Combinació de fàrmacs biològics:

una opció segura i eficaç per a l'espondiloartritis refractària?

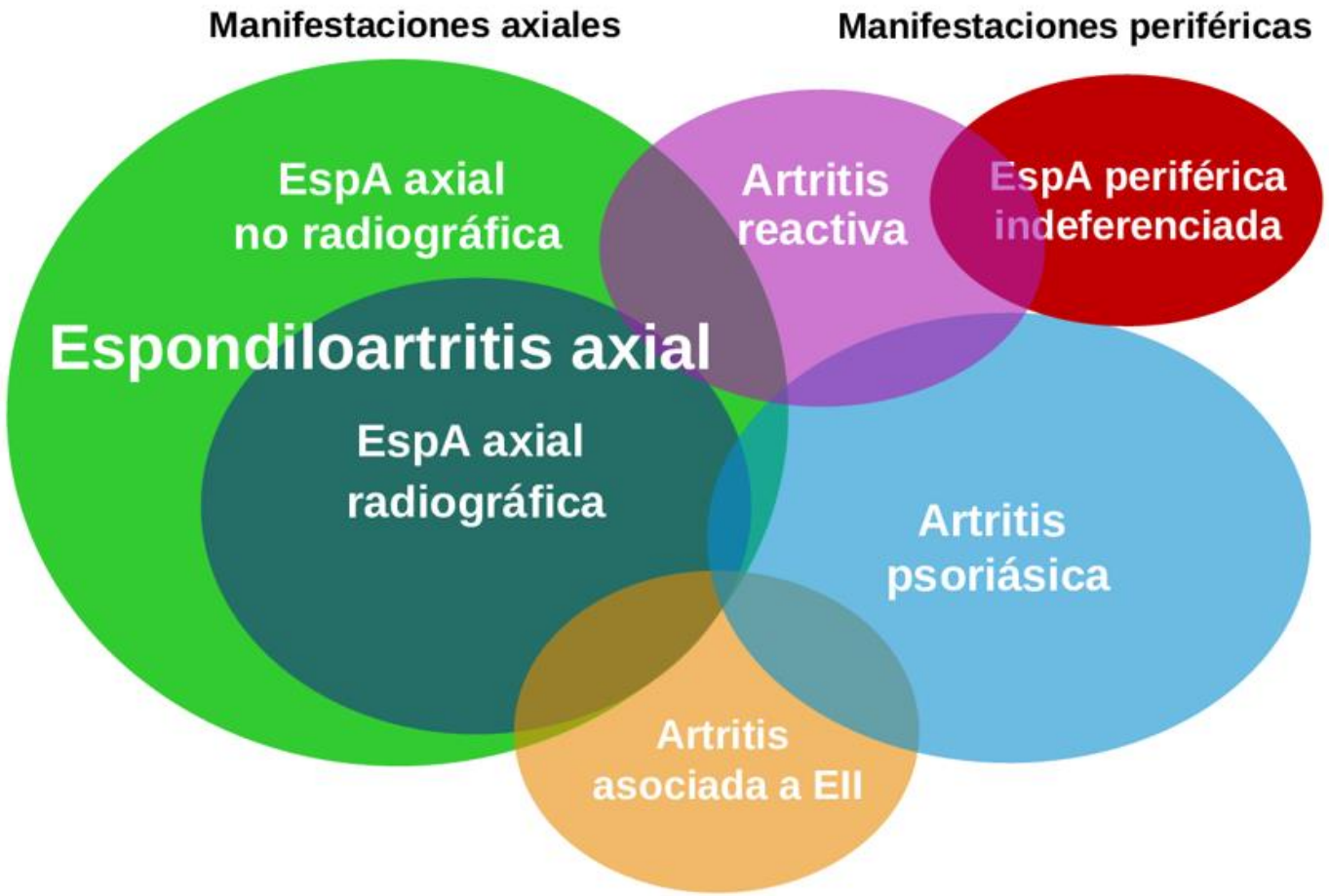
Meritxell Sallés, Judit Font, Julio Ramírez, Xavier Juanola, Ana Laiz,

