A review of TNFi cycling vs mechanism of action switching outcomes after first-line TNFi in rheumatic conditions

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OBJECTIVE

To review the literature comparing outcomes of TNFi cycling to MOA switching for treatment of rheumatic conditions after failure of first or later line TNFi therapy.

CONCLUSIONS

The majority of TNFi cycling vs MOA switch evidence comes from RWE studies in RA assessing change in clinical endpoints

The available literature suggests that MOA switch may result in better outcomes compared to TNFi cycling.

More studies are needed in PsA, axSpA, and other rheumatic conditions to adequately understand patient outcomes after TNFi cycling or MOA switching

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5. The remainder of references can be accessed through Scanning the QR code

Presented at the 2023 Academy of Managed Care Pharmacy (AMCP) Nexus Meeting; October 16-19, 2023

K Perkins completed this research as a participant in the AMCP Foundation/AbbVie, Inc. Specialized Summer Internship Program in Health Outcomes. P Zueger and K Onishchenko are employees of AbbVie and may own stock or options. N Mirza is a graduate intern at AbbVie.

AbbVie participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the poster. All authors contributed to development of the poster and maintained control over final content. No honoraria or payments were made for authorship.

Thank you to my mentors who helped me conduct this review and to AbbVie, Inc. funding the AMCP Foundation Specialized Summer Internship in Health Outcomes

INTRODUCTION

- Tumor necrosis factor inhibitors (TNFi) are often the first-line biologic therapy for treatment of moderate-to-severe rheumatic diseases
- After TNFi therapy failure, some guidelines advise switching to a biologic or targeted synthetic disease-modifying antirheumatic drug (DMARD) of different mechanism of action (MOA)[1,2]
- Real world studies suggest that prescribers frequently select treatment with another TNFi (cycling) over switching to a new MOA after initial TNFi failure[3, 4]
- There is a lack of consensus of which treatment strategy results in better outcomes for patients with rheumatic conditions

METHODS

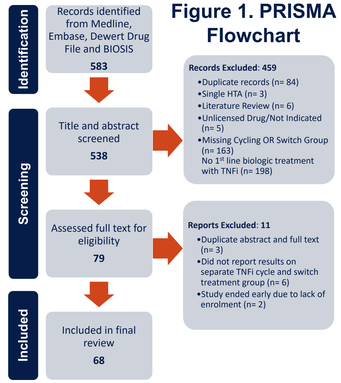
Study Design

- A targeted literature review was conducted in Medline, Embase, Derwent Drug File and BIOSIS Previews to identify studies comparing outcomes of cycling to a subsequent TNFi versus switching to another MOA after initial TNFi therapy failure in adults with rheumatic conditions.
- Title and abstract screening were performed independently by two reviewers, with data extraction divided and performed by one independent reviewer.

Inclusion Criteria

- Adult patients with RA, PsA or AxSpA
- Study type: real world evidence (RWE), randomized controlled trials (RCT), economic analysis, meta-analysis
- Prior treatment with TNFi
- Compared patients treated with a 2nd TNFi (cycling) to patients treated with a new mechanism of action (switching MOA)

Figure 1. PRISMA Flowchart



Study Characteristics

Endpoints

- Endpoints were categorized into clinical, economic, or medication-taking behavior outcomes

Endpoint Assessment

- Endpoints results were classified into 4 categories
  - Switch Preferred: statistically favored switching MOA
  - Cycle Preferred: statistically favored TNFi Cycling
  - No Difference: no statistically significant difference between cycling and switching groups
  - Inconclusive: statistics comparing cycling and switching not reported
- Modeling studies often did not report statistical significance of endpoints, in this case author summary was used to determine outcome of switch preferred, cycle preferred or no difference

RESULTS

- Studies found were published between 2007 – 2023
- Of the 68 studies in total, 51 of the studies were global and 17 focused solely on the US market.
- Study types consisted of real-world evidence (n=46), meta-analysis (n=7), and modeling studies (n=15), with most of studies conducted in RA (96%, n=65)
- In RA, a total of 113 outcomes were collected, 68 clinical (60%), 18 economic (16%) and 27 assessed medication taking behaviors (24%).
- The baseline characteristics of the MOA switch group often had higher disease activity compared to the patients in the TNFi cycling group

Table 1. MOA Switch Drug Classes

Class	Disease	# Studies
Anti-CD80/86	RA	39
Anti-CD20	RA	35
IL-6i	RA	35
JAKi	RA	11
IL-1i	RA	3
IL-17Ai	axSpA, PsA	1, 3
IL-12/23i	PsA	1

