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Rheumatoid arthritis: advances in treatment strategies

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Abstract

Rheumatoid arthritis (RA) is characterised by severe joint and bone damage due to heightened autoimmune response at the articular sites. Worldwide annual incidence and prevalence rate of RA is 3 cases per 10,000 population and 1%, respectively. Several genetic and environmental (microbiota, smoking, infectious agents) factors contribute to its pathogenesis. Although convention treatment strategies, predominantly Disease Modifying Anti Rheumatic Drugs (DMARDs) and Glucocorticoids (GC), are unchanged as the primary line of treatment; novel strategies consisting of biological DMARDs, are being developed and explored. Personalized approaches using biologicals targetspecific pathways associated with disease progression. However, considering the economic burden and side-effects associated with these, there is an unmet need on strategies for early stratification of the inadequate responders with cDMARDs. As RA is a complex disease with a variable remission rate, it is important not only to evaluate the current status of drugs in clinical practice but also those with the potential of personalised therapeutics. Here, we provide comprehensive data on the treatment strategies in RA, including studies exploring various combination strategies in clinical trials. Our systematic analysis of current literature found that conventional DMARDs along with glucocorticoid may be best suited for early RA cases and a combination of conventional and targeted DMARDs could be effective for treating seronegative patients with moderate to high RA activity. Clinical trials with insufficient responders to Methotrexate suggest that adding biologicals may help in such cases. However, certain adverse events associated with the current therapy advocate exploring novel therapeutic approaches such as gene therapy, mesenchymal stem cell therapy in future.

Keywords Rheumatoid arthritis · DMARDs · Biologicals · Therapy · Clinical trial

Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic disease, primarily characterised by synovial inflammation (synovitis), which further leads to cartilage damage and bone erosion. Early symptoms include general malaise, swollen and tender joints and morning stiffness. If untreated, chronic RA can lead to systemic inflammation resulting in abnormalities in heart, liver, intestine, muscle and in some cases can also cause cognitive decline [1]. It usually starts between the age group of 20 to 40 years and its prevalence rate varies from 0.3 to 1% [2]. Several factors are known to contribute to the development of this disease. Approximately, 60% of RA cases are linked to genetic predisposing factors, compounded by environmental factors. Among the contributing genes, single nucleotide polymorphisms (SNPs) in HLA-DRB1 alleles (DRB1*01 and DRB1*04; DQ8) are mostly involved. Exact mechanism of disease development has not been completely understood but pathogenic or non-pathogenic triggering events may be involved, such as bacterial/viral infections, microvascular damage or microtrauma [3]. Thus, presence of auto-reactive B and T cells along with generation of Neo-epitopes leading to loss of tolerance is found [4]. Deregulated factors such as cytokine and other inflammatory molecules along with immune cells like B, T and mast cells eventually accumulate in the synovial sites, causing the damaging effect. Certain biomarkers such as

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rheumatoid factor (RF), antibodies to citrullinated protein antigen (ACPAs), C-reactive protein CRP (CRP) and erythrocyte sedimentation rate (ESR) are useful in RA diagnosis [5].

The overall aim for treating RA is to achieve disease remission. Although Methotrexate is a staple drug for its treatment, the repertoire of therapeutic options for rheumatologists has increased over the past decade. DMARDs have been effectively utilised to target inflammation and prevent further joint damage. Besides these, Non-steroidal Anti-inflammatory drugs (NSAIDs); cause symptom improvement but no effect on disease progression and Glucocorticoids (non-specific immune suppression but with long term side effects) have also been used. DMARDs include those drugs which target rheumatoid inflammation and effectively control disease progression. Two categories of DMARDs are available for use (i) Synthetic DMARDs and (ii) Biological DMARDs. Synthetic DMARDs can be subdivided further into Conventional and Targeted DMARDs. Conventional DMARDs (cDMARDs) include routinely used drugs such as Methotrexate, Hydroxychloroquine and Sulfadiazine, whereas newer targeted DMARDs include JAK inhibitors (Baricitinib/Tofacitib). Biological DMARDs (bDMARDs) include antibodies against TNF-alpha, TNF-R, IL-6, IL6-R, co stimulatory molecules and B cell depleting antibodies. Importantly, combination therapies of two/three synthetic DMARDs or synthetic and biological DMARDs can also be used [6–11]. However, not all patients respond with therapy and multi-refractory (MR) patients showing insufficient response to at least three bDMARDs or bDMARDs with different mechanism of action have also been reported [12]. Further insights are required into biomarker development for early diagnosis of RA and early identification of non-responder population with cDMARDs, so that other treatment arms may be implemented to avoid disease progression.

Treat-to-Target approach is the newer strategy in RA treatment that engages in stringent observation of the disease progression and management if respective therapy is not encouraging [13]. The American College of Rheumatology (ACR), EULAR and the Asia Pacific League of Associations for Rheumatology (APLAR) have employed the treat-to-target approach in their recommendations [14, 15]. At present, RA treatment is focused on reducing disease activity followed by potential remission preventing joint deformities and disease progression [16, 17]. However, advanced approaches emphasise on the importance of attaining at least 50% improvement in disease activity within 3 months of drug administration [18]. In case the desired outcome has not been achieved, modification in treatment strategy is suggested depending upon patient's situation in order to improve disease management.

Methodology

PubMed and Google scholar sites were used for literature search of peer-reviewed articles. The main keywords used for search were "rheumatoid arthritis and therapy and DMARD". For including clinical trial data, we have referred to the NIH Clinical Trials website (https://clinicaltrials.gov/). Only Phase 3 and 4 studies with published results were included in the article. Figure of targeted therapy and mechanism of action of cDMARDs was generated originally using Biorender software. Algorithm of European League Against Rheumatology (EULAR) recommendation is adapted from published source. Systematic chart of inclusion and exclusion criteria is mentioned in Fig. 1.

Aetiology of rheumatoid arthritis

RA is a multifactorial disease and its progression and severity depends on both environmental and genetic factors. Genomic studies have identified more than 100 loci associated with this disease. Out of these, Major Histocompatibility Complex class II (MHC class II) encoding genes such as Human Leukocyte Antigen DR01/04 (HLA DR01/04) are prominently involved [19]. Products of HLADR01/04 (DR1 and DR4) help T-cells in preferential recognition of auto-reactive peptides [20]. Further, genes associated with inflammatory processes are also found associated with higher risk. Genome Wide Association Study (GWAS) have identified involvement of multiple genes like PTPN22, STAT4, PADI4, CTLA4, CD40, TNF in RA. Single Nucleotide Polymorphisms (SNPs) in genes such as HLA-DR, PTPN22, and TRAF1-C5 are associated with 40-fold higher risk. Recently, epigenetic modifications are also found associated with disease etiology [21]. Altered methylome signatures are found in synovial fibroblasts that contribute to their activation. Pathways associated with hypomethylated genes are involved in cell adhesion and migration and trans-endothelial migration, thus leading to a migratory phenotype [22]. In one of the studies, higher expression of polyamine-modulated factor 1-binding protein 1 (PMFBP1) and spermidine/spermine N1-acetyltransferase (SSAT1), hypomethylating factors, is reported in fibroblasts from RA patients [23]. Inhibition of PMFBP1 and SSAT1 downregulates Matrix MetalloProteinase 1 (MMP1), involved in cell migration and invasion, and hence can help in preventing disease progression [23]. In another study, inhibition of Histone Deacetylase (HDAC) leads to increased expression of Tumor Necrosis Factor A (TNFA) induced ICAM-1and VCAM-1 in synovial fibroblasts [24]. ICAM-1 and VCAM-1 level in blood is found to be positively correlated with RA severity [25] role. Comprehensive epigenetic profiling of fibroblasts like synoviocytes from RA patients found changes in expression

