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-
### Growth of MTX / T. Sokka

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Cohort, Reference</th>
<th>Enrolment Period</th>
<th>IM gold</th>
<th>AM</th>
<th>SSZ</th>
<th>MTX</th>
<th>Other DMARDs</th>
<th>No DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>Heinola Cohort, Janti et al. 2001 (46)</td>
<td>1970s 1973–75</td>
<td>56%</td>
<td>36%</td>
<td>0</td>
<td>0</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Finland</td>
<td>Jyväskylä 1983–85 Sokka et al. 2004 (28)</td>
<td>1980s 1983–85</td>
<td>70%</td>
<td>30%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Austria</td>
<td>Aletaha et al. 2002 (47)</td>
<td>1995 1985</td>
<td>87%</td>
<td>7%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6%</td>
</tr>
<tr>
<td>NL</td>
<td>Welsing et al. 2005 (23)</td>
<td>1995–90</td>
<td>na</td>
<td>na</td>
<td>60%</td>
<td>2%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>Aletaha et al. 2002 (47)</td>
<td>1995 1991–95</td>
<td>20%</td>
<td>46%</td>
<td>22%</td>
<td>4%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>Welsing et al. 2005 (23)</td>
<td>1995–90</td>
<td>na</td>
<td>na</td>
<td>82%</td>
<td>9%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>ERAS, Young et al. 2000 (48)</td>
<td>1995–94</td>
<td>8%</td>
<td>2%</td>
<td>61%</td>
<td>2%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Greece</td>
<td>Papadopoulos et al. 2002 (50)</td>
<td>1987–1995</td>
<td>5%</td>
<td>30%</td>
<td>0%</td>
<td>2%</td>
<td>21%</td>
<td>44%</td>
</tr>
<tr>
<td>USA</td>
<td>Western Consortium, Paulus et al. 1999 (14)</td>
<td>1993–1996</td>
<td>4%</td>
<td>17%</td>
<td>7%</td>
<td>36%</td>
<td>0</td>
<td>36%</td>
</tr>
<tr>
<td>Sweden</td>
<td>BARFOT, Forslind et al. 2004 (51)</td>
<td>1995–1997</td>
<td>0</td>
<td>34%</td>
<td>24%</td>
<td>8%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>Jyväskylä 1995–96, Sokka et al. 2004 (28)</td>
<td>2000s 1995–96</td>
<td>3%</td>
<td>1%</td>
<td>95%</td>
<td>1%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>France</td>
<td>Brittany, Saraux et al. 2002 (52)</td>
<td>2000s 1995–97</td>
<td>32%</td>
<td>34%</td>
<td>7%</td>
<td>10%</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Finland</td>
<td>Jyväskylä 1997, Makinen et al. 2005 (53)</td>
<td>2000s 1997</td>
<td>na</td>
<td>na</td>
<td>73%</td>
<td>20%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Sweden</td>
<td>Carl et al. 2006 (54)</td>
<td>2000s 1997</td>
<td>na</td>
<td>na</td>
<td>30%</td>
<td>23%</td>
<td>11%</td>
<td>33%</td>
</tr>
<tr>
<td>Austria</td>
<td>Aletaha et al. 2002 (47)</td>
<td>2000s 1998</td>
<td>1%</td>
<td>40%</td>
<td>29%</td>
<td>29%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>NL</td>
<td>Welsing et al. 2005 (23)</td>
<td>2000s 1996–2000</td>
<td>na</td>
<td>na</td>
<td>76%</td>
<td>10%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>ERATER, Sokka &amp; Pincus, 2002 (55)</td>
<td>2000s 1998–2003</td>
<td>0</td>
<td>7%</td>
<td>1%</td>
<td>82%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Sweden</td>
<td>Carl et al. 2006 (54)</td>
<td>2000s 2001</td>
<td>na</td>
<td>na</td>
<td>20%</td>
<td>54%</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>USA</td>
<td>SONORA, Bombardier et al. 2002 (56)</td>
<td>2000s Early 2000s</td>
<td>0</td>
<td>16%</td>
<td>5%</td>
<td>27%</td>
<td>17%</td>
<td>35%</td>
</tr>
<tr>
<td>Italy</td>
<td>GIARA, CER 2003 (57)</td>
<td>2000s Early 2001</td>
<td>na</td>
<td>18%</td>
<td>1.2%</td>
<td>19%</td>
<td>11%</td>
<td>51%</td>
</tr>
<tr>
<td>France</td>
<td>ESPOIR, Benhamou et al. 2009 (58)</td>
<td>2000s 2002–2005</td>
<td>1%</td>
<td>14%</td>
<td>10%</td>
<td>54%</td>
<td>Lef: 5%</td>
<td>20%</td>
</tr>
<tr>
<td>Latin America</td>
<td>GLADAR early RA database 2006 (15)</td>
<td>2000s 2004–2006</td>
<td>0</td>
<td>46%</td>
<td>12%</td>
<td>82%</td>
<td>Lef: 11%</td>
<td>8%</td>
</tr>
</tbody>
</table>

