Longterm Studies in Rheumatoid Arthritis — The German Experience

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ABSTRACT. We describe the aims and uses of a large rheumatological database, the national database of the German Collaborative Arthritis Centres. The database is a continuing registry of all patients with inflammatory rheumatic diseases seen at one of the member sites of the German Collaborative Arthritis Centres. The patients are recorded once a year with a clinical datasheet and a patient questionnaire. The database has been used for identification of deficits and trends in health care, description of current treatment practices, practice variations and individual burden of diseases, as well as for quality assessment. Large differences in disease modifying antirheumatic drug treatment between rheumatologists and nonspecialists as well as deficits in nonmedicinal therapies were identified. Considerable practice variation in German rheumatology with respect to drug and nondrug therapies was identified. The burden of disease (pain, disability, early retirement) was high in various patient subgroups. The database is useful for various aspects of health services research. It has, however, the important limitation that no specific followup procedure is applied. Therefore, longitudinal data exist only for patients in continuing rheumatological care. (J Rheumatol 2004;31 Suppl 69:22–26)

Key Indexing Terms:
DATABASE ARTHRITIS CENTERS HEALTH SERVICES RESEARCH

The national database of the German Collaborative Arthritis Centres is the most important source of information about patients treated in German rheumatology. It provides data on deficits, trends, and variations in health care provision and on outcomes in specialized care. It is also used for internal quality assessment by providing the participating rheumatologist with analyses of their own data compared with others.

The national database of the German Collaborative Arthritis Centres was started in 1993 as part of a government program. The Federal Ministry of Health supported the establishment of so-called arthritis centers, which are networks of rheumatologists who work at university departments, specialized hospitals, hospital departments, or in fee-for-service practices within defined regions. These arthritis centers were established in all parts of Germany, and nearly all of them are coordinated by a university department. Their major aim is to improve the collaboration among all levels and branches of rheumatology, i.e., from primary to tertiary care as well as among rheumatologists with a background in internal medicine or orthopedics. Further, the arthritis centers support general practitioners and other physicians without the rheumatological subspecialization in the care of patients with systemic inflammatory rheumatic diseases. In order to get more information on the health care that is supplied by these centers, the national database was implemented as an obligatory patient registry. This means that each patient with an inflammatory rheumatic disease seen in routine outpatient care is supposed to be documented once a year in all participating outpatient clinics and individual rheumatological practices with a standard clinical record form and patient questionnaire.

In 1997, German pediatric rheumatologists initiated a separate database of children with arthritis. The pediatric rheumatologists are integrated in the arthritis centers, and the pediatric database is similar to the adult database in its organization. Apart from adaptations to the specific situation of children, it contains the same items as the adult database.

The experiences with the national database led to the development of other, more specialized databases and cohorts. All are based on the item pool of the national database.

This article describes the methodological and organizational background, the general aims and uses, and the present developments concerning standard patient documentation in German rheumatology.

PATIENTS AND METHODS

Participation. Rheumatologists from 24 arthritis centers have participated in the database. In 2001, the total number of units that recorded at least 50 cases was 80; among them were 19 university departments in internal rheumatology, 3 university departments in orthopedic rheumatology, 23

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Supported by a grant from the German Federal Ministry of Health (FB2-433346-8/13) 1993 to 1999, and thereafter by a grant from the German Federal Minister of Education and Research (01GI/9944/3) within the Competence Network Rheumatology.

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departments of rheumatology at general hospitals or hospitals for rheumatic diseases, 10 rehabilitation hospitals (formerly spa clinics), and 25 rheumatologists in individual practices.

The database comprises newly referred as well as prevalent cases. Patients seen on a regular basis are registered once a year, possibly in the same month or at least the same quarter-year as in the previous year. Of these patients the same corpus of information is available for successive years. These followup patients form the longitudinal part of the database.

