Arthritis Care & Research
Vol. 63, No. 1, January 2011, pp 65–78
DOI 10.1002/acr.20338

REVIEW ARTICLE

Cost-Effectiveness of Biologic Response Modifiers Compared to Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis: A Systematic Review

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects approximately 1% of the population (1,2). The course of RA varies, but for a substantial proportion of patients it is characterized by persistent pain and stiffness, progressive joint destruction, functional disability, and premature mortality (3). RA also presents a serious socioeconomic burden in terms of direct medical costs (associated with resources consumed to research, detect, and treat RA) and indirect costs (associated with lost productivity, early mortality, and time contributed by caregivers) (4–9).

The pharmacologic management of RA has been transformed with the introduction of disease-modifying antirheumatic drugs (DMARDs), a large class of drugs that includes hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine. Whereas drugs such as nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids control symptoms, DMARDs slow the progression of joint damage that leads to loss of function (10,11). Guidelines advocate treatment with DMARDs as soon as RA is diagnosed to control symptoms and delay disease progression (12). Newly developed biologic response modifiers (biologics) offer even more hope, having a greater potential to suppress disease activity, improve quality of life, and inhibit joint destruction (13–15). But while biologics may have the greatest potential to slow the course of RA, these drugs cost substantially more than DMARDs. Consequently, current guidelines recommend biologics for patients with inadequate responses to DMARDs largely because higher costs preclude their widespread early use (12,16–18).

Therefore, at the core of the debate is whether the superior clinical outcomes achieved with biologics are worth their higher costs. Should earlier treatment with biologics be considered, given their potential to slow disease progression and extend productivity, thereby reducing downstream direct costs associated with health care utilization and indirect costs associated with lost productivity? Since the introduction of cyclooxygenase 2–inhibiting NSAIDs and DMARDs, RA drug costs have more than doubled, and now with the recent introduction of biologics, these costs are expected to increase (19). Not surprisingly, many agencies (including the National Institutes of Health in the US) have identified the cost-effectiveness of biologics as one of the highest-priority research topics in the pharmacologic treatment of RA. Decision makers in public and private health care systems need a synopsis of current economic evidence upon which to base funding decisions. An understanding of the existing literature is also essential to identify gaps in the current evidence and to inform the development of future economic evaluations. We therefore undertook a review of the literature to identify and critically appraise existing economic evaluations of biologics versus DMARDs for adults with RA and to determine whether the incremental cost-effectiveness is within the range of generally accepted medical interventions.

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Dr. Bombardier has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from AstraZeneca, Pfizer, Biogen Idec, PESI Healthcare, and Roche, and (more than $10,000 each) from Abbott Canada and Abbott International, Wyeth (Merck), and Schering (Merck).

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Submitted for publication January 29, 2010; accepted in revised form August 19, 2010.

Materials and Methods

Literature search. We performed an electronic search of Medline (1950 to September week 4, 2008), EMBase (1980 to week 39, 2008), the National Health Services Economic Evaluation Database (fourth quarter 2008), Ovid HealthStar (1966 to October 2008), EconLit (1969 to November 2008), and the Tufts Medical Center Cost-Effectiveness Analysis Registry (1976 to November 2008) for economic evaluations published in English, using a search strategy developed with a library scientist. Reference lists of identified economic evaluations and reviews were also manually searched.

Selection of studies. We included full economic evaluations of biologics (including, but not limited to, etanercept, infliximab, adalimumab, anakinra, abatacept, rituximab, natalizumab, golimumab, and efalizumab) (20) compared to any DMARD for the treatment of RA in adults. Full economic evaluations were defined as comparisons that considered costs (resource use) and consequences (health outcomes), including cost-effectiveness analyses (CEAs), in which results are usually expressed as a cost per unit of effect (e.g., cost per life year gained), and cost-utility analyses (CUAs), in which results are generally expressed as a cost per quality-adjusted life year (QALY) gained, or some variant (20). We excluded evaluations of biologics for other forms of arthritis, juvenile arthritis, and mixed populations where RA-specific results could not be extracted. Four reviewers (LI, MM, GvdV, WW) independently applied these criteria to identified citations during title and abstract screening and met in pairs for consensus audits to resolve discrepancies. A fifth reviewer (BP) was used to settle disagreements.

Data extraction. Data were extracted according to current recommendations using a standard collection form (21). We extracted study characteristics related to: 1) patients, 2) biologic therapy and DMARD comparator, 3) study design (country, analytic perspective, time horizon, price year, types of costs, discount rates, health effects, quality of life weight to calculate QALYs), and 4) study outcomes. All of the reported costs were converted to 2009 Canadian dollars using the Bank of Canada currency converter (online at www.bankofcanada.ca/en/rates/exchform.html) and adjusted for inflation/deflation using the Bank of Canada core Consumer Price Index (online at www.bankofcanada.ca/en/cpi.html). Three reviewers independently extracted data; all of the entries were verified in meetings with the 3 reviewers present.

Critical appraisal of selected studies. Selected studies were appraised with the British Medical Journal checklist and, for economic modeling studies, the checklist by Philips et al (22,23). These checklists provided a systematic overview of the selected studies' strengths and limitations. Three reviewers (LI, MM, GvdV) independently appraised the studies and met for consensus audits to resolve discrepancies. A fourth reviewer (BP) was used to reconcile disagreements.

Data summary. Tables and narrative synopses were used to summarize characteristics and methodologic qualities of selected studies. Incremental cost-effectiveness ratios (ICERs) were stratified by biologic agent and indications for the use of biologics in RA patients as described by the American College of Rheumatology (ACR) 2008 recommendations (i.e., patients with early RA [<6 months], patients with RA [6 months] who failed methotrexate monotherapy, and patients with RA [>6 months] who failed methotrexate combination therapy or after sequential administration of nonbiologic DMARDs) (12). We also reported results for RA patients with no previous DMARD exposure to determine the cost-effectiveness of biologics as a first-line treatment. It was not feasible to statistically pool cost-effectiveness estimates (e.g., measures of precision were mostly unreported), nor was it valid due to extensive heterogeneity across the studies (24). However, we reported median ICER values with corresponding minimum and maximum values. Costs were rounded to the nearest whole number in the tables and to the thousands in the text. Variables identified by sensitivity analyses that reportedly influenced the results were described.

