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Current treatment in rheumatoid arthritis: a review including nanotechnology and gene therapy

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ABSTRACT

Rheumatoid arthritis (RA) is a common inflammatory disease affecting approximately 1% of the adult population worldwide. Before new treatments were available, unchecked RA caused notable inability and mortality .It is now accepted that primary diagnosis and treatment are essential and useful. Progress in therapy of RA has made it possible to deeply influence signs and symptoms as the period that joint destructed in inflammatory arthritis. Earlier and more efficient treatment becomes visible to significantly improve the prognosis of this disease. In this article, the old and new methods for treatment rheumatoid arthritis and their limitation and benefits were reviewed. These methods include nonsteroidal anti-inflammatory drug (NSAIDs), glucocorticoids(GC) that are a class of steroid hormones, disease-modifying anti-rheumatic drugs (DMARDs), biological agents that can be divided in two groups of monoclonal antibodies and teeny molecules, bisphosphonate therapy, nanotechnology, oral tolerance, photodynamic therapy, gene therapy, bone marrow transplantation, liposomes, superparamagnetic iron oxide nano particles (SPIONs).

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Introduction

Autoimmune disorders (AIDs) are responsible for a large amount of disability and morbidity and these diseases affect nearly 8.5% of individuals worldwide (1).The term rheumatoid arthritis(RA) is used to describe a spectrum of diseases, which include symmetrical, continuous and destructive polyarthritis that some of them have rheumatoid factor and/or positive results for anti-cyclic citrullinated peptide(anti-CCP)antibodies (2). RA is a systemic chronic inflammatory disease that involves numerous joints in a symmetric pattern disorder affecting 0.5–1% of the world population (3). The female to male ratio of this disease is 2-4:1. The basis of gender difference is not clear, but it can be related to effects of the hormonal milieu on immune function. The RA is more frequent in adulthood, particularly aged 40-60 years (4) This disease is diagnosed by a chronic inflammation of synovial joints, which causes destruction of articular cartilage and bone erosion ,and eventually leads to sever disability of patient (5). The etiology and pathogenesis of RA is unknown, but it has genetic basis and a lot of genes have been involved in genome-wide association studies (GWAS)(6,7). Environmental factors such as infections, vaccines inoculations and emotional trauma also play a role in RA (8,9).

Identification of RA is important, especially in the earliest stages. It can affect disease period, and stop the progress of persistent inflammation and progressive joint damage.

Clinical diagnosis of RA is very complex and involves many features that are difficult to help the clinical diagnosis. American college of rheumatol-

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ogy has introduced the formal criteria to diagnose RA in early stages. Because of the nature of autoimmune arthritis, effective and complete suppression of the disease has been the early therapeutic goal (10). Recently, treatment of the RA has considerable progress due to the advent of new tools and new treatment that have been made and accredited, highlighting the need for guidelines focused on primary RA. The goal of treatment should now be to get clinical progression for preventing structural damage and inability. Currently, available treatment options include nonsteroidal anti-inflammatory drug (NSAIDs), glucocorticoids(GC) that are a group of steroid hormones, disease-modifying anti-rheumatic drugs (DMARDs), biological agents including monoclonal antibodies and small molecules, bisphosphonate therapy, nanotechnology, oral tolerance, photodynamic therapy, gene therapy, bone marrow transplantation, liposomes, superparamagnetic iron oxide nano particles (SPIONs).

Literature Review

Earliest treatment

NSAIDs have analgesic and anti-inflammatory properties, but they do not change the process of the disease or prevent joint destruction. The main mechanistic pathway of NSAIDs is protecting the enzyme cyclooxygenase (COX) and inflammation (11).

It is clear that the anti-inflammatory effect of NSAIDs is due to the inhibition of COX-2, an isoform of cyclooxygenase, whereas inhibition of the COX-1 isoform causes the problems in gastric and renal function (12).

Celecoxib, a new NSAlD that selectively protects the enzyme COX-2, is recommended by the US Food and Drug Administration (FDA) for treatment of RA. Nausea, diarrhea, and abdominal pain are the important effects of Celecoxib. Another new drug with a specific inhibitory effect on COX-2 is Rofecoxib. All the various effects are transient, and non- required patients can discontinue the therapy (13). In comparison with glucocorticoids and traditional NSAIDs, drugs such as celecoxib and rofecoxib do not have many of the side effects (14).

