

NEPHROLOGY

Rounds®

AS PRESENTED IN THE ROUNDS OF
THE RENAL DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
BOSTON, MASSACHUSETTS

Antineutrophil Cytoplasmic Antibodies (ANCA) in the Long-Term Management of Wegener Disease: How Should We Use Them?

By ANDREAS HERRLICH, MD, PhD

The diagnostic value of antineutrophil cytoplasmic antibodies (ANCA) in Wegener granulomatosis (WG) and other ANCA-associated vasculitis (AAV) syndromes is undisputed. Yet, significant controversy remains in the field about how useful ANCA levels are in the prediction of disease relapse and whether they can guide clinicians in treatment decisions. These issues are of particular importance when disease activity by other clinical or laboratory measures appears quiescent, since treatment carries the risk of significant toxicity. This issue of *Nephrology Rounds* provides a review of the available data with a particular focus on WG.

ANCA are highly sensitive in the diagnosis of WG and other AAV syndromes. The interpretation a clinician gives to serial ANCA levels during remission and the possibility of increased ANCA levels suggesting increased immunosuppression (IS) to prevent relapse is a matter of current debate. Increasing IS may expose patients to significant toxicity and side effects. Several studies in mice and humans question whether ANCA are causative in the disease and whether their levels correlate with disease activity. The Wegener Granulomatosis Etanercept Trial (WGET)¹ addressed the criticisms of previous trials by its prospective design, relatively large size, and the focus on a purely WG patient population. Contrary to previous reports, WGET results suggest that there may be no relationship between proteinase-3 (PR3)-ANCA titer changes and disease activity or relapse. Given these new findings, the available evidence regarding the use of serial ANCA titers for treatment decisions in WG will be reviewed. Therapeutic concepts in WG management will only be briefly reviewed in order to provide a basis for understanding the presented clinical trials. An excellent and more detailed review of the clinical features and therapy in AAV syndromes is also available in *Nephrology Rounds*.²

Therapeutic concepts in WG management

Patients require significant IS to achieve initial remission and for chronic maintenance therapy, since relapses are frequent. Before the introduction of intensive IS, most patients died within a year; currently, treatment protocols lead to remission in the majority of patients with AAV syndromes.^{3,4}

The current treatment concept has been developed over the last 60 years and originates from several retrospective clinical trials.⁵⁻⁷ Oral prednisone (1 mg/kg) and cyclophosphamide (CP; 500 mg–1 g/m²/day in the first week) are established first-line treatments for remission induction. In severe cases, pulsed high-dose intravenous (IV) methylprednisolone (MP, 1 g/day for 2–5 days) is added. Some evidence suggests that oral CP administration may be more effective than the IV route.⁸⁻¹⁰ Mycophenolate mofetil (MMF) may provide a less toxic alternative to CP in patients with limited disease and those who cannot be treated with CP.^{11,12} When serum creatinine is >5 mg/dL at presentation, plasmapheresis (PP) should be added and, when added to oral CP and oral prednisone, PP in comparison with IV methylprednisolone reduces the risk for progression to end-stage renal disease (ESRD) by 24% (from 43% to 19%) at 1 year.¹³ Oral CP (1-2 mg/kg/day) is usually tapered at 6-12 months. Toxic side effects due to IS are frequent, most notably bone marrow suppression and susceptibility to infections, osteopenia, increased risk of certain malignancies, and infertility. Current practice often switches patients to azathioprine (AZA), methotrexate (MTX), or MMF at 3–6 months or when remission is achieved,¹⁴ which helps avoid CP toxicity and reduces the need for steroids. Beginning in the first month of induction therapy, prednisone is slowly tapered every 3 months to ~0.1–0.15 mg/kg at 1 year



BRIGHAM AND
WOMEN'S HOSPITAL



HARVARD
MEDICAL SCHOOL
TEACHING AFFILIATE

Co-Editors

Joseph V. Bonventre, MD, PhD,
(Division Director)

Barry M. Brenner, MD, FRCP,
(Director Emeritus)

