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Changes in Use of Disease Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis in the U.S. for the period 1983–2009

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Abstract

Objective—Use of non-biologic disease-modifying antirheumatic drugs (nbDMARD) and/or biologic DMARDs (bDMARD) is generally recommended to improve the prognosis of patients with rheumatoid arthritis (RA). The objective of this study was to describe the changing trends in DMARD use for RA over the past two decades.

Methods—We analyzed data from an open longitudinal cohort of RA patients recruited from rheumatologists' practices in Northern California. We examined baseline demographic and clinical characteristics of the participants and their long DMARD use through annual comprehensive structured telephone interviews.

Results—A total of 1,507 established RA patients were recruited through 5 enrollment periods between 1983 and 2009. Between 1983 and 2009, the use of any DMARD increased from 71% of all patients to 83% (p for trend <0.0001). In 2009, 43% received a bDMARD, 34% were on both nbDMARD and bDMARD, and 40% were treated with only nbDMARDs. The four most commonly used nbDMARDs in 2009 were methotrexate (49%), hydroxychloroquine (30%), leflunomide (13%) and sulfasalazine (7%). Etanercept (20%) was the most commonly used bDMARD in 2009, followed by infliximab (10%), adalimumab (9%) and abatacept (6%). Use of oral steroids was common (40%–50%) and remained similar throughout the study period.

Conclusion—There has been a significant increase in the use of DMARDs for RA over the past two decades. However, 15% of the individuals with a clinical diagnosis of RA were not receiving DMARDs in 2009. Future research should focus on sociodemographic and clinical factors associated with DMARD use for RA.

INTRODUCTION

Over the past few decades, major advances have occurred in understanding of the pathophysiologic mechanism underlying rheumatoid arthritis (RA). Although there is still no

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Competing interests

Kim has received research support from Takeda Pharmaceuticals North America and Pfizer and tuition support for the Pharmacoepidemiology Program at the Harvard School of Public Health funded by Pfizer and Asisa.
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known cure for RA, treatment with non-biologic disease-modifying antirheumatic drugs (nbDMARDs) and/or biologic DMARDs (bDAMRDs) is considered the standard of care for RA.(1, 2) Prior research suggests that not all patients with RA receive these drugs and seeing a rheumatologist is associated with use of DMARDs.(3–5) The objective of this study was to describe the changing trends in both nbDMARD and bDMARD use over the past two decades, using data from a longitudinal cohort of RA patients in community-based rheumatology practices.

METHODS

Data Source

This study is based on data from the University of California, San Francisco (UCSF) RA Panel study which includes 1,507 patients with RA from the practices of a random sample of 57 of the 115 rheumatologist practicing in northern California.(6) The participation rate of 57 rheumatologists was 70%. Between 1982 and 1983, the initial RA Panel included 822 (97%) out of 847 patient that the participating rheumatologists provided names for. Four more enrollments occurred in 1989, 1995, 1999 and 2003, during which 203, 131, 122, and 169 patients were enrolled, respectively. The average patient attrition rate from year to year was 7% including deaths. Other details about the structure of the Panel and the validity of its measures are summarized elsewhere.(6–8)

The principal data collection method for the RA Panel study is an annual, 45-minute-structured telephone interview conducted by a trained survey worker. Basic demographic information, signs and symptoms of RA, extent of comorbidity, physical and psychological health status, functional status, health care utilization information, and characteristics of health insurance plans were collected. Use of RA treatment at any point in the year prior to the survey was also reported. The study was approved by the UCSF and Brigham and Women's Hospital's Institutional Review Boards.

