ΔΟΡΥΦΟΡΙΚΗ ΔΙΑΛΕΞΗ
«Παρουσίαση περιστατικών σε θεραπεία με βιο-ομοειδές της Ετανερσέπτης»

Δρ. Πηνελόπη Κωνσταντοπούλου

Ρευματολόγος

ΓΝΑ «Γ. Γεννηματάς»

Σύγκρουση συμφερόντων

- Τιμητική αμοιβή για την παρούσα ομιλία από τη φαρμακευτική εταιρεία DEMO

Περιγραφή 1ης περίπτωσης

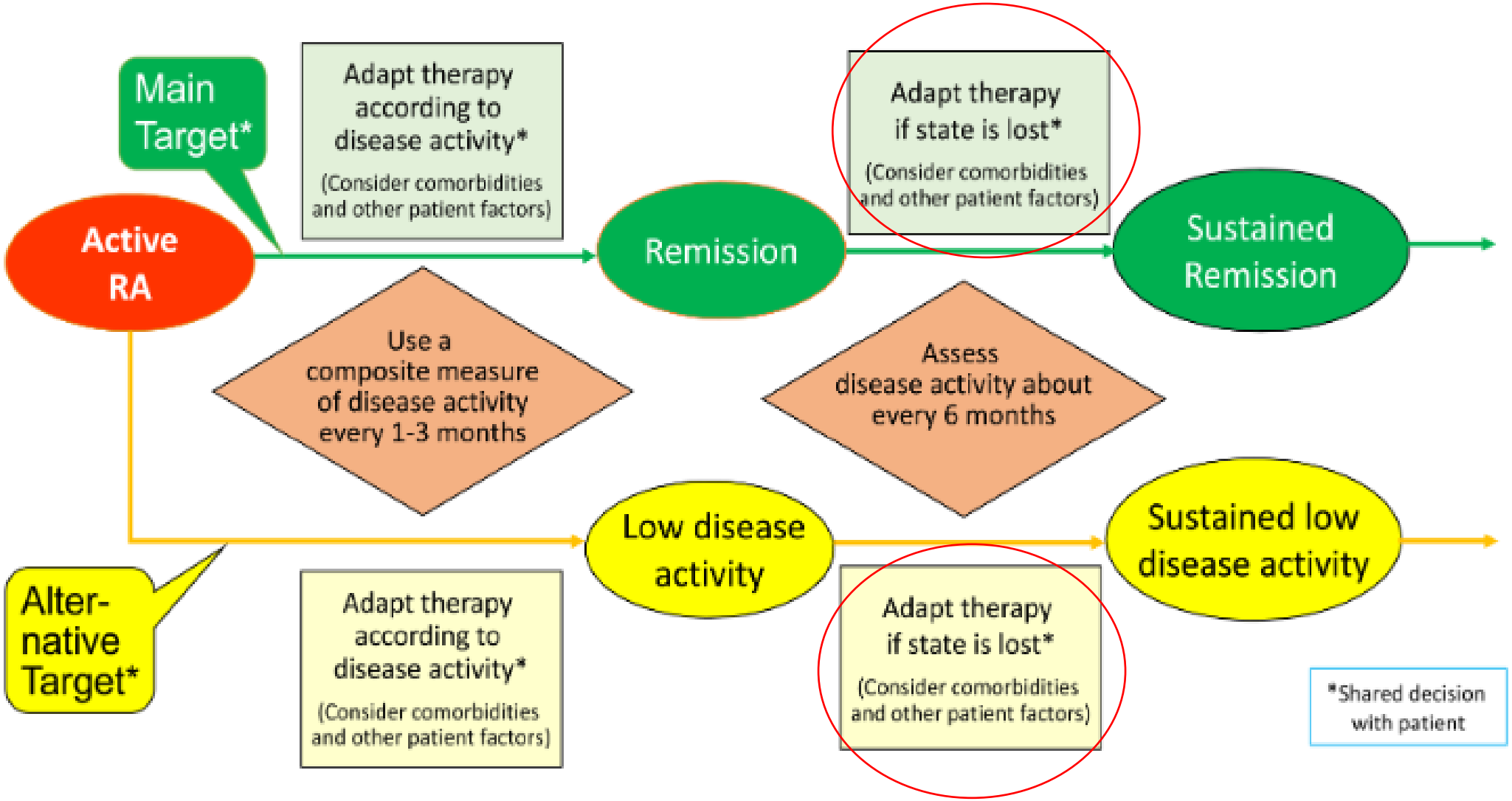
- Γυναίκα 67 ετών : αρθρίτιδα ΜΚΦ άμφω, ΕΦΦ άμφω, ΜΤΦ άμφω, τενοντίτιδα ώμων άμφω, πρωινή δυσκαμψία 3 ώρες, κόπωση από 4μήνου
  - RF=112 anti-CCP=2, CRP=20 (ΦΤ<5), ΤΚΕ=40, DAS28 (ΤΚΕ)= 5.82
  - Ακτινογραφίες άκρων χειρών και ποδών: οίδημα μαλακών μορίων, παραάρθρική οστεοπόρωση
  - **Διάγνωση: ρευματοειδής αρθρίτιδα**
- Ατομικό αναμνηστικό: υποθυρεοειδισμός, δυσλιπιδαιμία, αρτηριακή υπέρταση, ΣΝ υπό λεβοθυροξίνη 100mcg/ημ, ατορβαστατίνη 20 mg/ημ, βισοπρολόλη 10 mg/ημ, ακετυλοσαλικυλικό οξύ 100 mg/ημ
- Έναρξη πρεδνιζολόνης 10 mg/ημ, ΜΤΧ 15 mg/εβδ, φυλλικού οξέος 5 mg/εβδ

Recommendations_EULAR 2019

	Recommendations			
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A	9.8
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*	1a	A	9.7
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted.	2b	B	9.3
4	MTX should be part of the first treatment strategy.	1a	A	9.4
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9.0
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.	1a	A	8.9
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors*, other csDMARDs should be considered.	5	D	8.4
8.	If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors* are present, a bDMARD† or a tsDMARD‡ should be added.	1a	A	9.3
9.	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.	1a	A	8.9
10.	If a bDMARD# or tsDMARD## has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	#1b ##5	A D	8.9
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.	1b	A	9.2
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

Smolen JS, et al. Ann Rheum Dis 2020;79:685–699. doi:10.1136/annrheumdis-2019-216655

Treat To Target



Smolen JS,et al.Ann Rheum Dis 2016;75:3–15

Περιγραφή 1ης περίπτωσης

- 3 μήνες μετά: εμμένουσα αρθρίτιδα και πρωινή δυσκαμψία, DAS28 (TKE)= 4.5
- Πόνος και κόπωση αναφέρονται σταθερά από την ασθενή

Poor prognostic factors	▶ Persistently moderate or high disease activity despite conventional synthetic DMARD (csDMARD) therapy according to composite measures including joint counts ▶ High acute phase reactant levels ▶ High swollen joint count ▶ Presence of RF and/or ACPA, especially at high levels ▶ Presence of early erosions ▶ Failure of two or more csDMARDs

Recommendations_EULAR 2019

	Recommendations			
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A	9.8
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*	1a	A	9.7
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5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9.0
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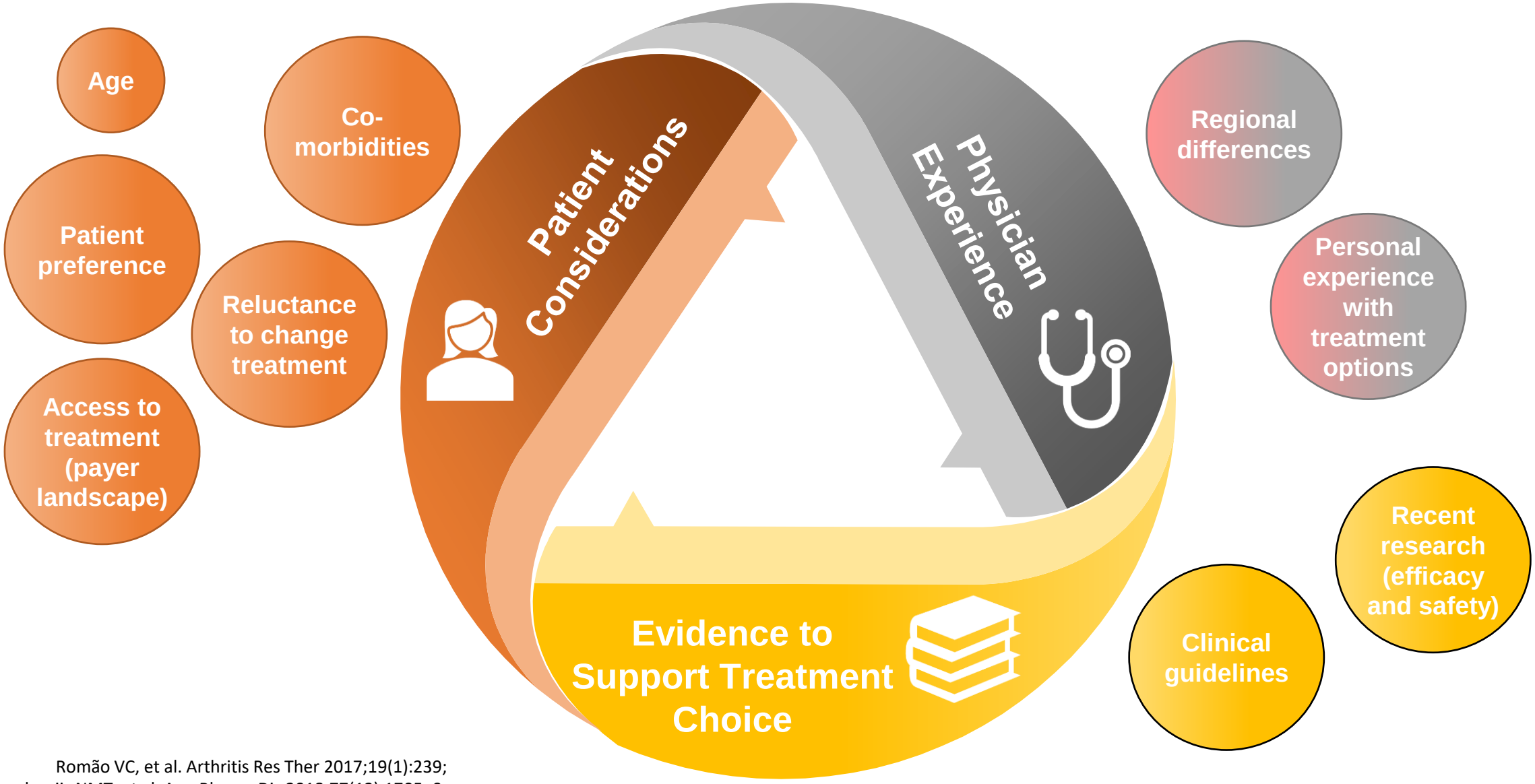
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.	1b	A	9.2
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

Smolen JS, et al. Ann Rheum Dis 2020;79:685–699. doi:10.1136/annrheumdis-2019-216655

Πως επιλέγουμε την κατάλληλη θεραπεία για τον κατάλληλο ασθενή την κατάλληλη στιγμή;



Romão VC, et al. Arthritis Res Ther 2017;19(1):239;
Roodenrijs NMT, et al. Ann Rheum Dis 2018;77(12):1705–9.

