Increases in use of methotrexate since the 1980s

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ABSTRACT

In this chapter, we review the use of DMARDs in several clinical RA cohorts and databases between the 1970s and the 2000s. The DMARD profile in the QUEST-RA database provides an overview of clinical use of MTX in recent years in 25 countries. The data show that (I) MTX is currently the most frequently used DMARD in RA, and (II) that this development has taken about 20 years to emerge.

Introduction

The use of Methotrexate (MTX) for rheumatoid arthritis (RA) was sporadic until the mid 1980s. Four randomised clinical trials confirmed the efficacy of MTX in 1984–85 in patients who did not respond to other anti-rheumatic drugs (1-4). Subsequently, MTX was approved by the Food and Drug Administration for use in RA. By the mid 1980s it also became apparent that most patients seen in rheumatology clinics with symptoms and signs of RA for longer than 3–6 months rarely experienced spontaneous remission, and most had a progressive disease (5, 6). It was recognised that short term drug efficacy was not translated into long-term effectiveness (7). These reports led to calls for early and aggressive use of disease modifying anti-rheumatic drugs (DMARDs) (8, 9) including aggressive strategies to prevent severe long-term outcomes of RA (10, 11).

Trends of MTX use in clinical cohorts and databases

Data reported from clinical cohorts in the 1980s indicate that MTX was almost never started as an initial treatment for RA (Table I) and 0–10% of all patients were taking MTX (Table II). Growth of MTX use in most rheumatology settings started only during the 1990s. In a survey from the USA, RA patients were taking MTX on 0.6% of visits in 1980–81, 4.9% of visits in 1985, 9.1% of visits in 1989–91, and 27.3% of visits in 1993–99 (12). In patients with early RA in the Wichita, Kansas database, the use of MTX increased from 6% in patients who were diagnosed in the 1970s *vs*. 45% in the 1990s, calculated as percentage of person-time in follow-up (13).

In European early RA cohorts in the 1990s, sulfasalazine was the most often used initial treatment while one third of patients in the USA (14) started MTX as the initial anti-rheumatic therapy (Table I). The same trend can be seen in cross sectional analyses in the 1990s: in European cohorts, about one third of patients were taking MTX while 57% of patients in the US Western Consortium were taking MTX (Table II). The use of MTX was lowest in established longitudinal cohorts from Bath, UK, Finland, and Sweden, in which 4–18% of patients were taking MTX (Table II).

In the 2000s, the majority of patients with early RA in most rheumatology settings were treated with MTX as the initial DMARD. However, published data indicate highly variable percentages, with low proportions at some sites: MTX was initial DMARD in 18 and 27% of patients in two cohorts, 54% in another two cohorts, and in 82% in another two cohorts, one of them from Latin America (15) (Table I). Various use of MTX was seen also in cross sectional analyses: 29% to 74% of patients were taking MTX (Table II).

Examples of growth of MTX use in selected early RA cohorts in 1970s – 1990s

Heinola cohort

An early RA cohort was established in Heinola, Finland in 1973–75. This cohort enrolled 103 patients (16), who were reviewed 1, 3, 8, 15, 20, and 25 years after enrolment (17). The treatment strategy in the Heinola Cohort was "early and active" therapy. On admission, 56% of patients began intra-muscular gold and 36% began anti-

Table I. The initial DMARD in selected early rheumatoid arthritis cohorts, according to period of time.

