Duration of Treatment With Glucocorticoids in Giant Cell Arteritis A Systematic Review and Meta-analysis

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Abstract

The aim of this meta-analysis was to estimate the mean duration of glucocorticoid (GC) treatment in patients with giant cell arteritis (GCA). PubMed, Embase and Cochrane databases were searched from inception till November, 30 2021. The outcome measures were the proportion of patients on GC at year 1, 2, and 5 after diagnosis and the mean GC dose (in the entire cohort and expressed in prednisone equivalents) at these time points. Twenty two studies involving a total of 1786 patients were included. The pooled proportions of patients taking GC at year 1, 2 and 5 were 89.7% [95% CI 83.2 – 93.9%], 75.2% [95% CI 58.7 – 86.6%] and 44.3% [95% CI 15.2 – 77.6%], respectively. The pooled GC dose at year 1 and 2 was 9.1 mg/d [95% CI 2.8 – 15.5 mg/d] and 7.8 mg/d [95% CI 1.4 – 14.1 mg/d], respectively. The proportion of patients taking GC at year 1 was lower in multicenter studies ($p = 0.003$), in randomized controlled trials ($p = 0.01$) and in studies using a GC tapering schedule ($p = 0.01$). There were no significant differences in the proportion of patients taking GC at year 1 and 2 according to study design (retrospective vs prospective), initial GC dose, use of pulse GC, publication year, enrolment period, duration of follow-up, age and sex. This meta-analysis showed that GCA is a chronic disease that requires substantial and prolonged GC treatment in a considerable proportion of patients. A predefined GC tapering schedule may help to avoid inadequately long GC treatment.

Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis that preferentially affects the cranial arteries, the aorta, and its proximal branches and is commonly associated with raised inflammatory markers.[1–3] The incidence of GCA increases with age and is estimated at 20 per 100 000 in persons over 50 years old.[3] GCA represents a heterogeneous group of patients with distinct presentations according to the pattern of vessel involvement (cranial versus large vessel vasculitis or combined). Manifestations of GCA may include 1) constitutional symptoms (such as fever, weight loss, anorexia, and malaise) due to systemic inflammation, 2) symptoms due to vasculitis (such as temporal headache, jaw or limb claudication or visual loss), and/or 3) polymyalgia rheumatica (PMR).[4,5]

Glucocorticoids (GC) remain the cornerstone of the treatment. High dose GC (40-60 mg prednisone/day according to the EULAR guideline[6] and 1 mg/kg prednisone/day with a maximum of 80 mg according to the ACR guideline[7] - if no visual symptoms) followed by a tapering scheme is recommended. GC therapy usually results in a rapid resolution of symptoms and inflammation and prevents further ischemic complications.[3] However, almost half of the patients experience disease relapse, prolonging the required GC treatment.[8] Long-term treatment increases the risk of GC-related adverse effects, including osteoporosis, hypertension, hyperglycemia, myopathy, easy bruising, cushingoid features and cataract.[9,10] High-quality evidence on the optimal duration of GC treatment is lacking. Guidelines prefer an individualized tapering regimen based on the disease activity, adverse events, relapses, and patient's and physician's preferences.[6,7] Tapering to 5 mg prednisone/day after 12 months and weaning of GC within 18 to 24 months is recommended.[6,11,12] It is generally assumed that GC treatment in GCA takes about 2-3 years and that only a minority of patients requires long-term treatment with low GC doses.[3,13,14] However, the mean duration of GC treatment in real-life practice is not well known.

The aim of this systematic review and meta-analysis is to gain insight into the duration of GC treatment in patients with GCA.

Materials and methods

This systematic review was informed by the Cochrane Collaboration Handbook and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[15,16] This study was registered in advance in PROSPERO database (CRD42022302782).

Search strategy

We performed a systematic literature search in PubMed, Embase, and Cochrane database from inception till November 2021. We used keywords for GCA and GC, using both free text and MeSH and Emtree terms. Full search terms are described in Supplementary Table 1. The search was limited to articles published in English, French or Dutch. The references of relevant articles were screened to identify additional studies.

