Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

An updated review of glucocorticoid-related adverse events in patients with rheumatoid arthritis

Mariana Luís, João Freitas, Flávio Costa, Frank Buttgereit, Maarten Boers, Da Silva JAP & Tânia Santiago

To cite this article: Mariana Luís, João Freitas, Flávio Costa, Frank Buttgereit, Maarten Boers, Da Silva JAP & Tânia Santiago (2019): An updated review of glucocorticoid-related adverse events in patients with rheumatoid arthritis, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2019.1615052

To link to this article: https://doi.org/10.1080/14740338.2019.1615052

Accepted author version posted online: 06 May 2019.
Published online: 14 May 2019.

EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2019.1615052

Taylor & Francis
Taylor & Francis Group

REVIEW

An updated review of glucocorticoid-related adverse events in patients with rheumatoid arthritis

Mariana Luís[a], João Freitas[a], Flávio Costa[a], Frank Buttgereit[b], Maarten Boers[c], Da Silva JAP[a,d,e] and Tânia Santiago [a,d]

[a]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [b]Department of Rheumatology and Clinical Immunology, Charité University Medicine, Berlin, Germany; [c]Department of Epidemiology and Biostatistics, Amsterdam Rheumatology and Immunology Center, Amsterdam University Medical Centers, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; [d]Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [e]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal

ABSTRACT

Introduction: Glucocorticoids represent a cornerstone in the treatment of rheumatoid arthritis. Their effect as a disease-modifying treatment in rheumatoid arthritis is well established. Despite this, the risk of adverse events of glucocorticoids, especially in high doses and over a long time, is constantly highlighted. Data on the prevalence and impact of glucocorticoid-related adverse effects in rheumatoid arthritis is needed, therefore, to be regularly revisited.

Areas covered: In this review, our primary aim was to provide an update of evidence from randomized controlled trials and observational cohort studies on the safety of glucocorticoid treatment in rheumatoid arthritis. Our secondary aim was to provide a critical overview of the concerns raised with both study designs – randomized clinical trials versus nonrandomized observational studies – regarding the assessment of the safety of glucocorticoids in rheumatoid arthritis.

Expert opinion: In the meantime, adherence to recommendations and consensus on standardized methodologies for monitoring and reporting adverse events is essential to improve our knowledge and competence in the best management of glucocorticoids.

ARTICLE HISTORY
Received 25 February 2019
Accepted 1 May 2019

KEYWORDS
Adverse events; glucocorticoids; rheumatoid arthritis; risk; safety; toxicity

1. Introduction

Glucocorticoids (GCs) are one of the oldest pharmacological treatments in the management of inflammatory diseases and remain a cornerstone therapy in a variety of conditions. In rheumatoid arthritis (RA), they have been proven to have a disease-modifying effect, i.e. reducing radiographic progression [1–4]. However, the current use of GC is always overshadowed by fear of adverse events (AEs). Evidence suggests that most of these AEs are dose and time-dependent effect [5], and most studies advocate that GCs have a favorable risk-benefit profile if kept at low-dose, defined as ≤7.5 mg/day prednisone-equivalent (PDN-eq) [6]. Clarifying the real magnitude of the GC-induced AEs has proved difficult because most studies are observational and thus exposed to confounding (bias) by indication: severe inflammation is associated with both higher cumulative doses of GCs and with systemic complications that coincide with many of the AEs attributed to GCs. These include, among others, accelerated cardiovascular disease, insulin resistance, altered bone metabolism and avascular necrosis of bone [7]. This bias is strong and cannot be resolved by statistical adjustments (e.g. propensity scores) in observational studies [8].

Unfortunately, high-quality data regarding the safety of GCs in RA is still limited, as randomized clinical trials have been designed and powered for benefit (i.e., they are frequently too short or too small for adequate risk assessment), and concerns have been raised over the representativeness of trial populations, as these are often selected to have less comorbidity (external validity). A previous comprehensive review by Santiago and Da Silva published in 2014 concluded that the evidence remains limited both in quantity and quality, hindering clear conclusions regarding GC safety [9].

In this paper, we update this review with the evidence from recent literature in RA on the safety of low- and medium-dose GC treatment.

2. Literature search

A PICO-structured search was made to identify relevant studies in Pubmed MEDLINE and Embase databases.

a. Population: RA population;
b. Intervention/test: Low-dose GC, defined as ≤10 mg/day;
c. Comparator/control: Any other GC dose or none;
d. Outcome: Adverse events of low-dose GC in RA patients;
e. Design: Observational studies (including cohort and case–control studies), systematic reviews, and randomized trials.

The search was performed with free terms and medical descriptors (e.g., MeSH terms). The terms used were:

CONTACT Tânia Santiago tlousasantiago@hotmail.com Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Praceta Prof. Mota Pinto, Coimbra 3000-076, Portugal

Article highlights

- Evidence to support clear conclusions regarding safety remains limited, both in quantity and quality.
- Observational data are often negatively affected by bias by indication and other methodological issues that hinder interpretation; such strong bias cannot be overcome by statistical techniques.
- More attention should be given to monitoring and reporting GC-AEs in clinical trials.
- Large prospective trials dedicated to the safety of low-dose GC are dearly needed.
- Adherence to guidelines/recommendations may contribute to reduce and better understand GC-related AEs and optimize their use for the benefit of patients.

This box summarizes key points contained in the article.

Rheumatoid arthritis, Glucocorticoids, Low-dose, Safety, Toxicity, and Adverse events.

2.1. Selection criteria and search strategy

In September 2014, Neuroimmunomodulation published a special supplement regarding 'Low Dose Glucocorticoids in Rheumatic Diseases'. This supplement included two important reviews: one focusing on randomized controlled trials [9] and other on observational studies [10]. The current paper is an updated review of these previous publications.

