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The Clinical Role of Glucocorticoids in the Management of Rheumatoid Arthritis

Hussein Al-Mossawi and John R. Kirwan
*Academic Rheumatology Unit, Bristol Royal Infirmary, Bristol
UK*

1. Introduction

In 1949 Hench & Kendall published the first report of a treatment that was to revolutionise the management of rheumatoid arthritis (RA) (Hench & Kendall, 1949) and indeed, much of medicine. Their work was based on the observation that RA seemed to improve in patients who were pregnant or jaundiced. The adrenal cortex extract they used contained the hormone 17-hydroxy-11-dehydrocorticosterone, and they set the scene for the use of glucocorticoid (GC) therapy in the management of RA. In the 62 years since that seminal publication, our knowledge of the mechanisms of action of GC has increased markedly. The extent of GC use has ebbed and flowed because of concerns about adverse effects and in the light of the subsequent discovery of new anti rheumatic agents, but nevertheless the role of GC in the clinic has endured and around 10 million new prescriptions for oral GC are written each year in the USA alone (Schäcke et al, 2002)

In recent years the importance of GC in preventing long term joint erosions has been confirmed (Kirwan et al., 1995). Today they are seen as an important “disease modifying” agent in their own right and are recommended by the UK National Institute for Health and Clinical Excellence (NICE) for the early treatment of rheumatoid arthritis (Rudolph, 2009). Moreover, they remain an effective clinical tool for achieving short term control of disease flares especially in high doses administered intravenously. Their use in intra-articular injections is also a mainstay for targeting disease flares in particular joints and thus GC continue to form an important part of the therapeutic armoury of rheumatological practice (van Vollenhoven, 2009).

The main clinical problem associated with the use of GC is the numerous adverse effects. The most serious of these include the development of glucose resistance or in some instances type 2 diabetes. Other important adverse effects include hypertension, osteoporosis, skin changes, sleep disturbance, weight gain and changes to body fat distribution (Schäcke et al., 2002). This wide spectrum of actions reflects the many physiological roles of endogenous GC.

As our knowledge of the action of GC increases, we can begin to tackle the two key challenges that lie ahead. Firstly, how can the benefits of these drugs be utilised while minimising their many adverse effects. Secondly, is it possible to identify a distinct subset of patients with inflammatory disorders who are resistant to GC. Apart from RA, clinical GC resistance can be found in a range of inflammatory conditions including asthma, inflammatory bowel disease and uveitis (Barnes & Adcock, 2009). GC-resistant disease is the

cause of considerable morbidity, as affected individuals are subject both to the adverse sequelae of on-going inflammation, and the systemic adverse effects of GC. The mechanisms underlying this phenomenon are becoming more apparent and understanding and overcoming GC resistance in a subset of RA patients may offer further insight into the pathophysiology of RA itself.

2. Glucocorticoid use in rheumatoid arthritis

GC are still widely used in the management of RA and between 25-75% of patients with RA are treated more or less continuously with GC (Johannes et al., 2010). They are used in high doses (including intra-articular injection which provides a high dose to the synovium) to rapidly control acute disease flares. Moreover, the anti-inflammatory effects of lower dose GC can also be beneficial for a large number of patients especially when starting standard disease modifying anti-rheumatic drugs (DMARDs) which often take weeks to months to have their full effect. Whether this anti-inflammatory effect persists in the long term over and above that achieved by standard DMARDs is a matter of debate.

The most recently confirmed role of GC is their use in preventing long term joint erosions as measured through radiological progression. In the last 10-15 years this observation (Kirwan et al., 2007) has put GC firmly back on the map as effective disease modifying agents in their own right.

2.1 High dose short term therapy

The use of high dose GC therapy to control life threatening complications of rheumatic diseases such as rheumatoid vasculitis is widespread. Intravenous methylprednisolone is often used in “pulsed therapy” at doses of around 1000mg. At these doses all GC receptors are saturated and there are undoubtedly non-genomic effects as discussed later in this chapter (Tyrrell & Baxter, 1995).

The necessity of such high doses in clinical practice remains a matter for debate due to the lack of large randomized controlled trials in rheumatoid arthritis which specifically address this question. The practice has been inherited largely from success in managing life threatening systemic lupus erythematosus and from transplant rejection rescue. In the clinical setting however, such doses seem to be successful and this success is captured in small non controlled and retrospective trials (Jacobs et al., 2001; Weusten et al., 1993). These small trials also demonstrate that short term pulsed therapy is relatively safe but there remains the concern over significant infection from profound immunosuppression. A review by Badsha et al in 2003 suggested that lower (but still high) doses may be just as effective (Badsha & Edwards, 2003).

2.2 Anti-Inflammatory effects of low dose therapy

GC therapy is often initiated shortly after diagnosis in RA usually in combination with disease modifying agents. Many patients find GC to be very effective in controlling their symptoms and continue the therapy long term. A recent Cochrane review confirmed the effectiveness of low dose (<15mg per day) GC therapy compared to traditional NSAIDs and placebo. It analysed 10 studies with 320 patients and the overall results showed an improvement in all parameters with GC therapy. These included pain scales, joint scores, morning stiffness, fatigue and improvement in acute phase reactant levels (Criswell et al., 2000; Gotzsche & Johansen, 2004). The therapeutic benefit is much greater than that of

other anti-inflammatory treatments, with an effect size of about 1.25. However, these results do not seem to be sustained in most patients after 6 to 12 months. In practice some patients are unable to completely come off GC therapy as they experience a recurrence of symptoms.

2.3 Role of low dose glucocorticoids in prevention of joint erosions

The first report of the disease modifying effects of long term low dose glucocorticoids was in 1995. The Arthritis and Rheumatism Council Low Dose Glucocorticoid Study was a double blind placebo controlled trial which studied the effects of 7.5mg of prednisolone (in addition to standard therapy for RA) on radiographic joint erosions. The results showed a significant benefit in the prednisolone group but no statistically significant difference in adverse events between treatment and placebo (Kirwan et al., 1995). This observation again confirms that low dose GC is relatively safe in clinical practice and in this case the risk versus harm balance clearly falls in favour of treatment with GC.

