# A bird's eye review of the recent literature

*Edited by C. Salvarani and N. Pipitone*

## ANCA-associated vasculitis

**Authors:** Finkielman JD, Merkel PA, Schroeder D, Hoffman GS, Spiera R, St Clair EW, Davis JC Jr, McCune WJ, Lears AK, Ytterberg SR, Hummel AM, Viss MA, Peikert T, Stone JH, Specks U; WGET Research Group.
**Title:** Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis.
*Ann Intern Med* 2007 Nov 6; 147(9): 611-9.
**Summary:** The utility of antineutrophil cytoplasmic antibody (ANCA) levels to guide the management of patients with Wegener granulomatosis remains controversial. The objective of this study was to determine whether pro-proteinase 3 (PR3)-ANCA levels are a better measure of disease activity than mature-PR3-ANCA levels, whether decreases in either level are associated with shorter time to remission, and whether increases are followed by relapse. 156 patients with Wegener granulomatosis enrolled during periods of active disease were prospectively evaluated. PR3-ANCA levels (by capture enzyme-linked immunosorbent assay) and disease activity (by the Birmingham Vasculitis Activity Score for Wegener granulomatosis) were measured. The ANCA levels were only weakly associated with disease activity across patients. The longitudinal association within patients was stronger, but changes in ANCA levels explained less than 10% of the variation in disease activity. Decreases in mature- and pro-PR3-ANCA levels were not statistically significantly associated with shorter time to remission, and increases in mature-PR3-ANCA levels (adjusted hazard ratio, 0.8 [95% CI, 0.4 to 1.9]; p=0.67) and pro-PR3-ANCA levels (adjusted hazard ratio, 1.0 [CI, 0.5 to 2.1]; p=0.99) were not associated with relapse. The proportion of patients who had relapse within 1 year of an increase in PR3-ANCA levels was 40% for mature-PR3 (CI, 18% to 56%) and 43% for pro-PR3 (CI, 22% to 58%). The results of this study suggest that pro-PR3-ANCA is no better than mature-PR3-ANCA as a measure of Wegener granulomatosis activity. Decreases in PR3-ANCA levels are not associated with shorter time to remission, and increases are not associated with relapse. These findings suggest that ANCA levels cannot be used to guide immunosuppressive therapy.

**Authors**: Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA, Peikert T, Hoffman GS, Merkel PA, Spiera R, St Clair EW, Davis JC Jr, McCune WJ, Tibbs AK, Ytterberg SR, Stone JH, Specks U; WGET Research Group.
**Title**: ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis.
*Am J Med* 2007 Jul; 120(7): 643.e9-14.
**Summary**: The pathogenic significance of antineutrophilic cytoplasmic antibodies (ANCA) in Wegener's granulomatosis is controversial. The objective of this study was to determine the frequency of ANCA in patients with active Wegener's granulomatosis and to assess the influence of disease severity on test results. Baseline serum samples from 180 patients were tested for ANCA by indirect immunofluorescence, direct enzyme-linked immunosorbent assay (ELISA), and capture ELISA. Disease activity was measured using the Birmingham Vasculitis Activity Score for Wegener's granulomatosis. All patients had active disease at enrollment. Patients were categorized as having severe (n=128) or limited (n=52) Wegener's granulomatosis. 166 patients (92%) were ANCA positive. 96% of patients with severe disease and 83% with limited disease tested positive for ANCA. These results suggest that ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis, and in 4 out of 5 patients with active limited disease are ANCA negative, reinforcing the role of ANCA in buttressing the diagnosis of Wegener's granulomatosis, particularly in patients with severe disease.

