Effect of Remission Definition on Healthcare Cost Savings Estimates for Patients with Rheumatoid Arthritis Treated with Biologic Therapies

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ABSTRACT. ***Objective.*** Sustained remission in rheumatoid arthritis (RA) results in healthcare utilization cost savings. We evaluated the variation in estimates of savings when different definitions of remission [2011 American College of Rheumatology/European League Against Rheumatism Boolean Definition, Simplified Disease Activity Index (SDAI) ≤ 3.3, Clinical Disease Activity Index (CDAI) ≤ 2.8, and Disease Activity Score-28 (DAS28) ≤ 2.6] are applied.

Methods. The annual mean healthcare service utilization costs were estimated from provincial physician billing claims, outpatient visits, and hospitalizations, with linkage to clinical data from the Alberta Biologics Pharmacosurveillance Program (ABioPharm). Cost savings in patients who had a 1-year continuous period of remission were compared to those who did not, using 4 definitions of remission.

Results. In 1086 patients, sustained remission rates were 16.1% for DAS28, 8.8% for Boolean, 5.5% for CDAI, and 4.2% for SDAI. The estimated mean annual healthcare cost savings per patient achieving remission (relative to not) were SDAI $1928 (95% CI 592, 3264), DAS28 $1676 (95% CI 987, 2365), and Boolean $1259 (95% CI 417, 2100). The annual savings by CDAI remission per patient were not significant at $423 (95% CI –1757, 2602). For patients in DAS28, Boolean, and SDAI remission, savings were seen both in costs directly related to RA and its comorbidities, and in costs for non-RA-related conditions.

Conclusion. The magnitude of the healthcare cost savings varies according to the remission definition used in classifying patient disease status. The highest point estimate for cost savings was observed in patients attaining SDAI remission and the least with the CDAI; confidence intervals for these estimates do overlap. Future pharmacoeconomic analyses should employ all response definitions in assessing the influence of treatment. (First Release July 15 2014; J Rheumatol 2014;41: 1600–606; doi:10.3899/jrheum131449)

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The cost of biologic therapies to control disease-modifying antirheumatic drug (DMARD)-refractory rheumatoid arthritis (RA) has driven the development and refinement of cost-effectiveness modeling using both clinical trial and registry data. These analyses incorporate the cost of the new treatment offset by improvements in work productivity and future reduced health resource utilization[1]. Cost-effectiveness models are recognized to vary greatly in their inputs, namely in the assumptions made around patient disease characteristics, disability progression, treatment sequences, cycle length, medication dosing and wastage, risk of adverse effects, disease complications and mortality, comorbidity, and fluctuations in Health Assessment Questionnaire (HAQ) scores that are used as a surrogate to estimate health utility for the estimates[2].

Another source of variation is in the choice of effectiveness data for the modeling, specifically the use of Disease Activity Scores (DAS)[3] or American College of

Rheumatology (ACR) responses[4]. For example, the cost-effectiveness systematic review performed by Chen, *et al* based on randomized controlled trial data used ACR20, ACR50, and ACR70 responses[5]. In the analysis from the British Society for Rheumatology Biologics Registry (BSRBR), the European League Against Rheumatism (EULAR) response based on the DAS28 and HAQ was used[6]. A recent report from the Swedish Rheumatology Register (SRR) evaluated 5 levels of the HAQ and the DAS28 low activity cutpoint (< 3.2) in their analysis[7]. Analysis from the Finnish national registry (ROB-FIN) used an ACR50 response as well as the DAS28 low activity cutpoint[8]. The cost per quality-adjusted life-year (QALY) in these studies ranged from 20,000 to 120,000 Euros. None of these studies compared estimates obtained using different disease activity indices in their analyses, and none examined newer composite measures proposed for clinical practice such as the Simplified Disease Activity Index (SDAI)[9] or Clinical Disease Activity Index (CDAI)[10]. As well, none of these considered remission status as compared to a minimum desired improvement in disease activity. It is already accepted that the stringency of the disease activity measure affects the proportion of patients classified as being in remission[11,12,13], raising the concern that estimates of cost-effectiveness modeling are particularly susceptible to the outcome measures used.

