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Running head: Glucocorticoids in the treatment of RA

The "official view" on glucocorticoids in rheumatoid arthritis. A systematic review of international guidelines and consensus statements

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ABSTRACT

Objective. To describe the perception on the current role of systemic glucocorticoids (GC) in the management of rheumatoid arthritis (RA) by examining their importance and the current level of evidence in recent guidelines, and to identify open questions to be addressed in future guidelines and research projects.

Methods. Systematic literature review using the databases PubMed, EMBASE and Cochrane for guidelines on the pharmacological treatment of RA. Retrieved articles were evaluated regarding their quality using the AGREE II tool and scrutinized for all relevant information concerning the use of GC.

Results. All guidelines agree that GC, especially if given at low dosages and for a short duration, are an appropriate option in the treatment of RA. However, many recommendations remain vague as reliable and detailed evidence is scarce. Important aspects of GC therapy are partially or completely neglected, and the existing nomenclature is not used uniformly. Quality evaluation revealed flaws in many articles, concerning not only GC specific recommendations but also guideline quality in general.

Conclusion. Current recommendations for use of GC in the management of RA are suboptimal. More rigorous evaluation of dosages, timing and duration of their use is needed. Existing nomenclature on glucocorticoid therapy should be used uniformly.

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SIGNIFICANCE AND INNOVATIONS

- There is general agreement that glucocorticoids are an important element of RA therapy, but recent recommendations lack evidence and guidance on dosages, timing and duration of their use.
- Existing nomenclature describing the use of glucocorticoids is not uniformly used, which may lead to uncertainty in interpretation and implementation of recommendations.
- High-quality studies examining glucocorticoids in RA are urgently needed, especially with regard to long-term benefit:risk ratio, optimal treatment duration and tapering strategies.

Rheumatoid arthritis (RA) is a chronic, disabling disease that poses a heavy burden on both affected patients and the society, causing annual societal costs of more than €45 billion for Europe alone (1). About one third of the patients suffer from such severe symptoms that they are unable to work (2). The life expectancy of patients with persistent high disease activity (DAS28 Score of > 5.1) is about 11 years less than the general population (3). Optimal management is thus a crucial issue.

Guidelines suggest that RA should initially be treated with synthetic disease-modifying anti-rheumatic drugs (DMARDs) in combination with glucocorticoids (GC) (4, 5). If the treatment target of remission or at least low disease activity with preserved function is not reached within 3–6 months, another synthetic or a biologic DMARD should be tried with or without concomitant GC therapy (4, 5). These recommendations underline the importance of GC and reflect convincing evidence for their beneficial effects (5).

However, there is also a high awareness of GC-associated adverse effects, especially when used at high doses for prolonged periods. Osteoporosis, diabetes mellitus, cardiovascular diseases, infections, weight gain and myopathy were among the most worrisome adverse effects mentioned in one survey by both patients and rheumatologists (6).

Despite over 60 years of use, the medical community has been inept at producing a solid evidence base for the proper application of GC therapy. Therefore, it is an important and timely task to achieve consensus on specific conditions and circumstances for which GC provide a positive benefit:risk ratio. One way is to assemble multidisciplinary task force groups of experts including patients with rheumatic diseases in order to elaborate recommendations based on existing and critically reviewed evidence, as recently completed for RA (5). Another approach is

to review current clinical practice guidelines. We have taken this approach to systematically examine the current role of systemic GC in the treatment of RA as described in recent international guidelines and consensus statements.

MATERIALS AND METHODS

Systematic literature search

A systematic search strategy was developed to identify all relevant publications. A detailed description of the search process, including the exact search strings for each database, a list of all scanned websites and precise eligibility criteria, is provided in the **Supplementary Material**.

Eligibility criteria

Articles published between January 1, 2011 and December 31, 2015 were included in this review if they were guidelines or consensus statements containing specific recommendations for the systemic pharmacological treatment of RA. For ease of readability, in this report the term “guideline” is used for both guidelines and consensus statements without differentiating between them. Corresponding to the language skills of the team, the search includes articles in English, French, German and Spanish. Articles were not considered if they excluded GC a priori, e.g. because they focused exclusively on the treatment with one specific drug. The intraarticular administration of GC, although undoubtedly important in the management of RA, is not covered by this review.

