



REVIEW

# Value of Remission in Patients with Rheumatoid Arthritis: A Targeted Review

Andrew J. Ostor · Ruta Sawant · Cynthia Z. Qi · Aozhou Wu ·  
Orsolya Nagy · Keith A. Betts

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## ABSTRACT

The treat-to-target strategy, which defines clinical remission as the primary therapeutic goal for rheumatoid arthritis (RA), is a widely recommended treatment approach in clinical guidelines. Achieving remission has been associated with improved clinical outcomes, quality of life, and productivity. These benefits are likely to translate to reduced economic burden in terms of lower healthcare costs and resource utilization. As such, a literature review was

conducted to better understand the economic value of remission. Despite the large heterogeneity found in RA-related economic outcomes across studies, patients in remission consistently had lower direct medical and indirect costs, less healthcare resource utilization, and greater productivity compared to those without remission. Remission was associated with 19–52% savings in direct medical costs and 37–75% savings in indirect costs. The economic value of remission should thus be considered in economic analyses of RA therapies to inform treatment and reimbursement decisions.

**Keywords:** Rheumatoid arthritis; Remission; Treat-to-target; Economic benefit; Direct cost; Indirect cost; Healthcare resource utilization

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A. J. Ostor  
Cabrin Medical Center, Monash University and  
Emeritus Research, Melbourne, VIC, Australia

R. Sawant · O. Nagy  
AbbVie, Inc., North Chicago, IL, USA

C. Z. Qi  
Analysis Group, Inc., Boston, MA, USA

A. Wu · K. A. Betts (✉)  
Analysis Group, Inc., 333 S. Hope Street, 27th Floor,  
Los Angeles, CA 90071, USA  
e-mail: keith.betts@analysisgroup.com

### Key Summary Points

Achieving remission has been associated with improved clinical outcomes, quality of life, and productivity in patients with rheumatoid arthritis (RA); however, the associated economic benefits are less understood.

This review provides an overview of clinical, humanistic, economic value of clinical remission, with a focus on quantifying remission-associated economic benefits, which could be used to better characterize the economic profile of RA treatments.

Achieving clinical remission was found to promote better disease control and was associated with substantial economic benefits.

Remission was associated with 19–52% reduction in direct medical costs and 37–75% savings in indirect costs, compared with not achieving remission.

The economic benefit of remission is an important component to consider when conducting economic analyses of RA therapies to inform treatment and reimbursement decisions.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory arthritis, affecting approximately 5 per 1000 adults worldwide [1]. RA has a significant negative impact on daily activities, including work and household tasks, and is associated with high burden and impaired quality of life (QoL) [1, 2].

During recent decades, the target of RA treatment has changed from symptomatic relief to clinical remission, which slows down radiologic damage and prevents disability [3, 4]. Emerging treatments, including biologics and

Janus kinase (JAK) inhibitors, have transformed the management of RA to the extent that remission is a reasonable expectation and is now a major therapeutic target to guide treatment in clinical practice [4, 5].

Multiple definitions of clinical remission are endorsed in clinical guidelines, including remission based on Disease Activity Score 28 (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and Boolean criteria [4, 6, 7]. Among them, DAS28 is the most commonly used remission definition in clinical practice, as well as in clinical trials [8–11], and can also be further characterized by incorporating composite parameters like C-reactive protein (i.e., DAS28-CRP) and erythrocyte sedimentation rates (i.e., DAS28-ESR) [12]. Nevertheless, all these remission definitions are useful outcome measures to characterize disease status. Despite the debate regarding which remission definition should be used as the treatment target, achieving remission has been associated with improved clinical outcomes, patient QoL, and productivity [13–15].

Additionally, achieving and maintaining remission is likely to be associated with substantial economic benefits due to several reasons. With sustained disease control, patients would have no or fewer disease flares and require less resources and costs for disease management (e.g., clinic visits, examinations, and physiotherapy). Additionally, patients in remission may maintain better physical function and work productivity [3, 4], which could lead to reduced disease-related indirect costs.