The rheumatologists are asked to register all outpatients with inflammatory rheumatic disease who agree to participate. In addition, inpatients as well as patients with osteoarthritis, soft tissue disorders, or back pain are recorded by some centers for their own study purposes. All central analyses are restricted to outpatients with inflammatory rheumatic diseases for whom complete data can be assumed.

In 2001, the number of patients recorded was 26,445. Considering only outpatients with complete data sets (patient and physician record form available) from the 80 sites mentioned above, data from 17,836 patients were available. Half of them (8752) had rheumatoid arthritis (RA), about 4000 ankylosing spondylitis (AS) or undifferentiated spondyloarthropathy, and 3986 connective tissue diseases such as systemic lupus erythematosus (SLE) or vasculitis. Data are published for different years[1-4]. The pediatric rheumatological database contains data of 3586 children with arthritis, among them 2511 cases with juvenile idiopathic arthritis seen in 2001. The national database for children with rheumatism is reported in detail by Minden, *et al*[5]. Here we report only results from the adult database.

Funding. The German Federal Minister of Health funded the database from 1993 to 1999 within the program "Regional Collaborative Arthritis Centers." In 1999, German rheumatology was lucky to be among the winners of a new governmental program to build up so-called "competence networks" in various fields of medicine ("Competence Network Rheumatology," http://www.rheumanet.org). Funds for 5 years are available in order to improve collaboration between basic science, clinical research, health services research, and health care in rheumatology. The network aims at enhancing understanding in the research area of the patients' problems and their clinical care in order to help researchers identify problems most relevant to patients, as well as making advances in research available as quickly as possible on the patient care level. The database was considered an indisputable part of clinical and epidemiological work in rheumatology. Funding includes a part-time employee in each of the arthritis centers to organize data collection, as well as staff for centralized data analysis. However, no funds are available for the work of participating physicians.

Clinical documentation and the patient questionnaire. The clinical data sheet contains demographic data of the patient (age, sex, insurance), onset of symptoms, onset of treatment in the institution, and up to 3 diagnoses by the rheumatologist. Therapies are reported as "current therapy" (day of registration) and "therapy within the previous 12 months" [analgesics, disease modifying antirheumatic drugs (DMARD), glucocorticoids, and osteoporosis therapy, as well as physio- and occupational therapy]. The type of surgery is recorded as "within previous 12 months" and "ever before." The physician gives a global assessment of the present disease activity (based on a numerical rating scale from 0 to 10), the severity of the disease (based on a 5-item Likert scale), and the functional status. The Steinbrocker functional class[6] was used in a modified form (intermediate values from I to II, II to III, III to IV were allowed) from 1993 to 1999 and — for reasons of better international comparability — has been used in its original form since 2000. The physician ratings of activity, severity, and function give global information on physician's judgment of the patient's condition. For patients with RA, 28-joint counts for swollen and painful joints as well as erythrocyte sedimentation rate and C-reactive protein are recorded by the physician, allowing for the calculation of the Disease Activity Score-28[7].

The diagnoses are registered using a list of 190 diagnoses of the musculoskeletal system, which was developed by a subcommittee of the German rheumatological association before the implementation of the database. Eighty of these diagnoses are indications of inflammatory rheumatic diseases. This list is more specific and detailed than the 9th revision of the International Classification of Diseases (ICD), but all diagnoses based on it can be transformed into ICD-9 or ICD-10 codes by a unified dictionary developed by a consensus group[8].

The patients complete a self-administered paper-and-pencil questionnaire. They give their treatment histories: onset of symptoms, first visit to a rheumatologist, number of visits to the primary physician within the previous 3 months, and visits to the rheumatologist in the previous year. The patients record their stays in hospitals or rehabilitation clinics, in- and outpatient treatment including physiotherapy, balneotherapy, occupational therapy, psychological support, patient education, etc., for the time window of 12 months. Other items examine self-help, social support, degree of help needed, and days of sickness or absence from work. The patients record their current pain, global function, and general well being (previous 7 days) on numerical rating scales (0 to 10). Disability is recorded using an 18-item scale, the Hannover Functional Status Questionnaire (FFbH), which measures limitations in various activities of daily living. The FFbH is similar to the Health Assessment Questionnaire (HAQ) but is more widely used in Germany. The 2 disability scales are highly correlated (r = 0.87). FFbH

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values can be transformed into HAQ values[9,10]. Demographic data of patients are recorded in a standardized way corresponding to official health statistics. Comorbidity and adverse events have been recorded by the patient since 2002.