Περιγραφή 1ης περίπτωσης

- Quantiferon, ηπατίτιδες, HIV, Ro θώρακος: κφ, EF=55%
- Έναρξη Erelzi (βιομοϊδές etanercept) 50mg/wk sc
- Έναρξη αντιοστεοπορωτικής αγωγής με διφωσφονικό και συνδυασμό Ca και vitD

Μελέτη EMPIRE, ταχεία έναρξη δράσης και επίτευξη ύφεσης

- Exploratory analyses showed a higher proportions of patients with DAS28-CRP<2.6 **in the MTX+ETN group at week 2 (38.5% vs 9.2%, adjusted OR 8.87 (2.53 to 31.17), p=0.001) and week 12 (65.1% vs 43.8%, adjusted OR 2.49 (1.12 to 5.54), p=0.026)**
- **Clinical responses, including DAS28-CRP<2.6, were achieved earlier with MTX+ETN combination therapy.**

Nam JL, et al. Ann Rheum Dis 2014;73:1027–1036. doi:10.1136/annrheumdis-2013-204882

Effectiveness of Etanercept in Rheumatoid Arthritis: Real-World Data from the German Non-interventional Study ADEQUATE with Focus on Treat-to-Target and Patient-Reported Outcomes

Eugen Feist . Xenofon Baraliakos et al. 2022 Rheumatol Ther https://doi.org/10.1007/s40744-021-00418-5

Results:

- ✓ The proportion of patients achieving remission was 24% at week 12 and 31% at week 24. The proportion of patients achieving LDA was 39% at week 12 and 45% at week 24.
- ✓ The proportion of patients achieving remission or LDA further increased beyond week 24 up to week 52.
- ✓ Improvement in pain and reduction in concomitant glucocorticoid treatment were observed. Improvements in patient-reported outcomes were also seen in patients who did not reach remission or LDA.
- ✓ No new safety signals were detected.

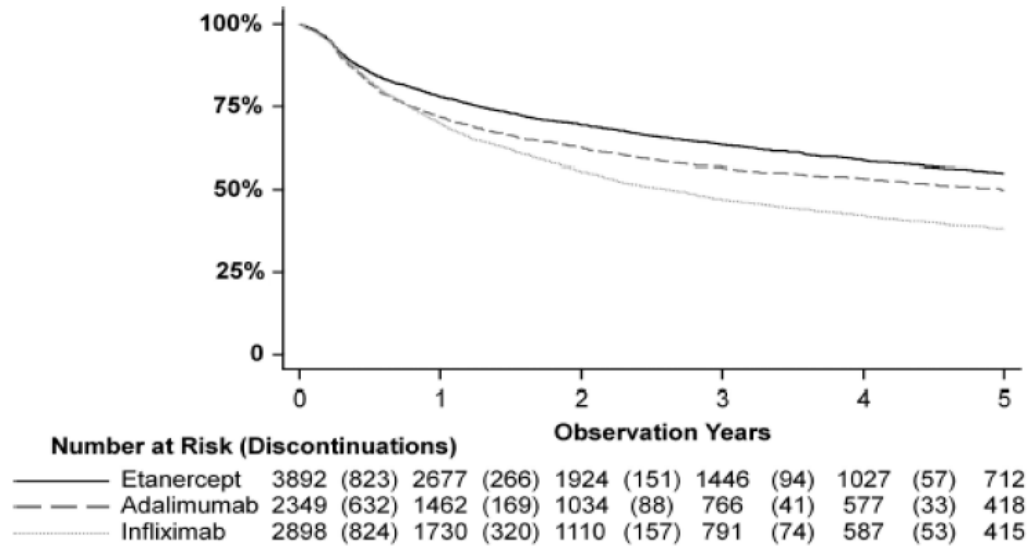
CONCLUSIONS

- ➢ In summary, our results show that decision making regarding continuation or switching of therapy is complex. Optimal treatment decisions should always take into account patient preferences.
- ➢ While the treat-to-target approach has proven clinical benefits, some patients may benefit from prolonged treatment with ETN beyond 12 weeks before considering switching treatment.
- ➢ Our findings confirm the effectiveness and safety of ETN in a real-world setting and highlight the potential benefits of continuing treatment with ETN in patients who have not reached their treatment goal after 12 weeks of treatment.

Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab

ARTIS Study group/SWE

2003-2011
- 9139 RA pts
- 5-years follow up

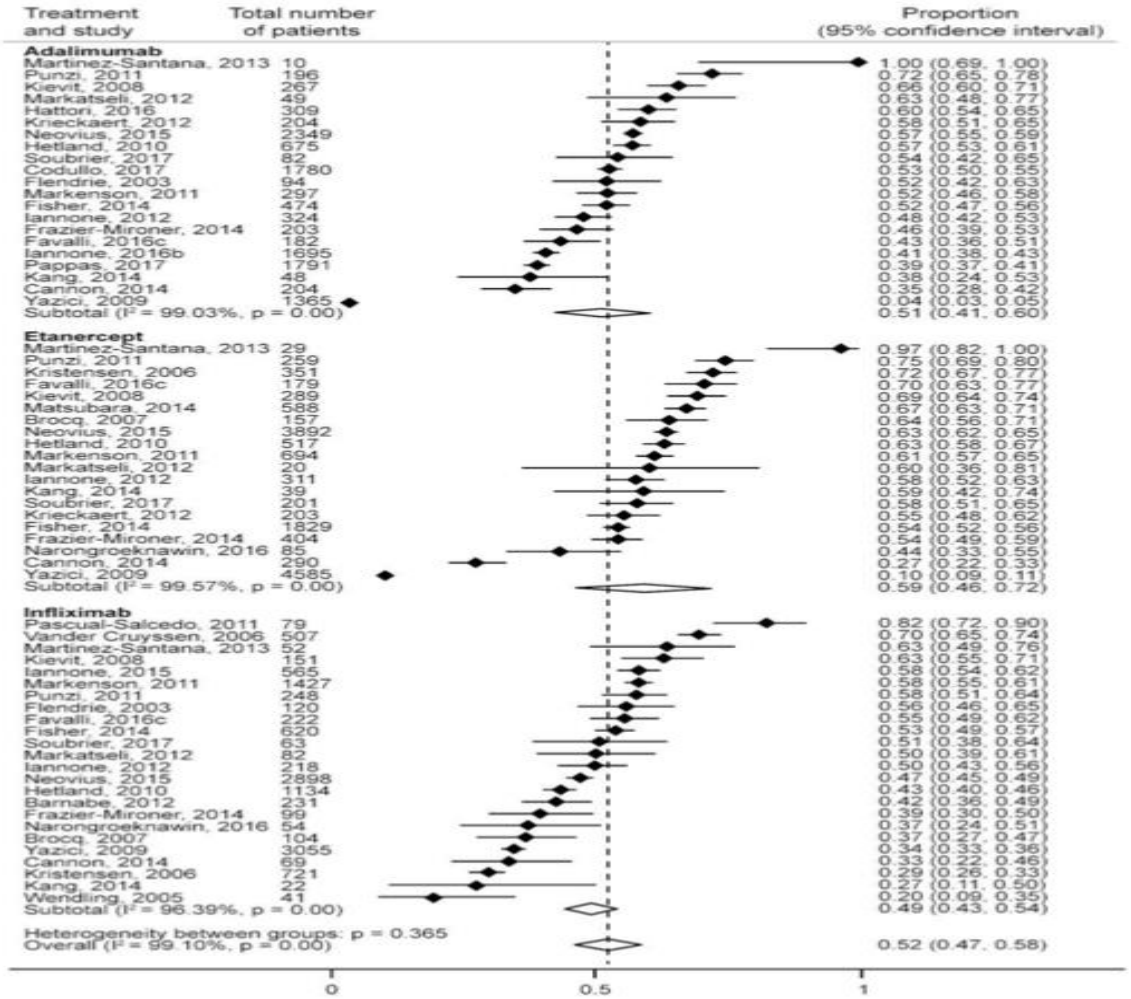


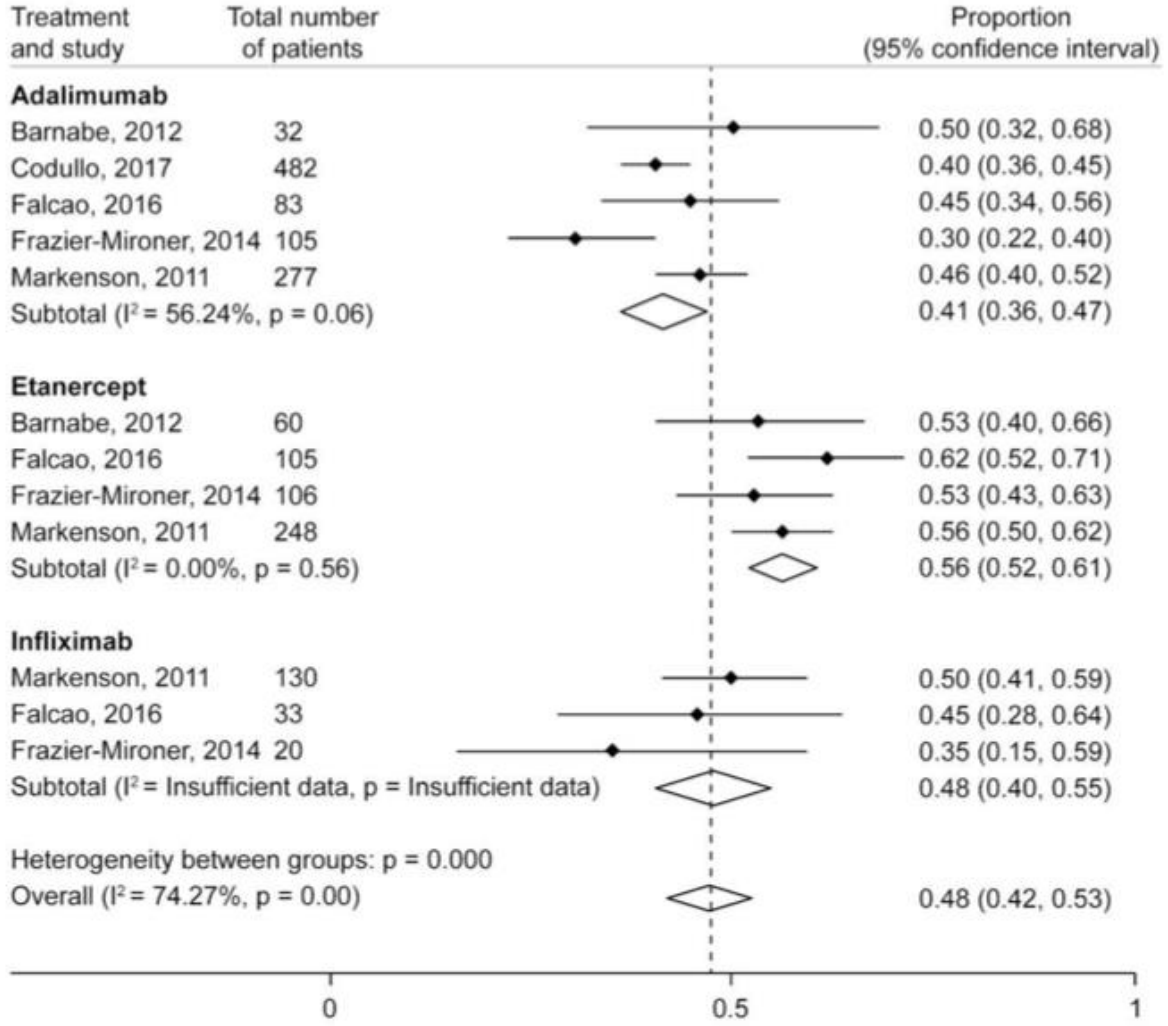
3782 discontinued
51% inefficacy, 36% adverse events

- At the end of the 5-year follow-up
- **38% of infliximab, 50% of adalimumab and 55% of etanercept** initiators remained on their first drug.

Neovius M et al. Ann Rheum Dis 2015

Long-term drug survival of tumor necrosis factor inhibitors in patients with rheumatoid arthritis: After >12 months of follow-up, more patients with rheumatoid arthritis receiving etanercept remain on treatment compared with other TNFi





Emery P, et al. J Rheumatol.2020;47(4):493-501

Out of all five TNFa blockers, data from the DANBIO registry (a nationwide registry of biological therapies in Denmark) revealed that etanercept was the best tolerated drug

Murray et al. Arthritis Research & Therapy (2021) 23:25

Table 2 A comparison of rheumatoid arthritis and psoriatic arthritis outcomes at biologic initiation, one year and 12 year reviews

	Baseline			1 Year Review			12 Year Review		
	RA (*n* = 274)	PsA (*n* = 129)	*p*	RA (*n* = 203)	PsA (*n* = 96)	*p*	RA (*n* = 179)	PsA (*n* = 87)	*p*
Biologic									
Adalimumab	144 (52.6%)	47 (36.4%)	0.002	76 (44.7%)	27 (31.0%)	0.034	43 (25.6%)	28 (33.3%)	NS
Etanercept	100 (36.5%)	68 (52.7%)	0.002	62 (36.5%)	45 (51.7%)	0.019	48 (28.6%)	30 (35.7%)	NS
Infliximab	18 (6.6%)	14 (10.9%)	NS	13 (7.6%)	11 (12.6%)	NS	3 (1.8%)	8 (9.5%)	0.004

Long-term remission and biologic persistence rates: 12-year real-world data

- **In the current study, both of the subcutaneous bDMARDs (etanercept and adalimumab) commenced at baseline showed excellent clinical outcomes.**
- There were no differences in remission or continuation rate by initial bDMARD agent in either disease.
- Indeed, there were no significant differences in any clinical outcome measure in RA.
- In PsA, patients on etanercept at baseline also had a lower CRP at 12 years (p = 0.041). However, given the normal values in both groups, this is of dubious significance.

Η συνολική χρήση του συστήματος υγείας μειώθηκε μετά την έναρξη της ετανερσέπτης. Οι ασθενείς που συμμορφώθηκαν περισσότερο με την ετανερσέπτη είχαν σημαντικά χαμηλότερη χρήση από τους λιγότερο συμμορφούμενους ασθενείς

Changes in Healthcare Utilization After Etanercept Initiation in Patients with Rheumatoid Arthritis: A Retrospective Claims Analysis Adv Ther (2017) 34:2093–2103 DOI 10.1007/s12325-017-0596-6 **Neil A. Accortt**

Results:

- Data from 6737 patients were analyzed; mean age was 49.8 years and 77.3% were female.
- Overall outpatient services, office visits, outpatient hospital services, laboratory visits, and emergency department visits were significantly lower in the post-index period compared to pre-index.
- RA-related pharmacotherapy use (oral corticosteroids, opioid analgesics, nonsteroidal anti-inflammatory drugs, and nonbiologic disease-modifying antirheumatic drugs) was significantly lower in the post-index period compared to pre-index.
- Rates of RA-related total joint arthroplasty, joint reconstructions, and soft tissue procedures were similar in pre-index and post-index periods.
- High etanercept compliance (PDC C80%) was associated with significantly lower rates of RA-related outpatient services, office visits, diagnostic imaging studies, and joint reconstructions compared with noncompliance.

- **Η ύφεση σε ασθενείς με PA, μειώνει τον καρδιαγγειακό κίνδυνο**
- **Disease Activity in Rheumatoid Arthritis and the Risk of Cardiovascular Events**
- Arthritis Rheumatol. 2015 Jun; 67(6): 1449–1455. doi: 10.1002/art.39098 DH Solomon et al.
-

Results. A total of 24,989 patients who had been followed up for a median of 2.7 years were included in these analyses. During followup, we observed 534 confirmed CV end points, for an incidence rate of 7.8 per 1,000 person-years (95% confidence interval [95% CI] 6.7–8.9). In models adjusted for variables noted above, a 10-point reduction in the time-averaged CDAI was associated with a 21% reduction in CV risk (95% CI 13–29). These results were robust in subgroup analyses stratified by the presence of CV disease, use of corticosteroids, use of NSAIDs or selective cyclooxygenase 2 inhibitors, and change in RA treatment, as well as when restricted to events adjudicated as definite or probable.

Conclusion. Our findings showed that reduced time-averaged disease activity in RA is associated with fewer CV events.

Οι anti-TNFα μειώνουν τον καρδιαγγειακό κίνδυνο

- After adjustment for a number of risk factors, the risk of CV events was significantly reduced following the use of anti-TNFα agents in patients with RA, psoriatic arthritis or ankylosing spondylitis

- The benefits of TNF inhibitors on CVD risk correlate with their impact on RA disease control, with data from the Swedish biologics register demonstrating that the 1-year risk of ACS for patients with a good EULAR response was approximately half that of patients with no EULAR response

- Improvements in the apolipoprotein profile, a biomarker of CVD risk, were observed in patients with RA who exhibited a good or moderate EULAR response to etanercept but not in EULAR non-responders

- Anti-TNFα may exert their effects through reducing systemic inflammation rather than by modifying traditional CV risk factors. Etanercept did not affect levels of traditional metabolic risk factors (including glucose, insulin, lipid and apolipoprotein parameters) despite reducing RA severity, as indicated by decreases in CRP

1. Lee et al. Arthritis Research & Therapy (2018) 20:171
2. Ljung L, et al. Ann Rheum Dis 2016;75:2087–2094
3.Jamnitski A, et al. Ann. Rheum. Dis. 2010, 69, 1929–1933
4. Deodhar A, et al. Clin. Rheumatol. 2016, 35, 3045–3052

Consistent with responses in younger subjects, elderly subjects with RA treated with etanercept experienced significant improvement in disease activity and function without incurring additional safety concerns

Response to Etanercept (Enbrel®) in Elderly Patients with Rheumatoid Arthritis: A Retrospective Analysis of Clinical Trial Results

ROY M. FLEISCHMANN, SCOTT W. BAUMGARTNER, ELIZABETH A. TINDALL, ARTHUR L. WEAVER, LARRY W. MORELAND, MICHAEL H. SCHIFF, RICHARD W. MARTIN, and GEORGE T. SPENCER-GREEN

Safety and Efficacy of Etanercept Treatment in Elderly Subjects with Rheumatoid Arthritis

JOAN M. BATHON, ROY M. FLEISCHMANN, DÉSIRÉE M. van der HEIJDE, JOHN R. TESSER, PAUL M. PELOSO, YUN CHON, and BARBARA WHITE

1. J Rheumatol 2003;30:691–6
2. J Rheumatol 2006;33:234–43

Τα αναφερόμενα ποσοστά φυματίωσης (TB) είναι επίσης ευνοϊκά για την ετανερσέπτη

Συγκριτικός κίνδυνος για TB - Δεδομένα εθνικού μητρώου

Συγκριτικός κίνδυνος για ανάπτυξη TB μεταξύ των αντι-TNF παραγόντων (95%CI)				
Πηγή δεδομένων	**Δείκτης μέτρησης κινδύνου**	**Ετανερσέπτη**	**Αδαλιμουμάμπη**	**Ινφλιξιμάμπη**
BSRBR (HB)[1]	Προσαρμοσμένος λόγος ποσοστού επίπτωσης σε σύγκριση με την ετανερσέπτη	1	4,2 (1,4-12,1)	3,1 (1-9,5)
ARTIS (Σουηδία)[2]	Σχετικός κίνδυνος (RR)	2,5 (1,0-6,1)	3,1 (1,1- 8,0)	5,2 (2,7-11)
RATIO (Γαλλία)[3]	Τυπικός λόγος επίπτωσης (SIR)	1,8 (0,7-4,3)	29,3 (20,3–42,4)	18,6 (13,4–35,8)

1. Dixon WG, et al. *Ann Rheum Dis* 2010;69:522–528· 2. Askling J, et al. *Ann Rheum Dis* 2009;68(Suppl3):422
3. Tubach F, et al.. *Arthritis Rheum.* 2009;60: 1884–94.

