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American College of Rheumatology
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REVIEW ARTICLE

Giant Cell Arteritis: A Systematic Review and Meta-Analysis of Test Accuracy and Benefits and Harms of Common Treatments

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This systematic review compares treatment options for patients with giant cell arteritis (GCA) and evaluates the test accuracy of studies used in diagnosing and monitoring GCA. These studies were used to inform evidence-based recommendations for the American College of Rheumatology (ACR)/Vasculitis Foundation (VF) vasculitis management guidelines. A systematic review and search of articles in English in Ovid Medline, PubMed, Embase, and the Cochrane Library was conducted. Articles were screened for suitability, and studies presenting the highest level of evidence were given preference. Three hundred ninety-nine full-text articles addressing GCA questions were reviewed to inform 27 Population, Intervention, Comparison, and Outcome questions. No benefit was found with intravenous glucocorticoids (GCs) compared with high-dose oral GCs in patients with cranial ischemic symptoms (27.4% vs 12.3%; odds ratio [OR] 2.39 [95% confidence interval (CI) 0.75-7.62], [very low certainty of evidence]). Weekly tocilizumab with a 26-week GC taper was superior to a 52-week GC taper in patients achieving remission (risk ratio 4.00 [95% CI 1.97-8.12], [low certainty of evidence]). Non-GC immunosuppressive therapies with GCs compared with GCs alone showed no statistically significant in relapse at 1 year (OR 0.87 [95% CI 0.73-1.04], [moderate certainty of evidence]) or serious adverse events (OR 0.81 [95% CI 0.54-1.20]; [moderate certainty of evidence]). Temporal artery biopsy has a sensitivity of 61% (95% CI 38%-79%) and a specificity of 98% (95% CI 95%-99%) in patients with a clinical diagnosis of suspected GCA. This comprehensive systematic review synthesizes and evaluates the benefits and harms of different treatment options and the accuracy of commonly used tests for the diagnosis and monitoring of GCA.

INTRODUCTION

Giant cell arteritis (GCA) is a granulomatous large vessel vasculitis that preferentially involves the cranial arteries, aorta, and its proximal branches. Inflammation of the vessel wall can result in damage, leading to stenosis, aneurysm formation, or occlusions (1). GCA is the most common form of systemic vasculitis, with an annual incidence between 15 and 25 per 100,000 persons (2). Clinically, GCA affects older patients and can result in severe ischemic complications, including visual loss, stroke, or limb claudication. The diagnosis of GCA can be challenging and is informed by clinical presentation, laboratory results, tissue sampling, and vascular imaging (3). Historically, management of GCA has relied on glucocorticoids (GCs), although more recently, newer biologic

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agents have been studied in several randomized controlled trials (RCTs), as well as observational studies, in this population. GCA is a chronic disease with frequent relapses, which contributes to the morbidity experienced by patients as well as the need for long-term monitoring and management.

The first aim of this systematic review is to search for and compare the benefits and harms of different treatment options for patients with GCA. This review includes RCTs and nonrandomized studies and presents the evidence and an assessment of its quality for important outcomes. The second aim of this systematic review is to determine the accuracy of commonly available diagnostic tests for GCA, which can be used to inform a combined strategy for diagnosis and management. Pooled estimates of sensitivity and specificity obtained in this systematic review were used to model different diagnostic and management strategies for patients with suspected GCA. The results of modeling were used to inform evidence-based recommendations on management strategies for GCA in the American College of Rheumatology (ACR)/Vasculitis Foundation (VF) vasculitis management guidelines.

MATERIALS AND METHODS

Search strategy and data sources. An information specialist conducted systematic searches of the published English-language literature in Ovid Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Health Technology Assessments) from the inception of each database through August 2018 to obtain direct evidence relating to vasculitis questions in patients with vasculitis (Supplementary Appendix 1). The information specialist updated the searches conducted on August 2019. The methods team used DistillerSR software to identify duplicate records (online at https://www.evidencepartners.com/products/distillersr-systematic-review-software/). The search was specific to address the Population, Intervention, Comparison, and Outcome (PICO) questions asked for each vasculitis type. The ACR/VF vasculitis management guideline core team developed 27 PICO questions for GCA that addressed relevant or commonly encountered patient diagnostic testing, treatment, and management scenarios (Supplementary Appendix 2).

Study selection. *Studies.* We included studies that would provide the highest certainty of the evidence. For questions addressing treatment options, we included RCTs first. When RCTs were not available, we included observational studies (cohort and case-control studies) that reported on patient-important outcomes for the intervention and comparison arms. When studies with comparative data were not available, we included case series that presented patient-important outcomes for either the intervention or the comparison arm. For questions addressing diagnosis and test-related options, we included studies that reported on diagnostic test accuracy (cohort studies, cross-sectional studies) for GCA.

Participants. Adult patients 18 years of age and older presenting to inpatient or outpatient settings with suspected or confirmed GCA were eligible for inclusion. When studies addressed multiple vasculitis types, we included data when results were presented separately or when greater than 80% of the included population were patients with GCA.

Interventions. Studies reporting outcomes comparatively for the intervention and comparison arms in the PICO questions or reporting outcomes for either the intervention or the comparison arm were included. In case of diagnostic questions, when test accuracy results were presented comparatively for the index test and the comparator or for either the index test or the comparator, the studies were included.

Exclusion criteria. Excluded studies were studies with an irrelevant population, intervention, or outcome; studies that had no primary data, such as letters, opinion pieces, and commentaries; narrative reviews; systematic reviews; epidemiological studies that only included prevalence or incidence results; any study that had less than 10 patients (if a study had greater than 10 patients but only less than 10 had vasculitis, it was excluded); any study that addressed an organ-limited vasculitis, except renal-limited vasculitis; and any study about basic research in animals.

Screening and data extraction. Pairs of two independent reviewers conducted the title and abstract screening and the full-text review in duplicate to identify eligible studies. Data extraction was also conducted independently and in duplicate, and conflicts were resolved by a third reviewer (MAK). Each pair of reviewers included at least one of five clinical experts (KB, ABD, KEJ, YCL, and JMS). Data extracted included general study characteristics (authors, publication year, country, and study design), duration of follow-up, outcome data for the intervention and/or comparison arm, and diagnostic index test and reference standard, along with parameters to determine test accuracy (ie, sensitivity and specificity of the index test) when relevant.

