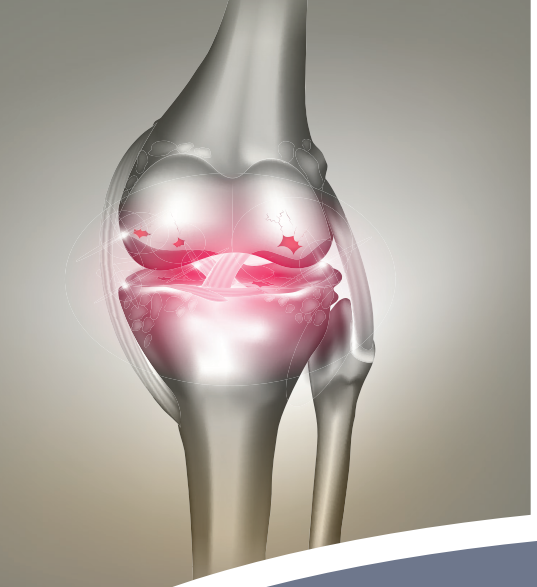

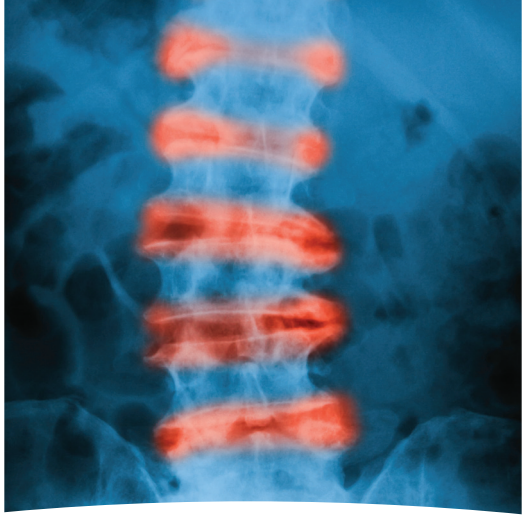

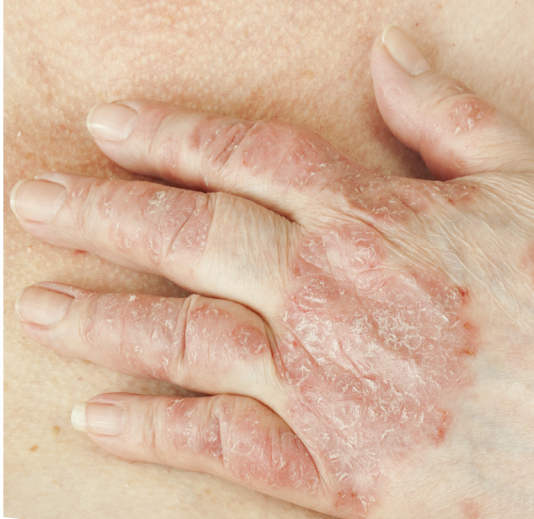

Biological Therapies for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Osteoarthritis: Comparative Effectiveness Based on Treatment Profiles and Guideline Recommendations

Program Director

Philip J. Mease, MD

Clinical Professor, University of Washington School of Medicine,
Director of the Rheumatology Clinical Research,
Division of Swedish Medical Center, Seattle, WA

Saturday, September 19, 2015

Courtyard Philadelphia Downtown
21 North Juniper Street • Philadelphia, PA 19107
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Statement of Need/Program Overview

This symposium is intended to provide paradigm shift in the treatment options for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and osteoarthritis. The format will include didactic lectures from known thought leaders; question and answer sessions, case report presentation and ample opportunity for participant interaction with faculty.

Target Audience

This symposium is directed primarily to rheumatologists, physician assistants, nurse practitioners, pharmacists, registered nurses, and other clinicians involved in the management of patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and osteoarthritis.

Learning Objectives

After completing this activity, the participant should be better able to:

- Review the data supporting the classification of RA by the ACR/EULAR and ACR updated treatment guidelines
- Utilize strategies to diagnose and identify RA patients who may benefit from early disease-suppressing therapy
- Identify current disease-modifying anti-rheumatic drugs (DMARDs) and newer combination and biological therapies to delay disease progression and improve outcomes in patients with RA
- Identify the role of biosimilars in the treatment of early stage rheumatoid arthritis
- Utilize algorithm for evaluation and implementation of treatment strategies to identify psoriatic arthritis patients who may benefit from early disease-suppressing therapy
- Identify newer biological therapies to delay disease progression and improve outcomes in patients with psoriatic arthritis
- Identify evolving concepts of spondyloarthritis and update on treatment options
- Identify the key components that contribute to the pathogenesis of knee osteoarthritis
- Discuss current clinical data and outcomes associated with the use of chondroitin sulfate, glucosamine and hyaluronic acid in osteoarthritis treatment
- Identify strategies to alleviate chronic widespread pain due to central sensitization in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis

Agenda

SATURDAY – September 19, 2015

7:00 AM	**Buffet Breakfast and Registration**	
8:25 AM	Opening Remarks and Introductions	*Philip J. Mease, MD*
	State of the Art Lectures – RHEUMATOID ARTHRITIS	
8:30 AM	Update on European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) Guidelines in the Treatment of Rheumatoid Arthritis	*Roy Fleischmann, MD*
9:05 AM	Discuss Optimal Strategy to Monitor Early and Established Patients with Rheumatoid Arthritis Disease Activity and Response to Novel Therapies	*Gregg J. Silverman, MD*
9:40 AM	Focus on Early Stage Rheumatoid Arthritis: Update on Role of Biosimilars	*Jonathan Kay, MD*
10:15 AM	Panel Discussion and Case Presentation	*Roy Fleischmann, MD / Gregg J. Silverman, MD / Jonathan Kay, MD*
10:35 AM	**BREAK**	
	PSORIATIC ARTHRITIS	
10:45 AM	Algorithm for Evaluation and Treatment Options for Patients with Psoriatic Arthritis	*Alexis Ogdie-Beatty, MD*
11:20 AM	Discuss Optimal Strategy to Monitor Early and Established Patients with Psoriatic Arthritis and Comparative Efficacy and Safety of Biological Therapies	*Philip J. Mease, MD*
11:55 AM	Panel Discussion and Case Presentation	*Alexis Ogdie-Beatty, MD, MD / Philip J. Mease, MD*
12:15 PM	**LUNCH**	
	ANKYLOSING SPONDYLITIS	
12:55 PM	New Concepts in the Diagnosis and Treatment of Ankylosing Spondylitis	*Muhammad A. Khan, MD*
	OSTEOARHTIRITS	
1:30 PM	Identify the Key Components in the Pathogenesis of Knee Osteoarthritis: Current Clinical Data and Outcome Associated with the Use of Chondroitin Sulfate and Glucosamine	*Marc C. Hochberg, MD*
2:05 PM	**BREAK**	
	SUPPORTIVE CARE ISSUES	
2:15 PM	Neurobiology of Central Sensitization in Conditions Such as Rheumatoid arthritis, Osteoarthritis and Ankylosing Spondylitis – How it Influences Standard Outcome Measures?	*Philip J. Mease, MD*
2:50 PM	Panel Discussion and Case Presentation	*Muhammad A. Khan, MD / Marc C. Hochberg, MD/ Philip J. Mease, MD*
3:10 PM	Closing Remarks and Adjourn	*Philip J. Mease, MD*

Faculty

Roy Fleischmann, MD
Clinical Professor of Medicine, University of Texas Southwestern Medical Center, Co-Medical Director Metroplex Clinical Research Center, Rheumatology Associates, Dallas, TX

Marc C. Hochberg, MD
Professor of Medicine, Head of the Division of Rheumatology and Clinical Immunology, University of Maryland School of Medicine, Baltimore, MD

Jonathan Kay, MD
Professor of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts; Director of Clinical Research, Division of Rheumatology, University of Massachusetts Memorial Medical Center, Worcester, MA

Muhammad A. Khan, MD
Professor of Medicine, Case Western Reserve University School of Medicine, Division of Rheumatology, Cleveland, Ohio

Philip J. Mease, MD
Clinical Professor, University of Washington School of Medicine, Director of the Rheumatology Clinical Research, Division of Swedish Medical Center, Seattle, WA

Alexis Ogdie-Beatty, MD
Assistant Professor of Medicine at the Hospital of the University of Pennsylvania, Philadelphia, PA.

Gregg Silverman, MD
Professor of Medicine and Pathology, NYU School of Medicine, New York, NY

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Jonathan Kay, MD	**Consultant**: Amgen, Inc., AbbVie Inc., AstraZeneca, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company, Crescendo Bioscience, Inc., Eli Lilly and Company, Epirus Biopharmaceuticals, Inc., Genentech, Hospira, Inc., Janssen Biotech, Inc., Merck Sharp & Dohme Corp., Nippon Kayaku Co. Ltd., Novartis Pharmaceuticals Corporation, Pfizer Inc., Samsung Bioepis, Roche Laboratories, Inc., UCB, Inc. **Research Support**: AbbVie, Inc., Eli Lilly and Company, Pfizer, Inc., Roche Laboratories
Muhammad A. Khan, MD	**Consultant**: AbbVie, Inc., Amgen, Inc., Novartis, Janssen Biotech, Inc., Celgene, Crescendo Bioscience, Inc., Sun Pharmaceuticals
Alexis Ogdie-Beatty, MD	No relevant financial relationships
Philip J. Mease, MD	**Consultant**: AbbVie, Inc., Amgen, Inc., Bristol-Myers Squibb, Celgene, Crescendo Bioscience, Inc., Corona, Genentech, Janssen Biotech, Inc., Lilly, Merck, Novartis, Pfizer, UCB, Inc. **Speaker's Bureau**: AbbVie, Inc., Amgen, Inc., Bristol-Myers Squibb, Celgene, Crescendo Bioscience, Inc., Genentech, Janssen Biotech, Inc., Lilly, Pfizer, UCB, Inc. **Research Support**: AbbVie, Inc., Amgen, Inc., Bristol-Myers Squibb, Celgene, Crescendo Bioscience, Inc., Genentech, Janssen Biotech, Inc., Lilly, Merck, Novartis, Pfizer, UCB, Inc.
Gregg Silverman, MD	**Consultant**: Pfizer, Lilly, Bristol-Myers Squibb

Kamatham A. Naidu, PhD	No relevant financial relationships

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- Participants can earn Continuing Education credits for this program by electronically logging onto the website https://ce.ahrevents.com/ and completing the session evaluation form for sessions attended.
  - **Nurses:** After completion of the evaluation, certificate of credit can be printed.
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REGISTRATION FORM Biological Therapies for Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Osteoarthritis: Comparative Effectiveness Based on Treatment Profiles and Guideline Recommendations

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Update on European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) Guidelines in the Treatment of Rheumatoid Arthritis

Roy Fleischmann, MD

Comparison of 2012 ACR Recommendations and the 2013 EULAR Guidelines for the Management of Rheumatoid Arthritis

Roy Fleischmann, MD, MACR
Clinical Professor of Medicine
University of Texas Southwestern Medical Center
Dallas, Texas

Conflict of Interest Disclosure

Consultant for:

- AbbVie, Akros, Amgen, Ardea, Astra Zeneca, Augurex, BMS, Celgene, Genentech, GSK, Iroko, Janssen, Eli Lilly, Pfizer, Roche, Sanofi Aventis, UCB

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The goal is remission

Low disease activity if remission cannot be reached

American Rheumatology Association Remission Criteria (1981)[1]

- ≥5 of the following criteria must be met for at least 2 consecutive months
  - Morning stiffness: 15 minutes
  - No fatigue
  - No joint pain (by history)
  - No joint tenderness or pain on motion
  - No soft tissue swelling in joints or tendon sheaths
  - ESR
    - Females <30 mm/h
    - Males <20 mm/h

1. Pinals RS, et al. Arthritis Rheum.

ACR/EULAR RA remission criteria[1]

- Developed by committee using data from clinical trials
- Assessed ability of candidate measures to predict: damage (change ≤0 in van der Heijde modified total Sharp score) and function (change in HAQ ≤0; HAQ ≤0.5) over 2 years
- Best results obtained by 2 proposed definitions:
  - TJC and SJC and CRP and Patient Global all ≤1 OR
  - SDAI ≤3.3 [SDAI = TJC (28) + SJC (28) + MD global (0–10 cm VAS) + Patient global (0–10 cm VAS) + CRP (mg/dL). Cut points: 3.3/11/26[2]

Stringent new RA remission criteria adopted (but not as stringent as 1981)

1. Felson DT, et al. Arthritis Rheum. 2011; 63(3):573-586. 2. Smolen J, et al. Rheumatology. 2003;42:244–57.

Proposed 2015 ACR recommendations for the treatment of RA

Recommendations and not Guidelines

Principles for 2015 RA Recommendations

- Focus on common patients, not exceptional cases
- Optimal dose of medication given for 3 months before therapy escalation or switching
- Disease activity measurement using one of ACR recommended measures should be performed in a majority of encounters for individuals with RA
- Panel considered cost as one of many possible conditions to recommendation; however, explicit cost-effectiveness analyses not conducted

8

Key Terms

DMARD combinations	Any combination of 2 drugs (MTX + HCQ, MTX + LEF, MTX + SSZ, SSZ + HCQ) or triple therapy – MTX + SSZ +HCQ
bDMARDs	ADA, CZP, ETN, IFX, GLM, ABA, RTX, TCZ, not anakinra, "tofacitinib"
Early RA	Disease duration < 6 months
Established RA	Disease duration > 6 months or meeting the 1987 ACR classification criteria
Disease Activity	Low, moderate or high per validated common scales
RA remission	ACR/EULAR definition of remission

Singh JA, et al. ACR 2014, Boston

Instruments to Measure RA Disease Activity and to Define Remission

Instrument	Thresholds of disease activity levels
Clinical Disease Activity Index (CDAI) (range 0-76)	REM: ≤ 2.8; LDA:>2.8-10; MDA: 11-22; HAD: >22
Disease Activity Score in 28 joints (DAS28-ESR) (range 0-9.4)	REM:<2.6; LDA:≥2.6-- <3.2; MDA: ≥ 3.2 - < 5.1; HDA: ≥ 5.1
Simplified Disease Activity Index (SDAI) (range 0-86)	REM: ≤3.3; LDA:>3.3 -≤ 11; MDA: ≥ 11 --≤ 26; HAD: ≥ 26

Singh JA, et al. Arthritis Care Res. 2012 ;64:625

Principles for 2015 RA Recommendations

- MTX is initial therapy in most RA patients
- Mono-DMARD therapy
  - most often MTX, but could also be SSZ, HCQ, or LEF
- All patients with RA should see a rheumatologist
- Glucocorticoid treatment should be limited:
  - lowest effective dose for shortest possible time
  - provides best benefit-risk ratio for patient

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Principles for 2015 RA Recommendations

- If patient is doing well and their RA is under control, switching from one therapy to another should be done only at discretion of treating physician in consultation with patient
  - Arbitrary switching between therapies should not be done.
- Functional status assessment using a standardized, validated measure should be performed routinely for RA patients
  - At least once per year, but more frequently if RA is active.

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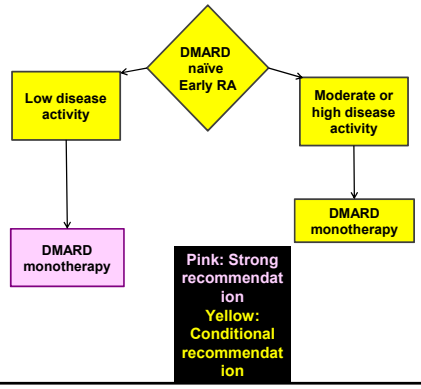
2015 Recommendations: Goals of RA Therapy

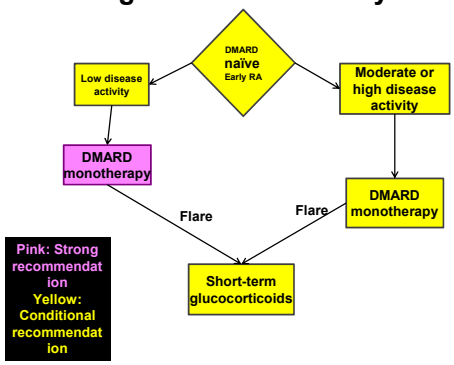
- ***Strongly recommend*** **using a treat-to-target strategy rather than a non-targeted approach in**
  - **Early RA**
  - **Established RA**
- **Ideal target should be remission or low disease activity if remission cannot be reached, determined by the clinician and patient**
  - In some cases, another target may be chosen because of risk, tolerance, comorbidities, etc.

13

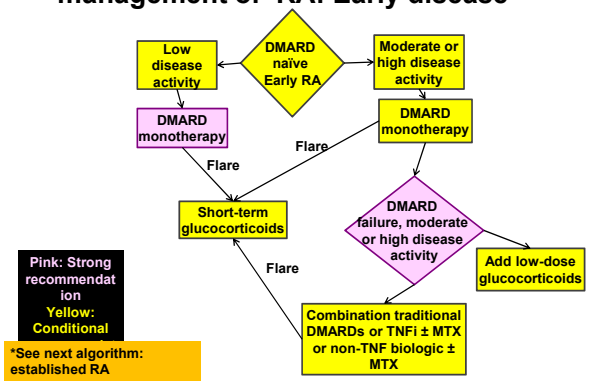
Draft 2015 ACR recommendations for management of RA: Early disease



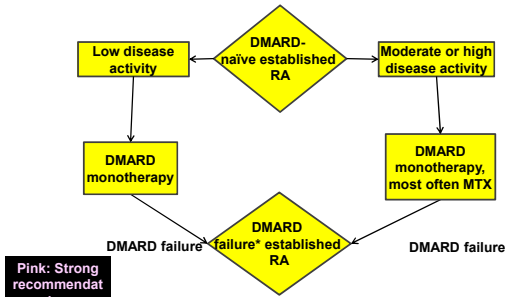
Draft 2015 ACR recommendations for management of RA: Early disease



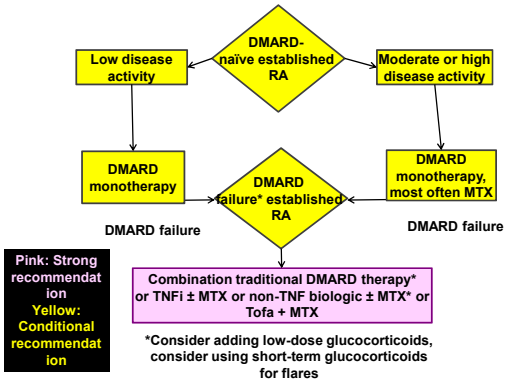
Draft 2015 ACR recommendations for management of RA: Early disease



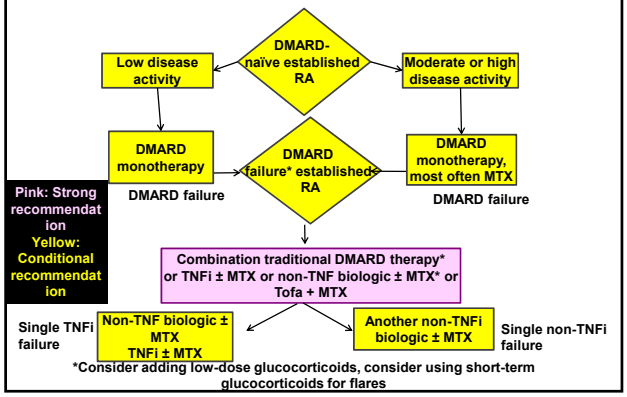
Draft 2015 ACR recommendations for management of RA: Established disease



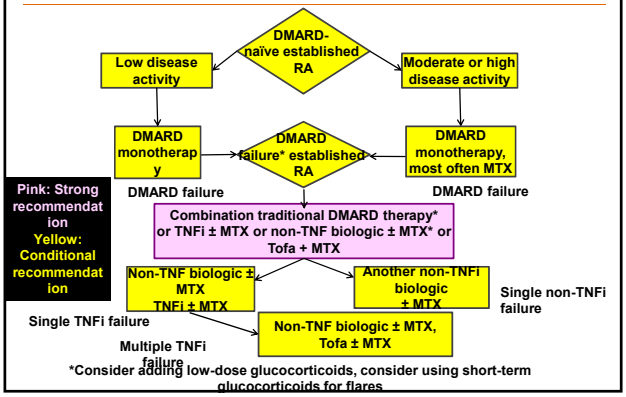
Draft 2015 ACR recommendations for management of RA: Established disease



Draft 2015 ACR recommendations for management of RA: Established disease



Draft 2015 ACR recommendations for management of RA: Established disease



Tapering or Discontinuing Therapy in Patients with Established RA

Should we or shouldn't we?

