AHRQ Comparative Effectiveness Review Surveillance Program

CER #54:
Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report

Original release date:
June 2012

Surveillance Report:
March 2013

Key Findings:

- Key Question 1: Conclusion regarding biologic Disease-Modifying Antirheumatic Drug (DMARD) plus oral DMARD compared to either alone is possibly out of date.
- Key Question 2: Conclusion regarding biologic DMARD plus oral DMARD compared to either alone is possibly out of date.
- Key Question 3: Conclusions up to date.
- Key Question 4: Conclusions up to date.

Summary Decision

This CER's priority for updating is **Low**

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Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report

1. Introduction

Comparative Effectiveness Review (CER) #54, Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report, was released in June 2012.[1] It was therefore due for a surveillance assessment in December 2012. At that time, we contacted experts involved in the original CER and subject experts to get their opinions as to whether the conclusions had changed and need to be updated. We also conducted an electronic literature search update. We also searched the U.S. Food & Drug Administration (FDA) and UK Medicines and Healthcare Regulatory Authority (MHRA) web sites for any warnings issued since the CER's release.

2. Methods

2.1 Literature Searches

Using the search strategy employed for the original report, we conducted a limited literature search. We searched PubMed for the time period October 2010 to October 2012; the search for the CER was conducted in February 2011. We searched the five most influential medical journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine) and the five top journals for arthritis research (Annals of Rheumatic Disease, Arthritis and Rheumatism, Clinical Rheumatology, Journal of Rheumatology, and Rheumatology).

In addition to the electronic database searches, we followed up on suggestions from the topic experts for studies not already included in the original report. We reference-mined articles that met inclusion criteria as well as systematic reviews identified by the literature searches to identify additional articles that may have been published since the CER.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER. We screened the titles and abstracts and obtained full text copies of publications accordingly.

2.3 Expert Opinion

We shared the conclusions of the original report with six experts in the field (including the original project leader, all original technical expert panel (TEP) members, and peer reviewers for their assessment of the need to update the report and their recommendations of any relevant new studies; three subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA or MHRA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

We conducted the search updates for rheumatoid arthritis (RA) and psoriatic arthritis (PsA) CERs simultaneously. This literature search identified 585 titles. After title and abstract review, we further reviewed the full text of 142journal articles. One additional article was suggested by the expert. The other studies were rejected because they did not meet the inclusion criteria of the original report.

Of these 143 articles, 127 studies included only RA patients. Two more studies included only Juvenile Idiopathic Arthritis (JIA) patients. Thus, 14 articles were reviewed for PsA. One study on PsA was rejected because it included fewer than 100 patients, while another was rejected for study design (non-systematic review). The remaining 12 articles were abstracted into an evidence table (Appendix B) for this assessment.[4-15]

3.2 Expert Opinion

The original project leader and two experts responded to our request for input. The project leader felt that all the conclusions were up to date. One expert did not know if any of the conclusions had changed, while another felt that all the conclusions were up to date.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and regulatory database searches, the experts' assessments, and the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update. All conclusions are up to date, with the exception that conclusions about the efficacy of combining a biological DMARD with an oral DMARD are possibly out of date. This CER's priority for updating is low.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
KQ 1: For patients with PsA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?				
Oral DMARDs				
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. (INSUFFICIENT) Compared with placebo in one study, leflunomide produced statistically significant, but not clinically significant, improvement in disease activity. (LOW) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo in one fair study, MTX resulted in greater improvement in physician assessment of disease activity than placebo. (LOW) Sulfasalazine: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo in one good systematic review study, sulfasalazine reduced disease activity. (MODERATE)	A new 6 month RCT of MTX versus placebo found no significant effect on: PsARC, ACR20, or DAS-28.[15]	No safety warnings since publication of the CER update.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know.	Conclusion is up to date.
Biologic DMARDs				
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: The current evidence was limited to two cohort studies. Compared to anti-TNF monotherapy	One new non-randomized, non-blinded 6 month controlled trial reported that adalimumab combined with cyclosporine led to	No safety warnings since publication of the CER update. Tocilizumab, a new	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did	Conclusion regarding biologic DMARD plus oral DMARD compared