There are now 14 randomised controlled trials included in a Cochrane meta-analysis (Kirwan et al., 2007) which concludes that low dose GC therapy in addition to standard therapy in rheumatoid arthritis significantly reduces the rate of joint erosions (Fig 1). The doses needed to achieve these effects are modest and hence associated with less adverse effects. Even in studies of patients not taking other conventional DMARDs alongside GC, the average reduction in the rate of joint progression was 70%.

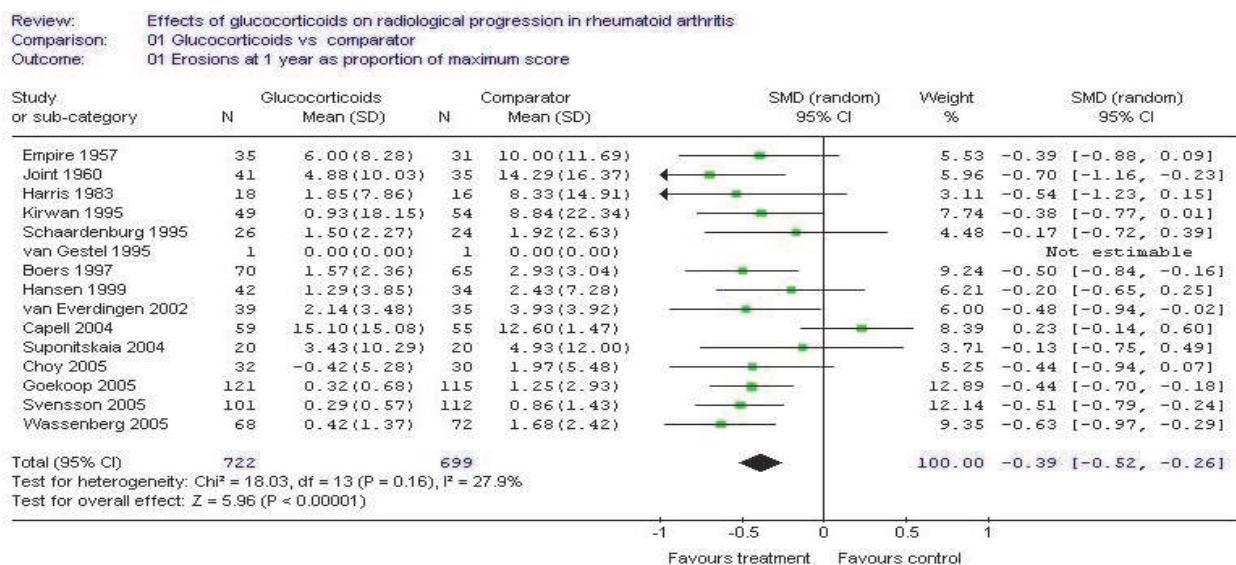


Fig. 1. Summary of data from Cochrane meta-analysis (Kirwan et al., 2007)

Subsequent analysis of longer term follow up data from some of these studies shows that the anti-erosive effects of GC persist several years after the treatment has been discontinued (Fig 2). In particular the data from the COBRA trial which compared sulphasalazine alone with combination sulphasalazine, methotrexate and a tapering dose of prednisolone showed anti-erosive benefits at 5 years in the GC group, long after the GC had been discontinued (Landewijde et al., 2002). The Utrecht trial (Johannes et al., 2006) which looked at the effects of 10mg prednisolone in a DMARD naïve group of patients also demonstrated a significant reduction in radiological joint progression at 2 years which was sustained at 5 years (2 years

after discontinuation of the prednisolone). This continued benefit of GC in preventing joint erosions long after their anti-inflammatory benefits have subsided is noteworthy. There is increasingly an appreciation in the literature for several simultaneous pathogenic processes taking place in the RA joint. In particular joint erosions and synovitis seem to be two distinct processes and their apparent dissociation in the case of GC therapy is therefore not surprising (Kirwan, 2004).

