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REVIEW

State-of-the-art glucocorticoid-targeted drug therapies for the treatment of rheumatoid arthritis

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ABSTRACT

Introduction: Glucocorticoids are steroid hormones broadly used for the treatment of several inflammatory and autoimmune diseases among other numerous indications, including rheumatoid arthritis.

Areas covered: For the purposes of this article, the authors have performed an extensive review of the literature to present the latest studies on glucocorticoid use in rheumatoid arthritis. They also provide the reader with their expert perspectives on future developments.

Expert opinion: The authors do not anticipate that glucocorticoids with be replaced in the near future by newer drugs. As such, rheumatologists should be fully aware of the possible side-effects and educate appropriately their patients to recognize and report them. Newer formulations, such as the liposomal/nanoparticle-based treatments, will result in less pronounced adverse effects, but the input of clinical experience along with the current recommendations for the glucocorticoid use will benefit both clinicians and patients with rheumatoid arthritis.

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KEYWORDS
DMARDs; glucocorticoids; liposomal treatment; rheumatoid arthritis; treatment strategies

1. Introduction

Glucocorticoids (GCs) are steroid hormones broadly used for the management of several inflammatory and autoimmune diseases among other numerous indications [1]. Rheumatoid arthritis (RA) is a systemic autoimmune disease that affects approximately 0.5–1% of the general population [2]. The hallmark of the disease is inflammation and proliferation of the synovial lining leading to destructive changes within the synovial-lined joints if left untreated [3].

1.1. Discovery of glucocorticoids

In 1946, Edward Calvin Kendall, among other notable contributions to biochemistry, managed to isolate several steroids from the adrenal glands, which he named compounds A, B, E, and F. Compound E or also known as "substance X," is the well-known in nowadays cortisol [4]. In 1948, a rheumatologist named Philip Hench, administered the "substance X" in the form of intramuscular injections of 50 mg, twice daily in a patient suffering from RA. The patient noticed a significant improvement of pain and stiffness on day 4, and later on, she was able of doing her everyday tasks with no problems. In 1950, Philip Hench and Edward Kendall managed to receive the Nobel Prize in medicine and Physiology [5,6].

1.2. Mechanism of action

GCs circulate as free glucocorticoid or bound to cortisol-binding globulin. Free GC diffuses into the cytoplasm and attaches to the glucocorticoid receptor (GR). When GC binds to the GR, an activated GR-GC complex is formed which can then translocate into the nucleus. This gives the ability to enhance or inhibit gene expression. The enhancement of gene expression takes place by binding to specific short sequences of DNA called glucocorticoid responsive elements (GRE) resulting in the induction of gene transcription, a process called transactivation. However, the inhibition of gene expression takes place by binding to transcription factors like the activated protein-1 (AP-1) or nuclear factor-κB (NF-κB) preventing their interaction with DNA and thus inhibiting protein synthesis, a process called transrepression (Figure 1). GCs can inhibit the inflammatory process exerting multiple effects on immune response cells, cytokines, and other mediators, which are capable of producing tissue injury, as it is shown in Table 1 [7–9]. More specifically, GCs wield their beneficial pleiotropic effects through numerous mechanisms, but the most important are two: genomic and non-genomic.

1.2.1. Genomic

Low-dose GCs diffuse passively across cell membranes, bind to and activate intracellular GRs, enter the nucleus, and interact with pro-inflammatory transcription factors (NF-κB, AP-1, etc) that have bound to DNA. This complex then recruits histone deacetylase 2 (HDAC2), which deacetylates histones resulting in the inhibition of genes causing decreased production of pro-inflammatory molecules (adhesion molecules, chemokines, cytokines, etc). Higher-dose GCs diffuse passively across cell membranes, bind to, and