Glucocorticoids (GCs) are a group of steroid hormones, and these drugs cab bind to the cortisol receptors and have many biological effects. They have potent anti-inflammatory and immunosuppressive effectives. Glucocorticoids are basically used for the treatment of RA (15).

Glucocorticoids are used in two ways, intra-articularly or systemically. Usually, prednisone 10 mg/day is used in decreasing short-term signs and symptoms in patients with RA. Therapy with GCs temporarily has some side effects, including weight gain , hypertension ,diabetes, cataracts and osteoporosis (16).

Disease-modifying anti-rheumatic drugs (DMARDs): the effect of this drug on the disease process will be clear within weeks or months. By comprising several handmade molecules, and biological DMARDs produced by genetic engineering, these drugs can be named traditional DMARDs (17).

DMARDs include Methoteroxate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), cyclosporine, gold salts, penicillamine, and azathioprine. According to radiological studies these drugs have had good effects, although their long-term effect on disability is not clear. It has been shown that early combined therapy with DMARDs is more useful and less dangerous than late monotherapy in patients (18).

Among the DMARDs, MTX is considered the most important drug and should be firstly used in the patients at risk of extending chronic disease (20).

When we use MTX weekly in small doses, the result is not dependent to the plasma concentration of the drug. It is shown that MTX does its function with decreasing the concentration of circulating purines and pyrimidines that cause decreasing the material for synthesis of DNA and RNA. This drug may also increase the immune cells and cytokines. During treatment of RA patients with MTX, increasing hepatocellular enzymes and serum alkaline phosphatase are common. The increase of enzymes is dependent to the length and definition of significant abnormality (18).

Two group of biological agents including monoclonal antibodies and small molecules that are added to the existing spectrum of DMARDs in RA (19).

1. Monoclonal antibodies

The monoclonal antibody therapy in rheumatology has shown a good effect in recent years. The main effect of these molecules may be attributed to chimeric antibodies with human constant regions of light and heavy chain and the several murine binding sites for the special molecule.

These antibodies act in some different method including frustrating target cytokine or its receptor, blocking exciting molecules, and stimulating cytolysis, apoptosis or depletion of the last cell molecules (20). Some results show that progressive anti-inflammatory treatment like biologic DMARDs decreases the level of bone loss in RA (7) (Table 1).

Macrophage migration inhibitory factor (MIF) has many biological activities, which is associated

with some immune diseases such as RA.

Table 1. Currently used biological therapies for rheumatoid arthritis.

Biological therapies
1.TNF-α inhibitors 2.Infliximab (Remicade)-chimeric monoclonal antibody 3.Etanercept (Enbrel)-TNF- α receptor 4.Adalimumab (Humira)- human monoclonal antibody 5.IL-1 inhibitor 6.Anakinra (Kineret)-IL-1 receptor antagonist 7.IL-6 inhibitor 8.Tocilizumab (Actemra)-humanized monoclonal anti-IL-6 receptor antibody 9.B-lymphocyte depletion 10.Rituximab (MabThera)-monoclonal anti-CD20 antibody 11.Inhibition of costimulation 12.Abatacept (Orencia)-fusion protein CTLA-4 with immunoglobulin
TNF: tumor necrosis factor; IL: interleukin; CTLA-4: cytotoxic T-lymphocyte antigen 4.

This protein is a potential therapeutic target because the serum level of MIF is increased in patients with RA. There is direct relation between high amounts of MIF with disease severity. Finding show that polymorphism in the promoter of MIF gene is associated with disease severity in RA patients (21).

2. Small molecules

Many of the new anti-inflammatory therapies in preclinical and clinical practice consisted small molecules with molecular weights of about 1 kDa.

These agents that are used for preoral administration should be less expensive; furthermore, they should have at least the same efficacy as the new biological therapies. Recently, new small molecules have a special impact on several intercellular factors or cell structures. For example, receptors, intracellular signaling pathways and enzymes have a function in the pathogenesis of RA.

Due to some problems of biologic DMARDs (parenteral administration), orally effective treatment options is also suggested for RA. Tofacitinib is a janus kinase (JAK) suppressor, and the first non-biologic DMARD that is used orally. This drug can be used with methotrexate or other non-biologic DMARDs (Table 2) (22).

