



Health Canada approves rituximab for induction of remission of severe GPA and MPA in adults

A Notice of Compliance (NOC) has been issued on December 13th, 2011, for rituximab following Priority Review for the following indication: rituximab (RITUXAN) in combination with glucocorticoids is indicated for the induction of remission in adult patients with severely active granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA). As a reminder, this same indication for rituximab has been approved in April 2011 by the FDA, based on the simultaneously published results of the RAVE and RITUXVAS trials. As stated at the end of official communication, consideration should be given to current treatment guidelines for vasculitis. This approval may eventually facilitate the access and coverage of this expensive drug (rituximab) for patients with severe GPA or MPA for whom it is indicated and there is no safe or appropriate alternative. However, this approval is only a (huge) first step. Now, it has to be approved by each Canadian province separately, before it changes anything in the patient access to rituximab and the coverage of the drug costs. - CPx, December 13, 2011.

More information soon on Health Canada website <http://www.hc-sc.gc.ca>

Neutrophil microparticles as potential pathogenic players in ANCA vasculitis (GPA)

Microparticles are membrane vesicles released upon activation or apoptosis from various cells, including platelets, endothelial cells or neutrophils. The two former types have been reported to be increased in the plasma of children with active ANCA vasculitis. Hong et al. studied here plasma neutrophils MPs from 9 children with active ANCA+ GPA (median age 16 years), 4 with inactive ANCA+ GPA, and 4 with other active (ANCA-) vasculitis (3 PAN, 1 KD). Eight healthy pediatric subjects were used as controls. In vitro, freshly isolated neutrophils from healthy adults released large amounts of MPs after being primed with TNF-alpha then exposed to polyclonal antiMPO or antiPR3 Abs from children with active GPA, but not if unprimed or after exposure to healthy control polyclonal IgG. These released MPs overexpressed PR3, MPO and CD11b as compared to spontaneously released neutrophil MPs. When incubating these MPs (released from primed neutrophils exposed to antiPR3) and HUVEC (human umbilical vein endothelial cells), a binding of MPs to HUVEC was observed, mediated by CD18 expression by MPs. Moreover, following this binding, HUVEC endothelial cells showed upregulation of ICAM-1 expression, an adhesion molecule which is also a surrogate marker for endothelial activation. The binding of MPs to HUVEC was also associated with an increased secretion by endothelial cells of IL6 and IL8. Notably, antiCD18 monoclonal Abs were able to block this binding of MPs to HUVEC as well as the activation of endothelial cells after the binding of MPs and the release of IL6 and IL8 by HUVEC. Authors further demonstrated that the upregulation of ICAM-1 after binding of MPs was related to the induction and increased production of intracellular endothelial reactive oxygen species, which could be inhibited by HUVEC pre-treatment with antioxidants (either a SOD mimetic manganese derivative (MnTBAP) or

apocynin). Finally, authors showed that these neutrophil MPs generated thrombin (suggesting a potential pro-thrombotic effect of MPs) and that children with active GPA had higher plasma levels of neutrophil MPs as compared to both children with inactive GPA or other vasculitis.

Neutrophil MPs may thus contribute to the pathogenesis of ANCA vasculitis (at least pediatric antiPR3+ GPA). After both neutrophil priming and exposure to ANCA, these MPs expressed PR3 and MPO, thereby potentially eliciting auto-immune and inflammatory response, and bound to endothelial cells, activating these latter. However, non-bound MPs have been previously shown by other groups to possibly exert opposite anti-inflammatory effects. The balance between the different MPs may thus be more subtle in vivo... New therapeutic agents, including antiCD18 m-Abs and anti-oxydant agents, or mechanisms by which adjuvant approaches act , such as plasma exchange to clear MPs, have to be further investigated based on these results. - CPx, December 11, 2011.

Hong Y, Eleftheriou D, Hussain AA, Price-Kuehne FE, Savage CO, Jayne D, Little MA, Salama AD, Klein NJ, Brogan PA. Anti-Neutrophil Cytoplasmic Antibodies Stimulate Release of Neutrophil Microparticles. J Am Soc Nephrol. 2011 Nov 3. [Epub ahead of print]. [Link](#)

Induction therapy for GPA/MPA based on oral cyclophosphamide is associated with a lower relapse rate, as compared to IV pulse cyclophosphamide, 4 years after CYCLOPS study closure

The EUVAS group reports on the follow-up of the patients enrolled in the CYCLOPS trial, which compared continuous oral cyclophosphamide (2 mg/kg/d until remission, then 3 additional months for consolidation, followed by azathioprine for maintenance) versus pulse IV cyclophosphamide (15 mg/kg on days 1, 14 and 28 then every 3 weeks until remission, then 3 additional pulses for consolidation, followed by azathioprine for maintenance) for induction in patients with either granulomatosis with polyangiitis (GPA, Wegener) or microscopic polyangiitis (MPA). At 9 months, the same proportion of patients achieved remission (BVAS=0, around 88% in each arm). Only the rate of leukopenia was more frequent in the oral CYC arm, but which was not associated with a higher risk of infection. At 18 months, 15% of the patients experienced a relapse, with a non-significant difference between groups (19% in the IV versus 9% in the oral group). With a follow-up post-closure of the trial of 4.3 years, this difference in the rate of relapse has become significant: 40% of the IV pulse recipients have experienced a relapse, as compared to only 21% of those having received continuous oral cyclophosphamide (HR=0.50, p=0.03). AntiPR3+ patients were also more likely to have experienced relapses, as compared to antiMPO+ patients. Conversely, there was no difference between arms for the frequency of infection, the progression to end stage renal disease (ESRD, IV 13% versus oral 11%), VDI scores, or rates of other adverse events. As a reminder, oral cyclophosphamide recipients had received a cumulative dose of 16 g, as compared to only 8 g for the IV pulse cyclophosphamide patients (the cumulative dose of prednisone was comparable between groups, as was the use of immunosuppressant drugs after trial closure, even though they have not been extensively gathered).

This follow-up analysis is interesting but was not planned on a statistical point of view and thus the results of this study remain only indicative and not definitive. This difference in the rate of relapse does not dismiss pulse IV cyclophosphamide as induction therapy, but illustrates the subtle balance between safety and toxicity of cyclophosphamide. A higher cumulative dose (using oral cyclophosphamide) is associated with a reduced relapse rate, but a lower cumulative dose could also reduce the risk of infection (even though no difference in infection rate was observed in the CYCLOPS and in this follow-up studies) and the risk of delayed cyclophosphamide-related toxicity, such as infertility or late cancers (even though a cumulative dose of 16 g is certainly not as toxic as what was used in the past, when patients were given oral cyclophosphamide for more than 1 year). - CPx, December 11, 2011.

Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, Tesar V, Vanhille P, Groot KD, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D; on behalf of EUVAS investigators. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann Rheum Dis*. 2011 Nov 29. [Epub ahead of print] [Link](#)