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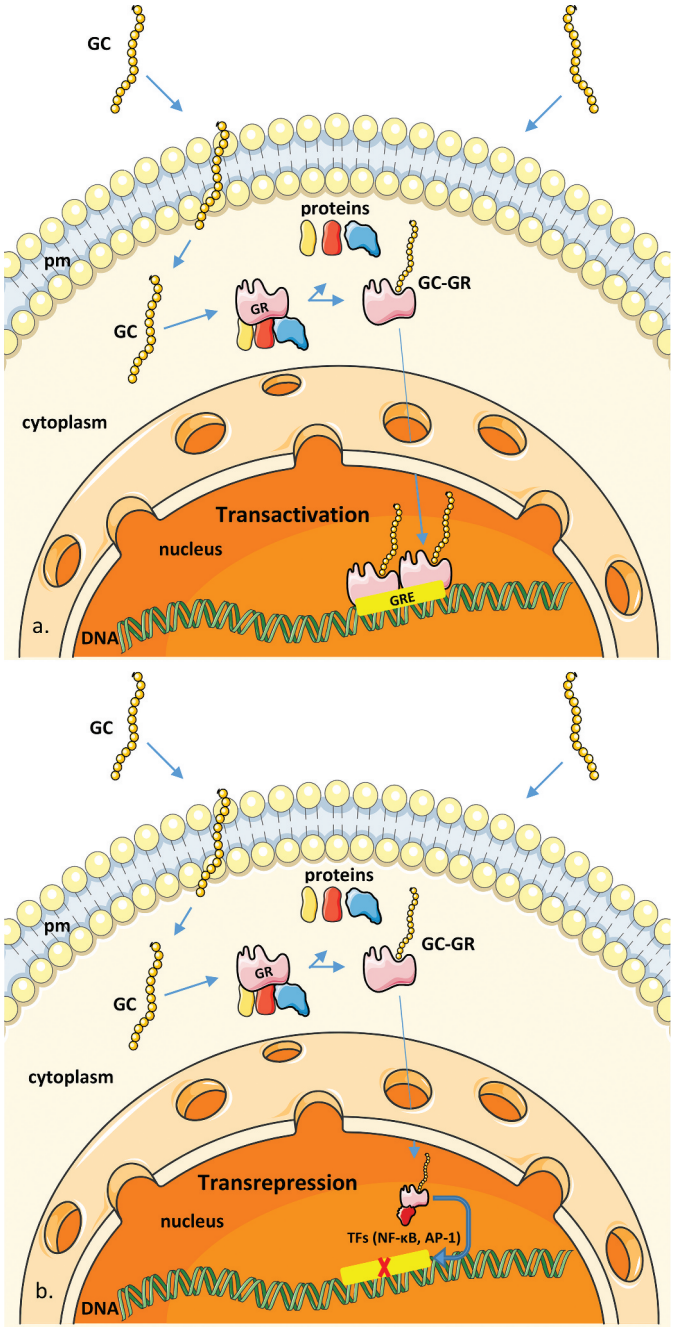

Figure 1. Mechanism of action of GCs – The genomic pathway.

GCs circulate as free GC and diffuses through the plasma membrane into the cytoplasm. Then, attaches to the GR which exists as a multi-protein complex in the cytoplasm. After binding of the GC to the GR, the proteins are released and an activated GC-GR complex is formed, which can then translocate into the nucleus. This gives the ability to enhance or inhibit gene expression. **a)** The enhancement of gene expression takes place by binding to specific short sequences of DNA called GREs resulting in the induction of gene transcription, a process called **transactivation. b)** The inhibition of gene expression takes place by binding to transcription factors preventing their interaction with DNA and thus inhibiting protein synthesis, a process called **transrepression**.

activate cytoplasmic GRs causing release from their chaperone proteins such as the heat shock protein-90, −70, −56, and −40. The GR-GC complex homodimerizes, enters the nucleus, and binds to GC response elements on DNA. This complex on the DNA binds cAMP response element-binding proteins (CREB), which acetylate histones exposing genes

Table 1. Effects of GCs on immune response cells.

Immune/Cellular effect	Immune cells	Effect
Production of anti-inflammatory cytokines	IL-10, IL-1Ra, annexin −1	⇑
Production of adhesion molecules	E-selectin, ICAM-1	⇓
Production of inflammatory cytokines	TNF, IL-2, IL-6	⇓
Processing of antigens by monocytes for presentation to lymphocytes	Monocytes, lymphocytes	⇓
Activation and proliferation of immune cells	Immature T lymphocytes, T-effector lymphocytes, natural killer cells, immature B cells	⇓
Expression of proinflammatory cytokines	TNF, IL-1, IL-2, IFN	⇓
Generation of other mediators of inflammation	Prostaglandins, nitric oxide	⇓

GCs: glucocorticoids; **IL**: interleukin; **ICAM**: intercellular adhesion molecule; **TNF**: tumor necrosis factor; **IFN**: interferon.

that code for anti-inflammatory proteins (e.g. IL-10). GCs saturate the GRs at doses of ≤30 mg/day of prednisone or equivalent. Higher doses have few genomic effects. GCs take >30 minutes to exert their genomic effects [10,11].

