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Mod Rheumatol (2008) 18:228–239
DOI 10.1007/s10165-008-0056-x

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Abstract Modern therapy for rheumatoid arthritis (RA) is based on knowledge of the severity of the natural history of the disease. RA patients are approached with early and aggressive treatment strategies, methotrexate as an anchor drug, biological targeted therapies in those with inadequate response to methotrexate, and “tight control,” aiming for remission and low disease activity according to quantitative monitoring. This chapter presents a rationale for current treatment strategies for RA with antirheumatic drugs, a review of published reports concerning treatments in clinical cohorts outside of clinical trials, and current treatments at 61 sites in 21 countries in the QUEST-RA database.

Keywords Rheumatoid arthritis · DMARDs · Methotrexate

Introduction

The history of rheumatoid arthritis (RA) includes a long period from the 1950s through to the mid-1980s in which RA was regarded “in the majority of patients as a disease with a good prognosis,” based on epidemiological data [1]. This traditional teaching was that RA could be controlled in most patients with bed rest [2], aspirin, and later with alternative nonsteroidal anti-inflammatory drugs. However, it was recognized during the mid-1980s from clinical cohorts that short-term drug efficacy was not translated into long-term effectiveness, as most patients experienced severe functional declines [3], radiographic progression [4], work disability [5], and premature mortality [3]. These reports led to calls for early and aggressive use of disease modifying anti-rheumatic drugs (DMARDs) [6–8], including aggressive strategies to prevent future damage and functional loss [7].

Gold sodium thiomalate was among the first drugs to be shown to be disease-modifying over the long term [9]. One of the earliest proposals for a more active treatment strategy in early RA was presented by Luukkainen et al. in 1978: “…In our opinion gold treatment ought to be started in the early stages of RA, before the development of erosions. We are treating not only the actual inflammation of the joints but also the quality of the patient’s life for many decades in the future” [10].

Currently, a strategy of early, aggressive and continuous treatment is the basis for therapies for early RA. This approach aims to reduce and possibly prevent damage to joints and other organs in most patients, analogous to the “tight control” of hypertension and diabetes [11], in which reducing elevated blood pressure or blood glucose (which are consequences of a dysregulation) reduces vascular damage and mortality rates. Lifelong therapy for RA is required in most cases, such as in hypertension and diabetes. Although the etiology of the dysregulation remains unknown in RA, the outlook for patients at this time is much better than in previous decades in many countries.
The traditional conservative approach to RA applied until the mid-1980s was based in part on evidence that many patients with inflammatory arthritis in population-based studies have a self-limited process rather than a progressive disease [12–15]. During the mid-1980s, it became apparent that most patients who present with symptoms in medical settings for longer than 3–6 months rarely experienced spontaneous remission [16, 17]. Furthermore, short-term drug efficacy of traditional DMARDs such as antimalarials and penicillamine, although significantly efficacious compared to placebo in clinical trials, had low rates of long-term effectiveness and/or high rates of toxicity, and did not prevent joint damage and poor outcomes [3, 18].

The contemporary approach applied to patients is based on the early use of available therapies, often in combination, to control inflammation as completely as possible; tight control according to quantitative monitoring in order to prevent long-term damage; the use of methotrexate as the anchor drug, as it is a far more effective and less toxic drug in the long term than earlier DMARDs; biological agents in about 20–30% of patients with inadequate responses to methotrexate; and an individualized approach to specific patients.

General principles of drug therapy for RA

Several general principles characterize the contemporary approach to patients with RA, as described below.

Early treatment

The term “rheumatoid arthritis” is used to describe a syndrome that has the capacity to lead to a destructive symmetrical polyarthritis [19]. Identification of RA in the early stages is both important and difficult. Criteria for RA have been developed since 1907 [20]. However, even the most recent criteria, the American Rheumatism Association (now the American College of Rheumatology) ACR 1987 revised criteria [21], do not differentiate patients with early RA from other types of recent onset inflammatory polyarthritis [22, 23]. Laboratory tests, which are traditionally emphasized by general physicians at the “front line” of diagnosis, are normal in about 40% of patients with RA [24, 25], including ESR, CRP, RF and anti-CCP, so that any patient with polyarthritis for longer than two weeks should be evaluated by a rheumatologist.

A “preventive” effort to reduce or avoid damage through the control of inflammation should begin as soon as there is evidence of joint swelling, and causes other than RA, such as infection, crystal arthropathy and reactive arthritis, have been excluded. Some patients may be treated unnecessarily using a “preventive” approach. However, the risks of “side effects” of RA are substantially greater than side effects of contemporary DMARDs [26]. Early treatment may prevent the development of RA [27], whereas even a short delay of therapy of four months reduces the likelihood of achieving remission [28].

Tight control

Therapy to control inflammation should be directed at “tight control,” with a goal of “preventing” joint damage and other undesirable consequences. Improvement at a 20% level (ACR 20) versus a placebo is sufficient for approval of marketing through the Food and Drug Administration (FDA), but this level of control is usually not sufficient to prevent long-term damage, which requires more extensive control of inflammation in most patients.

Several studies provide strong evidence that “target control” or remission is associated with better outcomes than ACR 20 or ACR 50 responses. The FIN-RACo trial included patients with early active RA with remission as a treatment goal. Among patients whose inflammation was controlled to a status of remission at six months, at five years, no patient was receiving work disability payments [29]. By contrast, 22% of patients who had ACR 20 or 50 responses and 54% of patients who did not have ACR 20 responses were receiving work disability payments at five years. The TICORA study documented that a strategy of intensive tight control of RA led to significantly better status compared to traditional therapeutic strategies in articular, functional, and radiographic outcomes over 18 months [30]. The goal of total remission is desirable, although “low disease activity” status may be acceptable for many patients, as a gold standard measure of remission does not exist [31].