Mireia Moreno, Manel Pujol i Emma Beltran en el grup EspoCat de la SCR

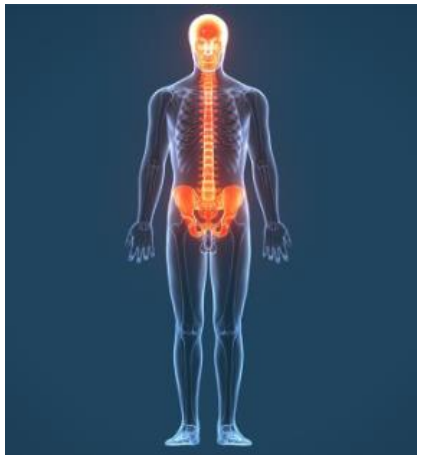
Conflictes interès

Cap per aquesta ponència

Introducció

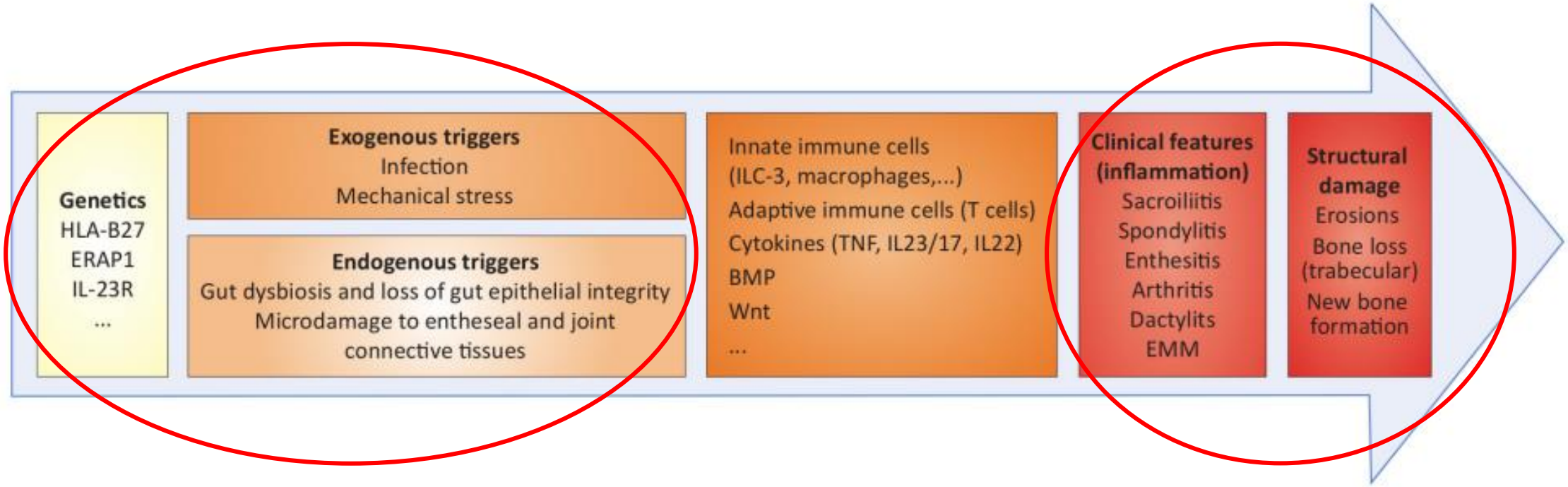


Modificado de Proft F et al. Ther Adv Musculoskelet Dis 2018;10:129-39

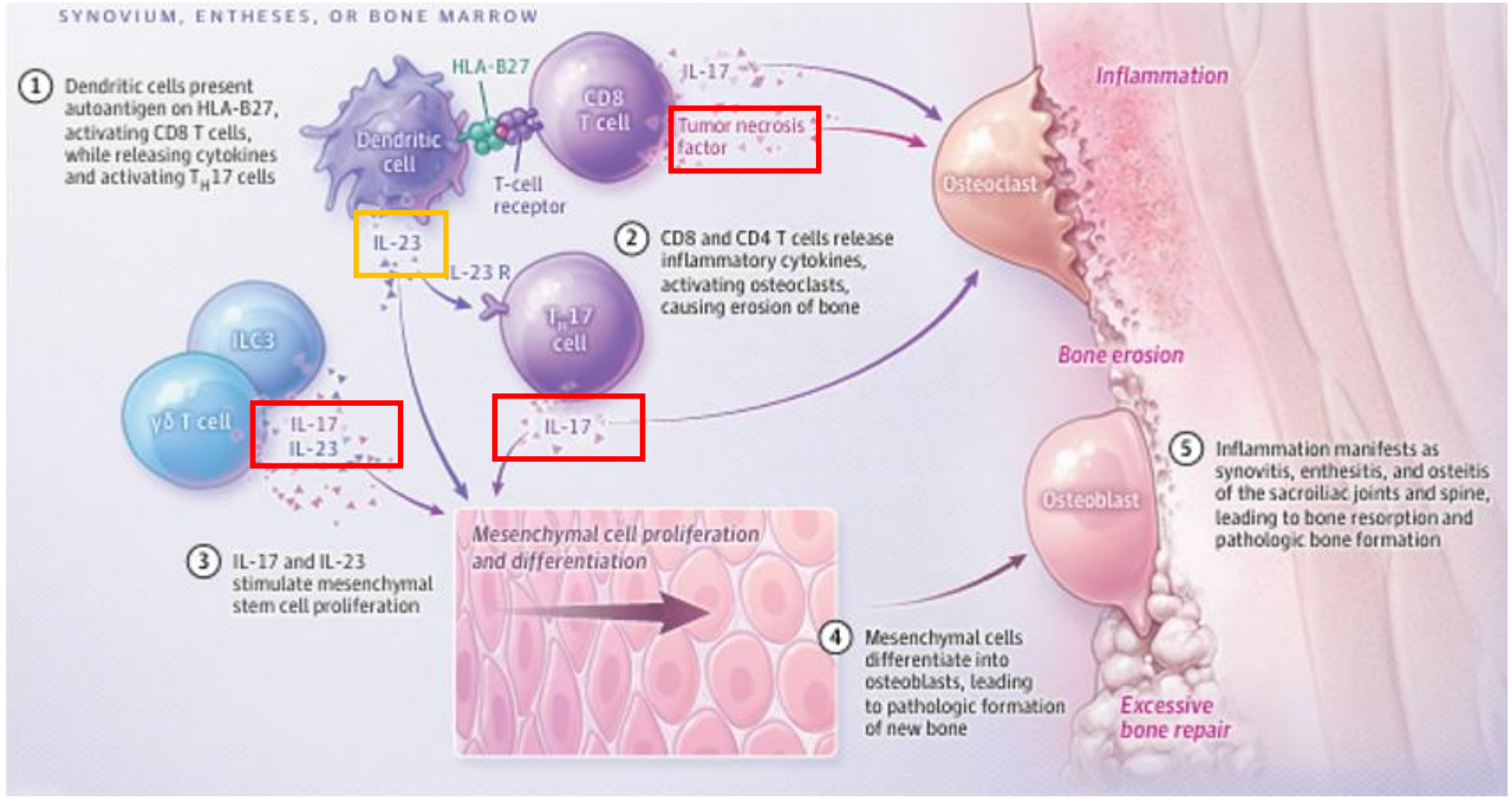


Patogènia Espondiloartritis

Patogènia Espondiloartritis

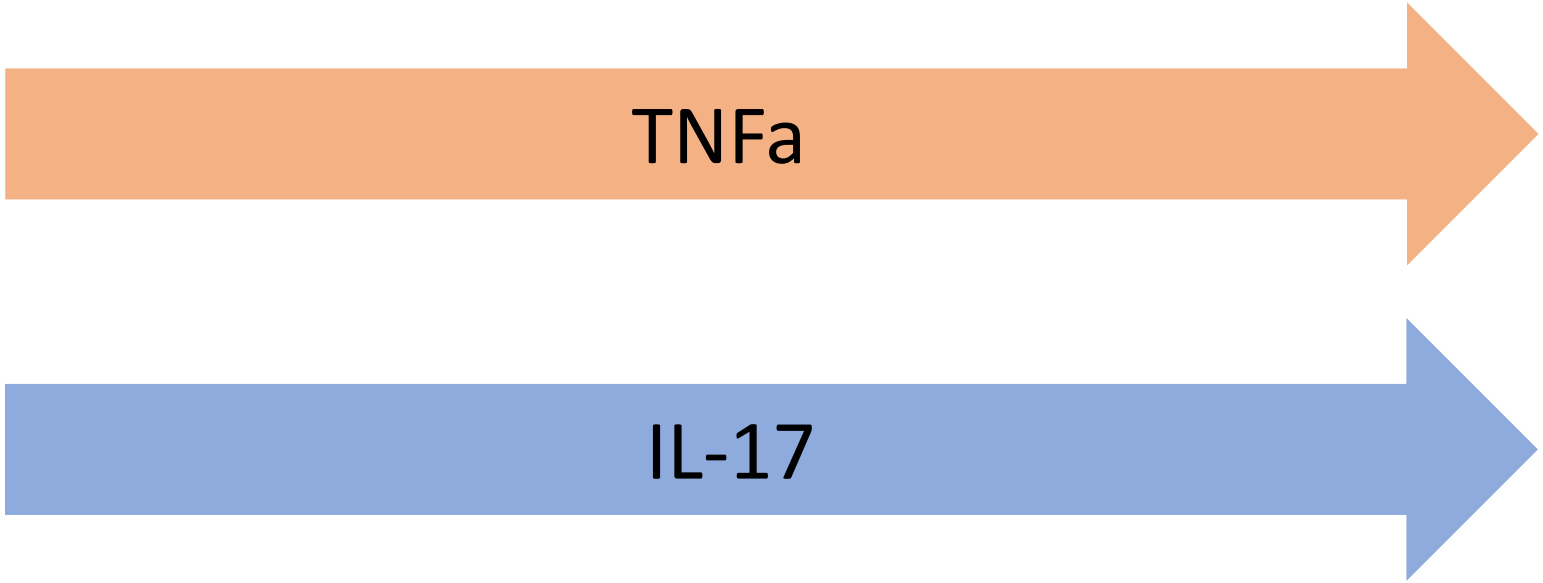


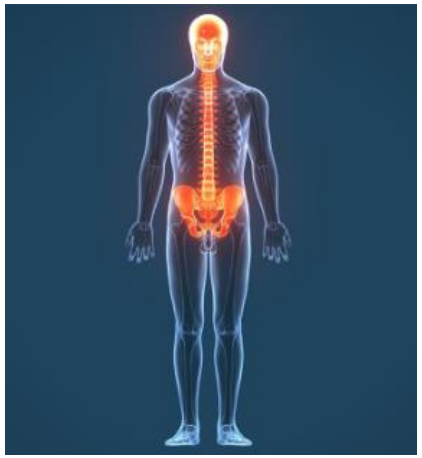
Patogènia Espondiloartritis



Bittar M. JAMA 2024

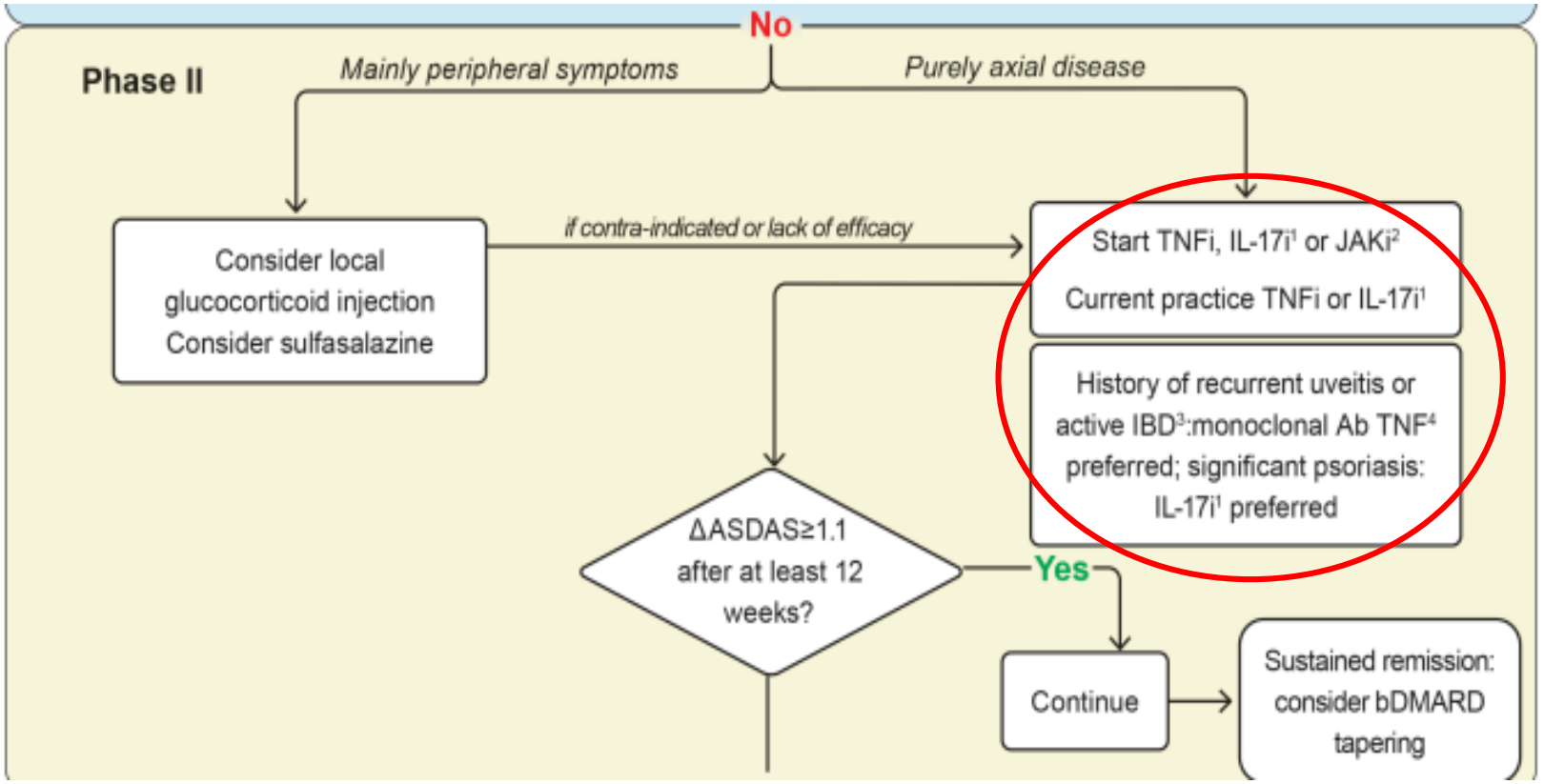
Patogènia Espondiloartritis

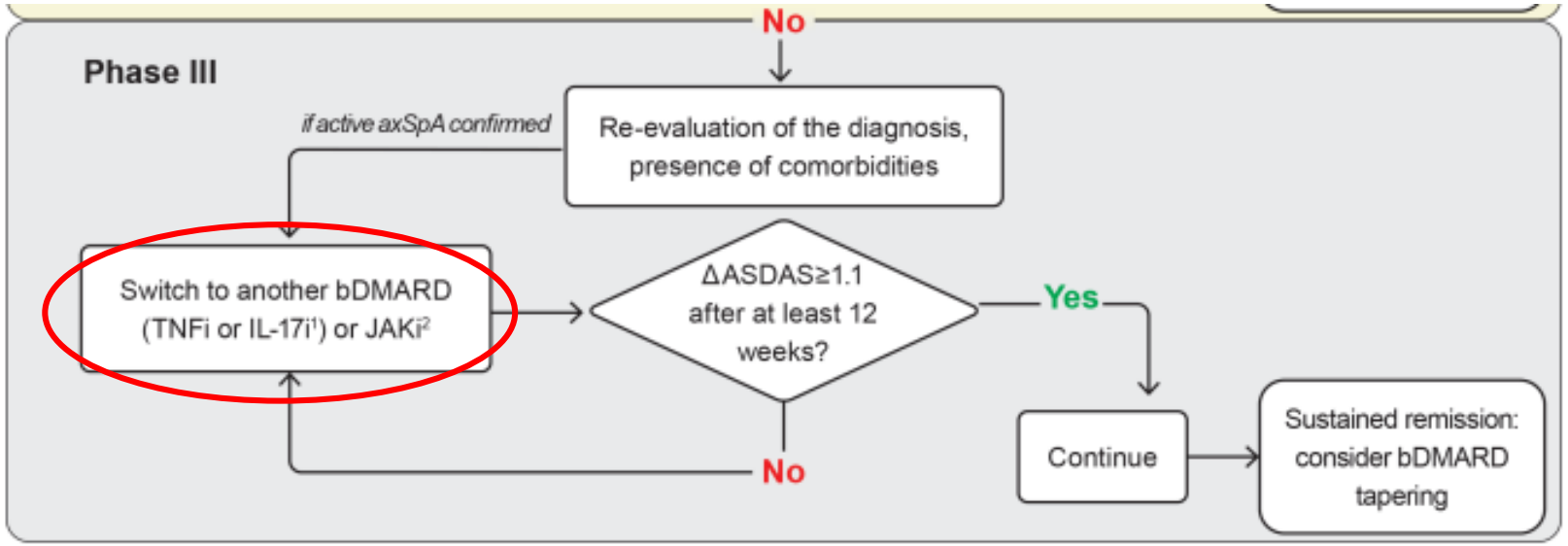




ASAS- EULAR recommendations for the management of axial spondyloarthritis: 2022 update