1.2.2. Non-genomic

GCs bind to GR causing release of inhibitory proteins such as Src, a tyrosine-protein kinase. This effect occurs with low-dose GCs within seconds to minutes. At doses ≥30 mg/day, GCs bind to membrane GRs on lymphocytes and monocytes leading to changes of the physicochemical properties of the biological membranes and in this way the exert their anti-inflammatory effects. Finally, at doses >100 mg/day of prednisone or equivalent, GCs' anti-inflammatory effects are credited to their ability to intercalate into cell membranes reducing calcium and sodium cycling across the membrane. This may explain the different effects of high-dose "pulse" steroids. A "pulse" is considered between 250 and 1000 mg/day for 1–3 days [12].

1.3. The role of 11β-HSD enzymes in rheumatoid arthritis

In RA but also in other chronic inflammatory disorders, corticotropin-releasing hormone (CRH), cortisol, and adrenocorticotropic hormone (ACTH) are not produced in a sufficient level as they should in a non-inflammatory state of the organism [13]. This is the result of a continuous activation of the hypothalamic-pituitary-adrenal (HPA) axis. In fact, as scientists try to explain the above, there is an evolutionary-adaptation hypothesis supporting that our organism in order to counterbalance infections and stress lowers the threshold of cortisol production [14]. As such, and because of the lower endogenous production, an iatrogenic/exogenous administration compensates the inflammation-induced down-regulation caused in RA [15]. Lately, a lot of interest has been shown about the hepatic 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) enzyme [16,17]. Through this enzyme, an interesting mechanism that is called "the systemic cortisone-to-cortisol shuttle" takes place by converting peripheral inactive cortisone into

cortisol. This mechanism conveys a negative feedback on ACTH release and cortisol production [18]. Moreover, 11β-HSD1 can be also found in the joints at the sites of inflammation. Furthermore, in human and murine models with RA, another enzyme, the 11β-HSD2, enhances cortisol degradation leading to down-regulation of its concentration in the inflamed sites. In this way, it may be a factor that diminishes the potential favorable action of the 11β-HSD1 enzyme [19]. That means that an iatrogenic/exogenous supplementation of GCs can restore the serum levels of cortisol and enhance its anti-inflammatory effects on inflamed tissues.

1.4. Modified pharmacokinetics

As our knowledge regarding GCs is improving constantly, we are trying to find new ways of adapting their pharmacokinetic properties to enhance their therapeutic properties and optimize the benefit–risk ratio, and in many instances, we have already achieved it [20]. In this direction, depot injections (slow release GCs) [21], timed-release preparations (mimic the circadian rhythm of cortisol) [22], and liposomal-based or nanoparticle-based treatments (selectively target specific tissues) are some of the novel approaches to minimize side-effects and increase GC potency [23–25].

Lodotra®/RAYOS® took its first approval in Europe in March 2009 [26], while in July 2012, it was approved by the Food and Drug Administration (FDA). Among other indications Lodotra®/RAYOS® has been approved for the treatment of moderate-to-severe RA in adults. Due to its mechanism of action and its pharmacokinetics, patients that could benefit mostly from this formulation were those with morning stiffness. But, what is Lodotra®/RAYOS® and why using it? It is a relatively new formulation that uses a timed-released low-dose prednisone engineered to address the circadian rhythm of endogenous cortisol and disease symptoms, which cannot be achieved by conventional prednisone. Two trials, the Circadian Administration of Prednisone in RA 1 and 2 (CAPRA-1 and −2), have been used to extract data for its safety and its efficacy [22–27]. In CAPRA-1, a 12-week, multicentre, randomized, double-blind trial, researchers included 288 patients with active RA and compared the modified-release prednisone tablet with an immediate-release prednisone tablet. The results shown that the former formulation was better than the latter in terms of duration of morning stiffness and it was well-tolerated by the patients. In CAPRA-2, a 12-week, double-blind, placebo-controlled study, the researchers included 350 patients with active RA and compared the use of modified-released prednisone with placebo on top of their standard treatment with a disease-modifying anti-rheumatic drug (DMARD). The results shown that the former combination achieved higher response rates and greater reduction in morning stiffness than the latter.

Except from the depot injections and the above programmed-release formulation of low-dose prednisone, the rest have not been on market yet. There is still a great interest for the liposomal/nanoparticle-based treatments, but other formulations such as the mapracorat, dagrocorat, and fosdagrocorat never received approval.

Mapracorat is a selective glucocorticoid receptor agonist (SEGRA) and has shown to have anti-inflammatory properties. In phase I clinical trials, mapracorat seemed to be an attractive new drug for RA, but due to its toxicity in higher doses, it has been withdrawn from the studies. Dacrocorat and Fosdagrocorat are steroid-like selective glucocorticoid receptor modulators (SGRM), but clinical studies for RA did not carry on after phase II [28–30].

