ABSTRACT

Tumor necrosis factor (TNF)-α is a potent trimeric cytokine which plays a fundamental role in the host immuno-inflammatory response, as well as in homeostasis and development. Although critical for canonical immune function, TNF-α has great destructive potential and is implicated in the development of multiple immune-mediated disorders. Within the context of rheumatoid arthritis (RA), TNF-α acts as a primary pathogenic driver by precipitating a pro-inflammatory cytokine cascade and coordinating the attraction and activation of immune cells, all of which culminate in damage to the synovium. The discovery of the paramount role of TNF-α in the pathophysiology of RA motivated studies to understand the effects of TNF blockade in vitro and in vivo. Promising preclinical results provided the impetus for clinical trials, spearheaded in the 1980s and 90s by Marc Feldmann and Ravinder N. Maini, which revealed significant improvements across RA symptom scores and finally led to approval by the Food and Drug Administration (FDA) in 1998. As of 2021, five TNF-α blocking agents have been widely applied clinically, including infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GLM) and certolizumab pegol (CZP). All of them successfully ameliorated symptoms of RA and the associated tissue damage, especially in patients not responding to traditional treatment methods. Anti-TNFs are most often administered in combination with methotrexate (MTX) as part of Phase II treatment (i.e., second line). Although the general availability of anti-TNFs has dramatically improved patient outcomes, sustained remission is rare, and the mechanism of RA remains incompletely understood. Thus, additional basic and translational research with the aim to develop novel RA treatments is warranted.
Introduction

Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease characterized by chronic and systemic inflammation, leading to progressive deterioration of joints. Symptoms of RA severely impact the quality of life of patients and can lead to marked functional impairment and disability. Traditional treatment regimens include glucocorticoids (GCs), nonsteroidal anti-inflammatory drugs (NSAIDs), and disease modifying antirheumatic drugs (DMARDs). However, these treatment regimens are often insufficient to produce sustainable limitations of disease progression and may even lead to disease exacerbation. Since the 1980s, continuous progress has been made in establishing tumor necrotic factor-α (TNF-α) as a critical mediator of the pathogenesis and progression of RA.

Role of TNF-α in Immunity and Homeostasis

Tumor necrosis factor (TNF) was named after its discovery process in the 1890s wherein Dr. Williams B. Coley, a pioneer of modern immunotherapy, successfully induced tumor necrosis by injecting inoperable sarcoma patients with crude bacterial extracts termed “Coley’s Toxin”. Although his treatment was largely successful, patients curiously developed systemic hyperinflammation. TNF, the molecule responsible for in vitro lysis, was later isolated from the serum of endotoxin-treated animals. In 1985, Nobel Prize winner Dr. Bruce Beutler purified TNF-α, originally named ‘cachectin’ due to its ability to induce cachexia, from the supernatant of endotoxin-treated macrophages.

TNF-α, a member of the TNF superfamily, is a conserved trimeric cytokine with diverse systemic and local effects. Although largely produced intracellularly by macrophages and dendritic cells, TNF-α can affect most immune and non-immune cells. TNF-α release is classically induced by lipopolysaccharide (LPS), however many other in vivo and in vitro stimulators of TNF-α are known. Two forms exist: the membrane-bound (mTNF-α) and soluble form (sTNF-α). The expression of TNF-α is NF-κB-dependent, as evidenced by multiple NF-κB binding sites present within the promoter region of the TNF gene. TNF-α exerts its molecular signalling functions, including the induction of tumor necrosis, via its interactions with TNF receptors (TNFRs), TNFR1 (expressed by a wide variety of cells) and TNFR2 (expressed mostly on lymphocytes, both of which are found in membrane-bound or soluble (e.g., p75) forms, instigating homodimerization and intracellular signaling cascades.