Risk of bias and data synthesis. When direct comparative results were available from RCTs, reviewers entered the results into RevMan version 5.3 software (The Cochrane Collaboration; online at http://tech.cochrane.org/revman), which was used to calculate pooled effect estimates. Reviewers evaluated the risk of bias using the Cochrane risk-of-bias tool (The Cochrane Collaboration; online at https://methods.cochrane.org/risk-bias-2).

When direct comparative results were available from observational studies (cohort and case-control studies), reviewers entered the results into RevMan version 5.3 software, which was used to calculate pooled effect estimates. Reviewers evaluated

the risk of bias using a modified Newcastle-Ottawa Scale for observational studies (online at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

When comparative results were not available, reviewers abstracted data describing details of the population, interventions, and results into summary tables.

When test accuracy results were available, reviewers abstracted test accuracy information and used the Quality Assessment of Diagnostic Accuracy Studies tool to assess the risk of bias in the included studies. When pooling was appropriate, the review team used OpenMetaAnalyst (online at http://www.cebm.brown.edu/openmeta/) to pool test accuracy results.

Two investigators familiar with the GRADEpro software (online at https://gradepro.org) (MAK and NMH) formulated Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary-of-findings tables for each PICO question when direct comparative data or test accuracy results were available. The investigators used the GRADE framework to assess overall certainty by evaluating the evidence for each outcome on the following domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Data analysis. For questions addressing treatment options, relative risks (risk ratios [RRs] and odds ratios [ORs]) were calculated by pooling results from RCTs and from observational studies comparing treatments. When no direct comparisons between treatments within a study were available, the risk of an event (or proportion) in a study (eg, disease relapse) was calculated, and then the weighted proportions from each study were combined and presented in the outcome description section of the summary tables.

For questions addressing diagnosis tests, the accuracy estimates from individual studies were combined quantitatively (pooled) for each test by using OpenMetaAnalyst. We conducted a bivariate analysis for pooling sensitivity and specificity for each of the test comparisons to account for variation within and between studies. Forest plots were created for each comparison. The Breslow-Day test was used to measure the percentage of total variation across studies due to heterogeneity (I^2); however, the results did not influence our judgment of the pooled estimates because the literature has discouraged its use for test accuracy.

RESULTS

Description of studies. The initial search yielded 13,800 nonduplicate studies, of which 2596 were included for the full-text review. Following the full-text review, we identified 1156 articles to be potentially eligible for data abstraction and inclusion in the systematic reviews of seven different types of vasculitis. For this review, we considered 399 articles for data abstraction for GCA. Figure 1 shows the study flow diagram for included studies.

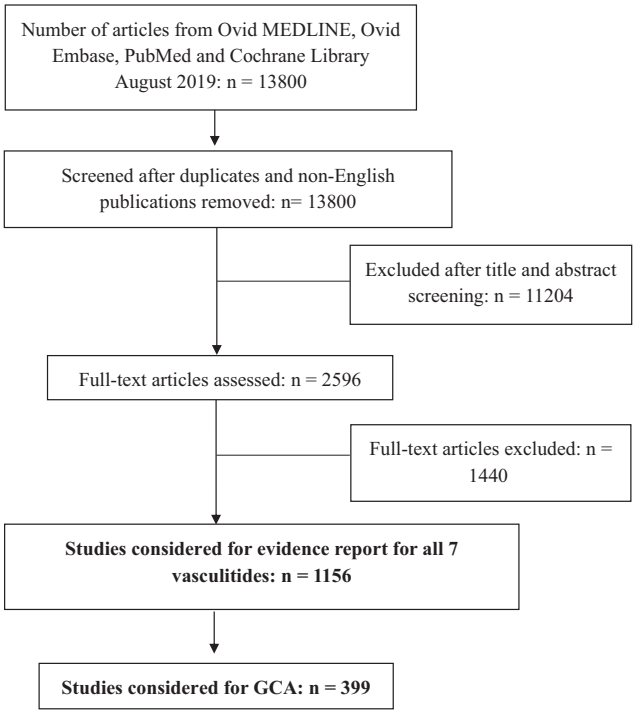

Figure 1. Flow diagram for the studies included in this systematic review for giant cell arteritis (GCA).

Benefits and harms of treatment options in GCA. *Intravenous versus high-dose oral glucocorticoids in patients with cranial ischemia.* Two retrospective studies evaluated intravenous (IV) glucocorticoids (GCs) versus high-dose oral GCs in patients with newly diagnosed GCA with features of cranial ischemia. In the study by Chan et al (4), which included 73 patients who presented to the ophthalmologist with biopsy-proven GCA and vision loss, 23% of patients who received IV GCs had improved vision, compared with 5% of those treated with oral GCs ($P = 0.01$). Those who received IV GCs had worse initial visual acuity at presentation ($P = 0.04$) (4). In the retrospective study by Hayreh et al (5), among 84 consecutive patients with biopsy-proven GCA with visual loss, visual improvement was seen in 7% of 41 patients treated initially with IV GCs versus 5% of 43 patients treated with oral GCs only ($P = 0.672$). Variable doses of IV steroid regimens were used in both of these retrospective studies, ranging from 500 to 1000 mg daily for 2 to 5 days. In the meta-analysis, there was no statistically significant difference in the proportion of patients showing visual improvement between those who received IV GCs and those who received oral GCs (27.4% vs 12.3%; OR 2.39 [95% confidence interval (CI) 0.75-7.62]) (very low certainty of evidence).

IV versus high-dose oral GCs in patients without cranial ischemia. Two RCTs evaluated outcomes of IV GCs versus high-dose oral GCs in patients with newly diagnosed GCA without manifestations of cranial ischemia (6,7). In the study by Chevalet et al (6), 50 patients with GCA were treated with 240 mg of IV methylprednisolone, followed by 0.7 mg/kg/day of

oral prednisone, and 53 patients were treated with 0.7 mg/kg/day of prednisone without an IV pulse. There were no significant differences in the cumulative GC dose at 1 year (P = 0.39) or in the time to normalization of C-reactive protein levels. Patients treated with IV GCs did not have significantly more infections (10 of 50 [20%]) when compared with those treated with oral GCs (6 of 53 [11.3%]; OR 1.77 [95% CI 0.69-4.50]) (Very low certainty of evidence). There were three deaths in this RCT, all seen in the IV GC group, although this was not statistically significant. In the double-blind, placebo-controlled RCT by Mazlumzadeh et al (7), 27 patients with biopsy-proven GCA were randomly assigned to15 mg/kg of IV methylprednisolone or IV saline for three consecutive days, followed by 40 mg/day of oral prednisone. More patients in the IV GC group were in remission at week 36 (71.4% vs 15.4%; OR 13.75 [95% CI 2.05-92.04]) (very low certainty of evidence) and week 52 (78.6% vs 15.4%; OR 20.17 [95% CI 2.80-145.30]) (very low certainty of evidence) compared with the oral GC group. The IV GC group showed fewer relapses (21 in 14 patients vs 37 in 13 patients; P = 0.028), a lower cumulative GC dose at week 78 (5636 mg [interquartile range (IQR) 4050-6690] vs 7860 mg [IQR 7373-9005]; P = 0.001), and no significant difference in adverse events (38 events in 14 patients vs 37 events in 13 patients) when compared with the oral GC group (7).

