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CYTOKINES IN RHEUMATOID ARTHRITIS: GENE POLYMORPHISMS AND THERAPEUTIC IMPLICATIONS

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ABSTRACT: Rheumatoid arthritis (RA) is an inflammatory disease that causes persistent systemic inflammation and progressive joint destruction, which can result in lifelong disability. RA pathogenesis involves a complicated network of cytokines that stimulate synovial cell growth and induce cartilage and bone degradation. Variations in cytokine expression profiles play a key role in the persistence of inflammation and joint damage in RA. The complex interactions have been emerged as an important factor regulating RA susceptibility, disease severity, and treatment effects. Production of these cytokines, at large, is affected by variations in cytokine genes. Targeted medicines that attempt to block specific cytokines or regulate intracellular signaling pathways have drastically altered RA treatment. Biologic disease-modifying antirheumatic drugs that target cytokines and small molecule inhibitors that disrupt intracellular signaling have shown efficacy in controlling RA symptoms and slowing disease progression. The present review collectively summarizes the association of cytokine gene polymorphisms in susceptibility toward RA in different populations. In addition, the various emerging biological therapies in RA involving cytokines as targets have been discussed. More research into the complex links between cytokine dysregulation, genetic variability and treatment responses will pave the way for more precise and successful RA management options.

Keywords: Autoimmunity, Biologicals, Genetic variations, Inflammation, Monoclonal antibodies, Polymorphisms

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1. INTRODUCTION

Cytokines are proteins/glycoproteins that are secreted predominantly by leukocytes in the effector phase of the immune response. These exhibit diverse functions including cell growth, angiogenesis, inflammation, etc. Based on their actions, cytokines can be broadly classified into pro-inflammatory and anti-inflammatory. A regulated immune response effectively demands a balance between these two types. Thus, any imbalance in terms of their overproduction or deficiency may lead to immunological disorders including systemic lupus erythematosus, Crohn's disease, inflammatory bowel disease, and Rheumatoid arthritis (RA). RA is a chronic inflammatory autoimmune disease characterized by, persistent synovitis and systemic extra-articular manifestations with progressive joint destruction [1]. The worldwide prevalence of RA is approximately 1% but may vary according to geographical location and race. In India, the prevalence of RA has been reported to be 0.7% [1]. Various infiltrating immune cells accumulated at the affected joint, leading to the production of a set of cytokines, which further set the course of the disease [2]. Production of these cytokines, at large, is affected by variations in cytokine genes. Extensive research on the role of cytokines in RA pathophysiology has led to the elucidation of the pivotal role of numerous cytokines in the disease process. The findings further set the pace to evaluate these cytokines as therapeutic targets in the management of RA. The present review collectively summarizes the association of cytokine gene polymorphisms in susceptibility toward RA in different populations. In addition, the various emerging biological therapies in RA involving cytokines as targets have been discussed.

CYTOKINE GENE POLYMORPHISMS IN RHEUMATOID ARTHRITIS

A growing body of evidence including case-control studies and meta-analyses demonstrated the association of various cytokine gene polymorphisms with susceptibility towards RA.

Genetic polymorphism in Pro-Inflammatory cytokines genes:

The various members of this category include Interleukin (IL)-1, IL-18, TNF-α, IL-6, IL-17, IL-15, IL-2, IL-12, etc. (Table 1).

Interleukin-1

A growing body of evidence supported the significant association of IL-1β -511C/T with increased risk of RA [3-7]. A significantly high frequency of TT genotype of this variant was observed in patients with positive anticitrullinated protein/peptide antibodies compared with the negative group [5], [8]. In contrast to this, another study showed no significant association of this SNP with

an increased risk of RA [(9]. No association of IL-1 β +3953 C/T with RA was observed in different populations [4,5,8]. In contrast, a study by Arman et al., (2006) showed a 3 significant difference in frequency distribution between cases and controls [7]. Furthermore, various independent studies showed no association of other IL-1 single nucleotide polymorphisms (SNPs) including rs2058660, rs2310173, rs13015714, rs3811047, and rs1143643 with RA [10-15]. Meta-analysis of IL-1α rs1800587 polymorphism showed no association with RA susceptibility [16]. Another meta-analysis found that IL-1α +4845G/T and IL-1β +3954C/T polymorphism showed a significant association with RA, but no association was found with IL-1α –889C/T, IL-1β –31T/C, and IL-1β –511C/T polymorphism towards RA disease [17]. Further, another meta-analysis found a significant correlation between IL-1β SNPs (rs1143634 C/T and rs1143627 C/T) and RA [18].

