

---

# Update on the management of systemic vasculitis: what did we learn in 2009?

---

B. Hellmich

---

Medizinische Klinik, Kreiskliniken  
Esslingen, Plochingen, Germany.

Please address correspondence and  
reprint requests to:

Prof. Dr. med. Bernhard Hellmich,  
Kreiskliniken Esslingen,  
Klinik Plochingen,  
Medizinische Klinik,  
Am Aussichtsturm 5,  
73207 Plochingen, Germany.  
E-mail: b.hellmich@kk-es.de

Received on January 21, 2010; accepted  
on February 1, 2010.

*Clin Exp Rheumatol* 2010; 28 (Suppl. 57):  
S98-S103.

© Copyright CLINICAL AND  
EXPERIMENTAL RHEUMATOLOGY 2010.

**Key words:** Vasculitis, treatment,  
cyclophosphamide, rituximab, ANCA

### ABSTRACT

*In the past two decades, the clinical investigation of systemic vasculitis has advanced from small case series and cohort studies to large multicentric randomised controlled clinical trials. The growing evidence gathered from all these trials led to the development of international consensus guidelines on the management of systemic vasculitides. The combination of cyclophosphamide and prednisone is still regarded the induction treatment of first choice for most types of generalised systemic vasculitis. However, treatment-associated adverse events of this regimen occur frequently and have a considerable negative effect on outcomes. Therefore, the major challenge in the treatment of systemic vasculitis is the search for treatments that are less toxic, but similarly effective compared to cyclophosphamide. In 2009, several studies have addressed these issues. It was shown that the cumulative dosage can be reduced by pulse versus oral administration without losing efficacy. Furthermore, new data indicate that targeted treatments such as rituximab might have the potential to replace cyclophosphamide in the future. In this article, the key studies in the field of vasculitis that might affect clinical management are reviewed and their potential relevance for patient care and future research is discussed.*

### Introduction

In the past two decades, the clinical investigation of systemic vasculitis has advanced from small case series and cohort studies to large multicentric randomised controlled clinical trials (RCTs). This success was largely driven by the continuous work of collaborative clinical research groups such as the European Vasculitis Study Group

(EUVAS), the Vasculitis Clinical Research Consortium (VCRC) and the French Vasculitis Study Group which allowed the conduction of RCTs with a sufficient number of patients despite the rarity of the diseases. A number of these studies such as CYCAZAREM, NORAM, MEPEX and WGET that were primarily designed to compare the efficacy and safety of different regimens for remission induction and maintenance have been published in the past couple of years (1). Many of these large cohorts were and are continuously followed to study long-term outcomes. The growing evidence gathered from all these trials led to international consensus recommendations on the management of systemic vasculitides (2, 3). Furthermore, consensus recommendations on trial methodology were developed in order to allow comparison of data between future different clinical trials (4).

Today, major challenges in the management of systemic vasculitis are the still significant morbidity related to treatment with glucocorticoids and cytotoxic drugs, particularly cyclophosphamide, and the treatment of refractory and relapsing disease. In order to address these issues, trials aimed to optimise the use toxic immunosuppressive drugs, *i.e.* by the use of pulse versus daily oral cyclophosphamide, have been conducted. Furthermore novel drugs, particularly biologic agents such as rituximab, are studied for their potential to replace conventional immunosuppressive drugs in the future. The results of some of these studies were reported within the past 12 months and are likely to influence the way we manage patients with systemic vasculitis in clinical practice. The aim of this review was therefore to summarise and comment on the most important studies on

*Conflict of interest: Professor Hellmich has received speaker honoraria from Roche Pharma and Abbott Immunology.*

the treatment, diagnosis and outcome of patients with vasculitis which were published after this topic was reviewed in the past vasculitis issue of this journal by Guilpain *et al.* in 2009 (5).

