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Rheumatoid arthritis: current therapeutics compendium

Hassan Dariushnejad [1], Leila Chodari [2], Mehrnoosh Sedighi [3], Soheila Akbari [4],
Vajihe Ghorbanzadeh [3]

[1]Department of Medical Biotechnology, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran; [2]Department of Medical Physiology, Urmia University of Medical Sciences, Urmia, Iran; [3]Cardiovascular Research Center, Shahid Rahimi Hospital, Lorestan University of Medical Sciences, Khorramabad, Iran; [4]Department of Obstetrics and Gynecology, Lorestan University of Medical Sciences, Khorramabad, Iran;
E-mail: vghorbanzadeh@gmail.com

Rheumatoid arthritis is a common chronic inflammatory disease with substantial economic, social, and personal costs. Its pathogenesis is multifactorial and complex. The ultimate goal of rheumatoid arthritis treatment is stopping or slowing down the disease progression. In the past two decades, invention of new medicines, especially biologic agents, revolutionized the management of this disease. These agents have been associated with an improved prognosis and clinical remission, especially in patients who did not respond to traditional disease-modifying anti-rheumatic drugs (DMARDs). Improvement in the understanding of the rheumatoid arthritis pathogenesis leads to the development of novel biologic therapeutic approaches. In the present paper, we summarized the current therapeutics, especially biologic agents, available for the treatment of rheumatoid arthritis.

Key words: rheumatoid arthritis, DMARD, biological therapeutics, monoclonal antibody

Rheumatoid arthritis is a common chronic autoimmune disease of unknown etiology leading to a progressive joint damage, fatigue, pain, limitation in motion, morning stiffness, systemic complicate, disability, and early death (Campbell et al. 2011; McInnes and Schett 2011). With the disease progression, atrophy of the muscles, prominent tissue injuries, and destruction of cartilages and bones result in a joint deformity. Eventually, various systemic features appear including pulmonary, cardiovascular, physiological, and skeletal disorders (Firestein 2003).

Rheumatoid arthritis has a poor long-term prognosis and 80% of people with this disease are disabled after 20 years (Scott et al. 1987). The prevalence of rheumatoid arthritis is estimated to be 1% worldwide (Rudan et al. 2015). The disease affects both sexes, but in women 2–3 times greater risk than in men has long been recognized (Neovius et al. 2011). The rheumatoid arthritis is also associated with a substantial financial impact on patients with medical expenses (direct), economic burden to society with early retirement or loos of productivity (indirect), and intangible costs that impact on quality of life, which is difficult to estimate (Osiri et al. 2007).

The rheumatoid arthritis diagnose is usually made based on the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria (Aletaha et al. 2010). Control of symptoms considered with administrating glucocorticoid joint injection and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients diagnosed with rheumatoid arthritis should be started on disease-modifying antirheumatic drug (DMARD) therapy (Am Coll Rheum Subcom Rheum Arth 2002). Methotrexate, a common DMARD standard

Corresponding author: Vajihe Ghorbanzadeh Razi, Cardiovascular Research Center, Shahid Rahimi Hospital, Lorestan University of Medical Sciences, Khorramabad, Iran; phone: +98 66 33336150; e-mail: vghorbanzadeh@gmail.com.

for rheumatoid arthritis, has been shown to be an effective agent in improving the rheumatoid arthritis symptoms and signs. However, treatment with methotrexate failed in many patients with long term use (Keystone et al. 2004).

Biological agents, as novel therapeutics, have emerged at the field of the inflammatory disease by intervening into the pathways related to the development and progress of the rheumatoid arthritis. Since DMARDs only control rather than cure the rheumatoid arthritis, anti-cytokine therapy represented the major advance in the treatment of this disease (Figure 1).

This review is focused on the conventional and emerging new therapeutic strategies for the rheumatoid arthritis treatment including biological agents. Biologic agents are divided into three groups: monoclonal antibodies, fusion proteins, and interleukin-1 (IL-1) antagonists. Each of them is briefly discussed below, whereas more emphasis will be placed on the recent insights into the biological therapies.

Chemical agents

The utilization of the non-biologic agents, called disease-modifying anti-rheumatic drugs (DMARDs), goes back to the middle of the 20th century. In the recent years, tofacitinib, a new small chemical molecule, is included into this group. These agents prescribed at the first line, periodically assessed the disease activity and the regimen was adjusted based on the clinical response. All the presently used DMARDs (Table 1) have toxicity problems, limited efficacy or both.

Non-biologic disease-modifying anti-rheumatic drugs (DMARDs)

Until now, five DMARDs are recommended by ACR including: methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and minocycline (Singh et al. 2012).