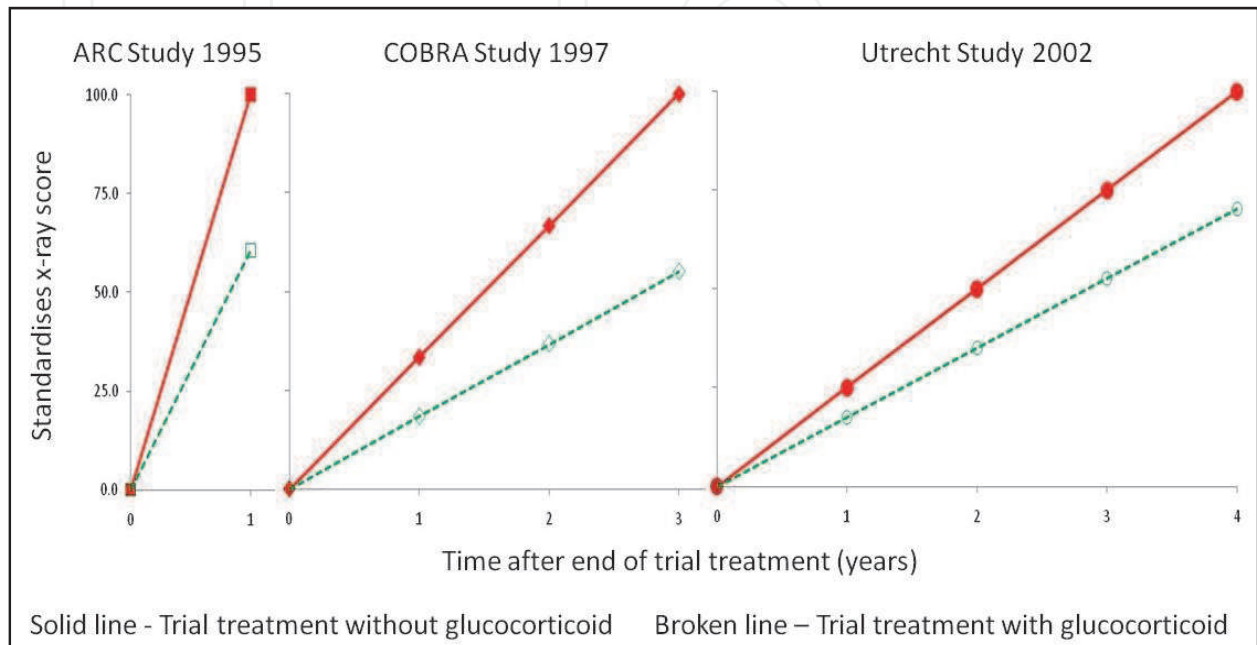


Fig. 2. X-ray progression after stopping trial therapy

2.4 Adverse effects of glucocorticoids in rheumatology practice

In 2007 Hoes et al published the EULAR evidence-based recommendations on the management of systemic GC therapy in rheumatic diseases (Hoes et al., 2007). The table of their key recommendations is reproduced below (Fig 3) but as part of their review process they quantified the incidence of reported adverse events in the glucocorticoid treated arms from 18 studies which included 963 patients taking 30mg or less of prednisolone (or equivalent) for the treatment of rheumatic diseases. The average dose across all studies was 8mg of prednisolone and the mean duration of follow up was 19.6 months. The results (Fig 4) are reported as adverse events per 100 patient years and provide an overview of the types of adverse events reported in GC use at these doses. (Not all these will actually be attributable to GC).

An important point to note when considering cardiovascular and osteoporotic fracture risk in the context of GC use is the underlying risk posed by the inflammatory disease itself. It has been shown that chronic inflammatory conditions are associated with an increased fracture risk and bone mineral density loss (Cooper et al., 1995; Staa et al., 2006; Hoff et al., 2007). Moreover, the increased cardiovascular risks associated RA and other inflammatory conditions are now very well established (Peters et al., 2010). Clearly the relationship between the beneficial effects of GC in controlling inflammation which, drives adverse events in these settings, and the GC contributions to the above risks are quite complex.

Proposition	Strength of Recommendation (0-100 VAS)
The adverse effects of GC therapy should be considered and discussed with the patient before GC therapy is started	92
<ul style="list-style-type: none"> This advice should be reinforced by giving information regarding GC management 	93
<ul style="list-style-type: none"> If GC are to be used for a more prolonged period of time, a "glucocorticoid card" is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens 	79
Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient	86
<ul style="list-style-type: none"> Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of GC 	57
When it is decided to start GC treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated; these include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidaemia and comedication with non-steroidal anti inflammatory drugs	92
For prolonged treatment, the GC dosage should be kept to a minimum, and a GC taper should be attempted in case of remission or low disease activity; the reasons to continue GC therapy should be regularly checked	86
During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient's risk, GC dose and duration	93
If a patient is started on prednisone >7.5 mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed	100
<ul style="list-style-type: none"> Antiresorptive therapy with bisphosphonates to reduce the risk of GC-induced osteoporosis should be based on risk factors, including bone-mineral density measurement 	93
Patients treated with GC and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively could switch to a cyclo-oxygenase-2 selective inhibitor	93
All patients on GC therapy for longer than 1 month, who will undergo surgery, need perioperative management with adequate GC replacement to overcome potential adrenal Insufficiency	93
GC during pregnancy have no additional risk for mother and child	87
Children receiving GC should be checked regularly for linear growth and considered for growth-hormone replacement in case of growth impairment	93

Fig. 3. Summary of EULAR recommendations for the use of GC in rheumatological practice. (VAS=visual analogue score)

Indeed a cohort study examining the interaction between GC therapy and cardiovascular risk in RA showed GC therapy to be associated with an increased risk only if patients were rheumatoid factor (RF) positive (Davis et al., 2007). In fact in RF negative patients GC were not associated with increased risk regardless of the cumulative dose and indeed showed a trend towards being protective.

Type of Adverse Event	Median:(25 th -75 th percentiles) AEs per 100 patient years
Cardovascular (dyslipidemia, oedema, hypertension, heart failure)	15 (3-28)
Infectious (viral, bacterial, skin infections)	15 (3-15)
Gastrointestinal (peptic ulcer, pancreatitis)	10 (4-20)
Psychological and behavioural (minor mood disturbance, psychosis)	9 (2-236)
Endocrine and metabolic (glucose intolerance, diabetes, fat redistribution)	7 (3-34)
Dermatological (cutaneous atrophy, acne, hirsutism, alopecia)	5 (2-80)
Musculoskeletal (osteoporosis, osteonecrosis, myopathy)	4 (3-9)
Ophthalmological (glaucoma, cataract)	4 (0-5)

Fig. 4. Reported adverse events in GC treated patients with rheumatological diseases.

In summary, GC are widely used in the management of RA and rheumatologists have over 60 years experience in their use. At low doses they act as to reduce the symptoms of RA in the first 6 to 12 months but in addition, their use early in the disease process substantially slows the progression of joint destruction and results in less disability in the long term. Remarkably this joint protective effect seems to be sustained years after GC are discontinued and for this reason GC can both be considered to be true “disease modifying” anti-rheumatic drugs (Bijlsma et al., 2010) and to have some kind of effect on the underlying long term disease process. At higher doses they are effective in treating severe and life threatening flares of disease. Adverse effects remain a significant problem but in the balance of risk versus benefit, GC (especially at lower doses) can be considered relatively safe. The summary of the EULAR recommendations in GC use are reproduced below and are a useful tool for clinicians to refer to in their daily practice.

3. Mechanism of action of GC

A better understanding of the mechanisms of GC action is crucial for understanding how to utilise these drugs more effectively in the clinical setting while minimising their adverse effects. In general terms the mechanisms of action can be divided into genomic and non-genomic. The genomic actions of GC are mediated through gene transcription and take hours to days to occur while the non-genomic actions are more rapid (Fig 5).

3.1 Genomic mechanisms

GC have a lipophilic structure and low molecular mass. They therefore pass easily through the cell membrane and exert their effects mainly through binding with the glucocorticoid receptor (GCR) in the cytoplasm (Rhen & Cidlowski, 2005). There are two isoforms of the GCR, α and β . GCR- α is the biologically active form of the receptor and mediates the intracellular effects of GC. GCR- β is an alternatively spliced form which may act as dominant negative inhibitor of GC action (Lewis-Tuffin, 2006). Over expression of GCR- β may be implicated in GC resistance as will be discussed later in this chapter.

