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REVIEW ARTICLE

IL-23/IL-17 axis in the pathogenesis and treatment of systemic lupus erythematosus and rheumatoid arthritis

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Abstract

Interleukin-23 (IL-23) and IL-17 are the gatekeepers of $CD4^+$ T helper 17 (Th17) cells where IL-23 is required for the development and expansion of Th17 cells that subsequently produce IL-17 to promote inflammation. Owing to such pro-inflammatory properties, the IL-23/IL-17 axis has emerged as an important mechanism in the pathogenesis of autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In recent years, therapeutic antibodies targeting IL-23 (*e.g.* ustekinumab, tildrakizumab, guselkumab) or IL-17 (*e.g.* brodalumab, secukinumab, ixekizumab) have been approved for the treatment of various autoimmune diseases. In this review, we describe the pathogenic mechanisms of IL-23/IL-17 axis in SLE and RA, as well as summarising the findings from phase II and III clinical trials of anti-IL-23/IL-17 therapeutic antibodies in SLE and RA patients. In particular, phase II study has demonstrated that the anti-IL-23 antibody (ustekinumab) confers enhanced treatment outcomes in SLE patients, while anti-IL-17 antibodies (secukinumab and ixekizumab) have shown improved clinical benefits for RA patients in phase II/III studies. Our review highlights the emerging importance of targeting the IL-23/IL-17 axis in SLE and RA patients.

Keywords: IL-23, IL-17, Systemic lupus erythematosus, Rheumatoid arthritis, Therapeutic antibodies

HIGHLIGHTS

1. IL-23/IL-17 axis plays vital pathogenic roles in autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).
2. Phase II study has demonstrated that the anti-IL-23 antibody (ustekinumab) yields promising treatment outcomes in SLE patients.
3. Anti-IL17 antibodies (secukinumab and ixekizumab) confer significant clinical benefits for RA patients in phase II/III studies.

Interleukin-17 (IL-17 or IL-17A)

IL-17 is a potent pro-inflammatory cytokine that mediates protective immunity[1] and acts as host defense against microbial pathogens.[2] The family members of IL-17 consist of IL-17A (also known as IL-17), IL-17B, IL-17C, IL-17D, IL-17E and IL-17F.[2] IL-17 is mainly produced by $CD4^+$ T helper 17 (Th17) cells[3,4] in response to their stimulation by IL-23 produced by macrophages and dendritic cells (DCs).[5,6] IL-17 is also produced by $CD8^+$ T cells, natural Th17 cells, innate lymphoid cells (ILCs), and natural killer T (NKT) cells[7-11] (Table 1). IL-17 is critical for the protection against extracellular bacteria, protozoa and fungal infections at mucosal and epithelial barriers.[12] IL-17 signals through a heterodimeric receptor complex, IL-17RA and IL-17RC, where IL-17RA is found ubiquitously but can only signal in the presence of IL-17RC.[13]

However, IL-17 signalling contributes to the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA) and spondyloarthritis (SpA) where IL-17 directly aggravates the inflammation site by stimulating immune cells to produce pro-inflammatory cytokines, chemokines and other inflammatory mediators including nitric oxide (NO), prostaglandins and matrix metalloproteinases (MMPs).[14] Aberrant production of IL-17 has also been implicated in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and psoriasis.[3,15]

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TABLE 1: Sources, production sites and mode of IL-17 production

Sources	Production sites	Mode of IL-17 production	Reference
CD4+ T cells	Thymus/ peripheral lymphoid tissues	Upon activation and expansion, CD4+ T cells develop into CD4+ Th17 cells with the production of IL-6 by DCs that induce IL-17 production	[9]
CD8+ T cells	Thymus/ peripheral lymphoid tissues	CD8+ T cells develop into Tc17 cells, inducing IL-17 production. In Tc17 cells maturation, IL-23 is required for their expansion and maintenance	[10]
	Skin		
Natural Th17 (nTh17) cells	Skin and mucosa	Both transcription factors, RORyt5 and RORα6 are expressed by Th17 cells, to produce IL-17 and also express the production of IL-23R	[11]
	Thymus	Similar with adaptive Th17, nTh17 cells also develop in the thymus and induce IL-17 production	[8]
Innate lymphoid cells (ILCs)	Gut and skin	Produce IL-17 in response to inflammatory cytokines and stress	
NKT	Thymus and liver	NKT cell subsets are categorised based on CD4 and NK1.1 expression, and tissue of origin. Activated $CD4^{-}NK1.1^{-}$ NKT cells produce high levels of IL-17	[7]

Interleukin-23 (IL-23)

IL-23 (p19/p40) is an important cytokine in the development, expansion and proliferation of Th17 cells[16] where it is produced by inflammatory myeloid DCs (mDCs), monocyte-derived DCs (Mo-DCs), intestinal macrophages, eosinophils and epithelial cells[17-21] (Table 2). IL-23 is involved in the development and maintenance of autoimmune inflammation.[22,23] IL-23 belongs to IL-12 cytokine family which includes IL-12, IL-23, IL-27 and IL-35, and IL-23 induces memory T cells to produce interferon-γ (IFN-γ) and potently enhances the expansion of Th17 cells for the production of IL-17.[22,24]

