JIA Guidelines Reflect Treatment Advances

BY AMY ROTHMAN SCHONFELD
FROM THE AMERICAN COLLEGE OF RHEUMATOLOGY AND EXPERT ANALYSIS

The American College of Rheumatology has issued its first guidelines for the treatment of juvenile idiopathic arthritis.

“Our goal was to provide evidence and consensus-based guidance that reflects the current state of the field and is useful to clinicians of all levels of experience with the treatment of JIA.”

The recommendations are important because the treatment of JIA has undergone major changes over the last decade with the introduction of biologic therapeutic agents,” Dr. Timothy G. Beukelman, lead author of the paper, said in an interview with RHEUMATOLOGY NEWS.

“The ACR says that the recommendations are not meant to dictate care, and it considers adherence to be voluntary.”

The guidelines are published in Arthritis Care and Research (2011;63:465-82).

Up until now, there have been no validated guidelines for the treatment of JIA. Recognizing this, in 2008, the ACR issued a formal request for proposals to develop recommendations. The recommendations were authored by a core expert panel of international pediatric rheumatology experts.

A separate task force panel that included internationally recognized pediatric rheumatology clinicians, a pediatric rheumatology nurse, a general pediatrcian, and a patient representative also provided input as the guidelines were being developed.

Dr. Thomas J.A. Lehman, professor of clinical pediatrics at Cornell University, New York, noted in an interview that: “While these new guidelines are useful in emphasizing the importance of promptly initiating appropriate disease management, they are all very well and good. But this body of knowledge and consensus is in rheumatology. In the outpatient setting, the outcomes of disease we treat are not something we can judge in 1, 5, or 10 years. The system is in rheumatology.”

Medicare physician fees should be increased by 1% in 2012, and an alternative must be found for the Sustainable Growth Rate formula, according to recommendations in the Medicare Payment Advisory Committee annual March report to Congress.

The recommendations of MedPAC are all very well and good. But this body of knowledge and consensus which answers to Congress, is due to be replaced by the Independent Payment Advisory Board (IPAB) as early as 2012 under the terms of the Affordable Care Act. The IPAB will set limits on Medicare spending and will be answerable to the President, noted Dr. Karen S. Kolba.

IPAB may undertake global payment reform of physicians’ fees for outpatient care, said Dr. Kolba, chair of the American College of Rheumatology’s Committee on Rheumatologic Care. It will be tricky to set up outpatient global fees. The model for global fees may be diagnosis-related groups, or DRGs, now used for inpatient services.

IPAB is due to replace MedPAC all too soon and may usher in an era of global outpatient fee reform.

When DRGs were in the offing, tertiary hospitals argued that the fees they were expected to accept did not reflect the fact that their patients were sicker and more difficult to treat than were those seen in community hospitals. So it is in rheumatology. “In the outpatient setting in rheumatology, the outcomes of disease we treat are not something we can judge in 1, 5, or 10 years. The system will never capture whether my treatment of a patient’s rheumatoid arthritis prevented the need for knee replacement. That will take 20 years,” said Dr.
Role of Methotrexate Debated

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modifying therapy for children with active juvenile idiopathic arthritis, they are flawed in their failure to recognize the many variations in the severity of the disease.

The recommendations are “as evidenced-based as possible,” and also to include expert opinion. They were developed after a systematic literature review that identified 244 pharmacotherapeutic studies, both controlled and uncontrolled. These studies were reviewed by the core expert panel, which then prepared a summary report of the scientific evidence. The core expert panel also prepared more than 1,500 clinical scenarios to evaluate the medications of interest, using a consensus approach to select five patients using all possible combinations of selected key clinical parameters, including JIA treatment group, disease activity, presence of features of poor prognosis, and current medications. By a formal group assessment process, the task force panel then made their recommendations, based on the published literature or expert opinion. However, there was insufficient evidence that was not available. While the current ILAR classification divides JIA into six distinct categories, these recommendations describe five JIA treatment groups: history of arthritis of five or more joints; active sacroiliac arthritis; systemic arthritis with systemic features and without active arthritis; and systemic arthritis with active arthritis and without systemic features. These alternate groups were chosen because currently children are not necessarily treated differently based upon JIA diagnosis alone, and therefore, none of these groupings were similar to any of the ILAR categories, for example psoriatic arthritis. Specific features for poor prognosis are described for each treatment group, as well as disease activity levels. For instance, the features of poor prognosis for group 1 of arthritis of five or more joints are anemia, fever, or more joints are satisfied at least one of the following: arthritis of the hip or cervical spine, positive rheumatoid factor or anti-CCP antibodies, or radiographic evidence of osteopenia or osteoporosis.

