Vasculitis
A bird's eye review of the recent literature

edited by N. Pipitone and C. Salvarani

Cryoglobulinemic vasculitis

Authors: Terrier B, Launay D, Kaplanski G, Hot A, Larroche C, Cathébras P, Combe B, de Jaureguiberry JP, Meyer O, Schaeverbeke T, Somogyi A, Tricot L, Zénone T, Ravaud P, Gottenberg JE, Mariette X, Cacoub P.
Title: Safety and efficacy of rituximab in nonviral cryoglobulinemia vasculitis: data from the French Autoimmunity and Rituximab registry.
Arthritis Care Res 2010; 62(12): 1787-95
Summary: There is limited evidence on the management of nonviral cryoglobulinemia vasculitis. Rituximab has emerged as a novel and promising therapeutic alternative, but data are scarce. The goal of this study was to evaluate the safety and efficacy of rituximab in nonviral cryoglobulinemia vasculitis in off-trial real-life patients. To this end, prospective data from the French AutoImmunity and Rituximab registry, which includes data on patients with autoimmune disorders treated with rituximab in off-label conditions, were analysed. Twenty-three patients received treatment with rituximab for cryoglobulinemia vasculitis. Eighteen had histologically confirmed systemic vasculitis (skin [n=7], kidney [n=6], and nerve [n=5]). Patients without histologically proven vasculitis (n=5) but with purpura and detectable cryoglobulinemia were considered to have small-vessel vasculitis. Nine patients (39%) had primary SS (including 1 patient with mucosa-associated lymphoid tissue [MALT] lymphoma and 1 with marginal zone lymphoma), 8 (35%) had B cell lymphoproliferative disorders (MGUS [n=3], follicular lymphoma [n=1], lymphoplasmacytic lymphoma [n=1], low-grade B cell NHL [n=1], MALT lymphoma [n=1], and marginal zone lymphoma [n=1]), and 8 patients (35%) had essential mixed cryoglobulinemia. The main clinical features of cryoglobulinemic vasculitis included purpura (74%), skin ulcers (43%), Raynaud's phenomenon (30%), skin necrosis (17%), nasal septum perforation (4%), peripheral nervous system involvement (52%), arthralgia/arthritis (35%), and kidney involvement (30%). Seventeen patients (74%) had type II cryoglobulin, 3 (13%) had type I cryoglobulin, and 2 (9%) had type III cryoglobulin. 65% of patients had received previous treatment, in the majority of cases glucocorticoids (57%) and cyclophosphamide (22%).
Rituximab was administered at 375 mg/m^2× 4 in 78% of patients, 1,000 mg×2 in 13%, and as part of other combined regimens in the remaining patients.
Data on clinical and immunologic responses to rituximab were available for 20 (87%) and 16 (70%) of the 23 patients, respectively. Clinical and immunologic efficacy was noted in all evaluable patients. In particular, a clinical response was noted in 94% (81% complete response) of patients with skin manifestations, 100% (83% complete response) of those with arthralgia, 91% (36% complete response) of those with peripheral nerve involvement, and 100% (67% complete response) of those with glomerulonephritis. Clinical relapses occurred in half of the patients after a median time of 13.5 months following rituximab administration, and were more frequent in patients refractory to previous immunosuppressive therapy than in previously untreated patients. Almost half of the patients experienced adverse events, including severe infections in 6 (26%) of 23, with a rate of 14.1 per 100 patient-years. These infections occurred in a particular subset of patients ages>70 years, with essential type II mixed cryoglobulinemia and renal impairment (glomerular filtration rate of <60 ml/minute), and receiving high-dose corticosteroids. Three of these patients died. This study shows efficacy with a steroid-sparing effect of rituximab, but also a significant rate of severe infections in elderly patients with renal failure treated with high-dose steroids. The role of rituximab in nonviral cryoglobulinemia vasculitis remains to be defined in well-designed randomised controlled trials.

