The role of low-dose glucocorticoids for rheumatoid arthritis in the biologic era

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ABSTRACT

In rheumatoid arthritis (RA), low-dose glucocorticoid (GC) therapy has a well-established effect on disease activity. Particularly in early RA, robust evidence demonstrates that GC treatment in association with standard disease-modifying anti-rheumatic drugs (DMARDs) is effective in inducing high remission rates, earlier and more persistently.

Despite international recommendations that discourage long-term concomitant GC use, the majority of the clinical trials and observational registries on biologic agents include a high proportion (up to 80%) of patients in treatment with GC.

From an analysis of the literature, a substantial lack of reliable information about the efficacy of GC in association with biologic agents emerges; in particular, the role of GC co-therapy in sustaining remission after biological therapy discontinuation remains to be clarified.

Given the increasing prevalence of patients in sustained remission, a rational discontinuation strategy should include low-dose GCs in the experimental design to elucidate their role in inducing and maintaining biologic-free remission, for efficacy, safety and pharmacoeconomic considerations.

Introduction

In rheumatoid arthritis (RA), low-dose glucocorticoid (GC) therapy has a well-established effect on disease activity (1, 2). Particularly in early RA, robust evidence demonstrates that GC treatment in association with standard disease-modifying anti-rheumatic drugs (DMARDs) is effective in inducing high remission rates, earlier and more persistently (3–5). Such an earlier and more stringent control of inflammation, as also revealed in imaging studies (6–8), may account for better functional (9) and structural outcomes (10).

GC co-therapy seems to have a role in a *treat-to target* and *tight control* strategy, as recently demonstrated by the CAMERA II study, in which RA patients treated with 10 mg/day of prednisone showed higher remission rate with respect to placebo-treated patients (3). This may allow a reduced rate of patients who need additional treatments, including biologic agents, with obvious economic and safety implications.

Systematic literature reviews and meta-analyses of randomised controlled trials (RCT) support a disease-modifying effect of GC in terms of reduced radiographic progression (10-12). Although clinically significant also in established disease (13), this disease-modifying effect is more evident in the early phases, prior to any joint damage. Accordingly, low-dose GC are currently recommended in early RA at least as bridging therapy (14, 15).

In real life, the use of GC is not limited to early RA; for example, in the QUEST-RA database, about two-thirds of patients analysed were receiving concurrent GCs (16). A general decline in GC dosages toward <5 mg/day regimens has been documented in the recent decades; such very low-dose GC is associated with low risk of adverse events, including diabetes mellitus, hypertension, cataract, with evidence of long-term effectiveness (17). Several RCTs also appear to confirm a favourable risk/benefit ratio for low-dose GC regimens in RA (18).

Glucocorticoids and biologic agents

Although the literature suggests a long-term disease-modifying effect of low-dose GC treatment, in most studies it is not possible to discriminate between the contributions made by different components in a combination regimen that includes both GC and synthetic DMARDs. This is even more difficult in analyses of clinical trials of biologic agents, in which potential additive or

multiplicative effect of GCs over biologics (and conventional DMARDs) has not been systematically investigated. As reported in a comprehensive review of RCTs, the percentages of patients receiving concomitant GC treatment range from 34% to 93%, at least 50% for each biologic agent: abatacept, 74.4%; golimumab, 67.9%; infliximab, 60.6%; certolizumab 57.5%; rituximab, 57.5%; etanercept, 54.4%; tocilizumab, 52.8%; adalimumab, 50.4% (19). It is difficult to assess the contribution of concomitant GC beyond the specific effect of a given biologic drug, as well as to compare and properly evaluate safety data. Moreover, reporting on concomitant treatments is not adequate to evaluate the effect of biologic agents in the subgroup of patients who take GC treatment (19).

Although the majority of the clinical trials on biologics include patients in treatment with GC, international recommendations discourage concomitant GCs (14). This is mainly due to the increased risk of infection of high-dose GC noticeable in observational settings – in which GC are administered based on disease severity and comorbidities – rather than in RCT (20, 21). The analysis of the complex interaction of anti-TNF alpha agents with concomitant risk factors and GC use supports a clinically important increased risk of infections in patients exposed to more than 7.5 mg of prednisone per day (22).

Since patients in clinical trials are drawn from clinical practice, a similar proportion of concomitant GC is seen in both clinical trials and clinical care. In observational registers, the prevalence of GC ranges from 40 to 84% (23, 24).

The efficacy of biologic agents may be accounted for in part by interaction with concurrent treatments, and it may be more appropriate to consider efficacy in the context of a disease-modifying drug combination strategy, rather than focusing on individual disease-modifying drugs (25). This concept of strategy has been clearly demonstrated by the BeSt study and other clinical trials, in which a treatment strategy rather than a specific agent has been evaluated. In the BeSt trial, concomitant treatment with prednisone (at a maintenance dose of 7.5 mg per day) and synthetic DMARDs resulted in clinical improvements comparable to those observed in patients receiving infliximab in conjunction with methotrexate in patients with recent-onset RA. Furthermore, the BeSt trial introduced the practical possibility to aim for persistent and even drug-free remission (26). Trials in early RA evaluating the efficacy of GCs over synthetic plus biologic DMARDs will elucidate possible interaction between these drugs in the context of a disease-modifying strategy, aiming for sustained remission even after down-titration and drug discontinuation.

