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# Benefit/risk of therapies for rheumatoid arthritis: Underestimation of the "side effects" or risks of RA leads to underestimation of the benefit/risk of therapies

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## ABSTRACT

*Most physicians are familiar with the side effects or risks of drugs used to treat rheumatoid arthritis (RA), but relatively less familiar with the "side effects" or risks associated with RA itself. RA is not thought to have the same potential severity as a cardiovascular or neoplastic disease by most physicians, the public, or even some rheumatologists, although relative rates of predicted mortality in some patients with RA are in the range of some people with coronary artery disease or Hodgkin's disease.*

*Many reasons may be identified to explain why the risks of RA have been underestimated: RA does not lead to acute life-threatening situations; population-based data have suggested that most people who meet criteria for RA have a mild or self-limited process; acute attributed causes of death in people with RA are superficially similar to those in the general population; clinical trials have suggested many therapies that are efficacious over a period of 3-12 months; few long-term longitudinal studies were performed prior to the 1980s; medical recommendations made during the 1950s-1980s suggested that simple therapies were adequate for most patients; and quantitative information concerning patient status is generally not included in standard rheumatology care.*

*As more information has emerged concerning severe long-term outcomes in the "natural history" of RA (as treated prior to the 1990s), new strategies of aggressive intervention have been developed. Furthermore, basic research has led to new therapies. It appears that the benefit/risk ratio of therapies for RA has increased substantially over the last two decades, and the outlook for patients with RA is much better at this time than in previous years.*

## Introduction

Analysis of the benefit/risk of therapies for rheumatoid arthritis (RA) has undergone a considerable change over the last two decades. A prerequisite for these changes has come from a more accurate knowledge of the risks in the natural history of RA than was available prior to the mid-1980s. At that time, the perception of RA was "in the majority of instances a disease with a good prognosis" (1) which "the majority of patients can control... with well-accepted, conservative regimens" (2). However, the natural history of risks of RA is now recognized to include severe long-term outcomes, including radiographic progression (3-8), declines in functional status (9-11), work disability (9,12-14), and premature mortality (15-18).

The benefit/risk of the traditional disease modifying anti-rheumatic drugs (DMARDs) for RA, primarily gold and penicillamine, during the 1970s and 1980s was relatively low, with a high level of toxicity, so that 50% of treatment courses were discontinued within 2 years and 80% by 5 years (19,20). At this time new therapies, notably methotrexate (21-23), cyclosporine A (24) and leflunomide (25,26); biologic agents to inhibit tumor necrosis factor alpha (TNF $\alpha$ ), including etanercept (27,28), infliximab (29,30), and adalimumab (31,32); and the interleukin-1 receptor antagonist anakinra (33,34), are available. These therapies appear to have far greater long-term effectiveness, with risks in the same range as or possibly less than traditional DMARDs. Therefore the "pyramid" strategy, in which physicians sought to avoid the introduction of DMARDs that were recognized to have high toxicities for a disease that was thought to have generally good outcomes, has been overthrown (35-42). The benefit/risk ratio of therapies for RA is viewed as being considerably more

**Table I.** Some side effects of drugs used to treat rheumatoid arthritis (RA)

NSAIDs	GI, renal, CNS, others
Hydroxychloroquine	Retinal, others
Gold salts	Hematologic, renal, others
Penicillamine	Hematologic, GI, others
Methotrexate	Hematologic, hepatic, others
Azathioprine	Hematologic, GI, others
Cyclophosphamide	Hematologic, bladder, others
Cyclosporine	Hypertension, renal, others
Corticosteroids	Osteopenia, diabetes, others
Leflunomide	Hepatic, teratogenic, others
Biological agents	Tuberculosis, ? lymphoma, others

favorable at this time than two decades ago, with great benefits and acceptable risks that support an aggressive approach toward remission (43-47).

Nonetheless, at this time most medical students, trainees, and practicing physicians can enumerate in great detail the side effects of drugs used to treat RA (Table I), but have limited knowledge of the "side effects" or risks of morbidity and premature mortality associated with this disease (Table II) (48). Patients who receive prescriptions for anti-rheumatic drugs are given extensive warnings concerning the risks associated with their drugs, with little or no information about the risks of not taking the drug, specifically the risks of RA (or how both the drug and disease risks may be substantially reduced). Many non-rheumatologist physicians, and even some rheumatologists, regard anti-rheumatic drugs as having lower benefit/risk than many antibiotics, statins, anti-hypertensives, and other drugs, which actually are more likely to be poorly tolerated and to cause adverse events than anti-rheumatic drugs.