ANCA-associated vasculitis

Authors: Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group.
Title: Rituximab versus cyclophosphamide for ANCA-associated vasculitis.
N Engl J Med 2010; 363(3): 221-32.
Summary: Cyclophosphamide and glucocorticoids have been the cornerstone of remission-induction therapy for severe antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis for 40 years. Uncontrolled studies had suggested that rituximab might be effective and possibly safer than a cyclophosphamide-based regimen. This multicenter, randomised, double-blind, double-dummy, noninferiority trial (Rituximab in ANCA-associated vasculitis, RAVE) compared rituximab (375 mg/m^2 of body-surface area per week for 4 weeks) with oral cyclophosphamide (2 mg per kilogram of body weight per day, control group) for remission induction. Nine centers enrolled 197 ANCA-positive patients with either Wegener's granulomatosis or microscopic polyangiitis. Baseline disease activity, organ involvement, and the proportion of patients with relapsing disease were similar in the two treatment groups. The two treatment groups received the same glucocorticoid regimen: one to three pulses of methylprednisolone (1000 mg each), followed by prednisone at a dose of 1 mg per kilogram per day. The dose was tapered

so that by 5 months, all patients who had a remission without disease flares had discontinued glucocorticoids. Patients in the control group who had a remission between 3 and 6 months were eligible to switch from cyclophosphamide to azathioprine (2 mg per kilogram per day). The primary end point was remission of disease without the use of prednisone at 6 months. Sixty-three patients in the rituximab group (64%) reached the primary end point, as compared with 52 patients in the control group (53%), a result that met the criterion for noninferiority (p<0.001). The rituximab-based regimen was more efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease; 34 of 51 patients in the rituximab group (67%) as compared with 21 of 50 patients in the control group (42%) reached the primary end point (p=0.01). Rituximab was also as effective as cyclophosphamide in the treatment of patients with major renal disease or alveolar haemorrhage. This study concluded that rituximab was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and that it could be superior in relapsing disease. However, there were no significant differences between the treatment groups with respect to rates of adverse events. Limitations of this study include the inclusion of only ANCA-positive patients and the exclusion of patients with severe alveolar hemorrhage requiring ventilatory support and of those with advanced renal dysfunction (serum creatinine >4.0 mg/dl). Therefore, the results of this study may not be generalised to ANCA-negative patients or to those with severe alveolar hemorrhage or advanced renal failure. Further data are needed to clarify whether duration of remission and relapse rates are similar in patients treated with rituximab and in those treated with cyclophosphamide.

Authors: Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group
Title: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis.
N Engl J Med 2010; 363(3): 211-20.
Summary: Cyclophosphamide induction regimens for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis are effective in about 80% of patients, but they are associated with high rates of adverse events. Uncontrolled observations suggest that rituximab may induce remission in over 80% of patients with refractory ANCA-associated vasculitis and that it may be safer than cyclophosphamide. This study (Randomised trial of rituximab versus cyclophosphamide for ANCA-associated vasculitis, RITUXVAS) compared rituximab with cyclophosphamide as induction therapy in ANCA-associated vasculitis. Fourty-four patients with newly diagnosed ANCA-associated vasculitis and renal involvement were randomly assigned, in a 3:1 ratio, to either the rituximab or to the control group. Both groups received intravenous methylprednisolone (at a dose of 1 g) and the same oral glucocorticoid regimen (1 mg per kilogram per day initially, with a reduction to 5 mg per day at the end of 6 months). Patients in the rituximab group received rituximab at a dose of 375 mg/m^2 per week, for 4 consecutive weeks, and intravenous cyclophosphamide at a dose of 15 mg per kilogram with the first and third rituximab infusions; these patients did not receive azathioprine to maintain remission. For patients in the rituximab group who had progressive disease within the first 6 months, a third dose of intravenous cyclophosphamide (at a dose of 15 mg per kilogram) was permitted. Patients in the control group received a validated regimen of intravenous cyclophosphamide for 3 to 6 months, followed by azathioprine. Further treatment with rituximab or cyclophosphamide was permitted in cases of relapse. Relapses occurring before a minimum of 6 months of sustained remission were considered failures with respect to the primary efficacy end point.
The median age was 68 years, and the glomerular filtration rate (GFR) was 18 ml per minute per 1.73 m^2 of body-surface area. Primary end points were rates of sustained remission at 12 months and of severe adverse events. Twenty-five patients in the rituximab group (76%) and 9 patients in the control group (82%) had a sustained remission (p=0.68). Severe adverse events occurred in 14 patients in the rituximab group (42%) and 4 patients in the control group (36%) (p=0.77). Six of the 33 patients in the rituximab group (18%) and 2 of the 11 patients in the control group (18%) died (p=1.00). The median increase in the GFR between 0 and 12 months was 19 ml per minute in the rituximab group and 15 ml per minute in the control group (p=0.14). This trial showed that rituximab was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis and that severe adverse events were similar with rituximab and cyclophosphamide therapy.
Like the RAVE, this study included only ANCA-positive patients. Therefore, the results of this study may not be generalised to ANCA-negative patients. Unlike the RAVE, in this study patients randomised to rituximab also received at least two doses of intravenous cyclophosphamide, whereas in the RAVE trial patients randomly assigned to rituximab did not receive cyclophosphamide. Outcome data were reported at 12 months (6 months in the RAVE study). Despite these differences, this study arrived at conclusions similar to those reached by the RAVE study with regard to the efficacy and safety profile of rituximab compared to cyclophosphamide.

