DOI: https://doi.org/10.61841/jhkrgs83 Publication URL: https://jarmhs.com/MHS/index.php/mhs/article/view/533

THE ANALYSIS STUDY OF SAFETY AND LONG-TERM EFFECTS OF GLUCOCORTICOIDS IN TREATMENT OF INFLAMMATORY RHEUMATIC DISEASE: A COMPREHENSIVE SYSTEMATIC REVIEW

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To Cite This Article: Rahman, F. F., & Istiana, S. (2024). THE ANALYSIS STUDY OF SAFETY AND LONG-TERM EFFECTS OF GLUCOCORTICOIDS IN TREATMENT OF INFLAMMATORY RHEUMATIC DISEASE: A COMPREHENSIVE SYSTEMATIC REVIEW. Journal of Advanced Research in Medical and Health Science (ISSN 2208-2425), 10(9), 6-15. https://doi.org/10.61841/jhkrgs83

ABSTRACT

Background: Glucocorticoids (GCs) are often the first-line therapy for autoimmune diseases including many neurological conditions. Their use is commonly associated with complications and comorbidities. These include both immediate and long-term complications that are often related to the dose and cumulative dose of GCs.

The aim: The aim of this study to show about safety and long term effects of glucocorticoids in treatment of inflammatory rheumatic disease.

Methods: By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: Eight publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles.

Conclusion: Glucocorticoids are effective drugs for many rheumatic diseases. However, there are serious adverse effects that can ensue. These are often dose related and related to the duration of therapy. Several of the complications occur in patients already at risk for these adverse events. The adverse effects, such as weight gain, osteoporosis, fracture, osteonecrosis, infections, ocular complications, cardiovascular effects, hyperglycemia, etc.

Keyword: Glucocorticoids, rheumatic, inflammation, effects.

INTRODUCTION

Glucocorticosteroids (GCs) have a long history of good efficacy and safety in the treatment of RA. This has resulted in their inclusion in guidelines for the management of this disease. For example, the European League Against Rheumatism (EULAR) guidelines recommend that GCs be added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) since they have been shown to provide benefit as an initial short-term treatment. However, it is also generally recommended that GCs should be tapered as rapidly as clinically feasible. The Canadian Rheumatology Association treatment recommendations state that GCs (oral, intramuscular or intra-articular) can be added to DMARD therapy as part of the initial treatment strategy for patients with RA, and may be an option for managing flares as bridge therapy while waiting for a DMARD to take effect, or for symptom control if no other options exist.[1–3]

Previously, outcome measures of RA reflected joint inflammation (morning stiffness, number of tender joints [tender joint count (TJC)]) and swollen joints [swollen joint count (SJC)], and limitation of joint motion), systemic inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] level), and joint destruction (radiographic evaluation). While the latter still is a separate outcome, clinical and biochemical variables have been integrated in composite disease activity scores and improvement scores, which may include TJC, SJC, ESR, and CRP.[4]

Prior to a discussion of the infection risk for immunomodulatory therapy, it must be acknowledged that patients with RA appear to be at increased risk for infection compared with the general population, independent of immunomodulatory medications. Among patients with RA, higher disease activity is associated with greater risk for infection, independent of treatment. Thus, the potential risks of therapy must be balanced with the benefits of controlling RA disease activity. For many patients, comorbidities and other risk factors for infections may be more important than the risks posed by their RA therapies.[5]

The most commonly self-reported adverse events by patients who are prescribed with longer-term GC use are weight gain (about 70 % of individuals), skin bruising (~55 %), sleeping problems (~45 %) and mood problems (~45 %) and all show a positive relationship with GC exposure. It might be added that a constructive patient-practitioner dialogue at the start of any GC therapy is very important. The adverse reactions associated with GC therapy have been described in more detail in recent reviews. From a clinical aspect, the more serious adverse reactions are outlined below.[6,7]

In the early 1990s, it was clear that GCs could negatively impact bone health, but the magnitude of effect was unclear. Confirmation of a bone demineralising effect of GC therapy accrued gradually throughout the 1990s with the publication of a review with meta-analysis and with the very large cohort analyses of the UK's GPRD database by van Staa et al. The latter group demonstrated that patients exposed to GCs had higher relative risk of fracture (versus age-matched non-exposed individuals), with relative risk ratios varying from 1.1 for forearm fracture, through 1.6 for hip, to 2.6 for vertebral fracture. Again, one of the major difficulties encountered in observational studies, is controlling for confounding factors, since the decision to prescribe a GC (and the dose selection) is greatly influenced by the activity of the underlying disease and the age of the patient. The rate of bone loss will vary also according to these factors, as well as others (patient sex, baseline BMD, previous fracture history).[6,8]

