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Review

Novel Targets for Refractory Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis (RA) is the most common form of chronic inflammatory arthritis that affects about 18 million people worldwide. Genetic and environmental risk factors initiate the onset of RA, while gene-environment interactions involving epigenetic mechanisms (such as aberrant DNA methylations and dysregulated histone modifications) trigger the upregulation of pro-inflammatory genes or the downregulation of anti-inflammatory counterparts. Given the presence of autoantibodies against rheumatoid factor and citrullinated proteins, it is considered an autoimmune disease involving accumulation and activation of several leukocyte subpopulations including T-cells releasing T-cell derived cytokines, B-cells with subsequent autoantibody responses and macrophage-like and fibroblast-like cells which produce large amounts of pro-inflammatory cytokines.

Disease management follows a stepwise approach using disease-modifying antirheumatic drugs to achieve sustained remission or at least low disease activity. Nevertheless, a significant proportion of patients show a refractory disease necessitating further research. Novel biologics are in development mainly targeting pathogenic B- and T-cell responses, inflammatory cytokines and co-stimulatory pathways or protein citrullination. Novel small molecules acting on certain melanocortin receptors may rebalance the immune system. Innovative cell therapies are emerging, including products based on T-cells with chimeric antigen receptors (CARs) that target B-cell proteins and have already demonstrated drug-free remission in individual case studies.

Keywords: Refractory Rheumatoid Arthritis, Biologics, JAK inhibitors, Novel drugs, CAR-T-cells

1. Introduction

1.1. Epidemiology

Rheumatoid Arthritis (RA) is the most common form of chronic inflammatory arthritis, affecting 0.24 to 2 % of the population depending on the geographic region, socioeconomic and environmental factors[1]. In 2020, an estimated 17.6 million people suffered from RA worldwide. The age-standardized global prevalence rate was 208.8 cases per 100,000 people, representing a 14.1% increase since 1990. About 31.7 million individuals will be living with RA worldwide by 2050. RA affects women two to three times more than men with onset occurring between 60 and 70 years of age[2]. The main characteristics of RA include a chronic destructive inflammatory synovitis, accompanied by co-morbidities particularly affecting systemic bone, vasculature, metabolic function and cognition[3]. Initially, RA primarily impacts the small joints. Over time, cumulative joint damage and other systemic comorbidities can lead to substantial physical disability and mortality. Patients with RA typically present with pain and stiffness in multiple joints, most commonly the wrists,

proximal interphalangeal joints and metacarpophalangeal joints. Patients will usually experience stiffness of the joints in the morning, lasting up to an hour or more. Synovitis may lead to visible boggy swelling of the joints or synovial thickening may be more subtle, with thickening palpable on joint examination. If left untreated, synovitis leads to the destruction of cartilage and bone - known as erosions - and to irreversible loss of function in the affected joints. Systemic symptoms include fatigue, weight loss and low-grade fever. Signs and symptoms of RA may flare, alternating with periods of remission. Serious extra-articular manifestations can include involvement of the heart, lungs, skin, eyes, kidneys and nervous system[4].

1.2. Pathogenesis

The onset, severity and progression of RA are largely determined by genetic factors. The most important genetic risk factor is located within the class II major histocompatibility (MHC) locus. In 1978, the B-cell alloantigen HLA-DRw4 was found in 70% of RA patients, as compared to 28 % of normal controls indicating that RA is associated with genes of the HLA-D region[5]. Thereafter, the dominant influence of the HLA system (particularly HLA-DRB1) has been confirmed strongly implicating arthritogenic peptide (and self-peptide) presentation and binding in RA pathogenesis. Multiple RA risk alleles within HLA-DRB1 have been identified and all RA-associated HLA-DR alleles encode the amino acid motifs QKRAA, QRRAA or RRRAA, known as 'shared epitopes' (e.g., DR1 and DR4 sharing epitope QKRAA). The 'shared epitope' hypothesis was born as the molecular genetics of susceptibility to RA, though the exact mechanism remains unknown[6,7]. Some HLA genotypes particularly associate with more aggressive erosive disease and with higher mortality, pointing to a crucial role of peptide binding[8,9]. In genetically predisposed individuals with RA risk alleles, environmental insults such as cigarette smoking, infections associated with periodontal disease as well as epigenetic and post-translational modifications of neutrophil proteases and fibroblast-like synoviocytes can lead to loss of tolerance with subsequent chronic articular and extra-articular manifestations[10-12].

Thus, genetic and environmental risk factors initiate the onset of RA, while gene-environment interactions involving epigenetic mechanisms (such as aberrant DNA methylations and dysregulated histone modifications) trigger the upregulation of pro-inflammatory genes or the downregulation of anti-inflammatory counterparts. Within the joint lesions, intercellular crosstalk prompts activated immune cells, fibroblast-like synoviocytes and bone-related cells to secrete pro-inflammatory cytokines and osteoclastogenic factors, exacerbating the inflammatory microenvironment. Involved inflammatory pathways include the JAK/STAT, PI3K/AKT, MAPK, NF-κB and Wnt/ß-catenin pathways which promote the transcription of inflammation-related genes, thereby exacerbating disease progression and resulting in synovitis, cartilage degradation and bone erosion[13].

Given the presence of autoantibodies against rheumatoid factor (RF) and citrullinated proteins (ACPA), RA is considered an autoimmune disease involving accumulation and activation of several leukocyte subpopulations including T-cells releasing T-cell derived cytokines; B-cells with subsequent autoantibody responses and macrophage-like and fibroblast-like cells which produce large amounts of pro-inflammatory cytokines[9,13-15]. RA disease activity is driven mainly by overproduction of tumor necrosis factor-alpha (TNF-α) by T and B-cells, synovial-like fibroblasts and macrophages[16]. Elevated levels of TNF-α trigger further secretion of deleterious cytokines, including IL-6, leading to a persistent inflammation, resulting in joint destruction[17]. Autoantibodies and multiple cytokines may occur in circulation years before RA symptoms occur, triggering aberrant immune responses resulting in joint synovial inflammation and destruction of bone, cartilage and tendons.

1.3. Biomarker Landscape in RA

Traditional RA biomarkers including RF and ACPA are still required for serological confirmation of RA diagnosis[18]. Some data suggest that patients with high ACPA titers respond particularly well to abatacept[19]. CRP and ESR remain integral to composite disease activity measures (DAS28, SDAI, CDAI) but reflect systemic inflammation rather than joint-specific pathology[20,21]. Nowadays, the biomarker landscape in RA is moving toward integrated, multimodal strategies enabling precision medicine approaches[22]: Among novel serological markers, 14-3-3η protein and anti-carbamylated protein (anti-CarP) antibodies show strong validation for seronegative disease and prognostic stratification. Calprotectin can be used for disease activity monitoring and de-escalation decisions. Emerging multi-biomarker disease activity scores provide an objective assessment but lack outcome trial validation. Musculoskeletal ultrasound offers easy access imaging biomarker capability, while MRI bone marrow edema remains the strongest structural progression predictor.

1.4. Management of RA

As RA is a heterogeneous disease, treatment decisions are patient-driven, considering individual factors like disease activity and progression of structural damage. The principal goal of RA management is to achieve sustained remission or at least low disease activity using disease modifying antirheumatic drugs (DMARDs). The recommended treatment options for RA include conventional synthetic (csDMARDs; e.g., methotrexate), biological DMARDs (bDMARDs; e.g., rituximab, TNF-α inhibitors [TNFi]) and targeted synthetic DMARDs (tsDMARDs; such as Janus kinase inhibitors [JAKi]). Additionally, glucocorticoids and nonsteroidal anti-inflammatory drugs are used as short-term symptomatic treatment options until the disease is controlled with DMARDs.

The recent update of the European Alliance of Associations for Rheumatology (EULAR) still recommends adhering to a stepwise approach for the management of RA[23]: MTX combined with short-term glucocorticoids are still recommended as first-line treatment for RA. When patients do not show sufficient response to first-line therapy within 3 to 6 months, the association recommends adding a bDMARD. After considering risks of major adverse cardiac events (MACEs), malignancies and/or thromboembolic events, targeted synthetic (ts) DMARDs such as JAKi may also be considered. If the first bDMARD (or tsDMARD) fails, any other bDMARD (from another or the same class) or tsDMARD (considering risks) is recommended. With sustained remission, DMARDs may be tapered but should not be stopped.

1.5. Refractory RA

Despite treatment according to the current management recommendations, a significant proportion of RA patients remain symptomatic. These patients are refractory to different types of DMARDs and are considered to have a difficult-to-treat (D2T) RA. To establish a uniform terminology to be used in the clinics and in clinical trials, the EULAR Task Force defined the following criteria as mandatory elements of the definition of D2T RA[24]: (1) Treatment according to EULAR recommendation and failure of ≥2 biological DMARDs/targeted synthetic DMARDs (with different mechanisms of action) after failing conventional synthetic DMARD therapy (unless contraindicated); (2) presence of at least one of the following: at least moderate disease activity; signs and/or symptoms suggestive of active disease; inability to taper glucocorticoid treatment; rapid radiographic progression; RA symptoms that are causing a reduction in quality of life; and (3) the management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient.

