«Δεδομένα από τη μείωση/διακοπή των φαρμάκων σε ασθενείς με αξΣπΑ σε ύφεση»

Ανδρέας Μπούνας

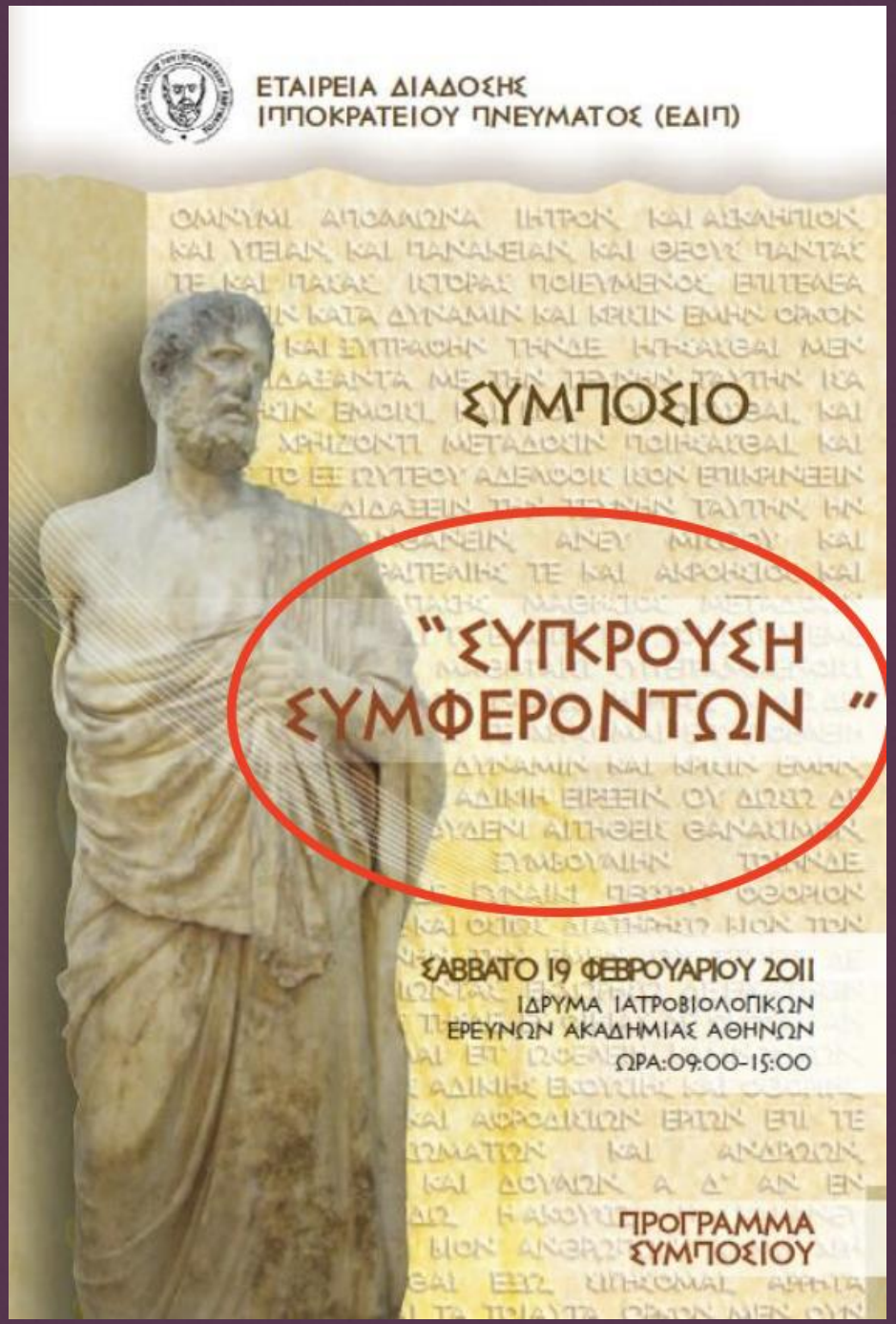
Ρευματολόγος

ΠΑΤΡΑ

16° ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ ΕΠΕΜΥ

με διεθνή συμμετοχή

3-6 ΟΚΤΩΒΡΙΟΥ 2024 Ξενοδοχείο Du Lac, ΙΩΑΝΝΙΝΑ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Εισαγωγή

- αξΣπΑ…εδώ και 2 δεκαετίες…η θεραπεία εξελίχθηκε σημαντικά !
- TNFi, IL-17Ai, JAKi
- Μείωση φλεγμονής, βελτίωση συμπτωμάτων, βελτίωση δεικτών ποιότητας ζωής, επιβράδυνση δομικών βλαβών

Danve A, Deodhar A. Treatment of axial spondyloarthritis: an update. Nat Rev Rheumatol. 2022; https://doi.org/10.1038/s41584-022-00761-z.

van der Heijde D, Baraliakos X, Hermann KA, Landewe RBM, Machado PM, Maksymowych WP. Limited radiographic progression and sustained reductions in MRI inflammation in patients with axial spondyloarthritis: 4-year imaging outcomes from the RAPID-axSpA phase III randomised trial. Ann Rheum Dis. 2018; https://doi.org/10.1136/annrheumdis-2017-212377.

Ho A, Younis I, Le QA. Impact of biologics on health-related quality of life in patients with ankylosing spondylitis: a systematic review and meta-analysis of randomized controlled trials. Semin Arthritis Rheum. 2022; https://doi.org/10.1016/j.semarthrit.2022.151996.

b-DMARDs

- Οφέλη …###…ανησυχία για ανεπιθύμητες ενέργειες
- Συχνό ερώτημα ασθενών (σε ύφεση)…η ΔΙΑΚΟΠΗ
- Έναρξη σε μικρή ηλικία ➔ αγωγή για 10ετίες ➔ Κόστος $$$ X 4

Curr Rheumatol Rep (2024) 26:155–163
https://doi.org/10.1007/s11926-024-01137-w

Walsh JA, Song X, Kim G, Park Y. Healthcare utilization and direct costs in patients with ankylosing spondylitis using a large U.S. administrative claims database. Rheumatol Ther. 2018; https://doi.org/10.1007/s40744-018-0124-4.