Search strategy

The Ovid EMBASE, PubMed MEDLINE and Cochrane Library databases were searched for relevant titles. **Supplementary Table 1 and Supplementary Box 1** present the exact search terms for each database. All articles retrieved by this search were screened independently by two authors for eligibility, and discrepancies were resolved by consensus.

Additionally, we conducted an extensive manual search for additional relevant literature according to the same inclusion criteria as specified above. This search included screening of the reference lists of included articles and an online search of relevant websites such as guideline clearinghouses and websites of rheumatology associations.

Quality appraisal

The AGREE II instrument, an internationally acknowledged state-of-the-art tool for the evaluation of quality and reporting of practice guidelines, was used to assess the quality of the included guidelines (7). AGREE II comprises 23 items in six domains (1. Scope and Purpose, 2. Stakeholder Involvement, 3. Rigour of Development, 4. Clarity of presentation, 5. Applicability, 6. Editorial Independence), each rated on a scale from 1 (lowest possible quality) to 7 (exceptionally good quality). Subsequently, the separate ratings are summed up to calculate one score for each domain, as well as an overall score for each guideline, both of which are provided as percentages of the maximum attainable score.

As recommended by AGREE II, the appraisal was conducted independently by two authors, whose ratings were calculated into a mean final score to minimize

subjectivity and to reduce the risk of systematic bias. Guidelines with a total score of < 40% were excluded from this review.

Data extraction

Data were extracted using pre-defined data extraction sheets. Separate tables were used to extract information concerning general information on the guidelines, the actual recommendations and the evidence supporting them, all provided parameters detailing the recommended GC therapy, and research agenda or points stated to lack sufficient evidence.

RESULTS

Search results

A total of 3742 articles were retrieved by the systematic search of literature databases, of which 15 were considered eligible for the final review. The manual search yielded 4 additional publications (8-11). Of these 19 articles, 4 were excluded due to insufficient quality after quality appraisal (11-14). Notably, all excluded guidelines had an AGREE II score of 30% or lower and also scored worst in “Rigour of Development”, considered the most important single domain by experts from the ADAPTE Collaboration (15). Finally, 15 guidelines were included for detailed analysis.

An overview of the search process is presented in **Figure 1**.

Characteristics of included guidelines

The included guidelines were developed by 13 different rheumatology associations and guideline networks from 5 continents; none was written by other individual working groups. From two associations, two guidelines each were included because they were developed by different authors for different purposes (8, 10, 16, 17).

Five of the included articles are based on systematic literature reviews specifically conducted for the development of the respective guideline (4, 8-10, 18). Six guidelines (16, 17, 19-22) are regional adaptations of a single other recommendation paper, mostly from EULAR (16, 17, 19-21), which have often been complemented by update or additional literature searches. In two cases, the ADAPTE framework was used to create a synthesis of existing guidelines (23, 24), whereas the remaining two do not specifically describe the provenance of the underlying evidence (25, 26). All included guidelines contain a list of references.

A summary of general information on the included guidelines can be found in **Supplementary Table 3.**

AGREE II ratings

The total scores of included guidelines ranged from 85% [Canada 2012; reference (24)] to 41% [Hong Kong 2011; reference (19)] with an average of 63% **(Supplementary Figure 1)**. Concerning the separate domains, the best average score was achieved in “Clarity of Presentation” (84%), whereas “Applicability” (50%) and “Editorial Independence” (52%) received the worst ratings **(Supplementary Figures 2-7)**. Comparison of the total ratings of both authors revealed that one author tended to interpret the single items slightly more strictly than the other, resulting in a mean difference of total scores of 5%. However, the final rankings

were almost identical, and no guideline ranked more than one position different in the ratings of one author compared to the other author.

Recommendations for the glucocorticoid treatment of rheumatoid arthritis

All included guidelines address the use of GC for the management of RA. Thirteen articles provide a separate paragraph for GC; one does not contain any drug-specific paragraphs at all (19), and another includes a shared paragraph for GC, analgesics and neuromodulators (22).

Eight of the included guidelines consider the use of GC an appropriate option in certain circumstances, while seven explicitly recommend it for at least one situation. For *early RA*, the majority of guidelines recommend the use of GC generally without further guidance (**Table 1**). For established RA, GC are only recommended for specific situations, mainly flares and as bridging therapy. In guidelines that do not differentiate between early and established RA, GC are most commonly recommended for the initial treatment strategy after the diagnosis of RA and as a bridging therapy.