**Authors**: Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, Sailler L, Delaunay C, Sadoun A, Guillevin L; French Vasculitis Study Group.
**Title**: Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients.
*Arthritis Rheum* 2008 Jan; 58(1): 308-17.
**Summary**: This multicenter, prospective study aimed to evaluate the safety and efficacy of intravenous immunoglobulins (IVIGs) administered for 6 months (at a dose of 0.5 gm/kg/day for 4 days per month) for 6 months to treat relapses of Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) occurring under treatment or within one year following steroid and/or immunosuppressant withdrawal. Corticosteroids could be maintained or reintroduced in case of a relapse; immunosuppressants could be continued but not reintroduced. Twenty-two patients were studied: 19 had WG, and 3 had MPA. The median Birmingham Vasculitis Activity Score (BVAS) 2005 score was 11 (range 3-25). At study entry, 21 patients were ANCA positive, and 21 patients were taking steroids and/or immunosuppressants. All patients experiencing relapse were treated with the same drug(s) plus IVIGs. All patients initially responded to IVIG therapy. By month 9 (end point), 13 patients had complete remission, 1 had partial remission, 7 had relapse, and 1 had treatment failure. In 8 of the 14 patients who had remission, the response persisted at month 24 (follow-up). Seven patients experienced minor side effects. The results of this study suggest that IVIGs may be considered as adjunctive therapy to treat relapses of WG or MPA.
**Authors**: Metzler C, Miehle N, Manger K, Iking-Konert C, de Groot K, Hellmich B, Gross WL, Reinhold-Keller E; German Network of Rheumatic Diseases.

**Title**: Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis.
*Rheumatology (Oxford)* 2007 Jul; 46(7): 1087-91.
**Summary:** In this multicentre, prospective randomized controlled clinical trial, patients with generalized Wegener's granulomatosis (WG) were treated either with oral leflunomide (LEF) 30 mg/day or oral methotrexate (MTX) starting with 7.5 mg/week and reaching 20 mg/week after 8 weeks for 2 years following induction of remission with cyclophosphamide. The primary endpoint was the incidence of relapses. Fifty-four patients were included in the study, 26 in the LEF-limb, 28 in the MTX-limb. In the LEF-group, six patients relapsed after a median time of 7 months, thereof one major relapse with a new pulmonary manifestation. In the MTX-group, 13 relapses occurred in 6 months, of which seven were major: rapidly progressive glomerulonephritis (n=4), pulmonary haemorrhage (n=2), and one cerebral granuloma. There was a significantly higher incidence of major relapses in the MTX-limb ($p$=0.037), which led to the premature termination of the study. In the LEF-limb, four patients were withdrawn due to hypertension (n=2), peripheral neuropathy (n=1) and leucopenia (n=1). LEF at a dosage of 30 mg/day appears to be effective in the prevention of major relapses in WG, however, this is associated with an increased frequency of adverse events.

**Authors**: Cohen P, Pagnoux C, Mahr A, Arène JP, Mouthon L, Le Guern V, André MH, Gayraud M, Jayne D, Blöckmans D, Cordier JF, Guillevin L; French Vasculitis Study Group.
**Title**: Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients.
*Arthritis Rheum* 2007 May 15; 57(4): 686-93.
**Summary:** This prospective multicenter study compared long and short durations of adjunctive cyclophosphamide for the treatment of severe Churg-Strauss syndrome (CSS). 48 patients with CSS with at least 1 poor-prognosis factor at baseline were treated with glucocorticoids and either 12 or 6 intravenous cyclophosphamide pulses. At 8 years, complete remission rates and severe side effects of therapy were comparable for both groups. The overall difference in relapses was not significant between the 12-pulse and the 6-pulse regimens. However, when considering only the number of mild relapses this difference was statistically significant, therefore the trial was prematurely discontinued due to the superiority of the 12-pulse regimen. This data may suggest that 12 cyclophosphamide pulses are superior to a 6-pulse regimen in controlling severe CSS.