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Vol. 71, No. 10, October 2019, pp 1599–1613
DOI 10.1002/art.41042

American College of Rheumatology
Empowering Rheumatology Professionals

SPECIAL ARTICLE

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Michael M. Ward,[1] Atul Deodhar,[2] Lianne S. Gensler,[3] Maureen Dubreuil,[4] David Yu,[5] Muhammad Asim Khan,[6] Nigil Haroon,[7] David Borenstein,[8] Runsheng Wang,[9] Ann Biehl,[1] Meika A. Fang,[10] Grant Louie,[11] Vikas Majithia,[12] Bernard Ng,[13] Rosemary Bigham,[14] Michael Pianin,[15] Amit Aakash Shah,[16] Nancy Sullivan,[17] Marat Turgunbaev,[16] Jeff Oristaglio,[17] Amy Turner,[16] Walter P. Maksymowych,[18] and Liron Caplan[19]

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to the recommendations within this guideline to be voluntary, with the ultimate determination regarding their application to be

21. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).†	Very low	17
22. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.†	Moderate	18
RECOMMENDATIONS FOR ADULTS WITH STABLE AS		
23. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Low to moderate	1
24. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both treatments.	Very low	11
25. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both treatments.	Very low	12
26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Very low to low	66

26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.

Table 2. (*Cont'd*)

Recommendation	Level of evidence	PICO
27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low to low	65
28. In adults receiving treatment with an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	63
29. We strongly recommend treatment with physical therapy over no treatment with physical therapy.†	Low	19
31. We conditionally recommend advising unsupervised back exercises.†	Moderate	20
32. We conditionally recommend fall evaluation and counseling.†	Very low	51
33. We conditionally recommend participation in formal group or individual self-management education.†	Moderate	48
34. In adults with spinal fusion or advanced spinal osteoporosis, we strongly recommend against treatment with spinal manipulation.†	Very low	21
35. In adults with advanced hip arthritis, we strongly recommend treatment with total hip arthroplasty over no surgery.†	Very low	25
36. In adults with severe kyphosis, we conditionally recommend against elective spinal osteotomy.†	Very low	26

27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.

ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update

Sofia Ramiro ,[1,2] Elena Nikiphorou ,[1,3] Alexandre Sepriano ,[1,4] Augusta Ortolan ,[5] Casper Webers ,[6] Xenofon Baraliakos,[7] Robert B M Landewé ,[8,9] Filip E Van den Bosch ,[10,11] Boryana Boteva,[12] Ann Bremander,[13,14] Philippe Carron ,[10,11] Adrian Ciurea ,[15] Floris A van Gaalen ,[1] Pál Géher,[16] Lianne Gensler,[17] Josef Hermann,[18] Manouk de Hooge ,[10] Marketa Husakova,[19] Uta Kiltz ,[7] Clementina López-Medina ,[20,21] Pedro M Machado ,[22,23,24] Helena Marzo-Ortega,[25] Anna Molto ,[26] Victoria Navarro-Compán ,[27] Michael J Nissen ,[28] Fernando M Pimentel-Santos,[4] Denis Poddubnyy ,[29] Fabian Proft ,[29] Martin Rudwaleit ,[30] Mark Telkman,[31] Sizheng Steven Zhao ,[32] Nelly Ziade ,[33,34] Désirée van der Heijde [1]

Handling editor Josef S Smolen

For numbered affiliations see end of article.

Correspondence to

ABSTRACT

Objectives To update the Assessment of SpondyloArthritis international Society (ASAS)-EULAR recommendations for the management of axial spondyloarthritis (axSpA).

Methods Following the EULAR Standardised Operating

than immediate discontinuation of a bDMARD, can be considered in patients in sustained remission (#13). The last recommendations (#14, 15) deal with surgery and spinal fractures.

Conclusions The 2022 ASAS-EULAR recommendations provide up-to-date guidance on the management of

Ann Rheum Dis: first published as 10.1136/ard-2022-223296 on 21 October 2022. D

9	TNFi, IL-17i† or JAKi‡ should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start a TNFi or IL-17i†.	1a/A	9.2 (1.2)	94
10	If there is a history of recurrent uveitis or active IBD§, preference should be given to a monoclonal antibody against TNF¶ In patients with significant psoriasis, an IL-17i† may be preferred.	2b/B (uveitis, IBD) 1a/B (psoriasis)	9.1 (1.8)	97
11	Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities.	5/D	9.5 (0.8)	97
12	Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i†) or a JAKi‡ should be considered.	2b/B (TNFi after TNFi failure) 1b/A (IL-17i after TNFi failure) 5/D (all other switches)	9.3 (1.1)	88
13	If a patient is in sustained remission, tapering of a bDMARD can be considered.	1a/B (TNFi), 5/D (IL-17i)	9.1 (1.2)	82
14	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity.	4/C	9.5 (0.8)	97
15	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.	5/D	9.6 (0.9)	97

*Level of recommendation: level 1a, systematic review with homogeneity of RCTs; level 1b, individual RCT (with narrow CI); level 1c, all or none; level 2a, systematic review with homogeneity of cohort studies; level 2b, individual cohort study (including low-quality RCT); level 2c, 'outcomes' research, ecological studies; level 3a, systematic review (with homogeneity) of case–control studies; level 3b, individual case–control study; level 4, case series (and poor-quality cohort and case–control studies); level 5, expert opinion

13 If a patient is in sustained remission, tapering of a bDMARD can be considered.

†The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAKi: age over 65 years, current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events.
§In patients with active IBD, IL-17i are contraindicated.
¶This includes a pegylated Fab' fragment.
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; b/tsDMARDs, biological/targeted synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; GCs, glucocorticoids; IBD, inflammatory bowel disease; IL-17i, interleukin-17 inhibitors; JAKi, Janus

Recommendation

2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis

Désirée van der Heijde,[1] Sofia Ramiro,[1] Robert Landewé,[2,3] Xenofon Baraliakos,[4] Filip Van den Bosch,[5] Alexandre Sepriano,[1,6] Andrea Regel,[4] Adrian Ciurea,[7] Hanne Dagfinrud,[8] Maxime Dougados,[9,10] Floris van Gaalen,[1] Pál Géher,[11] Irene van der Horst-Bruinsma,[12] Robert D Inman,[13] Merryn Jongkees,[14] Uta Kiltz,[4] Tore K Kvien,[15] Pedro M Machado,[16] Helena Marzo-Ortega,[17,18] Anna Molto,[9,10] Victoria Navarro-Compàn,[19] Salih Ozgocmen,[20] Fernando M Pimentel-Santos,[21] John Reveille,[22] Martin Rudwaleit,[23,24,25] Jochen Sieper,[26] Percival Sampaio-Barros,[27] Dieter Wiek,[28] Jürgen Braun[4]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-210770).