We recently described healthcare service utilization costs incurred by Canadian patients in a prospective population-based biologics registry, the Alberta Biologics Pharmacosurveillance Program (ABioPharm)[14]. Although this type of cost accounts for only a small fraction of the economic consequence of RA[15], it is a major consideration in justifying resource allocation in the healthcare system in Canada. In this study, patients achieving sustained remission (defined as greater than 1 continuous year in remission) had the greatest reduction in healthcare service utilization costs, relative to those patients who had persistent moderate or high disease activity. Savings were also observed for those achieving sustained remission compared to those whose remission period was not sustained, and for brief periods of low disease activity relative to those remaining in moderate or high disease activity. These estimates were all based on using DAS28 cutoff levels for disease activity[3]. This analysis considers the variation in estimates for direct costs based on remission defined by different disease activity measures, namely the ACR Boolean definition, the SDAI, and the CDAI. This is important, given expanded use of simpler composite disease activity measures in clinical practice, and the potential future need to perform global metaanalyses of the cost-effectiveness of biologic therapies.

MATERIALS AND METHODS

Data sources. ABioPharm was initiated in 2004 to identify the efficacy, safety, and cost-effectiveness of new biologic therapies for RA[16]. Patients were enrolled at initiation of biologic therapy; a comparison group of patients treated only with leflunomide was also enrolled in the study. Patients in Alberta qualify for anti-tumor necrosis factor (anti-TNF) therapy cost coverage if they have RA refractory to both oral and parenteral methotrexate in combination with at least one other DMARD, and a trial of leflunomide. They must achieve and retain a minimum DAS28 improvement of 1.2 units and a minimum improvement of their HAQ score by 0.22 units over their baseline scores at 12 weeks and every 6 months thereafter to continue receiving cost coverage for anti-TNF therapy. Patients who fail to meet these response criteria will be switched to another anti-TNF therapy or a biologic therapy with a different mechanism of action. Patients participating in the program (> 90% of all patients receiving biologics in our province) are assessed for disease activity, adverse events, effects on function and quality of life, healthcare utilization, and self-reported economic effects of their disease at the start of a new biologic agent, 12 weeks after initiation of that drug, and at 6-month intervals as long as they receive treatment with a biologic agent. Patients may be assessed more frequently if they contact the program reporting suspected treatment failure or adverse events that may require a treatment switch.

Clinical data from ABioPharm was linked with provincial administrative databases maintained by Alberta Health and Wellness to identify health services utilization and associated costs of the RA patients. Datasets include physician billing claims, outpatient department and emergency room visits (Ambulatory Care Classification System; ACCS), and hospitalizations (Discharge Abstract Database; DAD). Clinical data and provincial administrative data collected between April 1, 2004, and March 31, 2009, were used in our analysis. Patients continued to contribute data as long as they remained in the cohort (i.e., did not withdraw consent, continued taking leflunomide or biologic agent, and remained in the provincial healthcare system).

All patients provide informed consent in accord with ethical standards described in the Declaration of Helsinki. The study was approved by the University of Calgary Health Research Ethics Board and by the University of Alberta Research Ethics Board.

Determination of healthcare service utilization cost. We estimated the annual mean and median healthcare service utilization costs per patient during the study period, including all services and procedures provided during hospitalizations and emergency room visits, or ambulatory care contacts including same-day surgery, day procedures, and community rehabilitation program services occurring in publicly funded facilities, but not drug costs due to the limited availability of these data prior to 2008 in the provincial datasets. The cost of each inpatient stay was estimated by multiplying the Alberta average inpatient cost (derived from provincial Management Information System data) per patient-day by the length of stay. The cost of each outpatient visit was estimated by the average unit cost corresponding to the ACCS grouper code assigned to the visit. Physician billing claims for all patient encounters whether in hospital or the emergency room are also provided per individual. Before any analyses, we attributed costs as RA-related or not RA-related, determined by consensus of 4 rheumatologists (CB, JH, LM, WPM) who reviewed all the International Classification of Diseases diagnostic codes associated with physician billing claims, ACCS, and DAD datasets. RA-related costs were those directly associated with musculoskeletal disease, extraarticular manifestations, recognized comorbidities such as cardiovascular disease and osteoporosis, and treatment-related complications such as gastrointestinal ulcerations, infections, and malignancy. Non-RA-related costs were those encounters deemed not to be directly related to RA or its recognized complications, for example, endocrine, allergic or psychiatric conditions, or genitourinary or gynecologic disease.