Interleukin -2

A significant strong association of rs6822844 was found with RA susceptibility [19-22]. Another variant *i.e.* rs13151961 also showed a significant association with RA risk [23]. However, studies revealed no association of rs2104286, in interleukin-2Rα, with RA susceptibility [24-25]. Similarly, rs743777 in Interleukin-2Rβ showed no significant association of this SNP with RA risk [26]. Genotypic and allelic distribution of -330 promoter SNP of IL-2 showed no risk association, but a significant association with disease severity [27]. No association of -384 and 114 SNPs of IL-2 was observed with susceptibility towards RA [28].

Interleukin-6

A case-control study in the Chinese Han population revealed an association of IL-6 SNPs *i.e.*, rs1800797 and rs1474347 with increased RA risk [29]. The study revealed a significantly high prevalence of the GCCGCT haplotype in patients as compared to controls, whereas the GGCGCT haplotype was suggested as a protective factor towards RA. A promoter polymorphism of IL-6 *i.e.* rs1800795 (-174 G/C) has been extensively studied in RA. Two independent studies in the Chinese population showed an association of rs1800795 (-174G/C) with increased risk for RA [29,30]. However, no association has been observed for this SNP in the Kashmiri and Turkish populations [4,31,32]. Furthermore, this SNP was also found to be associated with improved disease outcomes in RA patients receiving anti-tumour Necrosis Factor-α (TNF- α) therapy and hence suggested as a genetic marker of responsiveness to anti-TNF-α therapy [33,34]. Conflicting results have been obtained regarding the association of this SNP with CVD risk in RA patients [35,36]. Additionally, rs12083537 in the IL-6R gene was found to be related to improved clinical outcomes in RA patients with therapeutic response to tocilizumab [37]. rs2243289 was linked with a lower risk of RA disease, while rs2069837 was associated with an increased risk of RA disease [38]. Another study in the Chinese Han population showed no significant difference in the genotypic/allelic distribution of rs6946864 between cases and controls, while a significant difference in allelic distribution of rs11265628, an SNP of IL-6R, was observed [39]. Another study showed a

significant association between rs4845618 and rs4453032, with an increased degree of joint destruction in RA [12]. Nisar et al., (2020) found that rs1800795 increased the risk of RA in the Pakistani population [40]. A further study reported no positive correlation between rs184229712 and rs36215814 of IL-6 with RA susceptibility [41]. A study by De Lima et al., (2020) showed no association between IL-6 rs1800795 SNPs and RA disease [42]. In a meta-analysis IL-6-174G/C polymorphism was significantly associated with RA but IL-6 -572G/C polymorphism showed no association [43]. In another meta-analysis, out of three polymorphisms (IL-6 rs1800795, IL-6R rs12083537, and IL-6R rs4329505), rs1800795 and responsiveness to Drug modifying antirheumatic drugs (DMARDs) were found to be significantly [44]. Also, a strong link was observed between the IL6R rs12083537 AA genotype and tocilizumab responsiveness in RA patients but no positive association was seen between IL-6R rs4329505 polymorphism and RA disease in response to tocilizumab. Furthermore, the two IL-6 SNPs *i.e.* rs1800796 and rs1800797, were significantly correlated with RA susceptibility [18].

Interleukin-8

A study in IL-8 3'-UTR 2767A/G polymorphism in RA showed no significant difference in genotypic and allelic distribution between cases and controls [45]. Another study in the Caucasian population showed an association of IL-8 781C/T with the onset of RA [46].

Interleukin-12

A genetic association study showed no significant difference in IL-12 SNP +1188 A/C in the Brazilian population [47]. IL-12B rs17860508 showed a positive association towards RA but no association was found between rs3212227 and RA in the Bulgarian population [48]. rs2243115 of IL-12A showed no association with RA in the Chinese population [49]. IL-12 B gene SNPs rs3212227 and rs6887695 were associated with RA in the Chinese population. However, meta-analyses showed no association of these SNPs with RA [50,51].