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Tapering or Discontinuing Therapy in Patients with Established RA

LDA and continuing MTX

- Continue
  - csDMARD(s)*
  - bDMARDs**
    - TNFi
    - Non-TNF bDMARD
  - Tofacitinib

Remission and continuing MTX

- Taper (Conditional Recommendation)
  - csDMARD
  - bDMARD
    - TNFi
    - Non-TNF biologic
  - Tofacitinib
- Do not discontinue all medications

Strong Recommendations

* = conventional synthetic DMARDs; ** = biologic DMARD

Safety

Malignancy

Malignancy	Conditional Recommendation	Strong Recommendation
Previously treated or untreated non-melanoma skin cancer (NMSC)	Combination DMARD or non-TNF biologic > TNFi	
Previously treated or untreated melanoma skin cancer	TNFi > Tofa	
Previously treated lymphoproliferative disorder	Combination DMARD	non-TNF biologic (ABA, TCZ or RTX) > TNFi
Previously treated solid organ malignancy	Same therapy as in patients without this condition	

Conditional recommendations: low level evidence; largely based upon expert opinion and clinical experience

Infection

SERIOUS INFECTION

Recommended	No Consensus
Combination csDMARD over TNFi	RTX over TNFi
ABA over TNFi	TCZ over TNFi

All conditional recommendations

HEPATITIS

	Strong	Conditional
Active hepatitis B infection and receiving effective anti-viral treatment	csDMARD: bDMARD (TNFi or non-TNF) or Tofacitinib	
Hepatitis C receiving effective anti-viral treatment		csDMARD, TNFi, non-TNF biologic, or Tofa

Live Attenuated Vaccines in RA Patients on Biologics

- **Ideally, patients aged ≥50 years should receive herpes zoster vaccine *before* biologic therapy**
  - **FDA approved for age ≥ age 50 although CDC recommendation is ≥ age 60**
- **Early and established RA, currently on biologics**
  - **Do not use live attenuated vaccines such as herpes zoster vaccine**

Conditional recommendations supported by low level evidence are largely based upon CDC recommendations, safety warning, expert opinion, and clinical experience

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2015 ACR Recommendations: Vaccinations

	Killed vaccines			Recombinant vaccines	Live attenuated vaccines
	Pneumococcal	Influenza (IM)	Hepatitis B	Human papillomavirus	Herpes Zoster
Before therapy					
DMARD mono	√	√	√	√	√
DMARD combo	√	√	√	√	√
Anti-TNF	√	√	√	√	√
Non-anti-TNF	√	√	√	√	√
During therapy					
DMARD mono	√	√	√	√	√
DMARD combo	√	√	√	√	√
Anti-TNF	√	√	√	√	X
Non-anti-TNF	√	√	√	√	X

Comparison of 2012 and 2015 ACR Recommendations

AGENT	2012	2015
DMARDS	Hydroxychloroquine	Hydroxychloroquine
	Leflunomide	Leflunomide
	Methotrexate	Methotrexate
	Minocycline	Minocycline
	Sulfasalazine	Sulfasalazine
	Combination of 2 or 3 DMARDs	Combination of 2 or 3 DMARDs
		Tofacitinib
bDMARDs: Non TNF	Abatacept	Abatacept
	Rituximab	Rituximab
	Tocilizumab	Tocilizumab
bDMARDs: TNF-i	Adalimumab	Adalimumab
	Etanercept	Etanercept
	Infliximab	Infliximab
	Certolizumab pegol	Certolizumab pegol
	Golimumab	Golimumab

Singh JA, et al. Arthritis Care Res. 2012 ;64:625

Comparison of 2012 and 2015 ACR Recommendations

	2012	2015
Switching between therapies	√	√
Monitoring Side Effects	√	√
Tb screening (initial/during therapy)	√	√
Use of bDMARDs in hepatitis, CHF and malignancy	√	√
Vaccinations (initial/during therapy)	Pneumococcal, influenza, hepatitis Human papilloma virus and HZ	Pneumococcal, influenza, hepatitis Human papilloma virus and HZ
Malignancy		√

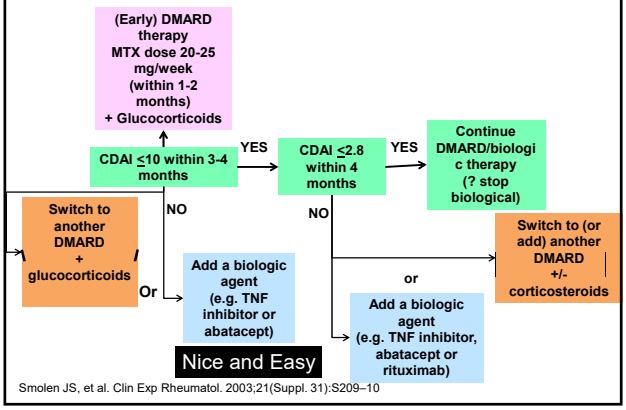
Singh JA, et al. Arthritis Care Res. 2012 ;64:625

Summary of 2015 ACR Recommendations

- **Literature search with expert opinion (but who defines whether they are experts?)**
- **Many recommendations are not based on well controlled studies**
- **Some recommendations based on few studies**
- **Includes recommendations for hepatitis, malignancy and vaccinations**
- **Advocates a Treat to Target approach but not clear on how often medication is changed**
- **Includes recommendation to use TNF-I monotherapy**
- **Does not address aggressive therapy with poor prognostic markers**

EULAR Recommendations for the Treatment of RA

EULAR Algorithm for Treatment of RA



Smolen JS, et al. Clin Exp Rheumatol. 2003;21(Suppl. 31):S209–10

2103 EULAR Guidelines for the Treatment of RA

2103 Update of the EULAR Recommendations

Overarching principles

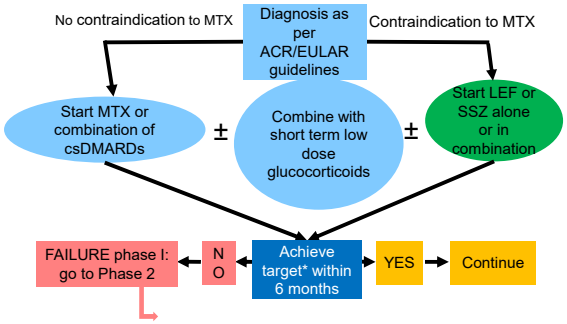
A. **Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist**

B. **Rheumatologists are the specialists who should primarily care for RA patients**

C. ***RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist***

Smolen et al, ARD 2014 73(3):492-509

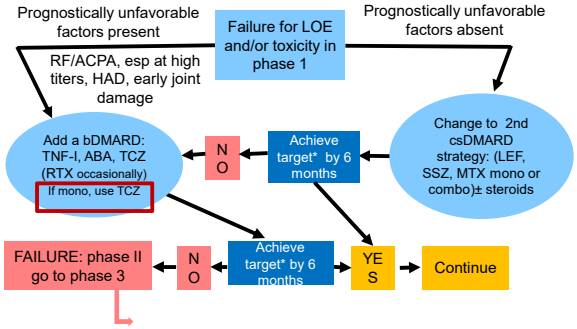
EULAR 2013 Treatment Algorithm for RA: Phase 1



*Target is ACR/EULAR remission or low disease activity; must have some response by 3 months

Smolen et al, ARD 2014 73(3):492-509

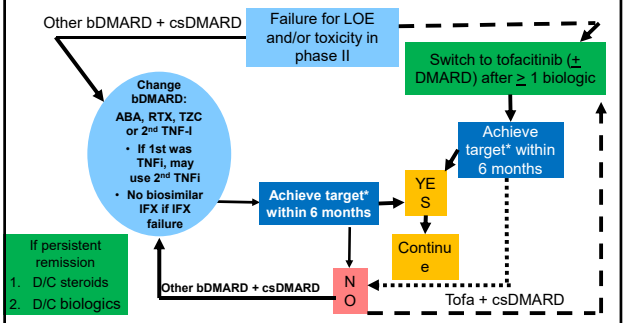
EULAR 2013 Treatment Algorithm for RA: Phase 2



*Target is ACR/EULAR remission or low disease activity; must have some response by 3 months

Smolen et al, ARD 2014 73(3):492-509

EULAR 2013 Treatment Algorithm for RA: Phase 3



*Target is ACR/EULAR remission or low disease activity; must have some response by 3 months

Smolen et al, ARD 2014 73(3):492-509

2103 Update of the EULAR Recommendations

Recommendations

1. Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2. Treatment of RA patients should aimed at reaching a target of remission or low disease activity in every patient
3. Monitoring should be frequent in active disease (every1-3 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
4. MTX should be part of the first treatment strategy in patients with active RA
5. In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the first treatment strategy
6. In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy of combination of csDMARDs should be used
7. Low dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
8. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered

Smolen et al, ARD 2014 73(3):492-509

2103 Update of the EULAR Recommendations

9. In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX.
10. If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or a biological with another MOA
11. Tofacitinib may be considered after biological treatment has failed
12. If a patient in is persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD
13. In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered , as a shared decision between patient and physician
14. When therapy needs to be adjusted, factors apart from disease activity such as progression of structural damage, comorbidities and safety issue, should be taken into account

Smolen et al, ARD 2014 73(3):492-509

Summary of 2013 EULAR Guidelines

- Expert opinion (but who defines whether they are experts?)
- Many recommendations are not based on well controlled studies
- Does not include recommendations for hepatitis, malignancy, CHF, Tb screening and vaccinations
- It is clear how often a patient is to be reassessed to change therapy
- States that metrics which are validated should be used
- Includes recommendation to use TZC but not other bDMARD monotherapy
- Does address aggressive therapy with poor prognostic markers

Many countries insist that EUALR guidelines be used

Summary

- Both the ACR recommendations and the EULAR guidelines rely on "expert opinion" with some evidence in the literature
- Neither determine treatment recommendation based on well controlled studies
- ACR recommendations include discussion of vaccination and treatment with co-morbid disease – EULAR guidelines do not
- EULAR guidelines address the use of TZC; ACR does not
- Both have major inconsistencies:
  - ACR:
    - Use of minocycline; no clear timing of change; TNF-I monotherapy; does not focus on poor prognostic markers and HDA; use of RTX with history of malignancy
  - EULAR:
    - Focus on costs; LEF in patients with contraindication to MTX (?); tofacitinib after a biologic; discontinuation of csDMARDs and bDMARDs but no threshold of remission.

Conclusion

- ACR recommendations are not binding; EULAR guidelines may be
- Better than nothing
- Both have strengths
- Both have weaknesses
- Both have too much "expert opinion" and not enough data
- Expect to see revisions every 2-3 years as new data becomes available and the "experts" need frequent flyer miles.

Thank you

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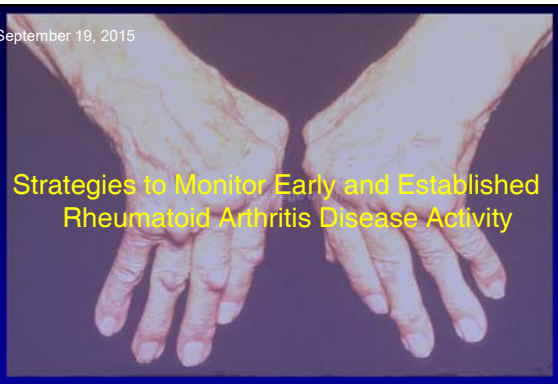
Discuss Optimal Strategy to Monitor Early and Established Patients with Rheumatoid Arthritis Disease Activity and Response to Novel Therapies

Gregg J. Silverman, MD

September 19, 2015



Strategies to Monitor Early and Established Rheumatoid Arthritis Disease Activity

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Conflict of Interest Disclosure

Consultant: Pfizer Inc., Genentech, Roche, BMS; Eli Lilly

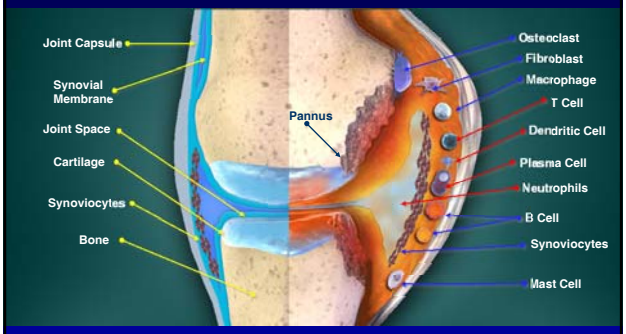
Grant support: NIH, RRF, Lupus Research Institute

Learning Objectives

- Describe prognostic factors for RA.
- Review the current diagnostic criteria.
- Review the clinical indices for monitoring of disease activity.
- Discuss the range of therapeutic options.
- Consider emerging concepts of optimal therapeutic targets and tools proposed for better measurement of disease activity

Explain that the features that edefine bad prognisis
Tools available for early diagnosis

Normal vs Symptomatic Rheumatoid Synovium



RA Diagnostic Criteria

- 1987 ACR criteria relied heavily on features associated with chronic RA disease and tissue injury.
- In 2010, the ACR and EULAR developed new RA criteria, primarily for clinical trials.
  - These criteria were designed to diagnose RA at earlier stages and included anti-CCP antibody testing linked to RA pathogenesis.

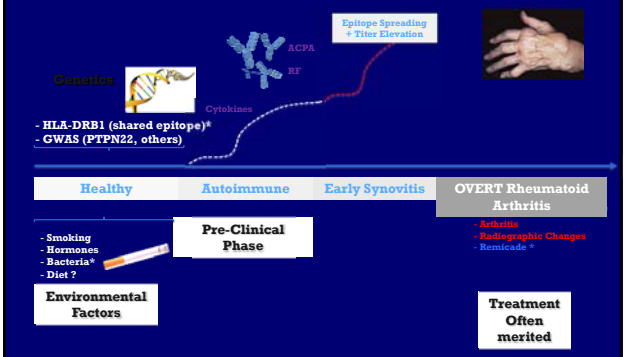
Arnett FC et al. *Arthritis Rheum.* 1988;31:315-324. Aletaha D et al. *Arthritis Rheum.* 2010;62:2569-2581.

ACPA-Positive vs ACPA-Negative Disease Characteristics

- ACPA-positive disease: Majority of patients with established disease[1]
  - Associated with:
    - Genetic signatures[1-3]
    - Worse erosive disease[4,5]
    - Cardiovascular disease[6]
- ACPA-negative disease: Not well understood[1]
  - More research needed
  - To date, has not been associated with[7]:
    - Genetic signatures
    - Environmental factors
    - Other characteristics of autoantibody-positive disease

1. Morgan AW et al. *Arthritis Rheum.* 2009;60(9):2565-2576.
2. Berglin E et al. *Arthritis Res Ther.* 2004;6(4):R303-308.
3. Pedersen M et al. *Arthritis Rheum.* 2007;56(5):1446-1453.
4. Goldbach-Mansky R et al. *Arthritis Res.* 2000;2(3):236-243.
5. El-Khoury GY et al. *Radiology.* 1988;168:517-520.
6. Södergren A et al. *Ann Rheum Dis.* 2007;66(2):263–266.
7. Källberg H et al. *Am. J. Hum. Genet.* 2007;80:867–875.

RHEUMATOID ARTHRITIS: HYPOTHESIS FOR STAGES OF DISEASE



Klareskog and others

ACR Response Criteria

ACR disease activity score enabled modern RA randomized clinical trials design

- Reported as percent overall clinical improvement, comparing baseline disease activity with a later time point (often after 6 months of therapy)
  - ACR20 is ≥20% improvement
  - ACR50 is ≥50% improvement
    - ACR50 responders include ACR20 responders
  - ACR70 is ≥70% improvement
    - ACR70 responders include ACR20 and ACR50 responders
- Used to discriminate effective treatment from placebo treatment in clinical trials
- However, not directly applicable to clinical practice

Felson DT et al. *Arthritis Rheum.* 1995;38:727-735.

2010 ACR/EULAR RA Classification Criteria *

2010 RA Classification Criteria

- ≥1 joint with synovitis (excluding the DIP, first MTP and first CMC joints)
- Absence of alternative diagnosis that better explains synovitis
- Achievement of total score of ≥6 (of 10) from individual scores in 4 domains
  - Joint involvement patterns
  - Serologic abnormality
  - Elevated acute-phase response
  - Symptom duration

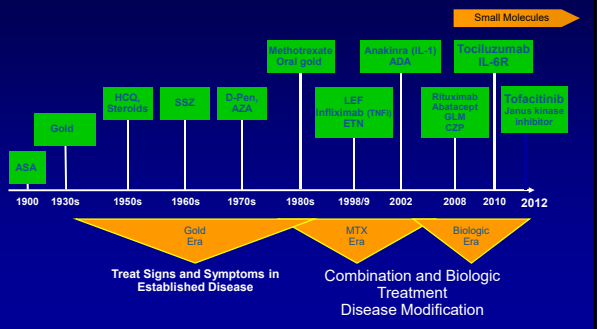
Swollen/Tender Joints	**(0-5)**
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints	3
>10 joints (≥1 small joint)	5
Serology	**(0-3)**
Negative RF AND ACPA	0
Low-positive RF OR ACPA	2
High-positive RF OR ACPA	3
Symptom Duration	**(0-1)**
<6 weeks	0
≥6 weeks	1
Acute Phase Reactants	**(0-1)**
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

Patients with a score of ≥6 have "definite" RA

DIP = distal interphalangeal joint; MTP = metatarsophalangeal; CMC = carpometacarpal; ACPA = anti-citrullinated protein antibody.

