

# Current treatment of ANCA-associated renal vasculitis

Zdenka Hruskova, Zuzana Rihova, Vladimir Tesar

Department of Nephrology, General Teaching Hospital and First Faculty of Medicine.  
Charles University, Prague, Czech Republic.

Received for publication: 13/12/2007  
Accepted: 06/03/2008

## ABSTRACT

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitides include Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and renal-limited vasculitis. While conventional immunosuppressive therapy with oral cyclophosphamide and corticosteroids has dramatically improved the prognosis of patients with these potentially life-threatening disorders, this therapy is associated with considerable mortality and morbidity, however. Thus there has been an urgent need to find novel effective treatment strategies and modalities with lower toxicity. Such an approach has been lately supported by major advances in understanding the disease pathogenesis. At present, remission induction treatment of renal vasculitis may involve pulsed cyclophosphamide, methotrexate or plasma exchange, according to disease severity. Azathioprine has proven successful for remission maintenance therapy. Newer promising therapeutic possibilities include mycophenolate mofetil, deoxyspergualin or leflunomide. Even though the benefit of TNF- $\alpha$ -blocking agent (etanercept) has not been demonstrated in a controlled trial, there have been positive reports on the use of other biologics, especially rituximab. In the oncoming years, emphasis has to be placed on the development of novel, safer and more effective targeted therapies.

### Key-Words:

ANCA; cyclophosphamide; infliximab; mycophenolate; plasma exchange; rituximab; vasculitis.

## INTRODUCTION

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) are a group of systemic immune-mediated diseases with a strong and highly specific association with ANCA (Anti-Neutrophil Cytoplasmic Antibodies).

Together with isolated "idiopathic" pauci-immune necrotising rapidly progressive glomerulonephritis (IRPGN) they are all ranked among ANCA-associated vasculitides (AAV). The disorders predominantly affect small-to medium-sized vessels. Basically, any organ may be affected in AAV, the most typical being kidney, lungs and ENT organs<sup>1,2</sup>.

ANCA are mainly IgG autoantibodies directed against several epitopes located in azurophilic granules of polymorphonuclear leucocytes and the peroxidase-positive lysosomes of monocytes. Several antigenic targets of ANCA have been identified. In WG, ANCA are usually directed against proteinase 3 (anti-PR<sub>3</sub>) and have a cytoplasmic immunofluorescence pattern when using ethanol-fixed neutrophils (c-ANCA). In MPA, the target antigen is mostly myeloperoxidase (anti-MPO) and the type of immunofluorescence is perinuclear (p-ANCA). Both anti-MPO and, less frequently, anti-PR<sub>3</sub> can also be found in CSS and IRPGN (also referred to as renal-limited vasculitis, RLV) (Table I)<sup>3</sup>.

**Table I**

Prevalence of ANCA positivity in AAV

	PR3-ANCA (% positive)	MPO-ANCA (% positive)
Wegener's granulomatosis	70-85	10
Microscopic polyangiitis	15-40	45-75
Churg-Strauss syndrome	up to 5	40
Renal-limited vasculitis	25-35	65

## ■ CLASSIFICATION OF ANCA-ASSOCIATED VASCULITIS BASED ON DISEASE SEVERITY

Given the similar response to therapy and difficulties in disease classification, it has been assumed that, regarding treatment, AAV can be studied together, despite clinical and pathological differences between WG and MPA (CSS notwithstanding), and despite different features of anti-PR3 and anti-MPO ANCA associated disease, respectively.

As the initial severity of the disease and its extent relate to the degree of damage at long-term follow-up<sup>5</sup>, it has been widely accepted that clinical studies should be tailored to patients' characteristics and needs. The European Vasculitis Study Group (EUVAS), established gradually during the first half of the 1990s, determined five subgroups to cover the spectrum of severity of AAV at presentation<sup>6</sup>. Pauci-immune small-vessel vasculitides were classified as follows: (i) localised vasculitis; (ii) early systemic vasculitis; (iii) generalised vasculitis; (iv) severe renal vasculitis; and (v) refractory vasculitis (Table II).

In this paper, emphasis is placed on the management of generalised and severe renal vasculitis. Newer therapeutic approaches and biological therapy might be of particular importance for patients

with refractory vasculitis and/or patients intolerant of standard therapy.