Country	Cohort, Reference[#]	Enrolment Period	Percentage of patients who started selected DMARDs					
			IM gold	AM	SSZ	MTX	Other DMARDs	No DMARDs
		1970s						
Finland	Heinola Cohort, Jantti *et al*. 2001 (46)	1973–75	56%	36%	0	0	4%	4%
		1980s						
Finland	Jyväskylä 1983–85 Sokka *et al*. 2004 (28)	1983–85	70%	30%	0	0	0	0
Austria	Aletaha *et al*. 2002 (47)	1985	87%	7%	0	0	6%	
NL	Welsing *et al*. 2005 (23)	1985–90	na	na	60%	2%	38%	
		Early 1990s						
Austria	Aletaha *et al*.2002 (47)	1992	20%	46%	22%	4%	8%	
NL	Welsing *et al*. 2005 (23)	1991–95	na	na	82%	9%	9%	
UK	ERAS, Young *et al*. 2000 (48)	Before 1994	8%	2%	61%	2%	11%	16%
UK	*NOAR, Bukhari *et al*. 2003 (49)	Early 1990s	3%	4%	37%	3%	1%	52%
Greece	Papadopoulos *et al*. 2002 (50)	1987–1995	5%	30%	0%	21%	44%	0
USA	Western Consortium, Paulus *et al*. 1999 (14)	1993–1996	4%	17%	7%	36%	0	36%
Sweden	BARFOT, Forslind *et al*. 2004 (51)	1993–1997	0	0	34%	24%	8%	34%
		Late 1990s						
Finland	Jyväskylä 1995-96, Sokka *et al*. 2004 (28)	1995–96	3%	1%	95%	1%	0	0
France	Brittany, Saraux *et al*. 2002 (52)	1995–97	32%	34%	7%	10%	4%	14%
Finland	Jyväskylä 1997, Makinen *et al*. 2005 (53)	1997	na	na	73%	20%	6%	1%
Sweden	Carli *et al*. 2006 (54)	1997	na	na	30%	23%	11%	33%
Austria	Aletaha *et al*. 2002 (47)	1998	1%	40%	29%	29%	1%	
NL	Welsing *et al*. 2005 (23)	1996–2000	na	na	76%	10%	14%	
		2000s						
USA	ERATER, Sokka & Pincus, 2002 (55)	1998–2003	0	7%	1%	82%	3%	7%
Sweden	Carli *et al*. 2006 (54)	2001	na	na	20%	54%	6%	17%
USA	SONORA, Bombardier *et al*. 2002 (56)	Early 2000s	0	16%	5%	27%	17%	35%
Italy	GIARA, CER 2003 (57)	#2001–02	na	18%	1.2%	19%	11%	51%
France	ESPOIR, Benhamou *et al*. 2009 (58)	2002–2005	1%	14%	10%	54%	Lef: 5% Biol: 2% Other: 2%	20%
Latin America	GLADAR early RA database 2006 (15)	2004–2006	0	46%	12%	82%	Lef: 11%	8%

IM gold: intra-muscular gold; AM: antimalarials; SSZ: sulfasalazine; MTX: methotrexate; na: not available; NL: The Netherlands; Lef: leflunomide; biol: biologic agents.
*early inflammatory polyarthritis; #early RA patients in the cohort included. Data for "other DMARDs" and "no DMARDs" were combined when detailed data were not available. Modified and updated from (59), with permission.

malarials. After eight years, 24% were taking intra-muscular gold, 25% antimalarials, and 8% other DMARDs although none was taking MTX by early 1980s (Fig. 1A) (18, 19). 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 (17, 19, 20).

Jyväskylä early RA cohorts

Increasing use of MTX was seen in the early RA cohorts established in Jyväskylä, Finland, in 1983–85, 1988–89, and 1996–97 (21). Only a few patients in the earliest cohort took MTX during the first 5 years (Fig. 1B), while 6–20% of Cohort 1988-89 were treated with MTX as single therapy or as part of a combination of DMARD during 2–5 years (Fig. 1C). In the most recent cohort, 24%, 50%, and 70% were taking MTX or a combination of DMARD at 6 months, 2 years, and 5 years, respectively (Fig. 1D).

Nijmegen early RA cohort

Patients with early RA were enrolled in an early RA program in Nijmegen, the Netherlands, between 1985 and 2000 (22). Sulfasalazine remained the most often used DMARD over 5 years in each of the 5-year sub-cohorts (1985–90; 1991–95; 1996–2000) (23). The 5-year use of MTX increased from <10% of time in the earliest cohort to >20% in the latest cohort.

Interval after presentation until treatment with MTX

A longitudinal study of all patients with RA seen in usual care between 1980 and 2004 included 1,982 consecutive patients in Jyväskylä, Finland and 738 consecutive patients in Nashville, TN, USA (Fig. 2) (24). The probability of initiating MTX within 5 years after presentation increased from <5% in Jyväskylä before 1989 to >90% in 2000–2004, and from 25% in Nashville in 1980-1984 to >90% since 1995. The median interval from presentation to MTX initiation in Jyväskylä was 14 years in 1980-1984, *versus* 8.6 in 1985-1989, 4.5 in 1990-1994, 1.8 in 1995-1999, and <1 year in 2000-2005; in Nashville, median intervals were 8.6 years in 1980–1984, 4.4 years in 1985-1989, and <2 months in

Table II. The DMARD profile in selected clinical cohorts and clinical databases, according to period of time.