For the purpose of this systematic review, studies were included for detailed analysis if: (1) they included adult patients with RA; (2) they focused on exposure to oral or intramuscular injections GC treatment (excluding intra-articular injections) in one arm and non-exposure in another, otherwise comparable, study arm; (3) GCs were used in doses ≤10 mg of prednisone or equivalent per day; (4) they lasted 6 months or longer. Published articles from July 2013 to October 2018, written in English, Spanish, French, Italian or Portuguese were searched. The last search was run on 29 October 2018, with weekly automatic email updates, until 1 December 2018. A manual search for recent publications without attribution of mesh terms was added on this date.

Publications reporting no original data or without a clear description of the research methods, were excluded. No search was made on conference abstracts or unpublished studies. Duplicates were removed and the selected references were imported into Microsoft Excel.

2.2. Study selection

Eligibility assessment was performed independently, on the basis of title and abstract, by two authors (ML and TS). Disagreements were resolved by discussion with the author/expert (JAPS). In case of doubt, the full text of the article was retrieved and discussed. Exclusion criteria were recorded after the full text screening. The inter-rater agreement between ML and TS for selection based on abstract and full text, measured by Cohen's kappa coefficient was 0.98.

3. Results

The selection of articles is reported in Figure 1. A total of 69 articles were identified from the two databases. Twenty-four articles were excluded after abstract reviewing. The main reasons for this were: case reports or case series, not RA, and not focused on safety. Another 14 articles were excluded after detailed review: 2 articles due to intra-articular GC formulations, 3 articles exploring the benefit of modified formulations of GC on circadian cycle, 3 articles related with low-dose GC efficacy rather than safety, 5 articles because GC exposure was not clearly defined, 1 article for the inclusion of pediatric patients.

In the end, 31 articles were included in this updated review: 18 observational studies, 7 reviews, 3 recommendations/guidelines, 2 meta-analyses, and one RCT. We also discuss the relevance of two ongoing RCTs.

The main focus of the observational studies was mortality, including all-cause and cardiovascular. Bone metabolism, endocrine disturbances, and infection risk were other topics covered. The studies included in this updated review are described in Table 1. Results are expressed as relative risk (RR) or odds ratio (OR) or hazard ratios (HR) with 95% confidence interval (CI).

3.1. Findings from randomized control trials and meta-analysis

In 2014, was published a systematic review on the safety of GCs in RA [9]. In this review, which compiled data from 11 RCTs the authors did not identify any strong signal of relevant toxicity of GC in doses of up to 10 mg of prednisone equivalent/day for up to 2 years [9]. However, the quantity (1100 patient-years of exposure) and the quality of evidence were too limited to support firm conclusions regarding this issue.

Since this review, only one RCT has been published. In the tREACH trial (3 arms: an arm comprising MTX + sulfasalazine + hydroxychloroquine + a bolus of IM GC (methylprednisolone 120 mg or triamcinolone 80 mg), an arm comprising MTX + sulfasalazine +hydroxychloroquine + oral GC, and an arm comprising MTX-only + oral GC), there were no significant differences in terms of adverse events between the two GC bridging therapies [11].

Meanwhile, results of long-term follow-up of the CAMERA [12] and BARFOT [13] trials have been published giving more insights into GC safety in RA (studies detailed below).

Two meta-analyses on specific GC safety issues have been published since our last review [9].

In 2015, a meta-analysis of 7 RCTs evaluated the effects of 6–12 mg/d of PDN-eq on bone mineral density (BMD) in RA patients (445 patients exposed to GCs and 347 controls) [14]. GCs were associated with a small negative effect on lumbar spine (standardized mean difference in change in BMD −0.30 (0.55–0.04)), but not hip BMD with significant heterogeneity across studies. The included RCTs had relatively short follow-up duration (20 weeks to 2 years). In the two RCTs that reported data on hand BMD, GCs were associated with less hand bone loss than control treatment (SMD change in BMD 0.51 (0.20, 0.81), p = 0.001, I2 = 0%).

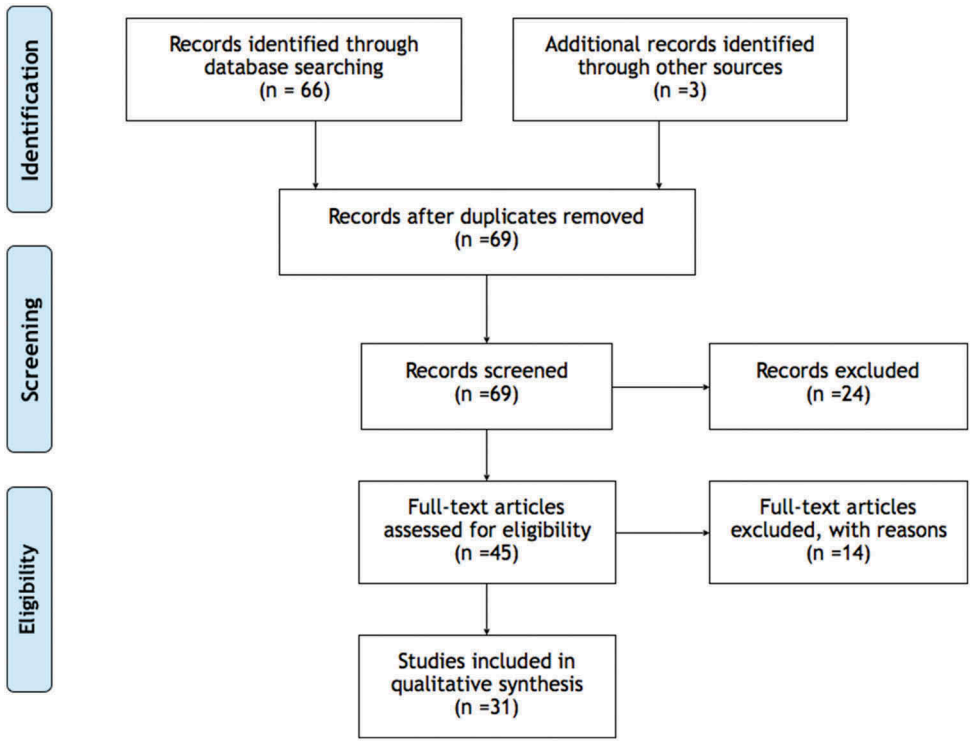

Figure 1. PRISMA flowchart.