While the clinical implications of achieving remission are well established, knowledge gaps exist regarding remission-associated economic value and potential savings to the healthcare system. Although a few studies have assessed healthcare costs and healthcare resource utilization (HRU) in patients with RA and different disease activity levels [i.e., remission, low disease activity (LDA), moderate/high disease activity (M/HDA)], heterogeneities exist between these studies regarding the country of interest, data sources, remission definition, and the approach of cost estimation, which render the evidence difficult to interpret and use to

guide treatment decision-making. A comprehensive evaluation of the economic value of remission and whether it varies by the definition of remission is needed. Considering the differential cost savings associated with treatments with different efficacy profiles [5, 16], evidence regarding the economic benefits of remission could be used to better characterize the economic profile of RA treatments, thus informing treatment decision-making.

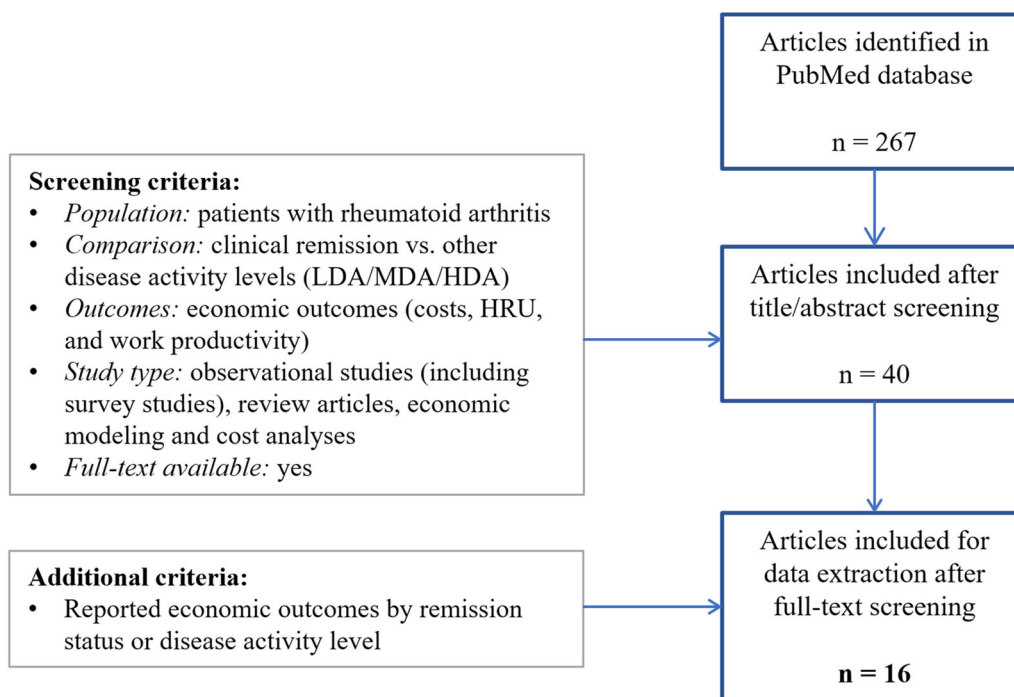
This review aimed to provide an overview of the clinical, humanistic, and economic value of clinical remission, with a focus on quantifying associated economic benefits. We summarized the significance of remission in clinical practice based on guideline recommendations, conducted a literature review, and synthesized evidence of clinical remission-associated healthcare savings from patient, payer, and societal perspectives.

## METHODS

First, existing clinical guidelines were identified to provide a summary of the current understanding and recommendations in clinical practice regarding achieving remission.

Second, a comprehensive literature review was conducted by searching the PubMed database (including MEDLINE and PubMed Central) to identify studies that reported economic outcomes by disease activity status in patients with RA, including direct medical costs, indirect costs, HRU, and work productivity. The search keywords and Medical Subject Heading (MeSH) terms listed in Table S1 in the supplementary material were used for the search strategy. On the basis of this search, 267 articles were identified, and 16 articles which reported economic outcomes (including direct medical costs, indirect costs, and HRU) by remission status were selected after abstract and full-text screening to be included in the summary (Fig. 1).