Analysis

Baseline demographics, such as age, sex, race, educational level, and insurance type, and clinical characteristics including RA duration, duration of morning stiffness, number of swollen joints and the health assessment questionnaire (HAQ) score were examined in each of the five enrollment periods. Proportions of patients receiving specific DMARD agents and category of DMARDs, either nbDMARDs or bDMARDs, were calculated for each calendar year. In this study, nbDMARDs include azathioprine, cyclophosphamide, cyclosporine, d-penicillamine, oral or injectable gold compounds, hydroxychloroquine, leflunomide, methotrexate and sulfasalazine. For bDMARDs, abatacept, adalimumab, anakinra, etanercept and infliximab were included. Data on rituximab or other newer bDMARDs, such as certolizumab and golimumab, were not available. The Cochran-Armitage trend test was used to test for time trend over the study period.(9)

RESULTS

Subject Characteristics

A total of 1,507 RA patients were recruited through 5 enrollment periods between 1983 and 2009. (Appendix 1) The mean (SD) age of the sample ranged from 55 (16) to 58 (13) years depending on the enrollment periods. Seventy five percent were women, 77% were non-Hispanic white, 9% were Hispanic, and 5% were Asian. Forty seven percent had a higher level of education than high school graduation, 53% had private health insurance, 33% had Medicare, and 5% had no insurance. At the start of follow-up, mean RA disease duration ranged from 9 to 16 years and mean HAQ scores from 0.9 to 1.3 depending on the

enrollment periods. The mean (SD) RA disease duration increased over time from 11 (10) years in 1983 to 24 (12) years in 2009. The mean (SD) number of swollen joints was 2.8 (2.7) in 1995 and 2.7 (2.6) in 2003. Nineteen percent had prolonged morning stiffness for more than two hours.

Patterns of Disease-Modifying Anti-Rheumatic Drugs Utilization

Between 1983 and 2009, the use of any DMARD increased from 71% of all patients to 83% (p for trend < 0.0001). (Figure 1) Since 1999 when the first bDMARD was introduced, the use of any bDMARD increased from 10% to 48% (p<0.0001), but the use of any nbDMARD remained similar between 70% and 80% (p<0.0001) from 1983 to 2009. The proportion of patients receiving only one nbDMARD gradually decreased from 60% to 25% between 1983 and 2009. Since 1999, less than 10% of all patients were on bDMARD monotherapy. The proportion of patients receiving both nbDMARD and bDMARD increased from 9% to 34% of all patients between 1999 and 2009.

The proportion of patients not receiving any DMARDs ranged from 13% to 18% since 1999. These patients were older and had a longer RA duration, compared to those who received any type of DMARDs. The mean ± SD HAQ score (1.0 ± 0.8) as well as patient global score (74 ±24) were similar in both patients who received any DMARDS or who did not. The mean ± SD number of swollen joints was slightly lower (2.2 ± 3.1) in patients who did not receive any DMARDs, compared to those who received a DMARD (2.7 ± 2.9). Although having Medicare as primary health insurance was more common in patients who did not receive any DMARDs than those who did, there was no difference in the prescription coverage between the two groups.

In 1983, injectable gold compound was the most commonly used DMARD at 40%, followed by d-penicillamine (26%), but the use of these drugs has drastically changed over time to 1% and 0% in 2004, respectively. (Figure 2) In recent years, methotrexate has been most frequently used and the proportion of patients receiving this drug increased from 3% in 1983 to 49% in 2009. Use of hydroxychloroquine, the second most commonly used drug in recent years, has increased from 13% in 1983 to 30% in 2009. The proportion of patients on sulfasalazine remained stable around 5–9% over the follow-up time. Leflunomide has been prescribed in 13–15% of patients since 1999. Among the patients receiving only nbDMARDs, the proportion of patients receiving more than two nbDMARDs was 17% in 1983, 35% in 1998 and 22% in 2009.

Etanercept (20%) was the most commonly used bDMARD in 2009, followed by infliximab (10%), adalimumab (9%) and abatacept (6%); anakinra was only used in 1–2% of subjects. (Figure 3) Among patients who received bDMARD, 77% to 90% used at least one nbDMARD concomitantly. Use of oral steroids was common (40–50%) and remained generally unchanged over the study period.

DISCUSSION

Our study illustrates a remarkable change in the use of DMARDs for patients with longstanding RA over the past two decades. The two most commonly used drugs in early 1980s, gold and d-penicillamine, are almost “extinct” in recent years. Methotrexate and hydroxychloroquine are the two most frequently used nbDMARDs and etanercept and infliximab were the two most commonly prescribed bDMARDs in 2000s.

