«Συνδυαστική θεραπεία (Combination Targeted therapy) στις Σπονδυλαρθρίτιδες. Πού βρισκόμαστε;».

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Disclosures

None

Outline

- Background
- Systematic literature review (SLR) for Combination targeted therapy (CTT)
- CTT in SpA
- Consideration

Background (1)

- Immune mediated inflammatory diseases (IMID):
  - Rheumatoid arthritis (RA)
  - Psoriatic arthritis (PsA)
  - Axial spondyloarthritis (axSpA)
  - Crohn's disease (CD)
  - Ulcerative colitis (UC)
  - Psoriasis (PsO)

- Although, biologic (b) and targeted synthetic (ts) DMARDs are very effective in many patients, still **approximately 60%** of them are **unable to reach low disease activity status.**

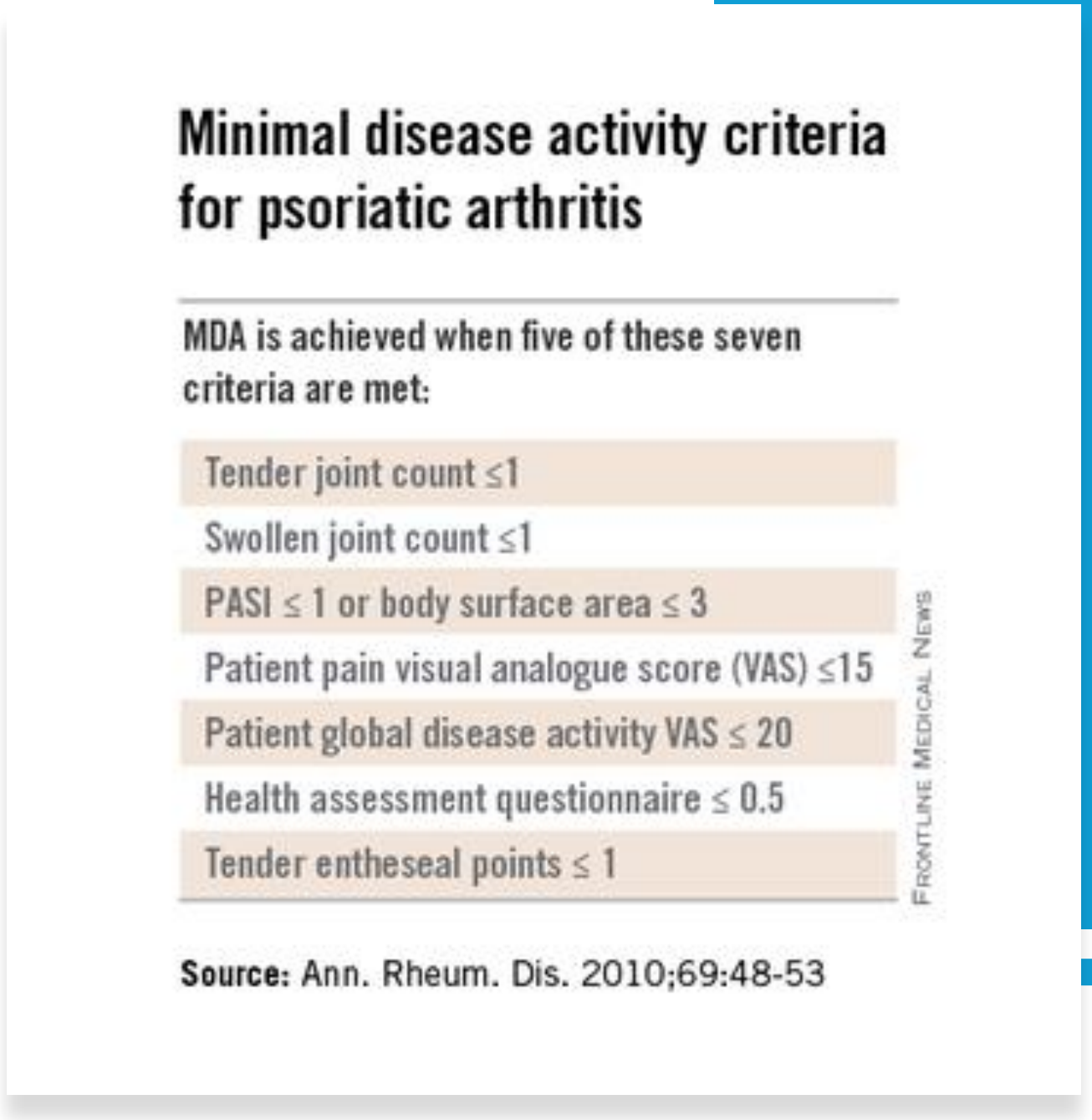
Zardin-Moraes M. et al. J Rheumatol. 2020.