For numbered affiliations see end of article

ABSTRACT

To update and integrate the recommendations for ankylosing spondylitis and the recommendations for the use of tumour necrosis factor inhibitors (TNFi) in axial spondyloarthritis (axSpA) into one set applicable to the full spectrum of patients with axSpA. Following the

INTRODUCTION

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease with a diverse clinical presentation.[1] Chronic back pain is the leading symptom of the disease and often inflammatory in nature with pronounced stiffness and improvement of pain and

6	Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated	5	D	8.8 (0.94) 100% ≥8
7	Glucocorticoid injections* directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids‡	2* 5‡	B* D‡	9.4 (0.78) 100% ≥8
8	Patients with purely axial disease should normally not be treated with csDMARDs§; sulfasalazine† may be considered in patients with peripheral arthritis	1a†	A	9.2 (0.78) 100% ≥8
9	bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (figure 1); current practice is to start with TNFi therapy	1a (TNFi); 1b (IL-17i)	A	9.6 (1.09) 93% ≥8
10	If TNFi therapy fails, switching to another TNFi* or IL-17i** therapy should be considered	2* 1b**	B* A**	9.6 (0.95) 97% ≥8
11	If a patient is in sustained remission, tapering of a bDMARD can be considered	2	B	9.1 (1.57) 97% ≥8
12	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity	4	C	9.4 (0.82) 100% ≥8
13	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed	5	D	9.9 (0.31) 97% ≥8

§1a (sulfasalazine; methotrexate); 1b (leflunomide); 4 other csDMARDs.
axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GoR, grade of recommendation; IL-17i, interleukin-17 inhibitor; LoA, level of agreement; LoE, level of evidence; NSAIDs, non-steroidal anti-inflammatory drugs; TNFi, tumour necrosis factor inhibitor.

can be assessed using the ASAS Health Index, which is based on the ICF.[46–48] As axSpA is an inflammatory disease, suppression of inflammation by drugs has a prominent place, in order to relieve symptoms, preserve physical function and maintain quality of life. And indeed, data have accrued that suggest a direct relation between clinical disease activity and syndesmo-

recommendations, the task force wanted to draw attention to the importance of non-pharmacological treatment by formulating it as an overarching principle.

4. Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the

The Current Evidence on Dose Tapering of bDMARDs in Axial Spondyloarthritis

- Αρχικά σειρές περιστατικών (case series) και
- μελέτες παρατήρησης (observational studies) → →→→→→ επιτυχημένο tapering

Lee J, Noh J-W, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. Clin Rheumatol 2010;29:1149–54.

Navarro-Compán V, Moreira V, Ariza-Ariza R, et al. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. Clin Rheumatol 2011;30:993–6.

Paccou J, BaclÉ-Boutry M-A, Solau-Gervais E, et al. Dosage adjustment of anti-tumor necrosis factor-α inhibitor in ankylosing spondylitis is effective in maintaining remission in clinical practice. J Rheumatol 2012;39:1418.

Breban M, Ravaud P, Claudepierre P, et al. Maintenance of infliximab treatment in ankylosing spondylitis: results of a one-year randomized controlled trial comparing systematic versus on-demand treatment. Arthritis Rheum 2008;58:88–97.

RCT Pts με axSpA σε ύφεση υπό etanercept

➔ standard dose treatment vs spacing of the dose interval

➔ follow-up of 22 months

➔ 90% Pts διατηρούσαν ύφεση

Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. Biologics. 2013; https://doi.org/10.2147/BTT.S31474.

Definition of terms

- **Tapering**

  - επιμήκυνση μεσοδιαστημάτων χορήγησης του φαρμάκου (spacing)

  - μείωση χορηγούμενης δόσης

- **Stepwise tapering** - σταδιακή μείωση της δόσης (multiple steps)

- **Instant tapering** - απευθείας μείωση (one single step)

Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice

Casper Webers[a,b,*], Elena Nikiphorou[c,d,e], Annelies Boonen[a,b], Sofia Ramiro[e,f]

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Review

Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice

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[a] Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, Maastricht, The Netherlands
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[c] Department of Rheumatology, King's College Hospital, London, United Kingdom
[d] Centre for Rheumatic Diseases, King's College London, London, United Kingdom
[e] Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands
[f] Department of Rheumatology, Zuyderland Medical Centre, Heerlen, The Netherlands

Table 1
Randomized controlled trials investigating tapering of bDMARDs in axSpA.

Strategy Study	Drug(s)	Population	Tapering entry criteria[a]	Induction[b]	Intervention *Comparator*	N	Time (wks)[c]	Outcome definition	Outcome	Tapering success[d]
Spacing										
Lukas, 2021 [11]	ADA, CZP, ETN, GOL, IFX	axSpA	BASDAI < 4 for ≥ 6m	No	TNFi spacing *Standard-dose TNFi*	197 201	52	BASDAI < 4 at 52w (non-inferiority)	88.0% 91.5%	+
Cantini, 2013 [6]	ETN	r-axSpA	BASDAI < 4, no PD or uveitis, CRP/ESR ≤ ULN	Yes (2y)	ETN 50 mg Q2W *Standard-dose ETN*	22 21	91–95	Maintain remission (see entry criteria)	86.3% 90.4%	+
Li, 2016 [8]	ETN	r-axSpA + hip involvement	None reported	Yes (4w)	ETN 25 mg QW *Standard-dose ETN*	26 17	8	BASDAI at 8w	1.42 1.40	+
Ruwaard, 2022 [13]	ETN	r-axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	ETN spacing[i] *Standard-dose ETN*	20 20	26	Maintain remission (ASDAS < 2.1)	55.0% 65.0%	+
C-OPTIMISE [15]	CZP	axSpA (early)	ASDAS < 1.3 at 32/36w and 48w of induction	Yes (48w)	CZP 200 mg Q4W *Standard-dose CZP*	105 104	48	Absence of flare[f]	79.0% 83.7%	NR
GO-BACK [16]	GOL	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	GOL 50 mg Q2M *Standard-dose GOL*	64 63	52	Absence of flare[f]	68.3% 84.1%	–
BIODOPT[g] [14]	ADA, CZP, ETN, GOL, IFX	axSpA[g]	Remission/LDA (not specified) for ≥ 12m	No	TNFi spacing *Daily practice TNFi*	95 47	78	Superiority: dose ≥ 50% reduced at 78w Equivalence: ASDAS at 78w	36.8% 2.1% 1.75 1.84	+ +

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Randomized controlled trials investigating tapering of bDMARDs in axSpA.