Table 2. Prospective biological therapies for rheumatoid arthritis in clinical trials.

Therapeutic aim/drug	Phase of clinical trial
Novel TNF- α inhibitors Golimumab- fully human monoclonal antibody, under regulatory review Certolizumab pegol (Cimzia)-humanized monoclonal antibody, under regulatory review	
Novel IL-1 inhibitors Canakinumab (ACZ885), humanized monoclonal antibody against IL-1	**II**
Inhibitors of cytokines from the TNF superfamily Atacicept/TACI-Ig — recombinant fusion protein of BAFF- and APRIL receptor	**II**
Inhibitors of other cytokines HuMaxIL-15-humanized monoclonal anti-IL-15 antibody	**II**
AIN457-monoclonal anti-IL-17 antibody	**I /II**
Inhibitors of osteclastogenesis Denosumab-monoclonal antibody against RANKL	**III**
Inhibitors of B-lymphocyte cell-surface markers Ocrelizumab-humanized monoclonal anti-CD20 antibody	**III**
Ofatumumab-fully human monoclonal anti-CD20 antibody	**III**
TRU-015-small antibody polypeptide (SMIP) blocking CD20	**II**
Small molecules Inhibitors of p38 kinase	**II**
Inhibitor of JAK3 kinase (CP-690,550)	II
Inhibitor of Syk kinase (Fostamatinib)	II
IL-12/IL-23 inhibitor (Apilimod, STA-5326)	II
Inhibitor of CD80-CD28 costimulation (RhuDex)	I

TNF, tumor necrosis factor; BAFF, B-cell activating factor; APRIL, a proliferation-inducing ligand; IL, interleukin; RANKL, receptor activator for nuclear factor κB ligand; SMIP, small modular immune pharmaceutical; MAPK, mitogen-activated protein kinase; JAK,Janus tyrosine kinase; Syk, spleen tyrosine kinase

New treatment

Bisphosphonate therapy in RA

Bisphosphonates include amino –and non-amino-containing compounds, depending on the presence or absence of a side-chain amino group, forming a "P-C-P" structure (23). Bisphosphonates can inhibit common bone loss. Osteoclast, known as the culprit in focal bone damage due to inflammatory illnesses like RA, is the main goal (24,25). This amino group influences drug potency by giving a various option for mechanism of actions. Thus, amino bisphosphonates such as pamidronate, alendronate, risedronate and zoledronate perform their inhibitory effects on osteoclast function by preventing farnesyl pyrophosphate synthase. In contrast, non-amino bisphosphonates such as etidronate and clodronate metabolize non-hydrolysable analogues of ATP and act as suppressor of ATP dependent enzymes, leading to increase osteoclast (26). Bisphosphonates are chemically steady analogs of inorganic pyrophosphate (27,28). So, bisphosphonates are an important group of drugs for the treatment of bone illness. Animal studies show that the bone resorption can be stopped after chymopapain injection into the rabbit knee joint (29,30).

Oral tolerance

Oral tolerance refers to a state that immune system does not response to protein antigens that have been stimulated by several exposures of the mucosal immune system to ingested protein antigens (31).

For treatment of chronic autoimmune diseases including RA, induction of oral tolerance is considered as a promising approach. T cells have been observed to increase osteoclast genesis by expression of receptor activator of nuclear factor kappa B ligand (RANKL) that is stimulated by cytokines, self-antigens, and other immune cells. Cytokines such as IL-23 and IL-15 stimulate T cells to secrete IL-17, which promotes osteoblasts and synoviocytest to produce RANKL, starting RANKL-associated osteoclast genesis and bone loss. Also, il-17 is associated with the severity of inflammation in the synovia of patients with RA (32,33).

Oral tolerance is a therapeutic method for regulating the autoreactivity of CII, which not only causes IL-17 production, but also induces RANKL expression in CD4+ T cells (34).

This method is useful for the treatment of autoimmune diseases because it has not many side effects in addition it has easy clinical implementation. However, protein antigens, administered orally are digested very fast and presenting of their effect is in short time, but these drawbacks can be dominated by encapsulating CII (35).

Photodynamic therapy

The function of photodynamic therapy (PDT) is mainly decreasing the hyperplastic synovium and this method is a custody approach to treat RA. Due to potential destruction of other tissues, choosing the appropriate method is important. Gabriel et al. made a new polymeric pheophorbide a prodrug that is cleaved by thrombin, which is up-regulated in a synovial tissue of RA patients (36).