Authors: Silva F, Specks U, Kalra S, Hogan MC, Leung N, Sethi S, Fervenza FC
Title: Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement - a prospective, open-label pilot trial.
Clin J Am Soc Nephrol 2010; 5(3):445-53.
Summary: Cyclophosphamide (CYC) plus corticosteroids (CS) is considered standard therapy for patients with renal involvement due to ANCA associated vasculitis (AAV), but treatment response is not satisfactory in all patients and CYC has a recognised toxicity. This prospective pilot trial explored whether mycophenolate mofetil (MMF) might represent an effective alternative to CYC for induction and maintenance of remission in the AAV microscopic polyangiitis (MPA) with mild to moderate renal involvement. Seventeen P-ANCA/MPO-ANCA-positive patients with MPA with

mild to moderate renal involvement received MMF (1000 mg orally, twice daily) and CS (intravenous methylprednisolone, 1 to 3 g, followed by oral prednisone at 1 mg/kg per day). Oral CS were discontinued by month 6; MMF was continued through month 18. The primary outcome measure was remission by month 6 and stable renal function. Secondary endpoints included major relapses necessitating a switch to CYC plus CS, minor relapses requiring an increase in CS dosage, and adverse events. Thirteen of 17 patients enrolled achieved the primary outcome, and 4 failed because of insufficient response, relapse, or MMF intolerance. Twelve patients remained in remission through month 18, renal function remained stable, and proteinuria improved. Side effects of MMF were mild, transient, and responsive to dose adjustments in nearly all patients except one. These results suggest that MMF may represent an alternative to CYC for induction and maintenance of remission in patients with MPO-ANCA-associated MPA with mild to moderate renal disease.

Authors: Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann
I, Tesar V, Wissing KM, Pagnoux C, Schmitt W, Jayne DR; European Vasculitis Study Group (EUVAS).
Title: Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomised controlled trial.
JAMA 2010; 304(21): 2381-8.
Summary: Current remission maintenance therapies for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are limited by partial efficacy and toxicity. This multicentric, open-label randomised controlled trial aimed to compare the efficacy of mycophenolate mofetil with azathioprine on the prevention of relapses in patients with AAV. Eligible patients had newly diagnosed AAV (Wegener granulomatosis or microscopic polyangiitis) and were aged 18 to 75 years at diagnosis. All patients initially received 1 mg/kg/d (maximum 80 mg) of oral prednisolone, which was reduced to 0.75 mg/kg/d after 1 week, 0.50 mg/kg/d after 2 weeks, 0.40 mg/kg/d after 4 weeks, 0.30 mg/kg/d after 7 weeks, 0.28 mg/kg/d after 10 weeks, and 0.25 mg/kg/d after 13 weeks; prednisolone was reduced to 15 mg/d at the start of the remission regimen, tapered to 5 mg/d after 12 months, and was withdrawn after 24 months. Patients were randomly assigned to azathioprine (n=80, starting at 2 mg/kg/d, reduced to 1.5 mg/kg/d after 12 months, 1 mg/kg/d after 18 months, and withdrawn after 42 months) or mycophenolate mofetil (n=76, starting at 2000 mg/d, reduced to 1500 mg/d after 12 months, 1000 mg/d after 18 months, and withdrawn after 42 months) after induction of remission with cyclophosphamide and prednisolone. The primary end point was relapse-free survival, which was assessed using a Cox proportional hazards model. The secondary end points were Vasculitis Damage Index, estimated glomerular filtration rate, and proteinuria. One hundred fifty-six patients were assigned to azathioprine (n=80) or mycophenolate mofetil (n=76) and were followed up for a median of 39 months. All patients were retained in the analysis by intention to treat. Relapses were more common in the mycophenolate mofetil group (42/76 patients) compared with the azathioprine group (30/80 patients), with an unadjusted hazard ratio (HR) for mycophenolate mofetil of 1.69 (95% confidence interval [CI], 1.06-2.70; *p*=03). The secondary outcomes of Vasculitis Damage Index, estimated glomerular filtration rate, and proteinuria did not differ significantly between groups. There were 22 severe adverse events in 13 patients (16%) in the azathioprine group and there were 8 severe adverse events in 8 patients (7.5%) in the mycophenolate mofetil group. Severe adverse events did not differ significantly between groups. The conclusion of this trial was that in patients with AAV mycophenolate mofetil was less effective than azathioprine for maintaining disease remission. Both treatments had similar adverse event rates.

