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Efficacy and Safety of Corticosteroid In The Treatment of Rheumatoid Arthritis

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Abstract

Therapy using corticosteroid in a patient of rheumatoid arthritis (RA) has modernized the debate of its risks and benefits. RA is a chronic clinical condition of inflammation leads to disability and deformity by affecting joints as well as connective, muscle, tendons, and fibrous tissue. In general, it tends to strike at the ages of 20 to 40. Treatment of RA using steroid has recently been renewed. Evidences suggesting rapid effects as well as disease modifying properties which of corticosteroids led it beneficial for the treatment of RA. Several attempts have been made to optimize its clinical benefits using low doses, subsequent step down of doses after high dose administration and limits its adverse effects also gives an interesting clue for the scientists to reconsider it as drug for real life setting in RA. It potentially acts by inhibition of inflammation though decrease in inflammatory mediators. Here we present recent updates to exemplify the significant potential of glucocorticoids for the treatment of RA with the special impact in terms of approaches of administration.

Keywords: glucocorticoids; rheumatoid arthritis; therapeutic advancement; corticosteroid

1. Introduction

Rheumatoid arthritis (RA) is a chronic condition of inflammation due to autoimmune defects. It affects overall prevalence of 1%, which may rise up to 2% in older population. Now-a-days 30 out of 100000 patients are suffering from rheumatoid arthritis [1]. The prevalence of this disease is 2-3 folds more in females of age group 40-60yr. The main hallmark of RA is synovial inflammation, long term prognosis of disease is poor [2]. Severe pain, stiffness with swelling of joints of hands, feet, knees in early stages are the characteristic features of RA [3, 4] RA

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commonly results in persistent synovitis, progressive joint destruction and ultimately alter the quality of life of the patients [3]. The articular and extra- articular progressive nature of RA leads to morbidity and mortality. Early symptoms of RA are nonspecific such as fatigue, musculoskeletal pain and stiffness [5] later on, synovial membrane gets thickened and lead to erosion of cartilages [6]. In RA, synovial membrane invades the joint and due to this joints get swollen which further leads to pain during movement [7, 8]. As per American Rheumatism Association morning stiffness develops to the individual which lasts for >1h for >6 weeks, arthritis of at least 3-joint areas takes place. Further hand joints, symmetrical arthritis develops and finally rheumatoid nodule followed by serum rheumatoid factor appears in the patients of RA. At the end, physicians reporting about with radiographic changes in wrist and hands [9]. Etiology of RA in precise way is not clearly known but microbial agents, smoking, obesity, or Schizophrenia ae causative factors for pathogenesis [10, 11]. Tyrosine phosphatase non-receptor type 22 gene has been identified in RA patients[12, 13]. The association between antigen HLA-DR4 and RA is much stronger, and is important in severe form of RA. Infectious agents linked to RA such as Epstein-Barr virus (80%), parvovirus, mycobacteria have also been linked to RA because of heat shock protein (HSP) that they express [14]. Various risk factors are used to consider while understanding the etiology of RA. Whenever an antigen attack on synovial membrane, production of cytokines causes activation of monocytes and macrophages [15]. Further, synovial fibroblast overproduces IL-1, IL-6 and TNF-α [16]. These mediators of inflammation trigger signal transduction pathways followed by activation of transcription factors e.g. matrix metalloproteinases (MMP's) present in joints. These are also involved in cartilage degradation and bone erosion [17]. Regular therapy of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) have many disadvantages which involves reduction of solubility, permeability, bioavailability and degradation of these drugs by the enzymes present in gastrointestinal system. These conventional medicines also undergoes first pass metabolism, interaction with food, and cause toxicity to the patients [3, 18-23]. Its treatment can be also provided using non conventional therapy which includes superoxide dismutase (SOD), antisense oligodeoxynucleotides, boron neutron capture therapy, and radioisotopes [3, 23]. Since remarkable advancement has been made in the medical sciences as well as in pharmaceutical sciences for clinical treatment of RA but it was regularly observed that long-term administration of anti-rheumatic drugs brings several adverse effects, required high doses for satisfactory pain relief and increased frequency dosing. It results in problems associated with major organ system like cardiovascular, hepatic and renal system. Hence, this review will focus on therapy with the help of glucocorticoids which is known to prevent RA in stepwise manner so that inflammatory process as well proliferative pathways can be limited in RA.