Since 2000, 82–88% of all patients in the RA panel received at least one DMARD, either non-biologic or biologic. Since 2003, 75–80% received at least one nbDMARD and over 40% of patients received a bDMARD. More than three-quarters of those who received a

bDMARD also used nbDMARDs. Half of patients were treated with only nbDMARDs and 10% with only bDMARD. An earlier study based on the data from a US RA patient registry (2002–2006) showed similar results; nearly a third of all RA patients were on a bDMARD and 70% of those taking a bDMARD were also on nbDMARDs.(10)

Our results are different from an earlier study using the data from the UK General Practice Research Database (1987–2002) which showed that about 50% of subjects with a clinical diagnosis of RA were prescribed any DMARDs at any time.(11) In the UK study, sulfasalazine was the most commonly used nbDMARD followed by methotrexate and less than 10% of the patients used combinations of DMARDs. Several important characteristics of our study may explain the differences in the results. First, health care reimbursement systems differ between the countries. Second, our study includes more recent years up to 2009. Lastly, all subjects in our study were under a rheumatologist's care; thus, these patients might not be representative of RA patients in the general population or primary care clinics.

Our study has several limitations. First, as the majority of the patients have established RA for longer than 10 years, this study was not designed to evaluate whether there has been an increase in the use of DMARDs for early RA. However, current American College of Rheumatology guidelines recommend a use of nbDMARD and/or bDMARD to achieve either low disease activity or remission in all patients regardless of disease duration.(1, 2) Second, some changes in the medication use in a shorter period of time might have not been well-captured since our study was based on the data from an annual telephone interview.

A population-based Canadian study using administrative billing data (1996–2000) showed that only 43% of the entire RA cohort received a DMARD at least once over 5 years, but 84% of patients followed by rheumatologists continuously were on treatment with DMARDs.(12) In the present study, it is noteworthy that nearly 15% of the individuals with RA were not receiving any DMARDs even in 2003–2009. Consistent results were also noted in a large longitudinal study of RA patients from rheumatology clinics in Germany, which reported that 13–19% of patients with RA received no DMARDs between 1997 and 2007.(13) There are several potential explanations for this finding. First, it is possible that some patients are not optimally treated because of patients' preference or lack of access to adequate and continuing care for RA. These patients should be the focus of quality improvement in RA. Second, some patients may have no or low RA disease activity; thus, do not need treatment with DMARDs. Third, some serious comorbidities may complicate treatment decisions and prohibit patients from receiving treatment with DMARDs.

In conclusion, this 23-year longitudinal study based on a cohort of established RA patients recruited from a random sample of rheumatologists highlights the changing trends in the use of DMARDs over the past two decades. While over 80% of RA patients were treated with DMARDs and half the patients receiving DMARDs were prescribed bDMARD in recent years, there are still a number of patients with RA who remained on no DMARDs. This may suggest room for improvement in care of RA patients but it is also possible that some patients with RA are poor candidates for treatment with DMARDs because of comorbidities, low disease activity or patient preference. To ensure optimal care for RA, further work is needed to characterize this group of untreated patients.

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Appendix 1. Baseline characteristics of rheumatoid arthritis (RA) patients, by recuritment year

	1983 (n = 882)	1989 (n = 203)	1995 (n = 131)	1999 (n = 122)	2003 (n = 169)
	Percentage or mean ± SD				
Demographic					

	1983 (n = 882)	1989 (n = 203)	1995 (n = 131)	1999 (n = 122)	2003 (n = 169)
Female	75	77	80	88	82
Age, years	57 ± 14	58 ± 13	56 ± 14	55 ± 16	56 ± 13
Race, White	78	87	82	81	78
Ethnicity, Hispanic	11	9	7	7	9
Socioeconomic					
Primary health insurance					
No insurance	7	5	2	2	1
Medicare	32	43	37	40	26
Medicaid	8	5	2	4	4
Private	53	47	59	54	69
Managed care					
FFS			44	13	15
HMO			54	50	47
PPO			0	35	38
Insurance pays for drugs			88	91	93
Educational attainment					
< High school	27	22	4	6	5
High school degree	34	34	38	22	18
> High school	39	44	58	72	76
RA disease activity					
Disease duration, years	11 ± 10	10 ± 10	10 ± 10	16 ± 11	9 ± 10
HAQ score	1.3 ± 0.8	1.0 ± 0.7	1.0 ± 0.7	1.0 ± 0.8	0.9 ± 0.7
Number of swollen joints			2.8 ± 2.7	2.1 ± 2.8	2.7 ± 2.6