## ■ TREATMENT OF ANCA-ASSOCIATED VASCULITIS

Without treatment, prognosis of systemic AAV is poor. In 1958, the average patient survival after diagnosis of WG was 5 months<sup>4</sup>. The unfavourable outcome of patients with AAV was dramatically improved in the early 1970s when Fauci and Wolff introduced an empirical therapeutic scheme consisting of daily oral cyclophosphamide (CYC, 1-2 mg/kg) administered for at least one year after remission achievement and corticosteroids (prednisolone 1 mg/kg/day on a tapered-off basis)<sup>7</sup>. Thus, remission was induced in approximately 80% of cases<sup>8</sup>. However, the toxicity of the regimen caused considerable morbidity and mortality (e.g. bone marrow suppression, infections, haemorrhagic cystitis, infertility, myelodysplasia or transitional cell carcinoma of the bladder)<sup>8</sup>. Moreover, a long-term follow-up has shown that at least 50% of patients relapse, even under continuing immunosuppression or when the therapy is reduced<sup>9</sup>.

Therefore, there has been an urgent need to find new effective treatment strategies and modalities

**Table II**

Classification of ANCA-associated vasculitides based on disease severity

Clinical subgroup	Constitutional symptoms	ANCA typically	Threat to vital organ function	Serum creatinine (μmol/L)
Localised	No	+ or –	No	< 120
Early systemic	Yes	+ or –	No	< 120
Generalised	Any	+	Yes	< 500
Severe renal	Yes	+	Yes	> 500
Refractory	Yes	+ or –	Yes	Any

with lower toxicity. Such an approach has been lately supported by major advances in understanding the disease pathogenesis. Over the last decade, results of several controlled randomised trials have confirmed the efficacy of some of the less toxic therapeutic alternatives, summarised in this paper. In addition, attention will be given to the current use of biological treatment in AAV. Finally, novel targeted therapeutic options, which might appear in oncoming years, will be briefly outlined.

## ■ REMISSION INDUCTION IN ANCA-ASSOCIATED RENAL VASCULITIS

As mentioned above, daily oral cyclophosphamide with a tapering dose of oral prednisolone has been considered the gold standard for systemic, generalised vasculitis. However, high treatment-related mortality and morbidity have led to a search for safer therapies. In recent years, most studies have aimed to limit the use of CYC, testing its intravenous administration and various dosage rates. A meta-analysis concluded that pulsed CYC may be as effective as daily oral CYC in remission induction, with fewer adverse events, but with a potential higher relapse rate<sup>9</sup>. Preliminary results of the EUVAS trial CYCLOPS (Randomized Trial of Daily Oral vs. Pulse Cyclophosphamide as Therapy for ANCA-associated Systemic Vasculitis) have confirmed the same efficacy of pulsed CYC (dosed 15 mg/kg every 2-3 weeks) and standard oral daily CYC. While pulsed administration significantly reduced the cumulative dose of CYC, there was no difference observed in relapse rates or in severe adverse events<sup>10</sup>.

Methotrexate (MTX) can also be considered as a therapeutic agent for remission induction in AAV but only in patients with early systemic disease with normal or near-normal renal function (serum creatinine < 177 µmol/L). The NORAM trial (designed by EUVAS) comparing methotrexate with oral CYC suggested that MTX can replace CYC for initial treatment of early AAV, even though the relapse rate was increased in the MTX group. However, patients with renal involvement were excluded from the study<sup>11</sup>.

In patients with life- or organ-threatening disease, standard immunosuppressive treatment does not

provide satisfactory results. Only a half of the patients presenting with advanced renal failure (severe renal vasculitis) were shown dialysis independent at 1 year<sup>12</sup>. Several studies reported on the addition of pulses of methylprednisolone and/or plasma exchange. In the MEPEX trial (Randomized Trial of Adjunctive Therapy for Severe Glomerulonephritis in ANCA-associated Systemic Vasculitis: Plasma Exchange vs. Intravenous Methylprednisolone), a large international randomised study conducted by EUVAS, plasma exchange was shown superior to pulsed methylprednisolone for recovery of renal function (69% vs. 49% at 3 months)<sup>13</sup>. These data confirmed the meta-analysis of several smaller studies<sup>14</sup> and strongly suggest that plasma exchange should be used as an adjunctive treatment in patients with ANCA-associated renal vasculitis with acute renal failure. Based on case series, while it seems plasma exchange might be beneficial also for patients with pulmonary haemorrhage<sup>15</sup>, this remains to be vindicated.