**Authors:** Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Lauque D, Puéchal X, Letellier P, Delaval P, Cordier JF, Guillevin L; French Vasculitis Study Group.
**Title:** Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients.
*Arthritis Rheum* 2008 Feb; 58(2): 586-94.
**Summary:** This multicenter, prospective, randomized, open-label therapeutic trial included 72 patients with newly diagnosed CSS without poor-prognosis factors (FFS of 0) treated with CS alone. At treatment failure or relapse, patients were randomized to receive 6 months of oral AZA or 6 pulses of CYC. Among the 72 patients studied, 93% achieved remission with CS therapy alone, and 35% relapsed, mainly during the first year of treatment. Among the 19 patients randomized to additional immunosuppression because of treatment failure or relapse, 5 of 10 receiving AZA and 7 of 9 receiving pulse CYC achieved remission, but the difference was not statistically significant. Survival rates in all patients at 1 and 5 years were 100% and 97%, respectively. At the end of followup, 79% of the patients whose disease was in remission required low-dose CS therapy, mainly to control respiratory disease. In CSS patients with an FFS of 0, survival was excellent. First-line therapy with CS achieved remission in most patients, but relapses were common, and one-third of them required additional immunosuppressive therapy. AZA or pulse CYC was fairly effective in treating CS-resistant disease or major relapses.

## Polyarteritis nodosa and cryoglobulinemia vasculitis

**Authors:** Henegar C, Pagnoux C, Puéchal X, Zucker JD, Bar-Hen A, Guern VL, Saba M, Bagnères D, Meyer O, Guillevin L; French Vasculitis Study Group.
**Title:** A paradigm of diagnostic criteria for polyarteritis nodosa: Analysis of a series of 949 patients with vasculitides.
*Arthritis Rheum* 2008 Apr; 58(5): 1528-38.
**Summary:** The abilities of individual descriptive items to predict a diagnosis of PAN were evaluated by screening available data from 949 patients from the French Vasculitis Study Group database, including 262 with PAN and 687 with control vasculitides. Selected items were tested in a logistic regression model to establish a minimal set of nonredundant PAN-predictive criteria. The discriminative accuracy of these items and of the American College of Rheumatology (ACR) 1990 criteria were assessed by reapplying them to the initial patient sample and a subgroup restricted to PAN and microscopic polyangiitis (MPA) patients. The analysis resulted in the retention of 3 positive predictive parameters (hepatitis B virus antigen and/or DNA in serum, arteriographic anomalies, and mononeuropathy or polyneuropathy) and 5 negative predictive parameters (indirect immunofluorescence detection of antineutrophil cytoplasmic antibody; asthma; ear, nose, and throat signs; glomerulopathy; and cryoglobulinemia) for the criteria set. These criteria yielded 70.6% sensitivity for all control vasculitides and 89.7% for MPA controls, with 92.3% specificity for all controls and 83.1% for MPA controls. The discriminant abilities of this set of items outperformed the ACR 1990 criteria in all analytical situations, showing better robustness to variations in the prevalence of individual vasculitides

**Authors :** Saadoun D, Resche-Rigon M, Sene D, Perard L, Piette JC, Cacoub P.
**Title :** Rituximab combined with Peg-Interferon-Ribavirin in refractory HCV-associated cryoglobulinemia vasculitis.
*Ann Rheum Dis* 2008 Jan 4. [Epub ahead of print] PMID: 18178690
**Summary:** Sixteen consecutive patients with severe HCV-MC vasculitis which were resistant (n=11) or relapser (n=5) to a previous combination therapy with standard (n=10) or Peg-IFNalpha2b (n=6) plus ribavirin were treated with rituximab (375mg/m(2) intravenously weekly for 4 weeks) combined with Peg-IFNalpha2b (1.5microg/kg/week subcutaneously) plus ribavirin (600-1,200 mg/day orally) for 12 months. Fifteen patients (93.7%) showed clinical improvement, 10 of whom (62.5%) were clinical complete responders (CR). HCV RNA and serum cryoglobulin became undetectable in all the clinical CR. Compared with clinical CR, the partial or non responders had a 3.6 times longer duration of vasculitis prior to therapy and a lower rate of early virologic response. Treatment was well tolerated with no infectious complications. Rituximab combined with Peg-IFNalpha2b-ribavirin represents a safe and effective therapeutic option in severe refractory HCV-MC vasculitis.