Interleukin-13

There are two studies have been documented to assess the role of IL-13 SNPs in susceptibility to RA. A case-control association study in the Chinese Han population indicated the association of this SNP with RA patients having ESR <25, while, no association of rs1800925 C/T polymorphism was observed in overall RA patients [52,53]. Another IL-13 variant rs1295686, showed no association with susceptibility towards RA [53].

Interleukin-1

A case-control study in the Tunisian population showed a significant association of rs10519613 with disease susceptibility [54]. Another study showed a significant association of -267C/T polymorphism with RA [55].

Interleukin-16

A significant association of rs1131445 polymorphism in the IL-16 gene was observed with risk

and clinical characteristics of RA in the Iranian population [56]. Patients with rs1131445 C allele had higher serum concentrations of C-reactive protein as well as blood urea nitrogen, triglyceride, and erythrocyte sedimentation rates.

Interleukin-17

A perusal of literature revealed the conflicting results regarding the association of rs2275913 (-197G/A) of IL-17 A with susceptibility towards RA. Some studies reported a significant association of this SNP with increased risk towards RA [57,58]. Other studies reported no association of this SNP with susceptibility toward RA [59-61, 40]. rs3819024, rs3819025, and rs8193036, other SNPs of IL-17 A, were significantly associated with RA in the Chinese population [57]. On the other hand, rs4711998 and rs8193037 of IL-17A did not show any association with RA susceptibility. A study by Amin *et al*., (2021) indicated a positive correlation of three SNPs (IL-17A gene (rs2275913), IL-17F gene (rs763780), and IL-17F gene (rs2397084) with RA in the Pakistani population [62]. rs8193037, rs2275913, rs3819024, and rs8193036 were not significantly associated with RA susceptibility [63]. Further, found no statistically significant links between IL-17A (rs2275913) and IL-17R (rs708567) polymorphisms and RA susceptibility [64]. Various case-control studies showed no association of rs763780 of IL-17 F with susceptibility towards RA [40,59-61,65]. Furthermore, this SNP was found to be significantly correlated with various disease activity parameters [65]. In contrast, a single study by Bogunia-Kubik *et al*., (2015) showed a significant association of this SNP with increased RA risk [66]. A Study in the Japanese population showed a significant association of rs3804513 with radiographic progression in RA patients [67]. Other IL-17F SNPs including rs2397084, rs11465553, and rs2397084 did not show any significant association with RA [57,59,61]. A meta-analysis revealed a significant association of IL-17A SNPs rs2275913 and rs763780 with RA susceptibility [68]. However, a meta-analysis could not find any conclusive links of rs2275913 with RA susceptibility [69].

Interleukin-18

There are two widely studied promoter SNPs of IL-18 *i.e.*, rs1946518 and rs187238 in RA. Several research including meta-analysis demonstrated the association of rs187238 with RA [70].

Interleukin-21

Hao *et al*., (2021) studied IL-21 SNPs (rs907715, rs2221903, rs2055979) in RA [71]. Out of these three SNPs, a significant correlation was found between rs2055979 and RA susceptibility. Higher plasma levels of IL-21 were also observed in the individuals carrying the AA genotype of rs2055979, intermediate levels in CA, and lower levels in the CC genotype.

Interleukin-23

In the Polish population, no association of three SNPs, (rs10889677, rs11209026, and rs2201841) of IL-23R was found with RA susceptibility [72]. A meta-analysis by Mohammadi *et al.*, 2019

assessed seven SNPs of the IL-23R gene (rs1343151, rs1004819, rs10489629, rs11209026, rs2201841, rs7517847, rs10889677) in RA susceptibility [69]. Out of these, two SNPs in the IL23R gene (rs1343151 and rs2201841) were found to be significantly linked to the risk of RA.

Interleukin-32

Only one single nucleotide polymorphism *i.e.* rs4786370 of IL-32 has been studied in susceptibility to RA [73]. Patients with the TT genotype showed higher mRNA expression of IL-32β. Patients with CC genotype on the contrary showed high IL-32γ mRNA expression. However, when PBMC was stimulated with rhTNF-α, patients with TT genotype expressed higher IL-32γ, when compared to the unstimulated cells and patients with the CC genotype.