## ■ REMISSION MAINTENANCE IN ANCA-ASSOCIATED RENAL VASCULITIS

To further reduce CYC toxicity after remission achievement, CYC was replaced by less toxic immunosuppressive drugs in several studies. In the EUVAS trial CYCAZAREM (Randomized Trial of Cyclophosphamide vs. Azathioprine during Remission in ANCA-Positive Systemic Vasculitis), patients at remission were after 3-6 months of therapy with oral CYC randomised to either continue cyclophosphamide or switch to azathioprine. Patient survival, relapse rate at 18 months and disease-free period did not differ between the groups<sup>16</sup>. Given the known long-term safety profile of azathioprine, the early switch to azathioprine seems superior to prolonged treatment with CYC in patients with generalised vasculitis as the treatment is comparably effective. Nevertheless, in the long-term follow-up, relapse-free survival was slightly lower in patients switched to azathioprine than in CYC group in retrospective studies<sup>17</sup>. Particularly the patients with positive anti-PR3 ANCA at the time of switch are at a higher risk of relapse and should be therefore monitored with caution<sup>18</sup>.

Not only azathioprine but also mycophenolate mofetil (MMF) or methotrexate were studied for remission

maintenance in generalised AAV. Whereas some authors report on the favourable outcome of the use of MMF<sup>19</sup>, higher relapse rates were observed by others<sup>20</sup>. Therefore, results of another EUVAS trial IMPROVE (International Mycophenolate mofetil to Reduce Outbreaks of Vasculitides), comparing MMF with azathioprine for remission maintenance, are awaited. French authors performed a randomised trial<sup>21</sup> comparing azathioprine with methotrexate. In this trial, MTX appeared as effective as azathioprine for remission maintenance. However, adverse events were slightly more frequent in the MTX group even though the difference did not reach statistical significance.

## ■ ALTERNATIVE THERAPEUTIC POSSIBILITIES

In patients with refractory vasculitis or those intolerant of standard immunosuppressive treatment, a wide range of alternative experimental therapies has been used. Generally, as the patient survival has improved, the problem of accumulated organ damage has emerged. The number of patients with repeated relapses and unacceptably high cumulative dose of CYC has gradually increased. Therefore, new therapeutic options have been intensely sought.

In patients intolerant of CYC, the potential use of MMF for remission induction has been investigated. However, only uncontrolled studies and case series have been reported so far. In a recent study<sup>22</sup>, complete remission was achieved in 78% (25/32) of patients with active vasculitis (15 of 32 patients with active renal disease) treated with MMF (2x1g/day). The median relapse-free survival was 16 months. Adverse events led to premature treatment termination in 2 patients (6%). Although the results seem promising, the use of MMF as induction therapy remains to be rationalised in a large randomised trial. EUVAS has recently launched the MYCYC trial, comparing MMF with CYC as an induction therapy.

The mechanism of action of 15-deoxyspergualin (DSG) includes inhibition of IL-1 synthesis and anti-proliferative effects. It appears to be an effective (70% of patients responded to therapy) and safe agent to treat patients with refractory vasculitis or with contraindications to standard immunosuppressants<sup>23</sup>,

even as a prolonged therapy<sup>24</sup>. In another study, the response rate was as high as 92%<sup>25</sup>. Adverse events mainly involved reversible bone marrow suppression in both studies. Experience with this drug is, however, still very limited.

Leflunomide, a pyrimidine antagonist used as a disease-modifying agent in rheumatoid arthritis, has been tested as a remission maintenance therapy for AAV with encouraging results<sup>26</sup>. A subsequent multicentre randomised trial comparing 30mg daily leflunomide with 20mg weekly methotrexate had to be prematurely terminated because of the significantly higher incidence of major relapses in the methotrexate group<sup>27</sup>. The authors concluded that while leflunomide (30mg/day) seems to be effective in preventing major relapses in generalised vasculitis, adverse events are, nonetheless, frequent.

As T-cells are most likely involved in the pathogenesis of AAV, T-cell directed treatment is also well-founded in AAV. Little data is available on the use of cyclosporin in AAV which is limited by nephrotoxicity. Some benefit of cyclosporin has been reported for remission maintenance in a very small study, which, however, supports data showing low rates of relapse in patients with vasculitis receiving cyclosporin after renal transplantation<sup>28</sup>.

