AxSpA is not just the spine….

A case of axial spondylarthropathy

George Fragoulis

“Laiko” hospital, Athens, Greece

Porto Heli, May 2025

Disclosures

- Consulting fees: Vianex, Lilly, Janssen, Boheringer-Ingelheim, GSK, AbbVie, Novartis, UCB, Pfizer, Aenorasis

Clinical case

The story of Konstantinos

- Male 38 years old presented in outpatient clinics (2022)
- Low back pain
  - starting ~ 2015
    - ✓ Getting worse over the last 8 months
  - Insidious onset
  - Improving with exercise but not with rest
  - Mild to moderate response to NSAIDs, prn

Clinical case

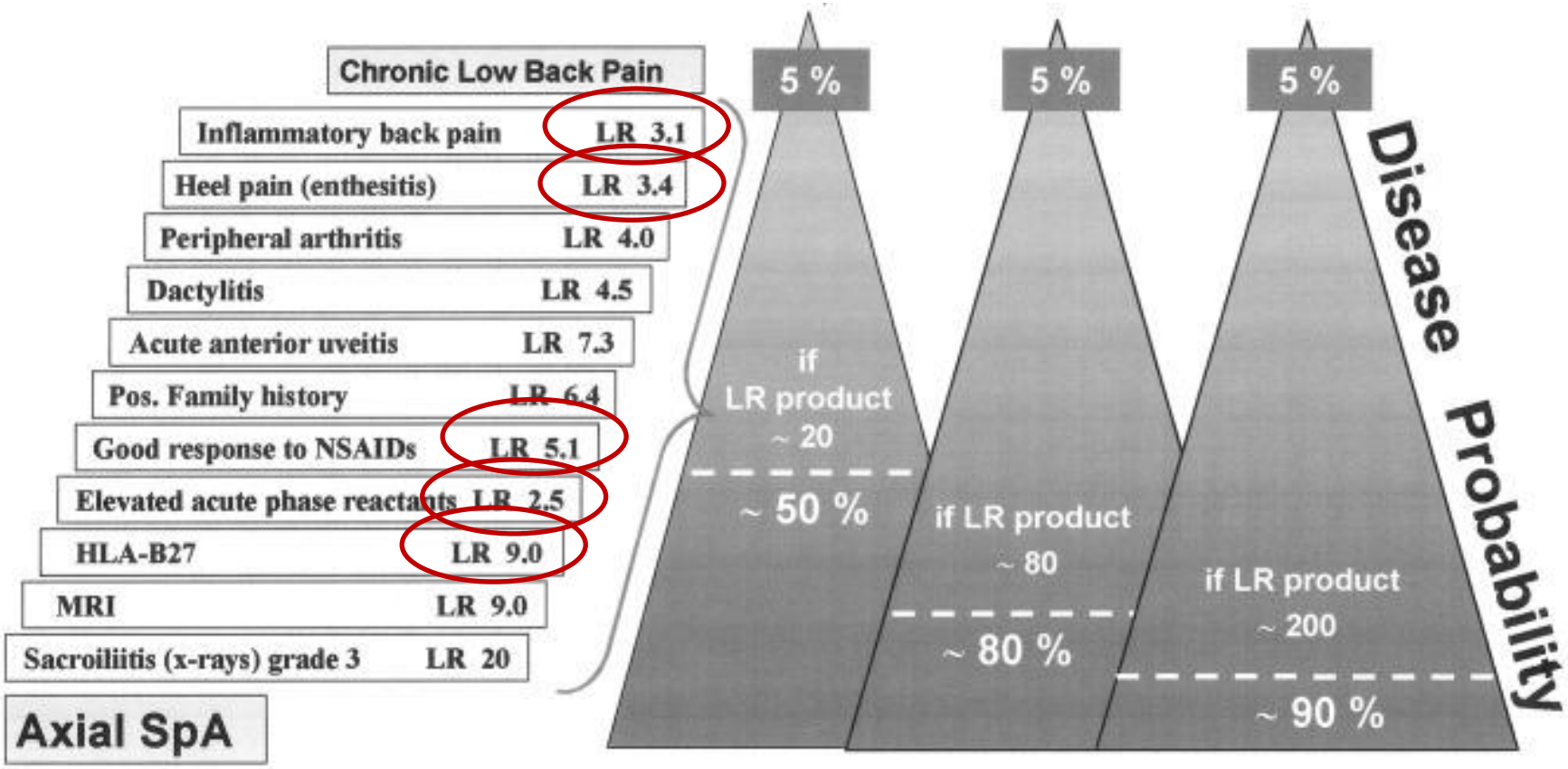
- Past medical history: unremarkable
- Family history: unremarkable
- Habits: smoker (15 pack-years)
- BMI: 27
- Work: mechanic

Clinical case

- Clinical examination: Faber test (+), enthesitis: +2 achilles, skin: -, arthritis: -
- Laboratory findings
  - ESR, CRP: increased
    - ESR: 50
    - CRP: 12mg/L
  - HLA-B27: (+)

Axial SpA

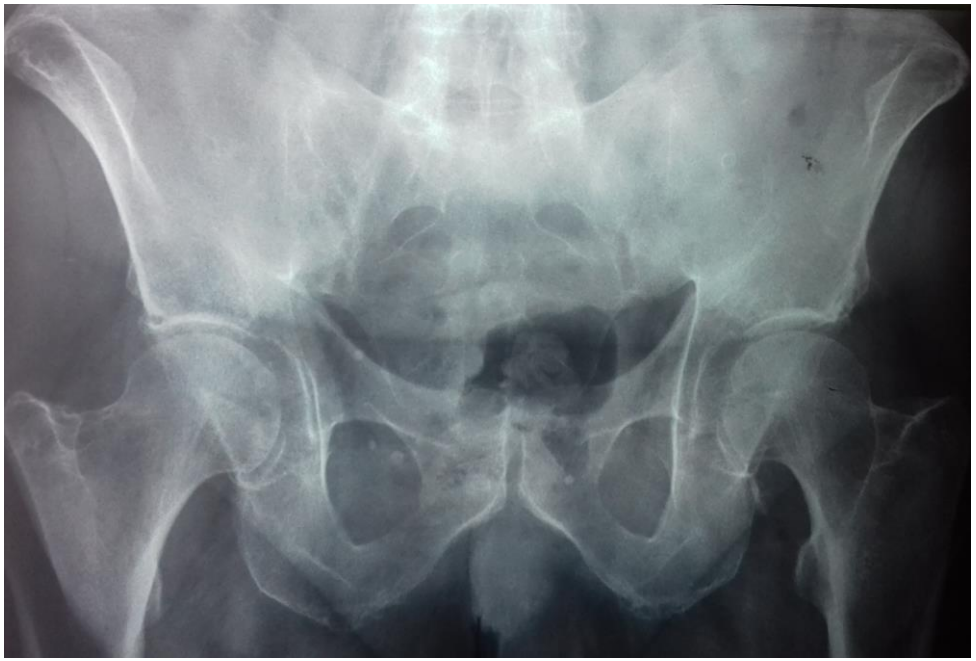
Most likely



(modif from) Rudwaleit M et al Arthr & Rheum 2005

Clinical case

Imaging



Treatment options in SpA

Condition	Monoclonal TNF inhibitors	Etanercept	IL-17-inhibitors	IL-23-inhibitors	JAK-inhibitors
AxSpA	++	++	++	-	++
Uveitis	++	- (?)	-	(?)	(?)
IBD	++	-	-	++	CD(?)/UC++
Psoriasis	++	+	+++	+++	++