Study selection

We included studies fulfilling the following criteria: (1) randomized controlled trials (RCT) or observational studies, (2) only involving patients with GCA (3) treated with GC alone (entire study or control arm of trials testing GC-sparing agents) (4) reporting on the duration of GC treatment. Studies with several treatment options were only included if results for the different treatment groups were presented separately or if at least 90% of patients were treated with GC in monotherapy. When several publications were based on a single cohort or database, the most extensive and recent study was selected.

Title and abstract screening were performed by a single investigator (LM). Afterwards, the full text of the obtained studies was screened by two investigators (LM and AB). Disagreements were resolved through discussion until consensus was reached.

Data extraction

Relevant data were extracted by two independent investigators (LM and AB) into a standardized electronic form in Excel. Following data were extracted: first author's name, publication year, enrolment period, country, study design (RCT or observational study, retrospective or prospective, single or multicenter), criteria for diagnosis of GCA, number of patients who received only GC therapy, overall duration of follow-up (in months), mean age, proportion of women, proportion of patients with relapse, initial GC dose, number of patients with GC pulse, presence of GC tapering schedule, proportion of patients on GC 1, 2 and 5 years after treatment initiation and mean GC dose 1, 2 and 5 years after treatment initiation (in the entire cohort, also including patients who have already stopped GC and expressed in prednisone equivalents, being 0 mg in patients off GC). Missing summary statistics for means were calculated based on the methods proposed by Wan et al[17] (2/22 studies for age and 2/7 studies for mean GC dose).

Risk of bias was assessed by two independent investigators (LM and AB). Disagreements were solved by discussion to reach a consensus. The 'Cochrane Collaboration risk of bias tool version 2' and an adapted version of the 'Newcastle-Ottawa scale' (Supplementary Table 2) were used for RCTs and observational studies, respectively.[18,19]

Statistical analysis

A meta-analysis was performed to estimate the proportion of patients on GC and the mean GC doses 1, 2, and 5 years after treatment initiation. Meta-analysis was only performed when a minimum of 3 studies were available.

We used logit transformed proportions to stabilize the variance. As we expected high between-study heterogeneity, a random-effects model was implemented with an inverse variance method to weigh each study. The 95% confidence intervals (95% CIs) were adjusted with the Hartung-Knapp method. Tau was calculated using the restricted maximum likelihood method. Heterogeneity was measured by the I^2 and Cochrane's Q statistic. If a minimum of 10 studies

were available, subgroup analyses and univariable meta-regression were performed to assess variables that could explain heterogeneity. A sensitivity analysis was performed excluding studies with a high risk of bias. To assess small-study effects (which could indicate publication bias), funnel plots in combination with the Egger's regression test were used, although these results should be interpreted with caution as we aimed to estimate a pooled proportion and mean of one group of patients rather than a comparison of interventions.[20] Small-study effects were only assessed for outcomes reported in ≥ 10 studies. A P value less than 0.05 was considered statistically significant. All analyses were performed using R Statistical Software (v2021.11.1) with the *meta* package. The risk of bias figures were constructed using RevMan 5.4 Software.

Results

Our PubMed, Embase and Cochrane database searches identified 8982 articles, resulting in 6740 articles after removal of duplicates (Figure 1). Title and abstract screening yielded 252 articles eligible for full text analysis, of which 22 studies were included involving a total of 1786 patients.[21–42] Several studies assessed multiple outcome measures. The characteristics of the included studies are presented in Supplementary Table 3. Most studies were observational (19 studies, n = 1616),[21–25,27–32,34,36–42] retrospective (14 studies, n = 1296)[21–25,28,29,31,32,34,36–38,40] and single-center (16 studies, n = 1215).[21,23–25,27,29–31,34–43] The follow-up ranged from 12 to 114 months.