Methotrexate as an “anchor drug”

The “anchor drug” for most patients with RA is weekly low-dose methotrexate [32–34], the most effective DMARD, with the lowest level of toxicities, particularly with use of concomitant folic acid. The better long-term drug continuation of methotrexate compared to other traditional DMARDs is an indication of the beneficial efficacy/tolerability profile of methotrexate [35, 36]. Weekly low-dose methotrexate for RA is anti-inflammatory, in contrast to high-dose methotrexate, which is cytotoxic, and associated with much higher levels of adverse events than lower doses. A large fraction of patients are controlled adequately with methotrexate alone or in combination with traditional DMARDs such as sulfasalazine and/or hydroxychloroquine, and do not appear to require biological agents [37].
Therapy must be individualized in each patient. It should be kept in mind that results of randomized controlled clinical trials and clinical observational studies are presented for groups of patients, and responses of individual patients to different agents vary considerably. In general, it is desirable for all patients with RA to take as high a dose of weekly methotrexate as needed or tolerated (up to 25–30 mg). Methotrexate should be discontinued at least three months before planned conception, and should be used with caution in patients with liver disease or chronic alcoholism. Methotrexate should not be discontinued because of modest (<2.5 times the upper limit of reference values) elevations of liver function tests (usually alanine aminotranferase)—often reducing the dose corrects the abnormality.

Biological agents

Five biological agents, including three which interfere with the actions of tumor necrosis factor alpha (TNFα)—etanercept, infliximab, and adalimumab, one with T-cell actions—abatacept, and one with B-cell actions—rituximab, are approved for use in RA in the US and other countries. These agents represent a major advance for the armamentarium of antirheumatic drugs for patients who have poor or incomplete responses to methotrexate monotherapy or a combination with other DMARDs. It is important to recognize such incomplete responses within 3–6 months of treatment, to prevent long-term damage in the 20–30% of patients who appear to require biological agents to control inflammatory activity [38]. According to guidelines in many countries, biological agents should be considered if patients do not respond to traditional DMARDs including methotrexate during the first few months [32, 39].

The use of glucocorticoids

Long-term high-dose glucocorticoid therapy (>10 mg equivalent of prednisone daily, for more than a few weeks) should be avoided in the treatment of RA. By contrast, the benefits of low-dose glucocorticoid therapy, in doses of 5 mg or less, are often greater than their potential harm, and may be continued over many years, particularly if the bones are protected with therapy for osteopenia. However, long-term low-dose use of glucocorticoid therapy remains controversial [32].

Improved outcomes of RA

Evidence is increasing of improved clinical status of RA patients at this time compared to previous decades, according to disease activity [40, 41], functional capacity [41–44], radiographic scores [41, 45, 46], the need for joint replacement surgery [47], and other clinical measures [41], including lower mortality rates in patients who responded to methotrexate [48, 49] and lower work disability rates in patients who responded to DMARDs [29]. These improvements are associated with early, aggressive treatment strategies in these countries. However, other reasons cannot be excluded, such as observations of less severe RA in the Western world compared to the past [50, 51]. Nonetheless, high disease activity is still observed in the majority of patients in many countries and in some patients in all countries [52].

Treatments for RA in selected clinical cohorts and cross-sectional studies

The initial DMARD for early RA

Few DMARDs were available for RA before the 1980s. If a DMARD was begun in early RA, it was most often intramuscular gold [36, 45, 53] (Table 1). During the 1980s–1990s, sulfasalazine was used as the first DMARD in most European countries [46, 54–56], while methotrexate was the first DMARD used, and was the anchor drug for RA, in many US rheumatology clinics [57–59], and is expanding to other clinics and other countries [33, 60]. However, in many published reports from the late 1990s and early 2000s, fewer than one third of patients began methotrexate as the initial treatment for early RA (Table 1). Biological agents were not used as the initial treatment for RA in the reviewed data because in many countries national guidelines allow biological agents to be used only after the failure of traditional DMARDs, as discussed above.

The use of DMARDs in selected early RA cohorts

The earliest cohort to enrol patients with early RA was established in Bath, UK, between 1957 and 1963 [61]. The use of DMARDs has been reported for over 40 years; over that time period 46% of patients took intramuscular gold, 70% antimalarials, 3% sulfasalazine, and 4% methotrexate [62]; 20% did not take any DMARDs. Another early RA cohort was established in Heinola, Finland in 1973–1975. This cohort enrolled 103 patients [63], who were reviewed 1, 3, 8, 15, 20, and 25 years after enrollment [64]. The treatment strategy in the Heinola Cohort was “early and active” therapy. On admission, 56% of patients began intramuscular gold and 36% began antimalarials. After eight years, 24% were taking intramuscular gold, 25% antimalarials, and 8% other DMARDs [45, 65]. Although the treatment strategy was active over the first few years, long-term benefits were limited due to discontinuation of the drugs. Therefore, severe
joint damage and/or amyloidosis was seen in many patients over the subsequent 20 years [64–66].

Patients with early RA were enrolled in an early RA cohort in Nijmegen, the Netherlands, in 1985 [67]. Sulfasalazine remained the most commonly used DMARD over five years in each of the five-year sub-cohorts (1985–1990; 1991–1995; 1996–2000) [56]. The five-year use of MTX increased from <10% of time in the earliest cohort to >20% in the latest cohort.