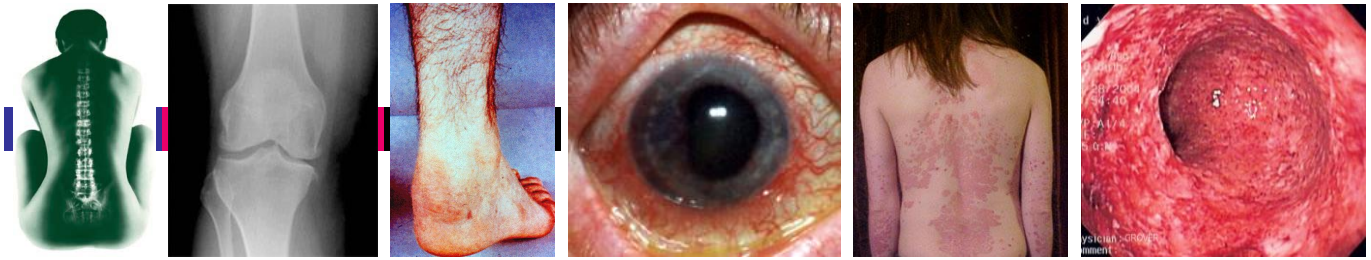
modif from Fragoulis GE & Siebert S Rheumatology (Oxf 2020)

Clinical case

- Treated: Started with etanercept
- In 2023
  - Two episodes of uveitis (treated by opthalmologists)
  - 3/2024, third episode of acute anterior uveitis

Spondyloarthritis

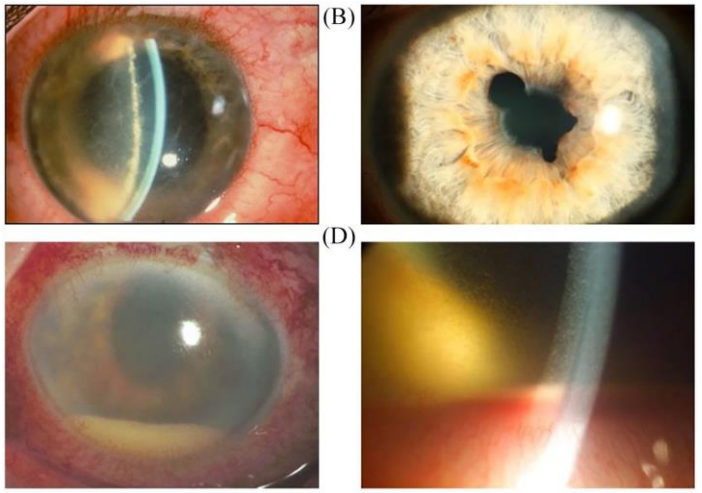
Clinical manifestations



Chandran et al J Autoimmun 2010

Uveitis in SpA

- The most frequent extra-articular manifestation in spondyloarthritis
- Anterior and unilateral in 90%
  - Acute onset
  - Redness/pain/photosensitivity
- Prevalence: 21% - 33%
  - ⇧ disease duration
  - ⇧ in HLA-B27 (+)
  - AxSpA >> PsA



Zeboulon et al. Ann Rheum Dis 2008
de Winter JJ et al. Arthritis Res Ther 2016
Stolwijk C et al. Ann Rheum Dis 2015
Rademacher J et al Ther Adv Mus Dis 2020

Uveitis

Treatment options

- Local Treatment
  - Steroids and cycloplegics
  - Intravitreal implants
- Systemic steroids
  - Especially in bilateral/refractory/posterior segmental
- cDMARDs (? – steroid sparing)
- TNFi (Off label – they are marketed for posterior uveitis)

Rademacher et al Ther Adv M Dis 2020

Uveitis

Treatment options - II

- Adalimumab
  - Approved for uveitis (non-anterior)
- Certolizumab, infliximab, golimumab
  - Have also good results
- Etanercept, Secukinumab
  - Not-effective
- JAKi and IL-23i
  - No data yet

Rademacher J et al Ther Adv Mus Dis 2020
Fragoulis & Siebert Rheumatology 2020
Dick AD et al. Ophthalmology 2013

Extra-articular manifestations

Uveitis

- Retrospective study 264 axSpA and 369 PsA patients from 4 centres in Greece (2018-2023)
- In axSpA, uveitis occurred in 11.7%
  - associated with HLA-B27
    - (OR=4.15, 95%CI 1.16-14.80, p=0.028)
  - ever-present peripheral arthritis
    - (OR=3.05 (1.10 – 8.41, p=0.031)
- Median uveitis recurrence rate was: 0.205 (axSpA)
- Ocular damage (e.g. synechiae) was seen in 16.1% of axSpA (all with recurrent uveitis)

Rheumatology International (2023) 43:2081–2088
https://doi.org/10.1007/s00296-023-05424-0

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

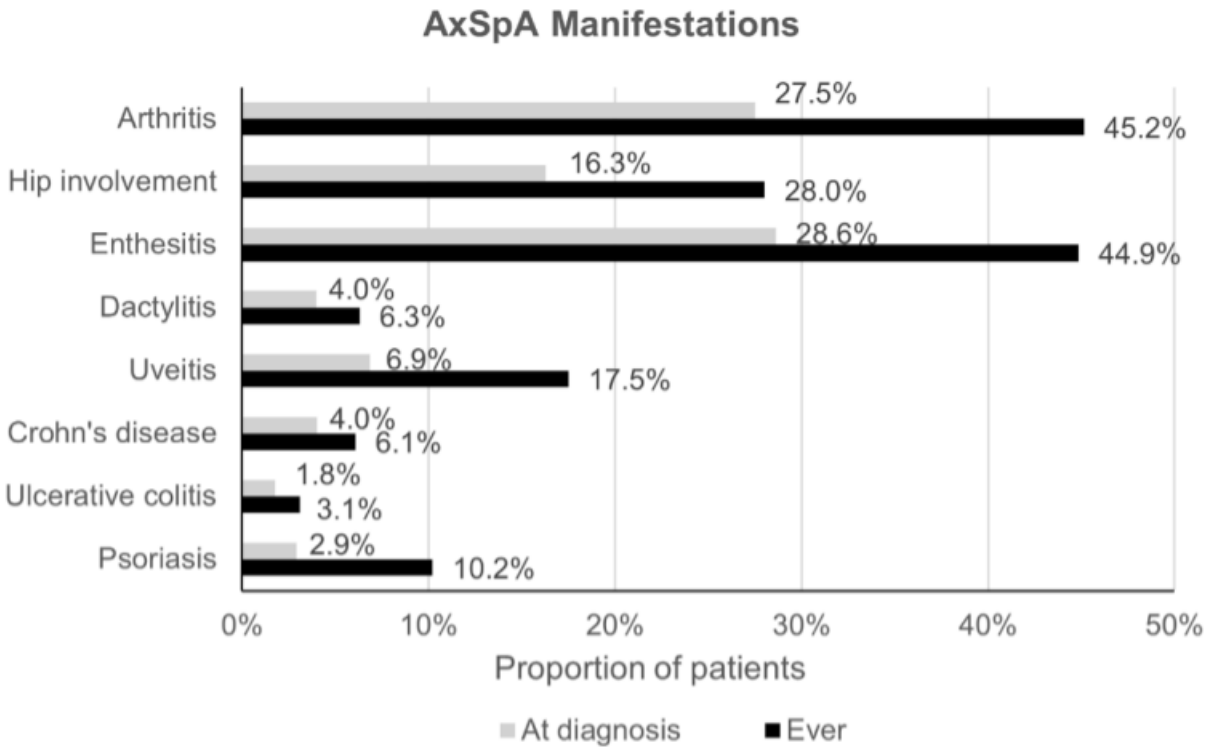
Higher frequency but similar recurrence rate of uveitis episodes in axial spondylarthritis compared to psoriatic arthritis. A multicentre retrospective study