The two classes of TNF-α receptors produce antagonistic effects: TNFR1 (death receptor with death domain) signaling induces inflammation, host defense, and apoptosis or necroptosis, whereas TNFR2 is anti-inflammatory and pro-cell proliferation. When TNFRs were knocked out in transgenic mice, they became more susceptible to infections and displayed a suppressed inflammatory response, as measured by a decreased response to LPS challenge. Disparate actions are mediated by the specific recruitment of adaptor proteins (e.g., TNFR-associated factors: TRAFs), activation of kinases, and phosphorylation/dephosphorylation events. Notably, TNF-α autocrine and paracrine induction of cytokines and/or cell survival factors is dependent upon NF-κB translocation to the nucleus.

The three main events mediated by TNF-α signaling are: acute and/or chronic inflammation (notably host response to infection), apoptosis, and necroptosis. TNF-α plays a fundamental role in the inflammatory and immune responses by recruiting immune cells to sites of infection, stimulating macrophage phagocytosis, as well as regulating and acting in concert with other pro-inflammatory cytokines. Although crucial for the local containment of infection, systemic release of TNF-α can induce septic shock. Homeostatic roles include, but are not limited to, effects on bone remodeling, and sleep-wake cycles, regulation of embryonic development and cell differentiation, as well as lymph node follicle and germinal center formation. Taken together, TNF-α is a potent pro-inflammatory cytokine implicated in multifaceted pathways across the immuno-inflammatory axis, in homeostasis, and in development, thereby demonstrating both destructive and protective potential.

Role of TNF-α in Rheumatoid Arthritis

One of the hallmarks of RA is an inflamed synovial membrane that continuously releases pro-inflammatory cytokines, leading to the destruction of bone and cartilage in the joints. Due to the potency of TNF-α as a pro-inflammatory cytokine, there have been continual efforts since the 1980s to investigate its role in inflammatory diseases such as RA. Researchers have gathered the following evidence to verify the involvement of TNF-α as a mediator in the pathogenesis of RA: (1) TNF-α is one of the most abundantly produced cytokines at the site of the inflamed synovial membrane; (2) the presence of high levels of TNF-α has been associated with active tissue damage; (3) both in vitro and in vivo experiments have demonstrated that TNF-α can induce damage to normal cartilage; (4) the induced tissue damage can be prevented by antagonization of TNF-α using neutralizing antibodies. As such, it is well-supported that TNF-α plays a crucial role in the propagation of inflammation and the destruction of tissues in RA.

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Figure 1: Pathogenesis and disease progression of rheumatoid arthritis. In a susceptible joint (knee joint illustrated herein), a not yet known trigger promotes inflammation in the synovium, initiating the infiltration of immune cells including, but not limited to, CD4+ T cells and macrophages. Autoreactive CD4+ T cells then activate macrophages, which produce a milieu of proinflammatory cytokines, including TNF-α. Stimulated by the foregoing cytokines, fibroblasts produce MMP, which causes direct tissue destruction, and RANKL, which activates osteoclasts. Together, the foregoing factors cause joint destruction. Graphics created with BioRender.com.

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The aforementioned cells, in concert with macrophages activated directly through TLR signaling, produce proinflammatory cytokines including TNF-α, which can be detected in the synovial fluid of RA patients. A critical node in the etiology of RA, TNF-α plays both systemic and local roles, and many of its effects have been reasoned in the reverse through studying blockade. Notably, TNF-α is a key regulator of the inflammatory cascade, inducing the production of a proinflammatory mosaic consisting of cytokines such as interleukin (IL)-1, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which jointly orchestrate cellular responses resulting in structural and functional damage to the joint. TNF-α is also thought to stimulate mesenchymal cells to release matrix metalloproteinases (MMPs), which destroy tissue, and to bolster MMP effects through the concomitant inhibition of MMP inhibitor production.

As a corollary, through the stimulation of IL-11, TNF-α indirectly promotes the development of osteoclasts, as well as drives osteoclastogenesis by stimulating the expression of receptor activator of nuclear factor kappa-B ligand (RANKL) and M-CSF. TNF-α also precipitates bone resorption through the upregulation of prostaglandins and leukotrienes, potentiates angiogenesis through the upregulation of vascular endothelial growth factor (VEGF), as well as induces the proliferation of fibroblasts and expression of adhesion molecules to facilitate trafficking of leukocytes to the joint.