Methotrexate is most famous and preferred conventional DMARD that is commonly chosen as the first agent for the rheumatoid arthritis treatment. It is a small chemical molecule, which can be administered by an intramuscular injection, subcutaneously or taken orally. It is one of the best tolerated drugs in patients. On the other hand, methotrexate cost is more effective than its biological effect (Cranwell-Bruce 2011; Jurgens et al. 2011).

Sulfasalazine efficacy has been proven in the placebo-controlled trials and positive risk/benefit ratio often used in the rheumatoid arthritis treating.

Hydrochloroquine and chloroquine are antimalarial agents with the similar structure. hydrochloroquine had a lower toxicity and for the clinic
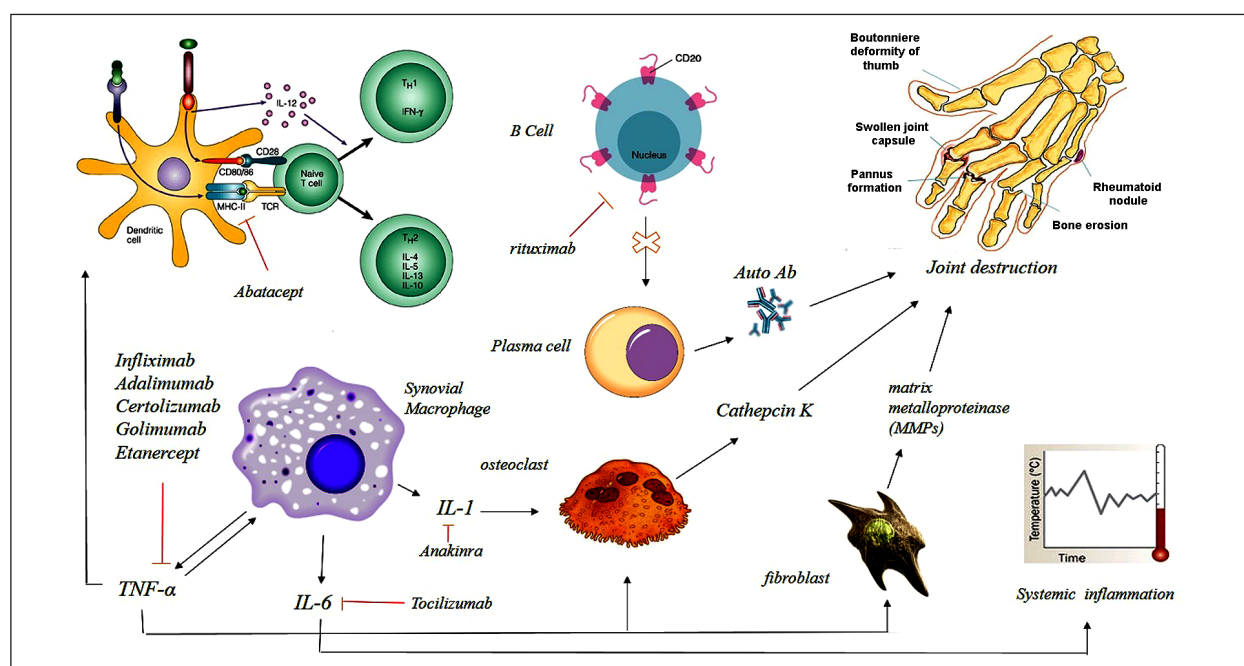
Figure 1. Schematic picture of the cytokine signaling pathways involved the inflammation of rheumatoid arthritis. Blocking these pathways by biologic agents is the key to stop inflammation in the rheumatoid arthritis patients.

Table 1
The advantages and common side effects of chemical agents used in the rheumatoid arthritis patients

Agent	Advantages	Most common side effects
Methotrexate	First choice for treatment, best tolerated drug in patients	Hepatotoxicity, ulcerative stomatitis, teratogenic – avoid in pregnancy, low white blood cell count
Sulfasalazine	Well tolerated, use in monotherapy or part of combination	Severe depression in young males, temporary infertility, thrombocytopenia, headache
Hydroxychloroquine	Low toxicity, quick gastrointestinal absorption, moderate clinical effect.	Mild nausea, stomach cramps, retinal damage
Leflunomide	Alternative to methotrexate in patients whose cannot tolerate methotrexate	Teratogenic – avoid in pregnancy, diarrhea, respiratory tract infections, hair loss, high blood pressure, abnormal liver function tests, gastroenteritis
Minocycline	Weak anti-inflammatory properties in comparison with other DMARDs	Diarrhea, dizziness, vomiting, hepatotoxicity, anorexia
Tofacitinib	Traded by XELJANZ® trade name and Pfizer company, JAK inhibitor approved in November 2012, small chemical molecule, tofacitinib with methotrexate use in patients who had failure with anti-TNF drug	Diarrhea, headache, upper respiratory infection and hypertension

Abbreviations: DMARDs – disease-modifying anti-rheumatic drugs; JAK – Janus activated kinase; TNF – tumor necrosis factor.

it was more often prescribed than the chloroquine. Both of them have been shown to be less effective in the rheumatoid arthritis treatment as the other DMARDs (Osiri et al. 2003; Jurgens et al. 2011; Singer and Gibofsky 2011).