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.

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 1990–1994.
### Table II. The DMARD profile in selected clinical cohorts and clinical databases, according to period of time.

<table>
<thead>
<tr>
<th>Country register or cohort, reference</th>
<th>Study period</th>
<th>Percentage of patients taking selected DMARDs</th>
<th>IM gold</th>
<th>AM</th>
<th>SSZ</th>
<th>MTX</th>
<th>Biol</th>
<th>Other DMARDs</th>
<th>No DMARD</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1970s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway Tromsø, Riise et al. 2001 (61)</td>
<td>15-yr follow-up</td>
<td>1970s</td>
<td>35%</td>
<td>55%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13%</td>
<td>na</td>
<td>ever used</td>
</tr>
<tr>
<td>USA Nashville TN, Pincus et al. 1984 (7)</td>
<td>1973</td>
<td>1980-1985</td>
<td>60%</td>
<td>26%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>na</td>
<td>na</td>
<td>ever used</td>
</tr>
<tr>
<td><strong>1980s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>USA Nashville TN, Pincus et al. 2005 (25)</td>
<td>1985</td>
<td>1980-1990</td>
<td>10%</td>
<td>5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9%</td>
<td>66%</td>
<td>cross sect</td>
</tr>
<tr>
<td>UK GPRD database, Edwards et al. 2005 (62)</td>
<td>1987</td>
<td>1980-1990</td>
<td>13%</td>
<td>0%</td>
<td>32%</td>
<td>2%</td>
<td>0</td>
<td>14%</td>
<td>39%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Finland Jyväskylä Cohort 1983-85, Sokka et al. 2004 (28)</td>
<td>1988-1990</td>
<td>1980-1990</td>
<td>19%</td>
<td>7%</td>
<td>9%</td>
<td>12%</td>
<td>0</td>
<td>30%</td>
<td>23%</td>
<td>cross sect</td>
</tr>
<tr>
<td>NL Leiden, van Schaardenburg et al. 1993 (63)</td>
<td>1989-1990</td>
<td>1980-1990</td>
<td>25%</td>
<td>63%</td>
<td>3%</td>
<td>0</td>
<td>0</td>
<td>9%</td>
<td>na</td>
<td>ever used</td>
</tr>
<tr>
<td><strong>1990s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland Jyväskylä Cohort 1988-89, Sokka et al. 2004 (28)</td>
<td>1990-1990</td>
<td>1990-1990</td>
<td>24%</td>
<td>0%</td>
<td>15%</td>
<td>18%</td>
<td>0</td>
<td>14%</td>
<td>29%</td>
<td>cross sect</td>
</tr>
<tr>
<td>USA Nashville TN, Pincus et al. 2005 (25)</td>
<td>1995-1998</td>
<td>1990-1990</td>
<td>47%</td>
<td>35%</td>
<td>35%</td>
<td>49%</td>
<td>0</td>
<td>&gt;63%</td>
<td>0</td>
<td>ever used</td>
</tr>
<tr>
<td>NL Leiden, van Schaardenburg et al. 1993 (63)</td>
<td>1995-1998</td>
<td>1990-1990</td>
<td>30%</td>
<td>6%</td>
<td>49%</td>
<td>36%</td>
<td>0</td>
<td>35%</td>
<td>6%</td>
<td>ever used</td>
</tr>
<tr>
<td><strong>2000s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain EMECAR, Gonzalez-Alvaro 2003 (72)</td>
<td>1999-2000</td>
<td>1999-2000</td>
<td>13%</td>
<td>29%</td>
<td>24%</td>
<td>40%</td>
<td>0</td>
<td>48%</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>France EMAR, Abasolo et al. 2008 (73)</td>
<td>1999-2005</td>
<td>2000-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>69%</td>
<td>0</td>
<td>9%</td>
<td>5%</td>
<td>ever used</td>
</tr>
<tr>
<td>USA Nashville TN, Pincus et al. 2005 (25)</td>
<td>2000-2005</td>
<td>2000-2005</td>
<td>1%</td>
<td>4%</td>
<td>0</td>
<td>73%</td>
<td>4%</td>
<td>5%</td>
<td>13%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Japan IORRA, Yamanaka et al. 2007 (74)</td>
<td>2000-2005</td>
<td>2000-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>34%</td>
<td>0</td>
<td>48%</td>
<td>18%</td>
<td>cross sect</td>
</tr>
<tr>