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Administered dose reduction										
ANSWERS [7]	ETN	r-axSpA	BASDAI 50% or ≥ 2 unit decrease, and spinal pain ≥ 2 unit decrease	Yes (26w)	ETN 25 mg QW *Standard-dose ETN (50 mg QW)*	23 24	26	Maintain response (see entry criteria, non-inferiority)	52.2% 83.3%	–
Combined[h]										
REDES-TNF [9]	ADA, ETN, GOL, IFX	axSpA	BASDAI ≤ 2, no PD, CRP ≤ ULN for ≥ 6m	No	TNFi tapering *Standard-dose TNFi*	55 58	52	BASDAI, PhGA. PtGA, night pain < 4 at 52w (non-inferiority)	81.3% 83.3%	+
DRESS-PS [12]	ADA, CZP, ETN, GOL, IFX	axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	T2T with tapering[i] *T2T without tapering*	39 19	52	ASDAS < 2.1 at 52w (non-inferiority)	66.7% 73.7%	+
Zhang, 2020 [10]	ETN[j]	r-axSpA	Group A: ASDAS < 1.3	Yes (12w)	Group A: Stepwise ETN tapering *ETN discontinuation*	106 36	36	Absence of flare[f]	91.0% 68.2%	+
			Group B: 1.3 ≤ ASDAS < 2.1		Group B: Stepwise ETN tapering Delayed ETN tapering *ETN discontinuation*	53 19 21	36	Absence of flare[f]	83.3% 68.7% 57.1%	–

after tapering (tapering to discontinuation, see "Effectiveness of discontinuation" below) [15,16].

Overall, the findings of these RCTs suggest that tapering of TNFi is possible, i.e. not inferior to standard-dose continuation, for maintaining response. The risk of relapse was often comparable in those who taper and those who do not (Table 1) [6,8,9,11–15]. These favourable results have been observed in both r-axSpA and nr-axSpA. Most studies used spacing as tapering method, which can be explained by the mode of administration of TNFi. For subcutaneously administered TNFi (adalimumab [ADA], certolizumab pegol [CZP], etanercept [ETN], golimumab [GOL]), spacing allows for a more pragmatic implementation, as it does not require changes to preparation of prefilled syringes. For intravenously administered TNFi (infliximab [IFX]), however, administered dose reduction is a more efficient way to maintain a minimal effective concentration [18].

Interestingly, in the only trial that strictly used reduction of

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Tapering…

- Οι περισσότερες RCTs → “spacing” → ΥΔ – SC inj
- Πιο ρεαλιστική εφαρμογή (για προγεμισμένες πένες, σύρριγγες)

- Για ΕΦ – IV → μείωση δόσης κυρίως (για διατήρηση ελάχιστης συγκέντρωσης)

Fautrel B, Den Broeder AA. De-intensifying treatment in established rheumatoid arthritis (RA): why, how, when and in whom can DMARDs be tapered? Best Pract Res Clin Rheumatol 2015;29:550–65.

- ANSWERS (50% ETN dose) → tapering was inferior !!!

Table 1
Randomized controlled trials investigating tapering of bDMARDs in axSpA.

Strategy Study	Drug(s)	Population	Tapering entry criteria[a]	Induction[b]	Intervention *Comparator*	N	Time (wks)[c]	Outcome definition	Outcome	Tapering success[d]
Administered dose reduction										
ANSWERS [7]	ETN	r-axSpA	BASDAI 50% or ≥ 2 unit decrease, and spinal pain ≥ 2 unit decrease	Yes (26w)	ETN 25 mg QW *Standard-dose ETN (50 mg QW)*	23 24	26	Maintain response (see entry criteria, non-inferiority)	52.2% 83.3%	–
Combined[h]										
REDES-TNF [9]	ADA, ETN, GOL, IFX	axSpA	BASDAI ≤ 2, no PD, CRP ≤ ULN for ≥ 6m	No	TNFi tapering *Standard-dose TNFi*	55 58	52	BASDAI, PhGA. PtGA, night pain < 4 at 52w (non-inferiority)	81.3% 83.3%	+
DRESS-PS [12]	ADA, CZP, ETN, GOL, IFX	axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	T2T with tapering[i] *T2T without tapering*	39 19	52	ASDAS < 2.1 at 52w (non-inferiority)	66.7% 73.7%	+
Zhang, 2020 [10]	ETN[j]	r-axSpA	Group A: ASDAS < 1.3	Yes (12w)	Group A: Stepwise ETN tapering *ETN discontinuation*	106 36	36	Absence of flare[f]	91.0% 68.2%	+
			Group B: 1.3 ≤ ASDAS < 2.1		Group B: Stepwise ETN tapering Delayed ETN tapering *ETN discontinuation*	53 19 21	36	Absence of flare[f]	83.3% 68.7% 57.1%	–

ANSWERS…(ενστάσεις)

- ΟΧΙ σταθερά σε ύφεση (πχ 6 μήνες) !
- Αρκούσε…1 φορά μόνο να πετύχουν ύφεση !!???
- (Το tapering [εδώ] → …κατώτερο)

Yates M, Hamilton LE, Elender F, et al. Is etanercept 25 mg once weekly as effective as 50 mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. J Rheumatol 2015;42:1177.

ANSWERS…(μηνύματα)

- Χρειάζεται ικανός χρόνος του ασθενή σε ύφεση…για επιτυχημένο tapering!!!

- Καλύτερο το …Stepwise tapering (σταδιακή μείωση της δόσης) (multiple steps) από το… Instant tapering

Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice

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Σχήματα tapering

- Παλαιότερες μελέτες ←→ single-step approach
- Οι νεώτερες ←→ stepwise tapering
- συχνά… disease-activity guided