Another meta-analysis investigated the association between GCs and the risk of developing cataract and/or glaucoma in RA [15]. The authors point out that only 3 of the 28 RCTs included reported ophthalmological AEs. There was insufficient data to determine the impact of dose and duration of treatment, and thus the risk could not be accurately quantified [15].

3.2. Findings from observational and cohort studies

3.2.1. All-cause and cardiovascular mortality and morbidity

The cardiovascular effects as well as morbidity and mortality associated with GCs have been addressed over recent years solely on the basis of observational data.

A study based on the German biologics register – Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (with ~8,900 RA patients) found a more than twofold mortality risk in patients with a sustained higher disease activity (HR: 2.43 (1.64–3.61)), even after controlling for GC treatment [16]. However, GC>5 mg/day during the most recent 12 months was significantly associated with increased mortality, independent of disease activity. No increased mortality was seen with treatment with <5 mg/d GC. Importantly, however, the authors acknowledged that due to the observational nature of this study and the long list of risk factors and confounders, residual confounding with an impact on the results cannot be ruled out.

Roubille et al. reached similar conclusions in a study based on the French cohort ESPOIR (~600 RA patients) [17]. Low-dose GC (<5mg/d, mean dose 3.1 ± 2.9 mg/d) showed a good safety profile in early RA with neither cumulative nor duration of GC treatment having a significant effect on survival as long as disease activity and prognostic risk factors are taken into the equation [17].

Despite the emphasis given to CV mortality, the leading cause of death in RA, Movahedi *et al.* found GC treatment (~16,760 RA patients) to be associated with death caused by neoplasms, HR 1.46 (1.42–1.49), specially respiratory and digestive [18]. This observation may be partly explained by perimortal bias, since patients with terminal illness are more likely to be prescribed with GC both as part of cancer therapy and as a substitute for other DMARDs. Also, classical risk factors related to several types of neoplasms were not included in the model such as body mass index, diet, sedentarism, and occupational exposure. However, for GC < 5mg/d, no increased mortality risk was found for any of the cause-specific mortality categories evaluated [18].

The Texas study group (~780 RA patients) concluded that 7.5 mg/d is the maximum daily dose that can be considered safe from the standpoint of mortality risk [19]. The threshold associated with increased mortality when considering GC cumulative dose was found to be 40 g or 7g/year [19]. This represents 22 years of 5mg/d, which can be reached in any chronic inflammatory disease as RA suggesting that low-dose GC may not be entirely safe in the long term [19]. All associations between GC exposure and death, either all-cause or cardiovascular-related, remained significant after correction for confounding factors, such as RA disease activity and severity, and cardiovascular risk factors. However, this study has some limitations including the small sample size, the retrospective nature of data collection and the fact that authors did not account for the use of low-dose aspirin.

Another retrospective study based on an administrative healthcare claims data (~84,000 RA patients) observed that

Table 1. Observational and cohort studies reporting on glucocorticoid adverse events.

			Glucocorticoid				
Author, year, ref	N (RA pt)	Outcomes/ type of AEs	Daily dose Mean	Treatment duration (yrs)	Follow-up (yrs)	Adjusted for confounders	Results
Okano, 2013 [25]	219	BMD BMM	3.0	NS	7	+	BMD (total hip) decreased ($p < 0.01$) in GC without bisphosphonates *vs* no GC or GC with bisphosphonates
Ajeganova, 2014 [13]	223	CV events and death	7.5	2–10	10	+	HR 1.8 (0.9–3.6) Composite CV event 1.6 (0.6–4.1) Death 3.7 (1.2–11.4) Stroke
Rincón, 2014 [19]	779	All-cause mortality	6.9	NS	NS	+	HR 1.8 (1.2–2.6) 8–15mg/day 2.8 (1.4–5.7)>15 mg/day 1.2 (0.7–1.9) < 5 mg/day 1.2 (0.9–1.7) 5–7 mg/day
Listing, 2015 [16]	8908	All-cause mortality	5.6	NS	4	+	HR 1.0 (0.8–1.4) ≤ 5 mg/day
Richter, 2015 [47]	947	Risk of sepsis Mortality		NS	NS	–	OR 1.3 (0.8–1.9) 5–10 mg/day 0.9 (0.5–1.8) 5–10 md/day 2.4 (1.0–5.6) >10 mg/day
Movahedi, 2016 [18]	16,762	All-cause Neoplasm	7.5	NS	13	+	HR 2.0 (1.8–2.2) 3.2 (2.7–3.9)
Ozen G, 2016 [36]	13,669	iDM	NS	NS	5		HR 1.3 (1.2–1.5) 1.3 (1.1–1.5) ≤10 mg/day 1.7 (1.2–2.2), >10 mg/day
Borresen, 2017 [39]	42	Adrenal insufficiency	5	6	–	–	39% (25–56)
Yang, 2017 [31]	45,423	Hepatitis B virus-related mortality	NS	NS	13	–	No difference between GC and non-GC ($p = 0.074$)
Spivey, 2017 [24]	25,542	All-cause AE			< 4	–	OR 1.1 (1.1–1.2)
Schenfeld, 2017 [35]	40,933	HIV	NS	< 2	NS	+	IR 3.9 (3.6–4.1 no GC 6.4 (5.7–7.2) <7.5mg/day 13 [12–16] >7.5mg/day
Roubille, 2017 [17]	602	New-onset safety events (all-cause mortality, CVD, severe infection and fracture)	3.1	3 (SD 2)	7	+	HR 0.9 (0.6–1.3)
Safy, 2017 [12]	218	GC-related comorbidities	10 (tapering)	2–12	2	–	No difference between GC and non-GC
Best, 2018 [20]	84,357	Any GC-related AE	10.2	NS	1	+	OR1.2 (1.1–1.3)
Cheng, 2018 [27]	425	BMD Fracture Risk	2.5–7.5	NS	NS	–	LS BMD baseline: 0.85 (0.20) vs 0.89 (0.20), $p = 0.05$. FRAX (major): 14 (15.5) vs 8 (8.6), $p < 0.0001$ FRAX (hip): 4.4 (8.4) vs 2 (3.9), $p < 0.0001$

