pilot study of rituximab was started involving 161 patients with seropositive rheumatoid arthritis[26].

All patients had active disease, andwere resistantto previous DMARD treatment not withstanding ofreceiving at least 10 mg/week of MTX. Randomly allocated patients were divided into four treatment groups:

Group A: Continuation of MTX alone

Group B: Rituximab alone

(two × 1 g i.v. Infusions)

Group C: Rituximab

(two × 1 g i.v. Infusions) pluscyclophosphamide (two × 750 mg infusions)

Group D: Rituximab

(two × 1g i.v. Infusions) pluscontinuing MTX.

All groups were received corticosteroids for the course of 17 days (methylprednsolone, 100 mg, i.v. Infusion on day 1st,3rd,15th and 17th, and 60 mg p.o. on days between 4-7; and Prednisolone, 30 mg p.o. on days between 8-14). Rituximab is consisting two i.v. Infusions. The primary end point observed at week 24th and patients ACR50 response was greater with the combination of rituximab-MTX (43%) and the rituximab with cyclophosphamide combination (41%) than with individual MTX (13%). The comparable response (33%) achieved with the combination of rituximab and high-dose steroids may be due the withdrawal of MTX. After 48 weeks, a highly significant ACR50 responses noticed between group A (5%), C (27%) and D (35%). The p values for A Vs C and A Vs D were 0.01 and 0.002, respectively. This phase II trial study demonstrated a substantial clinical improvement in treating refractory RA with a short regimen of rituximab alone, or combinational therapy using MTX or cyclophosphamide. Rituximab induces a more clinical response in combination with MTX than rituximab alone. In this trial, a transient hypotension has been observed with the first infusion within 24 hours and became less frequent in the subsequent infusions. The complement mediated activation and cytokine release mediated reactions were likely to be less frequent in patients with RA than NHL patients (due to the lysis of tumor or high WBC levels). AEs reported by 70-80% of NHL patients during the first infusion[27], by comparing with 36% of patients in this study. The DANCER (Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis) study is an international, randomized, placebo-controlled, double-blinded, multifactorial phase IIb trial of different treatment regimens. This study tested two drug dose levels of combination,i.e rituximab and glucocorticoids (and rituximab placebo alone) by a 3x3 configuration (rituximab placebo, 500 mg, or 1000 mg on day of 1st and 15th, with each patient also receiving a placebo glucocorticoid, methylprednisolone i.v premedication, or methylprednisolone i.v. premedication plus oral prednisone for two weeks) with the associated use of MTX 10-25 mg/week.

Recommendation for treatment with rituximab

Several experts formulated a consensus statement regarding the use of B cell targeted RA treatment with rituximab for the patients with RA[28].

The guidelines to be followed for the treatment of RA with rituximab as follows:

1. Patients are considered for the treatment who should have active disease that should have at least moderate disease activity composite score of DAS28 ≥3.2 or SDAI >11.
2. The screening of patients for hepatitis B is mandatory. Several studies reported that hepatitis C can be successfully treated with rituximab alone, and incombination with lamivudine suitable for treating hepatitis B patients[29,30]. Rituximab has been administered at a dose of 1g per infusion on day 1st and 15th. Patients should receive methylprednisolone 100 mg i.v. and histamine antagonists to reduce the severity of infusion reactions caused by rituximab infusions.
3. Repeat the treatment regimen, whether any patients had residual disease activity after at least 24 weeks.
4. The contraindication of rituximab in patients who are allergic to rituximab, severe heart problems. Or active infectious diseases.

