DANBIO: a nationwide registry of biological therapies in Denmark

M.L. Hetland

DANBIO, Copenhagen University Hospital at Hvidovre, Department of Rheumatology, Hvidovre, Denmark.

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Please address correspondence to: Assistant Professor Merete L Hetland, MD, PHD, DANBIO, Copenhagen University Hospital at Hvidovre, Department of Rheumatology 232, Kettegård Alle 30, DK 2650 Hvidovre, Denmark.
E-mail: merete.hetland@dadlnet.dk

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ABSTRACT

Since the year 2000, Danish rheumatologists have been collecting data on a routine basis in the nationwide DANBIO registry, which includes all rheumatologic patients receiving biological drugs. Demographic data, markers of disease activity, current treatment, serious and non-serious adverse events and reasons for discontinuation are registered at each visit either on paper forms or on-line. By June 2005, approximately 3000 treatment courses (18,000 visits) were in the registry, corresponding to close to 90% of eligible patients. Rheumatoid arthritis was the most prevalent diagnosis (75%) followed by ankylosing spondylitis (11%) and psoriatic arthritis (7%). Infections occurred in 43% of the treatment series.

Introduction

Denmark had no routine-based registration of rheumatoid arthritis (RA) patients on a wider scale up to the year 2000, as was the case in most other countries. Inspired by other registries in Europe (1-5), the marketing of tumour-necrosis-alpha (TNF)-inhibitors and other so-called biological drugs triggered the formation of a nationwide, voluntary registry of all rheumatologic patients receiving biological agents. Shortly after it was initiated in October 2000, the DANBIO registry has gained wide acceptance among Danish rheumatologists, with coverage of close to 90% of eligible patients (6). The status of this database in June 2005 is reviewed.

Materials and methods

Since October 2000, Danish rheumatologists have been encouraged to register all patients on a routine basis at the start of and during treatment with biological agents. Table I shows the variables that are collected at baseline and at each medical visit. They include demographic data, markers of disease activity, current treatment, serious and non-serious adverse events and reasons for discontinuation. The disease activity score based on 28 joint count and C-reactive protein (DAS28-CRP) (7) are calculated, together with the EULAR- and ACR- responses (7,8). The variables are collected in a standardised format. Data are entered into the database by scanning the forms using a commercially available software program (TELEform v. 7.1, Cardiff Software Inc., USA). The error-rate during validation has been found to be 0.45% with no evidence of systematic errors (6). Recently, an online-registration has been launched (9). The IT-platform of "DANBIO-online" is entirely based on so-called "Open Source software" de-

Table I. The variables that are collected in DANBIO.

At baseline
Age
Gender
Diagnosis
Years since diagnosis
Previous DMARDs
At each visit
Markers of disease activity in RA
Health assessment questionnaire
Visual analogue scale for pain
Visual analogue scale for patient's global
Visual analogue scale for physician's global
Number of swollen joints (28 count)
Number of tender joints (28 count)
Serum C-reactive protein
Current treatment
Current anti-TNF-therapy
Concomitant DMARD therapy
Concomitant glucocorticoid therapy
At treatment termination
Date for withdrawal
Reason for treatment termination
Adverse events
Serious
Not serious

DMARD: disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis; TNF: tumour necrosis factor.

veloped and supported by worldwide computer science communities, and available at no license-costs in terms of use, customisation for specific needs and sharing with other clinical databases. The most important software in use is the web application platform Plone (www.plone.org / Plone Foundation), the language for statistical programming R (www.r-project.org / R Foundation) and the database MySQL (www. mysql.org / MySQLAB).

DANBIO is run in collaboration with the Danish Society for Rheumatology and the Institute for Rational Pharmacotherapy; the latter organization also hosted and financed the registry until the end of 2003. Since January 2004, the three pharmaceutical companies that market the TNF-inhibitors in Denmark (Abbott Denmark, Schering-Plough Denmark and Wyeth Denmark) have been sponsoring the registry. The sponsors receive anonymous reports on adverse events, market shares etc. in return for their sponsorship and have no representation in the steering committee and no influence on the analysis and publication of data. The Danish Society of Rheumatology and the Institute of Rational Pharmacotherapy appoint the members of the steering committee. The Danish Data Registry has approved the registry, and patients give their written informed consent at inclusion.

Table II. The number of treatment series in DANBIO year by year.