To enable a fair comparison between studies, costs were annualized and converted to 2020



**Fig. 1** Diagram of study inclusion for targeted literature review. HRU healthcare resource utilization, LDA low disease activity, MDA moderate disease activity, HDA high disease activity

euros, adjusting for inflation and currency exchange rates. For studies that did not directly report the cost among patients without remission but instead reported costs among LDA, MDA, or HDA, non-remission costs were calculated as a weighted average of costs in subgroups without remission (e.g., LDA and M/HDA) based on the sample sizes, when applicable.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## RESULTS

### Value of Remission in Clinical Practice

#### *Application of Remission in Clinical Practice and Clinical Trials*

A review of the current clinical guidelines indicates that the treat-to-target strategy is widely recommended in international and national clinical guidelines, including those endorsed by the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and National Institute for Health and Care Excellence (NICE) in the UK [4, 6, 7]. The approach was found to not only be more effective than usual care [6] but was also cost-effective [17–19]. According to the 2014 treat-to-target recommendations and clinical guidelines, the primary therapeutic target for RA should be a state of clinical remission, which is defined as the absence of signs and symptoms of significant inflammatory disease activity [3, 6, 7]. If remission is not possible, LDA may be an alternative goal. Under the treat-to-target strategy, therapeutic interventions are used to abrogate the inflammation to reach and maintain explicitly specified and sequentially measured goals, usually assessed by a composite disease activity score [3]. Tight control, such as regular visits with disease activity assessments (e.g., every 1–6 months depending on the level of disease activity) and treatment adjustments at least every 3 months until the desired treatment target is reached, is applied to reach the goal [3]. In addition, besides assessing measures

of disease activity, structural changes, functional impairment, and comorbidities should also be considered when making clinical decisions [3]. Once achieved, the desired treatment target should be maintained throughout the remaining course of the disease. Importantly, patients are more likely to achieve clinical remission when treated earlier in the course of RA [4, 20, 21]. Therefore, initiating an advanced treatment which offers a higher probability of achieving remission, immediately after conventional synthetic disease-modifying antirheumatic drug (csDMARD) failure, may be preferred in order to maintain joint integrity and avoid disability in the long run [1].

Given the clinical value, remission measures are widely adopted as important outcomes in clinical trials to assess the efficacy of RA treatment [20, 22]. In the US Food and Drug Administration (FDA) guidelines for RA, clinical remission has been suggested as an important measure to characterize the efficacy of the drug product and its utility in clinical practice [23].

#### *Clinical and Humanistic Benefits of Achieving and Maintaining Remission*

Achieving and maintaining clinical remission is associated with several clinical and humanistic benefits for patients. Patients in remission have better disease control and as a result improved radiographic outcomes, physical functioning (e.g., halt of joint damage and no development of disability), and lower mortality [24–29]. These improvements are observed with clinical remission irrespective of how early or late it is achieved [30].

The improved outcomes and physical functioning observed with remission also translate to a number of humanistic benefits. Achieving and maintaining remission improve patient QoL and other patient-reported outcomes. For instance, patients in remission have been shown to have higher scores in the EuroQoL 5D and Short Form 36 (SF-36) health surveys, which assess QoL based on different domains, like physical mobility, pain, and mental health [14, 24, 31]. Of note, when comparing patients with varying levels of disease activity (i.e., remission, LDA, and M/HDA), QoL assessment scores trend downwards as disease activity

increases [14], demonstrating the considerable benefit of achieving remission on QoL measures. Domain-wise, patients in remission have better QoL in physical health, as indicated by less pain and fatigue [14, 31, 32], improved mental status (e.g., better sleep quality and less depression and anxiety) [31–34], and higher work productivity or capacity [14, 31, 35]. The aforementioned benefits of remission also exist in clinical and humanistic aspects when comparing to LDA, regardless of remission definition [13–15].

### Economic Value of Remission

The reviewed studies considered various remission measures, adopted different methodologies to evaluate economic outcomes, and represented a broad range of geographic regions. Among the 16 studies included in the summary, there were ten studies from Europe (Austria, Finland, France, Germany, Italy, Netherlands, Portugal, Spain, and Sweden) [14, 36–44], five from North America (USA and Canada) [24, 45–48], and one from Asia (Japan) [49].

