Unmet Needs in the Treatment of Rheumatoid Arthritis
By Jack Alan McCain Jr.

A review of recently published data
with a commentary for managed care decision makers
by Jonathan Kay, MD, FACP, FACR
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Rheumatoid arthritis (RA) imposes a considerable disease burden. Patients experience increased medical costs, comorbid conditions, and a widened mortality gap. Existing treatments are insufficient for the current clinical demand, which is expected to increase as the population ages.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder in which joints, usually those in the hands and feet, can become inflamed, swollen, painful, and stiff. Without appropriate treatment, the inflammation may become chronic and lead to irreversible destruction of bone and cartilage in the affected joints, as well as contribute to the development of clinically important comorbid conditions with attendant morbidity and mortality (Klareskog 2009).

The National Arthritis Data Workgroup, a consortium of experts in epidemiology, estimates that about 1.3 million U.S. adults (0.6 percent of the adult population) had RA in 2005 (Helmsick 2008), down from its previous estimate of 2.1 million (1 percent) for 1995 (Lawrence 1998). However, Helmsick notes that while these estimates can most likely be generalized to the Caucasian population, the ability to do so with other racial and ethnic populations is questionable (2008). Cohort studies conducted in Rochester, Minn., have found that, in a Caucasian population, the incidence of RA rises steadily from ages 35 to 44 up to ages 75 to 84 (from 33.7 to 119 per 100,000 residents), after which it declines precipitously (Gabriel 1999).

Since the 1960s, two trends in RA epidemiology have become evident: the incidence of RA has declined progressively, while the average age of persons with prevalent RA has risen (from 65.3 years in 1965 to 66.8 years in 1995), which points toward an increase in the disease burden associated with RA as the U.S. population ages (Helmsick 2008). Klareskog (2009) has suggested that criteria used for the past two decades (Table) are inadequate for addressing the disease burden of RA because by the time a physician detects rheumatoid nodules or radiographic erosion (criteria 5 and 7), the optimal time has passed for treatment initiation. These problematic criteria also are used in the American College of Rheumatology (ACR) decision tree for diagnosing RA (Arnett 1988). Moreover, other biomarkers have similar sensitivity but greater specificity than rheumatoid factor (criterion 6), notably antibodies to cyclic citrullinated peptides (ACCP), which defines two subsets of RA (ACCP positive and ACCP negative) (Klareskog 2008).

| TABLE |
| American College of Rheumatology criteria for diagnosis of rheumatoid arthritis |
| RA is defined by the presence of four or more of the following criteria; criteria 1 through 4 must have been present for 6 or more weeks |
| 1. Morning stiffness in and around joints lasting 1 or more hours before maximal improvement |
| 2. Physician-observed soft tissue swelling of three of more joint areas |
| 3. Swelling of one or more proximal interphalangeal, metacarpophalangeal, or wrist joint |
| 4. Symmetric swelling |
| 5. Subcutaneous rheumatoid nodules observed by a physician |
| 6. Presence of abnormal amounts of serum rheumatoid factor |
| 7. Radiographic erosions and/or bony decalcification localized in or adjacent to involved hand and/or wrist joints |

Source: Arnett 1988
patients with RA in 2005 were $11,109, nearly three times as high as the $4,488 in direct medical costs for matched controls (Figure). In the RA group, direct medical costs were evenly divided between charges related to RA and charges not related to RA, reflecting the prevalence of comorbid conditions in the RA population.

**Comorbid conditions.** Even before its clinical onset, patients with RA are at increased risk of coronary heart disease (CHD) (Maradit-Kremers 2005). This retrospective cohort study of 603 adults with RA and 603 age- and gender-matched adults without RA found that, prior to their ACR criteria-based RA diagnosis, the former group had a substantially higher risk of myocardial infarction (MI) resulting in hospitalization (Maradit-Kremers 2005). Moreover, as CHD manifests differently in RA, a higher risk of unrecognized MI and sudden cardiac death also was shown, along with a lower likelihood of angina symptoms (Maradit-Kremers 2005). RA patients also have been shown to possess traditional risk factors for cardiovascular disease (CVD) that are more weakly associated with CVD events (Gonzalez 2008). In this study of 1,206 patients, evenly split between those with and without RA, such risk factors as male gender, smoking, and a personal and family cardiac history were shown to impart a lower risk for CV events.

RA-associated fatigue is rarely a target of treatment and has been infrequently assessed (Kalyoncu 2009), but at least two studies have found fatigue to be common and intrusive. A study of 133 adults with longer duration of RA reports a high degree of fatigue that causes moderate distress, remains consistent during the course of a week, and affects discretionary and nondiscretionary activities of daily living (Belza 1993). In addition, Wolfe (1996) assessed 1,488 patients with RA and found fatigue to be a strong indicator of overall health status, along with work dysfunctionality.

Anemia of chronic disease also is common in RA patients, occurring in 40 to 49 percent of these individuals (Davis 1997, Peeters 1996). Furthermore, a study of 2,495 RA patients found anemia, particularly the presence of a low hemoglobin level at baseline, to be one of the independent contributors to disability and diminished physical function ($P < .001$) (Han 2007). A retrospective cohort study estimated the economic burden of anemia within six chronic diseases, and found that patients with the condition did indeed have increased health care costs (Ershler 2005).

**Mortality gap.** Between 1965 and 2005, mortality rates for patients with RA have remained relatively constant, at 2.4 and 2.5 per 100 person-years for women and men, respectively, while mortality rates for women and men in the general population declined from 1.0 and 1.2, respectively, in 1965 to 0.2 and 0.3 in 2000 (Gonzalez 2007). This widening mortality gap points out the need for a better understanding of the causes of this phenomenon so that appropriate interventions can be employed.

**Therapy for RA**

As no cure exists for RA, the goals of management are to prevent or control joint damage, prevent a loss of function, and decrease pain (ACR 2002). As such, the majority of patients with newly diagnosed RA should be given disease-modifying antirheumatic drugs (DMARDs) within 3 months of their diagnosis (ACR 2002). For patients with disease in which inflammation is not controlled, biologic DMARDs (also known as biologic response modifiers) can be used against specific molecular targets within the immune system that promote inflammation and joint and tissue damage.
Conclusion
Providing the right drug for the right patient at the right time is the goal of all pharmacotherapy, but numerous unmet needs continue to make it difficult to do so for patients with RA. Although there have been great strides in treatment, the evidence seems to support a need for more advanced therapies.

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**About the Author**

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