Monitoring patients with rheumatoid arthritis in routine care: experiences from a treat-to-target strategy using the DANBIO registry

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ABSTRACT

Objective. Advances in aggressive use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as well as biological DMARDs (bDMARDs) have improved the treatment armamentarium for rheumatologists, and modern treatment principles include a treat-to-target (T2T) strategy. However, little is known about the feasibility of a T2T strategy in patients with rheumatoid arthritis (RA) treated in routine care. The aim of the present study was to (i) present the annual number of patients included in DANBIO between 2006 and 2013 and their disease characteristics and (ii) estimate coverage of DANBIO by 2013.

Methods. Patients who were registered with RA for the first time in the nationwide Danish DANBIO database between year 2006 and 2013 were included. Baseline characteristics were assessed in patients treated with bDMARDs and csDMARDs, respectively. The fraction of patients with low/moderate/high disease activity (i.e. DAS28 (CRP-based, 4 variables) was calculated for each calendar year.

Results. From 2006-2013 the number of patients increased from 2,395 to 14,249. By 2013, 29.8% of patients were receiving bDMARD. Patients in the csDMARD group were older, had shorter disease duration, lower disease activity, less disability and radiographic damage. By 2013, 19% of csDMARD (15% of bDMARD) patients were in ACR/Boolean remission. Coverage had increased to between 41% and 79% for patients with RA, for the bDMARD group it was 94%.

Conclusion. Systematic monitoring of RA patients with real-time feedback to the physician is feasible, although the goal of treat-to-target is not achieved in a substantial proportion of patients in routine care.

Introduction

Rheumatoid arthritis (RA) is a heterogeneous disease, with well-recognised potential to cause declines in patients' functional status and quality of life (1). In this millennium, advances in aggressive use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) as well as the development of biological DMARDs (bDMARDs) have substantially improved the treatment armamentarium for rheumatologists and outcomes for the patients.

Superior efficacy of bDMARD combination therapy compared to a *placebo-arm* of methotrexate (MTX) monotherapy has been demonstrated in many randomised control clinical trials (RCTs), allowing marketing of these bDMARDs. Several countries, including Denmark, have established longitudinal observational studies (LOS) with the aim to monitor safety and efficacy of biological drugs in routine care (2-9). The majority of patients with RA, however, continue to be treated with csDMARDs. Investigator-initiated randomised clinical trials with long follow-up have demonstrated that a strategy involving aggressive use of csDMARD in early RA may have clinical and radiographic outcomes that are similar to those seen with bDMARDs (10-13). However, little is known about disease control in patients treated with csDMARD in routine care, since few LOS have published data on outcome in this group.

Modern treatment principles include a *treat-to-target* strategy (T2T-strategy),

i.e. treatment should be aimed at reaching a target of remission or low disease activity in every patient (14). Monitoring patients in clinical practice with regular assessment of disease activity (*e.g.* DAS28) is necessary as part of a T2T strategy. However, little is known about how feasible this is in a busy clinical setting.

In Denmark, systematic, prospective collection of data concerning patients with RA treated in routine care with biological agents since year 2000 and with all DMARDs since year 2006 has been conducted in the DANBIO registry in order to optimise treatment and monitoring of this patient group, regardless of which treatment they receive (15, 16).

The aim of this paper is (i) to present the annual number of patients included in DANBIO between 2006 and 2013 and their clinical characteristics, including achievement of low disease activity/ remission and disability and (ii) to estimate coverage of DANBIO by 2013.

Materials and methods

DANBIO is a nationwide, Danish database, for which data are collected electronically concerning adult patients with inflammatory rheumatic diseases (15). Initiated in year 2000, patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, for whom biological treatment was prescribed, were registered. More than 90% of patients who receive biological treatment are included in the registry, and several reports concerning treatment outcomes have been published (4, 17-19).

In 2006, the systematic collection of data was expanded to also include csDMARD-treated patients. Today, DANBIO serves as an electronic patient file in routine care, regardless of treatment.

