The Effect of Biologic and Targeted Synthetic Drugs on Work- and Productivity-related Outcomes for Patients with Psoriatic Arthritis: A Systematic Review

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ABSTRACT. Objective. To systematically review the effects of biologic therapies for psoriatic arthritis [secukinumab, ustekinumab, adalimumab, etanercept, certolizumab pegol (CZP), apremilast, golimumab (GOL), or infliximab (IFX)] on work productivity.

Methods. A systematic review of Medline, EMBASE, CENTRAL, and ClinicalTrials.gov was conducted to identify randomized controlled trials reporting on work productivity outcomes at the end of the placebo-controlled double-blind period.

Results. There were 7959 records identified. Full text of 377 records was further assessed for eligibility, of which 5 trials were included. All included trials were assessed with the Cochrane Risk of Bias Tool, and 4 out of 5 were judged to be of low risk of bias in most domains. Improvements in self-assessed work productivity were observed in 5 trials (IFX, GOL, CZP, ustekinumab, and apremilast), ranging from a mean difference of –0.9 to –1.8 on a 1–10 scale of self-assessed work productivity (negative change represents improvement), although statistical significance of the results was not reported for CZP and apremilast. Treatment with CZP resulted in a statistically significant reduction in absenteeism (200 mg) and presenteeism (200 and 400 mg). IFX and GOL reported a nonsignificant reduction of absenteeism. The Work Productivity Survey, the Work Limitations Questionnaire, and visual analog scales were used to measure work productivity.

Conclusion. Treatment with IFX, GOL, CZP, ustekinumab, and apremilast resulted in improvements in self-reported work productivity. A pooled analysis was not possible because of the clinical heterogeneity of the trials and variability in outcome reporting. (First Release May 1 2018; J Rheumatol 2018;45:1124–30; doi:10.3899/jrheum.170874)

Key Indexing Terms:
WORK PRODUCTIVITY PSORIATIC ARTHRITIS
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Psoriatic arthritis (PsA) affects 0.3 to 3% of the population and is associated with significant impairment of quality of life[1]. Traditional outcome measures have focused on the disease manifestations, including psoriasis, arthritis, and enthesitis. However, there is increased recognition of the effect of PsA on work productivity. Productivity loss is defined as the time lost because of treatment or disease and is often measured monetarily or through quality of life[2]. PsA often affects patients in their prime working years, and partial or complete loss of work productivity may have a substantial effect on both the individual and society[3,4]. About 16–39% of patients experience impairment of work productivity, and this is associated with worse physical function and longer disease duration[5]. Costs from lost work productivity are estimated to be $11,080 (2016 US dollars) per patient per year[6].

The advent of biologic disease-modifying antirheumatic drugs (DMARD), and more recently, targeted synthetic DMARD, have improved outcomes for patients with moderate to severe PsA[7]. There is now a wide range of new treatments available with a diverse range of targets including tumor necrosis factor-α, interleukin (IL) 12, IL-23, IL-17A, and phosphodiesterase 4[7]. While biologic and targeted synthetic treatments have been demonstrated to be highly effective, they are associated with high costs[3]. However, these costs need to be balanced with cost savings from improved disease control. Costs because of lost productivity

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have been estimated to account for 52–72% of total PsA costs, and to be as high as $3.5 billion annually in the United States[8]. Clarifying the effect of these drugs on work productivity is an important step to understanding further benefits of these drugs.

The objective of our study is to systematically review the effects of biologic therapies [secukinumab, ustekinumab, adalimumab (ADA), etanercept (ETN), certolizumab pegol (CZP), golimumab (GOL), or infliximab (IFX)] and a targeted synthetic DMARD (apremilast) used to treat PsA on work productivity. The goal was to generate data that can be used by patients, physicians, and clinical guideline developers to incorporate this socioeconomic determinant of health into PsA treatment decisions.