A summary of the quality assessment for specific bias domains of the included studies is presented in Figure 2. Overall, 33.3% of the RCTs had some concern of bias and 66.7% were at high risk of bias; 73.7% of the observational studies were at low risk of bias and 26.3% at high risk of bias. Supplementary Figure S1 shows the risk of bias analysis for the individual studies.

The proportion of patients taking GC 1, 2 and 5 years after treatment initiation were reported in 15 (n = 1290)[21,22,24,25,27,29,31–33,35,36,38,40–42], 14 (n = 1184)[21,22,24,25,27,29–31,34,36,38,40–42] and 9 (n = 943)[21,22,24,25,29,31,38,39,42] studies, respectively. The pooled proportion of patients with GC was 89.7% [95% CI 83.2 – 93.9%] at year 1, 75.2% [95% CI 58.7 – 86.6%] at year 2 and 44.3% [95% CI 15.2 – 77.6%] at year 5 (Figure 3). The heterogeneity between studies was high. Subgroup analysis and meta-regression were performed to explore between-study heterogeneity in the proportion of patients still taking GC 1 and 2 years after diagnosis (Supplementary Tables 4 – 7). The proportion of patients taking GC was significantly higher in single-center studies compared to multicenter studies at year 1 (92.1% [95% CI 85.3 – 95.9%] versus 81.7% [95% CI 77.4 – 85.4%], p = 0.003) and at year 2 (76.7% [95% CI 59.5 – 88.1%] versus 55.4% [95% CI 49.1 – 61.5%], p = 0.01). Studies that reported the use of a GC tapering schedule had a significantly lower proportion of patients still treated with GC at year 1 (82.2% [95% CI 72.2 – 89.1%] versus 92.9% [95% CI 85.3 – 96.7%], p = 0.01), but not at year 2 (57.5% [95% CI 12.3 – 92.9%] versus 80.8% [95% CI 65.0 – 90.5%], p = 0.16). A significantly higher proportion of patients were still taking GC 1 year after diagnosis in observational studies compared to RCTs (90.3% [95% CI 83.1 – 94.7%] versus 81.7% [95% CI 77.4 – 85.4%], p = 0.01). There were no significant differences in GC use after 1 and 2 years according to study design (retrospective vs prospective), initial GC dose, proportion of patients with pulse GC, publication year, enrolment period, duration of follow-up, age and sex. The number of studies reporting relapse rate was inadequate to perform meta-regression. A sensitivity analysis excluding the studies with high risk of bias showed similar results in the proportion of patients taking GC at year 1 (88.1% [95% CI 78.1 – 93.9%]) and at year 2 (68.2% [95% CI 48.5 – 83.0%]). The proportion of patients still treated with GC at year 5 was significantly lower in studies with a low risk of bias compared to studies with a high risk of bias (22.0% [95% CI 4.1 – 64.9%] versus 77.7% [95% CI 33.4 – 96.3%], p = 0.006).

The mean GC doses at year 1, 2 and 5 were available in 5 (n= 257) studies[23,27,28,39,43], 4 (n = 302) studies[27,34,37,39] and 1 (n = 24) study[39], respectively. The pooled mean GC dose in the

entire group of patients, also including those who have already stopped GC, was 9.1 mg/d [95% CI 2.8 – 15.5 mg/d] at year 1 and 7.8 mg/d [95% CI 1.4 – 14.1 mg/d] at year 2 after diagnosis, respectively (Figure 4 and 5). As only 1 study reported the GC dose at year 5, meta-analysis was not performed. In the study of Friedman et al. the mean GC dose at 5 years was 5.0 mg/d [95% CI 4.5 – 5.6 mg/d].[39] Because of the low number of studies, we did not perform a sensitivity analysis excluding studies with a high risk of bias and subgroup analyses and meta-regression for the mean GC dose.