Authors: Laurino S, Chaudhry A, Booth A, Conte G, Jayne D.
Title: Prospective study of TNF-alpha blockade with adalimumab in ANCA-associated systemic vasculitis with renal involvement.
Nephrol Dial Transplant 2010; 25(10): 3307-14
Summary: Tumour necrosis factor alpha (TNF-α) has been implicated in the pathogenesis of ANCA-associated systemic vasculitis (AASV). Uncontrolled studies have pointed to the efficacy of TNF-α blockade with infliximab in the induction of remission in systemic vasculitides. The hypothesis behind this study was that adjunctive treatment with the humanised anti-TNF-α monoclonal antibody, adalimumab, could permit more rapid remission and reduced prednisolone exposure in AASV. This phase II, open-label, prospective study enrolled 14 patients with acute flares of AASV either as first manifestation of disease or relapse. Mean age was 58 years and eight patients were male; all had kidney involvement. The Birmingham Vasculitis Activity Score (BVAS) was used to assess the activity of the disease and the response to treatment. Adalimumab (40 mg s.c.) was given every 2 weeks for 3 months. Concomitant therapy included intravenous cyclophosphamide, six to ten pulses at a dose of 15 mg/kg, reduced according to renal function and age in association with a reducing course of oral prednisolone from an initial dose of 0.5 mg/kg/day (0 week) to 0.1 mg/kg/day after three months. After the achievement of remission, between 3 and 6 months, patients were changed to maintenance therapy of azathioprine (2 mg/kg/day) or mycophenolate mofetil (500–1000 mg twice daily), if azathioprine intolerant, plus a reducing dose of oral prednisolone. Patients were followed up for 78 weeks after entering the study. Primary endpoints were: (i) induction of remission within the first 14 weeks (BVAS = 0); (ii) time taken to achieve remission; (iii) safety and tolerability.
Eleven (78.5%) patients achieved remission within 14 weeks (mean, 12 weeks). Remissions were sustained in eight patients, while there were six relapses (one major) in five patients. BVAS decreased from 11.9 (mean; 95% CI, 9.3–14.4) at baseline to 2.0 (mean; 95% CI, 0–4.4) at Week 14 ($p<0.01$). Prednisolone dose (in milligrammes per day) decreased from 37.1 (mean; 95% CI, 28.8–45.3) at entry to 8.1 (mean; 95% CI, 5.1–11.1) at Week 14 ($p<0.01$). Estimated glomerular filtration rate (in millilitres per minute per 1.73 m(2)) increased from 17.1 (mean; 95% CI, 8.9–25.2) at entry to 30.1 (mean; 95% CI, 18–42.2) at 12 weeks ($p<0.01$). One patient died

and three infections occurred. In this pilot trial, the addition of adalimumab to prednisolone and cyclophosphamide for the treatment of severe AASV was associated with response rates and adverse events similar to standard therapy alone but with a reduced prednisolone exposure. However, there was a sizeable number of infections in patients treated with adalimumab. Larger studies are needed to establish the role of TNF-α inhibition in AASV with renal involvement.