Interleukin-33

A significant association of rs3939286 was observed with the risk of subclinical atherosclerosis in RA patients, with the T allele associated with a protective role in the development of subclinical atherosclerosis in RA patients [74]. A significant association of rs7044343 was observed with susceptibility towards RA, while rs10975514 showed no significant association with risk towards RA in the Chinese Han population [75].

Tumor necrosis factor-α

A genetic association study found statistically significant links between rs1800629 and RA [76,77]. Another study found a significant association between rs361525 and RA [78]. A study by Ayón-Pérez *et al.,* (2019) reported no correlation between TNF-α -857C/T polymorphism and RA disease [79]. Various studies including a meta-analysis demonstrated the significant association of TNF-α -308 with susceptibility towards RA [80,81]. In contrast, other studies showed no significant association [82,83]. Furthermore, TNF-α -308 gene polymorphism was not found to be associated with the efficacy of therapy with TNF-α inhibitors in patients with RA [66]. A single study for rs1799964 did not show any significant association with RA susceptibility [83]. A study found no significant association between the rs1800630 and RA [84]. No association of rs1799724 was observed with RA in the Pakistani population [85]. A study by Sandoval *et al.,* (2018) found no association of studied SNPs with RA susceptibility [86].

Transforming growth factor- β

A study by Vasilev *et al.,* (2022) found no association between -509C/T promoter polymorphisms and RA [87]. CC genotype of +869T/C showed a protective association with RA in the Chinese population [88]. Another study reported the association of the T allele and TT genotype of this SNP with RA susceptibility in the north Indian population [89]. Various studies including meta-analyses showed a significant association of +869T/C with RA susceptibility in the Egyptian population [90-94]. In contrast, studies in the Turkish population showed no association of this SNP with RA [95,96]. Meta-analyses indicated TT genotype as a risk factor for RA only in Asians, but not in Caucasians [93,97]. Studies showed the association of this SNP with the risk of

osteoporosis (OP) and bone erosion, as disease severity factors in RA [92,98]. In contrast, another study reported no association of this SNP with the risk of OP in RA [99]. A significant association of +869T/C was found with susceptibility towards hypertensive risk factors in RA patients [100]. Genotypic distribution of -509C/T indicated a significant association with disease susceptibility [91]. Various Studies revealed no significant association of G915C with susceptibility toward RA [97,101].

Interferon-γ

A study revealed no association of rs2430561 with RA susceptibility and cardiovascular morbidity and mortality in RA patients [47,102]. However, another study revealed the association of this SNP with the risk of diabetes mellitus in RA patients [103]. Another SNP of IFN-γ rs2069705 was proposed to modulate the response to anti-TNF drugs in RA patients [104].

Allograft inflammatory factor-1

There are scanty reports regarding the association of AIF-1gene polymorphisms with susceptibility towards RA. A significant association of rs2269475 was observed with increased risk of RA, with positive correlation of T allele with Anti-cyclic citrullinated peptide (anti-CCP) production [105]. Another study in Polish RA patients showed no statistically significant association of rs2736182 and rs2259571 with susceptibility toward RA [106]. Lack of association of rs2269475, rs2736182, rs2259571 with response to sulphasalazine was observed in RA patients [107]. Another study showed a significant association of rs2259571 with methotrexate (MTX) therapy in RA patients. Patients having CC genotype of rs2259571 were shown to have poor response towards MTX therapy in RA. While, there was a lack of association for rs2269475 and rs2736182 with MTX therapy response [108].

Genetic polymorphism in Anti-Inflammatory cytokines genes:

These included IL-1Ra, IL-4, and IL-10 (Table 1).

Interleukin-4

Different studies reported the significant association of rs2243250 of IL-4 with RA [104,109]. A significant association of -590C/T has been observed with increased risk and activity of RA [29,110]. Studies showed an association of rs1805010 with RA [111-113]. A significant association of rs1801275 has also been reported with RA in two independent reports [112,113]. Another study suggested that a minor allele of rs1805010 may contribute towards enhanced Th17 cell frequency and clinical manifestations of the disease [114].