As a heterodimer, IL-23 is composed of p19 and p40 subunit, the latter being shared with IL-12 (p35/p40).[13,22] p19 expression is produced by antigen-presenting cells (APCs), T cells and endothelial cells, while p40 is particularly limited to APCs *e.g.* DCs, monocytes and macrophages.[22] IL-23 forms a disulphide-linked complex with p19 and p40 secreted by activated macrophages and DCs in peripheral tissues *e.g.* lung, skin and intestinal mucosa where the synthesis of both p40 and p19 subunits are within the same cell that produces IL-23.[22]

The IL-23 receptor, IL-23R, is found on activated memory T cells, NKT cells, macrophages, and DCs.[9,25] Naïve T cells do not express IL-23R, while the receptor is expressed on activated Th17 cells.[13] Binding of IL-23 with its receptor complex activates STAT3 signaling in Th17 cells that induce Th17 differentiation to gain effector functions including expression of pro-inflammatory cytokines IL-17, GM-CSF and IFN-γ.[26,27] IL-23 is involved in the onset of several autoimmune inflammatory diseases such as psoriasis, colitis, gastritis, and arthritis[22,28] and high serum levels of IL-23 have been demonstrated in patients with SLE.[16]

IL-23/IL-17 axis in autoimmunity

The initial steps of naïve CD4+ T cells differentiation into IL-17 producing cells does not require IL-23, however IL-23 plays an important role in stabilising the phenotypic features of the Th17 lineage. IL-23 is important in the expansion and maintenance of Th17 cells.[7] IL-23 acts mainly on effector and memory CD4+ Th cells to enhance secretion of IL-17 by Th17 cells[22] and IL-23 is thus an upstream regulator for the production of IL-17.[29]

The production of both IL-12 and IL-23 requires nuclear factor-kappa B (NF-κB), and

TABLE 2: Sources, production sites and mode of IL-23 production

Sources	Production sites	Mode of IL-23 production	Reference
Inflammatory myeloid dendritic cells (mDCs)	Bone marrow	gp120-treated with mDCs induced production of IL-23, which then upregulated the suppressor of cytokine signaling 1 (SOCS1) protein in T cells	[17]
Monocyte-derived DCs (Mo-DCs)	Bone marrow	Treatment with PGE2 has been demonstrated to act in a cAMP-dependent manner to elevate IL-23 production in human Mo-DCs	[21]
Intestinal macrophages	Intestine	As IL-10 is an anti-inflammatory cytokine which limits mucosal immune responses, the addition of IL-10 reduces IL-23 production by intestinal macrophages in mice	[19]
Eosinophils	Lung	Confocal microscopy on cells obtained by bronchoalveolar lavage 8- and 54-hours post-infection with *A. fumigatus* were performed to confirm that eosinophils produced IL-23p19 and IL-17A in mice	[18]
Epithelial cells	Gut (Intestinal epithelial cells)	Lymphotoxin beta receptor (LTβR) signalling in intestinal epithelial cells promotes self-repair after mucosal damage (wound healing) and essential for epithelial IL-23 production	[20]

these cytokines trigger initial immune responses leading to Th1 or Th17 cell-mediated immunity. Th17 cells differentiate from naïve T cells under the influence of TGF-β and IL-6, and their maintenance and expansion are mediated primarily by IL-23. Without IL-23, activated $CD4^+$ T cells in the presence of IL-6 plus TGF-β can produce high amounts of IL-17 but unable to fully develop into pathogenic Th17 cells and acquire bystander regulatory properties mediated by IL-10 production.[30]

Hence, in order for pathogenic Th17 cells to fully differentiate and exhibit effector functions, IL-23 is essential. In inflammation pathology, both IL-23 and IL-17 play vital roles where they correspond to the IL-23/IL-17 axis through the differentiation and activation of Th17 cells driving chronic inflammation and autoimmunity, leading to the onset of autoimmune diseases.[8]

IL-23/IL-17 axis in RA

RA is a chronic, systemic autoimmune disease that usually begins in small joints of the hands and feet, causing stiffness, pain, swelling, and reduces mobility and flexibility of the affected joints.[25] RA is characterised by the overproduction of autoantibodies leading to cartilage and bone destruction, negatively impacting RA patients' ability to perform daily living activities.[31]

Growing evidence has demonstrated the importance of IL-23/IL-17 axis in RA pathogenesis[14] involving synoviocytes, osteoclasts and immune cells regulated by cytokines and signaling molecules[25] Both IL-17 and IL-23 were absent in healthy joints, whereas their elevated levels were found in the serum and synovial fluid of RA patients[32,33], corresponding to the IL-23/IL-17 axis in the pathogenesis of RA.

