Rheumatoid Arthritis Treatment

Subjects: Immunology

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that deteriorates quality and function of the synovium membrane, resulting in chronic inflammation, pain and progressive cartilage and bone destruction. The mechanism of RA pathogenesis is associated with dysregulation of innate and adaptive immunity.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease that causes damage to joints, connective tissues, muscle, tendons, and fibrous tissue, and, as a result, has a major impact on society. Worldwide prevalence of RA is about 5 per 1000 adults. The disease is 2 to 3 times more frequently diagnosed in women than men, with a mean age of 55 years old [1][2]. The onset of the disease, also known as pre-RA phase, lasts months to years before clinical symptoms are presented and is subject to the presence of circulating autoantibodies, increased level of inflammatory cytokines and chemokines and altered cell metabolism [3]. The advanced form of the disease is characterized by severe and debilitating chronic pain that compromises patients' quality of life. Inadequate management further results in disease progression, which ultimately leads to joint erosion, destruction and deformities. Previously, more than 50% of RA patients were disabled, incapable of serving on a full-time work basis, and were subject to increased mortality. However, a better understanding of disease pathophysiology and remarkable progress in the treatment of RA have led to the development of more efficient treatment approaches with the improvement of the disease activity control, the degree of pain and joint damage [1][4].

Regarding therapeutic approaches in RA, currently used drugs include glucocorticoids (GCs) and synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) [5]. In addition to these, non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used drugs for pain relief. GCs, in combination with NSAIDs or DMARDs, are used due to their potent anti-inflammatory effects. Among the above indicated conventional treatments, DMARDs demonstrated a high potential to reduce disease symptoms and prevent disease progression in patients with RA, however, they constitute high financial costs and exhibit serious side effects [6]. Additionally, despite significant pain reduction reported in numerous randomized controlled trials, many patients still experience clinically meaningful levels of remaining pain despite the treatment, and continue to be intolerant or resistant to these therapies [7][8].

Considering the limitations of conventional RA drugs, a modern cellular therapy based on mesenchymal stem cells (MSCs) may be regarded as an alternative strategy [9]. MSCs have attracted the attention of scientists and

clinicians due to their capacity for self-renewal, tissue and organ regeneration and strong immunosuppressive properties. These characteristics enable suppression of the activity of pro-inflammatory cells of both innate and adaptive immune systems. It has been shown that MSCs are able to suppress the activation of natural killer (NK) cells and maturation of dendritic cells (DCs); inhibit the proliferation and function of T and B cells; promote macrophages' polarization toward an anti-inflammatory phenotype; and induce the generation of T regulatory cells (Tregs) [10]. Moreover, it was demonstrated that the immunomodulatory effect of MSCs is mediated by both cell-cell contacts and through the secretion of soluble factors [11][12]. MSCs produce transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), soluble form of protein HLA-G5, indolamine-2,3-dioxygenase (IDO), nitric oxide (NO) and interleukin-10 (IL-10) that are involved in the regulation and suppression of inflammatory responses [13]. All these mechanisms can contribute to controlling excessive inflammation in RA. To further improve the anti-inflammatory properties of MSCs for cell-based therapy, priming or preconditioning can be successfully applied. This approach allows for the use of bioactive substances (cytokines and growth factors), immune receptor agonists, hypoxia and 3D culturing [14]. Based on this wide range of immunomodulatory properties, the therapeutic potential of MSCs in RA treatment has been intensively studied in preclinical [15] and clinical studies [16][17][18][19][20][21][22]. Experimental animal models and human clinical trials demonstrated that MSCs have beneficial therapeutic effects in suppressing inflammation, bone erosion and joint destruction, as well as decreasing pannus formation through immunosuppression and immunomodulation.

2. Current Approaches in RA Treatment

The main goal in RA treatment is to achieve clinical remission or to reduce disease progression by inhibiting joint inflammation. Currently available conventional treatment methods include synthetic and biologic DMARDs and GCs [23].