PDT uses the photosensitizer (PS), tissue oxygen, and light irradiation at the same time to produce cytotoxic reactive oxygen species (ROS) that can damage tissues.

Nano technology

Drug Delivery

When the aim is to use new drug delivery system like nano particle, the drug should be in nano size. To get the best result, these principle should be note:

1. More specific drug targeting and delivery,
2. Maintaining therapeutic effects and reducing the toxicity
3. Greater safety and biocompatibility (37).

The only physiochemical properties of drug-loaded nano carriers that are joined with pathophysiological within inflamed joints and strengthen bioavailability and bioactivity of DMARDs; therefore, excite their optional targeting . FDA-approved injectable nano carriers include liposomes, micelles, nano crystals, nano particles, nano tubes and super magnetic iron oxide (38,39).

Liposomes

There are 4 synthetic polymers in colloid engineering (1. Polymeric nano spheres 2. Micelles 3. Liposomes 4. Oil-in-water emulsions (40).

Liposome that is an artificial spherical vesicle composed of a lamellar phase lipid is useful for its ability to cover therapeutic agents, increase the duration of action, and effective intracellular delivery (17). With these technology, scientists can investigate therapeutic factors that are toxic to release through a systemic route (41). The aim of drug delivery systems, and in particular liposomes, is to enhance the biodistribution and the target site accumulation as well as to reduce the toxicity of drugs (42,43).

For example, liposomal dexamethasone caused to release pro-inflammatory cytokine (specifically TNF, IL1β, and IL6) in cells that has not been stimulated although it decreases this reactance in inflammatory conditions (44). Furthermore, some results show that cartilage oligomer matrix protein (COMP) stayed close to normal in group with sketchy articular cartilage that use clodronate liposomes in comparison with a considerable loss of

COMP in the control groups (45). Liposome-based delivery systems have limitations such as limited drug capacity and physical instability (17).

Superparamagnetic iron oxide nano particles (SPIONs)

To achieve the goal of locally treating inflammatory conditions such as arthritis, SPIONs and the corticosteroid dexamethasone acetate (DXM) are co-encapsulated into Poly Lactic-co-Glycolic Acid (PLGA) microparticles. It can increase microparticle residence time in the joint; in addition, it is shown that these microparticles did not stimulate any inflammatory response in the joint (46).

To develop a macromolecular prodrug for RA treatment, three acute design factors must be investigated. First: to choose and/or allocate the macromolecular carriers. Second: a suitable chemical connector between the macromolecular carrier and the target. Third: complete understanding of the mechanism. Findings show that physicochemical properties and magnetofection effects are not changed by many different factors in the making of SPIONs (47). This new passive targeting method named as "ELVIS" indicates the macromolecular prodrugs permeation through permeable vessels and further inflammatory cell-mediated destruction (Table 3) (19,21).

Table 3. The macromolecularization of anti-rheumatic drugs.

Drug	Macromolecular carrier	Linkage between the drug and the carrier	Targeting moiety	Activation mechanism
NSAIDs (e.g. naproxen)	Dextran	Ester	None	Esterase-catalyzed hydrolysis
Methotrexate (MTX)	Human serum albumin (HSA)	Amide	None	Proteases-catalyzed hydrolysis
MTX	HSA	-Maleimide-D-Ala-Phe-Lys-Lys-	None	Proteases-catalyzed hydrolysis
MTX	HPMA copolymer	-Gly-Phe-Leu-Gly-Lys-	Biotin	Proteases-catalyzed hydrolysis
MTX	Dextran	-Pro-Val-Gly-Leu-Ile-Gly-	None	Matrix metalloproteinase II or IX (MMP2/MMP9)
MTX	Poly amido amine (PAMAM) dendrimer	Ester	Folate	Esterase-catalyzed hydrolysis
MTX	PAMAM dendrimer	Ester	MTX itself	Esterase-catalyzed hydrolysis
MTX	PAMAM dendrimer	Amide	RGD	Unclear
Glucocorticoids (e.g. cortisol)	Polyvinyl pyrrolidone (PVP)	Ester	None	Esterase-catalyzed hydrolysis
Dexamethasone (Dex)	N-(2-hydroxypropyl)-methacrylamide	Hydrazone	None	Acid-catalyzed hydrolysis
Dex	Linear multifunctional polyethylene glycol (click PEG)	Hydrazone	None	Acid-catalyzed hydrolysis
Dex	PEG	Hydrazone	None	Acid-catalyzed hydrolysis

Gene therapy

Gene therapy, that is another possible therapeutic way for RA, needs to optimize the following: gene delivery, vectors, nomination molecules and aims and methods to set transgene expression.