Taken together, the confluence of proinflammatory and physiological actions induced by TNF-α precipitates articular cartilage damage facilitated by osteoclasts, chondrocytes, and synovial fibroblasts, enabling synovial hyperplasia and formation of the pannus. TNF-α overproduction in arthritic joints can also

The genetic architecture coupled with environmental factors. Notwithstanding, convergent lines of evidence demonstrate that synovitis (inflammation of the synovial membrane), a hallmark of RA, is caused by the infiltration and local activation of mononuclear cells in the synovial membrane. In susceptible individuals, it is surmised that the foregoing process is triggered by the activation of innate immunity (primarily through TLR signaling), which enables antigen-presenting cells to display arthritis-associated antigens to T cells. Consequently, CD4+ T cells infiltrate the synovium whereupon they attract and coordinate the activation of lymphocytes, monocytes, macrophages, and fibroblast-like synoviocytes, among other events.

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promote increased circulating levels of TNF-α, driving cardiovascular disease through insulin resistance (due to tissue alterations), free fatty-acid release from adipocytes, and upregulation of pro-coagulant proteins, as well as induction of acute-phase protein production, and HPA axis dysregulation.21,22.

History of TNF-α blocking treatments in RA

Pre-clinical models

Prior to the advent of biologic agents for RA, treatment options consisted of repurposed or serendipitously discovered pharmacotherapies. The foregoing options produced unsatisfactory outcomes in a substantial patient subset (non-responders). As such, the development of novel treatments with the aim of improving patient outcomes was a key research focus.

The first cytokine to be implicated in the pathogenesis of RA was IL-1, detected in the synovial fluid of RA patients in 1982. Subsequently, through the utilization of cytokine assays of RA synovium culture supernatants, other cytokines including TNF-α, IL-6, and GM-CSF were discovered to be continuously produced in the diseased joint. However, due to their redundancy of action, it remained unclear which cytokine was paramount and could thus serve as a therapeutic target. The observation that TNF-α was the first cytokine produced by macrophages during an inflammatory response was one of the first clues towards its critical importance. Furthermore, a key experiment by Fiona Brennen and Marc Feldmann demonstrated that blocking the action of TNF-α in culture inhibited the production of IL-1 (and IL1B mRNA), another prominent cytokine thought to be implicated in RA due to known in vitro joint-damaging actions. To parse out the critical role of TNF-α at the apex of the pro-inflammatory cascade, experiments were conducted to demonstrate the efficacy of anti-TNF-α in downregulating the production of multiple inflammatory cytokines. The foregoing results strengthened the hypothesis implicating TNF-α as a key driver of RA pathogenesis, thus, investigators became optimistic that blocking TNF-α in vivo would ameliorate RA symptoms.

Marc Feldmann and Ravinder N. Maini conducted a pivotal preclinical investigation wherein anti-TNF-α antibodies were administered to genetically susceptible mice with collagen-induced arthritis (a model of RA). Results were encouraging; treatment before or after the onset of disease reduced paw swelling and other clinical indicators of disease progression. Other murine models of RA also responded positively to high-dose treatments, whereas exogenous administration of TNF-α worsened the disease course. Moreover, transgenic overexpression of the human TNF-α gene produced an RA-like phenotype in mice. Taken together with in vitro experiments, the foregoing results were the impetus to test TNF-α blockade in human RA patients; efforts facilitated by the pre-existence of human anti-TNF-α, which had been unsuccessfully developed for the treatment of septic shock.

