TITLE: Long-Term Sustained Clinical Remission after Stopping First-Line Anti-TNF Agents in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis: Clinical Effectiveness

DATE: 7 November 2014

RESEARCH QUESTION

What is the long-term clinical effectiveness (ability to maintain sustained clinical remission) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) who remain on methotrexate (MTX) after using an anti-TNF agent plus MTX as first-line treatment?

KEY FINDINGS

Two randomized controlled trials (RCTs) and one non-randomized study were identified regarding the long-term clinical effectiveness (not necessarily clinical remission) in patients with RA who remain on MTX after using an anti-TNF agent plus MTX as first-line treatment.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1 2010 and 28 October, 2014. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS)
Intervention	Anti-TNF agent plus methotrexate (MTX) for approximately one year followed by MTX alone
Comparator	• MTX as first-line treatment followed by an anti-TNF agent if disease progresses (standard of treatment) • Anti-TNF agents as first-line therapy, continue for lifetime • MTX monotherapy • None
Outcomes	Clinical effectiveness (sustained clinical remission [measured by radiography, ACR, DAS, HAQ, lab measures like ESR, CRP], harms)
Study Designs	Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs and non-randomized studies.

Two RCTs and one non-randomized study were identified regarding the long-term clinical effectiveness (not necessarily clinical remission) in patients with RA who remain on MTX after using an anti-TNF agent plus MTX as first-line treatment. No relevant health technology assessment reports, systematic reviews, or meta-analyses were identified. In addition, no relevant literature including patients with PsA or AS was identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Two RCTs and one non-randomized study were identified regarding the long-term clinical effectiveness in patients with RA who remain on MTX after using an anti-TNF agent plus MTX as first-line treatment. Results specifically related to clinical remission were not presented in any of the abstracts; however, the full text of the articles may contain this information.

The OPTIMA[1] and the HIT HARD[2] RCTs reported: maintenance of good clinical responses,[1] no difference in rates of adverse events,[1] no difference in clinical outcomes,[2] and reduced radiographic progression[1,2] in patients with early RA who remained on MTX after using adalimumab plus MTX as first-line therapy compared with placebo plus MTX. Patients with RA in the BeSt study[3] who remained on MTX after using infliximab plus MTX as first-line therapy had no change in the rate of radiographic progression within the year after cessation of infliximab. A detailed summary of findings can be found in Table 2.

Table 2: Summary of Findings				
Lead Author, Year	**Population**	**Intervention**	**Comparator**	**Outcomes**
Randomized Controlled Trials				
Smolen, 2014[1]	Patients with early RA (less than one year)	ADA + MTX 26 wks, followed by MTX monotherapy 52 wks	• Placebo + MTX 26 weeks, followed by MTX monotherapy 52 wks OR ADA + MTX 52 wks • ADA + MTX 78 wks	• Intervention group achieved and "mostly maintained" a higher proportion of good responses (low disease activity [DAS28 < 3.2] and radiographic non-progression) at week 78 • No difference in adverse events between groups
Detert, 2013[2]	DMARD naive Patients with early RA (less than one year)	ADA + MTX 24 wks followed by MTX monotherapy up to 48 wks	Placebo + MTX 24 weeks followed by MTX monotherapy up to 48 weeks	• No difference in DAS28, ACR, or HAQ scores between groups • Greater reduction in radiographic progression in intervention group
Non-Randomized Studies				
van den Broek, 2011[3]	Patients with RA	Infliximab + MTX until DAS ≤ 2.4 for 6 months followed by MTX monotherapy	None	• No change in rate of radiographic progression one year post MTX monotherapy • Reintroduction of infliximab in 48% of patients

ACR = American College of Rheumatology; ADA = adalimumab; DAS28 = 28 joint disease activity score with C-reactive protein; DMARD = disease modifying antirheumatic drug; HAQ = Health Assessment Questionnaire; MTX = methotrexate; RA = rheumatoid arthritis; wks = weeks

No relevant literature including patients with PsA or AS was identified, therefore no summary can be provided.

REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses
No literature identified.

Randomized Controlled Trials

1. Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet. 2014 Jan 25;383(9914):321-32. PubMed: PM24168956

2. Detert J, Bastian H, Listing J, Weiss A, Wassenberg S, Liebhaber A, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. Ann Rheum Dis. 2013 Jun;72(6):844-50. PubMed: PM22739990

Non-Randomized Studies

3. van den Broek M, Klarenbeek NB, Dirven L, van SD, Hulsmans HM, Kerstens PJ, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. Ann Rheum Dis. 2011 Aug;70(8):1389-94. PubMed: PM21515916

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

APPENDIX – FURTHER INFORMATION:

Systematic Reviews and Meta-analyses - Anti-TNF Agent Dose Reduction

4. van Herwaarden N, den Broeder AA, Jacobs W, van der Maas A, Bijlsma JWJ, van Vollenhoven RF et al. Down-titration and discontinuation strategies of tumor necrosis factor–blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2013;(9): CD010455.

Randomized Controlled Trials - Unclear Crossover Therapy

5. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, Han KH, Ronday HK, Kerstens PJ, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Ann Rheum Dis. 2011 Jun;70(6):1039-46.
PubMed: PM21415052

Non-Randomized Studies - Anti-TNF Agent Dose Reduction

6. Morck B, Pullerits R, Geijer M, Bremell T, Forsblad-d'Elia H. Infliximab dose reduction sustains the clinical treatment effect in active HLAB27 positive ankylosing spondylitis: a two-year pilot study. Mediators Inflamm [Internet]. 2013 [cited 6 Nov 2014];2013:289845. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3780705
PubMed: PM24089587

7. Cantini F, Niccoli L, Cassara E, Kaloudi O, Nannini C. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. Biologics [Internet]. 2012 [cited 6 Nov 2014];6:201-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3421476
PubMed: PM22904612

Review Articles

8. Tanaka Y, Hirata S. Is it possible to withdraw biologics from therapy in rheumatoid arthritis? Clin Ther. 2013 Dec;35(12):2028-35.
PubMed: PM24290736