Legend:
Results are shown in Odds ratio (OR),and Hazard ratios (HR) (95% confidence intervals) or mean (SD).
AE, adverse event; **BMD**, bone mineral density; **iDM**, incident diabetes mellitus; **IR**, incident rate; **HIV**, Hospitalized infectious events; **LS**, lumbar spine;; **Yrs**, years; **Plac**, placebo; PDN, prednisolone; **Mo**, months; **NS**, Not Specified; **±**, yes/no adjusted for confounders.

higher cumulative oral GC dose was associated with increased risk of potential GC-related adverse events [20]. Namely, a cumulative oral GC dose of >1.8 g prednisone equivalent was associated with an increased risk of 'any AE' during 1 year compared with no GC exposure (OR 1.19 (1.09–1.30)). In addition, GC cumulative doses of 0.8–1.8 g/year (≈2–5 mg/d for 1 year) were associated with greater risk of some GC-related adverse events, mainly opportunistic infections (OR 1.28 (1.02–1.60)) and bone-related adverse events (OR 1.24 (1.11–1.40)) [20]. In this study, these two types of adverse events were also responsible for the highest health-care costs (~38 900$ for hospitalization for opportunistic infections and ~15 500$ for aseptic necrosis). We emphasize that these results should be appreciated with caution. This study is intrinsically associated with a number of methodological issues that may obscure the interpretation of the results as we highlighted in the accompanying editorial [21]. Similarly to previous observational studies, Best et al., tend to attribute to GC all negative events that occur during GC treatment. Many of these AE may actually be manifestations of the RA itself or AE of concomitant medications [21].

Considering cardiovascular risk, a recent prospective study (~350 RA patients) followed for incident cardiovascular disease highlighted that confounding by indication probably distorts the relationship between GC exposure and CV disease in RA [22]. The authors also suggested that the finding of incident cardiovascular disease in RA patients exposed to GCs is strongly confounded by indication due to high disease activity [22].

Subsequently, the BARFOT study group (~220 RA patients) examined the long-term effects of early low-dose GC (defined as <7.5 mg/d PDN-eq) in RA patients [13]. The authors found that low-dose GC had no impact on the risk of coronary events or cardiovascular death, while an increased risk for cerebrovascular events was observed, HR 3.7 (1.2–11.4) [13]. Caution is needed before drawing firm conclusions due to the low number of registered events and the fact the medications were not controlled for, after the initial randomization period.

Long-term results of the CAMERA II trial (~218 RA patients) showed a low occurrence of AEs [12]. However, the authors suggested an increased cardiovascular risk for the patients with early RA treated with 10mg/d prednisone for at least 2 years. In addition, a higher number of cardiovascular comorbidities and mortality in the former MTX+PDN group than in MTX-placebo group was found, although not statistically significant. This result is in line with the findings of the BARFOT study.

This cardiovascular safety issue was appreciated in the 2014 reviews [9,10] with converging conclusions. Both reviews highlight the results of an important meta-analysis from 2011, in which 4 out of 6 studies found that low-dose GC (<10 mg/day PDN-eq) was associated with major CV events, particularly stroke (OR 4.36 (1.60–11.90)) [23]. No association was found regarding atherosclerosis and high blood pressure, while a protective effect on the serum lipid profile was suggested.

Overall, we conclude that low-dose GC therapy is relatively safe from the CV point of view although caution is advised in high-risk patients, especially concerning cerebrovascular events.

3.2.2. Health-care utilization and costs

Recently, Spivey *et al.* examined treatment patterns and associated burden of GC utilization before initiation of biologic DMARDs among RA patients [24]. This retrospective study (with ~25,540 RA patients, 41% GC users) showed that GC users compared to non-users had greater health-care utilization and costs prior to initiating biologic DMARDS. The authors speculate that health-care providers and RA patients who use GC, particularly for a longer time and/or at recommended lower dosages, may be hesitant to disrupt a stable treatment regimen by initiating biologic DMARDs [24]. This observational study has several methodological limitations, such as lack of controlling for confounders, data concerning disease activity and duration, and/or patient background factors, among others. Further, there is a lack of systematic evaluation of AEs as these were determined based on the patients' claims database.

In summary, these methodological issues hinder appropriate interpretation of the results. Issues around economic costs and burden surely need better robust studies.

3.2.3. Bone mineral density and fracture risk

Data concerning low-dose GC side effects on bone mineral density (BMD) and risk of fractures are scarce. In 2014, Okano *et al.* assessed, retrospectively, the effects of biologics, bisphosphonates (alendronate or risedronate 35 mg/week) and GC on BMD and bone metabolism markers, in 219 RA patients [25]. Patients (n = 79) receiving GCs without bisphosphonates showed a significant decrease in BMD of the total hip ($p < 0.01$) compared with patients not receiving GC or receiving GC with bisphosphonates [25]. However, co-treatment was not constant (i.e., there were variations in methotrexate and GC doses), an important limitation of this study.

An interesting meta-analysis published in 2016 provided data on 1-year GC-associated bone loss across GC-treated patients with chronic inflammatory diseases (low-dose) and transplants (high-dose) [26]. The authors concluded that in chronic inflammatory diseases, bone loss appears limited and most likely manageable if current antiosteoporotic strategies are implemented [26]. Further, within the two groups, bone loss was not related to GC dose. This study was not integrated in our analysis because the populations studied included several chronic inflammatory diseases and it had no unexposed control group.