EQUIRA: Σχεδιασμός μελέτης

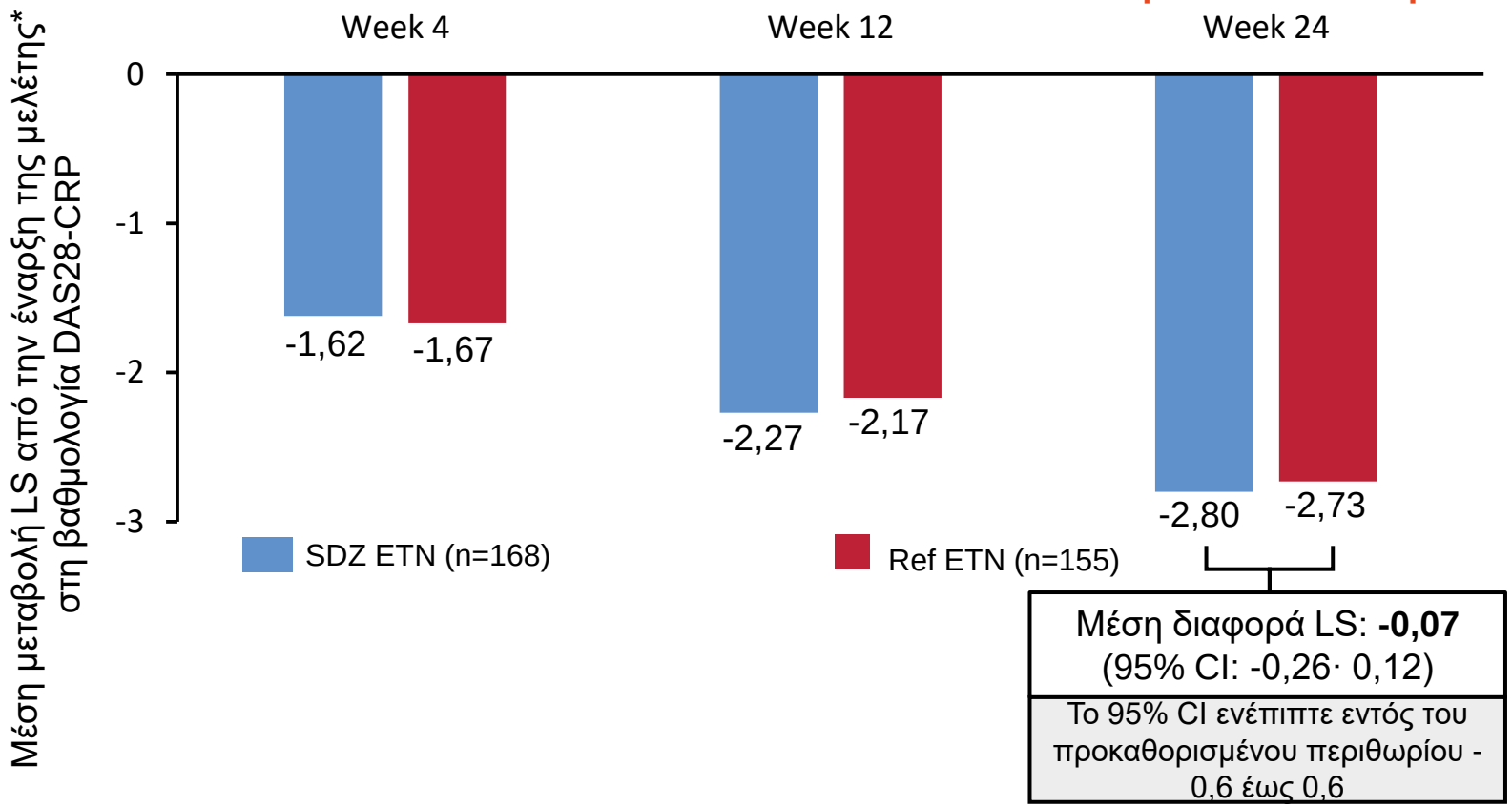
Δοσολογικό σχήμα:	50 mg SDZ ETN ή ref ETN εγκεκριμένης για χρήση στην ΕΕ, χορηγούμενης υποδορίως με προγεμισμένη σύριγγα, μία φορά την εβδομάδα
Συγχορηγούμενη θεραπεία:	Μεθοτρεξάτη (σταθερή δόση·10-25 mg/εβδομάδα) και φολικό οξύ (≥5 mg/εβδομάδα) καθ' όλη τη διάρκεια της μελέτης
Κριτήρια απόκρισης:	Οι αποκρινόμενοι ορίστηκαν σύμφωνα με τα κριτήρια απόκρισης κατά EULAR ως εξής: • DAS28 >3,2 και ≤5,1 την Εβδομάδα 24 και DAS28 βελτίωση από την έναρξη της μελέτης >0,6 ή • DAS28 >5,1 και DAS28 βελτίωση >1,2

DAS28, βαθμολογία ενεργότητας της νόσου σε 28 αρθρώσεις· ref ETN, ετανερσέπτη αναφοράς· SDZ ETN, ετανερσέπτη της Sandoz

Matucci-Cerinic M, et al. RMD Open 2018;4:e000757. doi:10.1136

Πρωτεύον καταληκτικό σημείο: Ισοδύναμη αποτελεσματικότητα στη DAS28-CRP μεταξύ της SDZ ETN και της ref ETN

Πρωτεύον καταληκτικό σημείο



*Μέση DAS28-CRP κατά την έναρξη της μελέτης: 5,43 και 5,55 για την ομάδα της SDZ ETN και την ομάδα της Ref ETN, αντίστοιχα
CI, διάστημα εμπιστοσύνης· DAS28-CRP, βαθμολογία ενεργότητας της νόσου σε 28 αρθρώσεις με βάση τη C-αντιδρώσα πρωτεΐνη· LS, ελάχιστα τετράγωνα· PPS, σύνολο κατά το πρωτόκολλο·
ref ETN, ετανερσέπτη αναφοράς· SDZ ETN, ετανερσέπτη της Sandoz· ΠΘ1, περίοδος θεραπείας 1
Matucci-Cerinic M, *et al*. *RMD Open* 2018;4:e000757. doi:10.1136

Η κλινική ισοδυναμία του GP2015 επιβεβαιώθηκε στη μελέτη EGALITY, μια επιβεβαιωτική μελέτη αποτελεσματικότητας και ασφάλειας στην ψωρίαση

Τυχαιοποιημένη, διπλά τυφλή, πολυκεντρική μελέτη για την κατάδειξη της ισοδύναμης **(e)** αποτελεσματικότητας και τη σύγκριση της ασφάλειας και ανοσογονικότητας ενός βιοομοειδούς της ετανερσέπτης (**G**P2015) και **(a)** του Enbre**(l)**® σε **(i)** ασθενείς με μέτρια έως σοβαρή χρόνια ψωρίαση τύπου **(ty)** κατά πλάκας #

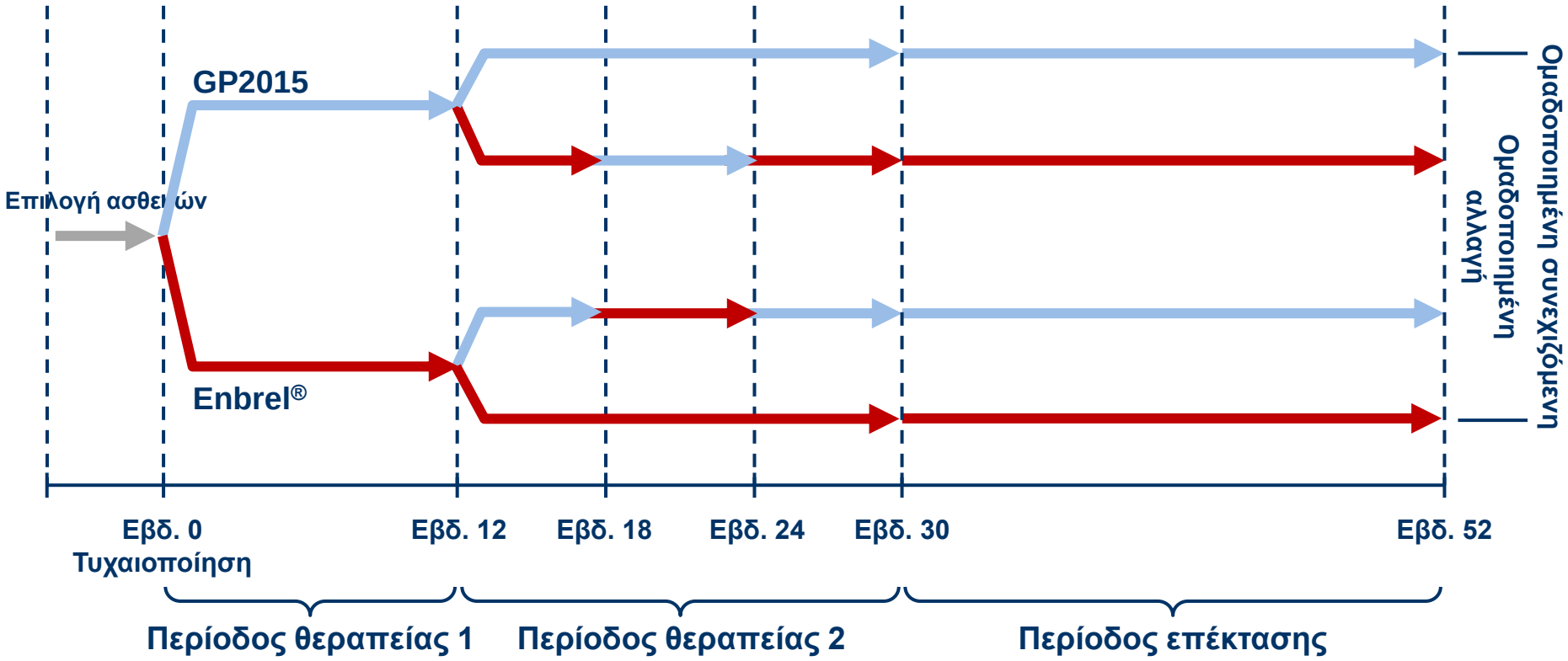
- **Περίοδος μελέτης:** Ιούνιος 2013 - Μάρτιος 2015
- **Τοποθεσία μελέτης:** 11 χώρες της ΕΕ + Νότια Αφρική
- **Κέντρα μελέτης:** 74 κέντρα μελέτης επέλεξαν τους ασθενείς
  71 κέντρα μελέτης τυχαιοποίησαν τους ασθενείς
- **Δημοσίευση δεδομένων:** Ψωρίαση 2016 (δεδομένα Εβδομάδας 12)
  EADV 2016 (δεδομένα Εβδομάδας 30)*