Nikolaos Kougkas[1] · Konstantina Magiouf[2] · Chrysoula G. Gialouri[2,3] · Gerasimos Evangelatos[4] · Maria Pappa[2] · Aikaterini Dimouli[5] · Alexios Iliopoulos[3] · Anastasios Karmanakos[5] · Theodoros Dimitroulas[1] · Maria G. Tektonidou[2] · Petros P. Sfikakis[2] · George E. Fragoulis[2]

Seminars in Arthritis and Rheumatism
Volume 71, April 2025, 152645

Disease characteristics, co-morbidities and treatment response in a contemporary axial spondyloarthritis cohort: Analysis of 717 patients from the Greek AxSpA registry

Charalampos Papagoras [a 1], George E. Fragoulis [b 1], Nikolaos Fytanidis [a], Michael Krikelis [c], Evangelia Mole [c], Sousana Gazi [c], Vasileios Skepastianos [d], Nikolaos Kougkas [d], Theodoros Dimitroulas [d], Nikolaos Koletsos [e], Evripidis Kaltsonoudis [e], Paraskevi V. Voulgari [e], Anastasios Karamanakos [b], Maria Pappa [b], Maria G. Tektonidou [b], Petros P. Sfikakis [b], Kalliopi Klavdianou [f], Eleni Kalavri [f], Konstantinos Kottas [g], Gkikas Katsifis [g]... Dimitrios Vassilopoulos [j]



CLINICAL SCIENCE

Anterior uveitis in patients with spondyloarthritis treated with secukinumab or tumour necrosis factor inhibitors in routine care: does the choice of biological therapy matter?

Ulf Lindström ,[1] Karin Bengtsson ,[1] Tor Olofsson ,[2] Daniela Di Giuseppe,[3] Bente Glintborg ,[4,5] Helena Forsblad-d'Elia,[1] Lennart T H Jacobsson,[1] Johan Askling [3]

Ann Rheum Dis 2021

Objectives & Methods

- **Objective**
  - to compare the risk of AU in patients with SpA treated with secukinumab or TNFi, in routine clinical care.
- Methodology
  - Retrospective, observational based on prospectively collected data from 4 registries (linked with personalized ID)
    - Rheumatology registry, outpatient's registry (ophthalmology), drug-registry, demographics registry
  - Patients
    - All axSpA or undifferentiated SpA starting TNF or SEC (2015-2018)

Methodology

Outcomes

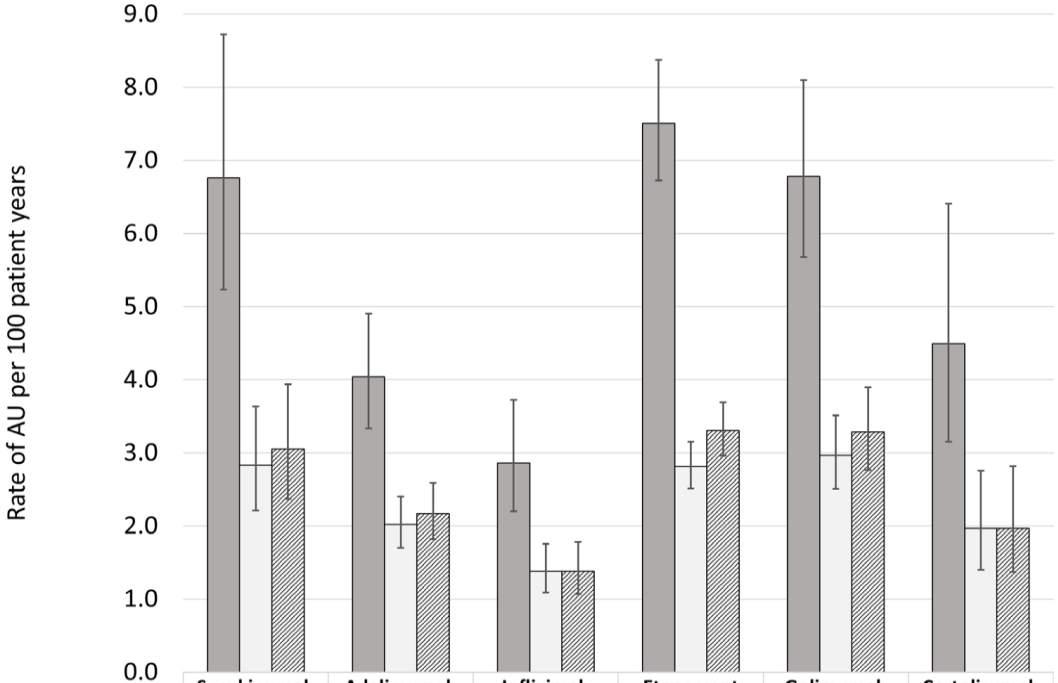
- Primary outcome
  - **Rate of AU-diagnoses** in outpatient ophthalmology care (based on the total number of all registered AU-diagnoses for each patient), per 100 patient-years
  - **Flare**: all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU-diagnosis OR all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).
- The secondary outcome
  - **risk of a first registered AU-diagnosis** in outpatient ophthalmology care (Vs Adalimumab (reference)

