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Frequency and trends of disease-modifying antirheumatic drug (DMARD) use in Germany

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Abstract

The aim of this study was to analyze the population-based frequency of classic (c-) and biologic (b-) disease-modifying antirheumatic drug (DMARD) use over time, selected underlying indications and the specialty of the prescribing physicians in Germany. Based on the claims data of the German Pharmacoepidemiological Research Database (GePaRD), yearly cross-sectional studies were conducted from 2004 to 2011. The prevalence of DMARD use was calculated as the number of persons with at least one dispensation per 1000 persons stratified by sex and age. In 2011, we also obtained the proportion of c- and b-DMARDs users with diagnoses of selected indications and the proportion of dispensations by specialty of the physician. Between 2004 and 2011, the annual prevalence of b-DMARD and c-DMARD use increased from 0.35‰ to 1.54‰ and from 6.53‰ to 8.93‰, respectively. In 2011, the study population comprised 12.8 million insurants with a mean age of 44.0 years. During this year, among c-DMARDs, methotrexate was prescribed most frequently (4.76‰), followed by azathioprine (1.72‰) and sulfasalazine (1.20‰). For b-DMARDs, adalimumab (0.57‰), etanercept (0.46‰), and rituximab (0.23‰) were most frequently used. Notably, b-DMARD users more often had a diagnosis of ankylosing spondylitis and psoriasis compared to c-DMARD-users (20.7% vs. 2.9% and 20.0% vs. 11.4%, respectively) and b-DMARDs were more frequently prescribed by rheumatologists and other specialists. Our population-based study highlights the increasing use of c- and b-DMARDs in Germany. Compared to c-DMARDs, b-DMARDs were commonly used for indications besides rheumatoid arthritis. Future research should therefore also focus on their prescription patterns and safety aspects in indications other than RA.

Abbreviations

ACR, American College of Rheumatology; ATC, Anatomical Therapeutic Chemical code; DDD, defined daily dose; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; MTX, methotrexate; TNF-α, tumor necrosis factor-alpha.

Introduction

In the last few decades, essential improvements in the treatment of rheumatoid arthritis (RA) and other autoinflammatory diseases have been made by the introduction of biologic disease-modifying antirheumatic drugs (b-DMARDs) (Roussy et al. 2013). While classic disease-modifying antirheumatic drugs (c-DMARDs) have been available for about 50 years, most b-DMARDs entered the market in the last 15 years. Up until 2011, nine b-DMARDs obtained approval in Germany (Kassenärztliche Bundesvereinigung & Arzneimittelkommission der

Deutschen Ärzteschaft [National Association of Statutory Health Insurance Physicians & Drug Commission of the German Medical Association] 2010). In the treatment of RA, b-DMARDs have been shown to be effective and can be used in monotherapy or in combination with c-DMARDs to control disease activity, to reduce joint destruction, and to improve quality of life. Thus, they are recommended by the clinical guidelines of the European League Against Rheumatism (EULAR) (Smolen et al. 2014) and the American College of Rheumatology (ACR) (Singh et al. 2012) if patients do not respond sufficiently to methotrexate (MTX) or other c-DMARDs. Besides RA and other labeled indications such as ankylosing spondylitis, inflammatory bowel diseases, and psoriasis, especially b-DMARDs are used in various off-label indications. For instance, tumor necrosis factor-alpha (TNF-α) inhibitors are also used in Wegener's granulomatosis, Behcet's disease, or hidradenitis suppurativa (Cessak et al. 2014).

Recently, a significant increase in any DMARD use in RA patients was observed in North America (Kim et al. 2013; Roussy et al. 2013), Germany, and the United Kingdom (Ziegler et al. 2010; Edwards et al. 2012). However, population-based analyses of DMARD use including patients with other DMARD indications are lacking, although DMARD indications have been extended increasingly (Cessak et al. 2014). In addition, prior studies from Europe were limited to c-DMARDs or did not investigate the recent development of b-DMARD use. Therefore, the primary objective of this study was to analyze the population-based frequency of c- and b-DMARD use over time in Germany. In addition, we examined underlying indications and the specialty of the physicians prescribing DMARD in the most recent study year available to us at the time of the analysis (2011).

Materials and Methods

Data source

We obtained data from the German Pharmacoepidemiological Research Database (GePaRD) which includes data from four German statutory health insurance providers (SHIs) representing approximately 17 million insurants. Because data of one small SHI covering approximately 350,000 insurants was not available up to 2011, this study was based on data from three SHIs only.