Several real-world studies have shown prevalence of D2T RA ranging from 5.9% to 27.5%[25]. Real-world data is also useful to identify differences in treatment effectiveness among different types of DMARDs and also within a specific class of DMARD and may guide clinical practice in the treatment of D2T RA. In this regard, there is growing evidence for the benefits of switching to a new mechanism of action after inadequate response or intolerance to a first TNF inhibitor. The recent phase 3b/4 head-to-head SELECT-SWITCH study (NCT05814627) evaluated the efficacy and safety of upadacitinib (RINVOQ®) 15 mg, once daily, compared to adalimumab (HUMIRA®) 40 mg, every other week, in adult patients with moderate-to-severe RA on a stable background of methotrexate (MTX) who had an inadequate response or intolerance to a TNF inhibitor other than adalimumab. A significantly higher proportion of patients who received the JAK inhibitor upadacitinib achieved low disease activity (DAS28-CRP≤3.2; primary endpoint) and remission (DAS28-CRP<2.6; ranked secondary endpoint) compared to adalimumab at week 12. The safety profile for upadacitinib was consistent with previously reported studies, with no new safety risks identified in the 12-week treatment period[26]. Real-world data also suggests differences in treatment effectiveness among different JAK inhibitors. A recent study analyzed data extracted from the Adelphi RA Disease Specific Programme™, a cross-sectional survey administered to rheumatologists and their patients in the EU, UK, Japan, Canada and the US from July 2021 to February 2022. Patients receiving upadacitinib 15 mg or other JAK inhibitors, including tofacitinib, baricitinib or peficitinib, for ≥ 6 months were included in the study. Patients taking upadacitinib had higher rates of reporting disease remission (54.3% vs. 44.1%), no pain (43.4% vs. 32.8%) and complete adherence to taking their medication (59.5% vs. 49.0%) compared with patients taking other JAK inhibitors[27].

Last but not least, there is emerging evidence that RA is often associated with metabolic dysfunction. RA patients are at 23% risk of diabetes mellitus incidence[28], particularly among those receiving glucocorticoids, while patients on hydroxychloroquine and biological DMARDs may be at lower risk[29]. A recent retrospective cohort study analyzed real-world data derived from the platform TriNetX in adult RA patients, who had at least 12 months of follow-up after DMARD initiation and who received DMARDs only, DMARDs and an SGLT2 inhibitor (SGLT2i) or DMARDs and a GLP-1 receptor agonist (GLP1RA). Post-initiation flare declined significantly in the SGLT2i group (34.1% to 12.0%, p = 0.0407) and non-significantly in the GLP1RA group (41.0% to 20.7%, p = 0.1525). The interpretation of these results is limited due to lack of standardized disease activity measures (e.g., DAS28), potential confounding factors and the inability to include DMARD escalation in pre-treatment and post-treatment analysis. Nevertheless, these findings support the need for further prospective studies to validate the anti-inflammatory potential of SGLT2 inhibitors in RA and further explore the effect of GLP-1 receptor agonists on RA flare[30].

2. Novel Targets for Refractory RA - Drug Pipeline

2.1. Biologics

2.1.1. Attenuators of B- and T-cell responses: RA is considered an autoimmune disease involving accumulation and activation of T-cells releasing T-cell derived cytokines; B-cells with subsequent autoantibody responses and macrophage-like and fibroblast-like cells which produce large amounts of pro-inflammatory cytokines[13]. In 2004, the therapeutic concept of B-cell depletion in RA was proven as effective using the anti-CD20 targeted antibody rituximab[31]. Shortly thereafter, the immune synapse between B-cells and T-cells was identified as a potential anchor for novel RA treatments leading to the concept of co-stimulation blockers. Abatacept (a fusion protein of cytotoxic T-lymphocyte–associated antigen 4 and IgG1) that inhibits T cell activation through interfering with the immune synapse between antigen-presenting cells, B cells and T cells has been proven as successful RA treatment[32]. Abatacept was approved by EMA (2007) as Orencia® and its use is recommended in combination with MTX for patients with difficult-to-treat RA[33]. In addition, tremendous progress has been made in the field of T-cell-engaging therapies in oncology. The first-in-class bispecific T-cell engager (BiTE) was blinatumomab, which has been approved as BLINCYTO® by the US-FDA (2024) for the treatment of patients with relapsed and/or refractory B-cell-precursor acute lymphoblastic leukemia[34]. Based on the action of BiTEs to kill B-cells by engaging T-cells as effectors, it was hypothesized that this principle may work also in the treatment of B-cell-mediated autoimmune diseases, including RA. Thus, the current RA drug pipeline includes several biologics specifically targeting B-cell responses including the BiTE antibody blinatumomab, the fusion protein telitacicept and the monoclonal antibody ianalumab, which are already in advanced stage of clinical development **(Figure 1)**. Furthermore, agonistic antibodies that mimic programmed cell death-ligand 1 (PD-L1) function to down-regulate T-cell activity are increasingly recognized as potential RA therapeutics. The anti-PD-1 (programmed cell death-1) agonist antibody rosnilimab mimics PD-L1 (programmed death-ligand 1) function to reduce T-cell activity and selectively depletes pathogenic PD-1 positive T-cells in inflamed tissue and peripheral circulation via effector function. Rosnilimab significantly reduced disease activity in RA patients previously treated with b/tsDMARDs in a phase 2b trial[35,36]. In the following, attenuators of B- and T-cell responses in late phase development for RA will be discussed in more detail.

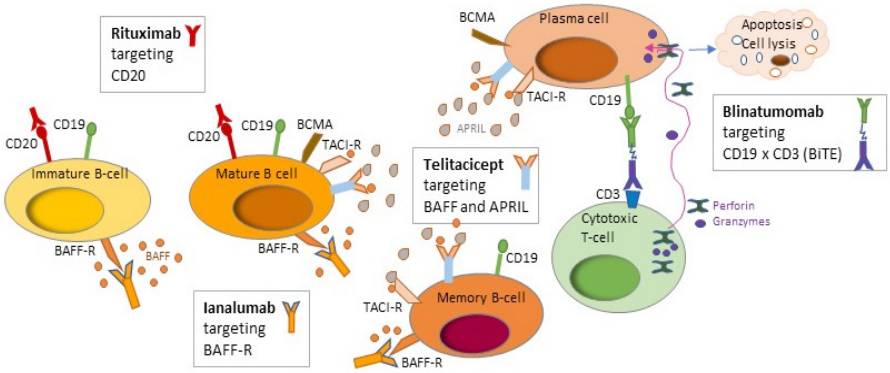

Figure 1: B-Cell Depleter - Mechanism of Action in Rheumatoid Arthritis.

Abbreviations: APRIL = a proliferation inducing ligand, BAFF = B-cell activating factor, BAFF-R = B-cell activating factor receptor, BCMA = B-cell maturation antigen, BiTE = bispecific T-cell engager, TACI-R = transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Note: BAFF is also known as BLyS = B-cell lymphocyte stimulator

Telitacicept (RC18) from Vor Bio (previously from RemeGen) is a first-in-class fusion protein in development for the treatment of autoimmune diseases. It is constructed with the extracellular domain of the human TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) receptor and the fragment crystallizable (Fc) domain of human immunoglobulin G (IgG). The TACI receptor mediates signaling through two cell-signaling molecules critical for B-cell development, namely BLyS (B-cell lymphocyte stimulator) - also known as BAFF (B-cell activation factor) - and APRIL (a proliferation inducing ligand). This way, telitacicept effectively reduces B-cell mediated autoimmune responses implicated in RA. Telitacicept was already granted conditional marketing approval by China's National Medical Products Administration (NMPA) to treat Systemic Lupus Erythematosus (SLE) in March 2021[37].

A phase 3 trial (NCT03016013) evaluated the efficacy and safety of telitacicept in moderate-to-severe RA patients with inadequate response to methotrexate. The randomized, double-blind and placebo-controlled 24-week treatment period was followed by an open-label follow-up period from week 25 to week 48. The study demonstrated that telitacicept 160 mg was effective and well-tolerated in this study population. Significant improvements in ACR20 response rate starting from Week 4 were shown, with high ACR20 response rates of 67.4% at Week 24 and 72.2% at Week 48. Joint structural damage was significantly delayed; 92.8% of participants had no radiographic progression at Week 24 and 89.9% at Week 48. In addition, telitacicept significantly improved the inflammatory level and physical function of participants and relieved pain; the proportion of participants reaching low-disease activity (DAS28-ESR $\leq$ 3.2) continued to increase until Week 48. Based on these study results, China's NMPA has accepted the New Drug Application for telitacicept as a new indication for the treatment of RA[38]. Meanwhile, telitacicept is approved in China also for the treatment of Sjögren's Disease (SjD) and generalized myasthenia gravis (gMG)[39].

Blinatumomab from Amgen is a bispecific T-cell engager (BiTE®) for targeted B-cell depletion. It is a bispecific CD19-directed CD3 T-cell engager that transiently links CD19-positive B-cells to CD3-positive T-cells (Figure 1). It was the first globally approved BiTE® immuno-oncology therapy engaging T-cells to CD19 positive cancer cells of B lineage origin resulting in T-cell (perforin) induced apoptotic cancer cell death[34]. A phase 2 open-label basket trial (NCT06570798) is currently evaluating the safety, tolerability and efficacy of blinatumomab in subjects with autoimmune diseases including active refractory RA. The primary endpoint in the RA part is the percentage of participants achieving remission (based on DAS28-CRP) at week 12.