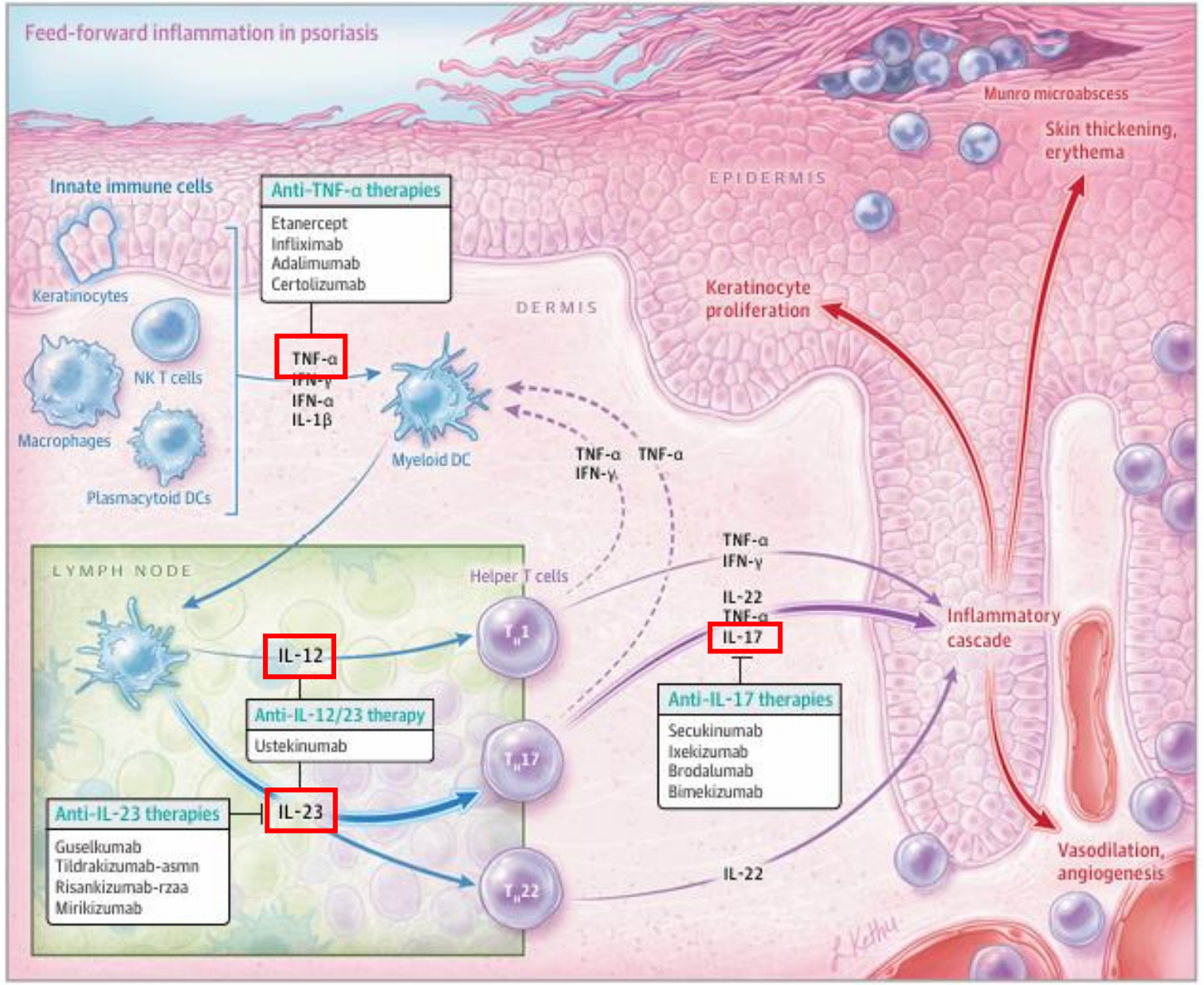
Ann Rheum Dis 2022;0:1–16


No
Phase II
Mainly peripheral symptoms
Purely axial disease
Consider local glucocorticoid injection
Consider sulfasalazine
if contra-indicated or lack of efficacy
Start TNFi, IL-17i[1] or JAKi[2]
Current practice TNFi or IL-17i[1]
History of recurrent uveitis or active IBD[3]:monoclonal Ab TNF[4] preferred; significant psoriasis: IL-17i[1] preferred
ΔASDAS≥1.1 after at least 12 weeks?
Yes
Continue
Sustained remission: consider bDMARD tapering


No
Phase III
if active axSpA confirmed
Re-evaluation of the diagnosis, presence of comorbidities
Switch to another bDMARD (TNFi or IL-17i[1]) or JAKi[2]
ΔASDAS≥1.1 after at least 12 weeks?
Yes
No
Continue
Sustained remission: consider bDMARD tapering