Leflumide is an immunomodulatory agent that inhibits the pyrimidine synthesis pathway *de novo*. In clinical trials, it has been shown to have similar efficacy to sulphalizine (Smolen et al. 1999).

Minocycline is basically an antibiotic derived from the tetracycline (Garrido-Mesa et al. 2013). In 1994 and 1995, the clinical trials showed that minocycline has anti-inflammatory properties in patients with the rheumatoid arthritis (Kloppenburg et al. 1994; Tilley et al. 1995). Zernicke et al. (1997) have shown the tetracycline anti-inflammatory effect in rats. A meta-analysis performed by Stone et al. (2003) has confirmed the beneficial effects of the previous studies. Despite the US Food and Drug Administration (FDA) approval and promising results, Greenwald (2011) has reviewed the effect of the tetracycline treatment and declared that tetracycline has a weak anti-inflammatory property. Therefore, this agent has been replaced by many other agents.

Immuno-suppressant agents

Tofacitinib, as an active immuno-suppressant agent, was as the first generated by Pfizer Inc. and introduced to the market with XELJANZ® trademark for the oral application. Tofacitinib is a Janus activated kinase (JAK) inhibitor, which plays a key role in the cytokine signal transduction that controls the lymphocyte survival, proliferation, differentiation, and apoptosis. Clinical evaluations have supported the use of tofacitinib in the monotherapy or combination with methotrexate (Fleischmann et al. 2012). Burmester et al. (2013a) have shown that combination of tofacitinib with methotrexate improved the physical function and the disease remission in patients with failed anti-tumor necrosis factor (TNF) agent medication. Nevertheless, results of the clinical trials have shown that the consumption of tofacitinib in the rheumatoid arthritis patients may induce different side effects such as diarrhea, headache, upper respiratory infection, hypertension, neutropenia, and elevated liver enzymes. On the other hand, this medicine, similarly with the other anti-inflammatory agents, increases the infection risk in the rheumatoid arthritis patients (van Vollenhoven et al. 2012; Burmester et al. 2013b; van der Heijde et al. 2013).

Biological agents

DMARDs are not always effective or the effectiveness of traditional DMARDs may decrease as the disease progresses and they may cause adverse effects. These reasons lead to a low tendency of DMARDs long-term use for a patient with a lifelong course.

For this reason, the biologic agents were introduced in the management of the rheumatoid arthritis. The biological agents revolutionized the management of the rheumatoid arthritis and radically altered its therapeutic areas. FDA has approved the use of these agents in the clinical cures (Table 2). The structures of the current biologic agents are depicted in Figure 2.

Monoclonal antibodies

Infliximab. TNF plays a crucial role in the rheumatoid arthritis patients' inflammation. This cytokine has both direct and indirect effects on the inflammation process (Dariushnejad et al. 2018). TNF stimulates macrophages and other immune cells to secrete proinflammatory cytokines like IL-1, IL-6, and IL-8. These cytokines lead to activation of T-cells and induction of adhesion molecule in endothelial cells. These events lead to T-cell infiltration, increase of angiogenesis, and keratinocyte proliferation (Choy and Panayi 2001). TNF engaged in differentiation and maturation of osteoclasts that pivotal cells involve in bone destruction (Redlich et al. 2002). On the other hand, TNF stimulates chondrocytes, fibroblasts, and osteoclasts to release proteinase, which destroys the bones and articular cartilages (Butler et al. 1995; Smolen and Steiner 2003). These evidences show central role of TNF in the rheumatoid arthritis pathogenesis and emerged TNF as a promising molecular target for rheumatoid arthritis treatment (Maini et al. 1995).

