Cleveland Clinic
R.J. Fasenmyer Center for Clinical Immunology

Novel Therapies PsA and SpA

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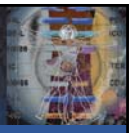
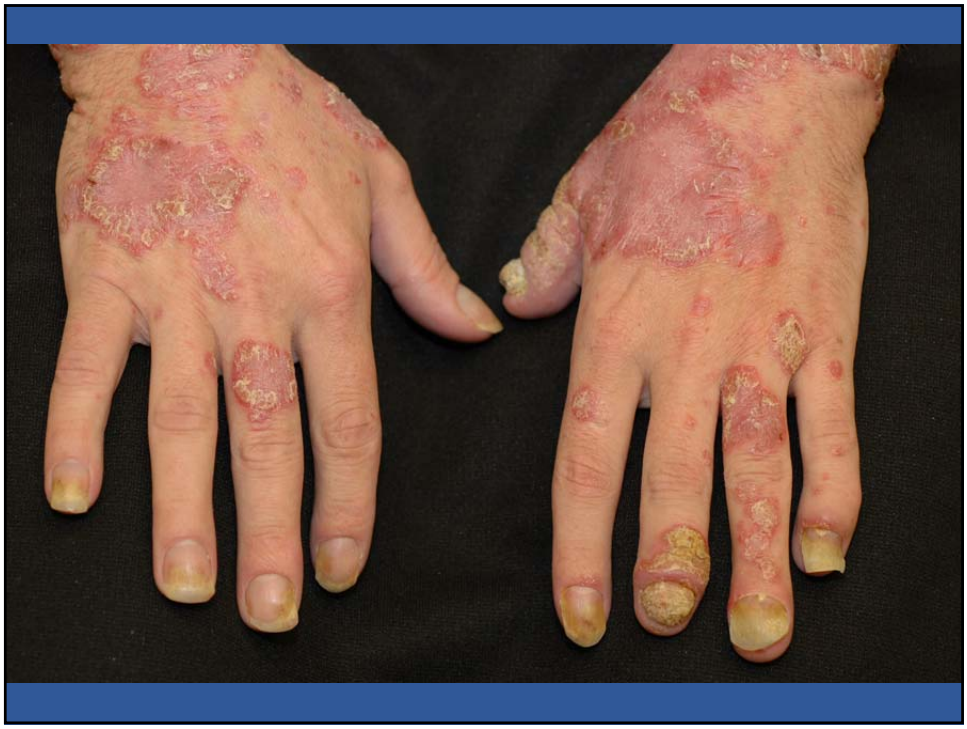
Learning Objectives

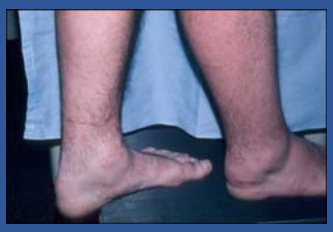


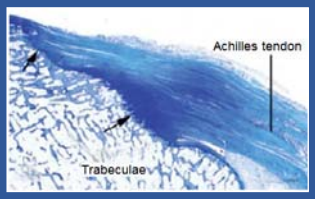
As a result of participating in this module, participants will be able to:

- Describe new concepts in the diagnosis and treatment of Psoriatic Arthritis and Ankylosing Spondylitis
- Review new treatment recommendations for Psoriatic Arthritis and Ankylosing Spondylitis
- Discuss novel and emerging therapies for Psoriatic Arthritis and Ankylosing Spondylitis



Mechanical Stress

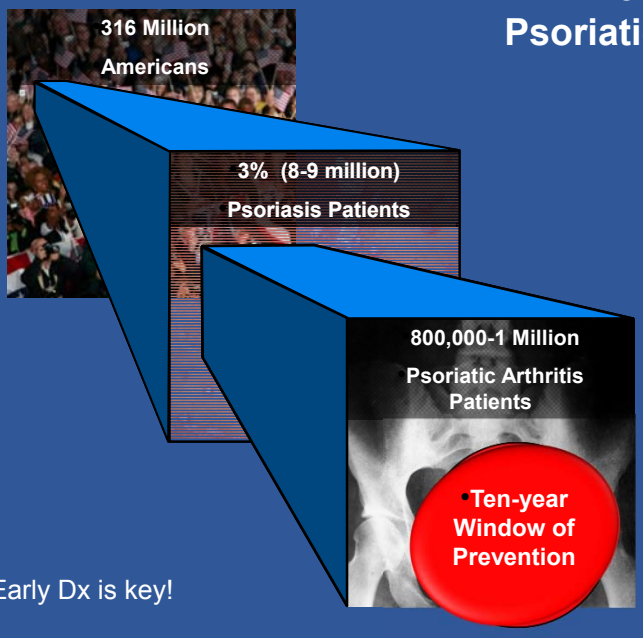




Achilles Tendon Enthesitis

Skin TNF, IL17, IL22, IL23

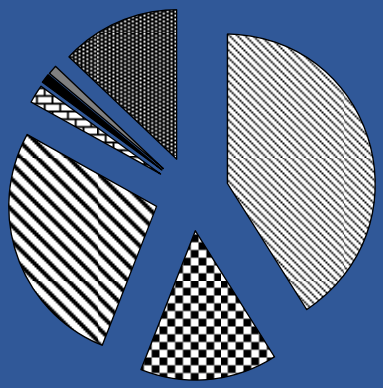
Who Will Get Psoriatic Arthritis?



Early Dx is key!

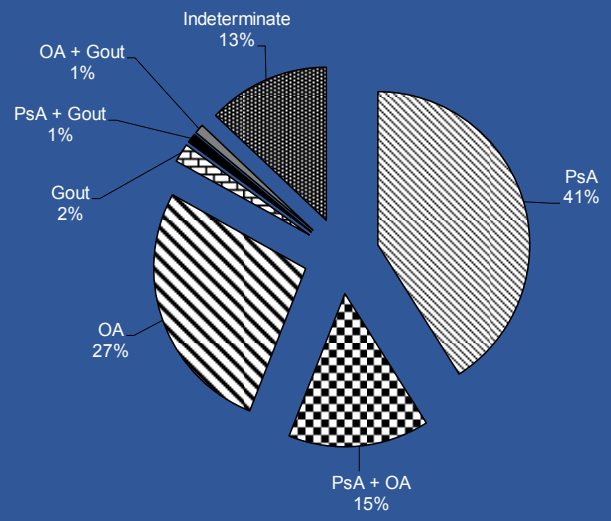
Adapted from C. Ritchlin MD

Diagnosis of patients presenting with musculoskeletal pain and psoriasis



Center for Skin and Related Musculoskeletal Diseases
Brigham and Women's Hospital

Diagnosis of patients presenting with musculoskeletal pain and psoriasis



Center for Skin and Related Musculoskeletal Diseases
Brigham and Women's Hospital

Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

PSORIATIC ARTHRITIS SCREENING AND EVALUATION (PASE) QUESTIONNAIRE

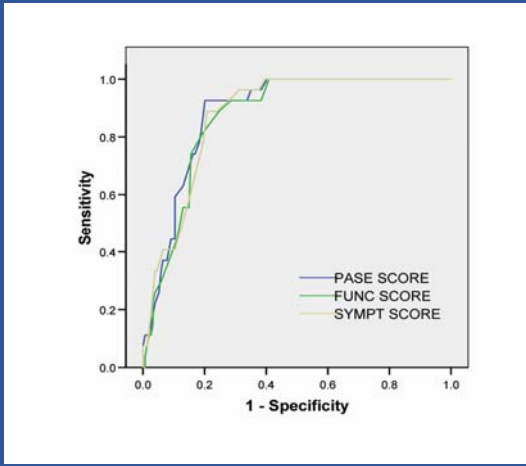
Please circle or mark **ONLY ONE** of the answers to the following questions. The answers to these questions will help us better understand your symptoms. This should take about 5-6 minutes to complete. You don't have to add up the numbers in each section if you don't want to. We can add them for you. Thank you for your time.

HAVE YOU EVER BEEN DIAGNOSED WITH PSORIATIC ARTHRITIS BY A RHEUMATOLOGIST? YES NO

YOUR SYMPTOMS	Strongly Disagree	Disagree	No Opinion	Agree	Strongly Agree
1. I feel tired during most of the day.	1	2	3	4	5
2. My joints hurt.	1	2	3	4	5
3. My back hurts.	1	2	3	4	5
4. My joints become swollen.	1	2	3	4	5
5. My joints feel "hot."	1	2	3	4	5
6. Occasionally, my entire finger or toe becomes swollen, making it look like a "sausage."	1	2	3	4	5
7. I have noticed that the pain in my joints moves from one joint to another. For example, my wrist will hurt for a few days, then my knee will hurt, and so on	1	2	3	4	5
					Total Symptom Score

YOUR ABILITY TO DO DAILY ACTIVITIES	Strongly Disagree	Disagree	No Opinion	Agree	Strongly Agree
8. I feel that my joint problems have affected my ability to work.	1	2	3	4	5
9. My joint problems have affected my ability to care for myself (for example, getting dressed or brushing my teeth)	1	2	3	4	5
10. I have had trouble wearing my watch or wearing rings on my fingers.	1	2	3	4	5
11. I have had trouble getting into or out of a car.	1	2	3	4	5
12. I am unable to be as active as I used to be.	1	2	3	4	5
13. I feel stiff for more than 2 hours after waking up in the morning.	1	2	3	4	5
14. The morning is the worst time of day for me.	1	2	3	4	5
15. It takes me a few minutes to get moving as well as I can, at any time of the day.	1	2	3	4	5
					Total Function Score
					Total PASE Score

PASE Tool: Sensitivity and Specificity



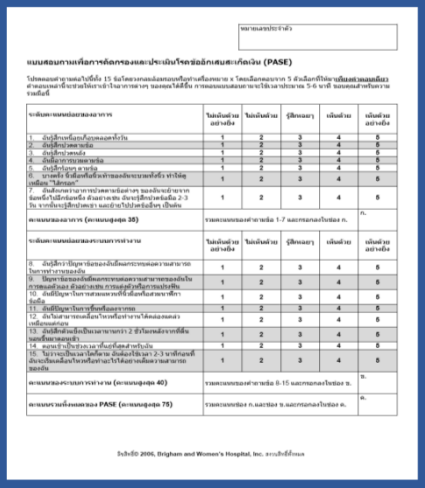
- Total PASE score cutoff 47:
- Sensitivity 93% (95% CI, 78-99)
- Specificity 80% (95% CI, 68-82)