The asymmetric funnel plot and significant Egger's test (p = 0.02) suggested a potential publication bias for the proportion of patients taking GC at year 1 (Supplementary Figure 2A). Trim-and-fill results showed that 4 additional studies would be required to achieve a symmetric funnel plot, resulting in a pooled proportion of 86.2% [95% CI 75.6 – 92.7%]. Visual inspection of the funnel plot and the Egger's test (p = 0.12) did not indicate publication bias for the proportion of patients taking GC at year 2 (Supplementary Figure 2B).

Discussion

While GC have been the mainstay of treatment for GCA for decades and they remain so today, the mean duration of GC treatment in real-life practice remained poorly defined. This meta-analysis showed that 89.7%, 75.2% and 44.3% of GCA patients were still treated with GC at year 1, 2 and 5 after diagnosis, respectively. In addition, patients were still receiving a considerable mean GC dose, 9.1 mg/d, 7.8 mg/d and 5.0 mg/d 1, 2 and 5 years after treatment initiation, respectively.

GCA and PMR are often seen as different manifestations of the same disease spectrum [2]. They may be found as isolated phenomena or in combination. In both diseases, GC are the cornerstone of the treatment with a slow tapering schedule to prevent relapses, however, with a higher initial GC dose in GCA compared to PMR. This meta-analysis revealed that the

proportion of GCA patients still taking GC is 13 to 24% higher at each time point compared to the GC duration of PMR patients reported in the meta-analysis of Floris et al.[44]

Several guidelines discuss some aspects of the duration of GC treatment in patients with GCA. The 2018 EULAR guideline for the management of GCA recommended tapering to ≤ 5 mg prednisone/day 1 year after treatment initiation and stated that in the majority of patients the treatment lasts approximately 2 years before GC discontinuation.[6] Both the EULAR and ACR guideline did not specify recommendations for the optimal GC treatment duration due to the lack of evidence.[6,7] The British Society of Rheumatology recommended a GC duration of 12 to 18 months.[11] The French Study Group for Large Vessel Vasculitis (GEFA) recommended tapering to 5 mg prednisone/day after 12 months and weaning of GC within 18 to 24 months.[12] In addition, several reviews mentioned that GC treatment in GCA generally takes about 2-3 years and that only a minor proportion of patients requires treatment with low doses of glucocorticoids for multiple years.[3,13,14] However, this meta-analysis showed that only 1 out of 4 patients discontinued GC at year 2. Moreover, even after 5 years, 44% of GCA patients are still on GC. In addition, we found that the mean GC dose 1 year after treatment initiation is significantly higher than the recommended dose of ≤ 5 mg prednisone/day proposed by the EULAR and GEFA guidelines. In fact, this dose seemed to be reached only at year 5.

In line with our expectations, subgroup analysis revealed a shorter GC duration in RCTs and in studies with a GC tapering schedule. The use of a predefined GC schedule appears to be important to avoid unnecessary long GC treatment. This may reflect the reluctance of clinicians to discontinue GC at an appropriate time, possibly due to concerns of microvascular and macrovascular complications and relapses.

Mainbourg et al. performed a meta-analysis assessing the relapse rate in patients with GCA and found that a shorter GC tapering schedule was associated with an increased risk of relapse.[8] In case of relapse, GC are typically increased in dose or reinitiated and subsequently tapered at a slower pace, prolonging the total duration of GC treatment. Unfortunately, the

number of studies reporting relapse rate was inadequate to perform meta-regression. Thus, an optimal GC treatment duration, which seeks a balance between the lowest possible relapse risk on one hand and the shortest GC duration with the lowest cumulative GC dose on the other hand, remains to be defined in future studies.

Chandran et al. compared GC usage between the time periods 1950–1979 and 1980–2009 and observed a higher cumulative GC dosage and a higher proportion of patients still taking GC at year 1, 2 and 5 after diagnosis in the second period.[22] However, in this meta-analysis we did not find a significant association between the proportion of patients with GC at year 1 and 2 and both publication year and enrolment period.