When referring to the purpose of GC prescription, three guidelines (18, 19, 22) address only short-term goals such as a rapid decrease of inflammation in flares, while eleven also mention long-term goals such as radiological or structural benefits. One paper exclusively addresses the long-term benefits (4). Four articles provide separate recommendations for these different purposes (8-10, 23).

None of the articles considers the timing or frequency of GC administration.

Dosage and administration

All included articles consider the use of low dose GC treatment for the management of RA, either by referring to “low dose” (n=10) or to “the lowest possible dose” (n=5) (**Figure 2A**). Only a small number of articles also recommend moderate or high doses (17, 20, 22, 26). Notably, high doses are only mentioned for the treatment of severe extra-articular manifestations (22, 26).

Particularly noteworthy is that not all guidelines provide the specific GC dosages corresponding to their descriptive terms **(Figure 2B)**. For oral predniso(lo)ne, most of the guidelines providing exact dosages consider ≤ 10 or ≤ 7.5 mg daily as “low” or “the lowest possible” dose, whereas one refers to ≤ 15 mg/d using the same descriptive terms (25). On the other hand, one guideline describes ≤ 10 mg/d as a “low or moderate dose” (20). Only one guideline gives a body weight-dependent recommendation of ≤ 0.15 mg/kg (in this review interpreted as ≤ 10 mg/d for **Figure 2B**) (21). A single guideline suggests an initially “moderately high” dose of 20 mg/d with subsequent tapering as an alternative to starting therapy with “low” doses of < 10 mg/d (8).

Oral use is the most frequently mentioned route of administration, and appears in all ten guidelines that specify the recommended administration method. Four guidelines mention intramuscular administration as an alternative (19, 23, 24, 26), one of which considers it preferable in certain situations as it may facilitate better dosing control (24). One guideline recommends intravenous GC (23), but exclusively for severe extra-articular manifestations. Another guideline suggests a potential advantage of parenteral methylprednisolone in comparison to oral therapy in avoiding weaning difficulties, but does not provide details about the parenteral administration (21).

Tapering and duration

There is a broad consensus that short term treatment with GC is an appropriate option for the management of RA, endorsed by 13 of the 15 included guidelines, while two provide no information about treatment duration at all **(Table 2)**. Six articles provide specific maximum treatment durations ranging from 3 to 24 months, while the others use imprecise descriptions such as “short term” or “shortest possible duration”.

Treatment durations longer than 6 months (i.e. 12-24 months) or referring to longer periods than “short term” (i.e. “medium-term” or “long-term”) are only considered by four guidelines (8, 9, 19, 25). They all provide caveats, and none explicitly recommends prolonged use. One of these guidelines (25) includes recommendations for use of GC for up to 24 months, but underlines that it should be discontinued as soon as possible. Another of these guidelines endorses “long term” GC treatment, but only for strictly defined situations if all other treatment options have been offered before (23). Finally, two publications merely state that prolonged continuation of GC therapy can be used to minimize radiological damage (8, 9) without clarifying if it should therefore be added to the basic treatment strategy.

Information concerning the optimal tapering strategy for GC therapy was scant and rarely provides additional guidance compared to the recommendations on duration. Five of the guidelines do not address tapering at all, and five merely state GC should be tapered as rapidly as possible. Two further articles, which also recommend rapid tapering, provide brief guidance: one advises tapering GC to ≤ 7.5 mg/d within 6 – 12 weeks and then rapidly to the lowest possible dose (17), while the other suggests only tapering GC after persistent remission for 6 months (23).

Three guidelines emphasize the importance of gradual dose reductions (10, 16, 20) or even a very slow tapering strategy (10) in order to avoid clinical recurrence.

As to the order of tapering the different RA medications of patients in persistent remission, five guidelines suggest first tapering GC before considering taper of biologicals and DMARDs (4, 17, 20, 21, 24), while one guideline treats GC and biologicals equally, stating they should both be tapered before DMARDs (25).