Different definitions of remission were used. The majority of the studies reported DAS28-based remission (i.e.,  $\text{DAS28} < 2.6$ ;  $n = 13$ ) [24, 36–46, 49], while a few studies also reported remission defined on the basis of SDAI (i.e.,  $\text{SDAI} \leq 3.3$ ;  $n = 4$ ) [14, 24, 46, 49], CDAI (i.e.,  $\text{CDAI} \leq 2.8$ ;  $n = 5$ ) [24, 46–49], and 28 joints-based Boolean criteria ( $n = 1$ ) [46]. Direct medical costs were the most common economic outcomes evaluated ( $n = 13$ ) [14, 36–47], followed by HRU ( $n = 4$ ) [24, 37, 38, 48], indirect costs ( $n = 3$ ) [14, 40, 44], and work productivity ( $n = 2$ ) [14, 49]. Different types of methodologies were adopted to evaluate the economic outcomes. For direct medical costs or HRU measures, the economic outcomes were either assessed using a claims/electronic health record (EHR) database or a patient/physician survey. For indirect costs or work productivity measures, the economic outcomes were estimated using patient-reported workday lost/disability. Of note, studies using claims/EHR databases to assess HRU/costs tended to report higher costs

compared to those using patient/physical surveys in general.

### Direct Medical Costs and HRU

Despite the variation in geographic focus, methodology, and remission definition, patients with remission consistently had lower direct medical costs or HRU compared to those without remission. In the 12 studies that reported direct costs by remission status (Table 1), patients with remission were reported to have a median annual medical cost of €2464 (range €821 [43] to €11,272 [47]) as compared to median costs of €4717 (range €1042 [43] to €16,879 [47]) among those without remission. The savings in direct costs between patients with remission and without remission ranged from 19% [46] to 52% [45]. Direct medical costs were assessed by disease activity levels (i.e., remission, LDA, and M/HDA) in nine articles (Table 2) [14, 36–40, 42, 45, 47]. Similarly, these studies showed cost savings associated with remission compared to both patients with LDA [median cost savings (percentage of saving) €285 (20%)] and patients with M/HDA [€3804 (51%)].

Despite the variation in reported direct medical costs across studies, similar cost components were considered, including outpatient/specialist visits, hospitalizations, medical exams/imaging/laboratory tests, surgery, physiotherapy, and orthosis. Some studies also included transportation, home care, and medications. Five studies evaluated the breakdown of direct medical costs by different components [36, 40, 43–45], with four indicating that physician and ambulatory care visits were the primary driver of the total medical costs [36, 40, 43, 44]. However, higher hospitalization rates may also drive the costs for patients without remission [36, 45]. Additionally, one study found that patients attaining sustained remission had lower orthopedic costs as compared to patients without sustained remission [46].

The economic benefits of remission on direct medical costs remain similar across different remission definitions. A study by Barnabe et al. concluded that a similar magnitude of cost savings was observed for remission defined on

**Table 1** Annualized direct and indirect costs by remission status in published literature

Author, year	Country	Study methodology	Population characteristics <sup>a</sup>		Cost components	Remission definition <sup>b</sup>	Annual cost by remission status (2020 euros) <sup>c</sup>		
			Age (years), mean (SD)	Female, %			Duration of RA (years), mean (SD)	Remission	No remission
Direct medical costs <sup>d</sup>									
Beresniak et al., 2013 [37]	Germany	Costs were estimated from claims/EHR database	58.4 (11.8)	76%	8.4 (8.4)	Specialist visits, hospitalization, surgery (inpatient and outpatient), general practitioner visits, physiotherapy, laboratory tests, ultrasound, orthosis, radiosynoviotrithesis, aids, medications (excluding biologics)	DAS28	N (%) 71 (21.1%)	266 (78.9%)
Neubauer et al., 2018 [41]	Germany	Costs were estimated from claims/EHR database	58.4 (11.8)	76%	8.4 (8.4)	Specialist visits, hospitalization, surgery (inpatient and outpatient), rehabilitation, medications (excluding biologics)	DAS28-CRP	N (%) NR	15,607