1.4.1. Liposomal/nanoparticle-based treatments

Liposomal/nanoparticle-based treatments have an emerging interest for scientists dealing with chronic inflammatory diseases. The vast majority of the clinical trials used intravenous GCs. Dexamethasone and prednisolone were the most studied drugs for liposomal delivery. The results showed, and still showing, that when comparing the liposomal form of the aforementioned GCs with their free forms, the former showed better results overall in terms of therapeutic effect, reduction in joint swelling, inflammation, and joint destruction. The interesting part is that their efficacy seems to be better for longer periods of time [31–36].

2. General aspects about glucocorticoids

Since the first administration of GCs in 1950 and their introduction into clinical medicine, a true revolution emerged for the treatment of several autoimmune/inflammatory diseases despite the advent of newer and more sophisticated treatments such as the biologic (b) and the targeted-synthetic (ts) DMARDs. The clinical benefit and the potency of GCs in RA patients is obvious, but not until recently, there was a clear guidance of how to use them correctly [37–40]. Most of the treatment schemes were based on pure clinical experience rather than being based on clinical trials. Moreover, different molecules have been emerged with different modes of administration (oral, intramuscular, intra-articular, creams/ointments, eye drops) and different biologic activity (Table 2), covering not only the arthritic symptoms but also some extraskeletal manifestations, including heart (pericarditis), lung (pleuritis), skin (vasculitis), and ophthalmic manifestations (episcleritis), or treatment side-effects. However, and due to the fact that GCs are used regularly by approximately 1–3% of the general population and especially the elderly [41,42], an objective safe dose should be standardized to be used with the minimum side-effects possible. In this direction, a European League Against Rheumatism (EULAR) task force examined and published an implementation on current recommendations for long-term GC treatment and its adverse effects [43]. Although the international bibliography lacks robust trials of this kind and results could be sometimes biased, a consensus has been

Table 2. GCs grouped in terms of biologic activity.

Short-acting half-life 12 hours	Intermediate-acting half-life 12 to 36 hours	Long-acting half-life 48 hours
Hydrocortisone (1)*	Prednisone (4)	Paramethasone (10)
Cortisone (0.8)	Prednisolone (4)	Betamethasone (25)
	Methylprednisolone (5)	Dexamethasone (30)
	Triamcinolone (5)	

GCs: glucocorticoids.
**GC potency in brackets. Potency is determined with cortisol as a reference value of 1.*

achieved by the task force. The task force concluded that, when a patient receives GCs for a long-term, but in a dosage scheme of ≤5 mg/day prednisone or equivalent, the adverse effects seem to be minimal. In those in need for long-term GC treatment using between 5 and 10 mg/day, the task force concluded that other specific parameters should be counted in (e.g. patient's risk factors) to estimate the risk of harm. The cutoff value of 10 mg/day of prednisone or equivalent in patients using GCs for a long period of time seems to bear an increased risk of the appearance of adverse effects [43]. In all circumstances, physicians should always bear in mind the serious effects of long-term GC use, taking in account not only the duration of the treatment but also specific risk factors of the patients. Some of the side-effect s being shown in Figure 2.

3. Glucocorticoids in rheumatoid arthritis

3.1. Current/updated recommendations and guidelines regarding the use of glucocorticoids

The ACR in the 2015 guidelines recommended low-dose, short-term GC use in patients not at target despite treatment with DMARD or biological therapies [44]. The 2021 update states that use of long-term GCs could lead to adverse effects including osteoporosis, reduced threshold for infections, and cardiovascular events. More specifically, the ACR 2021 recommendations on GC to treat RA states that initiation of a conventional synthetic (cs)DMARD without longer-term (>3 months) GCs in DMARD-naïve patients with moderate-to-high disease activity is strongly recommended over initiation of a csDMARD with longer-term GCs. Initiation of a csDMARD without short-term (<3 months) GCs in DMARD-naïve patients with moderate-to-high disease activity is conditionally recommended over initiation of a csDMARD with short-term GCs. Addition of/switching to DMARDs in patients that are taking GCs to remain at target is conditionally recommended over continuation of GCs. Finally, addition of/switching to DMARDs (with or without intraarticular GCs) in patients taking DMARD and not on target is conditionally recommended over use of intraarticular glucocorticoids alone [45].