Nephrology Division Brigham and Women's Hospital

Reza Abdi, MD
Jessamyn Bagley, PhD
Joseph V. Bonventre, MD, PhD
Barry M. Brenner, MD
Steven Brunelli, MD
Anil K. Chandraker, MB, MRCP
David M. Charytan, MD
Mary Choi, MD
Kenneth B. Christopher, MD
Gary C. Curhan, MD, ScD
Bradley M. Denker, MD
Jeremy Duffield, MD, PhD
John P. Forman, MD
Markus H. Frank, MD
Steven Gabardi, PharmD
Monica Grafals, MD
Indira Guleria, PhD
Dirk M. Hentschel, MD
Andreas Herrlich, MD, PhD
Li-Li Hsiao, MD, PhD
Benjamin D. Humphreys, MD, PhD
John J. Iacomini, PhD
Takaharu Ichimura, PhD
Vicki Rubin Kelley, PhD
Akio Kobayashi, PhD
Julie Lin, MD, MPH
Edgar L. Milford, MD
David B. Mount, MD
Nader Najafian, MD
Martin R. Pollak, MD
Mohamed H. Sayegh, MD
Johannes Schlondorff, MD, PhD
Julian L. Seifter, MD
Jagesh V. Shah, PhD
Alice M. Sheridan, MD
Ajay K. Singh, MB, MRCP (U.K.)
Theodore I. Steinman, MD
Jie Tang, MD, MSc
John K. Tucker, MD
Takuya Ueno, MD, PhD
Vishal Vaidya, PhD
Sushrut S. Waikar, MD
Xueli Yuan, MD, PhD
Kambiz Zandi-Nejad, MD
Jing Zhou, MD, PhD

Brigham and Women's Hospital

Website: www.brighamandwomens.org/renal

The editorial content of *Nephrology Rounds* is determined solely by the Renal Division of Brigham and Women's Hospital.

**Nephrology Rounds is approved
by the Harvard Medical School
Department of Continuing Education
to offer continuing education credit**

and often continued indefinitely. In some cases, IS has eventually been eliminated;^{11,12,15,16} however, most patients in remission eventually experience relapse (ie, a recurrence of disease activity irrespective of changes in ANCA titers) and require increasing IS or reinstatement of therapy.¹⁷⁻¹⁸

A more recent approach to treatment-resistant disease is B-cell depletion therapy with rituximab (a humanized antibody directed against CD20, a B-cell marker).¹⁹ The efficacy of rituximab may not solely be due to the destruction of plasma cells or other B-cells that produce ANCA. Since B cells modulate antigen presentation, they may be pathogenic in autoimmune disease in other respects than antibody production.^{20,21} The main advantage to rituximab is its safety profile, since several large studies have demonstrated no increase in the risk of infection or neoplasia and generally good tolerance.²¹

Birmingham vasculitis activity score (BVAS)

The BVAS for WG is a useful and validated tool for the assessment of disease activity that can be used to compare severity of disease in different study populations. The BVAS measures persistent, new, or worsened disease activity in all major organ systems, with a weighted scoring system for minor (1 point) and major items (3 points). Major items are generally those that would trigger the use of CP (eg, gangrene, scleritis, pulmonary hemorrhage, red blood cell [RBC] casts, glomerular filtration rate [GFR] reduction of >25% or a rise in creatinine of >30%, mononeuritis multiplex, and stroke). A severe flare is defined as ≥ 1 new/worse major item, and a limited flare as ≥ 1 new/worse minor item. Patients are considered in remission when the BVAS score is 0 (ie, no new/worse, and no persistent items present). The maximum BVAS/WG score is 68. The BVAS/WG score in the outpatient population (n = 117) used for original validation ranged from 0 to 13 (median 2).²²

ANCA testing

The reported sensitivity of ANCAs for patients with WG and other AAV syndromes varies widely, ranging from 50%–95%,^{23,24} with the differences dependent on the laboratory or the use of a commercial assay with high interassay variability.^{25,26} ANCAs are detected by immunofluorescent (IF) serum staining of fixed human neutrophils for specific antibodies against neutrophil cytoplasmic components (localization either cytoplasmic, cANCA, or perinuclear, pANCA). In addition, several enzyme-linked immunosorbent assays (ELISAs) for antibodies against the 2 most common antigens, PR3-cANCA and MPO-pANCA, are used. IF has less sensitivity and specificity than ELISA, but the combination improves diagnostic sensitivity and specificity.²⁶⁻²⁸ Although testing for pANCA and cANCA helps distinguish different AAV syndromes, they must be interpreted in the proper clinical context. Over 70% of ANCAs in WG are directed against PR3 and only 10%–30% have MPO-ANCA. The other AAV syndromes, microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS), are associated with a higher prevalence of MPO-ANCA (30%–70%) and only a few have PR3-ANCA. Significantly, a number of WG patients with clinically active disease are

ANCA-negative, despite the use of a novel PR3 capture ELISA with greater sensitivity and specificity than when using IF and standard PR3 ELISA combined.^{29,30} Nearly all WG patients with severe disease are ANCA-positive, but up to 20% of patients with limited disease are ANCA-negative.³¹ Some patients who are negative for classic ANCA may have antibodies against other targets, such as the lysosomal-associated membrane protein, LAMP-2,³² or against elastase, azurocidin, cathepsin G, and lactoferrin, which are involved in ANCA-positive drug-induced glomerulonephritis (GN).³³

ANCA and disease: a causal relationship?