Background (2)

- Prevalence of psoriatic arthritis patients achieving minimal disease activity in cross-sectional analyses is about 35%

Zardin-Moraes M. et al. J Rheumatol. 2020.

Minimal disease activity (MDA)



Minimal disease activity criteria for psoriatic arthritis

MDA is achieved when five of these seven criteria are met:

Tender joint count ≤1
Swollen joint count ≤1
PASI ≤ 1 or body surface area ≤ 3
Patient pain visual analogue score (VAS) ≤15
Patient global disease activity VAS ≤ 20
Health assessment questionnaire ≤ 0.5
Tender entheseal points ≤ 1

FRONTLINE MEDICAL NEWS

Source: Ann. Rheum. Dis. 2010;69:48-53

Difficult-to-treat/refractory Psoriatic arthritis

Rheumatology, 2024, **63**, 2427–2432
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Original Article

RHEUMATOLOGY

OXFORD

Clinical science

Identification and characteristics of patients with potential difficult-to-treat psoriatic arthritis: exploratory analyses of the Greek PsA registry

Konstantinos D. Vassilakis[1], Charalampos Papagoras[2], Nikolaos Fytanidis[2], Sousana Gazi[3], Evangelia Mole[3], Michael Krikelis[3], Paraskevi V. Voulgari[4], Evripidis Kaltsonoudis[4], Nikolaos Koletsos[4], Dimitrios Boumpas[5], Pelagia Katsimpri[5], Dimitrios Katsifis-Nezis[5], Theodoros Dimitroulas[6], Nikolaos Kougkas[6], Maria Boutel[6], Petros P. Sfikakis[1], Maria G. Tektonidou[1], Chrysoula Gialouri[1], Dimitrios Bogdanos[7], Theodora Simopoulou[7], Christos Koutsianas[8], Evgenia Mavrea[8], Gkikas Katsifis[9], Konstantinos Kottas[9], Maria Konsta[10], Matthoula Tziafalia[10], Evangelia Kataxaki[11], Eleni Kalavri[12], Kalliopi Klavdianou[12], Eleftheria P. Grika[13], Charalampos Sfontouris[13], Dimitrios Daoussis[14], George Iliopoulos[14], Ilias Bournazos[15], Dimitrios Karokis[15], Konstantinos Georganas[15], Dimos Patrikos[15], Dimitrios Vassilopoulos[8], George E. Fragoulis[1,16,*]

- About 15% of patients with Psoriatic arthritis are Difficult-to-treat (D2T)

Vassilakis et al (Rheumatology Oxford 2024)

Difficult-to-Manage Axial Spondyloarthritis

› Ann Rheum Dis. 2025 Feb 14:S0003-4967(25)00185-2. doi: 10.1016/j.ard.2025.01.035.
Online ahead of print.

The Assessment of SpondyloArthritis International Society (ASAS) Consensus-Based Expert Definition of Difficult-to-Manage, including Treatment-Refractory, Axial Spondyloarthritis

Denis Poddubnyy [1], Victoria Navarro-Compán [2], Murat Torgutalp [3], Suzanne Arends [4], Sibel Zehra Aydin [5], Simone Battista [6], Filip van den Bosch [7], Christine Bundy [8], Alberto Cauli [9], Jo Davies [10], Maxime Dougados [11], Tuncay Duruöz [12], Bassel El-Zorkany [13], Warren Fong [14], Floris van Gaalen [15], Rodrigo Garcia-Salinas [16], Marco Garrido Cumbrera [17], Pál Géher [18], Lianne Gensler [19], Simeon Grazio [20], Feng Huang [21], Mitsumasa Kishimoto [22], Robert Landewé [23], Ying Ying Leung [24], Pedro M Machado [25], Helena Marzo-Ortega [26], Bhowmik Meghnathi [27], Anna Molto [28], Elena Nikiphorou [29], Sofia Ramiro [15], Martin Rudwaleit [30], Carla G S Saad [31], Alexandre Sepriano [32], James Wei [33], Xenofon Baraliakos [34], Désirée van der Heijde [35]; ASAS

Affiliations + expand

PMID: 39955166 DOI: 10.1016/j.ard.2025.01.035

Figure. The ASAS Difficult-to-Manage Axial Spondyloarthritis Definition.