The first anti-TNF agent introduced to the market and assessed in the rheumatoid arthritis treatment was a chimeric human murine monoclonal antibody named infliximab with Remicide® trade name (sponsored by centocor Inc.) (Elliott et al. 1993; Knight et al. 1993). Trials showed an efficacy of infliximab in reliving the symptoms and signs of the rheumatoid arthritis (Elliott et al. 1994a, b). Maini et al. (1999) have shown that in-phase III trial declared treatment with infliximab was more effective than methotrexate alone in patients with active rheumatoid arthritis (51.8 % versus only 17% from methotrexate plus placebo). St. Clair et al. (2004) have demonstrated that infliximab plus methotrexate also provided significant improvement in radiology images, functional ability, and clinical outcomes of patients in the early treatment. Like any medicine, infliximab has side effects beside its beneficial prescription. Major side effects of infliximab include opportunistic intracellular infection, particularly reactivation of latent *Mycobacterium tuberculosis.* Intensification of the demyelinating disorder, severed neutropenia and thrombocytopenia (Antoni and Braun 2002; Day 2002; Vidal et al. 2003).

Adalimumab (Humera®) is a fully human monoclonal antibody isolated from the human Fab library for targeting TNF-α (Kempeni 1999; Bang and Keating 2004). In 2002, Abbott Laboratory received FDA approval and introduced this antibody as an anti-rheumatoid arthritis agent. In fact, adalimumab has been introduced for the treatment of immune mediated inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, chronic psoriasis, hidradenitis suppurativa,

Table 2
Biological agents approved in the rheumatoid arthritis treatments

Common/chemical name	Brand name	Sponsor company	Target	Form	Approval date
Infliximab	Remicide	centocor Inc.	TNF-α	Chimeric antibody	August 1998
Adalimumab	Humera	Abbott Laboratory	TNF-α	Human antibody	December 2002
Certolizumab pegol	Cimza	UCB	TNF-α	Humanized antibody	May 2009
Golimumab	Simponi	Johnson & Johnson/ Merck & Co.	TNF-α	Human antibody	April 2009
Rituximab	Rituxan	Roche	CD20	Chimeric antibody	November 1997
Tocilizumab	Actemra	Roche/ Chugai	IL-6	Humanized antibody	Late 2007
Etanercept	Enbrel	Immunex Corp.	TNF-α	fusion protein	November 1998
Anakinra	Kineret	Amgen	IL-1	IL-1 receptor antagonist (IL-1Ra)	November 2001
Abatacept	Orencia	Bristol-Myers Squibb	Co-Stimulation Modulators	Fusion protein	December 2005

Abbreviations: IL – interleukin; TNF-α – tumor necrosis factor α.
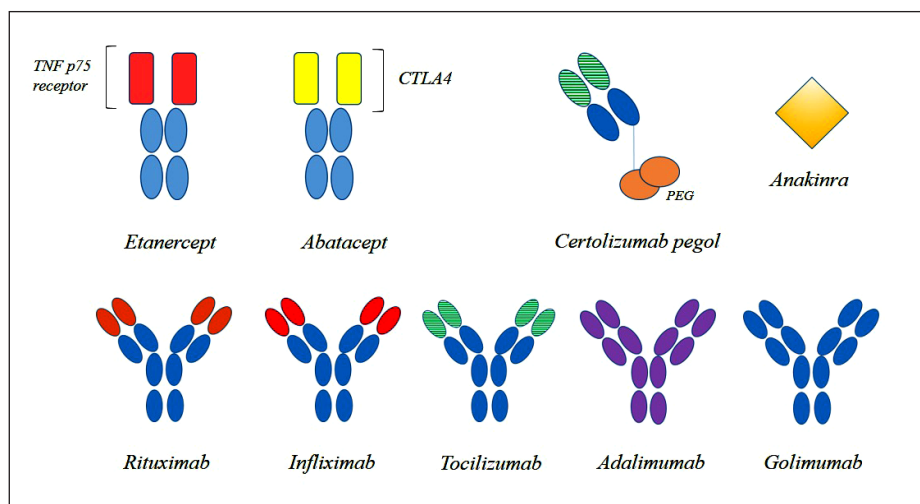
Figure 2. Schematic picture demonstrating the structure of several biologic agents. Anakinra is an IL-1 receptor antagonist; abatacept CTLA4–Ig fusion protein that inhibits T-cell activation; rituximab a chimeric anti-CD20 monoclonal antibody acting to deplete B cells; and tocilizumab a humanized antibody against the IL-6 receptor. The majority of the following agents of TNF targets: infliximab – chimeric IgG1; adalimumab – human monoclonal antibody; etanercept – TNF receptor – Fc fusion protein; golimumab – human monoclonal antibody; and certolizumab pegol – humanized antibody Fab' fragment linked to polyethylene glycol (PEG) molecules.

and juvenile idiopathic arthritis (Tracey et al. 2008). Weinblatt et al. (2003) have confirmed by ARMADA trials the efficacy of adalimumab in the treatment of rheumatoid arthritis patients with inadequate response to the methotrexate. In this trial, patients' response at 24 weeks was 67.2% in the adalimumab 40 mg versus 14.5% in placebo group (Weinblatt et al. 2003). Breedveld et al. (2006) have perform a 2-year follow-up and found that combination therapy of adalimumab and methotrexate was more effective in early diagnosed patients. Burmester et al. (2013b) studied 71 adalimumab clinical trials and declared safety analysis representing adverse events of adalimumab was same as in other anti-TNF agents.