Since there is not just one gene associated with RA, (48,49) first the appropriate gene should be chosen, because cytokines have strong positive feedback results, which can reinforce the impacts of the primary immune attack. Secondly, where these genes should be transferred? Results show that the anti-arthritic impacts of positional gene transfer is synovium (31).

For example, these genes (IL-1, IL-10, and Fas L) can be transferred with a suitable vector to the joint of patient; therefore, the impact of IL-35 gene delivery in an autoimmune and inflammatory RA model can be shown (50).

Moreover, another experiment shows that a non-tissue-particular cationic protein transduction domain (PTD-5) were joined to a peptide

(KLAK) that destruct microbes (2) to produce two proapoptotic peptides named DP2 and DP1 (G-protein–coupled receptors, DP1 and DP2 (CRTH2)). These peptides were able to promote programmed cell death of rabbit and human synovial cells in culture, and this can be clinically helpful for remedy of synovial hyperplasia (51).

The determinative step in gene therapy of RA is the capability to transfer genes efficiently and frequently to joints without creating destruction and long –term expression. The experimental data suggest that gene transfer may help repair the cartilage, ligaments, tendons, menisci, intervertebral discs and bone, but it is not yet definite that this method can be considered as a therapeutic option for RA (52).

Bone marrow transplantation

RA may be so progressed that it may need immune suppression to survive the patient. The most important determining factor in such immune suppression treatment is the danger of hemato ablation that can happen simultaneously. Findings indicate that many issues need further clarification: 1) choosing the best patient for hematopoietic stem cell transplantation (HSCT);2) fatality rates, especially in older people and weak patients; 3) recurrence rates over considerable follow-up; 4) graft manipulation before transplantation; and 5) prosperous keeping treatment with using MTX once in a week after HSCT (29).