Table 1 continued

Author, year	Country	Study methodology	Population characteristics <sup>a</sup>			Cost components	Remission definition <sup>b</sup>	Annual cost by remission status (2020 euros) <sup>c</sup>	
			Age (years), mean (SD)	Female, %	Duration of RA (years), mean (SD)			N (%)	No remission
Beresniak et al. (a), 2011 [38]	France	Costs were estimated using HRU reported in clinical guidelines and literature and unit costs from national tariff	NR	NR	NR	DAS28	N (%)	NR	NR
Miranda et al., 2012 [40]	Portugal	Costs were estimated using HRU from patient/physician survey and unit costs from national reports and public documents	59.3 (12.7)	84%	8.2 (8.6)	DAS28	N (%)	66 (19.9%)	266 (80.1%)
ten Klooster et al., 2019 [43]	Netherlands	Costs were estimated using HRU from EHR database and unit costs from national tariff and public documents	58.2 (14.1)	63%	NR	DAS28-ESR	N (%)	127 (51.8%)	118 (48.2%)
							Costs	1728	3223
							Costs	821	1042

Table 1 continued

Author, year	Country	Study methodology	Population characteristics <sup>a</sup>		Cost components	Remission definition <sup>b</sup>	Annual cost by remission status (2020 euros) <sup>c</sup>		
			Age (years), mean (SD)	Female, %			Duration of RA (years), mean (SD)	Remission	No remission
Radner et al., 2014 [14]	Austria	Costs were estimated from patient survey	59.9 (12.7)	80%	11.5 (10.2)	Outpatient visits, hospitalizations, surgery, imaging, home adaptations, transportations, home help	SDAI	N (%) 87 (24.4%)	269 (75.6%)
Curtis et al., 2017 [47]	USA	Costs were estimated from claims/EHR database	71 (median)	75%	13.3	All items covered in the Medicare Part A and Part B (outpatient visits, hospitalizations, emergency room visits, surgery, laboratory tests, skilled nursing facility, hospice, home health care, etc.)	CDAI	N (%) 952 (21.7%)	3429 (78.3%)
Barnabe et al., 2013 [45]	Canada	Costs were estimated from claims/EHR database	55.1 (13.3)	72%	13.6 (9.5)	Hospitalizations, emergency room visits, ambulatory care (same-day surgery and day procedures), community rehabilitation program services	DAS28	N (%) 175 (26.9%)	476 (73.1%)
								Costs 2465	5184



Table 1 continued

Author, year	Country	Study methodology	Population characteristics <sup>a</sup>		Cost components	Remission definition <sup>b</sup>	Annual cost by remission status (2020 euros) <sup>c</sup>			
			Age (years), mean (SD)	Female, %			Duration of RA (years), mean (SD)	Remission	No remission	
Barnabe et al., 2014 [46]	Canada	Costs were estimated from claims/EHR database	55.1 (13.3)	72%	13.6 (9.5)	Hospitalizations, emergency room visits, ambulatory care (same-day surgery and day procedures), community rehabilitation program services	DAS28	N (%) 175 (16.1%)	911 (83.9%)	
								Costs 2464	4717	
							SDAI	N (%) 46 (4.2%)	1040 (95.8%)	
								Costs 2318	4463	
							CDAI	N (%) 60 (5.5%)	1026 (94.5%)	
								Costs 3561	4414	
							Boolean	N (%) 95 (8.7%)	991 (91.3%)	
								Costs 2362	4552	
Indirect costs										
Miranda et al., 2012 [40]	Portugal	Costs were estimated on the basis of patient-reported workday lost and national average wage using human capital method	59.3 (12.7)	84%	8.2 (8.6)	Workdays lost (including workdays lost of family members)	DAS28	N (%) 66 (19.9%)	266 (80.1%)	
								Costs 135	540	

Table 1 continued

Author, year	Country	Study methodology	Population characteristics <sup>a</sup>			Cost components	Remission definition <sup>b</sup>	Annual cost by remission status (2020 euros) <sup>c</sup>		
			Age (years), mean (SD)	Female, %	Duration of RA (years), mean (SD)			Remission	No remission	
Radner et al., 2014 [14]	Austria	Costs were estimated on the basis of patient-reported workday lost/disability and national average wage using human capital method	59.9 (12.7)	80%	11.5 (10.2)	Workdays lost and work disability (salary loss due to early retirement)	SDAI	N (%)	87 (24.4%)	269 (75.6%)
							Costs	9023	14,273	

*CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *DAS* Disease Activity Score, *EHR* electronic health record, *ESR* erythrocyte sedimentation rate, *HRU* healthcare resource utilization, *NR* not reported, *RA* rheumatoid arthritis, *SD* standard deviation, *SDAI* Simple Disease Activity Index

<sup>a</sup>Patient characteristics reflect the study population from which the information of costs or HRU was collected. Beresniak et al. 2013 and Neubauer et al. 2018 derived the costs based on the same study population; Barnabe et al. 2013 and Barnabe et al. 2014 derived the costs based on the same study population

<sup>b</sup>Remission definition:  $DAS28 < 2.6$ ,  $SDAI \leq 3.3$ , or  $CDAI \leq 2.8$

<sup>c</sup>Annualized costs were extracted/calculated and converted to 2020 euros using consumer price index of healthcare based on the following sources and averaged currency exchange rates in the first half of 2020

Sources for consumer price index of healthcare: European countries: <https://fred.stlouisfed.org/searchresults/?st=health%20CPI>; accessed November 12, 2020; USA: <https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SAM>; accessed November 13, 2020; Canada: <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501>; accessed November 12, 2020

<sup>d</sup>All direct costs were healthcare resource-based costs, except for Miranda et al. 2012, which also included drug costs

**Table 2** Annualized direct and indirect costs by disease activity status (remission, LDA, or M/HDA) in published literature

Author, year	Country	Study methodology	Cost components	Disease activity definition <sup>a</sup>	N (%)	Annual cost by disease activity status (2020 euros) <sup>b</sup>		
						Remission	LDA	M/HDA
Direct medical costs <sup>c</sup>								
Beresniak et al., 2013 [37]	Germany	Costs were estimated from claims/EHR database	Specialist visits, hospitalization, surgery (inpatient and outpatient), general practitioner visits, physiotherapy, laboratory tests, ultrasound, orthosis, radiosynoviothrosis, aids, medications (excluding biologics)	DAS28	71 (21.1%)	39 (11.6%)	227 (67.4%)	227 (67.4%)
Beresniak et al. (a), 2011 [38]	France	Costs were estimated using HRU reported in clinical guidelines and literature and unit costs from national tariff	Medical visits, hospitalization, physiotherapy, laboratory tests, imaging, nursing, adaptive aids, transportation	DAS28	NR	NR	NR	NR
Beresniak et al. (b), 2011 [36]	Spain	Costs were estimated using HRU assessed from an expert panel and unit costs from national reports	Rheumatologists and other specialist visits, hospitalization, surgery, general practitioner visits, physiotherapy, laboratory tests, imaging, nursing, transportation	DAS28	NR	NR	NR	NR
Cimmino et al., 2011 [39]	Italy	Costs were estimated using HRU assessed from an expert panel and unit costs from national reports	Medical visits, hospitalization, laboratory tests, imaging, physical therapy, adaptive aids	DAS28	NR	NR	NR	NR
Puolakka et al., 2012 [42]	Finland	Costs were estimated using HRU assessed from an expert panel and unit costs from national reports	Specialist visits, hospitalization, general practitioner visits, nurse visits, rehabilitation care, laboratory tests, X-ray, orthoses, devices for daily activities, household workers	DAS28	NR	NR	NR	NR
					Costs	3173	3274	12,305
					Costs	1313	6784	13,947