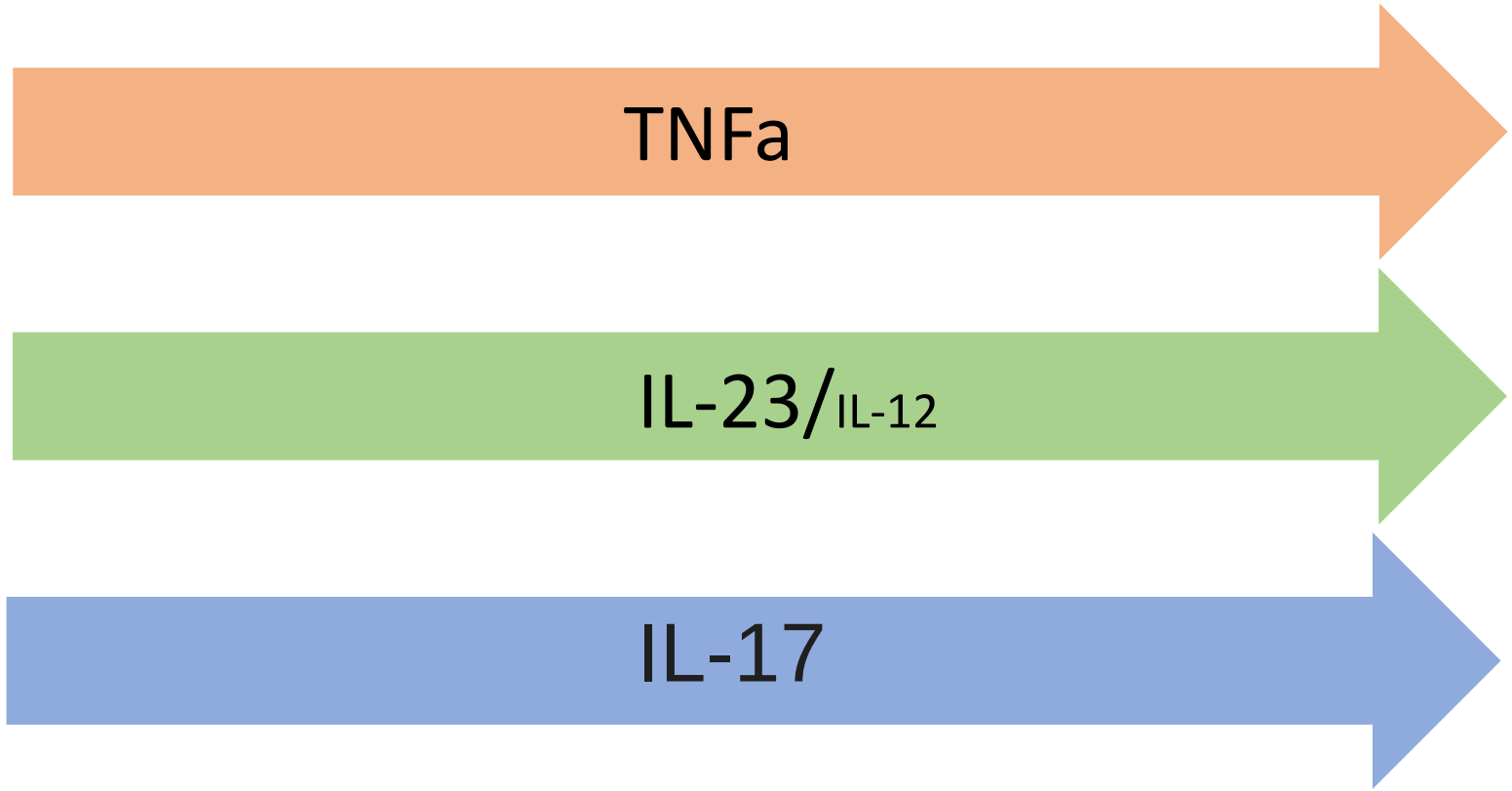
Patogènia Psoriasi/Artritis Psoriàsica

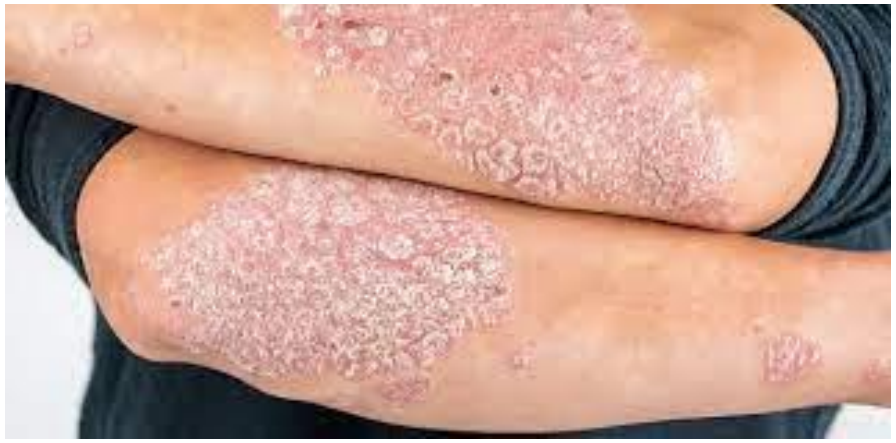
Patogènia Psoriasi



Armstrong AW. JAMA 2020;323:1945

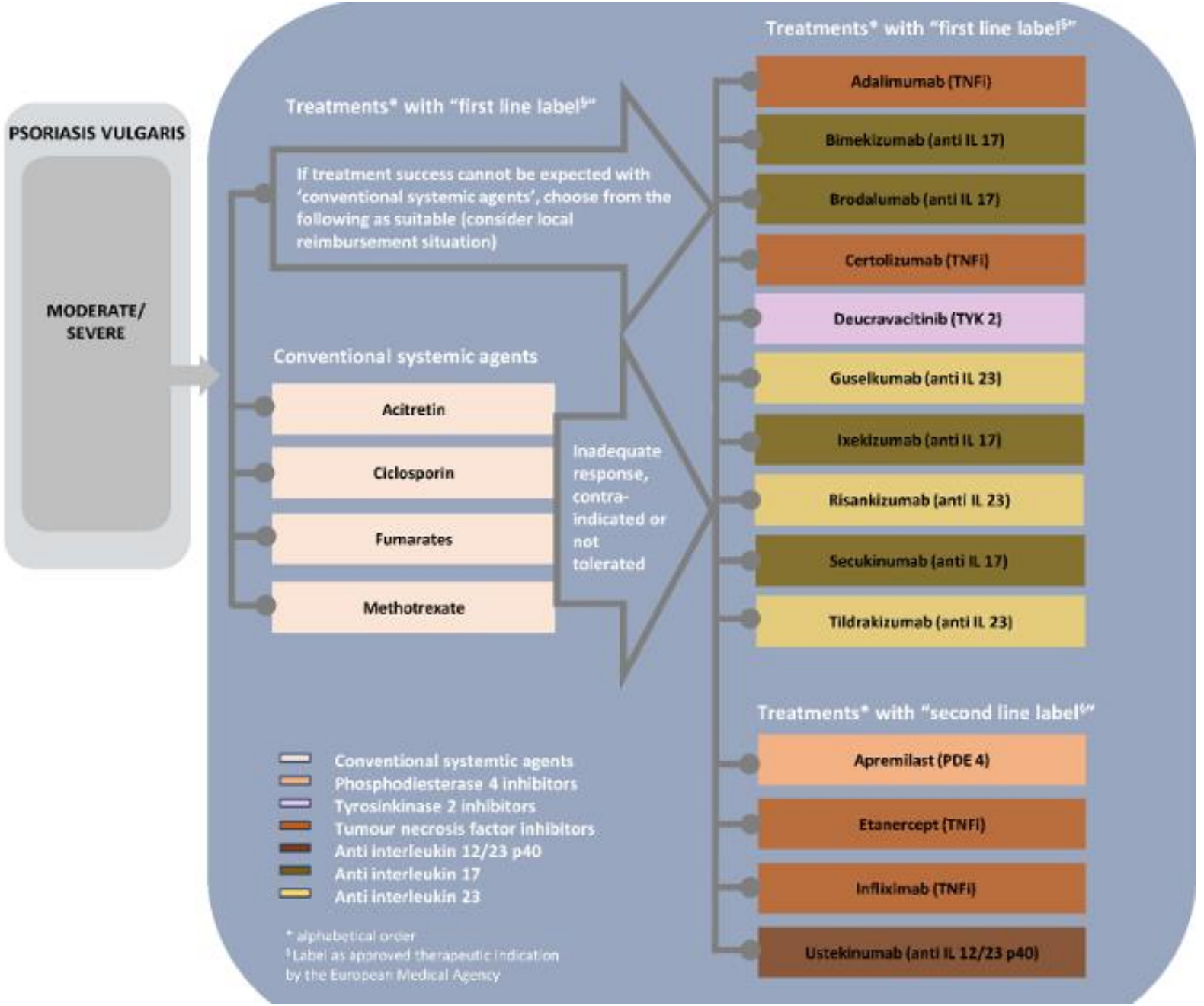
Patogènia Psoriasi/Artritis Psoriàsica





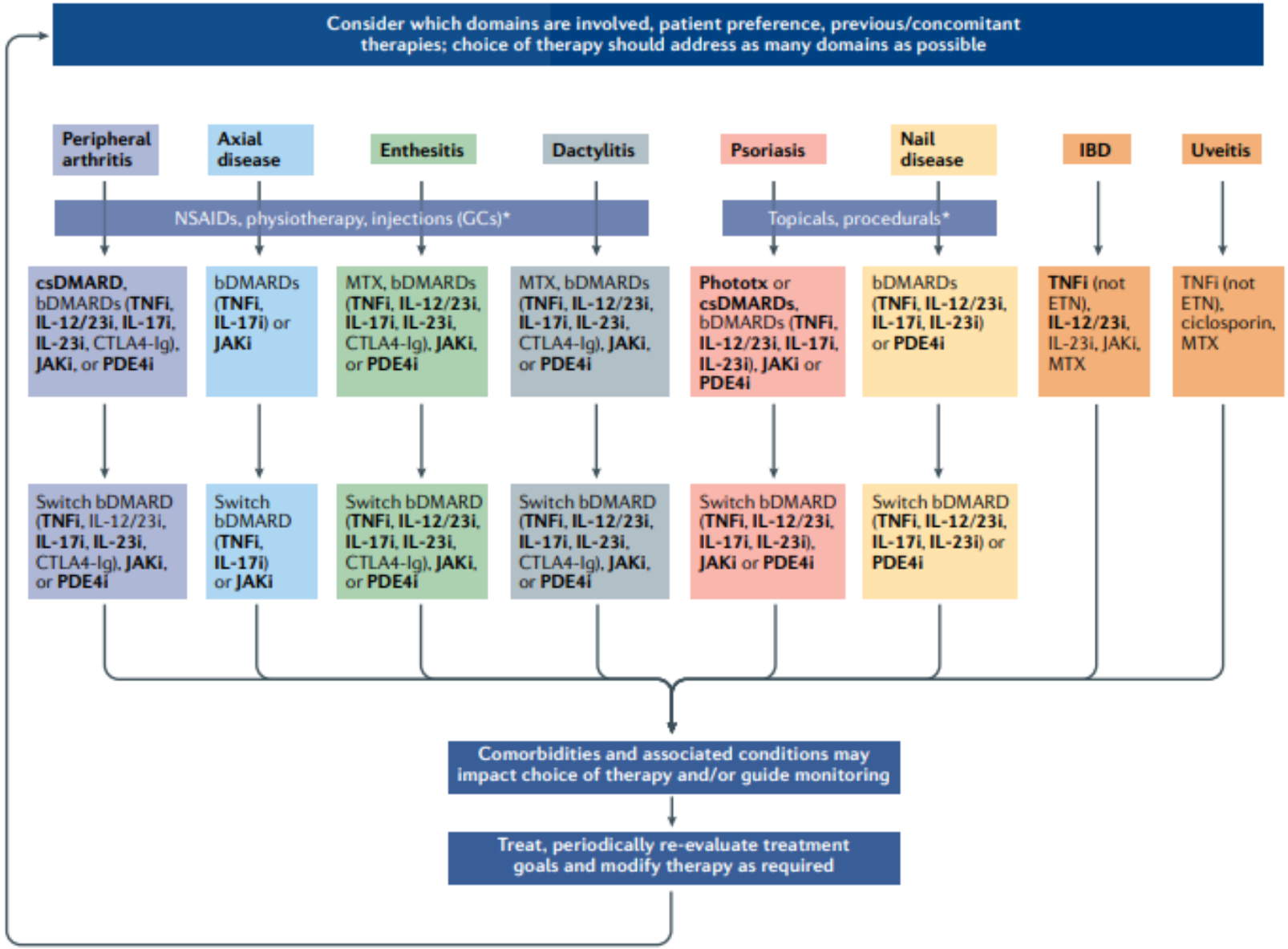
EuroGuiDerm Guideline for the systemic treatment of Psoriasis vulgaris

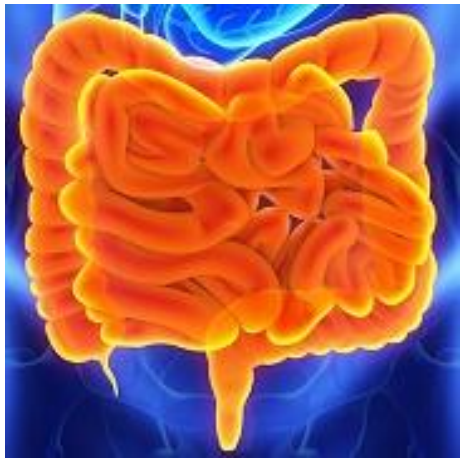
September 2023, revised version March 2024 *


PSORIASIS VULGARIS
MODERATE/ SEVERE
Treatments* with "first line label†"
If treatment success cannot be expected with 'conventional systemic agents', choose from the following as suitable (consider local reimbursement situation)
Conventional systemic agents
Acitretin
Ciclosporin
Fumarates
Methotrexate
Inadequate response, contra-indicated or not tolerated
Treatments* with "first line label†"
Adalimumab (TNFi)
Bimekizumab (anti IL 17)
Brodalumab (anti IL 17)
Certolizumab (TNFi)
Deucravacitinib (TYK 2)
Guselkumab (anti IL 23)
Ixekizumab (anti IL 17)
Risankizumab (anti IL 23)
Secukinumab (anti IL 17)
Tildrakizumab (anti IL 23)
Treatments* with "second line label†"
Apremilast (PDE 4)
Etanercept (TNFi)
Infliximab (TNFi)
Ustekinumab (anti IL 12/23 p40)
Conventional systemtic agents
Phosphodiesterase 4 inhibitors
Tyrosinkinase 2 inhibitors
Tumour necrosis factor inhibitors
Anti interleukin 12/23 p40
Anti interleukin 17
Anti interleukin 23
* alphabetical order
† Label as approved therapeutic indication by the European Medical Agency