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
activity response rates. (LOW) One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. (INSUFFICIENT) Biologic: No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. (INSUFFICIENT) Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in disease activity. (LOW to MODERATE)	drug alone.[7] An open label RCT reported a significantly higher percentage of patients on infliximab combined with MTX achieved an ARC20 response compared to those on MTX alone.[10] Improvements in C-reactive protein levels, DAS28 response and remission rates, dactylities, fatigue and morning stiffness duration were also significantly greater in the combo tx group. A new trial of adalimumab vs cyclosporine (CYC) vs a combination of both[7] found PsA Response Criteria (PsARC) were met by 65% of CYC group, 85% of adalimumab group, and 95% of combo group. ACR50 response rates were 36%, 69%, and 87% respectively (p= .0001 and .03, respectively). A new meta-analysis[9] found PsA Response Criteria (PsARC) response at 12-14 weeks was significantly greater for anti-TNFs than placebo. ACR20 response at 12-16 weeks was greater for both anti-TNFs and other biologics. ACR70 response at 12-16 weeks was greater with both anti-TNFs and other biologics than with placebo. Psoriasis area and severity index (PASI) response was greater	the FDA in October, 2012. This drug is not approved for PsA.		due to three new trials.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	for anti-TNFs and other biologics than placebo. A placebo controlled RCT comparing 3 dosages of abatacept reported all doses led to significantly improved ACR20 scores; 10 mg/kg was superior.[8] The GO-REVEAL trial reported a significantly lower percentage of golimumab patients had new erosions compared to placebo patients at 24 weeks according to radiograph. Erosion scores and JSN scores were also significantly lower in golimumab patients.[14]			
KQ 2: For patients with PsA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?				
Oral DMARDs				
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. (INSUFFICIENT) Compared with placebo in one study, leflunomide produced better improvement in health-related quality of life and statistically significant, but not clinically significant, improvement in functional capacity. (LOW) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. (INSUFFICIENT) Sulfasalazine: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. (INSUFFICIENT)	A new 6 month RCT of MTX vs placebo reported no significant effect on tender or swollen joint count, HAQ, and pain.[15]	No safety warnings since publication of the CER update.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know	Conclusion is up to date.
Biologic DMARDs				