In brief, GePaRD contains demographic characteristics, data on hospitalizations, information on outpatient care, as well as outpatient drug dispensation data for each insurant. Hospital data include information on the date of hospital admission and discharge, diagnoses, as well as diagnostic and therapeutic procedures. Claims of outpatient physician visits contain diagnoses including information on the level of diagnostic certainty (confirmed, suspected, ruled out, and status post), treatments, and procedures. All diagnoses are based on the German modification of the International Classification of Diseases, 10th revision (ICD-10-GM). Outpatient drug dispensation data comprise information on all dispensations of reimbursable drugs and include prescribing and dispensation dates as well as information on the prescribing physician. Dispensation data can be linked to a pharmaceutical reference database via the central pharmaceutical number of the drug providing additional information for each drug, for example, on the Anatomical Therapeutic Chemical (ATC) code, the amount of substance prescribed, or the defined daily dose (DDD). A more detailed description of GePaRD is available elsewhere (Garbe et al. 2011). For this study, we used data on demographic characteristics, such as age and sex, data on individual insurance periods, inpatient and outpatient diagnoses, and drug dispensation data. Previous analyses regarding the numbers of hospital admissions and outpatient dispensations have shown the database to be representative for Germany (Schink and Garbe 2010; Fassmer and Schink 2014).

Access to GePaRD is only granted to staff members of the Leibniz Institute for Prevention Research and Epidemiology – BIPS in the context of projects endorsed by the SHIs and approved by the responsible public authorities. For data protection reasons, information is pseudonymized and coarsened. Due to the pseudonymized nature of the data, an informed consent of the study participants and a vote of an ethics committee for this study were not required.

Study design and population

For this cross-sectional analysis, we defined one separate study population per year from 2004 to 2011. Insurants were included in the respective study population if they were continuously insured during the study year or their birth or death occurred during that time.

Drug exposure

We assessed all dispensations of the following c-DMARDs: azathioprine, chloroquine, cyclosporine, cyclophosphamide, hydroxychloroquine, leflunomide, MTX, natrium aurothiomalate, penicillamine, and sulfasalazine. All c-DMARDs were available during the whole study period from 2004 to 2011. As b-DMARDs, we considered abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Adalimumab, anakinra, etanercept, infliximab, and rituximab were available during the whole study

period, abatacept from 2007 onward, and certolizumab, golimumab, and tocilizumab from 2009 onward.

Outcome measures

The prescription prevalence of DMARD use was calculated as the number of patients exposed per 1000 persons (‰) in the respective year. Patients were considered as prevalent users if they had at least one outpatient dispensation of the respective DMARD in the study year. All estimates were calculated for the overall study population and stratified by age and sex. A Poisson regression analysis was performed to investigate the influence of increasing calendar year and the yearly prescription prevalence of DMARD use assuming a log-linear relationship between the year and the prescription prevalence (Nelder and McCullagh 1992).

Furthermore, we calculated the proportions of DMARD users with diagnoses of the DMARD indications in 2011 considering neoplasms (ICD-10-GM C00-C97), multiple sclerosis (G35x), myasthenia gravis (G70.0), Crohn's disease (K50x), ulcerative colitis (K51x), pemphigus vulgaris (L10.0), atopic dermatitis (L20x), psoriasis (L40x except L40.5), arthropathic psoriasis (L40.5, M07x, M09.0x), RA (M05x, M06x, M31.5, M35.1, M35.3), juvenile idiopathic arthritis (M08x), polyarteritis nodosa (M30.0), systemic lupus erythematosus (M32x), scleroderma (M34x), ankylosing spondylitis (M45.0x), and rejection after transplantations (T86x, Z94x). For this analysis, patients had to have at least two confirmed outpatient diagnoses or at least one hospital diagnosis during 2011. In addition, we obtained the proportion of c-DMARD and b-DMARD dispensations by the specialty of the physician.

All statistical analyses were conducted with SAS, version 9.3 (SAS Institute Inc.).

Results

In 2011, a total of 12,812,922 persons were eligible for analysis. The mean age of this study population was 44.0 years (standard deviation 22.7). Fifty-four percent of the population was female.