The possibility of antibodies causing a glomerular disease that is, by definition, pauci-immune on biopsy has been a conundrum, since the discovery of ANCA antigens in the 1980s.³⁴⁻³⁶ Several studies suggest a role for ANCA in the initial insult that leads to activation of neutrophils and other inflammatory cells. Although neutrophils are not a dominant feature of AAV renal pathology, it is possible that local neutrophil activation by ANCA incites a wider inflammatory response independent of neutrophils. Local immune complex formation on leukocytes or endothelial surfaces could mediate the initial glomerular and vascular insult. A supportive observation is that kidneys of myeloperoxidase (MPO)-immunized rats perfused with lysosomal extract containing MPO, both MPO and immunoglobulin G (IgG) localized transiently along the glomerular basement membrane (GBM), but 4 to 10 days later, at the time of maximal glomerular inflammation, MPO, IgG, and complement C3 were undetectable. Yet, MPO-perfused rats developed a dose-dependent proliferative GN with glomerular and extraglomerular pathology including the formation of granulomata and giant cells. Monocytes and neutrophils, and only a few T cells were found in the glomeruli and interstitial infiltrates.³⁷ Monocytes and macrophages are also known to express ANCA antigens and could be activated by ANCA through a similar mechanism. They are present in crescentic glomeruli of AAV patients³⁸ and are implicated in the development and progression of antibody-induced crescentic GN in a rat model where conditional ablation of macrophages significantly reduced disease severity.³⁹

Direct involvement of MPO-ANCA in human disease initiation and in mice *in vivo* is supported by several studies.⁴⁰ Two mouse models of MPO-ANCA-induced GN have been developed and report conflicting results. In the first model, purified MPO IgG (“MPO-ANCA”) injected into wild-type mice or into mice lacking B and T cells (but not neutrophils) induced focal necrotizing crescentic GN, suggesting that MPO-ANCAs are sufficient to cause vasculitis.⁴¹ In the second model, antibodies induced by human MPO immunization cross-reacted with mouse MPO and caused autoimmunity. This led to GN only when the glomerulus was predamaged by small doses of anti-GBM antibodies; GN was not dependent on the function of B-cells and depletion of T-helper cells ameliorated the disease. The fact that GN developed in the absence of B-cells (and therefore antibody production) could be explained by the presence of anti-MPO CD4+ T-helper cells that recognize MPO as a planted glomerular antigen and act together with macrophages to amplify

severe glomerular injury.⁴² This is supported by results obtained in autoimmune mouse models where complete absence of B cells prevented systemic autoimmunity; however, if antibody production of B cells was inhibited, autoimmunity developed normally. In this situation, inflammation is likely mediated by cell-cell or cell-matrix interactions alone, depending on where the antigen is localized.^{20,43,44}

Thus far, no straightforward mouse model for PR3-ANCA, the main antigen in WG, has been reported. One study from Israel potentially implicated both PR3- and MPO-ANCA. Mice were immunized with human ANCA and developed mouse ANCA against PR3 and MPO after 4 months, as well as antiendothelial autoantibodies. The mice developed proteinuria (but not hematuria), pulmonary mononuclear perivascular infiltration, and diffuse granular deposition of Ig in the kidneys.⁴⁵

ANCA and relapse

At least 50% of patients with WG have a tendency to relapse within 5 years, as opposed to about 30% in cases of MPA or renal-limited vasculitis.^{7,22,46,47} Given the possible ANCA involvement in the disease process, interval ANCA levels have been considered for guiding therapy, but absolute ANCA levels do not correlate well with disease activity across patients.²⁹ Nevertheless, if ANCA titers would reliably predict worsening disease, an incremental increase in baseline IS could potentially avoid relapse and the need for more toxic IS. Similarly, withholding intensified IS when ANCA levels are elevated or rising could increase morbidity and mortality secondary to irreversible damage incurred during the delay in initiation of therapy. Conceptually, ANCA tests and clinical disease assessments must be frequent enough to detect relationships between ANCA and disease activity, particularly when the goal is to detect ANCA increases prior to disease activity. For example, if intervals are too infrequent a rise in ANCA level may be detected too late (when disease is already present) or a trough of ANCA activity during remission may be missed. Therefore, it is important to know how ANCA titers behave over the normal course of induction therapy and whether relapses in clinical disease are usually ANCA-positive.