This essay presents a summary of the natural history of the risks of RA and evidence that this natural history may be altered substantially by currently available therapies. In view of the persistence of the traditional underestimation of the risks at this time, we also examine briefly how the risks of RA came to be underestimated in earlier decades.

### The risks or "side effects" of undertreated rheumatoid arthritis

It is now recognized that the risks or "side effects" for individuals who meet

the criteria for RA over more than one year involve a progressive disease (Table II), with frequent radiographic damage in the first 2 years of disease and radiographic progression (3-8), declines in functional status (9-11), work disability (9, 12-14), and premature mortality (15-18). At the present time, these risks are recognized to be favorably affected by an aggressive approach to induce remission, availability of new therapies, as well as possible secular changes in the severity of the disease. These phenomena are briefly summarized below.

### Radiographic progression

It was observed as early as 1966 (3) that radiographic changes could be seen in 86% of patients with RA of less than 5 years' duration, and in 1977 that 69% of patients had radiographic erosions within the first 3 years of disease, including 31% by 12 months and 64% by 24 months (4). It is now accepted that most patients with untreated RA have radiographic damage within the first 2 years of disease (5), although radiographic malalignment is unusual before 5 years of disease (6). Radiographic change is often detectable in many patients at presentation. Traditionally, these changes indicated irreversible end organ damage which could not be improved by medical treatment (49, 50).

It is now recognized that radiographic progression can be slowed considerably by the aggressive use of various therapies, including methotrexate and the new anti-TNF agents (51-53), as reviewed in this supplement by Strand (54).

Patients have less radiographic progression than in previous years as a result

**Table II.** Some severe 'side effects' of rheumatoid arthritis.

Joint destruction – radiographic damage
Declines in functional status
Work disability
Costs
Comorbid disease
Increased mortality rates

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of effective DMARD therapy (55). Healing phenomena are now recognized in some patients (52, 56, 57), as reviewed in this supplement by Rau (56). Nonetheless, radiographic progression over 5-10 years remains common in many patients with RA, despite improvement in the joint counts, functional status and laboratory tests.

### Declines in physical function

Declines in physical function have been reported in most patients with RA monitored over periods of 5 years or longer (9, 10, 58-62). In 75 patients monitored over 9 years between 1973 and 1982, who completed the same questionnaire at baseline and 9 years later (9), a decline in physical function (or death) was seen in almost all patients, documented according to questionnaires and physical measures of functional status (63). Long-term improvement was seen in fewer than 10% of patients. Morning stiffness was improved in many patients 9 years after baseline, suggesting that the markers of inflammatory activity may improve while damage occurs over time (64), as manifested by declines in functional capacity.

It was recognized in 1990 that a cohort of patients, most of whom were treated with methotrexate, had unchanged scores over 5 years on a modified health assessment questionnaire (MHAQ) (65), indicating the stability of physical function. Recent data suggest that the patients seen in the year 2000 who had been treated aggressively showed mean MHAQ levels in the range of 0.5 (66) compared to mean scores in the range of 1.0 seen 15 years earlier (67, 68).

Therefore, the physical function of patients appears to be improved by aggressive use of therapies for RA.

#### *Work disability*

Work disability has been observed historically in more than 60% of patients with RA seen in clinical settings who were younger than age 65 and who had been working at the onset of disease (9, 12, 14, 69, 70). These trends toward frequent work disability were also recorded in analyses of the entire U.S. population, in which more than 50% of individuals with symmetric polyarthritis, a surrogate for RA (13), were work disabled. The earnings of men and women with symmetric polyarthritis were only about 50% and 25%, respectively, of the earnings of individuals who did not have arthritis. Therefore, work disability in people with symmetric polyarthritis did not appear limited to patients seen at rheumatology referral centers.