Overall, the prescription prevalence of c-DMARDs was substantially higher compared to b-DMARDs in 2011 with 8.93‰ and 1.54‰, respectively. Figure 1 displays the prescription prevalence of b-DMARDs (A) and c-DMARDs (B) stratified by age and sex in 2011. The prevalence of c-DMARD use increased from 1.08‰ in the youngest age group to 17.42‰ in those 70–79 years old, followed by a strong decrease in the oldest age group. A similar pattern was observed for b-DMARD use with a maximum in the age group 60–69 years. While c-DMARDs were more frequently used in women across all

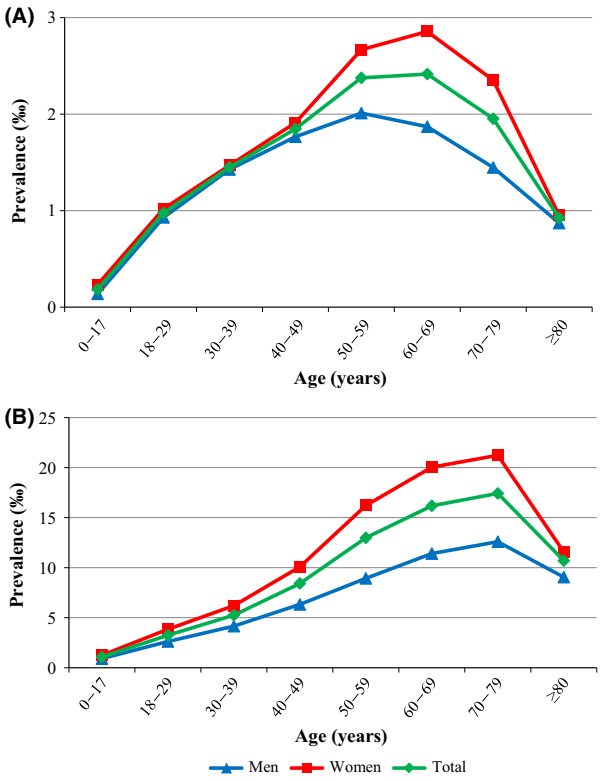

Figure 1. Prescription prevalences stratified by age and sex in 2011. (A) Biologic and (B) classic disease-modifying antirheumatic drugs.

age groups, a substantially higher prescription prevalence of b-DMARD use for women was only observed in those aged 50 to 79 years.

Among c-DMARDs, MTX was prescribed most frequently in 2011 (4.76‰), followed by azathioprine (1.72‰) and sulfasalazine (1.20‰). For b-DMARDs, the highest prescription prevalence was observed for adalimumab (0.57‰), followed by etanercept (0.46‰) and rituximab (0.23‰) (see Table 1). Comparing the two DMARDs with the highest prescription prevalence, MTX and adalimumab, regarding the number of dispensations in 2011, RA patients with MTX had on average three dispensations, while users of adalimumab received seven dispensations during this year.

The prescription prevalence for c-DMARDs as well as for b-DMARDs rose steadily during the 8-year study period (Fig. 2). For c-DMARDs, we found a relative increase of approximately 37% from 6.53‰ in 2004 to 8.93‰ in 2011 (P for trend <0.0001). In contrast, a more than fourfold increase was noted for b-DMARDs from 0.35‰ in 2004 to 1.54‰ in 2011 (P for trend <0.0001). No meaningful differences in trends over time between men and women were observed. Among c-DMARDs, MTX and azathioprine showed the strongest relative

Table 1. Development of prescription prevalences over study period from 2004 to 2011.

Study population (total)	2004 11,151,168	2005 11,799,064	2006 11,909,226	2007 12,004,771	2008 12,186,436	2009 12,883,876	2010 12,708,192	2011 12,812,922
Prevalence, total (‰)								
b-DMARDs	0.35	0.42	0.54	0.68	0.84	1.01	1.36	1.54
Abatacept	–	–	–	0.01	0.02	0.02	0.02	0.03
Adalimumab	0.07	0.11	0.18	0.25	0.34	0.42	0.49	0.57
Anakinra	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Certolizumab	–	–	–	–	–	<0.01	0.02	0.04
Etanercept	0.16	0.20	0.24	0.29	0.34	0.39	0.43	0.46
Golimumab	–	–	–	–	–	0.01	0.05	0.07
Infliximab	0.11	0.11	0.13	0.14	0.16	0.17	0.19	0.20
Rituximab	0.03	0.02	0.03	0.05	0.05	0.05	0.21	0.23
Tocilizumab	–	–	–	–	–	0.03	0.05	0.06
c-DMARDs	6.53	6.60	7.06	7.44	7.77	7.88	8.66	8.93
Azathioprine	1.34	1.36	1.45	1.52	1.57	1.59	1.68	1.72
Chloroquine	0.29	0.26	0.25	0.24	0.23	0.22	0.21	0.20
Cyclosporine	0.52	0.52	0.53	0.54	0.54	0.52	0.53	0.52
Cyclophosphamide	0.10	0.08	0.07	0.07	0.06	0.05	0.37	0.36
Hydroxychloroquine	0.51	0.53	0.58	0.63	0.70	0.74	0.80	0.84
Leflunomide	0.51	0.55	0.63	0.71	0.77	0.80	0.87	0.89
Methotrexate	3.02	3.08	3.42	3.67	3.89	4.11	4.56	4.76
Natrium aurothiomalate	0.05	0.04	0.03	0.03	0.03	0.02	0.02	0.02
Penicillamine	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Sulfasalazine	1.42	1.34	1.34	1.31	1.27	1.22	1.22	1.20