ANCA levels fall or become negative in 30%-80% of patients within the first 1-3 months of induction treatment. Persistence of ANCA beyond this point is usually associated with ongoing disease activity, but most patients ultimately reach remission and become ANCA-negative.^{18,48,49} A persistent or reappearing cANCA during the first year is associated with relapse in AAV syndrome,^{17,18,50-52} and relapse in patients with PR3- or MPO-ANCA who were ANCA-positive at diagnosis is associated with persistent or renewed positive ANCA in 80%-100%.^{18,47,48,50,52-56} Caution must be used when interpreting or comparing the studies addressing the correlation of ANCA levels with disease activity. Many studies are small and retrospective, with data on a mix of different AAV syndromes with PR3 and/or MPO-ANCA,^{16,57} as well, relapse definitions and methods of diagnosis differ with some failing to use BVAS or biopsy to support diagnoses. Often no distinction is made between participants who entered at initial presentation or at relapse. There is also a lack of standard-

ization of intervals between ANCA measurements, or between a rise in ANCA and the associated clinical event; differences in ANCA testing add another layer of complexity.⁵⁷

ANCA specificity and relapse

Some studies suggest that PR3-ANCA specificity has prognostic value for the prediction of relapse. Retrospective data from 2 large AAV cohorts, the American Glomerular Disease Collaborative Network (GDCN) and the French Vasculitis Study Group, identified PR3-ANCA and pulmonary involvement as independently associated with relapse.⁵⁸ Several other studies have reported an increased relapse rate for PR3- vs MPO-positive patients in combined datasets of different AAV syndromes.^{17,18,50,59} In a retrospective study of 137 patients with WG, those with PR3, as compared with MPO-ANCA had a higher relapse rate; however, the sample of MPO-ANCA-positive patients was rather small (n=13 vs n=124 for PR3-ANCA).⁵⁷ In 75 patients with MPA or renal limited vasculitis (RLV), who achieved remission, however, no difference was observed in the relapse rate between cANCA- or pANCA-positive patients.⁷

Positive ANCA when switching from CP to AZA in maintenance of remission

A positive ANCA may have prognostic value when IS is switched to a CP-sparing regimen after the patient achieves remission. A prospective study⁶⁰ compared 2 cohorts: 44 patients who were switched from prednisone and CP to prednisone and AZA after 3 months of clinical remission (irrespective of ANCA titer) and a historical control of 84 patients treated with prednisone and CP for remission induction in earlier years (1990-1996). There was a non-significant trend to increased relapse in the AZA group vs the CP group, but disease-free survival was similar in both groups at 2 and 4 years. In the AZA group, a positive PR3-ANCA titer at the moment of treatment switch (n=13) was significantly associated with relapse. Using a historical control and including several forms of AAV weaken the results of this study, since it is quite possible that treatment responses and duration of remission vary across AAV subsets. A switch to AZA therapy was carried out after 3-17 months of CP therapy, suggesting great variation in the length of CP treatment that may be particularly important in PR3-ANCA-positive patients switched to AZA. One potential interpretation of this study is that PR3-ANCA-positive patients should be continued on CP as long as they remain ANCA-positive, regardless of their clinical status;⁶¹ however, this approach would expose 2 out of 3 continuously PR3-ANCA-positive patients to unnecessary CP treatment.⁶⁰ The resulting CP-related toxicity could preclude patients from CP use in treating subsequent life-threatening AAV complications.

Falling or rising ANCA levels during remission

Falling ANCA titers are generally associated with a low risk of relapse;^{24,48,61,62} however, several studies suggest that increases in ANCA are often followed by disease relapse in 3-6 months. In one prospective study,⁵³ cANCA levels were

determined monthly in 58 patients with (biopsy-proven) WG in remission on CP and prednisone; 34% had an increase in ANCA titers over 2 years and were randomized to intensified CP and prednisone or left untreated. Almost all patients left untreated relapsed, most in the first 3 months, but none of the treated patients relapsed. In another prospective observational study by the same group,⁶³ 100 WG patients (85% PR3-ANCA, 15% MPO-ANCA) were studied over 2 years. ANCA levels were measured every 2 months; 37% of patients relapsed and, overall, most of those demonstrated a rise in ANCA levels preceding their relapse. The positive predictive value of an increase in ANCA titers for relapse was 57% for cANCA (by IF) and 71% for PR3-ANCA (by ELISA); however, 29% of those with a rise in PR3-ANCA (by ELISA) did not experience a subsequent relapse.⁶³

A prospective study of 60 patients with AAV⁵⁰ found clinical remission achieved in almost all patients on CP and prednisone, and ANCA was undetectable in 83%. ANCA was measured every month and the relapse rate over 1 year was 38% with the majority (57%) preceded by a rise in ANCA (mean of 7.8 weeks earlier), while almost all patients were ANCA-positive by the time of relapse. In 10% of patients a sustained rise in ANCA occurred without relapse, while clinical relapse occurred in <5% of ANCA-negative patients.