	Cumulated treatment series	Cumulated active treatment series	New treatment series per year	Withdrawn treatment series/year	Cumulated number of visits
-2000	85	68	85	17	241
2001	324	263	239	44	1520
2002	587	429	263	97	3870
2003	1183	790	596	235	7666
2004	2316	1475	1133	448	14049
2005*	3056	1944	740	271	18772

* 2005 covers approximately the first six months of the year.

Table III. Distribution of diagnoses in DANBIO.

Diagnosis	Total number of treatment series	Percentage of all treatment series
Rheumatoid arthritis	2231	76
Ankylosing spondylitis	319	11
Psoriatic arthritis	194	7
Other arthritides	115	4
Other rheumatologic diseases	54	2

Table IV. Adverse events.

Adverse events	Number of treatment series	Percentage of all treatment series
Infections	1293	43
Eczemas	818	27
Allergic reactions	359	12
Lupus-related symptoms	89	3
Other events	1036	34
Total with adverse events	1893	62

Results

The number of treatment series in DANBIO has been rapidly increasing during the five years of its existence, and by the first half of 2005, a total of 3056 treatment series (18.700 visits) were included in the registry. All 27 departments of rheumatology in Denmark report to DANBIO. Table II shows the distribution of new and withdrawn treatment series year by year.

Most of the patients have RA (76%), followed by ankylosing spondylitis (11%), psoriatic arthritis (7%), other arthritides (4%) and other rheumatologic diseases (2%) (Table III).

At baseline, 54% of the patients had severe disease activity (DAS28-score above 5.1), and 35% had moderate disease activity (DAS28-score between 3.2 and 5.1). Before initiation of a biological drug, 92% of the patients have been on methotrexate treatment, 82% on sulphasalazine, 43% on hydroxychlorochine, 27% on parenteral gold, 24% on leflunomide, 21% on azathiprine. Only 3% has not taken any previous DMARD. The median age at baseline was 54 years (inter quartile range: 43-62 years); disease duration 9 years (4-16 years); 64% were women.

Overall, adverse events were reported for 1863 of 3056 courses (62%) (Table IV). The most common adverse events were infections (43%), eczemas (27%), allergic reactions (12%), and lupus-related symptoms (3%). The total number of serious adverse events reported was 187, of which three were reactivations of latent tuberculosis.

Discussion

The rapid increase in the number of TNF-alpha treatment series in DANBIO reflects expanding use of these agents in standard clinical practise, and is similar to that observed in other European countries. Although we have found that the prescription practise has changed over the years towards shorter duration of disease and less severe disease activity at baseline, the majority of patients who were begun on anti TNF-alpha treatments had severe disease of long duration (10). The frequency and types of adverse events to the biological therapies are similar to what has been reported in other studies (2, 5).

After five years of registration in DANBIO, all departments of rheumatology in Denmark continue to report to the registry with a coverage of approximate-

ly 90% of eligible patients. Several factors probably contribute to this high level of participation:

DANBIO returns the collected data systematically to the physicians and departments in two ways: Reports on each patient showing graphically the changes over time in all core variables, DAS28-CRP, EULAR response and ACR–20, –50 and –70 responses since baseline have been sent at regular intervals, and are now available on-line [an example may be viewed at (9)]. This serves as a tool for the rheumatologist to monitor the treatment response in the individual patient. Improvement of treatment quality is also facilitated through regular reports to all departments, in which the indications for treatment, treatment responses etc. are shown for each department, allowing the departments to compare their results with each other [a sample may be viewed at (9)]. The on-line registration is expected to improve quality control even more by allowing true-time feedback on relevant clinical indicators, intra-organisational benchmarking and statistical analysis.

Data from DANBIO has been presented at national and international conferences (11,12), and in peer-reviewed articles (6,10) since 2003. These reports have shown that the registration of adverse events on a routine-based set-up results in a twenty-fold increase in the collection of non-serious adverse events, and a doubling of the report of serious adverse events in comparison with the mandatory reports to the Danish Medicines Agency (6). Thus, reporting to a clinical database appears to improve pharmacovigilance, especially the power to identify rare and late-occurring adverse events. The longitudinal feedback of data concerning efficacy gives important additional information to the results from the clinical trials (12). Since the registry monitors patients across different biological therapies, it has been possible to study the treatment response in "switchers" (11). The registry includes all rheumatologic diagnoses, which allows follow-up data on spondyloarthropathies (13) and other conditions, in addition to RA.

Plans for the future comprise expansion of the registry to include all new cases of RApatients regardless of treatment (from January 2006), assessment of health-related quality of life (from January 2006) and establishing a comparison group of patients with RA that are treated with conventional DMARDs.

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