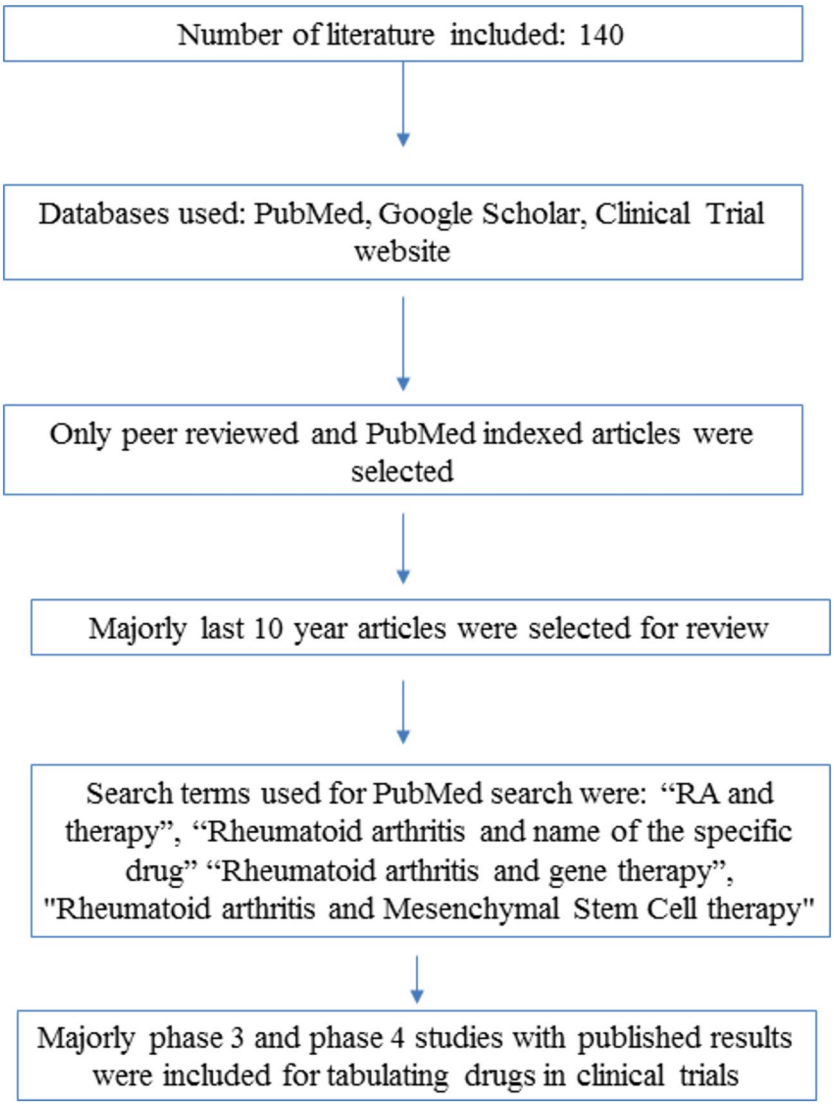

Fig. 1 Systematic chart of inclusion and exclusion criteria

of genes associated with pathways such as Protein Kinase A signaling, Clathrin-Mediated Endocytosis, role of osteoblasts, osteoclasts and chondrocytes and leukocyte extravasation signaling along with others [26].

Environmental factors such as smoking and infection play an important role as triggers for the disease development. Through epidemiological studies and in vivo models, the role of smoking has been established. In smokers, risk of developing RA is twofold higher than in non-smokers and in female smokers it is 1.3-fold higher than non-smokers [27]. Smoking can activate oxidative stress pathways by inducing free radical generation [28]. It can also induce Fas (CD95) and CD4 T-cell expression that can lead to increased cell death and autoimmune response contributing to synovial inflammation [29]. In smokers, higher expression of inflammatory molecules such as CRP, Fibrinogen, ICAM-1 along with other cytokines is found [27]. Cytokines such as IL-1α, IL-1β, IL-6 and IL-8 can be induced in FLS cells by condensate from cigarette smoke [30]. Smoking can increase the level of monocytes and macrophages in alveoli that can cause heightened inflammatory response and may contribute to disease development [31]. Smokers also show higher level of MMPs in their synovial fluid that contributes to joint destruction [32]. Further, smoking is reported to cause genome-wide methylation pattern in the MHC region [33].

Interestingly, dietary factors may affect RA risk. Studies have linked increased alcohol consumption with lower RA risk [34]. Study in Danish population has shown that consuming alcohol leads to decreased ACPA-positive RA. Certain foods can also increase susceptibility to disease development. Mediterranean diet is known to be the best for RA prevention. Study found that Mediterranean diet caused the decrease in disease activity score [35]. Calorie restriction methods like intermittent fasting also reduces inflammation. Although there is not much evidence regarding association

of poultry products and fish with RA risk. In one of the studies, red meat is shown to be associated with RA development [36]. Among other environmental factors, vitamin D is known to be strongly associated with RA risk. Vitamin D plays a major role in regulation of hormones and immune system [37]. Vitamin D being an immune regulator and suppressor of the inflammatory process, it is found to be associated with increased risk or disease severity.

Treatment strategies

Previously until early 1990s, unconfirmed diagnosis combined with the use of NSAIDs as first line therapy, led to chronic RA disease resulting in adverse consequences, with serious joint deformities and disabilities. However, the recent approach to treat any disease is primarily focused on achieving disease remission or reducing the disease activity and therefore multiple strategies, including combination of cDMARDs at the start and switching over to targeted or bDMARDs, are employed to decrease joint damage and related symptoms. In addition, advanced biological treatments that are currently being employed and some combinations under clinical trials, have shown to induce decreased activation of the immune system and inflammation [38]. According to the latest EULAR recommendations (2019), DMARDs are to be used either as monotherapy or in combination with a biological (TNF-inhibitors, IL-inhibitors etc.) depending upon response to respective drugs (Fig. 2, adapted from [39]) In addition, combination therapy with inclusion of NSAIDs and

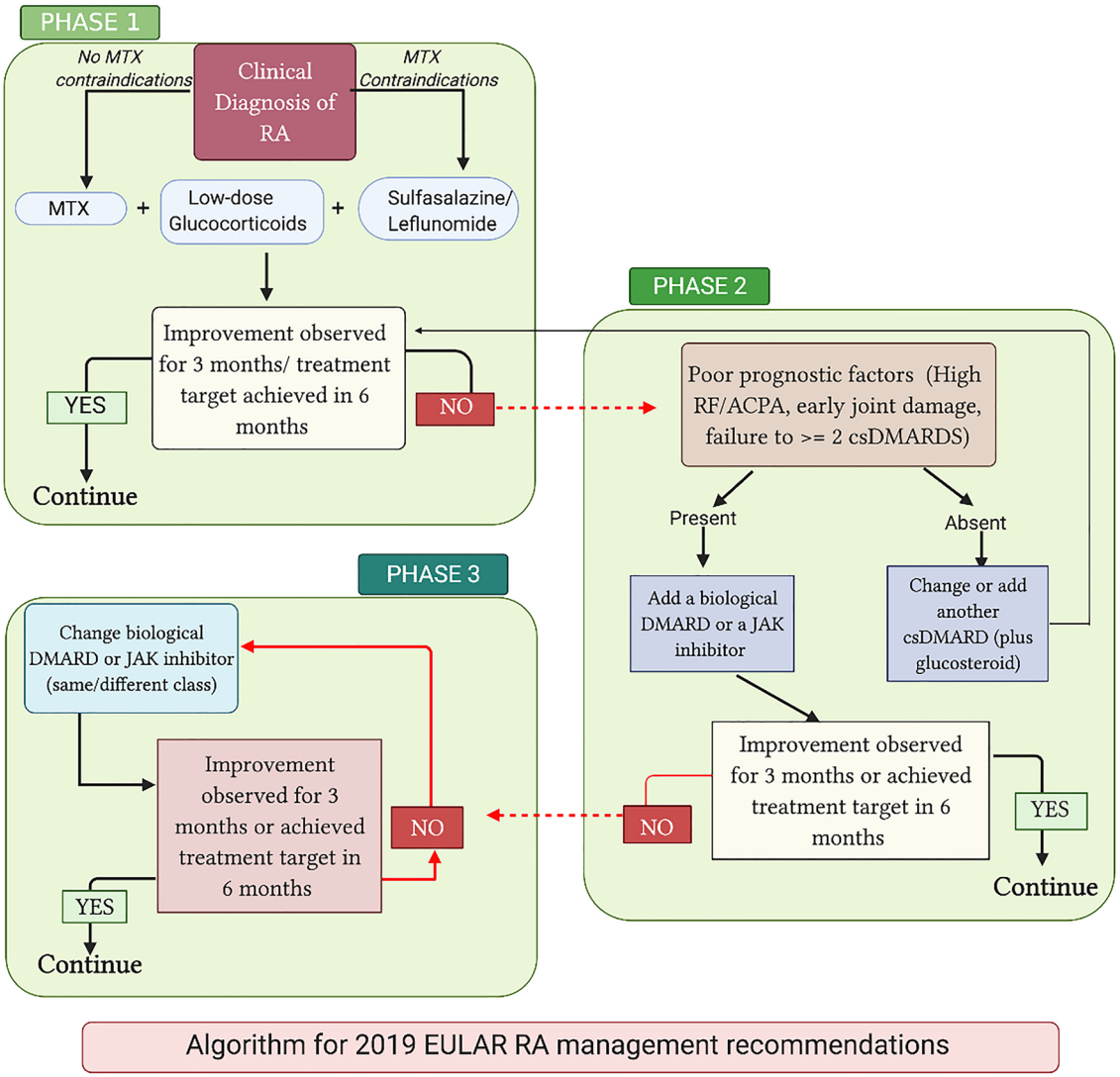

Fig. 2 Flowchart diagram for latest EULAR recommendations for disease management in rheumatoid arthritis