Aletaha D, et al. *Arthritis Rheum.* 2010;62(9):2569-2581.

Evolution of RA Treatment *



Algorithm for Treating RA to Target

Smolen JS, et al. *Ann Rheum Dis.* 2010;69(4):631-637.

Composite Measures of Disease Activity

Outcome Measures in RA

	ACR20/50/70	DAS28	SDAI	CDAI	RAPID
Patient function	+				+
Patient pain	+				+
Patient global	+	+	+	+	+
Physician global	+		+	+	
# Tender joints	+	+	+	+	
# Swollen joints	+	+	+	+	
ESR or CRP	+	+	+		

Yazici Y. *Bull NYU Hosp Jt Dis.* 2007;65(suppl 1):S25-S28. Zatarain E, Strand V. *Nat Clin Pract Rheumatol.* 2006;2:611-618.
Pincus T et al. *Rheum Dis Clin North Am.* 2009;35:773-778.

RA Disease Activity Score Continuous Measures Recommended for Use in Clinical Practice

	Categories of Disease Activity			
Instrument	Remission	Low	Moderate	High
DAS28	<2.6	≥2.6 to <3.2	≥3.2 to ≤5.1	>5.1
PAS or PAS-II	0 to 0.25	0.26 to 3.7	3.71 to <8.0	≥8.0
CDAI	≤ 2.8	>2.8 to 10.0	>10.0 to 22.0	>22.0
RAPID3	0 to 1.0	>1.0 to 2.0	>2.0 to 4.0	>4.0 to 10.0
SDAI	≤3.3	>3.3 to ≤11.0	>11.0 to ≤26.0	>26.0

PAS=Patient Activity Scale; RAPID3=Routine Assessment of Patient Index Data with 3 measures; CDAI=Clinical Disease Activity Index; DAS28=Disease Activity Score with 28-point counts; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; SDAI=Simplified Disease Activity Index.

Anderson J et al. *Arthritis Care Res.* 2012;64:640-647. Singh JA et al. *Arthritis Care Res*. 2012;64:625-639.

What is attainable clinical goal?

- Low Disease Activity ?
- Or even Remission?
- How do we gauge remission?

Table 1. Evolution of remission criteria.

Study (year)	Index used	Components	Remission definition	Ref.
Pinals *et al.* (1981)	ARA	Morning stiffness; fatigue; joint pain; joint tenderness or pain on motion; soft tissue swelling (joints and tendon sheaths); ESR	5 or more must be fulfilled for at least 2 consecutive months	[22]
van der Heijde *et al.* (1990) and Fransen *et al.* (2004)	DAS	Ritchie articular index, 44 SJC, ESR, PGA	≤1.6	[28,82]
Fransen *et al.* (2004) and Prevoo *et al.* (1995)	DAS28	28 TJC, 28 SJC, ESR, PGA	≤2.6	[82,29]
Smolen *et al.* (2003)	SDAI	TJC + SJC + PGA + MDGA + CRP	≤5	[34]
Aletaha *et al.* (2005)	CDAI	TJC + SJC + PGA + MDGA	–	[35]
Wolfe *et al.* (2005)	PAS	HAQ, pain, global health	<2	[36]
Wells *et al.* (2005)	Minimal disease activity	28 TJC, 28 SJC, ESR, PGA, pain, HAQ, physician's GA	DAS28 ≤2.85 OR meet 5 of 7 criteria	[23]
Pincus *et al.* (2008)	RAPID 3	Physical function, pain, patient global	≤3	[37]
Leeb *et al.* (2008) and Rintelen *et al.* (2013)	RADAI 5	5 questions + CDAI	<1.4 + CDAI ≤2.8	[38,39]
Felson *et al.* (2011) ACR/EULAR	Boolean index	TJC, SJC, CRP, PGA	All of the following: (a) TJC ≤1; (b) SJC ≤1; (c) PGA ≤1; (d) CRP ≤1 mg/dl	[83]
	SDAI		≤3.3	
	CDAI		≤2.8	

CDAI: Clinical disease activity index; CRP: C-Reactive protein; DAS: Disease activity score; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PGA: Patient global assessment; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint counts

Gul et al. Expert Rev. Clin. Pharmacol. 8(5), 575–586 (2015)

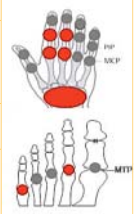
2014 EULAR Revised Recommendations

- **Primary target for treatment of RA should be a state of clinical remission**
- **Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity**
- **While remission should be a clear target, LDA may be an acceptable alternative therapeutic goal, particularly in long-standing disease**
- **Validated composite measures of disease activity, which include joint assessments, is needed to guide treatment decisions**
- **Choice of the (composite) measure of disease activity and target value should be influenced by comorbidities, patient factors and drug-related risks**
- **Measures of disease activity must be documented regularly, monthly if needed.**
- **Structural changes, functional impairment and comorbidity should be considered when making clinical decisions.**
- **Drug therapy adjusted at least every three months, until target attained.**
- **Desired treatment target should be maintained throughout course of disease**
- **The rheumatologist should involve the patient in setting the treatment target and the strategy to reach this target**

Ann Rheum Dis doi:10.1136/annrheumdis-2015-207524

Ultrasound in Rheumatologic Practice (German US Score)

	Wrist		Fingers		Toes	
Synovitis	Dorsal Palmar Ulnar	+PD +PD +PD	MCP II, III Palmar Dorsal PIP II, III Palmar Dorsal	 +PD only PD +PD only PD	MTP II, V Dorsal	+PD
Paratenonitis/ Tenosynovitis	Dorsal Palmar Ulnar	+PD +PD +PD	MCP II, III Palmar Dorsal	 +PD +PD		
Erosions			MCP II, III **Dorsal, Palmar** MCP II **Radial** PIP II, III **Dorsal, Palmar**		MTP II, V **Dorsal, Plantar** MTP V **Lateral**	
	1 Joint		**4 Joints**		**2 Joints**	

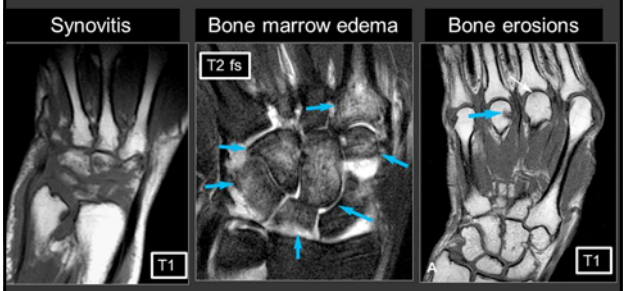


7 Joints

Gray-scale US and power Doppler US—synovitis, tenosynovitis/paratenonitis, and erosions from dorsal, palmar, and ulnar aspects of wrist, MCP, PIP and MTP joints.

Backhaus M, et al. *Arthritis Rheum.* 2009;61(19):1194-1201.

Key imaging findings in early RA



Courtesy of MANISA CELAL BAYAR UNI. - Istanbul/TR

MRI and RA

More sensitive than clinical examination and conventional x-ray for detection of inflammation (synovitis, bone marrow oedema (osteitis) and tenosynovitis) and damage (bone erosion and cartilage loss/joint space narrowing) in patients with rheumatoid arthritis (RA).

OMERACT RA MRI scoring system (RAMRIS) is a validated method for clinical trials can discriminate between different therapies regarding structural damage progression.

In routine clinical care, MRI can contribute to an earlier diagnosis of RA, can reveal subclinical disease activity, e.g. in the synovium (synovitis) and bone (osteitis), and can provide information of strong prognostic significance for the subsequent disease course.

The full benefits of MRI in clinical practice are not yet known.

Ostergard et al Clin Exp Rheumatol 2014 32(5 Suppl) S-17-22

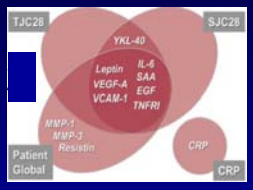
Multi-Biomarker Disease (MBDA) Panel

Biomarker	Biomarker Category	Primary Role
VCAM-1	Adhesion molecules	Cellular influx and tissue expansion
EGF	Growth factors	
VEGF-A		
IL-6	Cytokine-related proteins	Local inflammation and destruction
TNF-RI		
MMP-1	MMPs	Cartilage degradation and joint damage
MMP-3		
YKL-40	Skeletal-related proteins	Stromal activity and regulation (fibroblasts, chondrocytes, vascular cells)
Leptin	Hormones	Systemic inflammatory response
Resistin		
SAA	Acute phase proteins	
CRP		

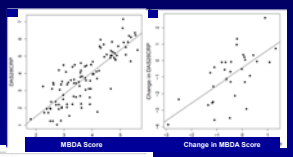
VCAM-1=vascular cellular adhesion molecule 1; EGF=epidermal growth factor; VEGF-A=vascular endothelial growth factor; IL-6=interleukin-6; TNF-RI=tumor necrosis factor-receptor 1; MMP=matrix metalloproteinase; SAA=serum amyloid.

Curtis JR et al. *Arthritis Care Res.* 2012;64:1794-1803.

Multi-Biomarker Disease Activity Score and validation with DAS28-CRP to Measure RA Disease Activity



- MBDA scores correlate with DAS28-CRP
- Changes in MBDA score over time correlate with changes in DAS28-CRP

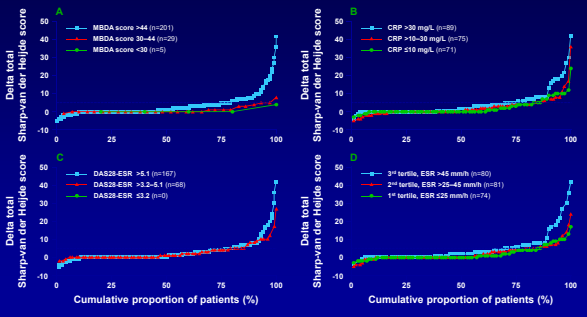


Disease activity category	DAS28-CRP definition	MBDA definition
Remission	<2.3	≤25
Low	≤2.7	≤29
Moderate	>2.7 & ≤4.1	>29 & ≤44
High	>4.1	>44

MBDA = multi-biomarker disease activity

Curtis JR, et al. *Arthritis Care Res (Hoboken).* 2012;64(12):1794-1803.

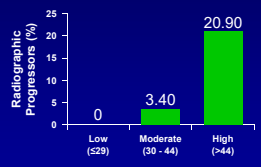
MBDA Score correlates with Rapid Radiographic Progression



Hambardzumyan K et al. *Ann Rheum Dis.* 2014;May 8, Epub ahead of print.

SWEFOT: Baseline MBDA Score Predicts Radiographic Progression (ΔSHS>5) over 1 Year

- Post hoc analysis of 235 patients from Swedish Farmacotherapy (SWEFOT) trial in DMARD-naïve early RA
- MBDA score measured in baseline serum samples as independent predictor of radiographic progression (↑ in SHS >5 points) after 1 year



High vs. Low/Moderate MBDA Score: OR=3.86, (95% CI 1.04 to 14.26)

- Future studies will help determine whether MBDA may identify a subgroup of patients at low risk of structural progression.

MBDA = multi-biomarker disease activity, SHS = Sharp-van der Heijde score.

Hambardzumyan K, Bolce R, Saevarsdottir, et al. Ann Rheum Dis Published Online First: 8 May 2014 doi:10.1136/annrheumdis-2013-204986

Conclusions

- RA is a chronic inflammatory condition that, if not treated early and effectively, often leads to deformity and disability.
- Routine use of validated disease activity measurements can guide therapy to attain LDA or remission more often.
- Patient preferences and values should be integrated in making treatment decisions and setting targets.
- The broad range of agents, administration routes, and MOA offers enhanced clinical opportunities.
- Optimal clinical monitoring is still in development.
- Newly developed serologic tests and imaging technologies may augment clinical evaluation and the measurement of disease activity.
- Compliance, individualized regimens, and effective patient-doctor relationships are key to the best outcomes.

September 19, 2015

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Focus on Early Stage Rheumatoid Arthritis: Update on Role of Biosimilars

Jonathan Kay, MD

Update on Biosimilars in the Treatment of Rheumatoid Arthritis

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Conflict of Interest Disclosure

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Learning Objectives

Upon completion of this program, the attendee will be able to:

1. **Distinguish between biosimilars and biomimics (intended copies) of biopharmaceuticals;**
2. **Identify biosimilars that are in development for treatment of rheumatoid arthritis;**
3. **Compare the regulatory pathways for approval of biosimilars in the European Union with that in the United States.**

Biosimilars: Concerns for the Clinician

- **Will a biosimilar be as effective as the originally licensed biopharmaceutical?**
- **Will a biosimilar be as safe as the originally licensed biopharmaceutical?**
- **If a pharmacist substitutes a biosimilar for a prescribed biopharmaceutical, will the patient be adversely affected?**
- **Will the availability of biosimilars reduce the high cost of targeted biological therapies for our patients?**

Overview

- **Definition of biosimilars**
- **Biomimics**
- **Biosimilars for inflammatory diseases**
- **Biopharmaceuticals**
  - **Structure**
  - **Changes in manufacture**
- **Regulatory aspects**
- **Clinical trials**
- **Immunogenicity**
- **Extrapolation of indications**
- **Interchangeability**
- **Cost**

What Is A Biosimilar?

- **A biosimilar is a legitimate copy of a biopharmaceutical, which no longer is protected by patent, that has:**
  - **Undergone rigorous analytical and clinical assessment, in comparison to its reference product, *and***
  - **Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation**

Biosimilars: Regulatory Definitions

A biosimilar is a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biologic activity, safety, and efficacy based on a comprehensive comparability exercise.

Committee for Medicinal Products for Human Use. *Guideline on similar biologic medicinal products. Draft.* London: European Medicines Agency; 2013.

Biosimilarity means "that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product"

US Food and Drug Administration. *Guidance for Industry. Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009.* Department of Health & Human Services, 2015.

Biosimilars: Varying Terminology

Country/Organization	Terminology
WHO	Similar biotherapeutic product (SBP)
EU & South Korea	Similar biological medicinal product
Canada	Subsequent-entry biological (SEB)
US & Australia	Biosimilar
Japan	Follow-on biologic
India	Similar biologic
Brazil	Biologic product
Mexico	Biocomparable

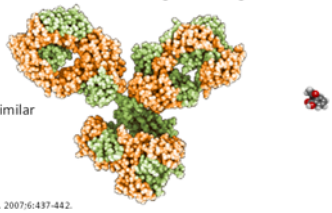
Biosimilars Are Not…

"Second-Generation" Biopharmaceuticals

- Structurally different from originally licensed biopharmaceutical
- Intended to improve performance while preserving mechanism of action
- Example:
  - Infliximab
  - Adalimumab
  - Golimumab
- Not considered to be biosimilar

Generic Drugs

- Biosimilars are more complex than small-molecule drugs
  - Manufacturing process is several orders of magnitude more complex
  - Regulated through different statutes



J Woodcock et al. *Nat Rev Drug Discov.* 2007;6:437-442.

What Is A Biomimic?

- **A "biomimic" (or "intended copy") is a replica of a biopharmaceutical that is *not* developed, assessed, or approved according to regulatory guidelines for biosimilars**
  - **Similarity *not* demonstrated by a stepwise and comprehensive comparability exercise**
  - **May have *differences* in primary structure from originator**
  - **May *differ* from originator in formulation, doses/dosing regimen, efficacy, safety, and immunogenicity; which may result in clinically significant differences**

Castañeda-Hernández G, et al. *RMD Open.* 2015;1:e000010. doi:10.1136/rmdopen-2014-000010.

