A Norwegian DMARD register: Prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases

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ABSTRACT

Information concerning the effectiveness of drug therapy cannot be obtained only from randomized controlled clinical trials, due to limitations such as a short time frame and narrow inclusion and exclusion criteria. Therefore, complementary longitudinal observational studies performed in a real life setting are required. NOR-DMARD, a Norwegian 5-center register, was established in December 2000. All DMARD prescriptions to patients with inflammatory arthropathies are included, and patients are followed longitudinally with a variety of assessments. As of 2005, 4683 DMARD regimens have been included. Methotrexate is the most commonly used DMARD in rheumatoid arthritis and psoriatic arthrits. The proportions of patients who have received anti-TNF drugs in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile arthritis and other diseases have been 22.5, 21.6, 53.8, 36.9 and 9.7%, respectively. The proportion of patients receiving anti-TNF drugs is considerably higher in 2004 than earlier, and criteria for prescribing anti-TNF drugs appear to be trending toward patients with less severe and active disease. Confounding by indication or channeling bias represents a challenge for the group comparisons of longitudinal effectiveness data, but can be addressed by modern statistical techniques. The NOR-DMARD register may in the future provide comparative real life effectiveness data that may also be used in cost-effectiveness analyses.

Introduction

Rheumatoid arthritis (RA) is a heterogeneous disease, with a natural history that often includes a disabling outcome and reduced life expectancy. Epidemiological studies in Scandinavia have revealed an annual incidence of 25 per 100,000 (1) and a prevalence of about 0.5% (2). The short-term therapeutic goal is usually to relieve symptoms and improve function by reducing inflammation to achieve the major long-term goals of stopping or slowing progression of radiographic damage, improving functional health status, and reducing mortality.

Traditional drug management includes the use of symptom-modifying therapies, mainly nonsteroidal anti-inflammatory drugs and corticosteroids, combined with disease modifying anti-rheumatic drugs (DMARDs). Several advances have been achieved during recent years regarding the practical use of traditional DMARDs. Withdrawal of DMARDs in patients with partial remission leads to the increased risk of disease exacerbation (3), indicating that DMARD therapy should be maintained when effective. Several studies have demonstrated the importance of early DMARD therapy after disease onset (4-7) and combinations of DMARDs have been shown to be more effective than single drug therapy, and with a similar tolerance (8-10).

Another major recent advance involves the development of biological agents, particularly anti-tumor necrosis alpha (anti-TNFα) agents. These compounds, including infliximab, etanercept and adalimumab, have been shown to benefit a large number of patients who fail or have partial responses to standard DMARD therapy. Several randomized controlled clinical trials have demonstrated that anti-TNF drugs are superior to methotrexate (MTX) in such patients (11-17). Their efficacy in retarding radiographic progression has been convincing (12). Leflunomide (LEF), a new DMARD, has also been shown to

have efficacy at least on the same level as traditional DMARDs in RA (18).

Randomized controlled clinical trials have several limitations. They are of short duration (maximum 2-3 years), especially when considering the long-term course of the disease (19). Secondly, the study populations do not necessarily reflect the real life patient populations that are exposed to the drug therapy in clinical practice, which is due to specified protocol requirements (20-23). Therefore, data from clinical trials (efficacy data) are less useful compared to real life data (effectiveness) when examining the cost-effectiveness ratio of therapies (24-26).

To provide data on the real life effectiveness of DMARDs and anti-TNF drugs, we established a Norwegian register of DMARD prescriptions for patients with inflammatory arthropathies, which we titled the NOR-DMARD register. Five rheumatology departments covering a total of 1.3 million inhabitants provide patient data. The overall objective is to examine the safety and effectiveness of DMARD regimens in clinical practise, and to collect data that can be useful for cost-effectiveness evaluations.