In cost-effectiveness analysis, ICERs are computed as the ratio of the difference in mean costs to the difference in mean health effects of the compared interventions. ICERs represent the additional cost per additional health benefit gained from an intervention. Whether an intervention is cost effective depends on the maximum the decision maker is willing to pay for an extra unit of health effect (the willingness to pay threshold). In most jurisdictions around the world, an acceptable cost-effectiveness threshold for a QALY has not been explicitly defined (25,26). We therefore used two willingness to pay thresholds to interpret the results: the commonly cited $50,000 per QALY, as well as $100,000 per QALY (25).

Results

We screened 918 nonduplicate citations, of which 861 were excluded by title and abstract screening (Figure 1). Fifty-eight studies were retrieved, of which 35 were excluded during full-text screening and 5 during data extraction (27–31). Eighteen economic evaluations were selected for inclusion.

Characteristics of selected studies. The 18 studies selected for inclusion were published inclusive of 2000–2007; 4 conducted CEAs (32–35) and 16 conducted CUAs (28,34–48) (Tables 1 and 2). The number of comparisons within each study ranged from 1 to 20, comprising a total of 116 comparisons. Biologic agents evaluated included adalimumab, etanercept, and infliximab, either as monotherapies (etanercept [n = 12], adalimumab [n = 3]) or combination therapies (etanercept + methotrexate [n = 4], adalimumab + methotrexate [n = 3], infliximab + methotrexate [n = 10]). One study evaluated biologics as a class (tumor necrosis factor α [TNFα] antagonists) (39). We did not identify evaluations of the interleukin-1 receptor antagonist anakinra, or newer (second-generation) biologics (e.g., abatacept, rituximab).

Biologics were compared to DMARD monotherapies (le-

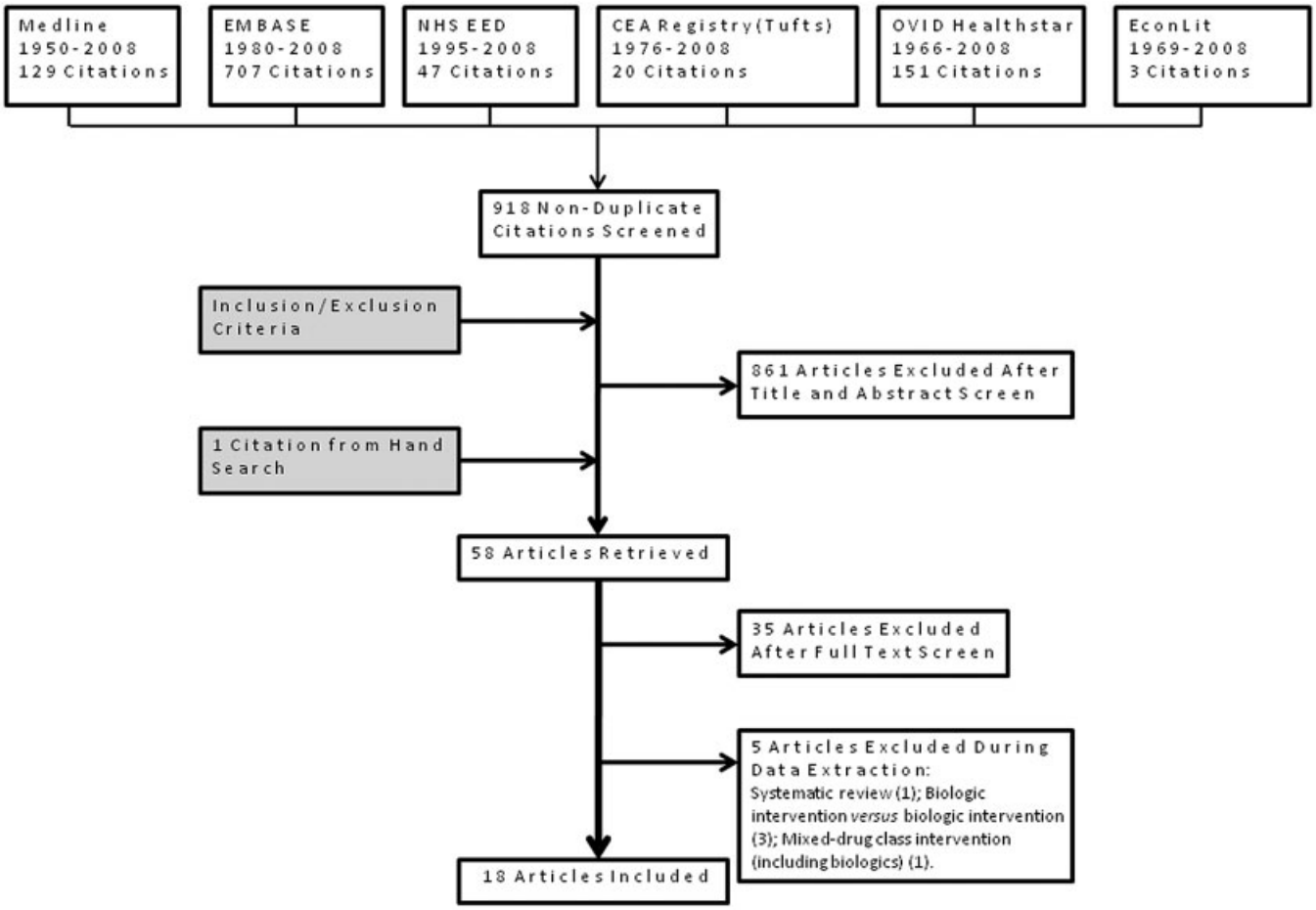

Figure 1. Flow chart of the study selection. NHS EED = National Health Services Economic Evaluation Database; CEA = Cost-Effectiveness Analysis.

flunomide [n = 1], methotrexate [n = 6], sulfasalazine [n = 1]) and combination therapies (cyclosporine + methotrexate [n = 1], hydroxychloroquine + sulfasalazine + methotrexate [n = 1]), DMARD sequences (n = 10), mixed drug treatments that included DMARDs and other drugs (e.g., NSAIDs; n = 1), and methotrexate + placebo (n = 1) (Table 1). Biologic treatment duration included 6 months (32,33), 1 year (34,42,43), 2 years (44), and depending on response and toxicity, up to 5 years (44,48), 10 years (44,45), or the patient's lifetime (28,35–41,46,47).