The cohort constitutes both incident and prevalent patients: ≈5,900 patients were registered in DANBIO within the first year after diagnosis, while the other patients had more established disease at the time of the initial registration. Patients are monitored prospectively and in principle indefinitely. Doctors are encouraged to enter longitudinal follow-up data concerning disease activity, treatments, adverse events, and other relevant data on the registered patients at least twice yearly.

An overview of the variables that are collected at each encounter has been published previously (15). They include patient reported outcomes (*e.g.* patient scores for pain, fatigue and global and disability as measured by the Health Assessment Questionnaire (HAQ)). The treating physician enters doctor's global score, number of swollen (SJC) and tender (TJC) joint counts (28-joint count), serum C-reactive protein (CRP), and medical treatments including joint injections and adverse events. To study trends in functional disability over time, patients were grouped into *no disability* (HAQ <1), *moderate disability* (1≤HAQ <2) and *severe disability* (HAQ ≥2).

It is a challenge to estimate coverage of RA in DANBIO, since the national registration of diseases ("Landspatientregistret") includes only patients who are treated in public hospitals, and the validity of this registration has been questioned (20). The only officially available estimate was published in a medical technology review in 2002 (21). Here, two separate surveys were used to estimate the prevalence of patients with RA in Denmark. First, in a public survey, which was conducted in year 1986–87, 1990–91, 1994 and 2000, representative samples of Danes were interviewed. Denmark had approximately 4.2 mill inhabitants >18 years old in those years (22, 23). The responses were based on how the individual respondent had understood the doctor's diagnosis. The average prevalence of RA was found to be 0.8% (range 0.7–0.9%), corresponding to approximately 35,000 patients. Interviews, however, may overestimate disease prevalence (24). In addition, the number of patients with RA followed by rheumatologists in one region of Denmark with 250,000 inhabitants was 900, corresponding to a prevalence of 0.47%. This prevalence is similar to two Norwegian studies in which the prevalence was estimated to be 0.47% and 0.6%, respectively (24). By extrapolation to the whole country, approximately 18,000 patients with RA are treated in rheumatology settings.

Statistics

Descriptive, non-parametric analyses were applied. We present clinical data

Table I. Characteristics of the DANBIO cohort from 2006 to 2013.

	bDMARD		csDMARD		*p*-value[*]
Age (years)	57	(47-65)	63	(52-71)	<0.0001
Follow-up time (years)	6	(3-8)	3	(1-5)	<0.0001
Gender (% women)	75%		71%		<0.0001
Disease duration (years)	6	(2-14)	2	(0-9)	<0.0001
HAQ (0-3)	1.25	(0.75-1.75)	0.625	(0.75-1.75)	<0.0001
SJC (0-28)	6	(3-9)	1	(0-4)	<0.0001
TJC (0-28)	8	(4-14)	2	(0-6)	<0.0001
Pain score (VAS 0-100)	60	(41-75)	34	(16-56)	<0.0001
Fatigue score (VAS 0-100)	63	(44-79)	40	(17-65)	<0.0001
Patient global score (VAS 0-100)	66	(48-80)	40	(18-65)	<0.0001
Doctor's global score (VAS 0-100)	41	(26-60)	15	(5-31)	<0.0001
C-reactive protein (mg/L)	12	(5-29)	6	(3-14)	<0.0001
DAS28 (4 variables, CRP)	5.0	(4.2-5.8)	3.3	(2.3-4.5)	<0.0001
Methotrexate (%)	70		61		<0.0001
Methotrexate (mg/w in those on drug)	20	(12.5-25)	15	(12.5-20)	<0.0001
Other sDMARD incl combinations (%)	24		21		<0.0001
Biological drugs in monotherapy	20		NA		<0.0001
Biological drugs in combination with sDMARD	80		NA		<0.0001
Prednisolone, oral (%)	32		11		<0.0001
Prednisolone (mg/day)	7.5		5		<0.0001
Erosive disease (%)[**]	74		52		<0.0001

[*]Mann-Whitney test for continuous variables, Chi-square test for dichotomous variables;
[**]As judged by the local department of radiology.
Shown are medians and interquartile ranges (IQR) unless otherwise indicated.
Data from the first registration in DANBIO (csDMARD patients) or at the initiation of the first biological treatment (bDMARD patients).

