

## CanVasc Literature Review

YEAR 2012



### A different cytokine environment and response to bacterial challenges in nasal mucosa of GPA patients?

The German group from Laudien et al. reports the results of their measurement study of *in vitro* secretions of 19 different cytokines by nasal mucosa epithelial cells from 20 GPA patients, aged around 50 years and diagnosed (and treated) for a median of 1.6 years (vs 10 healthy controls). After isolation and culture for 2 weeks of nasal epithelial cells from their study subjects, they observed at baseline a higher production of G-CSF but lower secretion of IL8 by GPA patient epithelial cells as compared to controls. Other measured cytokine levels did not differ between GPA and control subjects. After stimulation of these cultured epithelial cells (from 10 GPA patients and 10 controls) with *S. aureus* culture supernatant (secretory products), they also found that the induced additional IL8 secretion was lower in GPA patients than in controls.

Of course, measurements of cytokines in patients treated for months and in cultured cells can be seen as far from what may happen in GPA patients prior to and/or at the disease onset. It is also a little bit surprising that no differences in any other cytokines was observed (limited sample size? cytokine pattern changes during cell culture? or the difference is really and only limited to IL8 secretion?). Whatever, these results are interesting and suggest that local immune responses to bacterial challenges in GPA patients may be altered and might thus play some pathogenic role. Responses to other bacterial challenges would be interesting to study, if possible in treatment-naïve GPA patients, as well as in patients with chronic non-GPA-related sinusitis or rhinitis, sarcoidosis and/or nasal polyposis (due or not to EGPA).-CPx, October 09, 2012.

*J Wohlers et al. Aberrant cytokine pattern of the nasal mucosa in granulomatosis with polyangiitis. Arthritis Res Ther. 2012 Oct 2;14(5):R203. [Link](#)*

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### Rituximab approval by the Canadian Drug Expert Committee (CDEC)

After the FDA, Health Canada then Ontario Health Ministry, the Canadian Drug Expert Committee (CDEC) has released a positive decision regarding the treatment of GPA/MPA with rituximab. The actual working of the recommendation is as follows: The Canadian Drug Expert Committee (CDEC) recommends that rituximab be listed for the induction of remission in patients with severely active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) who have a severe intolerance or other contraindication to cyclophosphamide, or who have failed an adequate trial of cyclophosphamide. The CDR recommendation document and the link to the website is: [http://www.cadth.ca/media/cdr/complete/cdr\\_complete\\_Rituxan-Aug\\_16-12\\_e.pdf](http://www.cadth.ca/media/cdr/complete/cdr_complete_Rituxan-Aug_16-12_e.pdf). - CPx, August 24, 2012.

## **Genetic distinctions between antiPR3 and antiMPO ANCA vasculitis**

A new article on vasculitis in the NEJM! This time, this is a more fundamental and genetic study (GWAS/genome wide association study using SNP/Single-nucleotide polymorphism), conducted on 2,687 patients with ANCA-associated vasculitides (1,683 GPA and 489 MPA, including 1,521 antiPR3+ and 556 antiMPO+ ANCA) and 7,650 matched controls (data were not of sufficient quality for all patients and, at the end, the reported analyses include 2,395 patients and 6,925 controls). All subjects are from Europe (mainly U.K.). In a nutshell, the main finding is that the strongest genetic associations are with the ANCA antigenic specificity, rather than with the clinical syndrome (MPA vs. GPA): antiPR3+ ANCA vasculitis is associated with *HLA-DP*, the genes encoding alpha1-antitrypsine (*SERPINA1*) and proteinase 3 (*PRTN3*), whereas antiMPO ANCA vasculitis is associated with *HLA-DQ*. As already suggested by previous numerous clinical and therapeutic studies, one may eventually stop, one day, categorizing patients as having GPA or MPA, but rather as having antiPR3 or antiMPO disease (their respective treatments may also slightly vary).- CPx, July 21, 2012.

*Paul A. Lyons, Tim F. Rayner, et al. Genetically Distinct Subsets within ANCA-Associated Vasculitis. N Engl J Med 2012; 367:214-223. < a href= "http://www.nejm.org/doi/full/10.1056/NEJMoa1108735" target= \_blank> Link*

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## **PML in rheumatic diseases: new data**

Molloy and Calabrese already conducted and published a very good review of the litterature on progressive multifocal leukoencephalopathy (this dreadning opportunistic infection caused by JC virus) in rheumatic diseases. In this new article, they analyse the PML cases collected between 1997 and 2010 by the FDA using its Adverse Event Reporting System database. Among the 657 recorded cases, 34 with sufficient evidence of JC-PML occurred in the setting of rheumatic diseases. Most of the other cases occurred in HIV+ subjects.