DMARDs are the mainstay of RA therapy, which include heterogeneous drugs that inhibit disease progression and control symptoms [1]. Methotrexate (MTX), a conventional synthetic DMARD, is analogous to folic acid with anti-proliferative effects [24][25]. MTX causes the impairment of purine and pyrimidine metabolism, inhibits amino acid and polyamine synthesis and induces T cell and platelet apoptosis [26]. However, risks of skin cancer development and impairments in bone marrow as well as gastrointestinal, infectious, pulmonary and hematologic side effects have been observed in clinical practice [27][28].

Patients with moderate or severe disease should be initially treated with MTX as a monotherapy. In cases when disease inadequately responds to MTX, the treatment can be combined with a complementary drug, or fully replaced by other DMARDs if adverse effects are observed [29]. However, treatment with MTX is usually discontinued in less than 5% of patients due to side effects, which also can be reduced by prophylactic implementation of folates [30]. Alternative synthetic DMARDs include leflunomide, sulfasalazine, hydroxychloroquine and chloroquine. For patients with a mild disease course, hydroxychloroquine can be used as an initial therapy [31]. Leflunomide and sulfasalazine are also widely prescribed drugs for RA treatment, mostly in cases when patients have a contraindication to MTX [32]. Occasionally, a triple-drug therapy with MTX, sulfasalazine and hydroxychloroquine is applied [33]. Notably, MTX is preferred for use in patients because of its

economical and therapeutic efficacy [34]. However, a combination of MTX with other drugs is reported to be a better treatment strategy than MTX alone [4][35].

The American College of Rheumatology (ACR) and European League Against Rheumatism recommend treatment with MTX in combination with short-term GC application, which is another potential anti-inflammatory drug for RA treatment for newly diagnosed patients [8][36]. The immunological effect of GCs is mediated by apoptosis of immature CD4+CD8+ thymocytes, and by the reprogramming of DCs to a tolerogenic state (tDCs). tDCs induce the generation of Tregs and increase macrophage phagocytosis of apoptotic cells [37][38][39]. However, side effects after GC application are more severe in comparison to other drugs. A dose increase in GCs causes ecchymosis, cushingoid features, parchment-like skin, leg edema, sleep disturbance and immunosuppression. Other adverse effects involve weight gain, epistaxis, glaucoma, depression, hypertension and diabetes [40][41]. Despite the adverse effects of GCs, the combination of MTX and GCs could reduce RA signs in about 25% of patients within 6 months of treatment. Moreover, in conjunction with systemic administration of GCs, intra-articular (IA) injections can prevent local joint inflammation [42].

About 30–50% of patients are unresponsive to conventional DMARDs. If a 2–6 month treatment with MTX mono- or combinational therapy is inadequate, biologic DMARDs should be added [36][43]. Biologic DMARDs include tumor necrosis factor (TNF) inhibitors, costimulation modifiers, IL-6 inhibitors and B cell depleting drugs. Commercially available biological drugs, such as etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®) and certolizumabpegol (Cimzia®) are all TNF inhibitors that block cytokine signaling, reduce cell recruitment, normalize IL-6 expression level in serum and matrix metalloproteinase (MMP) expression levels in cartilage and bone, and as a result, slow bone destruction. Among the aforementioned biologic DMARDs, TNF inhibitors should be the initial drugs used in cases with an inadequate response to conventional synthetic DMARDs, and are often used in combination with other DMARDs, especially MTX [44][45]. Nonetheless, these drugs have serious side effects, such as increased risk of infections and neurological diseases, development of multiple sclerosis and lymphoma [46][47]. Additionally, TNF inhibition has previously resulted in the development of skin tumor Merkel cell carcinomas in patients affected by rheumatologic diseases [48]. Clinical trials with TNF inhibitors have revealed that a number of patients did not respond to treatment [49]. In this case, another DMARD, anakinra, that binds to IL-1 receptors and blocks inflammation, is considered for therapy. Anakinra is used in combination with other DMARDs or as a monotherapy, but the application is limited due to the risk of opportunistic and latent infections [50][51]. Anti-CD20 monoclonal antibody, rituximab, depletes B cells and is a typical medication for the treatment of lymphomas, leukemia and autoimmune disorders, and in RA patients, it can be added when there is an insufficient response to TNF inhibitors [52]. T cell activation can be blocked by abatacept, which is the fusion protein containing the domain of cytotoxic T lymphocyte-associated antigen 4 and prevents T cell activation by binding to CD80 and CD86 receptors on antigen-presenting cells (APCs), as well as blocks interaction between DCs and T cells. A clinical study of abatacept demonstrated significant results, however some patients were insensitive to this treatment, which was associated with the loss of CD28 expression on T cells [53][54]. Another biologic DMARD, tocilizumab, blocks IL-6 receptors and significantly reduces disease severity in RA patients who have not been effectively treated with traditional DMARDs [55]. A clinical study of anti-IL-17 antibody, secukinumab, and anti-IL-17RA antibody, brodalumab, has shown low response in RA patients in both cases [56][57]. Therapeutic

