Glucocorticoids in rheumatoid arthritis: balancing benefits and harm by leveraging the therapeutic window of opportunity

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Abstract

Glucocorticoids have been available since the early 1950s and have since become an integral part of the management of rheumatoid arthritis (RA). Due to their rapid effect, glucocorticoids have an appealing profile for treating flares or as “bridging” agents in early RA. The efficacy of glucocorticoids to treat RA has been well established, both to control disease activity and to delay the progression of joint damage. However, despite their benefits, glucocorticoids have equally well-known adverse effects. It is generally accepted that long-term use of glucocorticoids, particularly at higher doses, is not advisable, and recent guidelines for the management of RA therefore either recommend against the use of glucocorticoids or suggest using them only as bridging therapy. Perceptions on the harmful effects of glucocorticoids remain, mainly based on observational studies. Prolonged glucocorticoid therapy at low doses is still highly prevalent in clinical practice, but recent data suggested a rather favourable risk-benefit balance for this strategy, even in senior patients. Balancing the benefits and risks of treating RA with glucocorticoids thus remains a somewhat controversial topic. Therefore, this narrative review outlines the historical and current position of glucocorticoids in the management of RA, while summarising recent evidence on their beneficial and detrimental effects. Furthermore, practical strategies for the current use and tapering of glucocorticoids in RA were formulated.

Keywords: rheumatoid arthritis, glucocorticoids, tapering, bridging, treat-to-target, window of opportunity

Highlights:

- Using glucocorticoids as bridging therapy for early RA provides important cost-effective benefits, from prompt inflammatory disease control to improvement in several patient-preferred outcomes.
- New prospective data offer nuance on the perceived harmful effects of glucocorticoids that have, until recently, mainly been based on observational studies.
- Clinicians should seek to balance the benefits and risks of treating RA with glucocorticoids, by actively encouraging timely tapering and by aiming for the lowest dose and the shortest duration necessary to achieve inflammatory disease control.

Introduction

Glucocorticoids have been available since the early 1950s and have become an integral part of the management of rheumatoid arthritis (RA)(1). A crucial advantage is their rapid effect, particularly compared to conventional synthetic (cs-) disease-modifying antirheumatic drugs (DMARDs) like methotrexate. Consequently, glucocorticoids have an appealing profile for treating flares or as "bridging" agents in early RA pending the effect of csDMARDs, a strategy that has seen widespread use since the COBRA trial was published in 1997(2).

The efficacy of glucocorticoids to treat RA is well-established, both to control disease activity and to delay the progression of joint damage(3,4). However, despite their benefits, glucocorticoids have equally well-known adverse effects, including hyperglycaemia, osteoporosis, cataract, infections and cardiovascular events(5). These adverse effects have long shaped the perception on glucocorticoids in RA, particularly since biologic (b-) and targeted synthetic (ts-) DMARDs have become available as treatment options. It is generally accepted that long-term use of glucocorticoids, particularly at higher doses, is not advisable, and recent guidelines for the management of RA therefore either recommend against the use of glucocorticoids(6) or suggest using them only as bridging therapy(7).

Perceptions on the harmful effects of glucocorticoids remain, mainly based on observational studies(8). Prolonged glucocorticoid therapy at low doses is still highly prevalent in clinical practice(9,10), but recent data from the pragmatic GLORIA trial suggested a rather favourable risk-benefit balance for this strategy, even in senior patients(11). Balancing the benefits and risks of treating RA with glucocorticoids thus remains a controversial topic.

In this narrative review, we will outline the historical and current position of glucocorticoids in the management of RA, while summarising recent evidence on their beneficial and detrimental effects. Finally, we will formulate practical strategies for the current use and tapering of glucocorticoids in RA.