There was extensive heterogeneity across the selected evaluations. Patient populations were described as persons with early or late RA (n = 1), moderate to severe RA (n = 2), active refractory RA (n = 4), or simply persons with RA (n = 11). Within these populations, there were patients with no previous DMARD exposure (no previous methotrexate/DMARD exposure; n = 5) (33,35,40,41,46) or patients whose symptoms were not controlled by DMARDs (methotrexate resistant, ≥1 DMARD failure; n = 13) (Tables 1 and 2).

Most evaluations were conducted in the US (n = 7), followed by the UK (n = 4), Sweden (n = 3), Canada (n = 2), The Netherlands (n = 1), and Japan (n = 1). Economic perspectives included societal (n = 10) and payer (n = 11). Most evaluations considered a lifetime time horizon (n = 10). Other time horizons included 6 months (32,33), 1 year (43), 5 years (35,44,48), and 10 years (42,44,45).

The types of direct and indirect costs considered varied considerably. All of the studies considered direct costs, such as those related to drugs (price, administration, monitoring, toxicity, adverse events), patient visits (out-/inpatient, emergency) and care (home, ambulatory, palliative), imaging and laboratory tests, and joint replacement. Eleven studies considered costs related to productivity loss.

Seventeen of the 18 selected studies used model-based analytic approaches (Tables 1 and 2). The single empirical economic evaluation used observational data (43). All of the modeling studies used trial data to estimate patients' short-term responses to biologics and DMARDs except one, which used registry data (39). Long-term efficacy data were not available; therefore, evaluations with longer time horizons modeled trial data with observational data to extrapolate short-term effects. Efficacy data from the Anti–Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) (49,50) published in 1999 and 2000 were used in all of the studies that evaluated infliximab (28,34–36,40,42,45,46), except 3 studies that used registry or other data (37,41,43) (Tables 1 and 2). Two studies (40,46) also used response data in early RA

Table 1. Economic evaluations of biologics compared to DMARDs for rheumatoid arthritis*

Author, year (ref.)	Biologic (position in sequence)	Comparator(s)	Drug sequence(s)	Analysis	Perspective, country	Currency price, year	Time horizon	Discount rates
Patients with no previous DMARD exposure								
Choi et al, 2002 (33)	ETA	1: SSZ; 2: MTX; 3: LEF		CEA	Societal, US	US dollar, 1999	6 months	N/A
Jobanputra et al, 2002 (41)	ETA, INF + MTX (3rd)		SSZ > MTX > gold > HCQ > AZA > Pen > HCQ > LEF > CSA > CSA + MTX	CUA	Payer, US	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Barton et al, 2004 (37)	ETA, INF + MTX (3rd, 4th, 6th)		1: SSZ > MTX > LEF > gold > AZA > CSA > CSA + MTX; 2: SSZ > MTX > HCQ > gold > LEF > AZA > CSA > CSA + MTX	CUA	Payer, US	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Chen et al, 2006 (40)	ADA, ADA + MTX, ETA, ETA + MTX, INF + MTX (1st, 3rd, last)		1: MTX > MTX + SSZ > MTX + SSZ + HCQ > LEF > gold > AZA > CSA > CSA + MTX > Pen; 2: MTX > MTX + SSZ > MTX + SSZ + HCQ > LEF > gold > AZA > CSA > Pen; 3: MTX > SSZ > LEF > gold > AZA > CSA > Pen	CUA	Payer, US	British pound, 2004	Lifetime	Costs 6%, QALYs 1.5%
Coyle et al, 2006 (35)	ETA, INF + MTX (3rd, 4th)		MTX > MTX + SSZ > MTX + SSZ + HCQ > gold	CEA, CUA	Payer, Canada	Canadian dollar, N/R	5 years	Costs 5%, QALYs 5%
Spalding et al, 2006 (46)	ADA, ADA + MTX, ETA, INF + MTX (1st)		MTX > "pooled drug group" (complete range of possible optimal therapies)	CUA	Payer, US	US dollar, 2005	Lifetime	Costs 3%, QALYs 3%
Patients who failed prior MTX monotherapy								
Choi et al, 2000 (32)	ETA, ETA + MTX	1: MTX; 2: HCQ + SSZ + MTX; 3: CSA + MTX		CEA	Societal, US	US dollar, 1999	6 months	N/A
Wong et al, 2002 (34)	INF + MTX	MTX		CEA, CUA	Payer, societal, US	US dollar, 1998	Lifetime	Costs 3%, QALYs 3%
Kobelt et al, 2003 (42)	INF + MTX	MTX		CUA	Payer, societal, Sweden, UK	Euro, British pound, SEK, N/R	10 years	N/R
Marra et al, 2007 (45)	INF, INF + MTX	MTX		CUA	Societal, Canada	Canadian dollar, 2002	10 years	Costs 3%, QALYs 3%

(continued)