Rituximab for systemic vasculitis associated with rheumatoid arthritis

Xavier Puéchal et al. (France) report their experience with rituximab for the treatment of 17 patients with systemic vasculitis associated with rheumatoid arthritis (RA). These patients have been enrolled in a larger prospective cohort of 1,994 RA patients treated with rituximab at least at one occasion during the course of their disease (AIR registry). Mean age of these 17 patients, when receiving their first rituximab infusion, was 63.5 years and mean duration of RA was 29.5 months. Clinical manifestations of vasculitis mostly included mononeuritis multiplex (n=13) and/or cutaneous lesions (n=12). None had renal or CNS manifestations. Approximately one-third of the patients (only) had previously received cyclophosphamide and/or a TNF blocker. Rituximab induction regimens slightly varied, with 13 of the patients having received 1g, 2 weeks apart, in combination with corticosteroids in all but one of the patients and/or methotrexate in 8, cyclophosphamide in 1, and azathioprine in 1. Twelve (71%) of the patients achieved complete remission (modified BVAS for RA, not including arthralgias or arthritis, BVAS/RA= 0) at month 6; 4 (24%) achieved partial remission at month 6; 1 patient died at month 5 from gangrene and sepsis (active vasculitis with necrotic leg ulcers and mononeuritis multiplex). BVAS/RA fell from 9.6 at baseline to 3.6 at 3 months and 0.6 at 6 months; mean daily prednisone dose was reduced from 19.2 mg at baseline to 9.7 mg at month 6. Patients who received rituximab as first line therapy responded better than the relapsers and/or patients refractory to more conventional agents (87.5% achieved complete remission as compared to only 50%, respectively). Concerning RA itself, DAS28 synovitis score fell from 4.81 at baseline to 3.79 at month 6. Whether response to rituximab differed based on ACPA status was not studied/reported. Preemptive maintenance therapy was given to 6 of the patients who achieved complete remission, with a repeat infusion every 6 months. None of them relapsed. Conversely, 3 out of the 9 patients who received only methotrexate for maintenance or no maintenance therapy at all relapsed. Repeat rituximab induction therapy achieved complete remission again in these latter. In addition to the patient who died from gangrene with sepsis, 2 patients experienced severe infections (subcutaneous abscess due to *Fusobacterium nucleatum* at day 4 post-first rituximab infusion; relapse of an elbow prosthesis infection at month 6). - CPx, December 10, 2011.

Puéchal X, Gottenberg JE, Berthelot JM, Gossec L, Meyer O, Morel J, Wendling D, de Bandt M, Houvenagel E, Jamard B, Lequerr T, Morel G, Richette P, Sellam J, Guillevin L, Mariette X; on Behalf of the Investigators of the AutoImmunity and Rituximab registry. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis. Results from the autoimmunity and rituximab registry. *Arthritis Care Res (Hoboken)*. 2011 Nov 10. [Epub ahead of print] [Link](#)

Two excellent reviews: one on the pathogenesis of ANCA vasculitides and the other one on Churg-Strauss syndrome

The annual theme issue on vasculitis of *Current Opinion in Rheumatology* includes two excellent reviews by specialists in the fields. The first one on the pathogenesis of ANCA vasculitis is complete, updated and very clear. The second one on the Churg-Strauss syndrome is quite original and focused mainly on the latest data on pathogenesis. An issue not to be missed, especially for these two articles. - CPx, December 2, 2011.

Vaglio A, Moosig F, Zwerina J. Churg-Strauss syndrome: update on pathophysiology and treatment. *Curr Opin Rheumatol*. 2011 Nov 13. [Link](#) van Timmeren MM, Heeringa P. Pathogenesis of ANCA-associated vasculitis: recent insights from animal models. *Curr Opin Rheumatol*. 2011 Nov 13. [Link](#)

Interleukin-2 as a potential treatment for HCV-induced vasculitis

Every article on vasculitis published in the *New England Journal of Medicine* deserves to be highlighted. Such an event emphasizes the growing interest for vasculitis in the medical community and the fast-paced advances in therapeutic management of these rare but potentially severe diseases. David Saadoun and Michelle Rosenzweig et al. (Paris, France) report their experience with IL-2 in 10 patients with HCV-related vasculitis (open-label, phase 1-2 trial). This research group is already world renowned for its studies on HCV infection and HCV-related vasculitis. IL-2 is a potent T effector cell stimulator, increasing immune responses against cancer and infections, but it also induces survival of Tregs, that can exert opposite effects in cancer patients or hamper the clearance of infectious agents. Experimental model of IL2 knock-out mice suggested that IL-2 was essential for the development, expansion, activation and survival of Tregs to greater degree than for the stimulation of effector T cells. In HCV infected patients, mixed cryoglobulin can be detected in 40-60%, but only 5-10% of them will suffer of cryoglobulinemic vasculitis, ranging from arthralgias, purpura to severe mononeuritis multiplex or glomerulonephritis. HCV-induced vasculitis has been shown to be associated with a Treg quantitative deficiency. Therefore, the attempt to treat such patients with IL-2. Ten patients with chronic HCV infection (HCV RNA+ in sera, mixed cryoglobulinemia >0.05 g/l, active vasculitis, resistance to previous treatment with antiviral drugs - including Peg-IFN-alpha and ribavirin - and rituximab, absence of cirrhosis, and no co-infection with HIV or HBV) received IL-2 at low doses (1.5 million units per day of SQ aldesleukin for 5 days over one week, followed by 3 other 5 day-courses of 3 million units per day, given at weeks 3, 6 and 9). They were aged a median of 58.5 years, with 1:1 sex ratio. None were receiving concurrent antiviral drugs, immunosuppressant or corticosteroids. Eight of them had purpura, 8 had peripheral neuropathy and 1 had renal disease. All had type II cryoglobulin (median of 0.53 g/l with MC IgM kappa in all cases). The mean duration of HCV infection was 30.2 years, and most of the patients (n=7) had genotype 1 virus. Main adverse effects of IL-2 injections were minor and transient, including asthenia (n=4), flu-like syndrome (n=4) and hypertension (n=1). There was no vasculitis flare and a modest decrease in HCV viral load was observed, as well as of cryoglobulin levels. Tregs CD4+ CD25high FOXP3+ increased from 3.6% of the circulating CD4+ T cells at baseline (lower than in healthy blood donors) to 11.8% at week 9 (primary study end point, p= 0.004). This increase in Tregs peaked after the 3rd IL-2 course and corresponded to a 420% increase in the proportion of Tregs. In addition, at day 150 (week 19), the proportion of Tregs remained significantly higher (6.1%) than at baseline, i.e. close to the normal range of values for healthy subjects. These Tregs were demonstrated as functional in vitro, and accompanied by an increase in suppressor CD8+ CD25+ FOXP3+ T cell count. A decrease in (marginal-zone) B cell number and an increase in NK cell were also observed, both of which returned to normal after cessation of IL-2. Eventually, 8 of the 10 patients showed clinical improvement (purpura disappeared in all the 8 patients with skin lesions; only 2 patients with isolated neuropathy - both with type 4 HCV genotype - did not respond to IL-2 therapy). Improvement was noted as of the first infusion in two patients and after the 2nd course in the remaining six who improved. This study remains small-sized, rather exploratory and concerned patients with refractory vasculitis, but it elegantly demonstrates the safety (at least after 4 months of follow-up) and potential benefit of low-dose IL-2 treatment in such condition. At such dose, IL-2 favoured the development of Tregs rather than the stimulation of T effector cells, which would be potentially harmful in auto-immune and/or inflammatory diseases. - CPx 30 November 2011.

Saadoun D, Rosenzweig M, Joly F, Six A, Carrat F, Thibault V, Sene D, Cacoub P, Klatzmann D. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. *New Engl J Med* 2011;365:2067-77 - December 1st, 2011. [Link](#).

Granulomatous manifestations of GPA are less responsive to rituximab than vasculitic ones.

The impression that granulomatous GPA manifestations could be less often (or not as rapidly) responsive to rituximab has already been occasionally reported (Brihaye et al. Clin Exp Rheum 2007; Aries et al. Ann Rheum Dis 2006), but this larger retrospective study from the German group on 59 patients who received rituximab for refractory GPA is more demonstrative. The overall response to rituximab in these patients was 61.3% (26.7% were refractory) after a median of 7 months of follow-up post-rituximab, with no try of a second induction course in case of non-response and no rituximab-based maintenance regimen. Notably, 54.7% of the patients received concomitantly cyclophosphamide. The absence of response was more frequent in patients with retro-orbital tumors (33.3%) and/or pachymeningitis (33.3%), as compared to those with lung nodules ("only" 16.7%), alveolar hemorrhage (8.3%), renal disease (15.4%), neuropathy (0%) or arthralgias (0%). Surprisingly, subglottic stenosis was refractory in "only" 12.5% of the patients (1 among 8 patients). Globally, vasculitic manifestations were refractory or unchanged (stable but not improved) to rituximab in 9.4% of the cases as compared to 41.8% for the granulomatous manifestations (the same patients could have both types of manifestations of course - with 37% of the patients having 2 refractory manifestations or more). Finally, among the 36 patients who achieved complete remission, after a median follow-up of 13.5 months, 44.4% relapsed (at a median time of 13.5 months [3-54] post-rituximab induction). Three-quarters of these relapsers received a repeat rituximab-induction course and achieved again a good response. All patients had a decrease in their IgG/M levels but not correlated with infections (that occurred in 28.9% of the patients).