Authors: Flossmann O, Jayne DR.
Title: Long-term treatment of relapsing Wegener's granulomatosis with 15-deoxyspergualin.
Rheumatology (Oxford) 2010; 49(3): 556-62
Summary: Relapsing Wegener granulomatosis (WG) can be challenging to treat. This study aimed to determine the efficacy and safety of prolonged treatment with 15-deoxyspergualin (DSG, gusperimus) in patients with relapsing WG. Other immunosuppressants except corticosteroids were withdrawn and DSG, 0.5 mg/kg/day, self-administered subcutaneously for up to 21 days, in 28-day cycles. The cycle was terminated early for white blood cell count <4 x 10(9)/l. The prednisolone dose was adjusted according to the clinical state. End points were disease remission, relapse, Birmingham Vasculitis Activity Score (BVAS), prednisolone dose and safety. Eleven patients, five (45%) of whom were female, received 15 treatment periods with DSG. The median (range) duration of each treatment period was 6.8 (3.3–15.9) months. Ten (90.9%) patients responded in 13/15 courses after a median of 1.7 (0.7–2.7) months and six (54.5%) achieved remission after 7.7 (1.9–13.5) months. Two (18.2%) patients relapsed while continuing to receive DSG. Remission was maintained in other patients while DSG was continued. However, 7/8 relapsed after DSG withdrawal. The median BVAS fell from 10 (3-22) at baseline to 3 (0-16) at the end of each treatment period (p=0.002). Median prednisolone doses were reduced from 20 (5–30) mg/day at baseline to 10 (5–25) mg/day at the end of each treatment period (p=0.052). Three severe adverse events occurred in two patients. These observations showed that extended treatment with DSG was effective in the majority of patients with relapsing WG and permitted prednisolone reduction. There was no unexpected toxicity associated with prolonged DSG administration.

Authors: Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Puéchal X, Carli P, Kyndt X, Le Hello C, Letellier P, Cordier JF, Guillevin L; French Vasculitis Study Group.
Title: Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomised study of one hundred twenty-four patients.
Arthritis Rheum 2010; 62(4): 1186-97
Summary: This prospective, multicenter study had the goal of assessing the efficacy of systemic corticosteroids alone as first-line treatment of polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA) without poor-prognosis factors as defined by the Five-Factors Score (FFS), and to compare the efficacy and safety of azathioprine versus pulse cyclophosphamide as adjunctive immunosuppressive therapy for patients experiencing treatment failure or relapse. One hundred twenty-four patients with newly diagnosed PAN or MPA (FFS of 0) treated with corticosteroids alone were enrolled. At the time of treatment failure or disease relapse, patients were randomised to receive 6 months of therapy with oral azathioprine or 6 pulses of cyclophosphamide. Analyses was performed according to an intent-to-treat strategy. The mean followup (±SD) period was 62±33 months. Treatment with corticosteroids alone induced remission in 98 patients; 50 (40%) of these patients had sustained disease remission, 46 (37%) experienced a relapse, and 2 became corticosteroid dependent (daily prednisone dose > or = 20 mg). In 26 patients (21%), treatment with corticosteroids alone failed, and 49 patients (40%) required additional immunosuppression. Among the 39 patients randomised, 13 of 19 achieved remission with cyclophosphamide pulses, and 14 of 20 achieved remission with azathioprine. Among all patients, the 1-year and 5-year survival rates were 99% and 92%, respectively. Six deaths occurred in the cyclophosphamide-treated group compared with 2 deaths in the azathioprine-treated group. Disease-free survival was significantly lower for patients with MPA than for those with PAN (p=0.046). In conclusion, for patients with PAN or MPA with an FFS of 0, overall 5-year survival was good, but first-line corticosteroid treatment was able to achieve and maintain remission in only about half of the patients, and 40% of the patients required additional immunosuppressive therapy. Azathioprine or pulse cyclophosphamide were equally effective for treating corticosteroid-resistant disease or major relapses.