Patient specific factors

The examined guidelines contain few considerations of patient specific factors which might require special attention or present (relative) contraindications when deciding upon a GC regimen. Two guidelines explicitly allow the use of GC in pregnancy (10, 26). The possible effects and consequences of concomitantly used medications are only addressed by three guidelines, underlining the importance of gastric protection if GC are co-prescribed with nonsteroidal anti-inflammatory drugs (22, 25, 26). Only one guideline refers explicitly to GC when discussing several RA-associated comorbidities such as cardiological complications (10), and none of the articles contains any age- or sex-specific recommendations.

Open research questions

Eight of the guidelines included in this review state there is still insufficient evidence to provide adequate and confident recommendations for all aspects of GC therapy in RA. This lack of evidence concerns virtually all aspects of GC therapy, although “long-term safety”, “optimal tapering strategy” and “long-term efficacy/benefit” are the most frequently mentioned points **(Table 3)**.

DISCUSSION

This study represents a comprehensive overview of guidelines for the systemic use of GC in RA. We purposely excluded intraarticular administration as it would have required a separate assessment with regard to dosage, frequency, indications and outcomes, making an integrated overview difficult. Both oral and intraarticular GC are frequently used conjointly in individual patients in clinical practice. Clearly, intraarticular injections constitute another important and common way of administering GC and may influence the choice of dosing, duration and tapering of systemic prescription.

There is overall agreement about the potential usefulness of systemic GC for the treatment of RA, especially at low doses and for short durations. All included guidelines address their use and consider GC therapy appropriate for certain situations or disease phases. This is consistent with the widespread use of GC observed in recent studies, which report prescription rates for GC use sometime during the disease course ranging from 33% to as much as 74% (3, 27, 28).

There is increasing “official” recognition of the role of GC therapy in RA, reflected in more recent management guidelines. For example, the American College of Rheumatology (ACR) almost completely ignored GC in their 2012 guidelines update (29), but explicitly addressed their use in the 2015 ACR guidelines (18).

Still, the role of GC in the management of RA continues to be addressed with caution. Indeed, not even half of the articles explicitly recommend their use, even fewer specify the optimal treatment duration, and about one third abstain from providing exact dosage recommendations.

Only four of the included guidelines contain separate recommendations depending on the purpose for which GC are prescribed (8-10, 23). This may be either symptom

driven, for example with the short-term goal of flare management, or for their disease modifying properties. Since these different purposes also require different treatment approaches, recommendations regarding them and assessments of them should be considered separately in clinical practice guidelines. While it seems appropriate to advocate a dose as low and a duration as short as possible to rapidly decrease inflammation, some studies have reported successful use of specific dose ranges and durations for achieving long-term treatment goals. Examples include the COBRA-light regimen (30 mg/d prednisone and 10 mg/wk MTX for 9 weeks with a subsequent tapering of prednisone to 7.5 mg while increasing the MTX dose to 25 mg/wk), and the regimen used in the CAMERA-II trial (10 mg/d prednisone for two years added to a tight control MTX-based treatment strategy) (30, 31).

The dearth of detailed information about the proper use of GC has been commented upon by workers in other diseases such as psoriasis and psoriasis arthritis as well (32). An important reason for this relative neglect is likely the lack of evidence concerning various aspects of GC therapy. Authors of more than half of the guidelines analyzed in this review voiced concern about insufficient data for reliable and well-founded recommendations.

High-quality studies examining GC in RA are urgently needed which examine long-term benefit:risk ratio, optimal treatment duration and tapering strategies. The same issue has recently been addressed by a EULAR task force that aimed to define conditions for which long-term GC treatment has an acceptably low risk of harm (5). Based on the scarce available evidence, this expert group claims a positive benefit:risk ratio for long-term, that is, (3-)6 months or more, GC therapy at dosages of ≤ 5 mg/d prednisone equivalent, recognizing that the risk of harm is increased for the majority of patients at dosages of > 10 mg/d (5).

In addition to these points for which evidence is insufficient, we have identified several other potentially important clinical issues that are not addressed in any of the guidelines. The first of these issues is the timing and frequency of GC administration. The interval between doses of DMARDs and biologic drugs used in the treatment of RA is generally longer than that of GC dosing, and they are overall less affected by endogenous hormonal regulatory circuits. In contrast, the effects of daily GC therapy are highly influenced by their strong dependency on circadian rhythms. Thus, choosing the right administration schedule for GC may have a considerable impact on both efficacy and safety, by minimizing adverse effects on the hypothalamic-pituitary-adrenal axis or by allowing equal symptom control with lower dosages.