Table 2 continued

Author, year	Country	Study methodology	Cost components	Disease activity definition <sup>a</sup>	N (%)	Annual cost by disease activity status (2020 euros) <sup>b</sup>		
						Remission	LDA	M/HDA
Miranda et al., 2012 [40]	Portugal	Costs were estimated using HRU from patient/physician survey and unit costs from national reports	Outpatient visits, hospitalizations, urgency admissions, exams, physiotherapy, medications (excluding non-conventional medicine)	DAS28	N (%)	66 (19.9%)	48 (14.5%)	218 (65.7%)
Radner et al., 2014 [14]	Austria	Costs were estimated from patient survey	Outpatient visits, hospitalizations, surgery, imaging, home adaptations, transportations, home help	SDAI	N (%)	87 (24.4%)	150 (42.1%)	119 (33.4%)
Curtis et al., 2017 [47]	USA	Costs were estimated from claims/EHR database	All items covered in the Medicare Part A and Part B (outpatient visits, hospitalizations, emergency room visits, surgery, laboratory tests, skilled nursing facility, hospice, home health care, etc.)	CDAI	N (%)	952 (21.7%)	1631 (37.2%)	1798 (41.0%)
Barnabe et al., 2013 [45]	Canada	Costs were estimated from claims/EHR database	Hospitalizations, emergency room visits, ambulatory care (same-day surgery and day procedures), community rehabilitation program services	DAS28	N (%)	175 (26.9%)	138 (21.2%)	338 (51.9%)
Indirect costs								
Miranda et al., 2012 [40]	Portugal	Costs were estimated on the basis of patient-reported workday lost and national average wage using human capital method	Workdays lost (including workdays lost of family members)	DAS28	N (%)	66 (19.9%)	48 (14.5%)	218 (65.7%)
					Costs	135	145	627

Table 2 continued

Author, year	Country	Study methodology	Cost components	Disease activity definition <sup>a</sup>	N (%)	Annual cost by disease activity status (2020 euros) <sup>b</sup>		
						Remission	LDA	M/HDA
Radner et al., 2014 [14]	Austria	Costs were estimated on the basis of patient-reported workday lost/disability and national average wage using human capital method	Workdays lost and work disability	SDAI	87 (24.4%)	150 (42.1%)	119 (33.4%)	17,664

*CDAI* Clinical Disease Activity Index, *DAS* Disease Activity Score, *HRU* healthcare resource utilization, *LDA* low disease activity, *M/HDA* moderate/high disease activity, *NR* not reported, *SDAI* Simple Disease Activity Index

<sup>a</sup>Remission was defined as DAS28 < 2.6, SDAI ≤ 3.3, or CDAI ≤ 2.8; LDA was defined as 2.6 ≤ DAS28 < 3.2, 3.3 < SDAI ≤ 11, or 2.8 < CDAI ≤ 10; M/HDA was defined as DAS28 ≥ 3.2, SDAI > 11, or CDAI > 10

<sup>b</sup>Annualized costs were extracted/calculated and converted to 2020 euros using consumer price index of healthcare based on the following sources and averaged currency exchange rates in the first half of 2020

Sources for consumer price index of healthcare: European countries: <https://fred.stlouisfed.org/searchresults/?st=health%20CPI>; accessed November 12, 2020; USA: <https://beta.bls.gov/dataViewer/view/timeseries/CUUR0000SAM>; accessed November 13, 2020; Canada: <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000501>; accessed November 12, 2020

<sup>c</sup>All direct costs were healthcare resource-based costs, except for Miranda et al. 2012, which also included drug costs

the basis of DAS28, SDAI, CDAI, and the most stringent Boolean criteria [46].

With regards to HRU, detailed HRU associated with RA by disease activity level was described in four studies [24, 37, 38, 48]. Boytsov et al. quantified and compared three HRU aspects across the three disease activity levels of remission, LDA, and M/HDA, and found that remission was associated with lower rates of hospitalizations (64% reduction), joint surgeries (53% reduction), and radiographs (24% reduction) compared to M/HDA [48]. In a separate study, Alemao et al. found that patients who achieved remission had significantly lower use of durable medical equipment (including walkers, wheelchairs, standers, and patient lifts) and lower hospitalization compared with patients who did not achieve remission [24]. A dose–response relationship was also observed between lower disease activity indices and lower durable medical equipment use or hospitalizations. Furthermore, in two studies, Beresniak et al. determined that patients in remission had substantially lower HRU in terms of physician visits, laboratory tests, radiographs, physiotherapy visits, and surgery compared to patients not in remission [37, 38].

#### ***Indirect Costs and Work Productivity Loss***

A consistent benefit on indirect costs/work productivity loss was observed among patients with remission. The two studies evaluating indirect costs focused on different cost components [14, 40]. Miranda et al. assessed work productivity loss and reported a 75% reduction (€405) in indirect costs associated with remission (Table 1) [40]. In contrast, Radner et al. evaluated both work productivity loss and work disability (i.e., salary loss due to early retirement) and reported a 37% reduction (€5250) in annual indirect costs with achieving remission vs. not achieving it (Table 1) [14].