as medians and interquartile ranges. For comparison of bDMARD and cs-DMARD treated patients we used the Mann-Whitney test for continuous variables and the Chi-square test for dichotomous variables; A *p*-value of <0.05 was chosen as the level of significance. R-project (www.r-project.org) was used for statistical analyses.
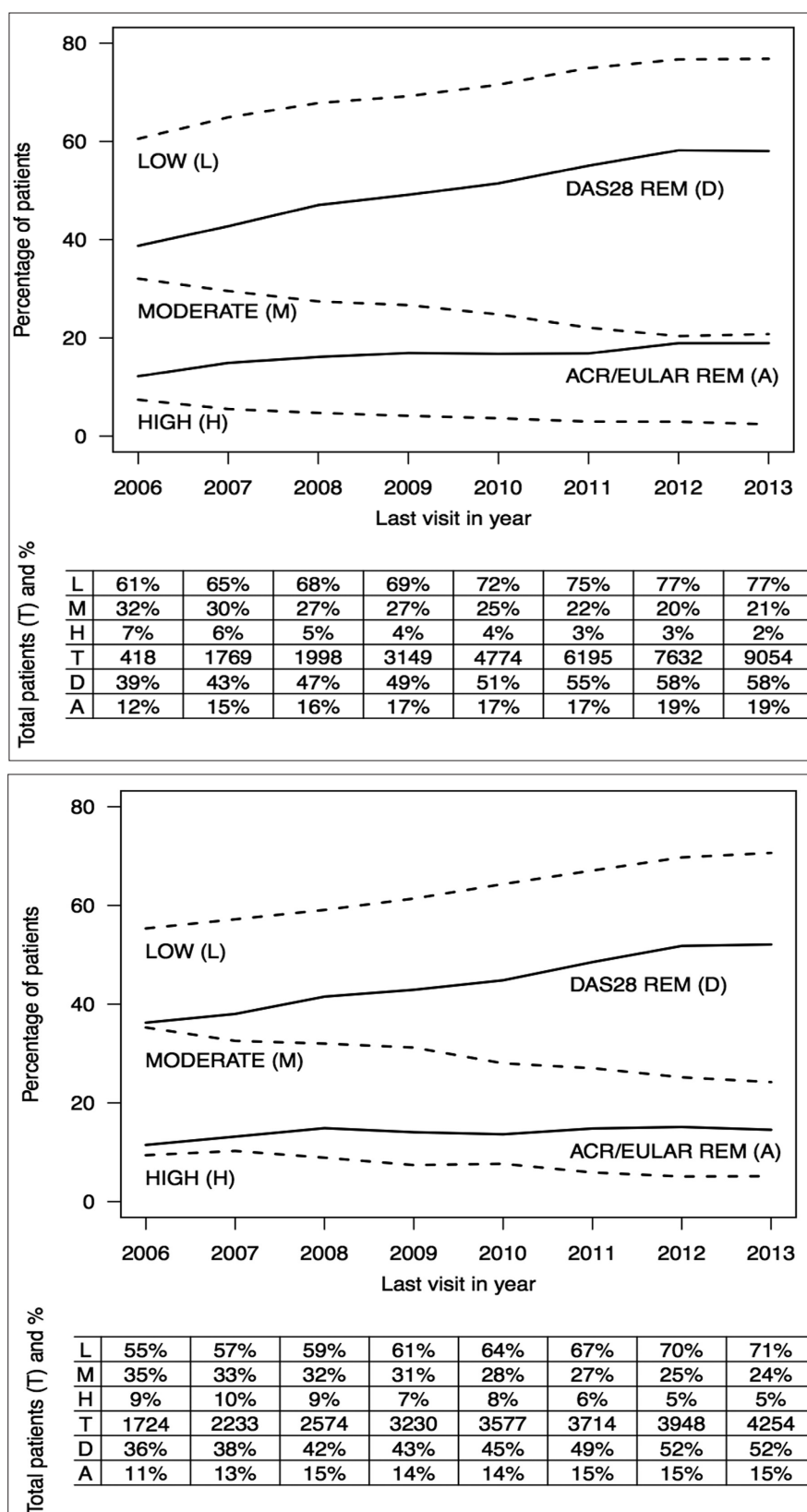
Results