Giant-cell arteritis

Authors: Arida A, Kyprianou M, Kanakis M, Sfikakis PP
Title: The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis.
BMC Musculoskelet Disord 2010; 11: 44.
Summary: Colour-Doppler sonography (CDS) of the temporal arteries may be used to demonstrate inflammatory changes in patients with giant cell arteritis (GCA). A previous meta-analysis of primary studies available through April 2004 concluded that CDS could indeed be helpful in diagnosing GCA. This review re-examined the diagnostic value of the CDS finding of the "halo sign", a dark hypoechoic circumferential thickening around the artery lumen, indicating vasculitic wall edema, in GCA. Original, prospective studies in patients with suspected GCA that examined CDS findings of temporal arteries using the ACR 1990 classification criteria for GCA as reference standard, published through 2009, were identified. Eight studies involving 575 patients, 204 of whom received the final diagnosis of GCA, fulfilled technical quality criteria for CDS. Weighted sensitivity and specificity estimates of the halo sign were assessed, their possible heterogeneity was investigated and pooled diagnostic odds ratio was determined. Unilateral halo sign achieved an overall sensitivity of 68% (95% CI, 0.61–0.74) and specificity of 91% (95% CI, 0.88–0.94) for GCA. The values of inconsistency coefficient of both sensitivity and specificity

of the halo sign, showed significant heterogeneity concerning the results between studies. Pooled diagnostic odds ratio, expressing how much greater the odds of having GCA are for patients with halo sign than for those without, was 34 (95% CI, 8.21–138.23). Diagnostic odds ratio was further increased to 65 (95% CI, 17.86–236.82) when bilateral halo signs were present (sensitivity/specificity of 43% and 100%, respectively). This study concluded that CDS of the temporal arteries is useful in patients with suspected GCA and that a bilateral halo sign has a 100% specificity for GCA.

Authors: Ball EL, Walsh SR, Tang TY, Gohil R, Clarke JM
Title: Role of ultrasonography in the diagnosis of temporal arteritis.
Br J Surg 2010; 97(12): 1765-71.
Summary: This is a systematic review performed of trials comparing temporal artery (TA) biopsy with Color-Doppler sonography (CDS) of the temporal arteries. CDS findings (halo sign, stenosis or occlusion) were compared with either TA biopsy findings or the American College of Rheumatology (ACR) criteria for the classification of giant cell arteritis (GCA). The performance of CDS was assessed with weighted independent sensitivity and specificity values. Seventeen eligible studies containing 998 patients were identified. Nine studies on 357 patients compared the halo sign with TA biopsy as the diagnostic standard. When the halo sign on CDS was compared with TA biopsy, the sensitivity was 75 (95% confidence interval 67 to 82) per cent and the specificity was 83 (78 to 88) per cent. The presence of any vascular alterations including stenosis and occlusion, compared with halo alone, seemed to improve sensitivity while retaining specificity, although there was significant between-study heterogeneity.
Six studies (401 patients) compared the halo sign with the ACR criteria as the diagnostic standard. The weighted sensitivity and specificity estimates were 69 (60 to 77) and 89 (84 to 92) per cent respectively. There was significant between-study heterogeneity. Start of glucocorticoid treatment before CDS did not appear to affect the findings. This review concluded that CDS of the TA is relatively accurate for diagnosing GCA.