DMARDs, disease-modifying antirheumatic drugs; b-DMARDs, biologic DMARDs; c-DMARDs, classic DMARDs; –, agent was not yet approved in this year.

increase from 2004 to 2011 with approximately 58% for MTX and 28% for azathioprine. Adalimumab and etanercept revealed the strongest elevation among b-DMARDs with a nearly eightfold and threefold relative increase, respectively (see Table 1).

The proportions of DMARD users with diagnoses of the most common indications in 2011 are shown in Table 2. Overall, nearly 50% of c-DMARD users were diagnosed with RA, whereas this was the case in only 35.8% of b-DMARD users. Patients with a combination therapy of c- and b-DMARDs most frequently had a diagnosis of RA with 63.7%. Notably, b-DMARD users more often had a diagnosis of ankylosing spondylitis and psoriasis compared to c-DMARD users (20.7% vs. 2.9% and 20.0% vs. 11.4%, respectively). Further indications more often diagnosed in b-DMARD compared to c-DMARD users were arthropathic psoriasis, Crohn's disease, and juvenile idiopathic arthritis.

With regard to the specialty of the prescribing physician, c-DMARDs were most frequently prescribed by general practitioners (50.0%). Dispensations from rheumatologists were also common with 20.3%, followed by general internists (5.5%), nephrologists (5.3%), and gastroenterologists (5.2%) (data not shown). On the contrary, b-DMARDs were predominantly prescribed by rheumatologists (50.4%), general practitioners (15.5%), gastroenterologists (8.8%), oncologists (6.7%), general internists (6.3%), and dermatologists (5.5%) (data not shown).

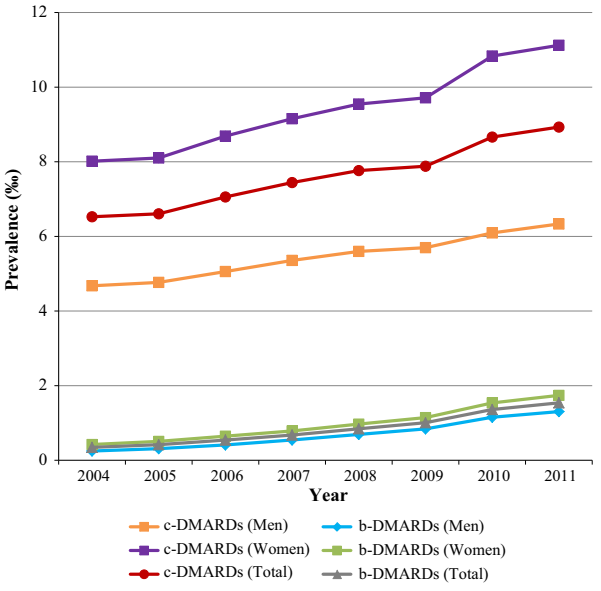

Figure 2. Prescription prevalence per 1000 users of classic and biologic disease-modifying antirheumatic drugs over the period 2004–2011.

Table 2. Proportions of diagnosed diseases in persons with at least one prescription (2011).