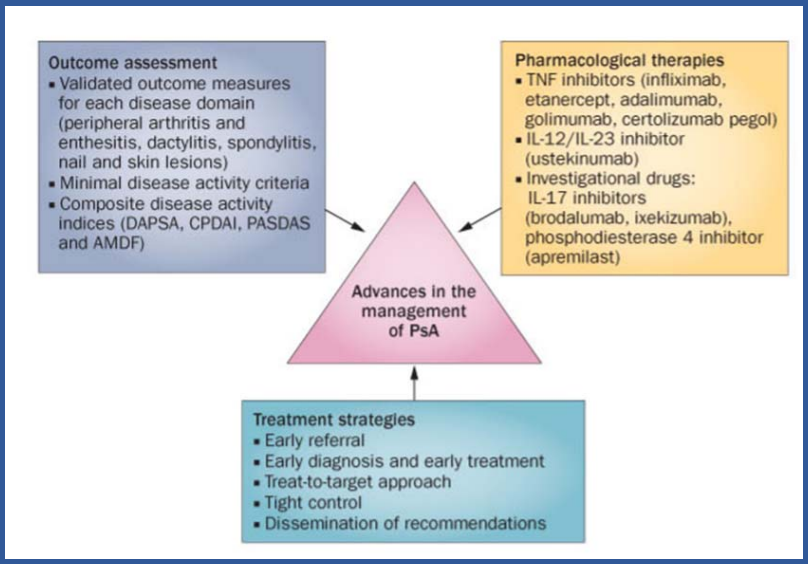
- Dominguez, P.D., et al., *Validity, reliability, and sensitivity-to-change properties of the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire*) submitted.

PASE translated in over 15 languages

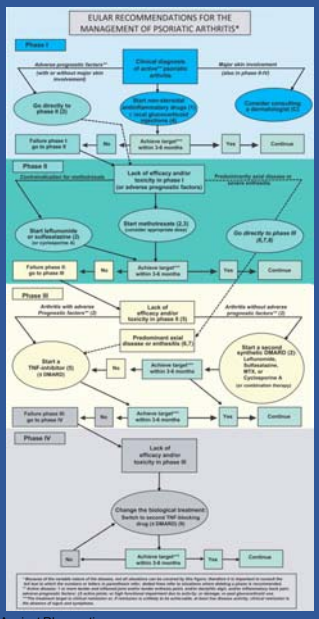
Korean

Thai





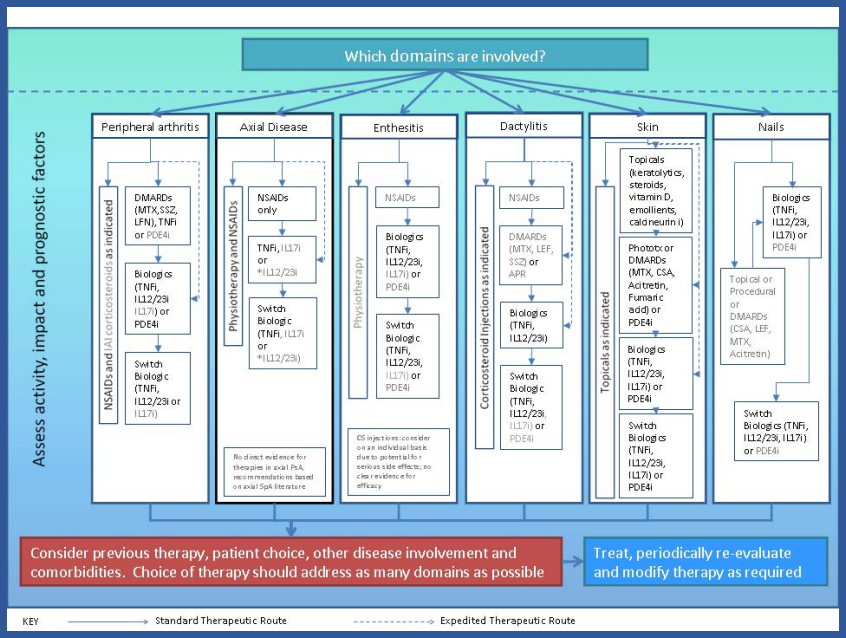
Management of psoriatic arthritis according to the European League Against Rheumatism recommendations.



L Gossec et al. Ann Rheum Dis 2012;71:4-12

ARD

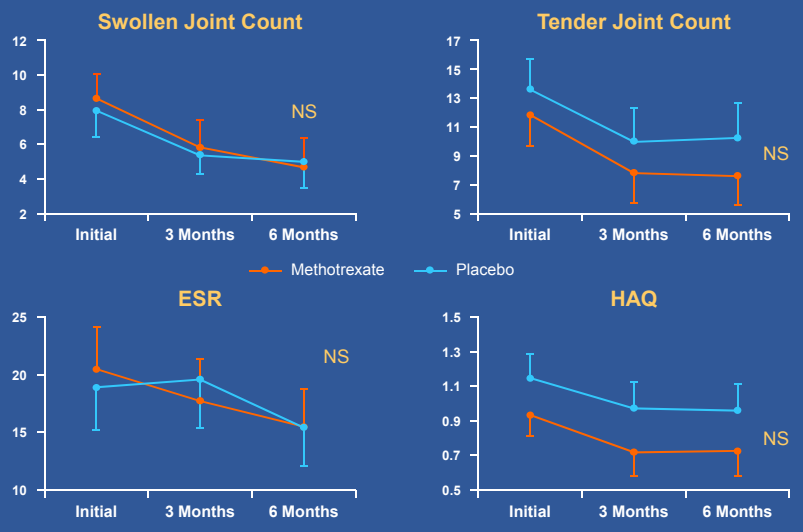
GRAPPA 2015 Treatment Recommendations



Coates L, et al. Arth Rheum. 2016 Jan 8 e ahead of print online

PSORIATIC ARTHRITIS TREATMENT

MIPA Trial Results:
Joint Counts, ESR and HAQ



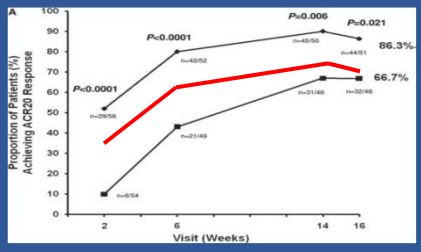
MIPA Trial Caveats

- Small numbers of patients with high dropout rate – may have been inadequately powered
- Target dose of MTX was 15 mg/week – too low?
- Mean joint count ~5 – to few to identify response?
- Very high placebo response

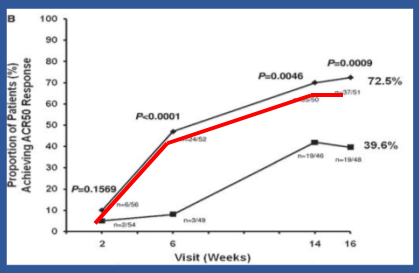
Does MTX really work in PSA ?
Can we even tell from available data?

Proportion of patients (%) achieving ACR response

ACR20



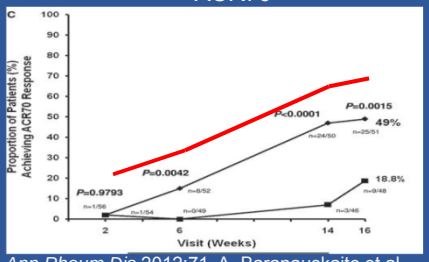
ACR50



IFX + MTX (n=56)

MTX (n=54)

ACR70



Ann Rheum Dis 2012;71. A. Baranauskaite et al

Methotrexate

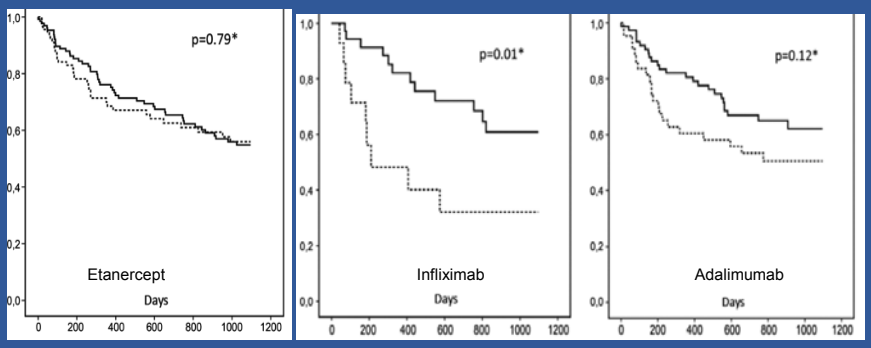
PsA STUDIES ON BIOLOGIC DMARD WITH AND WITHOUT MTX

TRIAL / STUDY	PsA SUBJECTS	EFFICACY
MIPA Trial [a] MTX in PsA	Off DMARD > 1 month	MTX Monotherapy Non-Effective @ 15mg/week
RESPOND TRIAL [b]	MTX Naïve	Infliximab + MTX > MTX Monotherapy
NOR DMARD PsA Study [c] **Longitudinal observational study (n=440) 1°TNFi: etanercept, infliximab, adalimumab**	aTNF naive	aTNF + MTX = aTNF Monotherapy aTNF drug survival ↑ with MTX
TICOPA TRIAL [d] **Q4week FU w/escalating Tx to Target vs Q12 FU w/ standard Rheum Care**	bDMARD naïve in Early PsA	82% of PsA subjects required an increase in MTX weekly dosage from 15 to 25mg in order to reach a target ACR20 in 48 weeks
Corrona Registry [e] **PsA patients from Corrona (NCT01402661)**	bDMARD naïve	aTNF + cDMARD (90%MTX) = aTNF Monotherapy Etanercept & Infliximab drug survival ↑ w/ cDMARD
SEAM TRIAL (Ongoing RCT) **Etanercept vs Etanercept/MTX vs MTX Mono**	bDMARD Naïve for PsA/PsO MTX Naïve for PsA only	No Published Results. Primary Outcomes Are •Efficacy at 24 weeks using ACR20 •Compare Etanercept/MTx vs Etanercept MonoTX vs MTX MonoTx

[a] Rheumatology (Oxford) 2012; 51:1368, [b] Ann Rheum Dis 2012 71: 541-548, [c] Rheum Dis 2014;73: 132–137, [d] Lancet 2015; 386:2489 , [e] Mease PJ, et al. RMD Open 2015;1:e000181.