### Methods

A systemic Medline search was performed using the term "vasculitis" (MeSH Terms and all fields). A number of 1953 articles that were published between January 1<sup>st</sup> 2009 and January 5<sup>th</sup> 2010 were retrieved and medline summaries and, if necessary, abstracts were screened. Among these articles, 43 were considered exceptionally important and were selected for this review. In addition, abstract books of the 14<sup>th</sup> International Vasculitis and ANCA Workshop and the annual scientific meetings of the EULAR and the American College of Rheumatology were screened for reports on RCTs in vasculitis.

### Results

#### ANCA-associated vasculitides

##### Treatment

The CYCLOPS trial, probably one of the key studies in vasculitis published in 2009, addressed the question whether pulse cyclophosphamide with a reduced cumulative dosage is similarly effective compared to oral treatment, previously considered the standard of care in patients with generalised ANCA-associated vasculitis (AAV) (6). Three previous studies comparing oral versus pulse CYC in AAV did not produce conclusive results due to limited statistical power (7). Therefore, the results of the CYCLOPS-trial that included 149 patients from 42 centers in 15 countries were desperately awaited. Patients who had generalised AAV according to EUVAS definitions but no immediately life-threatening disease were randomised 1:1 to receive prednisolone plus either oral cyclophosphamide (2mg/kg) or pulse cyclophosphamide (15mg/kg with adjustments for renal function and age) (6). In contrast to previous protocols, the first three pulses were administered in two-week intervals with three-week-intervals thereafter to a total of up to 10 pulses. Both groups were switched to azathioprine

once remission was achieved. There was no difference in the proportion of patients who achieved remission at 9 months (88.1% vs. 87.7%) and the time to remission (primary outcome). More patients in the pulse limb relapsed (13 vs. 6), but the study was not powered to detect differences in relapse rates. The median absolute cumulative cyclophosphamide dose in the pulse cyclophosphamide group was almost half of the dose needed in the daily oral group (8.2g vs. 15.9g;  $p < 0.001$ ) and rates of leukopenia were lower in the pulse group (HR 0.41 (CI 0.23-0.71)). In summary, these data show that in patients with generalised AAV cyclophosphamide exposure can safely be limited by using pulse instead of daily oral administration without the risk of lower efficacy to induce remission. Limiting cumulative cyclophosphamide dosage was associated with the short term benefit of lower leukopenia rates, but additional long-term benefits can be expected given the long-term toxic effects of the drug such as bladder cancer. Despite the limitations of a potentially somewhat higher relapse risk and yet short follow-up, these important data favor the use of pulse instead of daily oral cyclophosphamide in generalised AAV.

Another potential strategy to limit treatment-related morbidity is the avoidance of cytotoxic therapy by using alternative biologic agents. Results from a couple of case series and small open label studies indicated that in patients with refractory and / or relapsing AAV B-lymphocyte depletion by administration of rituximab may help to induce remission. In 2009, the yet largest series of patients which were analysed from retrospective multicentre survey in 65 patients provided further evidence for a potential efficacy of rituximab in refractory AAV. Patients received rituximab in two different regimens (4 infusions of 375 mg/m<sup>2</sup> weekly or 2 infusions with 1g with a two week interval) plus glucocorticoids in various doses and cyclophosphamide in 28 of the 65 patients (8). Complete remission was observed in 49 patients (75%), partial remission in 15 patients (23%) and lack of response in 1 patient. More than

half of the patients (57%) who achieved remission relapsed later on and an increase of B-cell counts preceded the flare in 52% of these patients. Of 38 patients who received two or more courses of rituximab, 32 (84%) remained in complete remission. Neither the type of rituximab regimen nor the continuation of other immunosuppressive agents did appear to affect treatment responses. A beneficial treatment effect was also reported in another single center series of 15 patients with refractory relapsing AAV of which 14 achieved remission following rituximab therapy (9). While earlier reports suggested that rituximab might be less effective in difficult to treat granulomatous manifestations of Wegener's granulomatosis (WG) such as retro-orbital granulomas (10), three recent case series with together 52 patients indicate that B-cell depletion appears to work also in granulomatous disease (11-13). Retro-orbital granulomas, chronic sinusitis, pulmonary nodules and subglottic stenoses improved in the vast majority of patients. An initial lack of response was seen in only 4 patients of one series with 34 patients, but all of these 4 patients achieved remission after a second course of rituximab (13). Overall, recent data cited above suggest efficacy of rituximab in refractory or relapsing AAV and open the question on whether B cell depletion might be an alternative to cytotoxic therapy also in non-refractory AAV. However, all published studies on the use of rituximab in AAV are limited by their uncontrolled design and the concomitant use of glucocorticoids and often other immunosuppressive agents. Therefore, final results from two randomised controlled clinical trials comparing rituximab and cyclophosphamide in new or relapsing AAV are urgently awaited: the RAVE trial (199 patients) conducted by the VCRC and the RITUXVAS trail (44 patients) conducted by the EUVAS. In 2009, preliminary results from both studies were reported in abstract format and indicate that rituximab is similarly effective compared to cyclophosphamide in the induction of remission in generalised AAV (14, 15). A subgroup analysis of the RAVE trial suggested that in patients with relapsing AAV,