Ianalumab (VAY-736) from Novartis is a fully human, afucosylated IgG1 mab with a dual mechanism of action. It is able to deplete B-cells while simultaneously inhibiting their activation and survival through blockade of the B-cell activating factor receptor (BAFF-R) on remaining B-cells. Binding of ianalumab to human FcγRIIIA is enhanced through afucosylation resulting in more efficient elimination of ianalumab-coated B-cells via antibody-dependent, cellular cytotoxicity (ADCC) and phagocytosis (ADCP). Ianalumab specifically targets B-cells, leading to sustained depletion of naive, transitional and memory B-cells in the blood and lymphoid organs. In an ADCC assay co-culturing purified natural killer (NK) cells with B-cells from healthy volunteers, ianalumab showed a 44-fold increased potency compared to rituximab. This increased potency was also observed when NK cells from patients with SjD and SLE were tested[40].

Ianalumab is currently investigated in a phase 2 trial (NCT06293365) to compare the pharmacokinetics of different injection devices for subcutaneous administration. The study is designed to demonstrate the comparability of ianalumab exposure following SC administration of one injection of 300 mg ianalumab/2 mL with an auto-injector versus two injections of 150 mg/1 mL with a pre-filled syringe (PFS). The study will also evaluate the safety and tolerability of ianalumab following the SC administration of both devices in participants with RA, SjD or SLE. In a second cohort, the comparability of pharmacokinetics of ianalumab between 1 x 2 mL PFS and 2 x 1 mL PFS will be tested. In January 2026, the US-FDA granted Breakthrough Therapy designation to ianalumab for the treatment of SjD. The designation builds on the Fast-Track status ianalumab received in 2016 and is supported by positive results from multiple clinical studies, including replicate phase 3 trials in this indication.

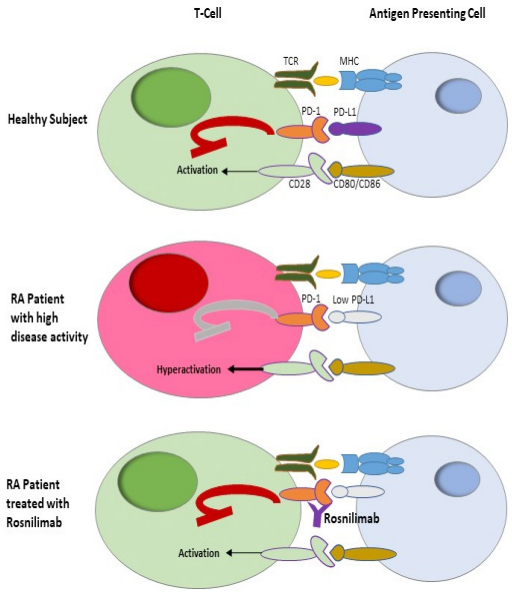

Figure 2: Rosnilimab - Mechanism of Action in Rheumatoid Arthritis.
Abbreviations: MHC = major histocompatibility complex, PD-1 = programmed cell death-1, PD-L1 = programmed death-ligand 1

Rosnilimab from AnaptysBio is a novel monoclonal antibody that directly targets programmed cell death- 1 (PD-1), a co-inhibitory receptor preferentially expressed on the surface of activated T-cells. Rosnilimab targets the PD-1 proximal binding region to induce agonism. It binds an epitope distinct from the programmed death-ligand 1 (PD-L1)-binding site thereby enhancing PD-L1 agonism[41]. Rosnilimab selectively depletes pathogenic T-cells (i.e., PD-1high T peripheral helper [Tph]/T follicular helper [Tfh] and T effector [Teff] cells) and agonizes the remaining PD-1+ T-cells to restore the immune system back to a state of homeostasis **(Figure 2)**. This is anticipated to result in specific immunological outcomes in both inflamed tissue and the periphery, such as reduction in T-cell proliferation, migration and cytokine secretion and reduction of plasma cell generation and autoantibody levels.

At the ACR Convergence Meeting 2025, positive data were reported from a phase 2b trial (NCT06041269) in which 424 adults with moderate to severe (≥6 tender and ≥6 swollen joints) seropositive RA on concurrent csDMARDs and less than 3 previous b/tsDMARDs were randomized 1:1:1:1 to receive SC rosnilimab 100mg Q4W, 400mg Q4W, 600mg Q2W or placebo[35,36]: The primary endpoint, mean change from baseline in DAS28-CRP at week 12, was met by all rosnilimab doses (-2.06, -2.12, -2.06 in 100mg, 400mg and 600mg arms) versus placebo (-1.69) ($p < 0.01$). At week 12, all rosnilimab dose arms had significantly greater changes in ACR20 and mean change in CRP versus placebo. ACR50, ACR70, CDAI≤10 (LDA) and patient reported outcomes (PROs) consistently demonstrated higher responses over placebo. 220 (69%) rosnilimab-treated participants reached CDAI≤10 LDA at week 14 and were eligible to continue into the All-Active cohort, in which response rates substantially increased from week 12 to week 28 for secondary endpoints (ACR50,70, LDA) and PROs (HAQ, pain VAS). After week 26, during the 12-14 week off-drug follow-up period, responses were generally maintained. In addition, the data show that for both b/tsDMARD-experienced and -naïve participants, rosnilimab demonstrated efficacy, safety and tolerability for seropositive RA. Translational data showed rapid depletion (>90%) of pathogenic T-cells of interest in blood with preservation of the total T-cell numbers through the 28 weeks treatment period, consistent with the durability of clinical outcomes. In general, rosnilimab treatment was well tolerated. No death or malignancy was reported. No serious or severe infections leading to treatment withdrawal were reported in rosnilimab-treated participants. Novel drugs which attenuate B- and T-cell responses and which may potentially be effective in refractory RA are summarized in **(Table 1)**.

Table 1: Current RA Drug Pipeline – Attenuators of B- and T-cell responses.

Product (Sponsor)	Target, Route of Administration	Development Phase
Telitacicept (Vor Bio)	Fusion protein of extracellular domain of TACI receptor and Fc domain of IgG targeting B-cell activation and BlyS and APRIL, SC injection	Phase 3: NCT03016013 Completed: DEC-2022 Positive results published[38].
Rosnilimab (AnaptysBio)	PD-1 agonist mab depleting pathogenic T-cells (PD-1high Tph/Tfh, Teff) with preservation of the total T-cell numbers, SC injection	Phase 2b: NCT06041269 Completed: May-2025 Positive results published[35].
Ianalumab (Novartis)	Afucosylated anti-BAFF-R mab (B-cell depletion through ADCC and blockade of BAFFR survival signaling), SC injection	Phase 2: NCT06293365 Active, not recruiting, SCE: APR-2029
Blinatumomab (Amgen)	CD19 x CD3 BiTE for targeted B-cell depletion, SC injection	Phase 2: NCT06570798 Recruiting, SCE: Aug-2028
A-319 (Huazhong University of Science and Technology)	CD19 x CD3 BiTE for targeted B-cell depletion, SC injection	Phase 1: NCT07347860 Recruiting, SCE: Aug-2027
CC312 (CytoCares)	CD19×CD3×CD28 tri-specific T-cell engager (TriTE™) for direct T-cell mediated B-cells depletion, intravenous administration	Phase 1: NCT06888960 Recruiting, SCE: NOV-2026
JADE201 (Jade Biosciences)	Afucosylated anti-BAFFR mab (deep B-cell depletion through ADCC and blockade of BAFFR survival signaling), SC injection	Phase 1: NCT07533955 Recruiting, SCE: Oct-2028
Abbreviations: ADCC = antibody-dependent-cellular cytotoxicity, APRIL = a proliferation inducing ligand, BAFF-R = BAFF receptor, BiTE = bispecific T-cell engager, BLyS = B-cell lymphocyte stimulator, BTLA = B- and T-lymphocyte attenuator, mab = monoclonal antibody, PD-1 = programmed cell death protein 1, SC = subcutaneous, SCE = study completion estimated, TACI = transmembrane activator and calcium modulator and cyclophilin ligand interactor, Tph = peripheral helper T-cells, Tfh = follicular helper T-cells, Teff = T effector cells		

Source: Based on data in public domain and on CLINICALTRIALS.GOV

2.1.2. Monoclonal antibodies targeting inflammatory cytokine signaling

CT-P13 (Zymfentra) from Celltrion is an anti-TNF antibody (biosimilar of infliximab) for which a phase 3 trial (NCT06738719) has been completed in April 2026. In the monocentric phase 3 trial, about 192 patients with moderate to severe RA and active disease on stable doses of MTX (10 to 25mg/week) received subcutaneous doses of CT-P13 for up to 12 weeks. The primary endpoint was the proportion of patients achieving clinical response according to the ACR20 criteria at week 12. A secondary endpoint in terms of efficacy was the change from baseline in HAQ-DI at week 12. Other secondary endpoints included the pharmacokinetics and safety of CT-P13 up to week 52. The study was completed in April 2026. Shortly thereafter, Celltrion filed global phase 3 studies of Zymfentra in patients with RA with the EMA and the U.S. FDA.

