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Polyarteritis Nodosa: A Systematic Review of Test Accuracy and Benefits and Harms of Common Treatments

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Objective. The object of this study was to analyze the benefits and harms of different treatment options and to analyze test accuracy used in the evaluation of patients with primary systemic polyarteritis nodosa (PAN).

Methods. A systematic search of published English-language literature was performed in Ovid Medline, PubMed, Embase, and the Cochrane Library from the inception of each database through August 2019. Articles were screened for suitability in addressing patient, intervention, comparison, and outcome questions, with studies presenting the highest level of evidence given preference.

Results. Of 137 articles selected for data abstraction, we analyzed 21 observational studies and seven randomized controlled trials (RCTs). The results showed indirect evidence that a deep skin biopsy provides good diagnostic accuracy. A combined nerve and muscle biopsy should be obtained for patients with PAN with peripheral neuropathy. Cyclophosphamide with high-dose glucocorticoids (GCs) is effective as an induction treatment for newly diagnosed active and severe PAN. GC monotherapy is adequate in the majority of patients with nonsevere PAN, although it has a high relapse rate with GC taper. There was insufficient data in determining the optimal duration of non-GC and GC maintenance therapy. Tumor necrosis factor inhibitors are effective treatment for patients with deficiency of adenosine deaminase 2 (DADA2) with stroke and vasculitis manifestations.

Conclusion. This comprehensive systematic review synthesizes and evaluates the harms and benefits of different treatment options and the accuracy of commonly used tests for the diagnosis of systemic PAN. Data for diagnosis and management of PAN and DADA2 are mostly limited to observational studies. More high-quality RCTs are needed.

INTRODUCTION

Polyarteritis nodosa (PAN) is a multisystemic necrotizing vasculitis that targets medium- and small-sized arteries. Although renal and visceral arteries are commonly affected, pulmonary arteries are generally spared. It does not cause glomerulonephritis because arterioles, capillaries, or venules are generally not involved. PAN is also not associated with antineutrophil cytoplasmic antibodies (1). PAN is more common in patients of European descent or White patients, and epidemiological data within European countries have reported an incidence of 0 to 1.6 cases per million and a prevalence of 31 cases per million (2–4). The reduction in incidence has been attributed to an increase in hepatitis B vaccination and its differentiation from microscopic polyangiitis (MPA) and other forms of systemic vasculitis (5). PAN-like vasculitis can also occur secondary to other causes, including viral infections (including hepatitis B, human immunodeficiency virus, varicella zoster, and parvovirus infections), hairy cell leukemia, and Sjogren syndrome. PAN may present with multisystemic organ involvement or be limited to one organ system (6). Most clinical

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presentations of PAN are nonspecific and subacute in onset, with a predilection for cutaneous, neurologic, renal, and gastrointestinal involvement (5,7). There are no specific laboratory or serologic markers for PAN. Although angiographic findings of fusiform narrowing and aneurysm in small- and medium-sized arteries are suggestive of PAN, a biopsy of an involved organ showing evidence of fibrinoid necrosis in medium-sized arteries remains the gold standard for diagnosis. However, a biopsy is rarely clinically feasible.

Untreated PAN has a poor prognostic outcome, with a mortality rate of between 10% and 20% in 5 years (8). The survival rate improves significantly with initiation of treatment. Systemic glucocorticoids (GCs) have been recommended for nonsevere PAN with a five-factor score (FFS) of 0. Cytotoxic and other immunosuppressive agents are given in addition to GCs for moderate-severe disease, particularly with an FFS of greater than 1. However, most treatment recommendations for PAN have been derived from studies with mixed cohorts that included patients with MPA and eosinophilic granulomatosis with polyangiitis (EGPA) (9,10).

Recently, PAN-like vasculitis with deficiency of adenosine deaminase 2 (DADA2) has been described. DADA2 is a monogenic disease that can present as a polyarteritis syndrome with a variety of symptoms, including early onset of stroke and cutaneous lesions. DADA2 can be diagnosed by sequence analysis of the *ADA2* (formerly known as *CECR1*) gene (11,12).