All three criteria must be present in a patient with axial spondyloarthritis diagnosed by a rheumatologist:

1. Treatment according to the ASAS-EULAR recommendations and failure of ≥2 b/tsDMARDs* with different mechanisms of action (unless contraindicated).**

2. Insufficient control of signs/symptoms of axSpA defined as ≥1 of the following:

a. High or very high disease activity (ASDAS ≥2.1);
b. Signs or symptoms suggestive of active disease (musculoskeletal or extra-musculoskeletal manifestations, elevated CRP***, active inflammation on MRI***);
c. Rapid radiographic spinal progression****;
d. Well-controlled disease according to the above-mentioned points (a-c), but still having axSpA symptoms that are causing a reduction in quality of life.

3. The present signs/symptoms are perceived as problematic by the rheumatologist and/or the patient.

**Including primary and secondary failure, as well as discontinuation because of side effects/intolerability/contraindications. Treatment failure but not discontinuation due to side effects/intolerability/contraindications is mandatory to conclude the presence of treatment-refractory disease.*
***Contraindications, which result in the inability to apply at least 2 b/tsDMARDs.*
****Objective signs of inflammatory activity (elevated CRP or active inflammation on MRI) are mandatory to conclude the presence of treatment-refractory disease.*
*****Defined as development of >2 new syndesmophytes/bony bridges in 2 years.*

ASAS: Assessment of Spondyloarthritis international Society, ASDAS: Axial Spondyloarthritis Disease Activity Score, axSpA: axial spondyloarthritis; bDMARDs: biologic disease-modifying antirheumatic drugs, CRP: C-reactive protein, EULAR: European Alliance of Associations for Rheumatology, MRI: magnetic resonance imaging, tsDMARDs: targeted synthetic disease-modifying antirheumatic drugs.

Is Combination targeted therapy (CTT) the solution?

Background (3)

- Combination targeted therapy (CTT) is the strategy of administering two b- or ts- DMARDs, with a different mechanism of action

- This approach has been used in the treatment of IMID

Background (4)

Indication for CTT:

- Refractory/ Difficult-to-manage disease
- Individuals with two diseases belonging to the same “spectrum” e.g. AxSpA and CD or UC – increased disease activity in one of the components

Background (5)

- Thus, there is a need about studies regarding CTT safety and efficacy among different immune mediated inflammatory diseases

- Most of the data are from inflammatory arthritis (RA, PsA, AxSpA) and IBD

CTT in bibliography

- Systematic literature review
- Title: "*Combination targeted therapy with two biologic/targeted synthetic DMARDs in 1200 patients with immune mediated inflammatory diseases. A Systematic Literature Review for current landscape in efficacy and safety*"

Objective of the study

- To present the current knowledge about efficacy and safety of combination targeted therapy in a wide range of IMID

Methods (1) - PICOs

Patient/intervention/comparator/outcome (PICO)-structure

P: adult patients (≥18 years old) with RA, PsA, AxSpA, CD, UC or PsO

I: receive, concomitantly or alternate, two or more b- or ts- DMARDs (including apremilast)

C: not applicable

O: efficacy (all outcomes were included as examined by the authors of the primary study) and safety (all adverse outcomes reported).

The SLR has been registered in PROSPERO (CRD42024583183).

Methods (2) – Search strategy

- PubMed, Scopus and Epistemonikos were searched from inception until June 1st 2024

- Multiple keywords were used
  - keywords: "inflammatory arthritis" OR "rheumatoid arthritis" OR "psoriatic arthritis" OR "axial spondyloarthritis" OR "axSpA" OR "non radiographic axial spondyloarthritis" OR “nr- axSpA” OR "inflammatory bowel disease" OR "crohn’s disease" OR "ulcerative colitis" OR "psoriasis" AND "dual therapy" OR "bispecific therapy" OR "bimodal Therapy" OR "dual treatment" OR "bispecific treatment" OR "bimodal treatment" OR "combination biologic" OR "combination targeted" OR "dual biologic" OR "dual targeted"

- Lack of definition for combination targeted therapy

Methods (3) - Inclusion & exclusion criteria

- Inclusion criteria were as defined in PICO

- Exclusion criteria: non-English literature, studies related to paediatric cases (<18 years-old), editorials, reviews, congress abstracts and studies based on non-approved for the disease given biologic or targeted synthetic DMARD