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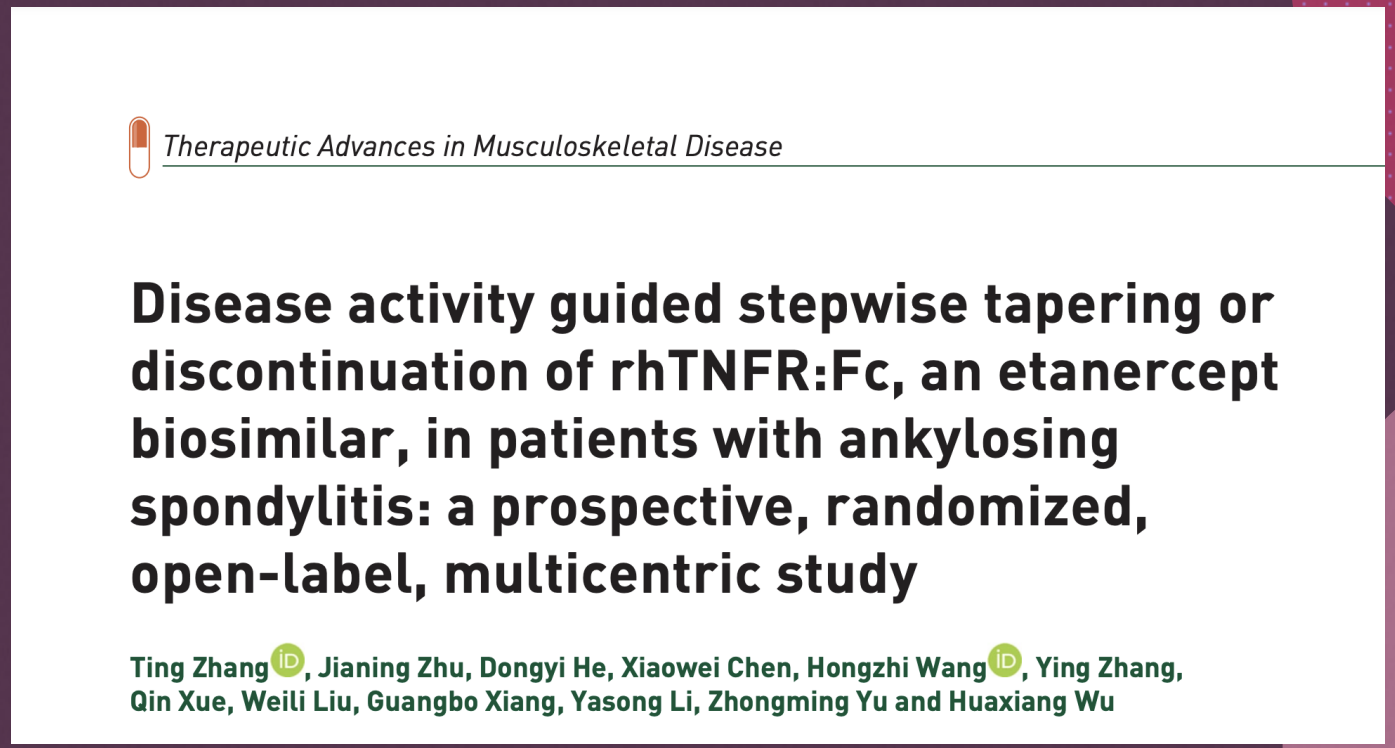
Μελέτη DRESS-PS

- Προκαθορισμένο πρωτόκολλο για tapering…
- Next step…μόνο αν διατηρούνταν η ύφεση ή η χαμηλή ενεργότητα
- Μετακίνηση στο προηγούμενο σκαλί αν συνέβαινε έξαρση
- Πλεονέκτημα: …“often regain control, while still maintaining some degree of tapering”
- Such schemes also allow for a more personalized approach.

Michielsens CA, den Broeder N, van den Hoogen FH, et al. Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial. Ann Rheum Dis 2022;81:1392–9.

Μελέτη Zhang (2020)

- Μείωση δόσης & Spacing (στην ίδια μελέτη) !!!



Therapeutic Advances in Musculoskeletal Disease

Disease activity guided stepwise tapering or discontinuation of rhTNFR:Fc, an etanercept biosimilar, in patients with ankylosing spondylitis: a prospective, randomized, open-label, multicentric study

Ting Zhang, Jianing Zhu, Dongyi He, Xiaowei Chen, Hongzhi Wang, Ying Zhang, Qin Xue, Weili Liu, Guangbo Xiang, Yasong Li, Zhongming Yu and Huaxiang Wu

Table 1
Randomized controlled trials investigating tapering of bDMARDs in axSpA.

Strategy Study	Drug(s)	Population	Tapering entry criteria[a]	Induction[b]	Intervention *Comparator*	N	Time (wks)[c]	Outcome definition	Outcome	Tapering success[d]
Administered dose reduction										
ANSWERS [7]	ETN	r-axSpA	BASDAI 50% or ≥ 2 unit decrease, and spinal pain ≥ 2 unit decrease	Yes (26w)	ETN 25 mg QW *Standard-dose ETN (50 mg QW)*	23 24	26	Maintain response (see entry criteria, non-inferiority)	52.2% 83.3%	–
Combined[h]										
REDES-TNF [9]	ADA, ETN, GOL, IFX	axSpA	BASDAI ≤ 2, no PD, CRP ≤ ULN for ≥ 6m	No	TNFi tapering *Standard-dose TNFi*	55 58	52	BASDAI, PhGA. PtGA, night pain < 4 at 52w (non-inferiority)	81.3% 83.3%	+
DRESS-PS [12]	ADA, CZP, ETN, GOL, IFX	axSpA[e]	ASDAS < 2.1 for ≥ 6m	No	T2T with tapering[i] *T2T without tapering*	39 19	52	ASDAS < 2.1 at 52w (non-inferiority)	66.7% 73.7%	+
Zhang, 2020 [10]	ETN[j]	r-axSpA	Group A: ASDAS < 1.3	Yes (12w)	Group A: Stepwise ETN tapering *ETN discontinuation*	106 36	36	Absence of flare[f]	91.0% 68.2%	+
			Group B: 1.3 ≤ ASDAS < 2.1		Group B: Stepwise ETN tapering Delayed ETN tapering *ETN discontinuation*	53 19 21	36	Absence of flare[f]	83.3% 68.7% 57.1%	–

Disease activity guided stepwise tapering or discontinuation of rhTNFR:Fc, an etanercept biosimilar, in patients with ankylosing spondylitis: a prospective, randomized, open-label, multicentric study

