Update in Rheumatology: Evidence Published in 2013

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The articles featured in this rheumatology update highlight the theme of delivering high-value, cost-conscious care to our patients. The search strategy used an automated query of the Ovid MEDLINE database for calendar year 2013, using Medical Subject Headings terms; results were filtered for high-impact journals. The articles were scored independently by the authors for relevance and validity of the methods.

Included in this update are studies comparing traditional (and less expensive) methods of treating rheumatoid arthritis (RA) and osteoarthritis with more novel (and expensive) therapies; the former have proven to be effective. Furthermore, with an expanding population seeking access to care, early referral is essential to limiting long-term complications of rheumatoid arthritis, including cardiovascular disease. New models of care that leverage team-based approaches and choosing medical resources wisely may improve access, reduce costs, and be more effective at providing value over traditional physician-based models of care.

Osteoarthritis

Functional Outcomes With Surgery and Nonoperative Intervention Did Not Differ in Symptomatic Meniscal Tears With or Without Knee Osteoarthritis

Katz JN, Brophy RH, Chaisson CE, et al. Surgery versus physical therapy for a meniscal tear and osteoarthritis. N Engl J Med. 2013; 368:1675-84. [PMID: 23506518]

Sihvonen R, Paavola M, Malmivaara A, et al; Finnish Degenerative Meniscal Lesion Study (FIDELITY) Group. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med. 2013;369:2515-24 [PMID: 24369076]

Background: Meniscal tears and osteoarthritis are highly prevalent and frequently treated surgically with arthroscopic partial meniscectomy (APM). Prior trials have shown that arthroscopic treatment was not superior to sham procedures or to nonoperative management for osteoarthritis. However, evidence is inconclusive about whether APM versus nonoperative therapy for meniscal tear with or without knee osteoarthritis results in better functional outcomes.

Findings: In the multicenter randomized, controlled trial (RCT) by Katz and colleagues, patients with symptomatic meniscal tear and radiographic evidence of mild to moderate osteoarthritis were randomly assigned to undergo APM and postoperative physical therapy ($n = 174$) or to a standardized physical therapy regimen ($n = 177$). In the double-blind, multicenter RCT by Sihvonen and associates, patients with symptomatic meniscal tear and no radiographic evidence of osteoarthritis were randomly assigned to undergo APM ($n = 70$) or sham surgery ($n = 76$). In both studies, participants had the option to cross over to surgery at the discretion of the patient and surgeon.

At 6 and 12 months, respectively, the trials found no significant differences between the surgical and nonsurgical groups in measures of physical functioning (the primary end point) or pain scores. Adverse events did not differ significantly between groups in either trial.

Cautions: In Katz and colleagues' study, only 9.2% of the 14 430 patients screened were eligible to participate and only one quarter underwent randomization, suggesting potential limitations in terms of generalizability. Furthermore, the results may be difficult to interpret in light of substantial crossover to the surgical group (30%). In such trials, recruiting patients who have no preference for either surgery or physical therapy is challenging and may result in selection bias. Sihvonen and associates' study addressed blinding with sham surgery but did not include physical therapy as an intervention; instead, both groups received exercise programs.

Implications: Patients assigned to undergo APM or a nonoperative intervention did not differ significantly in the degree of improvement in functional status and pain after 6 and 12 months. For patients with knee symptoms and a meniscal tear with or without knee osteoarthritis on radiography, the data support an initial nonoperative strategy, with referral for APM if substantial improvements are not achieved. Longitudinal assessments to determine progression of underlying osteoarthritis in both groups are under way (1).

Rheumatoid Arthritis

Triple Therapy Is Not Inferior to Biologics for Active RA

O'Dell JR, Mikuls TR, Taylor TH, et al; CSP 551 RACAT Investigators. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369:307-318. [PMID: 23755969]

Background: The decision to add tumor necrosis factor inhibitors to methotrexate compared with using combinations of disease-modifying antirheumatic drugs (DMARDs) has dramatic economic consequences. Biologic agents are far more costly than combination DMARD therapy, but few trials have compared combinations of conventional

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DMARDs with a biologic agent in the context of methotrexate failure.

Findings: In this double-blind noninferiority trial, 353 patients with active RA despite methotrexate therapy were randomly assigned to receive triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) or etanercept plus methotrexate. Patients who had not responded to therapy at 24 weeks were switched to the other intervention group. The primary end point was improvement in the Disease Activity Score for 28 joint counts (DAS-28) at week 48.