Case reports and case series were included

Methods (4) – Studies assessment

- Two blinded reviewers (AL, KDV)
- Titles and abstracts and subsequently the full-text articles
- Data extraction was performed by using a structured proforma sheet
- In case of disagreement, a third researcher (GEF) was consulted

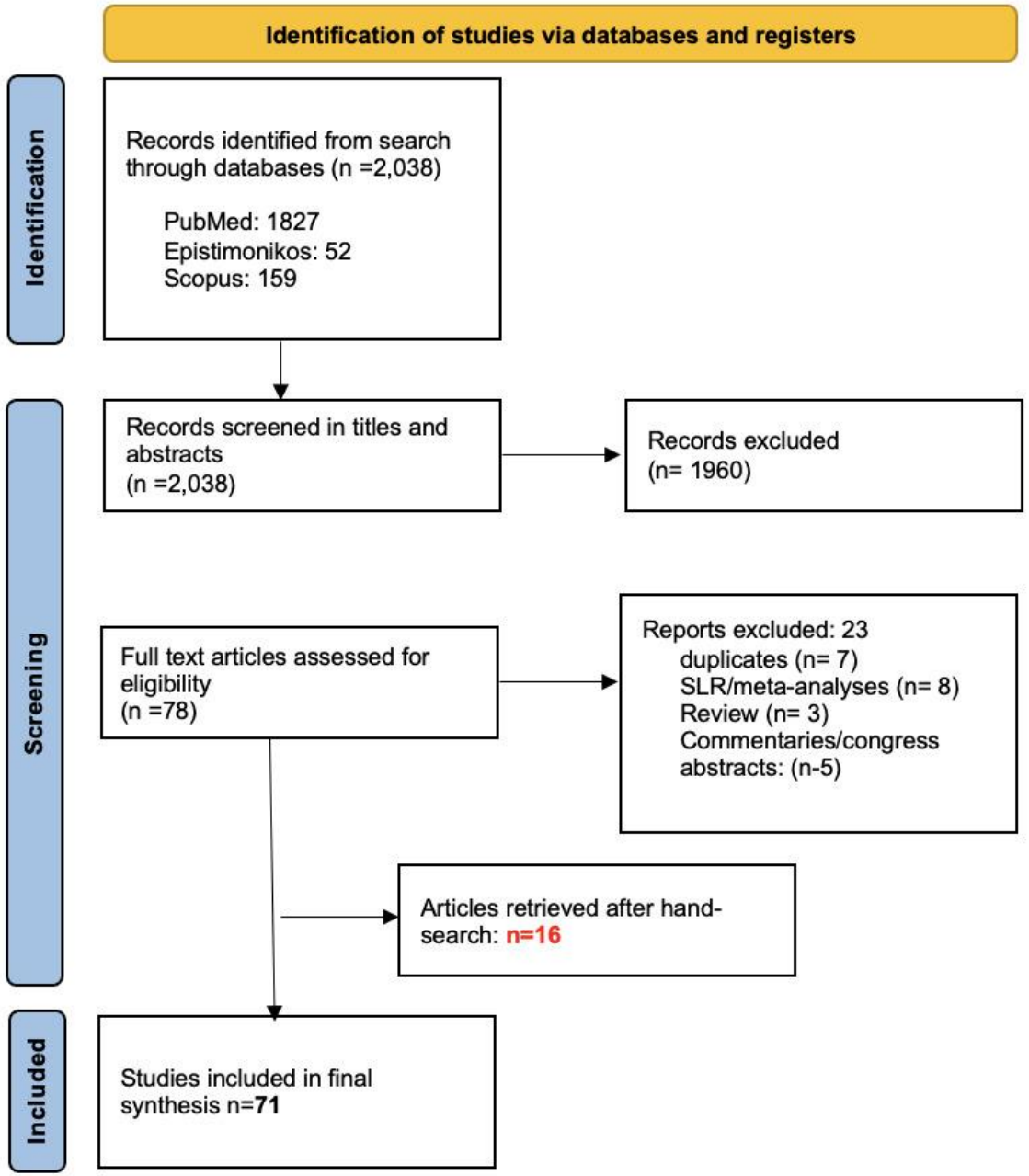
Methods (5) – Risk of Bias

- Newcastle-Ottawa (NOS) for observational studies
- Revised Cochrane risk-of-bias tool for randomized trials (RoB2) for RCTs
- JBI (Joanna Briggs Institute) critical appraisal checklist for case reports and case series