Isolated (single-organ) vasculitis

Authors: Salvarani C, Calamia KT, Crowson CS, Miller DV, Broadwell AW, Hunder GG, Matteson EL, Warrington KJ.
Title: Localised vasculitis of the gastrointestinal tract: a case series.
Rheumatology (Oxford) 2010; 49(7): 1326-35.
Summary: Vasculitis involving the gastrointestinal (GI) tract often occurs as part of a systemic inflammatory process and is a well-recognised manifestation of small- and medium-sized-vessel vasculitides. However, vasculitis of the GI tract may also occur in isolation ("localised vasculitis of the gastrointestinal tract [LVGT]). The objective of this study was to describe the clinical features, radiographic characteristics and outcomes of a series of patients with LVGT seen at a tertiary care centre. Medical records of 608 patients diagnosed with vasculitis involving the intra-abdominal vasculature and/or abdominal viscera between January 1996 and December 2007 at the Mayo Clinic (Rochester, MN, USA) were reviewed. Only patients with histopathological confirmation or typical angiographic findings of vasculitis localised to the abdomen were included. Eighteen cases with LVGT were identified over the 12-year study period. The patients were predominantly Caucasian (89%) and female (67%) with a median age at diagnosis of 53.5 (range 17.4-83.3) years. Most patients presented with multiple manifestations. Abdominal pain was the most frequent finding, present in almost all patients. Other GI manifestations were abdominal angina, nausea or vomiting, diarrhoea, haematochezia and melena. Twelve (66.6%) patients presented with an acute abdomen requiring surgical intervention. At diagnosis, the median ESR was 30.5 (range 4–77) mm/1st h. Autoantibody screening was generally unremarkable. Fifteen patients underwent abdominal angiography, which showed alterations consistent with vasculitis in 14 of them. Stenosis was the most frequent lesion, present in 13 (86.7%) patients, followed by dilatation in 8 (53.3%), aneurysm in 5 (33.3%), obstruction in 4 (26.7%) and wall thickening in 2 (13.3%). The most commonly involved blood vessel were the superior mesenteric artery (73.3%), followed by coeliac artery (60%), hepatic artery (53.3%), inferior mesenteric artery (46.7%), and splenic artery (40%). One patient had only abdominal MRA, which did not reveal vasculitic lesions. Abdominal CT was performed in 12 patients. Spleen infarcts were present in three patients, liver infarcts in two, bowel infarction in two, small intestine and/or large intestine wall thickening in three. Histological evidence of vasculitis was recorded in 5 (28%) patients, most commonly from gall bladder or small intestine specimens. Median duration of follow-up was 10.5 (range 2-156) months. No evidence of vasculitis outside the abdomen was observed at follow-up. Ten patients were treated medically and 8 were not. All the medically treated patients received oral glucocorticoids, while 5 patients also received other immunosuppressive agents. Eight of the 10 treated patients responded to therapy. At the last follow-up, of the eight untreated patients, three were in remission, one had relapsed, and four had died. Overall, 7 (39%) patients died during the follow-up period. Survival of the patient cohort (compared with an age-matched US white population) was significantly reduced. The results of this study suggest that LVGT is an uncommon form of vasculitis that can be associated with significant morbidity and mortality.

Authors: Salvarani C, Brown RD, Jr, Calamia KT, Christianson TJH, Huston J, III, Meschia JF, Giannini C, Miller DV, Hunder GG
Title: Rapidly progressive primary central nervous system vasculitis
Rheumatology (Oxford) 2011; 50: 349-358.
Summary: Primary central nervous system vasculitis (PCNSV) is a rare vasculitis that involves the brain and occasionally also the spinal cord. The aim of this study was to describe a subset of patients with a rapidly progressive clinical course extracted from a large cohort of 131 consecutive patients with PCNSV seen over a 25-year period at the Mayo

Clinic (Rochester, MN, USA). The diagnosis of PCNSV was based on brain or spinal cord biopsy, or on cerebral angiography. Patients were considered to have definite PCNSV if a brain or spinal cord biopsy specimen showed a transmural destructive inflammatory vessel wall infiltrate, or if angiograms showed changes highly suggestive of vasculitis (segmental narrowing, dilatation, or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes of atherosclerosis). Patients with high (≥5) scores of the modified Rankin scale indicating severe disability or death at diagnosis or within 6 months after the diagnosis were considered as having rapidly progressive disease. Patients with rapidly progressive PCNSV were compared to those without to identify features that might be associated with a rapidly progressive course. Three patients with rapidly progressive PCNSV received glucocorticoids alone and eight patients received glucocorticoids combined with immunosuppressants (six cyclophosphamide and two azathioprine). Despite the aggressive treatment, the outcome was poor for all the patients. Ten patients died and only one was alive at the end of follow-up but with severe neurological disability.

Compared with the 120 patients without rapidly progressive vasculitis, the 11 patients with rapidly progressive vasculitis had more frequently paraparesis/quadriparesis at presentation, angiographic signs of bilateral large-vessel vasculitis and MRI evidence of cerebral infarctions. Brain infarctions were more frequently multiple and bilateral, and were more frequently localised both in the cortex and in subcortical regions. Granulomatous and/or necrotising histopathological patterns of vasculitis were observed in patients with positive biopsies.