Whether patients with such refractory granulomatous manifestations who do not achieve remission (complete or partial) at month 4 to 8 post-rituximab should receive a second induction course of rituximab or be considered as failure to rituximab and switched to another treatment (which one?) remains to be determined. Subsequent treatments and outcomes of these rituximab-refractory patients are not mentioned in this, however, very interesting and good article. - CPx 20 November 2011.

Holle JU, Dubrau C, Herlyn K, Heller M, Ambrosch P, Noelle B, Reinhold-Keller E, Gross WL. Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis. 2011 Oct 21. [Epub ahead of print] [Link](#)

Lebrikizumab: a new kid on the block for (a specific subset of) asthma patients

This article is not on vasculitis, but might lead to some future researches in Churg Strauss syndrome (CSS). Results of the study have also been presented orally at the European Respiratory Society meeting, on September 26, 2011. Asthma is indeed the background condition of CSS, present in more than 90% of the patients at diagnosis (usually, late onset asthma). Lebrikizumab is a humanized IgG4 monoclonal antibody, further altered by a single point mutation in the hinge region to enhance its stability, and that specifically binds to IL-13 and inhibits its function. IL-13 is produced by Th2 helper T lymphocytes, which contribute to many key features of asthma (and also CSS). This double-blinded randomized placebo-controlled study evaluated 219 patients with uncontrolled asthma (Asthma control questionnaire - ACQ5 score higher than 1.5, despite the use of inhaled corticosteroids for at least 6 months, with FEV1 between 40% and 80%). Patients on maintenance oral corticosteroids were not eligible. Mean age of the patients was 44 years and ACQ5 was 2.5. All were taking inhaled corticosteroids and 80% were also on long-acting beta-agonists. Given subcutaneously once a month and for 6 months, lebrikizumab at the dose of 250 mg per injection achieved a greater increase in prebronchodilator FEV1 by a mean of 5.5% (95% CI, 0.8-10.2) as compared to placebo at week 12 (primary outcome measure). Notably, this improvement was mainly, if not exclusively, observed in patients with high level of periostine at baseline (a surrogate marker for IL-13 level, which is difficult to measure). Those latter with high periostine level represented almost half of

the enrolled patients and achieved a 8.2% (95% CI, 1.0-15.4) increase of their FEV1 as compared to placebo, whereas those with lower baseline periostine level had their FEV1 increased by only 1.6% (95% CI, -4.5-7.7) as compared to placebo. These differences were observed as soon as week 1 after the 1st injection and were sustained until the end of patient follow-ups at week 32. However, changes in ACQ5 and in the rate of asthma exacerbations were not significantly different between arms (there was a trend for a lower rate of exacerbation in those patients with higher periostine level). Whereas IgE level decreased, eosinophil count slightly increased in the lebrikizumab recipients (by a mean of 0.11x10⁹/l as compared to placebo, p<0.001). Safety analysis yielded similar results for both lebrikizumab and placebo (2 major asthma exacerbations requiring hospital admission in both arms; 1 patient in the lebrikizumab arm had pneumonia, whereas 1 in the placebo had shingles and another one had acute purulent meningitis). In summary, lebrikizumab led to a significant, though modest, improvement of the primary paraclinical outcome measure (FEV1) in patients with uncontrolled asthma, that was sustained over time and after the cessation of the drug (at least until month 26 post-termination of the injections). Clinical benefit was less obvious (no change in ACQ5 or rate of exacerbation). Patients with higher periostine at baseline (i.e., though indirectly, with higher IL-13 level) responded better to the biological agent. There was no particular safety issue, but eosinophil count slightly increased under lebrikizumab (because the blockade of IL-13 leads to less influx of eosinophils from the blood into the lungs, as suggested by authors? but one cannot exclude that an increase production of some other cytokine or chemokine causes this increase in eosinophil count, to compensate the inhibition of IL-13 signal); However, none of the patients developed vasculitis manifestation or CSS. The action of the drug in patients taking oral corticosteroids now deserves to be studied (most of the CSS patients because of persistent asthma), as well as in patients with more pronounced hypereosinophilia (allergic asthma or, again, CSS patients). – CPx, 26 Sept 2011.

Corren et al. Lebrikizumab Treatment in Adults with Asthma. N Engl J Med 2011;365:1088-1098. [Link](#) Editorial by Monica Kraft (Asthma Phenotypes and Interleukin-13 — Moving Closer to Personalized Medicine) - [link](#).

A comprehensive review on the roles of TH1 (IFN-gamma) and TH17 (IL17) pathways in GCA

C. Weyand et al. provide an excellent review on GCA pathogeny, emphasizing that both IFN-gamma- and IL17-producing T lymphocytes are implicated and respond differently to corticosteroid therapy. Whereas TH17 pathways is rapidly disrupted by corticosteroids, mainly through suppression of IL1-beta, IL6 and IL23, TH1 (IFN-gamma) pathway remains almost unaltered. As stated by authors, GCA is thus a chronic disease characterized by persistent TH1-inducing signals. Aspirin and supra-high doses of corticosteroids can alter TH1 pathway, but to a very limited degree. Hence, combined/new therapies are needed for better disease control (such as agents targeting TH1 pathways, like perhaps anti-IL12 or anti-IL32, or both TH1 and TH17 pathways, like NOTCH blockers/inhibitors). - CPx. 08 August 2011.

Weyand CM, Younge BR, Goronzy JJ. IFN- γ and IL-17: the two faces of T-cell pathology in giant cell arteritis. Curr Opin Rheumatol. 2011 Jan;23(1):43-9. [Link](#)

Further reading: Piggott K, Deng J, Warrington K, Younge B, Kubo JT, Desai M, Goronzy JJ, Weyand CM. Blocking the NOTCH pathway inhibits vascular inflammation in large-vessel vasculitis. Circulation. 2011 Jan 25;123(3):309-18. [Link](#)

Smell and taste alterations in granulomatosis with polyangiitis (Wegener's)

Many of our patients with GPA complain of smell and/or, less often, taste alterations. The reasons can be multiple, including adverse events of medications, sinusitis, sometimes with cacosmia or phantosmia due to mucosal crusting, or

olfactive and/or gustatory nerve involvement(s). In this study, 16 GPA patients were evaluated for their smell and taste using visual analogue scales (VAS) and different "Sniffin' sticks" (for 16 common odours) or paper taste strips (impregnated in 4 variable concentrations of sweet, sour, salty or bitter taste). Normative values for these tests are known and 16 healthy age- and gender-matched subjects were used in addition as controls. At the time of investigations, none of the patient had crusting rhinitis, but 62% had nasal septum perforation as damage. None was current smoker. Subjective olfactory function was rated a mean of 65.7/100 (vs. 83.8 for controls; $p=0.03$) and gustatory function 67.2 (vs. 83.5 for controls; $p=0.02$). For olfactory functions, all tests were affected but odour threshold was the main affected one, prior to odour discrimination and identification. For gustatory functions, there was no major difference between GPA patients and controls. There was only a non-significant tendency for GPA patients to have lower scores in the qualities of sour, salty and bitter sensations. For all these tests, there was no difference according to the other extra-ENT disease characteristics. Even though treatments were recorded in this study, authors were not able, due to the small sample size, to identify any association with taste or smell abnormalities and any of the received drugs. In the discussion, they mention studies on olfaction in rheumatoid arthritis that showed that low-dose corticosteroids, rather than anti-TNF-alpha or methotrexate, were associated with some olfactory threshold abnormalities. The impact of these gustatory and olfactory disorders on the patient quality of life should be taken into account more than it is at present. - CPx. 06 August 2011.