The privacy of the patients is ensured by coding all data.

Data collection. Governmental funds were provided to establish the position of coordinator in every arthritis center from 1993 to 1999. Since then, the centers themselves have been responsible for the maintenance of the coordinating position. These persons, usually rheumatologists, are also responsible for the supervision of documentation. A second person, usually a student, has been funded for study monitoring and for checking completeness and validity of data. This includes checks for completeness of case notification in the participating units. This post is still being funded within the new program. Data entry is performed centrally by an external company. All centers are provided with their own data files and with support for individual analyses. The study group at the German Rheumatism Research Centre regularly runs workshops to train coordinators and students in study monitoring and data analysis, and provides the centers with programs for data control and analysis. Validity checks are included in this software. After the local data sets have been tested and corrected, the data are sent to the group in Berlin for comprehensive, centralized analysis. They counter-check the data and send out reminders for missing data. The centers are obliged to complete the data at least for age, sex, disease duration, and diagnosis, whereas it is not possible to obtain missing data from a patient questionnaire.

The data sheets have different colors every year to facilitate discrimination between different years.

MAJOR RESULTS AND USES

The database has been used to identify the following:

1. Deficits in health care
2. Current treatment and trends in health care provision
3. Burden of illness in the various rheumatic conditions
4. Direct and indirect costs of rheumatic diseases
5. Outcomes of care under continuing rheumatological care
6. Quality assessment and practice variation (benchmarking)

Deficits in health care. A major aim of the arthritis centers is to offer cooperative treatment for patients with inflammatory rheumatic diseases to nonspecialized physicians to achieve early adequate care for a larger proportion of the population. Therefore, the database monitors how early patients are admitted and what kind of treatment they had before admission.

Between 1993 and 1999, the mean disease duration at first visit to a rheumatologist for patients with RA decreased from 2.0 years to 1.5 years. In the same time, the proportion of new patients with a disease duration less than 2 years who had already had a DMARD therapy over the previous 12 months decreased from 34% to 13%. Even at a disease duration of more than 2 years, less than half of newly admitted patients had previously been treated with DMARD, in comparison to 87% of those previously treated by a rheumatologist[3]. Other deficits concern the much lower prescription rates for osteoporosis medication and the differential use of glucocorticoids in the nonspecialized sector[1].

Current trends in health care. Over the years of observation, a shift in drug treatment and in inpatient treatment was observed. Current treatment has only been recorded as of 1995. Within the 4 years from 1995 to 1999, the proportion of methotrexate in the current treatment of patients with RA increased from 45% to 57%, and combination therapy increased from 8% to 16%. Further, drugs for the prevention or treatment of osteoporosis were used with increasing tendency. In the same time, the proportion of patients treated in inpatient care during a one-year period dropped from 27% in 1993 to 17% in 1999, and the mean duration of stays decreased from 27 to 20 days[3].

Burden of illness. The database is an important source of information about the individual burden of inflammatory rheumatic diseases in Germany. Specific analyses for the description of disease-related burdens in RA, AS, SLE, other vasculitides, and psoriatic arthritis have been carried out or are under way.

We showed that the burden of disease concerning pain, functional limitation, and reduced overall well being in patients with AS who were treated by a rheumatologist was similar to that of patients with RA[11]. Comparing matched pairs of patients with RA and SLE, a higher individual burden (pain, disability) was seen in RA, while work losses were higher in SLE[12].