The first aim of this systematic review is to conduct a comprehensive search and compare the benefits and harms of different treatment options for patients with primary systemic PAN. This review includes randomized controlled trials (RCTs) and nonrandomized studies and presents the evidence and an assessment of the certainty of evidence for important outcomes. The second aim of this systematic review is to determine the accuracy of commonly used diagnostic tests for PAN, which can inform a combined strategy for diagnosis. This review was used to inform evidence-based recommendations for diagnostic testing and management strategies for PAN by the 2020 American College of Rheumatology (ACR)/Vasculitis Foundation (VF) Guideline for the Management of PAN and Kawasaki Diseases.

METHODS

Search strategy and data sources. An information specialist made systematic searches of the published English-language literature, including in Ovid Medline, PubMed, Embase, and the Cochrane Library (including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, and Health Technology Assessment), from the inception of each database through August 2019 to obtain direct evidence in vasculitis patient populations relating to vasculitis questions (Supplementary Appendix 1). The information specialist updated the searches conducted August 2019. The team used DistillerSR software to identify duplicate records (Evidence Partners; online at https://www.evidencepartners.com/products/distillersr-systematic-review-software/). The search was specific to address the patient, intervention, comparison, and outcome (PICO) questions asked for PAN. The PICO questions were developed by the ACR/VF Vasculitis Guideline Core Team. A total of 21 PICO questions for PAN that addressed relevant or commonly encountered patient diagnostic testing, treatment, and management scenarios were developed (Supplementary Appendix 2).

Study selection. We included studies that provided the highest certainty of 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. When studies with comparative data were not available, we included case series that presented patient-important outcomes for either the intervention or the comparison. For questions addressing diagnostic testing, we included studies that reported on diagnostic test accuracy (cohort studies, cross-sectional studies) for PAN.

Adult patients 18 years of age and older presenting to inpatient or outpatient settings with suspected or confirmed primary systemic PAN were eligible for inclusion. Patients with DADA2 were also included. When studies addressed multiple vasculitis types, we included data when results were presented separately or when greater than 80% of the population included were patients with PAN.

Studies that compared outcomes between the intervention and comparison in the PICO questions or reported outcomes for either the intervention or the comparison were included. For questions examining diagnostic questions testing, studies that compared test accuracy results for the index test and the comparator or presented test accuracy results for either the index test or the comparator were included.

Studies were excluded if they had an irrelevant population, intervention, or outcome; had no primary data (eg, letters, opinion pieces, commentaries, or narrative reviews); were systematic reviews or epidemiological studies that only included prevalence or incidence results; had fewer than 10 patients with vasculitis under study; addressed cutaneous, single-organ, or hepatitis B–related PAN; or focused on basic research in animals. (Supplementary Appendix 4).

Screening and data extraction. Two independent reviewers conducted title and abstract screening and 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), the duration

of follow-up, outcome data for the intervention and/or comparison, and the 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). Reviewers evaluated the risk of bias using the Cochrane risk-of-bias tool (online at http://handbook.cochrane.org/).(Supplementary Appendix 5)

When direct comparative results were available from observational studies (cohort studies, case-control studies), reviewers entered the results into RevMan version 5.3 software. Reviewers evaluated the risk of bias using a modified New-Castle 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.

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 (eg, risk ratios and odds ratios [ORs]) were calculated 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.

RESULTS

Description of studies. The initial search yielded 13,800 nonduplicate studies, of which 2596 were included for full-text review. Following the full-text review, we found 1156 articles to be potentially eligible for data abstraction and inclusion in the systematic reviews of the seven different types of vasculitis. For this review on PAN, we considered 137 articles for data abstraction (Figure 1).

Of the 137 studies that were considered, 21 observational studies, 6 RCTs for single-arm analysis, and 1 RCT for two-arm analysis were included (Results from single arm studies are found in Supplementary Appendix 3). We noted that many studies were published prior to the newer classification of systemic vasculitis in 1994. Thus, the many study populations were heterogeneous and included patients with EGPA and MPA. There were also some studies that included hepatitis B–related PAN. Most noticeable was the paucity of RCTs.