Furthermore, in the 2019 update of the EULAR recommendations for the management of RA, there is a clear general recommendation of tapering GCs as quickly as the clinicians can, and if this is possible for the patients' clinical situation. Also, clinicians could consider the use of GCs, especially in those initiating or changing treatment with csDMARDs, but only in a short-term basis to avoid the adverse effects. The main question is how quickly we can taper GCs and what do we mean by "short-term." The recommendations underline that it is of utter importance to discontinue GCs within 3

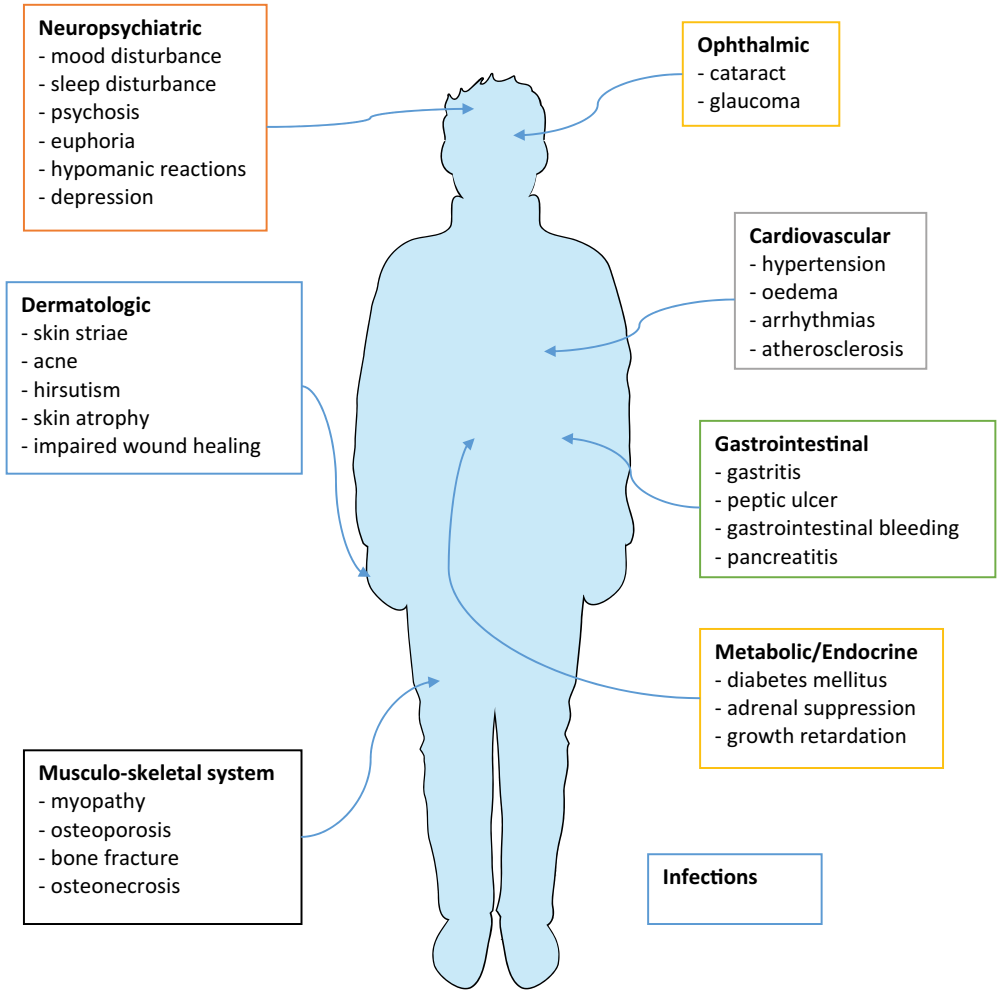

Figure 2. Glucocorticoid side-effects.

months, a period that is enough for the csDMARD to show its efficacy (bridging therapy). Moreover, if within 3 months the clinical response in not the one expected, there is an indication that the treatment strategy should change due to treatment failure and a different treatment path should be tried, such as a bDMARD or a tsDMARD on top of the csDMARD [46]. On the question whether clinicians should prefer the use of bDMARDs/tsDMARDS to csDMARDs plus GCs, there are now trials supporting and showing that the clinical response is similar in patients using methotrexate (MTX) plus GCs when compared with MTX plus bDMARDs [47–49].