Indication/ disease[1,2]	c-DMARDs *n* = 105,116 (100%)	b-DMARDs *n* = 10,457 (100%)	DMARD combinations *n* = 9282 (100%)
Arthritides			
Rheumatoid arthritis	50,809 (48.3%)	3745 (35.8%)	5914 (63.7%)
Psoriatic arthritis	9348 (8.9%)	1523 (14.6%)	1482 (16.0%)
Ankylosing spondylitis	3095 (2.9%)	2619 (20.7%)	663 (7.1%)
Systemic lupus erythematosus	2865 (2.7%)	30 (0.3%)	60 (0.7%)
Juvenile idiopathic arthritis	1379 (1.3%)	275 (2.6%)	373 (4.0%)
Scleroderma	1199 (1.1%)	17 (0.2)	25 (0.3%)
Polyarteritis nodosa	453 (0.4%)	11 (0.1%)	13 (0.1%)
Dermatoses			
Psoriasis	11,939 (11.4%)	2091 (20.0%)	1530 (16.5%)
Atopic dermatitis	2896 (2.8%)	282 (2.7%)	237 (2.6%)
Neurological disorders			
Myasthenia gravis	1532 (1.5%)	8 (0.1%)	11 (0.1%)
Multiple sclerosis	1507 (1.4%)	29 (0.3%)	21 (0.2%)
Inflammatory bowel diseases			
Crohn's disease	7904 (7.5%)	1444 (13.8%)	964 (10.4%)
Ulcerative colitis	6681 (6.4%)	582 (5.6%)	535 (5.8%)
Other serious conditions			
Neoplasms	13,634 (13.0%)	1863 (17.8%)	1012 (10.9%)
Rejection after transplantations	4089 (3.9%)	53 (0.5%)	51 (0.6%)

DMARDs, disease-modifying antirheumatic drugs; b-DMARDs, biologic DMARDs; c-DMARDs, classic DMARDs.

[1]At least two confirmed outpatient diagnoses or one hospital diagnosis during 2011.

[2]The same patients could have diagnoses for more than one indication.

Discussion

Using data from a large German health insurance database, we assessed the prescription prevalence of DMARDs over time. To the best of our knowledge, this is the first study investigating population-based trends of DMARD use and the specialties of the prescribing physicians without restriction to RA patients, thus allowing examination also of other underlying indications. In general, we found a trend for an increasing use of any DMARD between 2004 and 2011. Although c-DMARDs were more commonly used, the relative increase was more pronounced for b-DMARDs rising by 300% during the study period. Patients on c-DMARD monotherapy more often had a diagnosis of RA with 50% compared to patients on b-DMARDs alone with 36%. In contrast, b-DMARD users were more frequently diagnosed with ankylosing spondylitis and psoriasis. Overall, b-DMARDs were predominantly prescribed by rheumatologists and other specialists, whereas c-DMARDs were more often prescribed by general practitioners.

In 2011, we found a prescription prevalence of 1.54 ‰ for b-DMARDs. This is slightly higher than the result of another study using claims data from Germany by Windt et al. (2011), which found a prescription prevalence of 1.11‰ in the overall population. The lower proportion observed in their study is likely related to their focus on five TNF-α-inhibitors only. However, both studies showed that adalimumab and etanercept were the two most frequently used b-DMARDs. Unfortunately, Windt et al. (2011) did not investigate trends over time and possible underlying indications (Windt et al. 2011).

In every study year, we could observe sex-specific and age-related differences with regard to the prevalence of DMARD use. Although both DMARD classes were more commonly prescribed to women probably due to the sex distribution of RA as the main indication (Roussy et al. 2013), b-DMARD users were younger compared to c-DMARD users. These differences are most likely caused by more frequent b-DMARD use in diseases affecting younger populations, for example, ankylosing spondylitis or Crohn's disease.

Several other studies investigated the frequency and trends of c- and/or b-DMARD use over time in patients with RA in North America (Kim et al. 2013; Ng et al. 2013; Roussy et al. 2013), Europe (Ziegler et al. 2010; Edwards et al. 2012), and Japan (Katada et al. 2015). Due to their focus on RA patients, their results cannot directly be compared to ours, but all studies including b-DMARDs also observed a strong increase in their use over the study period (Ziegler et al. 2010; Kim et al. 2013; Ng et al. 2013; Roussy et al. 2013; Katada et al. 2015). With regard to individual DMARDs, Kim et al. (2013) also found a rise in etanercept and adalimumab use in RA patients over time (Kim et al. 2013). Several studies revealed a strong increase in treatment with MTX (Edwards et al. 2012; Kim et al. 2013; Katada et al. 2015). These findings were mainly explained by a trend toward more aggressive treatment in clinical practice with b-DMARD monotherapy and especially c- and b-DMARD combination therapy (Ziegler et al. 2010; Roussy et al. 2013; Katada et al. 2015), as recommended by clinical guidelines (Singh et al. 2012; Smolen et al. 2014). This may also have triggered the prescribing trends in our study, since RA was still the most frequently diagnosed indication in c- and b-DMARD users and its highest prevalence was observed in combination therapy. In