## ■ BIOLOGICAL THERAPY IN ANCA-ASSOCIATED RENAL VASCULITIS

The recent development of biological therapies, along with better understanding of the disease pathogenesis, have revealed a completely new area of therapeutic options in AAV. At present, biologics are still used more as a rescue therapy after conventional therapeutic regimens have failed. Nevertheless, in oncoming years they are likely to play a more important role in the therapy of AAV. Biologics currently used in AAV include intravenous immunoglobulins, anti-thymocyte globulin, and mainly rituximab and anti-TNF $\alpha$  therapy.

A number of studies have reported the beneficial effects of intravenous immunoglobulin (IV Ig) in patients with chronic grumbling vasculitis not reacting to conventional treatment or in patients with

acute disease. Jayne *et al.* conducted a small controlled trial of IV Ig given as a single course of a total dose of 2 g/kg in patients with chronic active disease. This treatment resulted in a significant clinical improvement, but the effect was short-lived and did not last beyond 3 months<sup>29</sup>. Moreover, still very little is known about IV Ig in patients with AAV and renal involvement even though beneficial effect has been proven in lupus nephritis<sup>30</sup>.

As for anti-T-cell-directed biologics, fifteen patients with active refractory WG were treated with anti-thymocyte globulin (ATG) in the SOLUTION protocol designed by EUVAS. Thirteen of these showed a favourable response to ATG. While the authors conclude that anti-T-cell-directed treatment with ATG may be a therapeutic option for severe refractory Wegener's granulomatosis, the therapy is, however, associated with a high risk of infection and toxicity and risk-to-benefit ratio should always be considered<sup>31</sup>.

Rituximab (RTX) is a genetically engineered chimeric monoclonal antibody that contains a human IgG1 constant region plus murine heavy and light chain variable regions directed against CD20. Rituximab causes a selective transient depletion of the CD20+ B cell subpopulation (i.e. the whole B cell population with the exception of plasma cells and pre-B cells), which typically lasts for at least 6 months with subsequent gradual reconstitution of B cell numbers.

Elimination of B cells by rituximab (4 weekly doses of 375 mg/m<sup>2</sup> or, occasionally, 2 doses of 1g 2 weeks apart) successfully induced complete but temporary remission in patients with AAV refractory to conventional therapy in several smaller studies<sup>32,33</sup>. However, some patients, especially those with predominantly granulomatous manifestations, seem not to respond to RTX<sup>34</sup>. Rituximab therapy was usually accompanied by prednisone, and also previous immunosuppressive therapy with cytotoxic agents was often continued. Safety did not appear to be a major problem but continued vigilance is warranted. Repeated rituximab administration was suggested and proven successful after B cell reconstitution but human anti-chimeric antibodies (HACA) and prolonged hypogammaglobulinaemia might occur<sup>35</sup>. Further studies are needed to clarify the effects of RTX and its indication. At present, two randomised controlled trials with rituximab (RITUX-VAS<sup>36</sup> and RAVE<sup>37</sup>) are underway.

The expansion of circulating TNF $\alpha$ -producing Th1-type CD28- effector memory T-cells and their presence as Th1-type cytokine profile-driving cell population within granulomatous lesions, together with further *in vitro* data supporting the role of TNF $\alpha$  in the pathogenesis of AAV, provide the rationale for using TNF $\alpha$ -blocking agents in refractory AAV. Both the chimeric monoclonal anti-TNF $\alpha$  antibody infliximab and the fusion protein consisting of a part of the human TNF $\alpha$  receptor linked to the Fc portion of human IgG1 etanercept have been successfully applied as additional therapy for refractory Wegener's granulomatosis in smaller studies<sup>38,39</sup>. Nevertheless, relapses were quite common and some severe infectious complications were noted.

The randomised WGET trial (Wegener's granulomatosis Etanercept Trial), in which patients were randomised to receive either etanercept or placebo in addition to standard immunosuppressive treatment, did not, however, confirm the efficacy of etanercept<sup>40</sup>. The time to remission, duration of remission or relapse rate did not differ between the groups. Intriguingly, 6 patients in the etanercept group developed solid organ cancers<sup>41</sup>. On the contrary, no cancer was observed in the placebo group even though the patients were also treated with CYC.

Despite the lack of efficacy of etanercept in the therapy of AAV, it is still possible that TNF $\alpha$  blockade with infliximab might be beneficial in the induction therapeutic regimens in AAV, which has to be clarified in future controlled trials. While etanercept binds to circulating TNF $\alpha$  only, infliximab also binds to TNF $\alpha$  complexed with TNF $\alpha$  receptors and might therefore have a different therapeutic mechanism. As in inflammatory bowel disease<sup>42</sup>, infliximab but not etanercept may therefore prove useful in the therapy of AAV.