<td>USA ERATER Sokka &amp; Pincus 2002 (55)</td>
<td>2001-2005</td>
<td>2001-2005</td>
<td>0%</td>
<td>16%</td>
<td>4%</td>
<td>89%</td>
<td>14%</td>
<td>22%</td>
<td>na</td>
<td>ever used</td>
</tr>
<tr>
<td>Finland Jyväskylä Cohort 1995-96, Sokka et al. 2004 (28)</td>
<td>2000-2001</td>
<td>2000-2001</td>
<td>7%</td>
<td>2%</td>
<td>10%</td>
<td>69%</td>
<td>1%</td>
<td>0</td>
<td>11%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Germany National database, Thiele et al. 2005 (75)</td>
<td>2001-2005</td>
<td>2001-2005</td>
<td>0%</td>
<td>5%</td>
<td>7%</td>
<td>56%</td>
<td>4%</td>
<td>17%</td>
<td>9%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Norway Norwegian DMARD register, Kvien et al. 2005 (76)</td>
<td>2001-2005</td>
<td>2001-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>24%</td>
<td>0</td>
<td>8%</td>
<td>10%</td>
<td>–</td>
</tr>
<tr>
<td>Brazil São Paulo, Chamont et al. 2008 (77)</td>
<td>2001-2003</td>
<td>2001-2003</td>
<td>na</td>
<td>47%</td>
<td>15%</td>
<td>88%</td>
<td>0</td>
<td>3%</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sweden Malmö RA register, Söderlin et al. 2007 (67)</td>
<td>2002-2005</td>
<td>2002-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>44%</td>
<td>14%</td>
<td>11%</td>
<td>31%</td>
<td>cross sect</td>
</tr>
<tr>
<td>UK GPRD database, Edwards et al. 2005 (62)</td>
<td>2002-2005</td>
<td>2002-2005</td>
<td>2%</td>
<td>8%</td>
<td>26%</td>
<td>30%</td>
<td>0</td>
<td>2%</td>
<td>32%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Hungary Röjkovich et al. 2007 (78)</td>
<td>2003-2005</td>
<td>2003-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>64%</td>
<td>na</td>
<td>Lef: 11%</td>
<td>na</td>
<td>cross sect</td>
</tr>
<tr>
<td>Norway Norwegian DMARD register, Kvien et al. 2005 (76)</td>
<td>2004-2005</td>
<td>2004-2005</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>8%</td>
<td>69%</td>
<td>13%</td>
<td>10%</td>
<td>–</td>
</tr>
<tr>
<td>Japan IORRA, Yamanaka et al. 2007 (74)</td>
<td>2006-2007</td>
<td>2006-2007</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>59%</td>
<td>3%</td>
<td>27%</td>
<td>11%</td>
<td>cross sect</td>
</tr>
<tr>
<td>UAE Dubai, Badsha et al. 2007 (79)</td>
<td>2006-2007</td>
<td>2006-2007</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>29%</td>
<td>2%</td>
<td>11%</td>
<td>58%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Germany National database, Ziegler et al. 2010 (80)</td>
<td>2007-2008</td>
<td>2007-2008</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>7%</td>
<td>8%</td>
<td>56%</td>
<td>16%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Denmark DANBIO, Hetland et al. 2010 (81)</td>
<td>2000-2009</td>
<td>2000-2009</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>76%</td>
<td>na</td>
<td>na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain Ide et al. 2009 (82)</td>
<td>2009-2009</td>
<td>2009-2009</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>59%</td>
<td>50%</td>
<td>na</td>
<td>Lef: 34%</td>
<td>cross sect</td>
</tr>
<tr>
<td>Brazil Ide et al. 2009 (82)</td>
<td>2009-2009</td>
<td>2009-2009</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>46%</td>
<td>0</td>
<td>Lef: 19%</td>
<td>na</td>
<td>cross sect</td>
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<tr>
<td>Argentina Buenos Aires, Tamborenea et al. 2010 (83)</td>
<td>2009-2009</td>
<td>2009-2009</td>
<td>0%</td>
<td>na</td>
<td>na</td>
<td>74%</td>
<td>na</td>
<td>excludedLef: 13%</td>
<td>13%</td>
<td>cross sect</td>
</tr>
</tbody>
</table>