Analysis categories. Remission was defined using 4 recognized definitions: the 2011 ACR/EULAR Boolean definition[17], SDAI ≤ 3.3[9], CDAI ≤ 2.8[10], and DAS28 ≤ 2.6[3]. As we wanted to specifically consider costs associated with sustained levels of disease activity, we identified patients who attained

a minimum 1-year continuous state of remission, with no changes in biologic, disease-modifying antirheumatic drug (DMARD), or corticosteroid therapy during that period. Annual costs for patients attaining remission by each definition at any time during the study period were compared to patients who did not attain remission by that same definition. We used a kernel propensity score matching technique[18,19,20] to compare the mean cost differences between disease activity categories. Propensity score matching identifies similar characteristics between subjects in each disease activity category, and compares the costs of these sets, to address the possibility that differences related to the disease activity state may be influenced by one or more confounders. Our propensity score matching technique accounted for confounding by variables affecting healthcare utilization, including specific therapy received, smoking status, age, sex, baseline function measured by the HAQ score, disease duration, and the presence of medical comorbidities scored using the Self-Administered Comorbidity Questionnaire[21]. Quantile regression was performed to calculate the median cost differences accounting for the same confounding factors. Stata MP 11.2 (StataCorp, College Station, TX, USA) was used for analyses. Our data agreement did not allow for access to healthcare utilization data prior to start of biologic therapy, thus baseline costs could not be included in the models. All the costs were converted to 2008 Canadian dollars to account for inflation using the Canadian Consumer Price Index.

RESULTS

Our cohort includes 1086 patients with established RA treated with leflunomide (n = 143) or biologic therapy (initial therapies n = 560 etanercept, n = 159 adalimumab, n = 208 infliximab, the remainder treated with anakinra, abatacept and rituximab) enrolled in ABioPharm between April 1, 2004, and March 31, 2009. Women comprised 72.1% of the cohort, and the mean age was 55.1 (SD 13.3) years. The mean disease duration was 13.6 (SD 9.5) years. At baseline, the mean HAQ score for the whole cohort was 1.5 (SD 0.7), with a mean DAS28 of 5.54 (SD 1.63), mean SDAI 49.6 (SD 38.2), and mean CDAI 32.8 (SD 15.9). At start of biologic, 49.9% remained on methotrexate, 29.7% on hydroxychloroquine, 36.6% on leflunomide, and 10.2% on sulfasalazine. Prednisone was taken by 11.2% of the cohort at a mean daily dose of 11.2 mg (SD 8.7). The mean disease activity measures at baseline for patients attaining remission and not, by each definition, are presented in Table 1.

The proportion of patients attaining a 1-year period of remission by the DAS28 definition was 16.1% (n = 175), compared to 8.8% for the ACR/EULAR Boolean definition (n = 95), 5.5% for the CDAI definition (n = 60), and 4.2% for the SDAI definition (n = 46). Only 20 patients were classified as in sustained remission by all the definitions. The mean reduction in HAQ score was similar across remission definitions, varying between 0.60 and 0.85.

Total healthcare service utilization costs were significantly higher in patients who did not attain sustained remission. Mean annual crude costs, presented in Table 2, were approximately $3000 per patient treated to sustained remission (with the exception of CDAI, with outliers affecting the analysis) compared to about $5700 per patient who did not achieve sustained remission. Median annual crude costs were about $2000 per patient achieving sustained remission, compared to $2700 when sustained remission was not reached.

The point estimates for healthcare cost savings varied numerically by the remission definition that was used, however, with overlapping confidence intervals (Figure 1). The mean annual total savings per patient attaining SDAI remission relative to those that did not using the propensity score matching technique was estimated at $1928 (95% CI 592, 3264), compared to $1676 (95% CI 987, 2365) for DAS28 remission, and $1259 (95% CI 417, 2100) for the ACR/EULAR Boolean definition of remission. The savings for those patients achieving CDAI remission was not statistically significant at $423 (95% CI –1757, 2602), again reflecting the outliers. Analysis of median costs using quantile regression also demonstrated cost savings for patients in remission for the SDAI, DAS28, and Boolean definitions only, with estimates that were similar to each other (SDAI $772 per year, DAS28 $814 per year, ACR/EULAR Boolean $715 per year). Due to the outliers noted, we also calculated cost savings for the 80th and 90th percentiles of patients (data not shown).