Lymphocyte depletion using humanised monoclonal anti-CD52 antibodies (alemtuzumab) has been reported in a series of patients with relapsing/refractory disease. Although most patients achieved remission, relapses and adverse events were common in the long run and further studies are needed<sup>43</sup>.

## ■ TRENDS FOR THE FUTURE

Increasing evidence for the pathogenic role of ANCA has emerged from both *in vitro* and *in vivo*



studies lately. Although the exact role for T-cells in the disease pathogenesis has yet to be elucidated, they are clearly involved in the pathogenic process. In oncoming years, better understanding of the disease pathogenesis might provide important clues for the development of new targeted therapies.

Many monoclonal antibodies to molecules involved in the disease pathogenesis have already been developed. For instance, interaction of CD28 on T-cells with CD80 and CD86 on antigen-presenting cells is required for T-cell activation. As CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4, receptor for both CD80 and CD86) is upregulated on T-effector memory cells in WG, blocking of CTLA4-mediated costimulation and upregulation of anti-apoptotic Bcl-2 expression by CTLA-4-immunoglobulin (Abatacept) might help to modulate pathologic immune response in AAV [44]. In the future, monoclonal antibodies inhibiting e.g. endothelium-neutrophil interactions, ANCA or directly suppressing signalling cascades triggered by ANCA could terminate the need for cytotoxic therapeutic regimens in AAV. At present, tailored therapy of AAV and the use of novel therapeutic options help to at least partially reduce disease- and treatment-related mortality and morbidity.

**Conflict of interest statement.** None declared.

## References

- Jennette JC, Falk RJ, Andrassy K, *et al.* Nomenclature of systemic vasculitides: proposal of an international consensus committee. *Arthritis & Rheum* 1994;37:187-192
- Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;337:1512-23
- Kallenberg CGM, Heeringa P, Stegeman CA. Mechanisms of Disease: pathogenesis and treatment of ANCA-associated vasculitides. *Nat Clin Pract Rheumatol* 2006;2:661-70
- Walton EW. Giant cell-granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958;2: 265-70
- Hogan SL, Falk RJ, Chin H, *et al.* Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 2005;143:621-31
- Jayne D. Update on the European Vasculitis Study Group trials. *Curr Opin Rheumatol* 2001;13:48-55
- Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. *Medicine (Baltimore)* 1973;52:535-61
- Hoffman GS, Kerr GS, Leavitt RY, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98
- De Groot K, Adu D, Savage COS. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol Dial Transplant* 2001;16:2018-27
- De Groot K, Jayne CRW, Tesar V, Savage COS for EUVAS. Randomised controlled trial of daily oral versus pulse cyclophosphamide for induction of remission in ANCA-associated systemic vasculitis. *Kidney Blood Press Res* 2005;28: 195
- De Groot K, Rasmussen N, Bacon PA, *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005;52:2461-69
- Booth AD, Almond MK, Burns A, *et al.*; Pan-Thames Renal Research Group. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003;41:776-84
- Jayne DR, Gaskin G, Rasmussen N, *et al.*; European Vasculitis Study Group. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180-88
- Jayne DR. Conventional treatment and outcome of Wegener's granulomatosis and microscopic polyangiitis. *Cleve Clin J Med* 2002;69 (Suppl 2):S11 110-5
- Klemmer PJ, Chalmerskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *Am J Kidney Dis* 2003; 42:1149-53
- Jayne D, Rasmussen N, Andrassy K, *et al.*; European Vasculitis Study Group. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36-44
- Sanders JS, Slot MC, Stegeman CA. Maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:2072-3
- Slot MC, Tervaert JW, Boomsma MM, Stegeman CA. Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. *Arthritis Rheum* 2004;51:269-73
- Nowack R, Göbel U, Klooker P, Hergesell O, Andrassy K, van der Woude FJ. Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: a pilot study in 11 patients with renal involvement. *J Am Soc Nephrol* 1999;10:1965-71
- Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. *Arthritis Rheum* 2004;51:278-83
- Mahr A, Pagnoux C, Cohen C, *et al.* for the French Vasculitis Study Group. Treatment of Anca-associated Vasculitides: Corticosteroids and Pulse Cyclophosphamide Followed by Maintenance Therapy with Methotrexate or Azathioprine: A Prospective Multicenter Randomized Trial (Wegent). *Kidney Blood Press Res* 2005;28:194
- Stassen PM, Cohen Tervaert JW, Stegeman CA. Induction of remission in active antineutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. *Ann Rheum Dis* 2007;66:798-802
- Birk R, Warnatz K, Lorenz HM, *et al.* 15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy. *J Am Soc Nephrol* 2003;14:440-47
- Schmitt WH, Birk R, Heinzl PA, *et al.* Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol Dial Transplant* 2005;20:1083-92
- Flossmann O, Jayne DR. Prospective clinical trial of guselimumab (deoxyspergualin) in refractory or relapsing Wegener's granulomatosis: an interim report. *J Am Soc Nephrol* 2005;16: 554A
- Metzler C, Fink C, Lamprecht P, Gross WL, Reinhold-Keller E. Maintenance of remission with leflunomide in Wegener's granulomatosis. *Rheumatology* 2004;43:315-20
- Metzler C, Miehle N, Manger K, *et al.*; German Network of Rheumatic Diseases. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology* 2007;46:1087-91
- Haubitz M, Koch KM, Brunkhorst R. Cyclosporin for the prevention of disease reactivation in relapsing ANCA-associated vasculitis. *Nephrol Dial Transplant* 1998;13:2074-76
- Jayne DR, Chapel H, Adu D, *et al.* Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 2000;93:433-39