Effect of Methotrexate on Biologic DMARD Drug Survival in PsA - NOR-DMARD study

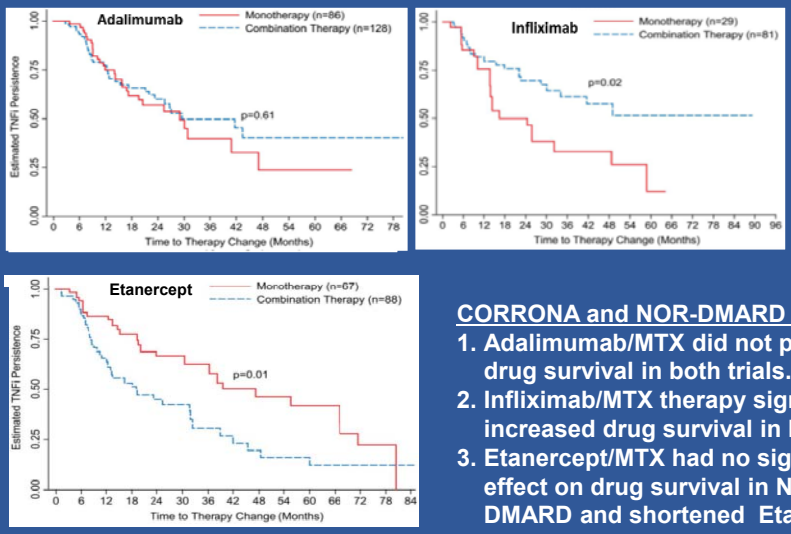
Anti-TNF / MTX Combination Tx in PsA NOR-DMARD observational study (n=440)



Biologic DMARD Monotherapy
Combination Biologic DMARD & MTX

Fagerli KM, Lie E, van der Heijde D, et al. Ann Rheum Dis 2014;73: 132–137.

Effect of Methotrexate on Biologic DMARD Drug Survival in PsA – CORRONA Registry (n= 519)



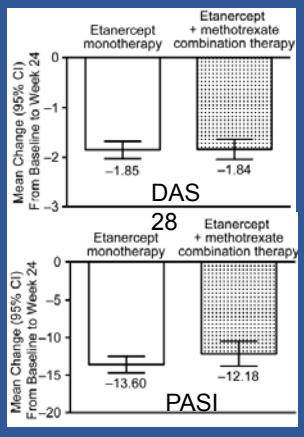
CORRONA and NOR-DMARD Trials

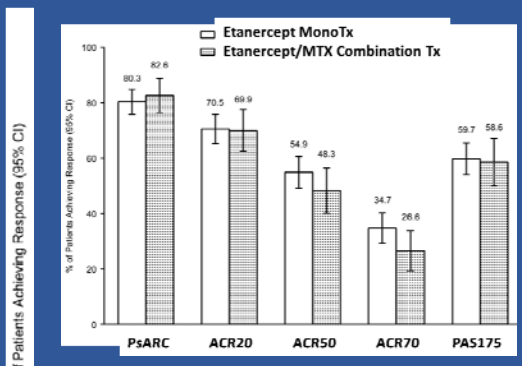
1. Adalimumab/MTX did not prolong drug survival in both trials.
2. Infliximab/MTX therapy significantly increased drug survival in both trials
3. Etanercept/MTX had no significant effect on drug survival in NOR-DMARD and shortened Etanercept drug survival in Corrona.

Mease PJ, et al. RMD Open 2015;1:e000181.

Etanercept with and without MTX Provided Similar Benefits in Active PsA: Results from 2 Etanercept Placebo-Controlled 24-Week Trials

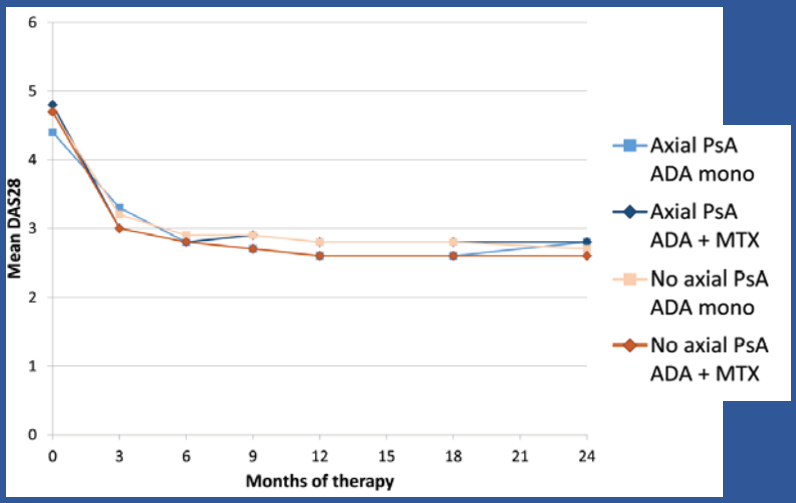
ETN (n = 322) ETN/MTX (n = 152)





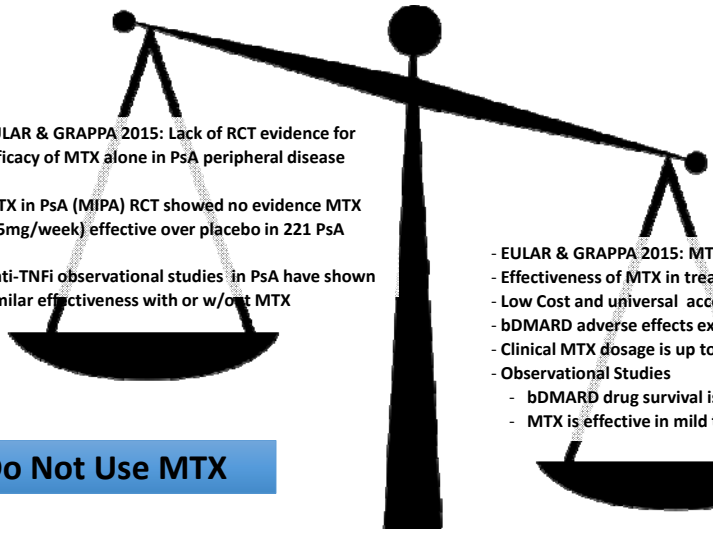
Bernard Combe, et al. **Comparison of Etanercept Monotherapy and Combination Therapy with Methotrexate in Psoriatic Arthritis: Results from 2 Clinical Trials**, J Rheumatol. 2016 Jun;43(6):1063-7

Effects of concomitant methotrexate (MTX) with adalimumab on treatment outcomes: retrospective observational analysis of PsA patients (n=1455)



Behrens, F et al. J Rheumatol 2016 Mar 15;43(3):632-9.

Weighing The Use of MTX in PsA



- EULAR & GRAPPA 2015: Lack of RCT evidence for efficacy of MTX alone in PsA peripheral disease
- MTX in PsA (MIPA) RCT showed no evidence MTX (15mg/week) effective over placebo in 221 PsA
- Anti-TNFi observational studies in PsA have shown similar effectiveness with or w/out MTX

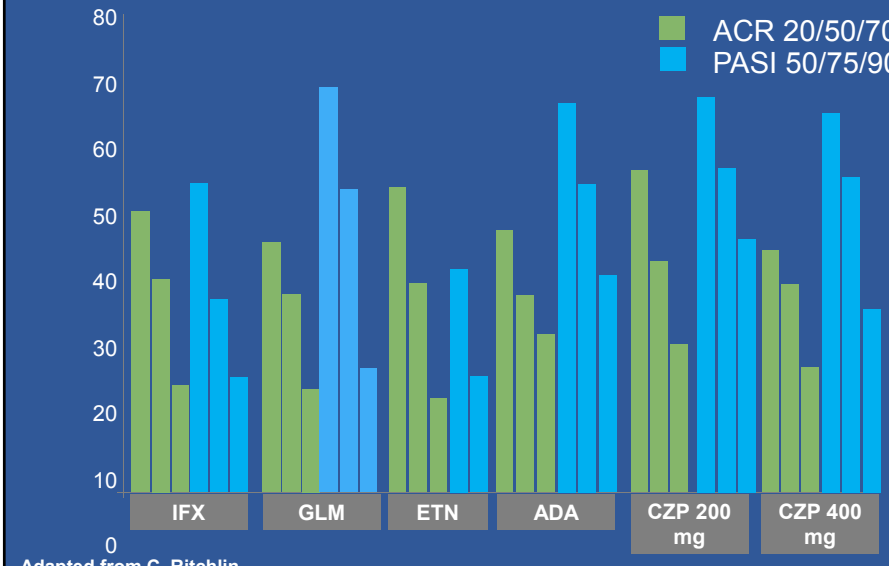
Do Not Use MTX

- EULAR & GRAPPA 2015: MTX is a first line.
- Effectiveness of MTX in treating Psoriasis.
- Low Cost and universal access of MTX
- bDMARD adverse effects exceed MTX
- Clinical MTX dosage is up to 25 mg/week
- Observational Studies
  - bDMARD drug survival is superior with MTX
  - MTX is effective in mild to moderate PsA.

