A bird's eye review of the recent literature

Edited by
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Treatment of ANCA-associated vasculitis

Authors: Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, Kyndt X, Lifermann F, Papo T, Lambert M, Le Noach J, Khellaf M, Merrien D, Puéchal X, Vinzio S, Cohen P, Mouthon L, Cordier JF, Guillevin L; French Vasculitis Study Group.
Title: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis.
N Engl J Med 2008 Dec 25; 359(26): 2790-803.
Summary: The aim of this prospective, open-label, multicenter trial was to compare azathioprine and methotrexate for maintenance therapy with regard to safety and efficacy in patients with Wegener's granulomatosis or microscopic polyangiitis who have achieved remission with intravenous cyclophosphamide and corticosteroids. Patients were randomly assigned to receive oral azathioprine (at a dose of 2.0 mg per kilogram of body weight per day) or methotrexate (at a dose of 0.3 mg per kilogram per week, increased within 2 to 4 weeks to 25 mg per week) for 12 months for maintenance. Among 159 eligible patients, 126 (79%) achieved remission with the induction protocol and were randomly assigned to receive a maintenance drug in two groups of 63 patients each. For a mean post-randomization follow-up of 29±13 months, adverse events occurred in 29 azathioprine recipients and 35 methotrexate recipients (p=0.29); grade 3 or 4 events occurred in 5 patients in the azathioprine group and 11 patients in the methotrexate group (p=0.11); and adverse events requiring discontinuation of the study drug or causing death, corresponding to the study primary end point, occurred in 7 azathioprine as compared to 12 methotrexate patients (p=0.21). There was one death in the methotrexate group. Twenty-three patients who received azathioprine and 21 patients who received methotrexate had a relapse (p=0.71); 73% of these relapses occurred after discontinuation of the study drug. These results suggested that the two agents are similar alternatives for maintenance therapy in patients with Wegener's granulomatosis and microscopic polyangiitis after initial remission. However, and even though no association between adverse events and renal impairment was observed in the méthotrexate patients, possibly due to the relatively small size of the study sample, authors wisely state that methotrexate dose should be adjusted or its use avoided in patients with severe renal impairment. Others points are that, despite this induction-maintenance approach, high relapse rates persist and the optimal duration of maintenance therapy remains to be determined.

Authors: Walsh M, Chaudhry A, Jayne D.
Title: Long-term follow-up of relapsing/refractory anti- neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H)
Ann Rheum Dis 2008 Sep; 67(9): 1322-7.
Summary: Since lymphocytes contributed to the pathogenesis of anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AASV), this study presented long-term follow-up results of the use of humanised monoclonal anti-CD52 antibodies (alemtuzumab, CAMPATH-1H) that selectively deplete lymphocytes, in patients with relapsing/refractory AASV.
This study, conducted between 1991 and 1999, included 71 patients with multiple relapses or refractory life threatening AASV. They received intravenous CAMPATH-1H on consecutive days at doses of 4, 10, 40, 40 and 40 mg (total 134 mg). Other immunosuppressive agents were discontinued and prednisolone was tapered to 10 mg/day.
Most of patients (79%) had previously received cyclophosphamide; 42% had renal involvement (including 8% dialysis-dependant) and 18% were critically ill requiring intensive care unit. Forty-six patients (65%) achieved a clinical remission requiring prednisolone ≤10 mg/day, no immunosuppressive agents and inactive disease; and 14 patients (20%) had a clinically significant improvement but required either prednisolone >10 mg/day or an immunosuppressive agent.
After a mean follow-up of 5 years, 43 relapsed (median 9.2 months); 24 had a remission >1 year, of which 10 had a remission >3 years. Adverse events were frequent and included infections (n=28), malignancies (n=3) and thyroid diseases (n=8). Thirty-one patients died; age >50 years, dialysis dependency and occurrence of severe infection during treatment were associated with an increased risk of death.
CAMPATH-1H represents an effective therapeutic option for relapsing/refractory AASV patients with, however, high adverse events and relapse rates.