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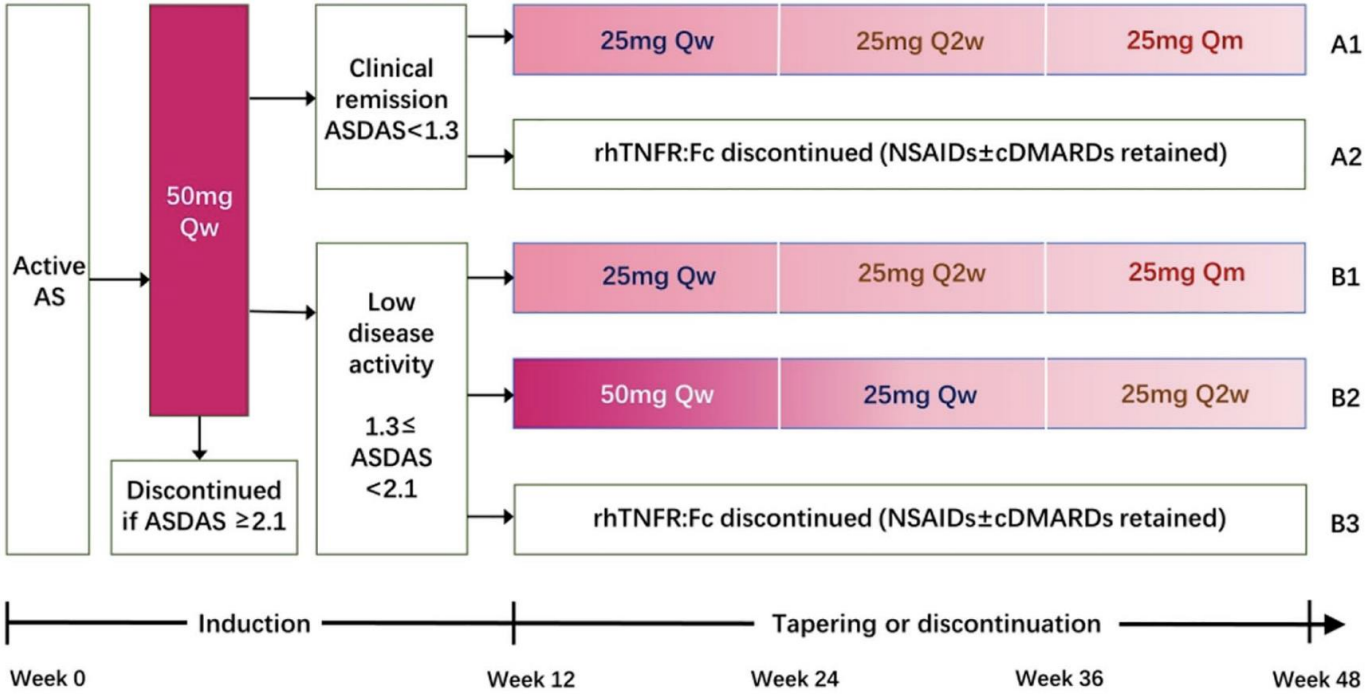

Figure 1. Study design.
Patients with AS enrolled were treated with rhTNFR:Fc 50 mg subcutaneously each week for 12 weeks, and then randomized into subgroups with different tapering or discontinuation strategies according to the ASDAS at the end of week 12.
AS, ankylosing spondylitis; ASDAS, ankylosing spondylitis disease activity score; cDMARDs, conventional disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; Q2w, each two weeks; Qm, each month; Qw, each week.

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Randomized controlled trials investigating tapering of bDMARDs in axSpA.

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					ETN discontinuation	36			68.2%	
			Group B: 1.3 ≤ ASDAS < 2.1		Group B: Stepwise ETN tapering	53	36	Absence of flare[f]	83.3%	–
					Delayed ETN tapering	19			68.7%	
					ETN discontinuation	21			57.1%	

ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IFX: infliximab; LDA: low disease activity; M/m: months; NR: not reported (not formally tested); PD: peripheral disease; ULN: upper limit of normal; W/w: weeks; Y/y: years.

[a] Eligibility criteria for patients to be included in (tapering phase of) the trial.

[b] Induction phase with (open-label) treatment as part of trial.

[c] Time in weeks from start of tapering (excluding induction phase, if applicable).

[d] Result of statistical analysis, interpretation: (+) = tapering non-inferior to comparator, or comparator not superior to tapering; (–) = tapering inferior to comparator or comparator superior to tapering (depending on design)..

[e] Study also included patients with PsA (DRESS-PS), or RA and PsA (Ruwaard); randomisation was stratified by diagnosis, and results shown here are for the axSpA subgroup only.

[f] Flare defined as: ASDAS ≥ 2.1 at two consecutive visits or ASDAS > 3.5 at any visit (C-OPTIMISE), ASDAS ≥ 2.1 at two consecutive visits or ASDAS increase ≥ 1.1 at any visit (GO-BACK), ASDAS > 2.1 at any point (Zhang). For C-OPTIMISE, no formal statistical comparison was made between the reduced dose and full dose arms.

[g] Study also included patients with RA or PsA; randomisation was stratified by diagnosis, and results shown here are for the overall population only (axSpA subgroup results not yet published).

[h] Strategies used: REDES-TNF: spacing for ADA/ETN/GOL, spacing and administered dose reduction for IFX. Zhang: initial reduction of administered, followed by spacing. DRESS-PS: spacing for ADA/CZP/ETN/GOL, administered dose reduction for IFX.

[i] Trial allowed for complete discontinuation (see Tables 2 and 3).

[j] ETN biosimilar (Yisaipu).

Προβλήματα σχεδιασμού μελετών για tapering σε axSpA

- Most trials on bDMARD tapering in axSpA were not blinded
- except for C-OPTIMISE and GO-BACK
- *Zhang et al.:* no full-dose continuation arm was included for reference

Landewe RB, van der Heijde D, Dougados M, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis 2020;79:920–8.
Merck S, Dohme LLC. Golimumab (MK-8259 SCH900259) treatment withdrawal in participants with non-radiographic axial spondyloarthritis (GO-BACK) (MK-8259-038). https://ClinicalTrials.gov/show/NCT032537962021.

Tapering - Ερωτήματα

- Ποιό σχήμα tapering είναι καλύτερο;
- Πότε ;;; (η έναρξη του tapering)
- Ποιά είναι η καταλληλότερη μείωση δόσης;
  (most trials, often ≥ 50% of full dose.)
- → Δύσκολη Απάντηση (Ετερογένεια μεταξύ των μελετών)

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The Current Evidence on Discontinuation of bDMARDs in Axial Spondyloarthritis

- (Ιστορικά, post-hoc) σε μελέτες TNFi… οι ασθενείς διέκοπταν την αγωγή… μετά την ολοκλήρωση της μελέτης
- Υποτροπή στις 48 wks …69% έως 98%
- (όμως δεν υπήρχε ομάδα σύγκρισης)

Baraliakos X, Listing J, Brandt J, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:R439.

Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48:1667–75.

Haibel H, Heldmann F, Braun J, et al. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. Arthritis Rheum 2013;65:2211–3.

Sieper J, Lenaerts J, Wollenhaupt J, et al. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2. Ann Rheum Dis 2014;73:108.

Song I-H, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2-year data of the ESTHER trial. Ann Rheum Dis 2012;71:1212.

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Table 3
Randomized/clinical controlled trials investigating discontinuation of bDMARDs in axSpA.

