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Cytokine targeting in rheumatoid arthritis

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1. Introduction

Rheumatoid arthritis (RA) is an inflammatory arthritis that afflicts roughly 1% of the population worldwide [1]. It is a disease that has been afflicting Man since ancient times. The first description of RA in modern medicine can be traced back to the 19th century but archeological findings dating back to ancient Egyptians and Vikings demonstrate skeletal findings that may be indicative of RA. Furthermore, although the first medical description of RA was not until the early 1800s, there exist descriptions from ancient Greece as well as artistic depictions during the Renaissance that would suggest that RA has been present since antiquity [2].

Prior to the development of modern treatments, RA could be a devastating disease leading to significant disabilities due to its chronic, destructive nature. The first major breakthrough was with the development of corticosteroid therapy by Phillip Hench, which led to his Nobel Prize in 1950. Since then, the past few decades have seen tremendous progress in the available treatments for RA – first with the development of conventional synthetic disease modifying rheumatic diseases (csDMARD) and more recently with the development of biologic therapy.

In this review, we will provide an overview of the cytokines that are thought to play a pivotal role in the pathogenesis of RA and the available treatments that target those cytokines (Table 1).

2. Pathogenesis

Although the exact etiology of RA is not fully understood, advances in the past three decades have convincingly established that it is a chronic inflammatory autoimmune disease whose risk factors encompass both genetic and environmental influences. The pathogenesis of RA appears to involve both the innate and adaptive immune system. Our current knowledge of the pathogenesis of RA is a model by which interactions between cells of the innate and adaptive immune system result in chronic inflammation of joint synovium leading to structural changes and eventual destruction of the underlying cartilage and bone [3].

With our growing insight into the immune cell types involved in the development of RA and what is known about the mediators of innate and adaptive immune interactions, this has opened the door to various areas of potential therapeutic interventions [4,5]. It is this elucidation of the pathogenesis of RA that has allowed for the relatively rapid development of treatments in the past 2 decades.

This review will focus exclusively on the cytokine aspect of RA pathogenesis and the treatments designed to specifically target this aspect of RA development.

3. RA treatment

3.1. Overview

RA treatments, collectively referred to as disease modifying antirheumatic drugs (DMARDs), can be divided into two broad categories: synthetic or biologic. Synthetic DMARDs (sDMARD) refer to conventional pharmacologic agents as well as small molecule inhibitors while biologic DMARDs (bDMARD) refer to treatments derived from monoclonal antibodies.

The mainstay of treatment of RA has primarily involved two primary approaches to intervention: 1) the direct manipulation of immune cells via alteration of metabolic pathways or direct depletion of cells versus 2) intervening on the cytokine signaling pathways that mediate the interactions between immune cells as well their function.

The first category of treatment encompasses sDMARDs such as methotrexate, leflunomide, and sulfasalazine, which modulate immune cell function by impairing nucleic acid synthesis; as well as biologic DMARDS such as abatacept and rituximab, which promote T-cell anergy and B-cell depletion, respectively.

The second category predominantly encompasses biologic DMARDs that directly antagonize cytokines involved in RA pathogenesis as well as csDMARDs such as tofacitinib that target signaling down-stream of cytokine pathways through inhibition of JAK (Janus kinase) family kinases.

3.2. TNF-α

Tumor necrosis factor-alpha (TNF-α) is a member of the TNF family of cytokines that plays an important role in mediating inflammatory responses as well as cell death. During the 1980s a series of publications identified TNF-α as a prominent player in the pathophysiology of RA [6,7]. Since then, TNF-α has been demonstrated to be a main mediator

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Table 1
Cytokine inhibitors investigated for the treatment of rheumatoid arthritis.

