

N-of-1 Trial of Low-dose Methotrexate and/or Prednisolone in Lieu of Anti-CCP, MRI, or Ultrasound, as First Option in Suspected Rheumatoid Arthritis?

Advances in therapy for rheumatoid arthritis (RA)[1,2] and recognition that the natural history of disease includes poor outcomes[3-5] have led to new efforts to establish a definitive diagnosis as early as possible after onset of symptoms[6-8]. That goal is complicated by at least 2 problems: First, no single pathognomonic test, such as blood pressure or serum cholesterol, is available to serve as a diagnostic gold standard[9]. Classification criteria for RA[10] have been developed for clinical trials and other research. However, the gold standard for diagnosis of RA (and most other rheumatic diseases) remains a physician's assignment. Second, about 75% of individuals identified as meeting classification criteria for RA in population-based studies have a self-limited process rather than a progressive disease[11]. Only 25% have evidence of rheumatoid factor (RF)[11], and many likely never consult a physician at all.

Recent reports from early arthritis clinics have confirmed the complexity of diagnosing early RA[12,13]. Most patients seen in these clinics have an "undifferentiated arthritis"[14], the outcome of which is far more favorable than in RA, with a natural remission rate of about 50% (apparently intermediate between 75% of patients who meet RA criteria in population-based cohorts and fewer than 10% of patients who meet these criteria in rheumatology clinical settings). Nonetheless, at least 25%–50% of patients with undifferentiated arthritis evolve into RA, and it is certainly desirable to recognize these patients as early as possible.

Over the last decade, several developments have improved the capacity to recognize early RA. Ultrasound and magnetic resonance imaging (MRI) indicate that significant inflammation may be present in joints that appear to be normal on physical examination[15-17]. Anti-cyclic citrullinated peptide (anti-CCP) antibodies identify patients with undifferentiated arthritis who have a significantly increased risk to meet American College of Rheumatology (ACR) classification criteria for RA at a later evaluation[18], some of whom have negative tests for RF. Therefore, it has been suggested that data from MRI, ultrasound, and anti-CCP antibodies might be widely used to establish an early definitive diagnosis of RA.

Anti-CCP, ultrasound, and MRI findings likely will further our understanding of the pathogenesis and course of RA, and emerging data from research centers will remain of considerable interest. However, standard clinical care outside of research settings is a different matter. Standard care of a patient for whom an anti-CCP, MRI, or ultrasound may appear indicated might involve the alternative strategy of an n-of-1 trial[19] of low dose methotrexate (MTX), and possibly low-dose prednisone (or prednisolone) over 30–180 days.

The n-of-1 trial principle has been developed for a clinical setting in which randomized controlled clinical trials might not apply or might be unavailable to treat an individual patient[19]. The goal of a treatment strategy defined by an n-of-1 trial is that a definite clinical answer is achieved with a high level of physician's confidence in the management plan. We propose that low-dose MTX and/or low-dose prednisone is associated with a high level of physician's confidence that it may provide greater benefit/risk and even more diagnostic information in patients with undifferentiated arthritis than an anti-CCP or imaging test.

The rationale for an immediate "n-of-1" trial in any patient with early undifferentiated arthritis is based on emerging evidence concerning the apparent benefit/risk of this approach. The efficacy of MTX is comparable to an anti-tumor necrosis factor (TNF) agent in most patients with early disease, although some patients respond more favorably to a combination of MTX and anti-TNF therapy, so that greater efficacy usually is seen in groups of patients who take anti-TNF compared to MTX only[20]. A recent randomized double-blind placebo controlled trial of patients with undifferentiated arthritis indicated that treatment with MTX for 1 year led to a clear reduction of joint damage and a lower proportion of patients who met ACR criteria for RA compared to treatment with placebo[21].

Weekly low-dose MTX is as well tolerated and safe as any therapy for a rheumatic disease, including all other DMARD. The likelihood of patients continuing MTX at 5 years was recognized to be 50% even in 1992, when

rheumatologists waited months to years before initiating disease modifying antirheumatic drugs (DMARD)[22,23]. In one recent study of patients treated between 1990 and 2002, 80% continued MTX for 5 years or longer; no discontinuations were seen because of laboratory abnormalities over this 12 year period[24], although patients were permitted 2 alcoholic drinks a day[24].