VDJ-001 from Beijing VDJBio is a novel humanized anti-IL-6 receptor IgG1 antibody (biosimilar of tocilizumab) with an already approved mechanism of action for RA. By modifying the amino acid sequences of tocilizumab, VDJ-001 displays an improved affinity and in vitro activity compared to tocilizumab. In a phase 1 trial, single intravenous doses of VDJ-001 (1-8 mg/kg) demonstrated an acceptable tolerability and safety[42]. The incidences of AEs in the test and placebo groups were 84.4% and 62.5%, respectively. The most common AEs that occurred in the verum group were laboratory findings (75.0%), followed by infections and infestations (21.9%). With escalated doses, Cmax increased linearly and AUC0-t and AUC0-∞ increased in a higher than dose-proportional manner, while clearance decreased and half-life prolonged. Immunogenicity monitoring of VDJ-001 revealed that 18.8% (6/32) of the subjects administered VDJ-001 had antigen-dependent antibodies (ADA). Among these ADA-positive subjects, one from the 2-mg/kg group tested positive for neutralizing antibodies (Nab). In the placebo group, one female subject was ADA-positive but Nab-negative. Based on results of the subsequent phase 2 trial (NCT05957107), a phase 3 pivotal trial (NCT06726096) is currently evaluating the efficacy of intravenous doses of VDJ-001 6mg/kg compared to tocilizumab 8mg/kg or placebo given once monthly for up to 24 weeks in patients with moderate to severe RA with poor response to MTX. About 615 RA patients will be enrolled by invitation at a single site in China.

Lutikizumab (ABT-981) from Abbvie is a novel human dual-variable domain immunoglobulin (DVD-Ig), which demonstrated simultaneous blockage of both IL-1α and IL-1ß and efficacy in a mouse model for osteoarthritis[43]–but failed to reduce pain scores and structural progression in erosive hand OA in a phase 2 trial[44]. With the FDA (2001) approval of anakinra (KINERET®), IL-1 receptor antagonism and thus complete inhibition of IL-1 signaling has been proven as an effective therapeutic approach for adult and juvenile RA. Thus, dual antagonism of IL-1α/ß by lutikizumab seems to be a promising approach as additional treatment option for RA. Lutikizumab is currently tested in a phase 2 trial (NCT06972446) as monotherapy and combined with ravagalimab (a novel anti CD40 antibody) in patients with moderate to severe RA. Approximately 180 participants who have failed 1 or 2 biologic or targeted synthetic DMARD therapies will be enrolled in the study. Lutikizumab is administered subcutaneously every other week up to 12 weeks. The combined primary endpoint for monotherapy and combination therapy will be analysed as the percentage of patients with ACR50 response and the number of patients with adverse events at week 12 compared to placebo.

SPY072 (formerly SP002-072) from SPYRE Therapeutics is a long-acting antibody targeting tumor necrosis factor-like ligand 1A (TL1A) that belongs to the tumor necrosis factor (TNF) ligand superfamily and is also known as TNF superfamily member 15 (TNFSF15). TL1A is produced by activated antigen-presenting cells (dendritic cells and monocytes/macrophages) and by synovial fibroblasts and endothelial cells after stimulation by TNFα or IL-1. Through its receptor death receptor 3 (DR3, TNFRSF25), which is expressed primarily on lymphocytes, TL1A stimulates T-cell activation, proliferation and production of various inflammatory cytokines. Decoy receptor 3 (DcR3), a soluble member of the TNF receptor superfamily, competes with DR3 for TL1A binding and inhibits functional signaling. TL1A, DR3 and DcR3 are significantly upregulated in inflamed intestinal and extraintestinal tissues and TL1A/DR3 signaling seems to critically participate in intestinal and extraintestinal inflammatory conditions that are frequently associated with inflammatory bowel disease known as the gut-joint-skin-eye axis[45].

SPY072 uses a 'YTE modification', incorporating the M252Y, S254T and T256E (YTE) triple substitution in the Fc region, which protects the antibody from immediate degradation and enables it to re-enter the circulation resulting in a prolonged drug activity. The prolonged half-life can reduce administration frequency, with potential for improved clinical outcomes through dose optimization and higher drug exposures. TL1A inhibition was effective in preclinical arthritis models and interim phase 1 results demonstrated that single doses of SPY072 up to 1500 mg were well tolerated. SPY072 exhibits a PK profile supporting potential quarterly or twice annual maintenance SC dosing and rapid and sustained target engagement[46]. SPY072 is currently evaluated in a proof-of-concept basket phase 2 trial (NCT07148414, SKYWAY) in patients with moderate to severe active RA, psoriatic arthritis or axial spondyloarthritis who have shown an inadequate response to conventional or advanced therapies. In the RA substudy, patients with moderately to severely active RA with inadequate response (defined as signs and symptoms of persistently active disease, loss of response or intolerance) to treatment with csDMARDs, bDMARDs or tsDMARDs will receive subcutaneous injections of SPY072 every 3 or 6 months. The change from baseline in DAS28-CRP and the proportion of RA patients who achieve an ACR20 response are the primary and secondary outcome measures, respectively.

Tulisokibart (MK-7240) from Merck Sharp & Dohme is a humanized monoclonal IgG1 antibody targeting TL1A also known as TNF superfamily member 15 (TNFSF15). TL1A and its receptor DR3 are essential for diverse animal models of autoimmune disease and may be pathogenic in RA[45]. TL1A is specifically elevated in RA from early in the disease course and in at-risk first-degree relatives. TL1A levels decline after TNF blockade and may be a useful biomarker for TNF activity in RA[47]. Tulisokibart is thought to bind both soluble and membrane-bound human TL1A. The investigational antibody has already entered phase 3 clinical development programs for ulcerative colitis and Crohn's disease and is also studied in other immune-mediated inflammatory diseases including RA[48]. A phase 2b trial

(NCT07176390) is ongoing to evaluate the efficacy and safety of different SC doses of tulisokibart in 182 patients with RA who are taking stable doses of MTX. Only bDMARD naïve patients or patients who did not respond to or tolerate up to a maximum of two classes of bDMARDs may participate. The study consists of a 12-week placebo-controlled period and a 116-week long-term extension (LTE), which is composed of a 44-week main extension and a 72-week optional extension. An overview of antibodies targeting inflammatory cytokine signaling currently in development for RA is given in **(Table 2)**.

Table 2: Current RA Drug Pipeline – Monoclonal antibodies targeting inflammatory cytokine signaling.

Product (Sponsor)	Target, Route of Administration	Development Phase
CT-P13 (Zymfentra) (Celltrion)	anti-TNFα mab (biosimilar of infliximab), SC formulation of Infliximab	Phase 3 (BE study): NCT06738719 Completed APR 2026
VDJ-001 (Beijing VDJBio)	anti-IL-6 receptor IgG1 mab, IV infusion	Phase 3: NCT06726096 Enrolling by invitation. SCE: DEC-2026
Lutikizumab (Abbvie)	anti-IL-1α/ß mab, SC injection	Phase 2: NCT06972446 Recruiting, SCE: NOV-2027
SPY072 (Spyre Therap.)	Long-acting anti-TL1A mab, SC injection (potential for a quarterly or half-yearly SC maintenance dose)	Phase 2 trial: NCT07148414 (SKYWAY-RD) Recruiting, SCE: MAR-2028
Tulisokibart (MK7240) (Merck Sharp & Dohme)	Anti-TL1A mab, SC injection	Phase 2: NCT07176390 Recruiting, SCE: MAR-2027 (12-week placebo-controlled period), SEP-2029 (116-week LTE period)

Abbreviations: BE = bioequivalence, IL = interleukin, mab = monoclonal antibody, SC = subcutaneous, SCE = study completion estimated, IgG = immunoglobulin G, LTE = Long-Term-Extension, TL1A = tumor necrosis factor-like ligand 1A, TNFα = tumor necrosis factor alpha

Source: Based on data in public domain and on CLINICALTRIALS.GOV

2.1.3. Therapeutic proteins targeting CD40-CD40L co-stimulatory pathway

CD40 (also known as TNFRSF5) and its ligand CD40L (CD154) belong to the TNF receptor superfamily. CD40 and CD40L are expressed by a variety of immune (antigen-presenting cells and lymphocytes) and non-immune cells[49]. Importantly, CD40L expression on activated platelets may cause an inflammatory reaction of endothelial cells[50]. CD40 and CD40L are both transmembrane proteins. A soluble form of CD40L has been reported with activities similar to the transmembrane form[51,52]. The CD40/CD40L signal transduction is essential for immune system modulation because it coordinates both adaptive and inflammatory responses. In particular, a functional CD40/CD40L interaction between the B lymphocyte CD40 receptor and the T lymphocyte CD40L is important in generating germinal centers, T-cell dependent humoral responses and generation of memory B lymphocytes.

