A Comparison of Patient Characteristics and Outcomes in Selected European and U.S. Rheumatoid Arthritis Registries[1]

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Purpose: Randomized controlled trials (RCTs) have demonstrated the efficacy of biologic agents in the treatment of rheumatic diseases. However, results from RCTs may not be generalizable to clinical practice because of their strict inclusion and exclusion criteria. Assessment of safety using RCT data also is limited by short duration of follow-up and relatively small sample sizes, which generally preclude analysis of longer term outcomes and rare adverse events. In rheumatology, various observational cohorts and registries have been created to complement information obtained from RCTs, some with the primary purpose of monitoring effectiveness and safety of biologic agents. Most registries are either drug based or disease based. These registries include patients with a variety of rheumatic diseases including RA.

Methods: To provide a qualitative comparison of selected U.S. and European rheumatoid arthritis (RA) biologics registries and cohorts including ARTIS, BIOBADASER, BSRBR, BRASS, CLEAR, CORRONA, NDB, RABBIT, SCQM, and VARA.

Results: A careful comparison of these registries, as provided in this article, can provide a basis for understanding the many similarities and differences inherent in their design, as well as societal context and content, all of which can significantly impact their results and comparisons across registers.

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Summary: The increasing use of biologic agents for treatment of rheumatic diseases has raised important questions about cost, safety, and effectiveness of these agents. The unique and variable features of patient populations and registry designs in Europe and the U.S. provide valuable and complementary data on comparative effectiveness and safety of biologic agents to what can be derived from RCTs.
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Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with chronic articular pain, disability, and excess mortality. There has been a growing emphasis on diagnosing and treating RA early and intensively with the goal of minimizing disability and mortality. The introduction of biologics in the past decade has revolutionized the treatment of RA because of their substantial impact on disease signs and symptoms as well as their ability to slow radiographic progression of joint damage. However, cost and safety concerns continue to be important considerations as these agents are used by an increasing number of patients, particularly those with less severe disease and with a greater burden of comorbidities than typically represented in randomized clinical trials (RCTs). Additionally, comparative effectiveness research is becoming increasingly important, and RCTs are unlikely to provide answers to many important comparative effectiveness questions.

To complement information obtained from RCTs, various observational cohorts and registries have been established in the last decade for patients with rheumatic diseases. A cohort is a structured organization of patients; as 1 type of cohort, a registry is typically prospective and enrolls patients for a specific reason (1). The registries are either drug based (ie, patient enrolled if they are starting particular medications) or disease based (ie, enrollment is predicated on a patient having a particular diagnosis such as RA), or both, and most allow evaluation of outcomes referent to a comparator group of RA patients. Many but not all drug-based registries enroll patients treated with a variety of medications for a given disease such as RA. In addition to broadly studying disease-related outcomes, an important purpose of most rheumatic disease registries is to monitor the long-term effectiveness and safety of new therapies. These registries are designed as longitudinal cohorts and can compare, for example, biologic users to nonbiologic users or to national population registers in a comparator arm. Many registries have unique features, such as a link to a national death database, bio-repositories, or access to laboratory data that makes them particularly suited to answer certain research questions. Some of the cohorts have reported results with differing magnitudes of effect or seemingly discrepant conclusions for the same safety questions. A careful comparison of the characteristics (similarities and differences) of these rheumatologic registries can lead to a better understanding of the reasons that may sometimes underlie heterogeneous results.

In this article, we present published and unpublished data to allow a qualitative comparison across European and U.S. RA registries and cohorts. The purpose of this approach was 4-fold, as follows: (1) to compare and contrast how similar information is collected and reported by the different registries; (2) to highlight the unique features of registries, the consequence of which results in certain registries being able to answer particular types of research questions; (3) to compare outcomes reported by the various registers; and (4) to explore how differences in registry design and analytic approaches may impact their results. In achieving these 4 goals, we compared registries across the domains of (1) recruitment methods and inclusion criteria for both biologic and comparator cohort patients; (2) demographics and comorbidities; (3) outcomes such as effectiveness and medication persistence; (4) safety; in particular, the rate of serious infections, acute myocardial infarction, and malignancy. Recognizing that harmonization of analytic approaches may improve the ability to compare result across registries, inherent differences in registry populations and the design features of the registry may provide results that are generalizable only to specific RA populations, a topic also addressed in this article.