efficacy of biologic DMARDs, when used as a monotherapy, is less effective compared to the combination with MTX [58].

It was shown that cytokines, such as TNF-α, IL-1, IL-6, IL-7, IL-15, IL-17, IL-18, IL-21, IL-23, IL-32, IL-33 and granulocyte-macrophage colony-stimulating factor (GM-CSF) were implicated in the pathogenesis of RA [59]. However, clinical trials with therapeutic strategies blocking IL-1, IL-18 or IL-17 have shown few benefits. On the other hand, TNF-α or IL-6 targeting therapy was successful in relieving symptoms and initiating disease remission [60]. Another approach in RA therapy is targeting small molecules. The Janus kinases (JAK) inhibitors are a type of targeted synthetic DMARD that recognize and regulate the activity of the JAK family of non-receptor tyrosine kinases, which transduce signals from several different cytokine receptors through the effects on the STAT family of transcription factors. Tofacitinib represents a targeted synthetic DMARD that inhibits IL-6 production by blocking JAK1 and JAK3 through the IL-6/gp130/STAT3 signaling pathway [61], and as a result, inhibits IL-17 and interferon-γ (IFN-γ) production and the proliferation of CD4+ T cells in patients with RA [62][63]. Another targeted synthetic DMARD, baricitinib, a JAK1/JAK2 inhibitor, was superior compared with the TNF-α antagonist adalimumab in patients with an inadequate response to the MTX [64]. Upadacitinib, which is a JAK1 inhibitor, significantly improves the efficacy of RA treatment in patients who are unresponsive to MTX or a TNF-α antagonist [65]. Thus, targeted synthetic DMARDs should be considered as a monotherapy or in combination with conventional synthetic DMARDs [66].

NSAIDs alongside GCs are commonly used as adjuvants to basic therapy. They are applied to decrease pain and inflammation during RA, however NSAIDs are not able to reduce bone and cartilage destruction [67]. NSAIDs are typically divided into two groups based on their chemical structure and selectivity: a group of non-selective NSAIDs, which inhibit both cyclooxygenase-1 (COX-1) and COX-2 and another group of COX-2 selective inhibitors. COX-1 plays a role in maintaining gastrointestinal mucosa lining, kidney function and platelet aggregation, whereas COX-2 is expressed during an inflammatory response. The most common NSAIDs applied in RA include acetylsalicylate, naproxen, ibuprofen and etodolac. Previously, NSAIDs were considered as first-line drugs, however low effectiveness in prevention of damage progression and side effects at high doses such as nausea, abdominal pain, ulcers and gastrointestinal bleeding, limited the implementation of these drugs [68].

Surgery is the final treatment approach for RA therapy in cases when the aforementioned nonsurgical methods are not sufficiently effective, which are becoming less frequent. Nowadays, various types of surgery are being applied, among them are tenosynovectomy, radiosynovectomy, arthroscopy, osteotomy and joint replacement. The final goal of surgical management is to relieve pain and restore joint function [69][70]. **Table 1** summarizes the current approaches for RA treatment with the route of administration, mechanism of action and major side effects.