Increased use of MTX was seen in the early RA cohort established in Jyväskylä in 1996–1997 [68]. Although these patients began with sulfasalazine as the first DMARD [46], after six months, two years, and five years, 24, 50, and 70%, respectively, were taking methotrexate alone or in combination with other DMARDs. In an early RA cohort from a US private practice, 83% started methotrexate as the first DMARD for early RA in 1998–2001, and 89% had taken methotrexate during the first year [69].

### Trends in the use of DMARDs

The use of methotrexate for the treatment of RA did not begin until the 1990s in many countries [70, 71]. In a survey from the USA, RA patients were taking methotrexate on 0.6% of visits in 1980–1981, 4.9% of visits in 1985, 9.1% of visits in 1989–1991, and 27.3% of visits in 1993–1999. In

| Country | Cohort, [reference] | Enrollment period | Percentage of patients who started selected DMARDs |
|---------|---------------------|-------------------|-----------------------------------------------|
|         |                     |                   | IM gold (%) AM (%) SSZ (%) MTX (%) Other DMARDs (%) No DMARDs (%) |
| 1970s   |                     |                   |                                              |
| Finland | Heinola Cohort, Jantti et al. [76] | 1973–1975 | 56 36 0 0 4 4 |
| 1980s   |                     |                   |                                              |
| Finland | Jyvaskyla Cohort1983–1985 Sokka et al. [46] | 1983–1985 | 70 30 0 0 0 0 |
| Austria | Aletaha et al. [53] | 1985 | 87 7 0 0 6 |
| NL      | Welsing et al. [56] | 1985–1990 | Na Na 60 2 38 |
| Early 1990s |                     |                   |                                              |
| Austria | Aletaha et al. [53] | 1992 | 20 46 22 4 8 |
| NL      | Welsing et al. [56] | 1991–1995 | Na Na 82 9 9 |
| UK      | ERAS, Young et al. [77] | Before 1994 | 8 2 61 2 11 16 |
| UK      | “NOAR, Bukhari et al. [78] | Early 1990s | 3 4 37 3 1 52 |
| Greece  | Papadopoulos et al. [79] | 1987–1995 | 5 30 0 21 44 0 |
| USA     | Western Consortium, Paulus et al. [80] | 1993–1996 | 4 17 7 36 0 36 |
| Sweden  | BARFOT, Forslind et al. [81] | 1993–1997 | 0 0 34 24 8 34 |
| Late 1990s |                     |                   |                                              |
| Finland | Jyvaskyla Cohort1995–1996, Sokka et al. [46] | 1995–1996 | 3 1 95 1 0 0 |
| Finland | Jyvaskyla 1997, Makinen et al. [82] | 1997 | Na Na 73 20 6 1 |
| Sweden  | Carli et al. [83] | 1997 | Na Na 30 23 11 33 |
| Austria | Aletaha et al. [53] | 1998 | 1 40 29 29 1 |
| NL      | Welsing et al. [56] | 1996–2000 | Na Na 76 10 14 |
| Early 2000s |                     |                   |                                              |
| USA     | ERATER, Sokka and Pincus [69] | 1998–2003 | 0 7 1 82 3 7 |
| Sweden  | Carli et al. [83] | 2001 | Na Na 20 54 6 17 |
| USA     | SONORA, Bombardier et al. [84] | Early 2000s | 0 16 5 27 17 35 |
| Italy   | GIARA, CER [85] | b2001–2002 | Na 18 1.2 19 11 51 |

Data for “other DMARDs” and “no DMARDs” were combined when detailed data were not available

IM gold intramuscular gold, AM antimalarials, SSZ sulfasalazine, MTX methotrexate, Na not available, NL The Netherlands