The concept of considering timing of GC administration in order to optimize the individual benefit:risk ratio is often referred to as “chronotherapy”. Although several studies have been reporting promising results concerning the potential benefit of chronotherapy for more than 50 years (33-35) and various authors have emphasized its importance (36-38), to date this topic has not been addressed by any of the included guidelines. A rather recent approach to this issue is the use of modified/delayed release prednisone (39), which will be another important point to be considered in future recommendations. The administration frequency, whether once daily or in multiple doses throughout the day, is being addressed in guidelines for other rheumatic diseases (40). It is of equal importance in RA, but remains to be tackled.

A second topic scarcely considered by any guideline to date is the potential influence of patient specific factors on the optimal treatment regimen. This is a significant deficit which should be addressed, since patient specific factors like

comorbidities, co-medications or other (relative) contraindications are of crucial importance in guiding GC therapy in individual patients (5). None of the available guidelines comments specifically on treatment of elderly patients with RA, which is an omission. Both incidence and prevalence of RA increase with age and therefore, elderly patients with RA represent a large segment of the RA population (41). In general, elderly have more comorbidities than young people, and this is even more true for elderly patients with RA. Such patients receive multiple concomitant drugs, which may influence RA treatment choices (42, 43). Also, elderly patients with RA are more likely than younger patients to suffer from GC related adverse effects such as osteoporosis, diabetes or hypertension.

As a third point, it is evident that the term “low dose” is still not uniformly used despite nomenclature suggestions published in 2002 (44). The prednisone dosages mentioned when referring to the term “low dose” range from ≤ 7.5 mg per day (4, 23) to as much as ≤ 15 mg per day (25), causing considerable confusion for the practicing clinician and investigators. For standardization, either the above-cited nomenclature should be uniformly used or, if considered inappropriate, a new nomenclature with sound justification should be developed.

Improvement of RA disease management requires not only critical assessment of the guideline passages referring specifically to GC, but also a general assessment of the respective guideline in which they are embedded. Our quality appraisal revealed several additional flaws in many of the examined articles, an issue already encountered in previous reviews of RA guidelines (45). Among the most neglected domains was “Editorial Independence” with a mean score of only 52%. This could be read to mean bias through external influences, but is more likely a problem of reporting. Specifically, five of the included publications do not state any funding

source, but all were published (and probably funded) by rheumatology associations. Nevertheless, a clear funding statement should always be included. Additionally, two (10, 26) of the five guidelines that received support from pharmaceutical enterprises lack a statement regarding any potential influence of the companies on the content.

"Applicability" was another domain with a poor score. This domain might even be of more immediate appeal to the end user, as it considers items such as the availability of tools to put the recommendations into practice and may be of key importance for the implementation of the guidelines. The potential for guideline implementation to affect practice can be anticipated by a recent observational study conducted in the United Kingdom, which found that 20% of patients with RA in primary care were receiving > 30 mg of prednisone equivalent per day (28), although there are no guidelines supporting such a dosage. As the discrepancy between guideline recommendations and actual practice is likely to be similar for other drugs used in the treatment of RA, the favorable effects of improved implementation would probably not be limited to a better use of GC, but might lead to an improvement of the management of RA in general.

Conclusion and perspective

Although the general usefulness of GC in the treatment of RA is widely acknowledged, there is still a shortage of specific recommendations for GC therapy, largely due to a lack of reliable evidence. New studies are needed to fill the existing gaps in the understanding of the balance between long-term safety and efficacy as well as the optimal tapering strategy and treatment duration. Future guideline updates should address chronotherapy, administration frequency and patient specific factors.

The GLORIA trial (Glucocorticoid Low-dose Outcome in RheumatoId Arthritis, ClinicalTrials.gov Identifier: NCT02585258) is currently underway to evaluate the safety and effectiveness of low dose GC therapy (5 mg/d prednisone for 2 years) versus placebo in 800 elderly patients with RA and might soon provide valuable new evidence.

