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To treat or not to treat rheumatoid arthritis with glucocorticoids? A reheated debate

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ABSTRACT

The therapeutic landscape of rheumatoid arthritis (RA) has rapidly evolved in the last few decades. At the same time, recommendations for the management of the disease suggest to minimize glucocorticoids (GCs) use in RA patients. Major concerns are the risk of long-term adverse events and the difficulties in discontinuing GCs once initiated. However, real-world data show that up to 50% of RA patients continue to take GCs during the disease course. Adverse events of GCs usually occur after a long-term use, which can limit the generalizability of randomized controlled trials (RCTs) proving no or minimal harm. Observational studies show conflicting results regarding the safety of GSs and are subjected to a high risk of bias, including indication bias. Thus, whether or not GCs should be used in the management of RA is still a matter of debate. The main reasons to support GCs use are the ability to rapidly suppress joint inflammation while waiting for the full effect of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and the acknowledged efficacy on radiographic progression in early RA. The main reasons to avoid GCs use in RA are that their potential risks may outweigh their benefits and there is no agreement on the minimal daily dosage of GC which can be considered safe.

1. Introduction

During the 7th CORA Meeting, held in Turin this year, two exceptional opponents (Professor Nagy and Professor Cutolo) passionately debated regarding the necessity of glucocorticoids (GCs) in treating rheumatoid arthritis (RA). They had a difficult task to overcome. Such a debate is not entirely new. Indeed, it has bothered researchers and clinicians for decades. We must stress that scientific and professional bodies of recognized authority, such as the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), have issued guidelines on that matter [1,2]. Those guidelines have shaped clinical practice worldwide and formed the basis for proper management and good clinical practice. In the evolving era of biologics and their unanimous efficacy in treating the disease, the widely held view is minimizing GC treatment in all autoimmune rheumatic diseases, including RA [3].

The "supporters" of ACR and EULAR views present a convincing argument based on the well-known adverse event profile of GCs. They argue that GCs play a role in the induction and perpetuation of troubling comorbidities, such as infections, hypertension, cardiovascular disease, diabetes mellitus, and osteoporosis [4,5]. Another point that cannot be ignored is that analyses so far indicate that patients on GCs appear to use

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more commonly non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). Emerging data also indicate that, despite using GCs (with or without) NSAIDs, patients with RA have higher disease activity and inflammatory markers compared to those whose pharmacological treatment is not based on GCs [6]. The fierce debate is even more profound when considering patients' perspectives on GCs' side effects and their willingness to achieve disease remission without GCs [7]. Many physicians are still uncertain about the actual benefit/risk ratio of GCs. However, the sights on this matter are eagerly mature over the years, based on the wealth of accurate and comprehensive data.

The opponent in favor of minimizing or discontinuing GCs in RA, Professor Nagy, has made a series of clear points. He referred to the issued recommendations, which consider the gathered data. In the updated ACR's management guidelines, long-lasting treatment with GC is primarily opposed due to the potentially serious side effects. In fact, in case of moderate to high disease activity, the guideline advises conditionally to initiate conventional synthetic DMARD (csDMARD) without short-term GCs (up to 3 months) over csDMARD and GC combination therapy. Moreover, the guideline strongly recommends commencing a csDMARD without long-term GC treatment, even in case of high disease activity [2].

The argument against GC treatment becomes more profound, given the 2022 update of the EULAR recommendations, which conditionally recommends using short-term GCs when initiating or changing csDMARDs, and,consequently, strongly advises that GCs should be tapered and discontinued as quickly as clinically feasible [1]. It becomes apparent that the long-term use of GCs is opposed by either body or even the short term of GCs is a matter of disputable arguments.

Why do we still treat RA patients with GCs if that would be the case? Despite the issued guidelines, GCs remain among the most prescribed drugs for treating RA [8]. In addition, many patients with early RA continue GC therapy for longer duration (>6 months), indirectly indicating the wish of patients and treating physicians to control disease activity and find an acceptable balance between efficacy and safety [9,10].