Table 1. Summary of current approaches for RA treatment.

Drug	Example	Administration/Dose	Mechanism of Action	Side Effects	Reference
Conventional Synthetic	MTX	Orally or intravenous (IV) injection (15 mg),	Impairs purine and pyrimidine	Skin cancer and gastrointestinal,	[27][28]

Drug	Example	Administration/Dose	Mechanism of Action	Side Effects	Reference
DMARDs		single subcutaneous (SC) or intramuscular (IM) injection (15–25 mg/week)	metabolism, inhibits amino acid and polyamine synthesis	infectious, pulmonary and hematologic side effects, bone marrow impairments	
	Leflunomide	Orally (50 mg/week or 10 mg/day)	Inhibits dihydroorotate dehydrogenase enzyme leading to inhibition de novo synthesis of pyrimidine nucleotides	Dyspepsia, nausea, abdominal pain and oral ulceration	[71]
	Sulfasalazine	Orally (500 mg/daily or 1 g/day in 2 divided doses up to a maximum of 3 g/day in divided doses)	Suppresses the transcription of nuclear factor-κB (NF-κB) responsive pro-inflammatory genes including TNF-α	Nausea, vomiting, anorexia, dyspepsia, male infertility (reversible), headache and skin rash	[72]
	Hydroxychloroquine	Orally (400 mg/day over a 30-day period)	Increases pH within intracellular vacuoles and alters processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes and post-translation modification of proteins in the Golgi apparatus	Retinal toxicity, neuromyotoxicity	[73][74]
Biologic DMARDs	Etanercept, Infliximab, Adalimumab, Golimumab, Certolizuma-bpegol	Etanercept—SC injection (50 mg/week or 25 mg/twice a week); Infliximab—SC injection (3–10 mg/kg every 4–8 weeks); Adalimumab	Blocks the biological activity of TNF	Infections, neurological diseases, development of multiple sclerosis and lymphomas	[75]

Drug	Example	Administration/Dose	Mechanism of Action	Side Effects	Reference
		—SC injection (25 mg/twice a week); Golimumab—SC injection (50mg/month); Certolizumab pegol—SC injection (400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks)			
	Anakinra	SC injection (75–150 mg or 0.04–2 mg/kg)	Binds to IL-1 receptors	Opportunistic and latent infections	[76]
	Rituximab	IV injection (1 gm twice separated by 2 weeks) with MTX and IV corticosteroid premedication	Anti-CD20 monoclonal antibody	Hypogammaglobulinemia, rarely serious infectious events	[77]
	Abatacept	IV injection (2–10 mg/kg on days 1, 15 and 30, and then every 4 weeks)	Contains the domain of cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), blocks interaction between DCs and T cells	Serious infections, increased risk of certain malignancies	[78]
	Tocilizumab	IV injection (8 mg/kg once every 4 weeks) or SC injection (162 mg/week)	Blocks IL-6 receptor	Serious infections, major adverse cardiovascular events, cancers, diverticular perforations, hepatic diseases, rarely lethal	[79]
	Secukinumab	SC injections (25–300 mg)	Primarily targets IL-17A	Nasopharyngitis or infections of the upper respiratory tract, mild-to-moderate candidiasis	[80]
	Brodalumab	SC injection (70–210 mg)	Prevents the nuclear factor kappa light chain enhancer of activated B cells, IL-6, IL-8,	Nasopharyngitis, upper respiratory tract infections, arthralgia, back pain, gastroenteritis, influenza, oropharyngeal pain, sinusitis	[81]