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. (INSUFFICIENT) Biologic: No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. (INSUFFICIENT) Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in functional capacity and health-related quality of life. (LOW to MODERATE)	An open label RCT reported patients on infliximab combined with MTX achieved significantly greater improvements in dactylities, fatigue and morning stiffness duration than patients on MTX alone.[10] A dosage study of abatacept vs placebo found significant improvement in HAQ and SF-36 scores compared with placebo, with 10 mg/kg greatest improvement.[8] The Go-REVEAL trial reported that change in HAQ scores at 24 months was not significantly different between patients taking golimumab than placebo.[14] An open label extension of the GO-REVEAL trial reported that patients who were on placebo for the first 24 weeks (all patients received golimumab after that) had significantly less improvement in the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and the dactylitis score at 52 weeks.[13] A new trial of adalimumab vs cyclosporine (CYC) vs a combination of both[7] reported improvement in HAQ disability index was significantly greater with combo tx than with either tx alone.	No safety warnings since publication of the CER update. Tocilizumab, a new biologic, was approved for RA by the FDA in October, 2012. This drug is not approved for PsA.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know	Conclusion regarding biologic DMARD plus oral DMARD compared to either alone is possibly out of date due to two new trials.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
KQ 3: For patients with PsA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?				
Oral DMARDs				
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of leflunomide and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo, leflunomide led to higher rates of withdrawals because of adverse events, diarrhea, and clinically significant increases in alanine aminotransferase. (INSUFFICIENT) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of MTX and other treatments. (INSUFFICIENT) Sulfasalazine: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of sulfasalazine and other treatments. (INSUFFICIENT)	A new RCT of MTX vs placebo reported more nausea / vomiting, respiratory infection, abdominal pain, and abnormal liver function in the MTX group. Statistical tests were not performed (perhaps because MTX was found ineffective).[15] A new cohort study[12] investigated the relationship between MTX and ischemic heart disease (IHD). Adjusted hazard ratio for new onset IHD for MTX patients compared to patients on non-biologics was 0.97 (0.79 - 1.19).	No safety warnings since publication of the CER update.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know	Conclusion is up to date.
Biologic DMARDs				
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: No head-to-head evidence met inclusion criteria; unable to draw conclusions on the comparative harms of biologic DMARD + oral DMARD and other treatments. (INSUFFICIENT) Biologic: Etanercept had a lower rate of withdrawals because of adverse events than infliximab in prospective cohort study (LOW) Additional evidence was limited to placebo controlled trials, where adverse events were not the primary outcome. Overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. However, compared with placebo, we noted the following: adalimumab and etanercept had	An open label RCT of infliximab combined with MTX vs MTX alone reported that 46% of the combo group experienced a treatment related adverse event, compared to 24% of MTX group. Two combo patients had serious AE compared to no one in MTX group. Liver enzyme changes were common. The GO-REVEAL trial report adverse events at 52 weeks; at this point, all patients had received golimumab for at least 28 weeks. 78.2% had at least one adverse event (AE), but only 4.6% had a	No safety warnings since publication of the CER update. Tocilizumab, a new biologic, was approved for RA by the FDA in October, 2012. This drug is not approved for PsA.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
more injection site reactions and adalimumab had fewer events of aggravated psoriasis than placebo (LOW) Golimumab was associated with more malignancies than placebo in one RCT (INSUFFICIENT)	serious AE. 51.0% had at least one infection; 0.8% had at least one serious infection.[14] A new trial of adalimumab vs cyclosporine (CYC) vs a combination of both[7] found adverse events generally mild to moderate in severity and intensity. 5% of CYC group, 9% of adalimumab group, and 7% of combination group had alanine aminotransferase or aspartate aminotransferase value over 3 times higher than upper limit of normal. Statistical tests were not conducted. A new cohort study[5] focused on diabetes Mellitus (DM) and calculated incidence rates per 1,000 person years: Anti-TNFs 19.7, methotrexate 23.8, hydroxychloroquine 22.2, other non-biologic DMARDs 50.2. Multivariate adjusted hazard ratios for DM were: anti TNF 0.62, 0.42-0.91, methotrexate 0.77, 0.53-1.13, and hydroxychloroquine 0.54, 0.36-0.80 compared to other nonbiologic DMARDs. Another cohort study focused on anti-TNFs and serious infection;[4] it found serious infection hospitalization rates were 5.41 per 100 person-years for anti-TNF, 5.19 for comparator PsA drugs, adjusted HR 1.10, 0.80 - 1.53. One other,[11] an individual patient meta-			

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
	analysis on adalimumab, found serious infectious events (SIEs) were the most frequently reported serious adverse events. The most commonly reported SIE in PsA patients was urinary tract infection (0.4 per 100 patient years). No serious opportunistic infections were reported.			
KQ 4: What are the comparative benefits and harms of drug therapies for PsA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?				
No pertinent evidence identified	A retrospective cohort of Danish patients found that male sex, CRP level > 10 mg/liter, concomitant methotrexate use, low health visual analog scale score were associated with longer drug survival in first time users of biologics (adalimumab, etanercept, or infliximab). 44% discontinued drug due to lack of efficacy.[6] CRP level > 10 was associated with improved ACR and EULAR scores. Study did not compare specific drugs.	No safety warnings since publication of the CER update.	EPC Investigator felt the conclusions were up to date. One other expert felt the conclusions were up to date. One expert did not know	Conclusion is up to date.