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• Bacterial, viral, and other infections due to opportunistic pathogens.

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MALIGNANCY
Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with TNF blockers, of which SIMPONI® is a member (see Warnings and Precautions).

INDICATIONS AND USAGE: Rheumatoid Arthritis SIMPONI® in combination with methotrexate is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis. Psoriatic Arthritis SIMPONI® alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis. Ankylosing Spondylitis SIMPONI® is indicated for the treatment of adult patients with active ankylosing spondylitis.

CONTRAINDICATIONS: None. Warnings and Precautions (See Warnings and Precautions).

INDICATIONS AND USAGE: Pediatric Rheumatology

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abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone, and the combination therapy, compared to the use of a TNF-blocker alone. The combination of TNF-blockers including SIMPONI® and astemizole is not recommended [see Drug Interactions]. Use with Antacids Concurrent administration of administration of an (oral) antacid and another TNF-blocker, was associated with a greater number of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of antacids with TNF-blockers, including SIMPONI® (see Drug Interactions). Hematologic Cytogenetic There have been post-marketing reports of pancycopenia, leukopenia, neutropenia, agranulocytosis, and thrombocytopenia in patients receiving golimumab. Although the incidence of severe cytopenias seen in the SIMPONI® clinical trials, caution should be exercised when used in patients with underlying bone marrow suppression or in patients with severe renal impairment. Vaccinations Patients treated with SIMPONI® may receive vaccinations, except for live vaccines. No data are available on the response to live vaccination or the risk of infection, or transmission of infection, from patients receiving SIMPONI®. In the Phase 3 P3a study, after pneumococcal vaccination, a similar proportion of patients (1%), received SIMPONI® and placebo experienced a serious adverse event. In the phase 3 study, response of at least 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine In both SIMPONI®-treated and placebo-treated patients, the proportions of patients with a ≥4 fold increase in antibody titers were similar in the treatment groups. Patients who were actively infected and hospitalized with patients not receiving MTX. The data suggest that SIMPONI does not suppress the human immune system to the extent that a patient cannot develop an infection. If clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, which are reflective of the conditions under which the drug was studied. Experience The safety data described below are based on 5 pooled, randomized, double- blind, controlled, 16-week Phase 3 trials (P3a, P3b, P3b2, P3c, and P3d) of SIMPONI® in patients with PsAr or AS. These 5 trials included 639 control-treated patients and 1595 SIMPONI®-treated patients including 1089 RA patients, 292 with PsA and 277 with AS. As the proportion of patients who discontinued treatment due to an adverse event (AE) for each treatment group that is greater than or equal to 5% is: Infections In controlled Phase 3 trials through Week 16 in RA, PsA and AS, infections were reported in 26% of SIMPONI®-treated patients compared to 19% of control-treated patients. Liver Enzyme Elevations There have been reports of severe hepatitis reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials through Week 16 in RA, PsA and AS for 2% of SIMPONI®-treated patients and 3% for placebo-treated patients. These patients did not appear to have a history of severe liver disease. Patients treated with SIMPONI® in the meantime have a trial week 16 were 3 (2%) patients with bilirubin ≥2 mg/dL and 1 (2%) patient with alanine amino transferase ≥3.0 IU/L. Patients treated with SIMPONI® had a post-baseline increase from basal of at least 2-fold increase in ALT elevation (≥2 ULN) occurring in 0.2% of control-treated patients and 0.7% of SIMPONI®-treated