Let us stick to the opponent's views favoring GCs treatment in RA. Professor Cutolo refers to a recent metanalysis convincingly demonstrating that there is very low to moderate quality of evidence for no harm with long-term low-dose GCs in RA, except an increased risk of infection [11]. Moreover, other pharmacological treatments also possess adverse effects, such as infections, which cannot be overlooked [12]. Professor Cutolo also refers to data from large multicenter trials showing that a very low daily dose of GCs has disease-modifying properties on radiographic progression in early RA [13]. These data seem to confirm that long-term low-dose GCs in RA is the best approach to obtain substantial therapeutical advantages, always in combination with csDMARDs, at least on joint damage in early RA. What about then GCs' side effects? Data have been presented supporting that low-dose GCs enables the delay of adverse effects induced by most standard csDMARDs. The argument is of profound importance. Do we prefer the risk of adverse effects related to low GC dosage or that of standard csDMARDs? The interpretation of the opponent of EULAR recommendations for the management of RA is quite distinct and argues that at the time of the diagnosis in early RA, initially GCs are recommended as bridging therapy to back the delayed biological effects of methotrexate (MTX). Data reporting a similar occurrence of adverse events and limited toxicity between those receiving low-dose GCs and placebo arguably add strength to that notion. More data are addressing the risk profile and argue that the risk of harm is low for most patients at long-term low dosages [14].

The jury must decide, and the judge must play an imperative role in accelerating an unbiased process which will benefit decision making for patients with early or established RA. The involving parties must accelerate research, data gathering and analyses. Let's be optimistic but cautious about what the future holds. We are very close.

2. The pros of using glucocorticoid therapy in rheumatoid arthritis

2.1. Endogenous cortisol and exogenous glucocorticoids in rheumatoid arthritis

The chronic inflammatory stimulus exerted by RA induces a persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis, with progressively insufficient production of endogenous corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and finally cortisol [15]. In this way, the exogenous supplementation of GCs should act as a "replacement therapy" to restore sufficient serum levels of cortisol.

2.2. Long-term GC use has a beneficial effect on radiographic progression in early RA

GCs are still far from being obsolete. Recently they have received a more differentiated re-evaluation as a possible disease-modifying agent if co-administered at low doses [16]. A systematic review and meta-analysis concluded that there is very low to moderate quality evidence for no harm with long-term low-dose GCs in RA, except for an increased risk of infections [11]. On the other hand, there is moderate to high-quality evidence of disease-modifying properties supporting the use of low-dose long-term administration of GCs. Clinical trials have shown that GCs therapy, especially long-term low dose, slows radiographic progression by at least 50% when given to patients with early RA, fulfilling the conventional definition for a DMARD [13,17,18].

A large multicenter, double-blind, placebo-controlled trial has shown that a shallow daily dose of 5 mg prednisolone given over two years in combination with background DMARDs therapy substantially decreased radiographic progression in early RA with a low level of risk [18]. Furthermore, in an open two-year extension study, clinical remission achieved after two years of treatment with low-dose prednisolone, in addition to csDMARDs in early RA, was significantly associated with reduced joint destruction that was still present after four years [19]. Interestingly, a retrospective, open-label study evaluated the incidence and severity of adverse effects in RA patients treated with csDMARDs with or without low-dose GCs [20]. The results suggested that low-dose GCs (7.5 mg/day of prednisolone) delay the occurrence of adverse effects caused by most standard csDMARDs and prolong the survival time of csDMARDs in patients receiving combination therapy. As expected, there was an increased incidence of side effects in GCs-treated patients compared to monotherapy patients. However, the undesirable effects were mainly of mild intensity (i.e., weight increase) [20]. Of note, even the authors confirmed a significant reduction in the frequency of erosive radiologically detected progression in RA patients treated with low-dose GCs [20,21].

Alongside other significant clinical benefits, although partially limited by dose-related side effects, GCs are still on the first line together with csDMARDs in early RA [15,22].

2.3. Role of GCs as bridging therapy

The 2022 update of EULAR recommendations for the management of RA confirms the previous ones; namely, at the time of the RA diagnosis, GCs are recommended as bridging therapy while MTX achieves the full biological effects. Inadequate response to this combination of drugs within 3–6 months should lead to an escalation of therapy according to individual risk factors [1]. Since there are concerns about the inability to discontinue GCs after the bridging time and the risk of serious adverse events in long-term users, a recent study showed that a shorter oral bridging schedule and a lower initial dose were associated with lower cumulative GCs doses and fewer patients on GCs at 18 months after bridging [9]. Therefore, RA patients who start a GCs bridging schedule to suppress inflammation rapidly can successfully discontinue GCs [9].