Due to the high number of cases in the database, labor force participation compared to the age and sex matched population could also be calculated for rare diseases. The standardized employment rates for women were 0.72 for RA, 0.69 for Wegener's disease, and 0.82 for SLE, but almost normal (0.97) for women with AS. In men, the figures were 0.77 both for RA and for systemic sclerosis, 0.82 for SLE, 0.91 for AS, and 0.92 for psoriatic arthritis[13]. Comparing federal states with high and low unemployment rates, strong influences of the general labor market and the education of the patient on the probability of employment could be shown for RA, AS, and SLE[14].

Costs of rheumatic diseases. Comparing RA, AS, and psoriatic arthritis, annual total costs between $11,441 US (women with RA) and $5510 US (men with psoriatic arthritis) were calculated. Direct costs (physician visits, drugs, surgery, nondrug therapies, inpatient treatment) accounted for one-third of the total costs[15]. Indirect costs were dominated by the costs of permanent work disability, which exceeded the costs of sick leave by the factor 2 to 3 (human capital approach).

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Outcomes of care. Concerning the prognosis of the diseases, the data are restricted to those patients who remain in rheumatological care. Therefore, the data cannot be applied to the whole spectrum of persons with the considered diseases. Those patients who are treated continuously tend to have higher disease activity and more functional limitations at baseline than dropouts. Bearing these limitations in mind, longitudinal data analyses are possible. One example is the identification of patients with very severe disease refractory to therapy, which might make them candidates for novel biologic therapies. Of all patients with RA seen for at least 3 years, 8% had a high disease activity despite DMARD and glucocorticoid therapy in 3 subsequent years[16].

Practice variation among rheumatologists. The database is used for the internal quality assessment of the participating units. Each unit annually receives a detailed analysis of its data, comparing patient spectrum, therapies, and outcomes to the data of other rheumatologists in the same arthritis center, as well as in the whole database. Moreover, variation in treatment is discussed in the annual meetings. The data show rather low variation concerning the use of DMARD therapy in RA, but higher variation concerning DMARD combination therapy, steroid therapy, and physiotherapy[17].

DISCUSSION

The database has proven useful for different purposes in rheumatology. In general, it has shown that the care provided by rheumatologists is significantly different from that provided by nonspecialists. This is important, considering that rheumatology has to fight against complicated budgetary conditions. One additional use of the database is made in the arthritis centers themselves: by relating the data to the local population, areas with a specific need for rheumatological care can be identified. This was used in the past in order to allocate rheumatologists. Another use of the database is sampling of patients for specific studies. By applying planned inclusion criteria to the database, it can be verified in advance whether sample sizes sought can be achieved.

The major and obvious shortcoming of our database is that patients are not regularly followed up, irrespective of returning to the rheumatologist. This was not possible in the past because the whole project was based on the idea that it could easily be integrated into routine care. We try to overcome this problem by various means:

1. *Followup of defined patient samples*. A followup interview of all patients who dropped out of the database over the years 1995 to 1998 was performed using the data of the Berlin arthritis center. Their present treatment and health status were compared to patients still in rheumatological care. Health care deficits in patients only seen by general practitioners could be verified (unpublished doctoral thesis).
2. *Establishment of specific research cohorts*. It is indisputable that complete followup of all patients must be performed for all research questions concerning prognosis. Within the "Competence Network Rheumatology," 3 large patient cohorts have been established. In all cases, the case report forms are based on the items of the national database; they are extended by modules according to the specific research question. Disease-specific international scales are included in the documentation. The network built up by the arthritis centers and their database was the prerequisite for the successful start of the following cohorts:

Early RA cohort. An early arthritis cohort (disease duration less than one year at onset of observation) with 300 cases and an observation period of 3 years was established within the rheumatology network (H. Burkhardt, Erlangen). Followup is continuing. This is the major source of patients and material for several experimental projects within the network. Research is carried out by several groups on antibodies and cell markers with suspected prognostic relevance.

Spondyloarthropathy cohort. Seven hundred patients with AS, undifferentiated spondylitis, reactive arthritis, and juvenile oligoarthritis will be observed over a 3-year period to evaluate novel genetic, immunological, and clinical markers of disease progression (J. Sieper, Berlin).