Use MTX

Gossec L, et al. Ann Rheum Dis. 2016 Mar;75(3):499-510
Coates, LC et al. Arthritis and Rheumatology, 2016 May;68(5):1060-71

TNFi therapy in PsA: Phase III trials



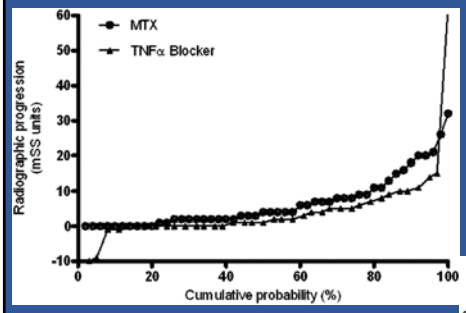
Adapted from C. Ritchlin

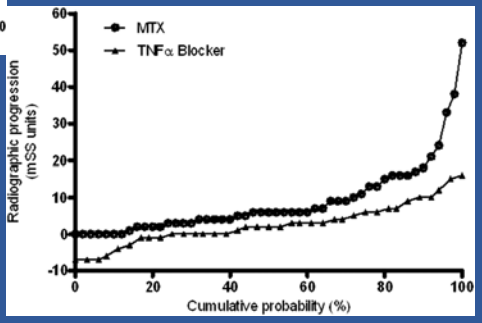
Anti-TNFs in PsA: Other Outcomes

- Enthesitis
  - ~60-75% improvement
  - Assessment methods evolving: 4-point, MASES, Leeds, SPARCC
- Dactylitis
  - ~60% improvement
  - Assessment methods evolving: Count, score, Leeds dactylometer
- Function
  - Significant improvement achieved as assessed by HAQ
- QOL
  - Significant improvements in SF-36, PsAQOL, DLQI, EQ-5D
- Fatigue
  - Significant improvement observed
- Structural damage
  - Inhibited

Mease P. Ann Rheum Dis. 2011;70:77-84; Mease P. Arth Care & Research. 2011:63;64-85

Tumour necrosis factor α blockers are more effective than methotrexate in the inhibition of radiographic joint damage progression among patients with psoriatic arthritis



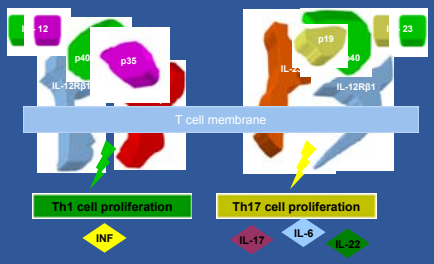


BEYOND ANTI TNF THERAPIES

Ustekinumab in PsA

- **PSUMMIT 1** – 615 pts with PsA despite DMARDs and/or NSAIDs
- **PSUMMIT 2** – 312 pts with PsA despite DMARDs, NSAIDs, and/or TNFi's (or intolerance/toxicity from TNFi)
  - Intended as TNFi failure trial, but recruitment lagged
- Both included 3 arms:
  - Placebo
  - Ustekinumab 45 mg wks 0, 4, q12 wks
  - Ustekinumab 90 mg wks 0, 4, q12 wks

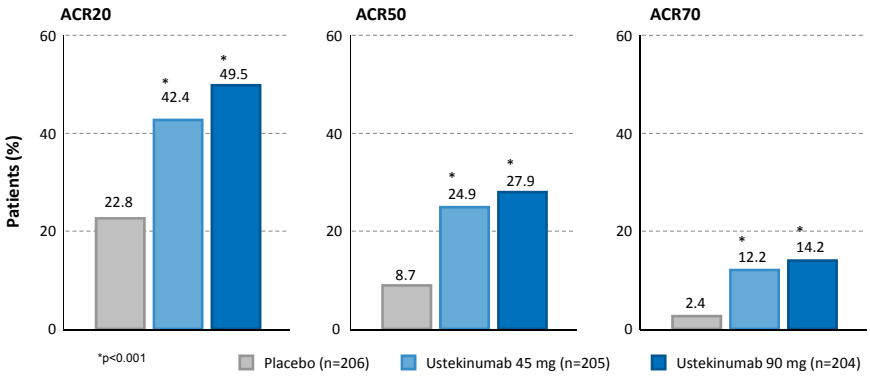
IL-12 & IL-23 Differences: p40 Subunit Is Common



Adapted from: Gutcher I, Becher B. *J Clin Invest.* 2007;117:1119-1127.

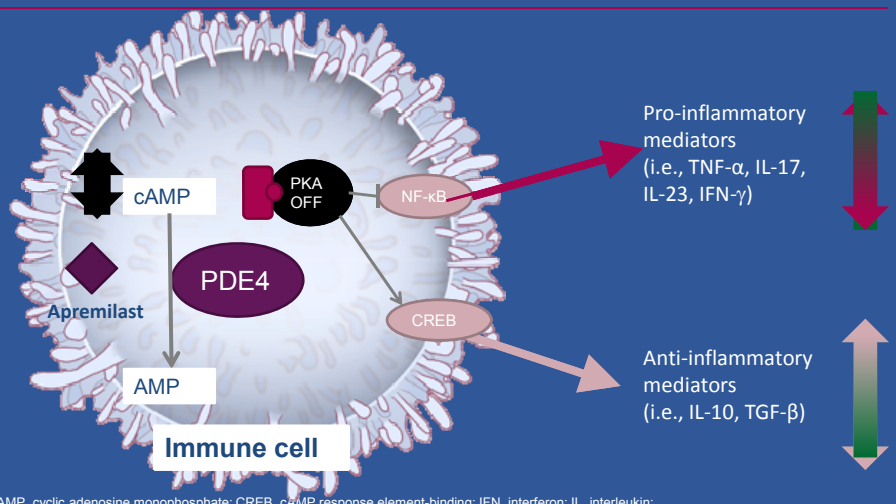
Ustekinumab PSUMMIT 1

Treatment response at Week 24



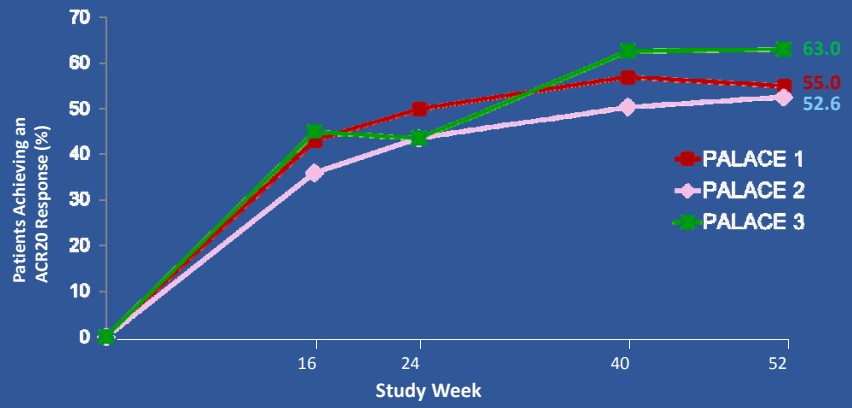
McInnes IB et al. Lancet 2013; 382(9844);780-9.

Apremilast (PDE4i) modulates the production of pro-inflammatory and anti-inflammatory mediators



cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding; IFN, interferon; IL, interleukin; NF-κB, nuclear factor kappa-B; PDE4, phosphodiesterase 4; PKA, protein kinase A; TGF, transforming growth factor

ACR20 Response Over 52 Weeks: PALACE 1, 2, 3
Apremilast 30 mg BID



PALACE 1 (Responders/n)	64/150	73/145	80/140	71/130
PALACE 2 (Responders/n)	52/145	60/138	61/121	61/116
PALACE 3 (Responders/n)	69/154	63/145	82/131	80/127

Kavanaugh A, et al. EULAR 2013 [oral presentation]. Cutolo M. SIR 2013 [oral presentation]. Cutolo M. ACR 2013 [oral presentation]. Edwards CJ, et al. ACR 2013 [poster 311].

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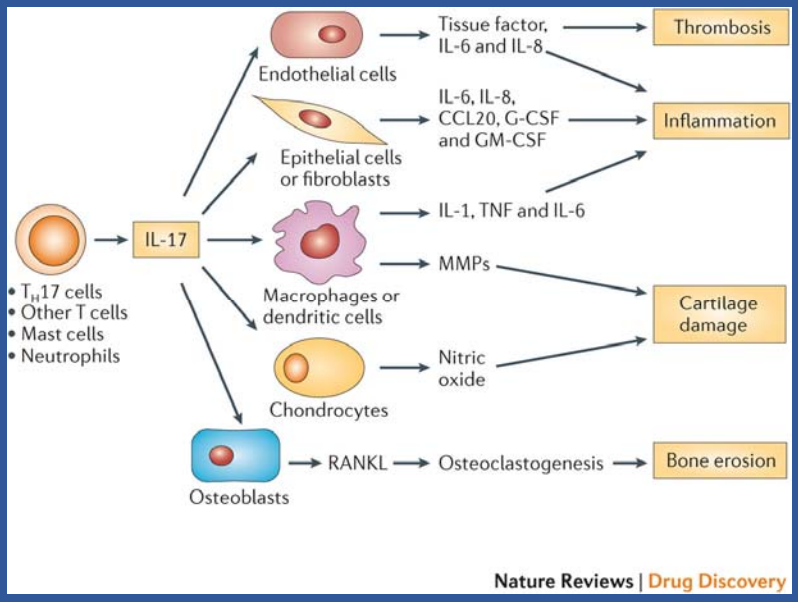
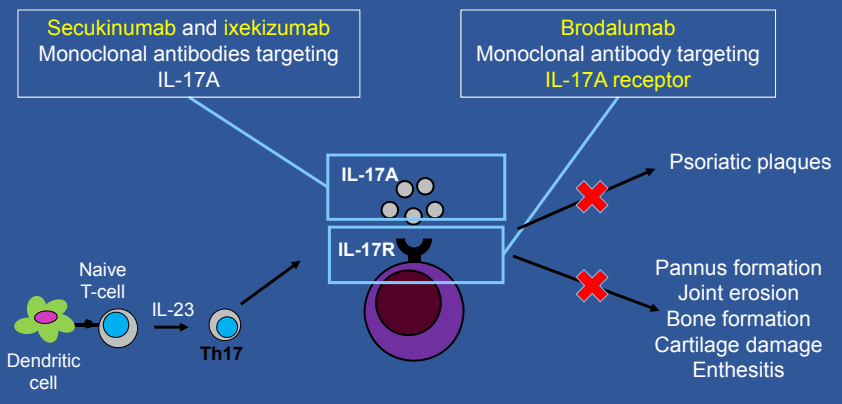
IL-17 ACTS ON VARIOUS CELL TARGETS



Mechanism of Action of IL-17 Inhibitors in Treating PsA



References in slidenotes.