Conclusion

RA is a very heterogeneous disease and the response to treatment is unpredictable. It has been proven that early treatment may lead to the reduction in structural damage and an improvement of incapacity in the long-term. Traditional therapies such as (NSAIDs), corticosteroids, and DMARDs may lead to decrease the severity of RA, but sometimes cause sustained remission and can have side effect and therefore cannot be used for long time. Using of DMARDs in early arthritis is suggested for preventing from more joint damage and instability. For patient that do not response well to DMARDs, biological therapies can be used. These drugs are expensive and they increase the possibility of catching infection in comparison with DMARDs. Hence, the treatment of RA can be successful with early diagnosis and using new drugs at the same time. Liposome formulations of the drugs causes long circulating of MTX, glucocorticoids, NSAIDs and super oxide dismutase; therefore, it may have better impacts and fewer side effects in comparison with free drug. Therefore, long-term using of this drug may be exhorting because of some severe allergic response in the reaction, especially in the activation part.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Hashemi M, Atabaki M, Daneshvar H, et al. Association of PTPN22 rs2476601 and EGFR rs17337023 Gene polymorphisms and rheumatoid arthritis in Zahedan, Southeast Iran. Int J Immunogenet. 2013;40:299-305.
2. Yuan F, Quan LD, Cui L, et al. Development of macromolecular prodrug for rheumatoid arthritis. Adv Drug Deliv Rev. 2012;64:1205-1219.
3. Sun J, Zhang Y, Liu L, et al. Diagnostic accuracy of combined tests of anti cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis: a meta-analysis. Clin Exp Rheumatol. 2014;32:11-21.
4. Subhashini V, Mahalakshmi AM, Suresh B. Current clinical strategies in rheumatoid arthritis: a review. Int J Pharm Pharm Sci. 2012;4:43-46.
5. Ho LJ, Lai JH. Small-molecule inhibitors for autoimmune arthritis: Success, failure and the future. Eur J Pharmacol. 2015;747:200-205.
6. Widler L, Jaeggi KA, Glatt M, et al. Highly potent geminal bisphosphonates. From pamidronate disodium (Aredia) to zoledronic acid (Zometa). J Med Chem. 2002; 45:3721-3738.
7. Bamonti F, Fulgenzi A, Novembrino C, et al. Metal chelation therapy in rheumathoid arthritis: a case report. Successful management of rheumathoid arthritis by metal chelation therapy. Biometals. 2011;24:1093-1098.
8. Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J Autoimmun. 2010;35:10-14.
9. Navarro Sarabia F, Blanco FJ, Álvaro Gracia JM, et al. Economic evaluation of rheumathoid arthritis monotherapy with tocilizumab and adalimumab. Rev Esp Salud Publica. 2013;87:343-350.
10. Lo SF, Wan L, Lin HC, et al. Association of rheumatoid arthritis risk with EGFR genetic polymorphisms in Taiwan's Han Chinese population. Rheumatol Int. 2012;32:2301-2306.
11. Urban MK. COX-2 specific inhibitors offer improved advantages over traditional NSAIDs. Orthopedics. 2000;23:S761-764.
12. Furst DE. Meloxicam: selective COX-2 inhibition in clinical practice. Semin Arthritis Rheum. 1997;26:21-27.
13. Vanniasinghe AS, Bender V, Manolios N. Manolios, The potential of liposomal drug delivery for the treatment of inflammatory arthritis. Semin Arthritis Rheum. 2009;39:182-196.
14. Nasonov EL. New approaches to pharmacotherapy for rheumatoid arthritis: perspective for use of tocilizumab (monoclonal antibodies to interleukin-6 receptor). Ter Arkh. 2010;82:64-71.
15. Quan L. Macromolecular Nanomedicine of Glucocorticoids for the Treatment of Rheumatoid Arthritis. J Nanomed Nanotechol. 2013;4:e126.
16. Combe, B. Early rheumatoid arthritis: strategies for prevention and management. Best Pract Res Clin Rheumatol. 2007;21:27-42.
17. Deighton C, Criswell LA. Criswell, Recent advances in the genetics of rheumatoid arthritis. Curr Rheumatol Rep. 2006;8:394-400.
18. Scully CJ, Anderson CJ, Cannon GW. Cannon, Long-term methotrexate therapy for rheumatoid arthritis. Semin Arthritis Rheum. 1991;20:317-331.
19. Sen D, Paul JR, Ranganathan P. Ranganathan, Pharmacogenetics in rheumatoid arthritis. Methods Mol Biol. 2014;1175:625-660.
20. Senolt L, Vencovský J, Pavelka K, et al. Prospective new biological therapies for rheumatoid arthritis. Autoimmun Rev. 2009;9:102-107.
21. Li S, Zhang R, Li P, et al. Development of a novel method to measure macrophage migration inhibitory factor (MIF)