rituximab might even be more effective than cyclophosphamide. In both trials, significant differences regarding safety were not observed during the short time period reported, but are likely to become evident during longer follow-up. Should the final reports of these two trials with extended observation confirm the preliminary findings and also demonstrate a significantly better long-term outcome, the results are likely to alter the standard of medical treatment of AAV, favouring the use of rituximab instead of cyclophosphamide, particularly in patients with high risk for cyclophosphamide-related damage like young women with child-bearing potential. However, rituximab is not a risk-free therapy. Recent reports indicate that multifocal leukoencephalopathy, a rare complication of rituximab therapy with case fatality rate of >90%, can also occur in patients with autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus (16, 17). Increased awareness of this severe treatment-related complication is therefore warranted, particularly in AAV patients with CNS involvement or who develop new neurologic symptoms.

In 2009, two new reports were published on the use of 15-deoxyspergualin (gusperimus), an immunosuppressive agent with a not fully understood mode of action that is licensed in Japan for avoidance of transplant rejection. In a prospective multicenter single-limb open label study, 44 patients with WG and refractory or relapsing disease (Birmingham vasculitis Activity Score (BVAS)  $\geq 4$ ) despite treatment with methotrexate or cyclophosphamide received 15-deoxyspergualin instead of their previous immunosuppressive therapy (18). Deoxyspergualin was given by daily subcutaneous injection at a dose of 0.5 mg/kg in 6 cycles of 21 days, each followed by a 7-day wash-out period. After 6 cycles treatment was switched to azathioprine. Of the 44 patients, 20 (45%) went into complete remission, 22 (50%) attained partial remission (reduction in BVAS > 50%) and 2 did not respond. Although apparently effective, a high rate (53%) of severe or life-threatening adverse events was observed, mostly due to reversible

treatment-related leucopenia. Another open-label study investigated the long-term use of 15-deoxyspergualin in 11 patients with WG (19). Of the 10 patients (=90%) who initially went into remission, two (=18.2%) developed a relapse on continued treatment (19). However, 7 out of 8 patients relapsed after the drug was finally discontinued, providing further indirect evidence for its efficacy in WG. Median prednisone doses were reduced at the end of each treatment cycle. New or unexpected safety signals were not reported. Although apparently effective, the potential role of this drug for the treatment of AAV is unclear, especially when considering the significant rate of adverse events, the relatively small number of studied patients and the emerging role of more targeted therapies such as rituximab. At present there is no EMEA or FDA approval for the use of 15-deoxyspergualin.

Currently used maintenance regimens based on azathioprine, methotrexate or leflunomide reduce the incidence of disease flares, but are still associated with a 5-year relapse rate of up to 50%. In view of several studies showing its efficacy in SLE, the value of mycophenolate mofetil (MMF) for maintenance of remission in AAV has recently been studied. In a series of 19 patients with AAV who received MMF after successful induction therapy no flares were reported during 18 months of treatment (20). After withdrawal of MMF, 31.5% of the patients relapsed. Like in previous reports on the use of MMF in AAV, the lack of a control group limits conclusions on the efficacy of MMF in AAV. Therefore, final results from a randomised multicentre trial (IMPROVE) conducted by the EUVAS that compared MMF and azathioprine for maintenance of remission in 175 patients with AAV will be of great interest. In fact, some preliminary data from that trial that were presented during the 2009 ANCA workshop do not suggest a superiority of MMF (21).