MATERIALS AND METHODS

Data sources and searches. A protocol for this systematic review was registered with PROSPERO (no. 52963). We searched the online databases (Medline, EMBASE, and the Cochrane Central Register of Controlled Trials) from database inception to October 21, 2016. Search terms combined MeSH headings and keywords for "psoriatic arthritis," drug names, and "randomized trial" (full Medline search strategy is found in Supplementary Data 1–4, available from the authors on request). We also searched the ClinicalTrials.gov trial registry using the terms "psoriatic arthritis" and [drug name] to identify unpublished or ongoing trials. No language or date filters were applied.

Eligibility criteria and study selection. We included any randomized trial in adults (aged > 18 yrs) with a diagnosis of PsA that compared any of the treatments of interest to placebo or another DMARD and reported any measure of work productivity. The treatments included were secukinumab, ustekinumab, ADA, ETN, apremilast, CZP, GOL, or IFX. To be eligible for inclusion, treatments had to be approved for PsA management by the US Food and Drug Administration. The search results were screened first by title/abstract, then by full text by 2 independent reviewers (NI, MH). Any article that either reviewer included at the title/abstract review stage was included for full-text review. Disagreements at the full-text stage of the review were settled by discussion until a consensus was reached by 2 reviewers (NI, MH).

Data extraction and quality assessment. We extracted relevant study characteristics and baseline characteristics of participants including demographics, medications, and baseline disease characteristics [enthesitis, dactylitis, 28-joint count Disease Activity Score (DAS28), Health Assessment Questionnaire–Disability Index (HAQ-DI), and Psoriasis Area and Severity Index (PASI)].

Risk of bias (ROB) was assessed using the Cochrane Risk of Bias tool at the study level across 7 domains: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues[9].

Our primary outcome of interest was any measure of work productivity at the end of the blinded period of the trial. Secondary outcomes included absenteeism and presenteeism. We had planned metaanalyses for work productivity, separately for biologic-naive and biologic-experienced patients. These were not conducted because of the clinical heterogeneity of the identified trials.

Work productivity measurement. There are different tools to measure work productivity for PsA. The visual analog scale (VAS) is a self-reported outcome between 0 and 10, where 10 represents total work impairment as a result of PsA, and 0 represents no impairment. The Work Productivity Survey (WPS) is self-reported and assesses the effect of arthritis on work and household productivity on a scale of 0–10. The Work Limitations Questionnaire (WLQ) index is a self-administered instrument that rates the patients' level of difficulty to perform work tasks in the past 2 weeks. Productivity loss can then be estimated from the scores. Statistical significance was considered at $p < 0.05$.

RESULTS

Identification of studies. Our search identified 6208 unique records (Figure 1), of which 377 remained after the title and abstract screening. After full-text review, 5 studies were included[10,11,12,13,14]. The studies evaluated work productivity for IFX, GOL, CZP, ustekinumab, and apremilast. No studies were included for ADA, secukinumab, or ETN. A trial for secukinumab mentioned work productivity outcomes, but no results were reported[15].

Baseline characteristics. Characteristics for the 5 included studies are presented in Table 1. The outcome measurement time ranged from 14 to 24 weeks across trials. Three trials included biologic-naive patients only. The remaining 2 (CZP and apremilast) included a mix of biologic-naive and -experienced patients. The proportion of methotrexate-experienced patients for the IFX, ustekinumab, and apremilast trials was 50%, and 63% for CZP[10,12,13,14]. The GOL trial had the smallest proportion, ranging from 33% to 38%[11]. The distribution of males and females was similar across treatment arms for all studies, except for the IFX trial.

The mean age of patients in the included studies ranged between 45 and 52 years. One trial excluded patients > 65 years of age[11]. Three trials did not report the proportion of employed patients[11,12,14]. On the other hand, close to 60% and 70% of patients were employed in the CZP and IFX trials, respectively[10,13]. The patients included had moderate to severe disease activity and disability, with mean Health Assessment Questionnaire–Disability Index (HAQ-DI) scores ranging from 1.0 to 1.3, and mean DAS28 ranging from 4.8 to 5.2[16] (Table 1). The percentage of patients with enthesitis ranged from 35% to 68%, and dactylitis ranged from 25% to 41%. PASI mean scores ranged from 7.0 to 11.4, indicating moderate skin disease manifestation[17].