Cytokine	Drug name	Trade Name/developmental Code	Description	Target	FDA approval for RA	FDA Indications
TNF-α	Etanercept	Enbrel	TNF receptor fusion	Membrane and soluble TNF	1998	RA, JIA, AS, PsA, PP
	Infliximab	Remicade	Chimeric mouse and human monoclonal	Membrane and soluble TNF	1998	RA, CD, UC, AS, PsA, PP
	Adalimumab	Humira	Human monoclonal	Membrane and soluble TNF	2002	RA, JIA, CD, UC, AS, PsA, PP
	Golimumab	Simponi	Human monoclonal	Membrane and soluble TNF	2009	RA, AS, PsA
	Certolizumab	Cimzia	PEGylated monoclonal Fab fragment	Membrane and soluble TNF	2008	RA, CD, AS, PsA
IL-1	Anakinra	Kineret	Recombinant IL-1Ra protein	IL-1 receptor	2001	RA, CAPS
	Rilonacept	Arcalyst	IL-1R1 and IL-1RAcP fusion protein	IL-1	Not approved	CAPS
	Canakinumab	Ilaris	Human monoclonal	IL-1β		CAPS, TRAPS, HIDS, FMF, sJIA
	Gevokizumab		Human monoclonal	IL-1β	Not approved	Ongoing investigation
IL-6	Tocilizumab	Actemra	Human monoclonal	Membrane and soluble IL-6 receptor	2010	RA, JIA, sJIA, GCA
	Siltuximab	Sylvant	Chimeric human and mouse monoclonal	IL-6	Not approved	MCD
	Sirukumab	Plivensia	Human monoclonal	IL-6	Not approved	Ongoing investigation
	Clazakizumab	ALD518, BMS-945429	Humanized rabbit monoclonal	IL-6	Not approved	Ongoing investigation
	Olokizumab		Humanized monoclonal	IL-6	Not approved	Ongoing investigation
	Sarilumab	Kevzara	Human monoclonal	IL-6 receptor	2017	RA
IL-17	Ixekizumab	Talz	Human monoclonal	IL-17A, IL-17A/F	Not approved	PP
	Secukinumab	Cosentyx	Human monoclonal	IL-17A	Not approved	PP, PsA, AS
	Brodalumab	Siliq	Human monoclonal	IL-17 receptor	Not approved	PP
IL-12/IL-23	Ustekinumab	Stelara	Human monoclonal	IL-12p40	Not approved	PP, PsA, CD
	Briakinumab	ABT-874	Human monoclonal	IL-12p40	Not approved	Withdrawn
	Tildrakizumab	MK-322	Humanized mouse monoclonal	IL-23p19	Not approved	PP
	Guselkumab	Tremfya	Human monoclonal	IL-23p19	Not approved	PP

RA- Rheumatoid Arthritis.
JIA: Juvenile Idiopathic Arthritis.
sJIA: Systemic JIA.
AS: Ankylosing Spondylitis.
PsA: Psoriatic Arthritis.
PP: Plaque Psoriasis.
UC: Ulcerative Colitis.
CD: Crohn's disease.
CAPS: Cryopyrin-associated Periodic Syndromes.
TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome.
HIDS: Hyperimmunoglobulin D Syndrome.
FMF: Familial Mediterranean Fever.
GCA: Giant Cell Arteritis.
MCD: Multicentric Castelman's Disease.

of inflammation in RA.

TNF-α is initially synthesized as a transmembrane protein that is then proteolytically cleaved to generate soluble TNF [8,9]. Released, solubilized TNF-α occurs as a homotrimer that then exerts its effects by binding to the TNF-α receptor which exists in 2 distinct forms – TNFR1 and TNFR2 [10]. TNFR1 is ubiquitously expressed while TNFR2 is restricted to particular cell types including immune cells. In RA, it is believed that TNF-α plays a pivotal role in disease pathogenesis by stimulating the release of pro-inflammatory cytokines such as IL-1 as well as type-I interferon and other NFk-b regulated cytokines, including IL-6. These cytokines may be expressed by synovial cells leading to the activation and recruitment of both innate and adaptive immune cells resulting in chronic inflammation of the synovial tissue and damage to the underlying bone and cartilage [11].

The first anti- TNF-α agent available was infliximab, which was developed by Jan Vilcek. Infliximab is a chimeric monoclonal antibody in which the constant region has been humanized but the variable region is murine in origin. Infliximab was initially approved for the treatment of Crohn's disease in 1998 and subsequently approved for the treatment of RA in 1999 after initial clinical trials demonstrated a substantial improvement in disease activity [12–14].