Fasunla JA, Hundt W, Lutz J, Förger F, Thürmel K, Steinbach S. Evaluation of smell and taste in patients with Wegener's granuloma tosis. Eur Arch Otorhinolaryngol. 2011 Jul 12. [Epub ahead of print]. [Link](#).

Relapse rate in GCA: anemia at the time of diagnosis as the best predictor of recurrence

The Spanish group from Gonzalez-Gay et al. reports that 71 (40.8%) of their 174 biopsy-proven GCA patients (diagnosed and followed between 1992 and 2006 at Lugo's hospital) experienced at least 1 relapse or recurrence (the latter being defined as a relapse occurring more than 1 month after cessation of prednisone). More precisely, 14 (8%) of the patients had 2 or more relapses and recurrences occurred in 32 (18.4%) patients. Relapses or recurrences were defined as ESR >20 mm/1st hr with clear new, recurrent or worsening clinical manifestation(s). The median follow-up was of 104 months for the entire cohort (a minimum of 1 year was required); the median time from diagnosis to relapse was 16 months (patients were under a median of 5 mg OD prednisone when relapsing) and 23 months for recurrences. Pertinently, none of the patients had visual loss or amaurosis at the time of their relapse(s) or recurrence(s). Anemia (Hb <12 g/dl) at the time of diagnosis was the best (and only identified) predictor of relapse or recurrence (OR 2.17; 95% CI, 1.02-4.62).

These results remind us of the non-negligible rate of relapse in GCA. Although being a retrospective study, patients were treated quite homogeneously (single center study). Because focusing only on biopsy-proven GCA patients, the study of course does not inform us on the relapse rate of GCA patients who are not biopsy-proven. Eventually, one important finding of this study is that, whereas anemia was earlier reported as a protective parameter for ischemic complications and stroke, it seems associated with a higher risk of GCA relapse or recurrence. As discussed by the authors, this latter result may suggest that a strong initial inflammatory syndrome can be associated with a lower risk of ischemic events but a higher relapse rate. However, higher ESR, leukocyte or platelet counts at diagnosis were not found to be associated with relapses or recurrences and, importantly, CRP level was not studied and/or included in the model to identify potential predictors of relapse. - 21 July 2011. CPx

Martinez-Lado L, Calviño-Díaz C, Piñeiro A, Dierssen T, Vazquez-Rodriguez TR, Miranda-Fillooy JA, Lopez-Diaz MJ, Blanco R, Llorca J, Gonzalez-Gay MA. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine (Baltimore). 2011 May;90(3):186-93. [Link](#)

What you wanted to know on FDG-PET scan in vasculitis

A (too?) brief and easy-to-read review by Dr. Blockmans (Leuven, Belgium) on FDG-PET in vasculitis. The interest of this imaging technique remains quite "limited" to GCA and Takayasu's arteritis (and other types of aortitis). In GCA, PET led to the demonstration that wide-spread involvement by the vasculitic process of large arteries throughout the body occurs much more frequently than originally thought. PET can be useful at diagnosis to further support the diagnosis of GCA or TA and study disease extension. However, as stated by Dr. Blockmans, "one should only rely on very clear pictures in order to distinguish from physiologic-uptake or atherosclerosis". PET value for follow-up and as a prognostic tool (to assess the risk of developing aneurism) remains more controverted and its place in medium- and small-sized vessel vasculitides is more than marginal. - 9 July 2011. CPx

Blockmans D. PET in vasculitis. Ann N Y Acad Sci. 2011 Jun;1228(1):64-70 [Link](#) (this article is part of a special issue on PET in inflammatory diseases).

Modified SerpinB1 as a specific inhibitor of PR3

Proteinase 3 (PR3) is a neutrophil serine protease that represents the main autoantigen of granulomatosis with polyangiitis (GPA; Wegener's), expressed both at the membrane surface and in the cytoplasm primary granules of neutrophils. Patients with GPA were shown to have a more frequent hereditary deficiency in alpha-1-antitrypsin, a natural inhibitor of several serine proteases, including human neutrophil elastase (HNE) and PR3 (but inhibited at a 100-fold lower rate), as well as cathepsin G. SerpinB1 (formerly called monocyte neutrophil elastase inhibitor) is another but so far less well known important physiological serine protease inhibitor, that is also not specific to PR3 and, indeed, inhibits HNE more efficiently than PR3. A French group from Tours and Marseille generated a PR3-specific SerpinB1 mutant, by inserting limited and precise mutations in the reactive center loop of SerpinB1 (however, the generated mutant was partially but more slowly degraded in presence of HNE). Adding mutant SerpinB1 to a suspension of activated neutrophils from healthy subjects resulted *in vivo* in the rapid inhibition of membranous expression of PR3 on neutrophils, without causing other cellular toxicity. The incubation of neutrophils with mutant SerpinB1 and plasma from a patient with GPA resulted in a significant decrease in binding of antiPR3-ANCA antibodies to activated neutrophils, thus supporting the removal of active PR3 from the cell surface by the inhibitor (however, this effect was not observed for quiescent neutrophils). Supplementation therapy with natural alpha-1-protease inhibitor is effective in patients suffering some forms of emphysema but the use of synthetic recombinant neutrophil serine protease inhibitors, administered systemically or by aerosols, e.g. in cystic fibrosis, led to less convincing results yet. Authors conclude by stating that the structure of their engineered SerpinB1 mutant is highly similar to that of the natural inhibitor, thus with an expected long half-life and potentially less toxicity than chemical inhibitors. - 2 July 2011. CPx

Jégot G, Derache C, Castella S, Lahouassa H, Pitois E, Jourdan ML, Remold-O'Donnell E, Kellenberger C, Gauthier F, Korkmaz B. A substrate-based approach to convert SerpinB1 into a specific inhibitor of proteinase 3, the Wegener's granulomatosis autoantigen. FASEB J. 2011 Jun 13. [\[Epub ahead of print\]](#)

Mycophenolate mofetil as a potential induction therapy for non severe ANCA-associated vasculitis?

The recently published IMPROVE trial results showed that MMF was inferior to azathioprine to maintain remission (when used as first line maintenance agent). However, they do not preclude from the potential place of MMF as an induction treatment in patients with non-severe ANCA disease. The ongoing EUVAS MYCYC trial (inclusions recently closed) is

indeed to compare MMF versus cyclophosphamide for induction in patients with non-severe non-life-threatening GPA or MPA.

The Chinese group from Hangzhou reports this month in *Am J Nephrol* on their 41 patients with non severe MPA (no life threatening manifestation, such as CNS or massive alveolar hemorrhage) treated in a open-labeled randomized study with either MMF (n=19) at relatively low dose (1 to 1.5 g/d for the patients >70 kg) or IV CYC (n=22) using their own protocol regimen (0.8 to 1 g every month), in addition to corticosteroids, for induction of remission. The treatment was continued for at least 6 months, time at which the response rate was assessed. All patients were antiMPO positive and had renal involvement, with a mean creatinine level around 310 micromol/l at diagnosis, similarly in the 2 groups. At month 6, remission rate was 63.6% in the CYC group and 78.9% in the MMF group ($p=0.23$). No patient relapsed over the 6-month duration of the study; there was no between-arm difference in the daily dose of corticosteroids at months 1 and 6, in the mean eGFR at month 6 or in the rate of adverse events (with 2 deaths in the CYC group and 1 in the MMF arm). Although interesting and adding some information to the current literature on MMF in ANCA vasculitis, the size of this study remains small and there was no statistical primary hypothesis at all, thus its very limited statistical power. In addition, the doses and treatment regimen schedules were quite unusual (not to mention that all patients had MPA and kidney disease - i.e. a specific patient population, and there is no information provided on what happened after month 6, including on subsequent maintenance strategy). However, there was no negative signal and the forthcoming results of the MYCYC trial are thus awaited with some renewed interest (but should not be available before 1 year from now). - 29 June 2011. CPx