Strategy Study	Population	Discontinuation criteria[a]	Induction[b]	Intervention *Comparator*	*n*	Time (wks)[c]	Outcome (definition)	Outcome (%)	Discontinuation success[d]
Instant discontinuation									
ABILITY-3 [29]	nr-axSpA	ASDAS < 1.3 at 16–28w of induction	Yes (28w)	PBO Q2W (ADA stop)	153	40	Absence of flare[e]	47.1	–
				Continue ADA 40 mg Q2W	152			70.4	
C-OPTIMISE [15]	axSpA (early)	ASDAS < 1.3 at 32w/36w and 48 w of induction	Yes (48w)	PBO Q2 W (CZP stop)	104	48	Absence of flare[e]	20.2	–
				Continue CZP 200 mg Q2W[f]	104			83.7	
RE-EMBARK [30]	nr-axSpA	ASDAS < 1.3 at 24w of induction	Yes (24w)	ETN stop (no PBO)	119	40	Absence of flare[e]	25.2	–
				Continue ETN (EMBARK)	NR			> 75	
GO-BACK [16]	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	PBO QM (GOL stop)	63	52	Absence of flare[e]	33.9	–
				Continue GOL 50 mg QM[f]	62			84.1	
COAST-Y [31]	axSpA	ASDAS < 1.3 at 16w/20w of induction, and < 2.1 at both	Yes (24w)	PBO Q2W	53	40	Absence of flare[e]	54.7	–
				Continue IXE 80 mg Q2/4W[g]	100			83.3	

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Strategy Study	Population	Discontinuation criteria[a]	Induction[b]	Intervention *Comparator*	*n*	Time (wks)[c]	Outcome (definition)	Outcome (%)	Discontinuation success[d]
Tapering to discontinuation[h]									
DRESS-PS [12]	axSpA[g]	ASDAS < 2.1 ≥ 6m pre-tapering, and maintained while tapering	No	T2T with TNFi tapering	39	52	No bDMARD use at 52w	20.5	NR
				T2T without TNFi tapering	19			5.3	
Ruwaard, 2022 [13]	r-axSpA[g]	ASDAS < 2.1 ≥ 6m pre-tapering, and maintained while tapering	No	ETN spacing → stop	20	26	No bDMARD use at 26w	14.3[i] (overall)	NR
				Continue ETN → spacing → stop	20				

ADA: adalimumab; CZP: certolizumab pegol; ETN: etanercept; GOL: golimumab; IXE: ixekizumab; M/m: months; NR: not reported; PBO: placebo; W/w: weeks.

[a] Eligibility criteria for patients to discontinue bDMARD.

[b] Induction phase with (open-label) treatment as part of trial.

[c] Time in weeks from start of discontinuation (excluding induction phase).

[d] Result of statistical analysis, interpretation: (+) = discontinuation non-inferior or superior to continuation; (−) = discontinuation inferior to continuation; (NR) = no formal (statistical) comparison.

[e] Flare defined as: ASDAS ≥ 2.1 at two consecutive visits (ABILITY-3), ASDAS ≥ 2.1 at two consecutive visits or ASDAS > 3.5 at any visit (C-OPTIMISE, COAST-Y), ASDAS ≥ 2.1 at any visit (RE-EMBARK), ASDAS ≥ 2.1 at two consecutive visits or ASDAS increase ≥ 1.1 at any visit (GO-BACK).

[f] Study also included a third arm with reduced dose (CZP 200 mg Q4W for C-OPTIMISE; GOL 50 mg Q2M for GO-BACK), which was formally only compared against the

Instant discontinuation of bDMARDs

- 55-80% υποτροπή…. (median time to flare 16 weeks)
- Vs 16-30% (those who continued)
- Ανεξαρτήτως …υπότυπου νόσου, σταδίου, φαρμάκου

Landewe R, Sieper J, Mease P, et al. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018;392:134–44.

Van Den Bosch F, Wei JCC, Nash P, et al. Etanercept withdrawal and re-treatment in patients with inactive non-radiographic axial spondyloarthritis at 24 weeks: results of re-embark, an open-label, phase iv trial. Ann Rheum Dis 2020;79:70.

Landewe RB, van der Heijde D, Dougados M, et al. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis 2020;79:920–8.

Merck S, Dohme LLC. Golimumab (MK-8259 SCH900259) treatment withdrawal in participants with non-radiographic axial spondyloarthritis (GO-BACK) (MK-8259-038). https://ClinicalTrials.gov/show/NCT032537962021.

C-OPTIMISE and GO-BACK

- Οι 2 ανωτέρω μελέτες → Instant tapering (50% dose)…και instant discontinuation
- Tapering … καλύτερο από…instant discontinuation

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C-OPTIMISE [15]	CZP	axSpA (early)	ASDAS < 1.3 at 32/36w and 48w of induction	Yes (48w)	CZP 200 mg Q4W *Standard-dose CZP*	105 104	48	Absence of flare[f]	79.0% 83.7%	NR
GO-BACK [16]	GOL	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	GOL 50 mg Q2M *Standard-dose GOL*	64 63	52	Absence of flare[f]	68.3% 84.1%	–

Table 3
Randomized/clinical controlled trials investigating discontinuation of bDMARDs in axSpA.

Strategy Study	Population	Discontinuation criteria[a]	Induction[b]	Intervention *Comparator*	*n*	Time (wks)[c]	Outcome (definition)	Outcome (%)	Discontinuation success[d]
Instant discontinuation									
C-OPTIMISE [15]	axSpA (early)	ASDAS < 1.3 at 32w/36w and 48 w of induction	Yes (48w)	PBO Q2 W (CZP stop)	104	48	Absence of flare[e]	20.2	–
				Continue CZP 200 mg Q2W[f]	104			83.7	
RE-EMBARK [30]	nr-axSpA	ASDAS < 1.3 at 24w of induction	Yes (24w)	ETN stop (no PBO)	119	40	Absence of flare[e]	25.2	–
				Continue ETN (EMBARK)	NR			> 75	
GO-BACK [16]	nr-axSpA (early)	ASDAS < 1.3 at 7m and 10m of induction	Yes (10 m)	PBO QM (GOL stop)	63	52	Absence of flare[e]	33.9	–
				Continue GOL 50 mg QM[f]	62			84.1	

Important considerations when interpreting these studies.(I)

- open-label induction φάσεις…σύντομες 24 έως48 εβδ
  (This might have negatively affected the flare rates)
- 20 – 50% πού διέκοψαν… 1 έτος μετά είχαν ύφεση !!
- Παρά το ρίσκο…σε συγκεκριμένους υποπληθυσμούς η διακοπή αγωγής…ίσως βιώσιμη

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Important considerations when interpreting these studies.(II)

- Ισως ένα αργό tapering…πριν την διακοπή…έχει καλύτερα αποτελέσματα (Ruwaard trial and DRESS-PS)

- Μεγαλύτερη διάρκεια ύφεσης πριν την έναρξη μείωσης και την διακοπή ;;;

- « ...Interestingly, the observed rates of successful discontinuation were

  notably higher for RA/PsA compared to axSpA… »

Michielsens CA, den Broeder N, van den Hoogen FH, et al. Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial. Ann Rheum Dis 2022;81:1392–9.
Ruwaard J, L'Ami MJ, Kneepkens EL, et al. Interval prolongation of etanercept in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a randomized controlled trial. Scand J Rheumatol 2022:1–8.