a Early inflammatory polyarthritis

b Early RA patients in the cohort included
| Country       | Register or cohort, [reference] | Study period | Percentage of patients taking selected DMARDs | Total                  |
|---------------|---------------------------------|--------------|-----------------------------------------------|------------------------|
|               |                                 |              | IM gold (%) | AM (%) | SSZ (%) | MTX (%) | Biol (%) | Other DMARD (%) | No DMARD (%) | Total                  |
| 1970s         |                                 |              |               |        |         |         |          |                  |                      |                       |
| UK            | Bath, Rasker et al. [86]        | 15-yr follow-up | 35  | 55  | 0       | 0       | 0       | 13     | Na            | Ever used               |
| USA           | Nashville, TN, Pincus et al. [3] | 1973         | 60  | 26  | 0       | 0       | 0       | Na    | Na            | Ever used               |
| 1980s         |                                 | Year of diagnosis  | 40  | 39  | 8       | 7       | 0       | 45     | Na            | % of started DMARDs     |
| Norway        | Tromsø, Riise et al. [87]       | 1979–1987     | 13  | 0   | 32      | 2       | 0       | 14     | 66            | 100%                    |
| USA           | Nashville, TN, Pincus et al. [41]| 1985         | 10  | 5   | 0       | 10      | 0       | 9      | 39            | 100%                    |
| UK            | GPRD database, Edwards et al. [88] | 1987         | 19  | 7   | 9       | 12      | 0       | 30     | 23            | 100%                    |
| Finland       | Jyväskylä Cohort 1983–1985, Sokka et al. [46] | 1988–1990 | 24  | 0   | 15      | 18      | 0       | 14     | 29            | 100%                    |
| NL            | Leiden, van Schaardenburg et al. [89] | 1989–1990 | 25  | 63  | 3       | 0       | 0       | 9      | Na            | Ever used               |
| Early 1990s   |                                 | Year of diagnosis 1988–1996 | 12  | 29  | 24      | 40      | 0       | 48     | Na            | % of started DMARDs     |
| Norway        | Tromsø, Riise et al. [87]       | 1988–1996     | 41  | 0   | 17      | 22      | 0       | >63    | 0             | Ever used               |
| Japan         | Tokushima, Hamada et al. [90]   | Enrollment 1980–1990 | 24  | 0   | 15      | 18      | 0       | 14     | 29            | 100%                    |
| Finland       | Jyväskylä Cohort 1988–1999, Sokka et al. [46] | 1993–1994 | 24  | 0   | 15      | 18      | 0       | 14     | 29            | 100%                    |
| Late 1990s    |                                 |              |               |        |         |         |          |                  |                      |                       |
| Finland       | Heinola, Jänitti et al. [65]    | 1995–1996     | 16  | 13  | 19      | 12      | 0       | 40     | 100%         |                       |
| UK            | London, Gordon et al. [91]      | 1996         | 18  | 12  | 15      | 36      | 0       | 8      | 11            | 100%                    |
| Norway        | Oslo RA register, Kvien [92]    | 1996–1997     | 47  | 35  | 35      | 49      | 0       | Na     | 18            | Ever used               |
| Sweden        | Malmö RA register, Söderlin et al. [93] | 1997 | Na  | Na  | Na      | Na      | 24      | 0      | 28            | 48            | 100%                    |
| USA           | Western Consortium, Paulus et al. [80] | 1995–1998 | 0   | 31  | 12      | 57      | 0       | Na     | Na            | 100%                    |
| Sweden        | BARFOT, Forslund et al. [81]    | 1997         | Na  | Na  | 15      | 33      | 0       | 19     | 33            | 100%                    |
| UK            | Bath, Minaur et al. [62]        | 40-year follow-up | 46  | 70  | 3       | 4       | 0       | 34     | 20            | Ever used               |
| Sweden        | Lund, Eberherdt et al. [94], Lindqvist et al. [95] | 1999 | 5   | 26  | 11      | 15      | 0       | 43     | 25            | Ever used               |
| Lithuania     | Vilnius, Dadoniene et al. [96]  | 1999         | 28  | 50  | 49      | 36      | 0       | 35     | 6             | Ever used               |
| Spain         | EMECAR, Gonzalez-Alvaro [97]     | 1999–2000     | 23  | 28  | 32      | 0       | 0       | 28     | 23            | 100%                    |
| Early 2000s   |                                 |              |               |        |         |         |          |                  |                      |                       |
| USA           | Nashville, TN, Pincus et al. [41] | 2000         | 1   | 4   | 0       | 73      | 4       | 5      | 13            | 100%                    |
| USA           | ERATER Sokka and Pincus [69]    | 2001         | 0   | 16  | 4       | 89      | 14      | 22     | Na            | Ever used               |
| Finland       | Jyväskylä, Cohort 1995–1996, Sokka et al. [46] | 2000–2001 | 7   | 2   | 10      | 69      | 1       | 0      | 11            | 100%                    |
| Germany       | National database, Thiele et al. [98] | 2001 | 2   | 5   | 7       | 56      | 4       | 17     | 9             | 100%                    |
| Norway        | Norwegian DMARD register, Kvien et al. [99] | 2001 | Na  | Na  | 24      | 38      | 10      | 28     | –             | 100%                    |
| Sweden        | Malmö RA register, Söderlin et al. [93] | 2002 | Na  | Na  | Na      | 44      | 14      | 11     | 31            | 100%                    |
patients with early RA in the Wichita, Kansas database, the use of methotrexate increased from 6% in patients who were diagnosed in the 1970s versus 45% in the 1990s, calculated as percentage of person-time in follow-up [72]. In many countries, the use of methotrexate appears to have increased to more than 50% of patients only during the 2000s (Table 2).

Limitations of available data concerning DMARDs

Quantitative data concerning patient clinical course and DMARDs for RA are not available at all in many countries. Most of the reported data concerning treatments for RA are based on cohort studies from specialized clinics with advanced treatment strategies in the US and Western European countries. Therefore, these data represent a small, selected minority of all patients.

A number of registries of biological agents have been established over the last few years in many countries to monitor patients outside of clinical trials [73]. These registers are not reviewed here as they often provide data only from the minority of patients who were treated with biological agents.

DMARDs in QUEST-RA

A need to collect further quantitative data concerning patients with RA seen in usual rheumatology care in many clinics in many countries has led to development of a program called Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA), which has two goals: (1) to promote the quantitative assessment of patients with rheumatic diseases in daily clinical practice, and (2) to develop a database of RA patients seen in regular care in many countries [52]. The initial design was to assess 100 patients with RA at each of three or more sites in different countries. Data collection was begun in January 2005. By July 2007, the program included 5,499 patients from 61 sites in 21 countries: Argentina, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, the Netherlands, Poland, Serbia, Spain, Sweden, Turkey, the United Kingdom, and the United States. All patients were assessed according to a standard protocol to evaluate RA (SPERA) [74].

Physicians completed three one-page forms: (a) review of clinical features, including classification criteria, extra-articular features, comorbidities, and relevant surgeries; (b) all previous and present DMARDs, their adverse events, and reasons for discontinuation; (c) a 42-joint count [75] which includes swollen and tender joints, as well as joints with limited motion or deformity. The patients completed a self-report questionnaire, which was translated into different languages, and included the Health Assessment Questionnaire (HAQ) to assess physical function, visual analog scales for pain, global status, and fatigue, as well as work status, and life-style choices such as smoking and amount of physical exercise. Disease Activity Score-28 (DAS28) was calculated to estimate disease activity.

In the QUEST-RA patients, the use of intramuscular gold as the first DMARD dropped from >60% in patients who were diagnosed with RA in the 1970s to <2% in patients who were diagnosed with RA in the 2000s, and the use of MTX increased from 2 to >50% as the initial DMARD.

