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THE SAFETY OF GLUCOCORTICOIDS IN THE TREATMENT OF INFAMMATORY RHEUMATIC DISEASE : A SYSTEMATIC REVIEW

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Abstract

Glucocorticoids have been utilized as a component of the treatment for rheumatoid arthritis ever since their introduction some decades ago. It has been established that glucocorticoids are effective in lowering the inflammatory activity induced by this condition and in slowing the course of erosive joint degradation. Both of these benefits can be attained by taking the medication. Unfortunately, they also have a wide variety of potentially adverse consequences, the severity of which may vary depending on the dosage and the length of the therapy. Nevertheless, the benefits of these medications far outweigh the risks associated with them. As a result of the rise in popularity of many alternative therapy alternatives, the use of glucocorticoids as a treatment method is currently being debated (such as biologic and targeted synthetic disease-modifying antirheumatic medicines). It is possible to provide corticosteroids by injecting them directly into the joint. Many people are opposed to the use of glucocorticoids because of the dose-dependent adverse effects that they can have, despite the fact that they continue to be an essential component in the treatment of a wide variety of inflammatory rheumatic diseases. The usage of glucocorticoids for an extended period of time is connected with a greater risk of experiencing adverse consequences. These problems are associated with an increased chance of developing cardiovascular disease, diabetes, and possibly mortality.

Keyword: *Arthritis; Glucocorticoids; Infammatory rheumatic disease; Prednisone*

INTRODUCTION

Arthritis is taken from the Greek for "joint illness." It is an acute or chronic joint inflammation that is frequently accompanied by pain and structural damage. Arthritis and arthralgia are not synonymous.[1] Arthralgia refers to pain that is localized to a joint, regardless of the cause of the discomfort (which may or may not be due to joint inflammation). Arthritis plagued both Neanderthals and ancient Egyptians, but the name "osteoarthritis" was not coined until 1886 by Dr. John K. Spencer. More than one hundred different forms of arthritis have been identified, with osteoarthritis or degenerative arthritis, which is non-inflammatory arthritis, being the most prevalent.[2,3]

Inflammatory arthritis can be caused by autoimmune processes (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, etc.), crystal deposition (gout, pseudogout, basic calcium phosphate illness), or infections (septic arthritis, Lyme's arthritis). Inflammatory arthritis may also occur in conjunction with other autoimmune connective tissue disorders, such as systemic lupus erythematosus, Sjogren syndrome, scleroderma, myositis, inflammatory bowel disease, celiac disease, etc.[4–6]

Imaging reveals that more than one-third of the US population has arthritis, and this proportion is likely to increase as the population ages. Osteoarthritis is the most prevalent arthritide. 19% to 30% of persons over the age of 45 years have knee osteoarthritis, 27% have hand osteoarthritis, and 27% have hip osteoarthritis. It is projected that 40% of men and 47% of women will get osteoarthritis throughout their lifetimes, with the prevalence rising to 60% if they have a body mass index of over 30.[7]

Gout is the most prevalent form of inflammatory arthritis in the United States, affecting more than 8 million people with a frequency of 3.9% and more than 9 percent in adults over 60 years old. The incidence of gout exceeds 45 per 100,000 people. Significantly, the incidence and prevalence of gout have increased by more than a factor of two in the last few decades. The frequency of pseudogout in the adult population is between 4% and 7%, with knee arthritis affecting more than half of individuals.[7–9]

The goal of osteoarthritic joint management should be to reduce pain while improving function. For optimal care, a combination of non-pharmacological (or conservative) and pharmacological treatments is usually required. Topical and oral medications are used in the pharmacologic management of osteoarthritis. Oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), topical capsaicin, and duloxetine are all commonly used medications.[6]

Corticosteroids can be injected into the joint directly. Glucocorticoids remain, deservedly, a cornerstone in the treatment of many inflammatory rheumatic disorders, but many are opposed to their use due to their dose-dependent side effects.[10]

This article review some research on safety of glucocorticoids in the treatment of infammatory rheumatic disease.

METHODS

For data collection, processing, and reporting, this study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project criteria. The regulations enacted were based on these considerations. This literature review investigates the safety of glucocorticoids in the treatment of rheumatoid arthritis with inflammation. The following are the significant issues raised by the present study: 1) Articles must always be written in English and must address the safety of glucocorticoids in the treatment of rheumatoid arthritis. 2) Publications published after 2014 but within the scope of this systematic review were evaluated. The anthology will exclude editorials, submissions without a DOI, reviews of already published articles, and pieces that are substantially identical to those in the journal.