Maintenance dosing of GC regimen. One RCT evaluated the impact of tapering off GCs by 6 months versus tapering off GCs over a period longer than 6 months in patients with GCA (8). This analysis included the two GCs-only arms of the four randomized arms in the trial evaluating tocilizumab (TCZ) (8). Patients were randomly assigned to a 26-week taper (n = 50) or a 52-week taper (n = 51). Both groups were initially treated with 60 mg of prednisone daily, which was tapered to 20 mg/day by week 7, at which point the tapering protocols diverged. There was no difference in patient ability to achieve remission between either arm (14% vs 17.6%; RR 0.79 [95% CI 0.32-1.97]) (low certainty of evidence), although the remission rate was low in both arms. There were numerically more flares in the 26-week taper arm (68%) compared with the 52-week taper arm (49%) (RR 1.39 [95% CI 0.99-1.95]) (moderate certainty of evidence). There were no statistically significant differences between the 26-week arm and the 52-week arm regarding serious adverse events (SAEs) (22% vs 25.5%; RR 0.86 [95% CI 0.43-1.74]) (low certainty of evidence) or infections (76% vs 64%; RR 1.17 [95% CI 0.91-1.52]) (moderate certainty of evidence) (8).

One RCT evaluated alternate-day dosing versus daily dosing of GCs in patients with GCA and found that remission at 4 weeks was achieved in 80% of those on daily dosing compared with 30% of those on alternate-day dosing (OR 0.11 [95% CI 0.03-0.46]) (low certainty of evidence) (9).

TCZ for induction. Two RCTs evaluated the efficacy and outcomes of TCZ for induction of remission in patients with newly diagnosed or relapsing GCA (8,10). In the trial by Stone et al (8), 251 patients were randomly assigned 2:1:1:1 to receive 162 mg of subcutaneous TCZ weekly or every other week combined with a 26-week GC taper or receive a placebo combined with a GC taper over either 26 or 52 weeks. The primary outcome was the rate of sustained GC-free remission at week 52 in each TCZ group as compared with the placebo group that underwent the 26-week prednisone taper. Sustained remission was seen in 56% of patients treated with weekly TCZ compared with 14% in the placebo plus 26-week prednisone taper group (RR 4.00 [95% CI 1.97-8.12]) (low certainty of evidence). When the weekly TCZ group was compared with the placebo plus 26-week GC taper group, flares were seen in 23% versus 68% (RR 0.34 [95% CI 0.23-0.51]) (moderate certainty of evidence), and there was no difference in serious infections (7% vs 4%; RR 1.75 [95% CI 0.38-8.12]) (Low certainty of evidence). In the trial by Villiger et al (10) of 30 patients (20 on weekly TCZ + GCs and 10 on GCs alone), relapse-free survival was achieved in 17 (85%) patients in the TCZ group and two (20%) patients in the placebo group by week 52 (risk difference 65% [95% CI 3-94]). When we included data from both of these trials, there was no statistically significant difference in SAEs (18.3% vs 26.7%; RR 0.69 [95% CI 0.40-1.19]) (low certainty of evidence).

Quality-of-life assessments were evaluated in the trial by Stone et al (8), and the mean increase (indicating clinical improvement) from baseline to week 52 in the 36-Item Short Form Health Survey (SF-36) physical component summary score was 4.10 in the group that received TCZ weekly, whereas the score decreased (indicating a worse condition) by –1.49 in the placebo group with the 52-week taper, with a difference of 5.59 points (99% CI 0.86-10.32; P = 0.002). This difference was not seen in the biweekly TCZ group. The mean change from baseline in the mental component summary score did not differ significantly between the group that received TCZ weekly (score change 7.28) and the placebo group that underwent the 52-week taper (score change 2.84). The average score on the patient global assessment of disease activity visual analog scale decreased by 19.0 in the weekly TCZ group, which was greater than the decrease of 7.2 in the placebo group with a 52-week GC taper (least-squares mean–11.8 [99% CI –27.2 to 3.6]; P = 0.048) (8).

Abatacept for remission maintenance. One multicenter RCT evaluated abatacept for remission maintenance in patients with newly diagnosed or relapsing GCA (11). Forty-nine patients were treated with 10 mg/kg of abatacept intravenously on days 1, 15, and 29 and week 8, together with prednisone administered daily. At week 12, 41 patients were in remission and underwent randomization to continue monthly abatacept or switch to a placebo. The prednisone taper was standardized as a daily dose of 20 mg at week 12 and discontinuation at week 28. The relapse-free survival rate at 12 months was 48% for those receiving abatacept and 31% for those receiving a placebo (P = 0.049) (low certainty of evidence). A longer median duration of remission was seen in those receiving abatacept compared with those receiving a placebo (median duration 9.9 vs 3.9 months; P = 0.023) (low

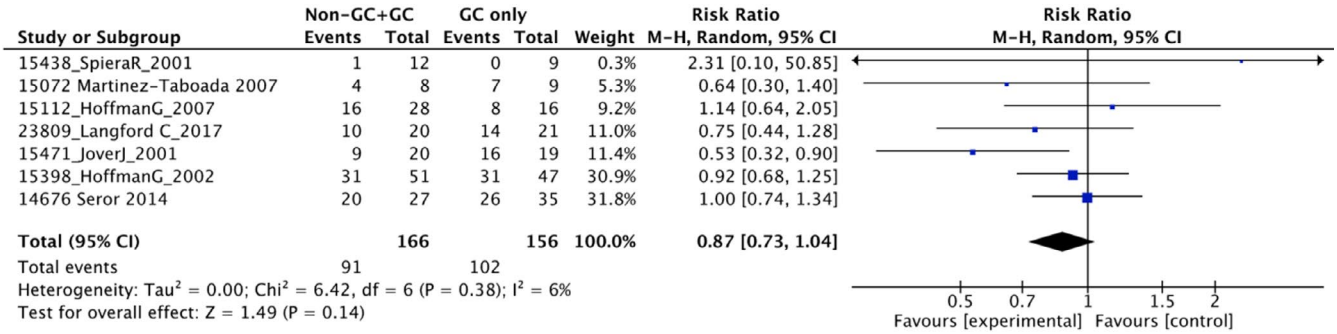

Figure 2. Relapse at 1 year in patients with giant cell arteritis (GCA) on glucocorticoids (GCs) and non-GC immunosuppressive therapies versus GCs alone. CI, confidence interval; df, degree of freedom; M–H, Mantel-Haenszel test.

certainty of evidence). There was no difference in the frequency or severity of adverse events (OR 1.63 [95% CI 0.47-5.63]) (low certainty of evidence), and no deaths were reported in either arm (11).