METHODS

Selection of Registries and Cohorts

While recognizing the existence of numerous RA registries, we identified published articles that report comparable data for the domains described above, with a particular focus on registries and cohorts that allowed for addressing questions related to patient characteristics and comorbidities and the effectiveness, safety, and adherence to biologics used for the treatment of RA. Based largely on size, the European registries selected for this qualitative comparison included the U.K. British Society for Rheumatology Biologics Register (BSRBR), the German Rheumatoid Arthritis oBservation of Biologic Therapy (RABBIT) registry, the Swedish Rheumatology Registers including the Biologics register, the Swiss SCQM registry, and the Spanish Registry of Biologics in Rheumatology (BIOBADASER). For U.S. registries, we described the Consortium of Rheumatology Researchers of North America (CORRONA), the National Data Bank (NDB) for Rheumatic Diseases, the Veterans Affairs Rheumatoid Arthritis Registry (VARA), the Consortium for the Longitudinal Evaluation of African Americans with Early

Table 1 Comparative Characteristics of Selected European and U.S. Rheumatoid Arthritis Registries and Cohorts

Cohort/Register	Funding Agency	Year of Inception	Physician/Clinical (eg, DAS)	Patient (eg, HAQ)	Add'l Labs Besides ESR/CRP
Administrative claims databases of health plans	Insurance company	N/A	No	No	Rarely
Swedish Rheumatology Registers (SRR): Early RA	Various public and private sources	1995	Yes	Yes	No
SRR: Biologics Register (ARTIS)		1999	Yes	Yes	No
BRASS[a]	Pharma/Diagnostics	2003	Yes	Yes	Yes
BSRBR United Kingdom	Pharma to British Society for Rheumatology	2001	Yes	Yes	No
CLEAR[b]	NIH	2001	Yes	Yes	Yes
CORRONA[c] (12,26)	Pharma	2001	Yes	Yes	Yes
Integrated health plans with electronic health records (eg, Kaiser Permanente)	Various	N/A	Physician notes available but no standardized exam (eg, joint counts)	No	Yes
National Data Bank for Rheumatic Diseases (26,27)	Pharma	1998	No	Yes	No
SCQM Swiss Registry of Inflammatory Arthritides	Various (Pharma, health authorities, foundations)	1997	Yes	Yes	Yes
RABBIT German Biologics Register	Pharma to German Rheumatism Research Centre	2001	Yes	Yes	Yes
Veteran's Affairs RA (VARA) Registry	Pharma, VA, NIH	2003	Yes	Yes	Yes
BIOBADASER Spanish Biologics Registry	Pharma, SFR, and AEMyPS	2000	Yes	No	No

BSRBR, U.K. British Society for Rheumatology Biologics Register; BIOBADASER, the German RABBIT registry, the Swedish Rheumatology Registers including the Biologics register, the Swiss SCQM registry, and the Spanish Registry of Biologics in Rheumatology; CORRONA, Consortium of Rheumatology Researchers of North America; NDB, the National Data Bank for Rheumatic Diseases; VARA, the Veterans Affairs Rheumatoid Arthritis Registry; CLEAR, the Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis; BRASS, the Brigham and Women's Rheumatoid Arthritis Sequential Study; Pharma, pharmaceutical companies; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; DMARD, disease-modifying anti-rheumatic drug; NIH, National Institutes of Health; SFR, Spanish Foundation of Rheumatology; AEMyPS, Spanish Medicines Agency.

[a]http://www.brassstudy.org/.

[b]http://medicine.uab.edu/rheum/70918.

[c]Some but not all CORRONA sites collect bio-specimens.

Table 1 Continued

Healthcare Utilization	Bio-respository	Frequency of Data Collection (mo)	Selection Criteria for Enrollment into Registry	Rheumatologic Diseases Captured
Yes, administrative data	No	Continuous	No restrictions Diseases defined on the basis of ICD-9 billing codes	All
Inpatient care, outpatients nonprimary care, and prescriptions	Limited	0, 3, 6, 12, 18, 24, etc from RA diagnosis	Diagnosis of RA <12 mo after symptom onset	RA
	Limited	0, 3, 6, 12, 18, 24, etc. from biologics treatment start	Rheum dx starting any biologic	Diseases for which biologics are prescribed
No	Yes	0, 6, 12, 18, 24, etc	No restrictions Disease-based registry	RA
No	Limited	0, 6, 12, 18, 24, 30, 36, then annual	Anti-TNF users: DAS usually >5.1 initiating biologic Comparator: New or prevalent nonbiologic DMARD users; guideline DAS >4.2	RA 2001-present, PsA and AS 2001-2006, other rheumatic diseases 2001-present
No	Yes		African American patients with early RA (<2 yr disease duration)	RA
No	Limited[c]	Usually every 3 to 4 mo (mean 4.5 mo)	No restrictions Disease-based registry	Predominantly RA and PsA; limited OA, and osteoporosis
Yes, administrative + clinical data	No	Continuous	No restrictions Diseases usually defined on the basis of ICD-9 billing codes + pharmacy data	All
Yes, patient-derived	No	6 monthly	No restrictions, disease-based registry	Predominantly RA, OA, SLE, fibromyalgia
No	Limited	Continuous	No restrictions Disease-based registry	RA, AS, PsA
Yes, patient-derived	No	0, 3, 6, 12 mo, and 6 monthly thereafter until month 120	Biologic users: initiators of a biologic Comparator: initiators of a nonbiologic DMARD after having failed prior DMARDs	Rheumatoid arthritis
Yes, administrative + clinical data	Yes	Coinciding with routine rheumatologic care	No restrictions, Veterans receiving rheumatologic care at participating center	RA
No	No	Continuous	RA Biologic users: DAS usually >3.2 initiating biologic Comparator: EMECAR propensity score matched on DAS28, RF+, disease duration, age	All