Study quality, ROB. Most studies were judged to be of low ROB in most domains (Table 2). However, the "incomplete outcome" domain was rated as unclear in all studies. Zhang, *et al* had an unclear ROB for most domains[14]. The proportion of employed patients was missing in 3 studies[11,12,14]. Additionally, 2 studies failed to report specific work productivity outcomes for subgroups of biologic-naive and -experienced patients[13,14]. Overall, 4 trials (80%) were rated as having a low ROB and 1 (20%) as having an unclear ROB[14].

Self-reported work productivity. Three studies used VAS[10,11,12], 1 used the WPS[13], and the last used the WLQ index[14] to assess work productivity. Lower scores reflect greater productivity in all scales.

All trials showed an improvement in self-reported work productivity (Table 3). Therapy with IFX compared to placebo resulted in a median score difference of –2.3 ($p < 0.001$)[10]. Results for GOL showed a mean score

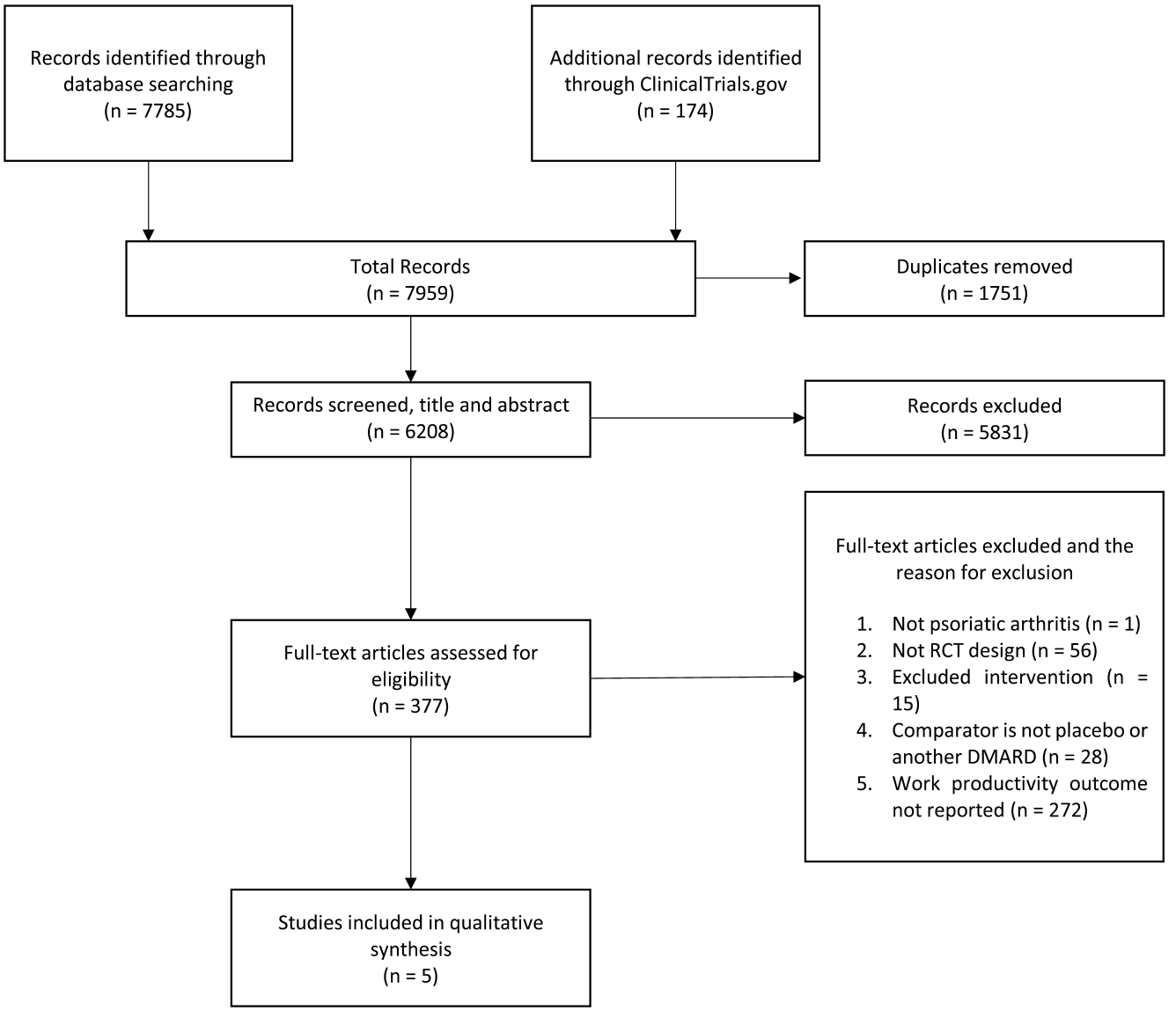

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. RCT: randomized controlled trial; DMARD: disease-modifying antirheumatic drug.

difference of –1.82 ($p < 0.001$) for the 50 mg dose, and –2.52 ($p < 0.001$) for 100 mg[11]. Treatment with ustekinumab (45 mg) resulted in a mean score difference of –1.04 ($p < 0.001$), and –1.86 ($p < 0.001$) for 90 mg[12]. The mean score difference between CZP and placebo was –1.7 for the 200-mg dose, and –0.9 for the 400-mg dose[13]. Statistical significance was not provided for these differences. Finally, the trial PALACE I reported that treatment with apremilast had a median percentage difference of –22.6% for the 20-mg dose, and –28.4% for the 30-mg dose compared to placebo (statistical significance not reported).

Other measurements of work productivity. Three out of the 5 included studies assessed absenteeism (missed work days) as a work productivity outcome (Table 3)[10,11,13]. CZP (200 mg) resulted in 0.8 fewer days missed from work compared to placebo, whereas the 400-mg dose group had no improvement compared to placebo. Statistical significance was not estimated for the difference in mean reduction of days of absenteeism from baseline between treatment arms and placebo for the CZP trial[13]. IFX resulted in 9.3 fewer days missed from work compared to placebo ($p = 0.138$). Both doses of GOL resulted in more days lost from work, but the results were not statistically significant ($p > 0.05$). Additionally, the CZP trial evaluated the time lost from work for caregivers. The absolute reduction of both doses compared to placebo was 0.9 days (unclear whether days/mo; $p < 0.05$ for both comparisons)[11].

The IFX trial assessed additional work productivity outcomes. Employment status was measured at baseline and after 14 weeks for both treatment arms. There were 11.4% of

Table 1. Characteristics of included studies.