Authors: Josselin L, Mahr A, Cohen P, Pagnoux C, Guaydier-Souquières G, Hayem G, Job-Deslandre C, Liferman F, Pourrat J, Guillevin L.
Title: Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients
Ann Rheum Dis 2008 Sep; 67(9): 1343-6. Epub 2008 Apr 29.
Summary: Data from small, uncontrolled studies with limited follow-up suggested that infliximab, a monoclonal anti-tumor necrosis α antibody, might be an effective add-on therapy to treat systemic necrotizing vasculitides (SNV)

refractory to conventional treatment. This retrospective study reported on the outcome of 15 patients with a variety of SNV (10 Wegener's granulomatosis, 1 microscopic polyangiitis, 3 rheumatoid arthritis-associated vasculitis, 1 cryoglobluline-mic vasculitis) who were treated with adjunctive infliximab (5 mg/kg per injection; range of time on infliximab: 2–31 months) for refractory disease. The follow-up from start of infliximab therapy was at least 2 years (median: 35 months). All 15 patients initially responded to infliximab and 5 achieved prolonged remissions of 6 months or more. Relapses were recorded in 10 patients including 3 while still receiving infliximab and 2 successfully re-treated with infliximab. Adverse events prompting infliximab discontinuation occurred in 2 instances and no malignancies were observed. The authors concluded that adjunctive infliximab might indeed be a useful salvage therapy for refractory SNV and should undergo further evaluation in this subset of difficult-to-treat patients.

ANCA-associated vasculitis

Authors: Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, Nachman PH.
Title: Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: Comparison of two independent cohorts.
Arthritis Rheum 2008 Sep; 58(9): 2908-18.
Summary: The objective of this collaborative study between the Glomerular Disease Collaborative Network (GDCN) in the southeastern US and the French Vasculitis Study Group (FVSG) was to evaluate the applicability of the predictors of treatment resistance and relapse earlier identified in the GDCN cohort of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Hogan *et al*., *Ann Intern Med* 2005;143:621-31). In this previous study, treatment resistance was associated with female sex, black ethnicity, and presentation with severe kidney disease, whereas the following factors seropositivity for anti-proteinase 3 (PR3) antibodies and disease of the lung or upper respiratory tract were associated with relapse. In the present study, including 434 patients from the French cohort and 350 from the GDCN cohort, with a median follow-up period of 44.5 months, only age (OR 1.32 per 10 years [95% CI 1.05-1.66]) predicted treatment resistance in the French cohort. Predictors of relapse in the French cohort were PR3 ANCA (HR 1.66 [95% CI 1.15-2.39]) and lung involvement (HR 1.56 [95% CI 1.11-2.20]), but not upper respiratory tract involvement (HR 0.96 [95% CI 0.67-1.38]). Notably, the French cohort included more patients with PR3-ANCA (58% vs. 40%), lung involvement (58% vs. 49%), and upper respiratory tract involvement (62% vs. 31%). Hence, older age is a predictor of treatment resistance, whereas PR3-ANCA and lung involvement are predictors of relapse in both cohorts. Authors hypothesized that the observed discrepancies in other predictors of treatment resistance may reflect differences in access to care, and differences in predictors of relapse may reflect variations in disease expression.

Authors: Allenbach Y, Seror R, Pagnoux C, Teixeira L, Guilpain P, Guillevin L; French Vasculitis Study Group.
Title: High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: a systematic retrospective study on 1130 patients
Ann Rheum Dis 2009 Apr; 68(4): 564-7.
Summary: Previous studies showed a higher incidence of venous thromboembolic events (VTE) in Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) patients than the general population. This study aimed to determine the frequency and risk factors of VTE in WG, MPA, and so far unstudied Churg–Strauss syndrome (CSS) and polyarteritis nodosa (PAN).
This retrospective, systematic included 1130 WG, MPA, CSS or PAN patients of the French Vasculitis Study Group cohort. VTE frequency was compared between the different vasculitides. Patients' characteristics were compared between VTE and non-VTE patients to identify VTE risk factors.During a mean follow-up of 58.4±45.8 months, 83 VTE occurred in 74 (6.5%) patients, with a median vasculitis-VTE-diagnosis interval of 5.8 months [-3 to +156]. VTE occurred in 7/285 (2.5%) PAN, 19/232 (8.2%) CSS, 30/377 (8%) WG, and 18/236 (7.6%) MPA patients. The WG, MPA and CSS patients had a significantly higher risk of VTE compared to PAN (adjusted odds ratio = 2.88 [1.27–6.50]; p=0.01). Age, male sex, prior VTE and stroke with motor deficit were associated with a higher VTE risk. Like WG and MPA, CSS patients are at greater risk of VTE, than those with PAN.

