



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

RHEUMATOID ARTHRITIS (RA)

NATURAL HISTORY AND OUTCOME

Disease Definition

Rheumatoid arthritis (RA) is a symmetric, peripheral polyarthritis of unknown etiology, mainly seen in adults age 35 or older. The disease usually presents with the abrupt onset of polyarticular joint pain and stiffness, particularly in the wrists, knees, and MCP joints of the hands. Any large joint may be involved.

Overview of Pain and Pathogenesis

Once the pathogenetic process is initiated, if it is untreated or is unresponsive to therapy, patients typically develop persistent swollen, painful joint capsules and frank joint effusions. Exquisitely tender and painful joints accompanied by the accumulation of inflammatory joint fluid significantly limits the ability of afflicted individuals to perform the activities of daily living. In severe active disease the joint effusions include massive lymphocytic and mononuclear cell infiltrates that stimulate the formation of a pathological stroma containing activated and proliferating fibroblasts. This pathological structure leads to joint space destruction and to the erosion of articular and subchondral bone. Unchecked joint space destruction and peri-tendous inflammation inevitably leads to marked mechanical dysfunction, deformity, and permanent destruction of joints.

Rheumatoid arthritis represents a disease continuum, having features in common with other so-called connective tissue diseases. RA has a spectrum of clinical expression, both in terms of populations that become symptomatic and within affected patients. Variations are seen in the age of onset, persistence, and severity of disease activity. At initial presentation it is not possible to predict the course and outcome of disease, particularly the time to progression to structural damage in joints. This variation in part reflects individual factors (genetic and environmental) that influence the disease process, including response to therapeutic interventions.

Some population-based natural history studies suggest that individual patients may experience periods of

spontaneous exacerbation followed by quiescence. These periods are characterized by an increase or decrease in symptoms, and may be modulated by the positive effects of drug therapy and exacerbated by withdrawal of therapy. Therapeutic goals include preservation of joint mobility, reduction of joint pain, and minimizing side effects of therapy.

Drug therapy is initiated in patients with probable RA based on the degree of disease activity. The goal of early therapy is to preserve mobility and prevent loss of joint function. Long-term functional outcome for patients depends on avoidance of irreversible structural damage to tendons and joints. The degree of damage is closely linked to cellular inflammatory processes, which are not directly measurable in the clinical setting.

However, clinical assessment plays a major role in disease management. Specialist rheumatologists base treatment decisions on global assessments of disease activity. These assessments include a total active joint count, joint tenderness, and range of motion; the characteristic radiographic signs of bone erosion associated with bone turnover and repair appear only after the disease is well-established. In one study, even with disease-modifying anti-rheumatic drugs (DMARD), only 25% met criteria for remission after three years of continuous treatment, and 20% after five years of DMARD (PJW Venables and RN Maini, Up To Date v.13.3).

The economic and social impact of RA has been studied in population-based assessments of disease prevalence. These studies, involving thousands of patients, do not distinguish between the three groups of patients that constitute the prevalence population: recent onset, established, and advanced.

Strictly speaking, patients are stratified into new onset (often reported as incidence), and a larger group, the so-called prevalence population containing two sub-groups: those with active erosive disease and patients with advanced end-stage RA that often have serious extra-articular tissue damage in the lungs and other organs.

- Recent-onset disease — Patients with early disease meet American College of Rheumatology (ACR) criteria for the diagnosis and classification of RA and have had evidence of active disease for a period of not more than three months.
- Established or persistent disease — Established RA is characterized by active, well-defined disease for at least six to 12 months. Significant and irreversible damage may be observed at this stage, leading to functional disability.
- Advanced end-stage disease — Patients with end-stage RA manifest significant destruction of previously involved joints and other affected organs

but may have little or no evidence of ongoing inflammation. The derangements of normal joint architecture are often the cause of fixed functional disability in the setting of limited active joint inflammation.

CLINICAL SUBSETS RELATED TO DISEASE ACTIVITY

In RA, cellular infiltration, particularly by lymphocytes, leads to peri-articular inflammation and damage to connective tissue structures in and around the joint capsule, including tendon inflammation, which often results in serious functional disability. This begins early in the course of RA. The longer active disease persists, the less likely the patient is to respond to current therapies.

Disease activity can be determined for the purpose of evaluating the efficacy of therapy. There are three distinct groups of patients with early RA: *mild, moderate, and severe.*

Early, Mildly Active RA

Patients with early RA have symptoms and or findings of synovitis which have persisted for three months or less and meet ACR criteria for RA.