We further examined whether these savings were directly attributable to reductions in healthcare utilization for RA and its comorbidities or treatment complications (Figure 2). Costs related to rheumatology visits were significantly reduced in patients achieving DAS28 remission compared to those that did not [mean annual savings per patient $340 (95% CI 174, 506)]. Annual orthopedic costs were reduced in patients attaining sustained remission with all definitions [DAS28 $355 (95% CI 174, 536); Boolean $251 (95% CI 90, 411); SDAI $320 (95% CI 20, 620); CDAI $285 (95% CI 33, 536)]. Patients in sustained DAS28 remission also had a reduction in costs associated with infections [annual savings $107 (95% CI 24, 191)].

Non-RA-related costs, such as those associated with nonautoimmune dermatologic, hematologic, renal, endocrine, respiratory, or psychiatric conditions, account for half of all healthcare service utilization costs in patients with RA, but were also significantly reduced in patients attaining sustained remission (Table 3). In particular, costs for nonautoimmune hematologic conditions, psychiatric disease, respiratory disease, lower gastrointestinal tract conditions, and ophthalmology conditions were significantly lower in patients achieving sustained remission by at least 1 definition.

DISCUSSION

We have demonstrated variations in the magnitude of the healthcare cost savings observed with biologic treatment according to the remission definition used in classifying RA patient disease status. In our program, the point estimates with the highest cost savings appear to be associated with attaining SDAI remission, followed by DAS28 remission and Boolean remission. We note that these estimates are

Table 1. Baseline disease activity measures in the Alberta Biologics Pharmacosurveillance Program, 2004-2009. All data are reported as mean (standard deviation).

Disease Activity Measure	Overall cohort	DAS28 Remission		ACR Boolean Remission		SDAI Remission		CDAI Remission	
		Yes	No	Yes	No	Yes	No	Yes	No
Tender joint count (28)	12.2 (8.6)	10.7 (8.5)	12.7 (8.5)	8.6 (7.8)	12.8 (8.6)	5.9 (6.5)	12.7 (8.7)	8.5 (8.2)	12.6 (8.7)
Swollen joint count (28)	8.1 (5.9)	7.1 (5.3)	8.5 (6.0)	6.1 (5.5)	8.5 (6.0)	4.1 (4.4)	8.3 (5.9)	5.5 (4.5)	8.3 (6.0)
ESR, mm/h	27.7 (24.4)	19.3 (18.4)	29.9 (24.9)	21.8 (19.7)	28.8 (24.8)	18.9 (19.4)	28.3 (24.8)	23.8 (20.2)	28.1 (24.9)
CRP, mg/dl	13.0 (28.5)	8.4 (27.2)	14.5 (28.9)	5.6 (15.2)	14.5 (30.2)	5.0 (11.7)	15.2 (30.6)	10.4 (20.9)	15.0 (30.6)
Patient global score, (0–10 scale)	5.7 (2.2)	4.7 (2.6)	5.9 (2.1)	4.1 (2.8)	5.9 (2.1)	3.4 (2.5)	5.8 (2.2)	4.4 (2.6)	5.8 (2.2)

DAS28: Disease Activity Score based on 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Total Healthcare service utilization costs (2008 Canadian dollars, crude) by disease status and remission definition.

Composite Disease Activity Score	Mean Annual Cost Per Patient (95% CI)		Median Annual Cost Per Patient (95% CI)	
	Sustained remission	Not in sustained remission	Sustained remission	Not in sustained remission
DAS28	n = 175, $3130 (2644–3617)	n = 911, $5992 (5333–6652)	n = 175, $1977 (1088–3923)	n = 911, $2791 (1467–5992)
ACR/EULAR Boolean	n = 95, $3000 (2356–3643)	n = 991, $5783 (5184–6383)	n = 95, $2009 (1047–3345)	n = 991, $2724 (1446–5922)
SDAI	n = 46, $2945 (1771–4120)	n = 1040, $5670 (5075–6266)	n = 46, $2007 (1265–3096)	n = 1040, $2779 (1458–5941)
CDAI	n = 60, $4524 (2091–6958)	n = 1026, $5607 (5019–6194)	n = 60, $2257 (1336–4558)	n = 1026, $2721 (1432–5787)

DAS28: Disease Activity Score based on 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism.