Efficacy and achievements ratio of corticosteroids

Glucocorticoids (GC) therapy has increased by more than 30% over the last 20 years [24, 25] as it is advantageous not only in RA but also in patients of asthma, and neoplastic state [24]. A recent survey reported that its therapy provides potential benefits in controlling pain, are not associated with worse results [26]. The misinterpretation regarding risk of corticosteroid can be avoided if corticosteroids should be given according to treatment-specific guidelines [27]. GC are responsible molecular as well as cellular effects. The known effects on GC can be illustrated as mentioned in fig.1 [28-30]. GC causes followings effects on cells [31]:

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1. Level of eosinophils decreases at the site of inflammation.
2. Decrease in proliferation, protein synthesis, synthesis of metalloproteins and also decrease in IL-6, IL-8, and GM-CSF due to action on fibroblasts.
3. It increases glycosaminoglycan and DNA synthesis on chondrocytes [29, 30, 32-67].

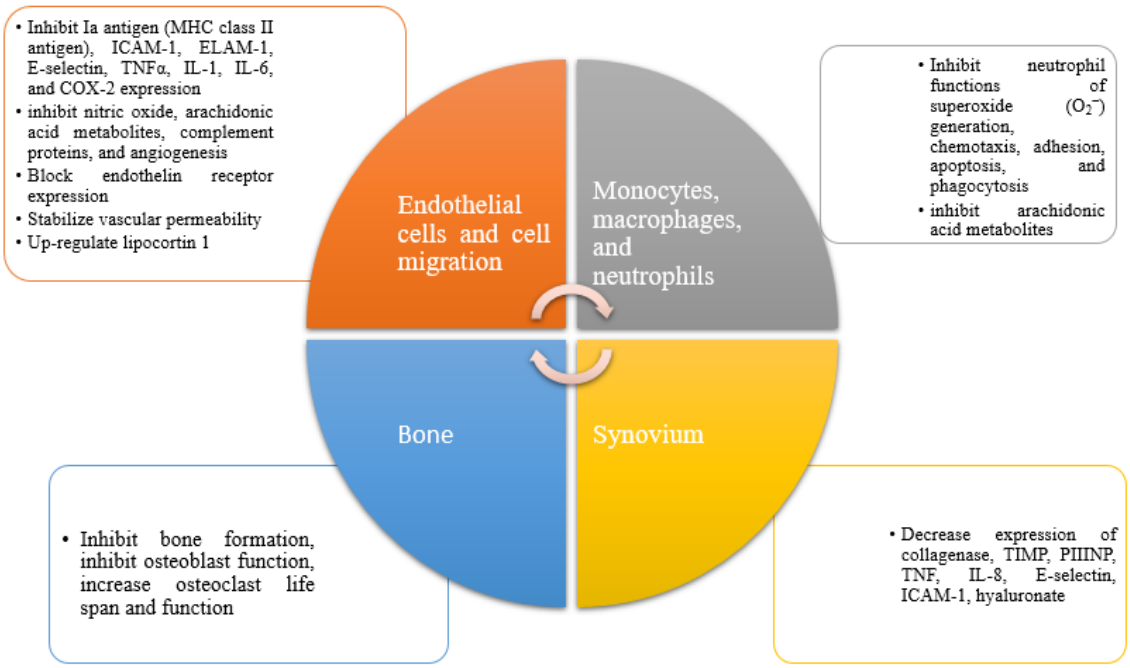

Fig.1. impact of GC on cells

Note: MHC = major histocompatibility complex; ICAM-1 = intercellular adhesion molecule 1; ELAM-1 = endothelial leukocyte adhesion molecule 1; TNF = tumor necrosis factor; IL-1 = interleukin-1; COX-2 = cyclooxygenase 2; NF-κB = nuclear factor κB; IFNγ = interferon-γ; GM-CSF = granulocyte–macrophage colony-stimulating factor; TIMP = tissue inhibitor of metalloproteinase; PIIINP = N-propeptide of type III procollagen.

Why to give GC in RA?