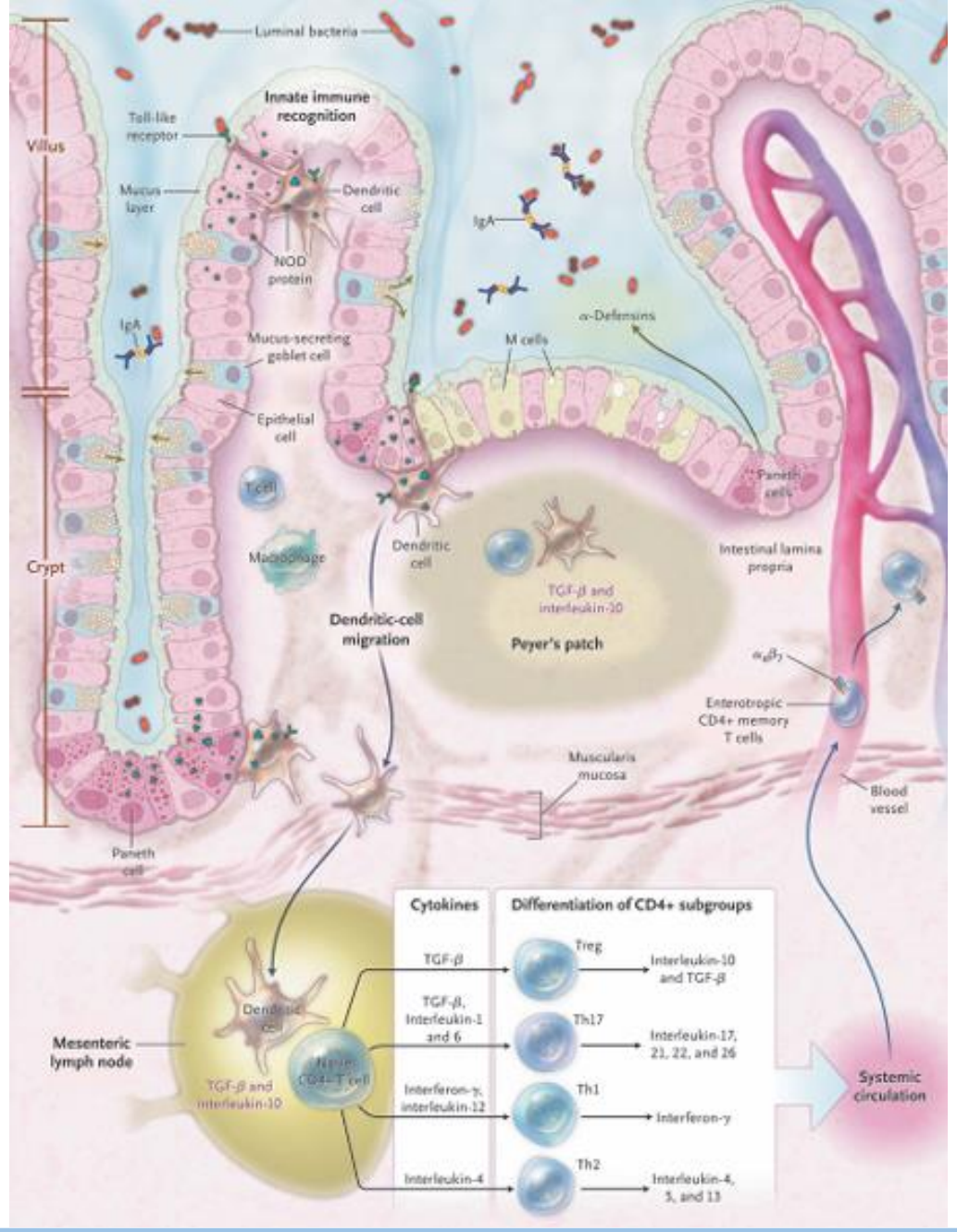
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021

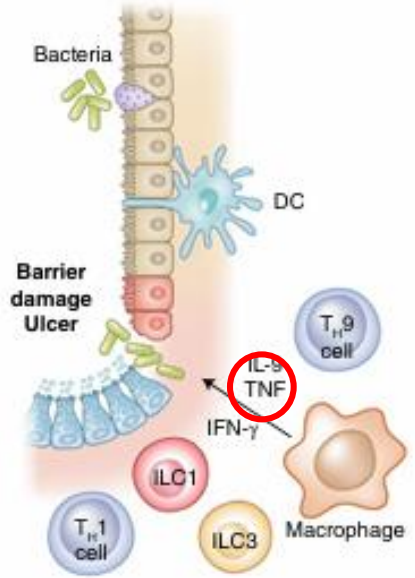
Nat Rev Rheumatol 2022;18:465

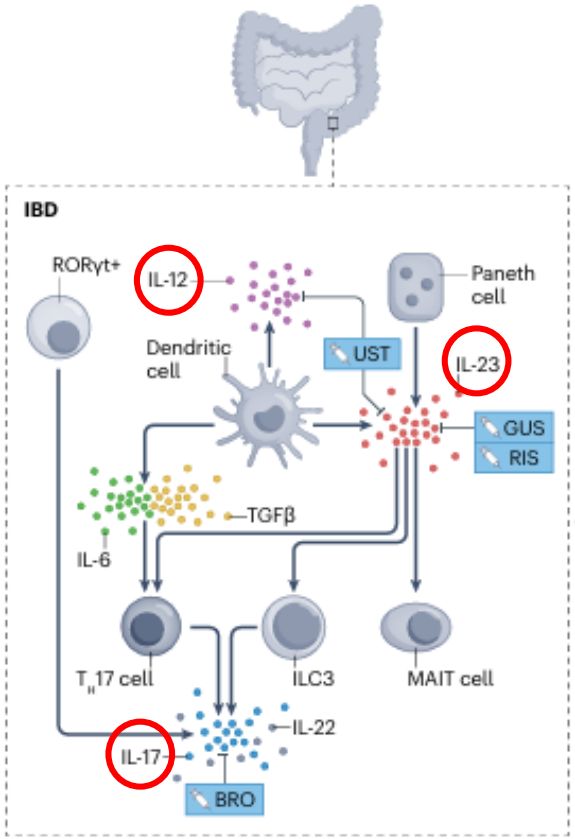

Consider which domains are involved, patient preference, previous/concomitant therapies; choice of therapy should address as many domains as possible
Peripheral arthritis
Axial disease
Enthesitis
Dactylitis
Psoriasis
Nail disease
IBD
Uveitis
NSAIDs, physiotherapy, injections (GCs)*
Topicals, procedurals*
csDMARD, bDMARDs (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
bDMARDs (TNFi, IL-17i) or JAKi
MTX, bDMARDs (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
MTX, bDMARDs (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
Phototx or csDMARDs, bDMARDs (TNFi, IL-12/23i, IL-17i, IL-23i), JAKi or PDE4i
bDMARDs (TNFi, IL-12/23i, IL-17i, IL-23i) or PDE4i
TNFi (not ETN), IL-12/23i, IL-23i, JAKi, MTX
TNFi (not ETN), ciclosporin, MTX
Switch bDMARD (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
Switch bDMARD (TNFi, IL-17i) or JAKi
Switch bDMARD (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
Switch bDMARD (TNFi, IL-12/23i, IL-17i, IL-23i, CTLA4-Ig), JAKi, or PDE4i
Switch bDMARD (TNFi, IL-12/23i, IL-17i, IL-23i), JAKi or PDE4i
Switch bDMARD (TNFi, IL-12/23i, IL-17i, IL-23i) or PDE4i
Comorbidities and associated conditions may impact choice of therapy and/or guide monitoring
Treat, periodically re-evaluate treatment goals and modify therapy as required



Patogènia Malaltia Inflamatoria Intestinal

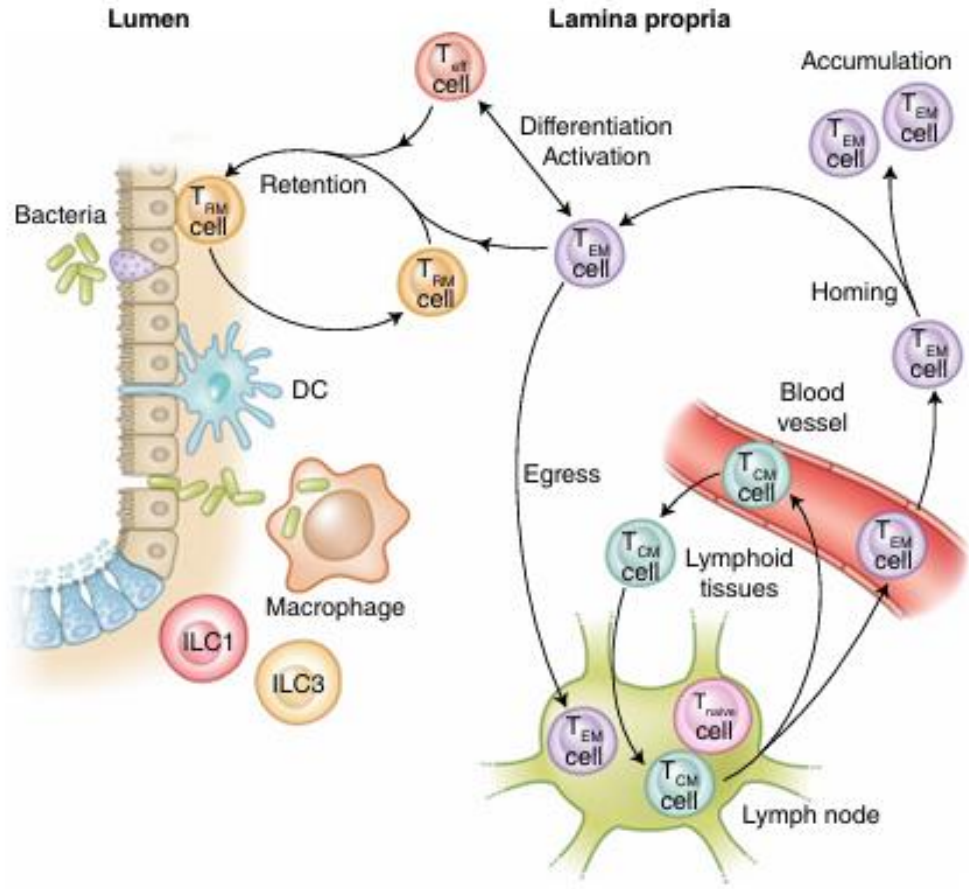


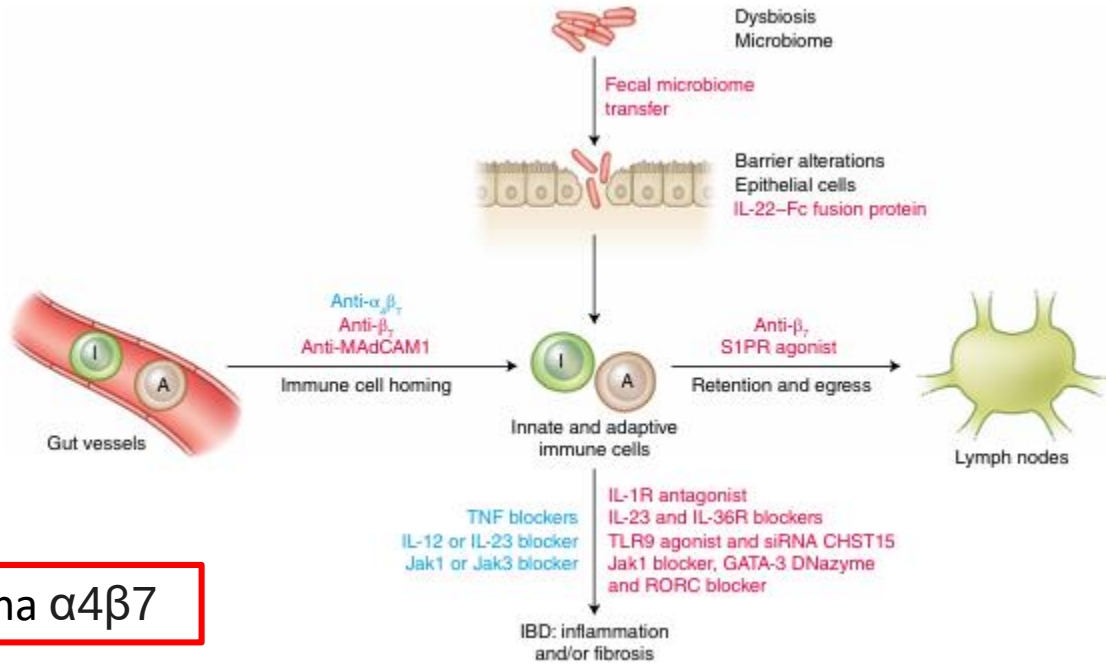




→ IL-17A independent de la IL-23 és protectora per intestí
→ IL-17 depenent de la IL-23 és patogénica per l'intestí