The engagement of CD40 by CD40L promotes the clustering of CD40 and induces the recruitment of adapter proteins known as TNFR-associated factors (TRAFs) or Janus Kinase 3 (JAK3) to the cytoplasmic domain of CD40. The signaling dependent or independent of TRAF proteins regulates different cellular and immune processes. The TRAF proteins activate different signaling pathways such as MAPKs (mitogen-activated protein kinases), PI3K (phospho-inositide-3 kinase), PLCγ (phospholipase Cγ) and JAK3 activates the STAT5 (signal transducer and activator of transcription 5) pathway. Subsequent signal transduction involves the activation of NF-κB (nuclear factor kappa B), NFAT (nuclear factor of activated T-cells) and AP-1 (activator protein-1) and the transcription of genes encoding pro-inflammatory cytokines (e.g., TNFα and IL-1), adhesion molecules (ICAM) or co-stimulatory molecules (CD80/B7-1, CD86/B7-2)[53]. There is a growing body of evidence that aberrant activity of the CD40-CD40L co-stimulatory pathway plays a crucial role in the initiation and development of RA[54]: CD40L over-expression on the surface of circulating T-cells and in the synovium of RA patients results in increased production of immunoglobulins by B-cells and increased secretion of IL-12 by dendritic cells and synovial macrophages. CD40 over-expression on fibroblasts and synovial cells by the presence of TNF-α and IFN-γ also increases the secretion of pro-inflammatory cytokines such as IL-6, IL-8, IL-15, IL-17, TNF and MCP-1, which amplifies RA-related inflammatory reactions and leads to joint destruction. Binding of CD40L from activated T-cells to CD40 from fibroblasts stimulates VEGF production and synovial neovascularization and increases the expression of adhesion molecules, such as E-selectin, ICAM-1 and VCAM-1, on the surface of fibroblasts, leading to the recruitment of immune cells to the inflammation site. In addition, very high serum levels of soluble CD40L are observed in RA patients - indicating a potential higher risk for cardiovascular events. In a mouse model, administration of an anti-CD40L monoclonal antibody prior to the initiation of collagen-induced arthritis (CIA) prevented the development of RA. Injection of this same treatment into mice that had already developed RA was however unable to reverse the complications induced by CIA.

Several novel biologics have already been developed to target CD40-CD40L costimulatory pathway in RA, however none of them has entered phase 3 development programs so far. Despite their effectiveness, the early anti-CD40L monoclonal antibodies had thromboembolic adverse effects consistent with expression of CD40L on platelets[55]. Thromboembolic toxicity observed with the first anti-CD40L antibodies has been associated mainly with their Fc fragment and FcγR crosslinking: endogenous monoclonal antibody-CD40L immune complexes can activate platelets via their surface IgG receptor (FcγRIIA), thereby promoting aggregation and thrombosis. Thromboembolic complications observed during the rupilizumab clinical trials were a setback to the field and safe alternative therapeutics targeting the CD40-CD40L pathway have since then been researched. Novel approaches targeting CD40L utilized Fc-silenced antibodies or pegylated anti-CD40L Fab′ fragments such as dapirolizumab pegol, but Fc silencing of anti-CD40L antibodies seems to

reduce their in vivo efficacy[56]. In recent years, novel Fc-silenced and non-lymphocyte depleting anti-CD40 antibodies, such as BI 655064, abiprubart and ravagalimab, were designed to reach clinically significant improvements combined with an acceptable safety profile in RA patients. In a phase 2a trial, BI 655064 showed a favorable safety profile but failed to show clinical efficacy in RA patients non-responding to MTX[57], whereas abiprubart demonstrated statistically significant reduction in disease activity and a good safety profile in refractory RA patients[58]. A phase 2 trial (NCT06972446) with ravagalimab is currently ongoing evaluating its efficacy and safety as monotherapy or in combination with lutikizumab (anti-IL-1α/ß mab) in RA patients, who have failed 1 or 2 biologic or targeted synthetic DMARD therapies. In a recent proof-of-concept study, ravagalimab was efficacious for inducing endoscopic improvement and clinical remission in patients with moderate-to-severe ulcerative colitis who had failed at least one prior biologic therapy or JAK inhibitor. Ravagalimab exhibited a favorable safety profile with no instances of thrombotic events[59]. These findings support further evaluation of ravagalimab as a potential therapeutic for inflammatory immune diseases including RA. In addition, the novel CD40L-specific fusion protein dazodalibep, designed to inhibit CD40-CD40L interaction, has demonstrated reductions in rheumatoid factor and disease activity in a phase 2 trial with RA patients[60]. In addition, a small molecule called C25-140 with less thromboembolic risks was identified, which selectively inhibits the activity of the TRAF6 protein and thus various pro-inflammatory NF-κB signaling pathways. In preclinical in vivo mouse models, C25-140 ameliorated inflammation and improved disease outcomes of autoimmune psoriasis and RA[61]. Whether these promising preclinical results can be translated into significant clinical improvements in RA patients remains to be investigated.

Abiprubart (KPL-404) from Kiniksa Therapeutics is a humanized monoclonal IgG4 antibody with a stabilized/functionally-silent Fc region that binds to CD40 and inhibits the CD40-CD40L costimulatory interaction without lymphocyte depletion. Abiprubart has demonstrated efficacy in a phase 2 trial (NCT05198310) which enrolled adult patients with moderate-to-severe active RA, who have had inadequate response to or have been unable to tolerate, at least one biologic DMARD or JAK inhibitor (i.e., refractory RA)[58]: Abiprubart was given every two weeks in the PK lead-in cohorts, in cohort 1 (2 mg/kg SC) and in cohort 2 (5 mg/kg SC). In cohort 2, a trend to improvement was observed in the change from baseline in DAS28-CRP at Week 12 (-2.00 [-2.43, -1.58] points, n=25) vs placebo (-1.65 [-2.07, -1.23] points, n=26) which did not reach statistical significance (LS (least-squares) mean difference = -0.35, p=0.2140). It was decided to increase dosing frequency for the POC (proof-of-concept) cohort 3 up to once weekly. In Cohort 3, the change in LS mean [95% confidence interval] from baseline in DAS28-CRP scores at Week 12 compared to placebo in the 5 mg/kg SC once weekly dosing group (-2.21 [-2.62, -1.80] points, n=27) vs placebo (-1.65 [-2.07, -1.23] points, n=26) was statistically significant (LS mean difference = -0.56, p=0.0487). In all cohorts, the 12 weeks treatment with abiprubart was well tolerated, with a PK profile that supports once weekly and possibly every two weeks SC dosing. These results support further clinical development of abiprubart in refractory RA.

Dazodalibep (VIB4920) is a fusion protein designed to inhibit CD40-CD40L interaction. Two Tn3 (human tenascin C) molecules were fused with human serum albumin, with each Tn3 domain engineered to bind specifically to CD40L. Dazodalibep has demonstrated clinical efficacy in the phase 2 dose optimization trial MIDORA (NCT04163991) where it was given as intravenous infusion in four different dosing regimens to patients with moderate-to-severe RA[60]. The change from baseline in DAS28-CRP (LS mean±SE) at day 113 (primary endpoint) was significantly greater for all dazodalibep groups (−1.83±0.28 to −1.90±0.27; $p<0.05$) relative to placebo (-1.06±0.26); significant reductions were also seen for all dazodalibep groups at day 309. Treatment effects at day 113 and the prolonged duration of responses after dazodalibep cessation support the use of longer dosing intervals. In addition, significant reductions in rheumatoid factor levels were observed starting from day 57 and sustained through day 113 for all dazodalibep dosage regimens. Dazodalibep treatment was associated with an acceptable safety and tolerability profile with no reported thromboembolic events. There was no imbalance of events in the infection and infestation system organ class between dazodalibep and placebo (32.3% and 31.3%, respectively); however, an imbalance in COVID-19 infections was observed, with COVID-19 infection reported by 12.9% (8/62) of dazodalibep recipients compared with 6.3% (1/16) who received placebo. These study results provide further evidence of the potential therapeutic benefits of targeting the CD40-CD40L pathway in RA and other autoimmune disorders. An overview of therapeutic proteins targeting the CD40/CD40L pathway is given in **(Table 3)**.

Table 3: Current RA Drug Pipeline - Therapeutic proteins targeting CD40-CD40L co-stimulatory pathway.

Product (Sponsor)	Target, Route of Administration	Development Phase
Abiprubart (KPL-404) (Kiniksa Therapeutics)	Fc-silenced, non-lymphocyte depleting anti-CD40 mab, SC injection	Phase 2: NCT05198310 Completed 2024 Positive results published[58].
BI 655064 (Boehringer Ingelheim)	Fc-silenced, B-cell reducing anti-CD40 antibody, SC injection	Phase 2a: NCT01751776 Completed 2015 Results published, showing good safety but no efficacy[57].
Dazodalibep (VIB4920) (Amgen)	Fusion protein designed to inhibit CD40-CD40L interaction, IV infusion	Phase 2: NCT04163991 Completed 2021. Positive results published[60].
Ravagalimab (Abbvie)	Fc-silenced anti-CD40 mab, SC injection	Phase 2: NCT06972446 Recruiting, SCE: FEB-2027
Abbreviations: CD40 = cluster of differentiation 40, CD40L = CD40 ligand, mab = monoclonal antibody, SC = subcutaneous, SCE = study completion estimated		

Source: Based on data in public domain and on ClinicalTrials.gov

2.1.4. Anti-inflammatory immunocytokines

Dekavil (F8IL10) from Philogen/Pfizer is a fully human fusion protein combining the F8 antibody, which targets the extra domain A (EDA) of fibronectin, with interleukin-10 (IL-10), an anti-inflammatory cytokine. Dekavil is designed to selectively deliver IL-10 to sites of inflammation, thereby increasing the therapeutic index of the cytokine while minimizing systemic side effects[62]. In January 2026, an open-label, non-randomized, ascending dose phase 1 trial (NCT07245992) commenced to assess the safety and tolerability of escalating doses of dekavil administered via intra-articular route 3 times every 4 weeks in patients with RA. Only patients with arthritis flare(s), who are suitable for intra-articular injection in a knee, ankle, shoulder, wrist or elbow, despite treatment are allowed to participate in the study. In addition, patients must be on stable doses (for at least 3 months) of DMARDs (conventional, biologic and targeted synthetic) as background therapy.