- Han F, Liu G, Zhang X, Li X, He Q, He X, Li Q, Wang S, Wang H, Chen J. *Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. Am J Nephrol. 2011;33(2):185-92. [Link](#)*

- IMPROVE. 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). *Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA. 2010 Dec 1;304(21):2381-8. [Link](#)*

MYCYC trial information: [Link](#)

Lack of evidence to support the systematic assessment of Thiopurine S-Methyltransferase activity prior to prescribing azathioprine

It has been and remains controversial whether testing for erythrocyte TPMT enzymatic activity or TPMT genotype prior to prescribing azathioprine was really of benefit, as compared to the regular and mandatory monitoring of CBC and liver enzymes. There have been several studies published over the past decade, but with conflicting results. In this systematic review published in the *Annals of Internal Medicine*, the authors (from Ottawa and Toronto) identified and analyzed 54 observational studies and 1 (the only one available so far) randomized control trial on this topic and found no evidence to support the systematic use of TPMT testing, even though they confirmed the clear association between leukopenia and myelotoxicity and TPMT reduced activity or variant genotype. Four to 11% of the general population is heterozygous for a variant TPMT allele and 0.3% are homozygous (perhaps more often in Africans), and have reduced or absent enzymatic activity, that can lead to the accumulation of toxic active metabolite of the drug, no further degraded. Genotyping can identify 4 of the most common alleles, accounting for 80 to 95% of persons with decreased TPMT activity (other variants are thus usually missed). However, TPMT status does not reliably predict all adverse events and up to 70% of patients suffering of azathioprine-related adverse events do not have abnormal TPMT activity. Seventy percent of the selected studies concerned patients with inflammatory bowel diseases; all but 2 included only white subjects. The OR to develop

myelotoxicity is 19.12 (CI, 4.56-80.24) for patients with low TPMT activity as compared to those with normal activity, and 2.56 (CI, 1.41-4.67) to develop leukopenia. Heterozygotes had an OR of leukopenia of 4.29 (CI, 2.67-6.89) and homozygotes of 20.84 (CI, 3.42-126.89) as compared to noncarriers. Withdrawal of the drug is more likely to be required in heterozygotes than noncarriers (OR 6.54; CI, 2.53-16.91). Although specificity of TPMT genotyping approaches 100%, sensitivity of genotyping to identify patients with low TPMT activity was only 70 to 86%.

For vasculitis patients, some small studies (Stassen et al. *Ann Rheum Dis* 2009 - included in this systematic review) suggested that regular CBC and liver enzyme monitoring (liver toxicity is less obviously associated with TPMT activity) was effective to early detect adverse events and prevent further and/or more severe toxicity. Finally, authors remind us that one must not forget that several drug interactions can also increase the risk of azathioprine-associated toxicity (as an example, remember that the concomitant use of azathioprine and allopurinol or any other xanthine oxidase inhibitor are contra-indicated).

The accompanying Editorial further emphasizes the lack of evidence on the clinical effectiveness and cost-effectiveness of preemptive TPMT testing and most of other pharmacogenetic testing so far. - 26 June 2011. CPx

- Booth RA, Ansari MT, Loit E, Tricco AC, Weeks L, Doucette S, Skidmore B, Sears M, Sy R, Karsh J. *Assessment of thiopurine s-methyltransferase activity in patients prescribed thiopurines: a systematic review. Ann Intern Med. 2011 Jun 21;154(12):814-23. [Link](#)*

- McLeod HL, Isaacs KL. *Preemptive pharmacogenetic testing: insufficient data equal unsatisfactory guidance. Ann Intern Med. 2011 Jun 21;154(12):842-3. [Link](#)*

- Stassen PM, Derks RP, Kallenberg CG, Stegeman CA. *Thiopurinemethyltransferase (TPMT) genotype and TPMT activity in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis: relation to azathioprine maintenance treatment and adverse effects. Ann Rheum Dis. 2009 May;68(5):758-9. [Link](#)*

Long- term (follow-up >10 years) outcomes of pediatric patients with ANCA vasculitis: the London UK experience on 8 patients.

ANCA-associated vasculitides are rare in childhood, but not exceptionnal (estimated annual incidence of 1 to 2 per million children below 15 years-old). The UK Londonian group of adult nephrology division reports on their 8 adult patients with ANCA-associated vasculitis diagnosed in childhood (before the age of 16 years) and followed for more than 10 years each (inclusion criteria). Mean age at diagnosis was 11.5 years; 6 were Caucasian and 2 African; 7 had GPA and 1 MPA; follow-up duration varied from 11 to 30 years after diagnosis (median 18.5 years). Five of them had renal involvement; only 4 had ENT manifestations at diagnosis and 1 developed subglottic stenosis. All patients received corticosteroids and all but one received cyclophosphamide as part of their therapies during the entire course of the disease. One patients never entered sustained complete remission and all of the remaining ones experienced at least 1 disease relapses, with a median of 4 relapses each (range 1 to 8 relapses). Whereas 1 patient died 25 years post-diagnosis (sudden death due to respiratory complications of GPA), only 1 progressed to end-stage kidney disease, but 4 became infertile (3 women and 1 man), 1 suffered of avascular necrosis of the hip and 1 developed malignancy (breast cancer at the age of 30 years). Infections were quite frequent, but none was severe.

In the second part of the article, authors made a review of the literature on ANCA-associated vasculitis in children, including only articles with information on outcomes (whatever the duration of follow-up). They thus identified a total of 86 additional patients. In those studies, female were also predominantly affected (up to 3/4 of the GPA patients), but

outcomes were relatively variable, with frequent relapses and damage (hearing loss, subglottic stenosis, infertility or chronic kidney disease in up to 1/3 of the patients).

The article is interesting to read (and brief) but authors missed the largest series on pediatric GPA patients from Toronto including 25 children, but with a shorter median follow-up of 32.7 months, and published in 2007 (Akikusa et al. *Arthritis Care & Research*, 57:837–844). However, it is true that if you search on PubMed for paediatric (with an -a-) vasculitis, this reference will not be listed...

As concluded by the authors, prospective cohorts are warranted to further study this specific population. There is indeed one already ongoing in Canada and USA, named ARChiVe, which started in 2005 under the impulse of Dr. Cabral (core member of CanVasc). More than 100 young GPA patients have already been enrolled, across 36 recruiting centers. - 25 June 2011. CPx

- Arulkumaran N, Jawad S, Smith SW, Harper L, Brogan P, Pusey CD, Salama AD. Long- term outcome of paediatric patients with ANCA vasculitis. *Pediatr Rheumatol Online J*. 2011 Jun 19;9(1):12. [Link](#) (free text).

- Akikusa JD, Schneider R, Harvey EA, Hebert D, Thorner PS, Laxer RM, Silverman ED. Clinical features and outcome of pediatric Wegener's granulomatosis. *Arthritis Rheum*. 2007 Jun 15;57(5):837-44. [Link](#) (free text).

Levamisole-adulterated cocaine-induced vasculitis

While awaiting for the publication of the cocaine-induced vasculitis patients from Ottawa (Dr. Milman, core member of CanVasc), the reading of this article may be useful. It is well illustrated and didactic. Authors report their experience on 6 patients recently seen in Los Angeles or New York and who had levamisole-adulterated cocaine-induced disease, including retiform purpura, characteristically necrotic with eschars and involving ears, nose and cheeks, with frequent neutropenia (half the patients) and p-ANCA (sometimes with c-ANCA and/or both antiPR3 and antiMPO on ELISA). Skin biopsy was done in 2 patients and showed leukocytoclastic vasculitis, with immune-complex deposits on IF.