On the basis of the evidence, work disability may be the driving component of indirect costs. Radner et al. reported substantially higher overall indirect costs compared to Miranda et al., which is due to the inclusion of costs associated with work disability [14, 40]. Indeed, the former found that 34% of patients with RA with a mean age of 60 years were in early

retirement due to RA [14]. Similarly, Boytsov et al. reported that 22% of patients with RA were retired early in the study sample, with a relatively lower percentage among patients with remission (17%) compared to patients without remission (19–25% depending on disease activity levels) [48]. Considering that patients in remission were able to delay or avoid early retirement, achieving remission early in the disease course and maintaining it can result in substantial cost savings.

Among patients who were currently employed, studies showed lower work productivity impairment in patients in remission, which is consistent with the findings of cost savings resulting from less work productivity loss. For instance, Radner et al. and Kim et al. reported a lower degree of RA-related impairment while working among patients with remission (8–12%), compared to LDA (21–27%) and M/HDA (30–46%) [14, 49]. A lower percentage of absenteeism was also seen among patients with remission (1%) compared to those with LDA (3%) or M/HDA (4%) [49].

Importantly, a large proportion of patients with RA also require care from relatives and friends with various issues, including household activities (cleaning, cooking, washing, etc.), personal care (dressing, eating, bathing, etc.), and other activities (gardening, shopping, etc.) [50]. While treating patients to remission may also have a positive economic impact by reducing the burden of informal care, not enough evidence has been provided in the literature.

In summary, this review has shown that remission was associated with lower direct and indirect costs and HRU compared with other disease activity levels. Major contributors to direct healthcare costs were physician visits, ambulatory care visits, and hospitalization. Of note, the time span of cost assessment in the studies included in this review ranged from 6 months [36–39, 41, 42] to 24 months [43]. Future studies with expanded data collection periods are needed to evaluate how remission impacts healthcare costs in the long term.

## DISCUSSION

In clinical practice, not all patients receiving RA treatment may be able to achieve remission, and the probability of attaining remission may depend on the application of treat-to-target strategy, type of therapy, and patient characteristics [20]. Innovative treatments that have improved efficacy profiles are usually associated with higher treatment costs [51]. However, these treatments may also offer a higher probability for patients to achieve and maintain clinical remission or LDA, especially if used early in the treatment sequence, potentially resulting in savings in direct medical costs and indirect costs. As such, savings in direct and indirect costs by disease activity status should be considered when quantifying the cost profile of RA treatments, particularly novel treatments with high remission rates. For example, JAK inhibitors are a new class of RA treatments that have favorable efficacy profiles among patients who have inadequate response to csDMARDs, with 24-week remission rates of up to 43% compared to 11% for csDMARDs in a meta-analysis of clinical trials [5]. Although JAK inhibitors have higher treatment costs (approximately \$20,000 to \$45,000 per year) than csDMARDs (e.g., methotrexate has an annual cost of \$796), they may not only allow more patients to achieve better disease control but may also result in direct and indirect cost savings [52]. Thus, the cost-effectiveness and economic benefits of novel RA treatments, such as JAK inhibitors, would be underestimated if treatment costs alone are considered in economic evaluations.

Including the direct and indirect costs related to different disease activity statuses would more accurately estimate the economic profile of RA treatments. However, very few studies have considered these cost savings due to remission when performing the economic evaluations of RA treatments [53–55]. The cost benefit may be tailored for the patient, payer, or societal perspective. These insights can then be used to guide treatment selection for clinicians and payers.

## CONCLUSION

Clinical remission is an important outcome in RA management and has wide applications in both clinical practice and regulatory approval of new therapies. Achieving clinical remission could promote better disease control and is associated with substantial economic benefits. On the basis of the literature review, patients with RA and clinical remission were found to have 19–52% savings in direct medical costs and 37–75% savings in indirect costs. Therefore, the economic value of remission should also be an important element to consider when performing economic analyses of different RA therapies to inform treatment and reimbursement decisions.

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