Interleukin-10

A significant association of rs1800896 was observed with RA susceptibility [3,42,65,80,115]. However, no association of rs1800890, rs3024495, and rs3024505 was observed with RA risk [116]. Furthermore, no association was found between rs1800896 and RA in the Bulgaria population [87]. De Lima *et al.,* (2020) found no association between the rs1800896 and RA in the

Brazil population but TT and CC genotypes was significantly associated with a high and low clinical disease activity index (CDAI) value respectively [42]. Comparison of genotypic/allelic distribution showed significant differences between RA patients with or without anti-cyclic citrullinated peptide antibodies [117]. A growing body of evidence including meta-analysis demonstrated the association of rs1800872 with RA [117-119].

Interleukin-35

A genetic association research in the Chinese population studied 10 SNPs (IL-12 rs2227314, rs2243115, rs2243123, rs2243131, rs568408, rs583911) [120]. Out of these, a significant correlation was seen between rs2227314, rs2243131 and rs583911 and RA susceptibility. A significant correlation was also observed between the genetic polymorphism (rs2227314, rs583911and rs9807813) and serum levels of IL-35 in RA susceptibility.

Interleukin-37

rs3811047 variant demonstrated a protective effect against severe RA activity in Chinese Han population [14]. However, no association with this variant was observed in the Egyptian population [121]. Another two studies have observed rs3211047 variant in the Chinese Han population, however, no positive association was observed with RA.

CYTOKINES AS THERAPEUTIC TARGETS IN RHEUMATOID ARTHRITIS

Traditional treatments used as therapeutics of RA mainly included DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs). Despite being extensively used, these drugs offer certain major concerns which mainly included non-responsiveness by subset of patients, remission of diseases flares, associated co-morbidities, adverse effects on long term usage *etc.* So, during last few decades the use of biologic agents was emerged as a boon for the treatment of RA. Being important mediators in inflammation, cytokines have been considered as one of the important molecules to target as therapeutics. Over the past years, various approaches have been developed to target these cytokines directly or indirectly. Some of these approaches have completed their clinical trials and are being effectively used in various autoimmune diseases [122,123]. The various strategies being used for modulating the cytokines expression in the pathogenesis of RA are given in Figure 1.