Results

Table 1 Baseline characteristics of patients starting secukinumab or a TNFi

	Secukinumab	Adalimumab	Etanercept	Infliximab	Golimumab	Certolizumab	Total
Treatment starts, n	**456**	**1006**	**1800**	**783**	**500**	**306**	**4851**
Sex, men, n (%)	190 (42)	507 (50)	909 (51)	405 (52)	289 (58)	124 (41)	2424 (50)
Age, years, mean (SD)	48 (13)	44 (14)	43 (14)	43 (14)	43 (14)	44 (14)	44 (14)
Diagnosis, AS n (%)	188 (41)	413 (41)	704 (39)	366 (47)	258 (52)	120 (39)	2049 (42)
BASDAI, mean (SD)	6.4 (2.0)	5.5 (2.1)	5.5 (2.0)	5.8 (2.0)	5.3 (2.3)	5.9 (2.1)	5.6 (2.1)
Missing n (%)	248 (54)	622 (62)	1053 (59)	462 (59)	283 (57)	190 (62)	2858 (59)
ASDAS, mean (SD)	3.4 (1.0)	3.0 (1.0)	3.0 (0.9)	3.2 (1.0)	3.0 (1.0)	3.2 (1.0)	3.1 (1.0)
Missing n (%)	257 (56)	669 (67)	1156 (64)	486 (62)	301 (60)	197 (64)	3066 (63)
Patient global assessment, mean (SD)	67 (21)	57 (23)	58 (22)	59 (23)	56 (24)	61 (23)	59 (23)
Missing n (%)	194 (43)	500 (50)	881 (49)	391 (50)	230 (46)	142 (46)	2338 (48)
CRP, mean (SD)	11 (22)	10 (16)	10 (16)	15 (29)	11 (20)	10 (16)	11 (20)
Missing n (%)	185 (41)	462 (46)	799 (44)	329 (42)	208 (42)	120 (39)	2103 (43)
Line of bDMARD treatment							
Line 1, n (%)	35 (8)	470 (47)	1202 (67)	539 (69)	242 (48)	79 (26)	2567 (53)
Line 2, n (%)	106 (23)	347 (34)	415 (23)	100 (13)	112 (22)	96 (31)	1176 (24)
Line 3, n (%)	129 (28)	109 (11)	93 (5)	86 (11)	76 (15)	65 (21)	558 (12)
Line ≥4, n (%)	186 (41)	80 (8)	90 (5)	58 (7)	70 (14)	66 (22)	550 (11)
IBD, n (%)	16 (4)	109 (11)	45 (3)	69 (9)	28 (6)	21 (7)	288 (6)
Psoriasis, n (%)	62 (14)	70 (7)	112 (6)	44 (6)	34 (7)	34 (11)	356 (7)
Previous AU, n (%)*	63 (14)	179 (18)	204 (11)	96 (12)	88 (18)	50 (16)	680 (14)
Concomitant csDMARDs							
Methotrexate, n(%)	73 (16)	168 (17)	255 (14)	215 (27)	77 (15)	47 (15)	835 (17)
Sulfasalazine, n (%)	27 (6)	80 (8)	164 (9)	71 (9)	41 (8)	30 (10)	413 (9)
csDMARD total, n (%)	102 (22)	251 (25)	414 (23)	282 (36)	119 (24)	82 (27)	1250 (26)

Higher rates for SEC and ETN



	Secukinumab	Adalimumab	Infliximab	Etanercept	Golimumab	Certolizumab
All AU diagnoses	6.8	4.0	2.9	7.5	6.8	4.5
Flare definition 1	2.8	2.0	1.4	2.8	3.0	2.0*
Flare definition 2	3.1	2.2	1.4	3.3	3.3	2.0*

Higher HRs for SEC and ETN

Table 3 HR of first on-treatment AU

	N with AU event/N total	Crude HR	Adjusted HR*
Adalimumab	25/1006	Ref	Ref
Secukinumab	13/456	1.53 (0.78–3.02)	2.32 (1.16–4.63)
Etanercept	52/1800	1.25 (0.77–2.01)	1.82 (1.13–2.93)
Infliximab	13/783	0.68 (0.35–1.32)	0.99 (0.49–1.96)
Golimumab	22/500	1.25 (0.71–2.21)	1.59 (0.90–2.80)
Certolizumab	6/306	0.90 (0.37–2.19)	1.12 (0.44–2.83)

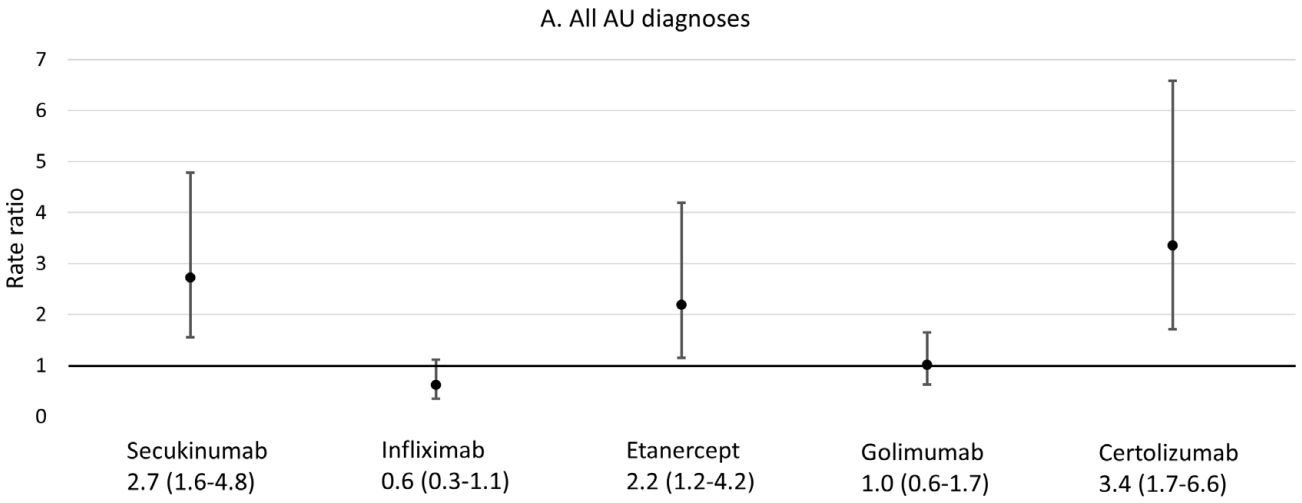
*Adjusted for sex, age, previous history of AU and patient global assessment.
AU, anterior uveitis.

- Conclusions
  - New-onset AU is rare during biological treatment
  - Monoclonal TNFi appear to be more effective choices for preventing AU in SpA patients, compared with etanercept and secukinumab.

Methods

sensitivity analysis

- In total, 1119 patients were included in the analysis comparing rate ratios of AU between a **subsequent** bDMARD treatment and a previous treatment with adalimumab.
- 74 patients were subsequently treated with secukinumab, 200 with infliximab, 516 with etanercept, 217 with golimumab and 112 with certolizumab



Meta-analysis

- Methods
  - PubMed, EMBase, and Cochrane from inception to May 3, 2020
  - placebo-controlled and H2H RCTs assessing TNFi or anti-IL17A in axSpA and reporting safety data on AU
- **Results**
  - 33 RCTs, comprising 4544 treated patients (TNFi: 2101, [ETN] 699, anti-IL17A 1744) and 2497 placebo

Roche et al Arthr Res Ther 2021

Meta-analysis

- Incidence of uveitis was lower with anti-TNF mAb versus placebo (OR = 0.46; CI 95% [0.24; 0.90]) and versus anti-IL17A (OR = 0.34; CI 95% [0.12; 0.92].