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.
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-
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 under-represented 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.

<table>
<thead>
<tr>
<th>Country</th>
<th>DAS28 mean</th>
<th>Patients, taking DMARDs</th>
<th>Delay to start DMARD, ever, % median</th>
<th>Number of DMARDs ever taken months</th>
<th>MTX ever, % of patients</th>
<th>Prednisone ever, % of patients</th>
<th>Biologics ever, % of patients</th>
<th>Any DMARD, % of disease</th>
<th>MTX, % of disease duration</th>
<th>Biologics, % of disease duration</th>
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<tbody>
<tr>
<td>Netherlands</td>
<td>3.1</td>
<td>99</td>
<td>5</td>
<td>2.3</td>
<td>92</td>
<td>30</td>
<td>23</td>
<td>87.6</td>
<td>45.0</td>
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</tr>
<tr>
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<td>3.3</td>
<td>100</td>
<td>7</td>
<td>4.0</td>
<td>86</td>
<td>74</td>
<td>17</td>
<td>109.6</td>
<td>25.7</td>
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<tr>
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<td>23</td>
<td>90.2</td>
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</tbody>
</table>

DAS28: Disease Activity Score; DMARD: Disease-Modifying Anti-Rheumatic Drug; MTX: Methotrexate; UK: United Kingdom; USA: United States of America; UAE: United Arab Emirates.
Modified from (39), with permission.

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 advanced 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.

Acknowledgments

QUEST-RA investigators and Theodore Pinus.