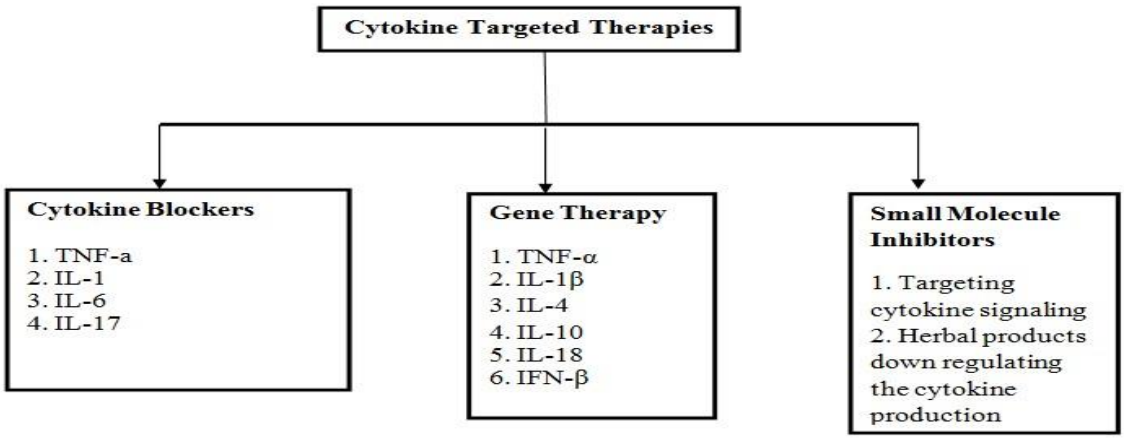

Figure 1: various strategies being used for cytokine-targeted therapies

Cytokine blockers

The various cytokines being targeted by use of their respective antibodies included TNF-α, IL-1, -6, -15, -17 (Table 2). Till date, five antibodies have been used against TNF-α for the treatment of RA [124]. Studies using these biologicals alone or in DMARD combination in RA patients, particularly poor responders of MTX, showed significantly improved outcomes [125]. Anti IL-1 drugs exhibit their action by blocking the activities of IL-1Rα or IL-1β [126-128]. All these drugs are either under clinical trials or completed clinical trials, but not validated for approval. Two Key phase III studies using Tocilizumab, an IL-6 inhibitor, showed approximately 60% positive outcomes in RA patients [129,130]. Olokizumab, another IL-6 inhibitor, binds specifically to IL-6 and neutralizes its activity by preventing the development of the extracellular signaling complex's hexamer, blocking transmembrane signaling, and showed significant improvement [131,132]. Further studies reported more effectiveness of olokizumab than methotrexate, and even better outcomes in combination [133,134]. Besides this, there are many other novel antibodies against IL-6, which are currently under clinical trials, including Sarilumab, Siltuxmab, and Sirukimab [135-138]. AMG714 (HuMax-1L-15), is the only drug to target against IL-15. Anti IL-17 antibodies have been targeted to IL-17A, IL-17E, IL-17F. The dual-variable domain immunoglobulins can additionally bind to TNF-α. Use of antibodies and decoy receptors specifically target at specific cytokine, rather than to induce overall immuno-suppression. So, in this way, this strategy offers an advantage over conventional methods, to be used as RA therapeutics [139]. A growing body of evidence indicated that combination therapy of anti-TNF-α drugs with MTX or other DMARDs resulted in the superiority of the drug over their use as monotherapy [140-142]. In contrast, the efficacy of tocilizumab appeared as its monotherapy over a combination with DMARDs [143,144].

Gene Therapy

This approach included either the downstream regulation of pro-inflammatory cytokines or upstream regulation of anti-inflammatory cytokines. The various genes targeted using this approach included TNF-α, IL-1β, IL-4, IL-10, IL-18 and IFN-β (Table 3).

Use of Small Molecule Inhibitors for Targeting Cytokines

Another approach adopted as therapeutics for RA included the use of small molecules which can inhibit cytokine production, rather than directly targeting the individual cytokine. Various naturally occurring inhibitors of cytokine signaling have been reported (Table 4) [145]. These molecules have been linked with reduced disease incidence and disease severity in murine models having adjuvant arthritis and CIA, improved the histologic and radiographic indicators of the disease [146-150]. Various studies reported the use of herbal products for their host anti-inflammatory and anti-arthritic properties [151,152]. The effects of these drugs were mediated by targeting various mediators involved in cytokine production. This included the inhibition of various cell signaling pathways which lead to down-regulation of cytokine synthesis (Table 4).

Other approaches:

A Perusal of the literature demonstrated the use of a low dose of IL-2 as an efficacious treatment of various autoimmune diseases [153-159]. Studies showed the efficacy and safety of IL-2 treatment in RA patients [160]. Furthermore, low-dose-IL-2 was suggested as a novel and safe therapeutic approach for RA that could synergize with methotrexate (MTX) to restore immune balance and reduce inflammation [161].

Limitations of using cytokines as therapeutics

Despite being so efficacious, these biologicals offer many limitations including short-lasting effect or remission of disease flares, susceptibility to various infections including tuberculosis (TB), Pneumonia, and viral infections including hepatitis B, herpes zoster, and hepatitis C, *etc.* in RA patients [162-166,179]. A few studies also showed the adverse effects of these drugs as cancer risk and anaphylactic reaction [167-169].

CRITICAL COMMENTS

Cytokines are pivotal molecules in inflammatory and autoimmune diseases including RA. Association of cytokines gene polymorphisms with RA risk, progression and severity has let to important findings. These observed differences in different studies may be attributed to ethnicity differences in the populations being tested or population stratification due to hospital-based studies. These findings necessitate the need of testing cytokines related treatment strategies in various population sets. Early interventions with various strategies using cytokines appear to have favorable outcomes, although coupled with some limitations.