Authors: Ormerod AS, Cook MC.
Title: Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales.
Intern Med J 2008 Nov; 38(11): 816-23.
Summary: Epidemiological data on the occurrence of primary systemic vasculitides (PSV) in the southern hemisphere is sparse. This population-based study aimed at describing the epidemiology of 4 PSV, *i.e*., Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS) and polyarteritis nodosa (PAN), in southeastern Australia for the period 1995-2004. Cases with PSV were searched in retrospect by screening inpatient databases of two teaching hospitals and through positive ANCA serologies obtained from a central immunology laboratory. A total of 75 cases of PSV fulfilling ACR (for WG, MPA and CSS) or CHCC criteria (for PAN) were identified for the investigated 10-year period. The overall annual PSV incidence was stable across the periods 1995-1999 and 2000-2004 (approximately 17/million adult population). For the period 2000-2004, the 5-year prevalence for PSV was estimated at 184/million adult population (95%CI 158.4-212.6) and disease-specific annual incidences at 8.4 for WG, 5.0 for MPA, 2.2 for CSS and 1.1 for PAN. There was a statistically significant 9-fold higher incidence of MPA in rural as compared to urban areas. This study indicates that in Australia, PSV occurs in similar rates than those previously reported from mostly western European countries. It was furthermore

suggested that the occurrence of ANCA-associated vasculitis might be more common in rural habitats.

Kawasaki's disease

Authors: Burns JC, Best BM, Mejias A, Mahony L, Fixler DE, Jafri HS, Melish ME, Jackson MA, Asmar BI, Lang DJ, Connor JD, Capparelli EV, Keen ML, Mamun K, Keenan GF, Ramilo O.
Title: Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease
J Pediatr 2008 Dec; 153(6): 833-8. Epub 2008 Jul 30.
Summary: The aim of this multicenter, randomized, prospective study was to investigate the safety, tolerability, and pharmacokinetics of the anti-TNF-alpha monoclonal antibody infliximab in paediatrics patients with intravenous immunoglobulin (IVIG)-resistant Kawasaki disease. A single infusion of infliximab (5mg/kg) was compared to a second infusion of IVIg (22g/kg) in 24 children (Mean age=21 months {8-38}; 7 females) with acute Kawasaki disease in whom fever persisted between 48 hours and 7 days after initial infusion of IVIG. The first IVIg infusion was given within the first two weeks of fever.
Cessation of fever within 24 hours in 11/12 patients treated with infliximab and in 8/12 patients treated with IVIG. One and 2 subjects treated with infliximab or IVIg respectively had 2 days of fever. Two additionnal patients in the IVIg-treated group were treated off-protocol with methylprednisolone because they had more than 2 days of fever. No infusion reactions or serious adverse events were attributed to either drug and no significant differences were observed between treatment groups in the change from baseline for laboratory variables, fever, or echocardiographic assessment of coronary arteries. As expected according to the literature data, 5 subjects (21%) developed a coronary artery aneurysm, including 4 patients randomized to infliximab and 1 randomized to IVIG who crossed over to infliximab). Notably, four of these patients with aneurysms had coronary artery abnormality on echocardiogram at study entry.
Infliximab appeared to be safe and well tolerated in this short population of children with IVIg-resistant Kawasaki disease. Infliximab could be used as an alternative to IVIg or intravenous corticosteroids. However, whether infliximab could prevent coronary aneurysms remains to be investigated and further studies are required to determine the best clinical practice in IVIg-resistant Kawasaki disease.

Authors: Hauser T, Mahr A, Metzler C, Coste J, Sommerstein R, Gross WL, Guillevin L, Hellmich B.
Title: The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: a case-crossover study
Thorax 2008 Aug; 63(8): 677-82. Epub 2008 Feb 14.
Summary: Numerous cases have been reported on the occurrence of Churg-Strauss syndrome (CSS) in asthmatics previously exposed to medications belonging to the class of leucotriene-receptor antagonists. This pharmacoepidemiological study was undertaken with the aim of analyzing the risk of CSS associated with intake of montelukast, the only leucotriene-receptor antagonist approved in the study area. Using various sources of information, the authors retrospectively retraced the medication histories prior to onset of CSS in 78 patients. Applying a case-crossover design, medication exposures during the 3-month "index" period preceding the onset of CSS were compared with those of four previous 3-month "control" periods. Computations yielded the following odds ratios (for risk of CSS onset associated with asthma medication exposure): montelukast 4.5 (95% CI 1.5–13.9), inhaled long-acting beta$_2$ agonists 3.0 (95% CI 0.8–10.5), inhaled corticosteroids 1.7 (95% CI 0.5–5.4), and oral corticosteroids 4.0 (95% CI 1.3–12.5). These results suggested that the association with CSS onset is not specific to montelukast but rather a phenomenon associated with the group of medications prescribed for long-term control of severe asthma. It was hypothesized that the link of CSS onset with montelukast and other asthma medications might account for confounding by indication reflecting the severity or the gradual worsening of asthma before the outbreak of vasculitis.