Drug	Example	Administration/Dose	Mechanism of Action	Side Effects	Reference
			COX-2, MMPs and GM-CSF		
Targeted Synthetic DMARDs	Tofacitinib	Orally (5 mg/twice daily)	Blocks Janus kinases (JAK1 and JAK3)	Cardiovascular events, neutropenia and lymphopenia, risk of infection (viral reactivation, herpes virus reactivation, opportunistic infections)	[82]
	Baricitinib	Orally (4 mg/day or lower dosage 2 mg/day) [86]	Inhibits JAK1/JAK2	Hyperlipidemia, viral reactivation, deep venous thrombosis and pulmonary embolism event	[83]
	Upadacitinib	Orally (15 mg/day or 30 mg/day)	Inhibits JAK1	Upper respiratory tract infection, nasopharyngitis, and urinary tract infections, gastrointestinal [87] perforation	[84]
GCs	Dexame-thasone, be-tamethasone, triamcinolone, prednisone, prednisolone	The addition of GCs, to either standard DMARD monotherapy or combinations of [88][89][90][91] synthetic DMARDs with low-dose GCs (< 7.5 mg/day) or high-dose GCs (up to 15 [92][93][94][95][96][97][98] mg/day)	Directly activates or represses gene transcription	Ecchymosis, cushingoid features, parchment-like skin, leg edema, sleep disturbance, immunosuppression, weight gain, epistaxis, glaucoma, depression, hypertension, diabetes	[40][41][85]

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phenotype, particularly, through decreasing populations of DCs, macrophages, NK cells, B and T cells, and by promoting anti-inflammatory phenotype [11][99][100][101][102]. Depending on the environment, MSCs have the ability of polarizing and acquiring either pro-inflammatory (MSC1) or anti-inflammatory phenotypes (MSC2). In the presence of the inflammatory milieu (high levels of TNF-α and IFN-γ), which is generated by the immune cells, MSCs become activated and adopt an anti-inflammatory phenotype [11]. The mechanism of immune cell suppression by MSCs is mediated by secretion of a number of soluble factors, such as enzymes, cytokines and growth factors, including IDO, PGE2, NO, TGF-β1, HGF, hemoxygenase (HO), COX-2, IL-6 and IL-10. The IDO secretion is presumably induced by inflammatory cytokine IFN-γ [103]. The mechanism of action of IDO is mediated by conversion of an essential amino acid tryptophan to kynurenine, which impairs the synthesis of various cellular proteins and leads to the suppression of T cell proliferation. IDO is also considered to be involved in the generation of Tregs and tDCs induced by MSCs [104]. Moreover, factors produced by MSCs include nitric oxide synthase (iNOS), which induces the production of NO from macrophages thus inhibiting the proliferation, secretory and cytolytic functions of T cells. Both soluble factors function in the process of immunosuppression. However, it is demonstrated that iNOS mediates immunosuppression by mouse MSCs, while IDO plays a similar role in human MSCs [105].

Together with constitutive secretion of TGF-β by MSCs, the environment favors generation of Tregs [13][106][107][108][109][110][111]. In the absence of an inflammatory environment (low levels of TNF-α and IFN-γ), MSCs may adopt a pro-inflammatory phenotype and enhance T cell responses by secreting chemokines (e.g, MIP-1a and MIP-1b, RANTES, CXCL9 and CXCL10) that recruit lymphocytes to the sites of inflammation; these chemokines bind to CCR5 and CXCR3 expressed on T cells. The levels of immune suppressive mediators, such as IDO and NO, are low when the pro-inflammatory phenotype is adopted [12][112].

The role of apoptotic MSCs for therapeutic applications have been recently investigated. A study by Galleu and colleagues demonstrated that infused MSCs undergo extensive caspase activation and apoptosis in the presence of cytotoxic cells, which is a requirement for their immunosuppressive function, in both preclinical and clinical studies [113]. The mechanism is explained by the engulfment of apoptotic MSCs by phagocytes, and the IDO production, which is ultimately necessary for mediating immunosuppression. Similar results were reported by another group. The MCSs effect is based on the hypoxia-induced activation of caspase 3-mediated apoptosis, recruitment of immune cells at the transplantation site and their further engulfment by locally circulating macrophages [114].

Thus, the mechanism of immunomodulation by MSCs is regulated by both cell-cell interactions and paracrine effect via the secretion of soluble factors. Considering the abovementioned immunomodulatory properties, MSCs are being widely investigated as a promising tool for the treatment of autoimmune diseases, including RA.

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