Legend: ACR: American College of Rheumatology; AE(s): Adverse Event(s); CER: Comparative Effectiveness Review; CYC: Cyclosporine; EPC: Evidence-based Practice Center; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; IHD: Ischemic Heart disease; JSN: Joint Space Narrowing; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MSX: Methotrexate; PsA: Psoriatic Arthritis; PsARC: Psoriatic Arthritis Response Criteria; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center; TNF: Tumor Necrosis Factor; Tx: Treatment

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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1/1/2011-10/15/2012

LANGUAGE:
English

SEARCH STRATEGY:
"Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH] OR "rheumatoid arthritis" OR "psoriatic arthritis"
AND
"Adrenal Cortex Hormones"[MeSH] OR corticosteroid* OR adrenal cortex hormone* OR "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH] OR methotrexate* OR leflunomide* OR sulfasalazine* OR hydroxychloroquine* OR "TNFR-Fc fusion protein"[Substance Name] OR TNFR-Fc fusion protein* OR etanercept OR "infliximab"[Substance Name] OR infliximab OR "adalimumab"[Substance Name] OR adalimumab OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab"[Substance Name] OR rituximab OR interleukin 1 receptor antagonist protein* OR anakinra OR "CDP870"[Substance Name] OR CDP870 OR CDP-870 OR certolizumab OR cimzia OR "efalizumab "[Substance Name] OR efalizumab OR raptiva OR "alefacept "[Substance Name] OR alefacept OR amevive OR "natalizumab"[Substance Name] OR natalizumab OR tysabri OR actemra OR "tocilizumab"[Substance Name] OR tocilizumab OR "golimumab "[Substance Name] OR golimumab
NOT
editorial[pt] OR letter[pt] OR practice guideline[pt]

NUMBER OF RESULTS: 1987

ENDNOTE FILTERED SEARCHES TO ELIMINATE:
ANIMALS
KEYWORD – "ANIMAL" NOT "HUMAN"
TITLE - MOUSE, MICE, MURINE, RAT, RATS, MONKEY(S)

CHILDREN/ADOLESCENTS –
KEYWORD - "CHILD OR ADOLESCEN" NOT ADULT
TITLE – "CHILD," "ADOLESCEN..."

NUMBER AFTER FILTERING: 1922

ADDITIONAL FILTERING TO INCLUDE ONLY THE FOLLOWING JOURNALS:
ANNALS OF INTERNAL MEDICINE
BMJ
JAMA
LANCET
NEW ENGLAND JOURNAL OF MEDICINE

ANNALS OF THE RHEUMATIC DISEASES
ARTHRITIS AND RHEUMATISM
ARTHRITIS RESEARCH THERAPY
CLINICAL AND EXPERIMENTAL RHEUMATOLOGY
CLINICAL RHEUMATOLOGY
JOURNAL OF RHEUMATOLOGY
RHEUMATOLOGY