Table 2 Comparative Characteristics of Rheumatoid Arthritis Patients, by Cohort and Drug Exposure

	ARTIS	United Kindgom BSRBR (2,19)		Germany RABBIT (28)		Spain (9)	NDB		CORRONA	
Drug Cohort	Bio	Bio	Comp	Bio	Comp	Bio	Bio	Comp	Bio	Comp
No. of patients enrolled, in thousands[a]	15	12	4	>5	>2	>5	>13	>12	>15	>12
Age (mean ± SD)	55	56 ± 12	60 ± 12	54 ± 12	56 ± 12	54 ± 13	59	60	58 ± 13	60 ± 13
Women, %	75	76	72	78	79	72	79	76	78	74
Household income, in $1000 units							35	35		
College graduate							26	25		
SF-36										
PCS							32.5	34.3		
MCS							49.3	49.8		
EuroQol (EQ-5D)							0.71	0.72		
Comorbidity[b]										
Current smoking, %		22	25	23	23	15	15	14	12	12
Ever smoker, %		60	65	47	47	—	43	42	36	36
Diabetes	4	5	6	8	9	7	8	9	6	7
Coronary artery disease, %	7	7	14	5	7	4	5	7	6	7
Chronic lung disease, COPD, or asthma, %	4	13	19	7	6	6	10	12	5	6
Fibromyalgia							19	17		
Baseline glucocorticoid use, %	51	44	19	84	76	52	50	39	38	39

Spain, BIOBADASER cohort; Bio, biologic cohort (for disease-based registries, represents persons who ever used biologics); Comp, comparator cohort; PCS, physical health component score; MCS, mental health component score; COPD, chronic obstructive pulmonary disease.

Data shown as %, median (IRQ), or mean ± SD, all % are reported as nearest whole integer.

[a]Cohorts continue to enroll, so number of participants is underestimated.

[b]Definitions for each comorbidity may differ across cohorts.

Rheumatoid Arthritis (CLEAR), and the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS). For comparative purposes, we also included an example of an RA cohort derived using administrative databases collected by large U.S. health plans.

We reported on published data that were available in more than 1 registry/cohort using similar enough methods to facilitate qualitative comparison. We also asked coauthors to provide information that was not captured in published form. A description of unique data captured by only a single registry was reported in the Appendix. Omission of certain data elements from a registry does not imply that the information is not collected, only that it was unavailable at the time of publication.

For the purposes of this report, RA patients were characterized as ever or never biologic users; in most drug-based registries, RA patients can contribute person-time to the nonbiologic cohort and subsequently to the biologic cohort; this transition can only occur once for each patient. In contrast, some cohorts (eg, RABBIT, the SCQM registry) allow for switching in both directions and contributing person time to different drug exposure categories. For disease-based registries, an ever user of a biologic was represented only in the biologic category.

RESULTS

Recruitment Methods and Inclusion Criteria

Table 1 summarizes the governance, nature of data reported, frequency of data collection, and selection criteria of the various cohorts. The European registers initiated by the national rheumatology societies of the respective countries had widely varied inclusion criteria for the biologic and comparator cohorts. The biologic arms generally enroll new users, although new disease-modifying antirheumatic drug (DMARD) use is often not required for the comparator cohorts. U.K. national guidelines restrict use of anti-TNF-α drugs to patients with active RA, defined as a Disease Activity Score (DAS28) >5.1 despite previous therapy with 2 DMARDs, 1 of which should be methotrexate. Within the BSRBR, patients initiating anti-TNF therapy and other biologic therapies are enrolled into the biologic cohort (2) up to a maximum of 4000 patients starting each of the 3 anti-TNF agents (etanercept, infliximab, adalimumab) and 1100 starting rituximab. The comparator cohort consists of patients with active RA with a DAS28 >4.2 despite current treatment with a conventional DMARD. New use of a nonbiologic DMARD is not required for comparator patients. The BSRBR initially sought to capture all patients with RA

Table 2 Continued

U.S. Health Plan (13)		VARA		CLEAR		BRASS		Swiss SCQM	
Bio	Comp	Bio	Comp	Bio	Comp	Bio	Comp	Bio	Comp
Variable may exceed tens of thousands		0.6	0.7	<0.1	0.3	0.5	0.5	~2.5	~3
50 ± 12	55 ± 13	64 ± 11	68 ± 12	51 ± 9	51 ± 13	58 ± 14	61 ± 15	53 ± 14	52 ± 15
73	73	11	8	82	100	86	79	70	64
						70 to 89	50 to 69	NA	NA
						52	51	27	29
						44 ± 12	49 ± 12	35.6	38.3
						36 ± 7	36 ± 6	45.9	48.3
						0.77 ± 16	0.82 ± 0.14	0.66	0.70
NA	NA	30	26	36	30	7	7	28	33
NA	NA	79	79	86	68	49	48		
8	10	18	23	14	18	8	7		
12	15	19	25	NA	NA	8	7		
8	9	19	22	NA	NA	22	18		
								NA	NA
56	56	43	47	93	86	47	34	45	28

treated with biologics in the country until recruitment targets were met. Comparator patients are enrolled from 29 geographically distinct rheumatology practices across the U.K. Because of the stringent requirements for biologic use, less than 10% of RA patients in the U.K. receive biologics.

