

IVIG Guidelines Highlight Autoimmune Uses

BY BRUCE JANCIN

BUDAPEST, HUNGARY — New European guidelines on high-dose intravenous immunoglobulin therapy in autoimmune dermatologic diseases restrict the first-line indications to toxic epidermal necrolysis, Kawasaki disease, and life-threatening, rapidly progressive cases of dermatomyositis.

With some exceptions, those recommended uses closely mirror standard practice in the United States, according to Dr. Eric Matteson, of the Mayo Clinic, Rochester, Minn.

“We use IVIG to manage Kawasaki disease and dermatomyositis. Beyond that, its use is generally limited to repletion therapy after plasma exchange, for example in patients with severe lupus or [antineutrophil cytoplasmic antibody]-associated vasculitis who develop pulmonary hemorrhage,” he said in an interview.

During his presentation at a satellite symposium that was devoted to the new guidelines and held in conjunction with the annual congress of the European Society for Dermatological Research, Dr. Alexander Enk said that the indications for IVIG as second-line therapy are broader. IVIG is deemed appropriate in the setting of an inadequate response or contraindications to conventional therapy in pa-



tients with any of the severe autoimmune blistering diseases, such as bullous pemphigoid, linear IgA dermatosis, and epidermolysis bullosa acquisita; for systemic vasculitic syndromes, including Wegener’s granulomatosis and polyarteritis nodosa; and in severe forms of systemic lupus erythematosus.

Dr. Enk chaired the guideline panel on behalf of the European Academy of Dermatology and Venereology and the European Dermatology Forum.

IVIG should be given as an adjunct to continued use of standard first-line corticosteroids and other immunosuppressive agents, barring contraindications.

The guidelines list several other diseases for which IVIG can be considered an option on the basis of case reports. These include atopic dermatitis, scleromyxedema, autoimmune urticaria, and pyoderma gangrenosum.

Dr. Enk was quick to concede that the evidence base for IVIG in autoimmune dermatologic diseases is limited. It consists overwhelmingly of small case series.

But in the absence of high-level clinical trial evidence, recommendations based upon expert consensus are the next-best option, said Dr. Enk, professor and chair of the department of dermatology at the University of Heidelberg (Germany). These are uncommon diseases with which most physicians have

limited experience, and it is all off-label therapy, he noted.

The guidelines were created to provide the medical community with the best practices of European experts, to provide physicians with protection against lawsuits, and to serve as a basis for attaining reimbursement, he said.

Speaking of reimbursement, Dr. Enk noted that although IVIG is quite expensive, it is relatively free of side effects and often induces prolonged remission.

An economic analysis conducted in Massachusetts concluded that when the cost of treating corticosteroid-induced osteoporotic fractures and other side effects of conventional chronic immunosuppressive therapy for autoimmune mucocutaneous blistering diseases was factored in, IVIG was a clear winner (Int. Immunopharmacol. 2006;6:600-6).

The guidelines spell out the recommended dosing, duration of therapy per cycle, and time interval between cycles (J. Dtsch. Dermatol. Ges. 2009;7:806-12).

The guidelines recommend dosing IVIG for all of the indicated disorders, except toxic epidermal necrolysis (TEN), at 2 g/kg of body weight given over 2-5 consecutive days to avoid adverse reactions. It should initially be given every 4 weeks, gradually extending the interval between infusions to 6 weeks if the response is good. If there is no response af-

ter six cycles, the recommendation is to halt IVIG therapy. Treatment for longer than 12 months is rarely warranted.

For TEN, the recommendation is 3 g/kg given over 3 days. As in Kawasaki disease, this is a one-time therapy.

Practice guidelines unsupported by clinical evidence leave much to be desired, noted guideline panelist Dr. Lars French. The chief obstacle to conducting randomized trials of IVIG has been a financial one. “The companies sell every gram of IVIG they make and have no incentive to fund a trial,” said Dr. French, professor of dermatology at the University of Zurich.

However, the European regulatory agency recently announced that IVIG manufacturers who fund clinical trials establishing efficacy in autoimmune diseases can win an indication for their product, Dr. French said.