At 61 QUEST-RA sites in 21 countries, 63% of patients were taking methotrexate and 20% were taking biological agents in 2005–2007, with considerable variation between countries (Table 3). Fewer than 20% of patients were

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### Table 2 continued

| Country | Register or cohort, [reference] | Study period | Percentage of patients taking selected DMARDs | Total |
|---------|---------------------------------|--------------|--------------------------------------------|-------|
|         |                                 |              | IM gold (%) | AM (%) | SSZ (%) | MTX (%) | Biol (%) | Other DMARD (%) | No DMARD (%) |
| UK      | GPRD database, Edwards et al. [88] | 2002         | 2           | 8      | 26      | 30       | 0        | 2                | 32            | 100%          |
| Norway  | Norwegian DMARD register, Kvien et al. [99] | 2004         | Na         | Na     | 8       | 69       | 13       | 10               | –             | 100%          |
| Japan   | IORRA, Yamanaka et al. [100]    | 2006         | Na         | Na     | Na      | Na 59    | 3        | 27               | 11            | 100%          |
| UAE     | Dubai, Badsha et al. [101]      | 2006         | Na         | Na     | Na      | Na 29    | 2        | 11               | 58            | 100%          |

IM gold intramuscular gold, AM antimalarials, SSZ sulfasalazine, MTX methotrexate, Biol biological agents, Na not available, NL The Netherlands, GPRD General Practice Research Database

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*a* Ever used by those who continued DMARD treatment for 10 years

*b* Includes 21% combinations

*c* “MTX” includes combinations with MTX, and “biol” includes combinations with biological agents “ever used”
currently taking oral glucocorticoids in Denmark and the Netherlands, in contrast to 83% of patients in Lithuania. More than 25% of the patients were taking biological agents in the USA, France, Sweden, Ireland, and Latvia, although the high percentage in some countries may be explained by prior participation of some patients in randomized clinical trials of biological agents. Fewer than 10% of patients were taking biological agents in Serbia, Estonia, Argentina, Turkey, Poland, and Lithuania (Table 3).

Methotrexate was taken at some time by 86% of all patients, prednisone 72%, sulfasalazine 46%, antimalarials 42%, any biological agent by 24%, intramuscular gold by 23%, and leflunomide by 22% of all patients (Table 4). Cyclosporine A, azathioprine, and D-penicillamine were taken at sometime by 7–10% of patients (Table 4).

Conclusions

A major transformation has been seen in the drug treatment of RA over the last few decades. Treatment with DMARDs only after erosions, i.e., joint damage, has been replaced by early, aggressive intervention. Judgment of efficacy as significant differences from placebo has been replaced by tight control of inflammation, with the goal of remission or low disease activity, to prevent joint damage. Intamuscular gold and penicillamine have been replaced by methotrexate, as monotherapy or used in combination with sulfasalazine and/or hydroxychloroquine, as well as targeted therapies with biological agents. Patient outcomes appear much improved at this time compared to earlier periods.

Table 3 Clinical characteristics and current use of prednisone, methotrexate, and biological agents in the QUEST-RA study

| Country     | Sites | Patients | Female (%) | Age (years) | Disease duration (years) | DMARD delay (months) | Education (years) | RF+ (%) | DAS 28 | HAQ | Taking now (%) |
|-------------|-------|----------|------------|-------------|--------------------------|----------------------|------------------|---------|--------|-----|----------------|
| Netherlands | 3     | 317      | 66.3       | 59.2        | 9.2                      | 5.5                  | 11.0             | 68.8    | 2.9    | 0.8| 16.1          |
| Greece      | 3     | 300      | 75.7       | 57.9        | 11.8                     | 7.0                  | 12.0             | 52.1    | 3.1    | 0.3| 70.7          |
| Finland     | 3     | 304      | 72.4       | 58.5        | 13.5                     | 7.0                  | 9.0              | 74.8    | 3.1    | 0.6| 51.0          |
| USA         | 3     | 301      | 72.9       | 57.5        | 9.3                      | 9.0                  | 13.0             | 70.9    | 3.2    | 0.6| 60.1          |
| Denmark     | 3     | 301      | 76.7       | 57.8        | 12.0                     | 10.1                 | 10.0             | 73.3    | 3.3    | 0.6| 14.6          |
| Spain       | 3     | 302      | 73.5       | 59.8        | 10.6                     | 14.0                 | 10.0             | 72.5    | 3.4    | 0.9| 46.7          |
| France      | 4     | 389      | 77.9       | 55.3        | 12.8                     | 8.0                  | 10.0             | 75.3    | 3.6    | 0.9| 60.9          |
| Sweden      | 3     | 260      | 71.8       | 59.4        | 12.5                     | 12.0                 | 10.0             | 81.6    | 3.6    | 0.9| 41.2          |
| Ireland     | 3     | 240      | 64.3       | 56.4        | 11.3                     | 11.0                 | 12.0             | 79.6    | 4.0    | 0.8| 31.3          |
| Turkey      | 3     | 309      | 85.6       | 51.9        | 11.6                     | 12.0                 | 5.0              | 67.6    | 4.1    | 0.9| 57.3          |
| UK          | 3     | 145      | 77.9       | 59.6        | 15.0                     | 12.0                 | 12.0             | 81.4    | 4.1    | 0.9| 28.3          |
| Germany     | 3     | 225      | 83.6       | 58.8        | 13.4                     | 15.0                 | 10.0             | 60.9    | 4.3    | 0.8| 26.7          |
| Canada      | 1     | 100      | 78.8       | 57.4        | 12.4                     | 12.0                 | 12.0             | 82.8    | 4.3    | 1.0| 25.0          |
| Italy       | 4     | 336      | 78.2       | 61.0        | 10.5                     | 9.0                  | 8.0              | 71.4    | 4.5    | 1.1| 51.8          |
| Estonia     | 3     | 168      | 85.5       | 55.8        | 11.8                     | 12.0                 | 12.0             | 68.1    | 4.7    | 1.1| 40.5          |
| Latvia      | 1     | 61       | 80.3       | 52.4        | 13.4                     | 23.0                 | 12.5             | 81.7    | 5.1    | 1.4| 55.7          |
| Hungary     | 3     | 153      | 87.4       | 57.9        | 12.6                     | 12.0                 | 12.0             | 92.8    | 5.2    | 1.4| 38.6          |
| Poland      | 7     | 642      | 86.7       | 53.2        | 11.5                     | 4.0                  | 12.0             | 70.3    | 5.3    | 1.4| 58.9          |
| Lithuania   | 2     | 300      | 82.9       | 54.1        | 10.7                     | 13.0                 | 13.0             | 78.4    | 5.6    | 1.4| 80.7          |
| Argentina   | 2     | 246      | 90.2       | 51.4        | 9.9                      | 13.0                 | 9.0              | 90.5    | 5.6    | 1.0| 63.4          |
| Serbia      | 1     | 100      | 88.0       | 59.2        | 10.1                     | 11.1                 | 8.0              | 71.4    | 6.1    | 1.6| 54.0          |
| Total       | 61    | 5,499    | 78.6       | 56.7        | 11.5                     | 10.0                 | 11.0             | 73.2    | 4.1    | 1.0| 48.6          |