In Germany, there are no strict guidelines on the use of biologic agents. However, recommendations presume high disease activity and failure of at least 1 conventional DMARD including methotrexate. Patients are eligible to be included in the biologic arm of the German RABBIT registry if they start new treatment with biologic agents. They are eligible to be in the control cohort if they initiate a new nonbiologic DMARD after the failure of at least 1 other DMARD (3). Participation in the registry by rheumatologists is voluntary. Based on countrywide sales figures of anti-TNF therapies, it is estimated that 5 to 10% of RA patients in Germany receive biologics (4).

In Sweden, the use of biologics is not restricted by health authorities (5). The Swedish Rheumatology Register hosts 2 overlapping modules: the Early RA Register of incident RA with less than 12 months of symptom duration at diagnosis, in operation since 1995 (n = 10,000); and the Biologics Register, which covers all treatment starts with any biologic for RA and for other rheumatology conditions, in operation since 1999 (n = 15,000 patients, of whom 10,000 have RA). A current estimate of the penetration of biologics in Sweden suggests that 12 to 20% of all the patients with RA (0.6% of the general population) receive biologics (6). There is no explicitly recruited Swedish biologic-naïve comparator cohort; several control groups are used including the Early Arthritis RA cohort and a national comparator encompassing the vast majority of prevalent patients with RA (or other rheumatology diseases, as needed), identified through the Inpatient Register or through nonprimary care outpatients visits. A variety of database linkages in Sweden exist including hospitalizations, nonprimary care outpatient visits (eg, rheumatologists), drug prescriptions (eg, DMARDs), cancer, and death. These databases can be linked to the Swedish Rheumatology Register using a national registration number (a 10-digit number assigned to all Swedish residents) for the detection of safety outcomes or comorbidities.

In Switzerland also, the use of biologics is not restricted by strict guidelines from health authorities. However, regulatory authorities have requested continuous monitoring of all patients receiving expensive biologic agents and selected the SCQM system for this task (7). Participation in the registry is voluntary, but rheumatologists are encouraged to enroll their patients by allowing them to deduct the costs of expensive biologic drugs from their global treatment expenditure scrutinized by the health authorities, which contributes to a very high enrollment rate. Based on a comparison with industry

Table 3 Comparative Characteristics of Rheumatoid Arthritis-Related Factors

	ARTIS	United Kingdom BSRBR (2,19)		Germany RABBIT (28)		Spain	NDB	
Drug Cohort	Bio	Bio	Comp	Bio	Comp	Bio	Bio	Comp
Disease duration, yr	11	12 (6-19)	7 (1-15)	9 (5-16)	6 (3-12)	9 (4-15)	13 (11)	14 (12)
DAS28	5.5	6.6 ± 1.0	5.0 ± 1.4	5.8 ± 1.2	5.1 ± 1.3	5.3 ± 1.3		
HAQ	1.4	2.1 ± 0.6	1.5 ± 0.8	1.6 ± 0.6[a]	1.3 ± 0.6[a]		1.1 ± 0.7	1.2 ± 0.7
RF+, %	87	65	58	81	72	90		

Bio, biologic cohort (for disease-based registries, represents persons who ever used biologics); Comp, comparator cohort.
Data shown as %, median (IRQ), or mean ± SD, all % are reported as nearest whole integer.
[a]Calculated from Hannover Functional Status Questionnaire (FFbH) by the formula HAQ = 3.16 − 0.028*FFbH (see Lautenschlaeger et al. German version of the Health Assessment Questionnaire (HAQ) and the Hannover Functional Status Questionnaire. Z Rheumatol 1997;56: 144-55 [in German]).
[b]The modified HAQ is collected, which generally is 0.3 to 0.4 units lower than the full HAQ (35).
[c]The Multidimensional-HAQ is collected in VARA.

sales data in 2004, approximately 70 to 80% of all Swiss RA patients receiving anti-TNF agents were included in SCQM, but this percentage might have decreased in recent years (8). Inclusion in the registry is not restricted to biologic users, but patients on biologic agents are overrepresented in the registry (~40% compared with approximately 15% in the general RA population).