## Large-vessel vasculitis

**Authors**: Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, Lavalley MP, Merkel PA.
**Title**: Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis.
*Arthritis Rheum* 2007 Aug; 56(8): 2789-97.
**Summary:** Three recent randomized placebo-controlled trials (*Clin Exp.Rheumatol* 2001, 19:495-501; Ann Intern Med 2001, 134:106-114; Arthritis Rheum 2002, 46:1309-1318) aimed at assessing the efficacy of methotrexate (MTX) ad adjunctive therapy in recent-onset giant cell arteritis (GCA) have produced discordant results. The Authors of this article performed an individual patient data meta-analysis of these trials to evaluate the effectivess of MTX. Time-to-event outcomes were compared between groups using Cox proportional hazards models stratified by trial, and continuous outcomes were compared by calculating weighted mean differences. 161 patients were analyzed, of whom 84 received MTX and 77 received placebo. The mean duration of followup was 54.7 weeks (SD 39.2 weeks). Hazard ratios (HRs) for a first and second relapse of GCA were 0.65 (p=0.04) and 0.49 (p=0.02), respectively, in patients receiving MTX as compared with patients receiving placebo. According to this data, 3.6 patients (95% confidence interval [95% CI] 2.2-56.8) and 4.7 individuals (95% CI 3.3-21.9) need to be treated with MTX to prevent the occurrence of one first or one second relapse, respectively, up to 48 weeks. MTX also resulted in a reduction in the corticosteroid cumulative dose by 842 mg within 48 weeks (p<0.001). Finally, MTX treatment was associated with a higher probability of achieving sustained discontinuation of corticosteroids for > or =24 weeks (HR 2.84, p=0.001). Dropout rates and occurrence of adverse events did not differ between treatment groups. In GCA, adjunctive treatment with MTX was effective in reducing the risk of relapse and the exposure to corticosteroids. At the same time, the onset of action of MTX was slow, and MTX use did not result in a decreased incidence of GC-related complications.

**Authors**: Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, Salvarani C, Xu W, Visvanathan S, Rahman MU; Infliximab-GCA Study Group.
**Title**: Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial.
*Ann Intern Med* 2007 May 1; 146(9): 621-30.
**Summary:** Tumor necrosis factor-alpha is expressed in the arteries of patients with giant cell arteritis. The aim of this randomized controlled trial was to evaluate the efficacy of the monoclonal anti-TNF-α antibody infliximab, in giant cell arteritis. 44 patients with newly diagnosed giant cell arteritis that was in glucocorticosteroid-induced remission were enrolled. Participants were randomly assigned in a 2:1 ratio to receive infliximab (5 mg/kg of body weight) or placebo. Sixteen patients were assigned to glucocorticosteroid plus placebo, and 28 patients to glucocorticosteroid plus infliximab. Primary end points were the number of patients who remained free of relapse through week 22 and adverse events. Secondary end points were time to first relapse, biomarkers, cumulative glucocorticosteroid dose, and the number of patients who remained relapse-free while the glucocorticosteroid dosage was tapered to 10 mg/d. In this trial, infliximab did not significantly increase the proportion of patients without relapse at week 22 compared with placebo (43% vs. 50%, respectively), nor did it increase the proportion of patients whose glucocorticosteroid dosages were tapered to 10 mg/d without relapse (61% vs. 75%, respectively). End points were measured through week 22, when an interim analysis resulted in early stopping of the planned 54-week trial.
Although the sample size of this trial is too small to draw definitive conclusions, this study provides evidence that infliximab as maintenance therapy in patients in glucocorticoid-induced remission of newly diagnosed giant cell arteritis is not beneficial. If infliximab has benefit, it is unlikely to be great.