The GCR- α in the cytoplasm is associated with various heat shock proteins (HSPs) including HSP40, HSP56, HSP 70 and HSP90 (McLaughlin & Jackson, 2002) which are released when the receptor binds to GC. After binding, the complex translocates to the nucleus where it exerts its effects on gene transcription (Davies et al., 2002). At the nucleus GCRs homodimerise and bind to GC response elements (GREs) in the promoter region of the target genes and lead to activation or inhibition of gene transcription. In addition the DNA bound GCR can also directly bind transcription co-activator molecules and exert further actions this way (Barnes, 2006).

In activated inflammatory cells there is an additional route for GC action. This is because inflammatory stimuli ultimately lead to the activation of nuclear factor κ B (NF κ B) which binds to specific κ B recognition sites on promoter regions of inflammatory genes in addition to coactivators such as cyclic AMP response element binding protein (CBP). The coactivators cause acetylation of core histones which leads to their unravelling and opens up the genes for transcription. Activated GCRs and the HSPs that are released when the GC binds to the receptor inhibit this effect directly by binding the coactivators and recruiting histone deacetylase (HDAC) 2 which inhibits acetylation (Rhen & Cidlowski, 2005). GC also switch on the transcription of certain genes including mitogen-activated protein (MAP) kinase phosphatase 1 (MKP1) hence inhibiting the MAP kinase pathway which is involved in proinflammatory gene transcription (Clark, 2003). The existence of this pathway has led to a search for ways of enhancing this GC effect, which would apply only in activated inflammatory cells and would therefore not be relevant to other body tissues, and hence would not contribute to adverse effects.

3.2 Non-genomic mechanisms

Some of the effects of GC occur within minutes of their administration especially at high intravenous doses (Croxtall et al., 2000). The mechanisms involved in mediating this rapid action are non-genomic as they are transcription independent. So far three such non-genomic actions of GC have been described. The first involved the observation of the rapid reversal by dexamethasone of epidermal growth factor-stimulated activation of phospholipase A2. It is thought that this effect is mediated by chaperone molecules such as Src which are rapidly released from the GCR-GC complex on ligation (Croxtall et al., 2000).

Non-specific non-genomic effects are seen at very high doses of GC therapy and are thought to be due to the saturation of all available GCRs in the cells at doses above 100mg prednisolone or equivalent (Tyrrell & Baxter, 1995). At these doses it is thought that GC molecules dissolve into the membranes and alter proton leak hence influencing membrane transport (Buttgereit & Scheffold, 2002).

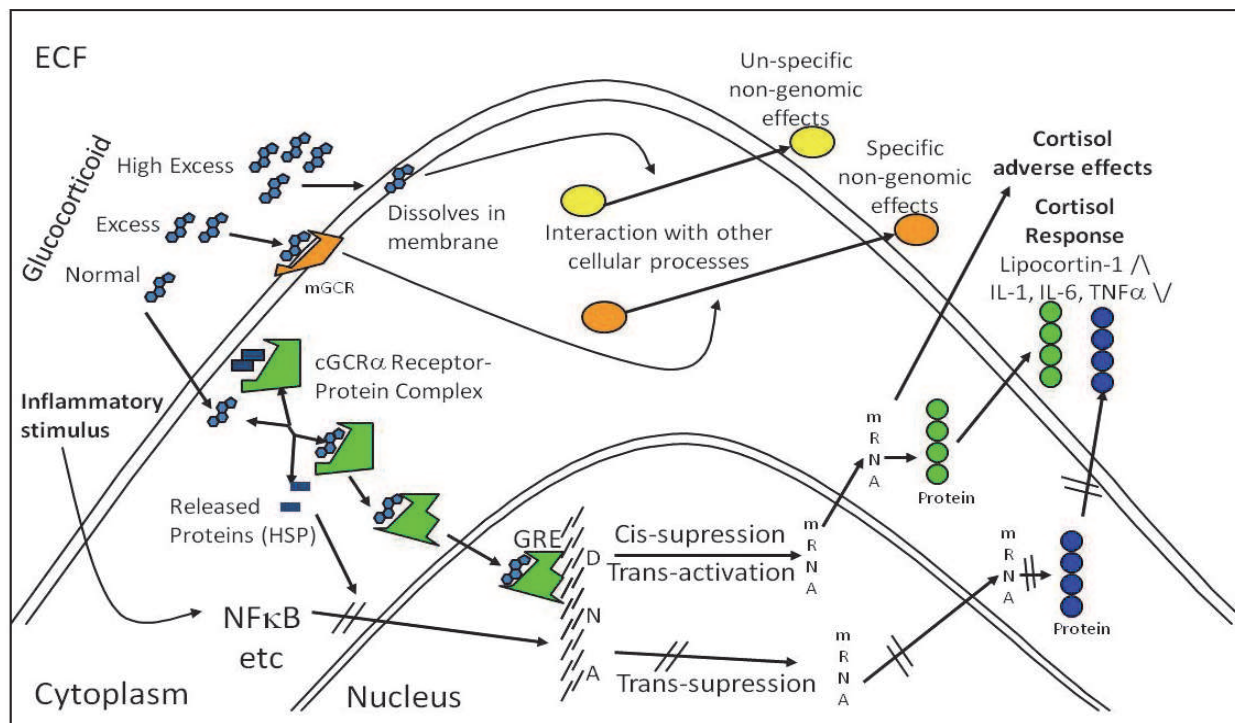


Fig. 5. Cellular action of glucocorticoids

It is now thought that GC also have specific non-genomic effects that are mediated through membrane bound GCRs which are found in small numbers on human peripheral blood mononuclear cells (Bartholome et al., 2004). Moreover, stimulation of these cells in vitro by lipopolysaccharide (LPS) increases the percentage of membrane GCR expressing monocytes indicating an active upregulation of this process (Bartholome et al., 2004). Interestingly in patients with RA who have an activated immune system, the percentage membrane GCR expressing monocytes is increased, in keeping with the in-vitro observations. These membrane expressed receptors are thought to be variants of the classical cytoplasmic GCRs (Löwenberg et al., 2007) and have recently been shown to also interact with the MAP kinase pathway (Strehl et al., 2011) Moreover, the engagement of these receptors is thought to inhibit T cell signalling by acting through downstream TCR associated signalling proteins lymphocyte-specific tyrosine kinase (LCK) and FYN oncogene (Lowenberg et al., 2006). It is possible that membrane glucocorticoid receptors will prove to have therapeutic implications.