Patogènia MII

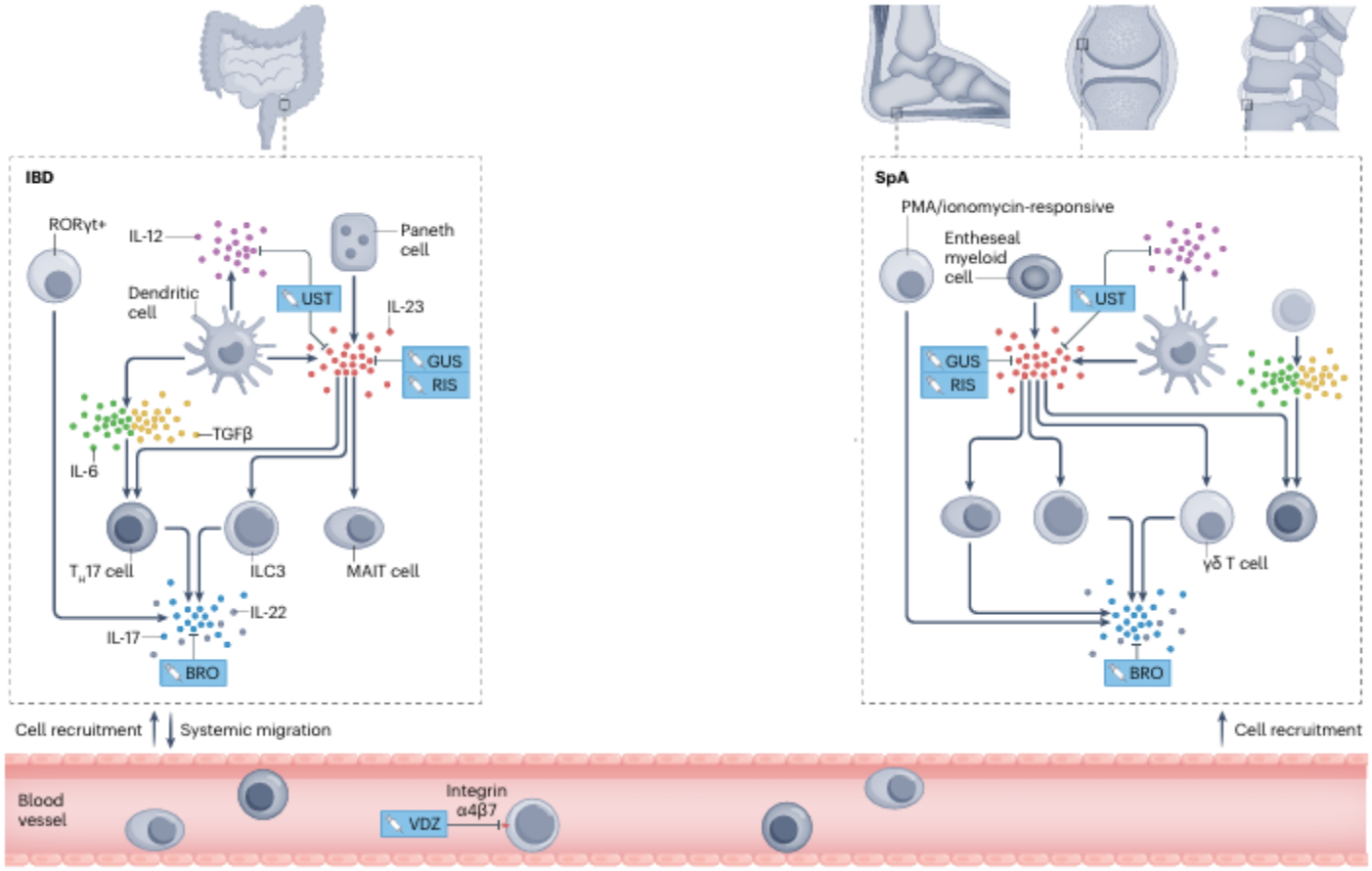




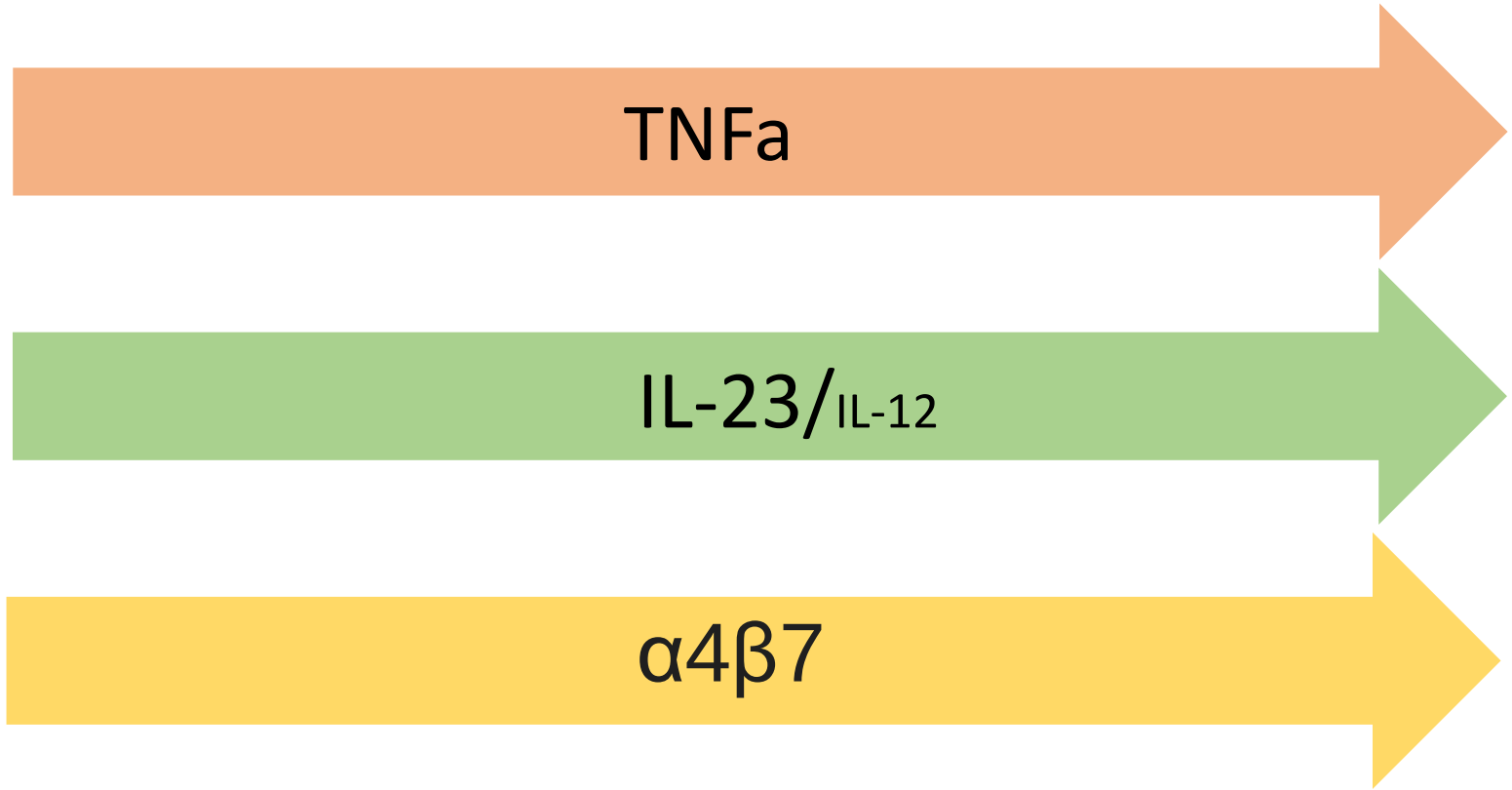
Integrina α4β7

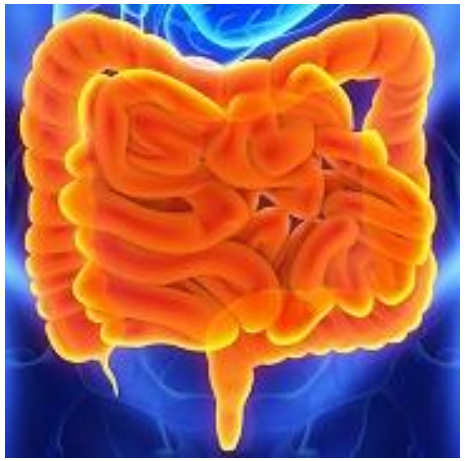
Neurath MF. Narure Immunology 2019

Eix intestí – articulació



Patogènia MII





ECCO Guidelines on Therapeutics in Crohn’s Disease: Medical Treatment

Journal of Crohn's and Colitis, 2024, 18, 1531–1555

	Induction [i]	Maintenance [i]	Perianal disease [ii]	Peripheral Spondylo-arthropathy	Axial Spondylo-arthropathy	Pregnancy	Over 65 years
Systemic corticosteroids	iv			iv	iv	iv	iv
Enteral release corticosteroids						v	v
Enteral Nutrition							
Thiopurines monotherapy						vi	vii
Methotrexate							
Infliximab							
Adalimumab							
Certolizumab							
Vedolizumab							
Ustekinumab							
Risankizumab				viii	ix		
Upadacitinib			x	xi	xii		xiii

Recommended

Can be considered

Not recommended

Insufficient evidence

3.9.1. Sequencing of advanced therapies in CD

Practice Point 3. There is currently insufficient evidence to direct how advanced therapies should be positioned in a therapeutic algorithm for luminal CD. Decisions should consider efficacy, safety, patient preferences and characteristics, disease characteristics, and cost or access to therapies. [Consensus: 97%]