Results (1)

- 2,038 records were identified
- 71 studies were finally included after the elimination process (7 RCTs, 11 cohort studies, 22 case series, 31 case reports)
- A total of 1200 patients, **previously ineffectively treated** with one or more bDMARDs, were included

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Results (2) – Combination targeted therapy categories

- TNFi+IL/23i (n=21 studies/245 patients), TNFi+IL/17i (n=3 studies/66 patients),
- JAKi+any b/tsDMARDs (n=9 studies/55 patients)
- Vedolizumab+JAKi (n=6 studies/14 patients), Vedolizumab+TNFi (n=17 studies/163 patients), Vedolizumab+IL/23i (n=14 studies/48 patients), Vedolizumab+ IL/17i (n=1 study/ 2 patients), Vedolizumab+ Ocrelizumab (n=1 study/ 1 patient)
- Apremilast+any b/tsDMARDs (n=14 studies/87 patients), Abatacept+any b/tsDMARDs (n=3 studies/289 patients), Rituximab+any b/tsDMARDs (n=5 studies/219 patients), Anakinra or Canakinumab+ any b/tsDMARDs (n=2 studies/ 166 patients) IL/17i+IL/23i (n= 2 studies/ 4patients), TNFi+TNFi (1patient)

Results (3) – Risk of Bias

- RCTs: 85.7% were estimated to have a low RoB
- Observational cohort studies: 72.3% scored 7 or higher in NOS, indicating a low RoB
- On the JBI critical appraisal checklist, 72.7% of case series scored ≥8 'Yes' answers, while approximately 65% of case reports scored 7 or more

Overall acceptable risk of bias

Results (4) – TNF-inhibitors

- TNFi and IL/23i CTT
  - favorable outcomes in about 40-60% of patients with PsA, axSpA or IBD
  - safety profile comparable to that of the approval studies of these drugs as monotherapy

- TNFi and IL/17i CTT
  - major clinical improvement (defined as improvement >85% in DAPSA for PsA, change in ASDAS-CRP >2 for SpA) in approximately 65% of patients with PsA/axSpA (understudied safety profile)
  - safe in RA, but the additional benefit appeared to be limited (one RCT)

First author -Year	Disease	Combination	N	Age	Gender	DTT exposure months (median)	Previous bDMARDs	AEs	Outcomes			Withdrawals (reason)		RoB
									Lab	Clinical	Scores	AEs	Inefficacy	
S. Glatt -2019	RA	BMK+CTZ	52	53	45F, 7M	8	N.A.	78.8% AEs: 50% infections 15,4% skin disorders 1,9% SAE: psoas abscess, haematoma	CRP ratio to week 8 (Geo CV [%]): 0.43(2.6)	^	48,1%: ACR20, 32%: ACR50, 21,1%: ACR70. 50% DAS28-CRP<3.2 PtGADA mean change -31.0 (26.6)	7,7%	-	Low †
C. Valero -2022	SpA	SEC+GOL (2) SEC+ETN (2) SEC+ADA IXE+ADA	6	60	3F, 3M	11	2	16,7%: S. aureus bacteremia, admitted for liver decompensation	N.A.	50%: MCI§ 33,3%: C.REM§ 16,7%: Inefficacy	DAS28-CRP: 2.8 (median) ASDAS-CRP: 2 (median)	16,7%	-	≥6
C.V. Martinez -2023	SpA	SEC+GOL SEC+ETN	2	37	2M	53	6	-	N.A.	100% MCI *, LDA->remission*	N.A.	-	-	Low ▸
	PsA	SEC+ETN (2) SEC+GOL SEC+ADA BRO+GOL IXE+ADA	6	61,5	5F,1M	8,5	6,5	16,7% Staph. bacteriemia	N.A.	66,7%MCI **	N.A.	16,7%	33,3%: MSK activity ±	Low ▸