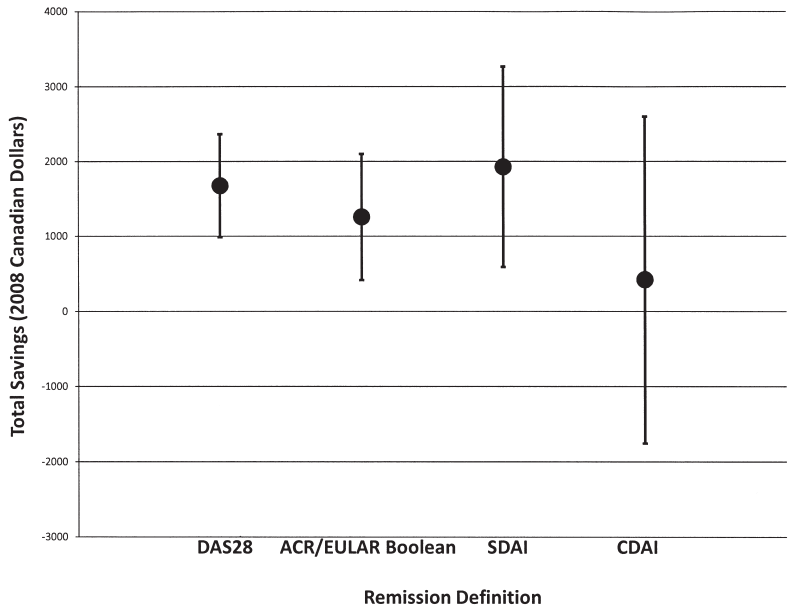

Figure 1. Mean cost savings estimates (2008 Canadian dollars) for patients in remission.

associated with overlapping confidence intervals, thus are not statistically different from each other. The healthcare cost savings for patients in CDAI remission was not statistically significant compared to patients not achieving remission related to outliers. The variation in our point estimates supports the concept that model-based cost-effectiveness evaluations are dependent on the specific disease activity measures used in their analyses, both through the number of patients classified to be in each disease activity state and through the cost savings attached to the sustained remission. As these models additionally use a variety of inputs, and rely on many assumptions and approximations,