Slide credit: clinicaloptions.com

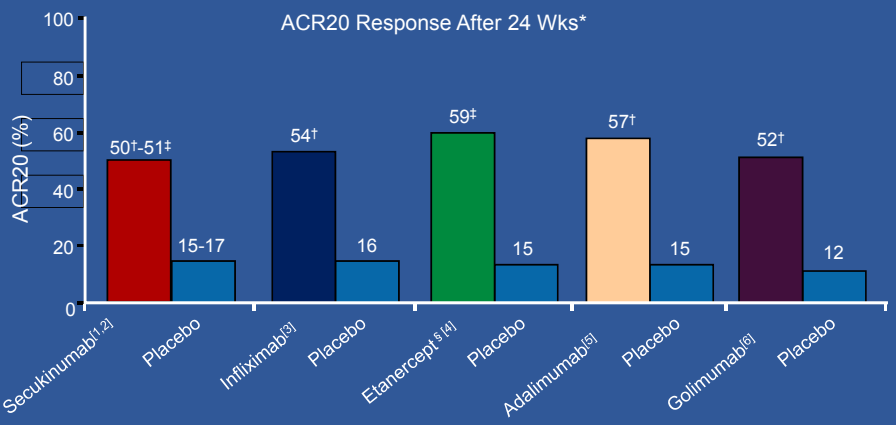
Secukinumab

ACR20 at week 24				
	Placebo	secukinumab 75 mg	secukinumab 150 mg	secukinumab 300 mg
FUTURE 1	17.3%	50.5% (P<0.001)	50% (P<0.001)	—
FUTURE 2	15%	29% (P=0.0399)	51% (P<0.0001)	54% (P<0.0001)
PASI75 at week 24				
	Placebo	secukinumab 75 mg	secukinumab 150 mg	secukinumab 300 mg
FUTURE 1	8.3%	64.8% (P<0.001)	61.1% (P<0.001)	—
FUTURE 2	16%	28% (P=0.1650)	48% (P=0.0017)	63% (P<0.0001)

CLEAR study

CLEAR study outcomes	secukinumab	ustekinumab	P value
PASI90 @ wk24 → wk52	79.0% → 74.9%	57.6% → 60.6%	P<0.0001
PASI100 @ wk24 → wk52	47.0% → 44.9%	35.2% → 36.7%	P=0.0333
Investigator's Global Assessment responses of clear/almost clear skin @ wk24 → wk52	82.9% → 78.1%	73.4% → 63.6%	P<0.0001

Secukinumab and TNFi Response Rates for Treating PsA



*Independent trials; no head-to-head comparisons. Results for PI-recommended PsA doses of each agent shown. †$P < .001$. ‡$P < .0001$. § Data given for Wk 12; results were sustained at Wk 24.

References in slidenotes.

Slide credit: clinicaloptions.com

Emerging PsA Therapies

- **Ixekizumab**
- **Brodalumab**
- **IL-23 blockers: Guselkumab and Tildrakizumab**
- **JAK inhibition (tofacitinib and baricitinib)**
- **CTLA4 co-stimulation (abatacept)**

Ixekizumab

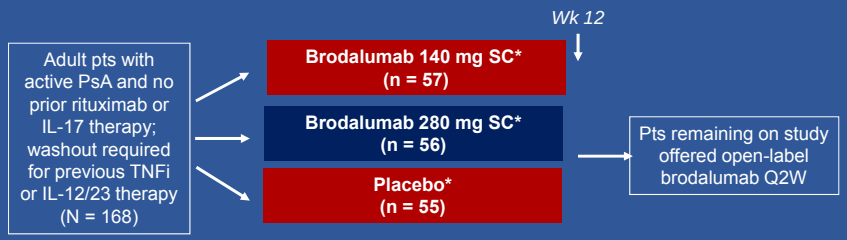
- Human monoclonal antibody targeting IL-17A
- FDA approved for the following patients:
  - Adults with moderate to severe plaque psoriasis
  - Patients eligible for systemic therapy or phototherapy[1]
- Clinical Trials
  - UNCOVER-1, -2, and -3 (N = 3,866) [2,3]
    - Randomized phase III studies investigating ixekizumab safety and effectiveness in psoriasis patients
    - Results: Ixekizumab treatment for 12 weeks significantly improved proportion of patients with PASI 75 response or sPGA score of 0-1 vs PBO in all trials and vs etanercept in UNCOVER-2 and -3.
  - SPIRIT-P1: randomized phase III study to investigating ixekizumab safety and effectiveness in PsA patients[4]

1. Ixekizumab [package insert]. March 2016.
2. Gordon KB, et al. N Engl J Med. 2016;375:345-356.
3. Griffiths CE, et al. Lancet. 2015;386:541-551.
4. Mease PJ, et al. Ann Rheum Dis. 2016;[Epub ahead of print].

Slide credit clinicaloptions.com

Brodalumab for Patients with Active PsA

- Randomized, double-blind, placebo-controlled phase II trial[1]

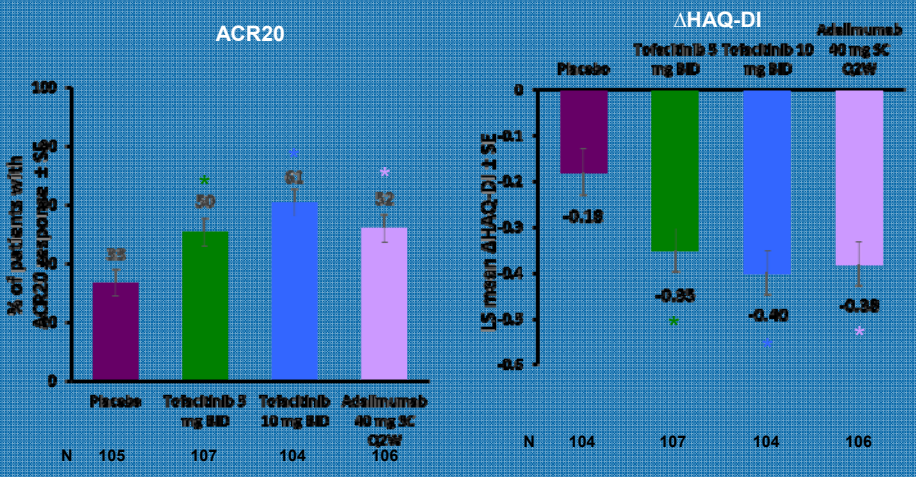


- At Wk 12, both 140-mg and 280-mg brodalumab significantly improved ACR20 and ACR50 vs placebo regardless of prior biologic therapy
- Phase III trials of brodalumab (eg, AMVISION-1/2) suspended by sponsor due to concerns about potential FDA labeling requirements regarding suicide ideation and behavior observed in phase III psoriasis trials[2]

1. Mease PJ, et al. N Engl J Med. 2014;370:2295-2306.
2. Ritchlin CT, et al. Curr Opin Rheumatol. 2016;28:204-210.

Slide credit: clinicaloptions.com

Tofacitinib in PsA: ACR 20 and HAQ at 3 mos



Mease P, et al. ACR 2016

IL-23 blockers: Guselkumab and Tildrakizumab

Target only IL-23 (not IL-12) via the p19 subunit

Guselkumab

- Phase 3 Psoriasis
- ACR abstract 149 patients PsA & >3% BSA
- Significant improvement in multiple domains

Tildrakizumab

- EULAR abstract 355 patients (56 PsA)
- Numeric improvement in PsA

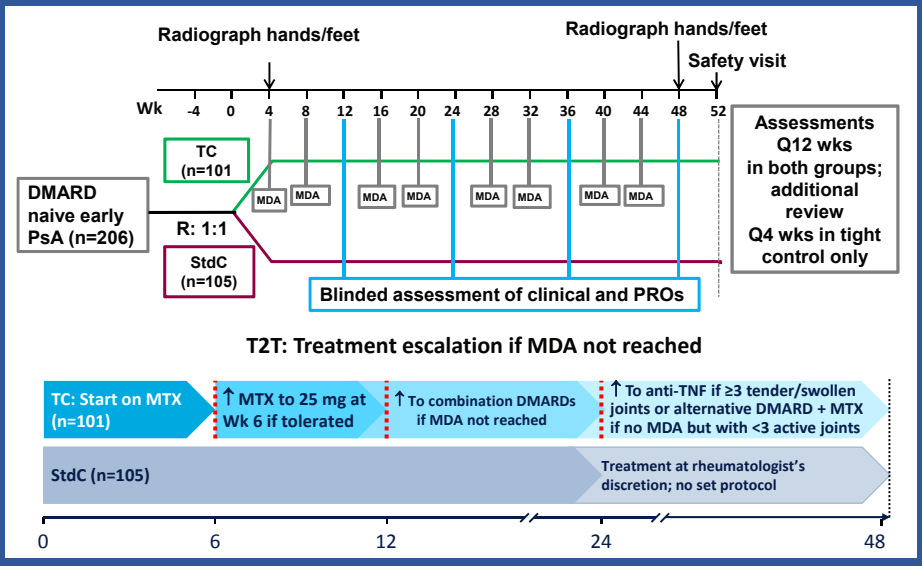
TREATMENT STRATEGIES

Minimal Disease Activity Criteria (MDA)

- A patient is classified as in MDA when they meet 5 of 7 of the following criteria:
  - tender joint count ≤1
  - swollen joint count ≤1
  - PASI ≤1 or BSA ≤3
  - patient pain VAS ≤15
  - patient global activity VAS ≤20
  - HAQ ≤0.5
  - tender entheseal points ≤1