References


22. WelsingPM, van Riel PL: The Nijmegen inception cohort of early rheumatoid arthri-

23. Welsing PM, Fransen J, van Riel PLCM: Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 to 2003 in an inception cohort of early rheumatoid arthri-


27. Alarcon GS: Methotrexate use in rheuma-

toid arthritis. A Clinician’s perspective. Immu-


29. Möttönen T, Hännonen P, Leirisalo-Repo M et al.: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-

RACo trial group. Lancet 1999; 353: 1568-

30. Hetland ML, Lindegaard IH, Hansen A et al.: Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response or adherence to therapy? Results from the nationwide Danish DANBIO Reg-


37. Ormestad M, Holmes T, Schettler JD, Fries JF: The methotrexate therapeutic re-


39. Aletaha D, Smolen JS: The rheumatoid arthri-
tis patient in the clinic: comparing more than 1300 consecutive DMARD courses. Rheum 2002; 41: 1367-74.

40. Young A, Dixey J, Cox N et al.: How does functional disability in early rheumatoid arthri-


42. Alarcon GS: Methotrexate use in rheuma-
toid arthritis. A Clinician’s perspective. Immu-


44. Möttönen T, Hännonen P, Leirisalo-Repo M et al.: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-

RACo trial group. Lancet 1999; 353: 1568-

35. Hetland ML, Lindegaard IH, Hansen A et al.: Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response or adherence to therapy? Results from the nationwide Danish DANBIO Reg-


37. Alarcon GS: Methotrexate use in rheuma-
toid arthritis. A Clinician’s perspective. Immu-


54. CARLI C, EHLIN AG, KLAERESKOG L, LIND- 
BLAD S, MONTGOMERY SM: Trends in dis-
ease modifying antirheumatic drug prescrip-
tion in early rheumatoid arthritis is influ-
enced more by hospital setting than patient or

55. SOKKA T, PINCUS T: Contemporary disease 
modifying antirheumatic drugs (DMARD) in 
patients with recent onset rheumatoid arthri-
tis in a US private practice: methotrexate as 
the anchor drug in 90% and new DMARD in 

56. BOMBARDIER C, DEATON RL, GREGERSEN 
P, MASSAROTTO E, FORMICA C, WEISMAN 
MH: Pattern of DMARD use in a North 
American cohort of patients with early 
rheumatoid arthritis (RA) (SONORA). Ar-
thritis Rheum 2002; 46 (9 Suppl.), S344.
(Abstract)

57. GIARA et al.: Aggressive 
rheumatoid arthritis registry in Italy. Charac-
teristics of the early rheumatoid arthritis sub-
type among patients classified according to 
the ACR criteria. Clin Exp Rheumatol 2003; 
21 (Suppl. 31): S129-S132.

58. BHENHAMOU M, RINCHEVAL N, ROY C et al.: 
The gap between practice and guidelines in 
the choice of first-line disease modify-
ing antirheumatic drug in early rheumatoid 
arthritis: results from the ESPOIR cohort. J 
Rheumatol 2009; 36: 934-42.

59. SOKKA T, ENVALDS M, PINCUS T: Treatment 
of rheumatoid arthritis: a global perspec-
tive on the use of antirheumatic drugs. Mod 

60. RASKER JJ, COSH JA: Radiological study of 
cervical spine and hand in patients with 
rheumatoid arthritis of 15 years’ duration: an 

61. RIBSE T, JACOBSEN BK, GRAN IT: Changes in 
therapy of rheumatoid arthritis during the pe-
riod 1979 to 1996. Scan J Rheumatol 2001; 

62. EDWARDS CJ, ARDEN NK, FISHER D et al.: 
The changing use of disease-modifying anti-
rheumatic drugs in individuals with rheuma-
toid arthritis from the United Kingdom Gen-
eral Practice Research Database. Rheumatol-

63. VAN SCHAARDENBURG D, HAZES JM, DE 
BOER A, ZWINDERMAN AH, MEIJERS KA, 
BREEVDELD FC: Outcome of rheumatoid ar-
thritis in relation to age and rheumatoid factor 

64. HAMADA Y, SHINOYAMA F, OKADA M, FUJI-
MURA T: Outcome of patients with rheuma-
toid arthritis treated by step-wise adminis-
tration of disease-modifying antirheumatic 
Drugs over a 10-year period. Mod Rheumatol 

65. GORDON P, WEST J, JONES H, GIBSON T: A 
10 year prospective followup of patients with 
rheumatoid arthritis 1986-96. J Rheumatol 

66. KVIENTK, UHLIG T, KRISTIANSEN IS: Cri-
teria for TNF-targeted therapy in rheumatoid 
arthritis: estimates of the number of patients 
potentially eligible. Drugs 2001; 61: 1711-
20.