Work disability remains an important problem in recent reports concerning patients with RA. A relatively high level of work disability is seen even in early RA in Europe (71, 72), which may in part reflect different social policies concerning work disability in the United States and Europe. However, recent analyses of the Finnish Rheumatoid Arthritis Combination Therapy Trial (FinRACo) indicated that work disability rates were significantly lower in patients who had received combination methotrexate, sulfasalazine, hydroxychloroquine plus prednisolone versus single DMARD therapy with or without prednisone (73). Furthermore, if inflammation was controlled to a status of remission at 6 months, after 5 years no patient was receiving work disability payments. In contrast, 22% of patients who had ACR 20 or 50 responses, and 54% of those who did not have ACR 20 responses, were receiving work disability payments (74). In a recent series of patients with early RA from the United States, work disability at 4 years was only 12% (75), considerably lower than in earlier series and in Europe at this time. Reduction in the rates of work disability would be a major advance in terms of the benefit/risk of therapies for RA (76).

#### *Premature mortality*

Premature mortality has been observed in all series of patients with RA in clinical settings over 10 years or more prior to 1990 (16-18, 60, 77-81). Mortality in RA is predicted by a number of measures indicating more severe clinical status, including poor functional status, involvement of more joints, comorbid cardiovascular disease, extra-articular disease, walking time, button test, grip strength, as well as higher age, and lower level of formal education (17, 82-84). Therefore, mortality is predicted by more severe disease, as in other chronic diseases, rather than being a random occurrence or a result of drug toxicity.

As noted, drug toxicity remains an important consideration in the treatment of patients, although the benefit/risk of therapies for RA is high. Nonetheless, the risks of drug toxicity in RA continue to be overestimated while the risks of severe disease have been underestimated (48). It appears that fewer than 0.5% of deaths in RA can be attributable directly to drug toxicities (85). This proportion is likely to be even lower at this time, with the decreasing use of gold and penicillamine.

In certain patients, RA may progress with a prognosis of 50% survival over the next 5 years, comparable to that of patients who have severe three-vessel coronary artery disease or Stage IV Hodgkin's disease (15, 38). Patients with RA who had more than 30 involved joints or poor functional status in terms of their activities of daily living showed subsequent 5-year survival rates of 40-50%, in the range of patients with three-vessel coronary artery disease seen at the Cleveland Clinic prior to widespread coronary bypass surgery (86) or Stage IV Hodgkin's disease seen at Stanford University prior to widespread chemotherapy (87). A smaller proportion of patients with RA were in the poorest prognostic categories compared to patients with cardiovascular or neoplastic diseases, and most patients with coronary artery disease or Hodgkin's disease were studied earlier in their course than patients with RA. Nonetheless, clinicians recognize that certain patients with RA experience long-term health problems that are as

severe as those in patients with cardiovascular or neoplastic diseases.

The relative risk of death over the subsequent 15 years for patients with a high number of involved joints and poor physical function on a patient questionnaire was 3-fold higher for those above versus those below the median level for these variables (88). These 3-fold relative risks were comparable to the relative risks of death over 12 years for individuals in the highest versus the lowest quintile for systolic and diastolic blood pressure, cholesterol, as well as smoking, in a large study of cardiovascular disease, the Multiple Risk Factor Intervention Trial (MR-FIT) (89). These data are not directly comparable, as the RA study involved patients while those in the cardiovascular study involved normal individuals. Therefore, the mortality estimates in RA are likely to be under- rather than overestimates, since the comparator group for those at highest risk did not consist of normal individuals, but those with milder disease. Again, this information is not widely known by the rheumatology community, much less the general medical community and public.

In recent years, some improvement in the survival of patients with RA has been seen. Several observers have reported similar mortality rates in the general population and in patients with RA (90, 91), although these observations appear to be due in part to patient selection criteria and to the fact that observations were made over a period of 5 or 10 years, rather than 15 or 20 years (92). Indeed, one recent survey suggested that higher mortality rates are seen in RA even in the community (93). However, two major reports indicate that a response to therapy with methotrexate appears to result in lower mortality rates (22, 23). This encouraging development remains to be further explored at other treatment centers.

#### **Why have risks of RA been underestimated?**

The above data suggest a favorable benefit/risk for therapies in RA, with a relatively urgent need for intervention in RA – which may be considered a type of "medical emergency" (43, 94-



96). Therefore, it appears important to analyze why RA remains underestimated by the general public and health professionals. Several possible explanations are discussed below (Table III).