The Spanish registry holds information not only on RA but on any rheumatic disease for which a biologic agent has been used (9). Patients are registered whenever they start the first biologic. Regarding RA, eligibility criteria for biologics is considered appropriate based on norms issued by the Spanish Society of Rheumatology and endorsed by the Ministry of Health (10,11). This guidance is a DAS28 >3.2 after a trial of a full-dose DMARD. RA patients treated with biologics are compared with a registry of RA patients (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide [EMECAR]) followed from 1999 to 2005. Inclusion criteria to be represented in EMECAR were fulfillment of ACR RA criteria; there are no disease duration or disease activity restrictions. EMECAR patients are recruited from 34 participating centers; all but 2 of these centers also contributed patients to BIOBADASER. In order to compare EMECAR and BIOBADASER patients, a propensity score matching process selects only EMECAR patients matched by propensity for biologic treatment with BIOBADASER patients. The propensity score is based on DAS28, rheumatoid factor (RF), RF positivity, age, and disease duration. The percent-

Table 4 Biologic Persistence at 6 Months After Initiating Etanercept, Infliximab, or Adalimumab

	ARTIS	UK BSRBR (15)	German RABBIT (16,29)	Spain BIOBADASER	NDB	CORRONA	BRASS	SCQM
Etanercept								9
Any discontinuation, %				13	13			
Discontinuation for efficacy,[a] %		19	23	4	5	15	11	4
Discontinuation for adverse events,[a] %		8	14	8	2	5	5	3
Discontinuation reason (other), %		9	9	2	4	2	2	1
Infliximab								
Any discontinuation, %				16	16			11
Discontinuation for efficacy,[a] %	13% discontinued for any reason	19	23	4	4	12	23	5
Discontinuation for adverse events,[a] %		8	12	10	3	4	16	5
Discontinuation reason (other), %		9	14	2	2	3	3	1
Adalimumab								
Any discontinuation, %			25[a]	16	20			8
Discontinuation for efficacy,[a] %			13[b]	6	7		5	4
Discontinuation for adverse events,[a] %			13[b]	6	9		3	4
Discontinuation reason (other), %				3	4		1	<1

Note. Not all cohorts in Table 1 are represented here due to the availability of data for this comparison.
[a]Numbers on these rows may not sum to the total since patients may have discontinued for more than 1 reason.

Table 3 Continued

CORRONA		VARA		CLEAR		BRASS		SCQM	
Bio	Comp	Bio	Comp	Bio	Comp	Bio	Comp	Bio	Comp
11 ± 10	10 ± 10	14 ± 11	14 ± 12	1.5 ± 0.6	1.0 ± 0.6	19 ± 12	15 ± 13	11 ± 9	10 ± 9
3.5 ± 1.6	3.3 ± 1.5	3.7 ± 1.4	3.7 ± 1.5	4.2 ± 1.0	4.0 ± 1.4	3.6 ± 1.6	3.2 ± 1.5	4.7 ± 1.5	4.4 ± 1.5
0.4 ± 0.4[b]	0.3 ± 0.4[b]	1.0 ± 0.6[c]	1.0 ± 0.7[c]	2.1 ± 0.8	1.6 ± 0.9	0.5 ± 0.7	0.5 ± 0.6	1.3 ± 0.7	1.1 ± 0.8
75	71	84	77	64	75	74	58	76	80

age of RA treated with biologics in Spain is estimated to be similar as in Germany and Sweden.

In the U.S., a number of rheumatic disease registries have been established, some but not all specific to RA. The CORRONA registry collects both physician and patient data from practices of participating academic- and community-based U.S. rheumatologists (12), for patients with RA and psoriatic arthritis. The NDB collects data from patients who have been referred by their rheumatologist after a rheumatic diagnosis has been established for RA or 1 of a variety of other rheumatic conditions (eg, osteoarthritis, systematic lupus erythematosus). Other U.S. registries have been created to facilitate RA research in specific patient populations. The CLEAR and the Veterans Affairs Rheumatoid Arthritis (VARA) Registry are examples targeting African Americans and U.S. veterans, respectively. Investigators at Brigham and Women's Hospital created a cohort of RA patients (the BRASS registry) with an emphasis on understanding the genetic basis of RA and identifying targets for new drug development. In addition to collecting disease-specific data, some but not all registries collect laboratory data that are available for research purposes. Likewise, some registries have an associated bio-repository. Additional unique features of each registry are described in the Appendix.

Other Databases Used to Conduct RA-Related Research

Some other databases that have been used for observational RA research in the U.S. come from large managed care or insurance plans (13). While some commercial health care organizations maintain databases with only administrative claims data used for billing purposes (and thus contain no clinical or RA-specific data), other databases such as Kaiser Permanente also have searchable inpatient and outpatient electronic medical records. U.S. government databases such as those available through the U.S. Veterans Affairs (VA) (14) are likewise available for research and also provide access to electronic medical records for the nation's veterans. RA-specific information is collected at several VA centers as part of the VARA registry and can be linked to administrative medical and pharmacy data.