Coates, L, et al. Ann Rheum Dis. 2010 Jan;69(1):48-53. Epub

TICOPA: Tight control/T2T in PsA



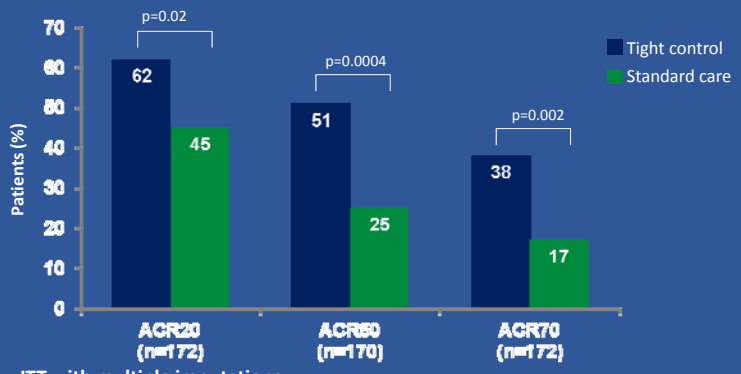
MDA, minimum disease activity; MTX, methotrexate; R, randomisation; StdC, standard care; TC, tight control; T2T, treat to target

Coates LC, et al. BMC Musculoskelet Disord. 2013 Mar 21;14:101. doi: 10.1186/1471-2474-14-101

47

Tight control was associated with significantly greater improvements in signs and symptoms of disease at Week 48

Primary outcome: Complete case analysis

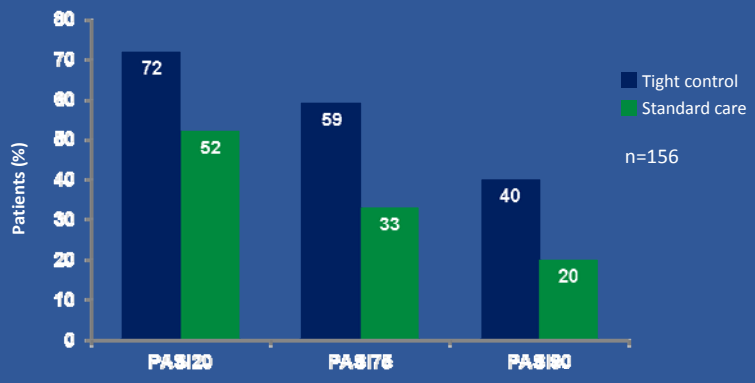


ITT with multiple imputations

Outcome measure	OR	Lower 95% CI	Upper 95% CI	p Value
ACR20	1.91	1.03	3.55	0.0392
ACR50	2.36	1.25	4.47	0.0081
ACR70	2.64	1.32	5.26	0.0058

Coates LC, et al. BMC Musculoskelet Disord. 2013 Mar 21;14:101. doi: 10.1186/1471-2474-14-101

Reduction in psoriasis severity was achieved in a higher proportion of patients in the tight control arm



Outcome measure	OR	Lower 95% CI	Upper 95% CI	p Value
PASI75	2.92	1.51	5.65	0.0015

Coates L, et al. BMC Musculoskelet Disord. 2013 Mar 21;14:101. doi: 10.1186/1471-2474-14-101

Effect of treatments on Cardiovascular Risk in PsA

- NSAIDs, 1st line of treatment for PsA
  - PRECISION Trial found selective and non selective NSAIDs have similar CV risks in OA and RA patients[1]
  - Net effects of NSAIDs are challenging[1]
- Biologic DMARDs
  - Reduction in carotid IMT [2]
  - Improve aortic stiffness [3,4]
  - Modify endothelial function [5]

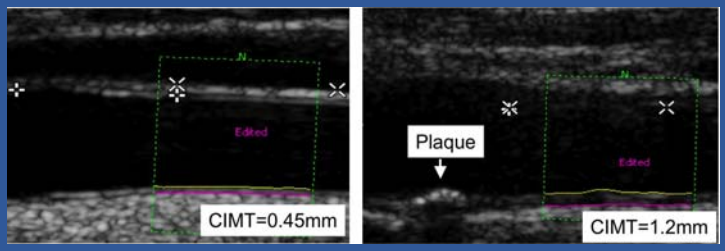
1. **Nissen S** *NEJM 2017*
2. **Tam L-S, Li EK, Shang Q**, *Annals of the Rheumatic Diseases*. 2011
3. **Angel K, Provan SA**, *Hypertension*. 2010
4. **Angel K, Provan SA**, *Fundamental and Clinical Pharmacology*. 2011
5. **Mazzoccoli G, Notarsanto I**, *Internal and Emergency Medicine*. 2010

Arthritis Care & Research
Vol. 66, No. 1, January 2014, pp 97–103
DOI 10.1002/acr.22144

SPECIAL THEME ARTICLE: CLINICAL IMAGING AND THE RHEUMATIC DISEASES

Relationship Between Metabolic Syndrome and Carotid Intima-Media Thickness: Cross-Sectional Comparison Between Psoriasis and Psoriatic Arthritis

YIH CHANG LIN,[1] DEEPAN DALAL,[1] SARAH CHURTON,[2] DANIELLE M. BRENNAN,[1] NEIL J. KORMAN,[2] ESTHER S. H. KIM,[1] AND M. ELAINE HUSNI[1]

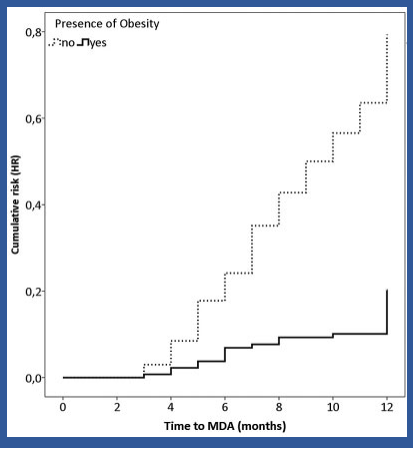


Obesity has an impact on therapy response

Odds of achieving MDA

Body Weight	OR
Normal	Ref
Overweight	**0.66 (0.50-0.87)**
Obese	**0.53 (0.41-0.69)**

*Adjusted for age, sex, duration, DMARD use, NSAIDs



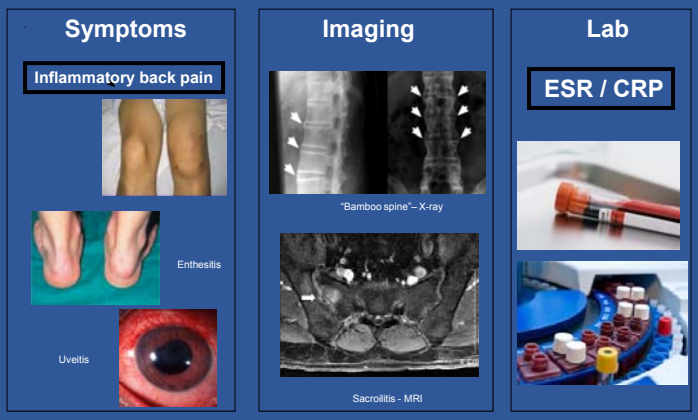
Time to Minimal Disease Activity

Eder et al Ann Rheum Dis 2014; Di Minno MN et al. AC&R 2013

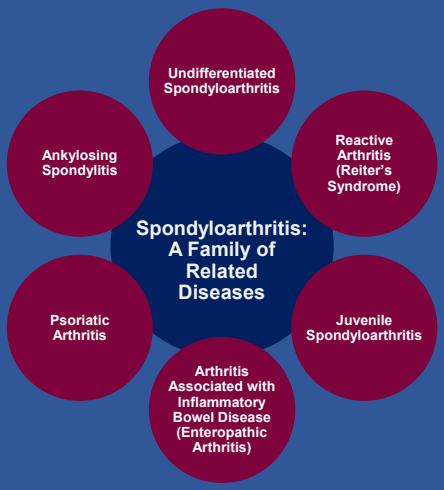
Conclusions

- Psoriatic arthritis is a unique inflammatory arthritis with diverse clinical features that occurs in ~ 30% of patients with psoriasis and remains underdiagnosed
- Early diagnosis and effective treatment is critical to minimize poor outcomes
- Co Management with dermatology and rheumatology can improve patient management
- Biologic therapy, in particular TNFi, can benefit all clinical domains and inhibit progressive structural damage
- A “treat to target” and “tight control” strategy has been shown to yield optimal clinical outcomes
- New therapies are emerging

Ankylosing Spondylitis

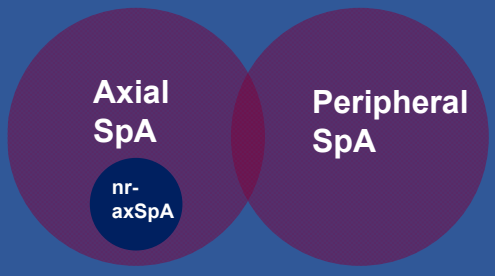


Classical Approach.....



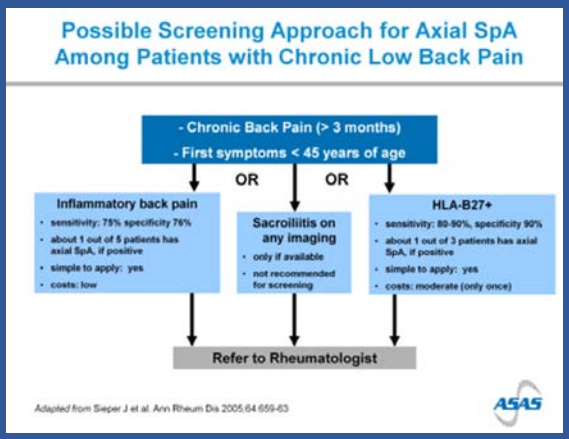
Spondylitis Association of America.

Defining the Patient Population

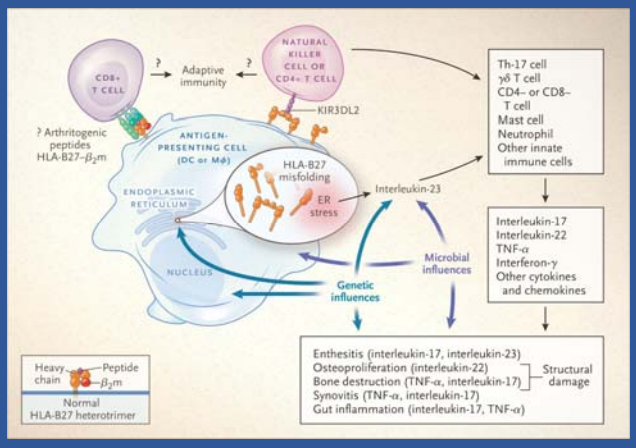


SpA: Spondyloarthritis; nr-axSpA: Non-Radiographic Axial SpA

Identifying Axial Spondyloarthritis



Pathogenic Mechanisms in Axial Spondyloarthritis.