Certolizumab pegol is an Fc-Free PEGylated and anti-TNF monoclonal antibody selected from a screen of hybridoma for human TNF-α binding parent antibody (Dariushnejad et al. 2019; Farajnia et al. 2020). The complementarity determining regions (CDRs) from murine antibody graft to the human Fab' IgG framework and subsequently PEGylated in the specific PEG attachment moiety (Fleischmann and Shealy 2003; Weir et al. 2006). UCB marketed certolizumab pegol as Cimza®, and FDA approved it in May 2009 for the rheumatoid arthritis treatment (Goel and Stephens 2010). Keystone et al. (2008) and Smolen et al. (2009a) have demonstrated the efficacy of certolizumab in the RAPID-1 and RAPID-2 trials

in methotrexate no responder patients. Fleischmann et al. (2009) have performed 24-week FAST4WARD trial and demonstrated efficacy of certolizumab monotherapy in patients who have failed in previous DMARD therapy.

Golimumab is the most recent anti-TNF-α monoclonal antibody that received FDA approval in April 2009. Golimumab (Simponi®) is a full-sized antibody and exhibit multiple glycosylation patterns. This antibody recognizes both trans membrane and soluble forms of TNF-α. HuMab (Medarex) transgenic mice that immunized with hTNF-α produced antibody secretory hybridoma clone (Mazumdar and Greenwald 2009; Shealy et al. 2010). Phase III GO-FORWARD trial has shown the efficacy of golimumab (Keystone et al. 2009). After 24 weeks, more patients in combination group (golimumab+methotrexate) responded to treatment rather than methotrexate or golimumab alone (Keystone et al. 2008). Phase III GO-BEFORE trial showed golimumab plus methotrexate response statistically significant in the treatment in early diagnosed patients (Emery et al. 2009). Smolen et al. (2009b) have also shown that golimumab could be efficacious in patients who did not respond to other anti-TNF drugs.

Tocilizumab (Actemra®) is a humanized anti-IL-6 receptor monoclonal antibody. This molecule is

humanized by CDR grafting method, in which CDRs of mouse anti-human IL-6 receptor is grafted to a human IgG1 framework. This antibody prevents the binding of IL-6 to both membrane and soluble expressed IL-6 receptors and blocks the pro-inflammatory reaction of IL-6/IL-6 receptor signaling cascade (Venkiteshwaran 2009). IL-6 participates in the rheumatoid arthritis pathogenesis and play an important role in the disease activity. Systemic levels of IL-6 and IL-6 receptors in blood stream correlate with magnitude of radiographic join damage, clinical symptoms, and signs of inflammation (Dasgupta et al. 1992; Kotake et al. 1996; Walsh et al. 2005). Clinical trials have proven the efficacy of tocilizumab as a monotherapy for the non-responded patients to conventional DMARDs (Dougados et al. 2013; Jones et al. 2010). Tocilizumab approved for monotherapy without association with methotrexate can be an alternative prescribe for patients who cannot tolerate methotrexate. Monotherapy is one of the biggest advantages of tocilizumab; however, randomized controlled trials have announced efficacy of its combination with methotrexate (Emery et al. 2008; Jones et al. 2010). In addition to the above-mentioned advantages, tocilizumab has side effects including decreased amount of platelet and neutrophil numbers and increased cholesterol and liver enzymes. Tocilizumab also induces cytochrome P450 expression. This enzyme increases the metabolisms of drugs and subsequently decreases the serum concentration of medicaments (Jones and Ding 2010).