3.9.2. Advanced combination therapies in treatment of CD

Practice Point 4. Advanced combination therapy may be necessary when there are uncontrolled extraintestinal manifestations or symptomatic immune-mediated disorders needing more than one agent to achieve remission. Advanced combination therapy may also be an option for refractory CD. There is currently no evidence to support advanced combination therapy in patients naïve to advanced therapies, even in high-risk patients. [Consensus: 100%]

Terapia combinada

Objectiu de la Terapia combinada

- Tractament més intens per una mateixa malaltia
- Tractar dues malalties diferents
- Evitar mecanismes d'escapament

Terapia combinada

Malaltia Inflamatoria Intestinal

MII

Estudi	Disseny	Població	Terapia combinada
Sands et al. (2007)	Randomized controlled trial	79 MC	Infliximab Natalizumab
Ahmed et al. (2022)	Systematic review and metanalysis	211 MC + 68 CU	
VEGA trial (2023)	Randomized, doble blind, controlled	214 CU	Guselkumab Golimumab
EXPLORER trial (2024)	Open-label trial	55 MC	Vedolizumab Adalimumab Metotrexat
Myatani et al. (2024)	Case series	10 MC	Ustekinumab Upadacitinib
Gilmore et al. (2021)	Case series	5 CU	Infliximab Tofacitinib

MII

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Gilmore et al. (2021)	Case series	5 CU	Infliximab Tofacitinib

Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis

Waseem **Ahmed** [1], Jonathan Galati [2], Anand Kumar [3], Paul J Christos [4], Randy Longman [1], Dana J Lukin [1], Ellen Scherl [1], Robert Battat [5]

Dual therapy		
Anti-TNF and anti-integrin	48%	138/288
Anti-TNF and ustekinumab	7%	20/288
Anti-TNF and tofacitinib	3%	10/288
Vedolizumab and ustekinumab	19%	54/288
Vedolizumab and tofacitinib	11%	32/288
Ustekinumab and tofacitinib	6%	16/288
Anti-TNF and other	3%	8/288
Vedolizumab and other	3%	8/288
Ustekinumab and other	1%	2/288

Remisió clínica	59%
Remisió endoscòpica	34%
Efectes adversos	31%
Efectes adversos greus	6%

MII

Estudi	Disseny	Població	Terapia combinada
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Ahmed et al. (2022)	Systematic review and metanalysis	211 MC + 68 CU	
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Gilmore et al. (2021)	Case series	5 CU	Infliximab Tofacitinib

Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial

Brian G Feagan [1], Bruce E Sands [2], William J Sandborn [3], Matthew Germinaro [4], Marion Vetter [4], Jie Shao [4], Shihong Sheng [4], Jewel Johanns [4], Julián Panés [5]; VEGA Study Group

Colitis Ulcerosa N:214

GUSELKUMAB + GOLIMUMAB vs monoterapia

Efectivitat a setm 12:

- TC millor resposta clínica, no diferencies en la resposta clínica + endoscópica

Seguretat a setm 50:

Sense diferencies en EA i EA greus

MII

Estudi	Disseny	Població	Terapia combinada
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Ahmed et al. (2022)	Systematic review and metanalysis	211 MC + 68 CU	
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Myatani et al. (2024)	Case series	10 MC	Ustekinumab Upadacitinib
Gilmore et al. (2021)	Case series	5 CU	Infliximab Tofacitinib

Vedolizumab, Adalimumab, and Methotrexate Combination Therapy in Crohn's Disease (EXPLORER)

Jean-Frederic Colombel [1], Ryan C Ungaro [2], Bruce E Sands [2], Corey A Siegel [3], Douglas C Wolf [4], John F Valentine [5], Brian G Feagan [6], Blue Neustifter [6], Harisha Kadali [7], Pradeep Nazarey [7], Alexandra James [7], Vipul Jairath [8], Rana M Qasim Khan [7]

Malaltia de Crohn naive a biològic N:55

VEDOLIZUMAB + ADALIMUMAB + MTX

Objectiu primari setm 26:

Remissió endoscopia → 34,5%

Remissió clínica → 61,8%

Seguretat setm 26:

Efectes adversos 87,3%

Efectes adversos greus 10,9%

MII

Estudi	Disseny	Població	Terapia combinada
Sands et al. (2007)	Randomized controlled trial	79 MC	Infliximab Natalizumab
Ahmed et al. (2022)	Systematic review and metanalysis	211 MC + 68 CU	
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Gilmore et al. (2021)	Case series	5 CU	Infliximab Tofacitinib

MII

Clinical Trials ID	Title/Objective	IBD Type	Therapy Combination	Study Design	Status	Target Population
NCT05242484 [91]	Guselkumab + golimumab in moderate to severe UC	UC	Guselkumab + golimumab	Phase 2b, randomized, placebo controlled	Ongoing	Patients with inadequate response to biologic therapies
NCT06095128 [90]	Vedolizumab + tofacitinib in moderate to severe UC	UC	Vedolizumab + tofacitinib	Phase 4, open label, multicenter	Ongoing	Patients with loss of response or intolerance to biologics
NCT05242471 [89]	Guselkumab + golimumab in moderate to severe CD	CD	Guselkumab + golimumab	Phase 2b, randomized, placebo controlled	Ongoing	Patients with active CD who failed advanced therapies
NCT06045754 [86]	Vedolizumab + adalimumab/ ustekinumab in moderate to severe CD	CD	Vedolizumab + adalimumab/ vedolizumab + ustekinumab	Phase 4, open label	Ongoing	Biologic-naïve or experienced patients with moderate to severe CD
NCT06520397 [87]	Upadacitinib + ustekinumab vs. intensified ustekinumab in CD	CD	Upadacitinib + ustekinumab	Randomized, controlled, multicenter	Planned	Patients with insufficient response to standard-dose Ustekinumab
NCT06227910 [88]	Vedolizumab + upadacitinib vs. vedolizumab monotherapy in moderate to severe CD	CD	Vedolizumab + upadacitinib	Phase 3b, randomized, placebo controlled	Ongoing	Patients with moderate to severe CD and prior biologic failure
NCT06453317 [93]	Ustekinumab + infliximab vs. either monotherapy in moderate to severe UC	UC	Ustekinumab + infliximab	Phase 2, open label	Planned	Adult, biologic-naïve patients with moderate to severe UC
NCT06095596 [92]	Upadacitinib + vedolizumab vs. either monotherapy in moderate to severe UC	UC	Upadacitinib + vedolizumab	Randomized, controlled, multicenter	Ongoing	Adult patients with moderate to severe UC

Terapia combinada

Psoriasi/Artritis Psoriasica

Combination Therapy with Apremilast and Biologics for Psoriasis: A Systematic Review

Mette Gyldenløve [1], Farzad Alinaghi [2], Claus Zachariae [2], Lone Skov [2], Alexander Egeberg [3]

N: 172 psoriasi
→ Bon perfil seguretat
→ Tan sols 2 abandonaments per inefiàcia

Combination Therapy with Apremilast and Biologics for Psoriasis: A Systematic Review

Mette Gyldenløve [1], Farzad Alinaghi [2], Claus Zachariae [2], Lone Skov [2], Alexander Egeberg [3]

N: 172 psoriasi
→ Bon perfil seguretat
→ Tan sols 2 abandonaments per inefiàcia

Combination Therapy With Tofacitinib and IL-12/23, IL-23, or IL-17A Inhibition for the Treatment of Refractory Psoriatic Arthritis: A Case Series

Megan Shurey [1], Ashley Yip [1], Olga Ziouzina [2], Jonathan Chan [3], Jan P Dutz

N:6
Tofacitinib + aIL-17
Tofacitinib + aIL-12/23
Tofacitinib + aIL-23

Combination of antitumour necrosis factor-α and anti-interleukin-12/23 antibodies in refractory psoriasis and psoriatic arthritis: a long-term case-series observational study

R Gniadecki [1], B Bang [2], C Sand [2]

Combined inhibition of tumour necrosis factor-alpha and interleukin-12/23 for long-standing, refractory psoriatic disease: a differential role for cytokine pathways?

Gabriele De Marco [1 2], Dennis McGonagle [1 2], Hannah R Mathieson [1 2], Mira Merashli [3], Conor Magee [4], Oliver FitzGerald [4], Mark Goodfield [5], Helena Marzo-Ortega [1 2]

NIH U.S. National Library of Medicine

ClinicalTrials.gov

☐ NCT05049798 Active, not recruiting

A Study of Guselkumab and Interleukin-17 (IL-17) Inhibitor Therapies in Participants With Psoriatic Arthritis in Routine Clinical Practice

☐ NCT05071664 Completed

A Study of Guselkumab and Golimumab Combination Therapy in Participants With Active Psoriatic Arthritis

Terapia combinada

Espondiloartritis

› Ann Rheum Dis. 2022 Jun;81(6):899-901. doi: 10.1136/annrheumdis-2021-221812. Epub 2022 Jan 27.

Effectiveness and safety of combined biological therapy in patients with refractory multidomain spondyloarthritis

Cristina Valero [1], Juan Pablo Baldivieso [1], Isidoro Gonzalez-Alvaro [1], Eva Tomero [1], Santos Castañeda [1 2], Rosario García-Vicuña [3 4]

Pot ser la combinació de dos fàrmacs biològics una terapia segura i eficaç en les espondiloartritis refractàries?

Pot ser la combinació de dos fàrmacs biològics una terapia segura i eficaç en les espondiloartritis refractaries?