Soon after the release of infliximab, this was followed by the release of etanercept for use in RA. Like infliximab, etanercept also antagonizes TNF-α. However, wherein infliximab is a monoclonal antibody that neutralizes TNF-α in both membrane and soluble form by inhibiting its ability to bind to its cognate receptor, etanercept is a recombinant protein in which the TNF-α receptor is fused to the constant region of an immunoglobulin. Etanercept is also able to bind to both soluble and membrane bound forms of TNF-α but neutralizes TNF-α activity by acting as a decoy receptor [15].

Since the release of infliximab and etanercept, 3 additional anti-TNF monoclonal antibodies have been approved for use in RA – adalimumab, golimumab, and certolizumab. Like infliximab, all three are monoclonal antibodies are able to bind to both the soluble and membrane form of TNF-α. Whereas infliximab is a chimeric monoclonal antibody, adalimumab and golimumab are fully humanized monoclonal antibodies in which the murine variable region has been grafted onto a human antibody. Certolizumab, on the other hand, is unique from the other anti- TNF-α s in that it is a truncated monoclonal antibody in which the Fc domain has been removed and the subsequent antigen recognizing Fab fragments have been conjugated to PEG. It is believed that the conjugation of Fab fragments to PEG may result in decreased

immunogenicity thereby lowering the risk of developing drug neutralizing antibodies [16] as well as affect the bioavailability of the drug [17].

Although, they all are able to bind to TNF-α, another difference between the monoclonal reagents and etanercept is the difference in avidity as etanercept, being a receptor fusion, is only able to bind TNF-α 1:1 while the monoclonals are able to bind 2 molecules of TNF-α per antibody molecule. Furthermore, it would also appear that the Fc regions found in the monoclonal antibodies may also confer some important differences between the two classes as it has been shown that etanercept may not be as effective as the monoclonals in the treatment of granulomatous diseases (and extra articular RA manifestations) and it has also been shown that etanercept is more resistant to the formation of host drug-neutralizing antibodies compared to the monoclonals [18,19]. This inherent resistance to ADAs (anti-drug antibodies) formation has been surmised to possibly be due to the difference in immunogenicity of etanercept owing to it being a receptor fusion protein rather than being a monoclonal antibody and may also be a result of the function of etanecept itself. Unlike the other anti-TNF- α drugs, etanercept is also capable of binding to and neutralizing lymphotoxin. This may contribute to the decreased immunogenicity of etanercept in that lymphotoxin is important in the generation of germinal center formation [20].

Overall, the anti- TNF-α s have revolutionized the treatment of RA these past 2 decades. Studies have consistently demonstrated that anti-TNF-α therapy is effective in both reducing inflammation as well as the joint damage seen in RA [21–26]. As such, it has served as a backbone of RA therapy in conjunction with methotrexate or as monotherapy.

3.3. IL-1

The IL-1 family of cytokines encompasses 11 different members that include IL-1α, IL-b, and IL-1 receptor antagonist (IL-1ra) as well as IL-18, IL-33, and IL-36 [27]. IL-1 cytokines are known to be involved in pro-inflammatory pathways mediating acute inflammation and has been implicated as the pathogenic cytokine in many auto-inflammatory disorders owing to its pivotal role down-stream of inflammasome activation [28].

IL-1α, IL-1β, and IL-1Ra has been of great interest in RA with a particular interest in IL-1β. IL-1β is initially produced as a pro-peptide that is then cleaved to produce the biologically active molecule that is then secreted [29]. Secreted, active IL-1β then binds to IL-1 receptor type 1 (IL-1R1) leading to the downstream activation of NFκb and the production of proinflammatory cytokines. In regards to IL-1α, it is less well studied compared to IL-1β, but it is known to bind to the same receptor and may be involved in the sterile inflammatory response [30]. IL-1ra, in contrast, serves as a negative regulator of IL-1 signaling. It is ubiquitously expressed and antagonizes IL-1 signaling by competitive inhibition of IL-1α /b binding at the IL-1 receptor [31].

IL-1 is of particular interest in RA patients in that it is enriched in their synovial fluid [32–34] It has been observed in mice that IL-1Ra deficiency results in a spontaneous, severe destructive arthritis [35]. As such, RA was the first disease in which antagonization of IL-1 was approved for clinical use with the approval of anakinra.

Currently, there are two strategies for IL-1 inhibition. One involves the usage of exogenous IL-1Ra to antagonize IL-1 signaling while the other strategy utilizes monoclonal antibodies that recognize and neutralizes IL-1β.