The Cleveland Clinic reported their experience on the use of rapamycin in 8 patients with severe refractory WG (22). Five of these patients discontinued rapamycin due to lack of efficacy

or adverse events. Four patients sustained remissions of at least 6 months duration. Overall, the risk/benefit ratio of rapamycin in refractory WG was not considered beneficial.

#### *Long-term outcome/comorbidities*

Factors contributing to early mortality in AAV were analysed in a large cohort of 524 patients with AAV that was derived from long-term follow-up of patients from four prospective randomised trial conducted by the EUVAS (23). In that combined cohort assembling patients with different disease stages including early systemic, generalised and severe AAV according to EUVAS definitions, one-year mortality was 11.1%. The majority of deaths (59%) were contributed to treatment and only 14% were related to active vasculitis. Particularly infections, leukopenia and impaired renal function were associated with early mortality. These data highlight the need for treatment protocols with a better safety profile.

The Chapel Hill group reported on the outcome of AAV with end stage renal disease (ESRD) (24). In a large cohort of 523 patients, 136 developed ESRD. In 51% of these patients ESRD was related to new onset vasculitis and in only 6% to a renal relapse. In the remaining 43% ESRD was due to chronic progressive renal failure without active vasculitis (24). Relapse rates were lower in patients on dialysis compared to patients with preserved renal function. Infections were twice as common in patients with ESRD who continued immunosuppressive therapy and contributed to mortality. The lower relapse rate and higher risk for infections in patients with ESRD who are in remission implies that less intense or shorter immunosuppressive therapy might be advantageous in this subgroup of patients.

A number of recent studies analysed the incidence and impact of comorbid conditions in patients of AAV. Previous epidemiologic studies raised the possibility that WG might be related to a higher risk of cancer even before the onset of cytotoxic therapy (25, 26). In a recent study of 293 patients with WG of which 26 developed various types of cancer before the onset of WG, the over-

all incidence of cancer before the onset of WG was not significantly increased over the general population (OR 1.6%; 95% CI 0.8-3.4) (27). Looking at different types of malignancies, only non-melanoma skin cancer occurred at an increased rate (OR 4.0%; CI 1.4-12).

A retrospective analysis in a cohort of 113 patients with AAV revealed an increased risk for cardiovascular events (OR 2.23; 95% CI 1.1-4.4) compared to matched controls (28). Within the cohort of patients with AAV, a history of previous cardiovascular events, smoking, age at diagnosis, dialysis dependency, high cholesterol and GFR at remission were the most strongly predictive factors for cardiovascular events. In a large cohort of 1130 patients with systemic vasculitis from the French Vasculitis Study Group, an elevated frequency of venous thromboembolic events ranging from 7.6 to 8.2% was reported for patients with WG, MPA and CSS during a mean follow-up time of 58.4 months (29). In contrast, venous thromboembolic events occurred in only 2.5% of patients with PAN. In line with previously reported data, venous thromboembolic events in AAV occurred early after the onset of vasculitis at a mean interval of 5.8 months (-3 to +156).

Infections are the major cause of early mortality in patients with AAV, as outlined above. Incidence of and risk factors for infections were reported from a retrospective study of 113 patients with WG (30). Overall, 53 major infections occurring in 35 patients were recorded, most of them bacterial infections of the airways, but also viral infections caused by viruses of the herpes group. Half of the infections occurred within 3 years after the diagnosis of WG. As expected, both cyclophosphamide and corticosteroids were independent risk factors for infections (30). All patients treated since 1993 had received chemoprophylaxis against *pneumocystis jirovecii* (PCJ). These data indicate that prophylactic administration of cotrimoxazole prevents the occurrence of PCJ-pneumonia in WG, but does not prevent other infectious complications. In this context, results from a randomised trial in 72 patients with WG are of clinical relevance, in which antibody response

to influenza vaccine was studied (31). All patients were in remission at the time of vaccination and achieved high seroprotection rates against 3 influenza, similar to those found in healthy controls. Only patients with A/H1 N1 vaccination reached lower seroconversion rates. Vaccination did not affect ANCA titers and adverse events in vaccinated patients did not differ from controls.