From Jan 1st 2006 to Dec 31st 2013, the total number of patients with RA registered in DANBIO increased from 2,395 to 14,249. Overall, the median age at the time of inclusion was 60 (IQR=50–59) years, 73% were women, 87% positive for IgM-rheumatoid factor (IgM-RF), 54% had erosive disease, disease duration was 4 (0–11) years, HAQ 0.75 (0.25–1.375) and DAS28 3.9 (2.7–5.1). Patients in the csDMARD group were older (median: 63 *vs*. 57 years) and had shorter disease duration (2 *vs*. 6 years) compared to the patients in the bDMARD group (Table I). They had lower DAS28(CRP)-score (3.3 *vs*. 5), fewer swollen (1 *vs*. 6) and tender (2 *vs*. 8) joints, lower serum CRP (6 *vs*. 12 mg/L), and fewer had erosive disease (52% *vs*. 74%). Gender distribution was similar in the two groups. The patient-reported outcomes showed lower HAQ (0.625 *vs*. 1.25), lower pain (34 vs. 60 mm), fatigue (40 *vs*. 63 mm) and global scores (40 *vs*. 66 mm).
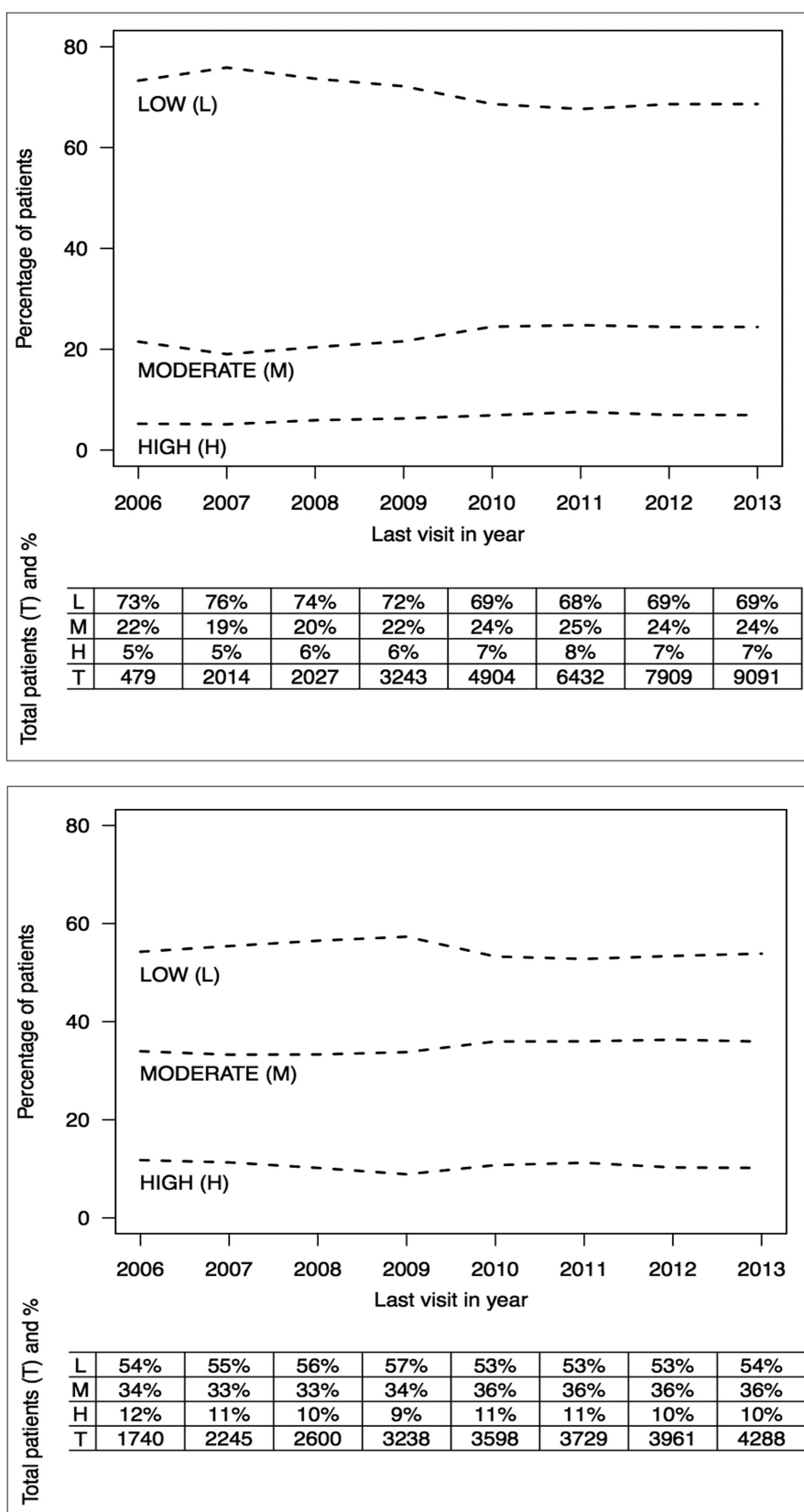
By 2013, 9,054 patients were bD-MARD naïve (MTX: 76%, other csD-MARD: 21%), 4,254 patients received bDMARD, of which etanercept (28%) and adalimumab (21%) were the most prevalent, 66% in combination with csDMARD), and 941 patients had formerly received bDMARD treatment. Therefore, 29.8% of patients were receiving bDMARD at the time of the most recent assessment, and 36.4% had received bDMARD at any time.