Many clinicians, particularly non-rheumatologists (but some rheumatologists as well), continue to regard the potential toxicity of weekly low-dose MTX as similar to that of daily high-dose MTX, as used in chemotherapy of neoplastic diseases. However, these 2 regimens have no more in common than the difference between, say, a glass of wine at dinner and a magnum of wine. The mechanism of weekly low-dose MTX is primarily antiinflammatory, while the mechanism of high-dose MTX is antimetabolic[25]. Since other DMARD such as hydroxychloroquine and sulfasalazine are likely to be replaced by MTX in more than 80% of patients within 2 years[22,23], why not begin with the agent that is most likely to provide longterm effectiveness? As noted, MTX does not provide adequate control of RA for some patients, who then require anti-TNF biological therapies. Why not establish this phenomenon early in disease?

In some respects, the search for a definitive diagnosis in a patient with possible RA is in part a holdover from an earlier period in which available DMARD, such as gold and penicillamine, had a great deal more toxicity, as well as lower efficacy in the majority of patients, compared to MTX. Rheumatologists wanted to be certain that they were treating a true inflammatory arthritis before initiating DMARD therapy. Toxicities such as nephritis or pancytopenia might appear suddenly, with severe and sometimes fatal consequences. By contrast, toxicities of low-dose weekly MTX (and prednisone) are rarely clinically unexpected. In almost all cases there is clinical warning to suggest reduction of the dose or discontinuation of MTX before "the bottom drops out," as was seen with earlier DMARD. The occasional toxicities of low-dose prednisone — bruising, skin thinning, and central nervous system changes — also become apparent clinically, and sudden disasters are not seen.

One consideration in all medical care is costs. An individual rheumatologist cannot reverse the problems of rising costs of medical care. At the same time, care today, unlike 30 years ago, is effectively being rationed; the concept of capitation, i.e., a fixed amount for a patient with a particular diagnosis, is increasingly applied regarding payment for diagnosis and treatment of specific diseases. If an increasing fraction of all costs for RA is directed to diagnostic studies, fewer resources will be available for therapies for patients or to support rheumatologists in prescribing these therapies, or to determine whether an anti-CCP test, MRI, or ultrasound is needed.

In many situations, laboratory tests may lack sensitivity for a definitive diagnosis (as is true for most clinical measures). For example, 50% of patients with recent-onset RA fulfilling the ACR classification criteria had negative tests for CCP[18], although treatment appeared to be required. Therapeutic decisions in many situations, such as a fever in a patient with systemic lupus erythematosus or vasculitis, may involve treatment with antibiotics in the absence of a definitive diagnosis. Even in standard non-urgent medical care, antibiotics, most of which have more adverse events than weekly low-dose MTX, may be prescribed, sometimes even over the telephone, as appropriate clinical care. Most antibiotics appear to be associated with greater toxicities than weekly low-dose MTX. Perhaps it is time to regard "possible" undifferentiated inflammatory arthritis as requiring urgent treatment with weekly low-dose MTX and possible low-dose prednisone < 5 mg/day.

This approach may lead to treatment of some individuals who may have fibromyalgia or a self-limited postinfectious polyarthritis. However, a strategy of "prevention" of damage, as has emerged for RA in recent years[26], will inevitably result in "overtreatment" for some patients. How many patients who are vaccinated for influenza, treated with an antibiotic, or even treated for hypertension or hyperlipidemia may not require these interventions?

We suggest that a 30 to 90 day n-of-1 trial of weekly low-dose MTX, and possibly 5 mg prednisone or less, be considered in any patient for whom a careful history and physical examination may indicate a pattern of joint distribution suggesting a possible inflammatory arthritis. This can be conducted as a formal trial, with alternating treatment and nontreatment periods of, say, 30 days each[19], or the patient may be instructed to continue treatment if there is a response. The most important principle is to prespecify a limited time span of, say, 1–6 months for use of the therapy[19], so that the treatment will not be continued indefinitely if no improvement is seen. In patients with undifferentiated arthritis, a response to a low-dose MTX and/or prednisone n-of-1 trial might be as likely as (or more likely than) a laboratory test or imaging procedure to identify a progressive inflammatory arthritis definitively, at a considerably lower cost than high-technology information. An n-of-1 trial of weekly low-dose MTX would appear to be a reasonable consideration for many, if not most, people with early undifferentiated inflammatory arthritis.

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