Non-GC immunosuppressive therapy with GCs versus GCs alone. A combination of 11 studies, including RCTs, case-control studies, and observational studies, evaluated the role of using non-GC immunosuppressive therapy (IS) in combination with GCs versus using GCs alone regarding disease-related outcomes and adverse events in patients with newly diagnosed GCA (8,10,12-20). Of the 11 studies, four evaluated methotrexate (MTX), including three RCTs (12,15,16) with 161 patients and one case-control study (20). One observational study evaluated leflunomide (LEF) (19). Six RCTs evaluated biologics, including infliximab (13), adalimumab (17), etanercept (18), abatacept (11), and TCZ (8,10).

Across seven of the studies evaluating MTX as well as biologics, there was no significant difference in relapse at 1 year between patients with GCA treated with non-GC IS in combination with GCs (91 of 166 [54.8%]) and those treated with GCs alone (102 of 156 [65.4%]; OR 0.87 [95% CI 0.73-1.04]) (moderate certainty of evidence) (11-13,15-18) (Figure 2). Across the six RCTs evaluating biologics in combination with GCs versus GCs alone, there was no difference in SAEs (OR 0.81 [95% CI 0.54 1.20]) (moderate certainty of evidence) (8,10,11,13,17,18) (Figure 3). Across the seven studies that reported on infections in patients with GCA, there was no significant difference between patients treated with non-GC IS in combination with GCs (63.4%) and those treated with GCs alone (52%) (OR 1.25 [95% CI 0.87-1.79]) (moderate certainty of evidence) (8,10,11,16-18) (Figure 4). Two studies (one with MTX, one with infliximab) reported on malignancies and found no significant difference between those on non-GC IS in combination with GCs (2 of 40 [5.0%]) and those on GCs alone (2 of 25 [8.0%]; OR 0.74 [95% CI 0.11-4.99]) (low certainty of evidence) (6,10).

TNF inhibitors. Hoffman et al (13) showed that infliximab therapy did not increase the proportion of patients without a relapse at week 22 when compared with a placebo (43% vs 50%, respectively; difference of –7 percentage points [95% CI –38 to 23 percentage points]; *P* = 0.65), nor did it increase the proportion of patients without a relapse whose GC dosages were tapered to 10 mg/day (61% vs 75%, respectively; difference, –14 percentage points [CI –42 to 14 percentage points]; *P* = 0.31). In another study of 70 patients with GCA (adalimumab, n = 34; placebo, n = 36) treated with 40 mg of adalimumab every other week for 10 weeks or a placebo, there was no difference in patient ability to achieve remission on less than 0.1 mg/kg of prednisone at week 26 (58.9% in the adalimumab arm and 50.0% in the placebo arm; *P* = 0.46) (17). Martinez-Taboada et al (18) observed eight patients on etanercept and nine patients on a placebo for 1 year. They found significantly less relapses in those

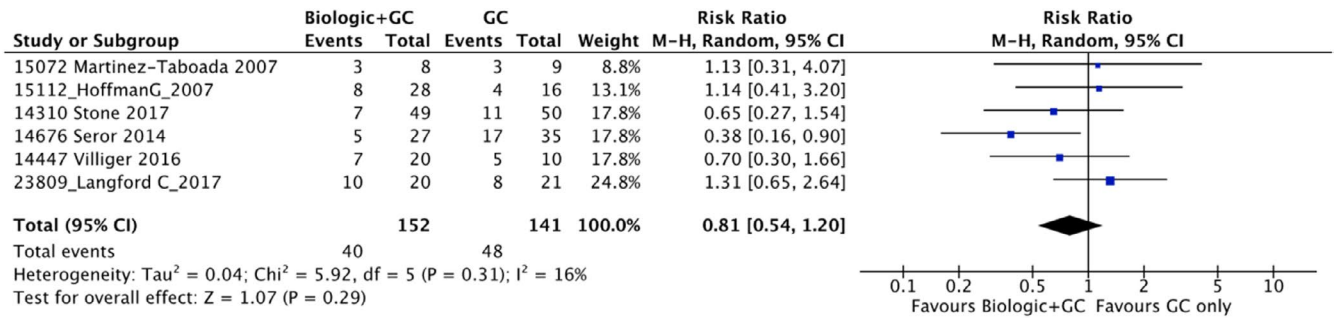

Figure 3. Serious adverse events (SAEs) in patients with giant cell arteritis (GCA) on glucocorticoids (GCs) and biologics versus GCs alone. CI, confidence interval; df, degree of freedom; M–H, Mantel-Haenszel test.

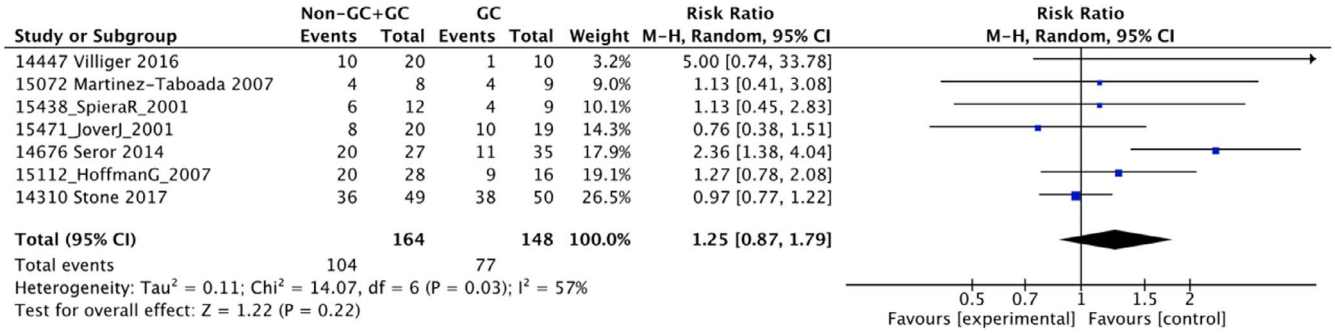

Figure 4. Infections in patients with giant cell arteritis (GCA) on glucocorticoids (GCs) and non-GC immunosuppressive therapies versus GCs alone. CI, confidence interval; df, degree of freedom; M–H, Mantel-Haenszel test.

treated with etanercept (2 of 8 [25.0%]) compared with those on GCs (9 of 9 [100.0%]; RR 0.29 [95% CI 0.10-0.85]) as well as a lower dose of accumulated prednisone during the first year of treatment (low certainty of evidence). The limited number of patients in this study makes it difficult to draw definitive conclusions on the efficacy of etanercept.

