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.

130 The proportion of patients taking GC 1, 2 and 5 years after treatment initiation were reported
131 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 =
132 943)[21,22,24,25,29,31,38,39,42] studies, respectively. The pooled proportion of patients with GC was
133 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%
134 [95% CI 15.2 – 77.6%] at year 5 (Figure 3). The heterogeneity between studies was high.
135 Subgroup analysis and meta-regression were performed to explore between-study
136 heterogeneity in the proportion of patients still taking GC 1 and 2 years after diagnosis
137 (Supplementary Tables 4 – 7). The proportion of patients taking GC was significantly higher in
138 single-center studies compared to multicenter studies at year 1 (92.1% [95% CI 85.3 – 95.9%]
139 versus 81.7% [95% CI 77.4 – 85.4%], p = 0.003) and at year 2 (76.7% [95% CI 59.5 – 88.1%]
140 versus 55.4% [95% CI 49.1 – 61.5%], p = 0.01). Studies that reported the use of a GC tapering
141 schedule had a significantly lower proportion of patients still treated with GC at year 1 (82.2%
142 [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%
143 [95% CI 12.3 – 92.9%] versus 80.8% [95% CI 65.0 – 90.5%], p = 0.16). A significantly higher
144 proportion of patients were still taking GC 1 year after diagnosis in observational studies
145 compared to RCTs (90.3% [95% CI 83.1 – 94.7%] versus 81.7% [95% CI 77.4 – 85.4%], p =
146 0.01). There were no significant differences in GC use after 1 and 2 years according to study
147 design (retrospective vs prospective), initial GC dose, proportion of patients with pulse GC,
148 publication year, enrolment period, duration of follow-up, age and sex. The number of studies
149 reporting relapse rate was inadequate to perform meta-regression. A sensitivity analysis
150 excluding the studies with high risk of bias showed similar results in the proportion of patients
151 taking GC at year 1 (88.1% [95% CI 78.1 – 93.9%]) and at year 2 (68.2% [95% CI 48.5 –
152 83.0%]). The proportion of patients still treated with GC at year 5 was significantly lower in
153 studies with a low risk of bias compared to studies with a high risk of bias (22.0% [95% CI 4.1
154 – 64.9%] versus 77.7% [95% CI 33.4 – 96.3%], p = 0.006).
155
156 The mean GC doses at year 1, 2 and 5 were available in 5 (n= 257) studies[23,27,28,39,43], 4 (n =
157 302) studies[27,34,37,39] and 1 (n = 24) study[39], respectively. The pooled mean GC dose in the

158 entire group of patients, also including those who have already stopped GC, was 9.1 mg/d
159 [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
160 diagnosis, respectively (Figure 4 and 5). As only 1 study reported the GC dose at year 5, meta-
161 analysis was not performed. In the study of Friedman et al. the mean GC dose at 5 years was
162 5.0 mg/d [95% CI 4.5 – 5.6 mg/d].[39] Because of the low number of studies, we did not perform
163 a sensitivity analysis excluding studies with a high risk of bias and subgroup analyses and
164 meta-regression for the mean GC dose.
165
166 The asymmetric funnel plot and significant Egger's test (p = 0.02) suggested a potential
167 publication bias for the proportion of patients taking GC at year 1 (Supplementary Figure 2A).
168 Trim-and-fill results showed that 4 additional studies would be required to achieve a symmetric
169 funnel plot, resulting in a pooled proportion of 86.2% [95% CI 75.6 – 92.7%]. Visual inspection
170 of the funnel plot and the Egger's test (p = 0.12) did not indicate publication bias for the
171 proportion of patients taking GC at year 2 (Supplementary Figure 2B).
172
173 **Discussion**
174 While GC have been the mainstay of treatment for GCA for decades and they remain so today,
175 the mean duration of GC treatment in real-life practice remained poorly defined. This meta-
176 analysis showed that 89.7%, 75.2% and 44.3% of GCA patients were still treated with GC at
177 year 1, 2 and 5 after diagnosis, respectively. In addition, patients were still receiving a
178 considerable mean GC dose, 9.1 mg/d, 7.8 mg/d and 5.0 mg/d 1, 2 and 5 years after treatment
179 initiation, respectively.
180
181 GCA and PMR are often seen as different manifestations of the same disease spectrum [2].
182 They may be found as isolated phenomena or in combination. In both diseases, GC are the
183 cornerstone of the treatment with a slow tapering schedule to prevent relapses, however, with
184 a higher initial GC dose in GCA compared to PMR. This meta-analysis revealed that the