Both groups had significant improvements over the course of the first 24 weeks ($P = 0.001$ compared with baseline values). In each group, 27% of participants required a switch in treatment at 24 weeks; these participants improved after switching ($P < 0.001$). In the intention-to-treat analysis, the change in the DAS-28 between baseline and 48 weeks was similar in the 2 groups (−2.1 with triple therapy and −2.3 with etanercept plus methotrexate; $P = 0.26$). Triple therapy was noninferior to etanercept plus methotrexate. The groups did not significantly differ in secondary outcomes, including radiographic progression, pain, health-related quality of life, or major adverse effects.

Cautions: The target sample size was not achieved because of funding; however, the 95% upper confidence limit of 0.41 for the difference in change in DAS-28 was below the margin of noninferiority of 0.6 ($P = 0.002$). The study sample included more men (many participants were from Veterans Affairs hospitals) than the general population of patients with RA, which affects generalizability. Methotrexate dosing was higher than in other trials, although this reflects real-world practice.

Of note, whereas the proportion of participants who achieved 20% improvement according to American College of Rheumatology criteria (ACR20) was nearly identical in the 2 groups, the percentage who achieved 70% improvement (ACR70) at 24 weeks was higher in the etanercept plus methotrexate group than the triple-therapy group. It is unclear whether a rapid response earlier in treatment translates into a longer-term benefit.

Implications: Managing patients first with triple therapy and switching to a biologic plus methotrexate in those who do not have an adequate response may be more cost-effective, without adversely affecting clinical outcomes. A recent study did not find a difference between biologics and triple therapy in time to return to work (2). Cost-effectiveness trials and long-term follow-up studies are needed to assess the durability of intermediate outcomes (such as disease activity) with patient-centered outcomes.

Fish Oil May Be an Effective Adjunctive Therapy in Recent-Onset RA

Proudman SM, James MJ, Spargo LD, et al. Fish oil in recent onset rheumatoid arthritis: a randomized, double-blind controlled trial within algorithm-based drug use. Ann Rheum Dis. 2013 Sep 30. [Epub ahead of print] [PMID: 24081439]

Background: Previous meta-analyses of RCTs have reported benefits of fish oil for patient-reported pain, morning stiffness, number of painful or tender joints, and reduction in use of nonsteroidal anti-inflammatory drugs. However, RCTs of adjunctive therapies, such as fish oil, have not been conducted for RA in conjunction with a treat-to-target, real-world practice. Use of a treatment algorithm for DMARDs that is responsive to disease activity and tolerability or toxicity, according to predefined rules, allows the extent of DMARD use to serve as an outcome measure. This is the first investigator-initiated, double-blind RCT of fish oil in recent-onset RA disease duration (<12 months), in which treatment outcomes were assessed in the context of contemporary best-practice therapy.

Findings: A total of 140 participants with early RA who were DMARD-naive were randomly assigned in a 2:1 ratio to receive fish oil (ω-3 fats: eicosapentaenoic acid and docosahexaenoic acid) at a high dose (5.5 g/d) or low dose (0.4 g/d). The low dose was given as a control rather than placebo because the taste of fish oil is difficult to mask.

All participants received methotrexate, sulfasalazine, and hydroxychloroquine, and doses were adjusted according to an algorithm that responded to disease activity and toxicity. The primary outcome was failure of triple DMARD therapy.

Triple DMARD therapy failed in fewer patients in the high-dose fish oil group than the low-dose group (hazard ratio, 0.24 [95% CI, 0.10 to 0.54]) after adjustment for smoking history, shared epitope, and baseline anti–cyclic citrullinated peptide levels. Rate of first ACR remission in disease activity was significantly greater in the high-dose fish oil group than the low-dose group (adjusted hazard ratio, 2.09 [CI, 1.02 to 4.30]). There were no differences between the groups in medication doses, disease activity scores, or adverse events.

Cautions: Adherence was lower in the high-dose group than the low-dose group; however, the intake of fish oil still exceeded the amount reported to exert anti-inflammatory effects.

Implications: Fish oil may be effective as adjunctive therapy in the context of modern treat-to-target drug management for recent-onset RA. If adjunctive therapy is effective in controlling RA disease activity, it may delay progression to biologic therapy. Findings will need to be replicated in the long term because the amount of fish oil necessary to reduce joint symptoms may be difficult for patients to tolerate.