3.3 Understanding adverse effects of GC therapy

The functions of endogenous GC are numerous. It is estimated that GC influence the transcription of ~1% of the entire genome and 20% of genes expressed on human leukocytes through their direct effects on transcription and their interaction with coactivators and transcription factors (Galon et al., 2002; Goulding & Flower, 2001). These include effects on metabolism, homeostasis and immune function. Most of the therapeutic effects are mediated via repression of gene activation in pro-inflammatory pathways. However, only certain adverse effects result from repression of gene transcription such as suppression of the hypothalamic-pituitary-adrenal axis while others are mediated via activation of gene transcription as is the case with diabetes. In some instances such as osteoporosis, there may be a complex interaction between gene activation and repression and the exact mechanism remains unclear in many cases (Schäcke et al., 2002) (Fig 6).

Adverse Effect	Primary Targeted Molecule	Mechanism [X= Confirmed, (X)= Possible]		
		DNA Dependent		DNA Independent
		Activation	Repression	Repression
Skin atrophy	Type I collagen			(X)
	Type II collagen		(X)	(X)
	Tensin C		(X)	(X)
	Sulfated glycosaminoglycans		(X)	(X)
Wound healing	Pro-inflammatory genes			X
Osteoporosis	Osteoblast/osteocyte apoptosis	X		
	OPG-L	X		
	OPG		(X)	(X)
	Osteocalcin		X	
	Type I collagen			(X)
Muscle atrophy	Glutamine synthetase	(X)		
	Ubiquitin-proteasome pathway	(X)		
Glaucoma	TIGR/MYOC gene product	X		
	Fibronectin	(X)		
	Type IV collagen	(X)		
	Type I collagen	(X)		
Psychiatric	5HT _{1A} receptor			X
HPA suppression	CRH			X
	POMC/ACTH		X	
Diabetes Mellitus	TAT	X		
	AAT	X		
	G6Pase	X		
	PEPCK	X		
Hypertension	α ENAC	X		
	sgk	X		

Fig. 6. Adverse effect associated proteins: regulation by GC and mechanisms. Reproduced from Schäcke et al, Pharmacology and therapeutics 96 (2002) 23-43

GC have a mixture of genomic and non-genomic therapeutic effects depending on the dosage used. Broadly speaking genomic effects occur at lower doses while non-genomic effects become relevant at higher doses with the combined effect of the two mechanisms accounting for the total effect of GC therapy (Fig 7). This has implications for therapeutics as at the lower doses not all the mechanisms are activated therefore the adverse effect profile may significantly differ. In essence low dose GC therapy is a very different treatment compared to high dose therapy both in terms of therapeutic effects and safety (Kirwan & Power, 2007).

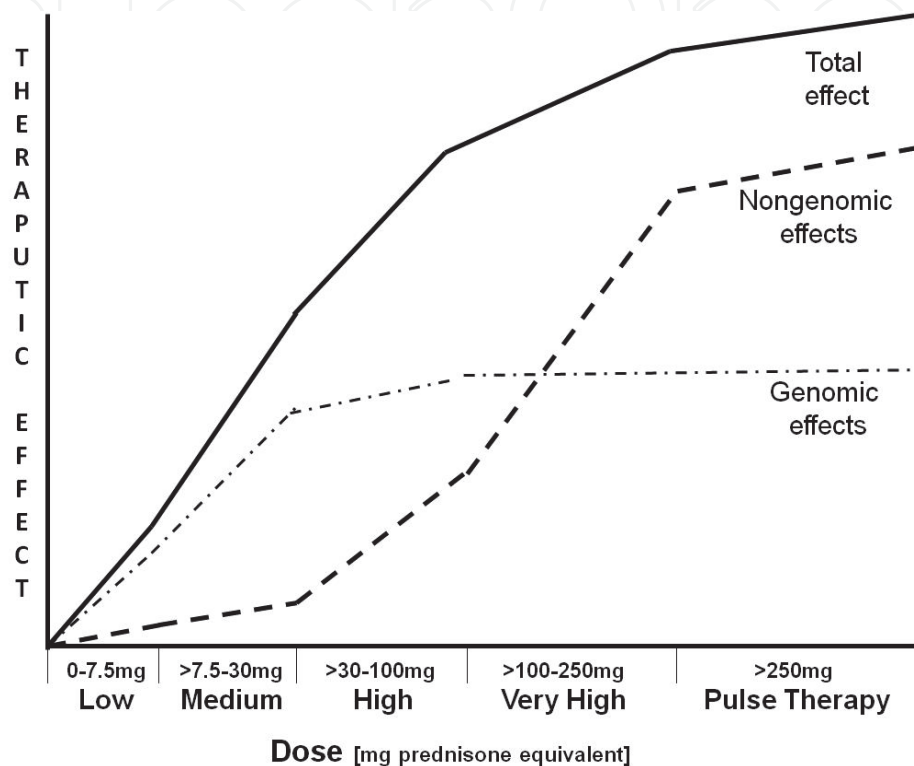


Fig. 7. Contribution of genomic and non genomic therapeutic effects of GC action is dose dependent.

4. New drug development in glucocorticoid therapy

There are several exciting developments in the world of GC therapy which aim to maintain the now well described benefits of this class of drugs whilst minimising adverse events. A better understanding of the mechanisms involved in GC action has made this goal a realistic one and there are already new licensed drugs on the market which are available for use in rheumatological practice. Broadly speaking there are two research strategies which are being pursued. The first approach aims to develop new GC analogues which can selectively reduce inflammation while minimising adverse effects (Kirwan & Power, 2007). This class of drugs are known as selective glucocorticoid receptor agonists or SEGRAs. This approach is based on the notion that the majority of therapeutic GC effects are due to the repression of gene transcription while the majority of the adverse effects are due to gene activation. Dissociating these two actions of GC is an attractive goal. The second approach utilises the improved understanding of the circadian HPA axis and its interaction with the inflammatory pathways and aims to develop new GC therapies that are better targeted to augment the natural diurnal variation.