In the meantime, he added that he has no qualms in recommending early administration of IVIG in patients with confirmed TEN. “There are numerous case reports in which it has proven potentially lifesaving,” he said.

Dr. Enk disclosed receiving grant support from IVIG manufacturer Biotest Pharmaceuticals Corp., which sponsored the satellite symposium. Dr. French and Dr. Matteson reported having no relevant financial conflicts of interest. ■

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DR. FRENCH



Combination Therapy Is ‘Cheap,’ ‘Effective’ for Pemphigus

BY BRUCE JANCIN

BUDAPEST, HUNGARY — When the off-label treatment of severe pemphigus vulgaris using anti-tumor necrosis factor- α agents is prohibitively expensive or medically contraindicated, consider treating with the TNF- α -lowering combination of sulfasalazine plus pentoxifylline, which proved to be safe and effective in a double-blind, randomized trial.

“Etanercept and infliximab

are very expensive, especially in developing countries, as in my country, Egypt, and they have some hazards. So we looked for other anti-TNF- α agents with fewer side effects and less cost,” Dr. Rania Abdel Hay said at the annual congress of the European Society for Dermatological Research.

“Our rationale in using sulfasalazine [plus] pentoxifylline as adjuvant therapy for pemphigus vulgaris is that they are cheap [and] effective, and have no seri-

ous side effects. Our rationale for combining them is they have synergistic effects and different mechanisms of action, so a more potent effect,” explained Dr. Abdel Hay, a dermatologist at Cairo (Egypt) University.

She presented a randomized, double-blind, placebo-controlled, 8-week clinical trial involving 64 pemphigus vulgaris patients. They were assigned 2:1 to the university dermatology clinic’s standard regimen of prednisone plus cyclophosphamide, and then to either the oral sulfasalazine-plus-pentoxifylline combination or a placebo.

After 8 weeks, 86% of patients in the sulfasalazine-plus-pentoxifylline group were classified as having excellent clinical improvement, compared with 18% of controls. (An excellent response was defined as no new lesions and a complete healing of baseline lesions.)

In all, 5% of patients on sulfasalazine plus pentoxifylline, and 18% of controls, were rated as having a poor response,

with the persistence of old lesions as well as the arrival of 10 or more new lesions per week, Dr. Abdel Hay said.

The degree of clinical improvement correlated with a decline in serum TNF.

The mean baseline TNF level in the sulfasalazine-plus-pentoxifylline group was 73 pg/mL. It fell to 56 pg/mL after 2 weeks, 34 pg/mL after 4 weeks, 20 pg/mL after 6 weeks, and 16.8 pg/mL after 8 weeks. In contrast, the mean TNF level after 8 weeks of prednisone, cyclophosphamide, and double placebo was 37.6 pg/mL. The mean serum TNF level in five healthy control patients was 15.5 pg/mL, she said.

The core treatment regimen common to both treatment arms was a 14-day cycle consisting of 500 mg of prednisone and 500 mg of cyclophosphamide given intravenously on day 1, followed by 500 mg of prednisone intravenously on days 2-5, then 100 mg of oral cyclophosphamide on days 6 and

7. On days 8 and 9, patients took 100 mg of oral cyclophosphamide and 60 mg of oral prednisone. Days 10-14 involved taking 100 mg of oral cyclophosphamide.

This cycle was repeated until patients cleared. Then they received oral prednisone and cyclophosphamide as maintenance therapy.

Sulfasalazine was given as a single 400-mg sustained-release tablet three times daily. Pentoxifylline was dosed at 500 mg three times daily, Dr. Abdel Hay said. She added that another attractive feature of this generic drug is that it has an anti-inflammatory effect comparable with that of methotrexate.

Pentoxifylline, which also has an anti-inflammatory effect, decreases TNF production by boosting cyclic adenosine monophosphate. Both agents have relatively few drug interactions, she said.

Dr. Abdel Hay did not disclose having any relevant conflicts of interest. ■



PHOTOS COURTESY DR. RANIA ABDEL HAY

Sulfasalazine and pentoxifylline therapy is cheaper than anti-TNF- α therapy, and it has been found safe and effective.