Griffiths CEM, et al. Έκτακτη ανακοίνωση στο Συνέδριο για την Ψωρίαση του 2016·[περίληψη αρ.1325].

British Journal of Dermatology (2017) 176 DOI 10.1111/bjd.15152

Η μελέτη EGALITY παρουσιάζει έναν καινοτόμο σχεδιασμό που περιλαμβάνει τρεις διαδοχικές περιόδους θεραπείας

Γενικός σχεδιασμός μελέτης



Κάθε περίοδος θεραπείας επεδίωκε την επίτευξη ξεχωριστού στόχου της μελέτης

Εβδ., εβδομάδα· Πηγές: Πρωτόκολλο μελέτης GP15-302 (Ενότητα 2)· Τελική αναφορά μελέτης (CSR) GP15-302 την Εβδομάδα 12 (Ενότητες 8.1 και 8.2); Griffiths CEM, et al.

Ενδιαφέρον λόγω των διαδοχικών αλλαγών θεραπείας

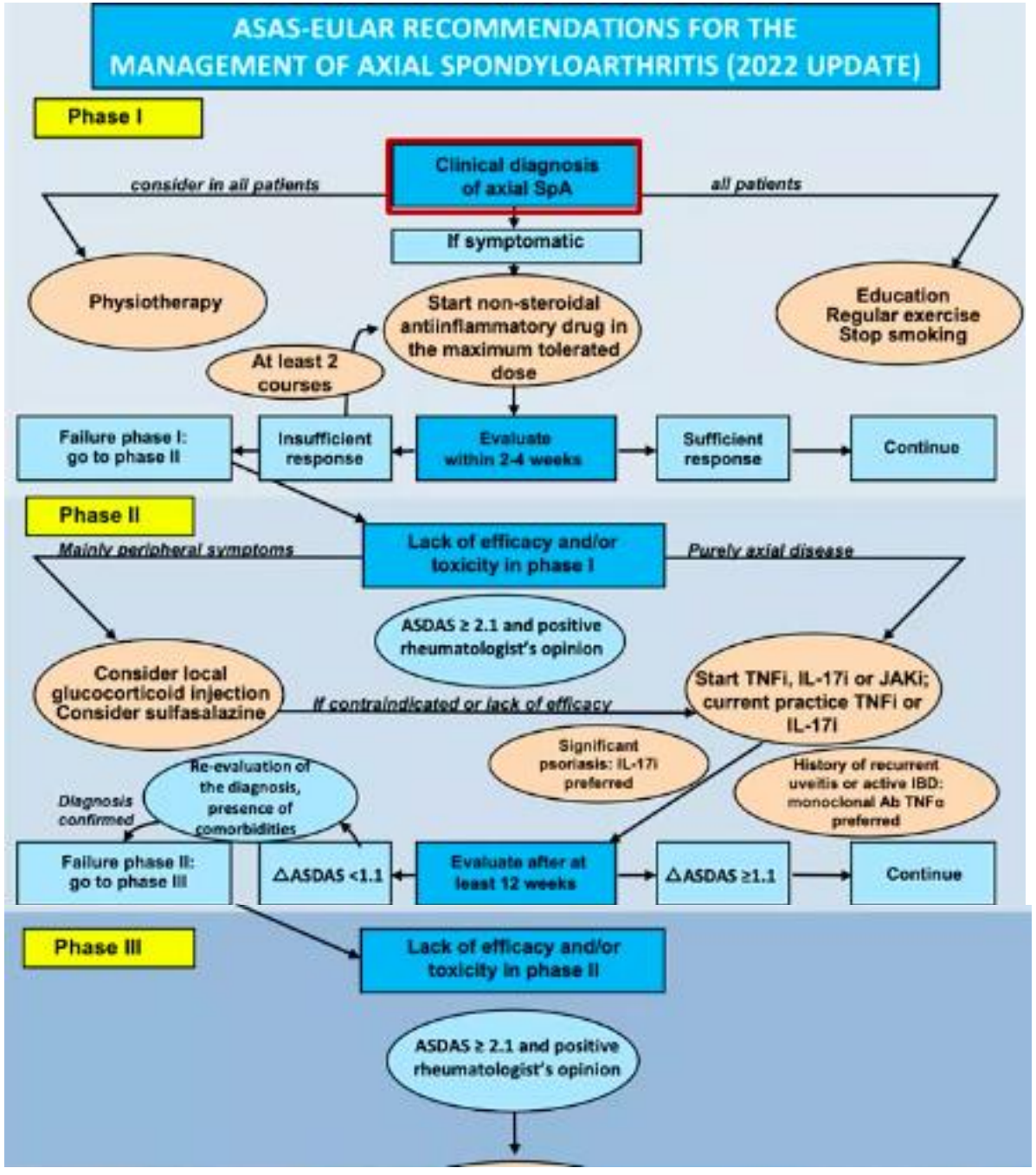
British Journal of Dermatology (2017) 176 DOI 10.1111/bjd.15152

Περιγραφή 1ης περίπτωσης

- 3 μήνες μετά: DAS28 (TKE)=2.9
- Λήψη πλέον 5mg πρεδνιζολόνης
- 6 μήνες μετά: πλήρης απογαλακτισμός από τα κορτικοειδή με DAS28 (TKE)=2.1
- Χωρίς πρωινή δυσκαμψία και κόπωση
- 6 μήνες μετά: Λήψη πλέον MTX 10mg/wk, Erelzi 50mg/wk με DAS28 (TKE)=1.8

Περιγραφή 2ης περίπτωσης

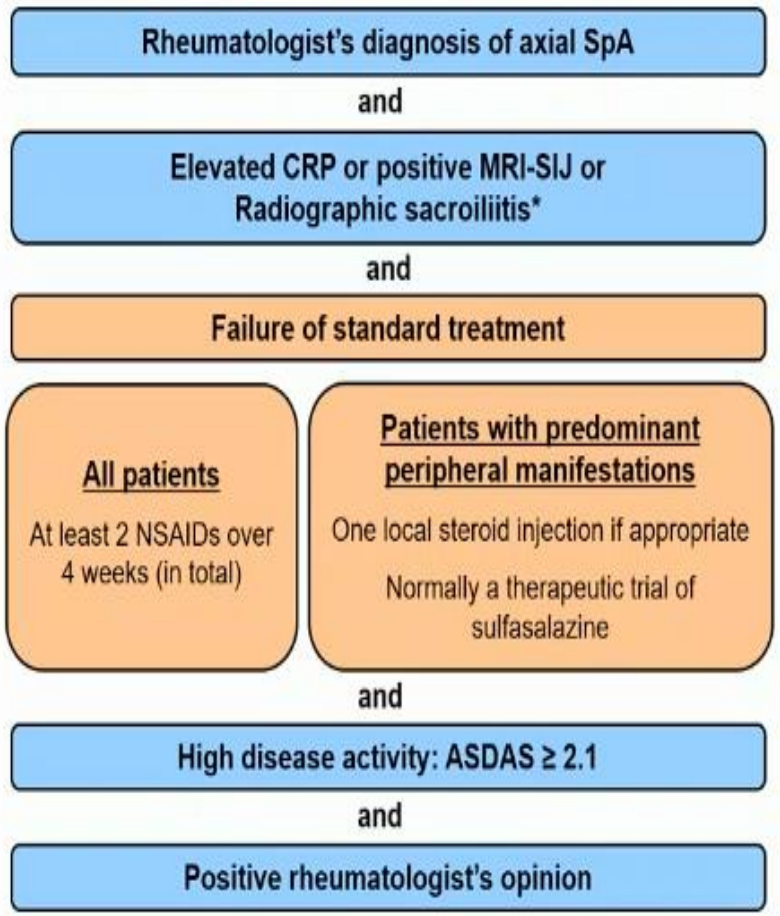
- Γυναίκα 38 ετών : χαμηλή οσφυαλγία με φλεγμονώδεις χαρακτήρες και πρωινή δυσκαμψία >2 ώρες προοδευτικά επιδεινούμενη από 6ετίας, αρθρίτιδα ΑΡ ΠΔΚ από 3 εβδομάδων
- Λοιπό ατομικό αναμνηστικό: ελεύθερο
- Οικογενειακό ιστορικό: αδελφός πατέρα με ΑΣ
- Schober: 11 cm
- Ακτινογραφία ιερολαγονίων: ιερολαγονίτιδα άμφω ΑΡ>ΔΕ με σκλήρυνση και στένωση των ιερολαγονίων
- MRI ιερολαγονίων: σκλήρυνση ιερολαγονίων με οστικό οίδημα ΑΡ>ΔΕ
- CRP=21 (ΦΤ<5), ΤΚΕ=70, HLAB27 (+)
- BASDAI = 7.5 ASDAS = 5.1
- Διάγνωση: αγκυλοποιητική σπονδυλαρθρίτιδα