Table 4 Percentage of patients with current or previous (ever) use of various DMARDs in QUEST-RA, including 5,499 patients from 61 clinics in 21 countries

| DMARD (%): | Prednisone | Intramuscular gold | Antimalarials | Sulfasalazine | Methotrexate | Any biological |
|------------|------------|--------------------|---------------|---------------|--------------|----------------|
| Pred       | 72         | 23                 | 42            | 46            | 86           | 24             |
| MTX        | 72         | 23                 | 42            | 46            | 86           | 24             |
| Any biological | 24     | 22                 | 9.6           | 7.5           | 6.9          | 7.5            |

234 Mod Rheumatol (2008) 18:228–239

Modified and updated from [52], with permission.
Methotrexate use may serve as an excellent indicator of the transformation of drug therapy for RA; it was implemented in only a few patients in a few clinical settings in the 1980s, with increases in the number of clinics and patients in the 1990s, and widespread use as the “anchor drug” in most settings in the 2000s. Nonetheless, data in published reports continue to include only a minority of all patients with RA. Further efforts are needed to promote the collection of quantitative data in all patients with RA, in all countries, at all visits, in order to facilitate tight control and better outcomes for all patients with RA.

Acknowledgments Abbott for financial support; Pekka Hannonen for comments; the QUEST-RA Group.

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References

1. Kelley WN, Harris ED Jr, Ruddy S, Sledge CB. Textbook of Rheumatology. 2nd ed. Philadelphia: W.B. Saunders; 1985.
2. Short CL, Bauer W. The course of rheumatoid arthritis in patients receiving simple medical and orthopedic measures. N Engl J Med. 1948;238:142–8.
3. Pincus T, Callahan LF, Sale WG, Brooks AL, Payne LE, Vaughn WK. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. Arthritis Rheum. 1984;27:864–72.
4. Scott DL, Grindulis KA, Struthers GR, Coulton BL, Popert AJ, Bacon PA. Progression of radiological changes in rheumatoid arthritis. Ann Rheum Dis. 1984;43:8–17.
5. Yelin E, Meenan R, Nevitt M, Epstein W. Work disability in rheumatoid arthritis: effects of disease, social, and work factors. Ann Intern Med. 1980;93:551–6.
6. Wilske KR, Healey LA. Remodeling the pyramid—a concept whose time has come. J Rheumatol. 1989;16:565–7.
7. Fries JF. Reevaluating the therapeutic approach to rheumatoid arthritis: the “sawtooth” strategy. J Rheumatol. 1990;17 Suppl 22:12–5.
8. Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? Ann Rheum Dis. 1995;54:944–7.
9. Luukkainen R, Kajander A, Isomäki H. Effect of gold on progression of erosions in rheumatoid arthritis using better results with early treatment. Scand J Rheumatol. 1977;6:189–92.
10. Luukkainen R, Kajander A, Isomäki H. Treatment of rheumatoid arthritis (letter). Br Med J. 1978;2:1501.
11. Pincus T, Gobofsky A, Weinblatt ME. Urgent care and tight control of rheumatoid arthritis as in diabetes and hypertension: better treatments but a shortage of rheumatologists. Arthritis Rheum. 2002;46(4):851–4.
12. Kellgren JH, Bier F. Radiological signs of rheumatoid arthritis: a study of observer differences in the reading of hand films. Ann Rheum Dis. 1956;15:55–60.
13. Lawrence JS, Bennett PH. Benign polyarthritis. Ann Rheum Dis. 1960;19:20–30.
14. Mikkelsen WM, Dodge H. A four year follow-up of suspected rheumatoid arthritis: the Tecumseh, Michigan, community health study. Arthritis Rheum. 1969;12:87–91.
15. O’Sullivan JB, Cathcart ES. The prevalence of rheumatoid arthritis: follow-up evaluation of the effect of criteria on rates in Sudbury, Massachusetts. Ann Intern Med. 1972;76:573–7.
16. Niissilä M, Isomäki H, Kaarela K, Kiviniemi P, Martio J, Sarna S. Prognosis of inflammatory joint diseases. A three-year follow-up study. Scand J Rheumatol. 1983;12:33–8.
17. Emery P, Gough A. Why early arthritis clinics? Br J Rheumatol. 1991;30:241–2.