Diagnostic testing. There were limited data on comparing deep and superficial skin biopsies in diagnosing PAN. In general, medium-sized vessels are primarily located in deep dermis and subcutaneous tissues, which can be obtained adequately with a deep punch biopsy. In patients with suspected PAN and peripheral neuropathy, we found that seven observational studies directly or indirectly suggested that performing a biopsy of both the nerve and muscle increases the diagnostic accuracy. However, many of the studies included other forms of vasculitis and were published prior to differentiation of MPA from PAN (5,13–19). A study by Pagnoux et al (5) that included 108 patients with PAN with peripheral neuropathy who satisfied the ACR and Chapel Hill Consensus Conference criteria showed presence of vasculitis in 83.3% of combined muscle and nerve biopsies, compared with only 65% of muscle biopsies only (20,21). Another study showed that the addition of muscle with nerve biopsy did not result in more tissue damage (19). Because of the study selection criteria, there were limited data on the utility of imaging modalities in the diagnosis of PAN.

Treatment of newly diagnosed active and severe PAN. For treatment of life- or organ-threatening PAN, there was no RCT identified that directly compared cyclophosphamide (CYC)plus high-dose GCs with high-dose GCs alone. However, one observational study showed that induction therapy with cyclophosphamide and high-dose GCs demonstrated better efficacy than GC monotherapy for severe PAN, with an OR of 2.40 (95% confidence interval 0.53-10.93) (22). However, it was not clear in the study if some of the patients received prior treatments from outside hospitals (Table 1). CYC is the most studied non-GC immunosuppressive agent for induction therapy. In one prospective randomized multicenter study, 24 patients underwent induction treatment with GCs and then were randomly assigned to two CYC regimens. Remission was achieved in 88% of patients, with a 32% relapse rate in 10 years and overall 5- and 10-year survival of 90% and 80%, respectively (23). Furthermore, three RCTs and three observational studies showed sustained remission after treatment with CYC ranging from 100% at 2 years' follow-up to 41% at 13 years' follow-up. Relapse rates ranged from 6% to 39% within 32 months to 9 years of follow-up. Five studies showed a mortality rate of 6% to 18% with follow-up from 32 months up to 13 years (10,23–27). One study reported a CYC-induced severe adverse event incidence of 44% with up to 13 years of follow-up (24). Two retrospective studies using GC monotherapy reported suboptimal survival outcome of 53% to 61% at 5 years (22,28). One RCT showed that the addition of plasmapheresis to CYC

Table 1. The impact of cyclophosphamide with high-dose glucocorticoids vs. high-dose glucocorticoids alone on disease-related outcomes and treatment-related adverse events in patients with newly diagnosed PAN with active and severe disease

	Certainty assessment						No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclophosphamide with high-dose glucocorticoids	High-dose glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)	Certainty
Death within 2 y of disease onset											
1	Observational study	Seriousa	Not serious	Not serious	Very seriousb	Strong association	4/9 (44.4%)	9/36 (25.0%)	OR 2.40 (0.53 to 10.93)	194 more per 1000 (from 100 fewer to 535 more)	⨁◯◯◯ Very low

Note. Reference: Cohen et al (22).
Abbreviations: CI, confidence interval; OR, odds ratio; PAN, polyarteritis nodosa.
[a] Patients may have received prior treatment at outside institutions; it is unclear how this was determined. Patients may have received other treatments not documented.
[b] Clinical actions and recommendations would differ based on the upper versus the lower boundary of the CI leading to very serious imprecision.

Table 2. The impact of plasmapheresis combined with cyclophosphamide and glucocorticoids vs. cyclophosphamide and glucocorticoids alone on disease-related outcomes and treatment-related adverse events in patients with newly diagnosed PAN with active and severe disease