Patients and methods

All consecutive DMARD prescriptions in adult patients (≥ 18 years) with inflammatory arthropathies are included. Each prescription of a DMARD regimen represents one case. For example: a patient receives a prescription for MTX monotherapy and is included in NOR-DMARD. After 4 months, due to lack of efficacy the patient continues MTX but receives in addition sulfasalazine (SSZ) and hydroxychloroquine (combination regimen). The case is then recorded as a termination of MTX monotherapy, and the patient is then re-included as a new case in NOR-DMARD under the category of combination regimen.

Study variables are collected at baseline, after 3, 6, 12 months and then yearly up to treatment termination. The variables collected at each visit include:

- Drug therapy
  - Current drug therapy
  - Final date of DMARD regimen (if applicable)
  - Reason for treatment termination (if applicable)
  - Concomitant medication
- Measures of disease process and outcome
  - Pain [100 mm visual analogue scale (VAS)]
  - Fatigue (100 mm VAS)
  - Patient global assessment (100 mm VAS)
  - Physician global assessment (100 mm VAS)
  - 28 swollen joint and 28 tender joint count (28-SJC and 28-TJC)
  - Modified health assessment questionnaire (MHAQ)
  - Erythrocyte sedimentation rate (ESR)
  - C-reactive protein (CRP)
  - Disease activity score [DAS-28, calculated on the basis of 28-SJC and 28-TJC, patient global and ESR (27)]
  - SF-36 [also used for calculation of SF6-D, a utility to be used in cost-effectiveness analyses (28)]
- Adverse events
- Employment status
- Health care utilisation

At baseline, we also record demographic variables (age, gender, years of education, smoking, coffee consumption), diagnosis, disease duration, previous DMARD regimens, IgM rheumatoid factor (yes/no), erosive disease (yes/no), rheumatic nodules (yes/no), and comorbidity (checklist).

The study has been approved by the Norwegian Data Inspectorate, the regional ethical committee and the drug regulatory authorities (as a phase IV observational study). Patients must complete a written informed consent form before their inclusion in the study.

Each center has a full- or part-time research nurse who usually performs the joint counts and organizes the logistics of data collection. Data are entered in a central secretariat where a designated person is responsible for data management. The course of the key outcome measures (e.g. DAS, MHAQ, joint counts and acute phase reactants) is displayed in a flow sheet which is sent from the secretariat to the clinic (Fig. 1). This flow sheet assists the clinician in therapeutic decisions during the patient follow-up.

The current annual budget of this register is NOK 2.5 mill (approximately Euro 300,000), which supports the costs of research nurses and the secretariat. A large percentage of this sum is provided by grants from pharmaceutical companies. The Norwegian government has also provided some financial support for the project.

Results

The number of prescriptions entered into the database as of June 2005 was 4,683. The mean (range) age of the patients was 51.8 (16.6–93.4) years, the disease duration was 8.5 (0–65) years, and the mean number of previous DMARD prescription regimens was 1.9 (range 0–19). The majority of patients had RA (n = 3.039); 448 had psoriatic arthritis (PA), 316 ankylosing spondylitis (AS), 141 juvenile arthritis with persistence into adult age (JA), and 739 had other diagnoses including unspecified arthritides. Of the RA patients 65.7% were rheumatoid factor positive, 54.8% had erosive disease and 19.7% had rheumatic nodules.

MTX monotherapy was the most frequently prescribed DMARD regimen (36.2%). MTX was also the anchor drug in most combinations (Table I). Some DMARDs that were extensively used in the 1980s and 1990s were (albeit infrequently) prescribed, including auranofin, azatioprine, cyclosporine, gold-thiomalate and D-penicillamine.

For practical purposes, the DMARDs are classified into seven major categories: anti-TNF-drugs used as monotherapies, anti-TNF-drugs in combination with MTX, MTX monotherapy, MTX used in combination with other DMARDs, LEF, SSZ and other. Table II shows how these seven categories of DMARD regimens were distributed across the various diagnoses. MTX was most widely prescribed in RA, PA and other inflammatory arthropathies, whereas anti-TNF drugs were most frequently prescribed in AS and JA(either as TNF monotherapy or TNF in combination with MTX). Overall, 22.5% of the prescriptions in RAwere with TNF-blocking agents (8.4% monotherapy, 14.1% in combination with MTX). The