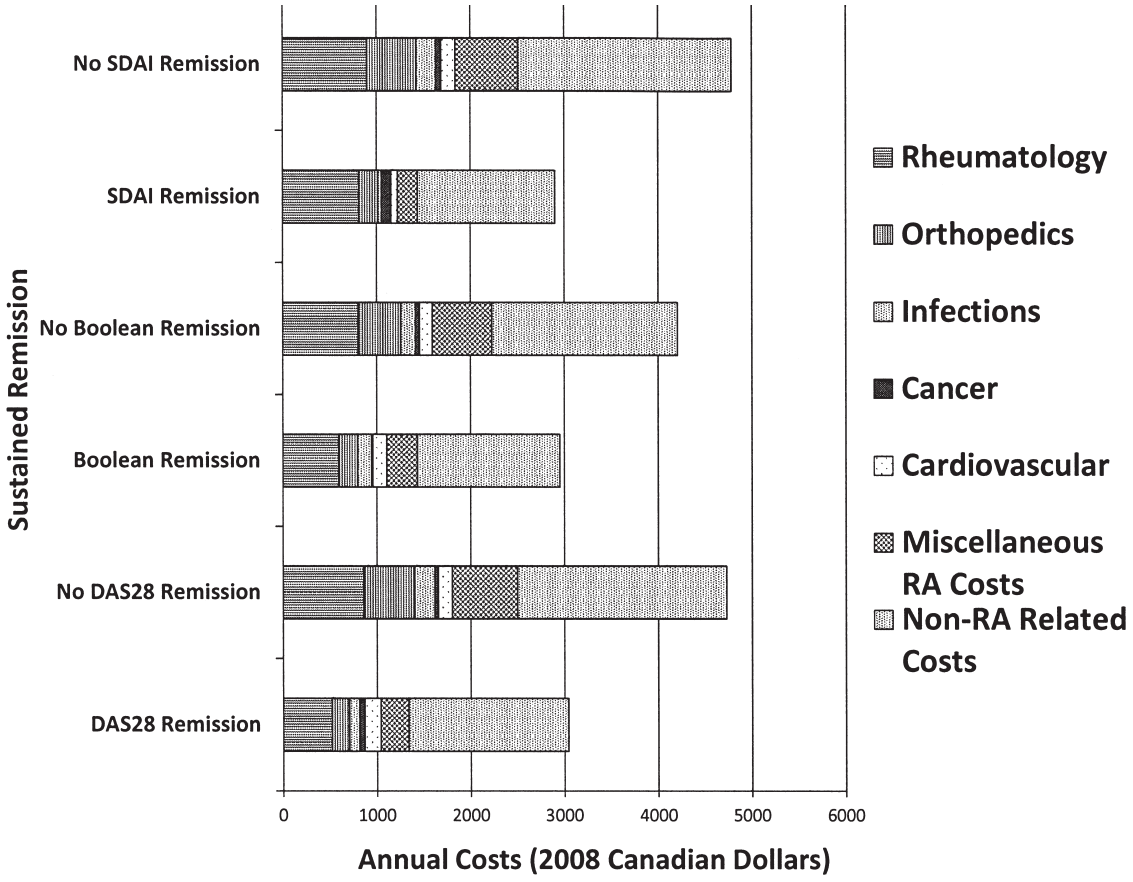

Figure 2. Distribution of costs per patient by remission status.

Table 3. Savings in non-RA-attributable healthcare service utilization costs [mean annual per patient (95% CI); 2008 Canadian dollars] for Patients in Sustained Remission (compared to not).

Cost Category	DAS28	ACR/EULAR Boolean	SDAI	CDAI
Total savings*	$518 (212, 958)	$458 (136, 839)	$802 (180, 1192)	$–287 (–2811, 1228)
Hematology	$18 (7, 30)	$22 (7, 37)	$24 (12, 36)	$24 (12, 35)
Psychiatry	$75 (–31, 180)	$63 (4, 122)	$131 (–15, 278)	$64 (–148, 275)
Arrhythmia	$–25 (–126, 77)	$27 (–11, 66)	$42 (10, 73)	$37 (13, 61)
Respiratory	$62 (21, 103)	$61 (–10, 132)	$52 (–4, 108)	$125 (–176, 426)
Gastrointestinal and liver	$88 (6, 170)	$50 (4, 95)	$104 (37, 171)	$5 (–198, 209)
Ophthalmology	$40 (29, 247)	$28 (–125, 190)	$-10 (–508, 252)	$-2 (–277, 260)
Health status/contact	$138 (43, 221)	$32 (34, 171)	$128 (83, 270)	$8 (33, 200)

*Negative values indicate higher costs in patients in sustained remission compared to those who are not. DAS28: Disease Activity Score based on 28 joints; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism.

it is critical that the reader understand the potential sources of variation when interpreting cost-effectiveness results.

There was variation in the number of patients classified as being in sustained remission using different definitions of remission, ranging from 4.2% for SDAI up to 16.1% for DAS28. This finding is not unexpected, as it is recognized that the DAS28 score has the least stringent remission definition[11]. Our CDAI sustained remission rates are strikingly similar to those of another North American cohort, the CORRONA study, where 5.8% of patients with established RA over 8 years achieved sustained remission (defined in their study as CDAI remission on 2 consecutive visits after the baseline visit, more than 2 but less than 6 months apart)[22]. Thus, sustained remission is a relatively rare event in clinical practice, limiting the power of the comparisons between the remission and nonremission groups for economic analyses. This is seen with our point estimates, which are nonsignificant but numerically distinct from each

other (mean annual cost savings estimate per patient of $1928 for SDAI remission, $1676 for DAS28 remission, and $1259 for Boolean remission).