Taurog JD et al. N Engl J Med 2016;374:2563-2574

The NEW ENGLAND JOURNAL of MEDICINE

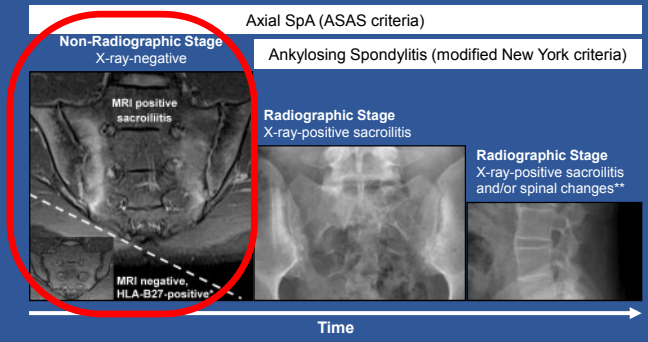
IBP: Three Different Criteria

Calin et al	Rudwaleit et al	Sieper et al
• Age at onset <40 years • Duration of back pain >3 months • Insidious onset • Morning stiffness • Improvement with exercise	• Morning stiffness >30 minutes • Improvement with exercise, not with rest • Awakening at second half of the night because of pain • Alternating buttock pain	• Age at onset <40 years • Insidious onset • Improvement with exercise • No improvement with rest • Pain at night (with improvement upon getting up)
IBP if 4/5 are present	IBP if 2/4 are present	IBP if 4/5 are present

IBP = inflammatory back pain.
Calin A, et al. *JAMA*. 1977;237:261. Rudwaleit M, et al. *Arthritis Rheum*. 2006;54:569-578.
Sieper J, et al. *Ann Rheum Dis*. 2009;68:784-788.

Spectrum of Axial Spondyloarthritis

Patients with chronic back pain ≤3 months and age of onset <45 years



*Clinical arm if nonradiographic axial SpA. **Radiographic evidence of inflammatory spinal changes, including, for example, syndesmophytes, fusion, or posterior element involvement.
Sieper J, et al. *Arthritis Rheum*. 2013;65(3):543-551.

Which of the following risk factors have been observed with patients progressing from axSpA to AS?

- Elevated CRP at presentation
- HLAB27 positivity
- Female Gender
- Risk factors have not been studied

Longitudinal Cohort Studies:Progression From nrAxSpA to AS

0 to 2 yrs from nrAxSpA diagnosis: 8% to 12% progress to AS

2 to 9 yrs from nrAxSpA diagnosis: 16% to 52% progress to AS

- Data from wide range of sources (N = 23 to 210)
  - Variable methodology and disease definitions used
  - Both mixed axial and peripheral disease at baseline
  - ASAS criteria for AxSpA was not used

Sampaio-Barros P, et al. J Rheumatol. 2010;37:1195-1199. Poddubnyy D, et al. Ann Rheum Dis. 2011;70:1369-1374. Schattenkirchner M, et al. Clin Rheumatol. 1987;6(suppl 2):83-86. Sany J, et al. Arthritis Rheum. 1980;23:258-259. Mau W, et al. J Rheumatol. 1988;15:1109-1114. Oostveen J, et al. J Rheumatol. 1999;26:1953-1958. Bennett A, et al. Arthritis Rheum. 2008;58:3413-3418.

Risk Factors Associated With Progression to AS

Consistent RF

- Baseline low-grade x-ray sacroiliitis[1,2]
- Baseline MRI inflammation[3]
- Elevated CRP[2]

Inconsistent RF

- HLA-B27 positivity inconsistent between studies[2,3]
- Male sex predictive for nrAxSpA but protective for AS[2]
- Buttock pain[4]
- Smoking[5,6]

1. Huerta-Sil G, et al. Ann Rheum Dis. 2006;65:642-646.
2. Poddubnyy D, et al. Ann Rheum Dis. 2011;70:1369-1374.
3. Bennett A, et al. Arthritis Rheum. 2008;58:3413-3418.
4. Sampaio-Barros P, et al. J Rheumatol. 2010;37:1195-1199.
5. Machado P, et al. Arthritis Rheum. 2011;63(suppl 10):1650.
6. Poddubnyy D et al Arthritis Rheum. 2012 May;64(5):1388-98

Which of the following risk factors have been observed with patients progressing from axSpA to AS?

- Elevated CRP at presentation
- HLAB27 positivity
- Female Gender
- Risk factors have not been studied

TREATMENT OF AXIAL SPONDYLOARTHRITIS

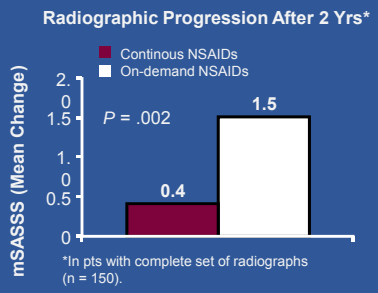
ACR/SAA/SPARTAN Recommendations for Active AS

Setting	Recommendation	Considerations
First-line	NSAIDs*	▪ No preferred NSAID ▪ Use continuously if active ▪ *Nonresponder*: lack of response to ≥ 2 NSAIDs over 1 mo or incomplete response to ≥ 2 NSAIDs over 2 mos
	Physical therapy*	▪ Active vs passive ▪ Land-based vs aquatic
	Not recommended: systemic GCs	▪ Consider if peripheral arthritis, pregnancy, or IBD flare
Active AS despite NSAIDs	TNFi*	▪ No preferred agent ▪ Recurrent iritis: IFX or ADA ▪ IBD: TNFi monoclonal
	If TNFi contraindication: SAARD	▪ Non-TNFi biologic not recommended
	If isolated sacroiliitis, peripheral arthritis, enthesitis: local GC	
Active AS despite TNFi	Alternative TNFi	

*Strongly recommended. †Conditionally recommended.

NSAID Therapy in AS: Radiographic Progression

- Open-label, randomized trial
- AS patients treated with continuous or on-demand NSAIDs for 2 yrs (N = 215)
  - All patients started on celecoxib (could switch NSAID if discontinued celecoxib)
  - Mean daily dose of celecoxib
    - Continuous-treatment group: 243 mg
    - On-demand group: 201 mg
    - Dose difference: 42 mg; *P* = .0001



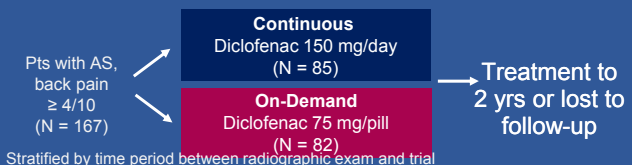
*In pts with complete set of radiographs (n = 150).

Wanders A, et al. Arthritis Rheum. 2005;52:1756-1765.

Slide credit: clinicaloptions.com

ENRADAS: Effects of NSAIDs on Radiographic Progression in AS

- Multicenter, randomized phase III trial



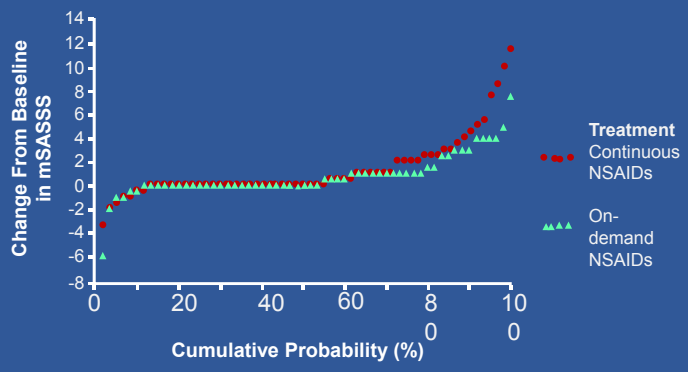
Stratified by time period between radiographic exam and trial inclusion.

- Primary endpoint: spinal radiographic progression (change in mSASSS)
- Mean daily dose: continuous tx, 113 mg; on-demand tx, 66 mg

Sieper J, et al. Ann Rheum Dis. 2015.

Slide credit: clinicaloptions.com

ENRADAS: Radiographic Progression



Sieper J, et al. Ann Rheum Dis. 2015.

Slide credit: clinicaloptions.com

Conclusions in NSAID treatment for AS

- NSAIDs have no disease-modifying effect
- NSAIDs should be used to treat symptoms in AS
- ACR/SAA/SPARTAN: conditionally recommend continuous NSAID treatment vs on-demand treatment for active AS
- If patients are stable on TNFi, NSAID continuation is not necessary.

Slide credit: clinicaloptions.com

Efficacy of Sulfasalazine and Methotrexate (Cochrane Meta-Analysis)

Sulfasalazine: 11 RCTs

Some Evidence of Benefit	No Evidence of Benefit
• ESR • Morning stiffness • Peripheral arthritis (2 trials)	• Physical function • Pain • Spinal mobility • Enthesitis • Patient and physician global assessment

Conclusion: Patients with early disease, with higher levels of ESR, and peripheral arthritis may benefit

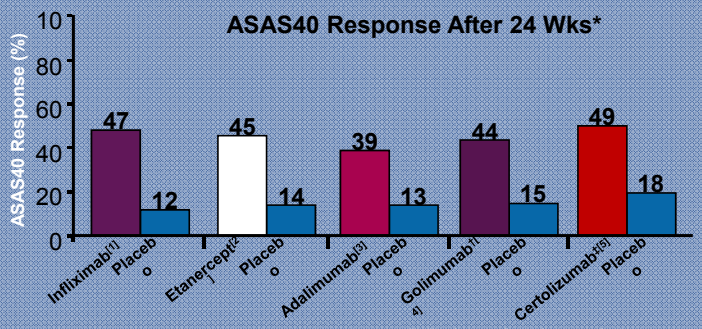
MTX: 2 Randomized Controlled Trials (N=81)

Outcomes	MTX + Naproxen vs Naproxen	MTX vs Placebo
• Function • Pain • Peripheral arthritis / enthesitis • Morning stiffness • PGA • CRP and ESR	No significant difference between intervention groups	

- **Conclusions:**
  - **MTX demonstrated no statistically significant benefit**
  - **Additional RCTs with larger samples, longer duration, and higher MTX dosages are needed**

Chen J, Liu C. *Cochrane Database Syst Rev.* 2005;(2):CD004800.
Chen J, Liu C. *Cochrane Database Syst Rev.* 2004;(3):CD004524.