N: Number of combinations, DTT: Dual Targeted Therapy, bDMARDs: Biologic Disease-Modifying Anti-Rheumatic Drugs, AEs:Adverse Events, RoB: Risk of Bias, RA: Rheumatoid Arthritis, SpA: Spondyloarthritis, PsA Psoriatic Arthritis, CTZ: Certolizumab, BMK: Bimekizumab, SEC: Secukinumab, GOL: Golimumab, ETN: Etanecept, ADA:Adalimumab, IXE: Ixekizumab, BRO: Brodalumab, F: Female, M: Male, N.A.: Not Applicable, SAE: Serious Adverse Event, CRP: C Reactive Protein, MCI: Major Clinical Improvement, C.REM: Clinical Remission, LDA: Low Disease Activity, ACR20, ACR50, ACR70, American College of Rheumatology 20%, 50%, 70% improvement criteria. DAS28-CRP, Disease Activity Score-28 joints count-C Reactive Protein, PtGADA: Patient Global Assessment of Disease Activity, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C Reactive Protein, MSK: Musculoskeletal

§MCI: change in ASDAS-CRP >2 and in DAS-28-CRP >1.2. C.REM: ASDAS-CRP <1.3 or DAS-28-CRP <2.6 for axial or peripheral disease, respectively.

*MCI: change in ASDAS-CRP >2, Remission: ASDAS-CRP <1.3. **MCI: improvement >85% in DAPSA

±1/6: high psoriatic activity but low MSK activity at start of DTT, so the efficacy in MSK domain was not analyzed

^ placebo+BMK: larger reductions in mean PtGADA, placebo: larger reductions in mean SJC, TJC (SJC: swollen joint count, TJC: tender joint count)

† Low: Low Risk of Bias using Rob Revised Cochrane risk-of-bias tool for randomized trials (RoB 2), ≥6: ≥6 yes answers in JBI Critical Appraisal Checklist for case series,

▸ Low : Low risk of Bias usingNew Castle Ottawa quality assessment scale (NOS) (Score 8)

Figure-2: TNF- and IL/17-inhibitor CTT in immune mediated diseases

Results (5) – JAK-inhibitors

- JAKi and bDMARD CTT
  - significant improvement in about 50% of the patients with inflammatory arthritis (RA, PsA, axSpA) – data mainly from PsA
  - significant improvement in 60-80% of the patients IBD
  - no important safety issues

First author-Year	Disease	DTT	N	Age (median)	Gender	DTT exposure months (median)	Previous bDMARDs (median)	AEs	Outcomes			Withdrawal (reason)			RoB
									Lab/ Endoscopy	Clinical	Scores	AEs	Inefficacy	Other	
M. Shurey-2022	PsO/ PsA	TOFA +IXE (2) +RIS (1) +GUS(1) +UST (1) +SEC (1)	6	55	4F, 2M	11	3	16,7%: CL. Difficle	66,7% CRP<1.7 (33,3% N.A.)	Improvement: 33,3%: joints, enthesis/ dactylitis, skin 33,3%: joints, skin/ dactylitis 33,3%: skin 33,3% symptoms' resolution	100%: BSA≤1%§§	temporary TOFA discontinuation, restarted due to flare of disease	-	-	≥6§
M G.Hren-2024	PsO/PsA	UPA +GUS(2) +IXE (1) +BRD(1) DCR +IXE (2)	6	50s	4F,2M	9,3	5	16,7%: bronchitis	N.A.	100% PsA: MDA **	83,3% BSA 0% 16,7% BSA 5% (75% improved)	-	33,3%: PSO flared, switched to BMK	16,7% efficacy	≥6
N. S. Barroso-2018	1 PsA	TOFA +TOCI	6	56.5	F	10.83 (mean)	4.83 (mean)	*! 83.3% GI, 83.3% other 66,7% Infections 50% hyperlipidemia 50% CNS 33,3% skin 16,7%: hematologic 16,7% MSK 16,7% endocrine	N.A.	N.A.	worsened CDAI	tocixity*!	-	-	≥6
	5 RA	TOFA +TOCI (3) +ETN (1) +RTX(1)									60%: transient response: CDAI improvement of 7.5-13.5. 40% CDAI worsended	20% tocixity *!	40%	-	
J. W. Chen 2022	RA	TOFA +ADA	1	48	F	>12	5	-	RF:20iU/ml ESR:8mm/h CRP:1mg/L	CS discontinuation.	DAS28-ESR:2	-	-	-	≥7
S. D. Lee - 2022	CD	TOFA +UST (11) +VEDO (7) +CTZ(1)	19	41,2 (mean)	10F, 9M	9.6 (mean)	4	36,8% ≥ 1 AE: minor infection or worsening of CD symptoms 5,7% BCC	54.4%: EI 18.2%: ER 18.2%: EH# CRP 5.1±5.5 mg/L(mean) 75% normal	60%: C.REM 80%: C.RES$ 100% PG resolution 15,7%: elective surgery during followup ***	SESCD 6.5 ± 4.0 (mean)	-	10,5%	10,5% insurance 5,3% to determine if 1 can maintain C.RES	▸ Low
Y. Miyatani - 2023	CD*	UPA +UST	10	35,5	6F,4M	10	4	40% mild infection, 20% nausea 10%: SBO 10% acne	N.A.	Active CD: ‡ 83,3%: C.REM 16,7%: C.RES 75% (N=3) CS discontinuation. No surgery required active EIM: 75% joint pain improvment	N.A.	10% nausea	-	-	≥6
R. Gilmore-2021	UC	TOFA +INFL	5^	25	2F, 3M	9^	≥ 1	20% varicella zoster	40% E.REM median: CRP: 4,2 mg/L FCP: 106 mg/mL	60% CS free remission 20% moderate flare, responded to TOFA escalation, CS. No colectomy recquired	100% ≥3 reduction in Mayo score (Median: 3)	-	-	-	≥6
N. Li - 2023	CD, SpA	UPA +UST	1	61	F	N.A.	3	-	N.A.	spinal symptoms well controlled	BASDAI <1	-	-	-	≥7
C.V. Martínez-2023	IBD,SpA	TOFA +INFL	1	25	M	22	5	-	N.A.	MCI±	N.A.	-	-	-	▸ Low