Discontinuation of glucocorticoids and biologic agents

The possibility to modulate treatment after the achievement of a persistent status of clinical remission is now one of the challenges of clinical research of RA, to improve patient outcomes, reduce adverse events, and lighten the economic burden of widespread and long-term treatment with high-cost biologic drugs. This goal is made feasible in practice by the high remission rates achieved by intensive therapeutic strategies applied in the early phases of the disease course (27). The recently updated EULAR recommendations for the management of RA suggest 'for patients in persistent remission, first taper down the corticosteroid dosage', and 'if remission persists consider tapering down treatment with any biological DMARD, especially if the patient is also receiving one or more synthetic DMARDs.

When examining data concerning long-term efficacy and safety of low-dose GCs in early RA, particularly in a perspective of pharmaceutical cost containment, a need to suspend GCs before the biologic DMARD may appear counterintuitive. However, the prescription of GC in clinical practice often is perceived as an indicator of disease activity and lack of adequate response to DMARDs. Also, GCs are thought to mask the actual disease activity, because of their symptomatic effect. This perception may be linked mainly to "confounding by indication," as, in clinical practice, patients with established RA who are receiving treatment with GC are more likely to be those with more severe disease.

Nevertheless, little prospective evidence is available concerning the best strategy for down-titration/withdrawal of combination therapy once a patient has achieved a status of sustained response to combination treatment including GCs, conventional DMARDs and biologics. Perhaps this will vary considerably in different individual patients, so that group data from a randomised trial will provide only guidelines for individual patients.

Several studies have evaluated discontinuation of biologic agents (28, 29). Table I reports the characteristics of withdrawal group of patients in studies evaluating biologic discontinuation. Interpreting the results from these studies is difficult due to their wide heterogeneity of patients and methods.

A first level of variability is related to the study samples, which vary in terms of disease duration, duration and type of exposure to biologic agents, and threshold of disease activity for discontinuation. Further differences in withdrawal strategy, presence of comparator, definition of the outcome, study duration and design render it infeasible to pool data for reliable figures and external validity.

Among all these issues, a further complexity relies on concurrent treatment during the discontinuation period: the use of concomitant non-biologic DMARDs and GC at the time of biologic discontinuation is highly variable. Out of 18 reported studies of biologic discontinuation in RA, 15 report concurrent exposure to GC, of which 12 allowed the use of low-dose GC (≤10 mg/day). The percentage of patients on treatment with GC is reported in 6 out of 12 studies, and ranges between 4% and 61%. Dosages are reported in 5 out of 12 studies, ranging from 2.5 to 3.8 mg/day. The overall rate of successful biologic discontinuation in the moderate term (6 to 12 months) ranges from 0 to 82%, with better outcome for studies recruiting early RA patients.

The influence of GC co-medication is not quantitatively evaluable. Only 4 studies report results on the impact of

Table I. Glucocorticoid use in the main biologic discontinuation studies.