Recently, in November 2021, the National Institute for Health and Care Excellence (NICE) released the updated guidelines for the management of RA. As initial pharmacologic approach, NICE recommends monotherapy with a csDMARD (MTX, leflunomide or sulfasalazine). The treatment should start immediately after recognition of the related symptoms and signs of the disease. Again, it is underlined that GCs, if used, should not exceed a period of 3 months in any form (per os, intramuscular, intraarticular) as bridging therapy to let csDMARDs to show their efficacy. In patients with uncontrollable disease or the appearance of a flare, NICE recommends the use of GCs to decrease inflammation and to control adequately all related symptoms but in a short-term period. In patients with longstanding disease (established RA), long-term treatment schemes with GCs could be a conditional solution but only after discussing all potential adverse effects with the patient making sure that he/she understands the advantages and disadvantages of their choice. In addition, to be able to reach this decision, clinicians should make sure that all treatment options accordingly to patient's clinical profile have been tried and offered including bDMARDs and tsDMARDs. Finally, NICE implies that the use of GCs as bridging therapy is not a panacea, as there is limited evidence from clinical trials that the short-term use of GCs is the most effective way of relieving symptoms and signs of the disease, underlying for once more that GCs should be used with caution and only in specific cases [50].

3.2. Treatment strategies and glucocorticoid efficacy in rheumatoid arthritis

Nowadays where novel targeted therapies have emerged, and a multitude of other drugs have been tried [51], GCs still play a pivotal role in the treatment of RA in combination with a correct treatment strategy [52]. Moreover, one should expect that after the introduction of targeted therapies the use of GCs would decrease, but this is not the case [53]. There are studies showing that the use of GCs not only is still in rise, but they represent the most frequently prescribed drugs to combat inflammatory responses [54,55]. GCs can be prescribed with all the other available drug classes and different therapeutic strategies have been tried so far. The literature has already showed the efficacy of GCs in terms of morning stiffness improvement, extraskeletal manifestations, and reduction in radiographic progression, points that have been also discussed in a Cochrane review [56]. Moreover, the investigators from the COBRA (COmbinatietherapie Bij Reumatoide Artritis) study compared the combination of csDMARDs with high dose of GCs (60 mg/day of prednisone to 7.5 mg/day in 6 weeks) versus monotherapy. What has been shown then, is that the combination of csDMARDs had better results in terms of disease outcomes when compared to monotherapy. Furthermore, except the better disease control, the adverse effects were shown to be less [57]. The next step for this successful study was 5 years later, where the investigators on top of the previous results (better disease outcomes with less adverse events) added that the radiological progression of those patients was less than that of the monotherapy group [58]. The investigators, explored disease outcomes after 11 years of follow-up, and they found out that their patients that were on the combination therapy arm presented lower mortality rates in comparison with those on the monotherapy arm [59]. Finally, 23 years of follow-up using the treat-to-target approach, patients on the combination treatment scheme with early RA had normalized mortality rates as compared to the general population, which is a huge achievement for this category of patients [60]. So, even in nowadays, GCs are one of the most used treatment choices in RA patients. Among different studies GCs seem to be used in an estimated 50% of patients with RA [61]. In the Course and Prognosis of Early Arthritis (CAPEA) multicentre cohort, 669 patients with early RA were followed for 2 years. Seventy-seven percent were on per os treatment with GCs. More specifically, 20/22/35% received prednisolone in a low (<7.5 mg/day), moderate (7.5–19 mg/day), and high dose (>20 mg/day) scheme, respectively. Within 6 months the GC dose in all treatment groups was tapered to 4 mg/day and an analysis of the data has been made. What was found was that in patients with the high GC dose scheme, there was a better disease control within 3–6 months when compared to the scheme with lower dosages of GCs. Furthermore, the comorbidities among the three groups were about the same even in patients with high-dose GC therapy [62]. The ESPOIR (Etude et Suivi des Polyarthrites Indefférenciées Récentes) cohort, investigated the safety profile of GCs in a 7-year follow-up of patients with early RA and how good they can be tolerated by those patients. Among the 602 patients that were included in the cohort, 64.1% were on low-dose prednisone for the hollow follow-up (the mean dose of prednisone was 3.1 mg/day). After data analysis of this 7-year follow-up, the researchers of the ESPOIR cohort showed the good safety profile of GCs in low doses, and more specifically, in doses <4 mg/day in patients with early RA [63]. In the CAMERA II trial, patients suffering from RA were treated either with MTX plus 10 mg prednisone or MTX plus placebo. The investigators tried to discontinue the use of prednisone in cases that was feasible.

In this trial, it has been shown that in early RA patients who received 10 mg of prednisone on top of their csDMARD treatment with MTX on a daily basis, the need of starting a bDMARD was significantly lower implying that there is a better disease control. Another important outcome was the decreased radiographic progression by using this strategy. Finally, it has been shown that the addition of 10 mg of prednisone did not lead to more comorbidities than the group that was using placebo instead of prednisone [64].