The search for studies to be included in the systematic review was carried out from March, 20th 2023 using the PubMed and SagePub databases by inputting the words: “glucocorticoids”, “safety” and “infammatory rheumatic disease”. Where *("glucocorticoids"[Pharmacological Action] OR "glucocorticoids"[MeSH Terms] OR "glucocorticoids"[All Fields] OR "glucocorticoid"[All Fields]) AND ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields]) AND ("inflammatories"[All Fields] OR "inflammatory"[All Fields]) AND ("rheumatic diseases"[MeSH Terms] OR ("rheumatic"[All Fields] AND "diseases"[All Fields]) OR "rheumatic diseases"[All Fields] OR ("rheumatic"[All Fields] AND "disease"[All Fields]) OR "rheumatic disease"[All Fields])* is used as search keywords.

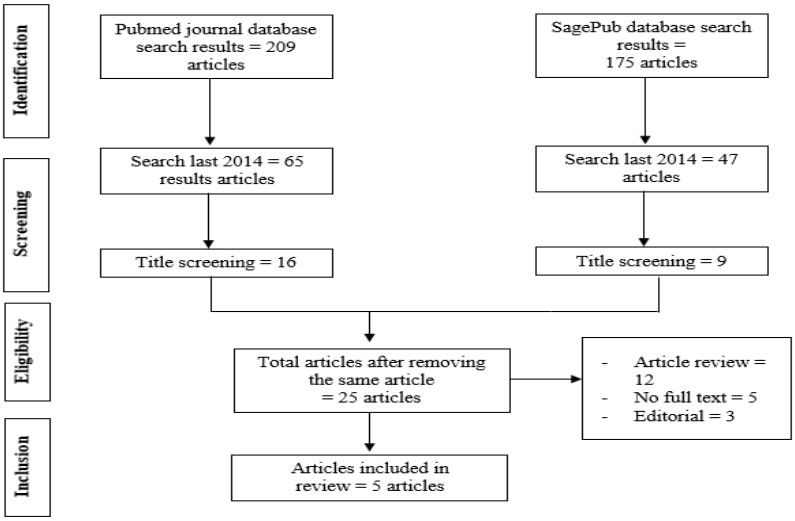

Figure 1. Article search flowchart

The abstract and title of each study were used to determine eligibility. As a result, historical literature serves as their primary source. Submissions in unpublished English are sought after reviewing multiple publications with identical results. The systematic review included only studies that met the inclusion criteria. This restricts the search results to only those that meet the specified criteria. The evaluation process follows. Authors, publication dates, location, activities, and parameters were all listed in the study's analysis. Duplicate articles were removed from the database after saving search results in EndNote. Each article's title and abstract were evaluated by two reviewers.

Each author read the title and abstract of each publication before deciding which manuscript to study. Following that, we'll go over all of the papers that meet the review's inclusion criteria. Following our investigation, we will look through relevant research articles. This rule governs which manuscripts are reviewed. It should be easier to decide which items to look into further. Which previous studies were included in the review, and why?

RESULT

Maarten, et al (2021)[11] were randomized 451 patients with established RA, a mean of 2.1 comorbidities, a mean age of 72, a mean disease duration of 11 years, and a DAS28 score of 4.5. Seventy-nine percent were on disease-modifying therapy, including fourteen percent on biologics. 63% of prednisolone patients and 61% of placebo participants completed the study. AE (both, 14%), active disease (3 vs. 4%) and other accounted for discontinuations; the mean duration of the study was 19 months. With prednisolone, disease activity was 0.37 points lower (95% CI = 0.23, p <0.01), and joint damage progression was 1.7% lower (95% CI = 0.7, p = 0.003). 60 vs 49% of patients suffered injury, adjusted relative risk (aRR) = 1.24 (95% CI = 1.04, p = 0.02), with the greatest difference in (mainly mild) infections.

Other study showed 17 incident composite CV events in 112 patients (15%) randomized to prednisolone and 15 occurrences in 111 patients (14%) randomized to placebo. In each group, there were nine deaths (8%). The age-adjusted relative hazards (HRs; 95% CI) for the first composite CV incident, first coronary event, and mortality were 1.80 (0.9 to 3.6), 0.98 (0.4 to 2.6), and 1.60 (0.6 to 4.1), respectively, in the prednisolone group against the group not treated with prednisolone. Those treated with prednisolone had a 3.7-fold greater relative hazard (95% confidence interval [CI]: 1.2-11.4) for their first cerebrovascular incident.[12]