Study, Yr	Treatment	Outcome Measurement Time, wks	Biologic-experienced Patients, %	Group Size	Age, Mean	Female, %	HAQ-DI, Mean (SD)	DAS28, Mean (SD)	PASI, Mean (SD)	Patients Employed, %
Kavanaugh, *et al*, 2006[10]	PBO	14	0	100	47	49	1.1 (0.6)	NR	10.2 (9.0)	66.7
	IFX, 5 mg/kg	14	0	100	46.5	29	1.1 (0.6)	NR	11.4 (12.7)	73
Kavanaugh, *et al*, 2009[11]	PBO	24	0	113	47	39	1 (0.5)	4.85 (1.02)	8.4 (7.4)	NR
	GOL, 50 mg	24	0	146	45.7	39	1 (0.6)	4.96 (1.10)	9.8 (8.6)	NR
	GOL, 100 mg	24	0	146	48.2	41	1.1 (0.6)	4.89 (1.06)	11.1 (9.5)	NR
Kavanaugh, *et al*, 2012[12]	PBO	24	0	206	47.4	47.6	1.3 (0.74)	5.2 (4.4–6.0)*	8.8 (7.3)	NR
	UST, 45 mg	24	0	205	47.1	48.3	1.3 (0.74)	5.2 (4.6–5.7)*	7.1 (8.9)	NR
	UST, 90 mg	24	0	204	46.8	43.1	1.3 (0.59)	5.2 (4.6–5.8)*	8.4 (7.3)	NR
Kavanaugh, *et al*, 2015[13]	PBO	24	19.1	136	47.3	58.1	1.3 (0.7)	NR	7.1	56.6
	CZP, 200 mg	24	22.5	138	48.2	53.6	1.3 (0.7)	NR	7	60.1
	CZP, 400 mg	24	17	135	47.1	54.1	1.3 (0.6)	NR	8.1	61.5
Zhang, *et al*, 2014[14]	PBO	16	24.4	168	51.1	47.6	1.2 (0.6)	4.9 (1.0)	9.1 (9.5)	NR
	APR, 20 mg	16	22	168	48.7	49.4	1.2 (0.6)	4.8 (1.1)	7.4 (8.7)	NR
	APR, 30 mg	16	24.4	168	51.4	54.7	1.2 (0.6)	4.9 (1.0)	9.2 (9.7)	NR

* Median (IQR). IFX: infliximab; PBO: placebo; GOL: golimumab; UST: ustekinumab; CZP: certolizumab pegol; APR: apremilast; HAQ-DI: Health Assessment Questionnaire–Disability Index; DAS28: 28-joint Disease Activity Score; PASI: Psoriasis Area Severity Index; IQR: interquartile range; NR: not reported.

patients who improved from unemployed at baseline to employed after 14 weeks, compared to 0% for patients in the placebo group ($p = 0.08$)[10]. Similarly, the proportion of patients improving from part-time to full-time employment was greater with IFX (30%) compared to placebo (10%; $p = 0.582$)[10]. The sample size of part-time employed at baseline was 10. Finally, the proportion of patients in the treatment arm who felt that their physical health was impeding their work or daily activities was reduced from 85% to 52.5% at Week 14, compared to an improvement from 88% to 84.4% in the placebo group ($p < 0.001$)[10].

The RAPID-PsA trial of CZP reported several additional outcomes. Presenteeism was measured as days with reduced productivity in the last month (Table 3)[13]. Additionally, this trial measured household work productivity. Compared to placebo, individuals in the 200-mg dose treatment arm had to hire outside help with less frequency after 24 weeks (–1.2 days in the last month, $p = 0.008$). Finally, both CZP treatment arms resulted in a statistically significant improvement in household work productivity. It was measured on a scale from 0 to 10, where 0 is no impairment and 10 full impairment. The mean difference between the 200-mg dose and placebo was estimated at –1.8 ($p < 0.001$), and at –1.5 for the 400-mg dose ($p < 0.001$).

DISCUSSION

In this systematic review, we identified 5 studies that measured work productivity outcomes for IFX, GOL, CZP, ustekinumab, and apremilast. No data were available for ETN, ADA, or secukinumab. All treatments resulted in improvements in self-reported work productivity. Treatment with CZP reduced absenteeism and presenteeism. IFX and GOL reported a nonsignificant reduction of absenteeism. A pooled analysis was not possible because of the clinical heterogeneity of the trials and variability in outcome reporting.