Two prospective studies^{50,54} reported a lack of association of ANCA rise and relapse. In the study of 72 WG patients in remission,⁵⁴ ANCA was measured by IF in 1-3-month intervals, 112 healthy subjects served as controls, and cANCA had an 88% sensitivity for active WG. In only 64% of patients were changes in serial titers temporally correlated with a change in disease status; only 24% who had been in clinical remission or had low-grade, smoldering disease had a cANCA titer increase preceding relapse.⁵⁴ However, this study had a low sensitivity and specificity with IF for ANCA detection. The other prospective study of 43 AAV patients⁵⁰ found that increases in ANCA titer had only a 28% (cANCA) and 12% (P3-ANCA) positive predictive value for relapse. There are limited data about the predictive value of a rise in MPO-ANCA titer.^{18,50,52,59,63}

A retrospective study by Han et al¹⁶ supports the notion that significant ANCA titer increases are associated with relapse. Forty-eight patients with AAV were followed in an outpatient clinic after remission (1990-2001). Patients had a mean BVAS score of 6 at study entry and renal disease was common; 56% were PR3-ANCA positive. Treatment consisted of CP for 3-12 months until remission and prednisone. During remission, CP was replaced by AZA, MTX, or MMF and prednisone was continued at low doses. Patients were clinically assessed and ANCA was measured every 2-3 months. In several patients, minor adjustments in therapy were made based on incremental ANCA changes. Of the 23 relapses in 16 patients, only 52% were

preceded by a 4-fold rise in ANCA titer. A total of 21 episodes of 4-fold rise in ANCA titer were observed. To focus on the value of ANCA titer rises, outcomes were assessed in 2 groups of patients with 4-fold rise in ANCA titer: Group 1 (n=8) had not been given increased IS and Group 2 (n=11) had received pre-emptive incremental increases in IS. All patients in Group 1 relapsed (mean 5.8 months) but only 2 relapses occurred in Group 2, suggesting that incremental increases in IS prevented relapse. The weaknesses of this study lie in its retrospective design, the small number of patients and the fact that different AAV syndromes are reported together. Interestingly, 10% of relapses had a concurrent ANCA rise and 25% occurred in the setting of falling or negative ANCA titers at the time of relapse.

The WGET trial

The National Institutes of Health-sponsored multicenter, prospective, randomized, placebo-controlled WGET¹ evaluated the effect of etanercept on maintenance of remission in 180 patients with WG. The primary outcome was sustained remission, defined as a BVAS of 0 for at least 6 months. Patients had a mean BVAS of 6 and received standard induction therapy in addition to etanercept or placebo. In remission, CP was tapered and replaced by AZA, MTX, or MMF. Steroids were tapered and discontinued by 6 months, if no relapse occurred; MTX was tapered after 12 months. There were no significant differences between the etanercept and control groups in the rates of sustained remission and relative risk of disease flares.

A second study²⁹ examined 134 PR3-positive and 22 PR3-negative patients included in WGET. Median follow-up was 34 months, and BVAS scores and ANCA measurements were obtained every 3 months and compared to the preceding 2 measurements, spanning a 6-month period. A 100% rise in ANCA titer over 6 months was defined as an increase, a 50% decline over 6 months as a decrease. Relapse was defined as any BVAS >0. Seventy-five percent of the PR3-positive patients reached remission and 50% subsequently relapsed. A similar number of PR3-negative patients relapsed and of those most relapses were again ANCA-negative. PR3-ANCA was significantly lower in remission as compared to study entry. However, multivariate analysis (adjusted for sex, age, disease severity, placebo or etanercept group, disease duration, baseline BVAS, and clinical center) revealed that decreases in PR3-ANCA levels were not associated with shorter time to remission and that increases were not associated with relapse. Only 40% of patients with an increase in PR3-ANCA relapsed over 1 year.²⁹

WGET confirms that WG has a high rate of relapse despite the therapies available and that patients usually have a lower ANCA titer when they reach remission compared with study entry. The lack of detection of a relationship between serial ANCA titers and disease

Table 1: Studies of antineutrophil cytoplasmic antibody increases as a predictor of disease relapse

Study	Patients (N)	PR3-ANCA, or cANCA (%)	ANCA interval (mo)	Detection method	Definition of increase	Total relapses (%)	Increase 3-6 months prior to relapse (%)
Tervaert et al, 1990 ⁴⁸	58	NS	1	IF	4-fold	54	54
Kerr et al, 1993 ⁵⁴	72	43*	1-3	IF	4-fold	62	24
Jayne et al, 1995 ¹⁸	60	65	1	ELISA	30%	38	57
Kyndt et al, 1999 ⁵⁰	43	17*	1-3	IF	2-fold	54	28
Boomsma et al, 2000 ⁶³	100	85	2	ELISA	75%	37	92
Han et al, 2003 ¹⁶	48	56	2-3	ELISA	4-fold	33	52
Finkelmann et al, 2007 ³¹	134	100	3	ELISA	100% over 6 months	46	40 ^o

