Ask the Expert

ANCA-Associated Vasculitis Management

Antineutrophil cytoplasm antibodies (ANCA) play an important role as markers for small-vessel vasculitis, and the ability to screen for them has routinely led to advances in the assessment, classification, and treatment of the ANCA-associated vasculitides, including Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis.

While there is no cure for these conditions, which often affect the lungs, sinuses, and kidneys, they are no longer acutely fatal thanks to the aggressive use of immunosuppressive treatment. Such therapy—typically a combination of cyclophosphamide and corticosteroids—can successfully induce initial remission in most patients.

BY LOÏC GUILLEVIN, PH.D.

However, because treatment must generally be long term to maintain remission and prevent relapses, it is associated with a significant risk of serious side effects and infective complications. For this reason, one of the major challenges in the clinical management of these patients is identifying those at greatest risk for relapse, and then trying to prevent and treat relapses with the least toxic regimens possible without compromising organ function, according to Dr. Loïc Guillevin.

In this month's column, Dr. Guillevin discusses recent advances in the management of ANCA-associated vasculitis, including the availability of new immunosuppressants and biologic agents.

Rheumatology News: What are the most important management concerns when dealing with ANCA-positive small vessel vasculitis?

Dr. Guillevin: It is important to consider the prognosis associated with the specific syndromes and target treatment appropriately. For example, patients with microscopic polyangiitis and Churg-Strauss syndrome with a score of zero on the five-factor scale [a prognostic index based on disease severity at onset] have a low probability of death and relapse, so remission can sometimes be obtained under steroid treatment alone, avoiding cytotoxic agents. If steroids alone fail, pulse cyclophosphamide or azathioprine can be prescribed to induce remission and to reduce steroid dose and limit its side effects. Patients with a five-factor score greater than one, indicating a poor prognosis, and every patient with Wegener's granulomatosis, should receive a combination of steroids and pulse cyclophosphamide, which has been proved effective and less toxic than oral cyclophosphamide. In all cases, the optimal cyclophosphamide treatment is 3-6 months, followed by maintenance treatment with azathioprine or methotrexate for 12-18 months.

RN: Are there any other options for induction therapy?

Dr. Guillevin: At the moment, we have no best induction treatment other than immunosuppressants and steroids, but anti-CD20 therapy [rituximab] is promising and is currently under investigation in an international prospective trial [Rituximab in ANCA-Associated Vasculitis, sponsored by the National Institute of Allergy and Infectious Diseases and the Immune Tolerance Network].

RN: What is the optimal management strategy for patients who relapse during or after treatment?

Dr. Guillevin: This is certainly the major concern, because relapse rates are high—50% in Wegener's, 33% in microscopic polyangiitis, and 25% in Churg-Strauss syndrome. When relapses occur, patients have sometimes already been heavily treated and the introduction of immunosuppressants increases the risk for side effects. Treatment strategies depend on the previous therapy administered and the time of occurrence of relapse, whether it's during treatment or after previous treatments have stopped. When relapse occurs months or years after stopping treatment, a new conventional treatment can be started. When relapse occurs under treatment, new combinations of conventional drugs and new biotherapies should be tried. In such cases, however, effectiveness can be difficult to obtain and side effects are frequent.

RN: Are there any other treatment options available or on the horizon?

Dr. Guillevin: The immunosuppressant mycophenolate mofetil is currently being tested as an alternative to azathioprine as a maintenance therapy in a trial by the European Vasculitis Study Group. Plasma exchanges have shown their effectiveness in improving renal function in patients with an initial creatinine level of 500 µmol/L or higher. Intravenous immunoglobulin also has been shown to be effective in controlling relapses and could have an indication as a steroid-sparing agent. Anti–tumor necrosis factor antibodies have successfully been used in severe vasculitis that is refractory to conventional therapies, despite the risk of developing infectious side effects. The anti-TNF drug etanercept, however, has not shown effectiveness as a maintenance treatment in Wegener's granulomatosis and was associated with an increased number of malignancies. ■

Dr. Guillevin is the head of the department of internal medicine at Hôpital Cochin in Paris, and is a member of the French Vasculitis Study Group.