#### *Outcome-assessment/classification*

A modified version of the BVAS (version 3) has been developed (32). BVAS 3 has a reduced number of items (56 instead of 66). Furthermore, the subscores for new/worse and persistent disease were unified. BVAS version 3 was validated in a prospective cross-sectional study in 313 patients with vasculitis and correlated well with BVAS 1 (Version 2) in patients with new/worse disease, BVAS 2 (Version 2) in patients with persistent disease, physician global assessment of disease activity, the vasculitis activity index and CRP serum levels (32). In accordance with the OMERACT filter for a useful assessment tool, the new BVAS proved to be repeatable, reproducible and sensitive to change. Another study compared different disease activity measures for AAV (33). The BVAS, BVAS 2003, BVAS/WG, the five factor score (FFS) and the disease extent index (DEI) were found to be highly correlated, allowing to some extent comparisons of data across clinical trials where different of these measures were used. Test and retest reliability was also high for all instruments.

Classification criteria for childhood WG developed by EULAR and the Paediatric Rheumatology European Society (PRES) were compared to ACR criteria for adult WG in a retrospective survey in 76 children with a clinical diagnosis of WG (34). Sensitivities and specificities of both sets of criteria did not differ significantly. The most frequent disease manifestations at disease onset were constitutional (89.2%), pulmonary (80%), ear, nose and throat (80%) and renal (75.4%) (34). For induction of remission, the majority of children (83.1%) were treated with cyclophosphamide and prednisolone with widely varying protocols.

#### *Biomarkers*

Two recent studies focused on new biomarkers for renal disease in AAV. In one study it was found that the presence of CD4+ effector memory (CD45RO+CCR7-CD3+CD4+) T-cells in urine was associated with renal involvement, independent of the presence or absence of active vasculitis in other organ (35). Flow cytometric analyses of the urine might therefore be a new tool for monitoring renal disease activity. Another publication reported on the diagnostic value of 18 urinary biomarkers which were selected from a set of 118 markers identified by proteomic analysis (36). These markers allowed to distinguish renal disease in AAV from other renal diseases with a sensitivity of 90% and a specificity of 86.7-90%. Furthermore a "remission-profile" of these urinary biomarkers was identified. Longitudinal studies are desirable to test whether flow cytometry and/or capillary electrophoresis are reliable tools to monitor renal disease activity without renal biopsy and to guide treatment decisions.

#### **Cryoglobulinemic vasculitis**

In line with previous reports on induction therapy, new data support the extended use of rituximab in patients with cryoglobulinemic vasculitis. Treatment of 20 patients with severe HCV-associated vasculitis with PEGylated interferon alfa-2b, ribavirin and rituximab led to complete remission in 80% of patients and to partial remission in 15% of cases (37). A complete or partial immunologic response was observed in 67 and 33% of patients, respectively. In 12 patients who received rituximab alone because of intolerance of antiviral treatments, a complete or partial clinical response was seen in 58 and 9% of patients respectively. Relapses were recorded in 22% of patients after a mean follow-up period of 23±12 months and these relapses were associated with loss of virologic control in all patients and with B cell recovery in 78% of cases.

#### **Giant cell arteritis**

It was previously shown that in patients with giant cell arteritis (GCA) and aortitis found on 15-FDG-PET-scans at the

time of diagnosis are more likely to develop thoracic aortic dilatation (38). A recent retrospective analysis of repeated aortic helical CT scans from patients with GCA revealed aortic involvement in 80% of cases (39). Unfortunately, the number of patients followed for more than 6 months was too small to conclude on the relevance of these CT data.