Table 1 List of important therapeutic classes for treatment of rheumatoid arthritis

Drug classification	Subclassification	Drug name	Mechanism of action	Side effects	References
Synthetic DMARDs	Conventional DMARDs	Methotrexate	Blocks 5-aminoimidazole-4-carboxamide ribonucleotide Transformylase (AICART)	Hepatic fibrosis, gastrointestinal issues	[6, 40]
		Leflunomide	Pyrimidine synthesis inhibitor	Hypertension, nausea	[41]
		Sulfasalazine	Anti-inflammatory and immunosuppressive	Nausea, abdominal discomfort	[40, 42]
		Hydroxychloroquine and Chloroquine	Immunomodulatory	Gastrointestinal infections	[40, 43]
	Targeted DMARDs (JAK Inhibitors)	Tofacitinib	Selective inhibitor of JAK 1, JAK2, JAK3 and Tyrosine kinase 2 (TYK2)	Pneumonia, gastroenteritis, cellulitis, UTI	[8]
		Baricitinib	selective and reversible JAK1 and 2 inhibitors	Elevated LDL levels	[9]
		Filgotinib	JAK 1 Inhibitor	Nausea, Neutropenia, mild decrease in platelet	[44, 45]
Biological DMARDs	TNF-inhibitors	Etanercept	Therapeutic neutralization of TNF-α	Sinusitis, upper respiratory tract infections, urinary tract infections and soft tissue infections	[10]
		Infliximab	Inhibits TNF receptor complex formation	Pneumonia	[11]
		Adalimumab	Prevents binding of TNF-α to its receptors	Hypertension	[11]
		Certolizumab pegol	Neutralizes membrane associated and soluble TNF-alpha	Hypertension Nasopharyngitis, High risk of serious infection	[11, 46]
		Golimumab	Binds to soluble and transmembrane forms of TNF-alpha	Demyelination, lymphoma at higher doses	[11]
	Interleukin-targeted therapy	Tocilizumab	IL-6 inhibition	Decrease in neutrophil count	[47]
		Anakinra	IL-1 inhibitor	Itchy rashes	[48]
	T-cell targeted therapy	Abatacept	Inhibits T cell activation by binding to CD80 and CD86	Pneumonia, malignancies	[49]
	Growth factor targets	Denosumab	RANKL inhibitor, decrease in DKK1 levels	Back pain, hand and feet pain, high cholesterol, hypocalcemia, osteonecrosis of jaw	[50, 51]
		Mavrilimumab	GM-CSF inhibitor	Pulmonary alveolar proteinosis	[52]

Glucocorticoids in the initial treatment regimen helps in pain management and general anti-inflammatory actions. The key therapeutic DMARD drugs and their mechanism of action are compiled in Table 1.

Synthetic DMARDs

Conventional DMARDs

RA being an inflammatory disease, first line of treatment involves cDMARDs along with NSAIDs that alleviate inflammation, pain and control radiographic progression at the joints. cDMARDs include Methotrexate (MTX),

Sulfasalazine, Leflunomide, and Hydroxychloroquine. NSAIDs and Glucocorticoids are also given initially to suppress pain and inflammation but they have limited benefit and do not reduce disease progression. Hence these are not categorised under DMARDs.

MTX has been a cardinal drug for RA therapy for more than two decades now. Its mechanism of action has been well reported [6]. It is folate analogue, which interferes with the activity of dihydrofolate reductase, thereby inhibiting nucleotide synthesis and metabolism. It has also been reported to increase adenosine release, thereby causing anti- inflammatory action. It is beneficial as it is reliable, affordable, effective and tolerable at low doses. On comparison with other cDMARDs, MTX is found most effective, however, certain patients are observed to be unresponsive or intolerable to MTX, as a consequence of which Hydroxychloroquine [7], Sulfasalazine and Leflunomide are included in the treatment. Potential side-effects may include ulcers, hepatitis, interstitial pneumonitis, cirrhosis, renal dysfunction and cytopenias. The mechanism of action of these cDMARDs is represented in Fig. 3.

Currently, MTX is given to every newly diagnosed RA patients but 50% of patients either do not show optimum clinical outcome or show some adverse events. In one of the studies, adverse events associated with MTX were evaluated on 1069 patients. Approximately, 77.5% of patients showed at least one adverse event. Some of the most common adverse events were of gastrointestinal, mucocutaneous, neurological and hematological types. Alcohol consumption and gender were also found to play role in these adverse events

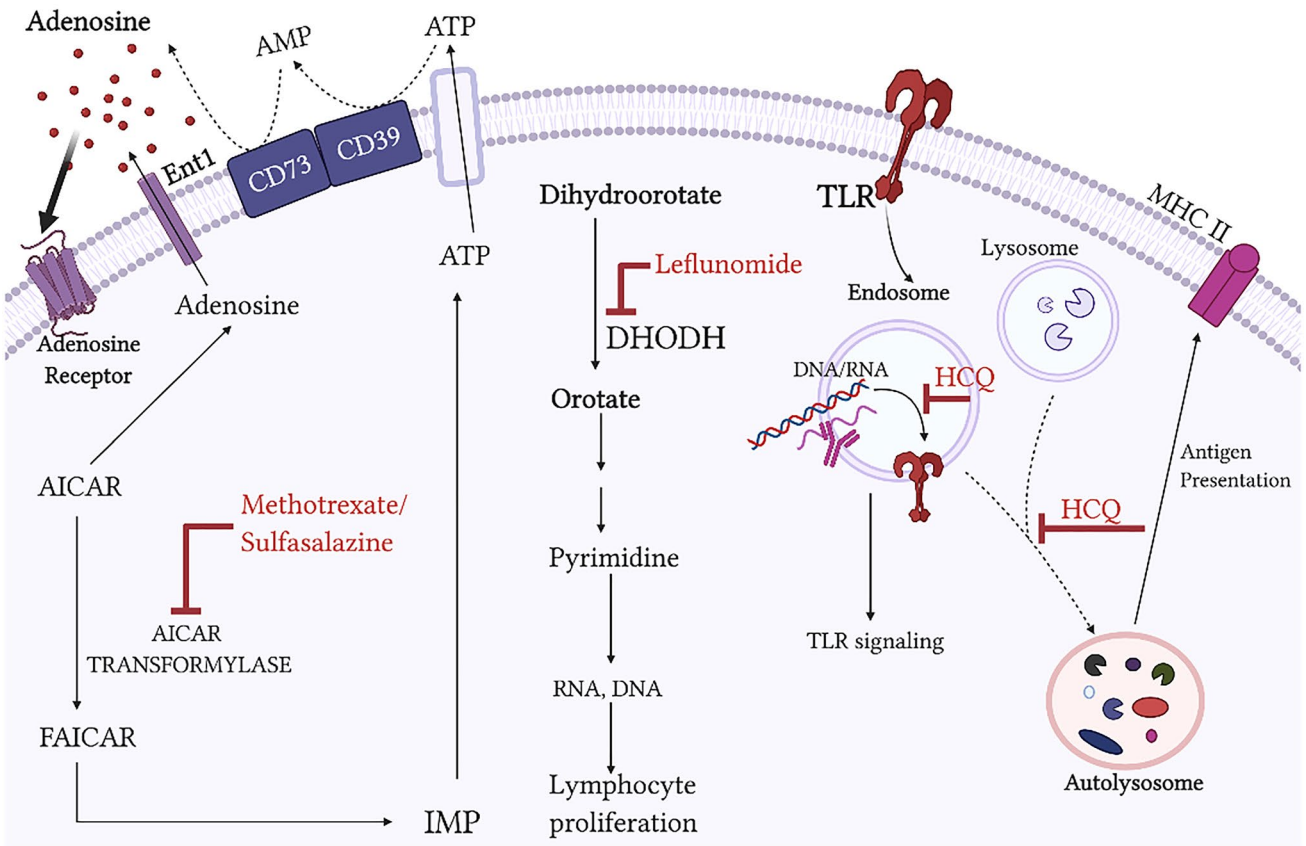

Fig. 3 Mechanism of action of csDMARDs. Methotrexate and Sulfasalazine share nearly similar mechanism of action. Although other potential mechanisms such as folate antagonism, adhesion molecules, generation of reactive oxygen species, alteration of cytokine profile and polyamide inhibition have been studies for Methotrexate, adenosine signalling happens to be the most acceptable. Methotrexate blocks 5-aminoamidazole-4-carboxamide ribonucleotide (AICAR) followed by its accumulation further blocking adenosine deaminase. Ent1 is the nucleoside transporter responsible for extracellular export of adenosine. Dephosphorylation of ATP and ADP to AMP takes place by CD39 and converted to adenosine by CD73. Leflunomide is an immunomodulatory drug and acts by inhibiting the enzyme dihydroorotate dehydrogenase (DHODH), which is essential for converting dihydroorotate to orotate. DHODH is one of the essential enzymes responsible for initiating pyrimidine synthesis, nucleic acids formation followed by lymphocyte proliferation. Mechanism of action of HCQ in RA is yet to be fully explored, however, molecular effects of HCQ include lysosomal activity, TLR signalling pathway and autophagy. HCQ interferes with immune activation by inhibiting several innate and adaptive immune processes. Specific molecular targets include TLR-signalling pathways and antigen-presentation cells (APCs). In APCs, HCQ inhibits antigen processing and MHC II presentation to T cells, thereby preventing T-cell activation and differentiation