Similar to other pharmaceutical fields, the field of GC continues to evolve. New formulations of GC are emerging, including modified/delayed release prednisone. Recently, selective GC receptor agonists (SEGRAs) have shown positive results in a phase II clinical trial, promising a reduction of adverse effects while preserving therapeutic activity (46), and liposomal prednisolone is currently being studied in a phase III clinical trial (47). While these developments may have a positive impact on the efficacy / toxicity balance of GC, they will also pose a challenge to guideline developers and clinicians, as more specific recommendations with regard to the different formulations will be needed.

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Tables

Table 1: Indications for glucocorticoids in rheumatoid arthritis

Indication	Number of mentions
Early RA	
Bridging therapy	1
Flares	1
Initial treatment	1
Other	1
Not specified	7
Established RA	
Bridging therapy	2
Flares	1
Other	2
Not specified	
Bridging	7
Flares	2
Initial treatment	7
Severe extra-articular manifestations	3
Other	1

Table 2: Number of guidelines addressing treatment duration

Specific recommendations	
Up to 3 months	1
Up to 6 months	4
Up to 12 – 24 months	1
Descriptive recommendations*	
Shortest possible duration	7
Short term	6
Medium term	2
Long term	3

*terminology mostly as used in respective guideline. Specific recommendations were integrated as “short term” for durations ≤ 6 months and “medium term” for ≤ 24 months. Formulations like “until DMARDs take effect” are listed as “shortest possible duration”.

Table 3: Items of missing evidence

Description	Number of guidelines
Long term safety	5
Optimal tapering strategy	5
Long term efficacy/benefit	4
Optimal duration of GC therapy	3
Other*	3

*points only mentioned by a single guideline, see Supplementary Table 6

Figure legends

Figure 1 Flow chart of search strategy

The Ovid EMBASE, PubMed MEDLINE and Cochrane Library databases were searched for articles published between 01.01.2011 and 31.12.2015. **Supplementary Table 1 and Supplementary Box 1** present the exact search terms for each database. The search was limited to articles published English, French, German and Spanish. Additional articles were retrieved by scanning the reference lists of included articles and by an online search of relevant websites such as guideline clearinghouses and websites of rheumatology associations. Two authors (in the figure identified as Reviewer 1 and Reviewer 2) independently reviewed abstracts and full-text papers selecting relevant articles. Any disagreement between the authors was resolved through discussion.

Figure 2 Dosage recommendations

Included articles were examined concerning their respective dosage recommendations for GC therapy, and the number of guidelines mentioning each dosage were counted. All examined guidelines provide descriptive recommendations, mainly referring to either “low dose” or “lowest possible dose”, whereas only a few guidelines also consider medium to high dosages (2A). Eleven guidelines provide specific recommendations for the maximum GC dosage to be used, ranging from 7.5 to 20 mg per day prednisone equivalent (2B). While

some guidelines differentiate between early and established RA, others remain nonspecific.