Levamisole-contaminated cocaine has been detected since 2003, and such vasculitis cases have been increasingly observed since 2008. Up to 70% of the cocaine currently circulating in the U.S. may be contaminated by levamisole, an anti-helminthic agent that may induce some dopamine release in the brain, thereby potentially enhancing psychoactive effects of cocaine. The interval between exposure to levamisole-adulterated cocaine and the appearance of the first skin lesions is usually brief (hours to days), with the lesions gradually worsening with the persistence of drug exposure (either snorted or smoked). Systemic treatment is often given (i.e. corticosteroids) because of the impressive necrotic skin lesions, but the clinical manifestations seem to resolve "spontaneously" in most of the cases, whether the drug exposure is completely and definitively stopped. Finally, it should be reminded that cocaine can also per se (i.e., even when not contaminated by levamisole) cause vasculitis, mainly skin vasculitis, but also cerebral vasculitis, potentially leading to severe and irreversible damage. - June 15, 2011. CPx.

Chung C, Tumei PC, Birnbaum R, Tan BH, Sharp L, McCoy E, Mercurio MG, Craft N. Characteristic purpura of the ears, vasculitis, and neutropenia—a potential public health epidemic associated with levamisole-adulterated cocaine. *J Am Acad Dermatol*. 2011 Jun 7. [\[Epub ahead of print\]](#)

UK recommendations for the use of rituximab in ANCA-associated vasculitides

A group of 11 vasculitis experts from the UK, including 5 nephrologists and 1 pediatrician, ended up after a systematic and structured process (DELPHI exercise, systematic review of the literature, categorization of evidence) to 15 graded recommendations for the use of rituximab. Results of studies on rituximab published in 2010 and 2011 have not been included in this literature review (done in late 2009), nor, of course, those of the RAVE and RITUXVAS studies after 18 months of follow-up, recently revealed at the 15th ANCA workshop and EULAR. Those latter studies already add some new considerations and would deserve some additional comments, but these recommendations may be very helpful for other initiatives, in other countries, for either national recommendations or drug approval by regulatory organizations.

These recommendations, further detailed and commented in the article, are as follows:

Recommendation 1		Level of evidence
	What are the indications for rituximab as a treatment of ANCA-associated vasculitis?	
	In newly diagnosed ANCA-associated vasculitis: Rituximab is as effective as CYC for remission induction of previously untreated patients. Rituximab may be preferred, especially when CYC avoidance is desirable.	1b
	In refractory and/or relapsing disease: Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended when conventional therapy has failed.	1b
According to patient subgroups		
	· WG with head and neck manifestations: Rituximab is an effective treatment of refractory head and neck manifestations of WG and can be recommended when conventional therapy has failed.	2b/4
	· Paediatric ANCA-associated vasculitis: Rituximab should be considered for the treatment of children with ANCA-associated vasculitis that fails to respond to conventional induction therapy with glucocorticoids and CYC; or for patients with relapsing disease where there is particular concern regarding cumulative glucocorticoid and/or CYC toxicity.	4
	· Churg-Strauss syndrome: Response rates in refractory and/or relapsing: Churg-Strauss syndrome appear similar to other vasculitides and rituximab may be considered when conventional therapy has failed.	4
Recommendation 2		
	What is the optimal induction dosage regimen?	
	Both commonly used rituximab protocols (375mg/m ² /week for 4 weeks; 1000mg repeated after 2 weeks) appear equally effective for induction	4

		of remission, but have not been formally compared; therefore, both can be recommended.	
Recommendation 3			
	What are the longer term outcomes of treatment with rituximab?		
		Relapse rate: The overall response to rituximab in refractory disease may be superior to that seen with alternative therapies in similar cohorts of patients. There is insufficient evidence on long-term outcomes with rituximab when compared with conventional therapy in newly diagnosed patients. Relapse after rituximab is common and patients should be monitored accordingly.	4
		Potential predictors of relapse: No biomarker reliably predicts relapse.	3
		Re-treatment with rituximab Repeat rituximab is recommended for a relapse following rituximab-induced remission.	4
		Pre-emptive re-treatment may be considered in order to reduce relapse rates.	4
Recommendation 4			
	How should other immunosuppressive therapies be prescribed in patients treated with rituximab?		
		Should CYC be administered concomitantly with rituximab? We do not recommend the routine use of CYC with rituximab. CYC may be considered in severe, life or organthreatening presentations such as rapidly progressive GN in order to achieve rapid disease control.	4
		Should other immunosuppressants be continued following rituximab? No conclusion can be drawn from current data regarding the prescription of other immunosuppressing drugs with rituximab.	N/A
		What glucocorticoid regimen should be adopted in patients treated with rituximab and can glucocorticoids be stopped? High-dose intravenous or oral glucocorticoids may be administered with the initial rituximab course in order to obtain rapid control of disease.	4
		There is no clear evidence to guide steroid tapering.	N/A

Recommendation 5		
	How safe is rituximab in ANCA-associated vasculitis?	
	There is no convincing evidence that rituximab increases the frequency of severe infections when used in the treatment of vasculitis. Other drug-related adverse events occur with similar frequency to that seen in other indications.	4
	We recommend that patients receive vaccinations at least 1 month before their first dose of rituximab.	3
Recommendation 6. Research agenda		

Level of evidence 1 is from meta-analysis of randomized controlled trials.

Level of evidence 4 is from expert committee reports or opinions and/or clinical experience of respected authorities.

June 11, 2011. CPx.

Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, Pusey CD, Salama AD, Scott DG, Savage CO, Watts RA, Jayne DR. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford). 2011 May 25. [\[Epub ahead of print\]](#)

Cancers during the post-close-out period of WGET (etanercept trial): 13 additional cases, but also in the placebo group

Over the mean 43 months post-trial close-out, there were 13 additional solid malignancies among the 153 WGET patients (who were alive and not lost of follow-up from the initial 180 WGET patients = etanercept or placebo, on top of corticosteroids and cyclophosphamide or methotrexate, for GPA patients - the study showed no benefit of adding etanercept in term of relapse rate, and 6 cancers occurred during the trial period, exclusively in the etanercept group). More precisely, there were 8 additional solid malignancies in the etanercept patients and 5 in the placebo group. Four (2 in each group) of these cancers were fatal. The risk of cancer in the etanercept recipients, after trial close-out, thus appears higher than in the general population (SIR=3.92) but not significantly different than in the placebo group (SIR=2.89; P= 0.39). Notably, all these cancers occurred in patients who had received cyclophosphamide with quite high cumulative CYC doses (mean of 56 g prior to the trial and 16 g during the trial - the dose received after trial closure was not recorded). Indeed, patients who developed cancer were more likely to have been enrolled with a disease relapse, have a longer disease duration and a past history of cancer. Three of the total 19 cancers that occurred since the trial onset were cholangiocarcinomas (2 in the etanercept group, 1 in the placebo).

The risk of cancer under etanercept thus remains significant, at least as compared to the general population, but there is a clear relationship with the combined and/or previous use of cyclophosphamide (at quite huge doses!). Nowadays, almost no GPA patient is any longer treated with TNF alpha blockers, even others than etanercept (i.e, infliximab or adalimumab which both have been used previously as rescue therapy in some patients, with quite good results sometimes). - 4 May 2011. CPx

Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, Spiera R, Sebastian JK, Davis JC Jr, St Clair EW, Allen NB, McCune WJ, Ytterberg SR, Specks U; for the Wegener's Granulomatosis Etanercept Trial Research Group. Solid

malignancies among patients with Wegener's granulomatosis treated with etanercept: Long-term follow-up of a multicenter longitudinal cohort. Arthritis Rheum. 2011 Apr 11 [\[Epub ahead of print\]](#)

Potential pathogenic role of TLRs (toll-like receptors) in initial phases of ANCA-associated vasculitides