[53]. Some studies show that bioavailability and response to MTX is partially determined by microbial composition of gastrointestinal tract of RA patients. Pharmacomicrobiology studies have identified several factors that alter the bioavailability and response to MTX [54]. Insufficient response to MTX has also been observed. Some patients are either unresponsive or show inadequate response within the first 6 months of treatment. Lack of response during the early window of opportunity has been a problem in making suitable therapeutic decisions and some biomarkers have been found to predict this. A multi-centric prospective observational study was conducted to identify baseline predictors of non-response to MTX. 43% (449/1050) of patients were classified as non-responders on the basis of RF-negativity (0.62), higher HAQ (Health Assessment Questionnaire) score (1.64), higher Tender Joint Count (1.06) and lower disease activity (0.29). Non-responders were thereby switched to biologicals (TNF or IL-1 inhibitors). This is the first study emphasising the importance of initial stratification of patients as responders and non-responders, further employing alternative approaches to ameliorate disease progression [55]. Another study highlights a significant correlation between gut microbiota and response to MTX. High-throughput metagenomic sequencing, conducted for drug-naive patients ($n=26$), indicated that the microbiota's metabolic capacity can influence MTX response. Thus, pre-treatment microbiome composition could be used as a predictor of MTX response [56]. Another study conducted for elucidating baseline levels of serum biomarkers representing the multi-biomarker disease activity (MBDA) test observed significant correlation between 4 biomarkers and response to MTX in DMARD-naive early RA patients ($n=298$) from SWEFOT trial. Reduced CRP, Leptin and higher levels of Tumor Necrosis Factor Receptor I (TNF-RI) and VCAM1 were found to be independently associated with reduced disease activity after 3 months of MTX therapy. A combination score of these biomarkers was found as a predictor of response to MTX after 3 months [57].

Targeted DMARDs

Targeted DMARDs were developed to specifically target the JAK-STAT pathway, which is a key cytokine mediated pro-inflammatory pathway. Cytokines like IL-6, IFN gamma, GM-CSF have a common mechanism of action after they bind to their respective receptors on cells. This binding activates the binding of JAK kinase to their receptors, which further phosphorylates these receptors, leading to phosphorylation and dimerisation of STAT molecules. This further causes the nuclear localisation of STAT and induction of further transcription of pro-inflammatory genes. Tofacitinib is a pan-JAK inhibitor inhibiting JAK-1/2/3, Baricitinib is a JAK1/2 inhibitor, and Filgotinib and Upadacitinib are selective JAK-1 inhibitors.

Encouraging results have been obtained from such drugs targeting JAK pathways [58, 59]. Tofacitinib with/without MTX was approved by the European Medicines Agency (EMA) in 2016–2017 for patients with moderate to active RA [60]. In addition, Baricitinib has also been approved for patients displaying non-efficacious response to DMARDs [61, 62]. In five rheumatology units including adults with RA initiating Baricitinib, retrospective longitudinal cohort study was conducted. Data from 182 patients found that patients treated with Baricitinib had long-standing and refractory disease. After 6 and 12 months of treatment initiation, high persistence and improvement in disease activity and pain were found [63]. Long-term safety was evaluated in RA patients from the completed extension trial of Baricitinib. Integrated analysis on data from the 3770 active RA patients found no new safety signals [64]. In one of the case studies, 35-year-old man with seronegative RA had bilateral severe non-granulomatous panuveitis which was resistant to steroid treatment, methotrexate, salazosulfapydine, adalimumab and infliximab. Patient was given Baricitinib which decreased the activity of systemic arthritis and also ameliorated the inflammatory activity in seronegative RA. It was found that Baricitinib was not effective only in refractory systemic arthritis but also in uveitis [65].

FL has shown good efficacy and safety in Phase II and III trials, both as a MTX add-on and as mono-therapy, in MTX inadequate responders over 24 weeks [66]. Rapid and significant improvements in disease activity have been found when FL was given alone or in combination with other conventional drugs. Phase 3 randomized, controlled FINCH 3 trial found significant improvement in Health Assessment Questionnaire-Disability Index was seen at week 24 of treatment along with sign and symptoms in active RA patients [67]. Another clinical trial, (DARWIN 3, a long-term, open-label extension study) on 739 patients found FL is well-tolerated in a 4-year safety profile [68]. Using integrated data from 7 trials (NCT01668641, NCT01894516, NCT02889796, NCT02873936, NCT02886728, NCT02065700 and NCT03025308), safety of Filgotinib was evaluated in moderately to severely active rheumatoid arthritis patients. Study on 3691 patients found that over a median period of 1.6 and maximum of 5.6 years of exposure, safety or tolerability of FIL200 and FIL100 were similar. Lower incidence of infections was found with FIL200 [69].

Upadacitinib (UPD) was also evaluated in Phase III study in Methotrexate Inadequate responders (MTX IR), and a significantly higher clinical and functional efficacy was observed with UPD (68–71%) as compared to continued MTX usage (41%) for 14 weeks. In a randomized controlled phase 3 trial (SELECT-COMPARE), long-term safety and efficacy of UPD vs Adalimumab (TNF inhibitor)

over 3 years was investigated in patients with active rheumatoid arthritis and inadequate MTX response. Comparative study between UPD and Adalimumab found that herpes zoster, lymphopaenia, hepatic disorder and CPK elevation were higher with UPD. However, UPD showed better clinical response than Adalimumab [70]. UPD vs placebo (PBO) and UPD vs Adalimumab was compared in RA patients who were on stable methotrexate treatment but had an inadequate response. Data from SELECT-COMPARE trial was taken for post-hoc analyses. Analysis found that UPD showed greater efficacy than Adalimumab as evidenced by DAS 28 score based on C-reactive protein [71].

To understand the mode of action of FL, secreted and cell-based biomarkers were studied from blood samples. Longitudinal analysis of these revealed that although lymphoid populations were unchanged, the RA pathophysiology related biomarkers were altered. Various key cytokine and molecules involved in mediating inflammation, leukocyte migration, angiogenesis and matrix adhesion were regulated by FL therapy [66]. Three phase III trials are also reported with FL in case of MTX-IR (Inadequate Responders), MTX-naive, bDMARD-IR patients. In MTX-IR study, FL showed significant improvement in signs and symptoms, physical function and prevented radiographic progression, compared to placebo. Also, its efficacy was found similar to Adalimumab, a TNF alpha inhibitor. In MTX naive patients, it was found that FL in combination with MTX led to significant improvements in signs and symptoms and patient-reported outcomes compared to MTX alone. Here, significant clinical response occurred as early as 2 weeks of treatment initiation [66].

Biological DMARDs

bDMARDs are class of drugs that are produced through living organisms and have a very selective anti-inflammatory mechanism of action and are usually prescribed upon failure of cDMARD therapy. bDMARDs execute their action by inhibiting mechanisms such as cytokine function or B/T cell activation. bDMARDs fall under different categories, like some of them are monoclonal and chimeric humanized fusion antibodies, whereas others are human immunoglobulin fused receptors or fused to inhibitors of certain signaling molecules.