addition, a general increase in the prevalence of several underlying indications in the last years might have contributed to the observed results, for example, for RA (Crowson et al. 2013; Widdifield et al. 2014), psoriasis (Danielsen et al. 2013), and inflammatory bowel diseases (Kappelman et al. 2013). To check this observation for GePaRD, the prevalences of these diseases were calculated for every separate study population from 2004 to 2011. We could also see an increase during this period (RA: from 1.42% to 1.69%; psoriasis: from 1.88% to 2.23%; ulcerative colitis: from 0.38% to 0.43%; Crohn's disease: from 0.30% to 0.35%). Another factor that could be associated with an increased b-DMARD use over time is the extension of licensed indications, for example, in 2009 for rituximab in combination with cyclophosphamide and fludarabine in patients with chronic lymphocytic leukemia (Castro et al. 2009). Nevertheless, our study reveals that DMARDs were used in a broad range of indications besides RA, since only 50% of c-DMARD and 36% of b-DMARD users had a diagnosis of RA. Particularly b-DMARD users frequently had a diagnosis of ankylosing spondylitis (20.7%), psoriasis (20.0%), and psoriatic arthritis (14.6%) for which the TNF-α-inhibitors adalimumab, etanercept, and infliximab are indicated (Cessak et al. 2014). Because TNF plays an important role in the pathophysiology of several diseases and approved indications have been extended widely during the last decade (Cessak et al. 2014), an ongoing trend toward an increasing use of these drugs as observed in our study is very likely.

With regard to the physician's specialty, b-DMARDs were predominantly prescribed by rheumatologists, but still 30% of all b-DMARD prescriptions were carried out by other specialists such as gastroenterologists and dermatologists. In contrast, c-DMARDs were more often prescribed by general practitioners. These findings are consistent with the results of the study by Roussy et al.(2013), in which patients with RA treated by rheumatologists in Canada were eight times more likely to receive b-DMARDs compared to those in general practitioner care. According to the German guidelines of RA (Schneider et al. 2011), it was expected that more severe cases and c-DMARD nonresponder will be treated with b-DMARDs by experienced rheumatologists. The same applies to other underlying indications, for example, psoriasis (Nast et al. 2012).

One strength of this study is the size of the underlying population, which allowed investigating the population-based prescription patterns of DMARDs in stratified analyses with a representative sample for Germany. Due to the nature of the administrative data, information and selection bias can be ruled out, since information on DMARD prescriptions is assumed to be complete for almost all drugs and even for older patients suffering from severe diseases.

On the other side, this study has some limitations. Due to the delayed data delivery to GePaRD, the study period was restricted to data up to 2011; however, all established DMARDs could be analyzed for at least 2 years. In addition, inpatient prescribing information is not available in GePaRD, so that DMARD use in this setting could not be analyzed. Outpatient dispensations of solutions for infusion or injection such as rituximab, cyclophosphamide, or methotrexate can partly not be identified in GePaRD. As it was not mandatory to name all components of solutions on outpatient prescriptions before 2010 in Germany (Hoffmann et al. 2010), we assume an underestimation of the prescription prevalence for these agents during the preceding study years. Moreover, direct linkage between prescriptions and diagnoses of possible indications is not possible. Although therapy switch in DMARD users has been shown to be frequent (Meissner et al. 2014; Jørgensen et al. 2015), the treatment regimen (switch, concurrent use) could not be assessed due to the cross-sectional study design per calendar year.

In conclusion, this 8-year study highlights the upward trend in the use of c- and b-DMARDs in the German population. Especially b-DMARDs were used commonly for indications besides RA, for example, ankylosing spondylitis and psoriatic arthritis. Considering the trends in our study and assuming a further extension of indications, the use of b-DMARD is likely to further increase. Therefore, information on safety and usage of these agents should also target other medical specialists (e.g., dermatologists and gastroenterologists). In light of high therapy costs, further research should also focus on prescribing patterns, safety aspects, and the effectiveness of these drugs in indications other than RA.

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Disclosures

E. G. was running and A. F. is and N. S. was working in a department that occasionally performs studies for pharmaceutical industries. These companies include Bayer, Celgene, GSK, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. E. G. has been a consultant to

Astellas, Bayer, Nycomed, Takeda, Teva, GSK, Schwabe, and Novartis. None of these activities are related to this study.

Author Contributions

A. F., E. G., and N. S. were involved in the development of the study protocol. A. F. performed this study and wrote the manuscript. E. G. and N. S. revised the manuscript. All authors approved the final manuscript.

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