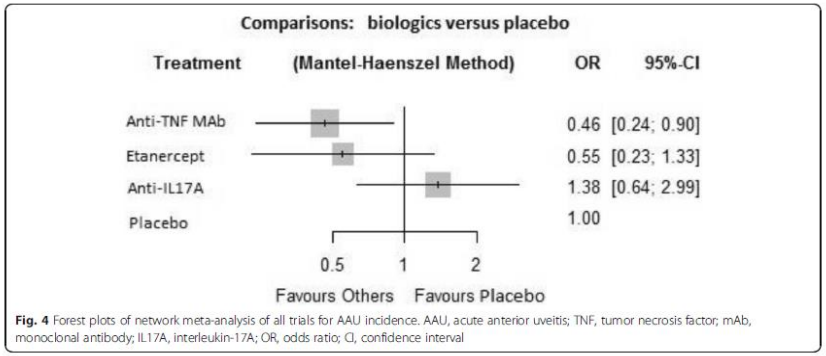


Fig. 4 Forest plots of network meta-analysis of all trials for AAU incidence. AAU, acute anterior uveitis; TNF, tumor necrosis factor; mAb, monoclonal antibody; IL17A, interleukin-17A; OR, odds ratio; CI, confidence interval

- Flares
  - Incidence of AU flares was lower with anti-TNF mAb compared to placebo and with anti-TNF Vs anti-IL-17

Table 2 Comparison for the preventive effect on AAU flares (OR and 95% CI)

Anti-TNF mAb			
0.8406 [0.2953; 2.3927]	Etanercept		
0.3369 [0.1240; 0.9157]*	0.4008 [0.1246; 1.2892]	Anti-IL17A	
0.4647 [0.2406; 0.8975]*	0.5528 [0.2299; 1.3288]	1.3792 [0.6357; 2.9921]	Placebo

OR Odd-Ratio, *CI* Confidence Interval, *AU* Anterior Uveitis, *TNF* Tumor Necrosis Factor, *mAb* monoclonal antibody, *IL17A* interleukin-17A
*$p < 0.05$

Roche et al Arthr Res Ther 2021

Treatment options in SpA

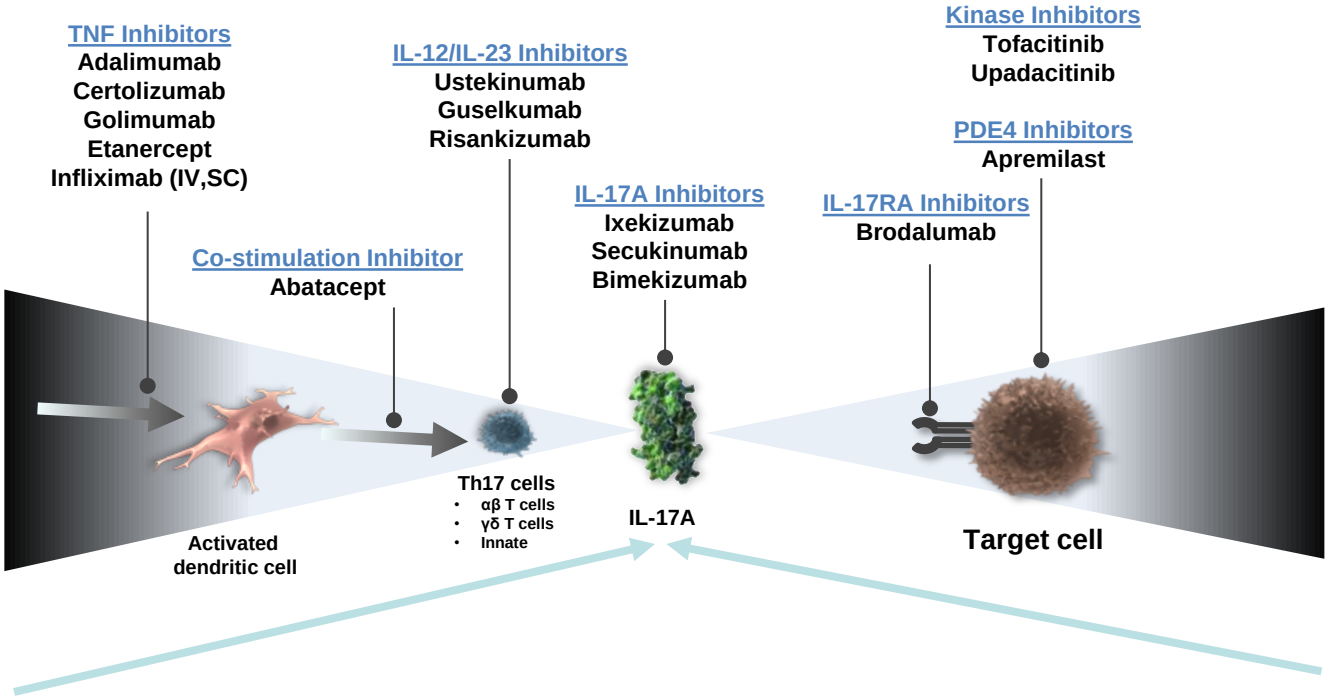
Condition	Monoclonal TNF inhibitors	Etanercept	IL-17-inhibitors	IL-23-inhibitors	JAK-inhibitors
AxSpA	++	++	++	-	++
Uveitis	++	- (?)	-	(?)	(?)
IBD	++	-	-	++	CD(?)/UC++
Psoriasis	++	+	+++	+++	++

- Treatment
  - Infliximab IV

modif from Fragoulis GE & Siebert S Rheumatology (Oxf 2020)

Treatment – the major players

tsDMARDs & Biologics



Nestle F et al. *N Engl J Med.* 2009

Kopf M et al. *Nat Rev Drug Discov.* 2010

Garber K. *Nat Biotechnol.* 2011

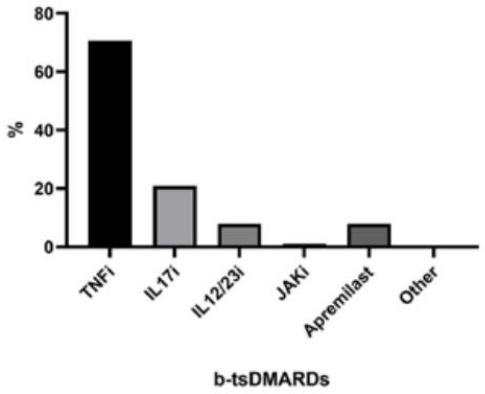
MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 34 4 2023

ORIGINAL PAPER

Disease Profile and Achievement of Therapeutic Goals in a Modern, Nationwide Cohort of 923 Patients with Psoriatic Arthritis

George E. Fragoulis[1*], Charalampos Papagoras[2*], Sousana Gazi[3], Evangelia Mole[3], Michael Krikelis[3], Paraskevi V. Voulgari[4], Evripidis Kaltsonoudis[4], Nikolaos Koletsos[4], Pelagia Katsimpri[5], Dimitrios Boumpas[5], Dimitrios Katsifis[5], Nikolaos Kougkas[6], Theodoros Dimitroulas[6], Petros P. Sfikakis[1], Maria G. Tektonidou[1], Chrysoula Gialouri[1], Dimitrios P. Bogdanos[7], Theodora Simopoulou[7], Christos Koutsianas[8], Eugenia 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]