Inflammation and hyperplasia are common manifestations in RA. There are several cytokines like TNF-α, IL-1, IL-7, IL-15, IL-17A, IL-18, IL-21, IL-23, IL-32, and IL-33 that participate in inflammatory process [72]. TNF-alpha and IL-6 are some of the key cytokines involved in RA development and progression. Monocytes, macrophages, B-cells, T-cells and fibroblasts mainly produce TNF-alpha, which is found to play a prominent role in synovitis. Fibroblasts are found to be stimulated by TNF-alpha that leads to expression of ICAM-1 [73]. Inhibiting TNF-alpha leads to reduction in the production of IL-1, IL-6, IL-8 and GM-CSF [74]. IL-6 is glycoprotein and is involved in activation of B-cell differentiation. In RA, IL-6 causes the production of autoantibodies by acting on plasmablasts [75]. IL-6 is also involved in bone destruction by inducing endothelial cells to produce IL-8 and MCP-1. This leads to the activation of adhesion molecules and leukocytes recruitment in joints [76]. Therefore, targeting TNF-alpha and IL-6 along with other cytokines can prove to be very effective in RA treatment.

TNF alpha-inhibitors

TNF alpha-inhibitors are either neutralising monoclonal antibodies (Infliximab, Adalimumab, Certolizumab), soluble TNAF-alpha receptor (Etanercept) or antibody fragments (Certolizumab pegol) [77, 78]. Their mechanism of action primarily involves inhibiting binding of TNF-alpha to their receptors on cells followed by complement-dependent response. TNF alpha inhibitor is clinically used as the second line of treatment if patients fail to respond to synthetic DMARDs. Choice of the inhibitor depends upon several factors including patient response to DMARDs, drug cost and other contributing factors.

Etanercept is a chimeric protein molecule which combines a TNF-receptor 2 subunit with the Fc domain of human IgG1 molecule. The best choice of anti-TNF therapy in RA patients was evaluated in one retrospective study. PubMed, EMBASE and Cochrane Library were searched and 72 randomized controlled trials (RCTs) with total of 28,332 subjects included. This study found that Certolizumab combined DMARDs therapy should not be recommended because of more adverse events and Etanercept monotherapy is the optimal choice for RA patients [79]. To estimate cost effectiveness of treatment with Etanercept in Japanese RA patients, markov modeling was used. This study found that the quality-adjusted life-years for the Etanercept 25 mg was increased by 0.841 compared to placebo group which suggests that maintenance treatment with Etanercept 25 mg is also cost-effective [80].

Insufficient response to TNF alpha inhibitors has also been observed but the reasons are still not completely understood. In one of the studies, potential predictive biomarkers and mechanism of insufficient response to Infliximab was explored. Analysis of differential gene expression was done on Infliximab responders and non-responders using two datasets GSE58795 (responders) and GSE78068 (non-responders). Module associated with nonresponse to Infliximab was identified by co-expression analysis and further enrichment analysis was done on the module genes. Gene signature was developed by least absolute shrink and selection operator (LASSO) regression for predicting therapeutic

effect of infliximab in RA. From the two datasets, 46 common genes were obtained in which 25 gene signatures were found to have potential predictive value for infliximab. Derlin-1 (DERL1) was identified as the hub gene which is found to be involved in regulation of autophagy and immune response. Expression of DERL1 was found to increase in synovial tissue of RA patients [81]. Multi-omics approach was used in another study to compare effects of MTX, Infliximab and Tocilizumab on peripheral blood signatures during a longitudinal analysis of patients and healthy controls up to 24 weeks of treatment. Molecular phenotyping revealed better normalization of molecular signatures using Infliximab and Tocilizumab than MTX, further emphasizing the need of personalized therapy in RA [82].

Golimumab (GLM) is a human IgG1κ monoclonal antibody which neutralizes TNFα and prevents inflammation and protects cartilage degradation and bone erosion. Decreased level of serum acute phase reactants and other inflammatory biomarkers were found when given alone or in combination with MTX in phase III clinical trial [83]. Serum level of cytokines such as serum amyloid A, E-selectin, MMPs, IL-6 and TNFR II is found to be reduced in patients treated with GLM. This drug also decreases the B and T cell number and macrophages [84].

However, anti-TNF alpha therapy have side effects like formation of Anti-Drug antibodies or drug-induced sarcoidosis-like disease. Usually the affected organs are lungs, skin, and lymph nodes. Retrospective study was done on RA patients from 2000 to 2021 in which 2492 patients were included. Out of these, 697 patients had received TNF-inhibitor therapy. Four patients in which sarcoidosis were induced by anti-TNF were studied. Patient 1 and 2 was classified as incomplete Heerfordt syndrome and sarcoid-like granulomatosis respectively. Patient 3 and 4 was classified as pulmonary sarcoidosis with hilar adenopathies. Patients 1, 2 and 3 were treated with Etanercept and patient 4 was given Infliximab. Also, they found that upon removal of anti-TNF agent and treatment with glucocorticoid, all of these patients recovered [85].

IL-6/IL-6R inhibitors

IL-6 blockers constitute an important group of bDMARDs which work by either (i) directly neutralising IL-6 (Siltuximab, Sirukumab) (ii) binding to IL-6R and directly blocking the anti-inflammatory signalling mediated by IL-6 (Tocilizumab, Sarilumab).

Tociluzumab is a humanised monoclonal antibody against IL-6R and is most commonly used for RA. Study done to evaluate effectiveness and safety of Toclizumab dose in RA patients revealed low disease activity (LDA) after treatment with Toclizumab. Nationwide cohort data of RA patients was collected in South Korea. 350 patients who were treated with Toclizumab and showed low disease activity were included in this study. Study found that after the achievement of low-disease activity, tapering tocilizumab dose increases the risk of losing LDA, whereas it does not significantly affect the safety [86]. After inadequate response (IR) to janus kinase inhibitors (JAKi) and Tocilizumab, effectiveness and safety of Sarilumab in RA patients was evaluated in a prospective, observational, 24-month single-arm PROSARA study (SARILL09661). Post-baseline effectiveness assessment was documented for 502 patients out of 536 patients. It was found that Sarilumab treatment for 6 months attenuated the disease activity in JAKi-IR, Tocilizumab-IR, bDMARD TH and b/tsDMARD-naïve patients to a similar extent [87]. 40% of patients showed poor clinical response despite targeted biological treatments. In more than 50% of RA patients, CD20+B cells, which are target for Rituximab are found to be either low or absent in joint synovium. This could be one of the reasons for failure of therapy in patients receiving Rituximab. It has been hypothesized that in such patients Tocilizumab could be more effective. 48-week, biopsy-driven, multicenter, open-label, phase 4 randomized controlled trial was done to compare the effect of Tocilizumab with Rituximab in RA patients. These patients had inadequate response to anti-TNF therapy stratified for synovial B cell status. Study found that Tocilizumab was more effective than Rituximab in patients with low or absent B-cell lineage expression signature [88].

B-cell depleting antibodies

Several B-cell-targeted therapies have been investigated in the past, with Rituximab being the only FDA approved for RA patients [89–91]. Rituximab is a chimeric monoclonal antibody targeting CD20 surface molecule on B cells. CD20 is a calcium channel being expressed at the pre-B cell stage only.

Rituximab is recommended for RA patients who fail to respond to cDMARDs and at least one anti-TNF therapy. Meta-analysis of clinical studies have shown good efficacy when Rituximab is used in combination with MTX [92]. In one of the retrospective studies, factors associated with Rituximab discontinuation was explored between the time period from 1998 to 2020. Analysis of 404 patients found that overall 31.2% of patients discontinued treatment due to primary inefficacy and patients who had previously failed other bDMARDs showed more chances of drug discontinuation [93]**.** A randomized, placebo-controlled, investigator-initiated clinical trial (AMARA study) was done in RA patients to check the Rituximab plus Leflunomide treatment. Study found that Rituximab

plus Leflunomide treatment showed clinical benefit compared to Leflunomide in secondary endpoints but this combination was associated with more adverse events [94]. However, incomplete B cell depletion is observed with Rituximab treatment as both memory and plasma B cells could be detected after the first infusion [90]. In addition, absence of autoantibodies, high DAS score and failure with other biologicals is found to be associated with reduced response to Rituximab [95].

Co-stimulation blocker/s

This is a new class of molecules which suppresses inflammation upstream to the inflammatory cascade. Abatacept is a chimeric antibody containing the extracellular domain of CTLA-4 fused to Fc portion of human IgG antibody. It neutralises binding of CTLA-4 part to either CD80/CD86 on activated APCs, hereafter interrupting pathways associated with T-cell activation [96, 97]. Abatacept is also found to target B cells, inhibit osteoclast differentiation and reduce expression of MMP1, 3 and 15 in fibroblast-like synoviocytes.