Estudi observacional ambiespectiu multicèntric en pràctica clínica real

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- Malalts que compleixen criteris de **Spa axial o perifèrica (Criteris ASAS) i Artritis psoriàsica (Criteris CASPAR)** que en algun moment hagin rebut simultaneament **dos agents biològics i/o dirigits amb diferent diana** del 4/2017 fins 12/2022
- Recollida dades:
    - Dades demogràfiques, clíniques i analítiques
    - **Eficàcia**: ASDAS-PCR, DAPSA
        - Millora clínica significativa:
            - Canvi ASDAS-PCR >2 i millora >85% DAPSA
        - La remisió/baixa activitat
            - ASDAS-PCR <1.3/<2.1, DAPSA <4/>14
    - **Efectes adversos**

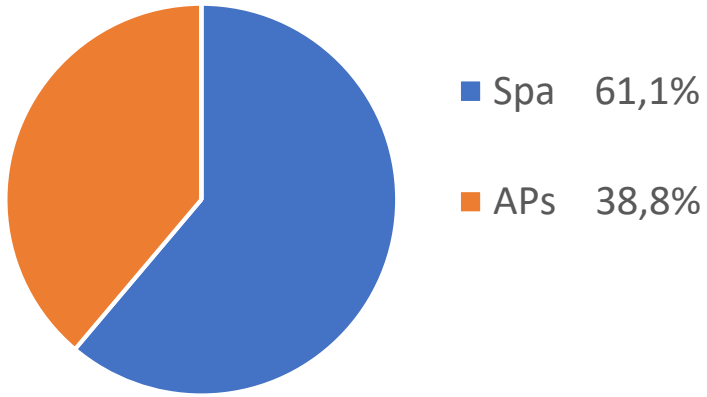
		EA	APs	Ps	CU	MC	Uv
aTNF	Etanercept	x	x	x			
	Infliximab	x	x	x	x	x	
	Adalimumab	x	x	x	x	x	x
	Golimumab	x	x	x	x		
	Certolizumab	x	x	x		x	
aIL-17A	Ixekizumab	x	x	x			
	Secukinumab	x	x	x			
aIL-17RA	Brodalumab			x			
aIL-17F i A	Bimekizumab	x	x	x			
aIL-23	Guselkumab		x	x			
	Risankizumab		x	x	x	x	
	Tildrakizumab			x			
	Mirikizumab				x		
aIL-23/12	Ustekinumab		x	x	x	x	
aIL-36R	Spesolimab			x			
a-integrin	Vedolizumab				x	x	
aCTLA	Abatacept		x				
iJAK	Tofacitinib	x	x		x		
	Upadacitinib	x	x		x	x	
	Filgotinib				x		
	Deucravacitinib			x			
PDE4i	Apremilast		x	x			

Resultats

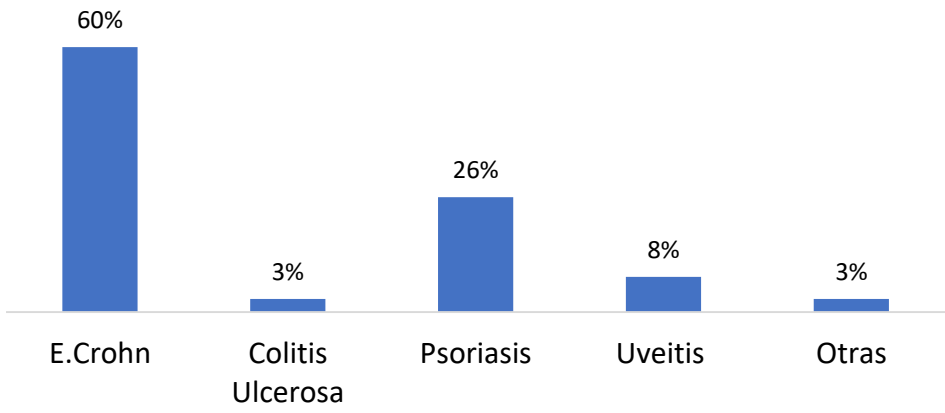
Terapies Combinades: 39

Pacients:	36
Sexe:	54,2% homes
Edat mitja:	47 anys (37-60)
HLA B27:	34,2%

Malaltia reumàtica



Clínica Extramusculoesquelética



Resultats

Nº FAMEb/d previs, mitjana (RIQ)		3 (1.5-5)
Tipus de FAMEb/d previ, n (%)	Anti-TNF	34 (97.1)
	Anti-IL17	13 (37.1)
	Anti-IL 12-23	13 (37.1)

A.Ps	**SpA**
5 ± 3	3 ± 2

88 %	una de les terapies havia fallat prèviament
70 %	naïve a una de les terapies
67 %	exposats a les dues dianes
55,3%	efecte advers associat a FAMEb previ

Resultats

Indicació de la TC, n (%)	
Articular	24 (61,5)
Articular + M.Inflamatòria Intestinal	10 (25,6)
Articular + Psoriasi	1 (2,6)
M.Inflamatòria Intestinal	3 (7,7)
Psoriasi	1 (2,6)

Moderada/alta activitat MSK
33/36

Resultats

aTNF + aIL-12/23 o (aIL-23)	**23**
aTNF + aIL-17	**8**
aTNF + Vedolizumab	3
aTNF + tofacitinib	1
Vedolizumab + aIL-12/23 o 23	2
aIL-17 + aIL-23	1
aIL-23 + ABT	1

Adalimumab + Ustekinumab

Certolizumab + Ustekinumab

Resultats

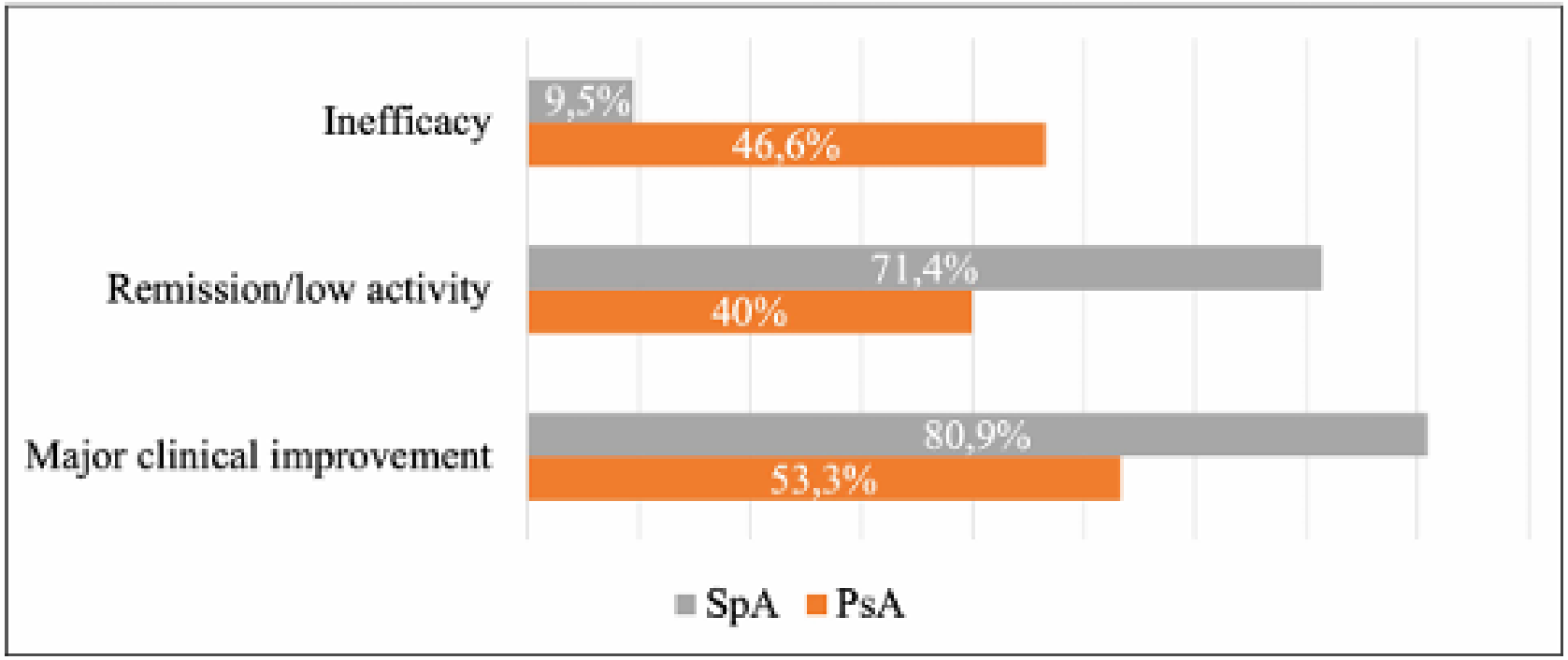
		n (%), al inici TC	
FAMEs concomitants	Cap	24 (61.5)	
	Metotrexat	10 (25.6)	
	Sulfasalacina	3 (7.6)	**38.3 %**
	Azatioprina	2 (5.1)	
Glucocorticoids		20 (**51.2%**)	

Resultats

Mitjana exposició a la TC	**14,8m** (8-20,2)

		n (%)			
Activitat Spa en la última evaluació	Remisió/Baixa activitat	**58,3**	(21/36)		
	Retirada corticoids	**55,0**	(11/20)		
Millora Clínica significativa	Naive a un biològic	76,0	(19/25)	**69,4**	(25/36)
	Exposats al biològic	54,0	(6/11)		
Status final	Mantenen TC	**69,4**	(25/36)		
	Suspensió	35,8	(14/39)		

Resultats


Inefficacy
9,5%
46,6%
Remission/low activity
71,4%
40%
Major clinical improvement
80,9%
53,3%
SpA
PsA

Resultats

<table>
<tr><td rowspan="4">Suspensió TC (14)</td><td colspan="2">Ineficàcia (9)</td></tr>
<tr><td rowspan="3">Efectes adversos (3)</td><td>Bacterièmia per staphylococcus (ETA + SECU)</td></tr>
<tr><td>Colitis per CMV i candidiasi esofàgica (ADA + VEDO)</td></tr>
<tr><td>Pneumonitis per hipersensibilitat (GOLI + USTE)</td></tr>
<tr><td colspan="2">Altres (2)</td></tr>
</table>

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Dual targeted therapy in patients with psoriatic arthritis and spondyloarthritis: a real-world multicenter experience from Spain

Cristina Valero-Martínez[1], Judit Font Urgelles[2], Meritxell Sallés[3], Beatriz E. Joven-Ibáñez[4], Alexia de Juanes[4], Julio Ramírez[5], Xavier Juanola[6], Raquel Almodóvar[7], Ana Laiz[8], Mireia Moreno[9], Manel Pujol[10], Emma Beltrán[11], José Antonio Pinto-Tasende[12], Laura Crespí[13], Luis Sala-Icardo[14], Santos Castañeda[1,15] and Rosario García-Vicuña[1,16*]

Conclusions

- La Terapia Combinada pot ser una alternativa terapèutica raonable i amb un perfil de seguretat acceptable en malalts seleccionats amb SpA refractaria i/o multidomini
- Et permet realitzar una estrategia en el bloqueig de les vies fisiopatològiques
- La combinació més utilitzada de la nostra serie ha estat **aTNF + aIL12/23** seguida de **aTNF + aIL-17**
- En la literatura predomina la combinació de **USTE i VEDO amb un altre FAMEb**, segurament per perfil de seguretat i selectivitat intestinal

Futur …

- Fàrmacs més selectius
- Seguint en aquesta linia ja s'están desenvolupant els Ac biespecífics
- Queda clara la inducció al tractament, però gens el manteniment
- Econòmicament insostenible, tot i que amb l'arribada de nous biosimilars si ho seria
- Col.laboració entre especialistes és básica