*RA does not lead to acute life-threatening situations*

Although the long-term consequences of RA may be as severe as those of hypertension and diabetes (47), there is no parallel in RA for the occurrence of acute events directly "due to RA", such as hypertensive crisis, stroke or diabetic ketoacidosis, in which an obvious acutely life-threatening situation requires urgent treatment. Occasionally, rheumatoid vasculitis or scleromalacia perforans demands urgent intervention, but the concept of "RA as a medical emergency" (43,94) has been difficult to promote, even though 15-20 year outcomes may be as severe in RA as in hypertension or diabetes.

The current approach to "tight control" for hypertension and diabetes, two chronic diseases with many parallels to RA (47), resulted in part from recognition that control of the dysregulation seen in these chronic diseases resulted not only in improved clinical measures, but also in changes in the long-term disability and survival of the patient (97, 98). Reports of improvement in mortality outcomes (22,23) appear to be a first step toward this objective. Some investigators have suggested that work disability may represent an urgent matter (47, 99), and certainly the economic consequences of RA may present substantial problems quite early in the disease (100). However, the absence of apparent acute life threatening events has led to difficulty in promoting the concept of RA as a medical emergency. Most physicians and the general public regard internal organs as more "vital" than the joints, e.g., an intact knee may appear less important to a gastroenterologist than a few hepatic cells to a gastroenterologist or a few glomeruli to a nephrologist. In the osteoporosis literature, it is inferred that a small reduction in bone densitometry with glucocorticoids is invariably undesirable, even though glucocorticoids are associated with disease modification in many pa-

tients with RA (101). Clearly, any degree of osteopenia is undesirable, but the possible benefit of preventing or reducing joint destruction may render a small decrement in bone density acceptable, although this is rarely taken into consideration. A greater awareness of the risks of RA exists at this time compared to perhaps 20 years ago, but an accurate assessment of the benefit/risk of therapies remains affected by a general underestimation of the severity of RA.

*Population-based studies suggest that most people who meet criteria for RA have a mild or self-limited process*

One reason for the traditional underestimation of RA may be traced back to observations made during population studies conducted during the 1960s on subjects who met the criteria for RA in general populations. Two such classic studies from Tecumseh, Michigan (102) and Sudbury, Massachusetts (103), indicated that about 1-2% of all individuals in a defined population met the 1958 American Rheumatism Association (ARA) Criteria for RA (104). When the individuals who met these criteria were then re-examined 3-5 years later, only about 25% showed evidence of RA. Furthermore, only about 25% of the subjects in population studies who met criteria for RA had rheumatoid factor (Table IV) (105-114). In contrast, more than 90% of patients with RA diagnosed in clinical settings show evidence of the disease 5 years later, often with progression (9-11). Furthermore, 70-90% of patients with RA in clinical settings have rheumatoid factor (115).

These observations are consistent with studies of early arthritis over the last few years. Reports from the United Kingdom (116) and The Netherlands (117)

show that fewer than half of patients diagnosed with early inflammatory arthritis develop sustained RA, as is discussed in another chapter in this supplement (118). It is likely that many patients with self-limited early arthritis have a post-infectious or other type of transient self-limited inflammatory polyarthritis, which generally resolves within a few months. However, the outcomes of early inflammatory polyarthritis within a community are not necessarily favorable. In the Norfolk Arthritis Register (NOAR), only 25% of subjects were in remission after 2 years (119), and almost a third had considerable disability 12 months after enrollment (120). Furthermore, the ACR criteria for RA (121) at baseline had little capacity to predict persistence of arthritis, development of radiographic erosions, or moderate disability ( $\text{HAQ} \geq 1$ ) (116), reinforcing that identification of those who are likely to develop persistent arthritis is difficult at the first visit. Previous hypotheses that patients with early arthritis identified in population-based studies were similar to clinical patients with sustained long-term RA has contributed to underestimation of the severity of RA. Many patients with self-limited transient polyarthritis are probably never seen by a physician, let alone a rheumatologist. Most patients with clinical RA who are seen by rheumatologists experience progressive disease which should be treated aggressively to achieve remission, as is discussed in another essay in this supplement (122).