Clinical trials

In 1992, Marc Feldmann and Ravinder N. Maini (with involvement of pharmaceutical company Centocor through Jim Woody) led a Phase I/II clinical trial to test the efficacy of anti-TNF-α antibodies in human RA patients at Charing Cross Hospital. The American College of Rheumatology criteria is most commonly used to assess the efficacy of RA treatments in clinical trials. Efficacy is operationalized as a composite 20% reduction of clinical and functional measurements (ACR20), including number of tender and number of swollen joints, functional ability measure, and CRP levels. Results of the 1992 trial were promising; 20 RA patients refractory to multiple treatments exhibited tolerability as well as rapid improvement in clinical symptoms (by ACR criteria) and decreases in serum pro-inflammatory cytokines. Although patients relapsed following discontinuation of treatment and the open study design was vulnerable to confounding by the placebo effect, promising preliminary results supported further investigation.

As such, in 1993 Marc Feldman and James Woody initiated a Phase II, randomized, double-blind placebo-controlled trial at 4 European centers. Treatment was well-tolerated, and the trial demonstrated formal proof of efficacy; by the endpoint at 4 weeks, 79% of patients had responded to 10 mg kg−1 (high dose), 44% to 1 mg kg−1 (low dose), compared to an 8% response to placebo 3. However, questions remained regarding long-term efficacy and tolerability as even fully immunized antibodies have the potential to produce immunogenicity. To address such concerns, Marc Feldmann and collaborators conducted a long-term Phase II 26-week, double-blind, placebo-controlled study evaluating the efficacy of anti-TNF-α alone or in combination with methotrexate in 101 RA patients. Results revealed that approximately 60% of patients achieved clinical improvement, operationalized as the 20% Paulus criteria for response to treatment. Low doses were effective at the start of treatment, however, only intermediate (3 mg kg−1) and high doses produced long-lasting effects. Furthermore, Feldmann’s 26-week RCT demonstrated that immunogenicity was tolerable, inversely related to dose, and reduced by co-treatment with methotrexate (MTX). The addition of MTX as a co-therapy produced improved outcomes in a Phase III trial lasting 2 years (termed ATTRACT) evaluating treatment of anti-
TNF-α (infliximab) for the reduction of RA symptoms and radiographic progression (cartilage damage and bone destruction)\(^{39}\). Moreover, patients receiving combination therapy reported improved quality of life, and approximately half demonstrated repairs in joint damage\(^{40}\). Clinical improvements in RA symptoms using anti-TNF-α were mediated by abrogation of many of the pathophysiological actions of TNF-α; reduction in the levels of pro-inflammatory cytokines, leukocyte trafficking, angiogenesis, joint destruction, decreased cardiovascular disease risk through hematological normalization, and overall normalization of the immune response\(^{39}\). Although anti-TNFs served to remove the linchpin of RA progression, they could not reverse existing damage. Notwithstanding, combination treatment consisting of an anti-TNF-α with MTX was approved for use in the United States and Europe in 1998\(^{24}\). Subsequently, multiple clinical trials were conducted to demonstrate the efficacy of other proprietary anti-TNFs\(^{39}\).

The three leading TNF-α blockade candidates for clinical trials were Infliximab (INF), Etanercept (ETA) and Adalimumab (ADA). The following section aims to discuss in further detail the efficacy and safety of INF, ETA and ADA, in addition to two newer TNF-α blocking agents, golimumab (GLM) and certolizumab pegol (CZP).

### Currently used TNF-α blocking agents

**Infliximab (INF)**

INF was the first TNF-α blocking agent to be clinically tested in RA patients. It is a chimeric monoclonal antibody with its constant region, or fragment crystallization (Fc) region, derived from human IgG1κ and its variable region, or fragment antigen binding (Fab) regions, composed of the Fab regions of a high-affinity neutralizing anti-TNF-α antibody of murine origin\(^{11-13}\). INF not only prohibits the binding of TNF-α to TNFRs, but also promotes the dissociation of TNF-α molecules from TNFRs\(^{44}\). INF has a half-life of 8-10 days and needs to be administered intravenously every 4-8 weeks\(^{41,42}\).