SD: standard deviation, FFS: fee-for-service, HMO: health maintenance organization, PPO: preferred provider organization, HAQ: health assessment questionnaire

Significance and Innovation

- A significant increase in the use of DMARDs for RA has been noted over the past two decades.
- Over 80% of RA patients were treated with DMARDs and half the patients receiving DMARDs were prescribed bDMARD in recent years.
- Sociodemographic and clinical factors associated with DMARD use and non-use should be further studied.

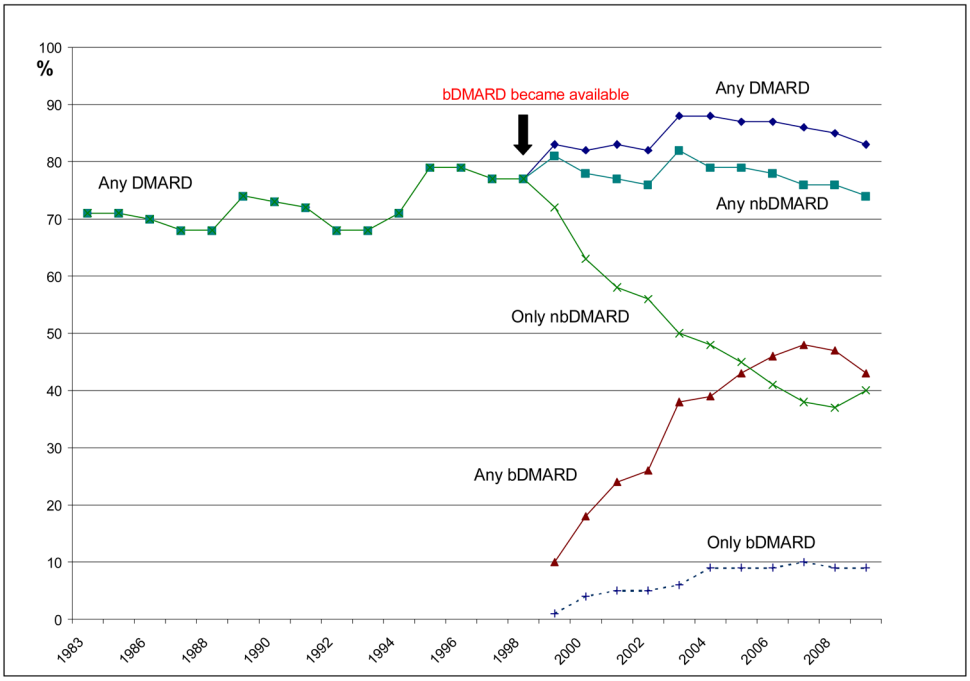

Figure 1.

Use of disease-modifying antirheumatic drugs (DMARDs) over the period 1983–2009 in Northern California. Values are percentage of patients receiving the specific DMARD categories, among 1,507 rheumatoid arthritis patients in the study cohort.

Any DMARD includes treatment with either biologic DMARD (bDMARD) or non-biologic DMARD (nbDMARD). nbDMARDs include azathioprine, cyclophosphamide, cyclosporine, d-penicillamine, oral or injectable gold compounds, hydroxychloroquine, leflunomide, methotrexate and sulfasalazine; bDMARDs are defined abatacept, adalimumab, anakinra, etanercept and infliximab