Charles-Schoeman et al. made a posthoc analysis of data from six phase III studies (ORAL start, ORAL solo, ORAL scan, ORAL standard, ORAL sync, ORAL step). RA patients, either MTX-naïve or with partial response to cs or bDMARDs, received tofacitinib 5 or 10 mg twice daily. Tofacitinib has been used alone or with a csDMARD by the concomitant use of GCs or without. For those patients that were on low-to-moderate dose of GCs before the initiation of the studies, they maintained a stable dose up to the termination of the studies. Across all studies, clinical efficacy of tofacitinib did not seem to be affected by the concomitant use of GCs. However, patients receiving MTX with GCs showed a better clinical response than those not on GCs [65].

An interesting abstract has been presented at the 2018 ACR meeting but never got published made an analysis of four randomized controlled trials (AMBITION, ACT-RAY, FUNCTION, ADACTA). At the results of the abstract, it has been shown that GCs used along with tocilizumab in RA patients made no difference on their clinical efficacy, implying that tocilizumab can be used alone without the use of GCs [66]. A previous study (STREAM) that got published in 2009, after a 5-year follow-up of RA patients receiving tocilizumab as monotherapy but allowing also the use of non-steroidal anti-inflammatory drugs or/and per os GCs (10 mg of prednisolone maximum), showed that 88.6% could taper their GC dose in lower levels and 31.8% were able to discontinue treatment with GCs [67]. The latest similar results came from a posthoc analysis of the TOZURA study. TOZURA was a multinational, open-label, single-arm, common-framework study programme. Tocilizumab has been used in RA patients as monotherapy or in combination therapy with or without GCs. The investigators then analyzed the results by the use of GCs. What they found is that there was no significant difference in the tocilizumab monotherapy group vs tocilizumab plus GCs but also in the tocilizumab in concomitant use with csDMARDs with GCs vs those without GCs. Furthermore, disease outcomes, adverse events, and safety profile were similar in all subgroups [68].

The BELIRA trial explored the hypothesis that low dose GC may confer resistance to higher doses. To get clarified the above hypothesis, the investigators enrolled 89 patients with active RA (41 with low-dose GCs and 48 without) into a 1-week trial of a total of 250 mg prednisolone. After analyzing the results, the authors did not find any significant differences between the two groups; thus, they concluded that a low-dose GC baseline treatment does not produce drug resistance and in case of a new flare in RA patients the results will remain unaffected [69].

As we mentioned above, there are no many robust clinical trials to use GCs correctly in a long-term basis. In the SEMIRA (Steroid EliMInation in Rheumatoid Arthritis) trial, Burmester et al. explored a specific dosage scheme for GCs rather than just continuing lowering the GCs per os in RA patients. The results shown that even if two thirds of the patients who were on tocilizumab and had low disease activity could taper their GC dose, continuing GCs at 5 mg/day for 24 weeks was a better treatment strategy with better results and turned out to be also a safe option [70].

The GLORIA (Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis) study, a pragmatic multicentre, 2-year, randomized, double-blind, clinical trial assessed the safety and effectiveness of a daily dose of 5 mg prednisolone or matching placebo added to standard of care in elderly patients with RA. Its results are eagerly awaited to implement them in the everyday clinical practice [71].

3.3. Different approach of the glucocorticoid use

An interesting study (NCT03763201) is aiming to measure the levels of glucocorticoid-induced tumor necrosis factor receptor-related protein (GITR) in the synovial fluid and serum of patients with recent onset RA. The measurements will be done before and after treatment [72]. Kiltz et al. in the TryCort study explored the clinical outcomes to a 3-day administration of 20 mg of prednisolone in patients with tender and swollen joints and suspicion of RA while trying to differentiate it from osteoarthritis. One gram of paracetamol daily for 5 consecutive days has been administered in all patients to see the responses in pain, while on the 3rd–5th days, patients were also received 20 mg of prednisolone as a single morning dose. This test has been named the pred-test, and after a clinical assessment, it showed a moderate sensitivity but a good specificity, being a simple-to-use method in specific cases that those two clinical entities is difficult to be differentiated [73]. In a phase IV, multicentre, double-blind controlled parallel-group randomized clinical trial from France, the investigators are trying to assess if a replacement therapy with hydrocortisone can help with the GC withdrawal at 1 year. The included patients are in low disease activity or remission, and they are compared to progressive decrease of GCs (NCT02997605) [74].