Marketed "Biomimics" Based On Biologic Agents Used To Treat Inflammatory Diseases

Drug*	Manufacturer (location)	Marketed in
Rituximab biomimics		
Reditux™	Dr. Reddy's Laboratories (India)	Bolivia, Chile, Ecuador, India, & Peru
Kikuzubam™	Probiomed (Mexico)	Withdrawn in March 2014 ~~Bolivia, Chile, Mexico, & Peru~~
Etanercept biomimics		
Yisaipu	Shanghai CP Goujian Pharmaceutical Co. (China)	China
Etanar™	Shanghai CP Goujian Pharmaceutical Co. (China)	Colombia
Etacept™	Shanghai CP Goujian Pharmaceutical Co. (China)	India
Etart™	Shanghai CP Goujian Pharmaceutical Co. (China)	Mexico
Infinitam™	Probiomed (Mexico)	Mexico

MA Scheinberg & J Kay. *Nat Rev Rheumatol.* 2012; 8:430–36
http://www.latinlink.com/tag/latin-america-pharma/

Current State of Biosimilars Market

Biosimilar	Reference Drug	Class	Company	EU Approval	Canada Approval	Japan Approval	US Approval
Abseamed	Eprex	ESA	Medice Arzneimittel Putter	Aug-07	—	—	—
Binocrit	Eprex	ESA	Sandoz (Novartis)	Aug-07	—	—	—
Epoetin alfa Hexal	Eprex/Erypo	ESA	Hexal (Novartis)	Aug-07	—	—	—
Retacrit	Eprex	ESA	Hospira	Dec-07	—	—	—
Silapo	Eprex	ESA	STADA Arzneimittel	Dec-07	—	—	—
Epoetin alfa BS	Espo	ESA	JCR Pharmaceuticals	—	—	Nov-09	—
Biograstim	Neupogen	G-CSF	CT Arzneimittel	Sep-08	—	—	—
Tevagrastim / Filgrastim NK	Neupogen	G-CSF	Teva / Nippon Kayaku	Sep-08	—	Feb-13	—
Zarzio (EU) / Filgrastim BS Injection (Japan) / Zarxio (US)	Neupogen	G-CSF	Sandoz (Novartis)	Feb-09	—	Nov-12	Mar-15
Filgrastim Hexal	Neupogen	G-CSF	Hexal (Novartis)	Feb-09	—	—	—
Nivestim	Neupogen	G-CSF	Hospira	Jun-10	—	—	—
Grastofil	Neupogen	G-CSF	Apotex / Stada	Oct-13	—	—	—
Accofil	Neupogen	G-CSF	Accord Healthcare	Sep-14	—		—
Omnitrope	Genotropin	hGH	Sandoz (Novartis)	Apr-06	Apr-09	May-09	—
Remsima	Remicade	TNF-α inhibitor	Celltrion / Nippon Kayaku	Sep-13	Jan-14	Jul-14	—
Inflectra	Remicade	TNF-α inhibitor	Hospira / Nippon Kayaku	Sep-13	Jan-14	Jul-14	—
Ovaleap	Gonal-f	FSH	Teva	Sep-13	—	—	—
Bemfola	Gonal-f	FSH	Finox Biotech	Mar-14	—		—
Abasaglar (previously Abasria)	Lantus	Insulin glargine	Eli Lilly	Sep-14	—	—	—

CT-P13

http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe; http://www.gabionline.net/Biosimilars/General/Subsequent-entry-biologics-approved-in-Canada; http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Japan

CT-P13: First Approved Biosimilar mAb

- July 23, 2012: Ministry of Food & Drug Safety (MOFDS) granted approval in South Korea
- June 27, 2013: CHMP recommended EMA approval
  - Remsima™ (Celltrion)
  - Inflectra™ (Hospira)
- September 10, 2013: European Commission granted approval
- Remsima™ launched in: Azerbaijan, Belarus, Bulgaria, Czech Republic, Finland, Georgia, Iceland, Kazakhstan, Latvia, Lithuania, Malta, Norway, Poland, Portugal, & Slovakia
- December 16, 2013: Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA) granted approval in Colombia
- January 15, 2014: Health Canada granted approval
- July 4, 2014: Pharmaceuticals Medical Devices Agency granted approval in Japan
- July 16, 2014: Ministry of Health granted approval in Turkey
- February 24, 2015: Inflectra™ launched in: Austria, Belgium, Denmark, France, Germany, Greece, Italy, Luxembourg, Netherlands, Spain, Sweden, & United Kingdom
- August 19, 2015: Therapeutic Goods Administration (TGA) granted approval in Australia

http://www.gabionline.net/Biosimilars/News/Biosimilar-monoclonal-antibody-approved-in-Korea;
http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002576/WC500144832.pdf;
http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002778/WC500144831.pdf;
http://www.gabionline.net/Biosimilars/News/Remsima-approved-in-Colombia;
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php;
http://www.gabionline.net/Biosimilars/News/Biosimilar-infliximab-receives-approval-in-Japan-and-Turkey;;
http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Australia

BOW015: Approved Biosimilar Infliximab

- Developed by EPIRUS Biopharmaceuticals, Inc.
- September 15, 2014: Drug Controller General of India (DCGI) granted approval
- Manufactured by Reliance Life Sciences at a facility in Mumbai, India
- December 1, 2014: Marketed in India as Infimab™ by Ranbaxy Laboratories Ltd.

http://www.gabionline.net/Biosimilars/News/Infliximab-similar-biologic-receives-Indian-approval
http://www.ranbaxy.com/ranbaxy-launches-indias-first-biosimilar-of-infliximab-drug-infimab-tm/

HD203: First Approved Biosimilar Etanercept

- Developed by Hanwha Chemical Corp. of South Korea

Hanwha

- November 11, 2014: Ministry of Food & Drug Safety (MOFDS) granted approval in South Korea

http://www.hcplive.com/conferences/acr-2014/HD203-Biosimilar-is-Clinically-Equivalent-to-Etanercept

ZRC-3197: First Approved Biosimilar Adalimumab

- Developed by Zydus Research Centre of India
  - "'Fingerprint match' with" Humira " in terms of safety, purity and potency"

Zydus

- December 9, 2014: Drug Controller General of India (DCGI) granted approval
- Marketed in India as Exemptia™ by Zydus Cadila
  - Indications: RA, JIA, PsA, & AS
  - Cost is 20% that of Humira

S Bandyopadhyay et al. Biosimilars. 2015;5:1-18;
http://www.exemptia.com

Biosimilars in Development To Treat Inflammatory Diseases*

- Adalimumab (11)
- Etanercept (9)
- Infliximab (5)
- Tocilizumab (2)
- Rituximab (7)

*As of July 2015.

Adalimumab Biosimilars in Development

Drug	Manufacturer (location)	Current status*
ABP 501	Amgen (US)	Clinical trials (Phase III completed in RA & PsO)
BI695501	Boehringer Ingelheim Pharmaceuticals (Germany)	Clinical trials (Phase III in RA)
SB5	Samsung Bioepis (South Korea)	Clinical trials (Phase III in RA)
GP2017	Sandoz (Switzerland)	Clinical trials (Phase III in PsO)
PF-06410293	Pfizer (US)	Clinical trials (Phase I completed; Phase III planned in RA)
CHS-1420	Coherus Biosciences (US)	Clinical trials (Phase III planned in PsO)
ONS-3010	Oncobiologics/Viropro (US)	Clinical trials (Phase I completed)
LBAL	LG Life Sciences (South Korea)/ Mochida Pharmaceutical (Japan)	Clinical trials (Phase I completed)
BCD-057	Biocad (Russian Federation)	Clinical trials (Phase I)
M923	Momenta Pharmaceuticals (US)/ Baxter International	Clinical trial planned
BOW050	EPIRUS Biopharmaceuticals (US)	Preclinical studies
	AET BioTech (Germany)/ BioXpress Therapeutics (Switzerland)	Preclinical studies

*As of July 2015.

T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print];
http://www.clinicaltrials.gov; https://www.clinicaltrialsregister.eu;
http://www.gabionline.net/Biosimilars/General/Biosimilars-of-adalimumab

Etanercept Biosimilars in Development

Drug	Manufacturer (location)	Current status*
SB4	Samsung Bioepis (South Korea)	Clinical trials (Phase III in RA - published)
GP2015	Sandoz (Switzerland)	Clinical trials (Phase III completed in PsO)
CHS-0214	Coherus Biosciences (US)/Baxter International/Daiichi Sankyo	Clinical trials (Phase III in RA & PsO)
TuNEX® (ENIA11)	TSH Biopharm Co., Ltd. (Taiwan)	Clinical trials (Phase III in RA)
LBEC0101	LG Life Sciences Ltd. (South Korea)	Clinical trials (Phase III in RA)
DWP422	Daewoong Pharmaceutical Co. Ltd. (South Korea)	Clinical trials (Phase I)
PRX-106	Protalix Biotherapeutics (Israel)	Clinical trials (Phase I)
Avent™	Avesthagen (India)	Preclinical studies
BX2922	BioXpress Therapeutics SA (Switzerland)	Preclinical studies

*As of July 2015.

T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print]; http://www.clinicaltrials.gov; https://www.clinicaltrialsregister.eu; http://gabionline.net/Biosimilars/General/Biosimilars-of-etanercept; http://www.protalix.com/development-pipeline/prx-106-autoimmune.asp; P Emery et al. *Ann Rheum Dis* annrheumdis-2015-207588 [Published Online First: 6 July 2015]

Infliximab Biosimilars in Development

Drug	Manufacturer (location)	Current status*
SB2	Samsung Bioepis (South Korea)	Clinical trials (Phase III in RA - published)
PF-06438179	Pfizer (US)	Clinical trials (Phase III in RA)
NI-071	Nichi-Iko Pharmaceutical Co.,Ltd. (Japan)	Clinical trials (Phase III in RA)
BCD-055	Biocad (Russian Federation)	Clinical trials (Phase I in AS)
ABP 710	Amgen (US)	Preclinical studies

Tocilizumab Biosimilars in Development

Drug	Manufacturer (location)	Current status*
BOW070	EPIRUS Biopharmaceuticals (US)	Preclinical studies
	BioXpress Therapeutics SA (Switzerland)	Preclinical studies

*As of July 2015.

T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print]; http://www.clinicaltrials.gov; https://www.clinicaltrialsregister.eu; http://www.gabionline.net/Biosimilars/General/Biosimilars-of-infliximab; http://www.amgenbiosimilars.com/our-products/our-pipeline; http://www.epirusbiopharma.com/programs/bow070-tocilizumab.php; J-Y Choe, et al. *Ann Rheum Dis* doi:10.1136/annrheumdis-2015-207764. [Published Online First: 28 Aug 2015]

Rituximab Biosimilars in Development To Treat Rheumatoid Arthritis

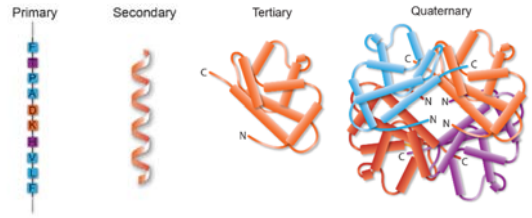
Drug*	Manufacturer (location)	Current status‡
BCD-020	Biocad (Russian Federation)	Clinical trials (Phase III in RA)
CT-P10	Celltrion (South Korea)	Clinical trials (Phase III in RA)
SAIT101	Samsung Electronics Co. Ltd. (South Korea)	Clinical trials (Phase I/III in RA) – *prematurely ended*
TL011	Teva Pharmaceutical Industries (Israel)	Clinical trials (Phase III in RA) – *prematurely ended*
PF-05280586	Pfizer (US)	Clinical trials (Phase I/II completed in RA)
GP2013	Sandoz Biopharmaceuticals (Switzerland)	Clinical trials (Phase I/II in RA)
MK-8808	Merck (US)	Clinical trials (Phase I completed in RA)
ABP 798	Amgen (US)	Preclinical studies
	iBio (US)/GE Healthcare	Preclinical studies

*As of July 2015.

T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print]; http://www.clinicaltrials.gov; https://www.clinicaltrialsregister.eu; http://www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab

Biopharmaceuticals (Originators & Biosimilars) Are Complex Proteins

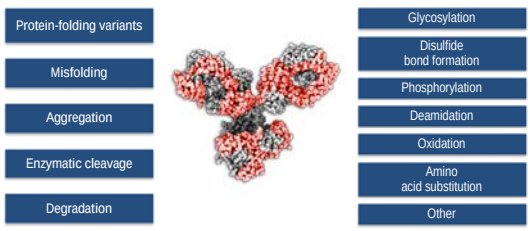
Four Levels of Protein Structure



Modified from: Shapiro M for the US Food and Drug Administration. Quality Considerations for Biosimilars. Presented August 8, 2012.

All Biopharmaceuticals (Originators & Biosimilars) Are Subject to Variability

Variability Can Be Due to Changes In



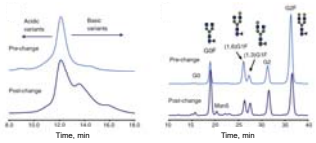
Kuhlmann M, Covic A. *Nephrol Dial Transplant*. 2006;21(suppl 5):v4-v8.

Range of Structural Relationships Between Biosimilars & Reference Product

- Most biosimilars are not identical to their reference product
- Proteins produced by recombinant DNA exhibit a range of structural similarities
  - Share primary amino acid sequence
    - May have N- and C-terminal modifications
  - Different post-translational modifications

Originator Manufacturing Process Changes

- Small modifications may result in gradual changes
- Chemical characterization of different commercial lots of etanercept and rituximab produced between 2007 and 2011 revealed variations in both C-terminal lysine content and glycosylation



Cation Exchange Chromatography Glycan Mapping Chromatogram

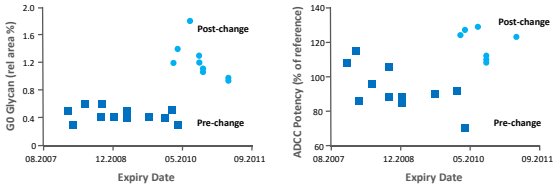
- Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label
- If large alterations occur, analytical (and possibly additional clinical studies) are required to compare post-change product with existing pre-change product

Schiestl M, et al. *Nature Biotechnology*. 2011;29(4):310-312.

Biosimilar Development Goal: Develop Product Highly Similar to Reference Product

Changes in Reference Product Manufacturing Process Create Products Highly Similar to Initially Approved Product

Comparison of Pre- and Post-Change Batches of Rituximab

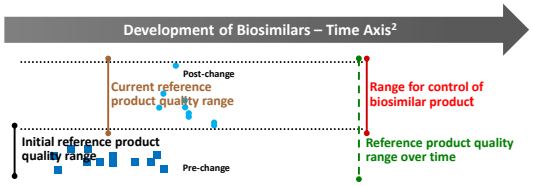


- Approximately 3-fold increase in unfucosylated G0 glycans in later batches of rituximab resulted in more potent ADCC

Schiestl M, et al. *Nature Biotechnology*. 2011;29(4):310-312.

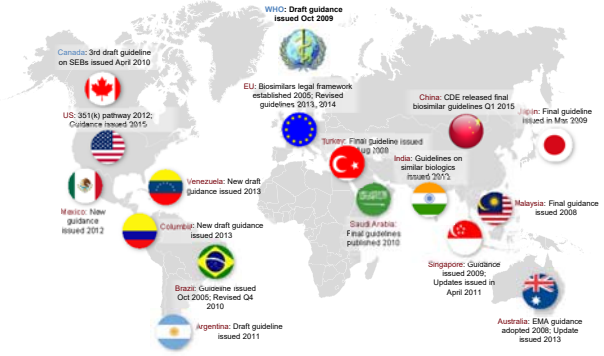
Biosimilar Development Goal: Develop Product Highly Similar to Reference Product

Exercise to Claim Biosimilarity Must Demonstrate Equivalence Within Prespecified Margins ("Goalposts")[1]



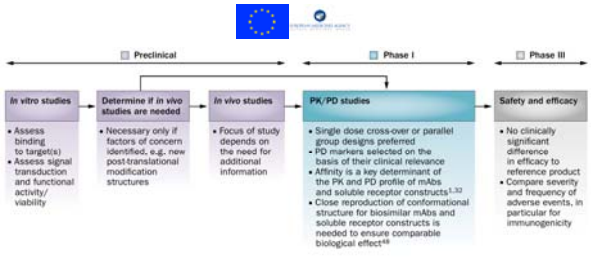
1. McCamish M, Woollett G. *Clin Pharmacol Ther*. 2012;91(3):405-417.
2. Figure adapted from McCamish M, Woollett G. *mAbs*. 2011;3(2):209-217. Worldwide experience with biosimilar development, Landes Bioscience, 2011.

Global Status of Biosimilar Guidelines



Modified from :Scheinberg MA, Kay J. *Nature Rev Rheumatol*. 2012;8(7):430-436.

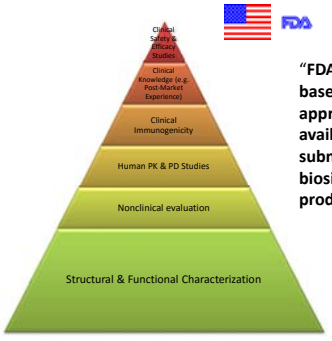
EMA Guidance on Biosimilars: A Stepwise Approach



Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2014.

T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print]

FDA Guidance on Demonstrating Biosimilarity: "Totality-of-the-Evidence" Approach



"FDA intends to use a risk-based, *totality-of-the-evidence* approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product."

S Koslowski et al. *N Engl J Med*. 2011;365:385-88; US Food and Drug Administration. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. Department of Health & Human Services, 2015.

EMA Guideline on Biosimilars (2006)

- Comparison of biosimilar with reference product is required
  - Preclinical
    - *In vitro* assays
    - *In vivo* animal studies
  - Clinical studies in patients
- If available:
  - Single- & multiple-dose PK studies
  - PD studies using biomarkers relevant to clinical efficacy of drug
- In most cases, 'comparative clinical trials' are also needed to:
  - Demonstrate clinical equivalence between biosimilar & already approved reference product
  - Assess potential immunogenicity with chronic dosing
- Careful post-approval pharmacovigilance monitoring is expected

Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency; 2006.

Biologics Price Competition and Innovation Act of 2009: Abbreviated Biological License Application

- Permits a biosimilar to be evaluated against only a single reference biological product
- To be considered for an abbreviated BLA, biosimilar & reference product must have same:
  - Presumed mechanism of action
  - Route of administration
  - Dosage form
  - Potency
- Biosimilar may only be reviewed & approved for indications for which FDA already has approved reference product

BLA = biological license application

FDA

Biosimilar Clinical Studies: Regulatory Expectations

- To support conclusion that there are *no clinically meaningful differences* between proposed biosimilar & reference product:
  - Comparative human PK & PD studies (if relevant PD measure exists)
  - Clinical immunogenicity assessment
  - Comparative clinical study or studies (if residual uncertainty about biosimilarity remains)
- "In cases where there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary."

Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2014.
US Food and Drug Administration. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry*. Department of Health & Human Services, 2015.

Phase 1 Double-Blind RCT of CT-P13 vs. Remicade® in Ankylosing Spondylitis

- 250 patients with active AS randomized 1:1 to receive either CT-P13 or Remicade® (5 mg/kg 2-hour IV infusion per dose)
  - Dose-loading phase: Weeks 0, 2, & 6
  - Maintenance phase: Weeks 14, 22, 30 , 38, & 46
- Assessments
  - Ratios of geometric means of primary PK parameters between Weeks 22-30 were subjected to ANCOVA analysis at 90% CIs
  - ASAS20 & ASAS40 at Week 30
  - Safety (incidence of AEs)
- Primary endpoint: Ratio of geometric means of PK parameters in CT-P13 & Remicade® arms (Weeks 22-30)
  - AUC_t: 1.05 (90% CI 0.94 to 1.16)
  - $C_{max,ss}$: 1.02 (90% CI 0.95 to 1.09)

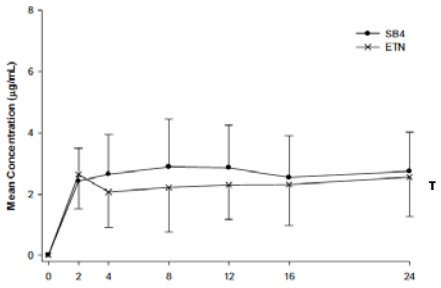
W Park et al. *Ann Rheum Dis.* 2013; 72:1605-1612

Phase 3 Double-Blind RCT of SB4 vs. Enbrel® in Rheumatoid Arthritis

- 596 patients with active RA despite MTX randomized 1:1 to receive either SB4 or Enbrel® SC weekly + MTX & folic acid for up to 52 weeks
- Primary endpoint: Proportion of patients achieving ACR20 at week 24
  - Equivalence between treatments: 95% CI of difference of ACR20 response rates between treatment groups had to be entirely contained within margin of ±15%
- Secondary endpoints
  - ACR50/70, ACR-N, AUC of ΔDAS28, EULAR response
  - Incidence of AEs & SAEs
- PK analyses performed on subpopulation of 79 patients (41 SB4, 38 ETN)
- Immunogenicity measured in all patients

Emery P, et al. *Ann Rheum Dis* [Published Online First: 2015 Jul 6] doi:10.1136/annrheumdis-2015-207588

SB4: Mean Serum Trough Concentrations (C_{trough})



AUC_t at week 8: 676.4 vs. 520.9 µg h/mL

Emery P, et al. *Ann Rheum Dis* [Published Online First: 2015 Jul 6] doi:10.1136/annrheumdis-2015-207588

Biosimilars: Clinical Trial Design Issues

- Patient benefit has already been established by reference product
- Biosimilar must be studied at the same dose that is licensed for the reference product
  - Dose-ranging studies (phase 2) are not needed for biosimilars
- Demonstrate similar efficacy & safety, compared to reference product
  - Double-blind, parallel-group, active comparator design
  - Patients with disease most responsive to reference product
  - Use clinical endpoint most sensitive to detect product-related differences, if present

US Food and Drug Administration. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry.* Department of Health & Human Services, 2015.
Committee for Medicinal Products for Human Use. *Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2011.
Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues.* London: European Medicines Agency, 2012.