Selective T-cell Costimulation Modulator (Abatacept)

T cells are considered to be an inflammatory and autoimmune components of RA for the production of immunomodulatory cytokines.Targeting T-cell activation approach can be helpful for treating RA. T-cell activation is done by the costimulation of T cells that recognizes antigen through T-cell receptor.The engagement of CD80/CD86 on APC (antigen-presenting cells) is the best characterized costimulatory pathway for T-cell activation. It is likely to be produced a positive costimulatory signal and helped for targeting T-cell activation.But, other T-cell activation pathways can cause downregulation of T-cell activity. CTLA-4 acts as T-cell activity downlregulator and has a more binding affinity with CD80/CD86 than CD28. Abatacept (CTLA-4 Ig) is a recombinant fusion protein consisting the extracellular domain of human CTLA-4 and Fc domain of human IgG1, and also modified for the prevention of complement fixation. Abatacept shows the high binding CTLA-4 avidity of CD80/CD86 on APCs. This prevents T-cell activation pathway by engaging CD28 present on T cells. The tolerability and efficacy of abatacept have already been reported for several international, double-blided, randomized and placebo-controlled trials in active RA patients, include patients with inadequate MTX response[31-33] or TNF antagonists[34].The examination trial reports of the safety, efficacy and the HRQoL outcomes of abatacept have been compared with placebo administration in RA patients receiving an associated RA medication; in the year, 2005, they have applied for FDA approval of the usage of abatacept in RA patients who earlier have an inadequate response by the use of MTX or TNF antagonists.

Phase III studies of abatacept treatment for RA

The AIM (Abatacept in Inadequate Responders to Methotrexate) study was a randomized, placebo-controlled, multicenter and double-blinded trial[35]. The main objective of the study was to determine the efficacy and safety of abatacept in patients with active RA has an inadequate response to MTX. In this study, an efficacy has been defined as achievement of ACR 70, ACR 50 and ACR20, and physical functional improvement, also defined by means of the HAQ DI, in 6-12 months. The higher ACR20 responses have been shown with the abatacept group than the placebo (67.9% vs. 39.7%, $p<0.001$) within 6 months. A true response was achieved with ACR50 (39.9%vs16.8%, $p<0.001$), and with ACR70 (19.8%vs. 6.5%, $p<0.001$).The beneficial effects were improved within 1 year for the group treated with abatacept (ACR70, 28.8% vs. 6.1%; ACR50, 48.3% vs. 18.2%; ACR20, 73.1% vs. 39.7%). The study also has been shown that abatacept can significantly control the radiographic progression of erosive disease within 1 year, by the reduction ofGenant-modified sharp scores i.e. 50% compared with that of the placebo recipients. The ATTAIN (Abatacept Trial in Treatment Of Anti-TNF Inadequate Responders) study was the placebo-controlled, randomized and double-blinded study for evaluating the efficacy and safety of abatcept in active RA patients and an insufficient response to TNF antagonists[36]. A significant difference has been observed in clinical efficacy as starting ACR20 response was noted by day 15 and continued till the 6-months study period (ACR20, 50.4% for abatacept vs. 19.5% for placebo, $p<0.001$).A group of patients significantly achieved a high of ACR50 and ACR70 responses in the abatacept group ((ACR50, 20.3% vs. 3.8%, $p<0.001$; ACR70, 10.2% vs. 1.5%, $p<0.01$).In addition, a significant improvements have been noted in the SF-36, HAQ and DAS28 scores in abatacept received patients.In conclusion, abatacept can be a safe and effective drug in treating active RA patients and those who had an inadequate response to anti-TNF therapy[36]. The safety of abatacept or placebo in combination with biologics or DMARD therapy can be determined by the ASSURE (Abatacept Study of Safety in Use with other RA Therapies) trial study[37]. Safety is the primary considerable factor for any class of therapy or new therapy to be introduced. The AIM trial suggesting that a slightly higher rate of SAEs (15% vs. 11.9%) has been due to the high rate of AEs (4.2% vs. 1.8%) than discontinuation in the abatacept groups Vs placebo groups, respectively.