Besides the VA health system, other U.S. governmental databases including those maintained by the Center for Medicare and Medicaid Services (CMS) are available for research. CMS data include administrative claims data used for billing purposes and covers a source population of tens of millions of people. These databases have high generalizability because they are nationally representative, at least for persons over the age of 65 (enrolled in Medicare) and lower income individuals (enrolled in Medicaid). CMS data and other administrative databases include complete health care utilization, including medication information and associated costs, but lack RA-specific information such as disease activity. Outside of the U.S., the United Kingdom General Practice Research Database (GPRD) covers approximately 6% of general practitioner visits in the U.K. and can be used to evaluate drug

Table 5 ACR Response of RA Patients 6 Months After Initiating Anti-TNF Therapy, by Cohort and According to Whether They Met Clinical Trial Criteria

	German RABBIT (17)	CORRONA (18)	VARA (30)
Infliximab ATTRACT			
Proportion of cohort meeting trial inclusion criteria, %	33	19	13
ACR20, %	52	52	—
ACR50, %	27	31	—
Etanercept monotherapy			
Proportion of cohort meeting trial inclusion criteria, %	23	13	6
ACR20, %	65	61	—
ACR50, %	37	37	—

Note. Not all cohorts in Table 1 are represented here due to the availability of data for this comparison.

Table 6 Incidence of Serious Adverse Effects in RA Patients Receiving Anti-TNF Agents, by Cohort and Treatment Group

	UK BSRBR (2,19)	German RABBIT (21)	Swedish ARTIS (6,20,31)	Spain BIOBADASER
Method to identify and confirm safety events	If event is reported from any of the 3 sources: consultant questionnaire or patient diary or UK malignancy and mortality register; hospital discharge summary and other supporting information is requested. Two physicians often independently verify the diagnosis. Verification criteria differ by outcome.	If a serious event is reported, a standardized query is sent to the reporting rheumatologist usually within 1 week after notification. The event specific queries ask for diagnostic details. They are used for the final coding of the event.	Safety outcomes are captured through 2 sources: (a) Physician AE reports, adjudicated at the Swedish medical Products Agency, (b) through linkages with pertinent registers, with/ without subsequent chart review	Physicians reported plus random in site audits comparing full clinical record and registry plus patient cross-check of hospitalizations.
Serious infections[a]	6.1 in TNF group 3.9 in DMARD group 1st 90 days: 7.2 in TNF group and 2.4 in DMARD group	6.2 in TNF group 2.3 in DMARD group	5.4	6.6
Fatal and nonfatal acute MI[a]	0.48 TNF group 0.59 DMARD group 0.94 in anti-TNF nonresponders vs 0.35 in anti-TNF responders		1.5 in TNF group	2
Malignancy[c]				
Malignancy (including nonmelanoma skin cancer)			9.3	7
Malignancy (excluding nonmelanoma skin cancer)				

Note. Not all cohorts in Table 1 are represented here due to the availability of data for this comparison.

Definition of serious infections: BSRBR, those that lead to death or hospitalization, or outpatient infection that required intravenous antibiotics; RABBIT, according to International Conference on Harmonization E2A guidelines; ARTIS, hospitalization with infection; CORRONA, described in (24); NDB, hospitalization or requiring intravenous antibiotics; U.S. Health Plan, 1 example described in (22); SCQM, infections leading to treatment discontinuation (34).

Definition of acute MI: BSRBR, definition according to modified ESC/ACC criteria, nonfatal and fatal. Sudden death included if MI on death certificate, and therefore, fulfilled above criteria; RABBIT, definition according to international conference on harmonization E2A guidelines; ARTIS, hospitalization with acute MI; NDB, hospital or physician records; CORRONA, nonfatal MIs reported by rheumatologist and adjudicated by cardiologist committee according to published RCT adjudication criteria based on American College of Cardiology/American Heart Association guidelines. Cardiovascular deaths included.

Definition of malignancy: ARTIS, reports to the Swedish Cancer Register (clinical + pathologic mandatory reporting, virtually all cases histological verified, chart review in biologics cohort to verify time sequence that drug exposure preceded cancer); CORRONA, reported malignancies confirmed by review of pathology reports/medical records in a majority of cases.

[a]Per 100 person-years.
[b]In the first 6 mo after starting therapy.
[c]Per 1000 person-years.
[d]Includes nonfatal MI and CV deaths.

safety and health outcomes across many disease states. However, the GPRD is not currently linked to the BSRBR; data is contributed by general practice physicians rather than rheumatologists, and the GPRD will therefore not be discussed further.

Demographics and Comorbidities, by Cohort and Drug Exposure

Table 2 reviews the demographics and comorbidities of RA patients enrolled in selected European and U.S. reg-

Table 6 Continued

CORRONA	NDB (32,33)	U.S. Commercial Health Plan (13)	SCQM
Serious adverse events are reported by the treating rheumatologist. A standardized follow-up adverse event form is completed by the physician. Hospital records and selected outpatient primary medical records are reviewed centrally by at least 2 physician researchers (eg, pathology reports for malignancy). CV events are adjudicated by cardiologist committee after review of primary medical records.	Preliminary information is obtained from patients at semiannual intervals. Reports of events are followed up on by patients and physician contact, and by review of medical records. If medical record data are not available, patient/family self-reported are sometimes accepted. Cases are categorized by level of evidence, and only strong evidence is accepted. National death records are searched for cause-specific mortality.	Highly variable. In some studies, administrative claims data are used to identify possible cases, and medical records are obtained for confirmation. Other studies rely on claims data alone for outcome ascertainment, particularly if a validation study is available showing claims alone can validly identify bona fide events	If a serious event is reported by the treating physician, a standardized query is sent to the reporting rheumatologist within 1 week after notification. The event specific queries ask for diagnostic details. They are used for the final coding of the event.
1.9 in TNF group		2.7 in TNF group 2.0 in Mtx group 1st 6 month: 2.9[b] in TNF group 1.4 in MTX group	2.3
0.11 in TNF group[d] 0.35 in MTX group 0.40 in DMARD group			
7.5	33.1		5.2
5.2	13.0		