in sera of patients with rheumatoid arthritis by combined electrochemical immunosensor. Int Immunopharmacol. 2008;8:859-865.
22. Lundquist LM, Cole SW, Sikes ML. Sikes, Efficacy and safety of tofacitinib for treatment of rheumatoid arthritis. World J Orthop. 2014;5:504-511.
23. Russell RG, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone. 1999;25:97-106.
24. Ding H, Yang L, Du W, et al. Bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2013;14:3337-3343.
25. Keizman D, Ish-Shalom M, Maimon N, et al. Are bisphosphonates an indispensable tool in the era of targeted therapy for renal cell carcinoma and bone metastases? World J Urol. 2014;32:39-45.
26. Romas E. bone loss inflamatory arthritis:mechanism and therapeutic approches with bisphosphonate. Best Pract Res Clin Rheumatol. 2005;19:1065-1079.
27. Russell RG, Rogers MJ, Frith JC, et al. The pharmacology of bisphosphonates and new insights into their mechanisms of action. J Bone Miner Res. 1999;14 Suppl 2:53-65.
28. Fick EM, Anzeneder T, Katalinic A, et al. Bisphosphonates and their Role in Therapy for Breast Cancer - Results from the PATH Biobank. Geburtshilfe Frauenheilkd. 2013;73:412-421.
29. Muehleman C, Green J, Williams JM, et al. The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage. Osteoarthritis Cartilage. 2002;10:226-233.
30. Forsblad D'Elia H, Larsen A, Waltbrand E, et al. Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis. Ann Rheum Dis. 2003;62:617-623.
31. Min SY, Park KS, Cho ML, et al. Antigen-induced, tolerogenic CD11c+,CD11b+ dendritic cells are abundant in Peyer's patches during the induction of oral tolerance to type II collagen and suppress experimental collagen-induced arthritis. Arthritis Rheum. 2006;54:887-898.
32. Lubberts E, Koenders MI, van den Berg WB. The role of T-cell interleukin-17 in conducting destructive arthritis: lessons from animal models. Arthritis Res Ther. 2005;7:29-37.
33. Cho ML, Kang JW, Moon YM, et al. STAT3 and NF-kappaB signal pathway is required for IL-23-mediated IL-17 production in spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice. J Immunol. 2006;176:5652-5661.
34. Ju JH, Cho ML, Jhun JY, et al. Oral administration of type-II collagen suppresses IL-17-associated RANKL expression of CD4+ T cells in collagen-induced arthritis. Immunol Lett. 2008;117:16-25.
35. Min SY, Hwang SY, Park KS, et al. Induction of IL-10-producing CD4+CD25+ T cells in animal model of collagen-induced arthritis by oral administration of type II collagen. Arthritis Res Ther. 2004;6:R213-219.
36. Rai P, Mallidi S, Zheng X, et al. Development and applications of photo-triggered theranostic agents. Adv Drug Deliv Rev. 2010;62:1094-124.
37. Misra R, Acharya S, Sahoo SK. Cancer nanotechnology: application of nanotechnology in cancer therapy. Drug Discov Today. 2010;15:842-850.
38. Rubinstein I, Weinberg GL. Weinberg, Nanomedicines for chronic non-infectious arthritis: the clinician's perspective. Nanomedicine. 2012;8 Suppl 1:S77-82.
39. Angell C, Xie S, Zhang L, et al. DNA Nanotechnology for Precise Control over Drug Delivery and Gene Therapy. Small. 2016;12:1117-1132.
40. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev. 2001;53:283-318.
41. Pham CT. Nanotherapeutic approaches for the treatment of rheumatoid arthritis. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2011;3:607-619.
42. Ozbakir B, Crielaard BJ, Metselaar JM, et al. Liposomal corticosteroids for the treatment of inflammatory disorders and cancer. J Control Release. 2014 28;190:624-636.
43. Alten R, Döring G, Cutolo M, et al. Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. J Rheumatol. 2010;37:2025-2031.
44. Bartneck M, Peters FM, Warzecha KT, et al. Liposomal encapsulation of dexamethasone modulates cytotoxicity, inflammatory cytokine response, and migratory properties of primary human macrophages. Nanomedicine. 2014;10:1209-1220.
45. Gomez-Barrena E, Lindroos L, Ceponis A, et al. Cartilage oligomeric matrix protein (COMP) is modified by intra-articular liposomal clodronate in an experimental model of arthritis. Clin Exp Rheumatol. 2006;24:622-628.
46. Butoescu N, Seemayer CA, Foti M, et al. Dexamethasone-containing PLGA superparamagnetic microparticles as carriers for the local treatment of arthritis. Biomaterials. 2009;30:1772-1780.
47. Prosen L, Prijic S, Music B, et al. Magnetofection: a reproducible method for gene delivery to melanoma cells. Biomed Res Int. 2013;2013:209452.
48. Balmayor ER, van Griensven M. van Griensven, Gene therapy for bone engineering. Front Bioeng Biotechnol. 2015;3:9.
49. Baum BJ. Gene therapy. Oral dis. 2014;20:115-118.
50. Quirke AM, Lugli EB, Wegner N, et al. Heightened immune response to autocitrullinated Porphyromonas gingivalis peptidylarginine deiminase: a potential mechanism for breaching immunologic tolerance in rheumatoid arthritis. Ann Rheum Dis. 2014;73:263-269.
51. Mi Z, Lu X, Mai JC, et al. Identification of a synovial fibroblast-specific protein transduction domain for delivery of apoptotic agents to hyperplastic synovium. Mol Ther. 2003;8:295-305.
52. Evans CH, Robbins PD, Ghivizzani SC, et al. Gene transfer to human joints: progress toward a gene therapy of arthritis. Proc Natl Acad Sci U S A. 2005;102:8698-8703.