MTX. Three RCTs and one case-control study evaluated the role of MTX in patients with GCA (12,15,16,20). Two RCTs did not find significant benefit with the use of MTX (12,16). Spiera et al (12) included 21 patients (12 receiving MTX, 9 receiving a placebo) and compared 7.5 mg/week of MTX (titrated up by 2.5 mg/week for disease flare to a maximum of 20 mg/week) in combination with GCs with a placebo in combination with GCs. GCs were tapered per the treating physician. There was no significant difference in the cumulative GC dose (6469 and 5908 mg, respectively; *P* = 0.6) the number of weeks to completion of GCs (68 and 60, respectively; *P* = 0.5), or major GC-related side effects between the two groups (12). The international multicenter RCT by Hoffman et al (16) randomly assigned 98 patients to either 0.15 mg/kg/week of MTX (increased to 0.25 mg/kg/week for a maximum weekly dosage of 15 mg) or a placebo with GCs (1 mg/kg/day with taper based on an alternate-day dosing regimen). Treatment failure was defined as two distinct relapses or persistence of disease activity after the first relapse despite increased GC therapy. At 12 months, 57.5% of patients in the MTX group failed treatment (95% CI 41.6%-73.4%) compared with 77.3% in the placebo group (95% CI 61.9%-92.8%; *P* = 0.26). There was no difference in cumulative GC dose or treatment toxicity (16).

Positive results were noted in the RCT by Jover et al (15) in Spain. Forty-two patients with new-onset, biopsy-proven GCA were randomly assigned to MTX (10 mg/week) in combination with GCs (60 mg daily with planned taper) or to a placebo in combination with GCs and were observed for 24 months. The MTX arm experienced less relapses than the placebo arm (45% vs 84.2%; *P* = 0.02), and the mean cumulative dose of prednisone was 4187 ± 1529 mg in the MTX group and 5489.5 ± 1396 mg in the placebo group (mean difference 1302 mg [95% CI 350-2253 mg]; *P* = 0.009). The rate and severity of adverse events were similar between groups (15). The single-center case-control study by Koster et al (20) had similar findings; however, MTX was initiated later (median [IQR] 39 [13-80] weeks) after the GCA diagnosis at a starting dose of 13.5 (IQR 10-15) mg/week. Relapse rates before and after the MTX initiation/index date were significantly reduced in both cases (RR 0.32 [95% CI 0.24-0.41]) and controls (RR 0.60 [95% CI 0.43-0.86]). Although both groups had a reduction in relapse rates, the decrease in relapse rates was significantly greater in patients taking MTX than in those taking GCs alone (*P* = 0.004) (20).

LEF. LEF was studied by Hočevar et al (19) in an observational open-label study of 76 patients with newly diagnosed GCA. At the time of diagnosis, all patients received GCs, and at week 12, 10 mg of LEF daily was recommended as an adjunctive therapy. The decision to start LEF was patient dependent, and 30 patients (39.5%) received LEF, whereas the remainder continued on GCs alone (n = 46). During the first 48 weeks of follow-up, 13.3% of patients on LEF and 39.1% of patients on GCs alone relapsed (OR 0.24 [95% CI 0.07-0.80]) (low certainty of evidence). Patients in the LEF group had a lower cumulative GC dose, and 56.7% were off of GCs by week 48 (19).

Temporal artery biopsy in diagnosis of GCA. *Accuracy.* Across six cohort and case-control studies of 856 patients, the pooled sensitivity of temporal artery biopsy (TAB) in patients with suspected GCA was 61% (95% CI 38%-79%) and the pooled specificity was 98% (95% CI 95%-99%) compared to a reference standard of a clinical diagnosis (supported by ACR criteria in the studies done after 1990) (21-26) (Table 1). There was overall very low certainty of test accuracy across these studies. In the studies by Bowling et al (22) and Luqmani et al (23), sensitivity was low and did not overlap with the CIs from other studies. The low sensitivity in the study by Bowling et al (22) may be in part due to the fact that many of the samples did not meet the average minimal length of greater than 1 cm, increasing the likelihood of missing skip lesions on pathology. Of the 129 TABs reviewed in this study that were performed in patients with suspected GCA, 13.2% were positive for GCA, 7.8% yielded insufficient samples, and

Table 1. The test accuracy of temporal artery biopsy in patients suspected to have GCA

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested		Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pretest probability of 20%	Pretest probability of 50%	
True-positives (patients with GCA)	6 studies (493 patients)	Cohort and case-control studies	Very serious[a]	Not serious	Very serious[b]	Very serious[c]	None	121 (76-144)	303 (191-360)	⊕◯◯◯ Very low
False-negatives (patients incorrectly classified as not having GCA)								79 (56-124)	197 (140-309)	
True-negatives (patients without GCA)	6 studies (363 patients)	Cohort and case-control studies	Very serious[a]	Not serious	Not serious	Serious[d]	None	785 (762-794)	491 (477-497)	⊕◯◯◯ Very low
False-positives (patients incorrectly classified as having GCA)								15 (6-38)	9 (3-23)	

Note. Sensitivity of 0.61 (95% CI: 0.38-0.79) and specificity of 0.98 (95% CI: 0.95-0.99); prevalence: 20%-50%.
Abbreviations: CI, confidence interval; CoE, certainty of evidence; GCA, giant cell arteritis.
[a] Different studies used different reference standards; also, the index test results were interpreted with knowledge of the results of the reference standard, and the reference standard results were interpreted with knowledge of the results of the index test.
[b] Unexplained heterogeneity. The CIs of the sensitivity from the studies by Bowling et al (22) and Luqmani et al (23) do not overlap with the CIs of other studies. The sensitivity ranges between 0.17 and 0.89.
[c] The pooled sensitivity has a broad CI. Clinical action would differ if the upper versus the lower boundary of the CI represented the truth.
[d] Wide CI of the false-positive, which may lead to a different decision on the basis of the extremes of the CI.