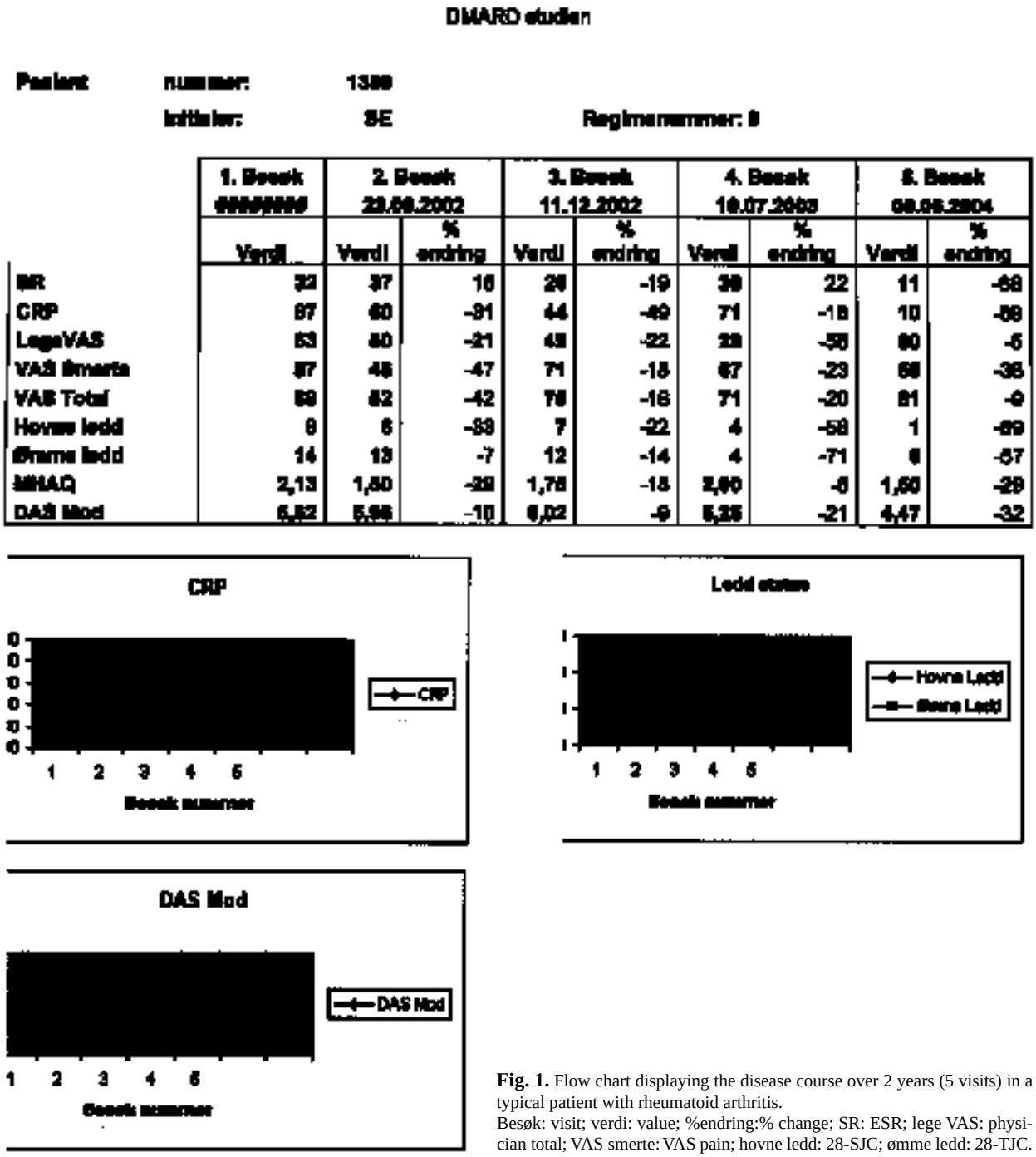

Fig. 1. Flow chart displaying the disease course over 2 years (5 visits) in a typical patient with rheumatoid arthritis.
Besøk: visit; verdi: value; %endring:% change; SR: ESR; lege VAS: physician total; VAS smerte: VAS pain; hovne ledd: 28-SJC; ømme ledd: 28-TJC.

proportions of anti-TNF drugs in PA, AS, JAand other diagnoses were 21.6%, 53.8%, 36.9% and 9.7%, respectively (Table II).