**Authors:** Salvarani C, Macchioni P, Manzini C, Paolazzi G, Trotta A, Manganelli P, Cimmino M, Gerli R, Catanoso MG, Boiardi L, Cantini F, Klersy C, Hunder GG.
**Title:** Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial.
*Ann Intern Med* 2007 May 1; 146(9): 631-9.
**Summary:** A reliable alternative to steroids for treating polymyalgia rheumatica has not yet been identified. The aim of this randomized controlled trial was to compare the efficacy of prednisone plus infliximab with that of prednisone plus placebo in patients with newly diagnosed polymyalgia rheumatica. 51 patients with newly diagnosed polymyalgia

rheumatica were treated with oral prednisone tapered from 15 mg/d to 0 mg/d over 16 weeks according to a standard protocol, plus infusions of placebo or infliximab, 3 mg/kg of body weight, at weeks 0, 2, 6, 14, and 22. The primary efficacy end point was the proportion of patients without relapse or recurrence through week 52. Secondary outcomes were the proportion of patients no longer taking prednisone, the number of relapses and recurrences, the duration of prednisone therapy, and the cumulative prednisone dose.
The proportion of patients who were free of relapse and recurrence at 52 weeks did not differ between groups (6 of 20 patients [30%] in the infliximab group vs. 10 of 27 patients [37%] in the placebo group; adjusted risk difference, -3 percentage points [95% CI, -31 to 24 percentage points]; $p$=0.80). The secondary outcomes at weeks 22 and 52 did not differ between the groups. Although too small to be definitive, the trial provides evidence that adding infliximab to prednisone for treating newly diagnosed polymyalgia rheumatica is of no benefit.

**Authors:** Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, López-Longo J, Figueroa M, Belzunegui J, Mola EM, Bonilla G.
**Title:** A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects.
*Ann Rheum Dis* 2008 May; 67(5): 625-30.
**Summary:** The aim of this randomized controlled trial was to evaluate the efficacy of etanercept in patients with biopsy-proven GCA with side effects secondary to corticosteroids.
Patients with GCA were randomly assigned to receive etanercept (n=8) or placebo (n=9) over 1 year together with corticosteroids that were reduced according to a predefined schedule. The primary outcome was the ability to withdraw the corticosteroid therapy and control the disease activity at 12 months. After 12 months, 50% of the patients in the etanercept group and 22.2% in the placebo group were able to control the disease without corticosteroid therapy ($p$-value not significant). Patients in the etanercept group had a significant lower dose of accumulated prednisone during the first year of treatment ($p$=0.03). There were no differences in the number and type of adverse events. The limited number of patients included in this study does not allow the authors to draw definitive conclusions. Etanercept therapy was well tolerated in this aged population. The therapeutic role of etanercept in patients with GCA should be evaluated in studies with a larger number of patients.

**Authors:** Salvarani C, Pipitone N, Boiardi L, Hunder GG.
**Title:** Do we need treatment with tumour necrosis factor blockers for giant cell arteritis?
*Ann Rheum Dis* 2008 May; 67(5): 577-9.
**Summary:** This paper summarizes the published evidence on the use of anti TNF agents in giant cell arteritis. A recent randomized controlled trial suggested that TNF blockade with etanercept suppresses disease activity in refractory GCA. However, a previous randomized controlled trial showed no effect of anti-TNF therapy with infliximab in GCA.
The major differences between the infliximab and etanercept trials were related to the respective study populations. In the infliximab trial the subjects enrolled were patients with newly diagnosed disease, while in the etanercept trial they were patients with refractory GCA (still treated with a median dose of 15 mg/day of prednisone after 10 months, median duration, of GC therapy). The efficacy of TNF blockers in patients with relapsing disease has a possible pathophysiological rationale. In fact, high TNF production was associated in GCA with longer steroid requirements and relapsing disease.
It is possible that TNF-blocking agents might be mainly effective in patients with GCA with relative GC-resistant disease, while their efficacy is less clear in patients with non-relapsing disease in whom TNF has a more limited pathophysiological role.