Rituximab (Rituxan®) is a monoclonal antibody that targets CD20+ B cells. It is genetically engineered chimeric antibody. FDA has proved it for the treatment of refractory or relapsed CD20+ non-Hodgkins lymphoma in combination with standard chemotherapy (Reff et al. 1994). This fact has proven that B cells clearly participate in the immune-pathogenesis of the rheumatoid arthritis. B cells act as antigen presenting cells that stimulate T cells macrophages activation and cytokine secretion. In addition, plasma cells derived from B cells in joint synovial membrane of patients produce rheumatoid factor. Rituximab depletes CD20+ B cells. Plasma or stem cells does not express CD20. B cell recovery and Ig secretion have been observed after a single rituximab course of use (Sell 1987; McLaughlin et al. 1998; Edwards et al. 2004). Cohen et al. (2006) have given rituximab to the patients that failed response to anti-TNF therapy for 2 weeks and improved Disease Activity Score in 28 joints (DAS28) compared with placebo. Keystone et al. (2012) have extended this trial and showed rituximab decrease damage of joints in radiographic images after for up to 5 years. Infusion reaction such as hypertension, hypotension, chills, rash, and fever have commonly been observed with rituximab. To overcome these problems, the patients should be pretreated with antihistamines, acetaminophens or corticosteroids. Another problem with rituximab is an increased risk of infections compared with placebo (Mease et al. 2010).

Sarilumab (Kevzara™), most recent monoclonal antibody, has been received its first global approval on February 2017 in Canada for the rheumatoid arthritis patients with moderately active disease, who had inadequate response to non-biological or biological agents (Scott 2017). Sarilumab is an IgG1 fully human monoclonal antibody against both soluble and membrane bound IL-6 receptors (sIL-6Rα and mIL-6Rα). This antibody is under regulatory review for use in other countries include Japan, EU and USA. Sarilumab is prescribed in combination with traditional DMARDs monotherapy in cases of methotrexate or other DMARDs intolerance (Ishii et al. 2018). The efficacy of sarilumab has been evaluated in two randomized, double-blind, multinational trials, SARIL-RA-MOBILITY Part A phase II trial, and SARIL-RA-MOBILITY Part B phase III trial. Patients received 150 and 200 mg of subcutaneous sarilumab or placebo plus methotrexate every 2 weeks for 52 weeks. In both trials, sarilumab plus methotrexate have provided significant improvement relative to placebo plus methotrexate (Huizinga et al. 2014; Tanaka et al. 2019). Injection site erythema, upper respiratory tract infections, neutropenia, and increased ALT levels are most frequent adverse reactions occurring in patients (Scott 2017).

Fusion proteins

Etanercept (Enbrel®, Immunex Corp) is a soluble dimeric TNF inhibitor fusion protein. This fusion protein, created by recombinant DNA technology and comprised of the TNF p75 receptor (TNF R2) conjugated to human IgG1-Fc moiety, includes CH2, CH3 domains and a hinge region (Mohler et al. 1993). It can be self-administered by subcutaneous injection as a monotherapy or in combination with methotrexate (Danila et al. 2008). Moreland et al. (1999) have reported efficacy of etanercept in patients, who previously failed to methotrexate respond. Etanercept efficacy has also been demonstrated in the early diagnosed patients (Bathon et al. 2000). Like other anti-TNF inhibitors, etanercept increases the risk of opportunistic infection and specially reactivation of the latent *Mycobacterium tuberculosis*. On

the other hand, skin infectious and chronic inflammation in the injection area have also been frequently reported (Lee et al. 2007).

Abatacept (Orencia®) is a selective T-cells co-stimulator modulator. Fully activation of T-cells requires, at least, two signals: the first is facing with antigen by MHC-peptide complex and the second by binding of a costimulatory receptor with a ligand on the antigen presenting cells. Interaction of CD28 on T-cells with CD80 or CD86 from antigen presenting cells is very important costimulatory signal (Siebert et al. 2015). CTLA4 (cytotoxic T-lymphocyte-associated antigen 4) is a high-activity receptor for both CD80 and CD86, which prevents these molecules from engaging with CD28 and stimulation of T-cells. Abatacept as CTLA4Ig is constructed by genetically fusing external domain of CTLA4 to the constant region of human IgG1 heavy chain (Kremer et al. 2003). Several clinical trials have proven the efficacy of abatacept in rheumatoid arthritis patients. Westhovens et al. (2009) have shown that combination of abatacept with methotrexate reduced the radiographic progression in early the rheumatoid arthritis patients. Abatacept is also effective agent in patients with an inadequate response to anti-TNF therapy (Genovese et al. 2005). Similarly, in 12-month trial, Schiff et al. (2008) have demonstrated that abatacept had greater reduction rather than infliximab in the rheumatoid arthritis disease activity. Weinblatt et al. (2006) have shown that adverse events of abatacept are same with other biologic agents in a clinical trial. Infusion related events, infections, headache, and dizziness are common abatacept side effects.