Anakinra is a recombinant IL-1Ra that was first approved for the treatment of RA based upon clinical studies that demonstrated improved pain and swelling as well as improved functional outcomes and protection from bone and cartilage destruction [36–39]. Although the findings were promising, it was eventually found that its overall clinical effects were only moderately successful in controlling inflammation in RA patients and a significant response to treatment was only observed in about half of the patients. Despite the fact that IL-1β inhibition does consistently reduce joint damage, due to the relative ineffectiveness at quelling inflammation seen in RA and low response rates, anakinra and IL-1 inhibition in general has been surpassed by other RA treatments.

In addition to anakinra, other IL-1β inhibiting agents include rilonacept which is an IL-1 receptor fusion protein that binds IL-1, and canakinumab and gevokizumab, which are monoclonal antibodies directed against IL-1β. Unlike anakinra, these IL-1 inhibiting agents have not been approved for RA but are often utilized in the treatment of monogenic auto-inflammatory disorders. IL-1 inhibition has also been clinically employed in gout treatment, although not FDA approved, because it is has a major role in the inflammasome assembly [40].

3.4. IL-6

IL-6 is an inflammatory cytokine that has wide-ranging effects. It exerts influence on both adaptive and innate immune cells. In the adaptive immune system, IL-6 promotes B-cell differentiation into plasma cells [41] as well as Th17 [42] and Tfh (T follicular helper cell) differentiation [43] while decreasing Treg (T regulatory cell) differentiation [44]. Together, this leads to a net proinflammatory effect by the adaptive immune system. It is also known to promote inflammatory cytokine production from endothelial and innate immune cells leading to localized inflammation [45,46] as well as mediate systemic inflammation through its effects on the liver leading to increased acute phase reactants such as complement, C-reactive protein, and hepcidin [47]. Furthermore, it plays a role in osteoclast differentiation that may lead to bone destruction [48] as well as mediates anemia due to chronic inflammation [49].

In RA, it is believed that the dysregulation of IL-6 expression is an important part of disease pathogenesis. Like TNFα and IL-1, IL-6 is found to be elevated in the serum of RA patients. More intriguingly, the levels of IL-6 are often highest within the synovial fluid and synovial cells are thought to be a major source of IL-6 production in RA [50,51,52]. In the past decade, IL-6 inhibition has emerged as a potent and effective treatment option for RA.

The first anti-IL-6 therapy developed was tocilizumab, which is a humanized monoclonal antibody against the IL-6 receptor thereby disrupting the binding of IL-6 to its cognate receptor. Tocilizumab is capable of disrupting the binding of IL-6 to both the membrane bound as well as soluble IL-6 receptor. It was approved for use in RA in the USA in 2010 and has proved to be effective in improving both clinical outcomes as well as radiographic progression in RA patients. In the past decade, a plethora of trials have demonstrated that tocilizumab is just as effective as anti-TNΦα or combination DMARD therapy [53].

Due to the effectiveness of IL-6 inhibition on inflammatory processes, it is also being investigated for use in a host of other autoimmune disorders and disorders of chronic inflammation, with recent approval for use in the treatment of giant cell arteritis [54,55]. In addition, given the wide-ranging immunologic implications of IL-6 signaling and the effectiveness in ameliorating inflammatory processes, other anti-IL-6 therapeutic options have been developed over the past half –decade and are currently being investigated in ongoing trials.

Current trials are ongoing to test the efficacy newer IL-6 inhibitors including siltuximab (chimeric monoclonal), sirukumab (fully humanized monoclonal), clazakizumab (humanized monoclonal), and olokizumab (humanized monoclonal), while sarilumab (human monoclonal) was FDA approved for RA in May 2017. Unlike tocilizumab, these agents disrupt IL-6 signaling by binding to IL-6 itself except for sarilumab, which, similar to tocilizumab, binds to the IL-6 receptor, rather than IL-6. One interesting phenomena which occurs specifically with IL-6 receptor inhibition is the observation that serum levels of both IL-6 and sIL-6R is increased by tocilizumab. This increase in IL-6 and sIL-6R is suspected to be due to the increased availability of free IL-6 due to decreased binding to its receptor while the increase in sIL-6R may be due to the delayed clearance of sIL-6R-tocilizumab complexes [56].