Table 1. *(Cont'd)*

Author, year (ref.)	Biologic (position in sequence)	Comparator(s)	Drug sequence(s)	Analysis	Perspective, country	Currency price, year	Time horizon	Discount rates
Patients who failed prior MTX combination therapy or sequential administration of DMARDs								
Brennan et al, 2004 (38)	ETA (1st)		Gold > LEF > CSA + MTX	CUA	Payer, UK	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Kobelt et al, 2004 (43)	ETA and/or INF (± DMARD[s])	Mixed DMARDs, NSAIDs, analgesic		CUA	Societal, Sweden	Euro, 2002	1 year	N/A
Welsing et al, 2004 (48)	ETA (1st, 2nd)		1: "usual care" = SSZ or MTX or other DMARDs; 2: LEF > "usual care"	CUA	Payer, societal, The Netherlands	Euro, N/R	5 years	Costs 4%, QALYs 4%
Bansback et al, 2005 (28)	ETA, ADA, ADA + MTX, INF + MTX (1st)		3 DMARDs (N/R)	CUA	Payer, Sweden	Euro, 2001	Lifetime	Costs 3%, QALYs 3%
Barbieri et al, 2005 (36)	INF + MTX > DMARDs		MTX + placebo > DMARDs (N/R)	CUA	Payer, UK	British pound, 2000	Lifetime	Costs 6%, QALYs 1.5%
Kobelt et al, 2005 (44)	ETA, ETA + MTX	MTX		CUA	Societal, Sweden	Euro, 2004	5, 10 years	Costs 3%, QALYs 3%
Tanno et al, 2006 (47)	ETA (1st)		MTX > SSZ > SSZ + MTX > no DMARDs	CUA	Societal, Japan	JPY, 2003	Lifetime	Costs 6%, QALYs 1.5%
Brennan et al, 2007 (39)	Anti-TNF (1st)		DMARDs (MTX, SSZ, LEF, HCQ, other) in each position based on weighted average of registry patients' DMARD use	CUA	Payer, UK	British pound, 2004	Lifetime	Costs 6%, QALYs 1.5%

* DMARDs = disease-modifying antirheumatic drugs; ETA = etanercept; SSZ = sulfasalazine; MTX = methotrexate; LEF = leflunomide; CEA = cost-effectiveness analysis; N/A = not applicable; INF = infliximab; > = followed by; HCQ = hydroxychloroquine; AZA = azathioprine; Pen = penicillamine; CSA = cyclosporin A; CUA = cost-utility analysis; QALY = quality-adjusted life year; ADA = adalimumab; N/R = not reported; SEK = Swedish kronor; NSAIDs = nonsteroidal antiinflammatory drugs; JPY = Japanese yen; anti-TNF = anti–tumor necrosis factor.

Table 2. Characteristics of economic evaluations of biologics compared to DMARDs for rheumatoid arthritis*

Author, year (ref.)	Quality of life weight	Model type	Costs reported to be included in the analysis	Health effect(s)	Funding	Efficacy source(s)
Patients with no previous DMARD exposure						
Choi et al, 2002 (33)	N/A	Decision tree	Drug, monitoring, toxicity, surgery, work capacity	ACR20/70 WR	N/R	13
Jobanputra et al, 2002 (41)	HAQ > EQ-5D	Discrete event simulation (preliminary BRAM)	Drug price, drug startup, monitoring, administration, toxicity, physician visits, home care, nursing care, self-care, palliative care, hospitalization, work disability	QALY	National Health Services	51, 52, 70
Barton et al, 2004 (37)	HAQ > EQ-5D	Discrete event simulation (BRAM)	Drug price, drug startup, monitoring, administration, toxicity, physician visits, home care, nursing care, self-care, palliative care, hospitalization, joint replacement	QALY	National Health Services	51, 70, 71
Chen et al, 2006 (40)	HAQ > EQ-5D	Discrete event simulation (BRAM)	Drug price, drug startup, monitoring, health practitioner (physician, specialist nurse), hospitalization (inpatient, outpatient), palliative care	QALY	National Health Services	13, 15, 49, 51–53, 55, 56, 72–74
Coyle et al, 2006 (35)	HAQ > EQ-5D	Markov	Drug price, monitoring, laboratory services, adverse events, physician visits, palliative care	ACR20/50/70, QALY	Health Canada	49–51
Spalding et al, 2006 (46)	HAQ > HUI-3	Markov	Drug price, administration, monitoring, adverse events, physician visits, hospitalization	QALY	University of Southern California	15, 50, 53, 55, 56, 75, 76
Patients who failed prior MTX monotherapy						
Choi et al, 2000 (32)	N/A	Decision tree	Drug price, monitoring, toxicity, surgery, work capacity	ACR20/70 WR	N/R	51, 52
Wong et al, 2002 (34)	VAS	Markov	Drug price, administration, monitoring, nurse, physician, therapist, nontraditional care, home care, tests, imaging, ER visits, surgery, rehabilitation, nursing home, employment	Life expectancy, QALY	Schering-Plough, Centocor, NIH	49, 50, 77, 78
Kobelt et al, 2003 (42)	EQ-5D	Markov	Drug price, hospitalization, surgery, ambulatory care, community care, work capacity (human capital approach)	QALY	Schering-Plough	49, 50
Marra et al, 2007 (45)	HAQ > HUI-2/3, SF-6D, EQ-5D	Markov	Drug price, long-term care, rehabilitation, nursing home, health professional visits, diagnostic tests, hospitalization, ER visits, ambulance, dialysis, surgery, productivity	QALY	CIHR, Canadian Arthritis Network	49

(continued)

Table 2. *(Cont'd)*

Author, year (ref.)	Quality of life weight	Model type	Costs reported to be included in the analysis	Health effect(s)	Funding	Efficacy source(s)
Patients who failed prior MTX combination therapy or sequential administration of DMARDs						
Brennan et al, 2004 (38)	HAQ > "utility"	Discrete event simulation	Drug price, monitoring, physician visits, outpatient care, hospitalization	QALY	N/R	51
Kobelt et al, 2004 (43)	EQ-5D	N/A	Drug price, hospitalization, surgery, work absence	QALY	Österlund & Kock Foundations	54
Welsing et al, 2004 (48)	EQ-5D	Markov	Drug price, physician, surgery, travel, work absence	QALY	N/R	51, 52
Bansback et al, 2005 (28)	HAQ > HUI-3	Markov	Drug price, administration, monitoring, toxicity, inpatient care, hospitalization, joint replacement	QALY	Abbott Laboratories	49, 51, 52, 54–56, 74
Barbieri et al, 2005 (36)	VAS	Markov	Drug price, administration, monitoring, adverse events, outpatient visits, hospitalization, joint replacement	QALY	Schering-Plough, Centocor	49
Kobelt et al, 2005 (44)	EQ-5D	Markov	Drug price, health care services, community services, investments, devices, transportation, informal help, sick leave, leisure time loss, early retirement	QALY	Wyeth Research	53
Tanno et al, 2006 (47)	HAQ > EQ-5D	Markov	Drug price, outpatient visit, guidance, home self-injection management, needles, monitoring, adverse events, hospitalization, lost productivity	QALY	Japanese Health Ministry	51
Brennan et al, 2007 (39)	HAQ > EQ-5D	Discrete event simulation	Drug price, administration, monitoring, hospitalization	QALY	BSR	BSR Biologics Registry