Early RA observational cohort. A second RA cohort (disease duration up to 2 years at inclusion), consisting of 1060 cases collected in the participating rheumatological units, will be followed for 3 years. Rheumatological assessment including radiographs is performed at onset and after 3 years. Patients are followed independently of where they receive health care. It is our objective to get information about the size of differential outcome to be observed between rheumatological and nonspecialized care (G. Westhoff, Berlin).

Longterm followup of patients receiving anti-tumor necrosis factor therapy. In summer 2001, a national controlled longterm followup study of RA patients receiving biologics was started (A. Zink, R. Rau, J. Listing, Berlin and Ratingen) with the aim to observe 1000 patients treated with etanercept, infliximab, and anakinra, in addition to 1000 patients treated with adalimumab (beginning September 2003), plus a control group of 2000 RA patients with a change of DMARD therapy (not initial therapy). The observation period will be 5 years, with followup data gathered after 3, 6, 12, 18, 24, 30, 36, 48, and 60 months. The study is completely investigator-driven, performed under the umbrella of the German Rheumatological Society and the Competence Network Rheumatology. Joint unconditional funds are given by Wyeth Pharma, Essex Pharma (Schering Plough), Amgen Inc., and Abbott Inc.

All 4 cohorts have benefited from experience with the national database and the structures that have been set up. Principles of the database — diagnosis, clinical assessment

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and drug therapy recorded by the physician, and nondrug therapies, as well as the outcomes pain, function, early retirement, etc., recorded by the patient — are the same in all cohorts. Identical scales are used wherever possible. This has an important advantage: outcomes can be compared across different cohorts and diagnoses.

CONCLUSION

The national database is an important tool for German rheumatology. It is, however, not a longitudinal database in the sense of complete individual followup of all patients. This would not be feasible given the number of patients included per year. Complete followup is restricted to the specific cohorts described here. It should be kept in mind that the database has been performing successfully now for 10 years, and its existence has been a prerequisite for other kinds of databases, of which the most recent is the registry of biologics noted above.

Still, these documentation components are pencil-and-paper based. To date this has been the only way to enable a great number of rheumatologists with very different experiences and electronic data processing equipment to participate. A group at the University of Duesseldorf (M. Schneider) will provide German rheumatology with an Internet-based client-server tool for registration of all patient data.

ACKNOWLEDGMENT

The establishment and continuation of the database would have been impossible without the enthusiasm and unpaid work of a large number of German rheumatologists: Collaborative arthritis centers and their speakers: Aachen/Koeln/ Bonn: E. Genth, Berlin: J. Sieper, Dresden: H.E. Schroeder, Duesseldorf: M. Schneider, Erlangen: B. Swoboda, Westliches Ruhrgebiet/Essen: C. Specker, Giessen/Bad Nauheim: K.L. Schmidt, Greifswald: H. Merk, Hannover: H. Zeidler, Heidelberg: U. Schneider, Jena: G. Hein, Leipzig: H. Haentzschel, Luebeck/Bad Bramstedt: W.L. Gross, Magdeburg/Vogelsang: J. Kekow, Mainz/Bad Kreuznach: R. Dreher, Muenchen: M. Schattenkirchner, Muenster: M. Gaubitz, Ostwestfalen/Lippe: H. Mielke, Regensburg/Bad Abbach: U. Mueller-Ladner, Rhein-Main: J.P. Kaltwasser, Rostock: M. Keysser, Saarland: M. Pfreundschuh, Suedbaden: H.H. Peter, Suedwuerttemberg: R. Maleitzke.

Speakers of the working group of collaborative arthritis centers: H. Zeidler, Hannover 1993-2002 and M. Schneider, Duesseldorf (since 2003). The national database was initiated in 1992 by E. Genth, H.H. Raspe, and A. Zink.

Data analyses were performed by J. Listing, S. Ziemer, K. Thiele, and M. Niewerth from the German Rheumatism Research Centre and the authors.

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