3.5. IL-17

The role of Th1 cells in the pathogenesis of RA has been well established but only within the past decade has the role of Th17 cells been appreciated [57,58]. It is now well accepted that Th17 cells play an important role in the development of autoimmune disorders including RA [59]. This has been based largely upon mouse models of inducible arthritis in which overexpression of IL-17 contributed to the development of arthritis [60] while genetic deletion of cytokines important for Th17 differentiation protected against the development of arthritis [61].

As such, IL-17 has been a focus of interest in the development of treatments for RA. Thus far there have been three clinical trials to test IL-17 inhibiting agents in RA: ixekizumab [62,63], secukinumab [64–66], and brodalumab [67]. Ixekizumab and secukinumab are both human monoclonal antibodies that recognize IL-17 while brodalumab is a human monoclonal antibody against the IL-17 receptor. All three have been approved for usage in plaque psoriasis and both secukinumab and ixekizumab have been approved for psoriatic arthritis.

Thus far the results from the ixekizumab trial had been promising with preliminary findings that demonstrate it is superior to placebo as an adjunctive therapy to oral DMARDs as well as being effective in patients who had an inadequate response to TNF inhibitors [62]. However, despite the initial promising results from phase 2 trials, subsequent results have failed to demonstrate a role for IL-17 inhibition in the treatment of RA due to inconsistent efficacy.

The efficacy of secukinumab, on the other hand, is not as clear-cut as some trials failed to meet their primary efficacy end-points despite an overall decrease in disease activity scores and CRP across most trials. Similarly, an early phase study with brodalumab, demonstrated no clinical efficacy in RA despite being effective in patients with psoriatic arthritis.

The inconsistent results of these trials suggest that IL-17 inhibition may only be effective in a subset of patients but does not have the same general efficacy observed in TNF and IL-6 inhibition. Furthermore, the discrepancy of efficacy between ixekizumab and secukinumab versus brodalumab suggests that IL-17 receptor blockade may not be as effective as IL-17 blockade in RA for unclear reasons [66]. At this time, it remains unclear what role anti-IL-17 therapy may play as a primary treatment for RA as more focus is being placed upon its role for the treatment of psoriatic arthritis which has been much more promising.

3.6. IL-23

IL-23 plays a role in the differentiation of Th17 cells [68] and, as such, has been of interest in the role it plays in the pathogenesis of RA [69]. Animal models of inducible arthritis in which IL23 has been genetically deleted demonstrate a decrease in the number of Th17 cells as well as protection from the development of arthritis [61]. It is believed that IL-23 dependent abrogation of Th17 differentiation is able to prevent the development of disease but does not stem disease activity once the disease process has been initiated [70].

IL-23 is a heterodimeric cytokine that is comprised of the IL-12p40, which it shares with Il-12, and the IL-23p19 subunit. It is recognized by the IL-23 receptor, which is comprised of the IL-23A and Il-12beta1 receptor [71]. Available drugs that target the IL-23 pathway fall in two categories – those that target both IL-12 and IL-23 via targeting of the IL-12p40 subunit versus those that specifically target IL-23 via targeting of the IL-23p19 subunit.

Ustekinumab and briakinumab are both human monoclonal antibodies that target IL-12p40 while tildrakizumab and guselkumab are monoclonal antibodies that target Il-23p19. Similar to Il-17 inhibition, these agents have been found to be effective in the treatment of psoriasis as well as psoriatic arthritis and may have a potential role in the treatment of ankylosing spondylitis with investigation currently under way [72].

With respects to RA, clinical trials testing the efficacy of ustekinumab and guselkumab did not demonstrate a significant response [73]. These results may reflect the findings in animal models that inhibition of IL-23 may be most effective in the early stages of disease initiation but does not significantly alter disease course once the inflammatory process is established. Given these disappointing findings, IL-23 inhibition as a potential therapeutic option for RA has largely been abandoned but continues to hold promise in the treatment of the spondyloarthropathies [74].

4. Discussion

Over the past few decades, as our understanding of the mechanisms that govern the pathogenesis of RA has progressed, this has allowed for the development of better and novel treatments. One area that has proven to be very effective and fruitful has been the targeting of cytokines. Although not all are efficacious the therapies that have been beneficial have revolutionized the way RA is treated since the first biologic was approved in 1998. Anti-TNF therapy has become first-line therapy and IL-6 inhibition is also emerging as a possible option for first line therapy with regards to RA therapies that specifically target cytokines.