NUMBER OF RESULTS AFTER FILTERING FOR JOURNALS: 585

Appendix B. Evidence Table

Author, Year	Study Design	Study name	Drugs	Year conducted	N, Population	F/U Length	Efficacy / effectiveness	Safety
Baranauskaite, 2012[10]	Open label RCT	RESPOND	Anti-TNF (Infliximab) plus non biologic DMARD (MTX) vs MTX alone	2006-2008	115 PsA patients naïve to MTX	16 weeks	86.3% of combo patients and 66.7% of patients receiving MTX alone achieved an ACR20 response ($p<.02$). Improvements in C-reactive protein levels, DAS28 response and remission rates, dactylities, fatigue and morning stiffness duration were also significantly greater in the combo tx group.	46% of combo group had treatment related adverse event, compared to 24% of MTX group. Two combo patients had serious AE compared to no one in MTX group. Liver enzyme changes were common.
Mease, 2011[8]	RCT	CASPAR	Anti-TNF: Abatacept. Study compared 3mg/kg, 10 mg/kg, and 30/10 mg/kg (2 initial doses of 30, followed by 10mg/kg) vs placebo		170 PsA patients with target lesion (TL) at least 2 cm who had previously taken DMARDs	6 months	All drug regimens resulted in significantly improved ACR20, MRI, HAQ, and SF-36 scores compared with placebo, with 10 mg/kg greatest improvement. The same is true for the proportion of patients achieving a minimum clinically important difference in the HAQ disability index and the mean change in physical component summary (PCS) scores on the SF-36.	One case of gastroenteritis in the 10 kg/mg arm and one case of osteomyelitis in the 30/10 arm were considered drug-related.
Glintborg, 2011[6]	Cohort	DANBIO registry, Denmark	Anti-TNFs (Adalimumab, Etanercept, Infliximab)	2000-2009	764 PsA patients initiating	5 years	Male sex, CRP level > 10 mg/liter, concomitant	Not stratified by drug. 44% stopped drug due to lack of

Author, Year	Study Design	Study name	Drugs	Year conducted	N, Population	F/U Length	Efficacy / effectiveness	Safety
					their first tx with an anti-TNF		methotrexate use, low health visual analog scale score were associated with longer drug survival. CRP level > 10 was associated with improved ACR and EULAR scores.	efficacy, 28% due to adverse events
Kingsley, 2012[15]	RCT	MIPA	MTX vs placebo	2003-2008	221 PsA patients in UK	6 months	MTX had no significant effect on: PsARC (OR 1.77, 0.97 - 3.23) ACR20 (OR 2.00, 0.65 - 6.22) DAS-28 (OR 1.70, 0.90 - 3.17) Also no significant effects on tender or swollen joint count, HAQ, pain	No statistical analyses. Common adverse events include: nausea/ vomiting, respiratory infection, abdominal pain, abnormal liver function.
Kavanaugh, 2012 Treatment of[13]	Open label extension of RCT	GO-REVEAL	Anti-TNF (Golimumab) vs placebo. At week 24, all patients began receiving golimumab.	2006-2007	405 PsA patients in US, Canada, and Europe	12 months	Patients who were on placebo for the first 24 weeks had significantly less improvement in the PsA-modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and the dactylitis score at 12 months.	NA
Kavanaugh, 2012, Golimumab[14]	Open label extension of RCT	GO-REVEAL	Anti-TNF (Golimumab) vs placebo. At week 24, all patients began receiving golimumab.	2006-2007	405 PsA patients in US, Canada, and Europe	12 months	At 24 weeks, a significantly lower percentage of golimumab patients had new erosions according to radiograph. Erosion scores and JSN scores were also significantly lower in golimumab patients. Change in	Adverse events were reported at 52 weeks; at this point, all patients had received golimumab for at least 28 weeks. 78.2% had at least one adverse event (AE), but only 4.6% had a serious AE.

Author, Year	Study Design	Study name	Drugs	Year conducted	N, Population	F/U Length	Efficacy / effectiveness	Safety
							HAQ scores was not significantly different between groups.	51.0% had at least one infection; 0.8% had at least one serious infection.
Ash, 2012[9]	Systematic review	NA	NSAIDs, corticosteriods, synthetic and biologic DMARDS	Included trials conducted 1962 - 2010	Meta-analyses included up to 8 anti-TNF trials, up to 3 trials on other biologic DMARDs in PsA patients	12 - 16 weeks	PsA Response Criteria (PsARC) response at 12-14 weeks was greater for anti-TNFs than placebo (RR 2.73, 2.36 - 3.15). ACR20 response at 12-16 weeks was greater for anti-TNFs (RR 4.39, 3.53-5.46) and other biologics (RR 2.12, 1.07-4.19) than placebo. ACR70 response at 12-16 weeks was greater with both anti-TNFs (RR 14.6,1 5.96-35.78) and other biologics (7.43, 1.37- 40.44) than placebo. Psoriasis area and severity index (PASI) response was greater for anti-TNFs (RR 6.89, 4.64-10.23) and other biologics (3.74, 2.49-5.61) than placebo.	No safety issues noted.
Karanikolas, 2011[7]	CCT (Non randomized, non blinded)	NA	Anti-TNF (adalimumab) vs non-biological DMARD (cyclosporine - CYC) vs combination	2007-2009	176 PsA patients with minimum 6 months tx with MTX	12 months	PsA Response Criteria (PsARC) were met by 65% of CYC group, 85% of adalimumab group, and 95% of combo group. ACR50 response rates were	Did not conduct statistical tests on adverse events data. Adverse events were generally mild to moderate in severity and intensity. 5% of