* ACR20 = American College of Rheumatology 20% improvement criteria; WR = weighted response; HAQ = Health Assessment Questionnaire; > = transformed to; EQ-5D = EuroQol; BRAM = Birmingham Rheumatoid Arthritis Model; HUI-3 = Health Utility Index 3; VAS = visual analog scale; ER = emergency room; NIH = National Institutes of Health; SF-6D = Short Form 6D; CIHR = Canadian Institutes of Health Research; BSR = British Society for Rheumatology. See Table 1 for additional abbreviations.

patients from the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset published in 2004 (15). Most studies that evaluated etanercept (28,32,35,37,38,40,41,47,48) used response data from two 1999 trials (51,52). Other sources of etanercept response data included the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes published in 2004 (53) used by 3 evaluations (40,44,46), a trial published in 2000 (13) used by 2 evaluations (33,40), and a prospective monitoring study (54) published in 2002 used by 2 evaluations (28,44). All of the studies that evaluated adalimumab (28,40,46) used data from the Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab (D2E7) in Rheumatoid Arthritis trial (55) published in 2003 and the Safety Trial of Adalimumab in Rheumatoid Arthritis published in 2004 (56); 2 of these (40,46) also used data from PREMIER published in 2006 (14).

Critical appraisal of data of selected studies. Methodologic limitations were largely associated with data and reporting practices. Most authors did not describe methods for identifying, selecting, and synthesizing data for key model parameters. Many did not adequately report point estimates and measures of precision for model parameters. Study design was not clearly described in many studies (e.g., failing to report the perspective) and methods (e.g., failing to report model estimates). Results were frequently poorly reported where, for example, mean costs, mean health effects, and incremental analyses were not reported.

Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131a) shows the appraisal of the economic evaluations using the British Medical Journal criteria. Several studies did not clearly state the research question (34,37,43,46) or provide the background on the importance of and rationale for the evaluation (28,33,34,37,38,43,46). Most studies did not describe quantities of resource use separately from unit costs (except 4 [36,37,40,41]) or approaches for currency conversion and inflation adjustment (except 4 [38–40,45]). Eleven of 18 studies reported incremental analyses, and 7 of 18 adequately presented disaggregated and aggregated outcomes. Of 15 studies that discounted costs and effects, 5 studies did not justify the discount rate (34,42,44,46,48). Only 3 studies satisfactorily reported ranges used for sensitivity analyses (37,40,41). Two of 12 studies that used stochastic data reported details of statistical tests and confidence intervals (40,45).

Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131a) shows the critical appraisal of the 17 modeling studies using the criteria by Philips et al. Eleven to 15 of 17 studies did not provide sufficient evidence of using transparent and systematic methods for identifying data or adequately describe the process for choosing between data sources, selecting key parameters, and identifying data for essential model parameters. Only 4 of 17 studies assessed the 4 types of uncertainty described by Briggs (57). Methodologic weaknesses were particularly clustered in the subsections "rationale for structure" (12 studies did not adequately describe whether competing theories about model structure were considered), "structural assumptions" (7 studies were not transparent about or justified assumptions), and "strategies/comparators" (most studies did not evaluate all feasible options or provide a justification for not doing so).

Results of CUAs. CUAs were conducted by 16 of the 18 selected studies. The quality of life weight most often used to calculate QALYs was a score derived from the EuroQol (EQ-5D) Index (35,37,39–45,47,48), followed by the Health Utility Index 3 (HUI-3) (28,45,46), visual analog scale (34,36), HUI-2 (45), and Short Form 6D scores (45) (Table 2). One study did not identify the weight used (38). In 10 of the 16 CUAs, weights were derived by transforming Health Assessment Questionnaire (HAQ) (58) scores using linear regression (28,35,37–41,45–47).

Patients with no previous DMARD experience: biologic DMARD sequence versus DMARD sequence. Five evaluations evaluated a DMARD sequence containing a biologic agent compared to a DMARD sequence without biologics in patients with no previous DMARD experience (35,37,40,41,46) (Tables 1–3). From a payer perspective, median incremental costs per incremental QALY for biologics inserted into the first, third, fourth, sixth, and last positions within a drug sequence were $207,000/QALY (range $84,000–$1,776,000/QALY), $134,000/QALY (range $75,000–$382,000/QALY), $124,000/QALY (range $106,000–$150,000/QALY), $125,000/QALY (range $109,000–$142,000/QALY), and $77,000/QALY (range $62,000–$106,000/QALY), respectively (Table 3). Therefore, biologic DMARD sequences were considered cost effective only when the willingness to pay threshold was $100,000/QALY (Table 3). ICER values tended to decrease as biologics were inserted later in a drug sequence. The overall median was $130,000/QALY (range $62,000–$1,776,000/QALY). Median ICERs by biologic therapy were all above $100,000/QALY (adalimumab: $111,000/QALY [range $106,000–$235,000/QALY], etanercept: $124,000/QALY [range $62,000–$141,000/QALY], adalimumab + methotrexate: $127,000/QALY [range $78,000–$354,000/QALY], etanercept + methotrexate: $105,000/QALY [range $63,000–$207,000/QALY], and infliximab + methotrexate: $142,000/QALY [range $100,000–$169,000/QALY]). There were no CUAs conducted from the societal perspective. All of the evaluations were conducted over a lifetime except one, which used a 5-year time horizon (35).

Overall, ICERs were fairly consistent across comparable studies, except where biologics were positioned first in a drug sequence: ICERs reported by Spalding et al (2006) (46) were lower those reported by Chen et al (2006) (40) (Table 3). In the study by Spalding et al (46), palliative care costs were not included and the authors assumed that following first-line biologic therapy, patients would receive optimal therapy with the same clinical effect and costs as other patients, which may have minimized differences between the interventions.