Patients with mildly active disease typically have most of the following clinical features:

- Arthralgias and morning stiffness
- Elevation in the erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) concentration
- At least three simultaneously inflamed joints
- No extra-articular disease
- No evidence of erosions or cartilage loss on plain radiographs
- No significant impairment of physical function.

Pharmacologic therapy for early, mildly active RA is evolving. Current interventions include use of non-steroidal anti-inflammatory drugs (NSAID), single DMARDs or combinations of DMARDs. Drugs in this class include azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold salts (Ridaura, Solganal, Aurolate, Myochrysine), hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate (Rheumatrex), penicillamine (Cuprimine), and sulfasalazine (Azulfidine). The role of anti-cytokine therapies (e.g., anti-tumor necrosis factor alpha agents) in patients with mild disease is uncertain.

Appropriate initial therapy of patients with mild disease consists of an NSAID at full therapeutic dose. Most physicians and patients prefer initiating therapy with an

NSAID rather than a salicylate, particularly since fewer tablets are required each day. However, NSAIDs do not prevent the development of erosive disease in those with continued disease activity. Thus, in the presence of signs of persistent synovitis (e.g., swollen joints, tender joints, or elevated acute phase response [ESR or CRP]), it is recommended that one or more DMARDs be added to the pharmacologic regimen within three months of continued symptoms and signs of disease.

Systemic glucocorticoids (e.g., oral prednisone or prednisolone) are used sparingly in patients with early mild RA. In contrast, intra-articular injections of long-acting glucocorticoids (e.g., triamcinolone hexacetonide) are used to reduce synovitis in particular joints that are more inflamed than others.

For patients with mildly active RA, use of DMARDs that have a relatively small risk of serious adverse effects is preferred. Thus the antimalarial drug hydroxychloroquine and sulfasalazine either individually or in combination are often used. An alternative to hydroxychloroquine and sulfasalazine include minocycline, which has benefit in some patients with early RA, probably through a weak inhibition of metalloproteinase activity. Combination DMARD therapy is superior to monotherapy in reducing the number of days of sick leave and overall work disability over a five-year period; a useful combination is sulfasalazine (500 mg to 1000 mg twice daily), methotrexate, (7.5 mg to 15 mg as a single weekly dose), hydroxychloroquine (300 mg per day), and prednisolone (≤ 7.5 mg per day).

Early, Moderately Active RA

To be classified as having moderately active disease, the patient should have some combination of the following clinical features:

- Between six and 20 inflamed joints
- Absence of extra-articular disease (most commonly)
- Elevated ESR or serum CRP concentration
- Positive rheumatoid factor or presence in serum of anti-cyclic citrullinated peptide (anti-CCP) antibodies
- Evidence of inflammation on plain film radiography, such as findings of osteopenia and periarticular swelling
- No erosions observed; however, a more sensitive modality such as ultrasonography or magnetic resonance imaging (MRI) may detect erosions of bone or cartilage destruction.

This constellation of findings places a patient at greater risk of developing joint damage and disability. Patients presenting with moderately active, previously untreated

(or only administered an NSAID) disease should receive DMARD therapy in addition to an NSAID. In the absence of contraindications to its use, methotrexate is recommended as the initial DMARD for patients with moderately active, early RA. Among those with moderate disease, anti-TNF therapy is currently recommended as an "add-on" to methotrexate therapy in patients with persistent disease activity despite adequate exposure to this DMARD. Oral glucocorticoids are also frequently added at a higher dose for a short period to the treatment regimen of the sicker patient to minimize disease activity while awaiting a clinical response to a DMARD.

Early, Severely Active RA

Early, severely active RA is defined as the presence of disease for three months or less with clinical features that suggest a disease course that includes progressive joint damage without effective therapy. Its features are:

- More than 20 persistently inflamed joints
- Rapidly declining functional capacity
- Elevated levels of ESR or CRP
- Anemia of chronic disease
- Hypoalbuminemia
- Positive rheumatoid factor test (often in high titer) or presence in serum of anti-cyclic citrullinated peptide (anti-CCP) antibodies
- Extra-articular disease manifestations (e.g., rheumatoid nodules, interstitial lung disease, or vasculitis).

Symptomatic treatment with NSAIDs is recommended unless there are contraindications such as a history of prior gastroduodenal damage or gastrointestinal bleeding due to these agents, renal disease, or heart failure.