^o No correlation of PR3-ANCA levels with disease activity of relapse after multivariate analysis; ELISA = enzyme-linked immunosorbent assay; IF = immunofluorescence; NS = not specified; PR3 = proteinase 3; ANCA = antineutrophil cytoplasmic antibody

activity could be based on the definitions for increase and decrease used in the study. A 3-month interval between ANCA measurements is relatively long when compared with other studies and changes are scored over 6 months (3 measurements at months 1, 3, and 6 of the interval). It is possible that a high ANCA titer flanked by 2 low ANCA titers (at the beginning of the interval and at the point of relapse) could be scored as a decrease or no change in ANCA and the relevant increase in ANCA preceding the relapse would be missed. WGET does not address the question whether treatment of such an interval ANCA rise would yield a better outcome irrespective of the ANCA titer at relapse. Since the BVAS reflects disease activity over the preceding 28 days, it is also possible that a given patient may have inactive disease at ANCA sample collection despite a BVAS >0, reflecting disease that has already subsided. This would bias against detecting a connection between ANCA titers and disease activity. Additionally, due to differences in follow-up length, the sensitivity and specificity of an increase in ANCA for the detection of relapse could not be calculated. Finally, it cannot be excluded that PR3-ANCA reflects involvement of only a particular organ and could be used successfully as a marker of relapse in a more specific setting. Table 1 combines the data available on serial ANCA titer increase and relapse in AAV.

Conclusion

ANCA level measurement is sensitive and specific for the diagnosis of AAV syndromes, but up to 20% of WG patients (mostly with limited disease) test negative. Negative or falling titers have a low risk of relapse. The data on a serial rise in ANCA titers and their impact on treatment decisions remain confusing. Given the overall evidence, a cautious approach to remission therapy in AAV and, particularly, WG remains best practice. Clearly, incremental adjustments in IS based on a rise in ANCA titer should be carefully correlated with clinical evidence for active disease at regular clinic visits. Severe or unabated clinical disease activity will

still require intensive IS with CP, prednisone, and potentially high-dose steroids, irrespective of the ANCA titer or its trend.

References

1. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med*. 2005; 352(4):351-361.
2. Duffield JS, Quatar A. Advances in the etiology and management of immune-mediated glomerulonephritides. *Nephrology Rounds*. 2008;6(10):1-6.
3. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J*. 1958;2(5091):265-270.
4. Hollander D, Manning RT. The use of alkylating agents in the treatment of Wegener's granulomatosis. *Ann Intern Med*. 1967;67(2):393-398.
5. Chasis G, Goldring W, Baldwin DS. The effect of nitrogen mustard on renal manifestations of human glomerulonephritis. *J Clin Invest*. 1950;29(6):804.
6. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med*. 1983;98(1):76-85.
7. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol*. 1996;7(1):33-39.
8. Rihová Z, Jancová E, Merta M, et al. Daily oral versus pulse intravenous cyclophosphamide in the therapy of ANCA-associated vasculitis – preliminary single center experience. *Prague Med Rep*. 2004;105(1):64-68.
9. Haubitz M, Schellong S, Göbel U, et al. Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study. *Arthritis Rheum*. 1998;41(10):1835-1844.
10. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol*. 1996;7(1):23-32.
11. Stassen PM, Cohen Tervaert JW, Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. *Ann Rheum Dis*. 2007;66(6):798-802.
12. Joy MS, Hogan SL, Jennette JC, Falk RJ, Nachman PH. A pilot study using mycophenolate mofetil in relapsing or resistant ANCA small vessel vasculitis. *Nephrol Dial Transplant*. 2005;20(12):2725-2732.
13. 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(7): 2180-2188.
14. Pagnoux C, Mahr A, Hamidou MA, et al; French Vasculitis Study Group. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med*. 2008;359(26):2790-2803.
15. 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(1):36-44.
16. Han WK, Choi HK, Roth RM, McCluskey RT, Niles JL. Serial ANCA titers: useful tool for prevention of relapses in ANCA-associated vasculitis. *Kidney Int*. 2003;63(3):1079-1085.
17. De'Oliviera J, Gaskin G, Dash A, Rees AJ, Pusey CD. Relationship between disease activity and anti-neutrophil cytoplasmic antibody concentration in long-term management of systemic vasculitis. *Am J Kidney Dis*. 1995;25(3):380-389.
18. Jayne DR, Gaskin G, Pusey CD, Lockwood CM. ANCA and predicting relapse in systemic vasculitis. *QJM*. 1995;88(2):127-133.
19. Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited Wegener's granulomatosis with refractory granulomatous manifestations. *J Rheumatol*. 2008;35(10): 2017-2023.