The diverse anti-inflammatory effects of glucocorticoids

The development of glucocorticoids was the result of extensive work by biochemists at the Mayo Clinic, who first discovered "cortisone" as a necessary component to maintain life in adrenalectomised animals(12). It was promptly recognised that this compound provided potent anti-inflammatory effects, and the early 1950s saw cortisone eventually become widely available as semisynthetic glucocorticoids. More recently, delayed-release formulations have also been developed to tackle the nocturnal increase in proinflammatory cytokines that seemingly contributes to morning stiffness in RA, a strategy termed "chronotherapy"(13).

Glucocorticoids are steroids, lipophilic hormones, that are produced in the adrenal cortex through regulation by the hypothalamic-pituitary-adrenal axis(14). Because of their lipophilic structure, glucocorticoids can pass cellular membranes to bind to the glucocorticoid receptor in the cytosol of nucleated cells. The hormone-receptor complex is then translocated into the nucleus to bind to DNA-binding sites on different target genes, or glucocorticoid response elements.

Following this binding, glucocorticoids exert several genomic effects, by activating the transcription of anti-inflammatory and regulatory proteins ("transactivation"), and by inhibiting the expression of proinflammatory proteins ("transrepression")(14). Interestingly, protein levels do not change directly after glucocorticoid administration, implying that these genomic mechanisms involve a certain delay. However, the rapid anti-inflammatory effects commonly reported with glucocorticoids point towards an additional contribution of non-

genomic effects. These rapid effects seem to depend on three different mechanisms: interactions with cellular membrane components, interactions with membrane-bound glucocorticoid receptors, and non-genomic effects mediated by the cytosolic glucocorticoid receptor(15). Together, glucocorticoids' genomic and non-genomic effects result in inhibition of inflammatory processes through various types of immune cells and their synthesis of cytokines and prostaglandins.

Glucocorticoids for RA: a brief history

Cortisone was first introduced into rheumatology at the Mayo Clinic, through a double-blind controlled study in patients with RA, resulting in spectacular clinical improvements(16). Although the early 1960s saw several trials confirm the efficacy of glucocorticoids for RA, even in daily doses as low as 7.5mg prednisone, side effects were also apparent and quickly dominated the perception on these drugs(17). Despite the overall conclusion that the optimal daily dose should not exceed 10mg prednisone, this low-dose approach was insufficiently adopted in practice and side effects continued to overshadow the benefits of glucocorticoids in RA for decades(12).

Only in the 1990s did important new evidence emerge, with several landmark papers that would give rise to two distinct approaches to treating RA with glucocorticoids: a continued low-dose approach and a bridging approach.

The continued low-dose approach

In 1995, a double-blind controlled study was published that compared prednisone at 7.5mg/day with placebo in early RA, while allowing for background treatment(18). The prednisone group showed improvements in joint pain, swelling, and damage over 2 years, confirming the results of the earlier trials from the 1960s. This pivotal study inspired several others in subsequent years to confirm the efficacy of low-dose prednisone in early RA over placebo, with or without concomitant DMARDs(19–21). More recently, the CAPRA-2 trial showed an equally clear efficacy for modified-release low-dose prednisone in a more established RA population(22).

Although trials like these have firmly established the clinical benefit of low-dose glucocorticoids in RA, uncertainty has remained regarding several key issues. First, concerns about cumulative glucocorticoid toxicity complicate their use in vulnerable patient populations. However, recent evidence has emerged through the pragmatic GLORIA trial, which purposely included patients with active, established RA aged 65 or above, with minimal exclusion criteria(11). Patients were randomised to receive either prednisolone 5mg daily or placebo for 2 years, as an add-on to other antirheumatic treatment. Although adverse events were indeed more common in the prednisolone group, they were mostly non-severe. Moreover, the trial's low-dose approach was clearly efficacious in this population, regarding both disease activity and radiographic progression, providing an overall favourable benefit-risk balance.