Figure 1

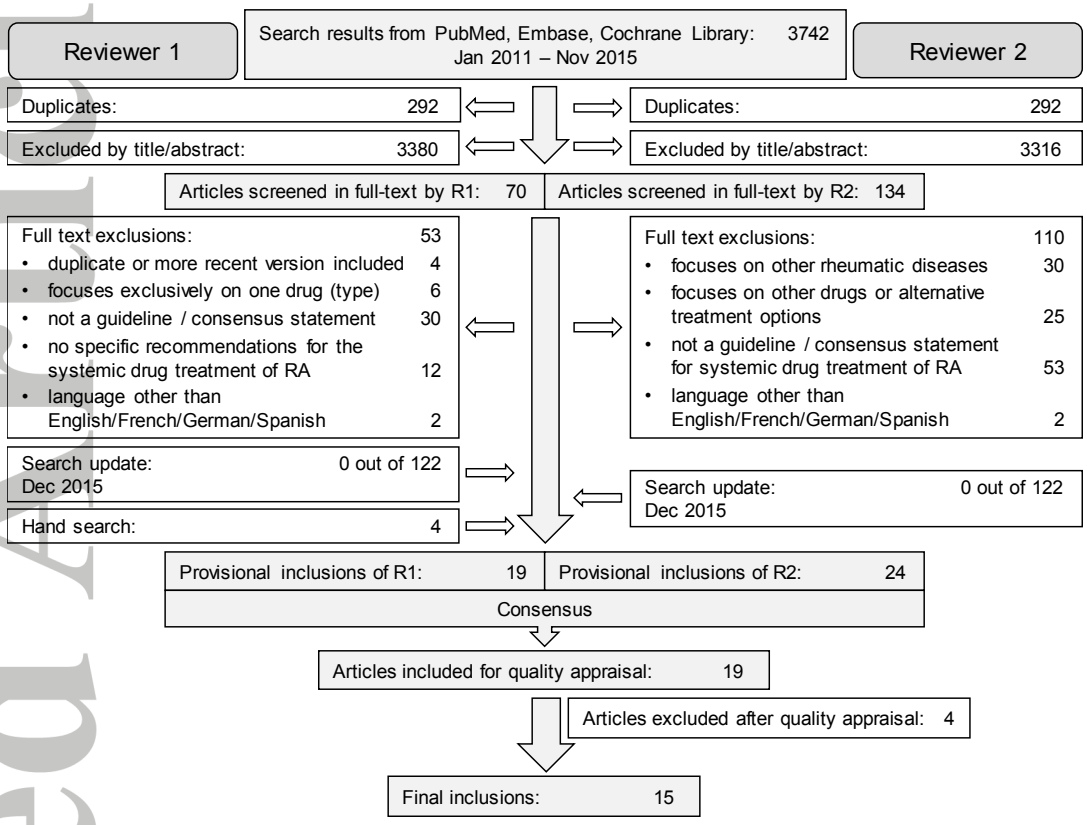
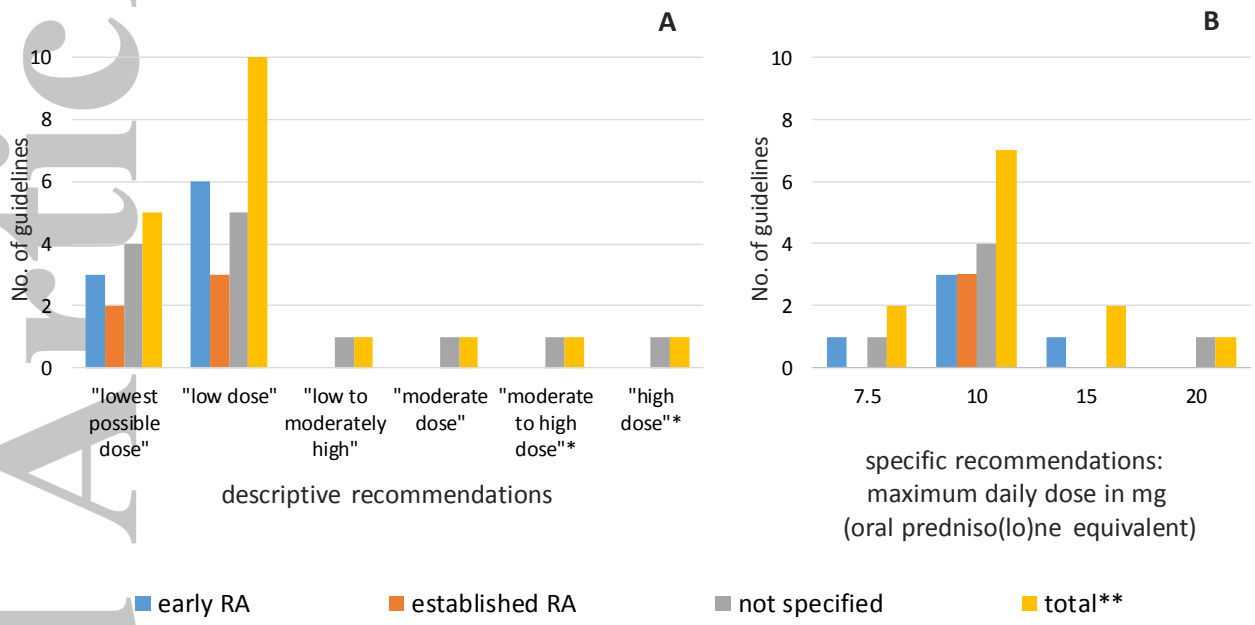


Figure 2



*only for severe extra-articular manifestations
**Note: some guidelines contain recommendations for more than one category
Note: terminology as used in respective guidelines