istries. The demographic characteristics of the patients are largely comparable across cohorts with only a few exceptions. The VARA registry has a much lower proportion of women given that the VA population consists mainly of men. The size of the various registries ranges from approximately one thousand (BRASS, VARA, and CLEAR) to many thousands. The prevalence of various comorbidities for these RA patients is shown in Table 2, although the definitions used to define these various conditions may differ. For all cohorts and registries, comparator patients

(ie, nonbiologic users) generally have as high or a higher burden of comorbidity compared with biologic-treated patients. Between cohorts, there are potentially important differences in the comorbidity profiles; some of these "differences" reflect true differences in the patients enrolled in each register, although dissimilarities in the definitions and methods of ascertainment of comorbidities may also underlie these apparent differences.

Approximately one quarter to one third of participants in the BSRBR, RABBIT, SCQM and CLEAR are current smokers, which is much higher than in BIOBADASER and some of the U.S. cohorts (prevalence of 12-15%). The reported prevalence of diabetes is higher in the VARA and CLEAR population (14-22%) versus 5 to 10% for other registries; the prevalence of chronic lung disease (including chronic obstructive pulmonary disease/asthma) is higher in VARA, BRASS, and the BSRBR (19-22%) than other registries. Other potentially important differences relate to the within-cohort prevalence of comorbidities contrasting biologic and nonbiologic users. For example, in RABBIT, the prevalence of chronic lung disease is quite similar between biologic and comparator patients at 6-7% for each, whereas in the BSRBR, it is approximately 50% higher in the comparator cohort (20%) than in the biologics cohort (13%). These differences are likely to significantly affect the absolute rates, as well as the relative rates, of conditions associated with chronic obstructive pulmonary disease such as pneumonia. Another salient difference relates to glucocorticoid use: the proportion of RA patients using glucocorticoids is much higher for patients in RABBIT (approximately 80%) compared with other cohorts.

Table 3 describes the RA-related factors of various registries, and several salient differences are noted. The mean DAS28 is quite high (5.8-6.6) in the biologic arm of the BSRBR, as might be expected given restrictions on biologic use in the U.K. In contrast, the mean DAS28 score in the biologic arm of the U.S. registers is substantially lower (3.5-3.6), which allows them to study not only patients with severe RA but also those with mild and moderate disease. Another factor that affects the mean DAS28 of biologic-treated patients relates to the age of the registry. The older registries generally enrolled patients with higher DAS28 and indices of RA severity. Similar trends are observed in the amount of disability, as measured by the Health Assessment Questionnaire (HAQ), although some of these differences may reflect different registries using different versions of the HAQ (the "full," 20-question HAQ, the 8 question modified HAQ, or the intermediate-length MD-HAQ). Differences in disease activity and disability among RA patients using biologics or comparator drugs may influence disease outcomes, medication effectiveness and safety. Also, for any European or U.S. registry that does not provide national representation, external validity is a potential concern since patients enrolled in the registry may or may not be representative of the entire RA population within that country. While this would not be expected to compromise the internal validity of results, it may affect generalizability. For example, the experience of the biologic users enrolled in the U.K. and Swedish registries are likely representative of the vast majority of RA patients within those respective countries because those registries capture most of their biologic-treated patients.

Outcomes: Biologic Persistence and Clinical Effectiveness

Comparable discontinuation data for new users of anti-TNF agents were found for the BSRBR, RABBIT, NDB, CORRONA, and BRASS and are shown in Table 4. The proportion of patients discontinuing therapy at 6 months was approximately similar across the cohorts; slightly higher rates of discontinuation were observed in BSRBR and RABBIT (19 and 23%, respectively) compared with NDB, CORRONA, and BRASS (15,16). It is possible, although speculative, that these small differences relate to baseline disease severity.

Table 5 describes the proportion of patients with RA who meet clinical trial eligibility criteria and also their associated American College of Rheumatology (ACR) response rates. Comparable data were available for RABBIT, CORRONA and VARA. Only between 6 and 33% of patients in RABBIT, CORRONA and VARA would have been eligible for the clinical trials that were reported in common (17,18). Among patients who were eligible for these trials, ACR20 and ACR50 responses were comparable between the observational cohorts (RABBIT and CORRONA) and the respective clinical trials.