In 2018, Cheng *et al.* retrospectively assessed the effect of low-dose GC (defined here as 2.5–7.5 mg/d PDN-eq) on BMD and fractures, in 425 RA patients (340 with low-dose GC – study group – *versus* 85 who never used GC – control group) [27]. Patients receiving GCs had a significantly lower vertebral BMD (LS1–4) (g/cm2) (0.85 (0.20) *versus* 0.9 (0.20), $p = 0.05$) in the control group. The 10-year probabilities of major fractures according to FRAX® were higher in the low-dose GC group (14.0 *versus* 8.0, $p < 0.0001$) [27].Several limitations can be found in this study that may bias the results. Fractures were narrated by a self-reported questionnaire, and a large proportion of the patients were receiving medications to reduce the fracture risk, which may impair the assessment of the association between fractures and GCs in this population.

In summary, there is considerable heterogeneity among the above-mentioned observational studies, which is mainly attributed to different GC doses, cumulative exposure, time-varying exposure, comedication, comorbidity, and the inherent bias by indication. The effects on GCs upon bone mineral density and fracture risk were assessed by both 2014 reviews [9,10]. Based on published RCTs, Santiago and Da Silva concluded that RCTs were either too small or too short in duration to allow definitive conclusions. Based on observational studies [10], the opinion was that very-low-dose exposure appears not to be associated with an increased risk of osteoporosis.

In summary, on the basis of the literature review, our main conclusion is that evidence suggests very limited risk regarding the effects of low dose GC on bone remains limited in both quality and quantity.

3.2.4. Infections

In 2011, Dixon *et al.* published a meta-analysis about the association between systemic GC treatment and the risk of infection in patients with RA [28]. The authors compiled data from 21 RCTs (1026 GC-treated patients with RA) and 42 observational studies. The estimated relative risk (RR) of infection associated with GC treatment differed significantly between the RCTs (RR 0.97 (0.69–1.36)) and the observational studies (RR 1.67 (1.49–1.87)).

Regarding, the risk of hepatitis B virus (HBV) reactivation as a result of GC, observational studies suggest that high dose GC treatment is strongly correlated with HBV reactivation [29,30].

Yan et al. [31] addressed this issue in a retrospective cohort study of ~2200 RA patients and HBV, identified from the National Health Insurance Research Database (1991 to 2011, in Taiwan) (please see Table 1). Treatment with prednisone <20mg/d for ≥3 months or equivalent did not increase liver-related mortality rate. Patients who received ≥20mg/d had the lowest mortality rate among four groups (no GC; GC <20 mg for ≥3 months; GC ≥20mg/day for 3 days; GC pulse treatment). The authors suggested that the most Taiwanese rheumatologists were aware of the need to prescribe prophylactic or preemptive antiviral agents for HBsAg-positive RA patients before or during high-dose GC. Overall, data from this study suggest that prescribing a long-term low-dose GC along with DMARDs for inactive HBV RA patients is safe.

In addition, large observational studies have suggested that low-dose GCs increase the risk of hospitalized infectious events. Although the definition of low and high dose varies between studies [32–34].

Recently, a retrospective study evaluated the impact of oral GC dose on rates of hospitalized infectious events among RA patients newly exposed to tumor necrosis factor inhibitor (TNFi) treatment [35]. A total of 40,933 patients were identified (mean age 53.0 years) from the data of the MarketScan claims database, between 2005 and 2014. Adult RA patients newly exposed to TNFi treatment were identified and assigned to three cohorts: no GC, low-dose GC (≤7.5 mg), and high-dose GC (>7.5 mg). The incidence rate (IR) was 3.9 (3.63–4.13) for no GC; 6.4 (5.68–7.16) for low-dose GC; and 13.3 (11.9–15.5) for high-dose GC. The adjusted rate ratio for variables was for low-dose GC vs no GC was 1.4 (1.19–1.58), for high-dose GC vs no GC was 2.8 (2.30–3.31), and for high-dose GC vs low-dose GC was 2.0 (1.65–2.44). Rates of HIEs were lowest for RA patients on no GC. The risk of hospitalized infectious events increased with increasing age, but did not increase with longer exposure to GCs. Glucocorticoids, regardless of the dose, significantly increased the risk of hospitalized infectious events among RA patients newly initiating TNFi treatment. The interpretation of these results is limited because of the absence of data concerning disease severity/activity and GC tapering.

This issue was approached in both 2014 reviews [9,10] again with conflicting results. On the one hand, none of the RCTs found an increasing incidence of any kind of infections over the 1–2 years of follow-up. On the other hand, observational studies showed a trend towards higher infection rates, which may be affected by disease severity and indication bias.

In summary, the association between low-dose GC and increased risk of severe infections is not resolved, and will probably remain unclear until powerful RCTs are conducted to clarify this issue.

3.2.5. Diabetes mellitus

Hyperglycemia and insulin resistance are well-recognized GC-AEs, although studies regarding whether and to what extent oral GC treatment lead to the development of diabetes mellitus are less clear. Importantly, no studies consider the impact of dosage, duration, and timing of GC use in the risk of diabetes mellitus.

A retrospective study including ~22,000 UK and ~12,700 US patients showed a HR for DM of 1.30 (1.17–1.45) and 1.61 (1.37–1.89) in current GC users compared to nonusers in the UK primary care database and in the US National Data Bank for Rheumatic Diseases, respectively [18]. Both cohorts showed that current use of GC at 5mg/day prednisone equivalent was not associated with a significantly increased risk of diabetes. The authors concluded that only GC doses taken within the preceding 6 months are associated with the current risk of diabetes mellitus. Risk increases with dose: each 5 mg increase of current oral GCs was associated with a 25–30% increased risk of diabetes [18].

Also, in a study based in a large database (National Data Bank for Rheumatic Diseases, ~13,670 patients with RA), the incidence of diabetes mellitus was found to be increased in association with GCs: adjusted HR for diabetes was 1.31 (1.15 to 1.49) [36].