Table 2. Comparative test accuracy of temporal artery biopsy versus temporal artery ultrasound in patients with suspected GCA

Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1000 patients tested				Test accuracy CoE
								Pretest probability of 20%		Pretest probability of 40%		
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Temporal artery biopsy	Temporal artery ultrasound	Temporal artery biopsy	Temporal artery ultrasound	
True-positives (patients with GCA)	1 study (257 patients)	Cross-sectional (cohort-type accuracy study)	Very serious[a]	Not serious	Not serious	Serious[b]	None	78 (67-91)	107 (95-120)	156 (133-182)	215 (190-240)	⊕◯◯◯ Very low
								29 fewer TPs in temporal artery biopsy		59 fewer TPs in temporal artery biopsy		
False-negatives (patients incorrectly classified as not having GCA)								122 (109-133)	93 (80-105)	244 (218-267)	185 (160-210)	
								29 more FNs in temporal artery biopsy		59 more FNs in temporal artery biopsy		
True-negatives (patients without GCA)	1 study (124 patients)	Cross-sectional (cohort-type accuracy study)	Very serious[a]	Not serious	Not serious	Serious[b]	None	799 (777-799)	646 (581-698)	599 (583-599)	484 (436-523)	⊕◯◯◯ Very low
								153 more TNs in temporal artery biopsy		115 more TNs in temporal artery biopsy		
False-positives (patients incorrectly classified as having GCA)								1 (1-23)	154 (102-219)	1 (1-17)	116 (77-164)	
								153 fewer FPs in temporal artery biopsy		115 fewer FPs in temporal artery biopsy		

Note. Temporal artery biopsy: sensitivity of 0.39 (95% CI: 0.33-0.46) and specificity of 1.00 (95% CI: 0.97-1.00); temporal artery ultrasound: sensitivity of 0.54 (95% CI: 0.47-0.60) and specificity of 0.81 (95% CI: 0.73-0.87); prevalences: 20%-40%.

Abbreviations: CI, confidence interval; CoE, certainty of evidence; FN, false negative; FP, false positive; GCA, giant cell arteritis; TN, true negative; TP, true positive.

[a] Bias in timing and flow was ultrasound and biopsy procedures within 10 days of starting treatment of suspected GCA. The reference standard bias was no independent gold standard diagnosis for GCA. The reference diagnosis used to determine accuracy was based on classification criteria for GCA that included clinical features at presentation and biopsy results.

[b] Results were based on one study with a small number of patients.

102 (79%) were negative for GCA. All patients with positive biopsy results or insufficient samples and 87% of those with negative biopsy results were continued on prednisone. There was an increased yield of positive TAB results when biopsies were done in less than 7 days. Only 83% of those who received biopsies met three or more ACR criteria for GCA. In the study by Luqmani et al (23), the sensitivity of TAB was 39% (95% CI 33%-46%) and the specificity was 100% (95% CI 97%-100%). The reference standard in this study was classification criteria for GCA that included clinical features at presentation as well as biopsy results. This was the only study that allowed for direct comparison of the test accuracy of TAB and temporal artery ultrasound in patients suspected of having GCA. Table 2 summarizes the comparative test accuracy of these two tests. Variable reference tests and the lack of an independent gold standard for the diagnosis of GCA increases the difficulty in interpreting the test accuracy of these studies. The other studies showed higher sensitivity (range 56%-97%) and specificity (range 92%-99 %), although wide CIs were observed (21,24-26) (Figures 5 and 6).

Biopsy characteristics. No comparative studies evaluated the impact of a unilateral versus bilateral TAB, but one prospective case series demonstrated that the rate of discordant biopsies was 4.4%, with only 2 of 250 patients returning for minor irritation and no cases of infection, unusual bleeding, or nerve injury (27). Four retrospective studies of 390 patients reported no complications from the TAB (24,25,28,29). Regarding the optimal TAB specimen length, no comparative studies were found, but in a retrospective case series of 3057 biopsies, the likelihood of a positive TAB result was significantly associated with a postfixation TAB specimen length greater than or equal to 30 mm (OR 1.58 [95% CI 1.06-2.36]; $P < 0.05$), as compared to a reference category of less than 10 mm in length (30). Other studies assessing long- or short-segment biopsy specimens did not present test accuracy with a reference test or discuss patient-reported outcomes.

In determining the ideal timing for obtaining a biopsy, no comparative studies evaluated the diagnostic accuracy of TABs done within 2 weeks of starting oral GCs versus after 2 weeks. Four single-arm studies evaluated this question (31-34). Of 119 patients who underwent a biopsy within 2 weeks of starting treatment, 50 of 119 (42%) had positive results (31-34). Of those who underwent a TAB after 4 weeks of treatment, 15 of 20 had positive results (75%) (31,32). The pretest probability of a positive biopsy result was not consistently described for categories of patients undergoing an early or late biopsy.

Other diagnostic imaging modalities. *Temporal artery magnetic resonance imaging.* Seven cohort and case-control studies of 395 patients showed that temporal artery magnetic resonance imaging (MRI) had a sensitivity of 73% (95% CI 0.60-0.83) and a specificity of 88% (95% CI 0.82-0.92) in diagnosing GCA when compared to a reference of clinical diagnosis of GCA (21,35-39). In six studies of 220 patients, temporal artery MRI showed low test accuracy, with a sensitivity of 82% (95% CI 0.64-0.93) and a specificity of 74% (95% CI 0.63-0.82), when compared with TAB (21,35-39).

Ultrasound. Compared with TAB, the test accuracy of a halo sign on ultrasound for diagnosing GCA showed a sensitivity of 40% to 67% and a specificity of 81% to 93% across two studies of 98 patients (40,41). Disease activity as measured by ultrasound was evaluated by Schmidt et al (42) in 176 patients who underwent ultrasound of the temporal artery, axillary artery, subclavian artery, and proximal brachial artery, with 30% of patients showing abnormalities. The axillary arteries were stenotic or occluded in 51 of the 53 patients found to have large vessel GCA (42).