Table 3. Results of cost-utility analyses of biologics versus DMARDs for RA in adults: patients with no previous DMARD exposure*

Biologic position†	Biologic	ICER (2009 Canadian dollar/ QALY)‡	Detail(s)	Author, year (ref.)
1st position	Adalimumab	138,445	Palliative care costs	Chen et al, 2006 (40)
		84,267	No palliative care costs	Spalding et al, 2006 (46)
	Etanercept	130,358	Palliative care costs	Chen et al, 2006 (40)
		118,629	No palliative care costs	Spalding et al, 2006 (46)
	Adalimumab + MTX	451,420	Palliative care costs	Chen et al, 2006 (40)
		257,139	No palliative care costs	Spalding et al, 2006 (46)
	Etanercept + MTX	206,842	Palliative care costs	Chen et al, 2006 (40)
	Infliximab + MTX	1,775,640	Palliative care costs	Chen et al, 2006 (40)
		541,163	No palliative care costs	Spalding et al, 2006 (46)
3rd position	Adalimumab	90,846	Early RA/palliative care costs	Chen et al, 2006 (40)
		381,850	Late RA/palliative care costs	Chen et al, 2006 (40)
	Etanercept	180,590	Palliative care costs	Jobanputra et al, 2002 (41)
		125,166	Palliative care costs	Barton et al, 2004 (37)
		128,197	Palliative care costs	Chen et al, 2006 (40)
		155,537	Palliative care costs	Coyle et al, 2006 (35)
	Adalimumab + MTX	79,522	Early RA/palliative care costs	Chen et al, 2006 (40)
		174,241	Late RA/palliative care costs	Chen et al, 2006 (40)
	Etanercept + MTX	75,001	Early RA/palliative care costs	Chen et al, 2006 (40)
		133,988	Late RA/palliative care costs	Chen et al, 2006 (40)
	Infliximab + MTX	237,375	Palliative care costs	Jobanputra et al, 2002 (41)
		169,277	Palliative care costs	Barton et al, 2004 (37)
		80,134	Early RA/palliative care costs	Chen et al, 2006 (40)
		379,891	Late RA/palliative care costs	Chen et al, 2006 (40)
		122,984	Palliative care costs	Coyle et al, 2006 (35)
4th position	Etanercept	110,816	Palliative care costs	Barton et al, 2004 (37)
		137,128	Palliative care costs	Coyle et al, 2006 (35)
	Infliximab + MTX	149,674	Palliative care costs	Barton et al, 2004 (37)
		105,668	Palliative care costs	Coyle et al, 2006 (35)
6th position	Etanercept	108,589	Palliative care costs	Barton et al, 2004 (37)
	Infliximab + MTX	141,603	Palliative care costs	Barton et al, 2004 (37)
Last position	Adalimumab	105,606	Palliative care costs	Chen et al, 2006 (40)
	Etanercept	62,213	Palliative care costs	Chen et al, 2006 (40)
	Adalimumab + MTX	77,452	Palliative care costs	Chen et al, 2006 (40)
	Etanercept + MTX	62,777	Palliative care costs	Chen et al, 2006 (40)
	Infliximab + MTX	100,366	Palliative care costs	Chen et al, 2006 (40)

* All economic evaluations were conducted from the payer's perspective. DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; MTX = methotrexate.
† Indicates position of biologic in a DMARD drug sequence.
‡ Costs have been converted and adjusted to 2009 Canadian dollars (rounded to zero decimal points).

Patients with early RA: biologic DMARD sequence compared to DMARD sequence. One study focused on early RA patients. DMARD sequences containing biologics were compared to DMARD sequences without biologics (40) (Tables 1–3). ICER values in early RA patients (range $75,000–$91,000/QALY) were consistently smaller than in late RA patients (range $134,000–$378,000/QALY), and cost effective at a willingness to pay threshold of $100,000/QALY.

Patients who failed methotrexate monotherapy: biologic combination therapy versus methotrexate monotherapy. Three studies evaluated biologic combination therapy (infliximab + methotrexate) in methotrexate-resistant patients (34,42,45) (Tables 1, 2, and 4). All of the studies took the societal perspective; 2 studies also took a payer perspective (34,42). All of the studies used efficacy data from the ATTRACT study (49), in which methotrexate-resistant patients were either randomized to receive infliximab + methotrexate or to continue on methotrexate monotherapy (rather than receive another DMARD). ICER values ranged from $6,000–$92,000/QALY. Therefore, all 20 comparisons conducted by these 3 studies found biologic combination therapy to be cost effective at a willingness to pay threshold of $100,000/QALY for the payer and societal perspectives. In contrast, 7 of 12 comparisons undertaken from the societal perspective and 2 of 8 comparisons undertaken from the payer perspective found this therapy cost effective at a willingness to pay threshold of $50,000/QALY. Jurisdiction-specific costing appears to have accounted for some variation. In one study, ICERs based on

Table 4. Results of cost-utility analyses of biologics versus DMARDs for rheumatoid arthritis in adults: patients who failed prior MTX monotherapy*