Abatacept has been shown to result in clinically significant disease reduction and is generally well tolerated in RA patients. A multicenter, randomized controlled study of active RA patients ($n=115$) concluded significant reduction in disease activity, maintained over a period of 12 months [98]. On the contrary, another multi-centre study concluded that use of Abatacept in combination with MTX had no significant improvement in treatment response in comparison with Abatacept monotherapy [99]. In another study, effectiveness and safety of Abatacept was evaluated in biologic-naïve RA patients over a period of 52 weeks. These patients were having moderate disease activity in the prospective, 5-year, observational study (ORIGAMI study) in Japan. Analysis of 325 patients found that Abatacept significantly improved disease activity, physical disability, and quality of life for up to 52 weeks [100]. In RA patients having MTX background therapy and positive for ACPA, safety and efficacy of Abatacept was evaluated in a post hoc analysis of a randomized, double-blind, placebo-controlled phase 4 study (NCT01758198). This study found that regardless of baseline MTX dose, similar efficacy and safety of Abatacept was observed in biologic naïve ACPA-positive RA patients [101].

RANK-L inhibitor

Receptor Activator of Nuclear Factor Kappa-B Ligand (RANK-L), a TNF superfamily member, binds to RANK and is involved in osteoclast development, survival and activation. Normally produced by osteoblast cells, RANK-L expression is induced in RA joints and immune cells and FLS cells become the main producers. Therefore, neutralisation of RANK-L prevents bone erosion and destruction.

Denosumab is a recently approved human monoclonal antibody, which targets RANK-L. Denosumab is also well tolerated in patients receiving conventional therapy. One of the studies found that Denosumab suppresses joint margin erosion and prevents narrowing of the joint space. Further, cartilage turnover marker, serum Cartilage Oligomeric Matrix Protein (COMP) was found unchanged but bone metabolism marker, C-telopeptide of type I collagen (CTX-I), was found reduced [102]. In a multi-centric observational study, changes in the bone mineral density (BMD) and erosion after Denosumab discontinuation in RA patients was investigated. Primary endpoint was change in lumbar spine (LS) BMD from baseline. Study on 59 patients found that compared to baseline, increased levels of serum C-telopeptide of type I collagen was observed after Denosumab discontinuation. Increased level of CTX-1 is associated with increased bone turnover. There was no significant difference in bone erosion score between on-treatment period and after Denosumab discontinuation that tells that considering patient's disease activity, denosumab discontinuation could be explored. On the other hand post discontinuation, numerical increase in bone erosion was observed [103]. Safety and efficacy of long-term Denosumab (60 mg dose) was evaluated in a 12 months, randomized, double-blind, placebo-controlled, multicenter phase 3 trial. After Denosumab initiation, BMD consistently increased in all groups irrespective of concomitant glucocorticoid administration. Post-Denosumab treatment, serum C-telopeptide of type 1 collagen was also found to be decreased. Study found that progression of joint destruction was inhibited after Denosumab treatment for up to 36 months. Regarding potential risk of infection there is no clear consensus on Denosumab in patients who are also receiving bDMARDs. In one of the studies, rate of infection in postmenopausal women who were receiving Denosumab and bDMARDs was compared. Similar rate of infections were found in the two groups here (4.5% vs 5%). Osteomyelitis of first metatarsal bone was other adverse events seen in bDMARDs plus Denosumab group [104]. Figure 4 is a comprehensive pictorial representation of key pathways and their targets, either approved or being explored for RA treatment.

Several drug combinations are being evaluated for their efficacy and are in different phases of clinical trials. Some of the promising and published results from Phase III and IV studies are compiled and listed in Table 2.

Secukinumab is one such promising monoclonal antibody against IL-17A, which has been tested as a long-term therapy in non-responder RA patients in a phase II study. In this 60-week long study, 237 non-responders with DMARDs and biologicals, were treated with different monthly doses of Secukinumab and significant improvement was observed

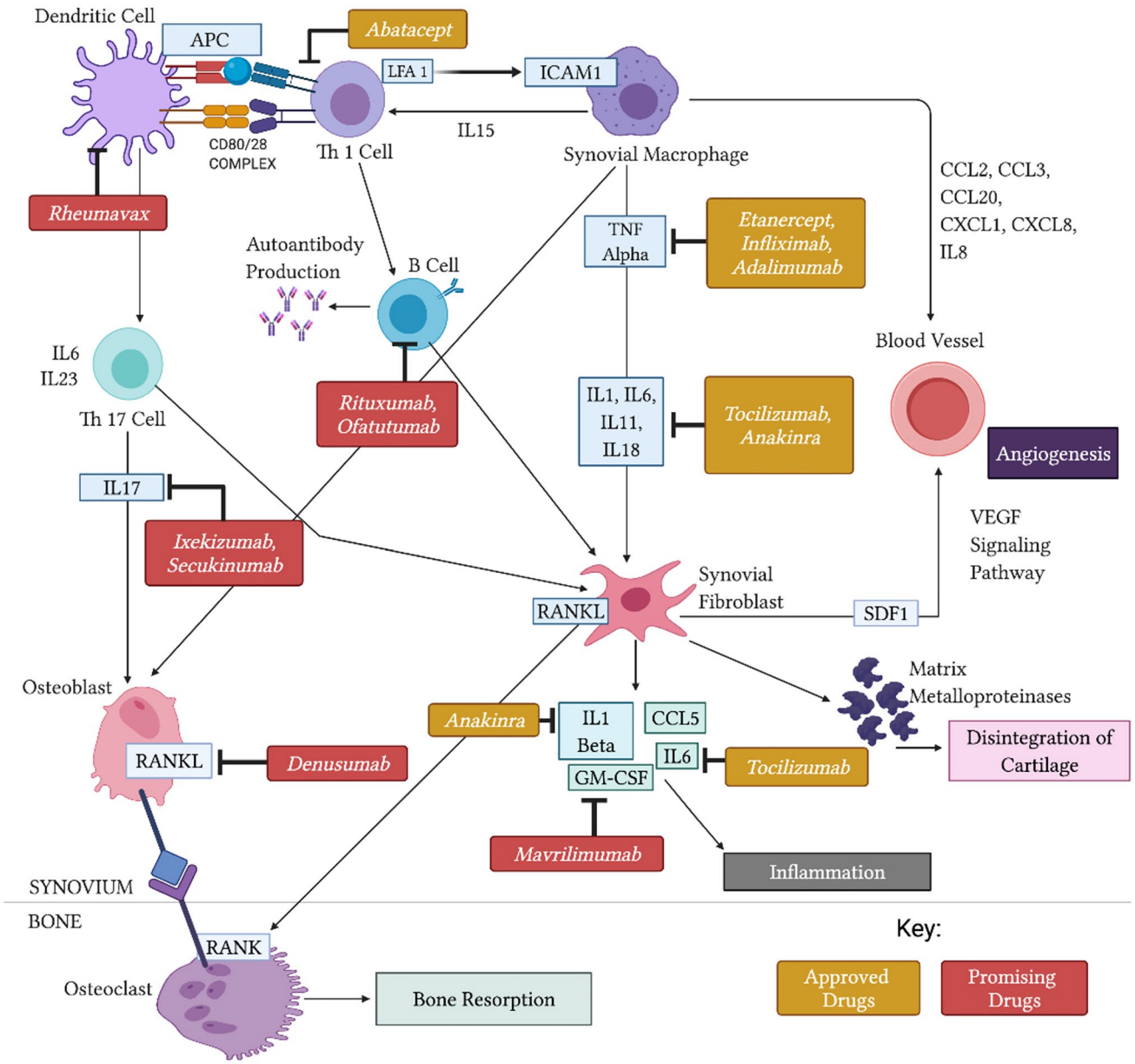

Fig. 4 Targeted therapy for rheumatoid arthritis (RA). T cells, B cells and macrophages play crucial roles in RA pathogenesis. This figure illustrates clinically approved and promising drugs for therapy and their respective targets. Abbreviations: *APC* Antigen Presenting Cell; *LFA1* Lymphocyte Function-Associated Antigen 1; *ICAM1* Intercellular Adhesion Molecule 1; *CCL* Chemokine Ligand; *CXCL* C-X-C Motif Chemokine Ligand; *IL* Interleukins; *TNF* Tumor Necrosis Factor; *VEGF* Vascular Endothelial Growth Factor; *SDF1* Stromal cell Derived Factor 1; *RANK* Receptor Activator of Nuclear Factor k B; *RANKL* Receptor Activator of Nuclear Factor k B Ligand

with 150 mg at 52 weeks. A recent meta-analysis on 1292 non-responders to TNF inhibitor, has also revealed better clinical efficacy with 150 mg Secukimumab at 16 weeks [113]. In bDMARD refractory patients, the proportion of FL receivers (66% for 200 mg and 57.5% for 100 mg) showed a significantly better clinical response (ACR20) as compared to placebo (33%) at week 12. Thus, FL holds great potential as therapy for all types of RA patients. Few TNF inhibitors (Certolizumab Pegol and Adalimumab) in combination with MTX have been evaluated in phase III and IV trials. It is evident that MTX along with ADA offers many benefits over mono therapy. Importantly, in both MTX naive and MTX-IR patients, greater efficacy (ACR50 response) was achieved despite reported MTX-related toxicity, which remained stable [111]. In addition, comparative trial between Certolizumab Pegol in combination with MTX and Adalimumab with MTX has completed phase IV trials. The study involves 915 patients receiving 200 ml Certolizumab injections,