This systematic review included data sources likely to publish previously completed trials, and ClinicalTrials.gov to identify ongoing trials. Multiple outcomes were identified and extracted from included studies, including several scales for work productivity, absenteeism, and presenteeism. Our study adds to a prior systematic review by Tillett, *et al*[5] that evaluated the burden of work impairment from PsA in observational studies and randomized trials. They found that work disability was high among patients with PsA and that it was associated with longer disease duration and disability. A positive treatment effect of IFX was briefly mentioned[5]. Our study adds to this review by specifically evaluating the effect of biologic therapy. Additionally, we included new agents that had not been reviewed (ustekinumab, apremilast, and CZP). Observational studies were not included because our study focused on a causal relationship between therapy and work productivity, for which randomized controlled trials provide the best available level of evidence. In addition to identifying the positive effects of biologic therapy on work productivity, our review summarizes how work productivity has been measured in PsA trials. To our knowledge, this is the first systematic review that attempted to determine the effect of biologic therapy on work productivity for patients with PsA.

However, our systematic review faced some limitations. There is a lack of consensus as to which tool should be used to assess work productivity. This resulted in inconsistent assessment of work productivity across trials. Some studies did not estimate statistical significance for comparisons of work productivity effects between treatment and placebo arms[13,14]. Standardized reporting of work productivity would facilitate comparison between biologic therapies with a pooled analysis. Two trials (apremilast and CZP) included a

Table 2. Cochrane Risk of Bias assessment.

Study, Yr	Random Sequence Generation		Allocation Concealment		Blinding of Participants and Personnel		Blinding of Outcome Assessment		Incomplete Outcome Data		Selective Reporting		Other Sources of Bias	
Kavanaugh, *et al*, 2006[10]	Stratified randomization with algorithm	*	Computer-generated	*	Administered by blinded investigators	*	Patients unaware of whether they received drug or PBO	*	No. patients for productivity assessment not provided	**	None identified	*	None identified	*
Kavanaugh, *et al*, 2009[11]	Centralized interactive voice-Web response system	*	Interactive voice response system	*	PBO and drug not distinguished	*	Assessed by independent assessors with no record access	*	No. employed participants not provided	**	None identified	*	None identified	*
Kavanaugh, *et al*, 2012[12]	Centralized interactive voice-Web response system	*	Interactive voice response system	*	Participant and physicians blinded to intervention and dosage	*	Not described	**	No. employed participants not provided	**	None identified	*	None identified	*
Kavanaugh, *et al*, 2015[13]	Stratified randomization with interactive voice response system	*	Interactive voice response system	*	Dose-blinded participants and personnel with blinded prefilled syringes	*	Not described	**	Biologic-naive not separated from biologic-experienced	**	None identified	*	None identified	*
Zhang, *et al*, 2014[14]	Not described	**	Not described	**	Not described	**	Blinded investigators	*	No. employed participants not provided	**	None identified	**	None identified	*

* Low ROB. ** Unclear ROB. ROB: risk of bias; PBO: placebo.

Table 3. Self-reported work productivity, absenteeism, and presenteeism.

Study, Yr	Treatment	Tool Used to Measure Work Productivity	Range*	Measurement of Self-reported Work Productivity	Change in Self-reported Work Productivity	Measure of Variability for Self-reported Work Productivity	Absenteeism◊	Presenteeism§
Kavanaugh, *et al*, 2006[10]	PBO	VAS	(0–10)	Median VAS score change from baseline	–0.3	IQR (–1.5, 1.5)	0	NR
	IFX, 5 mg/kg				–2.6**	IQR (– 0.5, –5)	–9.3	NR
Kavanaugh, *et al*, 2009[11]	PBO	VAS	(0–10)	Mean VAS score change from baseline	–0.08	SD (2.6)	0.4	NR
	GOL, 50 mg				–1.9**	SD (2.7)	1.6	NR
	GOL, 100 mg				–2.6**	SD (3)	2.3	NR
Kavanaugh, *et al*, 2012[12]	PBO	VAS	(0–10)	Mean VAS score change from baseline	–0.78	NR	NR	NR
	UST, 45 mg				–1.82**	NR	NR	NR
	UST, 90 mg				–2.64**	NR	NR	NR
Kavanaugh, *et al*, 2015[13]	PBO	WPS	(0–10)	Mean WPS score change from baseline	–1	NR	–1	–0.3
	CZP, 200 mg				–2.7[NR]	NR	–1.8[NR]	–3.9**
	CZP, 400 mg				–1.9 [NR]	NR	–1	–3**
Zhang, *et al*, 2014[14]	PBO	WLQ	(0–10)[Ŧ]	Median % improvement of productivity loss	0.37	NR	NR	NR
	APR, 20 mg				–1.89[NR]	NR	NR	NR
	APR, 30 mg				–2.47 [NR]	NR	NR	NR

