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REVIEW ARTICLE

Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs

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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.

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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 polyarthritides [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

Table 1 The initial DMARD in selected early rheumatoid arthritis cohorts, according to the time period

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	Jyvasyla 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	[a]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 Cohort 1995–1996, 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]	[b]2001–2002	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

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

Table 2 The DMARD profile in selected clinical cohorts and clinical databases, according to the time period

Country	Register or cohort, [reference]	Study period	Percentage of patients taking selected DMARDs							Total
			IM gold (%)	AM (%)	SSZ (%)	MTX (%)	Biol (%)	Other DMARD (%)	No DMARD (%)	
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										
Norway	Tromsø, Riise et al. [87]	Year of diagnosis 1979–1987	40	39	8	7	0	45	Na	% of started DMARDs
USA	Nashville, TN, Pincus et al. [41]	1985	10	5	0	10	0	9	66	100%
UK	GPRD database, Edwards et al. [88]	1987	13	0	32	2	0	14	39	100%
Finland	Jyväskylä Cohort 1983–1985, Sokka et al. [46]	1988–1990	19	7	9	12	0	30	23	100%
NL	Leiden, van Schaardenburg et al. [89]	1989–1990	25	63	3	0	0	9	Na	Ever used
Early 1990s										
Norway	Tromsø, Riise et al. [87]	Year of diagnosis 1988–1996	12	29	24	40	0	48	Na	% of started DMARDs
Japan	Tokushima, Hamada et al. [90]	Enrollment 1980–1990	41	0	17	22	0	>63	0	[a]Ever used
Finland	Jyväskylä Cohort 1988–1999, Sokka et al. [46]	1993–1994	24	0	15	18	0	14	29	100%
Late 1990s										
Finland	Heinola, Jäntti 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	24	0	28	48	100%
USA	Western Consortium, Paulus et al. [80]	1995–1998	0	31	12	57	0	Na	Na	100%
Sweden	BARFOT, Forslind 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	6	8	3	32	0	[b]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	Jyvaskyla, Cohort 1995–1996, Sokka et al. [46]	2000–2001	7	2	10	69	1	0	11	100%
Germany	National database, Thiele et al. [98]	[c]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%

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%
Late 2000s										
Japan	IORRA, Yamanaka et al. [100]	2006	Na	Na	Na	59	3	27	11	100%
UAE	Dubai, Badsha et al. [101]	2006	Na	Na	Na	29	2	11	58	100%

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

[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"

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 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, Hungary, 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 countires (Table 3). Fewer than 20% of patients were

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 (%)		
											Pred	MTX	Any biological
				Mean	Mean	Median	Median		Median	Median			
Netherlands	3	317	66.3	59.2	9.2	5.5	11.0	68.8	2.9	0.8	16.1	74.1	19.6
Greece	3	300	75.7	57.9	11.8	7.0	12.0	52.1	3.1	0.3	70.7	71.3	47.0
Finland	3	304	72.4	58.5	13.5	7.0	9.0	74.8	3.1	0.6	51.0	61.5	12.5
USA	3	301	72.9	57.5	9.3	9.0	13.0	70.9	3.2	0.6	60.1	71.8	27.6
Denmark	3	301	76.7	57.8	12.0	10.1	10.0	73.3	3.3	0.6	14.6	71.1	21.3
Spain	3	302	73.5	59.8	10.6	14.0	10.0	72.5	3.4	0.9	46.7	56.3	23.2
France	4	389	77.9	55.3	12.8	8.0	10.0	75.3	3.6	0.9	60.9	57.1	44.2
Sweden	3	260	71.8	59.4	12.5	12.0	10.0	81.6	3.6	0.9	41.2	65.8	26.9
Ireland	3	240	64.3	56.4	11.3	11.0	12.0	79.6	4.0	0.8	31.3	71.7	32.1
Turkey	3	309	85.6	51.9	11.6	12.0	5.0	67.6	4.1	0.9	57.3	69.3	5.8
UK	3	145	77.9	59.6	15.0	12.0	12.0	81.4	4.1	0.9	28.3	69.7	14.5
Germany	3	225	83.6	58.8	13.4	15.0	10.0	60.9	4.3	0.8	26.7	45.8	22.7
Canada	1	100	78.8	57.4	12.4	12.0	12.0	82.8	4.3	1.0	25.0	49.0	23.0
Italy	4	336	78.2	61.0	10.5	9.0	8.0	71.4	4.5	1.1	51.8	53.3	12.5
Estonia	3	168	85.5	55.8	11.8	12.0	12.0	68.1	4.7	1.1	40.5	53.6	0.6
Latvia	1	61	80.3	52.4	13.4	23.0	12.5	81.7	5.1	1.4	55.7	75.4	27.9
Hungary	3	153	87.4	57.9	12.6	12.0	12.0	92.8	5.2	1.4	38.6	62.7	12.4
Poland	7	642	86.7	53.2	11.5	4.0	12.0	70.3	5.3	1.4	58.9	65.0	6.1
Lithuania	2	300	82.9	54.1	10.7	13.0	13.0	78.4	5.6	1.4	80.7	55.7	9.3
Argentina	2	246	90.2	51.4	9.9	13.0	9.0	90.5	5.6	1.0	63.4	48.8	2.8
Serbia	1	100	88.0	59.2	10.1	11.1	8.0	71.4	6.1	1.6	54.0	54.0	0.0
Total	61	5,499	78.6	56.7	11.5	10.0	11.0	73.2	4.1	1.0	48.6	62.5	19.0

Modified and updated from [52], with permission

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).

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	72
Intramuscular gold	23
Antimalarials	42
Sulfasalazine	46
Methotrexate	86
Any biological agent	24
Leflunomide	22
Cyclosporin A	9.6
Azathioprine	7.5
D-penicillamine	6.9

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.

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.

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