Country	register or cohort, reference	study period	Percentage of patients taking selected DMARDs							Evaluation
			IM gold	AM	SSZ	MTX	Biol	Other DMARD	No DMARD	
		1970s								
UK	Bath, Rasker *et al*. (60)	15-yr follow-up	35%	55%	0	0	0	13%	na	ever used
USA	Nashville TN, Pincus *et al*. 1984 (7)	1973	60%	26%	0	0	0	na	na	ever used
		1980s								
Norway	Tromsø, Riise *et al*. 2001 (61)	year of diagnosis 1979-1987	40%	39%	8%	7%	0	45%	na	% of started DMARDs
USA	Nashville TN, Pincus *et al*. 2005 (25)	1985	10%	5%	0%	10%	0	9%	66%	cross sect
UK	GPRD database, Edwards *et al*. 2005 (62)	1987	13%	0%	32%	2%	0	14%	39%	cross sect
Finland	Jyväskylä Cohort 1983-85, Sokka *et al*. 2004 (28)	1988-1990	19%	7%	9%	12%	0	30%	23%	cross sect at 5 years
NL	Leiden, van Schaardenburg *et al*. 1993 (63)	1989-1990	25%	63%	3%	0	0	9%	na	ever used
		1990s								
Norway	Tromsø, Riise et al 2001 (61)	year of diagnosis 1988-1996	12%	29%	24%	40%	0	48%	na	% of started DMARDs
Japan	Tokushima, Hamada *et al*. 2003 (64)	enrollment 1980-1990	41%	0	17%	22%	0	>63%	0	†ever used
Finland	Jyväskylä Cohort 1988–89, Sokka *et al*. 2004 (28)	1993-1994	24%	0	15%	18%	0	14%	29%	cross sect at 5 years
Finland	Heinola, Jäntti *et al*. 2002 (19)	1995-1996	16%	13%	19%	12%	0	40%		cross sect
UK	London, Gordon *et al*. 2001 (65)	1996	18%	12%	15%	36%	0	8%	11%	cross sect
Norway	Oslo RA register, Kvien, 2001 (66)	1996-1997	47%	35%	35%	49%	0	na	18%	ever used
Sweden	Malmö RA register, Söderlin *et al*. 2007 (67)	1997	na	na	na	24%	0	28%	48%	cross sect
USA	Western Consortium, Paulus *et al*. (14)	1995-1998	0	31%	12%	57%	0	na	na	cross sect
Sweden	BARFOT, Forslind *et al*. 2004 (51)	1997	na	na	15%	33%	0	19%	33%	cross sect
UK	Bath, Minaur *et al*. 2004 (68)	40-yr follow-up	46%	70%	3%	4%	0	34%	20%	ever used
Sweden	Lund, Eberherdt *et al*.1998 (69), Lindqvist *et al*. 2002 (70)	1999	5%	26%	11%	15%	0	43%	25%	ever used
Lithuania	Vilnius, Dadoniene *et al*. 2003 (71)	1999	28%	50%	49%	36%	0	35%	6%	ever used
Spain	EMECAR, Gonzalez-Alvaro 2003 (72)	1999-2000	6%	8%	3%	32%	0	*28%	23%	cross sect
		2000s								
Spain	EMECAR, Abasolo *et al*. 2008 (73)	1999-2005	na	na	na	69%	0	9%	5%	ever used
USA	Nashville TN, Pincus *et al*. 2005 (25)	2000	1%	4%	0	73%	4%	5%	13%	cross sect
Japan	IORRA, Yamanaka *et al*. 2007 (74)	2000	na	na	na	34%	0	48%	18%	cross sect
USA	ERATER Sokka & Pincus 2002 (55)	2001	0	16%	4%	89%	14%	22%	na	ever used
Finland	Jyväskylä, Cohort1995-96, Sokka *et al*. 2004 (28)	2000-2001	7%	2%	10%	69%	1%	0	11%	cross sect at 5 years
Germany	National database, Thiele *et al*. 2005 (75)	#2001	2%	5%	7%	56%	4%	17%	9%	cross sect
Norway	Norwegian DMARD register, Kvien *et al*. 2005 (76)	2001	na	na	24%	38%	10%	28%	–	cross sect
Brazil	São Paulo, Chermont *et al*. 2008 (77)	2001-2003	na	47%	15%	88%	0	3%	–	prescribed over 1 year
Sweden	Malmö RA register, Söderlin *et al*. 2007 (67)	2002	na	na	na	44%	14%	11%	31%	cross sect
UK	GPRD database, Edwards *et al*. 2005 (62)	2002	2%	8%	26%	30%	0	2%	32%	cross sect
Hungary	Rojkovich *et al*. 2007 (78)	2003	na	na	na	64%	na	Lef: 11%	na	cross sect
Norway	Norwegian DMARD register, Kvien *et al*. 2005 (76)	2004	na	na	8%	69%	13%	10%	–	cross sect
Japan	IORRA, Yamanaka *et al*. 2007 (74)	2006	na	na	na	59%	3%	27%	11%	cross sect
UAE	Dubai, Badsha *et al*. 2007 (79)	2006	na	na	na	29%	2%	11%	58%	cross sect
Germany	National database, Ziegler *et al*. 2010 (80)	2007	na	7%	8%	56%	16%	Lef: 12%	15%	cross sect
Denmark	DANBIO, Hetland *et al*. 2010 (81)	2000-2009	na	na	na	76%		na	na	Of those starting TNF inhibitor
Spain	Ide *et al*. 2009 (82)	2009	0	na	na	59%	50%	Lef: 34%	na	cross sect
Brazil	Ide *et al*. 2009 (82)	2009	0	na	na	46%	0	Lef: 19%	na	cross sect
Argentina	Buenos Aires, Tamborenea *et al*. 2010 (83)	2009	na	na	na	74%	excluded	Lef: 13%	13%	cross sect