Biosimilars: Clinical Trial Design Issues

- Active comparator clinical trial must demonstrate equivalence within a prespecified margin
  - Based on historical information obtained from placebo-controlled clinical trials about treatment effect of reference product (difference in efficacy between active drug and placebo)
- Non-inferiority trial design is not usually adequate to assess biosimilarity
  - If proposed biosimilar is superior to the reference biopharmaceutical ('bio-better'), it is not biosimilar

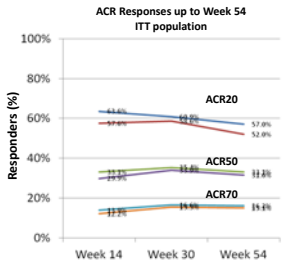
Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2014.
US Food and Drug Administration. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry.* Department of Health & Human Services, 2015.
Kay J & Smolen JS. Ann Rheum Dis 2013; 72: 1589-1593.

Phase 3 Double-Blind RCT of CT-P13 vs. Remicade® in Rheumatoid Arthritis

- 606 patients with active RA despite previous DMARDs randomized 1:1 to receive either CT-P13 or Remicade® (3 mg/kg 2-hour IV infusion per dose) + MTX & folic acid
  - Dose-loading phase: Wks 0, 2, & 6
  - Maintenance phase: Wks 14, 22, 30 , 38, & 46
- Primary endpoint: Proportion of patients achieving ACR20 at week 30
  - Equivalence between treatments defined using exact binomial test with 95% CIs within margin of ±15%
- Secondary endpoints
  - ACR50/70
  - Frequency of AEs

DH Yoo et al. *Ann Rheum Dis.* 2013; 72:1613-1620

Phase 3 Double-Blind RCT of CT-P13 vs. Remicade® in Rheumatoid Arthritis

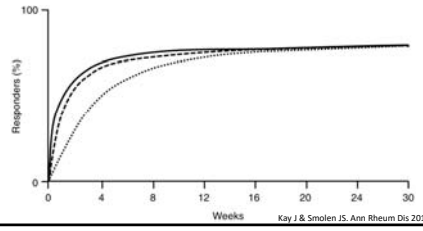


Related AEs (to Week 54)	CT-P13 (n=302)	Remicade® (n=300)
Total	131 (43.4%)	134 (44.7%)
Infections	69 (22.8%)	69 (23.0%)
Infusion reactions	23 (7.6%)	31 (10.3%)
TB	3 (1.0%)	0

DH Yoo et al. *Ann Rheum Dis.* 2013; 72:1613-1620
DH Yoo et al. *Ann Rheum Dis.* 2013; 72(Suppl3):73

Patterns of Pharmacodynamic Response Over Time

- Demonstration of equivalent clinical responses during early, rapid rise phase of time-response curve provides additional information on biosimilarity
  - Earlier portion of time-response curve affords greater sensitivity to detect differences in efficacy between study drugs than does plateau phase
  - Assessment of response to therapy over first 3 months of treatment allows comparison of rapidity of onset



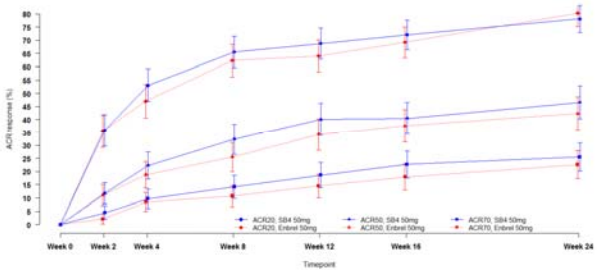
Kay J & Smolen JS. Ann Rheum Dis 2013; 72: 1589-1593.

Phase 3 Double-Blind RCT of SB4 vs. Enbrel® in Rheumatoid Arthritis

- 596 patients with active RA despite MTX randomized 1:1 to receive either SB4 or Enbrel® SC weekly + MTX & folic acid for up to 52 weeks
- Primary endpoint: Proportion of patients achieving ACR20 at week 24
  - Equivalence between treatments: 95% CI of difference of ACR20 response rates between treatment groups had to be entirely contained within margin of ±15%
- Secondary endpoints
  - ACR50/70, ACR-N, AUC of ΔDAS28, EULAR response
  - Incidence of AEs & SAEs

Emery P, et al. *Ann Rheum Dis* [Published Online First: 2015 Jul 6] doi:10.1136/annrheumdis-2015-207588

SB4: ACR Response Rates To Week 24*



*Per-protocol set

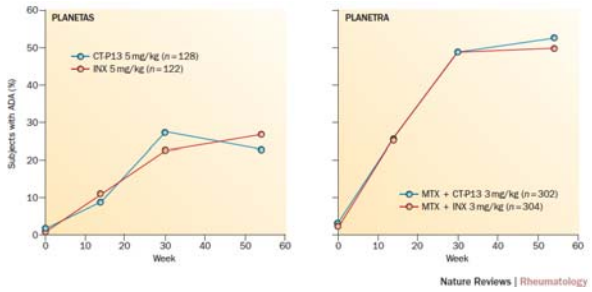
Emery P, et al. *Ann Rheum Dis* [Published Online First: 2015 Jul 6] doi:10.1136/annrheumdis-2015-207588

Clinical Immunogenicity Assessment

- **1-year follow-up immunogenicity data expected for biopharmaceuticals intended for chronic administration**
- **If extrapolating immunogenicity findings to other indications, use study population & treatment regimen *for which development of immune responses with adverse outcomes is most likely to occur* (e.g., patients who are not immunosuppressed)**
  - **Development of anti-drug antibodies may depend more upon dose used to treat underlying disease process than upon concomitant methotrexate use**

Committee for Medicinal Products for Human Use. *Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2014.
US Food and Drug Administration. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry.* Department of Health & Human Services, 2015.

CT-P13: Immunogenicity



Anti-drug antibodies were assessed by an electrochemiluminescent immunoassay using Meso Scale Discovery technology

W Park et al. *Ann Rheum Dis.* 2013; 72:1605-1612
DH Yoo et al. *Ann Rheum Dis.* 2013; 72:1613-1620
J Braun et al. *Arthritis Rheumatol.* 2014; 66(Suppl 11):3538-3539

Biosimilars: Differential Immunogenicity

- **Greater immunogenicity of proposed biosimilar, compared to reference product, would question biosimilarity**
- **Lower immunogenicity of proposed biosimilar would not preclude biosimilarity (e.g., SB4 vs. ETN: 0.7% vs. 13.1% tested + for ADA to wk 24)**
  - **Efficacy analysis of entire patient population could suggest that biosimilar is more effective**
  - **To establish that efficacy of biosimilar & reference product are similar, if not impacted by an immune response, pre-specify an *additional exploratory subgroup analysis of efficacy & safety in those patients that did not mount an anti-drug antibody response* during the clinical trial**

Committee for Medicinal Products for Human Use. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.* London: European Medicines Agency, 2014.
Emery P, et al. *Ann Rheum Dis* [Published Online First: 2015 Jul 6] doi:10.1136/annrheumdis-2015-207588

Biosimilars: Extrapolation of Indications

- **Extrapolation of data from a clinical trial of biosimilar conducted in one disease may be used to support approval for additional indications, for which reference product is already licensed**
- **In which inflammatory disease(s) should a biosimilar be studied to provide adequate information for extrapolation of indications?**
  - **Rheumatoid arthritis**
  - **Juvenile inflammatory arthritis**
  - **Ankylosing spondylitis**
  - **Psoriatic arthritis**
  - **Psoriasis**
  - **Inflammatory bowel disease**
    - **Crohn's disease**
    - **Ulcerative colitis**

CT-P13: Biosimilar Infliximab
Approved Indications

	Rheumatoid Arthritis	Ankylosing Spondylitis	Psoriatic Arthritis	Psoriasis	Crohn's Disease	Ulcerative Colitis
South Korea	X	X	X	X	X	X
European Union	X	X	X	X	X	X
Colombia	X	X	X	X	X	X
Canada	X	X	X	X		
Japan	X				X	X
Turkey	X	X	X	X	X	X
Australia	X	X	X	X	X	X

http://www.gabionline.net/Biosimilars/News/Biosimilar-monoclonal-antibody-approved-in-Korea; http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002576/WC500144832.pdf;
http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002778/WC500144831.pdf;
http://www.gabionline.net/Biosimilars/News/Remsima-approved-in-Colombia;
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php;
http://www.gabionline.net/Biosimilars/News/Biosimilar-infliximab-receives-approval-in-Japan-and-Turkey;
http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Australia

Biologics Price Competition and Innovation Act of 2009: Interchangeability

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

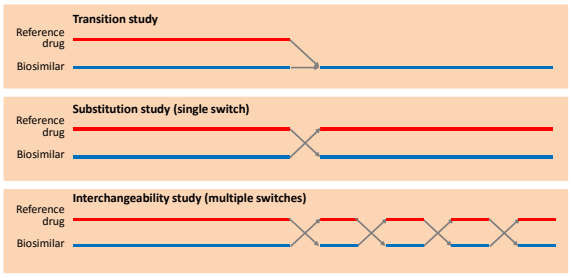
(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

"(3) The term 'interchangeable' or 'interchangeability', in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

Switching versus Substitution

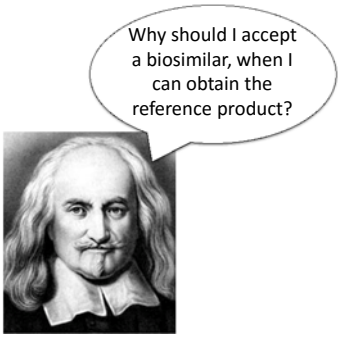
- **Switch = transition**
  - **Patient transitioned to biosimilar, after initial treatment with originator**
  - **Single switch study**
- **Substitution = interchange**
  - **Biologics Price Competition Act of 2009 affords 1 year of exclusive marketing rights to first biosimilar approved as being 'interchangeable' with reference product**
  - **Interchange could be initiated without prescriber input**
  - **Repeated switching study (although single switch study fulfills statutory requirement)**

Study Designs to Compare Efficacy & Immunogenicity of Reference Drugs & Biosimilars

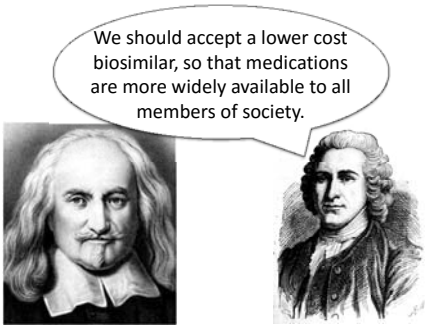


T Dörner & J Kay. *Nat Rev Rheumatol* 2015 Aug 18. doi: 10.1038/nrrheum.2015.110. [Epub ahead of print]

Biosimilars



Biosimilars: The Social Contract



Justification for Biosimilars

- **The potential risk to the individual of switching to a lower cost biosimilar should be outweighed by the potential benefit to society of expanding access to care for all.**

Infliximab Biosimilars for RA in Norway: Price Reduction for Tenders

Drug	Cost NOK	Cost US$	Discount c/w Remicade®
Infliximab (Remicade®)	84,787	14,131	---
Infliximab (Inflectra®)	56,987	9,497	32%
Infliximab (Remsima®)	51,588	8,598	39%

Based upon 75 kg patient treated with infliximab 3 mg/kg i.v. every 8 weeks

Slide kindly provided by Prof. T.K. Kvien

Biosimilars: Concerns for the Clinician

- Will a biosimilar be as effective as the originally licensed biopharmaceutical?
- Will a biosimilar be as safe as the originally licensed biopharmaceutical?
- If a pharmacist substitutes a biosimilar for a prescribed biopharmaceutical, will the patient be adversely affected?
- Will the availability of biosimilars reduce the high cost of targeted biological therapies for our patients?

Biosimilars: Concerns for the Clinician

- If a biosimilar is approved according to a regulatory pathway for biosimilars, it will be as effective & as safe as the reference product
- The designation of "interchangeability" is unlikely to be granted in the near future
- Insurance carriers & PBMs likely will dictate switching
  - Between originator & biosimilar
  - Between two biosimilars
- Currently marketed biosimilars are priced lower than their reference products

Thank you

Update on Biosimilars in the Treatment of Rheumatoid Arthritis

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Algorithm for Evaluation and Treatment Options for Patients with Psoriatic Arthritis

Alexis Ogdie-Beatty, MD

Evaluation and Treatment of Psoriatic Arthritis

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Conflict of Interest Disclosure

No relevant financial relationships

Objectives

- Review PsA classification and disease manifestations
- Examine assessment methods for disease manifestations
- Review principles of management
- Discuss management strategies for individual disease manifestations
- Consider how comorbidities associated with PsA may impact management

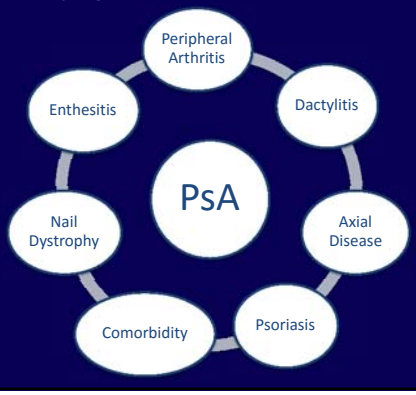
ClASsification Criteria for Psoriatic ARthritis (CASPAR)

Inflammatory musculoskeletal disease (arthritis, spondylitis, enthesitis) with three or more points from the following:

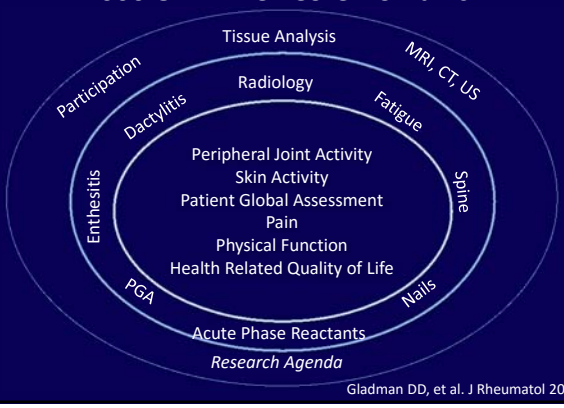
Evidence of psoriasis: a) Current psoriasis b) Personal history of psoriasis c) Family history of psoriasis	 2 1 1
Psoriatic nail dystrophy	1
Negative Rheumatoid Factor	1
Dactylitis (current or recorded by a rheumatologist)	1
Radiographic evidence of **juxta-articular new bone formation**	1

Taylor et al. Arthritis Rheum 2006

PsA is a highly heterogenous disorder with varying disease manifestations



Assessment of PsA: **2006 OMERACT Core Domains**



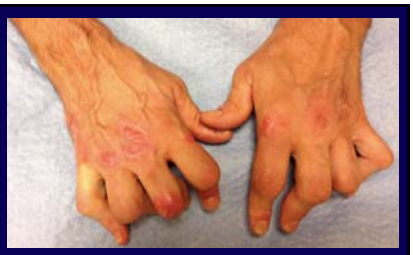
Gladman DD, et al. J Rheumatol 2007

Assessment of PsA in Clinical Practice

- Peripheral Joints
- Enthesitis
- Dactylitis
- Spondylitis
- Skin and Nail Disease
- Patient Reported Measures
  - Pain, Physical Function, and Quality of Life
- Comorbidities

Peripheral Arthritis

Poly-, Oligo- or Monoarticular



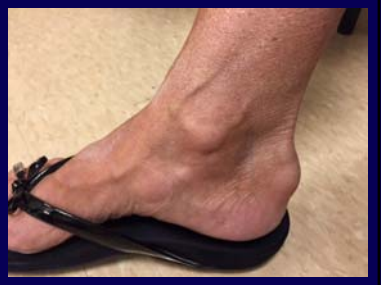
68 tender and 66 swollen joint count

Distal interphalangeal (DIP)
Proximal interphalangeal (PIP)*
Metacarpophalangeal joints (hands)*
Wrist*
Elbow*
Shoulder*
Acromioclavicular joints
Sternoclavicular joints
Temporomandibular joints
Hips
Knees*
Ankles
Midtarsal joints

**=included in 28 joint count*

Enthesitis

Inflammation where a tendon, ligament or joint capsule inserts onto a bone



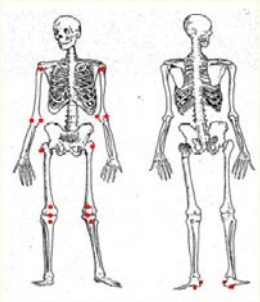
Apply ~4 kg/cm2 pressure to enthesis to assess for tenderness

Enthesitis Indices

	SPARCC	MASES	LEI	4-Point
1st costochondral		X		
7th costochondral		X		
Greater tuberosity of humerus	X			
Lateral epicondyle	X		X	
Medial epicondyle	X			
Posterior-superior iliac spine		X		
Anterior-superior iliac spine		X		
Iliac crest		X		
5th lumbar spinous process		X		
Greater trochanter	X			
Quadriceps insertion	X			
Inferior patella	X			
Tibial tuberosity	X			
Medial condyle femur			X	
Achilles	X	X	X	X
Plantar fascia	X			X

Mease. Arth Care & Res 2011; 63; S64-85; Sakkas et al. Seminars in Arth Rheum 2013; 43: 325-334

SPARCC enthesitis index



Score range 0 - 16
- Greater tuberosity of humerus (2)
- Lateral epicondyle (2)
- Medial epicondyle (2)
- Greater trochanter (2)
- Quadricepts insertion (2)
- Inferior patella (R + L)
- Tibial tuberosity (R + L) } (2)
- Insertion of Achilles tendons (2)
- Insertion of plantar fascia (2)