patients, and ALT elevation ≥5 ULN occurring in 0.1% of control-treated patients and 0.2% of SIMPONI®-treated patients. Since many of the patients in the Phase 3 trials were also taking medications that cause liver enzyme elevations (e.g. NSAIDs, MTX), the relationship between SIMPONI and liver enzyme elevations is not known. Antituberculosis The use of TNF-blockers has been associated with the formation of an anti- tuberculin purified protein derivative (PPD) reaction in patients previously exposed to tuberculosis. In controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, there was no association of SIMPONI® treatment and the development of newly positive anti-PPD antibodies. Injection Site Reactions Injection site reactions were reported in about 6% of patients treated with SIMPONI®. In controlled Phase 3 trials in patients with RA, PsA, and AS through Week 14, 1% of SIMPONI®-treated patients had nodules at the injection site. In patients with psoriasis, there have been reports of the use of TNF-blockers, including SIMPONI®. Cutaneous Reactions In clinical trials with TNF-blockers, including SIMPONI® use of any TNF-blocker, including SIMPONI®. Methotrexate and other biologic agents used in the treatment of JIA, specifically NSAIDs, intra-articular glucocorticoids injections, biologic DMARDs, biologic DMARDs, and systemic glucocorticoids for systemic arthri- tis. Methotrexate and other biologic agents used during pregnancy. For instance, for patients with arthritis of five or more joints, a patient on methotrexate should move on to a TNF-alpha inhibitor after 3 months if disease activity is low regardless of the presence of poor prog- nostic features. Dr. Lehman, who is also chief of the di- vision of pediatric rheumatology at the Hospital for Special Surgery in New York, noted, “It is very appropriate to ar- guge for the increased use of IL-1 inhib- itors, not only because of the disease activity.” However, there are several differ- ent diseases included in the other forms of juvenile idiopathic arthritis for many of which it is not appropriate to start with methotrexate. Indeed, in this era, one option is to delay therapy until after the right time for young children who could not have an adverse effect on disease activity and may suppress disease. Dr. Dr. Cron cited evidence showing the effectiveness of anakinra as a first-line disease-modifying therapy in 46 patients with JIA, preventing refractory arthritis in almost 90% of patients (Arthritis Rheum. 2011;63:545-51). In this series of case studies, use of anakinra reduced elevated sedimentation rates and ferritin levels, decreased the number of active joint counts, and significantly lowered the dose of concomitant ster- oid therapy. “It is the kind of therapy that kids appear to report it better with- in days or months with anakinra. It can be a wonderous drug for sick children with systemic JIA,” he added. Although it was not discussed in the recommendations, in his talk, Dr. Cron said he was encouraged by the current treatment of macropheage activa- tion syndrome (MAS) in systemic JIA (Rheumatology. 2011;50:417-9). Dr. Cron reported that he has used anakin- ra as initial therapy to treat two children with MAS, and he found dramatic re- ductions in ferritin levels and liver en- zymes within 2 days of initiation. Systemic JIA has a prevalence of about 1 in 10,000. It has multiple sys- temic manifestations, including a high fever (which follows a unique pattern: typically, a 103°F spike, a late-afternoon spike in 30% of patients at presenta- tion), rash, hepatosplenomegaly, lym- phadenopathy, pericarditis, pleural effu- sion, pulmonary vasculitis, and even CNS stroke or seizure. Early diagnosis and finding is asymp- tomatic of the jaw. According to Dr. Cron, up to 80% of children with all forms of arthritis, including systemic JIA, can have arthritis of the temporomandibul- lar joint (TMJ). “Kids often have a subtle finding that can be overlooked until significant erosion has occurred. However, early TMJ arthrograms can be detected with magnetic resonance imaging. Dr. Cron had no relevant financial disclosures. n