**Authors:** Pipitone N, Salvarani C.
**Title:** Improving therapeutic options for patients with giant cell arteritis.
*Curr Opin Rheumatol* 2008 Jan; 20(1): 17-22.
**Summary:** Glucocorticoids remain the mainstay of treatment of giant cell arteritis. The aim of this review is to establish the optimal schedule of glucocorticoid administration, and to ascertain which other treatments may be used as glucocorticoid-sparing agents. An initial dose of 40-60 mg/day of prednisone is usually adequate. Patients at risk of developing ischemic complications require dosages of around 1 mg/kg/day, whereas pulse glucocorticoid therapy is no more effective in preventing ischemic complications. In patients with longstanding disease or those at risk for glucocorticoid-related adverse events, methotrexate or azathioprine can be used as glucocorticoid-sparing drugs. Infliximab has been demonstrated to be efficacious in glucocorticoid-resistant disease in an open study, whereas a randomized controlled trial showed no efficacy in patients with recent-onset disease. Finally, two retrospective studies suggest that low-dose aspirin may decrease the rate of cranial ischemic complications secondary to giant cell arteritis.

**Authors:** Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, De Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R.
**Title:** EULAR Recommendations for the management of large vessel vasculitis. University of Oxford, United Kingdom.
*Ann Rheum Dis* 2008 Apr 15 [Epub ahead of print]
**Summary:** This paper reports the European League Against Rheumatism (EULAR) recommendations for the management of large vessel vasculitis. An expert group (10 rheumatologists, 3 nephrologists, 2 immunolgists, 2 internists representing 8 European countries and the USA, a clinical epidemiologist and a representative from a drug regulatory agency) identified ten topics for a systematic literature search through a modified Delphi technique. In accordance with standardised EULAR operating procedures, recommendations were

derived for the management of large vessel vasculitis. In the absence of evidence, recommendations were formulated on the basis of a consensus opinion. Seven recommendations were made relating to the assessment, investigation and treatment of patients with large vessel vasculitis. The strength of recommendations was restricted by the low level of evidence and EULAR standardised operating procedures.

**Authors:** Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, De Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R.
**Title:** EULAR Recommendations for the management of primary small and medium vessel vasculitis.
*Ann Rheum Dis* 2008 Apr 15 [Epub ahead of print]
**Summary:** This paper reports the European League Against Rheumatism (EULAR) recommendations for the management of small and medium vessel vasculitis. An expert group (consisting of 10 rheumatologists, 3 nephrologists, 2 immunologists, 2 internists representing 8 European countries and the USA, a clinical epidemiologist and a representative from a drug regulatory agency) identified ten topics for a systematic literature search using a modified Delphi technique. In accordance with standardised EULAR operating procedures, recommendations were derived for the management of small and medium vessel vasculitis. In the absence of evidence, recommendations were formulated on the basis of a consensus opinion. Fifteen recommendations were made for the management of small and medium vessel vasculitis. The strength of recommendations was restricted by low quality of evidence and by EULAR standardised operating procedures.

**Authors:** Pipitone N, Versari A, Salvarani C.
**Title:** Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: an update.
*Rheumatology (Oxford)* 2008 Apr; 47(4): 403-8.
**Summary:** Imaging studies play a central role in diagnosing and monitoring giant-cell and Takayasu arteritis. Deep, large vessels can be examined by CT or MRI, while colour Doppler ultrasound and MRI have been used with promising results to investigate the temporal arteries. Positron emission tomography is very sensitive in detecting large-vessel inflammation, although it does not delineate the vessel wall. Imaging procedures can also be used to monitor the disease course. However, imaging signs of inflammation may sometimes persist despite clinical remission and, conversely, seemingly unaffected vessels may develop alterations later on.