DMARDs are recommended for all patients with early, severely active RA, consisting of a methotrexate-based combination. Alternatives to methotrexate-based combinations include the use of a combination of hydroxychloroquine and sulfasalazine, or use of single agents such as leflunomide, anticytokine therapies (e.g., anti-TNF therapy, or anakinra).

Adjunctive therapies include simple analgesics (e.g., acetaminophen), oral glucocorticoids, and intra-articular glucocorticoid.

TARGET DISEASE POPULATION DEFINES MARKET OPPORTUNITY

Clinical trial results demonstrate that currently approved and available DMARDs and anticytokine agents can

control synovitis about a quarter to one-half of severely active RA patients. In some patients DMARDs may slow, or even stop, radiographic progression. These findings support an early aggressive approach to treatment. Interventions that are effective in preventing joint damage may be most effective in improving function when introduced as early as possible. There is a clear unmet need for earlier interventions that can effectively halt the disabling joint tenderness and arrest the waxing disease process at an early stage. Currently no therapy is effective in controlling pain and inflammation in the early active stage of the disease. Agents that could disrupt the pathogenetic cycle and improve mobility while also having the potential to alter the course of the illness would have a revolutionary impact on the cost, quality, and outcome of disease.

Table 1. Early RA Population

<i>Total U.S. Population</i>	<i>Female Population</i>	<i>Females Over 55</i>
281,421,906	143,368,343	approx. 33 million
<i>5% of Females Over 55</i>	<i>Females Over 20</i>	<i>40/100,000 Annual Incidence</i>
1.6-1.7 million	approx. 100 million	40,000 new cases per year

DISEASE EXPRESSION AND AFFECTED POPULATION

Rheumatoid arthritis affects women 2.5 to three times as often as men. The annual incidence of RA has been reported to be between 30 and 70 per 100,000 population, and it may affect any age group from children to the elderly. The disease prevalence is about 1% in North American Caucasians, but varies between 0.1% (in rural Africans) and to 5% of all adults (in Pima and Chippewa Indians).

Although RA may present at any age, most commonly patients are first affected in the third to sixth decades. The peak onset is between the ages of 30 and 55 and, because of the consistently higher rates in females, the prevalence of RA in females over 65 years is up to 5%¹. Others report a 5% incidence after age 55². In the U.K., between 1990 and 1991, the annual incidence rate was estimated to be 36/100,000 for women and 14/100,000 for men. RA was rare in men under 45 years of age. The incidence in men rose steeply with age. The

¹ Rheumatoid arthritis. Spector TD. *Rheum Dis Clin North Am.* 1990 Aug; 16(3):513-37

² Alan K. Matsumoto, M.D., Johns Hopkins, *Arthritis*

incidence in women rose up to age 45 years, reached a plateau at age 75, and fell in the very elderly³.

Table 2. Disease Demographics of RA in the U.S.

(estimated prevalence and incidence, by age group, from different U.S. and U.K. studies)

Age in Years:	15-44	45-54	55-64	75-79	Total
Females					
<i>U.S. Prevalence (n)</i>	171,945	843,952	1,048,234	1,027,269	3,091,400
<i>U.S. Prevalence (%)</i>	0.3%	4.4%	8.3%	23.5%	
<i>Incidence (n)</i>	22,926	57,542	44,203	13,114	137,785
<i>Incidence (per 100,000/yr)</i>	40	300	350	300	
Males					
<i>U.S. Prevalence (n)</i>	60,237	271,293	322,188	238,482	892,200
<i>U.S. Prevalence (%)</i>	0.1%	1.47%	2.77%	7.83%	
<i>Incidence (n)</i>	12,048	18,497	20,379	3,866	54,790
<i>Incidence (per 100,000/yr)</i>	20	100	175	127	
Combined Population					
<i>Prevalence (n)</i>	232,182	1,115,244	1,370,422	1,265,751	3,983,599
<i>Prevalence (%)</i>	0.2%	2.96%	5.65%	17.07%	
<i>Incidence (n)</i>	34,974	76,039	64,582	16,981	192,575
<i>Incidence (per 100,000/yr)</i>	30	202	266	229	

Sources: U.S. Census Data, 2000; U.K. RGCP Mortality Statistics from General Practice – 4th National Study (1991-1992); U.S. National Health Survey, 1960-62.

³ *Br J Rheumatol.* 1994 Aug;33(8):735-9