Using a mouse model (C57BL/6 mice injected intraperitoneally with MPO, with or without TLR-2 or TLR-9 ligands, then with anti-GBM globulin to trigger glomerulonephritis), Summers et al. demonstrate that TLR-2 ligation induces a Th17 response and production of IL-17A, while TLR-9 ligation favours a Th1 response with production of IFN-gamma. Both TLR ligands enhanced the immune response and production of antiMPO Abs, but with different CD4 subsets and ANCA IgG isotypes. Finally, both TLR ligands enhanced glomerular disease induced by antiGBM globulin, which were attenuated by subsequent injection of anti-IFN-gamma (in the TLR-9 model) or anti-IL17A (in the TLR-2 model). As stated by the authors, these findings support the hypothesis that infection can act as cofactor in the development of autoimmunity and renal disease in AASV, through TLR ligation. Gram-positive germs, including *Staphylococcus aureus*, are among the germs that can ligate TLR-2, whereas bacterial hypomethylated DNA or viruses can ligate TLR-9. - 23 April 2011. CPx

Summers SA, Steinmetz OM, Gan PY, Ooi JD, Odobasic D, Kitching AR, Holdsworth SR. Toll-like receptor 2 induces Th17 myeloperoxidase autoimmunity while Toll-like receptor 9 drives Th1 autoimmunity in murine vasculitis. Arthritis Rheum. 2011 Apr;63(4):1124-35. [Link](#)

FDA approval for rituximab (in combination with corticosteroids) for adults with severe forms of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis

The FDA approval for rituximab use for patients with severe forms of granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis is based on the National Institutes of Health-sponsored study known as RAVE (Rituxan in ANCA-Associated vasculitis). The news has been largely disseminated in 'public' health media and journals over the past weeks. You can read the press release [HERE](#). We hope that it will also soon be approved by Health Canada. However, based on expert opinion (including CanVasc), it should be clearly reminded here and emphasized that the indications of rituximab are (and should be for the moment) restrained to severe forms of these diseases that are, in addition, either refractory to conventional therapies and/or when there is clear contra-indication(s) to conventional therapies. - 21 April 2011. CPx

Another and excellent review on pathogenesis of ANCA vasculitis! NOT to be missed

There have been several (good) reviews on the pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis over the past months, but this one is not to be missed, because written by one of the ANCA vasculitis "popes", Dr. Charles Jennette. If you missed some steps in that moving topic, this is The article you need to read! Really updated, incisive, clear and complete. - 31 March 2011

Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. Curr Opin Nephrol Hypertens. 2011 Mar 18. [Link](#)

Is there any interest for a combination of rituximab and cyclophosphamide for induction therapy in ANCA-associated vasculitis?

Rituximab (RTX) has recently been shown as a potential alternative to cyclophosphamide (CYC) to induce remission of ANCA-associated vasculitis, based on their non-inferiority in the RAVE and RITUXVAS studies (New Engl J Med, 2010 – [link](#)). However, RTX use has not yet been approved in Canada and, thus, it remains at present restricted to refractory and/or multi-relapsing patients. Whether its combination with another immunosuppressive drug, like CYC (cf. RITUXVAS), during induction phase, has any interest, especially in severely affected patients and whether such a combination does not increase the rate of adverse event remain unanswered questions. N Mansfield, from the London (UK) group, reports 23 consecutive patients with newly-diagnosed or relapsing (1 patient only) renal ANCA-associated vasculitis treated with a customized combination of RTX, CYC and corticosteroids for induction, then azathioprine for maintenance. One-third of the patients were Indo-Asian and their median creatinine at diagnosis was 227 micromol/l. Patients with creatinine >500 micromol/l, alveolar hemorrhage, CNS disease and/or history of previous treatment with RTX were excluded from this study. The customized regimen included RTX (1 g at Days 0 and 14), IV CYC (10 mg/kg at Days 0 and 14, with a maximum of 750 mg per pulse, then every 2 weeks – Days 28, 42, 56 and 70 –, with a maximum of 500 mg per pulse) and oral prednisone (1 mg/kg/d, with a maximum of 60 mg/d, with a subsequent tapering scheme, aimed at reaching a dose of 10 mg/d at week 13, then maintained until month 12). As of month 3, patients were started on azathioprine (2 mg/kg/d) for maintenance. This regimen was devised in 2006, with RTX being considered a CYC sparing agent (median cumulative dose of CYC 3.44 g for induction).

At 6 weeks, all but one patient achieved remission with the assigned regimen (1 suffered severe systemic illness just after his 2nd CYC and RTX doses and, thus, did not receive further doses; he died at month 19, in remission of his vasculitis). At month 6, all patients had a BVAS of zero and “only” one had end stage renal disease requiring definitive dialysis. The median time to reconstitute B cells was 13.8 months in 14 patients; 3 of them had renal and extra-renal relapses and 1 had minor relapse (mainly arthralgias), for each of them within the 6 months following B cell reconstitution and preceded by a rise in ANCA titers. The remaining 9 patients were still B cell depleted after a median follow-up of 78 [27-130] weeks; 1 of them had a minor relapse (mainly arthralgias), while ANCA titers remained stable. All 3 major relapsers achieved remission with a repeat treatment including RTX, and the 2 minor relapsers with a transient prednisone increase alone. Concerning safety, in addition to the patient with severe systemic illness after receiving his 2nd doses of CYC and RTX, there were 5 minor urinary infections and 1 minor lower respiratory tract infection during the first 3 months, then 7 additional non-major infections afterwards (including 1 shingles). Two patients had to stop azathioprine because of hypersensitivity or leucopenia.

It is difficult to conclude based on the results of this open-label study whether a combination of CYC and RTX for induction confers any further benefit than one of these agents used alone for inducing remission and, thus, whether such a poly-chemotherapy has a place in the therapeutic armamentarium for (severe) ANCA-associated vasculitis. Whereas the remission rate was very good (almost 100%), the relapse rate is non negligible (all relapses 22%, major relapses 13%), despite the use of azathioprine for maintenance. However, one would expect a rate of 35% after a similar follow-up of 39 months using conventional staged-treatment with CYC alone then azathioprine, and the overall safety profile of the combination was considered “acceptable”. The relapse rate after remission has been achieved with RTX alone and without any maintenance treatment (RAVE trial design) should be revealed soon, for some additional indirect comparison. - 26 March 2011. CPx

Mansfield N et al. Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. Nephrol Dial Transplant. 2011 Mar 17. [Link](#)

Beware of crabs in Las Vegas: paragonimiasis as another (rare) cause of eosinophilic pneumonia after ingestion of crabs in the United States

Human paragonimiasis is a parasitosis (a plathelminthiasis) affecting the lungs (pleural effusion, pneumothorax, pleural and/or parenchymal lung nodules, possibly with cavitation, eosinophilic pneumoniae, sometimes with necrotizing granulomatous inflammation and/or eosinophilic vasculitis on histology). It can be acquired after ingestion of contaminated uncooked crabs, crayfishes or wild boar meat. Blood eosinophilia is usually present (but not constant). CNS, skin or other sites can occasionally be involved as well, depending on the migration of the flatworm. Endemic in several parts of the world, especially Southeast Asia and China, it has rarely been reported in North America, mainly in immigrants.

Authors report 4 patients, who had probably been infected within the United States, including one amazing 46-year-old patient who developed hemoptysis due to a cavitory lesion in his left upper lung 8 months after the ingestion of tiny live crabs served in a Martini at a sushi restaurant in Las Vegas! He suffered of cough for 2 months, then had hemoptysis, due to bilateral eosinophilic pneumonia and his lung cavity. He had blood eosinophilia, positive immunoblot CDC serology for *Paragonimus westermani*, and a lung wedge biopsy revealed eosinophilic infiltrates and granulomatous vasculitis (no paragonimus egg was observed). Usual treatment (praziquantel for 2 days) was given.

Human paragonimiasis is another, although rare in North America, possible differential diagnosis of eosinophilic pneumonia and Churg-Strauss syndrome. - 26 March 2011

Boland JM et al. Pleuropulmonary Infection by Paragonimus westermani in the United States: A Rare Cause of Eosinophilic Pneumonia After Ingestion of Live Crabs. Am J Surg Pathol. 2011 Mar 15. [Link](#)

Under the microscope: Epitope characterization of antiMPO ANCA

The lysosomal enzyme myeloperoxidase (MPO) is the main antigenic target of p-ANCA. Direct pathogenic role of antiMPO have been demonstrated in vitro and in animal models.