Safety of tapering and discontinuation

- Meta-analyses of RCTs in RA and axSpA did not observe statistically significant differences in odds for serious adverse events, serious infections, malignancies, cardiovascular events or death for tapering/discontinuation compared with continuation

- Overall, although it seems biologically plausible that tapering and discontinuation reduce the rate of adverse events, the currently available evidence does not clearly show this.

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Πότε και **σε ποιόν**;…tapering or discontinuation ?

- ASAS-EULAR 2022 →

  →Ασθενείς σε σταθερή κατάσταση (ύφεση ή LDA) at least **6ms**

  (όμως… expert opinion) !!!

ASDAS previously mentioned, ASDAS inactive disease or low disease activity could be used here. 'Sustained' has not been defined either, but the task force considered it appropriate to emphasise that before starting to taper treatment, a patient

should be in remission for a minimum period and that period should be (arbitrarily) at least 6 months. Existing data on tapering were restricted to TNFi.[13] For IL-17i, there was only one study with withdrawal of ixekizumab leading to a high proportion of flares and no data on withdrawal or tapering of JAKi.[13 14 140]

Recommendation 13

If a patient is in sustained remission, tapering of a bDMARD can be considered.

An accumulating body of evidence shows that abrupt bDMARD withdrawal may lead to a high proportion of flares, while tapering was shown to be successful in maintaining treatment response.[13 18 135–138] One double-blind trial with certolizumab in axSpA compared all three possible actions (continuing vs tapering vs stopping) directly and showed a significantly lower risk of flare for those who continued or tapered, compared with those who stopped.[139] Tapering has been mostly studied through spacing drug administration.[13] Although sustained remission has not been formally defined, in line with the advantages of the ASDAS previously mentioned, ASDAS inactive disease or low disease activity could be used here. 'Sustained' has not been defined either, but the task force considered it appropriate to emphasise that before starting to taper treatment, a patient

- in a large observational study the probability of inactive disease after one year with tapering was comparable to full dose if tapering was started if in remission, but lower if started in (non-remission) low disease activity

- **➔ ΥΦΕΣΗ καλύτερη από LDA**

Park JW, Kim HA, Shin K, et al. Effects of tapering tumor necrosis factor inhibitor on the achievement of inactive disease in patients with axial spondyloarthritis: a nationwide cohort study. Arthritis Res Ther 2019;21:163.

Σε ποια χρονική στιγμή (της ύφεσης) ;;;

- One post-hoc analysis found that the risk of flare following discontinuation was lower – but still high – in patients with sustained remission (8–12 weeks) compared to those with remission at a single timepoint (60% vs. 84%) after 40 weeks

Van Den Bosch F, Nash P, Wei JCC, et al. Efficacy outcomes following etanercept withdrawal by sustained remission status in patients with Nr-axSpA: results from RE-EMBARK. Arthritis Rheumatol 2020;72:2700–3.

Χαρακτηριστικά ασθενών για tapering ;;;

- **For tapering**, **(-)** female sex, higher CRP, HLA-B27 negativity, higher physician global score and smoking have been associated with higher failure rates in single studies, but not consistently

- **For discontinuation (-)** higher ASDAS/BASDAI at time of discontinuation, baseline sacroiliac joint MRI (MRI-SI) positivity together with increased CRP and smoking

Wetterslev M, Georgiadis S, Sorensen IJ, et al. Tapering of TNF inhibitors in axial spondyloarthritis in routine care – 2-year clinical and MRI outcomes and predictors of successful tapering. Rheumatology (Oxford) 2022;61:2398–412.

Zhao M, Zhang P, Fang L, et al. Possible predictors for relapse from etanercept discontinuation in ankylosing spondylitis patients in remission: a three years' following-up study. Clin Rheumatol 2018;37:87–92.

Moreno M, Gratacos J, Torrente-Segarra V, et al. Withdrawal of infliximab therapy in ankylosing spondylitis in persistent clinical remission, results from the REMINEA study. Arthritis Res Ther 2019;21:88.

The patient’s perspective

- a **shared decision**-making process

The tapering success rate was almost 95% in those who originally preferred to taper, and less than 50% in those who did not.

Van Rossen L, Chan A, Gilbert A, et al. Response to lower dose TNF inhibitors in axial spondyloarthritis; a real-world multicentre observational study. Rheumatol Adv Pract 2020;4:R439–44.

Interestingly, most patients do not think less frequent injections would positively affect home life, working life or travel !!!

Wallis D, Holmes C, Holroyd C, et al. Dose reduction of biological therapies for inflammatory rheumatic diseases: what do patients think? Scand J Rheumatol 2019;48:251–2.

Concluding remarks I

- Την τελευταία 10ετία εχουμε ενδείξεις για μείωση δόσης και (ίσως) διακοπή των βιολογικών στην αξΣπΑ
- Το **Tapering** είναι δόκιμη επιλογή σε ασθενείς με sustained low disease activity or remission state.
- **Spacing** is supported by the most evidence and seems the most practical method.

Concluding remarks II

- …περαιτέρω μελέτες για :

  1)για πόσο διάστημα να είναι ο ασθενής σε ικανό status … πριν την έναρξη παρέμβασης ;

  2)ποιο status εγγυάται επιτυχία ; LDA ή ΥΦΕΣΗ ;

- Discontinuation : το ρίσκο φαίνεται μεγάλο για εφαρμογή σε όλους τούς ασθενείς

…περαιτέρω μελέτες 1) για το κατάλληλο προφίλ ασθενών και

2) άμεση διακοπή ή προηγείται tapering ?(a more pragmatic approach)

Concluding remarks III

ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update

13 If a patient is in sustained remission, tapering of a bDMARD can be considered.

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.

27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.

Concluding remarks III

Healthcare providers have a societal responsibility to consider the costs incurred in the management of axSpA. Dose reduction, if done carefully, could free up valuable space in healthcare budgets and contribute to cost-effective use of bDMARDs

Van der Togt C, Van den Bemt B, Aletaha D, et al. POS0638 – Recommendations for cost-effective use of biological and targeted synthetic DMARDs in inflammatory arthritis: results from an international Delphi Study. Ann Rheum Dis 2022;81:588.

Obviously, the principle of best care outweighs any cost considerations

Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2022.

Complete discontinuation of bDMARDs in those in remission more often than not results in relapse and should not be recommended until we know how to select optimal candidates.

Tapering or discontinuation of biological disease-modifying antirheumatic drugs in axial spondyloarthritis: A review of the literature and discussion on current practice

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