67. SODERLIN MK, LINDRUTH Y, JACOBSSON 
LT: Trends in medication and health-related 
quality of life in a population-based rheu-
matoid arthritis register in Malmo, Sweden. 

68. MINAUR NJ, JACOBY RK, COSH JA, TAYLOR 
G, RASKER JJ: Outcome after 40 years with 
rheumatoid arthritis: a prospective study 
of function, disease activity, and mortality. 
J Rheumatol 2004; 31 (Suppl. 69): S3-8.

69. EBERHARDT K, FEX E: Clinical course and 
remission rates in patients with early rheuma-
toid arthritis: relationship to outcome after 5 

70. LINQVIST E, SAXNE T, GEBOREK P, EBER-
HARDT K: Ten year outcome in a cohort of 
patients with early rheumatoid arthritis: 
health status, disease process, and damage. 

71. DADDONIENE J, UHLIG T, STROPUVIENE S, 
VENALIS A, BOONEN A, KVIENTK: Disease 
activity and health status in rheumatoid ar-
thritis: a case-control comparison between 
Norway and Lithuania. Ann Rheum Dis 

72. GONZALEZ-ALVARO I, CARMONA L, BAL-
SA A et al.: Patterns of disease modifying antirheumatic drug use in a Spanish cohort of 
patients with rheumatoid arthritis. J Rheu-

73. ABASOLO L, JUDEZ E, DESCALZO MA, 
GONZALEZ-ALVARO I, JOVER JA, CARMO-
NA L: Cancer in rheumatoid arthritis: occur-
rence, mortality, and associated factors in a 
South European population. Semin Arthritis 

74. YAMANAKA H, INOUE E, SINGH G et al.: Im-
provement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large 
observational cohort study IORRA in Japan. 

75. THIELE K, BUTTGEREIT F, HUSCHER D, ZINK 
A: Current use of glucocorticoids in patients 
with rheumatoid arthritis in Germany. Arthri-


76. KVIENTK, HEIBERG MS, LIE E et al.: A Nor-
wegian DMARD register: prescriptions of 
DMARDs and biological agents to patients 
with inflammatory rheumatic diseases. Clin 
Exp Rheumatol 2005; 23 (Suppl. 39): S188-
94.

77. CHERMONT GC, KOWALSKI SC, CICONELLI 
RM, FERRAZ MB: Resource utilization and 
the cost of rheumatoid arthritis in Brazil. 

78. ROJKOVICH B, MÉSZÁROS G, DAGELENE 
S, BARATÁLO S: Changing pattern in the pre-
scription of DMARDs in Hungarian cohorts of 
RA patients. Hungarian Rheumatology 
2007; 48: 148. (Abstract)

79. BADSHA H, KONG KO, TAK PP: Rheumatoid 
arthritis in Dubai- delayed diagnosis and 
low usage of disease modifying antirheu-

80. ZIEGLER S, HUSCHER D, KARBERG K, 
KRAUSE A, WASSENBERG S, ZINK A: Trends 
in treatment and outcomes of rheumatoid 
arthritis in Germany 1997-2007: results from 
the National Database of the German Col-
laborative Arthritis Centres. Ann Rheum Dis 
2010. (Epub ahead of print).

81. HETLAND ML, CHRISTENSEN LJ, TARP U et al.: 

82. BADSHA H, KONG KO, TAK PP: Rheumatoid 
arthritis in Dubai- delayed diagnosis and 
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83. ZIEGLER S, HUSCHER D, KARBERG K, 
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