Clinical Factors Predict CNS Vasculitis Progression in Children

BY JOHN R. BELL
Associate Editor

The likelihood of progression of primary angiitis of the central nervous system in children can be predicted by using a high-risk profile comprising clinical features seen at diagnosis and on follow-up, according to new findings.

Dr. Susanne M. Benseler of the Hospital for Sick Children in Toronto and her colleagues found that in their study's cohort of patients with childhood primary angiitis of the central nervous system (cPACNS), progressive disease was associated with neurocognitive dysfunction, multifocal lesions as seen on MRI, and angiographic evidence of distal stenoses at presentation. Thus, they devised a high-risk profile encompassing those factors; the profile for their cohort had a high predictive value of disease progression (predicted $P = .002$; odds ratio 3.47; 95% confidence interval 2.11-8.24).

The investigators retrospectively assessed data from a consecutive cohort of children younger than 18 years who had been diagnosed with cPACNS over a 12-year period (1990-2002). Cases came from the institution's rheumatology database, as well as from the Canadian Pediatric Ischemic Stroke Registry (Arthritis Rheum. 2006;54:1291-7).

Criteria for having cPACNS were a clinical diagnosis of PACNS vasculitis and conventional CNS angiography and/or magnetic resonance angiography (MRA) findings of arterial stenosis that were not explained by other causes. The investigators excluded neonates and children with any various confounding conditions, such as systemic vasculitis.

The study's primary outcome was the presence or absence of stenosis progression more than 3 months after initial angiography. The researchers defined progression as "a decrease of at least 25% in the diameter at sites of initial stenosis or the appearance of new areas of stenosis."

Progressive disease was linked with neurocognitive dysfunction, multifocal lesions, and angiographic evidence of distal stenoses at presentation.

Specialists in stroke, neurology, and rheumatology followed up on all patients, collecting data on clinical presentation, underlying disease, stroke risk, and treatments from the databases.

Antithrombotic treatment had been administered according to established protocols; immunosuppressive treatment had been given in some individual cases. There were three treatment categories: antithrombotic therapy (heparin, aspirin, or warfarin) alone; antithrombotic therapy plus steroids; and antithrombotic therapy with steroids and intravenous cyclophosphamide.

The investigators then prospectively assessed patients in the stroke clinic at 3-6 months, 12 months, and 24 months post diagnosis, using the Pediatric Stroke Outcome Measure, an examination with five neurocognitive domains. They defined complete recovery as a neurologic deficit severity score of 0, with any other score indicating incomplete recovery.

In addition, laboratory tests were conducted, comprising an assessment of inflammatory markers, blood testing, prothrombotic testing, antibody profiling, and detection of abnormalities in cerebrospinal fluid. All children received MRI, MRA, or conventional cerebral angiography at diagnosis and follow-up, with results analyzed by blinded neuroradiologists.

Of the 62 children included in the study (38 boys and 24 girls), 20 patients (32%) were deemed to have progressive cPACNS, with the remaining 42 classified as nonprogressive. Among the most common symptoms in both groups were focal neurologic deficits: Hemiparesis was experienced by 60% of patients with progressive disease and 88% of those with nonprogressive disease; hemifacial weakness by 60% and 57%, respectively; hemisensory loss by 95% and 71%; and deficits in fine motor skills by 75% and 71%.

The differences between the two groups were more pronounced in their incidence of diffuse neurologic deficit. For progressive-disease patients, incidence in all three categories ranged from 60% to 75%, whereas in the nonprogressive group, incidence in those categories ranged from 7% to 19%. Likewise, progressive-disease patients experienced far more headaches than did children with nonprogressive cPACNS (95% vs. 38%).

Lesions and especially stenoses were more common in the progressive-cPACNS group. The largest lesion disparity was seen in the incidence of gray-matter lesions (90% for progressive vs. 48% for nonprogressive). For stenoses, as assessed via MRA, incidence was much greater among patients with progressive disease in all stenosis categories, except for proximal stenoses, for which the groups were equal. For multiple, bilateral, and distal stenoses, however, the differences in incidence were 30%, 33%, and 59%, respectively, between the two patient groups.

The researchers called for future trials assessing immunosuppressive therapy in children with features of nonprogressive disease. ■