Table III shows the distribution of the main groups of DMARDs within RA, PA, AS across the year of prescription from 2001 to 2004. The use of anti-TNF drugs has increased in all diagnostic groups during recent years. For AS, the total number of DMARD prescriptions is increasing, and this increase can be almost entirely attributed to the use of anti-TNF drugs (Table III).

We wanted to examine whether the increasing number of prescriptions of anti-TNF drugs is related to less stringent criteria for prescription. Table IV shows a consistent trend indicating that anti-TNF drugs are used in RApatients with less severe disease than before. Patients with RA receiving anti-TNF drugs in 2004 had a lower previous number of DMARDs, a lower likelihood of erosions, and lower swollen and tender joint counts, pain scores and DAS scores. Nonetheless, the average RA patient who received anti-TNF therapies in 2004 had severe and active disease (mean DAS 5.2) and had on average tried 3.7 previous DMARD regimens (Table IV).

Since one objective of this database is to compare the effectiveness of DMARDs, we need to take into

Table I. Distribution of 4,683 DMARD regimens prescribed to patients with inflammatory arthropathies in the NOR-DMARD register 2001-2005.

DMARD	n	%
MTX	1694	36.2
Sulphasalazine	624	13.3
Leflunomide	421	9.0
Infliximab + MTX	261	5.6
Etanercept	238	5.1
Etanercept + MTX	228	4.9
MTX + sulphasalazine	204	4.4
Other	164	3.4
Adalimumab + MTX	144	3.1
Antimalarials	130	2.8
Adalimumab	117	2.5
MTX + sulphasalazine + antimalarials	93	2.0
Infliximab	87	1.9
MTX + antimalarials	86	1.8
Gold thiomalate	41	0.9
Leflunomide + MTX	39	0.8
Auranofin	30	0.6
Azathioprin	27	0.6
Anakinra + MTX	21	0.4
Reumacon	14	0.3
Anakinra	8	0.2
Cyclosporin	8	0.2
Cyclosporin + MTX	3	0.1
D-penicillamine	1	0

MTX: methotrexate; SSZ: sulphasalazine; LEF: leflunomide.

account the fact that the various DMARDs are prescribed to patients with different levels of disease severity and activity. Table V displays the baseline characteristics of 3,039 patients with RA. Between 70-80% of the patients receiving anti-TNF-therapies had rheumatoid factor and/or erosive disease, whereas the numbers in patients treated with MTX and SSZ were 40-60 and 30-50, respectively. Similarly, there is also a consistent trend indicating that patients who received anti-TNF-therapies had scores reflecting greater severity for all patient reported measures, including higher joint counts, higher levels of acute phase reactants and a higher number of previous DMARDs. Ongoing analyses suggest that the crude responses are similar in groups receiving MTX, SSZ and anti-TNF, but that anti-TNF therapies appear to be more effective – in accordance with the results from randomized trials – after adjustment for channeling bias (data not shown).

Discussion

The NOR-DMARD database is an example of a register which provides real life research data concerning effectiveness. Such data are complementary to results from randomized controlled clinical trials, since the external validity of such trials can be questioned due to their stringent inclusion and exclusion criteria (20-23). Furthermore the register also serves an important role in the surveillance of the quality of care. The disease course is documented in all patients who are included, and the register provides opportunities to compare clinical practices across the 5 participating centers.