In the csDMARD group, 58% received MTX in monotherapy (median weekly dose 15 mg *vs*. 20 mg in the bDMARD group), 21% received other csDMARDs and 12% prednisolone either in monotherapy or in combination (Table I).

In 2006, 61% of the 418 patients who were taking csDMARD treatment had

	2006	2007	2008	2009	2010	2011	2012	2013
L	61%	65%	68%	69%	72%	75%	77%	77%
M	32%	30%	27%	27%	25%	22%	20%	21%
H	7%	6%	5%	4%	4%	3%	3%	2%
T	418	1769	1998	3149	4774	6195	7632	9054
D	39%	43%	47%	49%	51%	55%	58%	58%
A	12%	15%	16%	17%	17%	17%	19%	19%

	2006	2007	2008	2009	2010	2011	2012	2013
L	55%	57%	59%	61%	64%	67%	70%	71%
M	35%	33%	32%	31%	28%	27%	25%	24%
H	9%	10%	9%	7%	8%	6%	5%	5%
T	1724	2233	2574	3230	3577	3714	3948	4254
D	36%	38%	42%	43%	45%	49%	52%	52%
A	11%	13%	15%	14%	14%	15%	15%	15%

Fig. 1. DANBIO's cohort of patients with RA. For each calendar year, the percentage of patients with low (L), moderate (M) and high (H) DAS28 is shown in the figure (dotted lines) and in the table below. In addition, the fraction of patients in DAS28-remssion (D) and ACR/EULAR Boolean remission (A) are presented (full line). The total number of patients with available data (T) is presented in the table.
Figure 1A (top): Patients who are treated with csDMARD.
Figure 1B (bottom): Patients who are treated with bDMARD.

	2006	2007	2008	2009	2010	2011	2012	2013
L	73%	76%	74%	72%	69%	68%	69%	69%
M	22%	19%	20%	22%	24%	25%	24%	24%
H	5%	5%	6%	6%	7%	8%	7%	7%
T	479	2014	2027	3243	4904	6432	7909	9091

	2006	2007	2008	2009	2010	2011	2012	2013
L	54%	55%	56%	57%	53%	53%	53%	54%
M	34%	33%	33%	34%	36%	36%	36%	36%
H	12%	11%	10%	9%	11%	11%	10%	10%
T	1740	2245	2600	3238	3598	3729	3961	4288

Fig. 2. DANBIO's cohort of patients with RA. For each calendar year, the percentage of patients with low (L), moderate (M) and high (H) disability is shown in the figure (dotted lines) and in the table below. The total number of patients with available data (T) is presented in the table.
Figure 1A (top): Patients who are treated with csDMARD.
Figure 1B (bottom): Patients who are treated with bDMARD.

low disease activity (DAS28<3.2). By 2013, it was 77% of 9,054 patients. Similarly, the fraction of patients in DAS28 remission was 39% in 2006 and 58% in 2013, and for ACR/EULAR Boolean remission it was 12% and 19%, respectively (Fig. 1A). For bDMARD, the number of patients was increased from 1,724 to 4,254, and the corresponding figures for low disease activity and remission were slightly lower, but showed a similar pattern as for the csDMARD treated patients.