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Agent	Conclusion
Maarten, 2022[11]	Uni Europe	Double-blind randomised trial	451 patients with established RA	Prednisolone5 mg/day	With a trade-off of a 24% rise in individuals with largely non-severe AE, add-on low-dose prednisolone has beneficial long-term effects in senior adults who have established RA. This shows that there is a favorable balance of benefit and harm.
Ajeganova, 2014[12]	Sweden	Open randomised trial	223 patients with early RA	Prednisolone 7.5 mg/day in + disease-modifying antirheumatic drugs (DMARDs) with DMARD therapy alone	In this inception cohort study of low-dose prednisolone use during the first two years of RA disease, the incidence of ischaemic coronary artery events was similar in the two treatment groups, whereas the long-term risk of ischaemic cerebrovascular events was higher in the prednisolone group. The study was conducted on patients who had been diagnosed with rheumatoid arthritis (RA). There was a general downward tendency in terms of survival for those who were given prednisolone.
Listing, 2015[13]	Germany	Prospective study	31,378 patient	Glucocorticoids, TNF-α inhibitors and rituximab	Impaired function and therapy with glucocorticoids at doses greater than ≥5 mg/day were substantially related with an increased risk of death, and this association was irrespective of illness manifestation. Individuals whose disease activity has been consistently high over a lengthy period of time have a markedly elevated risk of passing away. The mortality rate is reduced when disease activity is effectively controlled. When it comes to mitigating this risk, it appears that TNF inhibitors and rituximab are more effective than standard DMARDs.
Roubille, 2017[14]	France	Cross sectional	602 patients with RA from the early arthritis	Low-dose prednisone	This examination of the ESPOIR cohort over a period of seven years lends support to the notion that very low-dose GC has a good safety profile for treating early active RA.
Movahedi, 2016[15]	United Kingdom	Prospective cohort study	UK primary care database (the Clinical Practice Research Datalink [CPRD]) including 21,962 RA patients (1992–2009) and the US National Data Bank for Rheumatic Diseases (NDB) including 12,657 RA patients (1998–2013)	5 mg of prednisolone equivalent dose	The usage of GC is a risk factor for diabetes that is clinically significant and can be quantified. The dosage and length of treatment both have an impact on the risk, but this is only true for recent usage of GC within the past six months.

Listing, et al (2015)[13] study showed 463 of 8908 patients died during the 31,378 patient-years of follow-up (standardised mortality ratio = 1.49 [95% CI = 1.36-1.63]). Patients with persistently high disease activity (mean DAS28 >5.1) had a significantly higher risk of death (adjusted HR [aHR] = 2.43; [95% CI = 1.64 to 3.61]) than patients with persistently low disease activity (mean DAS28 <3.2). Poor function and treatment with glucocorticoids ≥5 mg/d were associated with an increase in mortality, regardless of disease activity. Patients with TNF-α inhibitors (aHR = 0.64 [95% CI = 0.50-0.81]), rituximab (aHR = 0.57 [95% CI = 0.39-0.84]), or other biologics (aHR = 0.64 [95% CI = 0.42-0.99] had significantly lower mortality.

Roubille, et al (2017)[14] showed individuals with GC utilized more nonsteroidal anti-inflammatory medicines, synthetic and biological disease-modifying antirheumatic therapies, had more active disease impairment, and had higher C reactive protein and anticitrullinated protein antibody levels. 44 and 21 of the 65 occurrences (7 deaths, 14 cardiovascular disorders, 19 serious infections, and 25 fractures) occurred in patients with and without GC, respectively (p = 0.520). In individuals with GC, infections were more prevalent, although not significantly so (p = 0.09). Using weighted Cox proportional-hazards analysis using propensity score and inverse-probability-of-treatment weighting, and included age, gender, history of hypertension, and GC treatment, the outcomes did not differ between those with and without GC (p = 0.520; HR = 0.889; 95% CI = 0.620 to 1.245).

Movahedi, et al (2016)[15] conducted a study. They showed the hazard ratio (HR) was 1.30 (95% CI = 1.17–1.45) and 1.61 (95% CI = 1.37–1.88) for current GC users versus nonusers in the CPRD and the NDB. A variety of traditional statistical models indicated risk rises with increasing GC dosage and duration. The WCD model revealed that recent GC usage contributed most to the current risk of diabetes, but doses taken more than six months ago had little effect on the current risk. Compared to nonusers, 5 mg of prednisolone equivalent dose in the previous 1, 3, and 6 months was significantly linked with HRs of 1.20, 1.43, and 1.48 in the CPRD.