20. Chan OT, Hannum LG, Haberman AM, Madaio MP, Shlomchik MJ. A novel mouse with B cells but lacking serum antibody reveals an antibody-independent role for B cells in murine lupus. *J Exp Med*. 1999;189(10):1639-1648.
21. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. *Blood*. 1998;92(6):1927-1932.
22. Stone JH, Hoffman GS, Merkel PA, et al; International Network for the Study of the Systemic Vasculitides (INSSYS). A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). *Arthritis Rheum*. 2001;44(4):912-920.
23. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med*. 1992;116(6):488-498.
24. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis. A literature review and meta-analysis. *Ann Intern Med*. 1995;123(12):925-932.
25. Lim LC, Taylor JG 3rd, Schmitz JL, et al. Diagnostic usefulness of antineutrophil cytoplasmic autoantibody serology. Comparative evaluation of commercial indirect fluorescent antibody kits and enzyme immunoassay kits. *Am J Clin Pathol*. 1999;111(3):363-369.
26. Csernok E, Ahlquist D, Ullrich S, Gross WL. A critical evaluation of commercial immunoassays for antineutrophil cytoplasmic antibodies directed against proteinase 3 and myeloperoxidase in Wegener's granulomatosis and microscopic polyangiitis. *Rheumatology (Oxford)*. 2002;41(11):1313-1317.
27. Csernok E, Holle J, Hellmich B, et al. Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies directed against proteinase 3 in Wegener's granulomatosis: first results from a multicentre study. *Rheumatology (Oxford)*. 2004;43(2):174-180.
28. Choi HK, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. *J Rheumatol*. 2001;28(7):1584-1590.
29. Finkielman JD, Merkel PA, Schroeder D, et al; WGET Research Group. Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. *Ann Intern Med*. 2007;147(9):611-619.
30. Hellmich B, Csernok E, Fredenhagen G, Gross WL. A novel high sensitivity ELISA for detection of antineutrophil cytoplasmic antibodies against proteinase-3. *Clin Exp Rheumatol*. 2007;25(1 Suppl 44):S1-S5.
31. Finkielman JD, Lee AS, Hummel AM, et al; WGET Research Group. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. *Am J Med*. 2007;120(7):643.e9-e14.
32. Kain R, Matsui K, Exner M, et al. A novel class of autoantigens of anti-neutrophil cytoplasmic antibodies in necrotizing and crescentic glomerulonephritis: the lysosomal membrane glycoprotein h-lamp-2 in neutrophil granulocytes and a related membrane protein in glomerular endothelial cells. *J Exp Med*. 1995;181(2):585-597.
33. Yu F, Chen M, Gao Y, et al. Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis. *Am J Kidney Dis*. 2007;49(5):607-614.
34. Niles JL, McCluskey RT, Ahmad MF, Arnaout MA. Wegener's granulomatosis autoantigen is a novel neutrophil serine proteinase. *Blood*. 1989;74(6):1888-1893.
35. Goldschmieding R, van der Schoot CE, ten Bokkel Huinink D, et al. Wegener's granulomatosis autoantibodies identify a novel diisopropylfluorophosphate-binding protein in the lysosomes of normal human neutrophils. *J Clin Invest*. 1989;84(5):1577-1587.
36. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. *Am J Pathol*. 1989;135(5):921-930.
37. Brouwer E, Huitema MG, Klok PA, et al. Antimyeloperoxidase-associated proliferative glomerulonephritis: an animal model. *J Exp Med*. 1993;177(4):905-914.
38. Rastaldi MP, Ferrario F, Crippa A, et al. Glomerular monocyte-macrophage features in ANCA-positive renal vasculitis and cryoglobulinemic nephritis. *J Am Soc Nephrol*. 2000;11(11):2036-2043.
39. Duffield JS, Tipping PG, Kipari T, et al. Conditional ablation of macrophages halts progression of crescentic glomerulonephritis. *Am J Pathol*. 2005;167(5):1207-1219.
40. Bansal PJ, Tobin MC. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. *Ann Allergy Asthma Immunol*. 2004;93(4):398-401.
41. Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest*. 2002;110(7):955-963.
42. Ruth AJ, Kitching AR, Kwan RY, et al. Anti-neutrophil cytoplasmic antibodies and effector CD4+ cells play nonredundant roles in anti-myeloperoxidase crescentic glomerulonephritis. *J Am Soc Nephrol*. 2006;17(7):1940-1949.
43. Chan OT, Madaio MP, Shlomchik MJ. B cells are required for lupus nephritis in the polygenic, Fas-intact MRL model of systemic autoimmunity. *J Immunol*. 1999;163(7):3592-3596.