* *Equal contribution*



TNFi=392
ADA: 38%
IFX= 26%
ETN=18%
CZP: 12%
GOL=7%

Greek multicentre study

AxSpA

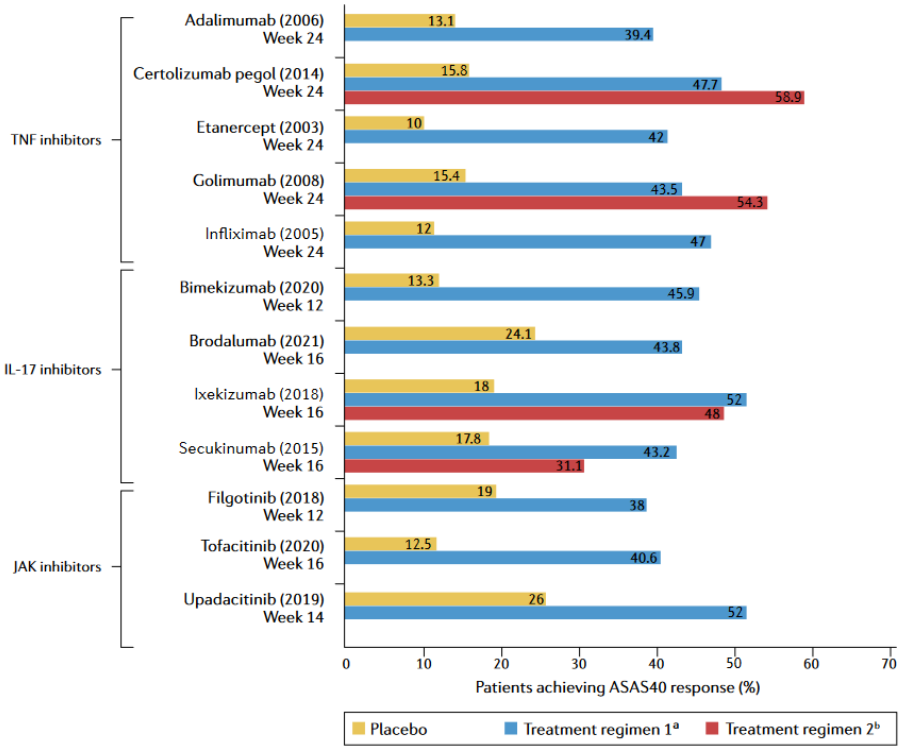
N=717

Current use of bDMARDs	
Adalimumab, n (%)	171 (24)
Certolizumab pegol, n (%)	54 (7.5)
Etanercept, n (%)	61 (8.5)
Golimumab, n (%)	53 (7)
Infliximab, n (%)	155 (22)
Ixekizumab, n (%)	3 (0.4)
Secukinumab, n (%)	54 (7.5)
Ustekinumab, n (%)	3 (0.4)

Papagoras et al (under review)

AxSpA treatments

Indirect comparison

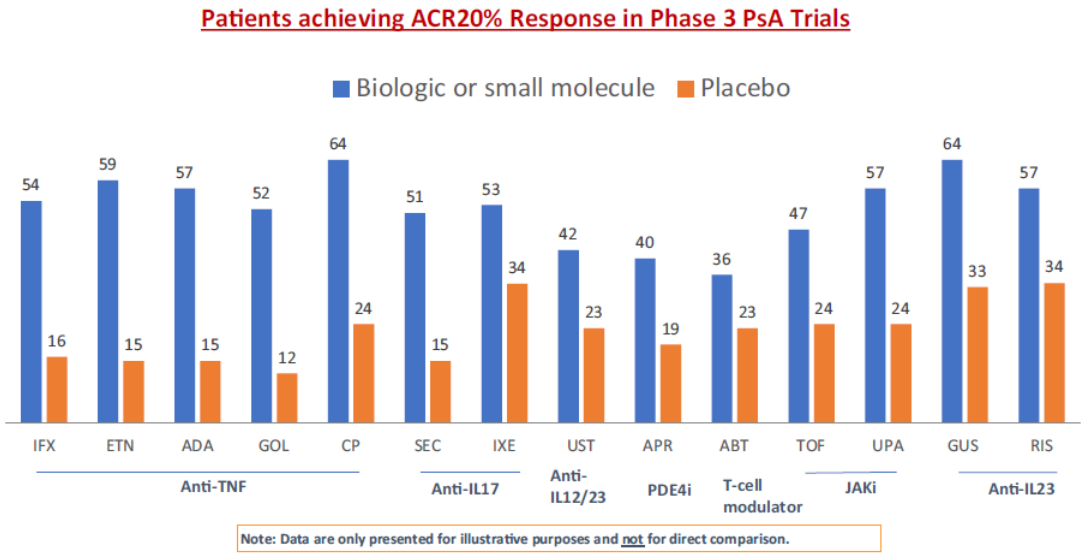


Danve & Deodhar Nat Rev Rheum 2023

PsA treatments

Indirect comparison

Biologic and Small-molecule Therapies for PsA: Efficacy Data from Registration Trials