Table 2 List of promising drugs undergoing clinical trials

Drug/Phase	Study AIM	Mechanism of action	Treatment regimen	Dose and duration	Results	References
Upadacitinib (Phase III randomized, controlled, double-blind study)	To compare UPD monotherapy vs MTX monotherapy in MTX-IR RA patients	Oral JAK-1 selective Inhibitor	UPD once daily vs continued MTX for 14 weeks 648 participants	15 mg or 30 mg once daily For 14 weeks	Statistically significant clinical (ACR20) and functional outcome observed with UPD monotherapy	105]
Tofacitinib vs Adalimumab (Phase IV randomized, double-blind Study)	To compare TFC + MTX vs ADL + MTX or TFC monotherapy	Partial and reversible JAK inhibitor	TFC + MTX, ADL + MTX, or TFC alone in MTX-IR patients (1152 participants)	Tofacitinib 5 mg two times per day for TFC monotherapy Tofacitinib 5 mg two times per day with MTX + Adalimumab 40 mg every other week + MTX	Improvement seen in PROs in all treatment arms. Combination therapy resulted in better clinically meaningful improvements than monotherapy.	[106,]
Tabalumab + Placebo (Phase III randomized2-period study)	**Period 1**: 24-week blinded treatment **Period 2**: 48-week post-treatment follow-up	Anti-BAFF antibody	1004 participants	Tabalumab 120 mg every 4 weeks or 90 mg every 2 weeks versus placebo	20% improvement in both tender and swollen joints	[107]
SB5 (Adalimumab biosimilar) (Phase III randomized trial)	To compare the efficacy, tolerability, safety and pharmacokinetics of SB5 vs ADL	TNF inhibitor	544 participants	40 mg every other week SB5 For 52 weeks	After 24 weeks, there was 20% reduction in the disease symptoms. Not much difference was observed between the two arms.	[108,]
Certolizumab Pegol + Methotrexate (Phase III randomized, Double-blind, Placebo-controlled Study)	To evaluate the efficacy & safety of CZP + MTX for early active RA	TNF inhibitor	CZP injections (200 mg/ml) and methotrexate 10 mg per week (430 participants)	400 mg CZP at weeks 0, 2 and 4 followed by 200 mg CZP every 2 weeks + 10 mg MTX once in a week for 24 weeks	20% or greater improvement in the clinical symptoms up to week 24	[109]
Certolizumab pegol + Methotrexate & Adalimumab + Methotrexate (Parallel Phase IV group study)	To evaluate the efficacy of CZP + MTX compared to ADL + MTX	TNF inhibitors and MTX combination	CZP injections + oral MTX & ADL + MTX injections (915 participants)	CZP 400 mg at 0, 2, 4 weeks followed by 200 mg CZP every 2 weeks + 15–25 mg MTX per week for 102 weeks 40 mg ADA at 0,2,4 weeks followed by 200 mg ADA every 2 weeks + 15–25 mg MTX per week for 102 weeks	MTX + CZP showed similar efficacy to ADL + MTX Highlights the clinical benefit and safety of switching to a second TNF inhibitor after failure to primary inhibitor	[110]

Table 2 (continued)

Drug/Phase	Study AIM	Mechanism of action	Treatment regimen	Dose and duration	Results	References
ADL + MTX (Phase IV randomized, parallel-arm study)	To study the efficacy of ADL + MTX	TNF inhibitor	Open-label ADL (40 mg) injection & blinded low-dose MTX(7.5 mg) once weekly (309 participants)	ADA + 2.5, 5, 10 or 20 mg per week MTX for 26 weeks (Patient with early RA from CONCERTO) ADA + 7.5 or 20 mg per week MTX for 24 weeks (Patient with an inadequate response to MTX from MUSICA)	Good response to the given drugs, however, after week 4, development of MTX-related toxicity was observed	[111]
Methotrexate + Sulfasalazine + Leflunomide + Prednisone (Phase IV Combination therapy trial)	Patients stratified as high risk & low risk according to the presence of prognostic biomarkers	MTX/SFS inhibits purine biosynthesis, LFL inhibits lymphocyte expansion, PRD is a glucocorticoid that inhibits inflammation	Received MTX weekly, SFS daily & PRD weekly (varied doses used among the high & low risk group) (400 participants	COBRA Classic-15 mg MTX weekly, 2 g SSZ daily and oral GCs (weekly step-down scheme 60–40–25–20–15–10–7.5 mg of oral PRD) COBRA Slim- 15 mg MTX weekly, oral GCs (weekly step-down scheme 30–20–12.5–10–7.5–5 mg of oral PRD) COBRA Avant-Garde- 15 mg MTX weekly, 10 mg LEF daily and weekly step-down scheme 30–20–12.5–10–7.5–5 mg of oral PRD For 16 weeks	Combining DMARD with glucocorticoids were effective for patients with early RA for 2 years. COBRA (slim) regimen, MTX + glucocorticoids bridging provided the best balance between safety and efficacy	[112]

The table enlists promising drugs with published Phase 3 and Phase 4 results in RA patients

UPD Upadacitinib, *MTX* Methotrexate, *TFC* Tofacitinib, *ADL* Adalimumab, *CZP* Certolizumab Pegol, *SFS* Sulfasalazine, *LFL* Leflunomide, *PRD* Prednisone

MTX orally administrated and Adalimumab plus MTX injections. Significant difference between the drug efficacies has not been reported. Certolizumab pegol (CZP) was evaluated in Canadian adults with moderate to severe, active RA in a 2 year prospective, observational study. DAS-28 Scores (DAS28) < 2.6 at week 104 was taken as the primary objective. Improvements in Patients' assessment of Arthritis Pain (PtAAP), fatigue, Health Assessment Questionnaire-Disability Index (HAQ-DI), and the proportion of patients achieving minimal clinically important differences (MCID) in HAQ-DI was taken as secondary endpoints. Study found that in Canadian practice, CZP was an effective RA treatment and no new CZP-related safety signals were identified [114]**.** A phase IV trial of combination of JAK inhibitor, Tofacitinib with MTX has been done. DMARDs have also been combined with glucocorticoids such as Prednisone and have been shown to produce good results.