Composite look at anti TNF therapy in AS patients



*Independent trials; no head-to-head comparisons between TNFis. †50 mg Q4W. ‡400 mg Q4W.
1. van der Heijde D, et al. Arthritis Rheum. 2005;52:582-591. 2. Davis J, et al. Ann Rheum Dis. 2005;64:1557-1562. 3. van der Heijde D, et al. Arthritis Rheum. 2006;54:2136-2146. 4. Inman RD, et al. Arthritis Rheum. 2008;58:3402-3412. 5. Landewé R, et al. Ann Rheum Dis. 2014;73:39-47

Slide credit: clinicalsolutions.com

Is Therapy with TNF-blockers More Effective in Patients with Shorter Disease Duration?

- Predictors of a good clinical response to TNF-blockers were studied
  - Short disease duration
  - Elevated CRP-serum levels
  - Younger age

Rudwaleit M, et al. *Ann Rheum Dis*. 2008;67(9):1276-1281.

TNF Blockade in the Management of AS

- AS Disease duration <3 years
  - 80% achieved BASDAI 50
- AS Disease duration >10 years
  - 14.3% achieved BASDAI 50

Rudwaleit M, et al. *Ann Rheum Dis*. 2008;67(9):1276-1281.

Anti-TNF Therapy in AS

S	=	Very effective, improves function, decreases XR damage
W	=	Not everyone responds
O	=	Improve on the long delay of dx AS and non-radiographic AS patients, tx extra spinal sx
T	=	Lack of early treatment algorithms, treat to target

SWOT = Strengths, Weaknesses, Opportunities, Threats.

ACR/SAA/SPARTAN Recommendations for Use of Specific TNFi

- For patients with active AS, no TNFi is preferred for treatment over another TNFi, EXCEPT when the pat has one of the following comorbidities:
  - IBD: strongly recommend use of TNFi monoclonal antibodies (eg, infliximab, adalimumab) over etanercept
  - Recurrent iritis: conditionally recommend use of infliximab or adalimumab over etanercept

Ward M, et al. Arthritis Rheum. 2016;68:282-298.

Slide credit: clinicaloptions.com

AS Treatment Beyond TNFi

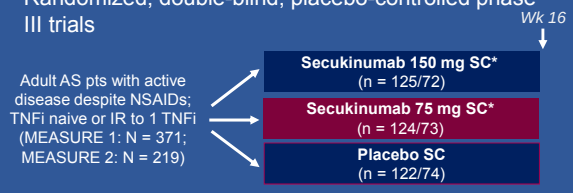
IL-6 in AS

- No significant response to IL-6 inhibition in two separate trials:
  - Tocilizumab – 99 pts 8 mg/kg IV q4 wks x 12 wks
  - Sarilumab (human anti-IL6R) – 100 pts 150 mg/kg SQ weekly x 12 wks
- No MRI improvement in sarilumab trial
- IL-6 doesn't appear to be a viable target in AS

Sieper J, et al. Ann Rheum Dis 2015 Jun;74(6):1051-7

MEASURE 1 and 2: Secukinumab for Active AS

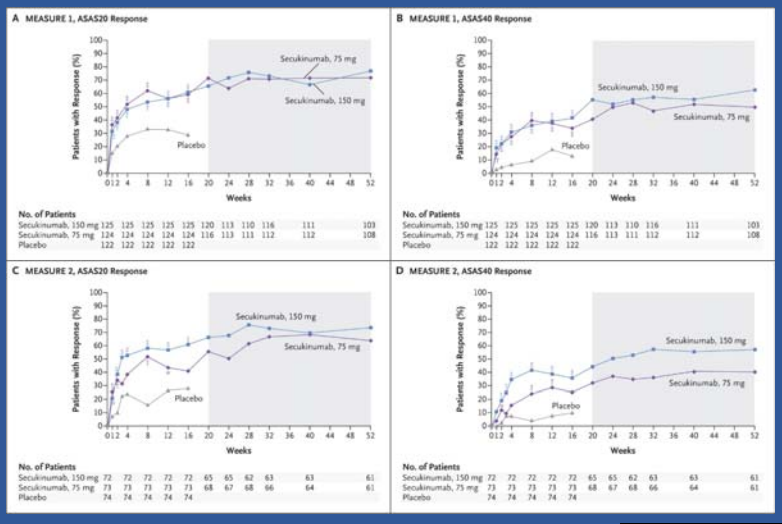
- Randomized, double-blind, placebo-controlled phase III trials



Pts could continue to receive MTX, SSZ, prednisone, or NSAIDs during the trial. *MEASURE 1: both dosage groups received 10 mg/kg IV at baseline, Wk 2, and Wk 4, then SC dosing every 4 wks starting at Wk 8.
MEASURE 2: SC dosing occurred at baseline and Wks 1-4, then every 4 wks.

Baeten D, et al. N Engl J Med. 2015;373:2534-2548.

Response Rates through Week 16 (Placebo-Controlled Phase) and through Week 52 among Patients Randomly Assigned to Secukinumab or Placebo at Baseline in MEASURE 1 and MEASURE 2.

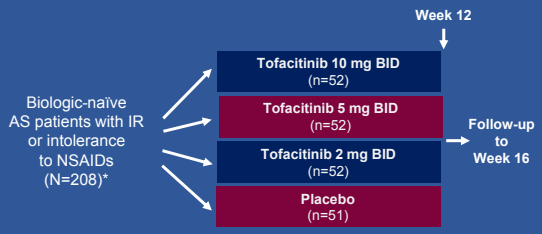


Baeten D et al. N Engl J Med 2015;373:2534-2548

The NEW ENGLAND JOURNAL of MEDICINE

Tofacitinib (Oral JAK inhibitor) for Biologic-Naïve Patients with AS

- **Randomized, double-blind, placebo-controlled, dose-ranging phase 2 trial**



Baseline characteristics

- Mean disease duration: 1.5-4.1 years; mean BASDAI score, 6.3-7.0
- Concomitant DMARDs: 27.5%-44.2%

*One patient not treated due to tibia/fibia fracture between screening and baseline.
van der Heijde D, et al. ACR/ARHP 2015. Abstract 5L.
Slide credit: clinicaloptions.com.

Tofacitinib for Biologic-Naive AS : Key Results

Wk 12, %	Tofacitinib 2 mg (n = 52)	Tofacitinib 5 mg (n = 52)	Tofacitinib 10 mg (n = 52)	Placebo (n = 51)
ASAS20 response (E_{max} model)*	56.0	63.0	67.4	40.1
▪ Difference vs placebo (95% CI)	15.8 (5.0-30.3)	22.9 (8.4-37.7)	27.3 (10.7-43.4)	--
ASAS20 (observed)	51.9	80.8†	55.8	41.2
BASDAI50	46.2‡	42.3‡	42.3‡	23.5
D/c for AE	0	1.9	1.9	5.9
TEAEs	44.2	53.8	51.9	43.1
Serious AEs	0	1.9	1.9	3.9

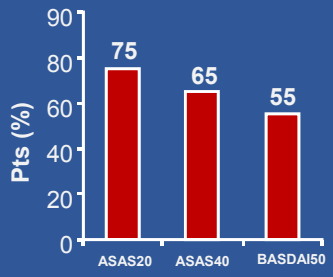
*Primary endpoint. †P < .001 vs placebo. ‡P < .05 vs placebo.

Tofacitinib treatment also associated with improvements in ASDAS, SPARCC MRI (joint and spine) scores vs PBO

van der Heijde D, et al. ACR/ARHP 2015. Abstract 5L.

TOPAS: Ustekinumab for Active AS 24 weeks

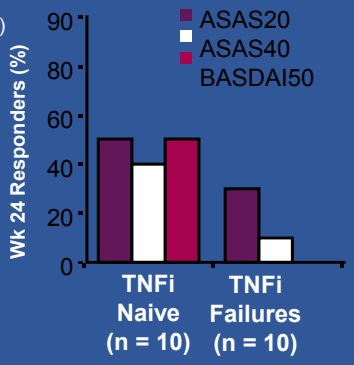
- **Ustekinumab: IL-12/23 inhibitor**
- **Phase II trial: pts with active AS and IR or intolerance to NSAIDs treated with ustekinumab 90 mg SC at BL, Wk 4, and Wk 16 (N = 20)**



van der Heijde D, et al. ACR/ARHP 2015. Abstract 5L

Rituximab for Active AS

- Rituximab: targets CD20+ B cells
- Phase II trial in active AS patients
  - rituximab 1000 mg at BL and Wk 2 (N = 20)



Song I, et al. Arthritis Rheum. 2010;62:1290-1297

Slide credit: clinicaloptions.co

What to do with anti TNF failures in AS?

- ACR/SAA/SPARTAN recommendations
  - Switch to a difference TNFi over adding non biologic DMARD (which have little efficacy for axial component)
  - Consider very low-quality evidence
- Secukinumab may be an option

Ward M, et al. Arthritis Rheum. 2016;68:282-298.

Summary

- First line teatment for active AS begins with NSAIDs
- Pts with active disease despite NSAIDs may use TNFi or secukinumab
  - If pt is stable on TNFi, NSAIDs may be stopped
- TNFi most effective if started < 10 yrs of disease onset, making early diagnosis essential
- Pts receiving TNFi should be monitored for general infection, TB, HBV, malignancy, and neurologic disorders; pts receiving secukinumab should be monitored for general infection, TB, and IBD
- Investigational agents tofacitinib and ustekinumab show promise in clinical trials for treating active AS