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18. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: Results after 20 years. Lancet. 1987;16:1108–11.
19. Symmons DPM, Hazes JMW, Silman AJ. Cases of early inflammatory polyarthritis should not be classified as having rheumatoid arthritis. J Rheumatol. 2003;30:902–4.
20. Allbutt T, Rolleston H. A system of medicine. London: Macmillan, 1907.
21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
22. Harrison BJ, Symmons DPM, Barrett EM, Silman AJ. The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. J Rheumatol. 1998;25:2324–30.
23. Saraux A, Berthelot JM, Chalès G, Le Henaff C, Thorel JB, Hoang S, et al. Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. Arthritis Rheum. 2001;44(11):2485–91.
24. Wolfe F, Michaud K. The clinical and research significance of the erythrocyte sedimentation rate. J Rheumatol. 1994;21:1227–37.
25. Pincus T, Sokka T. Prevalence of normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) on presentation of patients with rheumatoid arthritis (RA) at two rheumatology settings, one in the US and the other in Finland: Is a patient questionnaire a better quantitative measure of clinical severity? Arthritis Rheum. 2005;52(9):S127.
26. Pincus T, Callahan LF. The ‘side effects’ of rheumatoid arthritis: Joint destruction, disability and early mortality. Br J Rheumatol. 1993;32(suppl 1):28–37.
27. van Dongen H, van Aken J, Rolleston H, Korpela M, Nissila M, Kautiainen H, Hannonen P, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2007;56:1424–32.
28. Möttönen T, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, et al. Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum. 2002;46(4):894–8.
29. Puolakk K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. Arthritis Rheum. 2005;52(1):36–41.
30. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364:263–9.
31. Paulus HE. Defining remission in rheumatoid arthritis: what is it? does it matter? J Rheumatol. 2004;31(1):1–4.
32. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougdas M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007;66(1):34–45.
33. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol. 2003;21:S179–85.
34. Kremer JM. Toward a better understanding of methotrexate. Arthritis Rheum. 2004;50(5):1370–82.
35. Pincus T, Marcum SB, Callahan LF. Long-term drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second-line drugs and prednisone. J Rheumatol. 1992;19:1885–94.
36. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting anti-rheumatic therapy in rheumatoid arthritis: A 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol. 1990;17:994–1002.
37. Leirisalo-Repon M, Mottonen THP, Korpela M, Kauppi M, Kaipainen-Seppanen O, Luosujarvi R, et al. Does addition of infliximab to triple DMARD plus prednisalone therapy increase rate of remissions in patients with early active rheumatoid arthritis? A randomized double-blind placebo-controlled study. Arthritis Rheum; 2006;54(9 Suppl).
38. Sokka T, Hannonen P, Mottonen T. Conventional disease-modifying antirheumatic drugs in early arthritis. Rheum Dis Clin N Am. 2005;31(4):729–44.
39. Miyasaka N, Koike R. Treatment guidelines for the use of biologics in rheumatoid arthritis; present and future. Nippon Rinsho. 2007;65(7):1169–78.
40. Bergstrom U, Book C, Lindroth Y, Marsal L, Saxne T, Jacobsson L. Lower disease activity and disability in Swedish patients with rheumatoid arthritis in 1995 compared with 1978. Scand J Rheumatol. 1999;28:160–5.
41. Pincus T, Sokka T, Kautiainen H. Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. Arthritis Rheum. 2005;52:1009–19.
42. Sokka T, Möttönen T, Hannonen P. Disease-modifying antirheumatic drug use according to the ‘sawtooth’ treatment strategy improves the functional outcome in rheumatoid arthritis: Results of a long-term follow-up study with review of the literature. Rheumatology. 2000;39:34–42.
43. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med. 2003;115:371–6.
44. Heiberg T, Finset A, Uhlig T, Kvien TK. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. Ann Rheum Dis. 2005;64:191–5.
45. Sokka TM, Kaarela K, Möttönen TT, Hannonen PJ. Conventional monotherapy compared to a “sawtooth” treatment strategy in the radiographic procession of rheumatoid arthritis over the first eight years. Clin Exp Rheumatol. 1999;17:527–32.
46. Sokka T, Kautiainen H, Hakkinen K, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. J Rheumatol. 2004;31:1073–82.
47. Sokka T, Kautiainen H, Hannonen P. Stable occurrence of knee and hip total joint replacement in Central Finland between 1986 and 2003: an indication of improved long-term outcomes of rheumatoid arthritis. Ann Rheum Dis. 2007;66(3):341–4.
48. Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum. 2003;48:134–41.
49. Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359:1173–7.
50. Silman A, Davies P, Currey HLF, Evans SJW. Is rheumatoid arthritis becoming less severe? J Chronic Dis. 1983;36:891–7.
51. Aho K, Tuomi T, Palosuo T, Kaarela K, von Essen R, Isomaki H. Is seropositive rheumatoid arthritis becoming less severe? Clin Exp Rheumatol. 1989;7:287–90.
52. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund HM, et al. QUEST-RA: quantitative clinical assessment of
patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007;66(11):1491–6.
53. Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1300 consecutive DMARD courses. Rheum. 2002;41:1367–74.
54. Jobanputra P, Wilson J, Douglas K, Burls A. A survey of British rheumatologists’ DMARD preferences for rheumatoid arthritis. Rheumatology. 2003;42:1–5.
55. Hider SL, Silman AJ, Bunn D, Manning S, Symmons DP, Lunt M. Comparing the long-term clinical outcome between methotrexate and sulfasalazine prescribed as the first DMARD in patients with inflammatory polyarthritis. Ann Rheum Dis. 2006;65(11):1449–55.
56. Welsing PMJ, Fransen J, van Riel PLCM. Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. Arthritis Rheum. 2005;52:2616–24.
57. Willkens RF, Watson MA, Paxson CS. Low dose pulse methotrexate therapy in rheumatoid arthritis. J Rheumatol. 1980;7:501–5.
58. Hoffmeister RT. Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med. 1983;75(suppl 6A):69–73.
59. Kremer JM. Methotrexate update. Scan J Rheumatol. 1996;25:341–4.
60. Suzuki Y. Methotrexate for the treatment of rheumatoid arthritis in Japan—much more still remains to be resolved. Nippon Rinsho. 2002;60(12):2331–8.
61. Jacoby RK, Jayson MIV, Cosh JA. Onset, early stages, and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11-year follow-up. Br Med J. 1973;2:96–100.
62. Minaur N, Jacoby R, Cosh J, Taylor G, Rasker J. Outcome after 40 years with rheumatoid arthritis: a prospective study of function, disease activity and mortality. J Rheumatol. 2004;31(S69):3–8.
63. Kaarela K. Prognostic factors and diagnostic criteria in early rheumatoid arthritis. Scand J Rheumatol Suppl. 1985;57:1–54.
64. Sokka T. Early rheumatoid arthritis in Finland. Clin Exp Rheumatol. 2003;21:S133–7.
65. Jantti JK, Kaarela K, Belt EA, Kautiainen HJ. Incidence of severe outcome in rheumatoid arthritis during 20 years. J Rheumatol. 2002;29(4):688–92.
66. Kaarela K, Kautiainen H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. J Rheumatol. 1997;24:1285–7.
67. Welsing PM, van Riel PL. The Nijmegen inception cohort of patients with early rheumatoid arthritis. J Rheumatol. 2001;28:1102–5.
68. Bombardier C, Deaton RL, Gregersen P, Massarotti E, Formica C, Weisman MH. Pattern of DMARD use in a North American cohort of patients with early rheumatoid arthritis (RA) (SONORA). Arthritis Rheum. 2002;46(95):S344.
69. GIARA Registry Study Group. Aggressive rheumatoid arthritis registry in Italy. Characteristics of the early rheumatoid arthritis subtype among patients classified according to the ACR criteria. Ann Rheum Dis. 2004;63(9):1090–5.
70. Makinen H, Kautiainen H, Hannonen P, Sokka T. Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. A 5-year followup study. J Rheumatol. 2005;32:796–800.
71. Carli C, Ehlin AG, Klareskog L, Lindblad S, Montgomery SM. Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced more by hospital setting than patient or disease characteristics. Ann Rheum Dis. 2006;65(8):1102–5.
72. Rasker JJ, Cosh JA. Radiological study of cervical spine and hand in patients with rheumatoid arthritis of 15 years’ duration: an assessment of the effects of corticosteroid treatment. Ann Rheum Dis. 1978;37:529–35.
73. Rissel C, Jacobsen BK, Gran JT. Changes in therapy of rheumatoid arthritis during the period 1979 to 1996. Scan J Rheumatol. 2001;30:199–202.
74. Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP, et al. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology (Oxford). 2005;44(11):1394–8.
75. van Schaardenburg D, Hazes JM, de Boer A, Zwinderman AH, Meijers KA, Breedveld FC. Outcome of rheumatoid arthritis in early rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis. 2006;65(9):1192–7.
90. Hamada Y, Shinomiya F, Okada M, Fujimura T. Outcome of patients with rheumatoid arthritis treated by step-wise administration of disease-modifying antirheumatic drugs over a 10-year period. Mod Rheumatol. 2003;13:27–34.