Pathogenesis of RA is composed of two phases *i.e.* the priming phase involving the IL-23/IL-17 axis, and the effector phase involving bone and cartilage degradation.[34] In the priming phase, IL-23 induces Th17 cells

to produce IL-17 and IL-6. IL-17 stimulates production of inflammatory mediators such as TNF-α produced by macrophages. This subsequently upregulates RANKL expression in monocytes involved in regulating osteoclasts activation that act as the key factor for cartilage destruction and bone erosion.[33,35] Osteoclasts are multinucleated bone cells which play a role in bone resorption and they are activated by IL-17 and B cells via RANKL and autoantibodies production such as anti-citrullinated peptide antibodies (ACPAs).[36] In synovial fibroblasts of RA patients, IL-17 stimulates IL-23p19 mRNA and protein expression, and the synergistic actions of TNF-α and IL-17 stimulate the expression of IL-23p19 mRNA in fibroblast-like synoviocytes.[33,37] Through IL-6, naïve T cells differentiate into Th17 cells and Th2 cells, the latter are activated by IL-4.[38] Th2 and Th17 cells subsequently promote activation of B cells to produce autoantibodies including rheumatoid factor (RF) and ACPAs.[34,36] The autoantibodies lead to osteoclasts activation that cause inflammation and bone erosion. In synovial fluid, resident neutrophils generate two major cytotoxic mediators *i.e.* proteases and reactive oxygens (ROs) further causing bone and cartilage degradation[33] (Figure 1).

The significant role of IL-17 in RA is highlighted in a study by Genovese *et al.*, 2010, where they indicate the success of clinical trial of Ixekizumab (LY2439821), the neutralizing antibodies specific for IL-17[40] where IL-17 blocking during the reactivation of antigen-induced arthritis reduces bone erosion, joint swelling and inflammation.[25] In animal models, IL-17 contributes to arthritis pathogenesis and in collagen-induced arthritis and that IL-23/IL-17 axis is critical to the development of autoimmune arthritis including RA.[14]

IL-23/IL-17 axis in SLE

SLE is a systemic autoimmune disease of unknown aetiology in which the body's immune system becomes overactive and attacks healthy tissue through autoantibodies, resulting irreversible organ damage as a primary outcome.[41] The disease is characterised by polyclonal B cell activation and resultant autoimmunity with numerous cytokines and immunoglobulins production that can serve as biomarkers and predictors of disease activity.[42,43]

The IL-23/IL-17 axis contributes to the pathogenesis of SLE. In lupus-prone mice, it was shown that IL-23 receptor deficiency lowered IL-17 production, and more importantly these mice were protected from the disease onset.[44] High serum levels of IL-17 have been demonstrated in SLE patients and associated with higher SLE disease activity

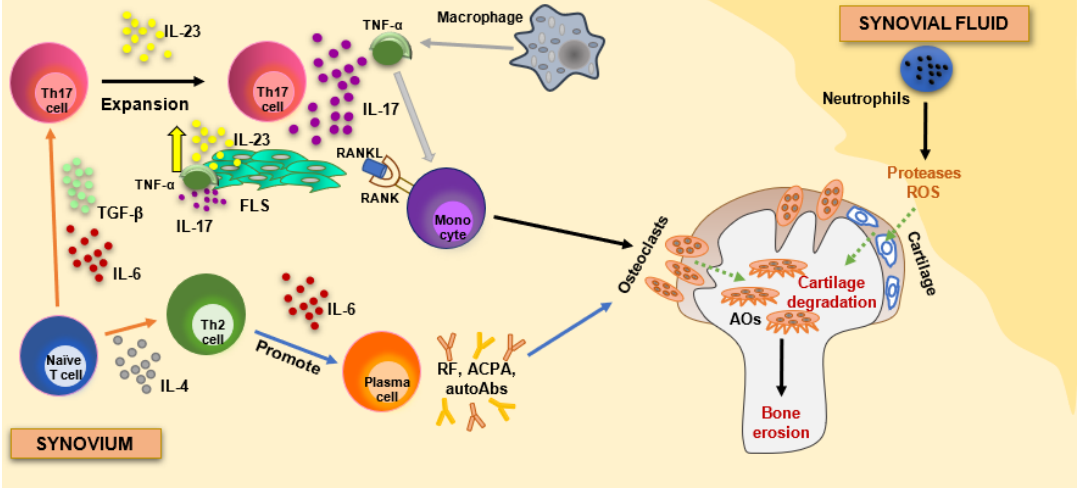

FIG. 1: **IL-23/IL-17 axis in RA pathogenesis.** $CD4^+$ naïve T cells upon stimulation with IL-6 and TGF-β differentiate into Th17. Subsequently, IL-23 induces Th17 expansion that in turn stimulates the production of IL-17. The IL-23/IL-17 axis promotes TNF-α production and RANKL expression, leading to osteoclastogenesis and subsequent cartilage degradation and bone erosion in RA patients. Other pathways contributing to the bone erosion and inflammation involve autoantibodies (autoAbs) including RF and ACPAs production by plasma cells, as well as neutrophils stimulated by pro-inflammatory cytokines to release proteases and reactive oxygen species (ROS). Sources: [33, 34, 39]

index (SLEDAI) score and it was elevated in SLE patients compared to controls.[15,45,46] Increased levels of IL-17 in the serum and increased numbers of IL-17-producing cells were demonstrated in SLE patients.[47] Moreover, increased levels of IL-17 in childhood-onset SLE (cSLE) were demonstrated in a study where 67 consecutive cSLE patients compared with 55 healthy controls.[48] In addition, higher IL-17 level was found in target organs such as skin, lungs, and kidneys, indicating a role of IL-17 in local tissue damage of SLE patients.[47]