	Certainty assessment						No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Plasmapheresis combined with cyclophosphamide and glucocorticoids	Cyclophosphamide and glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)	Certainty
Relapse 1	Randomized trial	Seriousa	Not serious	Not serious	Very seriousb	None	4/28 (14.3%)	3/34 (8.8%)	OR 1.72 (0.35 to 8.44)	54 more per 1000 (from 55 fewer to 361 more)	⨁◯◯◯ Very low
Mortality 1	Randomized trial	Seriousa	Not serious	Not serious	Very seriousb	Strong association	7/28 (25.0%)	4/34 (11.8%)	OR 2.50 (0.65 to 9.64)	132 more per 1000 (from 38 fewer to 445 more)	⨁⨁◯◯ Low
Cure: No vasculitis activity after 18 mo of no treatment 1	Randomized trial	Seriousa	Not serious	Not serious	Very seriousb	None	16/28 (57.1%)	22/34 (64.7%)	OR 0.73 (0.26 to 2.03)	75 fewer per 1000 (from 324 fewer to 141 more)	⨁◯◯◯ Very low

Note. Reference: Guillevin et al (29).
Abbreviations: CI, confidence interval; OR, odds ratio; PAN, polyarteritis nodosa.
[a] There is no mention of the randomization process or of allocation concealment.
[b] Clinical actions and recommendations would differ based on the upper versus the lower boundary of the CI leading to very serious imprecision.

and GCs was not superior to treatment with CYC and GCs alone. There was also no significant difference in 5-year cumulative survival rates of two groups (75% and 88%, respectively). However, the study included both patients with PAN and patients with EGPA in the cohort. The randomization process and the allocation of concealment were not mentioned leading to very low certainty in the evidence (29) (Table 2).

Treatment of newly diagnosed active and nonsevere PAN. For patients with PAN without life- or organ-threatening manifestations, we found limited data on non-CYC, non-GC treatments. One small retrospective study had seven patients treated with azathioprine (AZA), methotrexate, mycophenolate mofetil, or colchicine. However, four patients had relapsed (30). There were several studies showing the efficacy of GCs as monotherapy. Two observational studies showed that 93 of 115 patients (80%) with newly active nonsevere PAN achieved remission (31,32). However, three single-center retrospective observational studies showed a 5-year survival of 48% to 53%. Hypercortisolism and osteoporosis were the most common side effects noted. All three studies included patients with severe and nonsevere PAN and did not specify the outcomes of therapies in those with nonsevere PAN (22,28,33).

Maintenance of remission. There were very limited data on therapies used for the maintenance of remission. A single-center retrospective study by Fauci et al (25) in 1979 reported that eight patients were able to continue CYC (seven patients) and AZA (one patient) for 18 months. Five of the eight were able to discontinue GC treatment. However, two patients died after the 5-year follow-up: one of pneumonia and one of liver failure) (Table 3).

Treatment of refractory PAN despite GC monotherapy. In two heterogeneous studies, a total of 35 patients were given CYC for refractory PAN. Seventy percent of patients achieved remission. Complete remission was defined as the absence of clinical and biologic manifestations of active vasculitis after 3 months (25,31). The small cohort study by Ribi et al (31), which mainly involved patients with nonsevere disease, showed that induction of remission was achieved equally with CYC (13 of 19) and AZA (14 of 20) in patients who failed GC monotherapy. There were fewer reported deaths in the AZA group. However, it is important to point out that the outcomes were not differentiated between patients with PAN and patients with MPA (31).

Treatment of DADA2. In an observational study from 2019, Ombrello et al (34) reported on 15 patients with DADA2, aged 3 to 26 years, who had recurrent strokes despite treatment with multiple immunomodulatory therapies. They received adjunctive Tumor necrosis factor inhibitors (TNFis) (ie, adalimumab, etanercept, or infliximab), which resulted in a significant reduction in stroke events. Based on a matched follow-up time (733 patient-months), no strokes had occurred after initiation of TNFis ($P < 0.001$). After use of TNFis, all patients could be weaned off GCs with normalization of acute-phase reactants and improvement of anemia (34) (Table 3). The single-arm data for PAN and DADA2 are included in Supplementary Appendix 3.

DISCUSSION

The aim of this systematic review was to search and compare the benefits and harms of different treatment options and the accuracy of commonly used tests for the diagnosis of primary systemic PAN. The search strategy resulted in 137 articles that were considered, with 21 observational studies, 6 RCTs for single-arm analysis, and only 1 RCT for two-arm analysis, which were included in the final analysis. The results were used to inform evidence-based recommendations on the use of diagnostic testing and on management strategies for PAN developed by the ACR/VF.