A second source of persisting uncertainty regarding low-dose glucocorticoids relates to their added benefit in patients treated with bDMARDs. Although evidence to support clinicians remains scarce, some guidance can be obtained from the recent SEMIRA trial(23). In this double-blind randomised controlled trial, patients with RA in stable low disease activity under tocilizumab and low-dose glucocorticoids were randomised to either continue prednisone at 5mg daily or to taper prednisone to discontinuation over 16 weeks. The trial's tapering scheme involved reducing prednisone by 1mg every 4 weeks, with reinstitution in case of

flare. Overall, patients who continued prednisone in addition to tocilizumab retained better disease control than patients who tapered, although two-thirds of participants in the tapering group eventually managed to discontinue prednisone without experiencing flares. These results suggest that low-dose glucocorticoids are indeed efficacious even when added to a bDMARD, although these benefits should be weighed against the possible side effects and those of alternative DMARD options on a case-by-case basis.

The bridging approach

Despite the efficacy of continued low-dose glucocorticoids, the benefits reported in earlier studies of this strategy were often not retained after stopping prednisone, especially when used in monotherapy(18). Therefore, a different approach to treating early RA with glucocorticoids was spearheaded by the COBRA trial, published in 1997(2). Inspired by emerging evidence that early introduction of DMARDs might be more effective than the traditional stepwise approach, COBRA aimed to achieve disease control early by leveraging the rapid effects of glucocorticoids, before tapering and discontinuing them when the slower-acting DMARDs would take effect. In this landmark study, patients with early RA were randomised to receive either sulphasalazine alone or a combination of sulphasalazine with methotrexate and a step-down scheme of glucocorticoids starting at 60mg prednisolone daily, tapered to discontinuation by week 28. The combination regimen showed superior disease control and suppressed radiographic progression more effectively and more rapidly than sulphasalazine alone. Moreover, this reduction in structural progression remained apparent in COBRA's long-term follow-up studies(24).

Numerous strategy trials, including BeST(25), tREACH(26), IMPROVED(27), CareRA(28), IDEA(29), COBRA-light(30), NORD-STAR(31) and ARCTIC(32), have since confirmed the efficacy of combining a step-down scheme of glucocorticoids with csDMARDs to treat early RA (Table 1). Interestingly, results from many of these trials suggest that this approach is equally effective at starting doses of glucocorticoids below those in COBRA, namely 30mg per day in CareRA(33) and COBRA-light(30), 15mg in tREACH(26) and ARCTIC(32), and 10mg in the recent CORRA trial(34). Moreover, the current evidence suggests that the efficacy of combining bridging glucocorticoids with csDMARDs is not surpassed by first-line use of bDMARDs when treating-to-target, particularly considering the additional costs(29,31).

Consequently, the bridging approach, combining a csDMARD like methotrexate with a step-down scheme of glucocorticoids, is currently recommended by the European Alliance of Associations for Rheumatology (EULAR) as the first-line treatment for early RA(7). However, these recommendations do add that glucocorticoids should be tapered as rapidly as feasible, while the yet-unpublished 2022 update further specifies that discontinuation should be the aim whenever possible.

Bridging to leverage the therapeutic window of opportunity

Using glucocorticoids as bridging therapy for early RA provides several important benefits. A key advantage of glucocorticoids is their rapid effect, making them a particularly attractive treatment option when prompt inflammatory disease control is warranted. This is especially important during the early phase of RA, since it has long been evident that delaying treatment is associated with impaired outcomes. Over time, this realisation has resulted in the concept of a "window of opportunity", a crucial time in early disease during which its progression can be more effectively modified by DMARDs(35). More recently, evidence is emerging to suggest that our interpretation of the window of opportunity could be extended to a crucial time

frame where treatment should not only be started, but during which this should also result in a clinically meaningful treatment response.

A window for sustained disease control

Firstly, a favourable course of disease activity during the early treatment of RA is often associated with a higher probability of long-term remission(36). A compelling example comes from the IMPROVED trial. In this trial, patients with early rheumatoid or undifferentiated arthritis were started on a bridging treatment of step-down prednisone with methotrexate, before being randomised to one of two different second-line treatments when remission was not achieved after 4 months(37). Patients who achieved early remission had significantly better outcomes over time, including higher proportions of long-term remission and drug-free remission. These findings were confirmed in more recent work from the Leiden group(38). Similarly, in the CareRA trial, lower disease activity at month 4 was associated with a higher probability of sustained remission over 2 years(39), and early treatment response is commonly associated with reduced radiographic progression(40).