Anti-CD80/86: Inhibitor of CD80 and CD86 on T-cells, Selective T-Cell Costimulation Blocker; Anti-CD20: Inhibitor of CD20 on B-lymphocytes; IL-6i: Interleukin 6 inhibitor; JAKi: Janus Kinase Inhibitor; IL-1i: Interleukin 1 inhibitor; IL-17Ai: Interleukin 17A inhibitor; IL-12/23i: Interleukin 12/23 inhibitor

Table 2. Switching MOA Resulted in Improved Outcomes Across Endpoint Types in the Majority of Identified Studies

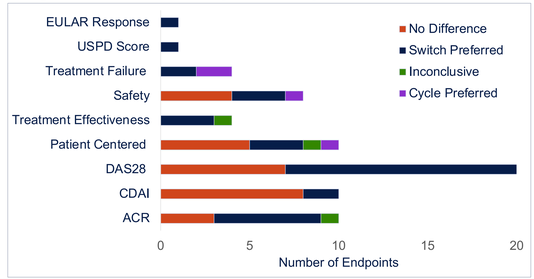
	Clinical	Economic	Medication Taking Behavior	Total (%)
TNFi Cycle Preferred	4	0	0	4 (4%)
Inconclusive	4	2	3	9 (8%)
No Difference	27	1	5	33 (29%)
MOA Switch Preferred	33	15	19	67 (59%)

Table 3. Study Characteristics

	Author, Year	Region	Study Type	Endpoint Types	Publication Type
RA	Finckh 2007[6]	Global	RWE	DAS28	Article
	Lebmeier 2009[7]	Global	Modelling Studies	Treatment Failure	Conference Abstract
	Russell 2009[8]	Global	Modelling Studies	Cost Effectiveness	Article
	Launois 2009[9]	Global	Modelling Studies	Direct Costs	Conference Abstract
	Merkesdal 2010[10]	Global	Modelling Studies	Cost Utility	Article
	Finckh 2010[11]	Global	RWE	DAS28	Article
	Hallinen 2010[12]	Global	Modelling Studies	Cost Utility	Article
	Carlos 2010a[13]	Global	Modelling Studies	ACR, Cost Effectiveness	Conference Abstract
	Carlos 2010b[14]	Global	Modelling Studies	ACR, Cost Effectiveness	Conference Abstract
	Salliot 2011[15]	Global	Meta Analysis	ACR	Article
	Johnston 2011[16]	US	RWE	Safety	Conference Abstract
	Du Pan 2012[17]	Global	RWE	Persistence	Article
	Schoels 2012[18]	Global	Meta Analysis	ACR, Safety	Article
	Finckh 2012[19]	Global	RWE	DAS28, Patient Centered	Article
	Johnston 2013[20]	US	RWE	Safety	Article
	Ryazhenov 2013[21]	Global	Modelling Studies	Cost Effectiveness	Conference Abstract
	Kim 2014[22]	Global	Meta Analysis	ACR, Patient Centered	Article
	Hirabara 2014a[23]	Global	RWE	CDAI, DAS28, Persistence	Conference Abstract
	Hirabara 2014b[24]	Global	RWE	DAS28, Persistence	Article
	Harrold 2015[25]	US	RWE	CDAI, ACR	Article
	Backhaus 2015[26]	Global	RWE	DAS28	Article
	Manders 2015[27]	Global	Modelling Studies	DAS28, Patient Centered, Cost Utility	Article
	Emery 2015[28]	Global	RWE	DAS28	Article
	Rotar 2015[29]	Global	RWE	Treatment Failure, Persistence	Article
	Choquette 2016a[30]	Global	RWE	Persistence	Conference Abstract
	Soubrier 2016[31]	Global	RWE	Treatment Failure, Persistence	Conference Abstract
	Choquette 2016b[32]	Global	RWE	Persistence	Conference Abstract
	Choquette 2016c[33]	Global	RWE	Persistence	Conference Abstract
	Falcão 2016[34]	Global	RWE	Persistence	Conference Abstract
	Chastek 2016[35]	US	RWE	Persistence	Conference Abstract
	Bonafede 2016[36]	US	RWE	RA Claims Algorithm	Conference Abstract
	Lopez-Olivo 2016[37]	Global	Meta Analysis	ACR, Persistence	Conference Abstract
	Bonafede 2016[38]	US	RWE	Treatment Effectiveness, Direct Costs, Adherence	Conference Abstract
	Harrold 2016[39]	US	RWE	CDAI, Patient Centered	Conference Abstract
	Huoponen 2016[40]	Global	Modelling Studies	Cost Utility	Conference Abstract
	Bonafede 2017[41]	US	RWE	Treatment Effectiveness, Direct Costs	Conference Abstract
	Chastek 2017[42]	US	RWE	Treatment Effectiveness, Direct Costs, Persistence	Article
	Flouri 2017[43]	Global	RWE	DAS28	Conference Abstract
	Lauper 2017[44]	Global	RWE	Safety, Treatment Failure, Persistence	Conference Abstract
	Wei 2017[45]	US	RWE	CDAI, DAS28, Persistence	Article
	Lopez-Olivo 2017[46]	Global	Meta Analysis	DAS28	Conference Abstract
	Bogas 2017[47]	Global	RWE	DAS28, ACR	Conference Abstract
	Nishino 2017[48]	Global	RWE	USPD Scores, Persistence	Conference Abstract
	Harrold 2017[49]	US	RWE	CDAI	Conference Abstract
	Sergio 2018[50]	Global	Modelling Studies	DAS28, Cost Effectiveness	Article
	Lopez-Olivo 2018[51]	Global	Meta Analysis	CDAI, Persistence	Conference Abstract
	Lauper 2018[52]	Global	RWE	Safety	Article
	Silva-Fernández 2018[53]	Global	RWE	Patient Centered	Article
	Soubrier 2018[54]	Global	RWE	Persistence	Article
	Choquette 2019[55]	Global	RWE	Persistence	Article
	Briones-Figueroa 2019[56]	Global	RWE	Persistence	Conference Abstract
	Harrold 2019[57]	US	RWE	CDAI, ACR, Persistence	Article
	Huoponen 2019[58]	Global	Modelling Studies	Patient Centered	Article
	Frisell 2019[59]	Global	RWE	Patient Centered, Persistence	Article
	Muszbek 2019[60]	US	Modelling Studies	Patient Centered, Cost Utility	Article
	Endo 2020[61]	Global	RWE	DAS28, CDAI, Persistence	Article
	Paul 2020[62]	US	RWE	Safety, Direct Costs	Article
	Lopatina 2021[63]	Global	RWE	Patient Centered, Cost Utility	Article
	Matusevich 2021[64]	US	Modelling Studies	Cost Effectiveness	Article
	Milgore 2021[65]	Global	Meta Analysis	ACR, Persistence	Article
	Matusevich 2021[66]	US	RWE	Direct Costs, Persistence	Article
	Bogas 2021[67]	Global	RWE	EULAR Response	Article
	Curtis 2022[68]	US	RWE	CDAI, DAS28	Article
	Pappas 2022[69]	Global	RWE	CDAI, Patient Centered, Persistence	Conference Abstract
	Shipa 2023[70]	Global	RWE	Persistence	Article
PsA	Lang 2016[71]	Global	Modelling Studies	Patient Centered, Cost Utility	Conference Abstract
	Pina Vegas 2022[72]	Global	RWE	Persistence	Article
axSpA	Weston 2020[73]	Global	RWE	BASDAI	Conference Abstract