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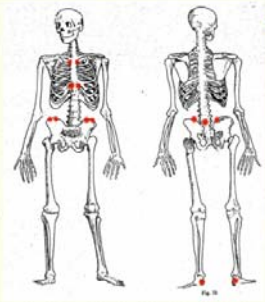
MASES enthesis index



Score range 0 - 13
- 1st Costochondral joints (2)
- 7th costochondral joints (2)
- Iliac crests (2)
- Ant sup iliac spines (2)
- Insertion of Achilles tendons (2)
- 5th lumbar spinous process (1)
- Post sup iliac spines (2)

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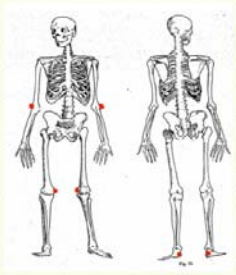
Leeds Enthesitis Index for Psoriatic Arthritis



Score range 0 - 6

- Lateral epicondyle of elbow (2)
- Medical condyle of femur (2)
- Achilles tendon insertion (2)

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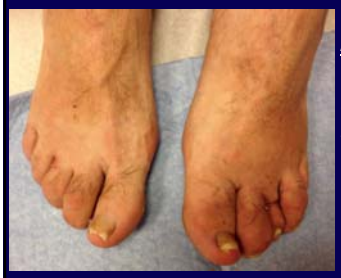
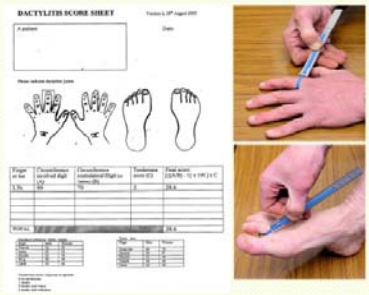
Dactylitis ("sausage digit")

" … swelling of an entire finger [or toe] due to synovitis, tenosynovitis, enthesitis, and soft tissue edema."
- Mease. Arth Care & Res 2011; 63; S64-85



Assessment Methods:
1) Number of digits affected
2) Severity: 0-3
3) Leeds Dactylitis Index
-Requires a "dactylometer"

Assessing dactylitis using the Leeds dactylometer



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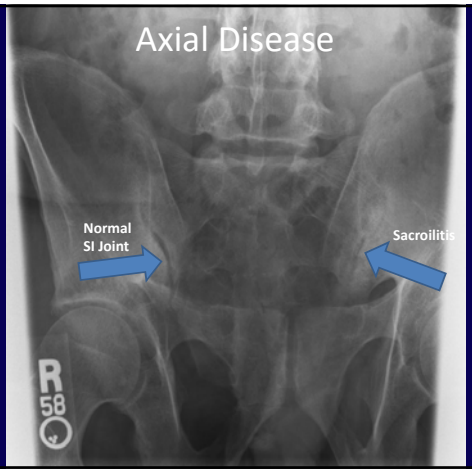
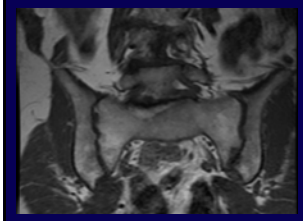
Healy PJ, Helliwell PS. J Rheumat 2007;34(6):1302-4.

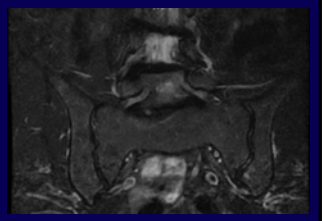
Axial Disease



Assessment of Axial Disease

MRI of the pelvis without gadolinium; attention to T1 and STIR images





Commonly Used Measures in AS

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
  - Fatigue
  - Neck, back or hip pain
  - Joint swelling
  - Tenderness
  - Morning stiffness (severity and length of time)
- Bath Ankylosing Spondylitis Function Index (BASFI)
- Bath Ankylosing Spondylitis Metrology Index (BASMI)

Psoriasis (skin disease)

1. Body Surface Area (BSA)
   – Patient's open hand ~1%
2. Psoriasis Area and Severity Index (PASI)
   – Redness, thickness, scale
   – Head, upper extremities, trunk, lower extremities
3. Physician Global Assessment (PGA)
   – 7-point scale from clear to severe

Psoriasis Assessment

1. Body Surface Area (BSA)
   – Patient's open hand ~1%
2. Psoriasis Area and Severity Index (PASI)
   – Redness, thickness, scale
   – Head, upper extremities, trunk, lower extremities

Body region	Erythema	Thickness	Scaling	# of palms in region
Head				
Upper limbs				
Trunk				
Lower limbs				

Derived PASI Score: _____

Psoriasis Assessment

3. Physician Global Assessment (PGA)

PGA: Physician's Global Assessment (Averaged over all lesions)

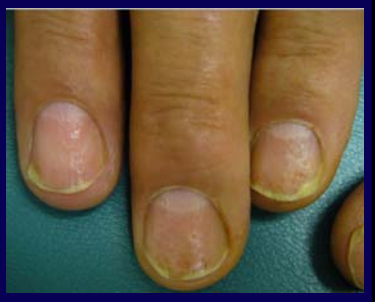
Induration (I)	Erythema (E)	Scaling (S)
0 = no evidence of plaque elevation 1 = minimal plaque elevation, ≈0.25mm 2 = mild plaque elevation, ≈0.5mm 3 = moderate plaque elevation, ≈0.75mm 4 = marked plaque elevation, ≈1mm 5 = severe plaque elevation, ≈1.25mm or more	0 = no evidence of erythema, hyperpigmentation may be present 1 = faint erythema 2 = light red coloration 3 = moderate red coloration 4 = bright red coloration 5 = dusky to deep red coloration	0 = no evidence of scaling 1 = minimal; occasional fine scale over less than 5% of the lesion 2 = mild; fine scale predominates 3 = moderate; coarse scale predominates 4 = marked; thick, nontenacious scale predominates 5 = severe; very think tenacious scale predominates
I =	E =	S =
	Total Average [(I + E + S)/3]	

Physician's Static Global Assessment based upon above total average:

0 = Clear; except for residual discoloration
1 = Minimal; majority of lesions have individual scores for (I+E+S)/3 that average 1
2 = Mild; majority of lesions have individual scores for (I+E+S)/3 that average 2
3 = Moderate; majority of lesions have individual scores for (I+E+S)/3 that average 3
4 = Marked; majority of lesions have individual scores for (I+E+S)/3 that average 4
5 = Severe; majority of lesions have individual scores for (I+E+S)/3 that average 5

Psoriatic Nail Involvement

Nail Bed Psoriasis
- Onycholysis
- Splinter hemorrhages
- Hyperkeratosis
- Oil-drop dyschromia



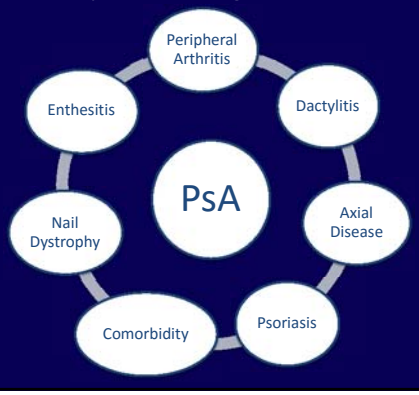
Nail Matrix Psoriasis
- **Pitting**
- Leukonychia
- Crumbling
- Red spots in the luna

Patient Reported Outcome Measures: Quality of Life and Functional Ability

- Quality of Life
  – Medical Outcomes Study Short Form (SF)-36
  – EuroQol 5-domain (EQ5D)
  – Dermatology Life Quality Index (DLQI)
- Functional Ability
  – Health Assessment Questionnaire (HAQ)
  – Routine Assessment of Patient Index Data-3 (RAPID3) often used in clinical practice (but not clinical trials)

Management of Psoriatic Arthritis

PsA heterogeneity also presents a challenge for optimal management



Additional Challenges

- Lack of data
  - For use of traditional DMARDs
  - On management of enthesitis, dactylitis, and spondylitis in PsA.
- Studies have focused on peripheral joints
- Little known about optimal therapy selection in setting of comorbidities

Principles of Treatment

- Goals of therapy:
  - control symptoms and inflammation
  - prevent joint damage
  - improve HRQOL, function and social participation
- Shared decision making
- Multidisciplinary care
- Therapy should be monitored and adjusted appropriately

Gossec L et al. Ann Rheum Dis 2012

Poor Prognostic Factors

- ≥5 active joints
- High functional impairment due to PsA activity
- Past glucocorticoid use
- Joint damage
- Elevated inflammatory markers

May require more aggressive management!

Gossec L et al. Ann Rheum Dis 2012

PsA Treatment Toolbox

NSAIDs

Glucocorticoids

Traditional Oral DMARDs

Methotrexate

Leflunomide

Sulfasalazine

Cyclosporine

TNF alpha inhibitors

Etanercept

Adalimumab

Infliximab

Certulizimab

Golimumab

Local Glucocorticoid Injections

IL 12/23-inhibitor

Ustekinimab

PDE4-inhibitor

Apremilast

In Development/Not Approved

IL 17-inhibitors

JAK/STAT inhibitor

CTLA Ig

B Cell therapy

IL 6-inhibitors

Adjunct Therapy

**Very limited evidence*

Physical therapy

Occupational therapy

Exercise

Weight Loss

Dietary Changes?

Acupuncture

Omega-3-FA

Patient Education

Social Support

Talk Therapy

GRAPPA ***2015 coming soon!***

Treatment recommendations for psoriatic arthritis

C T Ritchlin,[1] A Kavanaugh,[2] D D Gladman,[3] P J Mease,[4] P Helliwell,[5] W-H Boehncke,[6] K de Vlam,[7] D Fiorentino,[8] O FitzGerald,[9] A B Gottlieb,[10] N J McHugh,[11] P Nash,[12] A A Qureshi,[13] E R Soriano,[14] W J Taylor,[15] for the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)

Ann Rheum Dis 2009;68:1387–1394

EULAR

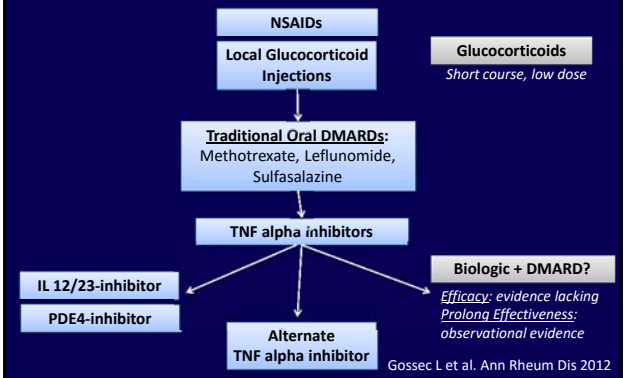
European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies

L Gossec,[1,2] J S Smolen,[3,4] C Gaujoux-Viala,[5,6] Z Ash,[7,8] H Marzo-Ortega,[7,8] D van der Heijde,[9] O FitzGerald,[10] D Aletaha,[3] P Balint,[11] D Boumpas,[12] J Braun,[13] F C Breedveld,[9] G Burmester,[14] J D Cañete,[15] M de Wit,[16] H Dagfinrud,[17,18] K de Vlam,[19] M Dougados,[1,2] P Helliwell,[7] A Kavanaugh,[20] T K Kvien,[17,18] R Landewé,[21] T Luger,[22] M Maccarone,[23] D McGonagle,[7,8] N McHugh,[24] I B McInnes,[25] C Ritchlin,[26] J Sieper,[27] P P Tak,[28] G Valesini,[29] J Vencovsky,[30] K L Winthrop,[31] A Zink,[32,33] P Emery,[7,8]

Ann Rheum Dis 2012;71:4–12.

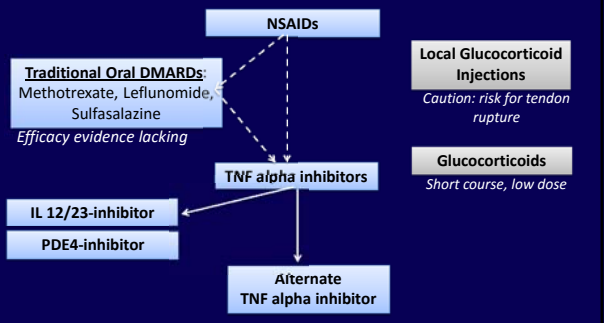
Both EULAR and GRAPPA present recommendations for therapy by disease manifestations

Peripheral Arthritis



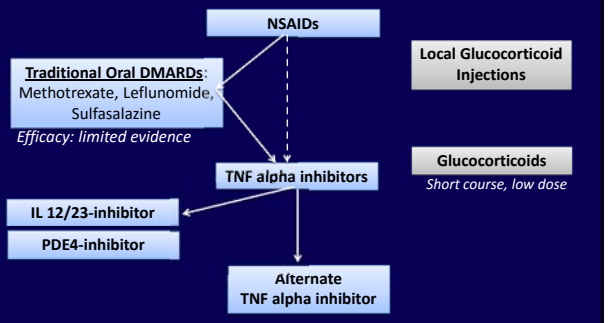
Gossec L et al. Ann Rheum Dis 2012
Acosta Felquer et al. J Rheumatol 2014

Enthesitis



Orbai A et al. J Rheumatol 2014
Gossec L et al. Ann Rheum Dis 2012

Dactylitis

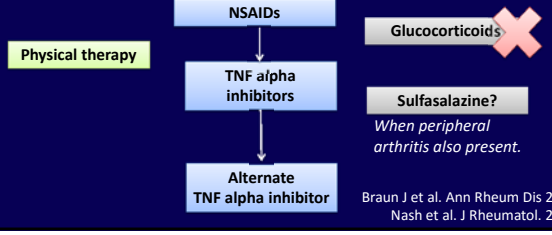


Rose S et al. J Rheumatol 2014
Gossec L et al. Ann Rheum Dis 2012

Axial Disease

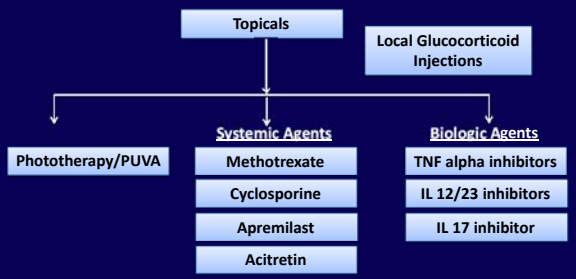
2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis

J Braun,[1,2] R van den Berg,[3] X Baraliakos,[1] H Boehm,[4] R Burgos-Vargas,[5] E Collantes-Estevez,[6] H Dagfinrud,[7,8] B Dijkmans,[9] M Dougados,[10] P Emery,[11] P Geher,[12] M Hammoudeh,[13] RD Inman,[14] M Jongkees,[15] MA Khan,[16] U Kiltz,[1] TK Kvien,[17] M Leirisalo-Repo,[18] WP Maksymowych,[19] I Olivieri,[20] K Pavelka,[21] J Sieper,[22] E Stanislawska-Biernat,[23] D Wendling,[24] S Özgocmen,[25] C van Drogen,[15] BJ van Royen,[26] D van der Heijde,[27]



Braun J et al. Ann Rheum Dis 2011
Nash et al. J Rheumatol. 2014

Skin and Nails



Armstrong A et al. J Rheumatol 2014
Crowley JJ et al. JAMA Dermatol 2015

Treat to Target in PsA

- *Tight Control of Early PsA (TiCOPA)*
- Minimal Disease Activity (MDA) defined as 5/7 of the following:
  - 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
- A balancing act:
  - Less progression in tight control arm
  - More adverse events associated with tight control

Coates & Helliwell. Curr Rheum Reports 2015

Comorbidities in PsA

Comorbidity	Screening Considerations
Cardiovascular Disease	Check blood pressure, lipid panel Encourage smoking cessation
Obesity	Council patients on the benefits of weight loss
Diabetes	Check fasting glucose or hemoglobin A1c
Inflammatory Bowel Disease	Ask about gastrointestinal symptoms in the ROS
Ophthalmic Disease	Ask about ophthalmic symptoms in the ROS
Malignancy	Consider yearly or periodic skin check for patients with a history of UV light therapy
Liver and Kidney Disease	Check LFTs, Cr, HBV/HCV serologies before starting therapy
Depression and Anxiety	Ask about symptoms of depression and anxiety

Ogdie et al. Curr Opin Rheumatol. 2015

Conclusions

- PsA is a heterogenous disease
- Assessment and therapy selection should be tailored to disease manifestations.
- Frequent monitoring of therapy and adjustment to attain treatment goals is important
- Some comorbidities are common in patients with PsA; assessment of comorbidities is important for therapy selection

Acknowledgments

- GRAPPA Slide Sets
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Thank you

Evaluation and Treatment of Psoriatic Arthritis

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Discuss Optimal Strategy to Monitor Early and Established Patients with Psoriatic Arthritis and Comparative Efficacy and Safety of Biological Therapies

Philip J. Mease, MD

Optimal Strategy to Monitor Early and Established Patients with Psoriatic Arthritis and Comparative Efficacy and Safety of PsA Therapies

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Conflict of Interest Disclosure

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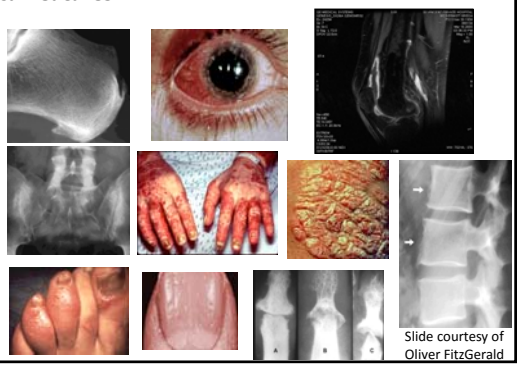
Research and Education Association Memberships

Executive board GRAPPA, member of ASAS, SPARTAN, Scientific Director of CORRONA SpA/PsA registry, Co-chair OMERACT PsA working group

Psoriatic Disease

Complex, polygenic autoimmune disease with diverse clinical features



Slide courtesy of Oliver FitzGerald

Extra-Articular, Extra-Cutaneous Manifestations of PsA and Comorbidities

Need for Teamwork with PCP, Opthalmology, GI, Psych

- Uveitis
- Colitis
- Cardiovascular disease
- Metabolic syndrome
  - Obesity, hypertension, hyperlipidemia
- Fatty liver (NASH)
- Depression, suicidal ideation
- Fatigue
- Fibromyalgia
- Osteoporosis

Assessment of Psoriatic Arthritis in Clinical Trials

Domains	Instruments
Joint assessment	68/66 T/S joint count, ACR, DAS, PsARC
Axial assessment	BASDAI, BASFI, BASMI
Skin assessment	PASI, Target lesion, Global
Pain	VAS
Patient global	VAS (global, skin + joints)
Physician global	VAS (global, skin + joints)
Function/QOL	HAQ, SF-36, PsAQoL, DLQI
Fatigue	FACIT, Krupp, MFI, VAS
Enthesitis assessment	Mander, MASES, Leeds, Berlin, SPARCC, 4-point
Dactylitis assessment	Leeds, present/absent, acute/chronic
Acute phase reactant	ESR, CRP
Imaging	Xray (modified Sharp or van der Heijde-Sharp), MRI, US

Mease P. *Arth Care & Research.* 2011;63:64-85. Mease P, et al. *Ann Rheum Dis.* 2005;64: ii49-ii54. Mease P, van der Heijde D. *Int J Adv Rheum.* 2006;4:38-48.