METHODS

PROTOCOL

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

CRITERIA FOR ELIGIBILITY

For the purpose of this literature review, we compare and contrast safety and long term effects of glucocorticoids in treatment of inflammatory rheumatic disease. It is possible to accomplish this by researching of the safety and long term effects of glucocorticoids in treatment of inflammatory rheumatic disease. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the safety and long term effects of glucocorticoids in treatment of inflammatory rheumatic disease. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

SEARCH STRATEGY

We used "safety and long term effects of glucocorticoids in treatment of inflammatory rheumatic disease." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Table 1. Search Strategy

Database	Search Strategy	*Hits*
Pubmed	*(("*Glucocorticoids*"[MeSH Subheading] OR "*Treatment*"[All Fields] OR "*Therapy*" [All Fields]) AND ("*effects*"[All Fields] OR " *Benefit*"[All Fields]) AND ("*Rheumatic*"[All Fields]) OR ("*Inflammatory rheumatic disease*" [All Fields]))*	195
Science Direct	*(("*Glucocorticoids*"[MeSH Subheading] OR "*Treatment*"[All Fields] OR "*Therapy*" [All Fields]) AND ("*effects*"[All Fields] OR " *Benefit*"[All Fields]) AND ("*Rheumatic*"[All Fields]) OR ("*Inflammatory rheumatic disease*" [All Fields]))*	2856
Sagepub	*(("*Glucocorticoids*"[MeSH Subheading] OR "*Treatment*"[All Fields] OR "*Therapy*" [All Fields]) AND ("*effects*"[All Fields] OR " *Benefit*"[All Fields]) AND ("*Rheumatic*"[All Fields]) OR ("*Inflammatory rheumatic disease*" [All Fields]))*	25

DATA RETRIEVAL

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.