Cryoglobulinemia

Authors: Saadoun D, Resche-Rigon M, Sene D, Perard L, Karras A, Cacoub P.
Title: Rituximab combined with Peg-interferon-ribavirin in refractory hepatitis C virus-associated cryoglobulinaemia vasculitis
Ann Rheum Dis 2008 Oct; 67(10): 1431-6. Epub 2008 Jan 4.
Summary: In this pilot study, the authors present the results of a treatment combining 2 antiviral agents, Peg-interferon alpha2b and ribavirin, with rituximab, an anti lymphocyte B agent, in patients with severe refractory hepatitis C virus-related mixed cryoglobulinaemia vasculitis.
Sixteen consecutive patients who were resistant (n=11) or relapser (n=5) after a previous course of antiviral therapy were included. They were all treated with rituximab (375 mg/m^2 intravenously weekly, for 4 weeks) combined with Peg-interferon alpha2b (1.5µg/kg per week, subcutaneously) plus ribavirin (600-1200 mg/d orally) for 12 months.Fifteen patients (93.7%) showed clinical improvement, 10 of whom were complete responders (CR). HCV RNA and serum cryoglobulin became undetectable in all the clinical responders. Compared with the clinical CR, the partial or non-responders had a 3.6 times longer duration of vasculitis prior to treatment and a lower rate of early virological response.
Peripheral blood B cell depletion was achieved in all patients (CD19+ cells, 111 (SD32)/mm3 at baseline versus 2 (2)/mm^3 after the fourth infusion of rituximab) with reconstitution starting at the end of the antiviral therapy. Treatment was well tolerated with no infectious complication.
After a mean follow-up of 19.4 months, 2 patients experienced clinical relapse with a simultaneous reappearance of HCV RNA and cryoglobulin and an increase in the number of B cells.

These results suggest that rituximab combined to Peg-interferon and ribavirin represents a safe and effective therapy in severe refractory HCV mixed cryoglobulinaemic vasculitis. However, the risk of long-term relapse is not yet known.

Pathogenesis of vasculitis

Authors: Kain R, Exner M, Brandes R, Ziebermayr R, Cunningham D, Alderson CA, Davidovits A, Raab I, Jahn R, Ashour O, Spitzauer S, Sunder-Plassmann G, Fukuda M, Klemm P, Rees AJ, Kerjaschki D.
Title: Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis.
Nat Med 2008 Oct; 14(10): 1088-96.
Summary: Herein, Kain *et al*. described a new target antigen recognized by autoantibodies in patients with pauci-immune necrotizing glomerulonephritis (including patients with proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA positive vasculitides). The recognized antigen is the lysosomal membrane protein-2 (LAMP2), which can be considered as a novel ANCA subtype, since it is expressed in the membranes of MPO- and PR3–containing intracellular vesicles and gives positive results in immunofluorescence assays. Anti-LAMP2 antibodies are found in almost all individuals, which represents an important help for the diagnosis of necrotizing glomerulonephritis. In addition, the immune tranfer of these autoantibodies to rats can trigger pauci-immune necrotizing glomerulonephritis, maybe through the induction of endothelial cell apoptosis. This is an important data for the pathogenic role of these autoantibodies. Furthermore, the human LAMP2 epitope (P41–49) recognized by patients' sera shares 100% homology with the bacterial adhesin FimH (from fimbriated pathogens) and anti-LAMP2 antibodies cross-react with FimH. Finally, the authors report a high prevalence (69%) of urinary infections with fimbriated pathogens during the 12 weeks before the onset of renal vasculitis. Because this study suggests that FimH-triggered autoimmunity to LAMP-2 could contribute to the development of necrotizing glomerulonephritis, it does provide an alternative view to the classical concept on ANCA-positive vasculitis. Additional studies are required to determine wheter anti-LAMP2 antibodies could be used as a clinical marker in systemic vasculitides.