ASAS-EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS (2022 UPDATE)
Phase I
Clinical diagnosis of axial SpA
consider in all patients
all patients
If symptomatic
Physiotherapy
Start non-steroidal antiinflammatory drug in the maximum tolerated dose
Education
Regular exercise
Stop smoking
At least 2 courses
Failure phase I: go to phase II
Insufficient response
Evaluate within 2-4 weeks
Sufficient response
Continue
Phase II
Lack of efficacy and/or toxicity in phase I
Mainly peripheral symptoms
Purely axial disease
ASDAS ≥ 2.1 and positive rheumatologist's opinion
Consider local glucocorticoid injection
Consider sulfasalazine
If contraindicated or lack of efficacy
Start TNFi, IL-17i or JAKi; current practice TNFi or IL-17i
Significant psoriasis: IL-17i preferred
History of recurrent uveitis or active IBD: monoclonal Ab TNFα preferred
Re-evaluation of the diagnosis, presence of comorbidities
Diagnosis confirmed
Failure phase II: go to phase III
ΔASDAS <1.1
Evaluate after at least 12 weeks
ΔASDAS ≥1.1
Continue
Phase III
Lack of efficacy and/or toxicity in phase II
ASDAS ≥ 2.1 and positive rheumatologist's opinion

Περιγραφή 2ης περίπτωσης

- Έναρξη ναπροξένης 500 mg x2
- Επανεκτίμηση σε 15 ημέρες: BASDAI = 7, ASDAS = 4.3
- Αλλαγή σε δικλοφαινάκη 75 mg x2
- Επανεκτίμηση σε 15 ημέρες: BASDAI = 6, ASDAS = 3.4
- Επιγαστραλγία

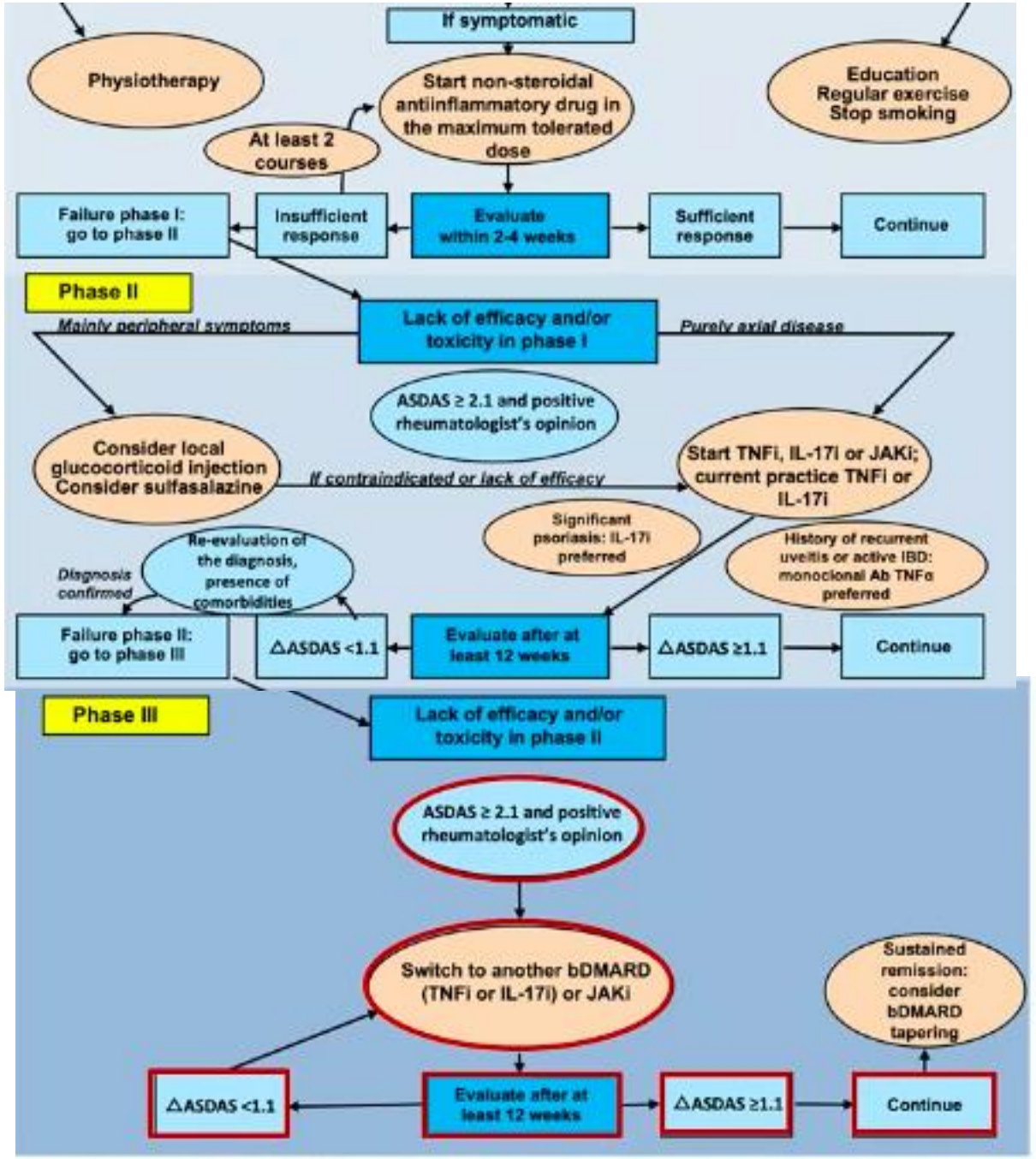
ASAS-EULAR Recommendations for the treatment of patients with axSpA with b/tsDMARDs



* Radiographic sacroiliitis is currently mandatory for infliximab and JAKi

ASAS Assessment of SpondyloArthritis International Society

eular


If symptomatic
Physiotherapy
Start non-steroidal antiinflammatory drug in the maximum tolerated dose
Education
Regular exercise
Stop smoking
At least 2 courses
Failure phase I: go to phase II
Insufficient response
Evaluate within 2-4 weeks
Sufficient response
Continue
Phase II
Mainly peripheral symptoms
Lack of efficacy and/or toxicity in phase I
Purely axial disease
ASDAS ≥ 2.1 and positive rheumatologist's opinion
Consider local glucocorticoid injection
Consider sulfasalazine
If contraindicated or lack of efficacy
Start TNFi, IL-17i or JAKi; current practice TNFi or IL-17i
Significant psoriasis: IL-17i preferred
History of recurrent uveitis or active IBD: monoclonal Ab TNFα preferred
Re-evaluation of the diagnosis, presence of comorbidities
Diagnosis confirmed
Failure phase II: go to phase III
ΔASDAS <1.1
Evaluate after at least 12 weeks
ΔASDAS ≥1.1
Continue
Phase III
Lack of efficacy and/or toxicity in phase II
ASDAS ≥ 2.1 and positive rheumatologist's opinion
Switch to another bDMARD (TNFi or IL-17i) or JAKi
Sustained remission: consider bDMARD tapering
ΔASDAS <1.1
Evaluate after at least 12 weeks
ΔASDAS ≥1.1
Continue

Περιγραφή 2ης περίπτωσης

- Απόφαση για έναρξη βιολογικού παράγοντα adalimumab 40 mg/2wks sc
- Mantoux (-), δείκτες ηπατίτιδας (-), HIV(-), Ro θώρακος =κφ
- 3 μήνες μετά : BASDAI = 2.2, ASDAS = 1.4
- 3 μήνες μετά : BASDAI = 0.6, ASDAS = 1
- 6 μήνες μετά κι ενώ εξακολουθεί να βρίσκεται σε ύφεση, εμφάνιση έντονης κι επώδυνης φλυκταινώδους ψωρίασης παλαμών και πελμάτων
- Παράδοξη ψωρίαση;