IL-1 antagonist

Anakinra (Kineret®) is a recombinant IL-1 antagonist currently used for the rheumatoid arthritis treatment (Vlieghe et al. 2010). Researchers have shown that IL-1 interferes in joint damage by tree mechanisms including stimulating matrix metalloproteinase secretion, cartilage repair process inhibition, and activation of osteoclasts. Under healthy condition, IL-1 receptor antagonist (IL-1Ra), neutralizes IL-1 in competitive manner, prevents signal transduction, and modulates the biologic action of IL-1 (van Beuningen et al. 1991; McDonnell et al. 1992; van de Loo et al. 1995; Xu et al. 1996). Anakinra significantly improves symptoms when is used as a monotherapy or in combination with methotrexate in controlled clinical trials (Bresnihan et al. 1998). Fleischmann et al. (2003b) have performed 6-month placebo-controlled study and demonstrated

that anakinra is safe and well tolerated in patients with the rheumatoid arthritis. Injection site reaction, decrease in neutrophil counts and serious infections were most common side effects of anakinra (Nigrovic et al. 2011).

Future directions for biologic agents

Since the rheumatoid arthritis is a complex and it is not driven from a cytokine or single factor, it does not seem that it could be cured by a miracle therapeutic. However, abundant biologic agents are under study or in different stages of *in vitro* or *in vivo* examinations. Most of them are newer versions of the current targets and some of them target new molecules. Table 3 summarizes some of the biological agents that are under the development.

IL-17 and **IL-23** are two important cytokines in the inflammatory pathways and noticed for development of some new biologic agents. Ustekinumab (Stelara) is a monoclonal antibody that inhibits IL-12/IL-23 function. IL-12 and IL-23 have a common chain with the same sequence; therefore, a single monoclonal antibody can target both of them at the same time. This monoclonal antibody is registered in the South Africa for psoriasis treatment and tested for various autoimmune diseases (Harmse and Reuter 2016). Secukinumab neutralizes the activity of IL-17A and has been shown to be an effective in the ankylosing spondylitis and psoriasis. A phase II trial in rheumatoid arthritis shows only a modest efficacy of this antibody in the rheumatoid arthritis (Genovese et al. 2013).

Another antibody against IL-17 is ixekizumab. This antibody neutralizes both IL-17A and IL-17F and is very effective in the psoriasis treatment. Phase II trial has shown its moderate efficacy in the rheumatoid arthritis patients (Genovese et al. 2014). Brodalumab binds to IL-17 receptor A and is very effective in psoriasis. Although this antibody did not show efficacy in rheumatoid arthritis treatment, the company that develops brodalumab has announced its continuing development and performing more clinical trials for this antibody (Martin et al. 2013). Granulocyte-monocyte colony stimulating factor (GM-CSF) has important immunoregulatory function, moreover of its role in hematopoiesis. Mavrilimumab targets GM-CSF and showed acceptable efficacy in a large phase II clinical trial in the rheumatoid arthritis (Burmester et al. 2011). Sirukumab is an antibody against IL-6 pathway, effective in phase II trial (Smolen et al. 2014). Clazakizumab and olokizumab are two humanized anti

Table 3
Monoclonal antibodies in rheumatoid arthritis that may be future therapeutic agents

Monoclonal antibody	Target	Mode of action	Status	References
Ustekinumab	IL-12/IL-23 antagonist	Fully human monoclonal antibody neutralizes both IL-12 and IL-23	In phase II clinical trials	Clinicaltrails.gov
Secukinumab	IL-17	Humanized monoclonal anti-IL-17	In phase III clinical trials	Clinicaltrails.gov
Ixekizumab	IL-17	Humanized monoclonal anti-IL-17	In phase III clinical trials	Clinicaltrails.gov
Brodalumab	IL-17	Humanized monoclonal anti-IL-17 receptor	In phase III clinical trials	Clinicaltrails.gov
Milatuzumab	MIF	Anti-CD74 (part of MIF receptor) monoclonal antibody	In phase I clinical trials	Clinicaltrails.gov
Natalizumab	VCAM-1	Fully human anti-a4 integrin (VCAM-1 receptor) antibody	FDA approved for treatment of MS. In phase II clinical trials for RA	Clinicaltrails.gov
Efalizumab	CD11a	It acts as an immunosuppressant by inhibiting lymphocyte activation and cell migration out of blood vessels into tissues	In phase II clinical trials	Clinicaltrails.gov

Abbreviations: IL – interleukin, MIF – macrophage migration inhibitory factor; VCAM-1 – vascular cell adhesion protein 1; FDA – US Food and Drug Administration; MS – multiple sclerosis; RA – rheumatoid arthritis.

IL-6 antibodies with the similar effectiveness as tocilizumab (Mease et al. 2012).

Milatuzumab is an anti-CD74 humanized monoclonal antibody for the therapy of the multiple myeloma, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia. The drug is the first anti-CD74 antibody that has been entered into the human checking out and is presently being studied for the cure of multiple myeloma. Milatuzumab has acquired orphan drug designation from the FDA in the United States for the remedy of the multiple myeloma and chronic lymphocytic leukemia (Congreve et al. 2018).