IL-23/IL-17 axis is involved in the pathogenesis in SLE where activated DCs produce inflammatory cytokines IL-6 and IL-23, stimulating Th17 cells to produce IL-17.[49] In addition, as IL-17 and IL-23 has a major role in both onset and progression of lupus nephritis (LN) pathology, Dedong *et al*., (2019) deduce that IL-17 involved in the LN inflammatory process and IL-23 is suggested to be a non-invasive method in assessing the aggravation of LN patients. The findings of this analysis explicitly showed that IL-23/IL-17 axis plays a crucial role in the LN pathogenesis and both cytokines may be useful as biomarkers for renal disease development[50] as IL-17 has been observed in LN glomeruli patients and IL-17 producing cells are found in the kidney tissue of LN patients.[51] Interestingly, IL-23/IL-17 seems to be active in renal activity, however further investigations need to be conducted to enhance our interpretation of the IL-23/IL-17 axis.

High levels of INF-α produced by plasmacytoid dendritic cells (pDCs) promote the activation of antigen presenting cells (monocytes, mDCs, B cells) that also activate Th17 cells to produce IL-17.[52] Activated monocyte induces the production of IL-17 by group 3 ILC cells, yδ T cells, and mast cells, as well as producing IL-6 and IL-23 which also trigger activation of Th17 cells.[49] Furthermore, autoantibodies production by activated B cells lead to activation of dendritic cells (DCs) to secrete IL-23, which also contributes to enhanced production of IL-17.[52] IL-17 induces inflammatory cytokines, RANKL, MMPs, and chemokines, resulting in the recruitment of neutrophils to mediate tissue inflammation and damage in SLE. As B cells play central roles in pathogenesis of SLE[53], upregulation of B lymphocyte stimulator (BLyS) in B cells is involved in SLE development.[52,54] BLyS acts as a survival factor for B cells as it inhibits B cells apoptosis, stimulates B cells proliferation and differentiation through the interaction with IL-17, and ultimately increases autoantibodies production.[52,54] The expansion of Th17 cells is also promoted by BLyS[52] (Figure 2).

Therapeutic Antibodies Targeting IL-23

Ustekinumab

Ustekinumab is a fully humanised IgG1 monoclonal antibody that binds to the p40 subunit to inhibit both IL-12 and IL-23, preventing them from binding to their receptors on the surface of immune cells.[55] The antibody interferes with the activities of Th1 and Th17 pathways and also keratinocyte activation.[30] Ustekinumab has been approved for the treatment of moderate to severe plaque psoriasis by the European Medicine Agency and US Food and Drug Administration (FDA).[56,57]

Ustekinumab in SLE

In terms of SLE, the safety and efficacy of ustekinumab in patients with active SLE were evaluated in a phase II study.[58] Placebo-controlled trial on seropositive (ANA, dsDNA, and/or anti-Smith antibodies) SLE patients was conducted and the patients had active disease (SLEDAI score ≥6, ≥1 BILAG A and/or ≥2 BILAG B scores) despite standard of care therapy. The patients (n=102) were randomised (3:2) to receive intravenous ustekinumab (~6 mg/kg) or placebo followed by subcutaneous injections of ustekinumab (90 mg) or placebo. Ustekinumab conferred significantly better efficacy compared with placebo where 60% of the patients receiving ustekinumab displayed an SLE response index (SRI) vs 31% in the placebo patients (p=0.0046), and the risk of a new British Isles Lupus Assessment Group (BILAG) flare was significantly lower in the ustekinumab vs placebo group (p=0.0078). Furthermore, the ustekinumab group demonstrated improved musculoskeletal and mucocutaneous disease features as well as improvements in anti-dsDNA and C3 levels.[58]

In terms of case reports, Meenakshi *et al*., (2017) showed that a patient with active psoriasis, PsA and SLE responded well to ustekinumab, and suggested that Th-17/IL-23 pathway as a therapeutic target in cutaneous (non-SLE) and SLE treatments.[59] In another case report, a 58-year-old woman with subacute cutaneous lupus erythematosus (SCLE) who was not responsive to standard treatments showed marked improvement after a single injection of ustekinumab, and remained in remission for