Efficacy of biological DMARDs

The efficacy of biologics can be tested by several randomized clinical trials in patients with RA, both in a short time and long time disease duration after failure of conventional DMARDs. These trials show the evidence of the biologics superiority in combination with methotrexate vs. methotrexate alone in both late and early disease. In addition, TNF inhibitors have also been shown superiority over methotrexate monotherapy. However, most of the patient groups, especially MTX-naïve population responds to MTX monotherapy than combinational therapy to treat RA.because the treatment with methotrexate is a less expensive and simpler than biologics.

Safety of biological DMARDs

The data from extensive clinical trials and registry studies provide an important safety information regarding DMARDs. An acceptable safety profile with a small risk of infections has been the most common adverse effect. An increased risk by the reactivation of tuberculosis with TNF inhibitors during treatment, thus screening for tuberculosis

before initiation of the TNF inhibitor drug regimen is highly recommended. The most common adverse effect of infliximab and rituximab has been infusion reactions. Demyelinating disease and Anti-TNF induced SLE are the rare complications of TNF antagonists.No data have not been found for any increase of risk caused by malignancies. A prospective observational studies and clinical meta analysis studies showed that no incremental growth of malignancies other than skin cancers by associating use of TNF inhibitors.

When to start biologic agents

The effectiveness of biological agents has been proved in several randomized clinical trials. Biologics become a first line treatment when no contraindications were reported with traditional DMARDs, and mostly with methotrexate. However, 70% of the patients who discontinue the treatment with methotrexate due to either intolerance or inefficacy. Hence, the combination of synthetic DMARDs (e.g. hydroxychloroquine and sulphasalazine) or biological agents are preferable.Few clinical trials have reported the results by direct comparison of these two treatments.In the SWEFOT trial, early RA patients have been administered with a combination of sulphasalazine and hydroxychloroquine or infliximab after inadequate response with MTX for 3months. The new combinational therapy has shown a significant results after 12 months of dosage regimen, 39% of RA patients reached the primary endpoint compared with 25% of the former group ($p=0.016$)[38]**.**No longer clinical significance has been observed in the 2 year follow-up assessment, but a significant disease progression reported in later group than the former group[39]**.**Almost identical results were observed in the BeSt trial[40,41]**.**in this BeSt trial, three treatment groups were involved. It includes group 1 (sequential DMARD monotherapy), group 2 (step-up combination therapy, group 3 (initial combination therapy with high-dose Prednisolone) and group 4 (infliximab).In this trial, groups 3 and 4 have shown a more aggressive treatment strategy than groups 1 and 2. But, initially, all groups have reported low disease activity. After 2 years, all patient groups had experienced the similar improvement in functional status and disease activity irrespective of initial treatment, maybe because of frequent treatment adjustments. An initial aggressive therapy resulting in some long-term gains with monotherapy.

When to stop biologic agents

The remission or low disease activity in patients with RA is possible with the use of biologics. According to European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR), the low disease activity or remission of rheumatoid arthritis has been defined as Creactiveprotein ≤ 1 AND swollen joint count ≤ 1 AND tender joint count ≤ 1 mg/dl AND patient global assessment ≤ 1 (on a 0-10 scale) (boolean-based definition) or a Simplified Disease Activity Index score of ≤ 3.3 (Index-based definition) (28). The discontinuation of biologic agents is possible when the patient experiences a state of low disease activity or remission for about 6 months period, and it is necessary to maintain a good clinical response of biologics against rheumatoid arthritis. Quinn et al. identified the induction of remission in several double-blind, randomized and placebo-controlled trial in early RA patient populations. The low disease activity or remission with the combination of infliximab and MTX leads to a significant reduction in erosions and synovitis within a 1 year period, and also achieving the quality of life and sustained functional benefits in 70% of the patients for a long period of time (2 years) despite the withdrawal of infliximab. Recently, Tanaka et al., studied the induction of remission or low disease activity in RA patients after discontinuing infliximab[42]**.** In this study, An average disease duration has been 5.9 years, it is suggested that the possibility of discontinuation of infliximab in early RA patients but also in more established RA patients.