The findings of this study suggest that rapidly progressive PCNSV is a subset of PCNSV at the worst end of the clinical spectrum of this vasculitis, characterised by bilateral, multiple, large cerebral vessel lesions and multiple CNS infarctions. Conventional treatment does not appear to significantly benefit these patients. It remains to be established whether other therapies including biological agents might be effective in this patients' subset.

Paediatric vasculitis

Authors: Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, Buoncompagni A, Lazar C, Bilge I, Uziel Y, Rigante D, Cantarini L, Hilario MO, Silva CA, Alegria M, Norambuena X, Belot A, Berkun Y, Estrella AI, Olivieri AN, Alpigiani MG, Rumba I, Sztajnbok F, Tambic-Bukovac L, Breda L, Al-Mayouf S, Mihaylova D, Chasnyk V, Sengler C, Klein-Gitelman M, Djeddi D, Nuno L, Pruunsild C, Brunner J, Kondi A, Pagava K, Pederzoli S, Martini A, Ruperto N; Paediatric Rheumatology International Trials Organisation (PRINTO).

Title: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria.

Ann Rheum Dis 2010; 69(5): 798-806.

Summary: This paper reports on the validation of the proposed classification criteria for Henoch-Schönlein purpura (HSP), childhood polyarteritis nodosa (c-PAN), c-Wegener granulomatosis (c-WG) and c-Takayasu arteritis (c-TA). The first step was a retrospective/prospective web-data collection for HSP, c-PAN, c-WG and c-TA, with age at diagnosis <or=18 years. The second step consisted of a blinded classification by consensus panel of a subgroup of 280 cases. Finally, in the third step a statistical evaluation was performed to assess sensitivity, specificity, area under the curve, and kappa-agreement using nominal group technique consensus evaluations. Overall, 827 patients with HSP, 150 with c-PAN, 60 with c-WG, 87 with c-TA and 52 with c-other were compared with each other. A patient was classified as HSP in the presence of purpura or petechiae (mandatory) with lower limb predominance plus one of four criteria: (1) abdominal pain; (2) histopathology (IgA); (3) arthritis or arthralgia; (4) renal involvement. Classification of c-PAN required a systemic inflammatory disease with evidence of necrotising vasculitis or angiographic abnormalities of medium-/small-sized arteries (mandatory criterion) plus one of five criteria: (1) skin involvement; (2) myalgia/muscle tenderness; (3) hypertension; (4) peripheral neuropathy; (5) renal involvement. Classification of c-WG required three of six criteria: (1) histopathological evidence of granulomatous inflammation; (2) upper airway involvement; (3) laryngo-tracheo-bronchial involvement; (4) pulmonary involvement (x-ray/CT); (5) antineutrophilic cytoplasmic antibody positivity; (6) renal involvement. Classification of c-TA required typical angiographic abnormalities of the aorta or its main branches and pulmonary arteries (mandatory criterion) plus one of five criteria: (1) pulse deficit or claudication; (2) blood pressure discrepancy in any limb; (3) bruits; (4) hypertension; (5) elevated acute phase reactant.

For HSP, the sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final HSP EULAR/PRINTO/PRES classification definition was 100%/87%/93.5%, respectively, with a κ-agreement of 0.90. For c-PAN, the sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final HSP EULAR/PRINTO/PRES classification definition was 89.6%/99.6%/94.6%, respectively, with a κ-agreement of 0.92. For c-WG, the sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final HSP EULAR/PRINTO/PRES classification definition was 93.3%/99.2%/96.3%, respectively, with a κ-agreement of 0.90. For c-TA, the sensitivities/specificities/AUC and κ-agreement (between the consensus panel and specific definition) of the final HSP EULAR/PRINTO/PRES classification definition was 100%/99.9%/99.95%, respectively, with a κ-agreement of 0.99.

The EULAR/PRINTO/PRES classification criteria for HSP, c-PAN, c-WG and c-TA have high sensitivity and specificity and should be used in future clinical trials.