Ταξινόμηση παράδοξης ψωρίασης

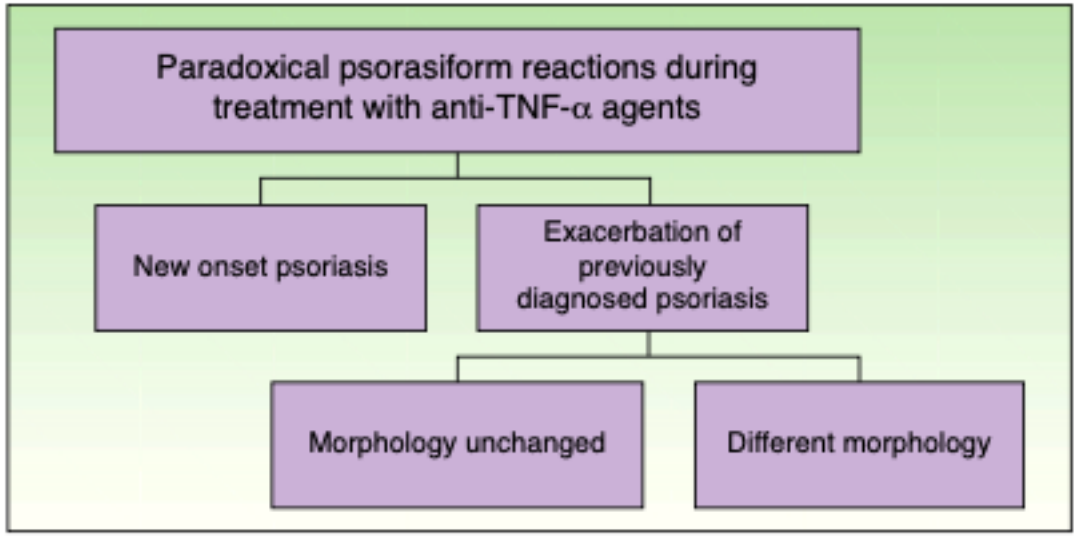
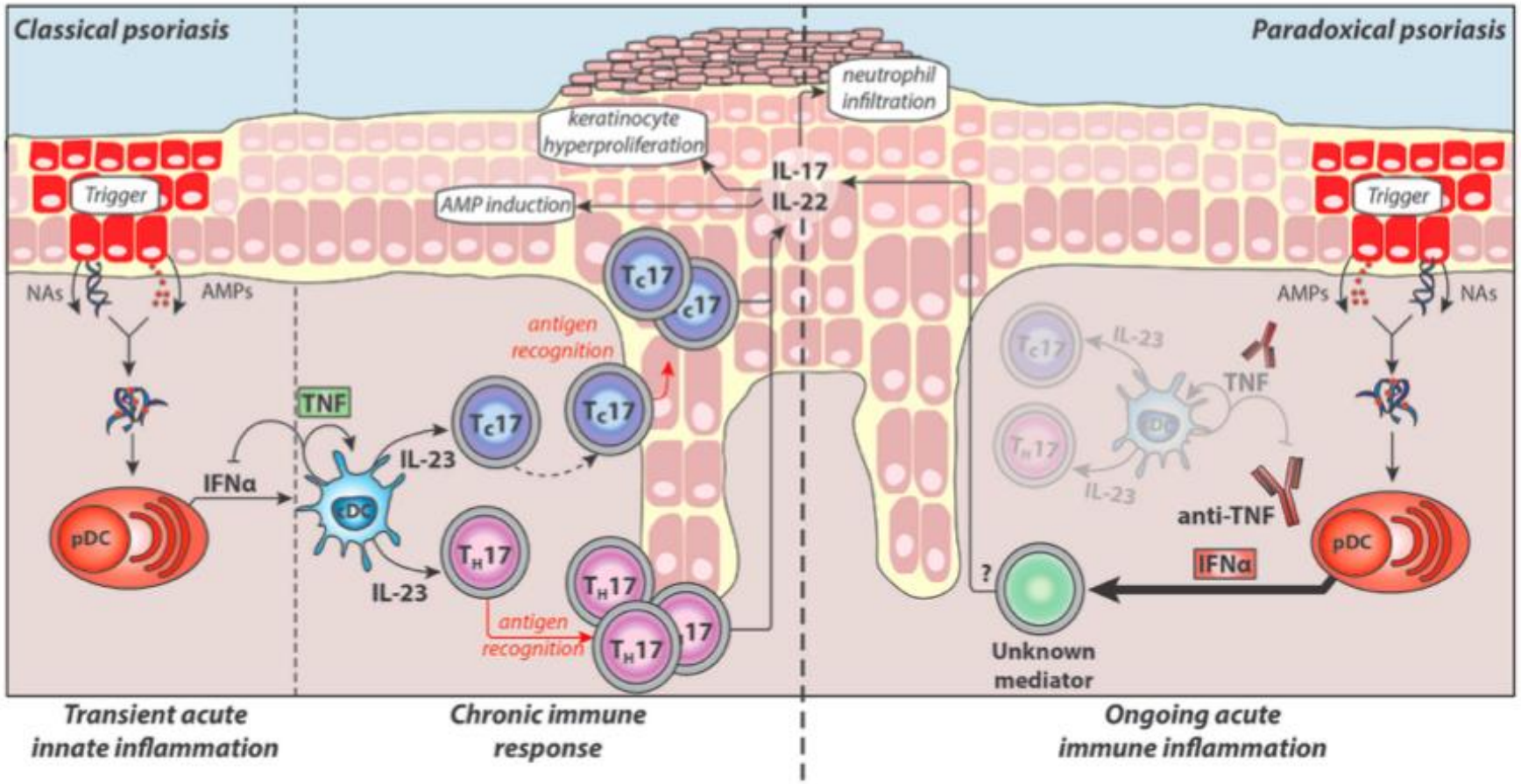


Figure 1 Classification of paradoxical psoriasiform reactions.

Navarro R and Daudén E. Actas Dermosifiliogr. 2014;105(8):752-761

Παράδοξη ψωρίαση



Mylonas A and Conrad C. Front. Immunol., 28 November 2018. https://doi.org/10.3389/fimmu.2018.02746

Αντιμετώπιση παράδοξης ψωρίασης

- According to published studies, almost 50% of patients will present an improvement or resolution of paradoxical skin lesions, following withdrawal of the BA.
- Another 45% of patients with anti-TNF-α induced psoriasis may present persistent or recurring cutaneous lesions, despite BA discontinuation.
- The more severe PR, such as generalized pustular psoriasis or psoriatic alopecia, can run a persistent course, only with partial improvement, after discontinuing the BA (Brown et al., 2017).
- Re-treatment with the same BA, after cessation of the cutaneous PR, should be evaluated on the basis of concomitant rheumatologic condition and availability of alternative treatment options. There is a substantial risk of recurrence of the cutaneous PR after re- treatment with the same BA, but there is no strong evidence in published studies (Wollina et al., 2008).
- Therapeutic switch of the PR-triggering BA with another BA of the same class (i.e., alternative TNFi) or of different class can be considered in moderate-to severe cutaneous PR, to control the underlying rheumatologic condition. Therapeutic switch to another BA is also indicated in the severe, paradoxical psoriasis subtypes, as in the case of generalized pustular psoriasis.

Navarro R and Daudén E. Actas Dermosifiliogr. 2014;105(8):752-761

Περιγραφή 2ης περίπτωσης

- Αλλαγή σε secukinumab 300 mg/mo μετά το σύνηθες σχήμα φόρτισης ανά εβδομάδα και χρήση τοπικών σκευασμάτων με οδηγία δερματολόγου
- 3 μήνες μετά: πλήρης εξαφάνιση του εξανθήματος
- 6 μήνες μετά: εμφάνιση φλεγμονώδους οσφυαλγίας, αρθρίτιδας ΑΡ και ΔΕ ΠΔΚ, ΑΡ 2^{ης} και 3^{ης} ΜΤΦ, πρωινή δυσκαμψία
- CRP=15, ΤΚΕ=40
- BASDAI=6.7 ASDAS= 4.4

Περιγραφή 2ης περίπτωσης

- Διακοπή secukinumab
- Εναρξη erelzi 50mg/wk sc
- 3 μήνες μετά: BASDAI= 4.4 ASDAS= 2.8
- 3 μήνες μετά: BASDAI= 1.7 ASDAS= 1.5
- 3 μήνες μετά: BASDAI= 0.9 ASDAS= 1.1
- Η ασθενής παραμένει σε ύφεση χωρίς υποτροπή του εξανθήματος

Table 1 Main randomized clinical trials analyzing the efficacy of etanercept in ankylosing spondyloarthritis

Reference	Year	Type	n	Duration (weeks)	Endpoints	*P*
Gorman et al[10]	2002	RCT	20/20	16	ASAS 20	0.004
Davis et al[11]		OLE	17	40		
Brandt et al[12,13]	2003	RCT	14/16	6	BASDAI 50, ASAS 20, BASDAI,	0.004
		OLE	23	54	BASFI, BASMI	
Davis et al[14,15]	2003	RCT	138/139	24	ASAS 20	0.0001
		OLE	128*	192		
Calin et al[16]	2004	RCT	45/39	12	ASAS 20, 40, 5/6, BASDAI	0.001
Dijkmans et al[17]		OLE	43	96		
van der Heijde et al[18]	2006	RCT	305/51	12	ASAS 20, 40, 5/6	0.001
Braun et al[19]	2007	RCT	305/51	12	BASFI, EuroQOL-5D, SF-36	0.001
Braun et al[20]	2011	RCT	379/187	16	ASAS 20, 40, 5/6, BASDAI, BASFI, BASMI	0.0001
Li et al[21]	2013	MET	1,570	-	ASAS 20, 40, 5/6, partial remission, BASFI, BASDAI, BASMI	0.00001

Table 2 Main adverse events occurring during treatment with etanercept in patients with ankylosing spondyloarthritis in randomized clinical trials and open-label extensions

Adverse event	AS-RCT[14]		AS-RCT[18]		AS-OLE[47]		AS-OLE[15]	AS-OLE[17]
	ETN (n = 138)	PL (n = 139)	ETN (n = 151)	PL (n = 51)	ETN TW (n = 54)	ETN OW (n = 54)	ETN (n = 257)	ETN (n = 81)
Injection site reactions	30%	9%	23%	12%	7%	8%	22%	37%
Upper respiratory tract infection	20%	12%	8%	14%	5%	8%	45%	53%
Headache	14%	12%	4%	0%	<3%	<3%	20%	20%
Diarrhea	8%	9%	4%	0%	<3%	<3%	18%	15%
Rhinitis	6%	6%	<3%	<3%	<3%	<3%	NA	14%
Rash	8%	6%	<3%	<3%	<3%	<3%	NA	NA

Note: Adapted with permission from D'Angelo S, Palazzi C, Cantini F, Lubrano E, Marchesoni A, Mathieu A. Etanercept in spondyloarthopathies. Part II: safety and pharmacoeconomic issues. *Clin Exp Rheumatol.* 2011;29:865–870.[89]

Abbreviations: AS, ankylosing spondylitis; RCT, randomized clinical trials; OLE, open-label extension; ETN, etanercept; PL, placebo; TW, twice a week; OW, once a week.

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Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis

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ARTICLE INFO

Keywords:
Switching
TNF inhibitor
Axial spondyloarthritis
Review

ABSTRACT

Objective: To assess the impact of switching tumor necrosis factor (TNF)-alpha inhibitors on patients with axial spondyloarthritis (axSpA).
Methods: PubMed literature searches were conducted using combinations of search terms including ankylosing spondylitis, spondyloarthropathy, spondyloarthritis, switch/switching, drug survival, and TNF/tumor necrosis factor to identify published articles with data on outcomes related to switching biologic therapies in patients with axSpA.
Results: Of the 134 studies screened, 21 were identified as reporting data on switching TNF inhibitors in patients carrying a diagnosis of axSpA or ankylosing spondylitis. The most common reasons for switching from the first TNF inhibitor were lack of efficacy (14–68%), loss of efficacy (13–61%), and adverse events/poor tolerability (13–57%). Switching TNF inhibitors was beneficial for a substantial proportion of patients with axSpA who failed to respond to initial or even second TNF inhibitor therapy and adverse effects were not enhanced. Drug survival rates were generally lower for the second (47–72% at 2 years) or third TNF inhibitor (49% at 2 years) than for the first TNF inhibitor (58–75% at 2 years). Predictors of responses in TNF-naïve patients included HLA-B27 positivity, absence of enthesitis, age ≤ 40 years, elevated C-reactive protein level, good functional status, and shorter disease duration. Predictors of drug survival included male sex and peripheral arthritis. Common characteristics of patients who switched TNF inhibitors included female sex, older age, more severe disease, greater symptom burden, higher erythrocyte sedimentation rate, complete ankyloses, and enthesitis.
Conclusion: When the first or even the second TNF inhibitor fails, switching to an alternate one is not an unreasonable clinical therapeutic decision.