Natalizumab is a monoclonal antibody, which pursuits a protein known as α4β1 integrin on white blood cells involved in the inflammation. By attaching to integrin, natalizumab is a concept to stop white blood cells from coming into the brain and spinal cord tissue, thereby lowering the inflammation and the ensuing nerve damage. The most frequent aspects of its effects are urinary tract infection, naso-pharyngitis (inflammation of the nose and throat), headache, dizziness, nausea (feeling sick), joint pain, and tiredness (Lundkvist et al. 2013). Natalizumab, bought beneath the brand title Tysabri amongst others, is a medicine used to deal with multiple sclerosis and Crohn's disease. It is a humanized monoclonal antibody in opposition to the cell adhesion molecule

α4-integrin. It is given through intravenous infusion each 28 days. The drug is believed to work through lowering the capability of inflammatory immune cells to connect and skip via the cell layers lining the intestines and blood-brain barrier. Natalizumab has been confirmed to be effective in treating the signs of each disease, preventing relapse, vision loss, cognitive decline, and considerably enhancing quality of existence in humans with multiple sclerosis, as properly as growing rates of remission and preventing relapse in multiple sclerosis (Dominguez-Mozo et al. 2020).

Efalizumab is the last one we want to deal with. Efalizumab, a previously accessible medication designed to treat autoimmune diseases, firstly marketed to deal with psoriasis. As implied with the aid of the suffix "-mab", it is a recombinant humanized monoclonal antibody administered once weekly through subcutaneous injection. Efalizumab binds to the CD11a subunit of lymphocyte function-associated antigen 1 and acts as an immunosuppressant via inhibiting lymphocyte activation and cell migration out of blood vessels into tissues (Talamonti et al. 2011). Known side effects consist of bacterial sepsis, viral meningitis, invasive fungal disorder, and modern multifocal leukoencephalopathy (PML). The brain infection brought about through reactivation of

latent JC virus infection. Four instances of PML had been said in plaque psoriasis patients, an incidence of about one in five hundred treated patients (Berends et al. 2007). In the recent years, a novel way, by using a vaccine like approach, rising the hopes in the rheumatoid arthritis treatment. In this method, autologous modified dendritic cells (Rheumavax) are injected to rheumatoid arthritis patient. In 2015, exploratory study demonstrated safety and bioactivity of this individual therapy (Benham et al. 2015).

Future trends

In the past two decades, researchers have introduced a variety of therapeutics for management of rheumatoid arthritis and we learned precious lessons from a decade of using biologic agents in clinical practice. Despite the scientists, medical biotechnologist and pharmaceutical companies attempt the rheumatoid arthritis remained problematic. The main goals in the rheumatoid arthritis treatment are achieved by disease inactivation or suppression, reduced disability, stopped joint damage, and maintaining of this state. Therefore, we need to improve our knowledge and skills at using biologic agents for achieving better therapeutic outcomes.

Since the rheumatoid arthritis is a complex and it is not driven from a cytokine or single factor, it does not seem that it could be cured by a miracle therapeutic. However, abundant biologic agents are under study or in different stage of *in vitro* or *in vivo* examination. Most of them are newer version of current targets and some of them target new molecules. These new molecules include: inhibitor of IL-1 converting enzyme, TNF-α converting enzyme, IL-6 receptor, IL-15 (HuMax-IL-15), CD22, anti-BLyS (B-lymphocyte stimulator), and many others.

Among expanded therapeutic options for patients, personal specific characteristics and side effects profiles should be considered when selecting therapy. On the other hand, an important issue for the patients, especially patients in developing countries, are the high cost of biologic agents. Therefore, the first choice for patients with low financial power is the use of conventional DMARDs and if needed, combination of biologic agent and DMARD with titrating their use to get preferred maximum response.

Conclusion

The clinician caring for patients with rheumatoid arthritis should consider the risk of infection. All patients should receive the pneumococcal vaccine at appropriate intervals and should have yearly influenza vaccinations (O'Dell et al. 1996). Clinicians should recommend that all patients should be tested for prior exposure to tuberculosis, when considering TNF inhibitors use (Ellerin et al. 2003). Since smoking has been associated with an increased severity of arthritis, its cessation may be beneficial. The risk factors for atherosclerosis should be strongly sought and addressed (Mattey et al. 2002). In addition, ACR guidelines may be helpful to clinicians to choose the best decision. Finally, the success of anti-cytokine therapy is a window of an opportunity for the rheumatoid arthritis effective treatment.

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