91. Gordon P, West J, Jones H, Gibson T. A 10 year prospective followup of patients with rheumatoid arthritis 1986–96. J Rheumatol. 2001;28(11):2400–8.

92. Kvien TK, Uhlig T, Kristiansen IS. Criteria for TNF-targeted therapy in rheumatoid arthritis: estimates of the number of patients potentially eligible. Drugs. 2001;61:1711–20.

93. Soderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology (Oxford). 2007;46(8):1355–8.

94. Eberhardt K, Fex E. Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. Br J Rheumatol. 1998;37:1324–9.

95. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis. 2002;61:1055–9.

96. Dadoniene J, Uhlig T, Stropuviene S, Venalis A, Boonen A, Kvien TK. Disease activity and health status in rheumatoid arthritis: a case-control comparison between Norway and Lithuania. Ann Rheum Dis. 2003;62(3):231–5.

97. Gonzalez-Alvaro I, Carmona L, Balsa A, Sanmarti R, Belmonte MA, Tena X, et al. Patterns of disease modifying antirheumatic drug use in a Spanish cohort of patients with rheumatoid arthritis. J Rheumatol. 2003;30:697–704.

98. Thiele K, Buttgereit F, Huscher D, Zink A. Current use of glucocorticoids in patients with rheumatoid arthritis in Germany. Arthritis Rheum. 2005;53(5):740–7.

99. Kvien TK, Heiberg MS, Lie E, Kaufmann C, Mikkelsen K, Nordvag B-Y, et al. A Norwegian DMARD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol. 2005;23:S188–94.

100. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283–9.

101. Badsha H, Kong KO, Tak PP. Rheumatoid arthritis in Dubai: delayed diagnosis and low usage of disease modifying anti-rheumatic drugs. Ann Rheum Dis. 2007;66(6):835.