Switching anti- TNFα in AS

Drug survival rates in switching studies in ankylosing spondylitis or axial spondyloarthritis

Study	Drug 1[a] survival	Drug 2 survival	Drug 3 survival
Glintborg et al. [11] DANBIO registry	58% at 2 years	47% at 2 years	49% at 2 years
Heinonen et al. [8]	75% at 2 years	72% at 2 years	NR
Lie et al. [5] NOR-DMARD registry	65% at 2 years	60% at 2 years	NR
Fabbroni et al. [22]	70% at 33.7 months	85% at 6 months	NR
Dadoun et al. [23]	65% at 1 year	60% at 1 year	NR

Not shown is that drug survival rate depends upon the reason for switching. Patients with a lack of response to the first TNF inhibitor are unlikely to respond to a second TNF inhibitor, while patients with a loss of response or intolerance to the first TNF inhibitor are more likely to respond to a second TNF inhibitor [6].
NOR-DMARD, Norwegian Disease-Modifying Antirheumatic Drug; NR, not reported; TNF, tumor necrosis factor.

[a] Drug 1 indicates patients were previously biologic-naïve.

Deodhar A and Yu D. Seminars in Arthritis and Rheumatism 47 (2017) 343–350

Baraliakos et al. Arthritis Research & Therapy 2013, 15:R67
http://arthritis-research.com/content/15/3/R67

arthritis research&therapy

RESEARCH ARTICLE Open Access

Long-term outcome of patients with active ankylosing spondylitis with etanercept-sustained efficacy and safety after seven years

Xenofon Baraliakos[1*], Hildrun Haibel[2], Claudia Fritz[3], Joachim Listing[3], Frank Heldmann[1], Juergen Braun[1] and Joachim Sieper[2]

Abstract

Introduction: Data from clinical studies on the long-term efficacy and safety of anti-tumor necrosis factor (TNF)-α therapy in patients with ankylosing spondylitis (AS) are scarce. This is the first report on continuous treatment with the TNFα fusion protein etanercept over seven years (y).

Methods: Overall, 26 patients with active AS were initially treated with etanercept 2 × 25 mg s.c./week with no concomitant disease modifying anti-rheumatic drugs (DMARDs) or steroids. The clinical response was assessed by standardized parameters. The primary outcome was the proportion of patients in the Spondyloarthritis International Society (ASAS) partial remission at seven years. AS disease activity scores (ASDAS) for status and improvement were compared to conventional outcome measures.

Results: Overall, 21/26 patients (81%) completed two years of treatment and 16/26 patients (62%) completed seven years. In the completer analysis, 31% patients were in ASAS partial remission at seven years, while 44% patients showed an ASDAS inactive disease status. Mean Bath AS activity index (BASDAI) scores, which were elevated at baseline (6.3 ± 0.9), showed constant improvement and remained low: 3.1 ± 2.5 at two years and 2.5 ± 2.2 at seven years, while ASDAS also improved (3.9 ± 0.7 at baseline, 1.8 ± 0.9 at two years, 1.6 ± 0.8 at seven years), all P <0.001. From the 10 dropouts, only 5 patients discontinued treatment due to adverse events. Patients who completed the study had lower baseline Bath AS function index (BASFI) scores vs. patients who discontinued. No other clinical parameter at baseline could predict any long-term outcome.

Conclusions: This study confirms the clinical efficacy and safety of etanercept in patients with active AS over seven years of continuous treatment. After seven years, more than half of the initially treated patients remained on anti-TNF therapy, and one-third were in partial remission.

Trial Registration: ClinicalTrials.gov: NCT01289743

Keywords: ankylosing spondylitis, TNFa, etanercept, ASDAS, BASDAI

CONCISE REPORT

Switching tumour necrosis factor α antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period

Fabrizio Conti, Fulvia Ceccarelli, Elisa Marocchi, Leonardo Magrini, Francesca Romana Spinelli, Antonio Spadaro, Rossana Scrivo, Guido Valesini

Ann Rheum Dis 2007;**66**:1393–1397. doi: 10.1136/ard.2007.073569

Objective: To evaluate the clinical response after switching from one tumour necrosis factor (TNF)α antagonist to another in patients with ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

Methods: In this ongoing, longitudinal, observational study, data were prospectively collected on efficacy and safety since 2000 for patients starting biological treatments. The present analysis was restricted to patients with a diagnosis of spondyloarthropathy (SpA) who switched from one TNFα antagonist to another because of inadequate efficacy or adverse events.

Results: In total, 589 anti-TNFα-naive patients were registered, of whom 165 had a diagnosis of SpA; 7 patients with AS and 15 with PsA received >1 TNFα antagonist. Two patients with PsA were treated with all the drugs. In all, 16 subjects switched from infliximab to etanercept, 7 from etanercept to adalimumab and 1 from etanercept to infliximab. Overall, a clinical response was seen in 75% of patients who changed from infliximab to etanercept, and in 57.1% who switched from etanercept to adalimumab.

Conclusions: The findings of this study on a selected population of patients with SpA indicate that the failure of an initial TNFα antagonist does not preclude the response to another one. Further trials are needed to confirm this preliminary observation.

In this paper, we report the
itudinal, observational study, and
after switching from one TNF
patients with AS and PsA within

PATIENTS AND METHODS

In this ongoing, longitudinal, ob
tively collected data since 2000 on
starting biological treatments in o

The present analysis was restrict
of SpA who switched from one TN
a minimum of 6 months' follow-u
(the first SpA patient started t
Patients with AS were classified a
York Criteria,[8] and patients with
Wright criteria modified by Helli
agent was based on clinical co
patients represented a 'real-life' s
TNFα antagonists. Infliximab
intravenously at weeks 0, 2 a
etanercept (25 mg twice weekl
alternate weekly) were given subc

Clinical assessment

Patients were evaluated by the sa
(before starting the TNFα antag
the last administration of the
graphics, diagnosis, date of diag

Infliximab to Etanercept Switch in Patients with Spondyloarthropathies and Psoriatic Arthritis: Preliminary Data

CAROLINE DELAUNAY, VALÉRIE FARRENQ, ANDRÉ MARINI-PORTUGAL, JEAN-DAVID COHEN, XAVIER CHEVALIER, and PASCAL CLAUDEPIERRE

ABSTRACT. ***Objective.*** To report early experience of switching anti-tumor necrosis factor-α (TNF-α) therapy from infliximab to etanercept in patients with spondyloarthropathy (SpA) and psoriatic arthritis (PsA).
Methods. Thirteen patients with various SpA (7 with ankylosing spondylitis and 6 with undifferentiated SpA) and 2 patients with PsA were receiving infliximab. Because they were experiencing inadequate response or adverse events, therapy was changed to etanercept. Patients were evaluated for response to the change in anti-TNF-α therapy at baseline, after 3 months, and then every 6 months.
Results. During the mean 10-month followup after the change in therapy, 9 of 13 patients with SpA and both patients with PsA responded to etanercept and none experienced intolerance to this agent.
Conclusion. These data suggest that switching between anti-TNF-α drugs may be useful for patients with SpA who are unresponsive or intolerant to a first anti-TNF-α agent. (J Rheumatol 2005;32:2183–5)

Key Indexing Terms:
SPONDYLOARTHROPATHY PSORIATIC ARTHRITIS ETANERCEPT
INFLIXIMAB SWITCH TREATMENT ANTI-TUMOR NECROSIS FACTOR

frontiers in Medicine

CLINICAL TRIAL
published: 30 October 2020
doi: 10.3389/fmed.2020.566160

Head-to-Head Comparison of Etanercept vs. Adalimumab in the Treatment of Ankylosing Spondylitis: An Open-Label Randomized Controlled Crossover Clinical Trial

James Cheng-Chung Wei[1,2,3], *Hsi-Kai Tsou*[4,5], *Pui-Ying Leong*[1,2], *Chia-Yin Chen*[1,2] *and Jin-Xian Huang*[6]*

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Background: Anti-tumor necrosis factor biological agents had been proved to have a dramatic effect in ankylosing spondylitis (AS). We aimed to determine the efficacy and safety of crossover effects of adalimumab vs. etanercept in AS patients.

Methods: A randomized, open-label crossover study was done in patients with active AS. Patients were randomized into two sequence groups, etanercept first (treatment arm) vs. adalimumab first (control arm) 8 weeks and then switched over for another 8 weeks. The primary endpoints were the difference of the Bath AS activity index and AS disease activity score (ASDAS)crp at week 16. Secondary endpoints were ASDASesr, ASAS20, and ASAS40 response rates and the proportion of patients achieving ASDAS inactive disease and low disease activity at weeks 8 and 16. Patient global assessment and preference was grading on a numerical scale.

Results: A total of 21 patients were screened, and 19 of them were randomly allocated into the treatment arm ($n = 9$) and control arm ($n = 9$). At baseline, age, sex, Bath AS activity index, and ASDAS of both arms were comparable ($p > 0.05$). Both arms showed dramatic improvement, whereas no significance was observed between the changes of ASDAScrp (0.90 ± 1.39 vs. 1.24 ± 1.40 at week 8, $p = 0.612$; 1.02 ± 1.22 vs. 1.26 ± 1.44 at week 16, $p = 0.707$, respectively). ASAS20 and ASAS40 response rates were also comparable at week 8 (33 vs. 44%, $p = 1.000$; 22 vs. 22%, $p = 1.000$) and week 16 (22 vs. 22%, $p = 1.000$; 22 vs. 22%, p = 1.000), respectively. Both arms were well-tolerated without a serious adverse event. Adalimumab was relatively more favorable by patients in both arms, with a total mean grading score of 0.4 (−5–5, $p = 0.218$).

Conclusion: Etanercept and adalimumab can both dramatically improve disease activity in 16 weeks. Crossover administration of etanercept and adalimumab revealed comparable efficacy and safety.


Ευχαριστώ πολύ