Economic analyses for RA are heterogeneous in methodology[23]. These studies may consider direct healthcare costs alone, both direct and indirect costs, and with or without medication costs, to consider the societal impact of the disease. Relatively few authors have reported analyses stratifying costs as RA-attributable or not, with variation in classification of these costs. For example, Weycker, *et al* defined RA-related costs to include rheumatology therapeutics and patient encounters, with all other care, medications, and all-cause hospitalizations being non-RA-related[24]. McBride, *et al* used a similar stratification for RA-related costs, with any patient encounters where the primary or secondary diagnostic code was for RA, as well as any nonbiologic DMARD or biologic DMARD or nonsteroidal antiinflammatory drug prescriptions, but with all other costs defined as non-RA-related[25]. However, it is evident from 1 publication that cost estimates vary once recognized RA comorbidities are taken into account. Joyce, *et al* demonstrated that the annual cost per RA patient per year in the United States was $11,404, but increased to $14,145 when RA patients also had cardiovascular disease, and $13,513 when they had both cardiovascular disease and depression[26]. This supports our decision to expand the list of RA-attributable costs to include not only RA directly, but also its recognized comorbidities and treatment complications.

Patients achieving remission also decreased utilization of healthcare in other non-RA related categories. In particular, costs for nonautoimmune hematology conditions and lower gastrointestinal tract conditions were reduced for patients across all remission definitions, whereas costs for psychiatric conditions, cardiac arrhythmias, respiratory conditions, and ophthalmologic conditions were decreased in at least one. The benefits of attaining good RA control with effective therapy thus affects other facets of a person's health and well-being. We propose that considering these non-RA-related costs in economic modeling will be beneficial, and will also likely affect indirect cost estimates. We encourage other groups to validate and refine our suggestions for RA- and non-RA-attributable cost classifications, and to also consider the use of general population comparators as an alternative to distinguish between cost categories.

We are not aware of any other reports that have compared cost estimates according to remission status, that have included the CDAI and SDAI, or even compared estimates in the same study using different disease activity measures. One study in early RA has done this using simulation models[27], demonstrating the wide variability in correlation between disease activity index states. For example, correlation was lowest for DAS28 (3 variables) with SDAI or CDAI (0.57), moderate for the CDAI and DAS28 (3 variables) (0.76), and highest between the original DAS with DAS (3 variables), and SDAI with CDAI (0.99). This variation affected simulated treatment decisions such as therapy intensification or tapering, and also the median estimates for medication costs, with simulated annual costs per patient at 318 Euros [interquartile range (IQR) 189–7733] for the DAS, 5267 Euros (IQR 214–8953) for the DAS28, 7657 Euros (IQR 298–10,233) for the SDAI, and 7050 Euros (IQR 298–10,214) for the CDAI. Our study represents an advance in the field by using real-world data for costs related to healthcare utilization to demonstrate variations according to the disease activity state of remission for patients with established RA.

There are limitations to our analysis. First, we acknowledge that our estimates reflect only a portion of the economic burden incurred in RA. Healthcare costs accounted for only 11.7% of total mean annual costs in a study performed in Sweden[15]. We have assumed stable levels of disease activity between evaluation times reflecting the evaluations occurring in standard clinical care. Our cost estimates also do not include privately funded services such as chiropractic treatments, massage therapy, and private mental health services, or costs associated with patient communication by healthcare providers by telephone or email. This analysis focuses only on direct costs; patients who do not achieve sustained remission will likely incur additional pharmaceutical costs and indirect costs that are not accounted for here. Our decision to categorize comorbidities common in RA as being entirely attributable to RA will result in an overestimate of costs, but still reflects the overall costs incurred by the patient. This work was conducted in a healthcare system that is publicly funded and the conclusions will require confirmation in other healthcare systems where access may be more restricted.

We have shown for the first time using real-world healthcare costing data that the definition of remission for disease activity influences estimates for cost savings in patients with RA. We propose that these costs should also be characterized to distinguish between RA- and non-RA-attributable costs. We have demonstrated that healthcare cost savings are observed for RA itself directly, as well as for related comorbidities and treatment complications. Our classification also provides estimates of healthcare savings realized in conditions not considered to be directly related to RA. We have proposed a definition for sustained remission in clinical practice that reflects measurable changes in economic outcomes. These analyses have major implications for economic modeling and we recommend that future analyses should address multiple definitions of disease status as well as both RA-attributable and non-RA-attributable costs. At the very least, utilization of a common "base case" that specifies the effectiveness measure used in at least 1 derivation of the modeling exercise is recommended, should any future metaanalyses be intended to evaluate the global effects of biologic therapies in RA.

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