4.1 SEGRAs

Dissociating the beneficial and adverse effects of GC was suggested over 10 years ago but has so far proved largely elusive. The first such compound was RU24858 which was described in 1997 by Vayssiere et al (Vayssi re et al., 1997). Despite showing initial promise in dissociation of GC mediated gene activation and repression, the in-vivo effects were more disappointing and the drug did not make it into clinical trials (Belvisi et al., 2001). Other drugs such as A276575 have again shown promise but fared little better (Lin et al., 2002). The only SEGRA in clinical trials at the moment is ZK 245186 which is in Phase III trials for topical use post cataract surgery after initial results from animal models showed promise (Proksch et al., 2011). The Phase II trial was concluded at the end of 2010 but results have not yet been released. The struggle to take SEGRAs from the bench to the bedside has been quite disappointing but not entirely surprising given the sheer number of biological mechanisms influenced by GC in vivo.

4.2 Modified release glucocorticoids

Modelling of the diurnal variation of the HPA axis and its effects on the secretion of systemic inflammatory cytokines in RA has been a novel approach which has yielded positive results. The cytokine IL-6 has been unequivocally shown to have a diurnal variation which causes an increase in serum concentrations during the night, before the natural increase in serum cortisol, and which reaches a peak at the time of morning waking (Perry et al., 2009). This has opened the door for the development of a modified release form of GC tablet which is taken at night and releases the active ingredients in the early hours of the morning (approximately 2 am) in order to target the peak in IL-6 levels (Kirwan, 2011). The rationale behind this approach suggests that better targeting of glucocorticoids within the HPA axis may produce better efficacy hence allowing clinicians to use smaller doses of GC. Indeed a multi-centre RCT comparing a modified release GC preparation with the equivalent prednisolone dose showed significant improvements in the duration of early morning stiffness in RA (Buttgereit et al., 2008). Interestingly, a recent study by Clarke et al. (Fig 8), which measured overnight cortisol concentrations as well as IL-6 in RA patients treated with modified release GC, showed the normal pre-treatment cortisol response to be suppressed in active RA and this suppression was reversed using the correctly timed modified release therapy with a corresponding decrease in IL-6 levels and clinical symptoms (Clarke et al., 2011).

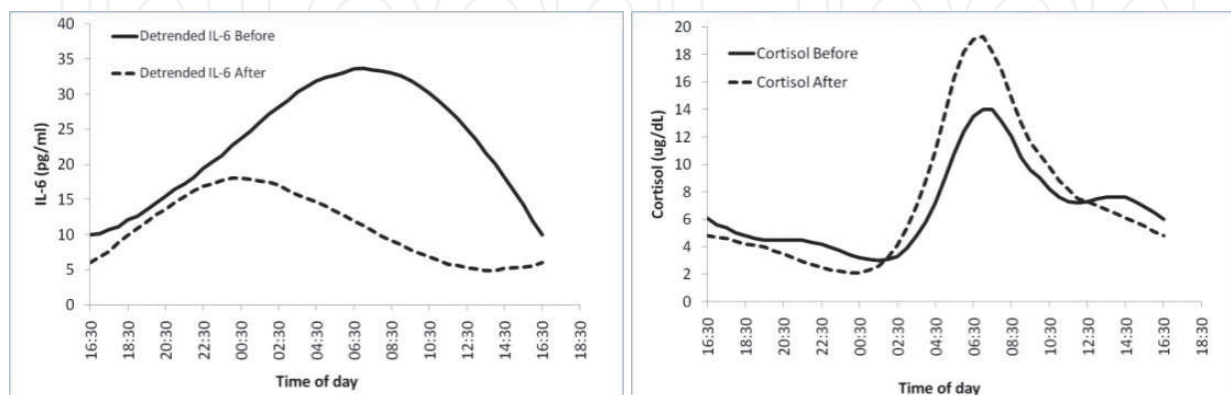


Fig. 8. Effects of modified release GC on 24 hour diurnal variation of systemic IL-6 and cortisol in RA patients

4.3 Other therapeutic advances

Another interesting approach in the use of GC has been their use in combination with drugs that can amplify their intracellular effects at low doses. One approach looked at a preparation which combines low dose prednisolone in combination with dipyridamole (Kvien et al., 2008). This combination seemed to enhance the ability of GC to suppress the pro-inflammatory NF κ B pathway (as mentioned in section 3.1) while sparing the gene-transcription element of GC action which is associated with adverse effects. Other novel strategies involve targeting of the GC to the site of inflammation by encapsulating them in long-circulating liposomes (Schiffelers et al., 2006). This approach has shown promise in animal models of inflammatory arthritis but clinical studies are still lacking. These advances represent a potential new dawn for the use of GC in rheumatoid arthritis and have implications for a number of other inflammatory diseases.

5. Glucocorticoid resistance

5.1 The problem of glucocorticoid resistance

GC resistance has been observed in the clinical setting for a long time and represents a challenge for clinicians as treatment requires larger doses of GC associated with an increased risk of adverse events. GC resistance may occur in a quarter to a third of RA patients. The emergence of this subgroup was first reported in a paper by Van Schaardenburg et al in 1995 (Van Schaardenburg et al., 1995). This study looked at elderly onset RA patients treated with oral prednisolone and a 30% discontinuation rate due to lack of efficacy was reported. Further confirmation of this phenomenon came in a study by Sliwinska-Stanczyk et al (Sliwinska-Stanczyk et al., 2007) who showed a 25% resistance rate in their 44 patients who had moderately active RA and who were not taking other disease modifying agents. This group went on to show that clinical GC resistance seemed to correlate with a failure of GC to adequately suppress *in vitro* peripheral blood mononuclear cell (PBMC) proliferation in the affected individuals.

The problem of GC-resistance is not unique to RA and has been observed in a range of inflammatory conditions including ulcerative colitis (UC), asthma and uveitis (Creed & Probert, 2007; Lee et al., 2009; Sousa et al., 2000; Barnes & Adcock, 2009). The proportion of 25-33% GC resistance seems to be preserved across the various diseases and the possible mechanisms underlying this are explored in the following sections.

5.2 Genetic and acquired glucocorticoid resistance

There is a rare but well described familial or sporadic mutation of the GCR gene which results in GC resistance. This leads to activation of the HPA axis and compensatory elevations in circulating adrenocorticotrophic hormone (ACTH) and cortisol. Patients with this disorder can develop adrenal hyperplasia as a result of the excess ACTH. Subsequent increase in mineralocorticoid and androgen release leads to a broad clinical spectrum whose manifestations depend on the severity of the disorder (Charmandari et al., 2008). This group of patients represents only a very small minority of GC resistance cases whilst acquired GC resistance in inflammatory conditions is quite common. In the last 10 years, more research effort has been focused on the problem of acquired GC resistance and several competing theories behind the underlying mechanism have emerged.