None of these 34 patients (including 17 lupus, 10 rheumatoid arthritis (RA), 2 cryoglobulinemic vasculitis and 2 granulomatosis with polyangiitis (GPA)) were HIV+. Nineteen of these 34 PML cases (including the 2 GPA patients) occurred in patients who had never received biologic therapy. Conversely, 15 cases occurred in patients who have received biologics (including the 2 with cryoglobulinemic vasculitis). Rituximab was the most recently used biologic agent in 14 of these latter 15 patients, with a median interval between the first infusion and the onset of PML of 1 year (range, 1-57 months). Six of these 14 rituximab-recipients were also receiving or had previously received cyclophosphamide. Six of the PML patients had earlier received (n=5, discontinued a median of 3 years prior to PML) or were receiving (n= 1) antiTNF-alpha agents at PML onset. Sixteen of the 34 PML patients have died; follow-up durations for survivors ranged between 6 months and 5 years; data on survival were missing for 5 patients.

As stated by the authors, "definitive attribution of causality is not possible, given the small numbers of cases, potential for reporting bias and existence of confounders in many cases. However, the relative paucity of confirmed cases in patients recently treated with anti-TNF therapies, despite their widespread use, suggests that a causal relationship is unlikely. In contrast, there is an increasing, specific signal emerging regarding the association between rituximab and the development of PML."

PML remains a rare complication but is worth to be reminded. Precise risk of PML can not be assessed. However, based on the number of RA patients treated with rituximab in the USA until May 2010, the results of this study would lead to a crude estimate of 5 per 100,000 exposed patients. The rare cases of PML reported in GPA so far

have all occurred in patients who received cyclophosphamide. No such PML cases have been reported yet in GPA patients treated with biologics.- CPx, March 23, 2012.

*Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: Evolving role of biologic therapies. Arthritis Rheum. 2012 Mar 15. [Epub ahead of print];*[Link](#)  
*Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum. 2007 Jul;56(7):2116-28.* [Link](#)

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### Become familiar with IgG4 related disease

Medical literature on IgG4 related disease has been growing fast within the past five years, since the first description of this condition by Japanese groups. It can cause aortitis, thus articles on this entity should be of great interest for every physician dealing with vasculitis. Here are three of the most recent and best reviews or original articles on this topic. Enjoy!- CPx, March 3rd, 2012.

*Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012 Feb 9;366(6):539-51.* [Link](#)

*Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore). 2012 Jan;91(1):57-66.* [Link](#)

*Ebbo M, Daniel L, Pavic M, Sèvre P, Hamidou M, Andres E, Burtey S, Chiche L, Serratrice J, Longy-Boursier M, Ruivard M, Haroche J, Godeau B, Beucher AB, Berthelot JM, Papo T, Pennaforte JL, Benyamine A, Jourde N, Landron C, Roblot P, Moranne O, Silvain C, Granel B, Bernard F, Veit V, Mazodier K, Bernit E, Rousset H, Boucraut J, Boffa JJ, Weiller PJ, Kaplanski G, Aucouturier P, Harlé JR, Schleinitz N. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. Medicine (Baltimore). 2012 Jan;91(1):49-56.* [Link](#)

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### The anti-LAMP2 controversy continues...

In 2008, Dr. Kain, from Vienna (Austria), reported in Nature Medicine, that up to 93% of 84 individuals with biopsy-proven active pauci-immune glomerulonephritis (95% being ANCA+) also had a specific subtype of ANCA autoantibodies directed towards human LAMP-2 (lysosomal membrane protein-2) in their sera either at presentation ( $n = 62$ ) or during relapse ( $n = 22$ ). Injection of anti-LAMP-2 caused pauci-immune GN in a rat model. In addition, a 100% homology of human LAMP2 and the bacterial adhesin FimH was described, and Wistar Kyoto rats immunized with FimH develop pauci-immune GN and antibodies to rat and human LAMP-2.

At the recent (May 2011) ANCA Workshop, Dr. Roth et al. from the famous Chapel Hill group (UNC, NC, USA) challenged these results. In their study on 329 subjects with ANCA GN, 104 with ANCA-negative GN, 104 with fimbriated, gram-negative Escherichia coli urinary tract infection, 19 disease controls and 124 healthy volunteers, anti-LAMP-2 reactivity was present in only 22% of ANCA GN group, 28% of ANCA-negative GN group, but also in 16% of the control group with urinary tract infection (and 9% of healthy controls)! Titers of anti-MPO and anti-PR3 were 1500-fold and 10,000-fold higher than anti-LAMP-2 titers and, in their hands, Wistar Kyoto rats injected with anti-LAMP-2 antibodies did not develop GN.

In this new article, Dr. Kain et al. provide new data to support their previous findings. They used three different assays (ELISA, Western-Blott and a indirect immunofluorescence assays) to detect anti-LAMP2 in 19 patients with pauci-immune GN from Vienna, 50 patients with ANCA-vasculitis from the Netherlands, 53 patients with pauci-immune GN from Cambridge (UK), 51 disease controls, and 80 healthy controls. In untreated patients at presentation, the frequencies of anti-LAMP-2 varied between 80 to 91% among the three groups of patients with ANCA-associated, but none in the disease control group was positive (2 SLE patients had discordant results within the 3 assays). Notably, anti-LAMP-2;rapidly became undetectable after the initiation of immunosuppressive treatment and frequently became detectable again during clinical relapse.