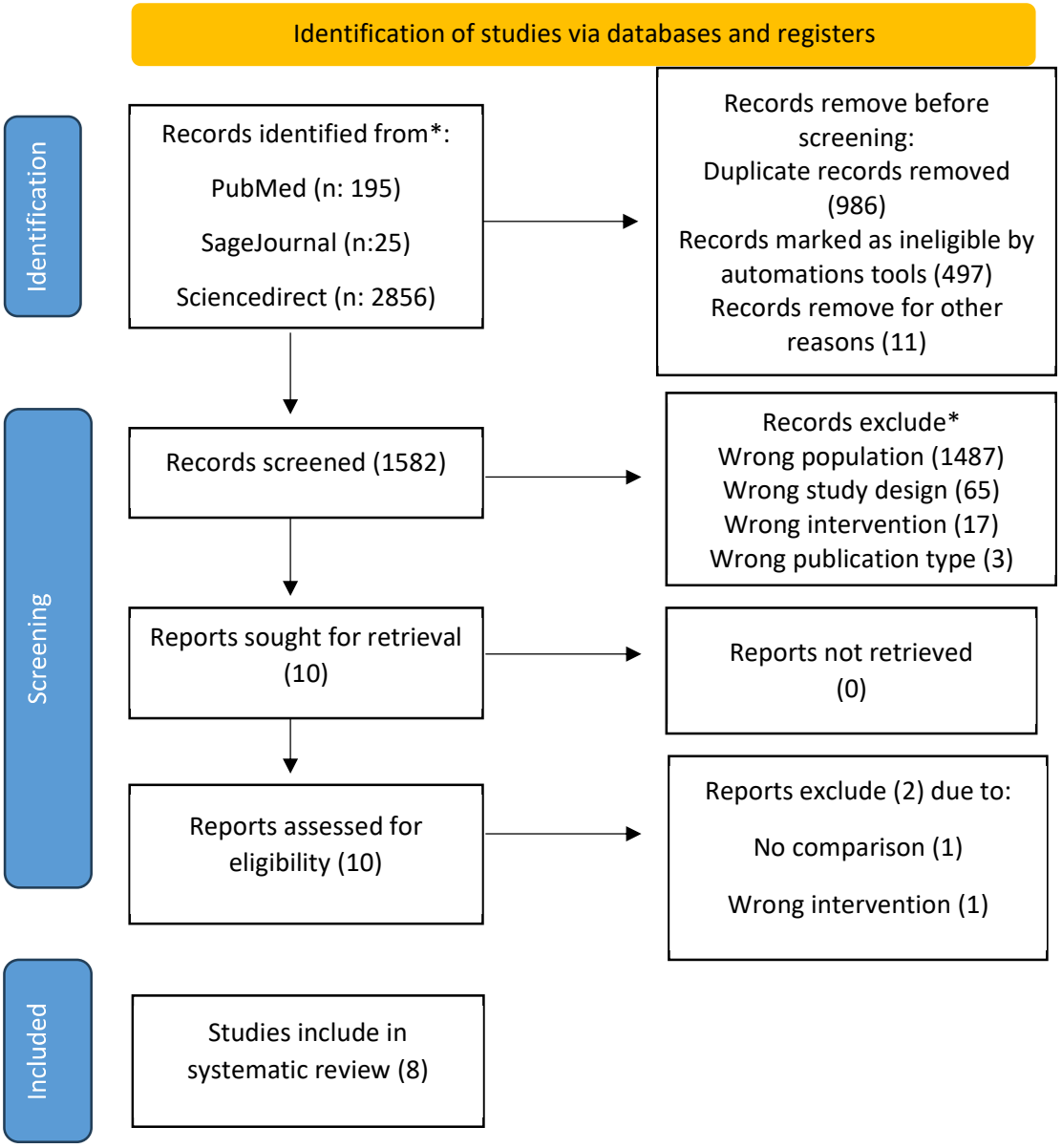

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

QUALITY ASSESSMENT AND DATA SYNTHESIS

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

Table 2. Critical appraisal of Study

Parameters	(Muller, S et al., 2022)	(Hua, L et al., 2020)	(So, H et al., 2023)	(Walje e, AK et al., 2017)	(Shbeeb, I et al., 2018)	(Barbulescu, A et al., 2023)	(Spinelli, FR et al., 2023)	(Boers, M et al., 2021)
1. Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	No	Yes	No	No	No	No	No	No
3. Bias related to confounding factors Were participants included in any comparisons similar?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No	No	No	No	No	No	No	No
5. Bias related to assessment, detection, and measurement of the outcome Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

way?								
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 3076 publications. A thorough three-level screening strategy was used to identify only eight papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Muller, S et al., 2022[9]	UK	Six hundred and fifty-two people with incident PMR were recruited from English general practices (2012–2014). Participants completed seven questionnaires over 2 years (used to allocate people to pain–stiffness trajectories) and a further long-term follow-up (LTFU) questionnaire a median of 5.16 years after diagnosis.	652	Of the 197 people completing the LTFUQ questionnaire, 179 people reported ever having taken glucocorticoids. Of these, 40.1% were still on treatment, with a median (quartile 1, quartile 3) daily dose of 5 (1.5, 9) mg. People still taking glucocorticoids were more likely to be older (72.5 *vs* 70.2 years, $P = 0.035$), live alone (31.8 *vs* 15.0%, $P = 0.01$) and have self-managed their glucocorticoid dose (39.1 *vs* 11.0%, $P < 0.0001$). They were also more likely to belong to a pain–stiffness trajectory class with sustained symptoms.
Hua, L et al., 2020[10]	China	Eighty untreated ERA patients were randomized into the trial (GCs + MTX + HCQ) and control (placebo + MTX + HCQ) groups, for 1-year treatment. Therapeutic evaluation	110	At 1st month, 55% and 20% cases in the experimental and control groups achieved ACR20 response, respectively, indicating a significant difference ($\chi^2 = 16.157$, $P < .001$). This trend continued until 6th month. At 12th month, the number of patients achieved ACR20 response was similar in both groups. At 1st to 6th month, DAS28- ESR scores in