Although there were a large number of studies included in this review, there were very limited numbers of RCTs and comparative studies available. Most data were obtained from single-arm observational studies. This is most likely due to the rarity of systemic PAN and decrease-in-disease prevalence after the change of its nomenclature in 1994 (20). Hepatitis B–related PAN was also excluded. There were also many studies that included heterogeneous cohorts of patients with MPA and EGPA.

In diagnosing PAN, a deep punch biopsy should be attempted to obtain a good sample of medium-sized vessels, which are primarily located in deep dermis and subcutaneous tissues. In patients who presented with PAN and peripheral neuropathy, a combined nerve and muscle biopsy provides superior diagnostic results than a muscle biopsy alone (5,17). Because of the study selection criteria, sufficient studies were not available to compare the utility of noninvasive vascular imaging to conventional catheter-based imaging in patients with PAN presenting with gastrointestinal symptoms.

In patients with newly diagnosed PAN with active and severe disease (FFS greater than 0), multiple observational studies have shown efficacy of CYC plus high-dose GCs as induction treatment (10,23–27). One observational study showed that treatment with the combination of CYC and high-dose GCs had a better outcome than high-dose GCs alone. However, there was serious bias and imprecision with the study (22). CYC use is typically limited up to 3 to 6 months because of its known toxicities. Most of the experience with CYC has been derived from other forms of systemic vasculitides. A randomized trial did not show the benefit of plasma exchange in induction of remission. However, the study did not mention the randomization process and allocation of concealment. Because of its risk of bias and imprecision, the study data has very low certainty (29). Plasmapheresis is mostly reserved for severe hepatitis B–related PAN. There were limited

Table 3. The impact of TNF-α inhibitors (eg, infliximab, etanercept, adalimumab) vs. glucocorticoids alone on disease-related outcomes and treatment-related adverse events in patients with PAN and adenosine deaminase 2 deficiency

	Certainty assessment						№ of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNF-α inhibitors (eg, infliximab, etanercept, adalimumab)	Glucocorticoids alone	Relative (95% CI)	Absolute (95% CI)	Certainty
Cumulative number of strokes											
1	Observational study	Not serious	Not serious	Not serious	Not serious	Strong association	The No. of strokes before administering anti-TNF (while on glucocorticoids) was 37. The No. of strokes after administering anti-TNF became 0.	–	–	–	⨁⨁⨁◯ Moderate
Normalization of acute-phase reactants											
1	Observational study	Not serious	Not serious	Not serious	Not serious	None	15/15 (100.0%)	5/15 (33.3%)	RR 1.5000 (0.6739 to 3.3389)	167 more per 1000 (from 109 fewer to 780 more)	⨁⨁◯◯ Low

Note. Reference: Ombrello et al (34).
Abbreviations: CI, confidence interval; PAN, polyarteritis nodosa; RR, risk ratio; TNF-α, tumor necrosis factor α.