2.1.5. Monoclonal antibody reducing protein citrullination

AZD1163 from AstraZeneca is a novel bispecific antibody that inhibits the activity of extracellular Peptidyl Arginine Deiminases (PADs) 2 and 4, enzymes responsible for protein citrullination. Increased PAD2 and PAD4 activity and citrullinated proteins are present in the joints of RA patients. In susceptible individuals, citrullinated proteins activate a cascade of T-cell driven events, promoting B-cell maturation and activation, leading to the production of pathogenic ACPA[63,64]: Development of ACPAs occurs earliest in the course of RA and they are present in the largest percentage of patients followed by the development of PAD4 antibodies in some patients. Both types of autoantibodies can occur preclinically and their prevalence increases over time. With increased disease duration, a small subset of anti-PAD4 antibody-positive patients may develop cross-reactive antibodies for PAD3 and PAD4 (anti-PAD3 and PAD4 antibodies). An ACPA-expressing B-cell undergoes B-cell receptor-mediated endocytosis of a PAD enzyme citrullinated protein intermediate complex and presents peptides from both proteins on MHC class II molecules to autoreactive T-cells. Stimulation of a PAD4-reactive T-cell or a citrullinated protein-reactive T-cell by the ACPA-expressing B-cell initiates intermolecular epitope spreading, thereby shifting the immune response from the citrullinated protein products to PAD enzymes themselves. The activated autoreactive T-cell then stimulates a PAD4-reactive B-cell, which produces anti-PAD4 antibodies. The PAD4-reactive B-cell can then undergo somatic hypermutation to generate PAD3 and PAD4 cross-reactive B-cells.

As preclinical data demonstrated that AZD1163 reduces protein citrullination by inhibition of increased PAD activity present in serum and synovial fluid samples from patients with RA, it was considered a promising new approach that may be used early in disease or even in first-degree relatives of RA patients. The first-in-human study with AZD1163 revealed that subcutaneous doses of AZD1163 were well tolerated in healthy volunteers, with dose proportional exposure increase in the dose range studied and a mean elimination half-life of 38 days. A significant, dose dependent inhibition of PAD2/PAD4 activity was observed, with maximum inhibition exceeding 95%, confirming target engagement[65]. A phase 2 trial (NCT07276581) is currently evaluating the efficacy and safety of different SC doses of AZD1163 in ACPA positive adults with moderate-to-severely active RA on standard-of-care therapy including csDMARDs or TNFα inhibitors with or without csDMARD.

2.2. Small Molecules

2.2.1. JAK inhibitors

Girocitinib (TLL-018) from Hangzhou Highlightll Pharmaceutical is a highly selective JAK1/TYK2 inhibitor designed to modulate key immune-inflammatory signaling pathways for the treatment of multiple autoimmune and inflammatory diseases. Girocitinib is currently being evaluated in phase 3 clinical trials in China for chronic spontaneous urticaria and RA. In April 2026, Highlightll Pharmaceutical announced positive topline results of a phase 3 clinical trial (NCT06020144) with girocitinib compared to tofacitinib in RA patients, who had inadequate response or were intolerant to biologics[66]: A total of 459 subjects were randomized to receive daily oral doses of girocitinib or tofacitinib for 52 weeks. The primary efficacy endpoint, the percentage of patients achieving ACR50 response at week 24, was met. Girocitinib demonstrated superior efficacy over tofacitinib in this trial. Girocitinib also outperformed tofacitinib in all secondary efficacy endpoints ($P<0.0001$), including the ACR20/70 rates, the proportion of subjects with DAS28≤3.2 and DAS28<2.6 and the proportion of subjects with low disease activity (LDA) who achieved CDAI≤10. In addition, patients who did not reach ACR50 in the tofacitinib group achieved better efficacy after being transferred to the girocitinib group, indicating that girocitinib may still be effective in patients with poor response to both biologics and JAK inhibitors (i.e., difficult-to-treat RA patients). The incidences of adverse events, severe adverse events and serious adverse events between the girocitinib and tofacitinib groups were similar and the adverse event profile is consistent with other JAK inhibitors with no new safety signal. The follow-up of this pivotal trial is ongoing. In addition, an open-label extension (OLE) study is currently assessing the long-term safety, tolerability and efficacy of girocitinib in RA patients, who have completed the pivotal phase 3 trial (NCT06020144).

Zemprocitinib (LNK01001) is a selective JAK1 inhibitor, which has been jointly developed by Simcere and Lynk Pharmaceuticals. Preclinical data showed that zemprocitinib has a higher selectivity and potentially better safety than other marketed JAK inhibitors. Zemprocitinib has already been studied in a phase 2 study (NCT06099535) in about 156 patients with moderately to severely active RA with an inadequate response or intolerance to conventional synthetic DMARDs. Significant differences in efficacy compared with placebo were seen in both low dose and high dose groups of zemprocitinib[67]: The primary endpoint (ACR20 at week 12) and key secondary endpoints at week 12 were met. In addition, ACR20 rates of both low dose and high dose groups reached over 90% at week 24. The overall safety and tolerability of the study drug was very good. Based on these positive results, a pivotal phase 3 trial COURAGE-RA (NCT06276998) has commenced in China in 2023. The trial evaluated the efficacy and safety of LNK01001 in 430 patients with moderate-to-severe RA, who are on stable doses of conventional synthetic DMARDs and have had an inadequate response or intolerance to at least one biologic DMARD. Randomized patients received oral doses of zemprocitinib (12 mg) or placebo twice daily over a period of 24 weeks. Positive topline results from this phase 3 trial have been announced in the

first quarter of 2026[68]: The primary endpoint and key secondary endpoints were met: the ACR20 response rates at week 12 and week 24 versus placebo were 74.0% versus 29.9% (P < 0.0001) and 79.1% versus 39.7% (P < 0.0001), respectively. The ACR50 response rates at week 12 and week 24 versus placebo were 41.4% versus 9.3% (P < 0.0001) and 55.8% versus 22.0% (P < 0.0001), respectively. The proportion of patients achieving DAS28 (CRP) ≤ 3.2 at Week 12 and Week 24 versus placebo was 51.2% versus 15.0% (P < 0.0001) and 67.0% versus 23.4% (P < 0.0001), respectively. In terms of safety, zemprocitinib was generally well tolerated. Patients may continue study treatment for further 52 weeks (open-label extension period).

2.2.2. Melanocortin receptor agonists

In the last two decades, targeting activated fibroblasts has evolved as a novel therapeutic strategy to promote pro-resolving mechanisms and termination of inflammatory responses in several fibroblast-mediated diseases, including RA. For example, cartilage and bone destruction in RA are mediated by abnormally activated fibroblasts that fail to switch from acute resolving to persistent activation of immune cells resulting in chronic inflammation[69]. Growing evidence is pointing at the melanocortin system as a potential new target for the treatment of diseases associated with aberrantly activated fibroblasts. New melanocortin drugs (primarily agonists with varying selectivity for each of the five melanocortin receptors, MC1R to MC5R) have demonstrated in several animal models and clinical trials that they can reduce collagen deposition, myofibroblast activation, pro-inflammatory mediators and scar formation or have already been approved for use in humans[70]. Expression of MCRs (MC1R, MC3R, MC4R and MC5R) has been found in synovial fibroblasts obtained from RA patients and selective MC1R agonism by the novel compound BMS-470539 reduced proliferation and attenuated the aggressive phenotype typically exhibited by these cells. Thus, selective activation of the MC1R may be a viable strategy to induce cellular senescence, affording a distinct way to control joint inflammation and arthritis[71].

While BMS-470539 has not entered a clinical development program for RA so far, the selective MC1R and MC3R agonist resomelagon (also known as AP1189) from SynAct Pharma has already entered phase 2 of clinical development. The compound selectively stimulates the MC1R and MC3R on target cells in the immune system, which are directly involved in inflammation and its resolution. As the compound does not stimulate the MC2R, the anti-inflammatory and immune resolution effects are not associated with an unwanted increase in the cortisol level and related side effects, as seen with adrenocorticotropic hormone (ACTH) based therapies. Furthermore, resomelagon does not stimulate melanocortin pathways that are responsible for off target activity such as skin hyperpigmentation. Resomelagon has shown 'proof of concept' results in the ADVANCE study (NCT06671054), a phase 2b randomized placebo-controlled dose range multi-center study conducted in the US and in Europe. A total of 246 patients with newly diagnosed RA, who displayed a high disease activity (CDAI>22; DAS28-CRP >5.1; hsCRP>3 mg/L) have been enrolled. The trial evaluated the efficacy, safety and tolerability of 12 weeks daily treatment of oral resomelagon (AP1189) at the doses of 40, 70 or 100 mg in combination with oral MTX (RES+MTX) compared to oral MTX alone ('placebo'). As expected, dose-response for resomelagon was non-linear and 40 mg resomelagon given once daily was identified as the most effective dose. Due to a large placebo effect, the primary endpoint (DAS28-CRP at week 12) was not met: 1.98 [SE 0.14] in the 40 mg RES+MTX group versus 1.79 [SE 0.14] in the placebo group (p=0.168). However, a significant reduction in SDAI at week 12 was observed: 35.9 in the 40 mg RES+MTX group versus 28.5 in the placebo group (p=0.03). A favorable safety profile without signs of immunosuppression was observed[72].