**Authors:** Maksimowicz-McKinnon K, Clark TM, Hoffman GS.
**Title:** Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients.
*Arthritis Rheum* 2007 Mar; 56(3): 1000-9.
**Summary:** The aim of this study was to describe the clinical, laboratory, and radiographic manifestations of Takayasu arteritis (TA) in a cohort from the US, evaluate the response to interventions, remission and relapse rates, and disease progression, and compare these observations with those from other cohorts in the US, Japan, India, Italy, and Mexico. Seventy-five patients were retrospectively studied using a uniform database that included clinical, laboratory, and imaging data. Vascular imaging studies were performed at least yearly to monitor disease progression. Common manifestations at disease onset included loss or asymmetry of pulses (57%), limb blood pressure discrepancy (53%), and bruits (53%). Eleven percent of patients were asymptomatic prior to disease diagnosis. Initial angiographic studies showed aortic abnormalities in 79% of patients and frequent involvement of the subclavian (65%) and carotid (43%) arteries.Ninety-three percent of longitudinally followed patients attained disease remission of any duration, but only 28% sustained remission of at least 6 months' duration after prednisone was tapered to <10 mg daily. Both angioplasty and vascular surgery were initially successful, but recurrent stenosis occurred in 78% of angioplasty and 36% of bypass/reconstruction procedures. More than two-thirds of patients had difficulty performing routine daily activities and approximately one-fourth of all patients were unable to work. This cohort was similar to the National Institutes of Health, Italian, Japanese, and Mexican cohorts. Although improvement of symptoms in TA usually follows glucocorticoid therapy, relapses usually occur with dosage reduction. Attempts to restore vascular patency are often initially successful, but restenosis occurs frequently.

**Authors:** Gonzalez-Juanatey C, Lopez-Diaz MJ, Martin J, Llorca J, Gonzalez-Gay MA.
**Title:** Atherosclerosis in patients with biopsy-proven giant cell arteritis.
*Arthritis Rheum* 2007 Dec 15; 57(8): 1481-6.
**Summary:** The aim of this study was to examine the presence of atherosclerosis in a series of giant cell arteritis (GCA) patients attended to in a community hospital and to determine whether clinical features or steroid therapy might be associated with the development of atherosclerotic disease. Forty consecutive patients diagnosed with biopsy-proven GCA, periodically followed at the rheumatology outpatient clinic of Hospital Xeral-Calde, Lugo (Spain), who had ended steroid therapy and had at least 3 years of follow-up were assessed for the presence of atherosclerosis by determination of the carotid intima-media thickness (IMT) and carotid plaques using high-resolution B-mode ultrasound. Forty matched controls were also studied. GCA patients exhibited less carotid artery IMT than did matched controls (mean ± SD 1.01±0.16 mm versus 1.13 ± 0.20 mm; $p$=0.005; difference in means 0.12, 95% confidence interval 0.04-0.20). Patients who required steroid therapy for >2 years had greater mean±SD carotid IMT (1.04±0.17 mm versus 0.95±0.15 mm) but the difference was not statistically significant ($p$=0.10). A positive correlation between age at the time of the study and the carotid artery IMT in GCA patients was observed ($r$=0.673, $p$<0.001). However, adjusting for age, sex, and classic atherosclerosis risk factors, no significant correlation between carotid IMT and the routine laboratory markers of

inflammation assessed at the time of disease diagnosis, disease duration, or cumulative prednisone dose was found. The present study demonstrates that atherosclerotic macrovascular disease is not increased in patients with GCA.

## Primary central nervous system vasculitis

**Authors:** Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Weigand SD, Miller DV, Giannini C, Meschia JF, Huston J 3rd, Hunder GG.
**Title:** Primary central nervous system vasculitis: analysis of 101 patients.
*Ann Neurol* 2007 Nov; 62(5): 442-51.
**Summary:** The aim of this study was to analyze the clinical findings, response to therapy, outcome, and incidence of primary central nervous system vasculitis (PCNSV) in a large cohort from a single center. 101 patients with PCNSV, selected by predetermined diagnostic criteria, who were seen during a 21-year period were retrospectively studied. Clinical findings and outcomes were compared among patients categorized by method of diagnosis, response to therapy, survival, and degree of disability. An annual incidence rate was calculated. Seventy patients were diagnosed by angiography and 31 by central nervous system biopsy. Three histological patterns were observed during biopsy. Although most patients responded to therapy, an increased mortality rate was observed. Relapses occurred in one fourth of patients. Mortality rate and disability at last follow-up were greater in those who presented with a focal neurological deficit, cognitive impairment, cerebral infarctions, and angiographic large-vessel involvement but were lower in those with prominent gadolinium-enhanced lesions when evaluated by magnetic resonance imaging. The annual incidence rate of PCNSV was 2.4 cases per 1,000,000 person-years. PCNSV is a rare disease that may result in serious neurological outcomes or death. Angiography and brain biopsy may complement each other when determining the diagnosis. Early recognition and treatment may reduce poor outcomes. PCNSV is a variable syndrome that appears to consist of several subsets of heterogeneous diseases.