Together, these results support the existence of an early window where achieving disease control improves the probability of retaining good long-term clinical outcomes.

A window for improved patient-reported outcomes

Crucially, a favourable treatment response within this window might also facilitate long-term improvements in patient-reported outcomes. For instance, less fatigue over up to 2 and 5 years of follow-up was reported for patients who achieved remission early in the ARCTIC and CareRA trials, respectively(41,42). Similarly, patients who were in remission after 4 months in IMPROVED had more favourable 5-year scores on the Health Assessment Questionnaire(37), and early remission in CareRA was associated with improved psychosocial wellbeing and self-efficacy after 1 and 2 years(43,44). Interestingly, additional mediation analyses on CareRA data suggested that early treatment response exerted its positive influence on long-term fatigue and psychosocial outcomes mostly through improvements in psychological aspects, rather than directly through improved inflammation(42,44). Stated differently, there might also be a "psychosocial window of opportunity" during which the achievement of early disease control leads to a more positive long-term outlook for patients regarding their disease.

Bridging glucocorticoids optimise chances to seize the window at personal and societal level

These results illustrate why clinicians should prioritise treatment strategies for early RA that allow for prompt inflammatory disease control. By including fast-acting agents like glucocorticoids in their first-line treatment, clinicians can maximise the probability of favourably affecting disease activity within the therapeutic window, leading to long-term benefits in disease control and overall patient wellbeing. These benefits even extend to a societal level, with a noteworthy example again coming from CareRA: patients who were treated with methotrexate and bridging glucocorticoids, rather than methotrexate alone, had a significantly lower risk of chronic analgesic consumption(45), and cost-effectiveness analyses also favoured the bridging approach(46).

Taken together, ample evidence supports that glucocorticoids, with their rapid effect, remain an important part of the initial treatment for early RA. However, recent guidelines from the American College of Rheumatology (ACR) and EULAR each in their own way recommend

restricting glucocorticoid use to short terms and low doses, for instance as part of a bridging approach with discontinuation whenever possible.

The downsides: glucocorticoid-related adverse effects

Ever since the earliest records of glucocorticoid use, side effects have been reported, which are usually dose and time dependent. Although the extensive list of possible glucocorticoid-related effects additionally includes cataract, myopathy and others, arguably the most important side effects are osteoporosis, cardiovascular and metabolic effects, and increased risk of infections(8).

Osteoporosis

Prolonged glucocorticoid use at daily doses >10mg prednisone has undisputed negative effects on bone health, increasing the risk of osteoporosis(47). However, the relationship between glucocorticoid use and bone mineral density (BMD) is also mediated by other aspects, including disease activity.

For instance, a recent observational study found no effects on BMD in patients with inflammatory rheumatic diseases for daily prednisone doses of ≤5mg, while doses of >7.5mg were negatively associated with BMD only for those patients in moderate or high disease activity(48). Moreover, short-term glucocorticoid bridging therapy was associated with limited bone loss over 4 years in the COBRA-light trial(49). Finally, increased fracture risk with glucocorticoids was mainly found in observational studies that did not fully account for differences in disease activity(50). In all, evidence suggests that at lower doses, the deleterious effects of glucocorticoids on bone health are offset by their beneficial effects on inflammatory disease control.

Cardiovascular and metabolic effects

Glucocorticoids have well-known detrimental effects on lipid metabolism and glucose homeostasis, contributing to hyperglycaemia and impaired cardiovascular outcomes. However, recent evidence suggests that these risks are mainly evident at daily doses of ≥5mg prednisone and at higher cumulative doses and longer durations(51). Moreover, managing cardiovascular and metabolic risk in RA additionally requires adequate control of inflammation, and the success of glucocorticoids in this regard might partially compensate for their detrimental effects on cardiovascular and metabolic health(52).