*The acute causes of death in RA are superficially similar to those in the general population*

The acute causes of death listed for

**Table III.** Why have the risks of RA been underestimated ?

1. RA does not lead to acute life-threatening situations.
2. Population-based studies have suggested that most people who meet the criteria for RA have a mild or self-limited process.
3. The acute causes of death in RA are superficially similar to those in the general population.
4. Clinical trials have suggested many efficacious therapies for RA.
5. Few long-term longitudinal studies were performed prior to the 1980s.
6. Medical recommendations during the 1950s-1980s suggested the efficacy of simple therapies.
7. The absence of quantitative information concerning patient status in standard rheumatology care.
8. The benefit/risk of traditional DMARDs was considerably less than currently available therapies.

**Table IV.** Prevalence of rheumatoid factor (RF) in individuals identified in population-based studies as meeting the criteria for rheumatoid arthritis (RA).

	Wensleydale England (1960)	Tecumseh Michigan (1959-1960)	Jerusalem Israel (1962-64)	Blackfeet Indians Montana (1961)	Pima Indians Arizona (1961)	Heinola Finland (1961)
Reference number	(106, 107)	(108)	(109, 110)	(111-113)	(111-113)	(114)
RF test	Latex fixation	Latex fixation	Latex fixation*	Bentonite flocculation	Bentonite flocculation	Waal- er-Rose
RF titer	> 1:80	> 1:20	> 1:320	> 1:128	> 1:128	≥ 64
Number of individuals tested	870	6590	1602	1046	959	539
ARA criteria	Definite & probable	Definite, probable & possible	Definite & probable	3-7 criteria	3-7 criteria	Definite
RA prevalence by criteria (%)	4.9%	6.1%	2.4%	3.6%	4.5%	3.5%
Prevalence of a positive RF test in individuals who met the ARA criteria for RA (sensitivity) (%)	24%	19%	25%	24%	33%	21%

\*Data also available for Rose-Waaler RF tests, in which only 12% of individuals meeting the ARA criteria for RA had positive tests, while the specificity was 99%.

patients with RA appear superficially to be quite similar to those in the general United States population (which are similar to those in Western Europe) (Table V) (15). In particular, cardiovascular disease was found to be a cause of death in approximately 40% of patients with RA, as in the general population. Although a higher prevalence of renal, pulmonary, infectious and gastrointestinal disease has been seen in patients with RA compared to the general population, a rheumatologist with 300 patients with RA would expect to have 1 per month die from an acute cause of death similar to the general population. The only way to determine whether the mortality rate might be higher would be to observe patients over long periods and compare mortality rates to those in the general population. All such studies have indicated a higher mortality rate for patients with RA, with a lifespan shortened by 5-15 years (15).

It is of interest to note that infection was 9-fold more common as a cause of death in reports prior to 1986 – that is, prior to the widespread use of methotrexate, leflunomide and anti-TNF agents. This phenomenon illustrates that an important and perhaps predominant basis for higher rates of infection in patients with RA is likely to be the disease itself, with a higher rate associated with more severe disease, as discussed in this supplement (123). Furthermore, over the last decade evidence for cardi-

ovascular disease as an inflammatory disease has emerged (124), and RA may be regarded as a risk factor for development of cardiovascular disease (125). However, these concepts are not widely recognized at this time in the medical community.

#### *Clinical trials have suggested many efficacious therapies for RA*

The randomized controlled clinical trial is the "gold standard" to compare one treatment to another or to a placebo (126), mimicking a "scientific" laboratory experiment by isolating a single variable, the therapy, and using randomization to adjust for additional variables which might affect the results (127). At this time, all new therapies designed for standard care require documentation of their efficacy and acceptable toxicity based on a randomized controlled clinical trial. Furthermore, the term "evidence-based medicine" has come to mean largely "evidence from clinical trials, rather than from clinical observational studies and case reports" (128). Nonetheless, limitations to randomized controlled clinical trials exist, as is true of all scientific methods, as has been described extensively in reports by many observers (40, 127, 129-144), including previous commentaries by us (145-149).