Although bDMARDs are shown to be effective for RA treatment, but some patients either show inadequate response or do not respond to this line of therapy after some time. In one of the studies, researchers had included 7540 RA patients in which they found 2527 showed response to bDMARDs whereas 5013 were non-responders. The study concluded that non-responders faced a higher economic burden in terms of increased healthcare resource use, direct medical costs etc. [115]. Therefore, it is important to identify early biomarkers which can predict response to bDMARDs therapy. In one study, gene expression classifier was identified to predict response to anti-TNF Infliximab therapy, by training classifier based on published blood gene expression data sets. RA patients were treated with Infliximab and therapy response was assessed after 14–16 months post treatment. Study identified 18 signaling mechanisms associated with higher TNF-mediated inflammatory signals. Mostly these 18 markers in the classifier were found to regulate pathways associated with wounding, which is an inflammation affecting small blood vessels in the skin (FOXA2, ERBB2, IL1, MAP2K3, MST1R, NOS2, NR2F6, PPARG, S100A8) and development of nervous system (FOXA2, MEIS1, NF1, PPARG, norepinephrine, gamma secretase complex) [116]. Another study reported using machine-learning algorithm that rate of remission with TNF alpha inhibitor was 5 times more in T allele carriers of a TLR-9 gene polymorphism (rs352139) (https://pubmed.ncbi.nlm.nih.gov/34635730/). Response to Abatacept (ABA) was studied in a different study to identify responders and non-responders. Here, differential expression of 610 genes (218 genes up-regulated and 392 genes down-regulated) was observed in responders. Gene ontology analysis of 218 genes identified response Interferon type I (Type I IFN) score as a marker for ABA responsiveness in RA patients. It was observed that type I IFN score decreases in ABA treated responders vs non-responders to ABA. Further, higher expression levels of nine genes (BATF2, LAMP3, CD82, CLEC4A, IDO1, STAT1, STAT2 and TNFSF10) was observed in ABA responders [117]. Similarly, type I IFN network genes (LY6E, HERC5, IFI44L, ISG15, MxA, MxB, EPSTI1 and RSAD2) can also be used to discriminate responders and non-responders in Rituximab-treated RA patients. Lower expression levels of these genes were found to be associated with responders [117]. In another study, thirty-two patients who were treated with Anakinara (100 mg/day) (IL-1 receptor antagonist), in combination with MTX were studied to identify responsiveness to treatment. Gene expression profiling of PBMCs isolated from treated patients identified 52 transcripts that can be used to discriminate responders and non-responders to combination therapy of Anakinara and MTX. Study identified 34 genes out of which 56% were found to have role in IL-1β-dependent pathway. Further analysis found that these genes are regulated by transcription factors, not very specific to IL-1-β pathways. Some of the identified transcription factors and their targets are: JUN (BST2), CEBPβ (RUNX1T1, ELF2), HIF1A (EP300), ESR1 (EMP2), CTNNB1 (CDH5, EIFS12), TP52 (CDK8) and STAT3 (LEPR). IL-1β pathway associated genes like co-stimulator ligand F (ICOSLG) and Transthyretin (TTR) were also identified in this study. In one of the studies, Anti-Drug Antibody (ADA) against GLM was explored in RA patients to assess the clinical response. ADA is found to be associated with low drug levels and low response rates. Lower GLM levels were found in non-responder RA patients as compared to responders after 28 weeks of treatment [119]. Some of the common side effects of using bDMARDs are infection of bacteria, fungus or viruses [120]. In few cases, tuberculosis reactivation is also observed [121]. Further, suppression of bone marrow and liver toxicity has been found to be associated with bDMARDs. In certain cases, congestive heart failure and demyelination of nervous system was reported with anti-TNF agents. Side effects associated with IL-6 inhibitors are hyperlipidemia and pancytopenia. Inflammatory bowel disease can be worsened by IL-17 inhibitors. Multifocal leukoencephalopathy has been observed in Rituximab-treated patients [122].

Novel therapeutic approaches

Epigenetic modifications such as DNA methylation and histone modifications are also found associated with RA pathogenesis [123]. Distinct epigenetic clinical markers are currently being explored for early diagnosis and targeted therapy. Presently, inhibitors of DNA Methyltransferase (DNMT) and Histone Deacetylase Inhibitors (HDAC) are available as therapeutic drugs. Preclinical studies have concluded that HDAC inhibitors are involved in reducing inflammation, edema, synovial angiogenesis and joint damage [124,125]. A HDAC inhibitor, Trichostatin A, has been

shown to interfere with production of inflammatory mediators in synoviocytes [126]. Also, MI192 is shown to exhibit an inhibitory effect on expression of TNF and IL-6 [127]. Other HDAC inhibitors (Vorinostat, Entinostat) were found to repress NF-kB pathway in synovial fibroblasts thereby downregulating inflammatory cytokines. A case–control study evaluated effect of a DNMT inhibitor, delineating its effect on hypomethylation of a gene (SFRP4) involved in RA pathogenesis [128]. However, epigenetic therapy is still in its nascent stage for RA and clinical trials are required for its validation.

In addition, inhibiting PAD4 activity, which is critical for generation of citrullinated proteins responsible for disease pathogenesis, could also be an effective therapeutic strategy. Though several reversible (streptonigrin, GSK199, GSK484) and irreversible inhibitors (Cl-amidine, F-amidine, YW-356, TDFA, and TCDA) have emerged, their clinical efficacy is yet to be proven in clinical trials. Synthesising novel PAD4 inhibitors which may synergistically and effectively target hypercitrullination and NET (Neutrophil Extracellular Traps) formation might be a good approach in future.

Gene therapy, specific DNA or RNA, is administered using viral vectors to modify expression of the gene of interest. In development and progression of RA, overproduction of inflammatory cytokines by FLS cells play a very important role. Therefore, inhibiting pro-inflammatory cytokines or overexpression of anti-inflammatory cytokines are strategies for RA therapy [3]. In Collagen-Induced Arthritis (CIA) animal models, gene therapy with IL-4 and IL-10 showed protection of joint and reversed degradation of cartilage but clinical trials have not shown much efficacy. In a novel approach, fusion protein of IL-4 and IL-10 (IL4-IL10 FP) was employed for RA therapy. In this synergetic approach, glycosylated IL-4-IL-10 FP showed decreased severity of proteoglycan-induced arthritis (PGIA) in mice [129]. In animal models, administration of the immunosuppressive cytokine IL-35 significantly exacerbated RA progression which could be due to indirect effect of IL-35 on the Th17 [130].

miRNAs also play a key role in the regulation of inflammatory responses and could be effective therapeutic targets in the future. In cells and tissues of RA patients, upregulation of miR-155 and miR-146a was found. Increased expression of miR-155 in RA patients is found to be associated with repression of MMPs. In RA patients, upregulation of miR-146a causes persistent production of TNF-alpha [131]. Inhibition of proliferation, migration and invasion of RA-FLS cells was observed after downregulating miR-135a [132]. In another study, miRNA-21 inhibition in RA-FLSs led to decreased proliferation of RA-FLSs. On the other hand, overexpression of miRNA-21 increased the rate of proliferation of normal FLSs [133]. Expression of MMP-3/13 and IL-1β was found to be inhibited by miR-124a [134]. In FLS cells from RA patients, miR-27a expression was found to be significantly decreased in serum, synovial tissues, and FLS compared to healthy controls. miR-27a targets pro-inflammatory mediators such as Follistatin-Like protein 1 (FSTL1). miR-27a overexpression downregulates expression of MMPs and Rho family proteins [135]. In RA-FLSs, gastric adenocarcinoma predictive long intergenic noncoding RNA is found to be overexpressed. Proliferation and migration of FLSs is found to be negatively regulated by Lowly expressed in rheumatoid fibroblast-like synoviocytes (LEFRS) lncRNA. Overexpression of zinc finger NFX1-type 1 containing 1 antisense RNA 1 (ZFSA1) is also found in RA-FLS. LEFRS positively regulates the invasion and migration of FLSs [136]. In PBMCs of RA patients, Nuclear Enriched Abundant Transcript 1 (NEAT1) is found to be overexpressed. This lncRNA is involved in restrained immune cell differentiation and helps in decreasing inflammation in CIA mice [137].

Mesenchymal stem cell (MSC) therapy could be another therapeutic option for RA treatment because it can exert immunosuppressive functions in both adaptive and innate immune cells. There are 14 MSC-based therapies listed in clinical trials for RA. Reduced erythrocyte sedimentation rate, improvement on DAS28 clinical score and diminished on the serum anti-cyclic citrullinated peptide (anti-CCP) antibody level was found upon intravenous infusion of allogenic bone marrow and umbilical cord-derived MSC in a small group of refractory RA patients. These patients were resistant to the anti-TNF monoclonal antibody therapy [138]. In a study, safety and effectiveness of allogenic UC-MSCs were demonstrated in large number of RA patients. In 172 active RA patients, MSCs and DMARDs were co-administered intravenously which resulted in significant increase in the percentage of regulatory CD4+T cells in the blood. For up to 6 months, significant clinical improvement was also seen [139]. However further clinical studies with conclusive results are required to demonstrate their safety and efficacy.

Summary and conclusion

Management of Rheumatoid Arthritis depends on early diagnosis and identifying various factors to minimise disease progression. The challenge still lies in the early identification of the disease before it has progressed to the clinical stage of joint damage. Efforts are ongoing to develop novel biomarkers for this. Therapeutic approaches, using conventional DMARDs comprising of MTX, Leflunamide, Sulfasalzine and Hydroxycholoroquine, have proven to be very effective. However, there is still a non-responder or insufficient responder population. To overcome this, a combination therapy approach is employed using either two DMARDs as the primary line of action or using a cDMARD and targeted

DMARD/bDMARD combination in insufficient responders. Various such novel combinations, are undergoing clinical trials, and hold great promise . More efforts are required to find key biomarkers to stratify patients based on disease severity and responder/non-responder population. Since various adverse events are associated with cDMARDs and bDMARDs both, exploring gene therapy approaches and mesenchymal stem cell-based therapy would be beneficial for RA patients in future. Further, various nanoparticle based formulations of Methotrexate being developed would also help navigate the adverse effects because of targeted release of the drug.

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