Infections

Glucocorticoids work by inhibiting the activity of various immune cells, necessarily increasing the risk of infections. A recent retrospective cohort study identified an increased risk of serious infections for patients with RA under stable DMARD treatment who were additionally treated with glucocorticoids(53). Although this risk was dose-dependent, small but significant effects were apparent even at daily doses <5mg prednisone. Other observational studies have shown similar associations, with risks usually depending on glucocorticoid dosage and duration(54).

Adverse effects particularly worrisome to patients

Research has additionally identified several glucocorticoid-related side effects that seem particularly worrisome to patients(55). Among others, these include fatigue, palpitations, and aesthetic changes like skin atrophy. To optimally manage glucocorticoid-associated side

effects, clinicians should therefore additionally consider adequate patient education and counselling, with emphasis on the patient's perspective.

Observational data and the GLORIA trial

Recent studies have shown that concerns about glucocorticoid-related side effects often exceed the published evidence, hampering the optimal use of these drugs(56,57). In part, this seems due to an overreliance on observational studies, which carry an inherent risk of confounding by indication(8). Conversely, randomised controlled trials have generally provided more reassuring safety data(47), but high-quality trials powered to detect adverse events were largely unavailable until recently.

This knowledge gap was the main rationale behind the GLORIA trial, which was not only statistically powered to detect safety signals, but also purposely included senior patients, who are more prone to experiencing adverse treatment effects(11). Consequently, GLORIA likely provides the most reliable evidence currently available to assess the safety of low-dose glucocorticoids in RA. Overall, the trial reported an increased proportion of patients with at least one adverse event (49% in the placebo group, 60% in the prednisolone group). However, this was mostly caused by mild to moderate infections, while no important differences were seen in other areas of possible concern. Given the trial's high-risk population, these results likely reflect a "worst-case scenario" for this dose and duration of glucocorticoid use. Moreover, some adverse effects, including bone loss, were seemingly counteracted by improved inflammatory disease control.

Together, the available evidence on the use of glucocorticoids in RA suggests that these drugs can provide a favourable balance of benefit and harm if they are used at the minimum dose and duration required to achieve disease control(47).

Balancing benefit and risk: from guidelines to clinical reality

The knowledge that many glucocorticoid-related side effects can be mitigated by restricting dosage or duration of use is reflected in the most recent ACR and EULAR guidelines for the management of RA. Specifically, the 2021 ACR guideline conditionally recommends initiating a csDMARD in monotherapy over a bridging approach with short-term glucocorticoids(6), while the 2019 update of the EULAR recommendations indicates that short-term glucocorticoids should be considered whenever a csDMARD is initiated or changed(7). However, the EULAR recommendations add to this that glucocorticoids should be "tapered as rapidly as clinically feasible", further expanded to "tapered and discontinued" in the soon-to-be-published 2022 update. Additionally, the 2022 EULAR recommendations will allow for glucocorticoids to be initiated at varying doses and routes of administration. Nevertheless, despite their differences, both US and European guidelines aim to avoid continued use of glucocorticoids.

Indeed, the probability of glucocorticoid treatment throughout follow-up for RA seems to have decreased since the early 2000s, and time trends over the past decades also show a clear decline in the mean dose that is used(58). However, long-term glucocorticoid use appears to still be widespread in routine RA care, and real-world practice patterns seem highly variable. For instance, several recent RA cohort studies have reported relatively high proportions of chronic glucocorticoid use. In the Canadian CATCH cohort, 30% of patients who received glucocorticoids still used them 2 years later(10), and up to 55% of patients treated with glucocorticoids in the French ESPOIR cohort continued them for more than 2 years(59).