2.4. Safety profile of low-dose GCs

The safety of low-dose GCs is another critical issue during RA treatment. A large meta-analysis reported a similar rate of adverse events and limited toxicity with low-dose GCs (mean dose 6.5 ± 2 mg/day of prednisolone or equivalent) compared to placebo [23]. In addition, a prominent trial evaluated the seven-year tolerability profile of GCs use among 602 early active RA patients, in which 64.1% received very low-dose prednisone (mean 3.1 ± 2.9 mg/day for the entire follow-up), and 68% started GCs during the first six months (68%) with a mean duration of GCs treatment of 1057 ± 876 days [14]. The rigorous statistical evaluation on weighted Cox proportional-hazards analysis, using propensity score and inverse-probability-of-treatment weighting, including age, gender, history of arterial hypertension, and GCs treatment, showed that outcomes regarding the safety did not differ with and without GCs [24].

A EULAR task force aiming at defining conditions in which long-term GCs treatment has an acceptably low level of harm supported the critical role of using low-dose GCs [4]. The final agreement was that the risk of harm is low for most patients at long-term dosages of ≤5 mg/day prednisone equivalent, between >5 mg/day and ≤ 10 mg/day, patient-specific characteristics influence the risk of harm, whereas at dosages of >10 mg/day, there is an elevated risk of harm [4]. Those conclusions are in line with the results of a recent large multicenter pragmatic double-blind, randomized trial that compared two years of prednisolone (5 mg/day) to a placebo in patients aged 65+ with active RA (GLORIA-Glucocorticoid Low-dose in Rheumatoid Arthritis) [25]. Regarding safety, 60% versus 49% of RA patients experienced a harmful outcome with adjusted relative risk 1.24 (95% CL 1.04, $p = 0.02$) and with the most significant contrast in non-severe infections. Reasons for treatment discontinuation were adverse events (14% in both arms), active disease (3 vs. 4%), and other reasons (19 vs. 21%).

3. The cons of using glucocorticoids therapy in rheumatoid arthritis

3.1. Time to go forward glucocorticoids in RA

Although 75 years after their introduction into clinical medicine, GC therapy remains essential in managing many rheumatic and musculoskeletal diseases (RMDs), there is a clear, modern tendency to minimize GC treatment in all conditions, especially RA. New medications, including targeted therapies like biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), and innovative management strategies enabled to reach and maintain treatment goals (remission or low disease activity) in many patients without using GCs. Concomitant use of GCs and tsDMARDs may also be unnecessary, as demonstrated by a posthoc analysis of six phase III studies of Tofacitinib [26].

3.2. There is no truly safe dosage for GCs

Increasing evidence supports the potential risks of GCs, which exceed the benefits [1,2,5]. GC therapy is associated with several severe adverse events, mainly when used for an extended period or at high doses. Although safety concerns about GCs arise more frequently after more than five years of use, it is important to note that there is no truly safe dosage for GCs [5]. Despite some undisputed beneficial effects of GCs, the fear of potential side effects, even at low dosages, represents a significant limitation in clinical practice. Prolonged use of GCs is associated with multiple side effects, such as infections, hypertension, cardiovascular disease, hyperglycemia and diabetes mellitus, obesity, osteoporosis, myopathy, skin fragility, cataract, and glaucoma. When prescribing GCs, it is mandatory to consider both treatment-related factors (such as dosage and duration) and individual patient characteristics (such as gender, age, genetics, multimorbidity, and lifestyle) as they affect the overall safety profile of GCs [14]. The GLORIA trial evaluated the efficacy and safety of add-on low-dose prednisone in elderly patients over two years [25]. It is crucial to interpret the results cautiously since many side effects appear after prolonged treatment exceeding five years. In most cases, low-dose GC use is associated with a good safety profile, whereas increased dosage of GC treatment raises adverse effects, including mortality. Nevertheless, the evidence is insufficient to establish a definitive safe dose and duration for different safety outcomes [5,14].