Several randomized, placebo-controlled clinical trials tested the safety and efficacy of INF in treating RA patients\(^{45-48}\). The doses they tested ranged from 3-10 mg/kg. Significant improvements were seen in patients treated with a combination of INF and MTX as compared to MTX plus placebo as assessed by ACR criteria\(^{45-47}\). The amelioration of joint destruction was long-lasting, as evident upon radiographing\(^{46}\). Interestingly, there was no significant correlation between clinical outcomes and the dosage of INF treatments\(^{45-48}\). The major side effects associated with INF treatment include common infusion reactions (e.g., injection site pain) and increased risk of infection\(^{4,11,49,50}\). The rates of serious infection and life-threatening infusion reactions, however, were similar in groups treated with INF plus MTX and placebo plus MTX\(^{4}\). There also exists the possibility that the risk of malignancies and of cardiovascular conditions is elevated among the INF-treated group\(^{50}\).

**Etanercept (ETA)**

ETA is a dimeric fusion protein with the Fc domain of IgG1 linked to the extracellular portion of the TNFR2. Since ETA has a higher affinity for TNF-α than natural TNFRs, it inhibits the activity of TNF-α signalling pathways by salvaging soluble TNF-α. ETA is a fully human protein, so the risk that it will induce neutralizing antibodies is lower than the risk that chimeric proteins will. ETA has a half-life of 3-5.5 days and is administered subcutaneously every 1-2 weeks\(^{51}\).

Several randomized, placebo-controlled clinical trials tested the safety and efficacy of ETA in treating RA patients\(^{52-55}\). The recommended dose for ETA is 50 mg/kg when administered once a week\(^{66}\). Patients treated with ETA showed significant improvements when compared to placebo controls as assessed by the ACR criteria\(^{53,51}\). Furthermore, treating with a combination of ETA with MTX resulted in greater improvements than treating with ETA or MTX alone did\(^{8}\). Increasing the dose to 50 mg/kg twice a week, did not yield significantly better results than the recommended dose\(^{46}\). The major side effects of ETA include infusion reactions and hypertension, although the symptoms are often mild to moderate. No difference in the rate of severe adverse effects, including infections, was observed between the ETA-treated group and the control group\(^{41,57}\).

**Adalimumab (ADA)**

ADA is a high-affinity and fully human monoclonal antibody for TNF-α molecules\(^{58,59}\). This recombinant monoclonal antibody is of class IgG1. Its mechanism of inhibiting the activities of TNF-α is similar to that of INF (i.e., prevention of receptor binding). Since ADA is structurally indistinguishable from natural human IgG1 molecules, there is minimal risk of decreased half-life attributed to the induction of neutralizing antibodies\(^{60}\). ADA has a half-life of 10-20 days and the FDA recommends intravenous or subcutaneous injections twice a week\(^{41}\).

Several randomized, placebo-controlled clinical trials tested the safety and efficacy of ADA in treating RA patients\(^{61-64}\). The doses ranged from 0.5-10 mg/kg for intravenous injections or 10-80 mg/kg for subcutaneous injections. Greater improvements were observed in patients treated with ADA as compared
### Table 1: Summary of half-life, dose and administration route, therapeutic outcomes, side effects, and structure of anti-TNFα agents.

Dosing recommendations, therapeutic outcomes, and side effects have been extracted from the clinical trials that led to the approval of these agents by the FDA and Health Canada.
to placebo controls, according to the ACR criteria. As with INF, ADA treatments ameliorated the progression of radiographic joint damage\textsuperscript{63}. Moreover, regimens combining ADA and MTX treatments showed superior clinical and functional improvements as compared to those treated with ADA or MTX alone\textsuperscript{65}. Overall, severe adverse effects associated with ADA were rare, signifying a high level of tolerance. Common side effects of ADA include infusion reactions and increased risk of infections, with the most elevated risk of serious infections at the 40 mg/kg dose\textsuperscript{41,63}.