Clinical trials during the 1970s-1990s indicated improvement over a 3 to 6-month period with disease modifying

anti-rheumatic drugs (DMARDs), as well as many new nonsteroidal anti-inflammatory drugs (NSAIDs) (145). Even at this time, the criterion of 20% improvement in the American College of Rheumatology Core Data Set criteria (ACR 20) is met in trials involving cyclooxygenase 2 (COX-2) selective inhibitors, although these drugs are not thought to be "disease-modifying", and can be used on an "as needed" basis to relieve symptoms, rather than as a required component of treatment. These phenomena illustrate some of the limitations of clinical trials as applied to long-term outcomes (127, 145). A report in this supplement by Strand (54) emphasizes a new trend toward longer term observations over 2-5 years in clinical trial settings. Nonetheless, emphasis on short-term improvements over 30 years in the literature on RA has led to an underestimation of the longer term outcomes.

#### *Few long-term longitudinal studies were performed prior to the 1980s*

Few long-term observational studies were available prior to the 1980s to enable researchers to study the severe morbidity and increased mortality rates in RA. Even at this time most observational research studies receive no support from foundation or government sources, and resources to optimally estimate the long-term consequences of RA are limited. Most of the published

**Table V.** Attributed causes of death (%) in 2,262 patients with rheumatoid arthritis in 13 centers.

Series	Cobb <i>et al.</i> 1953	Van Dam <i>et al.</i> 1961	Duthie <i>et al.</i> 1964	Uddin <i>et al.</i> 1970	Monson & Hall 1974	Lewis <i>et al.</i> 1980	Allbeck <i>et al.</i> 1981	Rasker & Cosh 1981	Vanden brouke <i>et al.</i> 1984	Pincus <i>et al.</i> 1984	Prior <i>et al.</i> 1984	Mutra <i>et al.</i> 1985	Mitchell <i>et al.</i> 1986	Cum- ulative total	1977 U.S. pop- ulation
Reference no.	(77)	(78)	(59)	(78)	(157)	(158)	(79)	(60)	(80)	(9)	(159)	(18)	(16)		
No. of deaths	130	229	75	94	570	46	84	43	165	20	199	356	251	2262	
Attributed cause of death	Percentage of deaths in each series attributed to listed causes														
Cardiovascular disease	24.6	38.5	36.0	51.0*	43.3	41.3	48.8	41.9	43.0	40.0	31.2	46.6	42.6	42.1	41.0
Cancer	11.5	15.2	13.3	7.4	12.6	28.3	23.8	11.6	19.5	25.0	15.1	11.8	13.1	14.1	20.4
Infection	24.6	12.6	14.7	19.1	NL	13.0	2.4	18.6	2.4	20.0	2.0	2.0	13.5	9.4**	1.0
Renal disease	13.1	7.8	17.3	4.2	4.4	NL	0	9.3	5.5	0	3.0	20.5	3.2	7.8	1.1
Respiratory disease	3.1	NL	4.0	4.2	10.0	6.5	1.2	NL	12.1	5.0	14.6	8.1	4.8	7.2	3.9
RA	NL	NL	NL	NL	6.7	2.2	4.8	NL	10.3	5.0	17.1	NL	10.0	5.3	NL
Gastrointestinal disease	6.2	6.5	8.0	2.1	4.0	2.2	6.0	NL	5.5	5.0	5.5	NL	6.0	4.2	2.4
CNS disease	9.2	NL	5.3	NL	11.2	NL	6.0	18.6	NL	0	0	NL	1.0	4.2	9.6
Accidents	0	NL	1.3	NL	NL	NL	NL	NL	0.6	0	0	4.0	4.0	1.0	5.4
Miscellaneous	7.7	16.9	NL	3.2	7.8	6.5	7.1	NL	1.2	0	3.5	7.9	2.0	6.4	15.2
Unknown	NL	2.2	NL	8.5	NL	NL	NL	NL	0	0	0	0	0	0.6	NL

\*Pulmonary embolus classified as "Cardiovascular Disease."

\*\*Percentage calculation does not include Monson and Hall's 570 cases, as infection was not listed as a cause of death.

NL: This cause of death not listed in this series.

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literature concerning RA involves short-term benefits, and an underestimation of long-term outcomes might not be surprising. This phenomenon illustrates the importance of possible increases in support for long-term observational studies by public agencies and pharmaceutical companies.