Perspective and biologic	ICER (2009 Canadian dollar/QALY)†	Detail(s)	Author, year (ref.)
Societal: infliximab + MTX	13,972	Discount: costs 3%, QALYs 0%	Wong et al, 2002 (34)
	15,584	No discounting	Wong et al, 2002 (34)
	16,381	Discount: costs 3%, QALYs 3%	Wong et al, 2002 (34)
	18,271	Discount: costs 0%, QALYs 3%	Wong et al, 2002 (34)
	6,451	1-year Swedish analysis	Kobelt et al, 2003 (42)
	29,864	2-year Swedish analysis	Kobelt et al, 2003 (42)
	56,795	1-year British analysis	Kobelt et al, 2003 (42)
	78,449	2-year British analysis	Kobelt et al, 2003 (42)
	62,015	QOL weight = HUI-2	Marra et al, 2007 (45)
	37,209	QOL weight = HUI-3	Marra et al, 2007 (45)
	80,620	QOL weight = SF-6D	Marra et al, 2007 (45)
	54,148	QOL weight = EQ-5D	Marra et al, 2007 (45)
Payer: infliximab + MTX	47,828	Discount: costs 3%, QALYs 0%	Wong et al, 2002 (34)
	48,365	No discounting	Wong et al, 2002 (34)
	56,074	Discount: costs 3%, QALYs 3%	Wong et al, 2002 (34)
	56,704	Discount: costs 0%, QALYs 3%	Wong et al, 2002 (34)
	52,992	1-year Swedish analysis	Kobelt et al, 2003 (42)
	82,559	2-year Swedish analysis	Kobelt et al, 2003 (42)
	67,563	1-year British analysis	Kobelt et al, 2003 (42)
	91,484	2-year British analysis	Kobelt et al, 2003 (42)

* DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; QOL = quality of life; HUI-2 = Health Utility Index 2; SF-6D = Short Form 6D; EQ-5D = EuroQol.
† Costs converted and adjusted to 2009 Canadian dollars (rounded to zero decimal points).

British costing were higher than those based on Swedish costing (42).

Patients who failed methotrexate combination therapy or sequential administration of DMARDs: biologic DMARD sequence versus DMARD sequence. Eight evaluations analyzed the cost utility of inserting a biologic monotherapy or combination therapy into a DMARD sequence compared to a DMARD sequence in patients who failed ≥2 DMARDs (28,35–37,39–41,48) (Tables 1, 2, and 5). All of the analyses took a payer perspective, with one evaluation also taking the societal perspective. ICER values ranged from $45,000–$612,000/QALY. Of 35 comparisons, biologic DMARD sequences were cost effective in 1 comparison and in 14 comparisons at the $50,000/QALY and $100,000/QALY willingness to pay thresholds, respectively. Median ICERs by biologic were $81,000/QALY (range $63,000–$383,000/QALY) for adalimumab, $79,000/QALY (range $60,000–$175,000/QALY) for adalimumab + methotrexate, $127,000/QALY (range $45,000–$612,000/QALY) for etanercept, $75,000/QALY (range $72,000–$134,000/QALY) for etanercept + methotrexate, and $133,000/QALY (range $80,000–$378,000/QALY) for infliximab + methotrexate. There were no consistent trends across the results.

Results of CEAs. CEAs were conducted by 4 of the 18 selected studies (32–35) (Table 1). Health effect measures included life expectancy and response categories based on the ACR core set of activity measures (ACR 20%/50%/70% response criteria [ACR20/50/70]) (59).

Two studies examined the cost-effectiveness of biologics in patients with no previous DMARD exposure (33,35). Choi et al (2002) (33) examined the incremental cost per patient achieving an ACR20 and ACR70 weighted response for etanercept monotherapy versus DMARD monotherapies in patients with no previous methotrexate exposure (Tables 1 and 2). ICER values for all analyses that only included direct costs were larger than those that included direct and indirect costs. ICERs for comparisons including direct costs ranged from $70,000–$90,000 and $70,000–$77,000 for an ACR20 and ACR70 weighted response, respectively, and those including direct and indirect costs ranged from $66,000–$78,000 and $62,000–$74,000 for an ACR20 and ACR70 weighted response, respectively. Coyle et al (2006) (35) compared a biologic DMARD sequence with biologics inserted into the third and fourth positions to the identical sequence without biologics (Tables 1 and 2). The incremental cost per additional year with an ACR20, ACR50, and ACR70 response ranged from $18,000–$28,000, $23,000–$36,000, and $93,000–$101,000, respectively.

Two studies evaluated biologics in methotrexate-resistant patients (32,34) (Tables 1 and 2). Choi et al (2000) (32) compared the cost per patient achieving either an ACR20 or ACR70 weighted response of etanercept (monotherapy or etanercept + methotrexate) versus methotrexate continuation and 2 DMARD combination therapies (Tables 1 and 2). The most favorable ICERs were for etanercept mono- or combination therapy compared to methotrexate; these ranged from $23,000–$35,000 depending on whether direct or direct and indirect costs were considered. ICER values were larger for analyses that considered only direct

Table 5. Results of cost-utility analyses of biologics versus DMARDs for RA in adults: patients who failed prior MTX combination therapy or sequential administration of DMARDs*

Perspective	Biologic position†	Biologic	ICER (2009 Canadian dollar/QALY)‡	Detail(s)	Author, year (ref.)
Societal	1st position	Etanercept	545,049		Welsing et al, 2004 (48)
	2nd position	Etanercept	299,510		Welsing et al, 2004 (48)
Payer	3rd position	Adalimumab	71,628		Bansback et al, 2005 (28)
			90,964	Early RA	Chen et al, 2006 (40)
			382,546	Late RA	Chen et al, 2006 (40)
		Adalimumab + MTX	60,190		Bansback et al, 2005 (28)
			79,388	Early RA	Chen et al, 2006 (40)
			174,811	Late RA	Chen et al, 2006 (40)
		Etanercept	44,501		Brennan et al, 2004 (39)
			611,953		Welsing et al, 2004 (48)
			63,641		Bansback et al, 2005 (28)
			177,214		Jobanputra et al, 2002 (41)
			126,293		Barton et al, 2004 (37)
			127,559		Chen et al, 2006 (40)
			155,537		Coyle et al, 2006 (35)
		Etanercept + MTX	71,627		Bansback et al, 2005 (28)
			74,906	Early RA	Chen et al, 2006 (40)
			133,912	Late RA	Chen et al, 2006 (40)
		Infliximab + MTX	83,300		Bansback et al, 2005 (28)
			90,090		Barbieri et al, 2005 (36)
			245,556		Jobanputra et al, 2002 (41)
			169,823		Barton et al, 2004 (37)
			80,057	Early RA	Chen et al, 2006 (40)
			377,999	Late RA	Chen et al, 2006 (40)
			122,985		Coyle et al, 2006 (35)
	2nd position	Etanercept	324,216		Welsing et al, 2004 (48)
			111,524		Barton et al, 2004 (37)
			137,127		Coyle et al, 2006 (35)
		Infliximab + MTX	150,103		Barton et al, 2004 (37)
			105,669		Coyle et al, 2006 (35)
	3rd position	Etanercept	108,098		Barton et al, 2004 (37)
		Infliximab + MTX	143,491		Barton et al, 2004 (37)
	Last position	Adalimumab	63,340		Chen et al, 2006 (40)
		Adalimumab + MTX	77,588		Chen et al, 2006 (40)
		Etanercept	62,340		Chen et al, 2006 (40)