5.3 Glucocorticoid receptor β expression

GCR- β is an alternatively spliced form of the GC receptor and its over-expression has been linked with GC resistance in asthma, RA and inflammatory bowel disease (Hamid et al., 1999; Sousa et al., 2000; Kozaci et al., 2007; Orii et al., 2002). GCR- β does not bind GC and in fact its natural ligand (if it has one) remains unknown (Lewis-Tuffin, 2006). However, it does compete with GCR- α for the GRE binding sites on DNA, thus acting as a dominant negative inhibitor. Another anti-GC mechanism may be the disruption of active GCR- α translocation to the nucleus since the down regulation of GCR- β in the alveolar macrophages of patients with asthma leads to enhanced GCR- α localization and a greater response to GC. Moreover, it has been shown that various pro-inflammatory cytokines can up regulate the expression of GCR- β and this may explain why patients seem to develop clinical GC resistance with worsening of their inflammatory disease (Webster et al., 2001).

5.4 Defects in histone acetylation

The role of defective histone acetylation in acquired GC resistance has emerged principally from studies on patients with asthma and chronic obstructive pulmonary disease (COPD).

As described previously, inflammatory stimuli ultimately lead to the activation of NF κ B which binds to specific κ B recognition sites on the promoter regions of inflammatory genes in addition coactivators which cause acetylation of core histones. This leads to their unravelling and opens up the genes for transcription. Activated GCRs inhibit this effect directly by binding the coactivators and recruiting histone deacetylase (HDAC) 2 which reverses the acetylation (Rhen & Cidlowski, 2005). GCRs themselves become acetylated upon ligand binding to allow them to bind GREs and can be targeted directly by HDAC2.

HDAC2 activity has been shown to be reduced in alveolar macrophages of GC resistant asthma patients and patients with COPD (Ito et al., 2005; Hew et al., 2006). This reduced activity is thought to be secondary to the oxidative stress resulting from smoking (Rahman & Adcock, 2006). Smoking and obesity, both causes of oxidative stress, are both risk factors for developing rheumatoid arthritis (Symmons et al., 1997). In COPD it has been shown that low dose oral theophylline can reverse GC resistance by restoring HDAC2 activity (Ito et al., 2005). This effect is independent of phosphodiesterase inhibition and is mediated via the selective inhibition phospho-inositide-3-kinase- δ (PI3K δ). This is an enzyme which is activated by oxidative stress in patients with COPD (To et al., 2010). This pathway has not been studied in rheumatoid arthritis and presents a novel way of reversing GC resistance.

5.5 T Helper-17 cells and glucocorticoid resistance

T helper (Th) cells differentiate into distinct phenotypes under the influence of the inflammatory cytokine milieu which is largely dictated by cytokines released from monocyte derived macrophages. IL-17 producing T-helper cells (TH-17 cells) have recently been identified as a distinct pro-inflammatory T-helper subset and their role in various autoimmune processes including RA (Kirkham et al., 2006), multiple sclerosis (Matusevicius et al., 1999), psoriasis and inflammatory bowel disease (Duerr, 2006) is becoming more apparent. They seem to have a reciprocal relationship with regulatory IL-10 secreting T helper cells (McGeachy, 2007) and drive an inflammatory response which is dominated by

neutrophils (Miossec et al., 2009). There is increasing evidence to suggest they play a role in GC resistance in a variety of inflammatory diseases.

The earliest reports of TH-17 cell involvement in GC resistance emerged from the asthma research community. McKinley et al. showed in a mouse model of asthma that naive T cells which were polarized to the TH-17 phenotype during differentiation (by adding IL-23, IL-6 and TGF- β in vitro) were less sensitive to dexamethasone compared to cells which differentiated to the TH-2 phenotype (McKinley et al., 2008). Subsequent work has shown an expanded TH-17 subset within PBMC cultures of patients with UC and uveitis (Lee et al., 2009; Lee et al., 2007). The data from the uveitis and UC studies seems to suggest that the TH-17 phenotype is inherently GC resistant when tested using in-vitro stimulation assays. It seems that their number is expanded in patients with clinical GC resistance.