In this study, Bruner et al. attempted to better characterize antiMPO target epitopes, using serum samples of 12 p-ANCA positive patients (matched with 12 healthy controls). They synthesized 369 different peptides based on the published sequence of MPO and tested patient's serum reactivity with each of them in a solid-phase assay and a modified conformatory ELISA. They eventually identified 7 major significant epitopes (bound by >33% of the patients), the 2 most significant ones (epitopes 2 and 6) being bound by 42 and 58% of the patients, respectively. None of these epitopes was bound among the controls. Based on the known and published crystal structure model of MPO (Fiedler et al. 2000, [link](#)), they further determined that only one of these 7 epitopes (epitope 3, i.e. SARIPCFLAG-aa 393-402) was within close proximity to the active site of MPO, and that another one (epitope 1) was located in the pro-peptide region, thus not present on the processed mature form of MPO. Two others (epitopes 6 and 7, i.e. RLDNRYQPMEPN-aa 511-522 and IFMSNSYPRD-aa 717-726, respectively) were close to each other in the structural form of MPO (i.e. the MPO heavy chain), with one or both of them being bound by 11 of the 12 patients. Biostatistical epitope prediction tools further supported the identification of these major epitopes.

In Goodpasture disease, anti-GBM antibodies react with only 1 epitope of the GBM. The identification of >5 different potential targets for antiMPO ANCA is thus of interest and provide some (new) interrogations. Unfortunately, authors did not mention the precise disease status or characteristics of the tested patients, nor did they tested their patients at different disease stages or activity levels. As they acknowledge, it would now have to be further investigated, on a larger scale. - 26 March 2011. CPx

Bruner BF et al. Epitope specificity of myeloperoxidase antibodies: identification of candidate human immunodominant epitopes. *Clin Exp Immunol*. 2011 Mar 14. [Link](#)

HCV-related vasculitis: prognostic factors

Among patients with active chronic hepatitis C (HCV) infection and related mixed cryoglobulinemia (MC), 5 to 10% develop symptomatic MC vasculitis (usually affecting small-sized vessels). Less frequently, vasculitis may occur in HCV-infected patients without cryoglobulinemia (often a PAN-like vasculitis). Benjamin Terrier and Fabrice Cacoub studied 151 consecutive patients with HCV infection and vasculitis (135 with MC, 16 without MC) followed-up between 1993 and 2009 in their Parisian center. The main HCV genotype was type 1 (62%), and 33% had severe liver fibrosis (Metavir score = 3). The main clinical vasculitis features were peripheral neuropathy (74%), purpura (69%), arthralgia/arthritis (50%) and kidney disease (33%).

With a median follow-up of 54 months, 21% of the patients died (26 patients with MC vasculitis and 6 with PAN-type vasculitis), mainly of infection and end-stage liver disease. Factors associated in multivariate analysis with a poor prognosis were the presence of severe liver fibrosis (HR 10.8), the Five Factor Score (HR 2.49 – however, in patients with Metavir score =3, FFS no longer had prognostic value), and the use of immunosuppressants (HR 4.05, after adjustment for severity of vasculitis). Conversely, the use of the Peg-interferon plus ribavirin combination was associated with a good prognosis (HR 0.34) and short-term corticosteroids, rituximab and/or plasmapheresis had no significant effect on outcome.

As stated by the author, HCV-vasculitis has a negative impact on the global prognosis of HCV-infected patients, whose mortality rate is eventually as high as that observed in HBV-related PAN patients. In addition, their findings emphasize the higher frequency of severe liver fibrosis in these patients, that also impacts on their prognosis. The more optimistic finding is the beneficial effect of antiviral agents and the absence of negative effect of short-term corticosteroids, rituximab and/or plasmapheresis. Finally, the study “validates” the use of FFS in HCV-related vasculitis, at least in those patients without severe liver fibrosis, in whom liver disease overweighs all other parameters. - 19 March 2011. CPx

Terrier B et al. Prognostic factors in hepatitis C virus patients with systemic vasculitis. *Arthritis Rheum*. 2011 Mar 11; Epub. [Link](#).

Granulomatosis with polyangiitis (GPA): the new name of Wegener's granulomatosis

It is now official. In an effort to get rid of eponyms for disease names, starting from the most controversial ones, an international group of vasculitis experts has renamed Wegener's granulomatosis. It is now to be named Granulomatosis with polyangiitis (Wegener's). The reference to Wegener will remain in brackets for several years, until being completely abandoned. Among other reason and justifications, its acronym wil thus be GPA, as opposed to its 'cousin' microscopic polyangiitis (MPA). - March 5, 2011. CPx

Falk R et al. Granulomatosis with Polyangiitis (Wegener's): An alternative name for Wegener's Granulomatosis; *Arthritis & Rheumatism* 2011; Epub 3 March 2011. [Link 1](#), [link 2](#). *Annals of Rheumatic Diseases* 2011;70:704,[link 1](#), [link2](#). *JASN* 2011;Epub 3 March 2011, [link 1](#). (these articles -similar- are not on free access now - you will need to have your own subscriber or institution access to read the full text of the articles).

Physiopathology Review of ANCA-associated Vasculitides

Cees Kallenberg, an internationally renowned expert on vasculitis from Groningen in the Netherlands, has extensively proven to write some of the best, most comprehensive, up-to-date and mind-opening reviews on vasculitis pathogenesis. Here is one of the latest, reviewing all most important findings since the discovery of ANCAs, in vitro and animal experience suggesting a potential pathogenic role of ANCA (at least antiMPO), and recent findings on the possible links with infection (molecular mimicry with *Staphylococcus aureus*, antiLAMP2 antibodies and gram negative bacteria). Update your knowledge! - March 5, 2011. CPx

Kallenberg CG. Pathogenesis of ANCA-associated vasculitides. Ann Rheum Dis . 2011 Mar;70 Suppl 1:i59-63. [Link](#) . (this article is not free of access - you will need to have your own subscriber or institution access to read the full text of the article).

Biologics for Churg-Strauss Syndrome?

There are very few data and studies on biologics such as rituximab (antiCD20, anti B cells) and mepolizumab (antiIL5) in Churg-Strauss syndrome. One recent article from the Boston group reports their experience with short-term use of mepolizumab (only 4 monthly infusions) on 7 patients. All were also receiving prednisone and methotrexate (chronic, moderately active disease) prior to and when receiving mepolizumab (adjunctive therapy). Safety profile appeared good (transient headaches in 3, mild pruritus in 1, no infection or anaphylactoid reaction, no burst of CSS during treatment). All patients were able to taper prednisone dose while receiving mepolizumab, but on cessation of mepolizumab, CSS manifestations recurred in all but 1 patients. The Rochester group reported their experience with rituximab on 3 ANCA-positive patients with glomerular involvement (thus a specific subset of CSS patients). All patients achieved renal remission using RTX and corticosteroids (but no other immunosuppressant) and none developed severe adverse event (one common upper respiratory tract infection) at 1 year of follow-up. These are very preliminary data and focused on very selected patients. Mepolizumab is currently under investigation in ongoing trials. There have been several promising cases reported with rituximab, but also some more concerning (major bronchospasms in some patients with ANCA-negative CSS; *Bouldouyre et al. Ann Rheum Dis. 2009 Apr;68(4):606 - [link](#)*). - March 5, 2011. CPx

- *Cartin-Ceba R et al. Rituximab for the treatment of Churg-Strauss syndrome with renal involvement. Nephrol Dial Transplant. 2011 Feb 16. [Epub ahead of print] [Link](#) (this article is not free of access - you will need to have your own subscriber or institution access to read the full text of the article).*

- *Kim S et al. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol. 2010 Jun;125(6):1336-43. [Link](#) (this article is not free of access - you will need to have your own subscriber or institution access to read the full text of the article).*