#### *Medical recommendations during the 1950s-1980s suggested the efficacy of simple therapies*

One contributing factor in the underestimation of RA could involve the opinion leaders of an earlier era, many of whom were greatly influenced by a report published in the *New England Journal of Medicine* in 1948 (150), which suggested that simple medical and orthopedic measures were adequate in most patients with RA. It is of interest to note that the "simple treatment" involved 3 weeks to 3 months of hospitalization at that time. Nonetheless, a careful review of the data shows that only 53.2% of patients were regarded as "improved" and 34% of them were "worse;" only 22% of patients with "marked" severity were "improved" (Table VI) (150).

In retrospect, these results in which the condition of only one-third of patients was regarded as worse, at a time when few therapies were available, may appear satisfactory. However, as effective therapies have become available, this outcome over long periods is not acceptable. Furthermore, in a follow-up paper in 1953, the same center was the first to report significantly increased mortality rates in RA (77). Nonetheless, the view of RA as being "well-controlled with simple measures" remained prevalent for another 40 years (1,2,38), in part based on the opinion of senior rheumatologists, with few exceptions (151). This phenomenon illustrates that the interpretation of data is often as important as the data themselves.

#### *Absence of quantitative information concerning patient status in standard rheumatology care*

The primary problems affecting patients with rheumatic disease – functional disability, pain, fatigue and psychological distress – traditionally have

not been measured quantitatively in clinical care. Furthermore, quantitative joint counts are generally not performed in most patients at most visits [see (152)]. In the majority of patients the only quantitative data collected are laboratory tests. However, the erythrocyte sedimentation rate may be normal in as many as 40%-70% of RA patients (153, 154). The increased use of patient questionnaires in clinical care, as discussed in this supplement (152), might be of considerable value to address the underestimation of the risks of RA.

*The benefit/risk of traditional DMARDs was considerably less than currently available therapies*

DMARDs available prior to the 1980s, most notably injectable gold and penicillamine, had considerable toxicity and were poorly tolerated. Fewer than 50% of treatment courses of these drugs were continued for longer than 2 years, and fewer than 20% after 5 years (19, 20). Therefore, any reference to these drugs as "remission inducing" was incorrect, as fewer than 2% of patients experienced long-term remission (155). A most fortunate development in the treatment of RA is that methotrexate not only is much more likely to be associated with an improvement in the patient status compared to gold or penicillamine, albeit rarely leading to actual remission, but is much better tolerated (156). Furthermore, methotrexate does not appear to be associated with a loss of efficacy over months to years, as was frequently seen with gold and penicillamine. More than 50% of courses were continued for longer than 5 years (20). The newer DMARDs, leflunomide, and biological agents also appear to have more favorable tolerability and safety profiles compared to gold salts and penicillamine. Nonetheless, when patients read about anti-rheumatic drugs on the Internet or fill prescriptions for these drugs, they are warned of the extensive possible complications and adverse events (Table I), but not of the potential "side effects" of RA if left untreated (Table II).

## Conclusion

In summary, the risks of RA indicate a progressive disease, with a natural his-

tory of radiographic damage, functional declines, work disability, and premature mortality in most patients. In view of these findings, a new approach to therapy involving "tight control" of RA, analogous to the modern treatment of hypertension and diabetes, is recommended. Aggressive treatment is possible because of the favorable benefit/risk of methotrexate, leflunomide and biological agents, particularly if full recognition is given to the risks of RA. However, to obtain maximum efficacy, these therapies must be administered prior to the development of joint damage. The need for two, three, or more drugs to achieve maximum control of inflammatory activity can usually be recognized within one year. With effective therapies available, RA should be viewed as an urgent medical problem – a "medical emergency" – in order to control the long-term consequences of the disease process.

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**Table VI.** Results in 250 patients with rheumatoid arthritis receiving simple medical and orthopedic measures.

Status of disease	No. of cases	Percentage improved
Improved:	133	53.2%
In remission	38	15.2%
Moderately improved	43	17.2%
Slightly improved	52	20.8%
Stationary	32	12.8%
Worse	85	34.0%
Total severity of disease process:	No. of cases	Percentage improved
Mild	59	79.7%
Moderate	150	51.3%
Marked	41	21.8%

Source: Short CL, Bauer W: The course of rheumatoid arthritis in patients receiving simple medical and orthopedic measures. *New Engl J Med* 238:142-148, 1948.



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