3.3. Role of GCs in current recommendations for the management of RA

The last update of the ACR RA management guidelines opposed GC treatment due to increasing evidence of their negative impact on long-term patient outcomes, including risk for infection, osteoporosis, and cardiovascular disease [2]. The guideline conditionally recommends initiating csDMARD without short-term GCs (up to 3 months) over csDMARD and GC combination therapy. Notably, the guideline strongly recommends against initiating a csDMARD with long-term GCs, even in patients with high disease activity [2].

Similarly, the 2022 update of the EULAR recommendations for the management of RA also amended its position regarding GC treatment. The new recommendation suggests considering short-term GCs when initiating or changing csDMARDs but strongly advises to taper and discontinue GCs as quickly as clinically feasible. An essential difference between the recommendation published in 2019 and 2022 is that the current version explicitly supports GCs discontinuation [1,27]. The EULAR strongly advocates minimizing and discontinuing GC treatment as soon as feasible, more unequivocally than in all previous versions, especially chronic GC use.

The advantages of using GCs as a bridging therapy are limited. In line with the EULAR recommendations, using a step-down scheme of GCs as bridging therapy in low-risk early RA patients was beneficial in the CareRA trial for rapid remission induction. However, after two years, MTX monotherapy demonstrated similar disease control at the endpoint compared to MTX combined with GCs [28]. Another study by Hua et al. also showed the initial advantages in disease activity of csDMARDS combined with low-dose GC versus placebo in early RA. Despite these positive effects observed with the early administration GCs, after 12 months of treatment, the two groups had no significant differences in the assessed indicators [29].

Furthermore, it can be challenging to reduce or completely stop GC treatment. A systematic literature review demonstrated that clinical trials that prespecify GC's tapering and discontinuation scheme are successful in most cases (88%) [9]. In contrast, findings from registry and cohort analyses indicate that approximately half of the patients continue to use GCs, suggesting that discontinuation might be more challenging in the real world compared to the controlled environments of clinical trials [30–32].

3.4. Lesson from D2T-RA

Many RA patients (30%) still experience symptoms of clinically active disease despite receiving appropriate treatment according to current recommendations. The EULAR recently developed the definition of difficult-to-treat RA (D2T-RA) to improve the classification and treatment of these patients [33]. The current definition of D2T-RA includes the inability to taper GCs below 7.5 mg/day of prednisone or equivalent as part of the signs suggestive of active/progressive disease. To address proper management of D2T patients, It is crucial to distinguish those with multiple therapy-resistant refractory RA (PIRRA) from those with persistent measured disease activity in the absence of inflammation (NIRRA) [34].

Even though patients may occasionally require GC therapy, especially D2T [35], overtreatment is still prevalent and can result in severe consequences [36].

The points to consider for the management of D2T-RA emphasize the

importance of a more comprehensive approach instead of just escalating treatment. These include evaluating the inflammatory disease activity, reassessing the diagnosis, optimizing treatment adherence, managing comorbidities, and pharmacological and non-pharmacological treatment [37,38]. The proposed algorithm, in line with the current EULAR and ACR guidance, can effectively reduce the use of GCs.

4. Conclusions

Despite substantial treatment advances in RA, GCs are still widely prescribed. While GCs provides some benefit when combined with csDMARDs, combination with b/tsDMARDs may unnecessarily prolong patients' exposure. We must consider that international recommendations for disease management aim to support patients' care based on the best currently available evidence. However, they do not dictate the care of the individual patient. The association between long-term GC use and adverse events is complex and can be significantly affected by indication bias. Given the high prevalence of multimorbidity in RA patients, if GCs are needed, we need to perform and accurate risk assessment and implement measures for harm reduction. Control of disease activity is a priority, and the goal of therapy should be set up with the patient. Non-inflammatory pain mechanisms must be considered, especially in the ones with long-standing disease or D2T-RA, and treated accordingly.

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CRediT authorship contribution statement

Maurizio Cutolo: Conceptualization, Writing – review & editing, Supervision. **Yehuda Shoenfeld:** Conceptualization, Writing – review & editing, Supervision. **Emanuele Gotelli:** Writing – review & editing. **Mariangela Salvato:** Writing – review & editing. **Lilla Gunkl-Tóth:** Writing – review & editing. **György Nagy:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

None.

Data availability

No new data were created. Data sharing is not applicable.

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