**Authors:** Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG.
**Title:** Primary central nervous system vasculitis with prominent leptomeningeal enhancement: a subset with a benign outcome.
*Arthritis Rheum* 2008 Feb; 58(2): 595-603.
**Summary:** This study was undertaken to evaluate the clinical features and outcomes among patients with primary central nervous system vasculitis (PCNSV) who presented with prominent gadolinium meningeal enhancement on magnetic resonance imaging (MRI). Through retrospective review using the Mayo Clinic medical records linkage system, 101 consecutive patients with PCNSV based on brain biopsy or conventional angiography (or both) were identified between January 1, 1983, and December 31, 2003. Data on demographics, clinical findings, laboratory studies, imaging, biopsy of brain or spinal cord (or both), treatment, and neurologic outcome were evaluated. MRIs showed prominent leptomeningeal enhancement in 8 of 101 patients with PCNSV. In 6 of those 8, cerebral angiography or magnetic resonance angiography results were normal, but biopsy of the brain or spinal cord showed vasculitis in all 8. Granulomatous vascular inflammation was found in 6 specimens and was associated in 4 cases with vascular deposits of beta-amyloid peptide. All 8 patients had a prompt response to therapy, with resolution of the MRI meningeal enhancement. Although 3 of the 8 patients had relapses during followup, the overall outcome was favorable. Patients with meningeal enhancement, compared with patients without enhancement, more commonly had substantial abnormalities of cerebrospinal fluid (100% *vs*. 58%; $p$=0.02) and amyloid angiopathy (50% *vs* 12%; $p$=0.03). Prominent gadolinium leptomeningeal enhancement on MRI may point to a distinct subtype of PCNSV with small leptomeningeal artery vasculitis and rapid response to therapy.

**Authors:** Salvarani C, Brown RD Jr, Calamia KT, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG.
**Title:** Efficacy of tumor necrosis factor alpha blockade in primary central nervous system vasculitis resistant to immunosuppressive treatment.
*Arthritis Rheum* 2008 Feb 15; 59(2): 291-6.
**Summary:** Two patients with primary central nervous system vasculitis (PCNSV) who did not respond to treatment with corticosteroids and immunosuppressive medication were succesfully treated with tumor necrosis factor (TNF) blockers.

**Authors:** Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB.
**Title:** Narrative review: reversible cerebral vasoconstriction syndromes.
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**Summary:** Reversible cerebral vasoconstriction syndromes (RCVS) comprise a group of diverse conditions, all characterized by reversible multifocal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without associated neurologic deficits. Reversible cerebral vasoconstriction syndromes are clinically important because they affect young persons and can be complicated by ischemic or hemorrhagic strokes. The differential diagnosis of RCVS includes conditions associated with thunderclap headache and conditions that cause irreversible or progressive cerebral artery narrowing, such as intracranial atherosclerosis and cerebral vasculitis. Misdiagnosis as primary cerebral vasculitis and aneurysmal subarachnoid hemorrhage is common because of overlapping clinical and angiographic features. However, unlike these more ominous conditions, RCVS is usually self-limited: Resolution of headaches and vasoconstriction occurs over a period of days to weeks. In this review, we describe our current understanding of RCVS; summarize its key clinical, laboratory, and imaging features; and discuss strategies for diagnostic evaluation and treatment.