IM gold: intra-muscular gold; AM: antimalarials; Lef: leflunomide, SSZ: sulfasalazine; MTX: methotrexate; biol: biologic agents; na: not available; NL: The Netherlands; GPRD: General Practice Research Database.

†ever used by those who continued DMARD treatment for 10 years; * includes 21% combinations; # "MTX" includes combinations with MTX and "biol" includes combinations with biologic agents "ever used". Modified and updated from (59), with permission.

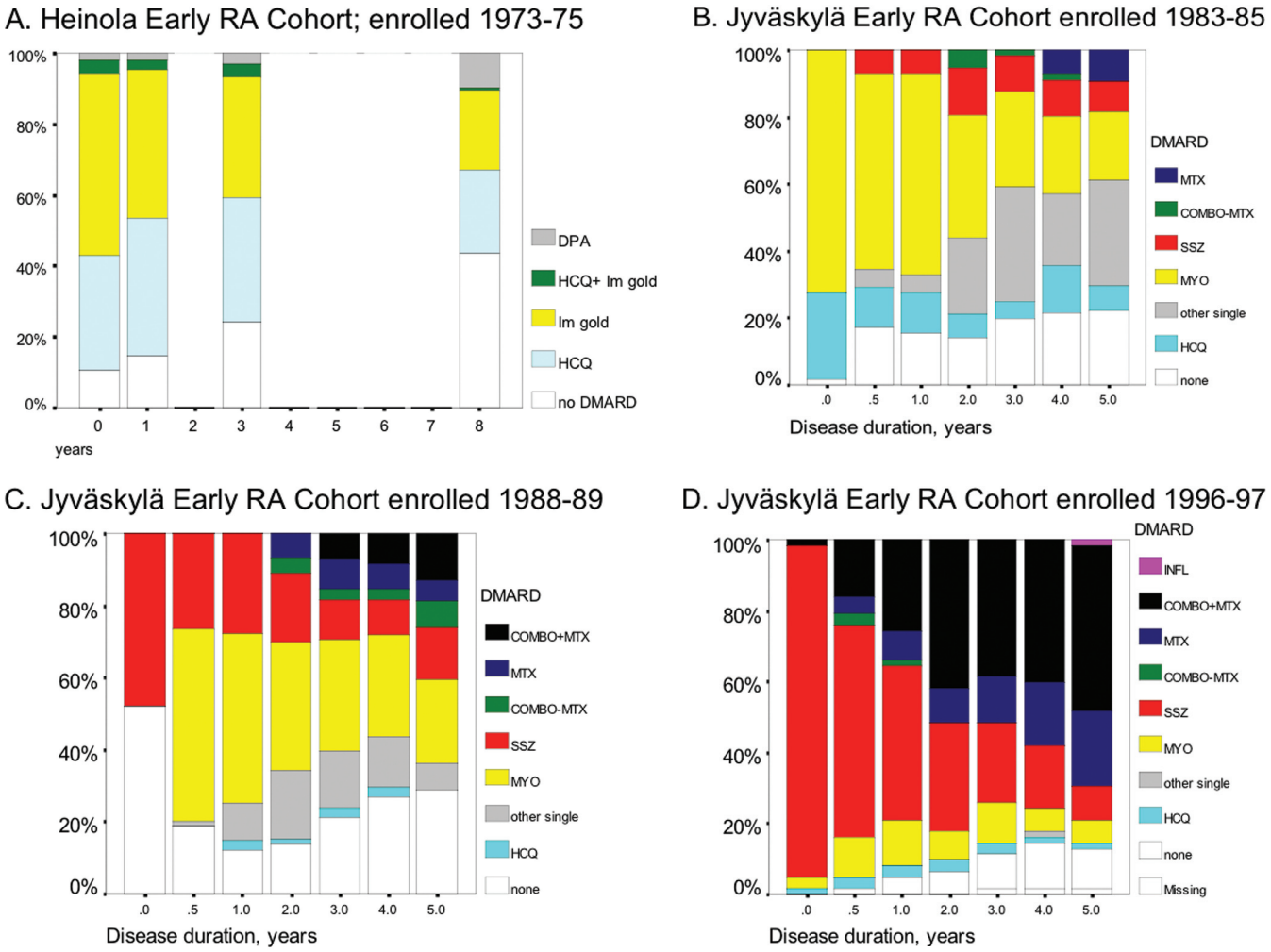

Fig. 1A-D. – DMARDs taken by patients with early RA in 5 separate early RA cohorts. A-D indicate percentages of patients taking each drug or combination at each time point. .
DPA: D-penicillamine, HCQ: hydroxychloroquine, Im gold, MYO: intra muscular gold, DMARD: disease modifying anti rheumatic drug, MTX: methotrexate, SSZ:sulfasalazine, COMBO+MTX:combination including MTX, COMBO-MTX: combination without MTX, INFL: infliximab, Anti-TNF: anti-tumour necrosis factor

1990–1995, 1995–2000, and 2000–2005 (Fig. 2) (24). This comparison of two longitudinal databases indicates that the interval from diagnosis to initiation of MTX at the U.S. site antedated the Finnish site by about a decade.

Growth of MTX use is associated with improved outcomes of RA

The outcomes of RA are much better at this time (25) compared to previous years. Improved patient status may be in part the result of other factors in addition to possible benefits of earlier and more aggressive therapy for RA, including changes in the natural history of disease toward milder disease (analogous to milder cardiovascular disease at this time than in previous decades (26)), earlier referral to treatment centres, and better general medical care for infections, cardiovascular disease and other comorbidities. In observational studies, it is impossible to distinguish definitively between these possibilities, but there is little doubt that the clinical status of patients with RA at this time is considerably better than two or three decades earlier, most of which antedated biological agents.

Analyses of RA cohorts and databases of consecutive patients in Jyväskylä, Finland, and Nashville, TN, USA, indicated improved outcomes of RA concerning clinical status (25), functional status (25, 27), radiographic outcomes (25, 28), and joint replacement surgery (29), concomitantly with more aggressive treatment strategies including growth of MTX use (25, 28).

Trends of long-term disability from 1977 to 1998 were studied in 3035 patients with RA in the ARAMIS database (30). Average disability for each patient over the follow-up period, according to HAQ scores, declined by approximately 40% between 1977 and 1998. Improved treatment strategies were recognised as a possible reason for the observation. Reduced mortality has been documented in patients who respond to MTX treatment (31, 32).

Increases in MTX doses

In the 1980s, the maximum recommended MTX dose for RA was 15mg/week (33). This was reflected in clini-