Due to potent anti-inflammatory properties, GC relieve joint pain, swelling, stiffness and prevent structural damage [68]. Long-term follow-up studies suggest that, GC therapy may positively alter course of disease even after its discontinuation [69]. Many international guidelines recommends using the lowest possible dose and duration of GC treatment [70]. Modified drug delivery to improve the therapeutic index of glucocorticoids [3, 55] are also available. Prednisolone are also available in Liposomes, Microspheres Prolonged release and Nanoparticles like drug delivery system which makes them more tissue targeting [71], prolonged release [72] and improved efficacy[73] respectively.

Formulations of corticosteroid

Table 1 and 2 indicates different formulations of glucocorticoids has been shown to lead in the antiarthritic effect [3].

Table 1. Different formulation aspects of corticosteroids

Name of drug	Formulation type	Animals tested/route	Outcome	Reference

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		of administration		
Hydrocortisone	Multilamellar liposomes	Rabbit (Intra-articular)	Anti-inflammatory effect enhancement	[74]
Prednisolone phosphate	PEG-liposomes	Mice (Intravenous)	Protection of cartilage	[75]
Methyl prednisolone hemisuccinate	Nanoliposomes	Beagle dog (intravenous)	More encapsulation and increased therapeutic efficacy	[76]
		Lewis rat (Intravenous or Subcutaneous)	Decrease in chemical mediator of inflammation, decreases arthritis	[77]
Dexamethasone phosphate	Oligolamellar, multilamellar vesicles	Rabbit (intra articular)	Increase retention of drug at joints	[78]
	RGD-PEG Liposomes	Lewis rat (intravenous)	Target vesicular endothelial sites	[79]
	Non-PEGlyated liposomes	Rat (intravenous)	Decreased joint swelling	[80]
Betamethasone	Nanoparticles	Rats	Prolonged release	[81, 82]
Dexamethasone	With HPMA-copolymer	Male Lewis rats	pH-sensitive drug release	[82, 83]

In order to achieve antiarthritic effect, following parameters must be fulfilled by a delivery system:

1. Sustained stabilization and extended bioavailability of the drug
2. Modification of the drug at molecular level
3. Availability of drug to the reach and released sites of inflammation with high specificity efficacy and in controlled manner [82].

Table 2. Clinically and preclinically tested formulation of corticosteroids

Drugs	**Prepared formulation**	**Doses**	**Clinically (CL) /preclinically tested (PCL)**	**Remarks**	**Reference**
Prednisone	Modified release	(2.5-10 mg/day)	CL	Improvements in morning stiffness	[84]
	Delayed release		CL (No. of pateints = 375, 144 for delayed release, 144 for immediate release)		[85]
Methyl prednisolone hemisuccinate	Proliposomal Gel	1.Lewis rats = 10 (mg/kg) 2.Beatle dog = 6.3 (mg/kg)	PCL (Rats and Beagle dog)	94% encapsulation	[76]
Dexamethasone	Intrasubcuta-neously	2.25 mg/kg	PCL(Lewis Rats)	Lower doses of corticosteroids may be sufficient to suppress the cytokines	[86]
Prednisone	Modified release	5 mg/day	CL(n=350)	Low-dose MR prednisone added to existing DMARD treatment produced rapid and relevant improvements in RA.	[87]

Safety: Drug interactions

Significant interactions between GC and other drugs provide an additional benefit. So that safety criteria must be adopted while administrating these drugs. It is well documented that some drugs reduce the systemic GC concentration which results in decrease in efficacy. They include:

1. At increased doses of aluminium/magnesium hydroxide causes decreased bioavalability of prednisone by 30– 40%

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2. Anticonvulsant drugs (phenobarbital, phenytoin), increases the metabolism of GC [88-95].
3. Rifampicin promotes the metabolism of synthetic GC. Rifampicin-induced adrenal crisis in with patients receiving GC [88-95].

It is also reported that some drugs raise the systemic GC concentration. They are:

1. Some oral contraceptives [96, 97], antibiotics (erythromycin and troleandomycin) [98, 99], antifungal agents, particularly ketoconazole decrease GC metabolising enzymes [100].
2. NSAIDs (indomethacin) and naproxen, increase GC concentrations[101]
3. GC may affect serum concentration, efficacy, or toxicity warfarin and salicylates [102, 103].

Conclusion

Monotherapy of corticosteroid should be avoided as they cause severe side effects but it is very important to remember that the doses in which it is required to administer must be tapered to the lowest possible level and can be given in combination with DMARDs. Hence, this review is fulfilling the giant gap to utilize corticosteroids in treatment of RA.

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