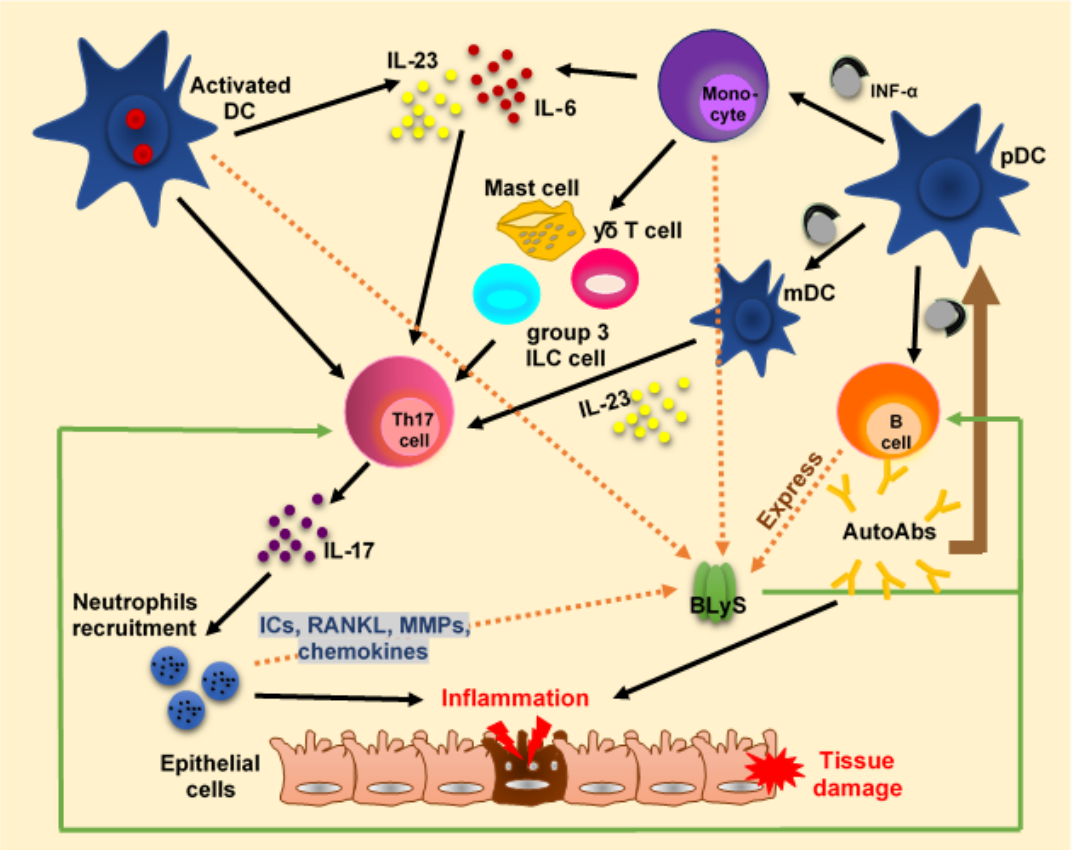

FIG. 2: **IL-23/IL-17 axis in SLE pathogenesis.** Activated DCs synthesise inflammatory cytokines IL-6 and IL-23, and promote the differentiation and expression of Th17 cells. BLyS expressed by B cells, monocytes, activated DCs, and neutrophils stimulate B cell differentiation and survival. BLyS also promotes Th17 cells expansion. pDC promotes the activation of monocytes, mDC, and B cell contributing to the induction of IL-23/IL-17 axis, which subsequently upregulates inflammatory cytokines (ICs), RANKL, MMPs, and chemokines. These result in the recruitment of neutrophils that trigger tissue inflammation and damage. Sources: [52-54]

seven months with continuous ustekinumab without side effects or adverse events.[60]

Ustekinumab and guselkumab in RA

A randomised phase II study was conducted to evaluate the efficacy and safety of subcutaneously administered ustekinumab and guselkumab (anti-IL-23 antibody) in active RA patients who were previously treated with methotrexate (MTX). Patients were randomly assigned to receive placebo (n=55), ustekinumab (90 mg; n=55), guselkumab (50 mg; n=55) and guselkumab (200 mg; n=54) every 4 weeks.[61] However, not all patients who enrolled completed the study due to lack of efficacy, adverse events (AEs), death and withdrawal of consent. By week 28, 22 patients (10%) discontinued in the study, while the remaining patients continued a stable dose of MTX (10-25 mg/week) where the primary endpoint showed at least 20% improvement in American College of Rheumatology criteria (ACR20), and safety of the therapies was monitored. However, no significant reduction in signs and symptoms of RA patients treated with ustekinumab or guselkumab where the primary endpoint (ACR20 at week 28) was not met for both antibodies.[61]

Therapeutic Antibodies Targeting IL-17

Brodalumab in and RA

Brodalumab (AMG 827) is a humanised, anti-IL-17RA monoclonal antibody where it binds and blocks the activities of interleukins 17A, 17F, 17A/F heterodimer, and 17E (IL-25).[62] In the phase Ib, multicenter, randomised, double-blind, placebo-controlled, multiple ascending dose study (NCT00771030), RA patients (n=40)

from 11 sites (7 in the United States, 2 in Canada and 2 in Mexico) were recruited. Patients were randomised 3:1 to receive brodalumab (50, 140, or 210 mg subcutaneously every 2 weeks for 6 doses per group; or 420 or 700 mg intravenous infusion every 4 weeks for 2 doses per group) or placebo. Multiple doses of subcutaneous and intravenous brodalumab were tolerated by active RA patients, however, there was no evidence of positive clinical response in the brodalumab group compared to placebo.[63]