		indices were American College of Rheumatology (ACR) 20 of ACR, disease activity score (DAS) 28-erythrocyte sedimentation rate (ESR), visual analog scale scores, joint function, health assessment questionnaire-disability index score, morning stiffness duration, C-reaction protein and ESR.		the experimental group were significantly lower than control values (all $p<.05$). The experimental group showed improved inflammation, quality of life and radiological symptoms. Bone erosion remained unchanged in the experimental group, while worsening in control group. Correlation coefficients between RA duration and DAS28-ESR score were 0.496, 0.464, 0.509, and 0.550 at 1st, 3th, 6th, and 12th month, respectively. No differences were found in adverse events between the 2 groups.
So, H et al., 2023[11]	China	Patients with RA without MACE at baseline were recruited from a Hong Kong citywide database from 2006 to 2015 and followed till 2018.	12233	Among 12 233 RA patients with 105 826 patient-years of follow-up and a mean follow-up duration of 8.7 years, 860 (7.0%) developed MACE. In the time-varying analyses after controlling for confounding factors, a daily prednisolone dose of ≥5 mg significantly increased the risk of MACE (erythrocyte sedimentation rate model: HR 2.02, 95% CI 1.72 to 2.37; C reactive protein model: HR 1.87, 95% CI 1.60 to 2.18), while a daily dose below 5 mg was not associated with MACE risk, compared with no GC use. In patients receiving daily prednisolone ≥5 mg, the risk of incident MACE was increased by 7% per month.
Waljee, AK et al., 2017[12]	USA	Retrospective cohort study and self controlled case series.	548945	Of 1 548 945 adults, 327 452 (21.1%) received at least one outpatient prescription for short term use of oral corticosteroids over the three year period. Use was more frequent among older patients, women, and white adults, with significant regional variation (all P<0.001). The most common indications for use were upper respiratory tract infections, spinal conditions, and allergies. Prescriptions were provided by a diverse range of specialties. Within 30 days of drug initiation, there was an increase in rates of sepsis (incidence rate ratio

				5.30, 95% confidence interval 3.80 to 7.41), venous thromboembolism (3.33, 2.78 to 3.99), and fracture (1.87, 1.69 to 2.07), which diminished over the subsequent 31-90 days. The increased risk persisted at prednisone equivalent doses of less than 20 mg/day (incidence rate ratio 4.02 for sepsis, 3.61 for venous thromboembolism, and 1.83 for fracture; all P<0.001).
Shbeeb, I et al., 2018[13]	USA	Using a population-based inception cohort, details of GC therapy were abstracted from medical records of all patients diagnosed with PMR in 2000–2014.	359	The study included 359 patients with PMR and 359 comparators. The median time to taper below 5 mg/day for 6 months was 1.44 years (95% confidence interval [95% CI] 1.36–1.62), while the median time to permanent discontinuation was 5.95 years (95% CI 3.37–8.88). The mean ± SD cumulative dose of GC at 2 and 5 years was 4.0 ± 3.5 grams and 6.3 ± 9.8 grams, respectively. The mean ± SD daily dose of GC at 2 and 5 years was 6.1 ± 7.6 mg/day and 7.2 ± 9.5 mg/day, respectively. There were no differences in rates of AEs between patients with PMR and comparators for diabetes mellitus, hypertension, hyperlipidemia, or hip, vertebral, or Colles fractures ($P > 0.2$ for all). Cataracts were more common in patients with PMR than comparators (hazard ratio 1.72 [95% CI 1.23–2.41]).
Barbulescu, A et al., 2023[14]	Sweden	We included 9654 newly diagnosed RA patients from the Swedish Rheumatology Quality Register between 2007–2018 and followed them for three years after the first rheumatology visit.	9654	An increased incidence of serious infections was associated with higher compared with lower doses and with more recent compared with past glucocorticoid exposure. Over 3 years of follow-up, the marginal structural models predicted one additional serious infection for every 83 individuals treated with low GC doses for the first 6 months, and for every 125 individuals treated with high GC doses for the first 3 months, compared with no GC use.
Spinelli, FR et al., 2023[15]	Italy	The project is a monocentric, prospective, open label,	30	We enrolled 30 patients (26 F: 4 M, mean age 60 ± 13 years, mean disease duration 13.2 ± 7.8 years). The primary