Figures 2A-B illustrate the fraction of patients in each of the three categories over time in the csDMARD and bDMARD groups from 2006 to 2013. Overall, more patients in bDMARD treatment had moderate ($\approx$36%) to high ($\approx$10%) disability than in the csDMARD group ($\approx$24% and $\approx$7%, respectively). The fractions remained largely unchanged during the period.

Based on the assumption that there are between 18,000 and 35,000 patients with RA in Denmark (5.6 mill inhabitants), DANBIO's coverage may thus be estimated to be between 41% (14,249)/35,000) (for patients with self-reported RA) and 79% (14,249)/18,000) (for patients attending rheumatology clinics and departments with a diagnosis of RA). For the subgroup receiving bDMARD, coverage is 94% (25).

Discussion

The demographic characteristics of the *real-life* DANBIO cohort are typical for RA, and it covers a wide range of disease states regarding treatment, disability and disease activity.

DANBIO collects different types of data on a routine basis: Patient-reported outcomes (PROs), *i.e.* HAQ, pain, fatigue and patient global scores are entered by the patient on touch screens in the waiting room (16). The doctor (or nurse) enters the 28 joint counts and the global score, as well as laboratory (serum CRP) and imaging results during the routine visit in addition to information about medication and adverse events. DANBIO calculates the DAS28 (4 variables including CRP) immediately and presents it to the rheumatologist, thus facilitating escalation of treatment if inflammation is not well

controlled. The outcome measures have been largely unchanged since registration began in year 2000, where they were largely copied from randomised clinical trials. They have proven feasible in a busy clinical practice, where DANBIO is used as an electronic patient file as part of routine care.

The data presented in this paper demonstrate that Danish rheumatologists are committed to monitor not only patients on bDMARD, but also patients on csDMARD treatment, thereby creating a data repository for quality improvement and research purposes. Thus, the number of csDMARD patients in DANBIO has increased from 418 in 2006 to 9054 in 2013, of which >1,800 were recruited during year 2013. The total number of csDMARD patients in DANBIO (including 941 who has withdrawn from bDMARD) exceeds14,500, which is almost three times as many as the bDMARD patients. The true number of patients with RA in Denmark is not known, but has been estimated to be approximately 18,000 for patients who attend rheumatology clinics and departments, and 35,000 for patients with self-reported disease (21). An estimate of DANBIO's coverage by 2013 is thus between 41% and 79%, which is a considerable increase since 2006. As a metaanalysis has suggested that approximately 71% of RA patients are IgM-RF positive (26), the high fraction of IgM-RF positive patients in DANBIO (87%) indicates that some selection may have occurred, *i.e.* patients with more severe disease are more likely to be registered in DANBIO, whereas patients with mild disease are recruited at a slower pace. Furthermore, the results show that an increasing fraction of patients in the csDMARD group fulfil the treatment goal set up by the EULAR (Smolen 2014). By 2013, 3 of 4 patients on csDMARD had low disease activity with a DAS28 of less than 3.2, 58% were in DAS28 remission (DAS28<2.6) and 19% in ACR/EULAR Boolean remission. As expected in a cross sectional study, the patients taking biological DMARDs had poorer clinical status, on the basis of more severe disease. Longitudinal data, exploring the treatment responses in the different groups of patients over

time would be needed to further recognise levels of possible improvement. In conclusion, systematic monitoring of real-life RA patients with a treat-to-target strategy with real-time feedback to the physician is feasible, although the goal of treat-to-target is not achieved in a substantial proportion of patients in routine care.

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