Disease Factors in Early RA Are Associated With Differential Risks for Cardiovascular Events

Ajeganova S, Andersson ML, Frostegård J, et al. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. J Rheumatol. 2013;40:1958-66. [PMID: 23950188]

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Background: Rheumatoid arthritis is associated with an increased risk for cardiovascular disease (CVD), which is the leading cause of death. Traditional CVD risk factors, systemic inflammation, and RA therapies are associated with the development of CVD; however, it has been difficult to show which factors predict excess risk. Inception cohorts permit the study of patients during the first crucial years of intervention.

Findings: In the Better Anti-Rheumatic Pharmacotherapy inception cohort, persons with RA were evaluated from 1993 to 1999. Over a 10-year observational period, 177 CVD events and 151 deaths occurred. In persons aged 65 years or older who developed RA, factors associated with an increased risk for CVD included glucocorticoid exposure, whereas decreases in C-reactive protein level and erythrocyte sedimentation rate and methotrexate exposure reduced the risk. For persons younger than 65 years, a positive rheumatoid factor or anti–citrullinated peptide antibody titer, C-reactive protein level, and erythrocyte sedimentation rate contributed to excess risk. The hazard ratios were adjusted for age, sex, and traditional CVD risk factors. In both groups, elevated markers of inflammation and reduced functional status scores were associated with poorer survival.

Cautions: This was an observational study with no control group. The CVD outcomes were identified by using codes from the International Classification of Diseases, Ninth and Tenth Revisions and were not adjudicated.

Implications: Rheumatoid arthritis is associated with increased cardiovascular events. Targeted therapy by both primary care and rheumatologists for patients at higher risk, such as those with positive autoantibody titer and persistent systemic inflammation, may reduce CVD events.

Psoriatic Arthritis

Ustekinumab Is Effective in Psoriatic Arthritis

McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780-89 [PMID: 23769296]

Background: Ustekinumab is a fully human IgG monoclonal antibody that binds to the p40 subunit of interleukin-12 and -23 and is responsible for T-helper–17 inflammatory cell suppression. Ustekinumab is injected subcutaneously every 12 weeks and is highly effective in psoriasis.

Approximately 30% of patients with psoriasis will develop psoriatic arthritis, which is often associated with poor quality of life and increased morbidity and mortality. This study sought to evaluate the efficacy of ustekinumab for alleviating symptoms of psoriatic arthritis.

Findings: This multinational phase 3 RCT assigned 615 patients in a 1:1:1 ratio to receive either placebo or ustekinumab, 45 mg or 90 mg. During the trial, 50% of participants were receiving methotrexate and 75% were receiving nonsteroidal anti-inflammatory drugs.

At week 24, more ustekinumab recipients (42.4% in the 45-mg group and 49.5% in the 90-mg group) than placebo recipients (22.8%) achieved the primary end point of an ACR20 response ($P < 0.001$ for both comparisons). This response was maintained at week 52. Adverse events were similar between the groups, with upper respiratory infections most commonly reported.

Cautions: This was an industry-sponsored trial. Although the results were promising, the 24-week follow-up period was short. Larger studies with long-term follow-up are needed to better assess the safety profile, work-related outcomes, and cost-effectiveness of ustekinumab.

Implications: Ustekinumab effectively treats psoriasis and psoriatic arthritis. On the basis of these data, ustekinumab was approved by the U.S. Food and Drug Administration in 2013 for the treatment of psoriatic arthritis and serves as an alternative biologic treatment.

Alternative Approaches to Health Care Delivery

Patient Satisfaction Sustained With Nurse Visits for Inflammatory Arthritis

Koksvik HS, Hagen KB, Rødevand E, et al. Patient satisfaction with nursing consultations in a rheumatology outpatient clinic: a 21-month randomised controlled trial in patients with inflammatory arthritides. Ann Rheum Dis. 2013;72:836-43. [PMID: 23393144]

Background: The ACR recommends following patients with inflammatory arthritis every 3 months after initiation of DMARD therapy for response to treatment; this is known as a "treat-to-target" strategy. In the United States, shortages of rheumatology providers and clinic time are barriers to meeting these recommendations.

In Europe, clinical nurse specialists (CNSs) are trained to evaluate patients for therapy management with an emphasis on patient education. Midlevel providers may be a critical resource to help patients maintain low disease activity while enhancing satisfaction with patient care (3).

Findings: Patients with inflammatory arthritis who had high disease activity and had begun receiving a DMARD within 3 months of study entry were assessed by a rheumatologist and then randomly assigned to have 30-minute visits with a CNS ($n = 35$) or a physician ($n = 33$) every 3 months. The CNSs had open access to rheumatologists and provided education and counseling for patients in addition to usual care. The primary outcome was the Leeds Satisfaction Questionnaire (LSQ) score (range, 1 to 5).