		pilot study. Since no previous prospective studies has evaluated any GC-tapering schedule in RA patients treated with tofacitinib, the sample size of 30 patients was estimated assuming a 12-weeks response rate of 30% with a confidence interval of 90% and a margin of error of 15%.		endpoint was achieved: 9 patients (30%) discontinued GCs at week-12. At week-24, other 12 patients (46%) withdrew GCs. The median prednisone dose decreased from 5 mg/day (interquartile range 5–10 mg) to 2.5 (0–5) mg/day at week 12 and 48 ($p < 0.00001$ vs baseline). At week 48, 12 out of 30 patients (40%) had discontinued prednisone. The percentage of patients achieving remission or low disease activity increased throughout the follow-up without any difference between patients who discontinued or not the GC.
Boers, M et al., 2021[16]	Netherlands	The GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) pragmatic double-blind randomised trial compared 2 years of prednisolone, 5 mg/day, to placebo in patients aged 65+ with active RA	451	We randomised 451 patients with established RA and mean 2.1 comorbidities, age 72, disease duration 11 years and DAS28 4.5. 79% were on disease-modifying treatment, including 14% on biologics. 63% prednisolone versus 61% placebo patients completed the trial. Discontinuations were for AE (both, 14%), active disease (3 vs 4%) and for other (including covid pandemic-related disease) reasons (19 vs 21%); mean time in study was 19 months. Disease activity was 0.37 points lower on prednisolone (95% CL 0.23, $p<0.0001$); joint damage progression was 1.7 points lower (95% CL 0.7, $p=0.003$). 60% versus 49% of patients experienced the harm outcome, adjusted relative risk 1.24 (95% CL 1.04, $p=0.02$), with the largest contrast in (mostly non-severe) infections. Other GC-specific events were rare.

DISCUSSION

Glucocorticoids are commonly used for their anti-inflammatory and immunomodulatory properties in the treatment of a wide range of inflammatory, immunological, allergic and malignant diseases and in the prevention of graft rejection after transplantation. A recent population study from Denmark found that the annual prevalence of systemic (oral and injectable) glucocorticoid use was ~3%, increasing to 6.7–7.7% in people aged 60–79 years and to 9.7–11% in those aged ≥80 years. In 2018 in England, 8 million prescriptions for systemic glucocorticoids, 21 million prescriptions for inhaled glucocorticoids and 12 million prescriptions for topical glucocorticoids were dispensed in the community. Glucocorticoids bind to glucocorticoid receptors, which are expressed in almost every cell in the body and have pleiotropic effects on multiple signalling pathways. This makes them highly effective anti-inflammatory drugs, but also causes diverse serious adverse effects that limit their use.[17–19]

Historically, the development of GC-induced side effects was thought to relate to both dose and duration of treatment with therapeutic benefit escalating in parallel with adverse effects. However, the precise association of dose and duration with increased risk of adverse effects is still not well established. Importantly, the severity of inflammation can be associated

with both higher cumulative doses of GCs and systemic complications that may mimic the side effects attributed to GCs, and this cannot be resolved by statistical adjustments in observational studies.[20–22]

Despite being in use for six decades of intense medical progress, glucocorticoids (GCs) still have a pivotal role in the management of rheumatoid arthritis (RA), resisting persistent (and sometimes alarming) news about their toxicity. The recent accumulation of solid evidence supporting their ability to reduce radiographic progression and modify the disease course, even at low dose, has stressed the need for a balanced re-assessment of risks and benefits. The concept that adverse events (AEs) are potentially serious and depend on the dose and duration of use support recommendations that the minimum dose should be used for the shortest possible time, always in combination with other disease-modifying anti-rheumatic drugs.[23,24]

However, the evidence required on which to base such decisions remains very limited. Theoretical constructs about the potential direct toxicity of GCs must acknowledge their potential benefits derived from the systemic reduction of inflammation. Data derived from observational studies need to be critically appraised in terms of the risks of bias by indication and the effect of unaccounted confounders [5] . RA is, per se, associated with a higher risk of many AEs, which are also considered as side effects of GCs, such as cardiovascular disease, osteoporosis and fractures, and decreased insulin sensitivity Patients with higher disease severity are more likely to be prescribed GCs and in higher dosages. Consequently, negative effects arising as a consequence of the disease per se and its co-morbidities may be attributed to the concomitant GC treatment. Disentangling such confounding issues cannot be achieved through observational studies. Valid and robust conclusions can only be obtained through properly designed prospective controlled trials.[23,25]

CONCLUSION

In conclusion, glucocorticoids are effective drugs for many rheumatic diseases. However, there are serious adverse effects that can ensue. These are often dose related and related to the duration of therapy. Several of the complications occur in patients already at risk for these adverse events. The adverse effects, such as weight gain, osteoporosis, fracture, osteonecrosis, infections, ocular complications, cardiovascular effects, hyperglycemia, etc.

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