Cranial ischemic complications represent a major challenge in patients with GCA. In a large series of 287 consecutive patients with GCA the incidence of cranial ischemic manifestations at the time of diagnosis was studied (40). Within the time period of first GCA-related symptoms to 4 weeks after the onset of corticosteroid therapy 8 (2.8%) of patients developed an ischemic stroke which affected the vertebrobasilar territory in 7 of the 8 cases. Permanent visual loss, and arterial hypertension were the strongest risk factors for those ischemic events. Smoking was the best predictor of vertebrobasilar strokes while anemia appeared to be protective. In another study, ophthalmic complications were found to unrelated to findings on temporal artery sonography (41). Interestingly, ischemic ocular events occurred less frequently, if vasculitis of the proximal arm was found on sonography, suggesting that patients with large-vessel GCA might be less prone to ophthalmic complications.

Based on data from several retrospective studies, platelet inhibition with acetylsalicylic acid (ASA) has been recommended for all patients with GCA for prophylaxis of ischemic complications. Results from two recent studies challenge this recommendation. A recent retrospective chart review of 85 patients with GCA did not show an association of ischemic complication with either ASA treatment or platelet size and count (42). Of 22 patients receiving ASA 15 (68%) developed an ischemic event. In another recent study involving 180 subjects with GCA, the risk for cranial ischemic events was even higher in patients on anti-platelet or anticoagulant therapy ( $p=0.03$ ) (43). However, in all these studies ASA was prescribed before the onset of GCA because of other vascular comorbidities or risk factors which increase the risk

for cerebrovascular events. Therefore the question remains how these patients would have done without ASA?

### Kawasaki disease

The use of oral methotrexate (10 mg per body surface area once weekly) was studied in an open label trial of 17 patients with Kawasaki disease with persistent fever and coronary aneurysms despite treatment with intravenous immunoglobulin (IVIG) (44). A reduction of body temperature and CRP levels was observed within a few days after the first dose of methotrexate. Given the long half-life time of methotrexate, the reported beneficial effects might well be due to co-medications. Furthermore, the outcome of coronary disease was not reported.

A recent large survey regarding treatment of Kawasaki disease in the USA revealed that infliximab is increasingly used in patients with IVIG-resistant disease (45). Interestingly, in a murine model of Kawasaki disease therapeutic concentrations of IVIG reduced the immune response leading to TNF-alpha expression (46), suggesting that TNF-alpha inhibition could be a relevant molecular mode of action of IVIG in this disease.

### References

- JAYNE D: Treatment of ANCA-associated small-vessel vasculitis. *APMIS* 2009; 117 (Suppl. 127): 3-9.
- MUKHTYAR C, GUILLEVIN L, CID MC *et al.*: EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; 68: 310-7. Epub 2008 Apr 15.
- MUKHTYAR C, GUILLEVIN L, CID MC *et al.*: EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2009; 68: 318-23. Epub 2008 Apr 15.
- HELLMICH B, FLOSSMANN O, GROSS W *et al.*: EULAR Recommendations for Conducting Clinical Studies and/or Clinical Trials in Systemic Vasculitis: Focus on ANCA-associated vasculitis. *Ann Rheum Dis* 2007; 66: 605-17.
- GUILPAIN P, DE MENTHON M, PAGNOUX C, SEROR R, MAHR A, COHEN P: A bird's eye review of the recent literature. *Clin Exp Rheumatol* 2009; 27 (Suppl. 52): S5-S9.
- DE GROOT K, HARPER L, JAYNE DR *et al.*: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-80.
- DE GROOT K, ADU D, SAVAGE C: The value of pulse cyclophosphamide in ANCA-associated

ciated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant* 2001; 16: 2018-2027.