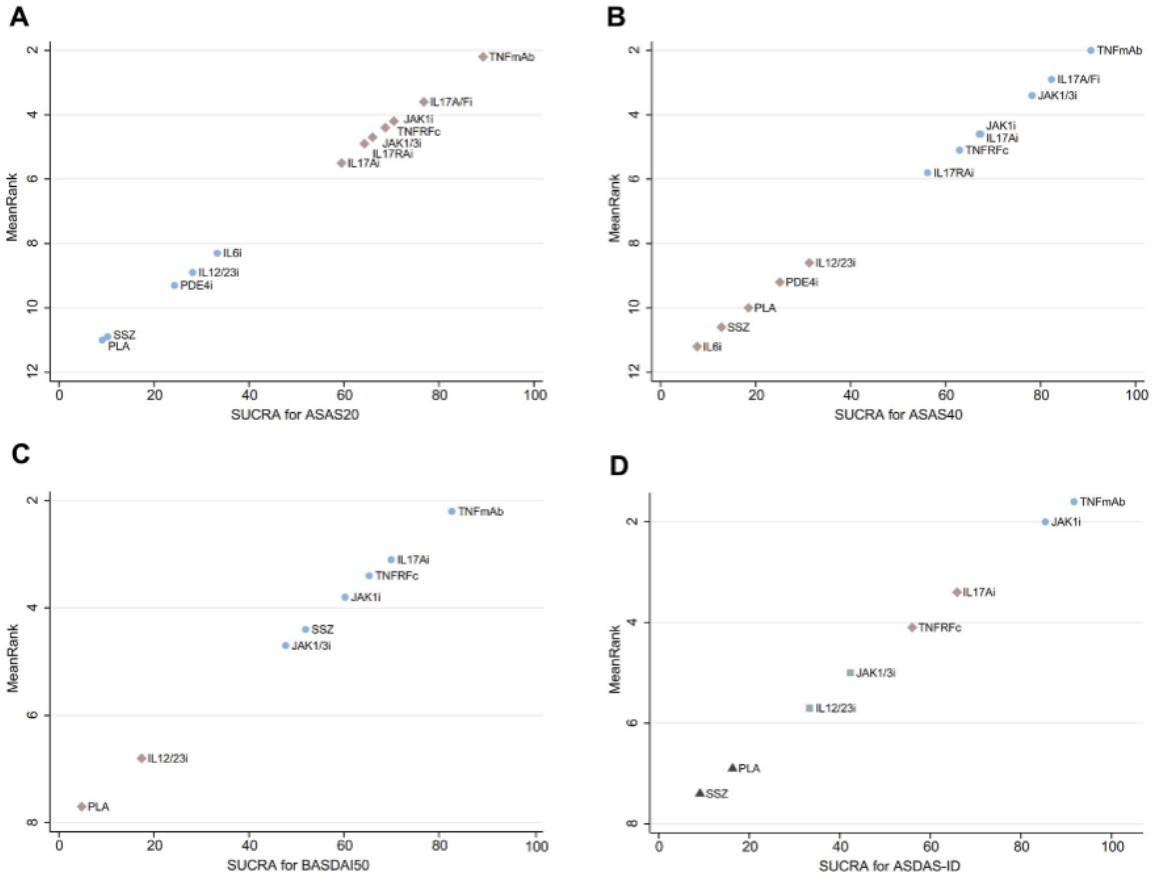


Lubrano et al Rheum Ther 2023
Kumthekar et al Clin Rheum 2023

AxSpA

Network meta-analysis

- surface under the cumulative ranking (SUCRA)
- 57 RCTs
- 11.800 pts



Zhou et al Front Pharmacol 2023

Clinical case

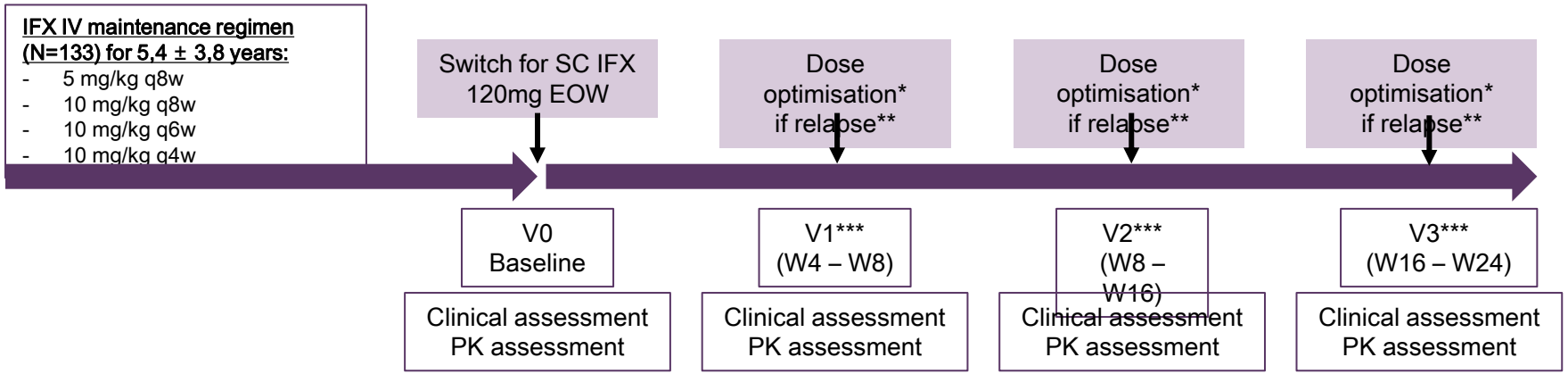
- 10/2024
  - No other uveitis episodes
  - ASDAS: 1.0
  - switch from IV to SC

Effectiveness of Switching From Intravenous to Subcutaneous Infliximab in Patients With Inflammatory Bowel Diseases: the REMSWITCH Study

Anthony Buisson,[1,2] Maria Nachury,[3] Maud Reymond,[1] Clara Yzet,[6] Pauline Wils,[3] Kayre Payen,[1] Marie Laugie,[1] Luc Manlay,[1] Nicolas Mathieu,[4] Bruno Pereira,[5] and Mathurin Fumery[6]

[1]Service d'Hépato-Gastro Entérologie, 3iHP, INSERM, Centre Hospitalier Universitaire de Clermont-Ferrand, Université Clermont Auvergne, Clermont-Ferrand, France; [2]M2iSH, USC-INRA 2018, INSERM U1071, 3iHP, Université Clermont Auvergne, Clermont-Ferrand, France; [3]INSERM U1286 - INFINITE - Institute for Translational Research in Inflammation, Centre Hospitalier Universitaire de Lille, Université de Lille, Lille, France; [4]Department of Hepato-Gastroenterology and Digestive Oncology, Grenoble Alpes University Hospital, Grenoble, France; [5]Unité de Biostatistiques, Direction de la Recherche Clinique et de l'Innovation, Centre Hospitalier Universitaire de Clermont-Ferrand, Université Clermont Auvergne, Clermont-Ferrand, France; and [6]Unité Peritox, Centre Hospitalier Universitaire de Amiens, Université de Picardie Jules Verne, Amiens, France

REMSWITCH- Σχεδιασμός μελέτης

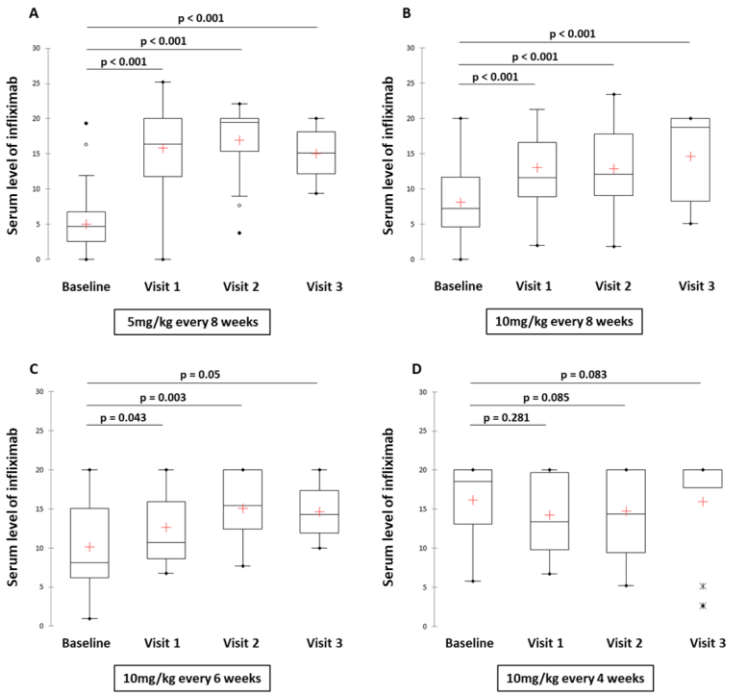


* Dose optimisation: 120mg EOW → 240mg EOW
** Relapse defined as clinical relapse or increase of faecal calprotectin > 150µg/g compared to baseline
*** At the theoretical day of IV infusion between 4 to 8 weeks

EOW, every other week; HBI, Harvey-Bradshaw index; IFX, infliximab; IV, intravenous; q4w, every 4 weeks; q6w, every 6 weeks; q8w, every 8 weeks; SC, subcutaneous; V, visit; W, week