4. Expert opinion

There is no doubt that GCs have played (and are still playing) a pivotal role in Rheumatology patients and as a consequence in RA treatment. A rheumatologist's drug armamentarium has been equipped with more sophisticated molecules since the first use of the "substance X"/compound E, or later cortisol, that endowed Philip Hench and Edward Kendall the Nobel Prize in medicine and Physiology in 1950. The adverse effects of GCs are numerous, and it has to be clear that physicians should be aware of those but should also be cautious when using them to achieve the best possible personal optimization of the benefit–risk balance. Thus, the systemic use of GCs should be appropriately selected case by case, and a basic knowledge regarding their pharmacologic properties along with the clinical guidelines, and the potential devastating adverse effects of these agents is critical. As mentioned above, until recently, the use of GCs was more a matter of doctors' experience in their daily clinical practice rather than being led by robust data and recommendations. The "miraculous" drug started to show its side-effects early, so after observation of the RA patients that were on treatment with GCs in their very first year of treatment (1950), developed moon faces, acne, and other skin manifestations including cutaneous striae, hirsutism, muscle weakening or muscle wasting, edema, increased appetite, abnormal menses,

euphoria, and depression. Within a decade from the use of GCs, hypertension, hyperglycemia, cardiovascular disease, telangiectasias, infections, peptic ulcer, osteoporosis, compression fractures, and posterior subcapsular cataracts were some of the side-effects that had been added to this list [75]. The known side-effects are still present, and there are other, numerous that have been added so far. Luckily, since the recognition of the side-effects, rheumatologists can now minimize them by applying different strategies. For example, dietary restrictions can minimize leg edema and hyperglycemia, vitamin D supplementation can minimize the effects of the GCs on bones, the use of proton pump inhibitors have contributed to lessen the appearance of gastrointestinal disorders, and finally, new drugs can now be used for long-term maintenance therapy permitting discontinuation of GCs or low-dose schemes where appropriate. In this direction, a minute patient history is mandatory to anticipate any specific side-effects that may appear, and patients should be closely monitored and checked for the most common. When long-term GC treatment is needed, all other available drugs should be considered and tried, always bearing in mind that a steroid-sparing therapy is not a panacea and may also confer a variety of side-effects. Furthermore, because all the new agents (cs/b/tsDMARDs) cannot fulfil all requirements of a patient who suffers from RA, GCs are still needed, mostly at the beginning of therapy but also during a disease flare. In the everyday clinical practice, it seems that with the appropriate measures and by instructing our patients appropriately to recognize any possible side-effects, we can achieve the best results with the minimum side-effects. In the near future, liposomal/nanoparticle-based treatments will be available for human use. Up to date, in animal studies, there are promising results. These drugs can act directly at the inflammatory tissues, and therefore, the side-effects will be less pronounced.

Abbreviation

11β-HSD	11β-hydroxysteroid dehydrogenase
ACCP	anti-cyclic citrullinated protein
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
AP-1	Activated protein-1
b	Biologic
CAPEA	Course And Prognosis of Early Arthritis
CAPRA	Circadian Administration of Prednisone in RA
COBRA	COmbinatietherapie Bij Reumatoide Artritis
CRH	corticotropin-releasing hormone
cs	conventional synthetic
DMARD	disease-modifying anti-rheumatic drug
ESPOIR	Etude et Suivi des Polyarthrites Indefférenciées Récentes
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GC	Glucocorticoid
GITR	glucocorticoid-induced tumour necrosis factor receptor related protein
GR	Glucocorticoid receptor
GRE	Glucocorticoid responsive elements
HDAC2	histone deacetylase 2
HPA	hypothalamic-pituitary-adrenal
ICAM	Intercellular adhesion molecule
IFN	Interferon
IL	Interleukin
MRM	multiple reaction monitoring
MTX	methotrexate
NF	Nuclear factor
NICE	National Institute for Health and Care Excellence
RA	Rheumatoid arthritis
RF	rheumatoid factor
SEGRA	selective glucocorticoid receptor agonists
SEMIRA	steroid elimination in rheumatoid arthritis
SGRM	selective glucocorticoid receptor modulators
TNF	Tumour necrosis factor
ts	targeted-synthetic

Highlights box

- GCs are broadly used for the management of rheumatoid arthritis despite the appearance of novel drugs.
- Side-effects are a great concern.
- Lately, recommendations and treatment guidelines are trying to harmonize the use of GCs at the lowest possible dose and the shortest duration.
- Low-dose GCs seem to bear less significant side-effects, but the benefit should always be weighed against risk.
- Novel formulations are pending aiming at avoiding as much as possible the known side-effects of GCs.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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