**Golimumab (GLM)**

GLM is another fully human monoclonal antibody targeting TNF-α of the IgG1 subclass. It was one of the newer TNF-α blocking agents and was approved by the FDA in 2009\textsuperscript{66}. GLM is generated in an in vivo system where genetically modified mice are immunized with human TNF-α molecules. The mechanisms behind the TNF-α neutralizing actions of GLM are similar to that of INF and ADA, principally by promoting dissociation between TNF-α and TNFRs\textsuperscript{67,68}. GLM has a half-life of approximately 12 days and the FDA recommends monthly subcutaneous administrations\textsuperscript{68}. Several randomized, placebo-controlled clinical trials tested the safety and efficacy of GLM in treating RA patients\textsuperscript{41,69,70,67}. The clinical trials tested two doses, 50 mg and 100 mg, with no statistically significant difference between the two in terms of clinical efficacy\textsuperscript{41,68}. According to the ACR criteria, patients treated with GLM plus MTX exhibited reduced RA symptoms and decreased risk of radiographic progression as compared to those treated with placebo plus MTX\textsuperscript{41,67}. The most commonly reported adverse effects of GLM treatment include infusion reactions, hypertension, and increased risk of infections\textsuperscript{68}. The adverse effects were more prominent at the 100 mg dose, prompting the recommended dose to be set at 50 mg\textsuperscript{68}. These side effects are rare and the severity generally ranges from mild to moderate, demonstrating that GLM is generally well-tolerated\textsuperscript{41}.

**Certolizumab pegol (CZP)**

CZP is another newly developed TNF-α blocking agent and was approved for clinical use by the FDA in 2009. Unlike INF, ADA, and GLM, CZP contains only a single humanized Fab fragment with a high affinity for TNF-α, which is artificially conjugated to polyethylene glycol (PEG)\textsuperscript{71}. Due to its unique structure, its mechanism of action is different from the other aforementioned TNF-α blocking agents\textsuperscript{72,73}. Specifically, due to the lack of an Fc region, CZP does not induce Fc-mediated cytotoxic effects, including complement-dependent cytotoxicity and antibody dependent cell-mediated cytotoxicity\textsuperscript{71}. As well, as compared to other TNF-α blocking agents, CZP has a longer half-life (around 2 weeks) and improved bioavailability\textsuperscript{71,72}. The FDA recommends CZP to be administered subcutaneously twice at 200 mg (for a total of 400 mg) initially at weeks 2 and 4, respectively, followed by a single 200 mg injection every two weeks.

Several randomized, placebo-controlled clinical trials tested the safety and efficacy of CZP in treating RA patients\textsuperscript{74-77}. Similar to other TNF-α blocking agents, when combined with MTX, GLM treatments led to significantly better clinical outcomes as compared to the placebo plus MTX control\textsuperscript{81}. In addition, patients who underwent GLM monotherapy also showed rapid reductions in RA symptoms and slowed radiographic progression as compared to baseline\textsuperscript{73, 77}. Increasing the dose from 200 mg to 400 mg did not provide a higher level of clinical improvements, however, the severity of adverse events was higher in the 400 mg dose group\textsuperscript{41,77}. The most prominent adverse effect of CZP is an increased risk for tuberculosis. Other side effects include pain in the injection area and hypertension. These adverse events were mostly mild or moderate\textsuperscript{76}.

**Risk and Adverse Effects of Anti-TNFs**

Although anti-TNF biologics have had a dramatic impact on the quality of life of many RA non-responders, utilization is not without risk. Of critical importance is the consideration that blocking the effects of TNF-α dampens general immunity. As such, RA patients treated with anti-TNF biologics are at an increased risk of serious viral, bacterial, and fungal infections - notably opportunistic pathogens and intracellular bacteria\textsuperscript{78}. Furthermore, there is an increased risk of lymphoma and non-melanoma skin cancers, as well as reactivation of latent tuberculosis due to the breakdown of granuloma\textsuperscript{79}. Rarely, patients undergoing anti-TNF treatment may develop new or worsening demyelinating diseases and/or drug-induced lupus 80. Common side effects of anti-TNF biologics, many of which are injection-site reactions, include headaches, rashes, anemia, upper respiratory tract infections, cough, diarrhea, nausea, and abdominal pain\textsuperscript{80}.