A phase II study was done for RA patients who have inadequate response on MTX (n=252) to evaluate the efficacy and safety of brodalumab, an IL-17R antibody inhibitor in RA patients. Patients were randomised to receive brodalumab through subcutaneous injections (70 mg, 140 mg, or 210 mg) or placebo. It is reported that there were no significant effects of treatment throughout the study while one death of patient was reported approximately 1 week after the last dose of brodalumab in 140 mg group due to cardiopulmonary failure. Thus, the study does not find meaningful evidence of clinical efficacy with treatment of brodalumab in patients with inadequate response to MTX.[64]

Secukinumab in RA

Secukinumab (AIN457) is an IgG1k, fully human monoclonal antibody that targets IL-17A and blocks its interaction with the receptor, IL-17R.[65] A phase II, double-blind, randomised and placebo-controlled study[66] was conducted to evaluate the one-year efficacy and safety profile of secukinumab in RA patients (n=237). RA patients on MTX and responded to DMARD or other biologics were randomised (1:1:1:1) to receive monthly subcutaneous injections of secukinumab or placebo for 48 weeks (25, 75, 150, 300 mg). A total of 174 patients (73.4%) completed the study and the authors reported that active RA patients who failed to respond to DMARD and other biologics showed an improvement after treatment with 150 mg of secukinumab as indicated by improvements in ACR responses and Disease Activity Score in 28 joints (DAS28) scores over time up to a year, as well as reduction in CRP levels, improvement in DAS28 using the C-reactive protein level (DAS28-CRP) <2.6 rates, and HAQ-DI scores (Table 3).

Another phase II study was conducted to evaluate the efficacy and safety of secukinumab, administered with an intravenous or subcutaneous loading regimen versus placebo, in patients with active RA (n=221).[67] RA patients on MTX were randomised to receive the following: (i) secukinumab intravenous loading 10 mg at baseline on weeks 2 and 4, then subcutaneous 150 mg every 4 weeks (n = 88); (ii) secukinumab subcutaneous loading 150 mg once weekly for 5 weeks, then every 4 weeks (n = 89); (iii) matching placebo followed by secukinumab 150 mg every 4 weeks starting in week 16; n = 44). The authors reported that the results did not meet the primary efficacy endpoint (ACR20 response) at week 12 for secukinumab compared with placebo (p=0.3559), but secukinumab demonstrated improved efficacy in reducing disease activity over placebo as measured by DAS28 and other secondary endpoints.

To evaluate the efficacy and safety of secukinumab in patients with active RA patients (n=551) who had an inadequate response to or intolerance of tumour necrosis factor (TNF) inhibitors, a phase III study (NURTURE 1) was conducted.[68] A total of 551 patients were randomised (1:1:1:1) to receive intravenous secukinumab at a dose of 10 mg/kg (at baseline and weeks 2 and 4) followed by subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks or, alternatively, abatacept or placebo on the same dosing schedule. The primary endpoint was the proportion of patients achieving 20% improvement in disease activity according to ACR20 at week 24 in patients receiving 150 mg secukinumab was significantly higher compared with placebo. The ACR20 response rates at week 24 were 30.7% in patients receiving 150 mg secukinumab (p=0.0305), 28.3% in those receiving 75 mg secukinumab (p=0.0916), and 42.8% in those receiving abatacept, compared with 18.1% in the placebo group. A significant reduction in the DAS28-CRP was seen in patients treated with 150 mg secukinumab (p=0.0495), but not in patients treated with 75 mg secukinumab. The authors concluded that secukinumab at 150 mg resulted in improvement in signs and symptoms with reduced disease activity in patients with active RA who had an inadequate response to TNF inhibitors.

Another phase lll study was conducted by Dokoupilova *et al*., (2018) to assess the efficacy and safety of secukinumab in patients with RA who failed to respond to TNF-α inhibitors. A total of 242 RA patients were randomised (1:1:1) to subcutaneous secukinumab 150 mg, 75 mg or placebo at baseline (weeks 1, 2, 3, 4 and every 4 weeks), where ACR20 response at week 24

TABLE 3: Summary of anti-IL-23 or anti-IL17 therapeutic antibodies examined in phase II/III clinical trials for SLE and RA patients