- JONES RB, FERRARO AJ, CHAUDHRY AN *et al.*: A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009; 60: 2156-68.
- LOVRIC S, ERDBRUEGGER U, KUMPERS P *et al.*: Rituximab as rescue therapy in antineutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients. *Nephrol Dial Transplant* 2009; 24: 179-85. Epub 2008 Aug 6.
- ARIES PM, HELLMICH B, BOTH M *et al.*: Lack of efficacy of Rituximab in Wegener's Granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006; 65: 853-8.
- TAYLOR SR, SALAMA AD, JOSHI L, PUSEY CD, LIGHTMAN SL: Rituximab is effective in the treatment of refractory ophthalmic Wegener's granulomatosis. *Arthritis Rheum* 2009; 60: 1540-7.
- SEO P, SPECKS U, KEOGH KA: Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations. *J Rheumatol* 2008; 35: 2017-23. Epub 2008 Aug 1.
- MARTINEZ DEL PERO M, CHAUDHRY A, JONES RB, SIVASOTHY P, JANI P, JAYNE D: B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. *Clin Otolaryngol* 2009; 34: 328-35.
- JONES R, COHEN TERVAERT JW, HAUSER T *et al.*: Randomized trial of rituximab vs. cyclophosphamide for ANCA-associated renal vasculitis: RITUXVAS. *APMIS* 2009; 117 (S127): 78 (Abstract).
- STONE J, MERKEL PA, SEO P *et al.*: Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: a randomized controlled trial (RAVE). *Arthritis Rheum* 2009; 62: (S1).
- CARSON KR, EVENS AM, RICHEY EA *et al.*: Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009; 113: 4834-40. Epub 2009 Mar 5.
- FLEISCHMANN RM: Progressive multifocal leukoencephalopathy following rituximab treatment in a patient with rheumatoid arthritis. *Arthritis Rheum* 2009; 60: 3225-8.
- FLOSSMANN O, BASLUND B, BRUCHFELD A *et al.*: Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. *Ann Rheum Dis* 2009; 68: 1125-30. Epub 2008 Aug 19.
- FLOSSMANN O, JAYNE DR: Long-term treatment of relapsing Wegener's granulomatosis with 15-deoxyspergualin. *Rheumatology* 2009; 23: 23.
- IATROU C, ZERBALA S, REVELA I *et al.*: Mycophenolate mofetil as maintenance therapy in patients with vasculitis and renal involvement. *Clin Nephrol* 2009; 72: 31-7.
- HIEMSTRA T, WALSH M, DE GROOT K *et al.*: Randomized trial of mycophenolate mofetil vs. azathioprine for maintenance therapy in ANCA-associated vasculitis (IMPROVE).