**Comparing TNF-α blockade to other rheumatoid arthritis therapies**

**Glucocorticoids and non-steroidal anti-inflammatory drugs**

Despite the potential for such adverse effects, TNF-α blockade is a striking improvement in the management of RA. In addition to lifestyle and physical approaches (e.g., exercise, occupational therapy), previous pharmacotherapies were largely diverted from other conditions. Willow bark derivatives (i.e., salicylates) have been used to provide symptomatic relief since antiquity. Furthermore, GCs and NSAIDs
can function rapidly to reduce pain and swelling, so they are often prescribed shortly after the onset of clinical symptoms81. NSAIDs, salicylate derivatives which inhibit cyclooxygenase (COX)-1 and 2 in order to reduce the production of prostaglandins, emerged in the mid-20th century, and derive their name by means of comparison to glucocorticoids (e.g., steroids such as cortisone), which were concurrently shown to reduce joint inflammation82. With the progression of RA symptoms, however, GCs and NSAIDs often lose effectiveness, creating an unmet demand for more effective treatments, such as DMARDs and anti-TNFα blockade. Moreover, chronic use of NSAIDs may lead to gastrointestinal abnormalities (e.g., bleeding, nausea, ulcers), tinnitus and hearing loss.

**Disease-modifying antirheumatic drugs**

Drugs which slow the course of RA are termed disease-modifying antirheumatic drugs (DMARDs). Treating RA patients with DMARDs presents several advantages, including low cost, reliability, and low incidents of side effects1. Therefore, DMARDs are often used as second-line medication in RA patients. Significant challenges arise, however, in patients that show persistent resistance to DMARDs83. Novel strategies such as anti-TNFα blockade are therefore especially in need to treat patients not responding to DMARDs.

In 1950, Philip Hench was awarded the Nobel Prize for his application of cortisone (introduced 1949) for the treatment of RA82. Corticosteroids were initially thought to be the cure for RA; they rapidly suppress symptoms and decrease bone erosion. However, symptoms recur following discontinuation and corticosteroids are associated with numerous profound side effects including immune, endocrine, and HPA axis suppression62. Antimalarials including quinine and cinchonine, isolated from the cinchona tree at the same time as salicylates, were also proven effective for the treatment of RA in the early 1950s82.

Among the DMARDs used to treat RA patients, MTX has been shown to be one of the most reliable, effective, and well-tolerated84,85. Since its introduction for RA in the 1980s, methotrexate (MTX) has been the gold standard treatment. Although it was initially shown to provide symptomatic relief for RA in 1951, MTX was largely used as a chemotherapeutic agent, curtailed due to the initial success of corticosteroids. MTX functions as a competitive inhibitor of dihydrofolate reductase, however, the exact mechanism of action within the context of RA is incompletely understood82. Hypotheses include folate antagonism, adenosine signaling, generation of ROS, inhibition of angiogenesis, and alteration of cytokine profiles86. However, MTX is still not as effective as newer treatment strategies, such as anti-TNFα, even in responding patients. Overall, the low cost and reliability of DMARDs currently confer enough advantages for them to often be considered first-line options in treating RA patients1.

**Novel or prospective treatment options**

In addition to TNF-α blocking strategies, there are several other novel treatment strategies currently available or in development 1. These novel strategies include inhibitors to other pro-inflammatory cytokines such as IL-1 and IL-6, and inhibitors of more upstream inflammatory pathways, such as the Janus-activated kinase (JAK) pathway and the co-stimulatory pathways required for T-cell activation1. The IL-1 blocking agent anakinra showed lower efficacy and higher incidence of adverse effects and is therefore only recommended for patients intolerant to TNF-α blocking agents87,88. Co-stimulation blockers and JAK inhibitors, on the other hand, are showing promising results regarding the efficacy and adverse effects, especially in combination with MTX89,90. More clinical trials are needed to determine whether these newer strategies are indeed more advantageous than TNF-α blocking agents.