Therapeutic antibodies	Trial	Phase	Disease	Patient Population	Treatment	Outcomes
Ustekinumab	NCT02349061 [77]	II	SLE	Active SLE patients (n=102) - Ustekinumab group (n=60) - Placebo group (n=42)	• Ustekinumab IV • Placebo Infusion • Placebo SC • Ustekinumab SC • Concomitant Medication	At week 24, 62% in the ustekinumab group (n=37) and 33% in the placebo group (n=14) achieved an SRI-4 response (percentage difference 28% [95% CI 10-47], p=0·006). Between week 0 and week 24, 47 (78%) of 60 patients in the ustekinumab group and 28 (67%) of 42 patients in the placebo group had at least one adverse event.
	NCT01645280 [61]	II	RA	Active RA patients who were previously treated with MTX (n=274)	• Placebo + methotrexate (MTX) • Ustekinumab 90 mg + MTX • CNTO1959 (guselkumab) 50 mg + MTX • CNTO1959 200 mg + MTX	No differences in the proportion of patients achieving an ACR20 response Treatment with ustekinumab or guselkumab did not significantly reduce in symptoms or signs of RA
Brodalumab	NCT00950989 [64]	II	RA	RA patients who have inadequate response to MTX (n=252)	• AMG827 70 mg • AMG827 140 mg • AMG827 210 mg • Placebo	ACR50 occurred in 16% (70 mg & 140 mg), 10% (210 mg) and 13% (placebo) At secondary endpoint, no significant treatment effects were observed

TABLE 3: Summary of anti-IL-23 or anti-IL17 therapeutic antibodies examined in phase II/III clinical trials for SLE and RA patients

Therapeutic antibodies	Trial	Phase	Disease	Patient Population	Treatment	Outcomes
Secukinumab	NCT01770379 [69, 72]	III	RA	RA patients (n=242)	• Secukinumab 150 mg • Secukinumab 75 mg • Placebo (1:1 ratio to secukinumab)	At week 24, ACR20 response rates for both secukinumab 150mg and 75 mg respectively, were not statistically significant to placebo, and the secondary endpoints were not met
	NCT01359943 [67]	II		RA patients on MTX (n=221)	• Secukinumab IV • Secukinumab SC • Placebo	Did not meet the primary efficacy endpoint (ACR20 response) at week 12 for secukinumab and placebo. However, DAS28, patient's and physician's global assessment of disease activity, patient's assessment of RA pain, and high-sensitivity C-reactive protein levels were improved significantly with pooled secukinumab Secukinumab demonstrated improved efficacy to reduce disease activity
	NCT01350804 [68, 72]	III		Active RA patients who had inadequate response to TNF inhibitors (n=551)	• Secukinumab • Placebo • Abatacept (Doses: 10, 75, 150 mg)	20% improvement in ACR20 at week 24 in 150 mg secukinumab group Reduction of DAS28-CRP in 150 mg secukinumab group (p=0.0495)
	NCT00928512 [66]	II		RA patients on MTX and responded to DMARD (n=237)	• Secukinumab • Placebo (Doses: 25, 75, 150, 300 mg)	ACR responses and DAS28 scores improved with 150 mg secukinumab
	NCT01426789 [70]	II		Biologic-naïve subjects with RA (n=100)	• Secukinumab 10 mg/kg i.v • Placebo	At week 12, secukinumab was significantly more effective than placebo in reducing DAS28-CRP (-2.41 vs -0.71; $p < 0.0001$) and producing ACR20 responses (87.1% vs 25.0%; $p < 0.0001$)
	NCT01377012 [71, 72]	III		Active RA patients (n=637)	• Secukinumab 10 mg/kg • Secukinumab 150 mg or 75 mg	Improvements in secondary endpoints were greater in secukinumab groups when compared to placebo Secukinumab 150 mg showed significant better clinical therapeutic option

TABLE 3: Summary of anti-IL-23 or anti-IL17 therapeutic antibodies examined in phase II/III clinical trials for SLE and RA patients

Therapeutic antibodies	Trial	Phase	Disease	Patient Population	Treatment	Outcomes
Ixekizumab	NCT00966875 [75, 76]	II	RA	Part A: Biologics-naïve RA patients (n=260)	• Ixekizumab + DMARDs • Placebo + DMARDs	Significant dose-response relationship at week 12 in biologics-naïve RA patients (p=0.031)
				RA patients with an inadequate response to TNF inhibitors (n=188) [75]		For patients with an inadequate response to TNF inhibitors, ACR20 responses at week 12 were significantly better with ixekizumab than placebo (p<0.05)
				Part B: RA patients who completed previous study, biologics-naïve RA patients (n=232)	• Ixekizumab 160 mg • Placebo	AE occurred in 72% biologic-naïve and 73% TNF-IR patients during OLE
				TNF-IR RA patients (n=158) [80]		ACR20, ACR50, ACR70, and DAS28-CRP observed at week 16 were maintained or improved through week 64

was the primary endpoint, meanwhile secondary outcomes included DAS28-CRP, HAQ-DI, and ACR50 at week 24. ACR20 response rates at week 24 for both secukinumab 150mg and 75 mg were not statistically significant to placebo respectively, and the secondary endpoints were not met for both doses. The authors concluded that, inhibition of IL-17A with secukinumab did not provide benefits or advantages to RA patients.[69]