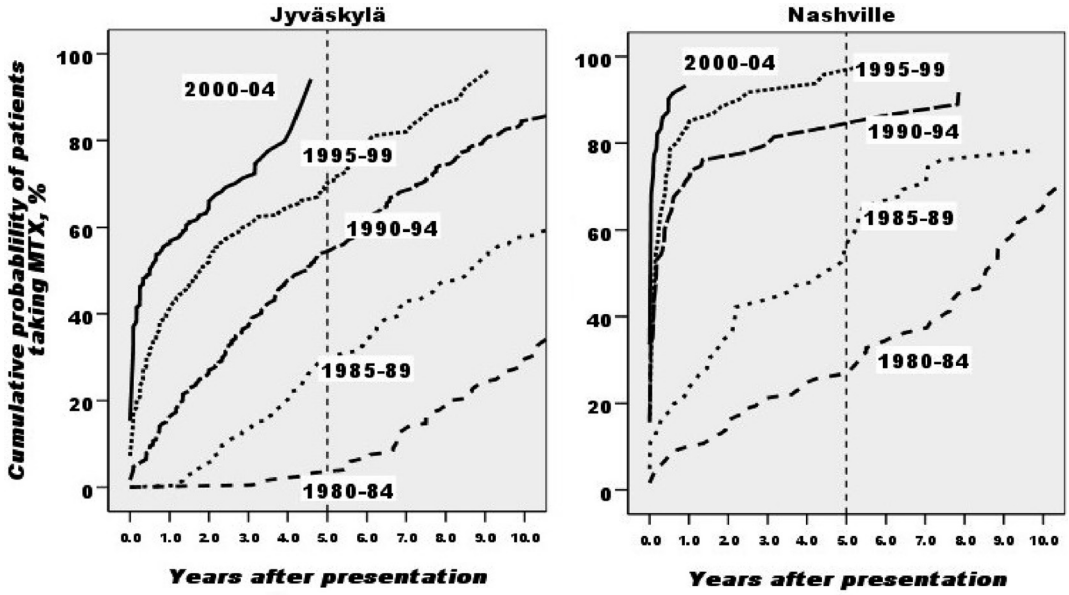

Fig. 2. Interval between patient presentation and initiation of MTX in Jyväskylä, Finland, and Nashville, Tennessee, according to the period of patient presentation.

cal studies and in clinical trials, e.*g*. in an inception cohort from Polynesia, the maximal MTX dose was 15mg per week in 1984–89 (34). In the FINRACo trial, the maximal MTX dose was 15mg/week, combined with other DMARDs (35). In usual care, the average MTX doses have remained considerably lower until recent years.

In the Danish biologic database DANBIO, the median MTX dose increased from 12.5mg/week in 2000/2001 to 20mg/week in 2005 in patients who started biologic treatments (36). In the IORRA database (37), MTX dose increased between 2000 and 2006 and was associated with better clinical outcomes, although average MTX doses in Japan generally remain <10mg/week.

MTX in QUEST-RA database from 25 countries

A collaborative program called Quantitative Standard Monitoring of Patients with RA (QUEST-RA) was established in 2005 to review patients who receive usual care in many countries (38).

As of April 2008, the program included patients from 25 countries representing a typical RA cohort in demographic features, with mean age of 56 years, 79% females, and mean disease duration of 11 years (39). DMARDs were taken by 88–100% of all patients in the 25 countries (Table III); the mean number of DMARDs taken over disease course was 2.7. The median delay between first symptoms and initiation of the first DMARD ranged from <6 months in three countries to one year or more in 10 countries. MTX was taken by 69–98%, prednisone by 30–97%, and biologic agents by 1–54% of patients. DMARDs were taken for less than 50% of disease duration in the UK, Ireland, Hungary, Latvia, Lithuania, and Argentina, and for more than 100% (percentages greater than 100 indicate simultaneous use of two or more DMARDs) in Finland, Greece, and Brazil. MTX covered 21–57% of disease duration, and the use of biologics covered 0.2–14% (Table III).

Limitations of available data concerning usual clinical care

Recent medical literature concerning RA has been dominated by targeted biological agents including clinical trials and national databases of patients who receive biologic treatments. The ascendancy of early treatment with weekly low-dose MTX for RA over the past 25 years remains relatively underrecognised although MTX has been recognised as an anchor drug for RA (40).

We found data concerning initial treatment for early RA in usual care from 10 countries. Clinical cohorts and databases provide data from 15 countries, and QUEST-RA represents 25 countries. Therefore, quantitative data concerning patient clinical course and DMARDs for RA are not available at all in the majority of countries. Apparently most of the reported data concerning treatments for RA are based on cohort studies from specialised clinics with advanced treatment strategies in the US and Western European countries. Therefore, these data represent a small, selected minority of all patients with RA.