Outcomes: Serious Adverse Events

As shown in Table 6, the incidence of serious infections in RA patients on anti-TNF therapy was comparable for most of the European registers (5-6 per 100 person-years). The rate was lower for RA patients in the U.S. registries (13,19-21). As 1 example of methodologic differences that may impact absolute incidence rates, the lower incidence reported in U.S health plan (2.9 per 100 patient-years) could be attributed to the "case definitions" for infections used in that study that incorporated clinical, microbiologic and radiologic results. These were perhaps more specific for an infection but decreased sensitivity (and thus the absolute rate). Although the case definitions for infections are not identical across cohorts, there are now available case definitions and a classification system to gauge the certainty of an infection (22-24). Moreover, some but not all registries have access to primary medical records, which may impact the certainty of infections and thus event rates, since unconfirmed reports of infections can be excluded. All of these factors could impact the absolute rate of serious adverse events SAEs, although the relative rates (comparing biologic to comparator patients) would be unaffected as long as these methodologic considerations applied equally to both the biologic and the comparator RA patients. In the future, better standardization of

case definitions and criteria for confirmation of infections and other SAEs may improve the comparability of absolute event rates between registries.

Besides possible differences in outcome definitions and factors such as demographics, several other factors might account for different event rates across cohorts for serious safety outcomes. Registries in countries with fewer restrictions on biologic use generally include patients with lower disease activity that may have an associated lower susceptibility to SAEs. Comorbidity profiles are also quite different within and between the biologic and DMARD arms of each cohort, as previously described in Tables 2 and 3. Differences in the relative rates of infections (comparing biologic to nonbiologic users) reported by the various registries may in part depend on the comorbidity profiles of the patient populations within each registry, particularly for the comparator RA patients not using biologics. As a point of similarity, both U.S. and European cohorts have demonstrated that the risk of infection is time dependent and is highest in the initial 3 to 6 months after initiation of therapy with TNF antagonists (19,20,25).

Finally, 1 possible area for potential harmonization is in adopting similar analytic methods for attributing events to drugs (risk windows) (19). Patients may be instructed to discontinue medications if they experience symptoms (eg, chest pain, or angina) consistent with an impending adverse event. If one attributes outcomes to exposure only while patients are actively receiving medications of interest, important safety events (eg, subsequent myocardial infarction) related to medication exposure can be missed. For that reason, the "risk window" that patients are considered exposed is often extended for some amount of time, which may differ based on the outcome. For infections, extending the risk window by 30 to 90 days would seem to be reasonable (19). The most appropriate risk window for other outcomes such as cardiovascular events and malignancy is unclear. Agreeing on the range of risk windows to be used for each outcome may provide better comparability in comparing results between registries.

CONCLUSION

Because results from RCTs may not be generalizable to clinical practice, biologics registries and cohorts have been set up in various countries to bridge the gap in our knowledge regarding the effectiveness and safety of these agents. The large size of these registries and long duration of follow-up allows analysis of rare events, which generally is not possible with RCTs. Our work highlighting the unique features of several of these cohorts points out their various characteristics that may make them more or less suitable to answer particular research questions. Ongoing work to possibly standardize definitions for outcomes and comorbidities and to harmonize analysis methodologies are likely to result in even greater knowledge from these valuable information sources. Ultimately, the existence of these population-specific registries in Europe and the U.S. from countries with markedly different biologic usage, patterns of comorbidity, and different sociodemographic and geographic factors (eg, background rates of opportunistic infections) will provide valuable information that complements RCT data to study comparative effectiveness and safety of rheumatic disease therapies.

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Appendix Unique Features of Individual RA Registries (provided by investigators affiliated with each cohort)	
ARTIS (Sweden)	Capture (estimated to 90% of all eligible patients with RA) the entire Swedish treatment experience with biologics in RA, possibility to use multiple control groups including the general population experience; linkages to external registers allow for capture also of outcomes that are not predefined (as long as they are captured by the registers)
BRASS	Recruitment from a single academic arthritis center, data collected from patients and their rheumatologists including laboratory, pharmacoeconomics, quality of life and radiographs with Sharp scores. Extensive biorepository including serum and DNA on over 1100 pts
BSRBR	High proportion of all UK patients recruited (estimated >80% until recruitment targets met). Linkage with national mortality and malignancy registers
CLEAR	Exclusive African American enrollment. Bio-repository available. Longitudinal radiographs and DXA performed
CORRONA	Disease-based U.S. registry collecting data from both physicians and patients, including laboratory data. Also includes pharmacogenetics bio-repository of >1000 patients prescribed biologics
NDB	Outcomes included direct and indirect medical costs, work disability, health utility measures, household income, job classification, joint replacement, psychological scales, SF-36, widespread pain scales, comparisons with other rheumatic diseases (eg, OA, SLE), cause-specific mortality, index, and scale development
RABBIT	Internal control group of DMARD switchers. After termination of biologic treatment, patients contribute to a second control group
SCQM	Radiographic damage assessed for all RA patients
VARA	Bio-repository with baseline serum, plasma, and DNA; links with digital radiographs of hands/wrists; links with VA administrative datasets including Pharmacy Benefits Management (PBM) data