- APMIS* 2009; 117 (Suppl. 127): 77-8 (Abstract).
22. KOENING CL, HERNANDEZ-RODRIGUEZ J, MOLLOY ES, CLARK TM, HOFFMAN GS: Limited utility of rapamycin in severe, refractory Wegener's granulomatosis. *J Rheumatol* 2009; 36: 116-9.
  23. LITTLE MA, NIGHTINGALE P, VERBURGH CA *et al.*: Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. *Ann Rheum Dis* 2009; 1: 1.
  24. LIONAKI S, HOGAN SL, JENNETTE CE *et al.*: The clinical course of ANCA small-vessel vasculitis on chronic dialysis. *Kidney Int* 2009; 76: 644-51. Epub 2009 Jun 17.
  25. KNIGHT A, ASKLING J, GRANATH F, SPAREN P, EKBORN A: Urinary bladder cancer in Wegener's granulomatosis, risks and relation to cyclophosphamide. *Ann Rheum Dis* 2004; 63: 1307-11.
  26. HELLMICH B, KAUSCH I, DOEHN C, JOCHAM D, HOLL-ULRICH K, GROSS WL: Urinary bladder cancer in Wegener's granulomatosis: is it more than cyclophosphamide? *Ann Rheum Dis* 2004; 63: 1183-5.
  27. FAURSCHOU M, MELLEMKJAER L, SORENSEN IJ, THOMSEN BS, DREYER L, BASLUND B: Cancer preceding Wegener's granulomatosis: a case-control study. *Rheumatology* 2009; 48: 421-4. Epub 2009 Feb 12.
  28. MORGAN MD, TURNBULL J, SELAMET U *et al.*: Increased incidence of cardiovascular events in patients with antineutrophil cytoplasmic antibody-associated vasculitides: a matched-pair cohort study. *Arthritis Rheum* 2009; 60: 3493-500.
  29. ALLENBACH Y, SEROR R, PAGNOUX C, TEIXEIRA L, GUILPAIN P, GUILLEVIN L: 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; 68: 564-7. Epub 2008 Nov 17.
  30. CHARLIER C, HENEGAR C, LAUNAY O *et al.*: Risk factors for major infections in Wegener granulomatosis: analysis of 113 patients. *Ann Rheum Dis* 2009; 68: 658-63. Epub 2008 May 26.
  31. HOLVAST A, STEGEMAN CA, BENNE CA *et al.*: Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. *Ann Rheum Dis* 2009; 68: 873-8. Epub 2008 Jul 14.
  32. MUKHTYAR C, LEE R, BROWN D *et al.*: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32. Epub 2008 Dec 3.
  33. MERKEL PA, CUTHBERTSON DD, HELLMICH B *et al.*: Comparison of disease activity measures for anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis. *Ann Rheum Dis* 2009; 68: 103-6. Epub 2008 Jul 29.
  34. CABRAL DA, URIBE AG, BENSELER S *et al.*: Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. *Arthritis Rheum* 2009; 60: 3413-24.
  35. ABDULAHAD WH, KALLENBERG CG, LIMBURG PC, STEGEMAN CA: Urinary CD4+ effector memory T cells reflect renal disease activity in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2009; 60: 2830-8.
  36. HAUBITZ M, GOOD DM, WOYWODT A *et al.*: Identification and validation of urinary biomarkers for differential diagnosis and evaluation of therapeutic intervention in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Mol Cell Proteomics* 2009; 8: 2296-307. Epub 2009 Jun 28.
  37. TERRIER B, SAADOUN D, SENE D *et al.*: Efficacy and tolerability of rituximab with or without PEGylated interferon alfa-2b plus ribavirin in severe hepatitis C virus-related vasculitis: a long-term followup study of thirty-two patients. *Arthritis Rheum* 2009; 60: 2531-40.
  38. BLOCKMANS D, COUDYZER W, VANDER-SCHUEREN S *et al.*: Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. *Rheumatology* 2008; 47: 1179-84. Epub 2008 May 31.
  39. MARIE I, PROUX A, DUHAUT P *et al.*: Long-term follow-up of aortic involvement in giant cell arteritis: a series of 48 patients. *Medicine (Baltimore)* 2009; 88: 182-92.
  40. GONZALEZ-GAY MA, VAZQUEZ-RODRIGUEZ TR, GOMEZ-ACEBO I *et al.*: Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. *Medicine (Baltimore)* 2009; 88: 227-35.
  41. SCHMIDT WA, KRAUSE A, SCHICKE B, KUCHENBECKER J, GROMNICA-IHLE E: Do temporal artery duplex ultrasound findings correlate with ophthalmic complications in giant cell arteritis? *Rheumatology* 2009; 48: 383-5. Epub 2009 Jan 29.
  42. BERGER CT, WOLBERS M, MEYER P, DAIKELER T, HESS C: High incidence of severe ischaemic complications in patients with giant cell arteritis irrespective of platelet count and size, and platelet inhibition. *Rheumatology* 2009; 48: 258-61. Epub 2009 Jan 7.
  43. SALVARANI C, DELLA BELLA C, CIMINO L *et al.*: Risk factors for severe cranial ischaemic events in an Italian population-based cohort of patients with giant cell arteritis. *Rheumatology* 2009; 48: 250-3. Epub 2008 Dec 24.
  44. LEE TJ, KIM KH, CHUN JK, KIM DS: Low-dose methotrexate therapy for intravenous immunoglobulin-resistant Kawasaki disease. *Yonsei Med J* 2008; 49: 714-8.
  45. SON MB, GAUVREAU K, MA L *et al.*: Treatment of Kawasaki disease: analysis of 27 US pediatric hospitals from 2001 to 2006. *Pediatrics* 2009; 124: 1-8.
  46. LAU AC, DUONG TT, ITO S, YEUNG RS: Intravenous immunoglobulin and salicylate differentially modulate pathogenic processes leading to vascular damage in a model of Kawasaki disease. *Arthritis Rheum* 2009; 60: 2131-41.