Study	Year	Drug	Number	Design	Duration of biologic use	Discontinuation criterion	Duration required	Concurrent DMARD	Concurrent GC (PDN)	GC	GC dose	Outcome (failure)	Time	Absence of failure
Aguilar-Lozano *et al*. (34)	2013	TCZ	45	LTE	5 years	DAS28<2.6 SJC28=0	Cross sectional	100%	?	?	?	SJC28>0	12 months	26.6%
DREAM (33)	2013	TCZ	187	LTE	Median 7.8 years	DAS28 <3.2	2-3 time points	0%	Y (stable <10mg/d)	34.2%	2.8mg/d	DAS28 ≥3.2 drug-free	At 52 wks	13.4%
PRESERVE (35)	2013	ETN	200	RCT	8 months	DAS28 <3.2	Cross sectional	100%	Y (stable <10mg/d)	61%	?	DAS28 ≥3.2	At 52 wks	42.6%
CERTAIN (36)	2013	CZP	17	LTE	6 months	CDAI ≤2.8	Cross sectional	100%	?	?	?	CDAI >2.8	28 wks	17.6%
HIT HARD (37)	2013	ADA	87	LTE	6 months	N/A	N/A	100%	Y (<10mg/d)	?	?	DAS28 ≥2.6	24wks	N/A
ADMIRE (38)	2012	ADA	15	RCT	Median 43.3 months	DAS28 <2.6	≥3 months	100%	Y (stable <10mg/d)	?	?	DAS28 ≥2.6	At 28wk	33.3%
BRIGHT (31)	2012	ADA	22	LTE	Mean 45.8 months	DAS28 <2.7	Cross sectional	13.6%	Y	40.9%	3.7mg/d	DAS28 ≥2.7	At 52 wks	18.2%
DOSERA (39)	2012	ETN	23	RCT	Mean 35.3 months	DAS28 <3.2	11 months	100%	Y (≤7.5mg)	?	?	DAS28 ≥3.2 and Δ ≥0.6	48wks	13.0%
HONOR (40)	2012	ADA	51	SA	Mean 16.6 months	DAS28 <2.6	6 months	100%	N	0%	0	DAS28 ≥2.6	12 months	36%
Van der Maas *et al*. (41)	2012	IFX	51	SA	Mean 67.2 months	DAS28 <3.2	6 months	100%	Y	4%	?	Stopping/ dow-titration	54 wks	16%/45%
OPTIMA (32)	2012	ADA	102	RCT	26wks	DAS28 <3.2	4 wks	100%	Y?	?	?	DAS28 ≥3.2	At 52wks	81.2%
BeSt (42)	2011	IFX	104	LTE	Median 11 months	DAS ≤2.4	6 months	100%	N	0%	0	DAS >2.4	12 months	≈80%
ALLOW (43)	2011	ABA	80	RCT	12 wks	DAS responders	Cross sectional	100%	Y (stable <10mg/d)	55%	3.8mg/d	DAS28 ≥2.6	At 12 wks	N/A
Saleem *et al*. (44)	2010	ADA INF ETA	47	SA	19mo (27) 120mo (20)	DAS28 <2.6	>6 months	100%	N	0	0	DAS28 ≥2.6 or Δ>1.2	24 months	40.4%
RRR (30)	2010	IFX	102	SA	?	DAS28 <3.2	24 weeks	100%	Y (<5mg/d)	?	2.5mg/d	DAS28 ≥3.2	12 months	55%
Brocq *et al*. (44)	2009	ADA ETN IFX	21	SA	Mean 40.3 months	DAS28 <2.6	6 months	66.7%	Y (≤5mg/d)	14.3%	2.7mg/d	DAS28 ≥3.2	12 months	25%
Quinn *et al*. (46)	2005	IFX	10	LTE	12months	N/A	N/A	100%	Y	?	?	DAS28	58wks	N/A
ATTRACT (47)	2004	IFX	17	LTE	24 months	N/A	Cross sectional	100%	Y	?	?	Loss of ACR20	15wks	0%

TCZ: tocilizumab; ABA: abatacept; ETA: etanercept; ADA: adalimumab; CZP: certolizumab pegol; INF: infliximab; PDN: prednisone equivalent; LTE: long-term extension trial; RCT: randomised controlled trial; SA: single arm trial; DAS: disease activity score; CDAI: clinical disease activity index; N/A: not available or applicable.

concurrent GC treatment on the discontinuation outcome.

The RRR, a single-arm clinical study of infliximab discontinuation in RA patients, analysed the influence of low dose of GC (mean prednisone dosage of 2.5 mg/day) on the persistency of low disease activity (LDA) over 1 year, without finding any significant difference in univariable logistic models (30).

The BRIGHT study, an open-label extension of a RCT of adalimumab (ADA) monotherapy, evaluated the persistence of LDA after ADA discontinuation over 52 weeks of follow-up in 46 RA patients. Though no formal statistical analyses were carried out because of the low power of the study, patients who achieved the primary endpoint of persistent LDA had shorter disease duration (4.4 *vs*. 18.1 years) and higher use of GC (75% *vs*. 33%) (31).

In the OPTIMA study, outcomes after 52 weeks of double-blind withdrawal or continuation of ADA were assessed in early RA patients who achieved a stable LDA target of DAS28 <3.2 at weeks 22 and 26 with initial ADA+MTX. GC use at baseline was not significantly associated with 'Biologic-Free Comprehensive Disease Control' (defined as DAS28 remission, absence of functional disability and radiographic progression) over 52 weeks of follow-up (32).

The DREAM study, a long-term extension study of clinical trials, included 187 patients on monotherapy with tocilizumab (TCZ) and DAS28 remission or LDA, followed up for 54 weeks after withdrawal of TCZ. About one third of patients were in low-dose GC treatment. Patients on GC treatment showed a lower probability of persistency in LDA (HR 0.64; 95%CI 0.46, 0.88) in univariable analyses, which however was not significant (HR 1.1; 95%CI 0.76, 1.59) when adjusted for disease activity and severity measures (33).

From an analysis of the literature, a substantial lack of reliable information about the relationship between GC and biologic drugs emerges, and the role of GC co-therapy in sustaining remission after biological therapy discontinuation remains to be clarified. Even if more detailed information on concurrent treatment in biologic discontinuation studies were available, no inference on the effect of GC would be possible. Since exposure to GC is not included in the experimental design, it is probably prescribed in patients with more severe disease, leading to confounding by indication.

Conclusion

Although there is a definite role of GC in the induction therapy of early RA, as well as the role of long-term (up to 2 years) low-dose GC in reducing structural progression, their use in the next phases of the clinical pathway of RA is still to be clarified. At present, GC comedication in biologic-treated RA looks like *something that most rheumatologists do but do not wish to talk about*. Given the increasing prevalence of patients in sustained remission, a rational discontinuation strategy is desirable for effectiveness, safety and pharmaco-economic considerations. Future studies should include GCs in the experimental design, trying to elucidate their role in inducing and maintaining biologic-free remission.

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