Figure-3: JAK-inhibitors plus any bDMARD CTT

Results (6) - Vedolizumab

- Data from IBD in which vedolizumab is approved

- Vedolizumab and TNFi CTT
  - improvement in 30-50% of the cases
  - acceptable safety profile

- Vedolizumab and ustekinumab CTT
  - Ustekinumab even more efficacious compared to TNFi as add on therapy to vedolizumab
  - Potential signal for *c. difficile* infection – more data are needed

- Vedolizumab and JAKi CTT
  - Data are few to interpret

Results (7) - Rituximab

- Data from RA
- Rituximab and TNFi CTT
  - acceptable safety profile
  - Additional efficacy was not well demonstrated

Results (8) – Apremilast

- Data mainly from PsO
- Apremilast and bDMARD CTT
  - skin improvement
  - no additional safety concerns

  - **efficacy in musculoskeletal manifestations though is unknown**

Results (9) – Other combinations

- Combination of bDMARDs with abatacept or anakinra
  - does not seem to have any benefit in RA
  - **under-investigated in other diseases, in SpA**

- Few data for other combinations
  - e.g. IL/17i + IL/23i or TNFi + TNFi

Conclusion - SpA and CTT

- Numerous b/tsDMARDs combinations
  - ✓ improvement in about half of the treatment-refractory patients
  - ✓ no important safety issues
- Most of the studies from IBD and SpA
- In SpA: Data more robust for:
  - ➢ **TNFi + IL/23i**
  - ➢ **JAKi + any bDMARD**
- Vedolizumab + TNFi CTT on IBD
- More data are needed to improve knowledge on efficacy and safety of the combination of targeted therapies

Considerations (1)

- CTT: >2 b/tsDMARDs with different mechanism of action - What about combination of b/tsDMARDs from the same drug class i.e combination of two different TNFi or two different IL/17i

Considerations (2)

- Full or half dose of the second b/tsDMARDs? – no safety concerns so far, as most of the studies used full dose regimens

- Once disease control is achieved, should we withdraw one of the two b/tsDMARDs? If yes, which one of them?

Considerations (3) - same CTT in another disease

- A combination might not have worked for one disease IMID, but it could be beneficial has not been evaluated for another IMID
  - IL-17i plus TNFi not efficacious in RA; What about AxSpA or PsA?
  - IL-1i plus TNFi CTT did not show any significant improvements in RA; SpA and auto-inflammatory features?

Considerations (4)

- Other factors should also be taken into consideration:
  - Long-term safety
  - Cost-effectiveness

Limitations

- some data could not be extracted, as they were not provided in the primary studies
- Potentially patients who displayed adverse outcomes or studies with early termination were not reported/published and therefore not included in the SLR
- Limited duration of CTT in primary studies; no data on long term safety or evolution of patients after CTT discontinuation

Authors

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ΛΑΪΚΟ
ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

Thank you for your attention

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