Burmester *et al*., (2016) conducted a phase II study to assess the association of HLA-DRB1 alleles with the clinical responses to secukinumab in active RA patients. 100 of biologic-naïve RA patients were randomised 2:1 to secukinumab 10 mg/kg i.v. or placebo every 2 weeks until week 10. As a result, secukinumab was reported as significantly more effective than placebo, reducing DAS28-CRP and producing ACR20 responses, however, there was no significant relation between HLA-DRB1*04 allelic group and response of secukinumab vs placebo. Secukinumab was concluded that the signs and symptoms of RA were significantly reduced when compared with placebo.[70]

In addition, another phase III study were reported by Tahir *et al*., (2017) and Huang *et al*., (2019) recruiting active RA patients who have an inadequate response to anti-TNFα (n=637). The patients were randomised 1:1:1 to receive intravenous secukinumab 10 mg/kg during baseline, week 2 and week 4, followed by subcutaneous secukinumab 150 mg or 75 mg. Secukinumab demonstrated efficacy in reducing disease activity over placebo as measured by ACR20 in active RA patients, promising a safety profile similar to other biologics currently approved for RA treatment.[71] Meanwhile, as secukinumab 150 mg showed significantly better clinical efficacy with no increased risk of AEs and serious AEs compared with placebo as reported by Huang *et al*., (2019), it is concluded that secukinumab may be the best therapeutic option for treatment if RA.[72]

Ixekizumab in RA

Ixekizumab (LY2439821) is a recombinant, high-affinity and humanised IgG4 monoclonal antibody that targets IL-17.[73] In early 2016, it has been approved by European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) for the treatment of psoriasis.[74]

A randomised, double-blind study was conducted to evaluate ixekizumab in two populations of RA patients: biologics-naïve patients (n=260) and patients with an inadequate response to TNF inhibitors (n=188)[75] conducted a randomised, double-blind study, to evaluate ixekizumab in 2 populations of RA patients: biologics-naïve patients (n=260) and patients with an inadequate response to TNF inhibitors (n=188). Placebo or ixekizumab was administered subcutaneously at weeks 0, 1, 2, 4, 6, 8, and 10 with concomitant DMARDs. Significant dose-response relationship was observed as measured by ACR20 response rates at week 12 in biologics-naïve patients (p=0.031). For patients with an inadequate response to TNF inhibitors, ACR20 responses at week 12 were significantly better with ixekizumab than placebo (p<0.05). Decreases in the DAS28-CRP, Clinical Disease Activity Index (CDAI), and CRP level from baseline were observed at week 12 in the ixekizumab groups in both populations (p<0.05 vs placebo). The authors concluded that ixekizumab improved the signs and symptoms of RA patients who were either naïve to biologics treatment or had an inadequate response to TNF inhibitors.

This study was continued by another phase II study for safety and effectiveness in both biologic-naïve and TNF-inadequate responder (TNF-IR) of RA patients through 64 weeks.[76] Patients who completed the 16-week double-blind period of a phase II study were eligible to enter the open-label extension (OLE) for an additional 48 weeks of ixekizumab treatment. After a treatment between weeks 10 to 16, biologic-naïve patients (n=232) and TNF-IR patients (n=158) entered the OLE with all patients receiving 160 mg ixekizumab at weeks 16, 18, and 20, and then every 4 weeks through week 64. The authors reported that 201 (87%) biologic-naïve and 99 (62%) TNF-IR patients completed the OLE and adverse events (AE) occurred in 168 (72%) biologic-naïve and in 115 (73%) TNF-IR patients during the OLE. Ixekizumab was well tolerated, and safety findings in the OLE were consistent overall with those in the double-blind period of this study. Clinical improvements observed with ixekizumab through week 16 were maintained or improved in patients participating in the OLE through week 64. Authors concluded that, Ixekizumab was well tolerated and shows consistent safety findings in OLE.

CONCLUSION

As IL-23/IL-17 axis is involved in the pathogenesis of autoimmune diseases, therapeutic antibodies

targeting IL-23 (ustekinumab, guselkumab and tildrakizumab) or IL-17 (brodalumab, secukinumab, and ixekizumab) have translated into clinical trials for these diseases. Our literature searches showed that an anti-IL-23 therapeutic antibody, ustekinumab has been studied in SLE and RA with better efficacy and no significant differences, respectively, compared to placebo or control group. In particular, ustekinumab has been approved for treatment of psoriasis while phase II (NCT02349061)[77] and phase III (NCT03517722)[78,79] trials are ongoing to assess the safety and efficacy of ustekinumab in SLE patients.

On the other hand, anti-IL17 antibodies (secukinumab and ixekizumab) have shown improved clinical benefits for RA patients in phase II/III studies. Studies involving anti-IL-17 antibodies in SLE patients are lacking and thus recommended for future investigations. Finally, as the IL-23/IL-17 axis plays key roles in the pathogenesis of SLE and RA, and the successful clinical trials of anti-23 or anti-17 therapeutic antibodies in other autoimmune diseases, we suggest that dual antibodies targeting IL-23 and IL-17 represent a potential treatment option for SLE and RA.

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