REMSWITCH- Αποτελέσματα

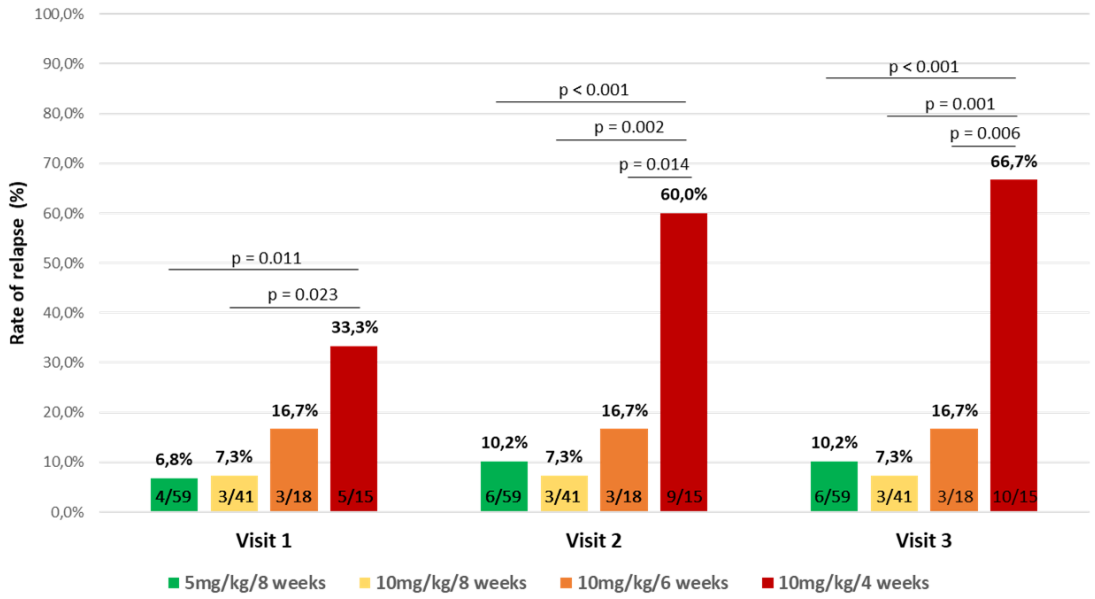
Εξέλιξη των επιπέδων του IFX στον ορό μετά την αλλαγή από IV σε SC



Τα επίπεδα IFX στον ορό αυξήθηκαν σημαντικά μετά το switch σε όλες τις ομάδες πλην της ομάδας που λάμβανε 10 mg/kg q4w

REMSWITCH- Αποτελέσματα

Αθροιστικά ποσοστά υποτροπής στην Επίσκεψη 1, 2 και 3 με βάση το αρχικό IV σχήμα



Το ποσοστό των ασθενών που υποτροπίασε μετά το switch ήταν πολύ μικρό,
Συμβατό με το 10-20% υποτροπής σε ΙΦΝΕ σε ένα χρόνο
πλην της ομάδας που έπαιρνε 10 mg/kg/4 weeks IFX IV

Qiu et al J Gastroenterol 2017

REMSWITCH- Αποτελέσματα

- ✓ **Η αλλαγή από IFX IV σε IFX SC120mg ανά 2 εβδομάδες είναι εφικτή και καλώς αποδεκτή και οδηγεί σε χαμηλό κίνδυνο υποτροπής σε ασθενείς με ΙΦΝΕ, συμπεριλαμβανομένων ασθενών με εντατικοποιημένο δοσολογικό ενδοφλέβιο σχήμα**

- ✓ Παρόλα αυτά, οι ασθενείς με σχήμα 10 mg/kg ανά 4 εβδομάδες θα πρέπει να λάβουν υψηλότερη δόση SC (240mg ανά 2 εβδομάδες)
  - ✓ 93,3% (14/15) των ασθενών πέτυχαν κλινική ύφεση και 80% (12/15) πέτυχαν συνδυασμό κλινικής και βιολογικής ύφεσης (FC<150μg/g)

Clinical Gastroenterology and Hepatology 2023;■:■–■

Switching From Intravenous to Subcutaneous Infliximab is Safe and Feasible in Patients With Inflammatory Bowel Disease Suffering From Obesity: A Post Hoc Analysis of the REMSWITCH Study

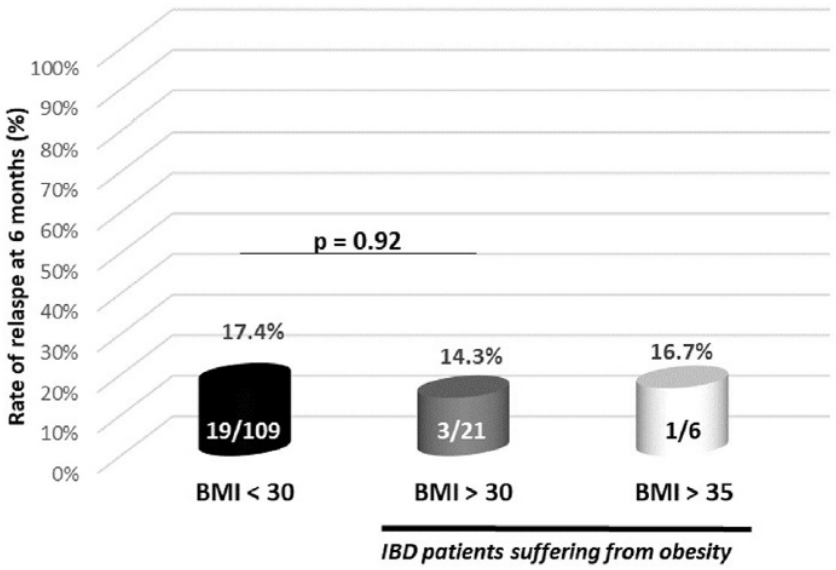
Post-hoc REMSWITCH

21 από τους 130 ασθενείς (16,2%) ήταν παχύσαρκοι, ενώ 6 (28,6%) από αυτούς είχαν BMI >35 kg/m^2

Δοσολογικό σχήμα IFX IV πριν το switch σε 120 mg q2w

8/21 → 5 mg/kg/q8w
8/21 → 10 mg/kg/q8w
4/21 → 10 mg/kg/q6w
1/21 → 10 mg/kg/q4w

Post-hoc REMSWITCH- Αποτελέσματα



Τα ποσοστά υποτροπής μετά το switch από IFX IV σε IFX SC δεν επηρεάστηκαν από το ΔΜΣ των ασθενών

Greek Multicentre study

SWITCHING FROM IV TO SC INFLIXIMAB IN PATIENTS WITH IMMUNE MEDIATED DISEASES IN CLINICAL REMISSION

Viazis N[1], Karamanakos A[2], Mousourakis K[1], Fousekis F[3], Mpakogiannis K[3], Koukoudis A[3], Katsanos K[3], Christodoulou D[3], Cheila M[2], Tzouvala M[4], Zacharopoulou E[4], Giouleme O[5], Katsoula A[5], Liatsos Ch[6], Kyriakos N[6], Zampeli E[7], Papathanasiou E[7], Theodoropopoulou A[8], Karmiris K[8], Psaroudakis I[8], Tribonias G[9], Gazi S[10], Mole E[10], Dimitroulas Th[11], Koutsianas Ch[12], Vasilopoulos D[12], Fragoulis GE[13], Michalakeas N[13], Papagoras C[14], Panagakis P[15], Papoutsaki M[15], Chasapi V[15], Stratigos A[15], Katsikas G[2]

- Retrospective, n=344
- CD, UC, SpA (n=52), RA (n=7), PsA (n=38), PsO
- Receiving IFX-IV for maintenance of remission
  - switched to IFX-SC
  - Only 3.5% (n=12) discontinued treatment (SpA=2, PsA=2)
    - After a mean (SD) period of 8 (4) months
    - 1.5% worsening
    - 2% side effects

Viazis et al 20224 (In Press)

Clinical case

- 3/2025
  - Last seen in the clinics
  - No other uveitis episodes
  - Still in remission

Thank you for your attention ☺