TABLE 1: ROLE OF VARIOUS PRO-INFLAMMATORY CYTOKINES IN THE PATHOGENESIS OF RA

Cytokines	**Cellular Source**	**Functions**
	Pro-inflammatory cytokines	
IL-1	Macrophages, monocytes, microglia, lymphocytes, keratinocytes,	Monocyte activation, increased osteoclast activation, oxidative burst, chemokine release
IL-2	Activated T cells, dendritic cells, NK cells	The proliferation of effector T and B cells, differentiation and proliferation of NK cells, and growth factors for B cells
IL-6	Mononuclear phagocytes, vascular endothelial cells, fibroblasts	Pannus formation, neutrophil recruitment, osteoclast activation
IL-7	Epithelial cells, Keratinocytes, B cells, monocytes	Synthesis induction of inflammatory mediators in monocytes, megakaryocytes maturation
IL-8	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, synovial cells	Chemoattractant for neutrophils, NK cells, T cells, basophils, eosinophils, angiogenesis
IL-12	Monocytes, macrophages, neutrophils, microglia,	Induce T_H1 Cell differentiation and cytotoxicity
IL-13	Basophils, eosinophils, mast cells, T cells, NK cells	Activation of eosinophils and mast cells, recruitment and survival of eosinophils
IL-15	Dendritic cells, monocytes, macrophages, Skeletal muscle cells	Recruitment and activation of T lymphocytes in the synovium.
IL-16	T-cells, fibroblasts, dendritic cells, epithelial cells and eosinophils	In joint destruction, T cells infiltrate articular tissues
IL-17	Activated T-cells	Increased cartilage damage, amplification of immune response, osteoclast activation
IL-18	Monocytes, dendritic cells, platelets, endothelial cells, kuffer cells, keratinocytes, Osteoblast	T cells effector polarization, NK activation, adhesion molecule expression, monocyte release
IL-21	Activated T helper 17, follicular T helper cells, Fibroblast-like synoviocytes, B cells, and macrophages	Activates STAT-3, PI3K/Akt, and MAPK, resulting in aberrant cellular proliferation and inflammatory processes in RA pathogenesis
IL-23	Dendritic cells, macrophages, and monocytes	Differentiate Th-17, induced autoimmune tissue inflammation, osteoclastogenesis, juxta articular bone resorption, and destruction of extracellular matrix

IL-32	T cells, natural killer cells, epithelial cells, and monocytes	joint swelling, infiltration of inflammatory cells, and cartilage damage
IL-33	Macrophages, fibroblasts, mast cells, dendritic cells, endothelial cells	Drive production of other cytokines including IL-13
TNF-α	Adipocytes, activated monocytes, macrophages, B cells, T cells and fibroblasts	T cells apoptosis, collagen synthesis, increase endothelial adhesion molecule expression
TGF-β	All leukocytes	Immune and stem cell regulation and differentiation
	Anti-inflammatory cytokines	
IL-4	Basophils, eosinophils, mast cells, T cells, B cells	Induce T_H1 Cell differentiation, upregulation of class II MHC expression on B cells, role in tissue adhesion and inflammation
IL-10	T cells, B cells, monocytes, macrophages, dendritic cells	Immune suppression, role in autoimmunity and in allergic disease
IL-35	Tregs, immature dendritic cells, vascular endothelial cells, epithelial cells, and smooth muscle	The proliferation of Tregs inhibited the differentiation of Th17 cells, synovial inflammation, and joint destruction
IL-37	Monocytes	Inhibit expression and production of cytokines from various cells

TABLE 2: CYTOKINE INHIBITORS TESTED FOR TREATMENT OF RHEUMATOID ARTHRITIS

Target	**Generic Name**	**Type**	**Half life**	**Clinical trials/Approved status**
TNF-α	Infliximab	Full-length recombinant IgG1 mAb	8-10 days	Licensed
	Adalimumab	Recombinant IgG1 mAb	14 days	Licensed
	Golimumab	Humanized monoclonal antibody	12± 3	Licensed
	Etanercept	A soluble fusion protein of p75 and Fc portion of IgG1	70 hours	Licensed
	Certolizumab	Humanized Fab conjugated to PEG	14 days	Licensed
IL-1	Anakinara	Recombinant IL-1Ra	3-6 hours	Licensed
	Canakinumab	Human IgG1 mAb	21-30 days	Licensed
	Gevokizumab	Humanized IgG2 mAb	-	Passed/under clinical testing
	LY2189102	Humanized IgG4 mAb	-	Passed/under clinical testing
	Rilonacept	Fusion of IL-1RI and human IgG1	-	Passed/under preclinical