Considering the dose-related diabetogenic effect, 2 different short-term treatment of GC (one week of 30 and 60 mg/d PDN-eq) were tested in 41 patients with high disease activity [37]. Despite an increase of impaired glucose tolerance and in the number of patients progressing to diabetes, this effect was found to be reversible after 1 week. In addition, several patients who were prediabetic at baseline actually normalized their glucose tolerance during the week of GC treatment. These findings suggest active RA is a diabetogenic factor, and that there is a balance in the diabetogenic and the anti-inflammatory effects of GC therapy in early active RA patients, making short-term exposure to high-dose prednisone a safe treatment option, from a metabolic view [37]. Both reviews from 2014 have addressed this issue [9,10]. In the seven RCTs reviewed, there were no relevant differences in the number of

cases of new-onset diabetes. In the review by Hwang and Saag [10], the authors concluded that the development of new-onset diabetes after starting low-dose GC treatment is rare, but the progression of preceding glucose intolerance to diabetes is more common. Contrary to these reviews, the observational studies published by Movahedi et al. [18] and Ozen et al. [36] suggest that GC increases the risk of diabetes. Caution is certainly warranted in this respect until the issue if fully resolved.

3.2.6. Adrenal insufficiency

Whether adrenal insufficiency is a clinically significant problem during long-term low-dose GC treatment remains unclear. In 2016, a systematic review found adrenal insufficiency to range between 0% and 100% (median 37.4%) in systemic GC treated patients [38]. This was particularly true at <5mg/day PDN-eq or cumulative dose <0.5 g, <4 weeks of exposure and following tapered withdrawal. However, the included studies were small, with heterogeneous methodologies and results too divergent to draw firm conclusions [38].

Later, an interesting study has shown that 20 out 42 48% (33–62%) RA patients treated with 5mg/d PDN-eq for a minimum of 6 months had an insufficient adrenal response to the Synacthen test [39]. This suggests that significant adrenal insufficiency occurs not only after GC withdrawal but also during ongoing low-dose treatment [39]. The clinical relevance of these findings is unclear. Further, Synacthen test does not fully reveal the response of the hypothalamo-hypophyseal axis, and a normal test does not exclude a risk of adrenal insufficiency [40].

4. Future?

In each of the adverse events sections described above, we have highlighted the recent evidence about the safety of GCs, essentially low-dose, based mainly on observational studies. As noted, these studies have major limitations that obscure the interpretation of the results. These methodological issues include the confounding/bias by indication: in brief, patients with higher disease activity are more likely to be treated with GC and also more likely to experience AEs that are associated both with the medication and with the disease itself [41]. The actual origin of these negative events cannot be precisely ascertained, but they tend only to be attributed to GC treatment. Thus, we can conclude that the safety of GCs, essentially low-dose, remains widely discussed but inadequately studied.

Hopefully, in the near future, we will have robust data with two ongoing large prospective pragmatic investigator´s initiative trials (CORRA and GLORIA). The evaluation and monitoring of AEs are not clearly specified in the protocol of the 'Comparison of the efficacy and safety of two starting doses of prednisolone in early active rheumatoid arthritis' (CORRA) trial [42]. This trial is focused on 3-month bridging strategies (GC high and low dose) compared to placebo. On the other hand, the 'Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis' (GLORIA) was designed specifically to consider GCs' AEs in the elderly (65+ years) treated with 5 mg prednisolone or placebo for two years [43]. Safety will be fully evaluated according to GCP standards, including spontaneous reports, and a 57-item symptom list completed by the patients at the beginning and the end of the study [44].

We expect that the results of these studies will result in a substantial revision of the existing guidelines on RA treatment.

Meanwhile, adherence to recommendations on standardized methodologies for the registration and report of GC-AEs must be fulfilled [7,45].

In 2016, EULAR published updated recommendations for RA management [46]. Here the authors defend their use as a 'bridging therapy', whenever DMARDs need adjustment. As in its previous version, it is recommended that GCs should be used for as short time as possible. However, in the 2016 update, the 6-month maximum period of exposure was replaced by the expression 'as rapidly as clinically feasible', suggesting a change of awareness towards a more acceptable safety profile of low-dose GC [46].

Later, a multidisciplinary EULAR Task Force specified conditions where long-term GCs have an acceptably low risk of harm in the treatment of chronic inflammatory rheumatic diseases [6]. Another important aspect conveyed by this task force was the concept that the risk of GC-associated harm depends on a combination of individual risk factors (age, comorbidities, smoking status, osteoporosis, and cardiovascular risk factors), drug-specific characteristics (dose, duration), and/or preventive measures (vaccination status, weight lost, exercise, sufficient vitamin D/calcium intake) [6]. The risk of harm conveyed by long-term GC treatment is dose-dependent with dosages of ≤5 mg/day giving an acceptably low risk level in almost every patient (with the exception of patients at high CV risk). At >10mg/day the risk is elevated. This report also states that patient-specific parameters (healthier lifestyle, early diagnosis, low disease activity, low cumulative GC dosage, monitoring and treatment of additional risk factors and comorbidities) clearly modify the actual risk of harm and that these need consideration when evaluating actual and future benefit–risk balance of long-term GC treatment, especially at dosages between >5 and ≤10 mg/day [6].

5. Conclusion

Overall, the conclusions concerning the safety of low-dose GC treatment in RA in 2018 are approximately the same as those of 2014 [9,10]. We maintain those conclusions, i.e., evidence based on RCTs indicate that the toxicity of low-dose GC dose in RA used for 2 years is mild and not statistically different from placebo [9]. The RCTs published are still scarce, with insufficient dimension and duration and with a limited assessment of adverse events.

Regarding our update on observational studies, this indicates a trend towards higher cardiovascular risk, higher risk of infections, higher risk of diabetes, and higher mortality among RA patients taking GCs even at low doses [16–19,36,47]. Interpretation of these results must be cautious due to the numerous methodological issues inherent to their observational nature. Moreover, observational studies are often of lower quality: high risk of bias (especially confounding by

indication), poor documentation of GC exposure and differing models of risk attribution. Consequently, results can be contradictory and their interpretation is sometimes biased.