- <sup>30</sup> Aries PM, Hellmich B, Gross WL. Intravenous immunoglobulin therapy in vasculitis: speculation or evidence? *Clin Rev Allergy Immunol* 2005;29:237-45
- <sup>31</sup> Schmitt WH, Hagen EC, Neumann I, Nowack R, Flores-Suárez LF, van der Woude FJ; European Vasculitis Study Group. Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients. *Kidney Int* 2004;65:1440-8
- <sup>32</sup> Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med* 2006;173:180-87
- <sup>33</sup> Stasi R, Stipa E, Del Poeta G, Amadori S, Newland AC, Provan D. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. *Rheumatology* 2006;45:1432-36
- <sup>34</sup> Aries PM, Hellmich B, Voswinkel J, *et al.* Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006;65:853-58
- <sup>35</sup> Jayne D. What place for the new biologics in the treatment of necrotising vasculitides. *Clin Exp Rheumatol* 2006; 24 (Suppl 41):S1-5
- <sup>36</sup> Jones R, Savage C, Peh CA, *et al.* Rituximab: A novel remission induction agent in ANCA associated vasculitis. The design of an international, randomised trial (RITUXVAS). *J Am Soc Nephrol* 2007;18:972A
- <sup>37</sup> Available online at: [www.immunetolerance.org/RAVE](http://www.immunetolerance.org/RAVE)
- <sup>38</sup> Booth A, Harper L, Hammad T, *et al.* Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 2004;15:717-21
- <sup>39</sup> Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. *Arthritis Rheum* 2001;44:1149-54
- <sup>40</sup> Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005;352: 351-61
- <sup>41</sup> Stone JH, Holbrook JT, Marriott MA, *et al.*; Wegener's Granulomatosis Etanercept Trial Research Group. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum* 2006;54:1608-18
- <sup>42</sup> Sieper J, Van Den Brande J. Diverse effects of infliximab and etanercept on T lymphocytes. *Semin Arthritis Rheum* 2005;34 (Suppl 1):23-27
- <sup>43</sup> Walsh M, Chaudhry A, Jayne DR. Long-term follow-up of relapsing/refractory ANCA associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). *Ann Rheum Dis* 2007 Nov 29 [Epub ahead of print]
- <sup>44</sup> Abdulahad WH, Stegeman CA, van der Geld YM, Doornbos-van der Meer B, Limburg PC, Kallenberg CG. Functional defect of circulating regulatory CD4+ T cells in patients with Wegener's granulomatosis in remission. *Arthritis Rheum* 2007;56:2080-2091

#### Correspondence to:

Prof. Vladimír Tesar  
Department of Nephrology, 1st School of Medicine and General  
University Hospital  
Charles University, U nemocnice 2  
128 08 Prague 2, Czech Republic  
e-mail: [vladimir.tesar@lf1.cuni.cz](mailto:vladimir.tesar@lf1.cuni.cz)