Fluorodeoxyglucose positron emission tomography/computed tomography. Two test accuracy studies of 94 patients with GCA evaluated the diagnostic accuracy of fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) compared with TAB and showed a sensitivity of 73.3% to 92%, a specificity of 83.3% to 85%, a positive predictive value of 61% to 88%, and a negative predictive value of 77% to 98% (43,44). Disease activity measured by FDG-PET/CT was evaluated in six single-arm studies (45-50). Two studies used FDG-PET at baseline before treatment was initiated (45,46). FDG-PET demonstrated a higher sensitivity in patients with high

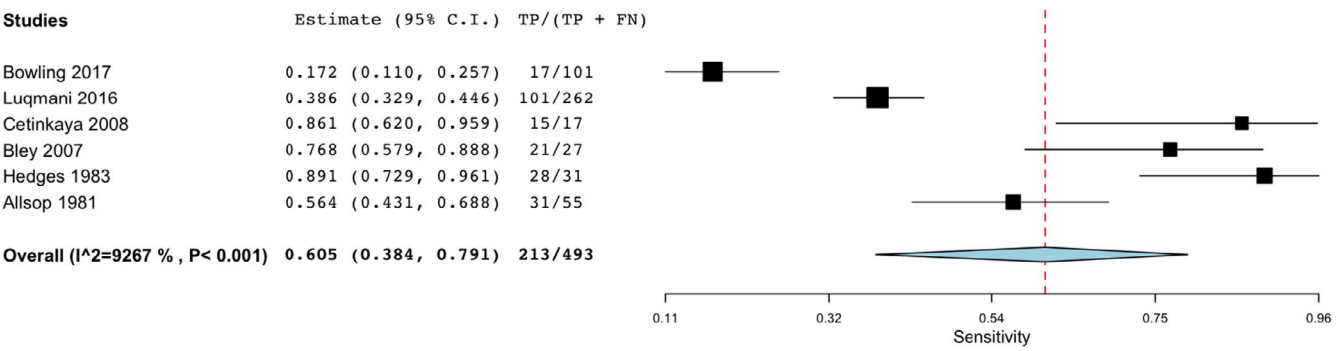

Figure 5. Sensitivity of temporal artery biopsy in diagnosis of giant cell arteritis (GCA). C.I., confidence interval; FN, false negative; TP, true positive.

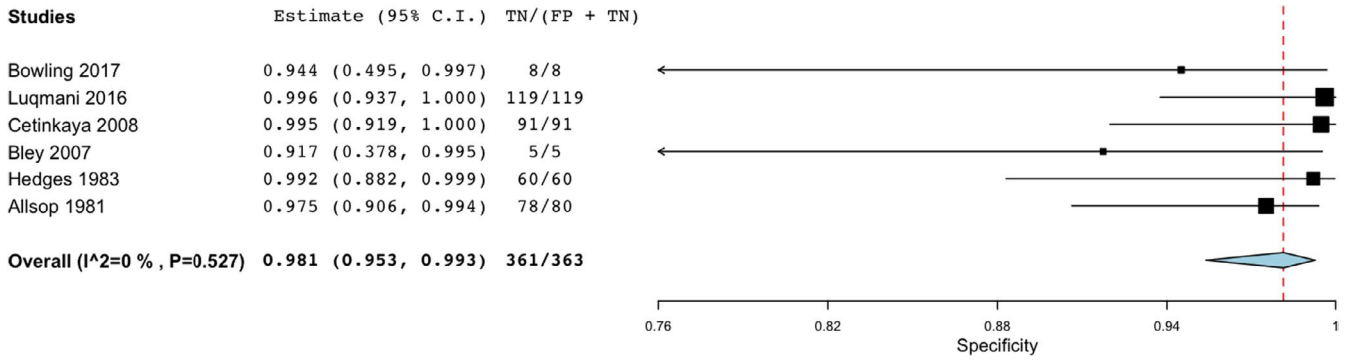

Figure 6. Specificity of temporal artery biopsy in diagnosis of giant cell arteritis (GCA). C.I., confidence interval; FN, false negative; TP, true positive.

C-reactive protein levels compared with erythrocyte sedimentation rate. Overall agreement between FDG-PET and magnetic resonance angiography was found to be 72% in 35 patients with GCA (Cohen's κ = 0.27) (49). The use of GCs significantly reduced the diagnostic accuracy of FDG-PET after 10 days of treatment, with a diagnostic window of 3 days (50). In a study of 63 patients with suspected GCA and a negative TAB result, FDG-PET showed large vessel involvement in 22 patients, 14 of whom were ultimately diagnosed with GCA. Forty-one patients had a negative FDG-PET result, nine of whom were ultimately diagnosed with GCA (51).

Monitoring disease activity. Although no studies have directly compared routine imaging versus clinical observation in the management of large vessel vasculitis, one observational study evaluated the impact of routine monitoring (such as every 6-12 months) with noninvasive vascular imaging on disease-related outcomes and diagnostic testing–related adverse events in patients with GCA (45). This study evaluated 35 patients with repeat PET scans at 3 and 6 months. Of the 29 patients who underwent routine imaging, 14 (48.3%) relapsed, compared with 66.7% of those who did not undergo routine imaging (OR 0.47 [95% CI 0.07-2.96]). At diagnosis, vascular FDG uptake was noted in 29 patients (83%), especially in the subclavian arteries (74%); there was a decrease in the total vascular score (TVS) with a repeat PET scan at 3 months (7.9 ± 5.5 at baseline to 2.4 ± 3.5 on a repeat PET scan at 3 months; $P < 0.0005$), but it did not further decrease at 6 months. The patients who relapsed had similar earlier decreases in the TVS compared with those who did not relapse (45). Grayson et al (52) evaluated the correlation between clinical examination findings in patients with large vessel vasculitis (n = 32 with GCA) and angiography (including a magnetic resonance, computerized tomographic, or catheter-based angiogram) of the carotid, subclavian, and axillary arteries. Individual physical examination findings (assessing pulse, bruits, blood pressure, and claudication) had a sensitivity ranging from 14% to 50% and a specificity ranging from 71% to 98% to detect arteriographic lesions. Even when physical examination findings in combination were considered, at least 30% of arteriographic lesions were missed.

DISCUSSION

This review presents pooled estimates of patient-important outcomes for treatment options as well as test accuracy for diagnostic methods in patients with GCA.