Which group did rub too strongly its Aladdin LAMP? Would European patients be different serologically from North American patients? Would assays, materials and/or hands differ so much between the two continents to explain these differences? Results from other groups are awaited, but who really wishes to join the party?

To add to this discussion, one can mention this other new article on anti-LAMP2 in adults with Henoch Schönlein purpura from the Japanese group of Drs. Kawakami and Soma. The mean level of antiLAMP2 in the sera of 24 HSP was much higher than in those of 8 MPA patients and 24 healthy controls (mean level was even higher in healthy subjects than MPA patients!). However, one can still argue that these patients are from another ethnic background that the time of blood sample withdrawal is not mentioned in the article (active MPA versus in remission and under therapy?).- CPx, March 3rd, 2012

Kain R, Tadema H, McKinney EF, Benharkou A, Brandes R, Peschel A, Hubert V, Feenstra T, Sengölge G, Stegeman C, Heeringa P, Lyons PA, Smith KG, Kallenberg C, Rees AJ. High Prevalence of Autoantibodies to hLAMP-2 in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis. *J Am Soc Nephrol.* 2012 Mar;23(3):556-66. [Link](#)

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. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. *Nat Med.* 2008 Oct;14(10):1088-96. [Link](#)

Roth AJ, Brown MC, Smith RN, Badhwar AK, Parente O, Chung HC, O'Dell D, Bunch, McGregor JG, Hogan SL, Hu Y, Yang JJ, Berg EA, Niles J, Jennette JC, Preston GA, Falk RJ. Anti-LAMP-2 Antibodies Are Not Prevalent in Patients With Antineutrophil Cytoplasmic Autoantibody Glomerulonephritis. *J Am Soc Nephrol.* 2012 Mar;23(3):545-55. [Link](#)

Kawakami T, Takeuchi S, Arimura Y, Soma Y. Elevated anti-lysosomal-associated membrane protein-2 antibody levels in patients with adult Henoch-Schönlein purpura. *Br J Dermatol.* 2012 Feb 6. doi: 10.1111/j.1365-2133.2012.10884.x. [Epub ahead of print] [Link](#)

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## IVIg as an alternative option for orbital GPA

Drs. D. Wiwatwongwana, J.M. Esdaile, V.A. White and P.J. Dolman report the case of one of their patients with GPA who had bilateral orbital disease (intraconic granulomatous tissue). His symptoms were mainly pain and discomfort, as well as conjonctival reddishness (possibly alternating with episcleritis). He did not tolerate corticosteroids and cyclophosphamide or methotrexate (leukopenia), thus was given IVIg (polyvalent IV immunoglobulins) at the dose of 400 mg/kg for 4 consecutive days every 3 weeks. The response was good (resolution of the pain), but an attempt to decrease the dose after 2 years of this regimen was not tolerated. The patient's ocular disease is still under control after 10 years of this treatment.

This case perfectly illustrates the potential place of IVIg in the management of GPA patients. IVIg represent an alternative treatment to control disease in patients with some refractory disease, like pachymeningitis, cutaneous lesions or such granulomatous orbital pseudo-tumor, especially in patients with ongoing severe infection or treatment-related leukopenia, which may both preclude the use of conventional immunosuppressants. However, and as repeatedly reported (UK series from D. Jayne and the French IGANCA study), IVIg effects, whenever a good response is achieved, are usually suspensive and/or transient. Like in this patient, once IVIg have been started, it is often difficult to ever stop them thereafter when effective. Doses and infusion schedules are among the same ranges in all publications, usually about 1 g/kg per course (given over 1 to 5 consecutive days), every month. Progressive spacing of the infusions or decrease in the dose can be attempted once the disease is stabilized.- CPx, March 3rd, 2012.

Wiwatwongwana D, Esdaile JM, White VA, Dolman PJ. *Intravenous immunoglobulin (IVIG) for orbital Wegener's granulomatosis*. Can J Ophthalmol. 2012 Feb;47(1):82-3. [Link](#)

Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, Sailler L, Delaunay C, Sadoun A, Guillemin L; French Vasculitis Study Group. *Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients*. Arthritis Rheum. 2008 Jan;58(1):308-17. [Link](#)

Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, Lockwood CM. *Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity*. QJM. 2000 Jul;93(7):433-9. [Link](#)

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**Quick overview of main abstracts presented at past ACR meeting (Chicago, IL) in November 2011 ->[click here](#)**

This summary is for you to have a quick overview of the main abstracts but, of course, we invite you to read the full abstracts, of which you are interested in, and have a look on the (few) ones not included in this selection (including the very good abstract #2372, page S925 of the abstract book and to be published soon in extenso +++) and the one on rituximab in vasculitis-associated rheumatoid arthritis, whose article has been published since and is commented below on this page). - CPx, January 17, 2012.

*Link to download the 2011 ACR abstract book [HERE](#) (free access for the moment).*