**Standard Protocol for the Treatment of RA**

Approximately 10-20% of patients do not respond to non-biologic DMARDs and are subsequently recommended for anti-TNF therapy24. Phase I of the standard protocol for the management of RA as developed by the European League Against Rheumatism (EULAR) recommends starting the patient on MTX and short-term glucocorticoids91. If the patient presents any contraindication for MTX, leflunomide or sulfasalazine can be used in its stead. Progression to Phase II is dependent upon symptomatic improvement; initiated if the patient does not present symptomatic improvement at 3 months and/or clinical remission at 6 months91. Upon initiation of Phase II, if the patient does not exhibit poor prognostic factors, the DMDAR is changed, or a second DMARD is added. However, if the patient does in fact present poor prognostic factors, a biological DMARD or JAK-inhibitor is added91. Anti-TNF-α biologics fall within the former category, along with abatacept (CTLA4-Ig), IL-6 inhibitors such as tocilizumab, and rituximab, a monoclonal anti-CD20 antibody91. Notably, methotrexate is utilized as a co-therapy in 70% of RA patients treated with anti-TNF-α biologic agents, as combination therapies have demonstrated synergistic effects39.

Both biologic and non-biologic DMARDs may be administered orally, subcutaneously, or intravenously. Phase III treatment is initiated if symptom improvement at 3 months and/or clinical remission at 6 months is not achieved after Phase II and involves switching out the biologic DMARD or JAK-inhibitor for an agent of the same or different class91. A 2019 meta-analysis
ascertained a 24% patient remission rate (according to Disease Activity Score 28 [DAS28] remission criteria) at 24 months, indicating that despite adequate symptom management, sustained remission is rare and there is significant room for improvement insofar as unmet needs is warranted. Response to RA treatment, including anti-TNFs, is thought to be dependent on both genetic and environmental factors. For example, one study reported that patients who achieved DMARD-free sustained remission were rarely anti-citrullinated protein antibodies (ACPA) or rheumatoid factor-positive. As such, the pharmacogenomics of anti-TNF treatment response are currently under investigation using GWAS, genomic, and transcriptomic analysis methodology towards the aim of generating genetic screening methods to predict treatment response.

**Current clinical applications and future perspectives**

Currently, the five TNF-α blocking agents discussed previously are FDA- and Health Canada-approved for the treatment of RA. From a clinical perspective, TNF-α blocking agents are usually considered third-line therapy; they are prescribed in patients not responding to DMARDs such as MTX. One of the factors precluding more widespread use of TNF-α blocking agents is its high cost as compared to MTX. Another aspect worth considering is the presence of adverse effects, especially the increased risks of infections, in patients treated with TNF-α blocking agents. It is worth pointing out that while TNF-α blocking agents are effective in limiting joint damage, they cannot reverse existing joint damage, and a substantial proportion of patients continue to demonstrate radiographic progression. Thus, TNF-α blocking agents are not cures for RA. With several new strategies showing promising results, combinational therapy has the potential of enhancing the efficacy of anti-TNF-α blockade. More targeted TNF-α blocking strategies have also been proposed, such as specifically targeting pro-inflammatory macrophages within the heterogeneous population implicated in RA.

**Conclusion**

The potent pro-inflammatory cytokine, TNF-α, plays a central role in the pathogenesis and progression of RA. Landmark in vitro, in vivo, and clinical studies conducted in the 1980s and 90s culminated in the general availability of anti-TNF-α therapies at the end of the 20th century. Currently, anti-TNFs are most commonly used in combination with MTX as part of Phase II treatment (i.e., second-line) for RA. Although patient outcomes have improved dramatically, sustained remission is rare; more research into the biology of RA, as well as the development of novel RA therapies, is warranted.

**COMPETING INTERESTS**

No competing interests declared by the author. Felicia Ceban has recused themselves from the editorial process, which was conducted independently by a different team of editors.

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