44. Chan O, Madaio MP, Shlomchik MJ. The roles of B cells in MRL/lpr murine lupus. *Ann N Y Acad Sci*. 1997;815:75-87.
45. Blank M, Tómer Y, Stein M, et al. Immunization with anti-neutrophil cytoplasmic antibody (ANCA) induces the production of mouse ANCA and perivascular lymphocyte infiltration. *Clin Exp Immunol*. 1995;102(1):120-130.
46. Gordon M, Luqmani RA, Adu D, et al. Relapses in patients with a systemic vasculitis. *Q J Med*. 1993;86(12):779-789.
47. Guillevin L, Durand-Gasselín B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum*. 1999;42(3):421-430.
48. Tervaert JW, Huitema MG, Hené RJ, et al. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet*. 1990;336(8717):709-711.
49. van der Woude FJ, Daha MR, van Es LA. The current status of neutrophil cytoplasmic antibodies. *Clin Exp Immunol*. 1989;78(2):143-148.
50. Kyndt X, Reumaux D, Bridoux F, et al. Serial measurements of antineutrophil cytoplasmic autoantibodies in patients with systemic vasculitis. *Am J Med*. 1999;106(5):527-533.
51. Girard T, Mahr A, Noël LH, et al. Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. *Rheumatology (Oxford)*. 2001;40(2):147-151.
52. Ara J, Mirapeix E, Rodriguez R, Saurina A, Darnell A. Relationship between ANCA and disease activity in small vessel vasculitis patients with anti-MPO ANCA. *Nephrol Dial Transplant*. 1999;14(7):1667-1672.
53. Gaskin G, Savage CO, Ryan JJ, et al. Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. *Nephrol Dial Transplant*. 1991;6(10):689-694.
54. Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. *Arthritis Rheum*. 1993;36(3):365-371.
55. Franssen CF, Stegeman CA, Oost-Kort WW, et al. Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerulonephritis. *J Am Soc Nephrol*. 1998;9(10):1915-1923.
56. Gaskin G, Pusey CD. Plasmapheresis in antineutrophil cytoplasmic antibody-associated systemic vasculitis. *Ther Apher*. 2001;5(3):176-181.
57. Stegeman CA. Anti-neutrophil cytoplasmic antibody (ANCA) levels directed against proteinase-3 and myeloperoxidase are helpful in predicting disease relapse in ANCA-associated small-vessel vasculitis. *Nephrol Dial Transplant*. 2002;17(12):2077-2080.
58. Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: Comparison of two independent cohorts. *Arthritis Rheum*. 2008;58(9):2908-2918.
59. Pettersson E, Heigl Z. Antineutrophil cytoplasmic antibody (cANCA and pANCA) titers in relation to disease activity in patients with necrotizing vasculitis: a longitudinal study. *Clin Nephrol*. 1992;37(5):219-228.
60. 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(2):269-273.
61. Hoffman GS, Stone JH, Langford C. Implications of antineutrophil cytoplasmic antibody status when switching to maintenance therapy. *Arthritis Rheum*. 2005;53(1):1-2.
62. Specks U, Wheatley CL, McDonald TJ, Rohrbach MS, DeRemee RA. Anticytoplasmic autoantibodies in the diagnosis and follow-up of Wegener's granulomatosis. *Mayo Clin Proc*. 1989;64(1):28-36.
63. Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CG, Limburg PC, Tervaert JW. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. *Arthritis Rheum*. 2000;43(9):2025-2033.

Upcoming Scientific Meeting

4 – 6 February 2010

29th Annual Advanced Nephrology: Nephrology for the Consultant

La Jolla, CA

Contact: Conference Secretariat: UCSD CME

Tel: 858-534-3940

Fax: 858-822-5908

Email: ocme@ucsd.edu

Disclosure: Dr. Herrlich has no disclosures to announce in association with the contents of this issue.

This activity is supported by an educational donation provided by

Amgen

©2009 Renal Division, Brigham and Women's Hospital, Boston, Massachusetts, which is solely responsible for the contents. The opinions expressed in this publication do not necessarily reflect those of the publisher or sponsor, but rather are those of the author based on the available scientific literature. Publisher: **SNELL Medical Communication Inc.** in cooperation with the Renal Division, Brigham and Women's Hospital. [®]*Nephrology Rounds* is a registered trademark of **SNELL Medical Communication Inc.** All rights reserved. The administration of any therapies discussed or referred to in *Nephrology Rounds* should always be consistent with the recognized prescribing information as required by the FDA. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.