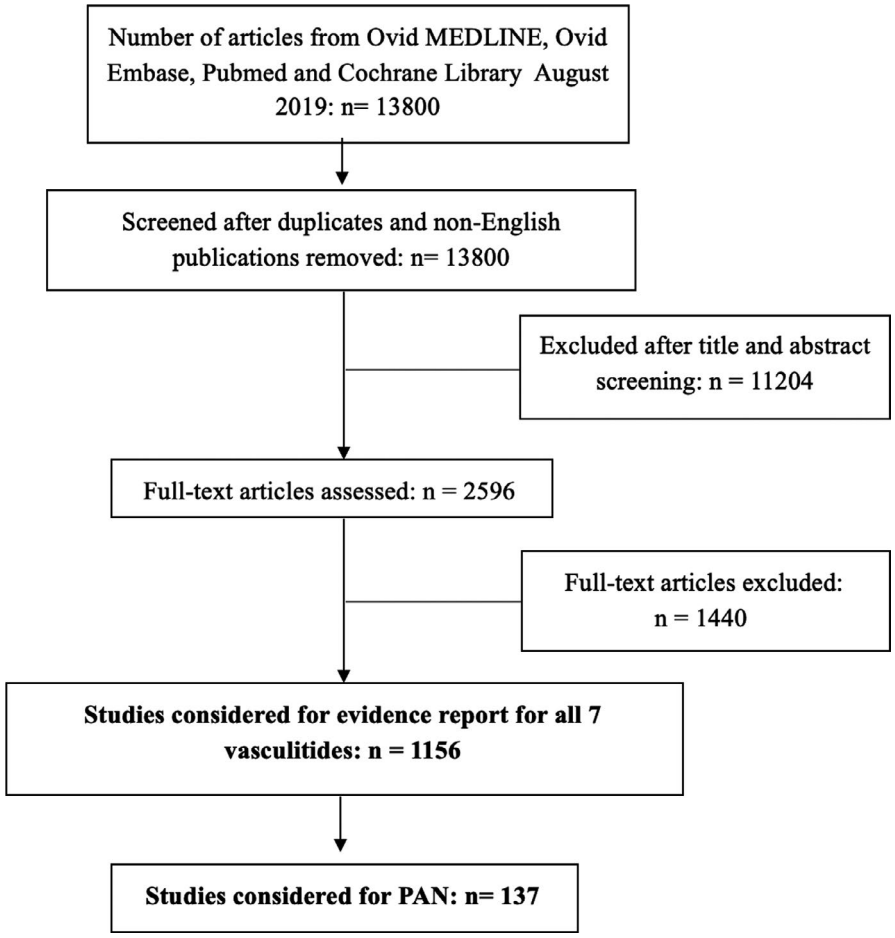

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for included studies. PAN, polyarteritis nodosa.

data regarding the use of other conventional and biologic immunosuppressives for induction treatment of severe PAN.

In patients presenting with newly diagnosed active nonsevere PAN, GC monotherapy is highly effective in achieving remission, although there is a high relapse rate with tapering of GCs (32). Conventional or biologic immunosuppressive agents are not commonly used in initial treatment. However, non-GC and nonbiologic immunosuppressive therapies (eg, methotrexate, AZA) can be used in patients who failed or had side effects with GCs (4,5).

In patients with refractory disease with GC monotherapy, the addition of CYC (severe and nonsevere disease) and AZA (nonsevere disease) can achieve remission in approximately 70% of patients (25,31). There were insufficient data in determining the optimal duration of non-GC and GC maintenance therapy. There was also a paucity of data regarding switching CYC to less toxic disease-modifying antirheumatic drugs. However, adequate duration of remission maintenance therapy is needed because there is a high rate of relapse and mortality, particularly in patients with a high FFS (5).

DADA2 can closely mimic PAN and can result in catastrophic outcomes. One small observational study showed a major reduction in stroke events in all 15 patients with DADA2 after treatment with TNFis. All patients were weaned off GCs. There was also a significant reduction in acute-phase reactant levels (25). TNFis should be used as first line therapy for this condition.

This review has several strengths. Our study had made an extensive systemic search of literature from the inception of each database through August 2019. 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 noted a few limitations in this comprehensive systematic review. We limited our review to the English language. Many of the studies had included cohorts of patients with MPA and EGPA. Some studies included hepatitis B–related PAN. In heterogeneous populations, we only included studies with 10 or more patients with primary systemic PAN. Also, there was a paucity of high-quality RCTs. However, we have included single-arm comparative studies and observational studies to extract the best possible evidence. Although these indirect comparative studies provide a lower quality of evidence because of potential selection bias, we believe these data still provide invaluable information for clinical decision-making and formulation of treatment guidelines for PAN.

In summary, this comprehensive systematic review synthesizes and evaluates the harms and benefits of different treatment options and the accuracy of diagnostic testing for primary systemic PAN. The results from this review were used to model diagnostic and management strategies and inform evidence-based recommendations for the 2020 ACR/VF Vasculitis Management Guidelines. Larger, more high-quality multicenter RCTs are needed to further determine the optimal management and therapy for primary systemic PAN and DADA2.

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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. Dr. Kalot had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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