185 proportion of GCA patients still taking GC is 13 to 24% higher at each time point compared to
186 the GC duration of PMR patients reported in the meta-analysis of Floris et al.[44]
187
188 Several guidelines discuss some aspects of the duration of GC treatment in patients with GCA.
189 The 2018 EULAR guideline for the management of GCA recommended tapering to ≤ 5 mg
190 prednisone/day 1 year after treatment initiation and stated that in the majority of patients the
191 treatment lasts approximately 2 years before GC discontinuation.[6] Both the EULAR and ACR
192 guideline did not specify recommendations for the optimal GC treatment duration due to the
193 lack of evidence.[6,7] The British Society of Rheumatology recommended a GC duration of 12 to
194 18 months.[11] The French Study Group for Large Vessel Vasculitis (GEFA) recommended
195 tapering to 5 mg prednisone/day after 12 months and weaning of GC within 18 to 24 months.[12]
196 In addition, several reviews mentioned that GC treatment in GCA generally takes about 2-3
197 years and that only a minor proportion of patients requires treatment with low doses of
198 glucocorticoids for multiple years.[3,13,14] However, this meta-analysis showed that only 1 out of
199 4 patients discontinued GC at year 2. Moreover, even after 5 years, 44% of GCA patients are
200 still on GC. In addition, we found that the mean GC dose 1 year after treatment initiation is
201 significantly higher than the recommended dose of ≤ 5 mg prednisone/day proposed by the
202 EULAR and GEFA guidelines. In fact, this dose seemed to be reached only at year 5.
203
204 In line with our expectations, subgroup analysis revealed a shorter GC duration in RCTs and
205 in studies with a GC tapering schedule. The use of a predefined GC schedule appears to be
206 important to avoid unnecessary long GC treatment. This may reflect the reluctance of clinicians
207 to discontinue GC at an appropriate time, possibly due to concerns of microvascular and
208 macrovascular complications and relapses.
209 Mainbourg et al. performed a meta-analysis assessing the relapse rate in patients with GCA
210 and found that a shorter GC tapering schedule was associated with an increased risk of
211 relapse.[8] In case of relapse, GC are typically increased in dose or reinitiated and subsequently
212 tapered at a slower pace, prolonging the total duration of GC treatment. Unfortunately, the

213 number of studies reporting relapse rate was inadequate to perform meta-regression. Thus,
214 an optimal GC treatment duration, which seeks a balance between the lowest possible relapse
215 risk on one hand and the shortest GC duration with the lowest cumulative GC dose on the
216 other hand, remains to be defined in future studies.
217
218 Chandran et al. compared GC usage between the time periods 1950–1979 and 1980–2009
219 and observed a higher cumulative GC dosage and a higher proportion of patients still taking
220 GC at year 1, 2 and 5 after diagnosis in the second period.[22] However, in this meta-analysis
221 we did not find a significant association between the proportion of patients with GC at year 1
222 and 2 and both publication year and enrolment period.
223
224 Furthermore, the proportion of patients with GC at year 1 and 2 after treatment initiation was
225 significantly lower in multicenter studies. However, this difference in GC duration between
226 single-center and multicenter studies was not explained by the use of a GC tapering schedule.
227 It also could not be explained by any other study, patient or treatment characteristics that were
228 included in this study.
229
230 This meta-analysis showed that GCA is a relapsing-remitting disease that requires treatment
231 with considerable doses of GC for years and evolves into a chronic condition in the majority of
232 patients. As the adverse effects of GC are very common, increase with a longer GC duration
233 and higher cumulative dose and are harmful,[10] GC-sparing and ideally disease modifying
234 agents continue to be a major need for patients with GCA. Tocilizumab has been the first
235 biological introduced and reimbursed for the treatment of GCA.[45] For methotrexate and
236 abatacept, there are inconsistent results.[3,46] Recently, two small trials showed promising
237 results with the anti-GM-CSF monoclonal antibody mavrilimumab and the JAK inhibitor
238 baricitinib, but these results need to be confirmed in larger trials.[47,48] Trials with several other
239 promising targeted drugs are ongoing.
240

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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407 **Figure legends**

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

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

410

411 **Figure 2:** Risk of bias summary for the included studies. A. Randomized controlled trials B.

412 Observational studies. Low risk of bias Some concern of bias High risk of bias

413

414 **Figure 3:** Forest plot of pooled mean proportion of patients with glucocorticoids 1, 2 and 5

415 years after treatment initiation.

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

417

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

419 1

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

421

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

423 2

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

425