PsA Management

GRAPPA PsA Treatment Evidence Review

	Peripheral Arthritis	Skin and Nail Disease	Axial Disease*	Dactylitis	Enthesitis
NSAIDs	x		x		
Intra-articular steroids	x				
Topicals		x			
Physiotherapy			x		
Psoralen UVA/UVB		x			
DMARDS (MTX, SSZ, Lef)	x	x			
Biologics (anti-TNF antagonists)	x	x	x	x	x

*Based on data from ankylosing spondylitis trials (used as surrogate for PsA spondylitis)

Kavanaugh A, Ritchlin C (eds). *J Rheum.* 2009 33;1417-1456.
Mease P. *Ann Rheum Dis.* 2011; 70 (Suppl 1): 77-84.

GRAPPA Treatment Grid for PsA Based on Disease Activity and Impact

	Mild	Moderate	Severe
Peripheral arthritis	<5 joints No damage on X-ray No LOF QOL-minimal impact Pt evaluation mild	≥5 joints (S or T) damage on X-ray IR to mild Rx Moderate LOF Moderate impact on QoL Pt evaluation moderate	≥5 joints (S or T) severe damage on X-ray IR to mild-moderate Rx Severe LOF Severe impact on QoL Pt evaluation severe
Skin disease	BSA <5 PASI <5 Asymptomatic	Non-response to topicals DLQI PASI <10	BSA >10 DLQI >10 PASI >10
Spinal disease	Mild pain No loss of function	Loss of function or BASDAI >4	Failure of response
Enthesitis	1–2 sites No loss of function	>2 sites or loss of function	Loss of function or >2 sites and failure of response
Dactylitis	Pain: Absent to mild Normal function	Erosive disease or loss of function	Failure of response

Ritchlin C, *et al. Ann Rheum Dis* 68:1387-94 2009

2015 Update of GRAPPA Evidence-Based Review of Therapies for PsA

- New data since prior recommendations regarding
  - Ustekinumab
  - Apremilast
  - Secukinumab
- Co-morbidities

Coates L, et al. J Rheum Supplement 2014

Controlled Trials of DMARDs in Psoriatic Arthritis

Compound	Arthritis	Skin
SSZ[1]	Marginal	None
MTX[2-4]	Improvement in global assessments only	Improvement in area of skin involvement only
CsA[4]	Marginal	Good
Gold[5]	Marginal	None
Azathioprine[6]	Marginal	None
Leflunomide[7]	PsARC 59% ACR 20 36.3%	Mean PASI improvement 22.4%

ACR = American College of Rheumatology; PASI = Psoriasis Area and Severity Index; PsARC = Psoriatic Arthritis Response Criteria.
1. Clegg DO, et al. *Arthritis Rheum.* 1996;39:2013-2020. **2.** Wilkens RF, et al. *Arthritis Rheum.* 1984;27:376-381. **3.** Kingsley GH, et al. *Rheumatology.* 2012;51:1368-1377. **4.** Spadaro A, et al. *Clin Exp Rheumatol.* 1995;13:589-593. **5.** Palit J, et al. *Br J Rheumatol.* 1990;29:280-283. **6.** Nash P, Clegg DO. *Ann Rheum Dis.* 205;64(suppl II):i74-i77. **7.** Kaltwasser P. *Arthritis Rheum.* 2004; 50:1939-1950

MIPA Trial: MTX Is Not a DMARD in Psoriatic Arthritis[1]

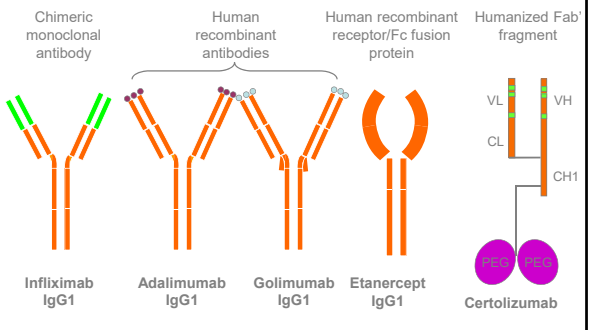
- Double-blind, parallel-group randomized controlled trial (N = 221)
- Patients randomized to receive MTX (target dose 15 mg/week) or PBO

Global Index	OR (95% CI)	*P* Value
PsARC (primary endpoint)	1.77 (0.97, 3.23)	0.06
ACR 20 responders	2.00 (0.65, 6.22)	0.23
DAS28 responders	1.70 (0.90, 3.17)	0.10

- There was no difference between groups in CRP/ESR, SJC, or TJC at 3 months or 6 months
- There were significant differences in improvement in patient and physician global assessment and PASI scores (*P* = 0.02, 0.01, and 0.02, respectively)
- There was no evidence MTX improves inflammatory synovitis in active PsA and thus that it has true DMARD activity

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MIPA = Methotrexate in Psoriatic Arthritis; OR = odds ratio; PBO = placebo; SJC = swollen joint count; TJC = tender joint count.
1. Kingsley GH, et al. *Rheumatology.* 2012;51:1368-1377.

TNFα Inhibitors*:



*Structural differences do not indicate differences in efficacy or safety. No head to head trials of these agents have been conducted.

CDR = Complementarity-determining region, PEG = Polyethylene glycol

Anti-TNF Therapies in PsA: ACR and PASI Responses

Trial	n	ACR20 %		ACR50 %		ACR70 %		PASI75 %[X]	
		Rx	P	Rx	P	Rx	P	Rx	P
Adalimumab 2/3[x]	315	58	14	36	4	20	1	59	1
Certolizumab 3+	409	58	24	36	11	25	3	62	15
Etanercept 2*	60	74	14	48	5	13	0	26*	0*
Etanercept 3*	205	59	15	38	4	11	0	23	3
Golimumab[X]	405	52	8	32	3.5	18	0.9	61	1
Infliximab 2+	100	69	8	49	9	29	0	68	0
Infliximab 3**	200	58	11	36	3	15	1	60	1

**12 weeks; **14 weeks + 16 weeks; [X]24 weeks*
Mease et al. Lancet 2000;356:385-90; Antoni et al, A8R 2005; 52:1227; Mease et al. A&R 2004;50:2264-72; Antoni et al. ARD 2005; 64:1150; Mease et al A&R 2004; 50:2264; Mease et al, ARD 2005; 52:3279; Kavanaugh et al. Arthritis Rheum 2007; Mease et al, Ann Rheum Dis. 2014 Jan;73(1):48-55

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

Safety of TNFi in PsA Using Example of Adalimumab AE Rates in Different Indications

Serious adverse event (Event/100 PY)	RA n=10,050 PY=12,506	Early RA n=542 PY=917	AS n=393 PY=423	Psoriasis n=142 PY=135	PsA n=395 PY=484	CD n=1459 PY=1506
Serious infections	5.05	1.85	1.18	0.74	2.07	5.98
Tuberculosis	0.27	0.11	0.00	0.00	0.00	0.20
Lymphomas	0.12	0.00	0.24	0.00	0.41	0.07
Demyelinating disease	0.08	0.00	0.00	0.00	0.00	0.13
SLE/Lupus-like syndrome	0.10	0.00	0.00	0.00	0.00	0.07
CHF	0.28	0.11	0.00	0.00	0.00	0.00

Studies of adalimumab in various populations: AS = ankylosing spondylitis; CD = Crohn's disease; CHF = congestive heart failure; PsA = psoriatic arthritis; PY = patient years; RA = rheumatoid arthritis. *Burmester GR, et al. ACR, Washington DC 2006, #467*

Current RA Therapies – Use in PsA/SpA?

- **IL-1 Inhibitors, e.g. Anakinra (Kineret) – not effective**
- **Co-stimulatory blockade: Alefacept (Amevive) (LFA3-CD2), Abatacept (CTLA4Ig) (B7-CD28)**
- **B cell ablators and modulators (minimally effective)**

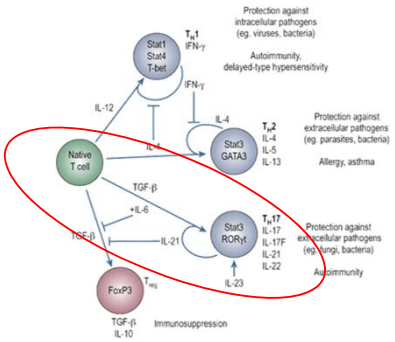
Mease P. Ann Rheum Dis. 2011;70:77-84

Recently Approved and Emerging Therapies for PsA

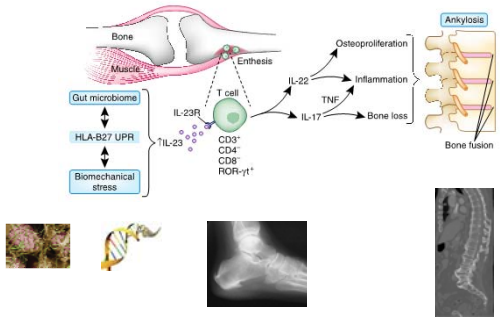
- **IL12-23i**
  - **Ustekinumab – approved for psoriasis and PsA**
- **Phosphodiesterase 4 (PDE4)i (Poly-cytokine inhibition)**
  - **Approved for psoriasis and PsA**
- **IL-17i**
  - **Secukinumab approved for psoriasis**
  - **Secukinumab in PsA and AS; Ixekizumab in psoriasis, PsA, AS in development**
- **IL-6 and IL-6Ri**
  - **Clazakizumab phase 2 study in PsA**
- **JAK (Poly-cytokine inhibition)**
  - **Tofacitinib approved for RA; being developed in psoriasis, PsA, AS**

Mease P. *Ann Rheum Dis.* 2011; 70 (Suppl 1) 77-84.

T Cell Differentiation Pathways

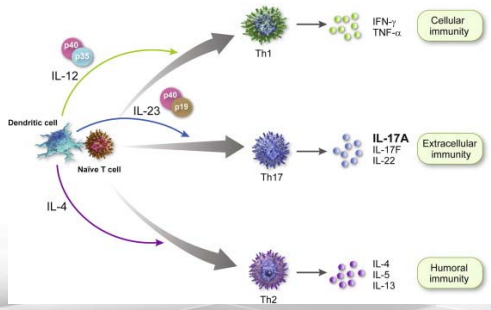


IL-23 and Resident T-cells Promote Enthesitis and Osteoproliferation



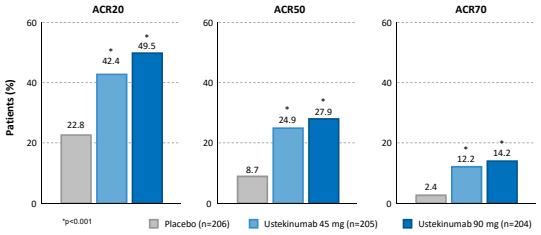
Lories R. *Nature Med*. 2012;18(7):1018.

Ustekinumab: p40 inhibitor



Ustekinumab* Treatment response at Week 24

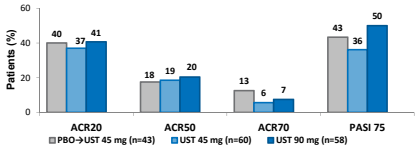
PSUMMIT I



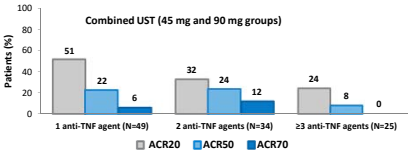
McInnes IB et al. Lancet 2013; 382(9844);780-9.

Ustekinumab*: PSUMMIT2 Efficacy in anti-TNF-experienced patients at Week 52

ACR and PASI responders



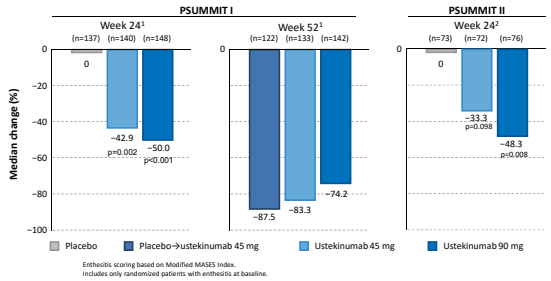
ACR20\50\70 responders



1. Gottlieb AB, et al. Poster presented at EADV, Oct 2-6 2013, Istanbul. Poster P1214.
2. Ritchlin C, et al. Ann Rheum Dis 2014;73:990–999

Ustekinumab* Median percent change from baseline in enthesitis scores at Week 24 and Week 52

PSUMMIT I and PSUMMIT II

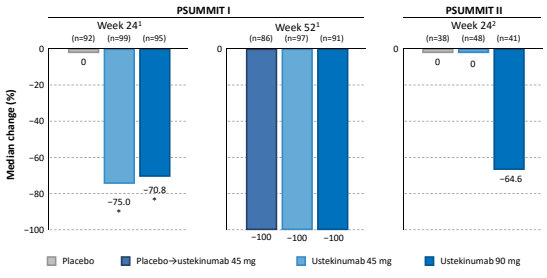


Enthesitis scoring based on Modified MASES Index.
Includes only randomized patients with enthesitis at baseline.

1. McInnes IB et al. Lancet 2013; 382(9844);780-9.
2. Ritchlin CT, et al. ACR/AHRP 2012, November 10-14, Washington, DC, USA. Abs 2557.

Ustekinumab* Median percent change from baseline in dactylitis scores at Week 24 and Week 52

PSUMMIT I and PSUMMIT II



*p<0.001

1. McInnes IB et al. Lancet 2013; 382(9844);780-9.
2. Ritchlin CT, et al. ACR/AHRP 2012, November 10-14, Washington, DC, USA. Abs 2557.

Ustekinumab*
Safety summary through Week 52

PSUMMIT I

	EE & CO (PBO → 45 mg)	UST 45 mg	UST 90 mg
Patients treated, n	189	205	204
Avg. duration of f/u, wks	29.8	50.4	50.2
Patients with AEs	78 (41.3%)	137 (66.8%)	132 (64.7%)
Patients with Infections	39 (20.6%)	77 (37.6%)	84 (41.2%)
Patients with SAEs	10 (5.3%)	12 (5.9%)	7 (3.4%)
Patients with ≥1 malignancy	0	0	0

Through Week 52:

- No cases of TB, opportunistic infections, or malignancies were reported
- There were 3 MACE events: 2 MIs in PBO→45 mg group, 1 CVA in the UST 45 mg group, and no events in the UST 90 mg group

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

IL-17 Inhibitors in Development for PsA

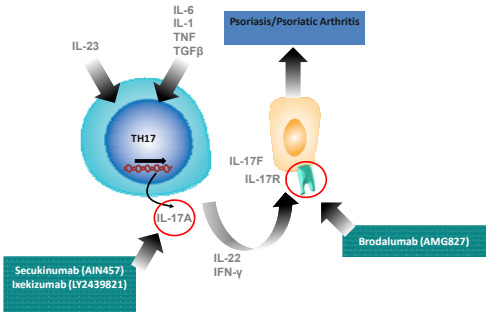
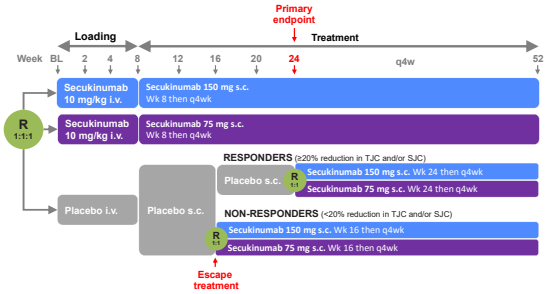


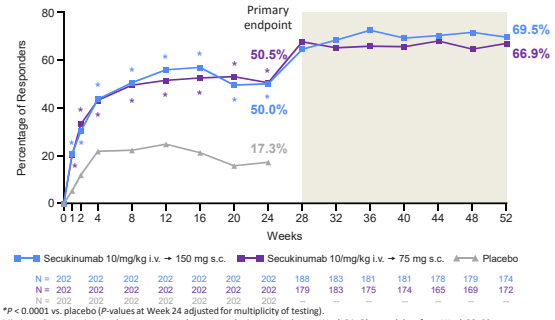
Figure adapted from Strzepa A, et al. Pharmacol Reports. 2011;63(1):30-44.

Secukinumab: FUTURE 1 Study Design
Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study



Mease P, et al. ACR 2014; Mease P, et al. New Engl J Med 2015, accepted

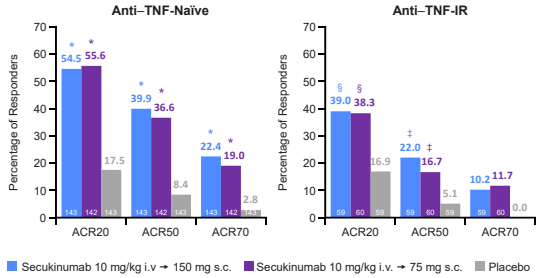
ACR20 Responses Through Week 52



*P < 0.0001 vs. placebo (*P*-values at Week 24 adjusted for multiplicity of testing).
Missing values were imputed as nonresponse (nonresponder imputation) up to Week 24. Observed data from Week 28–52.

Mease P, et al. ACR 2014; Mease P, et al New Engl J Med 2015 accepted

ACR 20/50/70 Responses in Anti–TNF-Naïve and Anti–TNF-IR Subjects at Week 24

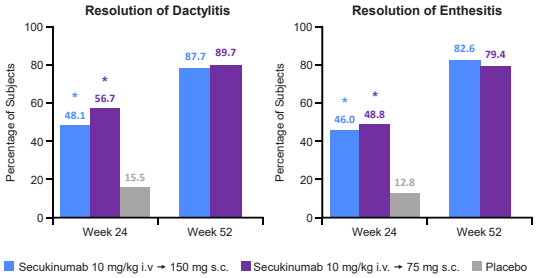


- Responses were sustained through Week 52 in both subgroups of subjects

*P < 0.0001, §P < 0.01; †P < 0.05 vs. placebo. Missing values were imputed as nonresponse (nonresponder imputation).
Statistical analysis of ACR70 response in the anti–TNF-IR subjects not performed due to lack of responders in the placebo arm.