These proportions are generally in stark contrast with data from clinical trials. A recent meta-analysis investigated the success rates of glucocorticoid tapering in clinical trials applying a bridging approach(60). In general, glucocorticoid discontinuation was mostly successful when protocolised, with only 10% of the patients who started bridging therapy in these trials still using glucocorticoids after 2 years. However, discontinuation rates were variable, ranging from approximately 40% after 1 year in both arms of the COBRA-light trial to 100% successful discontinuation after 1 year in arm 2 of the IMPROVED study. These differences illustrate that the success of glucocorticoid discontinuation seems to depend at least partly on the protocolised treatment steps(60).
In all, the current evidence from clinical trials, further corroborated by 5-year follow-up data from the CareRA and IMPROVED studies(33,37), suggests that successful discontinuation of glucocorticoids is feasible as long as clinicians actively encourage this, particularly when protocolised.

Stated differently, balancing the benefits and risks of glucocorticoid treatment in RA seems a realistic goal. A general approach to facilitate this could be:

1. Following EULAR recommendations, initiate treatment with a csDMARD, preferably methotrexate, and a step-down bridging scheme of glucocorticoids in a treat-to-target approach as soon as a diagnosis of RA is made. Based on recent evidence, daily starting doses of 30mg prednisone or less might be sufficient.
2. Timely tapering of glucocorticoids should be actively encouraged, aiming for discontinuation whenever possible. An attempt to taper glucocorticoids should be made in every patient who achieves low disease activity, through shared decision-making. Guidance on specific tapering regimens is still lacking, although a trial is currently underway (the STAR trial, NCT02997605). Pending the results of this trial, the only available guidance comes from the SEMIRA trial, during which tapering with 1mg/day every four weeks in patients on concomitant treatment with tocilizumab was feasible and safe in most cases.
3. However, clinicians should be aware that tapering glucocorticoids might not be successful for some patients, e.g., when treatment is complicated by multimorbidity or contraindications. In these cases, the recent evidence on the efficacy and relative safety of continued low-dose glucocorticoids suggests that the decision to switch to the next line of DMARDs should be weighed against the option of continuing glucocorticoids for a longer time at low doses, preferably ≤5mg/day prednisone. In this decision, the side effects of b- or tsDMARDs as alternative options should also be considered on a case-by-case basis.
4. Finally, when glucocorticoid tapering is mostly unsuccessful due to pronounced morning symptoms, clinicians could consider glucocorticoid chronotherapy, evening dosing or splitting doses to twice daily, given the underlying physiology of nocturnal inflammation. In any case, the intention should be to aim for the lowest possible daily dose.

Conclusion

Glucocorticoids remain an effective treatment for RA, even in the age of b- and tsDMARDs. Their rapid effect and cost-effectiveness make them a particularly suitable option as part of bridging therapy for early RA, helping to achieve disease control early and thus leveraging the therapeutic window to improve long-term clinical, societal and psychosocial outcomes.

Recent evidence from clinical trials supports the feasibility of tapering glucocorticoids to discontinuation after the bridging phase, as long as clinicians actively encourage this and are guided by a protocol. Evidently, adverse effects are common and should be considered, but the current literature suggests a favourable balance of benefit and harm when glucocorticoids are used at the lowest dose and for the shortest duration necessary to achieve inflammatory disease control.

In other words, although timely tapering of glucocorticoids after the bridging phase should always be encouraged, continuing glucocorticoids at doses ≤5mg prednisone could be considered as an alternative to DMARD escalation when tapering is not successful. In these cases, the known adverse effects of low-dose glucocorticoids should be weighed against those of specific DMARDs at the individual patient level, via a process of shared decision-making with the patient.

Table 1. Overview of randomised controlled trials applying a bridging approach with glucocorticoids in early rheumatoid arthritis.