2.2.3. Tim receptor agonists

The T-cell immunoglobulin and mucin domain (Tim) family of receptors are important regulators of the immune response. Human Tim proteins are phosphatidyl serine receptors, which are mainly expressed on the surface of T helper cells and antigen-presenting cells but also on B-cells, natural killer cells and mast cells. There are three Tim genes expressed in humans: HAVcR1 (which encodes Tim1), HAVcR2 (which encodes Tim3) and TIMD4 (which encodes Tim4)[73]. Tim molecules are typeI cellsurface glycoproteins that comprise an extracellular IgV domain, a mucinlike domain, a transmembrane domain and an intracellular cytoplasmic tail. Tim4 is unique because it has an RGD (integrin-binding) motif, but no tyrosine phosphorylation motif[74]. Researchers found that certain polymorphisms in Tim genes seem to be associated with a higher risk of developing RA in Chinese[75-77], Korean and Egyptian[78,79] populations. The Tim protein family affects immunomodulatory function and is involved in pathways of several autoimmune diseases, including RA[80]. Emerging data show that a decreased expression of Tim-3 on CD4+ and CD8+ T-cells in the peripheral blood and synovial fluid correlates with progression of RA[81]. Other researchers observed that the number of Tim3+ and Foxp3+ Treg cells (which are potent inhibitors of effector T-cells) is decreased in RA[82]. Thus, Tim3 receptor agonism may favor Treg expansion and restore the immune system's self-tolerance, enabling patients to more effectively and gently combat autoimmune disease.

LPX-TI641 from LAPIX Therapeutics is an oral small-molecule compound designed to bind the phosphatidylserine binding pocket on Tim-3 and Tim-4 receptors. It will be developed as novel treatment option for RA and Psoriatic Arthritis as well as for Psoriasis and Atopic Dermatitis. LPX-TI641 promotes antigen-independent immune tolerance through Tim receptor agonism and Treg expansion[83]. The results of a phase 1a trial (NCT05853835) showed that LPX-TI641 was safe and well tolerated when given to healthy subjects as single oral doses up to 150 mg and as multiple oral doses up to 120 mg once daily for up to 7 days. Adverse events were primarily mild and were not linked to dosage levels. Mild headaches were the most reported adverse event. Exploratory pharmacodynamic data from the study revealed an LPX-TI641 exposure dependent and statistically significant increase in circulating CD4+/Foxp3+ T-cells (T-regs) and CD25+/CD19+ B-cells (B-regs) compared to pooled placebo group[84]. A phase 1b trial (NCT06628206) is now investigating the safety, tolerability and pharmacokinetics of multiple ascending doses of LPX-TI641 given as solid-dose capsules orally for 28 days in patients with RA and Psoriatic Arthritis. An overview of small molecules that are currently in development for RA is given in **(Table 4)**.

Table 4: Current RA Drug Pipeline – Small Molecules.

Product (Sponsor)	Target, Route of Administration	Development Phase
Girocitinib (TLL-018) (Hangzhou Highlightll Pharmaceutical)	Highly selective JAK1/TYK2 Inhibitor, oral administration	Phase 3: NCT06020144 (pivotal trial) Active, not recruiting. Positive topline results announced[66]. Phase 3: NCT06887127 (LTE of NCT06020144), Recruiting, SCE: DEC-2027
Zemprocitinib (LNK01001) (Simcere and Lynk Pharmaceuticals)	Highly selective JAK1 inhibitor oral (twice daily) administration	Phase 3: NCT06276998 Active, not recruiting. SCE: NOV-2026 Positive topline results announced[68].
Resomelagon (AP1189) (SynAct Pharma)	Selective MC1R and MC3R agonist oral once daily administration	Phase 2: NCT06671054 Completed in Q2 2026. Positive topline data demonstrating 'proof of concept' announced[72].
LPX-TI641 (LAPIX Therapeutics)	Selective Tim3/Tim4 agonist, oral once daily administration	Phase 1b: NCT06628206 Recruiting, SCE: JAN-2026
Abbreviations: JAK1 = Janus kinase 1, LTE = Long-Term-Extension, MCR = melanocortin receptor, SCE = study completion estimated, Tim3 = T-cell/transmembrane immunoglobulin and mucin domain containing-3, Tim4 = T-cell/transmembrane immunoglobulin and mucin domain containing-4, TYK2 = Tyrosine kinase 2		

Source: Based on data in public domain and on ClinicalTrials.gov

2.3. Cell Therapies for RA

2.3.1. CAR T-Cell Therapies

Chimeric Antigen Receptor (CAR) T-cells are cell-based therapies whereby the patient's T-cells are extracted from their blood and engineered to express a CAR protein on the surface of the T-cells that redirects them towards target cells. The engineered T-cells are expanded in-vitro before being infused back into the same patient. CAR proteins are genetically engineered utilizing retroviral or lentiviral viral vectors as these vectors integrate the CAR gene into the T-cell genome to mitigate against gene loss following T-cell expansion prior to infusion back into the patient. Current approved CAR therapies are second generation CAR constructs consisting of an extracellular single chain variable fragment specific for antigen(s) on the target cell linked through a transmembrane domain to intracellular signaling domains derived from the T-cell receptor CD3 ζ chain and one co stimulatory domain CD28 or 4-1BB[85]. The CAR protein can be tailored to target essentially any antigen on the surface of the target cell. The interaction of the CAR molecule with its antigen on the target cell activates the T-cell via phosphorylation of the intracellular domains of the CD3 ζ and co-stimulatory domains by endogenous kinases, resulting in the production of perforin/ granzyme and inflammatory cytokines that promote target cell death. CAR function can be fine-tuned by adding further costimulatory domains or co-expression of inflammatory cytokines/antibodies.

CAR T-cell therapy has transformed the treatment of hematologic malignancies over the past decade by genetically altering T-cells to target associated CD19 and BCMA antigens, eliciting an immune response against malignant cells. Evidence is growing that these cell-based therapies can also target B-cell driven autoimmune diseases including RA. CAR T-cell therapy has delivered unique results for the treatment of ACPA positive, difficult-to-treat RA patients via depletion of CD19/CD20 and BCMA positive B-cells. Preliminary data of clinical case studies suggests that a single infusion of these CAR T-cell therapies could mediate long term suppression of inflammatory disease, an 'immune reset' and drug-free remission in RA patients[86-91]. Long-term outcomes for these patients in terms of clinical efficacy (drug-free remission) and safety including the risk of Cytokine Release Syndrome (CRS), Immune Cell Associated Neurotoxicity Syndrome (ICANS), infections and relapse are unknown. Several clinical trials are currently ongoing to evaluate CAR T-cell therapy in refractory (difficult-to-treat) RA patients **(Table 5)**.

Table 5: Current RA Drug Pipeline – Novel CAR T-Cell Therapies.

Product (Sponsor)	Target, Route of Administration, Study Population	Development Phase
KYV-101 (Kyverna Therapeutics/ Charite University Berlin, Germany)	CD19-targeting CAR T-cells, IV infusion in patients with refractory RA (compared to rituximab treatment)	Phase 1/2: NCT06475495 (COMPARE) Active, not recruiting. SCE: JUN-2027
EB CAR-T (BAH247) (Essen Biotech)	CD19/BCMA-targeting CAR T-cells, IV infusion in patients with relapsed-refractory autoimmune diseases including RA	Phase 1/2: NCT06428188 Recruiting, SCE: DEC-2026
Rapcabtagene autoleucel (YTB323) (Novartis)	CD19-targeting CAR T-cells, IV infusion in difficult-to-treat RA and severe, refractory Sjögren's Disease with organ involvement	Phase 1/2: NCT07048197 Recruiting, SCE: NOV-2028
ADI-001 (Adicet Therapeutics)	Allogenic CD20-targeting CAR-γδ T-cells, IV infusion in patients with refractory RA	Phase 1: NCT07100873 Recruiting, SCE: MAR-2028
BMS-986515 (Juno Therapeutics / Bristol-Myers Squibb	Allogenic CD19-targeted CAR T-cells, IV infusion in patients with severe, refractory autoimmune diseases including RA	Phase 1: NCT07115745 Recruiting, SCE: AUG-2030
CC-97540 (BMS-986353) (Juno Therapeutics / Bristol-Myers Squibb)	CD19-targeted Nex-T CAR T-cells, IV infusion in patients with severe, refractory autoimmune diseases including RA	Phase 1: NCT05869955 Active, not recruiting, SCE: AUG-2028
HBI0101 (Polina Stepensky)	BCMA-targeting CAR T-cells, IV infusion in refractory B-Cell autoimmune diseases including RA	Phase 1: NCT07085676 Recruiting, SCE: NOV-2030

Product (Sponsor)	Target, Route of Administration, Study Population	Development Phase
SBT777101 (Sonoma Biotherapeutics)	Autologous CAR Treg cell therapy, IV infusion	Phase 1: NCT06201416 Recruiting, SCE: NOV-2026
SCAR02 (The First Affiliated Hospital of University of Science and Technology of China)	BCMA/CD19-targeting CAR T-cells, IV infusion in patients with refractory autoimmune diseases including RA	Phase 1: NCT06503224 Recruiting, SCE: APR-2030
Abbreviations: ADCC = antibody-dependent-cellular cytotoxicity, BCMA = B-cell maturation antigen, CAR = Chimeric Antigen Receptor, IV = intravenous, SCE = study completion estimated		