Authors: Voswinkel J, Assmann G, Held G, Pitann S, Gross WL, Holl-Ulrich K, Herlyn K, Mueller A.
Title: Single cell analysis of B lymphocytes from Wegener's granulomatosis: B cell receptors display affinity maturation within the granulomatous lesions
Clin Exp Immunol 2008 Dec; 154(3): 339-45. Epub 2008 Sep 23.
Summary: In most cases, Wegener's granulomatosis (WG) is characterised by presence of circulating anti-neutrophil cytoplasm antibodies (ANCA) directed against autoantigen proteinase 3 (PR3). The site where these antibodies are produced is still not elucidated, even though there are some arguments suggesting this could take place in the granulomas, where aggregates of B lymphocytes and plasma cells have been described and could participate in forming tertiary lymphoid structures. The aim of this study was to perform a single B cell analysis from cyo-preserved endonasal biopsies of three WG patients, using laser-assisted microdissection. Subsequently, their immunoglobulin variable heavy (VH) and light (Vk, Vl) chain were analysed by single cell polymerase chain reaction (PCR) and sequencing, and compared to sequences of peripheral VH genes from healthy volunteers. Sixteen immunoglobulin VH-Vk or VH-Vl chain gene couples were characterised. Twelve of these gene couples resembled memory B cells, with high rate of mutation reflecting an antigen driven process. Except for one couple, the complementary determining region 3 (CDR3) contained aspartic acid at position 116 which might be a hint towards selection against a positively charged molecule, such as PR3. VH genes representing 39 single B cells of WG tissues displayed significantly more mutations than VH genes from peripheral blood of a healthy donor. In one WG patient, two separately analysed single B cells carried the same rearrangement VH3-21, suggesting clonal expansion in the granuloma. Interestingly, the CDR3 featured six negatively charged amino acid residues that, potentially, favour affinity to the positively charged PR3. In conclusion, these results demonstrate presence of B cells which underwent selection and maturation in the granuloma. This could support the idea that an autoimmune response directed against PR3 may take place in Wegener's granuloma.

Authors: Abdulahad WH, Stegeman CA, Limburg PC, Kallenberg CG.
Title: Skewed distribution of Th17 lymphocytes in patients with Wegener's granulomatosis in remission
Arthritis Rheum 2008 Jul; 58(7): 2196-205.
Summary: The role of recently described Th17 lymphocytes has not been studied so far in Wegener's granulomatosis (WG). Recent data suggest that these cells might play a role in several autoimmune inflammatory diseases such as rheumatoid arthritis, multiple sclerosis or systemic lupus erythematosus. The aim of this study was to determine the distribution of Th1/Th2/ Th17 cells in peripheral blood of WG patients in remission (determined by BVAS score at 0) and also to investigate the presence of Th17 cells specific for proteinase 3 (PR3). Peripheral blood from patients with WG (n=26) and healthy controls (n=10) was stimulated in vitro with PR3 or other stimuli (staphylococcal enterotoxin B (SEB), tetanus toxoid (TT), PMA-iono) together with anti-CD28 and anti-CD49d. The frequency of the various CD4+ T cells was determined by 7-color flow cytometric detection of CD3, CD8, CD69 (early activation marker), and intra-cellular cytokines (IL-2, IL-4, IL-17 and IFNγ).
A significant decrease in CD69 expression was observed in CD4+ T cells from WG patients upon stimulation with PR3 antigen, compared to healthy controls. Among activated CD69+CD4+ T cells after stimulation, increased percentages of Th17 and Th2 T cells were observed in patients, compared

to controls. Upon stimulation with PR3 autoantigen, a significant increase in Th17 cells was seen in ANCA-positive patients, compared to ANCA- negative and healthy controls while increased percentages of Th17 cells in response to TT and SEB was observed both in ANCA- positive and negative patients. These results show a skewed Th17 response in ANCA-positive WG patients following stimulation with PR and suggest a role of Th17 cells in the pathogenesis of WG. Targeting IL-17 cells could be a new therapeutic way in WG.

Authors: Knight A, Sandin S, Askling J
Title: Occupational risk factors for Wegener's granulomatosis- a case control study
Ann Rheum Dis Epub 2009 12 April
Summary: The etiology of Wegener's granulomatosis (WG) is unclear but environmental factors, *e.g.* silica exposure or farming, have been identified as putative risk factors. In this study, Swedish investigators studied the occupational exposures in 2,228 patients prior to development of WG in comparison to a matched control population. WG patients were identified through a national registry for inpatient care. Census data were used to obtain information on employments for WG cases and controls. Analyses focused on 32 occupations which were selected because they involve substantial exposure to inhaled particles or animal contact. The odds ratios (OR) for developing WG were 1.1 (95% CI 0.9–1.3) for the combined group of 32 occupations and ranged from 0.6–1.9 for the individual occupations. The highest risk increases for WG were observed for bakers (OR=1.6), paperworkers (OR=1.8), miners (OR=1.9) and animal keepers (OR=1.8) but none of these estimates reached statistical significance. The authors concluded that there is no general association between WG and occupational exposure to inhaled agents or to livestock farming.