Trial (publication year)	*Initial therapy*	*Glucocorticoid starting dose*	*Glucocorticoid tapering schedule*
COBRA (1997)(2)	▪ Combination arm: GC + MTX (7.5mg/week) + SSZ (2g/day) ▪ Control arm: SSZ monotherapy	Prednisolone 60mg/day (combination arm)	Tapered to 7.5mg/day over 7 weeks. Discontinuation after 28 weeks
BeST (2005)(25)	▪ Arm 1: sequential csDMARD monotherapy ▪ Arm 2: step-up csDMARD combination therapy ▪ Arm 3: GC + MTX (7.5mg/week) + SSZ (2g/day) ▪ Arm 4: MTX (25-30mg/week) + infliximab	Prednisone 60mg/day (arm 3)	Tapered to 7.5mg/day over 7 weeks. Discontinuation after 8 weeks depending on DAS
tREACH (2013)(26)	▪ Arm 1: GC intramuscularly + MTX (25mg/week) + SSZ (2g/day) + HCQ (400mg/day) ▪ Arm 2: GC orally + MTX (25mg/week) + SSZ (2g/day) + HCQ (400mg/day) ▪ Arm 3: GC orally + MTX (25mg/week)	▪ Arm 1: methylprednisolone 120mg or triamcinolone 80mg ▪ Arm 2 & 3: 15mg/day	Tapered to discontinuation over 10 weeks (arm 2 & 3)
IDEA (2014)(29)	▪ Infliximab arm: infliximab + MTX (10mg/week) ▪ GC arm: GC intravenously + MTX (10mg/week)	Methylprednisolone 250mg (GC arm)	-
IMPROVED (2014)(27)	All patients: GC + MTX (25mg/week).	Prednisone 60mg/day	Tapered to 7.5mg/day over 7 weeks. Discontinuation after 20 weeks depending on DAS
COBRA-light (2015)(30)	▪ COBRA arm: high dose GC + MTX (7.5mg/week) + SSZ (2g/day) ▪ COBRA-light arm: moderate dose GC + MTX (25mg/week)	▪ COBRA arm: prednisolone 60mg/day ▪ COBRA-light arm: prednisolone 30mg/day	▪ COBRA arm: tapered to 7.5mg/day over 7 weeks ▪ COBRA-light arm: tapered to 7.5mg/day over 9 weeks ▪ Both arms: discontinuation after 32 weeks depending on DAS
CareRA (2015)(28)	High-risk patients: ▪ COBRA Classic: high dose GC + MTX (15mg/week) + SSZ (2g/day) ▪ COBRA Slim: moderate dose GC + MTX (15mg/week)	▪ COBRA Classic: prednisone 60mg/day ▪ COBRA Slim & COBRA Avant-Garde: prednisone 30mg/day	▪ COBRA Classic: tapered to 7.5mg/day over 7 weeks, further tapered from week 28

	▪ COBRA Avant-Garde: moderate dose GC + MTX (15mg/week) + leflunomide (10mg/day) Low-risk patients: ▪ COBRA Slim ▪ Step-up monotherapy MTX		▪ COBRA Slim & COBRA Avant-Garde: tapered to 5mg/day over 6 weeks, further tapered from week 28 ▪ All arms: discontinuation after 34 weeks depending on DAS28
ARCTIC (2016)(32)	All patients: GC + MTX (25mg/week)	Prednisolone 15mg/day	Tapered to discontinuation over 7 weeks depending on DAS
NORD-STAR (2020)(31)	▪ Arm 1: MTX (25mg/week) + either GC OR SSZ (2g/day) and HCQ (200mg/day) and intra-articular GC ▪ Arm 2: MTX (25mg/week) + certolizumab pegol ▪ Arm 3: MTX (25mg/week) + abatacept ▪ Arm 4: MTX (25mg/week) + tocilizumab	Prednisolone 20mg/day (arm 1)	Tapered to 5mg/day over 9 weeks. Discontinuation after 9 months
CORRA (2022)(34)	▪ Arm 1: high dose GC + MTX (15mg/week) ▪ Arm 2: low dose GC + MTX (15mg/week) ▪ Arm 3: MTX monotherapy (15mg/week) + placebo	▪ Arm 1: prednisolone 60mg/day ▪ Arm 2: prednisolone 10mg/day	All arms: tapered to discontinuation over 12 weeks

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