Furthermore, the proportion of patients with GC at year 1 and 2 after treatment initiation was significantly lower in multicenter studies. However, this difference in GC duration between single-center and multicenter studies was not explained by the use of a GC tapering schedule. It also could not be explained by any other study, patient or treatment characteristics that were included in this study.

This meta-analysis showed that GCA is a relapsing-remitting disease that requires treatment with considerable doses of GC for years and evolves into a chronic condition in the majority of patients. As the adverse effects of GC are very common, increase with a longer GC duration and higher cumulative dose and are harmful,[10] GC-sparing and ideally disease modifying agents continue to be a major need for patients with GCA. Tocilizumab has been the first biological introduced and reimbursed for the treatment of GCA.[45] For methotrexate and abatacept, there are inconsistent results.[3,46] Recently, two small trials showed promising results with the anti-GM-CSF monoclonal antibody mavrilimumab and the JAK inhibitor baricitinib, but these results need to be confirmed in larger trials.[47,48] Trials with several other promising targeted drugs are ongoing.

Our meta-analysis has several limitations. First, all outcome measures had high between-study heterogeneity, which was only partially explained with prespecified subgroup analyses. These results reflect the significant variability in GCA treatment strategies, which potentially result from a lack of clear, evidence-based guidelines on the duration and tapering of GC treatment. Second, many studies had an observational design, which results in a meta-analysis with a lower grade of evidence, compared to a meta-analysis only consisting of RCTs. Third, the proportion of patients with GC at year 5 after treatment initiation can be overestimated since not all patients were followed up long enough and since patients who are not treated anymore with GC have a higher change to be lost to follow up. In addition, we realize that a considerable number of hypothesis tests have been conducted. Therefore, interpretation should be done with caution, especially for p-values that approach the cutoff value of $p = 0.05$. Finally, many different outcome measures are used in literature to evaluate the duration of GC treatment in GCA patients, decreasing the number of studies per outcome measure in this meta-analysis. The limited number of studies hampered the power of subgroup analyses and meta-regression to detect significant interactions and decreased the confidence in the mean GC dose estimates. As a consequence, we also included studies with high risk of bias. Sensitivity analyses, however, did not show a significant difference after exclusion of studies with a high risk of bias, except for the proportion of patients with GC at year 5 after treatment initiation.

In conclusion, the majority of GCA patients are treated with high doses of GC for multiple years. GCA patients receive considerable longer courses and higher doses of GC than recommended by current practice guidelines, which results in a higher cumulative GC dose and an increased risk of GC-related side effects. Early introduction of GC sparing agents in addition to the development of an optimal GC tapering schedule which seeks a balance between the lowest relapse risk and the shortest GC duration, will be crucial to avoid unnecessary long GC treatment.

Note

The study protocol and data extracted from the included studies are available upon reasonable request.

Keywords: Giant cell arteritis – treatment – glucocorticoids

Supplemental digital content: MA GCA GC supplemental final JCR revision.doc

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Figure legends

Figure 1: PRISMA flow chart of study selection from literature search

Abbreviations: GCA, giant cell arteritis; PMR, polymyalgia rheumatica

Figure 2: Risk of bias summary for the included studies. A. Randomized controlled trials B. Observational studies. Low risk of bias Some concern of bias High risk of bias

Figure 3: Forest plot of pooled mean proportion of patients with glucocorticoids 1, 2 and 5 years after treatment initiation.

Abbreviations: 95%-CI, 95% Confidence Interval, GC, glucocorticoids

Figure 4: Forest plot of pooled mean glucocorticoids dose (in prednisone equivalents) at year 1

Abbreviations: 95%-CI, 95% Confidence Interval ; SD, Standard Deviation

Figure 5: Forest plot of pooled mean glucocorticoids dose (in prednisone equivalents) at year 2

Abbreviations: 95%-CI, 95% Confidence Interval ; SD, Standard Deviation