* Lower VAS, WPS, and WLQ scores represent greater work productivity. ** Statistically significant difference compared to PBO at a 0.05 level. ◊ Days missed from work per month. § Days with reduced productivity per month. Ŧ Scores were transformed from a 0–100 scale. PBO: placebo; IFX: infliximab; GOL: golimumab; UST: ustekinumab; CZP: certolizumab pegol; APR: apremilast; VAS: visual analog scale; WPS: Work Productivity Survey; WLQ: Work Limitations Questionnaire; IQR: interquartile range; [NR]: statistical significance level not reported; NR: not reported.

mix of biologic-experienced and -naive patients. Neither reported work productivity outcomes for these populations separately. Biologic-experienced patients would be expected to have more severe disease and potentially greater work disability. Additionally, the difference in the proportion of female participants between treatment groups in the IFX trial is considerably large. Results of these studies might be biased if sex and previous line of treatment were effect modifiers of biologic therapy efficacy on work productivity. Additionally, the GOL trial excluded patients > 65 years[11]. This sample is probably not representative of the PsA patient population. This could lead to bias, because age and disease severity are positively correlated[18]. However, patients > 65 years are less likely to be employed. This limits the effect of this bias on estimates of work productivity. Finally, although abstracts were identified and included from EMBASE, it is possible that some were missed. ClinicalTrials.gov was searched for unpublished outcome data to mitigate this ROB.

The effect of biologic therapy on work productivity has major clinical and economic implications. Work productivity loss has been associated with pain, disability, and worse mental health for similar conditions[19]. Several economic evaluations have been conducted to assess whether these treatments are cost-effective by taking into account health-related consequences and associated monetary costs[20,21,22]. However, seldom have these studies included productivity costs, which is a significant limitation given that these represent more than half of the economic burden of disease for PsA[8]. While we could not calculate a monetary summary estimate across studies because this is country- and population-specific, productivity costs can be estimated from our results by converting self-reported work productivity, absenteeism, and presenteeism outcomes into estimates of lost salary to the population of interest[23]. The importance of including these indirect costs will depend on the perspective of the analysis[4]. Many decision makers take a healthcare system perspective that excludes costs and outcomes that do not affect the healthcare system directly. Alternatively, decision makers may take a societal perspective, which attempts to account for all costs and outcomes[24].

Accounting for productivity costs in economic analyses, however, is debatable, because it raises ethical issues[2]. The benefits of increased productivity and therefore the value of the treatment depend on the patient's wage and ability to

work. Including productivity costs in the valuation of a treatment infers that treating patients who work or have higher wages are preferred to treating patients who do not work or who have a low income[2]. This way, more money is spent on patients who work at the expense of those who do not work. Thus, the tradeoff between the potential benefit of including productivity costs against these equity issues needs to be considered[2].

Our study identifies the positive effect of 5 biologic therapies on work productivity. To our knowledge, this is the first systematic review that attempted to determine the effect of biologic therapy on work productivity for patients with PsA. Our systematic review adds to the current body of literature by demonstrating that biologic therapy related to PsA improves work productivity. Given the heterogeneity of the studies, including variability in outcome reporting and lack of direct comparisons, it was not possible to compare agents, which remains a limitation of the current literature. However, for jurisdictions that take a societal perspective, our review may help inform decisions about which treatments should be reimbursed by providing evidence needed to quantify how each biologic therapy reduces productivity costs.

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