Hopefully, in the near future, we will have more robust data about GC safety based on randomized clinical trials such as GLORIA [42,43].

Until then, we should abstain from giving strong and wrong advice based on weak observational data [48]. We should adhere to evidence-based recommendations for patient education, monitoring, and prevention of GC-related AEs and consensus on specific conditions of long-term GC treatment. These represent crucial steps towards a better ability to reduce the GC-related AEs in RA and optimize their use for the benefit of patients.

6. Expert opinion

Although constantly 'accused' of numerous and serious adverse events, GCs remain a pillar in the treatment of RA. Regarding the safety of low-dose GC, there is no strong scientific evidence of their harm, as the published literature remains limited both in quantity and quality.

We did not identify any new RCT published since our 2014 review. Two randomized pragmatic clinical trials are currently ongoing [42,43]. On the other hand, observational studies continue to pile up. They have considerable limitations when compared to RCTs, but also some advantages, namely larger number of participants, closer proximity to real-life use of medications and longer follow-up. Although their conclusions need to be interpreted with caution, they suggest, overall, that the main adverse events (infection, cardiovascular risk, infection, and diabetes) are relatively rare with low-dose GC, across different types of 'real-life' RA populations.

GC harm depends on drug-specific (i.e., type, dose, and duration) and patient-specific aspects (i.e., individual risk factors and/or preventive measures). Both aspects should be considered, discussed and optimized with patients before and during GC treatment is started [6].

When referring to long-term low-dose GC treatment, the potential advantages of using GC cumulative dose instead of daily dose deserve consideration. However, the use of GC cumulative dose carries an almost inevitable loss of precision and practicality due mainly to daily dose modifications through time, because of disease activity, surgical or infectious complications or occurrence of adverse events and adherence. Also, this would only be relevant in a very long term (years), which decreases the likelihood of it being considered in RCTs due to financial and ethical issues.

There is an urgent need for a large and long-lasting RCT on low-dose GC in RA with appropriate standardization in the definition and monitoring of AEs. Some limitations/barriers can be anticipated: 1) RCTs are quite expensive, making long follow-up periods hard to accomplish; 2) RCTs are generally designed and powered for benefit; 3) pragmatic, i.e. their eligibility criteria need to be non-restrictive, or the results will be less relevant for patients in real life practice; 4) patients frequently set their GC dose according to their complaints, even against medical advice; 5) use of co-interventions for the treatment of RA add to confounding; 6) certain GC-related AEs are difficult to standardize in terms of screening and diagnosis (such as, GC-induced skin atrophy, vascular fragility or cushingoid appearance, and others).

In practice, clinicians need to standardize questionnaires and define GC-specific core outcome parameters, including safety [6]. Certainly, this will provide better monitoring and reporting as well as quantification and communication of the GC-adverse events within rheumatologists and in clinical studies. Also, this could allow us to predict or identify patients at a higher risk of developing GC-related AEs.

An interesting attempt to standardize and quantify GC AEs was performed by Miloslavsky et al. with the proposal of the Glucocorticoid Toxicity Index [49]. The real value of this index for assessment of GC toxicity is still unknown, awaiting publications on its use in (research) practice.

Until then, we should all keep Jones' advice in mind when prescribing low-dose GC: 'Medication risk must be balanced with benefit, not fear' [50].

Funding

This paper was not funded.

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

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Tânia Santiago http://orcid.org/0000-0002-1562-4022

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Kirwan JR1, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007;1:CD006356.
2. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum. 2005;52(11):3360–3370.
3. Bakker MF, Jacobs JW, Welsing PM, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012;156(5):329–339.
4. Montecucco C, Todoerti M, Sakellariou G, et al. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther. 2012;14(3):R112.
5. Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65(3):285–293.
6. Strehl C, Bijlsma JW, de Wit M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of

harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis. 2016;75(6):952–957.
• **EULARrecommendations regarding specified conditions where long-term GCs have an acceptably low risk of harm in the set of chronic inflammatory rheumatic diseases.**
7. van der Goes MC, Jacobs JW, Boers M, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. Ann Rheum Dis. 2010;69(11):1913–1919.
8. Santiago T, Jacobs JW, Saag KG, et al. Balancing the benefits and risks of low-dose glucocorticoid in rheumatoid arthritis. Acta Reumatol Port. 2015;40(1):10–22.
9. Santiago T, Da Silva JA. Safety of glucocorticoids in rheumatoid arthritis: evidence from recent clinical trials. Neuroimmunomodulation. 2015;22(1–2):57–65.
•• **Systematic Review of low-dose GC AEs RCTs.**
10. Hwang YG, Saag K. The safety of low-dose glucocorticoids in rheumatic diseases: results from observational studies. Neuroimmunomodulation. 2015;22(1–2):72–82.
•• **Review of low-dose GC AEs observational studies.**
11. de Jong PH, Hazes JM, Han HK, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis. 2014;73(7):1331–1339.
12. Safy M, Jacobs J, IJff ND, et al. Long-term outcome is better when a methotrexate-based treatment strategy is combined with 10 mg prednisone daily: follow-up after the second computer-assisted management in early rheumatoid arthritis trial. Ann Rheum Dis. 2017;76(8):1432–1435.
13. Ajeganova S, Svensson B, Hafström I, et al. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. BMJ Open. 2014;4(4):e004259.
14. Siu S, Haraoui B, Bissonnette R, et al. Meta-analysis of tumor necrosis factor inhibitors and glucocorticoids on bone density in rheumatoid arthritis and ankylosing spondylitis trials. Arthritis Care Res (Hoboken). 2015;67(6):754–764.
15. Black RJ, Hill CL, Lester S, et al. The association between systemic glucocorticoid use and the risk of cataract and glaucoma in patients with rheumatoid arthritis: a systematic review and meta-analysis. PLoS One. 2016;11(11):e0166468.
16. Listing J, Kekow J, Manger B, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis. 2015;74(2):415–421.
17. Roubille C, Rincheval N, Dougados M, et al. Seven-year tolerability profile of glucocorticoids use in early rheumatoid arthritis: data from the ESPOIR cohort. Ann Rheum Dis. 2017;76(11):1797–1802.
18. Movahedi M, Beauchamp ME, Abrahamowicz M, et al. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2016;68(5):1089–1098.
19. Del Rincón I, Battafarano DF, Restrepo JF, et al. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol. 2014;66(2):264–272.
20. Best JH, Kong AM, Lenhart GM, et al. Association between glucocorticoid exposure and healthcare expenditures for potential glucocorticoid-related adverse events in patients with rheumatoid arthritis. J Rheumatol. 2018;45(3):320–328.
21. Jacobs JWG, Pereira DA, Silva JA. Glucocorticoids are always under suspicion - is the perception of their risks unbiased? J Rheumatol. 2018;45(3):293–296.
22. van Sijl AM, Boers M, Voskuyl AE, et al. Confounding by indication probably distorts the relationship between steroid use and cardiovascular disease in rheumatoid arthritis: results from a prospective cohort study. PLoS One. 2014;9(1):e87965.
23. Ruyssen-Witrand A, Fautrel B, Saraux A, et al. Cardiovascular risk induced by low-dose corticosteroids in rheumatoid arthritis: a systematic literature review. Joint Bone Spine. 2011;78(1):23–30.
24. Spivey CA, Griffith J, Kaplan C, et al. A retrospective analysis of corticosteroid utilization before initiation of biologic DMARDs among patients with rheumatoid arthritis in the United States. Rheumatol Ther. 2018;5(1):255–270.
25. Okano T. [Bone metabolism and cardiovascular function update. Role of vitamin D in the bone and vascular intercommunication]. Clin Calcium. 2014;24(7):45–52.
26. Lems WF, Baak MM, van Tuyl LH, et al. One-year effects of glucocorticoids on bone density: a meta-analysis in cohorts on high and low-dose therapy. RMD Open. 2016;2(2):e000313.
27. Cheng TT, Lai HM, Yu SF, et al. The impact of low-dose glucocorticoids on disease activity, bone mineral density, fragility fractures, and 10-year probability of fractures in patients with rheumatoid arthritis. J Investig Med. 2018;66(6):1004–1007.
28. Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. Arthritis Res Ther. 2011;13(4):R139.
29. Cheng J, Li JB, Sun QL, et al. Reactivation of hepatitis B virus after steroid treatment in rheumatic diseases. J Rheumatol. 2011;38(1):181–182.
30. Xuan D, Yu Y, Shao L, et al. Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy – a report of long-term follow-up of serial cases and literature review. Clin Rheumatol. 2014;33(4):577–586.
31. Yang SS, Hung CT, Li SF, et al. Hepatitis B virus-related mortality in rheumatoid arthritis patients undergoing long-term low-dose glucocorticoid treatment: A population-based study. J Formos Med Assoc. 2018;117(7):566–571.
32. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford). 2010;49(1):82–90.
33. Curtis JR, Yang S, Patkar NM, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(7):990–997.
34. Atzeni F, Sarzi-Puttini P, Botsios C, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev. 2012;12(2):225–229.
35. Schenfeld J, Iles J, Trivedi M, et al. Dose relationship between oral glucocorticoids and tumor necrosis factor inhibitors and the risk of hospitalized infectious events among patients with rheumatoid arthritis. Rheumatol Int. 2017;37(7):1075–1082.
36. Ozen G, Pedro S, Holmqvist ME, et al. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. Ann Rheum Dis. 2017;76(5):848–854.
37. Den Uyl D, van Raalte DH, Nurmohamed MT, et al. Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: balance between diabetogenic effects and inflammation reduction. Arthritis Rheum. 2012;64(3):639–646.
38. Joseph RM, Hunter AL, Ray DW, et al. Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Semin Arthritis Rheum. 2016;46(1):133–141.
39. Borresen SW, Klose M, Baslund B, et al. Adrenal insufficiency is seen in more than one-third of patients during ongoing low-dose prednisolone treatment for rheumatoid arthritis. Eur J Endocrinol. 2017;177(4):287–295.
40. Klose M, Lange M, Rasmussen AK, et al. Factors influencing the adrenocorticotropin test: role of contemporary cortisol assays, body composition, and oral contraceptive agents. J Clin Endocrinol Metab. 2007;92(4):1326–1333.
41. Buttgereit F, Bijlsma JW. Glucocorticoids in rheumatoid arthritis: the picture is shaping up. Ann Rheum Dis. 2017;76(11):1785–1787.
• **A critical and bright editorial regarding the risk of bias by indication and the problem of attribution of certain events to GC in the context of chronic inflammatory diseases.**
42. Trampisch US, Krause D, Trampisch HJ, et al. Comparison of the efficacy and safety of two starting dosages of prednisolone in early

active rheumatoid arthritis (CORRA): study protocol for a randomized controlled trial. Trials. 2014;15:344.
43. Hartman L, Rasch LA, Klausch T, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. Trials. 2018;19 (1):67.
44. Pincus T. Electronic multidimensional health assessment questionnaire (eMDHAQ): past, present and future of a proposed single data management system for clinical care, research, quality improvement, and monitoring of long-term outcomes. Clin Exp Rheumatol. 2016;34(5 Suppl 101):S17–S33.
45. Duru N, van der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2013;72(12):1905–1913.
- **EULAR recommendations on the managing of GC in chronic inflammatory rheumatic diseases.**
46. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3–15.
47. Richter A, Listing J, Schneider M, et al. Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(9):1667–1673.
48. Boers M. Observational studies on glucocorticoids are harmful! Lupus Sci Med. 2017;4(1):e000219.
49. Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a glucocorticoid toxicity index (GTI) using multicriteria decision analysis. Ann Rheum Dis. 2017;76(3):543–546.
50. Jones KW. Medication risk must be balanced with benefit, not fear. Ann Pharmacother. 2010;44(4):737–739.