DISCUSSION

Since several decades ago, glucocorticoids have been utilized as part of the treatment for rheumatoid arthritis. It has been demonstrated that glucocorticoids are useful in reducing the inflammatory activity caused by this condition and in halting the course of erosive joint deterioration. However, they also have a wide variety of potentially harmful effects, the severity of which might vary depending on the dosage and length of the treatment. The utilization of glucocorticoids is currently up for discussion as a result of the proliferation of alternative therapy options (such as biologic and targeted synthetic disease-modifying antirheumatic medicines).[16]

Low-dose prednisolone had positive long-term effects on disease activity and damage progression in people with RA who were already getting standard care that let them get the most out of their treatment. In exchange, 11% more patients were found to have at least one adverse event of special interest (AESI), like: any AE (except worsening of disease) leading to discontinuation; myocardial infarction, cerebrovascular or peripheral arterial vascular event; newly occurring: hypertension, diabetes, infection, cataract, glaucoma requiring treatment; and symptomatic bone fracture. Most of the increase was due to mild to moderate infections that needed treatment. These are things that are usually linked to GC. Even though these results are concerning, they should be seen in the context of the high-risk trial population, which is similar to patients in clinical practice.[11]

It is widely acknowledged that oral GC therapy is a significant risk factor for DM. To date, however, this risk has not been well quantified, and no studies have examined the impact of GC dosage, duration, and timing on the risk of DM. We generated validated measures of DM risk for various patterns of GC use using two distinct data sets of RA patients. The risk rises with dosage—every 5 mg increase in current oral GCs was associated with a 25-30% increase in the risk of DM. We also discovered that only GC doses taken within the previous 6 months are linked to the current risk of DM. The use of two data sets with distinct study designs and geographic settings increases the findings' validity significantly. Despite differences in populations, methods of determining DM, and definitions of exposure, the incidence of DM and estimates of risk for different models of GC therapy were nearly identical in the two studies.[15,17]

It has been found that the tolerability profile of GC changes depending not only on the dose but also on the time of exposure. In point of fact, in addition to having a better tolerability profile than a high-dose regimen, long-term usage of low-dose GC has been related with increased mortality when compared with shorter exposures.[18] This is the case despite the fact that low-dose GC has a superior tolerability profile. Most notably, two studies that were conducted not too long ago suggested a dose-dependent increase in mortality in RA; del Rincón et al revealed a daily threshold dose of 8 mg at which all-cause mortality increased with GC dose (adjusted HR=1.78; 95% CI = 1.22 to 2.60), and in the German register Rheumatoid Arthritis oBobservation of BIologic Therapy (RABBIT), use of GC >5 mg/ day was associated with increased mortality risk, independent of RA activity.[18–20]

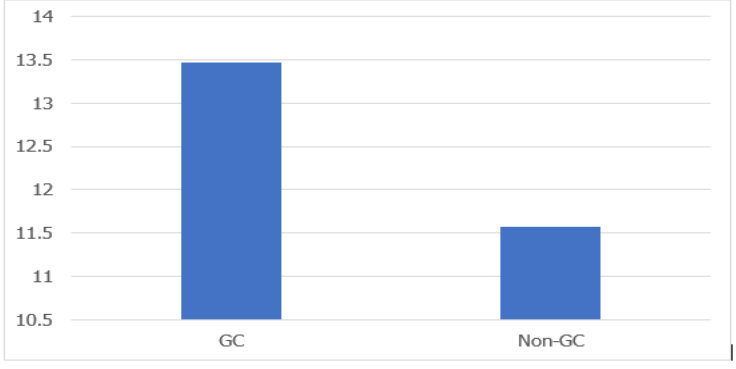

Figure 2. Percentage of patients experiencing adverse events in those on GC and non-GC

When administering treatment, it is essential for clinicians to have an understanding of the differences in the potency of various systemic corticosteroids. This is due to the fact that every corticosteroid has its own unique duration of action, in addition to glucocorticoid and mineralocorticoid actions that are distinct from one another. High dosages of corticosteroids, which are three to ten times higher than the physiological amount, are required for their anti-inflammatory effects.[21,22]

While treating severe and acute illnesses, it is necessary to administer high dosages of corticosteroids without generating serious adverse effects. In some circumstances, more extensive treatment over a longer period of time is required to achieve the desired therapeutic outcome. Due to the fact that corticosteroids have an influence on the majority of the body's organs, it can be challenging to prevent their adverse effects. Because of this, deciding whether or not to administer systemic corticosteroids in a patient calls for careful analysis of the risk to benefit ratio.[21,22]

CONCLUSION

The usage of glucocorticoids for an extended period of time is connected with a greater risk of experiencing adverse consequences. These problems are associated with an increased chance of developing cardiovascular disease, diabetes, and possibly mortality.

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