The NOR-DMARD register also allows the documentation of changing patterns of drug therapy over the years. This report illustrates that anti-TNF drugs are currently used more widely than in earlier years (Table III) and that the prescriptions are based on less stringent disease activity and severity criteria. We have previously shown that the prescription of anti-TNF drugs in RA are similar in Denmark and Norway, but that these countries have less stringent disease activity criteria than the United Kingdom (29). One particular strength of NOR-DMARD is the inclusion of DMARD prescriptions of all types of inflammatory arthropathies. Since we include a generic assessment tool (SF-36), we can also compare responses across diseases. One such analysis showed that anti-TNF drugs are at least as effective in AS as in RA (30). The increasing evidence of the efficacy and effectiveness of anti-TNF drugs in AS (31-33) has also been followed by the increasing use of etanercept and infliximab for this condition (Table IV).

The primary objective of NOR-DMARD was to compare the effectiveness of different DMARD regimens. Such comparative analyses raise special statistical challenges. Crude data comparing treatment groups present an incorrect picture of the relative effectiveness as they do not account for channeling bias or confounding by indication (Table V). Adjustment using propensity scores is one statistical technique that could be used to account for these differences at outset (34). We also attempt to use logistic regression analyses to examine the odds for achieving a good EULAR response with anti-TNF versus other DMARDs, adjusting for factors that are assumed to influence the treatment response (rheumatoid factor, baseline DAS, erosive disease, age, sex, number of previous DMARDs (35).

A primary challenge in observational

Table II. Distribution of main categories of DMARD regimens (n = 4,683) across groups of diagnoses.

	Rheumatoid arthritis		Psoriatic arthritis		Ankylosing spondylitis		Juvenile arthritis		Other diagnoses		Total	
TNF mono	256	(8.4)	36	(8.0)	106	(33.5)	23	(16.3)	21	(2.8)	442	(10.4)
TNF + MTX	428	(14.1)	61	(13.6)	64	(20.3)	29	(20.6)	51	(6.9)	633	(14.9)
MTX	1072	(35.3)	215	(48.0)	39	(12.3)	35	(24.8)	333	(45.1)	1694	(40.0)
MTX + DMARD	325	(10.7)	25	(5.6)	9	(2.8)	13	(9.2)	53	(7.2)	425	(10.0)
LEF	335	(11.0)	31	(6.9)	3	(0.9)	8	(5.7)	44	(6.0)	421	(9.9)
SSZ	300	(9.9)	53	(11.8)	81	(25.6)	12	(8.5)	178	(24.1)	624	(14.7)
Other DMARD regimens	323	(10.6)	27	(6.0)	14	(4.4)	21	(14.9)	59	(8.0)	444	(9.5)
Total	3039		448		316		141		739		4683	

TNF mono: anti-TNF drug monotherapy; MTX: methotrexate; SSZ: sulphasalazine; LEF: leflunomide; DMARD: disease-modifying antirhumatic drug.

Table III. Distribution of main categories of DMARDs across year of prescription in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.

	Psoriatic arthritis				Rheumatoid arthritis				Ankylosing spondylitis			
	2001	2002	2003	2004	2001	2002	2003	2004	2001	2002	2003	2004
TNF mono	31 (5.5)	16 (2.2)	80 (11.0)	109 (13.0)	3 10.3)	2 (2.4)	7 (5.2)	19 (12.8)	2 (4.0)	2 (3.6)	18 (26.9)	58 (55.8)
TNF + MTX	51 (9.0)	66 (9.2)	112 (15.4)	157 (18.7)	0 (0)	2 (2.4)	22 (16.3)	29 (19.5)	7 (14.0)	11 (20.0)	17 (25.4)	22 (21.2)
MTX	173 (30.7)	283 (39.3)	254 (34.9)	300 (35.8)	11 (37.9)	54 (65.9)	63 (46.7)	62 (41.6)	12 (24.0)	10 (18.2)	6 (9.0)	7 (6.7)
MTX + DMARD	64 (11.3)	88 (12.2)	73 (10.0)	77 (9.2)	0 (0)	5 (6.1)	7 (5.2)	12 (8.1)	3 (6.0)	3 (5.5)	3 (4.5)	0 (0)
LEF	99 (17.6)	95 (13.2)	74 (10.2)	53 (6.3)	0 (0)	4 (4.9)	11 (8.1)	11 (7.4)	1 (2.0)	1 (1.8)	1 (1.5)	0 (0)
SSZ	70 (12.4)	71 (9.9)	61 (8.4)	81 (9.7)	7 (24.1)	9 (11.0)	16 (11.9)	12 (8.1)	24 (48.0)	21 (38.2)	20 (39.9)	14 (13.5)
Other	76 (13.5)	101 (14.0)	74 (10.2)	62 (7.4)	8 (27.6)	6 (7.3)	9 (6.7)	4 (2.7)	1 (2.0)	7 (12.7)	2 (3.0)	3 (2.9)
Total	564	720	728	839	29	82	135	149	50	55	67	104