				testing
	Anti IL-1 β	Human IgG1 monoclonal antibody	-	Passed/under preclinical testing
IL-6	Tocilizumab	Monoclonal antibody	3-6 hours	Licensed
	Olokizumab	Monoclonal antibody	-	Passed/under clinical testing
	MRA	Humanized mAb	-	Passed/under clinical testing
	MAB406	mAb	-	Passed/under preclinical testing
	Sarilumab	Full-length human IgG1	8 days	Licensed
	Sirukimab	Monoclonal antibody	-	Under clinical trials
	Siltuxmab	Chimeric anti IL-6Ra IgG1	-	Passed/under preclinical testing
IL-17	Secukinumab	Human monoclonal IgG1κ antibody	-	Passed/under clinical testing
	Brodalumab	Human monoclonal antibody	-	Passed/under clinical testing
	Ixekizumab	Human monoclonal IgG4 antibody	-	Passed/under clinical testing
	ABBV-25	Dual-variable domain immunoglobulin	-	under clinical testing
	ABT122	Dual-variable domain immunoglobulin	-	Passed/under clinical testing
IL-15	HuMax-IL-15	Full length human IgG1 mAb	-	Under clinical testing

TABLE 3: ROLE OF CYTOKINES IN GENE THERAPY

Cytokines	**Findings**	**References**
Pro-inflammatory cytokines		
IL-4 Targeting IL-1β via Amelioration of LPS-	Gene therapy in various animal arthritic [170,171] models	
	induced arthritis in rats by injecting [172] rAAV encoding IL-1Rα cDNA into knee joints. Recurrent inflammation induces IL-1Rα expression, suppressing arthritic activities.	
Ex-vivo transfer of IL-1Rα	gene into metacarpophalangeal [173,174] joints of post-menopausal women under safety concerns.	
Clinical responses in human	arthritis patients with *ex-vivo* [175] intra-articular delivery of retrovirus, MFG-IRAP, carrying IL1Rα transgene. Reduced pain, swelling, MMP-3, and IL-1β expression observed.	
TNF-α Electrotransfer of	three TNFR variants in murine CIA model [176,177] reduces synovitis, cartilage erosion, and other disease symptoms.	

Anti-inflammatory cytokines		
IFN-β	Effective in animal models of RA. However, no significant effects observed in RA patients with the injection of adenoviral vector containing the IFN-β gene.	[178]
IL-18 BP	Injection of adenoviral vector containing IL-18 binding protein into arthritic mice resulted in reduced inflammation.	[179]
IL-10	Lentiviral vector encoding IL-10 injected into arthritic mice resulted in reduced inflammation.	[180]
IL-14	Reduced production of IL-1β and TNF-α in arthritic mouse model upon injection of adenoviral vector encoding the human IL-14 gene.	[180]

TABLE 4: ROLE OF SMALL MOLECULE INHIBITORS FOR TARGETING CYTOKINES

S.No.	Inhibitors	Effect	References
1	SH2-Containing phosphatase	Suppress cytokine signaling, inhibit protein inhibitors of activated STAT families, inhibit Mitogen-activated protein kinases, NF-kB signaling, ERK2, P38, and JNKs	[145]
2	Tofacitinib	Drug against JAK3 pathway	[146]
3	Baricitinib	Inhibits JAK1 andJAK2	[148]
4	GSK2982772	Blocks RIPK1-mediated cytokine production and cell death by binding an allosteric region of RIPK1 domain.	[181]
5	Natural bioactive compounds: Sinomene, Triptolide, and Withanolides derived from *Sinomenium acutum, Tripterygium*	Inhibits NF-kB activation Pathway leads to inhibition of various pro-inflammatory cytokines.	[182]
5	*wilfordi and Withania somnifera* Herb Derived: Calestrus derived from *Celastrus aculeatus*	Reduced bone damage in joints	[152,183]

2. CONCLUSION

Given the heterogeneity and complexity of RA, the exact etiology of disease is still not known. Complex network of various immune cells along with the interplay of cytokines are proposed to play an important role in the pathophysiology of RA. So, in future, current developments to target cytokines coupled with novel approaches may have a potential impact on the treatment and management of RA. An important aspect is to understand the orchestral networking of cytokines in RA, so that appropriate cytokines can be prioritized as a potential target in the management/therapeutics of RA.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

There is no conflict of interest in this paper.

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