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At 21 months, the LSQ score was significantly higher in the CNS group than the physician group (4.64 vs. 3.95; $P < 0.001$). The CNS group had improved LSQ scores in all subcategories by 21 months; in contrast, the physician group had reduced scores in "access to care" and "provision of information." Regarding secondary outcomes, DAS-28 improved from baseline in both groups, and there were no group differences at 21 months. Fatigue, quality of life, coping, and pain were similar between groups.

Cautions: This was a single-center, unblinded trial in Europe. Nurses had 10 years of clinical experience in rheumatology.

Implications: With the expected increase in the number of patients seeking care owing to implementation of the Patient Protection and Affordable Care Act, we must embrace alternative models of health care delivery to meet established standards of care for quality and effectiveness.

Mechanisms Identified to Reduce Delays in Access to Care for Rheumatology Patients

Villeneuve E, Nam JL, Bell MJ, et al. A systematic literature review of strategies promoting early referral and reducing delays in the diagnosis and management of inflammatory arthritis. Ann Rheum Dis. 2013;72:13-22. [PMID: 22532640]

Background: Treating patients with inflammatory arthritis early and aggressively has been shown to result in better long-term outcomes. In the United States, the Institute of Medicine has challenged providers to deliver quality care that includes both access and coordinated care. Studies from the Geisinger Health System have found cost savings and improved patient satisfaction with systems-based clinic redesign to facilitate access to rheumatologists (4).

In the United Kingdom, studies have shown that compared with a primary care setting, patients who were seen by rheumatologists received a diagnosis and were treated earlier and had better outcomes; in addition, management was more cost-effective. However, delays in referral to a rheumatologist are common in the United States.

Findings: This systematic literature review sought to determine the most effective strategies to reduce referral delays for patients with arthritis. After more than 8000 articles were screened, 47 were selected by using the patient, intervention, comparison, outcome (PICO) framework; the focus was on delays in identification of symptoms, diagnosis of disease, and initiation of therapy. To promote referrals to a rheumatologist, primary care education programs and patient questionnaires assisted in identification of patients with arthritis. For rheumatologists, reduction in the delay from referral to assessment came about with triage plus referral forms, early arthritis clinics, and rapid access services.

Cautions: The included studies were international, and implementation of strategies will need to be adapted to meet U.S. objectives.

Implications: Patient access to care is integral to the quality directives set forth by the Institute of Medicine and has been shown to be attainable in the United States (3). A coordinated effort will be needed by primary care and rheumatology to facilitate early recognition, early referral, and access to rheumatologists.

Choosing Wisely: Top 5 Tests Rheumatologists Should Question

Yazdany J, Schmajuk G, Robbins M, et al; American College of Rheumatology Core Membership Group. Choosing wisely: the American College of Rheumatology's top 5 list of things physician and patients should question. Arthritis Care Res (Hoboken). 2013; 65:329-39. [PMID: 23436818]

Background: The United States is focusing more attention on health care quality, value, and affordability. To that end, the American Board of Internal Medicine Foundation launched the Choosing Wisely campaign to promote open dialogue between physicians and patients regarding tests that may have low value or harmful consequences in patient care.

Findings: The ACR designated a task force to identify topics, engage U.S. rheumatologists, and perform the critical literature reviews to support the list. The preliminary list was constructed using the Delphi method and was then circulated to ACR members for voting. The common themes that were generated underwent a systematic literature review and were rated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. The final version was approved by a patient panel.

The top 5 list is as follows:

1. Do not test antinuclear antibody subserologies without a positive antinuclear antibody titer and clinical suspicion of immune-mediated disease (Grade 1C).

2. Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings (Grade 1A).

3. Do not perform magnetic resonance imaging of the peripheral joints to routinely monitor inflammatory arthritis (Grade 1B).

4. Do not prescribe biologic agents for RA before a trial of methotrexate (or other conventional nonbiologic DMARD) (Grade 1A).

5. Do not routinely repeat dual-energy x-ray absorptiometry scans more often than once every 2 years (Grade 1C).

Cautions: This list was derived from practicing rheumatologists; however, the precise estimates of the prevalence of these practices is unknown. The implications of these recommendations, namely cost savings and quality improvement, will need to be evaluated prospectively. The recommendations do not supplant clinical judgment.

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Implications: As health care reform broadens its scope, we must embrace efforts to improve quality and safety in order to deliver high-value, cost-conscious care.

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