GCs have been the mainstay of treatment for patients diagnosed with GCA, and although that are effective in preventing ischemic complications, including vision loss, they have a well-known toxicity profile (53). Both IV and high-dose oral GCs have been used in patients with GCA at the time of diagnosis. Across studies, there was significant variability in IV dosing regimens, and although the two retrospective studies that evaluated patients presenting with cranial ischemic symptoms did not demonstrate overall improvement in visual acuity in the patients treated with IV GCs, the study by Chan et al (4) demonstrated an increased likelihood of improved vision in patients who received IV GCs (40%) compared with those who received oral GCs (13%). Given the possible outcome of irreversible vision loss in patients with GCA, IV GCs are often initiated at variable doses in patients who present with signs of cranial ischemia, including transient, partial, or complete vision loss. In patients without cranial ischemia, there were discordant results, with one RCT demonstrating improved outcomes in patients treated with IV GCs (7) and the other showing no benefit or a decrease in the cumulative GC dose (6). In light of the toxicities of GCs, especially in the elderly population primarily affected by GCA, we are consistently trying to minimize GC exposure. In two of the four arms of the study by Stone et al (8), a 26-week GC taper was compared with a 52-week taper, and there was no difference in patient ability to achieve remission of GCA, although remission rates were low in both arms (14% and 17.6%, respectively). Additionally, daily GC dosing was found to be more effective in patients achieving remission than alternate-day dosing (9). Across many of the studies evaluating therapies for GCA, there was a high rate of relapse as GCs were tapered.

There have been increasing efforts to find alternative effective, GC-sparing therapies for patients with GCA, and other IS medications, including biologics, have been investigated. The trial by Stone et al (8) demonstrated that weekly TCZ with a 26-week GC taper was superior to the 52-week GC taper in patients achieving sustained GC-free remission at 1 year. Importantly, patient-reported outcomes, including the SF-36 physical component summary score and the patient global assessment of disease activity, were better in the TCZ-treated group (8). Abatacept inhibits T-cell activation and has a favorable side effect profile. It was evaluated in an RCT of patients who were able to achieve remission by 12 weeks with a combination of abatacept and GCs. Continuation of abatacept was associated with a higher relapse-free survival rate at 12 months (48% vs 31%; $P = 0.049$) and demonstrated a longer median duration of remission (9.9 vs 3.9 months) when compared to placebo (11).

MTX, LEF, and TNF inhibitors have also been studied in patients with GCA, and across multiple studies, we did not find a significant difference in relapse rate at 1 year, SAEs, infections, or malignancies when we compared MTX, LEF, and TNF inhibitors with GCs alone. Infliximab and adalimumab did not increase remission rates, decrease relapses, or demonstrate a GC-sparing effect, and the study with etanercept was too small to draw definitive conclusions (13,17,18). Data around the efficacy of MTX in patients with GCA have been debated. Two RCTs did not demonstrate a benefit of MTX in maintaining remission or providing GC-sparing effect in patients with GCA (12,16). However, doses of MTX in these trials were between 7.5 and 20 mg weekly (12,16). In the Hoffman et al (16) trial, although statistically, there was no benefit with MTX, numerically, 57.5% failed treatment in the MTX group compared with 77.3% in the placebo group. Additionally, an alternate-day GC dosing regimen was used, which may have negatively influenced the overall remission rate. The RCT by Jover et al (15) demonstrated less relapses and a lower cumulative GC dose in patients in the MTX arm. LEF similarly showed less relapses and a lower cumulative GC dose in an open-label study (19). There are many patients with GCA who do not achieve full remission, suffer from relapses, or cannot tolerate GC side effects. Modest benefits have been seen with the use of abatacept, MTX, and LEF, and significant benefits in relapse reduction and GC-sparing effects have been seen with weekly TCZ.

TABs have been considered the reference standard for diagnosis of GCA. The pooled sensitivity and specificity of TAB in patients with suspected GCA were 73% and 94%, respectively, across multiple studies, as compared to a clinical diagnosis of GCA. The pretest probability of obtaining a positive biopsy result can strongly affect the yield of a positive result, and some patients with a clinical diagnosis of GCA are continued on GC therapy even in cases with negative biopsy results (22). There can be skip lesions in pathologic specimens, and to increase yield, a postfixation TAB specimen length greater than or equal to 30 mm is preferable (30,54). Although TAB is a surgical procedure, it is relatively safe, and most patients did not experience any major complications. Ideally, patients would obtain a TAB soon after initiating GC therapy, but yield remains high even after 2 weeks of prednisone therapy (31-34).

Temporal artery MRI had a high sensitivity and specificity in diagnosing GCA when compared to a reference of clinical diagnosis of GCA (73% and 88%, respectively) and also when compared with TAB (82% and 74%, respectively). Ultrasound has gained significant interest in diagnosing and monitoring GCA. Ultrasound has the benefit of being noninvasive, inexpensive, and easily accessible. The test accuracy of identifying a halo sign for diagnosing GCA showed moderate sensitivity (40%-67%) but high specificity (81%-93%) (40,41). The study by Luqmani et al (23) analyzed 381 patients who underwent both an ultrasound and biopsy within 10 days of starting treatment of suspected GCA. The sensitivity of the biopsy was 39% (95% CI 33%-46%) and was inferior to that of the ultrasound (54% [95% CI 48%-60%]); the specificity of the biopsy (100% [95% CI 97%-100%]) was superior to that of the ultrasound (81% [95% CI 73%-88%]) (23). Ultrasound can also be used to image the axillary, subclavian, and proximal brachial arteries to evaluate for large vessel involvement. Ultrasound shows promise as a tool in both diagnosis and monitoring in GCA, although it requires operator expertise.

Large vessel involvement in GCA is important to recognize because the incidence has been reported to be between 25% and 70% and up to 100% in postmortem studies of patients with GCA (55-57), and patients with large vessel involvement have more relapses and require higher cumulative GC doses (58). FDG-PET/CT can be used in diagnosis and for assessment of large vessel involvement in GCA. Diagnostic accuracy in our review showed a sensitivity of 73.3% to 92% and a specificity of 83.3% to 85% of FDG-PET/CT compared with TAB. FDG-PET has the ability to identify early vascular inflammation and can rule out alternative diagnoses, such as infection or malignancy. Limitations of PET include high cost, inconsistent access, and a significant decrease in diagnostic utility after 10 days of GC use (50).

This review has several strengths. The comprehensive and systematic approach for identifying studies makes it unlikely that relevant studies were missed. Additionally, we assessed the certainty of evidence in this area and identified sources of bias. We note a few limitations in this comprehensive systematic review. We limited our review by English language. Additionally, the outcome data were combined on studies that had heterogeneous designs. For the majority of the studies, CIs remained wide and outcomes were reported with low confidence, reflecting smaller numbers of patients in these trials.

This comprehensive systematic review synthesizes and evaluates the benefits and harms of different treatment options and the accuracy of commonly used tests for the diagnosis of GCA. Estimates of benefits and harms, as well as sensitivity and specificity, from this review were used to model diagnostic and management strategies and inform evidence-based recommendations for the ACR/VF vasculitis management guidelines.

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AUTHORS CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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