Author, Year	Study Design	Study name	Drugs	Year conducted	N, Population	F/U Length	Efficacy / effectiveness	Safety
							36%, 69%, and 87% respectively (p= .0001 and .03, respectively). Improvement in HAQ disability index was significantly greater with combo tx than with either tx.	CYC group, 9% of adalimumab group, and 7% of combination group had alanine aminotransferase or aspartate aminotransferase value over 3 times higher than upper limit of normal.
Chen, 2012[12]	Cohort	NA	MTX vs nonbiologic drugs (oral retinioids, cyclosporine, azathloprine, mycophenelate, mofetil)	1996-2008	12,050 psoriasis patients, of which 10% had PsA. 6,578 patients on MTX vs 5,472 on non-biologics	12 years	NR	Adjusted hazard ratio for new onset ischemic heart disease (IHD) for MTX patients compared to patients on non-biologics was 0.97 (0.79 - 1.19)
Solomon, 2011[5]	Cohort	NA	Anti-TnF, MTX, Hydroxychloroquine, any other non-biologic DMARDs	1996-2008	13,905 RA or PsA patients	5.8 months	NR	Diabetes Mellitus (DM) incidence rates per 1,000 person years: Anti-TNFs 19.7, methotrexate 23.8, hydroxychloroquine 22.2, other non-biologic DMARDs 50.2. Multivariate adjusted hazard ratios for DM were: anti TNF 0.62, 0.42-0.91, methotrexate 0.77, 0.53-1.13, and hydroxychloroquine

Author, Year	Study Design	Study name	Drugs	Year conducted	N, Population	F/U Length	Efficacy / effectiveness	Safety
								0.54, 0.36-0.80 compared to other nonbiologic DMARDs.
Grijalva, 2011[4]	Cohort	NA	Any anti-TNF or non-biologic DMARD	1998-2007	3,113 PsO-PsA - As patients	12 months	NR	Serious infection hospitalization rates were 5.41 per 100 person-years for anti-TNF, 5.19 for comparator drugs, adjusted HR 1.10, 0.80 - 1.53
Burmester, 2012[11]	Individual patient meta-analysis	NA	Anti-TNF: Adalimumab	Included trials conducted 2000 - 2010	837 PsA patients (among a larger sample with RA, PsA, JIA, or Crohn's disease)	Up to 5 years	NR	Serious infectious events (SIEs) were the most frequently reported serious adverse events. The most commonly reported SIE in PsA patients was urinary tract infection (0.4 per 100 patient years). No serious opportunistic infections were reported. The number of deaths was similar to that expected in the general population.