Source: Based on data in public domain and on CLINICALTRIALS.GOV

KYV-101 is a novel CD19-targeting CAR T-cell therapy based on technology developed by Kyverna Therapeutics for which a phase 1/2 clinical trial (NCT06475495) is currently conducted at the Charité University Hospital of Berlin (Germany). KYV-101 based CD19-targeting CAR T-cells have already demonstrated excellent results in two case studies for the treatment of RA co-existing with other inflammatory diseases. In the first case, a 37-year-old woman with myasthenia gravis (MG) developed ACPA-positive RA in 2020[88]: The patient was unresponsive to glucocorticoids and rituximab or other conventional therapies and had high disease activity for both MG and RA. The patient's T-cells were isolated and engineered with a lentiviral vector encoding a second generation CD19-specific CAR T construct comprising a fully human CD19 binding domain with CD3 ζ and CD28 costimulatory domains. The cell product was mainly comprised of CD4 + helper T-cells and was well tolerated with grade 1 CRS following infusion. Disease activity scores for both MG and RA indicated disease remission, with undetectable ACPA levels reported for RA. Circulating B-cells were undetectable at day 4 post CAR T-cell infusion and slowly returned by day 150. The patient achieved symptom-free remission and remained in remission during follow-up.

Similar results were observed in a second case, where a 32-year-old woman with a six-year history of Systemic Sclerosis and ACPA-positive RA was treated with autologous T-cells engineered with KYV-101[89] **(Figure 3)**: The patient developed grade 2 CRS that was treated with tocilizumab and corticosteroids. Circulating B-cell counts were undetectable for 56 days and reappeared in the blood and bone marrow as naïve/transitional B-cell subsets by week 16. The level of ACPAs declined below the cut-off values within 21 days and remained below baseline for 6 months. The patient remained in stable clinical remission for RA, while Systemic Sclerosis-associated symptoms, including vasculopathy and fibrosis, improved despite the complete discontinuation of immunosuppressive, vasodilative and antifibrotic treatment. These preliminary results are promising and highlight the potential of anti-CD19 CAR T-cells engineered with KYV-101 as a safe and effective treatment option for patients with ACPA-positive and treatment refractory RA coexisting with B-cell driven autoimmune diseases.

A phase 1/2 trial (NCT06475495, COMPARE) is currently evaluating the safety and efficacy of CD19-targeting CAR T-cell therapy engineered with KYV-101 in comparison to CD20-targeting therapy with rituximab in active, ACPA positive and treatment refractory RA patients. Participants in the test-arm will receive a single intravenous dose of KYV-101 engineered CD19 CAR T-cells; the comparator group will receive 2x1000 mg rituximab intravenously on Day 0 and Day 14. Safety outcome will be evaluated based on the number of adverse events occurring during the study with a special focus on the incidence of CRS, ICANS and Serious Adverse Events within the first 4 weeks after anti-CD19 CAR T-cell therapy. Key efficacy endpoints are the percentage of patients with ACPA seroconversion (i.e., ACPA level <20 mU/ml) at week 16, the drug free survival time (in the test arm only), the time to relapse or flare from week 7 to week 52 and the percentage of patients achieving remission based on DAS28-CRP up to week 52.

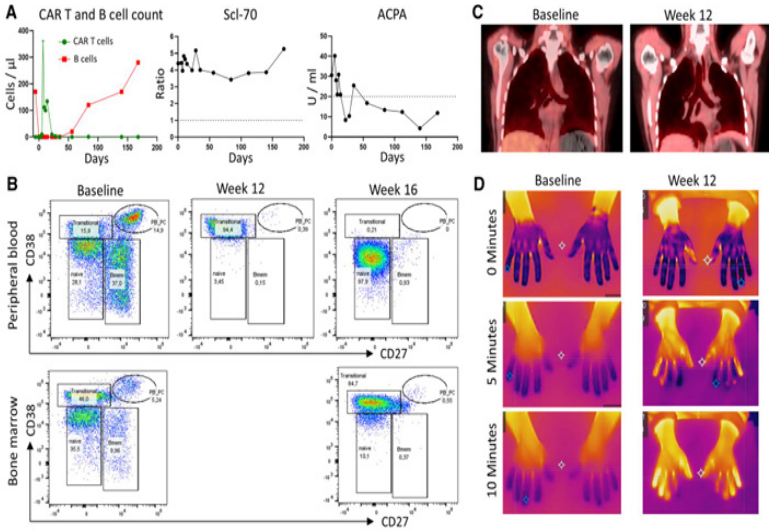

Figure 3: Patient with Systemic Sclerosis and ACPA-positive RA treated with KYV-101 (anti-CD 19 CAR T-cells).
(A) Anti-CD19 CAR T-cell and B-cell counts and auto- antibody levels before and after anti-CD19 CAR T-cell therapy. (B) Fluorescence-activated cell sorting (FACS) analysis showing B-cell subpopulations in peripheral blood and bone marrow before and after anti-CD19 CAR T-cell therapy. (C) FAPI PET/CT of the lung before and after treatment. (D) Thermography of the hands after 1 min bath in 10 °C cold water, 5 and 10 min later, before (left panel) and after anti-CD19 CAR T-cell therapy (right panel).
Abbreviations: ACPA = anticitrullinated protein antibodies, CAR = chimeric antigen receptor
Source: Figure adopted from[89].

2.3.2. NK Cell therapies

AlloNK® (AB-101) is a non-genetically modified, allogeneic, off-the-shelf, cryopreserved cord blood-derived NK cell therapy, which has been developed by Artiva Biotherapeutics. An open-label Phase 2a basket trial (NCT06991114) is currently evaluating the safety and efficacy of AlloNK® in combination with rituximab in relapsing forms of B-cell dependent rheumatologic diseases, including RA, Sjögren's Disease, Idiopathic Inflammatory Myopathies and Systemic Sclerosis. In the RA arm of the study, therapy refractory patients with at least moderate disease activity will receive one intravenous infusion of AlloNK® (after a conditioning regimen) combined with rituximab in an ascending dose design. The primary endpoint is the DAS28-CRP at week 52.

CD19 CAR NK cells (KN5501) are CAR Natural Killer cells targeting CD19 developed by 'The First Affiliated Hospital with Nanjing Medical University' (China). KN5501 is currently evaluated in an early phase 1 study (NCT06613490), which uses an open-label dose-escalation design to evaluate the safety and efficacy of 3 infusions of KN5501, as well as the expansion and persistence of KN5501 in patients with refractory antisynthetase antibody syndrome and in patients with refractory RA. All patients will receive fludarabine/cyclophosphamide lymphodepletion followed by anti-CD19 CAR NK cells infusion. The primary endpoint is a composite of the incidences of dose-limiting toxicity and treatment emergent adverse events. A summary of NK cell therapies currently in development for refractory RA is given in **(Table 6)**.

Table 6: Current RA Drug Pipeline – Novel NK and CAR-NK-Cell Therapies.

Product (Sponsor)	Target/ Route of Administration	Development Phase
AlloNK® (AB-101) (Artiva Biotherapeutics)	Non-genetically modified, allogenic, off-the-shelf, cryopreserved cord blood-derived NK cell therapy, IV infusion	Phase 2a: NCT06991114 Recruiting, SCE: JAN-2029
CD19 CAR NK cells (KN5501) (The First Affiliated Hospital with Nanjing Medical University, China).	CD19 CAR NK Cells, IV infusion after lymphodepletion with fludarabine/ cyclophosphamide	Early Phase 1: NCT06613490 Recruiting, SCE: OCT-2026
Abbreviations: CAR = Chimeric Antigen Receptor, SCE = study completion estimated		

Source: Based on data in public domain and on CLINICALTRIALS.GOV

3. Concluding Remarks

Despite the development of DMARDs and refined treatments, RA remains an incurable disease. By using different combinations of DMARDs, many patients experience remission of symptoms or at least low-disease activity over long periods. However, a large number of patients still do not respond to available therapies to date, indicating the necessity to develop novel treatment strategies.

Several novel therapies for RA are on the horizon including novel biologics targeting pathogenic B- and T-cell responses such as CD19xCD3 BiTE and CD19xCD3xCD28 TriTE for targeted B-cell depletion or the PD-1 agonistic antibody rosnilimab for targeted T-cell depletion. Novel monoclonal antibodies are targeting the inflammatory cytokine TL1A (e.g., SPY072 and tulisokibart), inhibiting the CD40/CD40L co-stimulatory pathway (e.g., abiprubart and dazodalibep) or reducing protein citrullination (e.g., AZD1163). The novel MCR1/MCR3 agonist resomelagon displays immune resolution effects and seeks to rebalance the immune system. In addition, novel cell therapies are emerging including allogenic Natural Killer cells and several CAR-T-cell and CAR-NK cell products primarily targeting B-cell proteins. Some of these novel therapies are already in advanced stages of clinical development and will hopefully lead to better treatment options, particularly for patients with refractory RA.

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Data availability statement

The data underlying this article are available in the article.

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