TNF mono: anti-TNF drug monotherapy; MTX: methotrexate; SSZ: sulphasalazine; LEF: leflunomide; DMARD: disease-modifying antirhumatic drugs.

Table IV. Disease characterstics in different years of prescription of 622 patients with RA receiving anti-TNF drugs between 2001 and 2004.

	2001 (n=82)	2002 (n=82)	2003 (n=192)	2004 (n=266)	p-value
Disease duration	13.0 (10.0)	10.3 (7.8)	10.5 (8.5)	11.5 (9.7)	0.14
Number of DMARDs	5.0 (2.1)	4.6 (2.3)	3.8 (2.5)	3.7 (2.5)	< 0.001
% rheumatoid factor	81.3	84.1	75.0	77.3	0.34
% erosive disease	88.5	81.5	76.2	71.4	0.01
Pain (VAS)	60.3 (22.0)	58.0 (23.4)	52.2 (24.1)	52.3 (22.5)	0.01
Patient global (VAS)	64.9 (20.8)	61.9 (22.8)	57.5 (23.5)	55.5 (22.1)	0.004
28-SJC	11.1 (6.5)	10.0 (6.1)	8.7 (5.8)	8.5 (5.8)	0.002
28-TJC	12.5 (8.0)	10.9 (7.3)	9.4 (7.0)	9.3 (7.1)	0.002
Physician global	60.3 (18.4)	53.7 (19.5)	47.9 (18.4)	46.1 (18.9)	< 0.001
ESR	36.3 (24.0)	41.1 (27.5)	36.1 (26.5)	28.7 (22.8)	< 0.001
CRP	33.2 (30.2)	40.2 (45.4)	33.1 (35.3)	28.6 (34.2)	0.08
SF-36 physical	33.6 (20.7)	33.0 (23.0)	39.7 (22.2)	42.0 (23.3)	0.002
SF-36 bodily pain	25.0 (16.0)	26.2 (17.6)	29.9 (17.2)	31.1 (16.2)	0.01
MHAQ	2.04 (0.51)	1.97 (0.54)	1.92 (0.56)	1.79 (0.47)	< 0.001
DAS	5.94 (1.34)	5.85 (1.24)	5.50 (1.17)	5.20 (1.30)	< 0.001

studies involves the completeness of data. Resources are not available for the same levels of close monitoring as in randomized clinical trials. In the NOR-DMARD register we have estimated that 15% of all candidates for inclusion in the register are lost, either due to unwillingness to be included or insufficient time for the doctors and nurses to enter the patient into the register. These 15% also include the patients who were assigned to ongoing randomized controlled clinical trials in the various centers. In addition, it appears that about 10% of patients still on therapy are lost to follow-up per year. About 5-10% of patients in randomized trials are lost to follow-up over the course of the trial.

Regular meetings with the participating centers, as well as telephone conferences, are regarded as important to maintain enthusiasm concerning the project. There is no financial incentive for any of the participating centers except that each center is provided with money to cover the salary for a part-time or full-time research nurse. The research nurses are regarded as essential to the success of the project. It is also important to have a professional secretariat to manage data and report back to the centers when data are missing. An addi-

Table V. Baseline disease characterstics across different categories of DMARD regimens in 3,039 rheumatoid arthritis patients.