Legend: ACR: American College of Rheumatology; AE(s): Adverse Event(s); CER: Comparative Effectiveness Review; CCT: Case Controlled Trial; CYC: Cyclosporine; EPC: Evidence-based Practice Center; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; IHD: Ischemic Heart disease; JSN: Joint Space Narrowing; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MSX: Methotrexate; PsA: Psoriatic Arthritis; PsARC: Psoriatic Arthritis Response Criteria; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center; TNF: Tumor Necrosis Factor; Tx: Treatment

Appendix C. Questionnaire Matrix

Title: Drug Therapy for Psoriatic Arthritis in Adults: Update of a 2007 Report

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
KQ 1: For patients with PsA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?			
Oral DMARDs			
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. (INSUFFICIENT) Compared with placebo in one study, leflunomide produced statistically significant, but not clinically significant, improvement in disease activity. (LOW) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo in one fair study, MTX resulted in greater improvement in physician assessment of disease activity than placebo. (LOW) Sulfasalazine: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo in one good systematic review study, sulfasalazine reduced disease activity. (MODERATE)	☐	New Evidence:	☐
Biologic DMARDs			

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: The current evidence was limited to two cohort studies. Compared to anti-TNF monotherapy (adalimumab, etanercept, or infliximab), MTX plus anti-TNF produced similar disease activity response rates. (LOW) One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. (INSUFFICIENT) Biologic: No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. (INSUFFICIENT) Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in disease activity. (LOW to MODERATE)	☐	New Evidence:	☐
KQ 2: For patients with PsA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?			
Oral DMARDs			
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of leflunomide and other treatments. (INSUFFICIENT) Compared with placebo in one study, leflunomide produced better improvement in health-related quality of life and statistically significant, but not clinically significant, improvement in functional capacity. (LOW) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative efficacy of MTX and other treatments. (INSUFFICIENT) Sulfasalazine: No head-to-head studies met inclusion	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
criteria; unable to draw conclusions on the comparative efficacy of sulfasalazine and other treatments. (INSUFFICIENT)			
Biologic DMARDs			
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: One systematic review of TNF inhibitors found that both TNF inhibitors and sulfasalazine are effective (similar withdrawals due to lack of efficacy); however, the data were insufficient to determine if the effect reached MCID. (INSUFFICIENT) Biologic: No head-to-head trials met inclusion criteria; unable to draw conclusions on the comparative efficacy of biologics and other treatments. (INSUFFICIENT) Compared with placebo, adalimumab, etanercept, golimumab, and infliximab led to greater improvement in functional capacity and health-related quality of life. (LOW to MODERATE)	☐	New Evidence:	☐
KQ 3: For patients with PsA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?			
Oral DMARD			
Leflunomide: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of leflunomide and other treatments. (INSUFFICIENT) Current evidence was limited to placebo-controlled trials. Compared with placebo, leflunomide led to higher rates of withdrawals because of adverse events, diarrhea, and clinically significant	☐	New Evidence:	☐

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
increases in alanine aminotransferase. (INSUFFICIENT) Methotrexate: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of MTX and other treatments. (INSUFFICIENT) Sulfasalazine: No head-to-head studies met inclusion criteria; unable to draw conclusions on the comparative harms of sulfasalazine and other treatments. (INSUFFICIENT)			
Biologic DMARDs			
Biologic DMARD + Oral DMARD vs. Biologic DMARD or Oral DMARD: No head-to-head evidence met inclusion criteria; unable to draw conclusions on the comparative harms of biologic DMARD + oral DMARD and other treatments. (INSUFFICIENT) Biologic: Etanercept had a lower rate of withdrawals because of adverse events than infliximab in a prospective cohort study (LOW) Additional evidence was limited to placebocontrolled trials, where adverse events were not the primary outcome. Overall adverse event profiles appeared to be similar for biologic DMARDs and placebo. However, compared with placebo, we noted the following: adalimumab and etanercept had more injectionsite reactions and adalimumab had fewer events of aggravated psoriasis than placebo (LOW) Golimumab was associated with more malignancies than placebo in one RCT (INSUFFICIENT)	☐	New Evidence:	☐
KQ 4: What are the comparative benefits and harms of drug therapies for PsA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?			
No pertinent evidence identified		New Evidence:	

Conclusions From CER Executive Summary and Strength of Evidence	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
	☐		☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			