Studies included in literature review sorted chronologically by disease state.
RA: Rheumatoid Arthritis; PsA: Psoriatic Arthritis; axSpA: Axial spondyloarthritis; RWE: Real World Evidence; DAS28: Disease Activity Score-28; ACR: American College of Rheumatology Score, CDAI: Clinical Disease Activity Index, EULAR: European Alliance of Associations for Rheumatology; PD: Power Doppler; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, Treatment Effectiveness: based on validated claims algorithm for RA[5]

Figure 3. Clinical Endpoints Reported in RA Studies



EULAR Response: European Alliance of Associations for Rheumatology (EULAR) criteria classify level of disease activity; USPD Score: Ultrasound Power Doppler Score; Treatment Failure: one study defined as "not achieving ACR20 response", the others did not define failure; Safety: infection rates, hospitalization rates, cardiovascular events, undefined safety issues; Treatment Effectiveness: based on validated claims algorithm for RA[5]; Patient Centered: patient reported functional ability, Health Assessment Questionnaire Disability Index (HAQ-DI) scores, total QALYs gained; DAS28: Disease Activity Score-28; CADI: Clinical Disease Activity Index; ACR: American College of Rheumatology Score

Figure 4. Economic Endpoints Reported in RA Studies

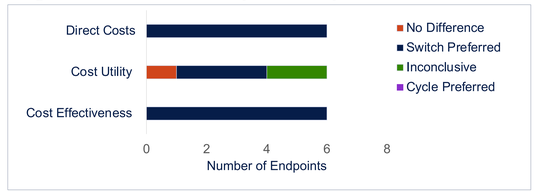
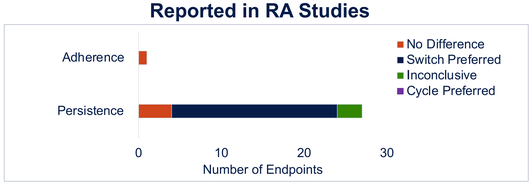


Figure 5. Medication Taking Behavior Endpoints Reported in RA Studies



Limitations

A risk of bias assessment was not completed as part of this review

Statistical analysis of endpoints was not performed as part of this review

The medications compared in many of the identified studies are not fully representative of the treatments approved for moderate-severe rheumatic conditions