* DMARDs = disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; MTX = methotrexate; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
† Indicates position of biologic in a DMARD drug sequence.
‡ Costs have been converted and adjusted to 2009 Canadian dollars (rounded to zero decimal points).

costs compared to those that considered direct and indirect costs. CEAs based on an ACR20 response produced larger ICER values than those based on an ACR70 response. Wong et al (2002) (34) compared the cost-effectiveness of infliximab + methotrexate to methotrexate (Tables 1 and 2). Cost-effectiveness ratios of cost per life year gained based on direct and indirect costs ranged from $34,000–$48,000, and those based on direct costs ranged from $116,000–$118,000 (variations in ICER values across these perspectives were the result of discounting or not discounting costs).

Results of sensitivity analyses. A wide array of factors was considered for sensitivity analyses. Results were sensitive to factors related to rates (compliance, effectiveness, withdrawal, adverse event, mortality, survival, discount), costs (drug, monitoring, toxicity, time lost), and other factors (time horizon, treatment duration, HAQ conversion factor). Results were sensitive to the type of quality of life weight used to calculate the QALY in all of the studies that examined this factor (28,39,41,45). Results were consistently sensitive to HAQ-related disease progression scores (28,37,38,40,44,46), position of biologic in a DMARD sequence (37,40,41), and biologic drug costs (32–34,42,44,46).

Discussion

Our systematic search identified 18 economic evaluations of biologic monotherapies/combination therapies compared to DMARDs. We stratified the results by biologic agent and indications for use in RA patients as described by the ACR 2008 recommendations (12). We used two willingness to pay thresholds to assess cost-effectiveness: $50,000 and $100,000 per QALY gain. At a willingness to

pay threshold of $50,000 per QALY gain, biologics were not cost effective in patients with no previous DMARD exposure and patients who failed methotrexate combination therapy or sequential DMARD administration. There was evidence of cost-effectiveness in patients who failed methotrexate monotherapy; however, this may have been partly due to the choice of comparator, where methotrexate-resistant patients continued to receive methotrexate. Several studies reported ICERs within the cost-effectiveness threshold of $100,000 per QALY gain. In patients with no previous DMARD exposure, a small proportion of ICERs (23%) fell below this threshold. In patients who had failed methotrexate monotherapy, all of the comparisons found biologic combination therapy to be cost effective; however, the comparator for these analyses was continued methotrexate therapy. In patients who failed methotrexate combination therapy or sequentially administered DMARDs, 14 of 35 comparisons found a biologic sequence to be cost effective. The most cost-effective approach for managing RA appears to be to treat with a DMARD early in the course of the disease, move through a sequence of other DMARDs, and with continued nonresponse, add a biologic, while moving through this sequence before late stages of RA are reached.

Our systematic search identified evaluations for 3 biologics (adalimumab, etanercept, and infliximab), yet in North American countries there are at least 6 biologics approved for RA: TNFα antagonists abatacept, adalimumab, etanercept, infliximab, and rituximab, and the interleukin-1 receptor antagonist anakinra. Absent in the literature were evaluations of newer biologics compared to DMARDs.

We identified other gaps. Prospective data on long-term responses to biologics are lacking. Research is needed to determine how to standardize CUA outcomes given that different quality of life weights yield different ICERs (45). There is no consensus on the appropriate way to measure quality of life weights (60). Investigation is also needed to determine the validity of assuming a linear relationship between functional status measures (e.g., the HAQ) and multiattribute utility measures (e.g., the EQ-5D). Another important issue is how to validly determine the potential of biologics to reduce downstream costs. Since biologics may have greater potential to reduce long-term costs related to RA disability, and since RA is a chronic disease, evaluations should consider lifetime time horizons (61). Finally, indirect costs have been estimated to account for 55.1% of the cost of illness of RA (4). We believe that studies should conduct separate analyses excluding and including indirect costs (38,61,62), and authors should justify their rationale for not including indirect costs. In cases where the rationale is that the payer's perspective was considered, authors should justify not using the societal perspective. It is likely that biologics would have been more economically attractive had indirect costs been included in analyses (Table 5) that excluded indirect costs.

As in previous studies that examined the quality of economic evaluations (63–65), the prevalence of methodologic problems was high. Unlike previous studies (63,64), we did not find that reporting improved over time. Many evaluations did not follow recommendations in existence since the mid-1990s (66–68). Poor reporting makes it difficult to judge whether results can be accepted with reasonable confidence. Posting materials on journal web sites would partly help.

We followed current recommendations for conducting reviews of economic evaluations (21,69). Reviewers were not blinded because even if journals and authors were concealed, reviewers could identify them by formatting style, references to previous work, or expertise with the literature. Lack of blinding may have influenced quality appraisal results favorably or unfavorably. Likewise, pairs of reviewers might have judged differently whether studies fulfilled quality criteria.

Economic evidence suggests that biologics are not cost effective compared to DMARDs for RA in adults at a cost-effectiveness threshold of $50,000 per QALY. There is mixed evidence of cost-effectiveness in selected populations at a willingness to pay threshold of $100,000 per QALY. Definitive conclusions are difficult to make given the lack of consistent, high-quality studies. Economic evaluations of biologics are hindered by lack of data on long-term responses and consequence of responses on downstream health utilization and productivity.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. van der Velde had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Van der Velde, Pham, Machado, Bombardier, Krahn.

Acquisition of data. Van der Velde, Pham, Machado, Ieraci, Witteman.

Analysis and interpretation of data. Van der Velde, Pham, Machado, Ieraci, Krahn.

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