Why are reports of usual clinical care infrequent? Some explanations can be suggested:

1 – Most usual clinical rheumatology care continues to be conducted according to physicians' impressions rather than quantitative measures, which are used primarily in clinical trials and other clinical research. Laboratory tests which are frequently normal, and contribute little to documentation of long-term outcomes, generally are the only quantitative measures available in medical records from usual care (41).

2 – Clinical registries to monitor patients outside of clinical trials (42) generally include only selected patients, *e.g*. patients with early disease or patients who receive certain therapies, *e.g*. biological agents, which may be taken by only a minority of patients in most settings.

3 – The methodology to collect clinical data in electronic format as part of usual care has become available only recently, and remains underutilised in most settings; until recent years, documentation of clinical care has been a privilege of advanced clinics with re-

Table III. Treatment-related variables in the QUEST-RA study in 25 countries, in descending order of disease activity.

Country	DAS28 mean	Patients, taking DMARDs	Delay to start a DMARD, ever, % median	Number of DMARDs ever taken months	MTX ever, % of patients	Prednisone ever, % of patients	Biologics ever, % of patients	Any DMARD, % of disease	MTX, % of disease duration duration	Biologics, % of disease duration
Netherlands	3.1	99	5	2.3	92	30	23	87.6	45.0	4.4
Finland	3.3	100	7	4.0	86	74	17	109.6	25.7	2.2
USA	3.3	98	9	2.1	85	77	33	83.8	39.5	8.5
Greece	3.4	100	7	2.9	94	94	54	104.2	50.8	14.6
Denmark	3.4	99	10	2.8	86	44	23	65.6	25.5	2.9
Spain	3.5	98	13	2.8	87	68	27	67.4	30.9	4.4
France	3.7	99	8	3.7	87	83	53	77.0	31.0	8.9
Sweden	3.8	94	12	2.8	84	69	33	73.7	31.1	7.2
UK	4.0	95	12	2.4	83	54	20	51.3	24.6	1.9
Ireland	4.1	98	10	2.4	93	71	42	55.7	28.9	6.6
Canada	4.1	95	11	3.0	76	62	28	77.6	22.1	5.0
Turkey	4.2	99	12	2.4	89	75	7	75.3	33.4	0.7
Brazil	4.2	100	8	3.0	98	81	27	115.7	57.6	3.7
UAE	4.3	88	11	1.8	73	56	10	70.2	31.3	1.9
Germany	4.4	92	15	2.7	80	54	29	66.5	28.8	6.3
Italy	4.5	96	9	2.4	81	72	27	66.9	28.9	2.9
Estonia	4.7	98	12	2.8	83	76	1	67.4	23.8	0.3
Russia	5.0	88	10	1.8	73	41	18	64.0	28.6	9.7
Hungary	5.1	96	12	2.6	85	58	16	54.3	20.1	0.7
Latvia	5.2	98	24	2.2	92	79	23	52.9	28.0	1.6
Poland	5.3	99	4	3.0	89	80	10	64.0	26.3	0.9
Argentina	5.3	88	13	1.5	68	83	3	46.3	24.5	0.5
Lithuania	5.5	96	13	2.3	84	97	11	45.3	21.2	1.7
Serbia	5.9	96	11	2.0	69	88	2	64.6	25.2	0.3
Kosovo	6.0	100	3	2.0	82	95	1	82.4	36.8	0.2
Total	4.2	97	9	2.7	85	71	23			

DAS28: Disease Activity Score; DMARD: Disease-Modifying Anti-Rheumatic Drug; MTX: Methotrexate; UK: United Kingdom; USA: United States of America; UAE: United Arab Emirates.
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sources allocated to data collection, analyses, and reporting.

4 – Clinical data from single clinics often are regarded as "anecdotal," and generally not recognised as sufficiently "scientific" for publication in the rheumatology literature. Therefore, national and international programs such as QUEST-RA are valuable as collaborative efforts to publish data concerning patients who receive usual clinical care.

Conclusions

MTX is currently the most frequently used DMARD in RA. Increases in number of patients treated with MTX and growth of the doses are universal (13, 43, 44). However, use of MTX can still be recognised suboptimal being too little and too late (45) although reviewed data apparently represent most advantaged rheumatology clinics. Further efforts should be directed toward collaborative programs of quantitative assessment of all RA patients in many more countries using electronic tools for more feasible data collection, storage, and analyses. The ultimate goal of these efforts would be to provide data that can be generalised concerning usual clinical care and therapies of patients with RA, and to improve outcomes for patients in many countries over future years.

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