Several conclusions have been made by different clinical phase studies about discontinuation of biologic DMARDs, which include:

- Discontinuation of biologics is the long-term therapeutic goal for the safety of patients with RA and also for health economics, after achieving the low disease activity and sustained remission in a considerable proportion of patients.
- The risk of deterioration of diseased condition increases with discontinuation of treatment until the initiation of the biologic treatment, therefore it has been suggested that early introduction of biologic treatment leads to better results and also increases the possibility of remission achieved by the withdrawal of biologic agents.

Principles for use of biologic treatment in rheumatoid arthritis

Several advantages of biologic treatment such as the rapid progress and advancement of biologic treatment, and the potential long term safety,etc. guide the physicians to make use of these agents in clinical practices. An initial goal of the rheumatologist is to achieve remission of RA, if not possible,at least can achieve a low disease activity[43]**.**A synthetic DMARDs (most often methotrexate) are prescribed at an early diagnosis of RA with or without association of corticosteroids. If disease control is not achieved within 3 months, it is advisable to administer an additional DMARDs or biologic agents. An early

aggressive and strong treatment should be prescribed to the patients with multiple negative prognostic factors, such as high disease activity, radiographic progression and seropositivity. It is prescribable to the switching of synthetic DMARD before starting the biologic treatment. Biologics can provide a better results in patients with active RA who earlier have not treated with DMARDs. Biologics are not widely used due to several factors such as high cost, safety and the possibility of the good effect of methotrexate. TNF inhibitor is the first biologic agent, it is also available with the combination of MTX; clinical evidences state that TNF combinations are more efficient than its monotherapy. Other biologic agents with different mechanism of action (abatacept or tocilizumab, rituximab) can also be chosen if any contraindications observed with TNF inhibitor therapy.

Optimize dose of biologic

The TNF inhibitors have a different dosage regimen for etanercept (once weekly) and infliximab (once every 8 weeks). During the optimization of infliximab dose, unexpected data have been available. Four different treatment regiments have been selected for optimization of infliximab in ATTRACT trial. Similar ACR (American College of Rheumatology) responses have been observed within 24 weeks duration. However, at 48 weeks, significantly different ACR 50 responses were observed, suggesting that change of treatment interval or dose increase can yield better results in patients with secondary loss of efficacy to infliximab[44,45]**.** In contrast, Pavelka et al., studied no significant efficacy observed with two dosages of infliximab (3 and 5 mg/kg) after initial lower dosage failure leads to remission[46]**.** In an observational study, it was confirmed that a reduction in the disease activity score DAS 28 in patients with RA when the higher dosage of infliximab has been administered[47]**.**However, controlled patient groups (patients receiving a stable dose of etanercept and those with no change in infliximab dose) also shown a significant improvement in DAS 28. In conclusion, evidences suggesting that an increased dosage regimen of infliximab may result in higher cost, loss of time and more potential side effects with no significant efficacy in most RA patients.

Conclusion

The biological agents provide a unique and potent addition to the patients with RA. Recently, several biological agents have been emerged and begun a new era in the treatment of RA. Treatments with cytokines such as IL-1 and TNF have been the only approved targeted therapies in the past. The new targets such as B cells, interleukin-6 and T-cell activation providesan important information about the pathogenesis of RA disease.However, other new licensed biological agents have higher efficacy against infections than placebo, have unrevealed long-term effects, unable to cure RA even if they are more efficacious against it and do not show remission in most RA patients who do respond. Thus, the requirement of an additional new drugs is essential for successful treatment of RA.An introduction of biologic DMARDs has changed the field of RA treatment. But a few factors limiting the usage of DMARDs in regular clinical practices.Such an approach is crucial, taking into consideration the increasing number of biologic agents, their high cost and the importance of choosing the right treatment from the beginning. These are some of the important challenges of clinical, epidemiological and basic rheumatologic research.

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