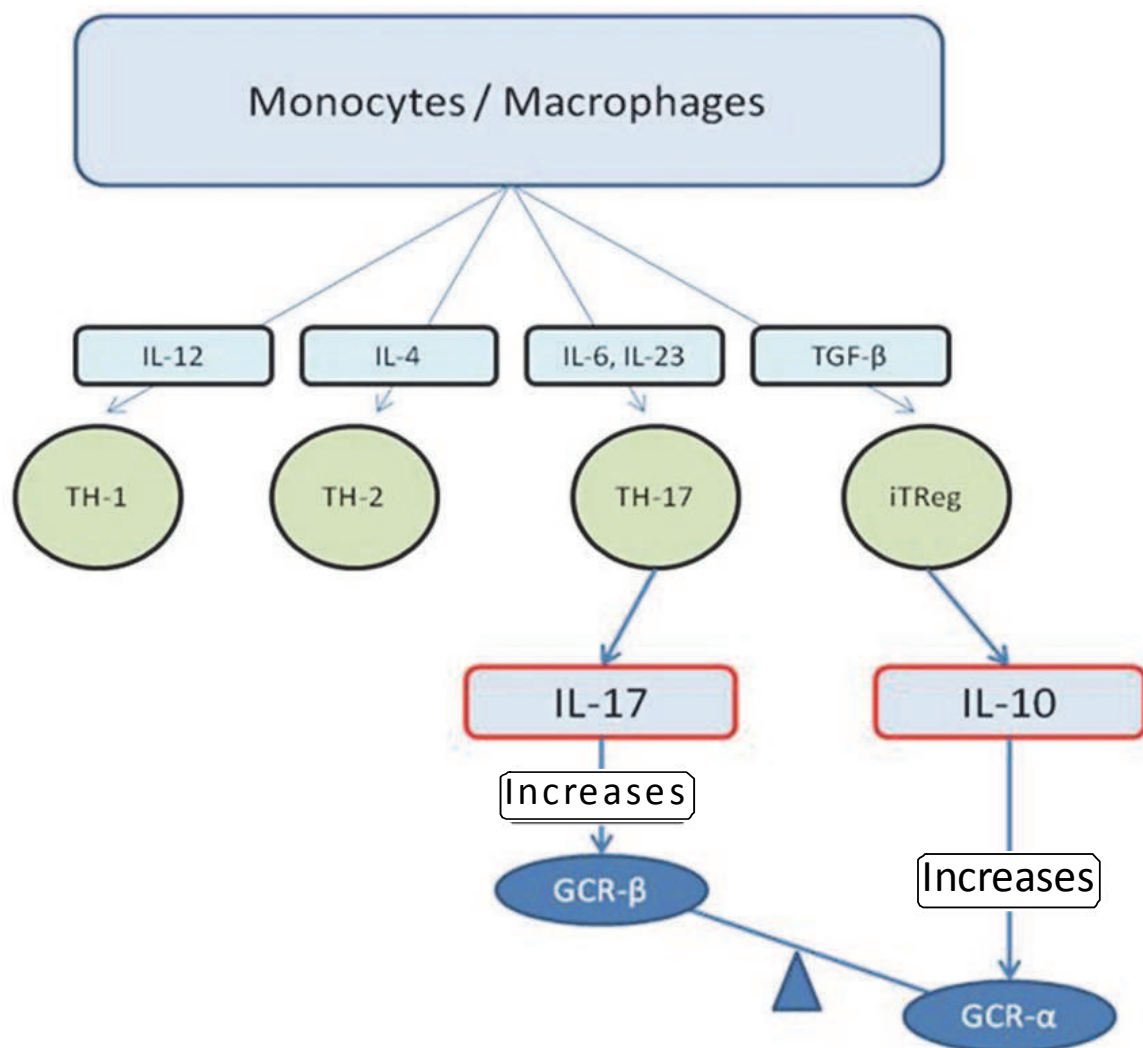


Fig. 9. The proposed model for GC resistance. Monocyte derived macrophages influence T helper cell phenotype differentiation through various cytokines. The balance of pro-inflammatory TH-17 cells and induced regulatory iTRegs alters the balance of IL-17, which increases GCR- β expression and hence reduces response to GC, and IL-10, which increases GCR- α expression and hence increases responsiveness to GC. The balance between these cytokines determines the balance between GC resistance and GC responsiveness.

Other work in this area has shown higher levels of IL-17 mRNA in the bronchial biopsies of asthmatic patients compared to controls with increased expression of GCR- β in response to IL-17. Dexamethasone was unable to decrease IL-17 induced IL-6 expression in these asthmatic patients (Vazquez-Tello et al., 2010). Conversely, the synthetic GC dexamethasone (Dex) normally induces the anti-inflammatory cytokine IL-10 in Th cells, and a deficiency in IL-10 up regulation in response to GC has been demonstrated in GC-resistant asthma (Xystrakis, 2005). Importantly IL-10 has been shown to enhance expression of GCR- α (Xystrakis, 2005). Very little work has been carried out in this field in the context of RA but these findings suggest that a disturbed balance of T cell derived cytokines may be causing GC resistance by altering the balance of GCR subtype expression.

5.6 A unifying model for glucocorticoid resistance

The emerging concept is that the human GC-resistant phenotype is disease independent, and observations of immune responses in GC-resistant individuals across medical specialities strongly supports this (Barnes & Adcock 2009; Schewitz et al., 2009; Norman & Hearing, 2002). Moreover, the data suggests that T helper cell responses in GC-resistant individuals are biased against IL-10 and in favour of IL-17. Importantly, there is also evidence that such a cytokine profile may be instrumental in regulating the ratio of glucocorticoid receptor (GCR) isoforms. IL-10 has been shown to enhance expression of GCR- α (Xystrakis, 2005), which augments GC-responses (Lewis-Tuffin, 2006), and IL-17 upregulates the level of GCR- β (Vazquez-Tello et al., 2010), which attenuates GC-responses. Consistent with this, PBMCs from GC-resistant patients with RA express higher levels of GCR- β (Kozaci et al., 2007) as do bronchoalveolar lavage washings from patients with GC-resistant asthma (Vazquez-Tello et al., 2010). As mentioned earlier, monocyte derived macrophages and dendritic cells have a huge influence on T helper phenotype differentiation and their precise role in this model requires further research. Macrophages may well be the master regulators of this GC-resistant phenotype through their influencing of the T helper cells (Fig 9).

It is interesting to note that there seems to be no resistance to the action of GC in terms of adverse effects. The most likely reason for this is that adverse effects are predominantly mediated by the excess activation of the transcription pathways which mediate the physiological role of GC action. Therefore administered exogenous GC potentially acts on all cells while the anti-inflammatory effects of GC are only mediated via their action on activated pro-inflammatory cells. Thus if these pro-inflammatory cells become GC resistant, GC resistant inflammation will occur alongside GC mediated adverse events. One key weakness of this model is that it does not take into account the important findings relating to histone acetylation which Barnes and colleagues have elucidated over the last 20 years and it would be interesting to study the effects of T helper derived cytokines on HDAC2 expression.

6. Conclusions

Glucocorticoids have become an even more important therapeutic intervention in rheumatoid arthritis both for the control of acute disease flares and for the long term prevention of joint erosions. A better understanding of their mechanisms of action has

begun to address the two key challenges which limit their use: developing better targeted GCs which achieve clinical benefit while minimising adverse effects, and reversing GC resistance. There is likely to be progress on both fronts over the next few years.

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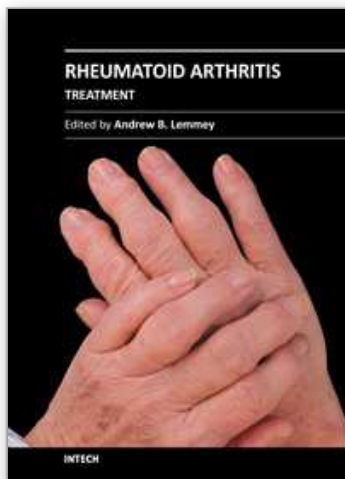
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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