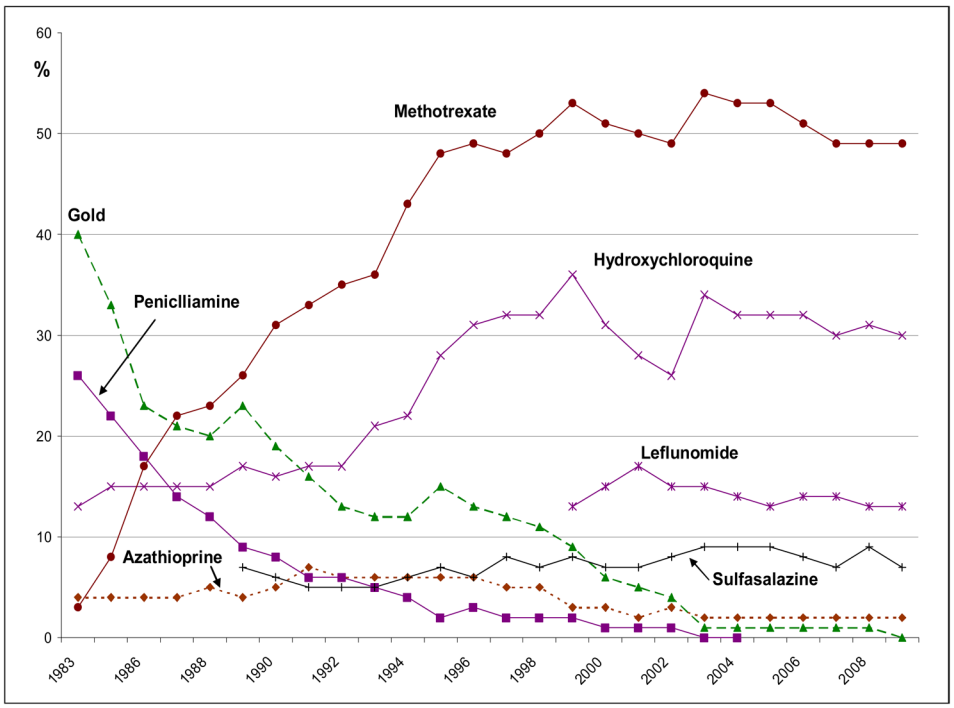

Figure 2.

Use of non-biologic disease-modifying antirheumatic drugs (nbDMARDs) over the period 1983–2009 in Northern California. Values are percentage of patients receiving specific nbDMARD agent, among 1,507 rheumatoid arthritis patients in the study cohort.

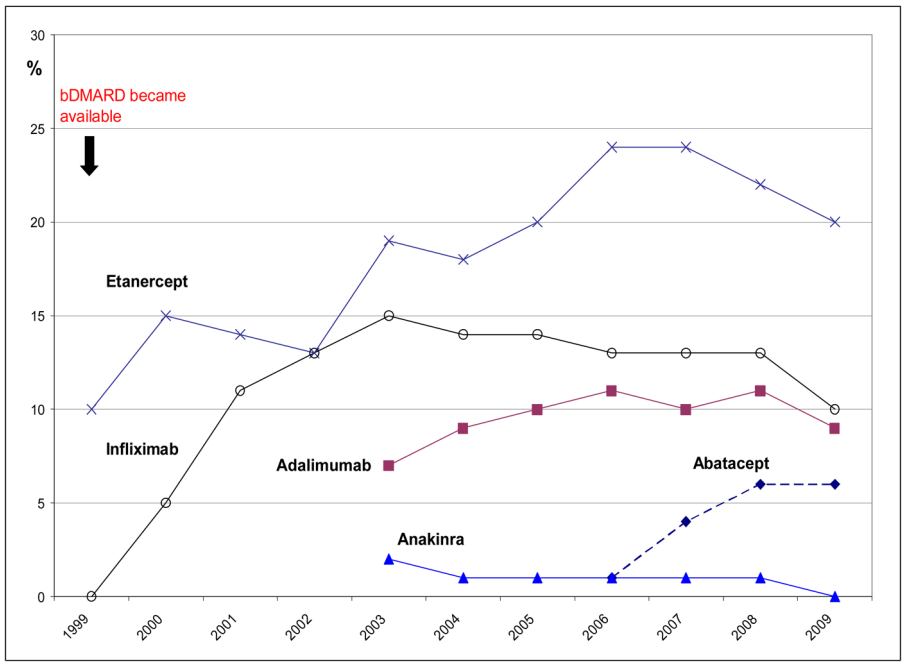

Figure 3.
Use of biologic disease-modifying antirheumatic drugs (bDMARDs) over the period 1999–2009 in Northern California. Values are percentage of patients receiving specific bDMARD agent, among 1,507 rheumatoid arthritis patients in the study cohort.