Thus far, the majority of therapies that have been designed to disrupt the cytokine pathways have depended primarily upon the generation of monoclonal antibodies to specific cytokines or cytokine receptors with a minority of approaches depending upon the generation of fusion receptor proteins.

With the success of monoclonal antibody-mediated neutralization of cytokines for the treatment of RA, there continues to be ongoing research to develop better and higher affinity antibodies. As such, over the next few years, the number of available drugs within a class will see an increase as more biosimilars become approved [75].

Another strategy that is being investigated is the generation of combination antibodies in which a single monoclonal antibody is engineered to recognize distinct cytokines by each variable region. One such dual antibody is ABT-122 that recognizes TNF as well as IL-17. Initial studies have established the relative safety of ABT-122 in comparison to the placebo group [76] and initial findings from a phase II trial yield promising results [77].

A review of clinical trials that are ongoing or completed at clinicaltrials.gov found that other cytokine targets are being explored such as GM-CSF and CX3CL1. Mavrilimumab and lenzilumab are both monoclonal antibodies that target GM-CSF, which is pivotal in macrophage and granulocyte development and survival, and have completed phase 2 [78] or are undergoing phase 1 trials (ClinicalTrials.gov Identifier: NCT02546284), respectively. CX3CL1, is a chemokine that is believed to play a role in RA by recruiting immune cells to the synovial space [79,80]. E6011 is a monoclonal antibody against CX3CL1 with promising results in its initial clinical trial (ClinicalTrials.gov Identifier: NCT02196558) and additional trials are in progress to assess its efficacy in RA (ClinicalTrials.gov Identifier: NCT02960438 and NCT02960490).

One other pharmacologic modality that impacts cytokine signaling is the inhibition of the JAK-STAT pathway [81,82]. Unlike the monoclonal antibodies that serve to neutralize cytokine signaling by disrupting cytokine binding to its cognate receptor, JAK-STAT inhibition involves small molecule inhibitors that interact with Janus kinase family members. Upon cytokine binding to its receptor, this leads to the activation of Janus family kinases resulting in STAT activation and translocation to the nucleus to initiate transcription [83]. Inhibition of the JAK-STAT pathway would affect any cytokine that is dependent upon a specific JAK kinase. JAK inhibitors have had a well-established role in cancer therapy but have emerged as a therapeutic option in the treatment of RA in the past half-decade. Tofacitinib is a small molecule inhibitor of JAK1 and JAK3 that was approved for use in the treatment of RA in 2012 and clinical trials have continued to demonstrate its efficacy and safety [84–86]. Accordingly, many other JAK inhibitors are

being investigated for use in RA as well as other autoimmune diseases [87–89]. One such drug is baricitinib, which is a JAK1/JAK2 inhibitor that was approved in the EU in 2017 for use in moderate to severe RA. Although baricitinib have demonstrated to be efficacious in clinical trials [90–92], the FDA delayed approval for the medication in the treatment of RA citing the need for further clinical data to assess appropriate dosage as well as to clarify its safety profile. Baricitinib has since undergone re-submission to the FDA and its approval is currently under review.

5. Future directions

As our understanding of the pathogenesis of RA grows, so do the available targets for intervention. Cytokine targeting has proved to be an effective approach to the treatment of RA. Considerations for future therapies continue to be informed by our understanding of the cytokines involved in RA. Studies done in both humans as well as animal models have provided a number of cytokine targets that may be of interest in the future. Examples of potential areas of interest include other cytokines within the IL-12 and IL-1 family of cytokines.

The IL-12 family of cytokines includes IL-27and IL-35 [93]. The IL-1 family cytokines includes IL-33, IL-36, IL-37, and IL-38 [94]. These may be of interest for future development as available data have demonstrated increased levels of these cytokines in the serum or synovium of RA patients compared to healthy donors and there is also preclinical data that suggests a potential role for these cytokines in the development of inflammatory arthritis [95].

Tremendous progress has been made within the past twenty years, with respect to RA treatment options. As our understanding of the pathogenesis of RA continues to improve, so do the potential avenues for better and safer interventions.

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