	TNF mono (n = 256)	TNF+MTX (n = 428)	MTX (n = 325)	MTX+ DMARD (n = 325)	LEF (n = 335)	SSZ (n = 300)	Other (n = 323)	p-value
Disease duration	12.4 (9.3)	10.3 (8.8)	5.9 (8.5)	7.2 (8.0)	11.9 (9.5)	5.3 (8.5)	9.9 (9.6)	< 0.001
Number of DMARDs	4.4 (2.2)	3.6 (2.5)	1.1 (1.8)	1.8 (1.5)	3.2 (2.0)	0.8 (1.3)	3.1 (2.8)	< 0.001
% rheumatoid factor	79.5	76.5	60.6	64.8	72.7	50.7	65.2	< 0.001
% erosive disease	79.1	73.2	41.1	54.5	69.3	33.0	61.5	< 0.001
Pain (VAS)	53.2 (24.6)	53.4 (23.3)	47.7 (23.7)	48.7 (23.5)	52.3 (21.5)	44.8 (23.9)	50.5 (23.5)	< 0.001
Patient global (VAS)	57.2 (24.3)	58.0 (21.9)	50.3 (23.9)	52.7 (23.0)	56.2 (21.9)	47.0 (24.4)	52.7 (23.7)	< 0.001
28-SJC	8.7 (6.2)	9.1 (5.9)	8.0 (5.9)	8.3 (5.7)	8.7 (5.7)	5.7 (4.4)	6.9 (5.1)	< 0.001
28-TJC	10.5 (7.7)	9.5 (7.1)	8.5 (6.8)	8.4 (7.0)	8.6 (6.7)	6.5 (5.7)	7.4 (6.4)	< 0.001
Physician global	48.0 (19.9)	49.6 (19.1)	41.4 (17.0)	44.3 (17.0)	45.1 (17.0)	33.6 (15.8)	38.7 (18.0)	< 0.001
ESR	32.4 (23.9)	33.9 (25.6)	30.1 (23.2)	28.3 (23.4)	31.1 (23.2)	23.5 (20.1)	30.2 (24.9)	0.003
CRP	27.0 (28.3)	34.1 (38.9)	24.9 (28.5)	26.4 (32.0)	26.8 (25.7)	18.6 (27.5)	25.1 (28.2)	< 0.001
SF-36 physical	39.5 (23.6)	39.4 (22.3)	47.9 (24.2)	47.6 (24.0)	40.8 (22.8)	52.4 (25.8)	43.0 (24.9)	< 0.001
SF-36 bodily pain	29.1 (17.2)	29.8 (16.9)	32.8 (17.8)	33.3 (17.3)	31.0 (15.1)	35.4 (18.6)	31.1 (16.5)	0.003
MHAQ	1.92 (0.57)	1.88 (0.50)	1.70 (0.52)	1.68 (0.52)	1.82 (0.48)	1.62 (0.48)	1.75 (0.57)	< 0.001
DAS	5.49 (1.31)	5.41 (1.32)	5.08 (1.30)	5.01 (1.43)	5.27 (1.23)	4.47 (1.34)	4.90 (1.35)	< 0.001

TNF mono: anti-TNF drug monotherapy; MTX: methotrexate; SSZ: sulphasalazine; LEF: leflunomide, DMARD: disease-modifying antirheumatic drugs.

tional benefit for the centers is achieved through the flow sheet, which displays the disease course of individual patients and is useful in therapeutic decisions at an individual level (Fig. 1).

Registers of drug therapy are considered especially important for the detection of infrequent adverse reactions (e.g. severe infections, malignancies, haematological adverse reactions etc.). The NOR-DMARD register is not as suitable for this purpose as some of the nation-wide registers in countries with a much higher population than Norway (36). As shown in Table II, about 1000 anti-TNF regimens have been included during 4 years, which does not provide sufficient power to generage meaningful data concerning infrequent adverse reactions.

Despite this limitation, the 5-center NOR-DMARD register provides other opportunities, as it includes all DMARD regimens and DMARD prescriptions to all inflammatory arthropathies. This longitudinal register with a range of assessed endpoints will also with time provide data that will be important for cost effectiveness analyses.

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