Mease P, et al. ACR 2014; Mease P, et al. New Engl J Med 2015 accepted

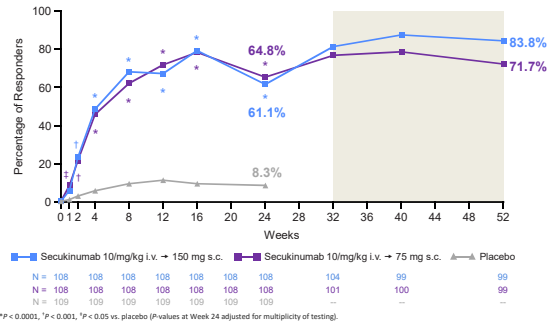
Resolution of Dactylitis and Enthesitis at Weeks 24 and 52



*P < 0.0001 vs. placebo.
Resolution of dactylitis and enthesitis amongst those subjects with these symptoms at baseline (dactylitis: n = 104 [150 mg], 104 [75 mg] and 116 [placebo]; enthesitis: n = 126 [150 mg], 129 [75 mg] and 117 [placebo]).
Missing values were imputed as nonresponse (nonresponder imputation) at Week 24. Observed data presented at Week 52.

Mease P, et al. ACR 2014; Mease P, et al. New Engl J Med 2015 accepted

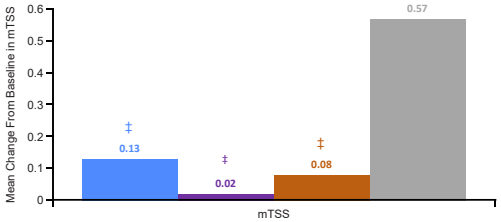
PASI 75 Responses Through Week 52



N =	108	108	108	108	108	108	108	104	99	99
N =	108	108	108	108	108	108	108	101	100	99
N =	109	109	109	109	109	109	109	--	--	--

*P < 0.0001, †P < 0.001, ‡P < 0.05 vs. placebo (*P*-values at Week 24 adjusted for multiplicity of testing).
Analysis performed in subjects with psoriasis ≥ 3% body surface area that were randomized.
Missing values were imputed as nonresponse (nonresponder imputation) up to Week 24. Observed data from Week 32–52.
Mease P, et al. ACR 2014.; Mease P New Engl J Med 2015 accepted

Mean Change from Baseline in mTSS at Week 24



‡P < 0.05 vs. placebo
P-values for pooled secukinumab group adjusted for multiplicity of testing.
Mease P, et al. ACR 2014; Mease P, et al. New Engl J Med 2015. Accepted

Secukinumab: FUTURE 1: Adverse Events of Special Interest

Variable	Any secukinumab 150 mg s.c. (n = 295)	Any secukinumab 75 mg s.c. (n = 292)	Placebo (n = 202)
Exposure to treatment, mean days	439.4	437.6	128.5
AEs, exposure-adjusted incidence rate (number of cases per 100 patient-years)			
Malignant or unspecified tumors	0.3	0.9	1.4
MACE	0.3	1.4	0.0

Candida infections
- Oral candidiasis in 8 (1.3%) subjects (4 with 75 mg; 4 with 150 mg); 1 (0.2%) case of esophageal candidiasis
- All cases of candidiasis were considered mild or moderate and responded to oral therapy; subjects continued in study

Neutropenia
- Grade 3 in 3 (0.5%) subjects (1 with 75 mg, 2 with 150 mg); no subject discontinued treatment. No Grade 4 cases were reported

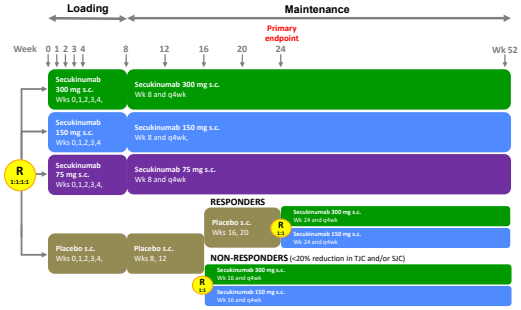
Treatment-emergent anti-secukinumab antibodies
- Treatment-emergent anti-secukinumab antibodies detected in 1 (0.2%) subject; no loss of efficacy

Grade 3 neutropenia: < 1.0–0.5 x 10^9 neutrophils/L; Grade 4: < 0.5 x 10^9 neutrophils/L; MACE, major adverse cardiac event.

Mease P, et al. ACR 2014; Mease P, et al. New Engl J Med. 2015

FUTURE 2: Study Design

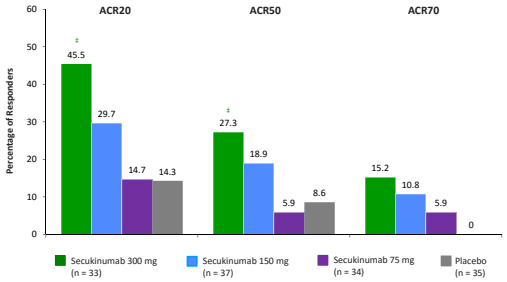
Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study



Randomization stratified by prior anti-TNF therapy (being anti–TNF-naïve or anti–TNF-IR). Only benefitting subjects continue after Week 52 q4wk, every 4 weeks; R, randomization; s.c., subcutaneous; SJC, swollen joint count; TJC, tender joint count; wk, week

McInnes I Lancet 2015

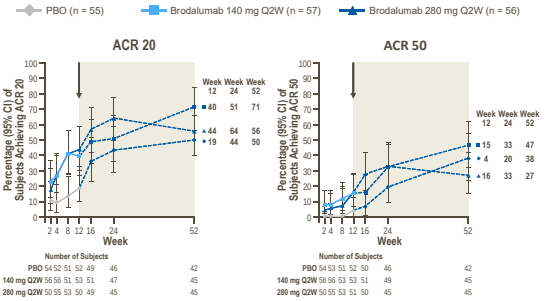
ACR Responses at Week 24 in Anti–TNF-IR Subjects



‡P < 0.05 vs. placebo
Missing values were imputed as nonresponse (nonresponder imputation).

McInnes I Lancet 2015

Brodalumab in PsA: ACR 20 and 50 Responses Through 52 Weeks: Observed Analysis



↓ = indicates time point at which all subjects began receiving 280 mg Q2W brodalumab
SE = standard error.

Mease P, et al. New England J Med. 2014. 370: 2295-306

Two-Year Clinical Response to Brodalumab, an Anti-IL-17 Receptor Antibody, in Patients With Psoriatic Arthritis

Exposure-adjusted Adverse Event Rates (per 100 Patient-Years), Week 12 to 108

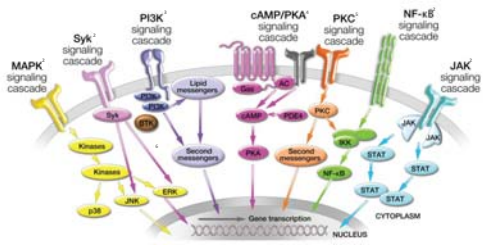
Treatment-emergent AE, n (r)	Prior Placebo (Pt-yr 81.1) N = 52	Brodalumab 280/210 mg Q2W OLE: Prior 140 mg Q2W (Pt-yr 97.8) N = 56	Brodalumab 280/210 mg Q2W OLE: Prior 280 mg Q2W (Pt-yr 95.5) N = 56	Brodalumab 280/210 mg Q2W OLE: Total (Pt-yr 274.5) N = 164
Any	351 (432.8)	554 (566.2)	539 (564.2)	1444 (526.1)
Grade ≥ 2	222 (273.7)	296 (302.5)	293 (306.7)	811 (295.5)
SAE	8 (9.9)	13 (13.3)	16 (16.7)	37 (13.5)
Infectious events	2 (2.5)	3 (3.1)	4 (4.2)	9 (3.3)
Malignancies	0 (0.0)	2 (2.0)	2 (2.1)	4 (1.5)
Leading to discontinuation of IP	7 (8.6)	13 (13.3)	12 (12.6)	32 (11.7)
Serious	2 (2.5)	5 (5.1)	2 (2.1)	9 (3.3)
Non-serious	5 (6.2)	8 (8.2)	10 (10.5)	23 (8.4)
Leading to discontinuation from study	6 (7.4)	11 (11.2)	11 (11.5)	28 (10.2)
Serious	1 (1.2)	5 (5.1)	2 (2.1)	8 (2.9)
Nonserious	5 (6.2)	6 (6.1)	9 (9.4)	20 (7.3)
Adverse events of interest				
Candida infection	9 (11.1)	8 (8.2)	9 (9.4)	26 (9.5)
Neutropenia	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.4)
Suicidal ideation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.4)
Life-threatening	2 (2.5)	0 (0.0)	1 (1.0)	3 (1.1)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Mease P, et al. EULAR 2015

What's Coming Along in the TH17i Pathway?

- Potential future approvals of IL-17is, secukinumab, ixekizumab in PsA, brodalumab uncertain
- IL-23i: guselkumab, tildrakizumab, BI-655066
- Dual inhibitors: TNFi/IL-17i

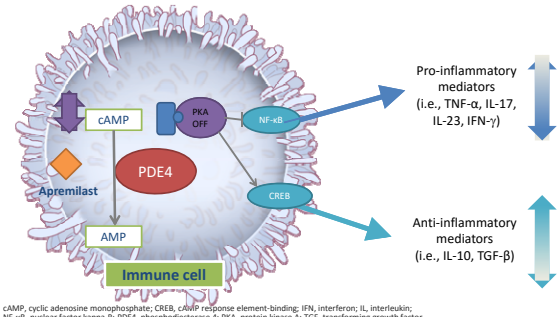
Cytokine signaling pathways



AC, adenylyl cyclase; BTK, Bruton's tyrosine kinase; cAMP, cyclic adenosine monophosphate; ERK, extracellular signal-related kinases; IKK, inhibitor of kappa B kinase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa B; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; PK, protein kinase; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase.

- 1. O'Sullivan L, et al. Molec Immunol. 2007;44:2497–2506;
- 2. Mavers M, et al. Curr Rheum Rep. 2009;11:378–85;
- 3. Rommel C, et al. Nat Rev Immunol. 2007;7:191–201; 4. Tasken K, et al. Physiol Rev. 2004;84:137–67;
- 5. Baier G, et al. Curr Opin Cell Biol. 2009;21:262–7; 6. Ruderman E, et al. Arthritis Res. Ther 2011;13:125.

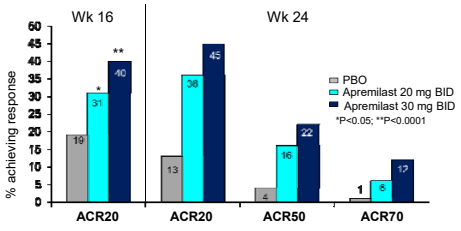
Apremilast (PDE4i) modulates the production of pro-inflammatory and anti-inflammatory mediators



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

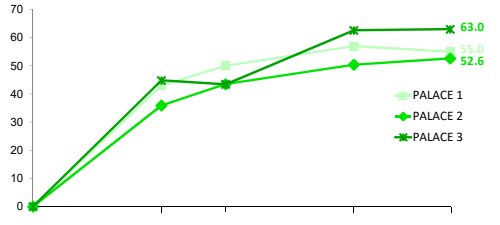
PDE4i in PsA: Apremilast Palace 1

- Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor
- RDBPC trial stratified for DMARD use, n=489, 1:1:1 randomization
- Major AEs diarrhea and nausea, resolve over time



Kavanaugh A, et al. Ann Rheum Dis. 2014 Jun;73(6):1020-6

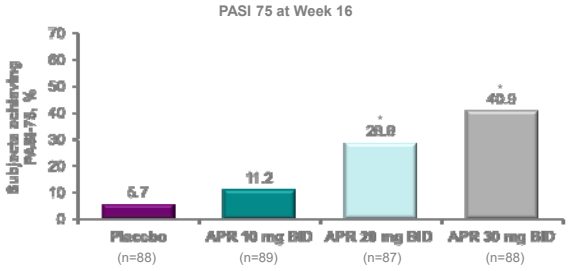
ACR20 Response Over 52 Weeks: PALACE 1, 2, 3
Apremilast 30 mg BID



PALACE 1 (Responders/n)	64/150	73/145	80/140	71/130
PALACE 2 (Responders/n)				
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].

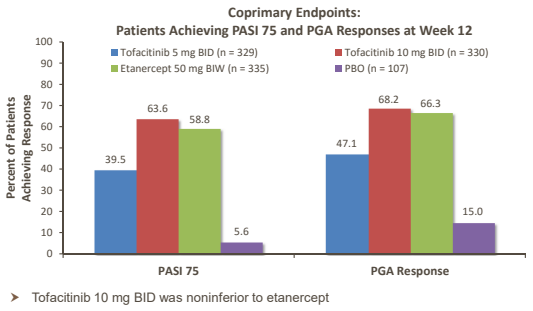
Efficacy of Apremilast in Psoriasis Skin Lesions in PsA



*P<0.001 vs placebo
Oral administration; Phase 2b

Papp K, et al. Lancet. 2012 Aug 25;380(9843):738-46

Efficacy of Tofacitinib in Psoriasis



➤ Tofacitinib 10 mg BID was noninferior to etanercept

PGA = Physician's Global Assessment.
1. Bachelez H, et al. Presented at: AAD, Denver, CO, March 21-25. 2014.

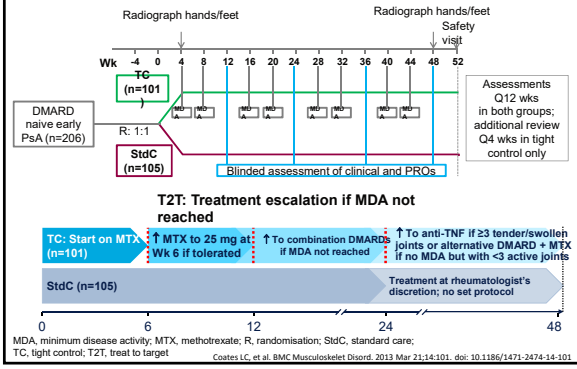
Treating to Target in PsA

Minimal Disease Activity Criteria (MDA) (GRAPPA)

- 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

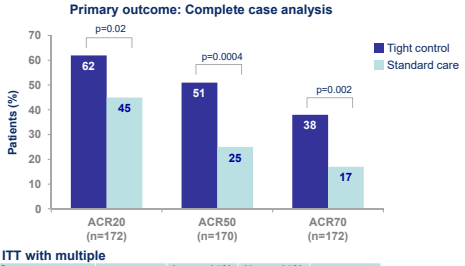
TICOPA: Tight control/T2T in PsA – Study Design



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

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

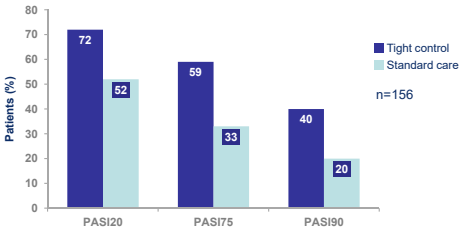


ITT with multiple

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

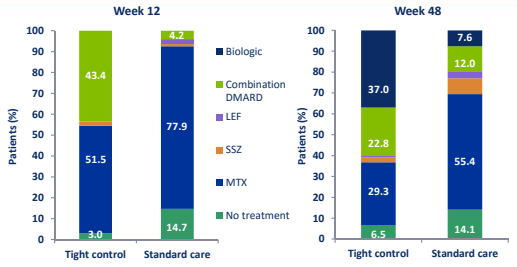
Reduction in Psoriasis Severity was Achieved in a Higher Proportion of Patients in the Tight Control Arm



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

Prescribed therapy at Weeks 12 and 48 in the TICOPA study



More combination Tx with MTX in TC arm at Week 12

More biologic Tx in TC at Week 48

Prescribed therapy: 37.0% of TC patients were receiving biologics at Week 48 versus 7.6% of patients on standard care

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

Incidence of AEs and SAEs up to Week 48

Number of AEs

	Tight control	Standard care
Any AE	622	249
AE related to study drug (%)	423 (68.0)	179 (71.8)
Common AEs		
Nausea	54	38
LFT abnormality	37	39
URTI – common cold	46	14
GI upset	35	13
Fatigue	33	8
Deaths	0	0
SAE	25 (14 pts)	8 (6 pts)
Drug-related SAE	8	2

Short-term 48-week data assessment:
Long-term study period required for adequate safety assessment

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

Rheum/Derm/PCP Collaboration for Optimal Outcomes

- Rheum/Derm combined clinic for integrated teaching and treatment model available in some academic centers
- Successful 'real-world' Rheum/Derm/PCP collaboration is facilitated by
  - Good communication between specialties
  - EMR/phone communication
  - Mutual access to a network of local dermatologists and rheumatologists
  - Use of screening questionnaires to improve sensitivity and specificity of referral of psoriasis pts who might have PsA

Conclusions

- **PsA is manifest by a variety of clinical features which may elude recognition**
- **Teamwork between PCPs, dermatologists, and rheumatologists is important to recognize the disease early and institute appropriate treatment**
- **Evolving understanding about pathophysiology is ushering in new, more targeted therapies**
- **Methotrexate can be helpful for symptoms of PsA, although evidence for its effectiveness is incomplete**
- **Biologic therapy can benefit all clinical domains of PsA**
- **A "treat to target" and "tight control" strategy has been shown to yield optimal clinical outcomes**
- **New therapies are emerging**

THANK YOU

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New Concepts in the Diagnosis and Treatment of Ankylosing Spondylitis

Muhammad A. Khan, MD

New Concepts in the Diagnosis and Treatment of Ankylosing Spondylitis

Muhammad Asim Khan, *MD, FRCP, MACP*
Professor *Emeritus* of Medicine
Case Western Reserve University
MetroHealth Medical Center
Cleveland, OH

Conflicts of Interest Disclosure Statement

Consultant/Speaker

AbbVie, Amgen, Novartis, Celgene, Janssen, Pfizer, Crescendo, Sun Pharmaceuticals

Khan MA, S van der Linden, I Kushner: Symptomatic ankylosing spondylitis without radiographic sacroiliitis in B27-positive relatives. Clin Res 31: 804A, 1983.

van der Linden S, Cats A, Valkenburg HA, Khan MA: Evaluation of the diagnostic criteria for AS: a proposal for modification of the New York criteria. Clin Res 31: 734A, 1983.

Spondylitic Disease Without Radiographic Evidence of Sacroiliitis. 1985	Ankylosing Spondylitis (Modified New York Criteria). 1984
Khan MA, et al. Arthritis Rheum. 1985; 28: 40-3.	van der Linden S, et al. Arthritis Rheum. 1984; 27:361-8

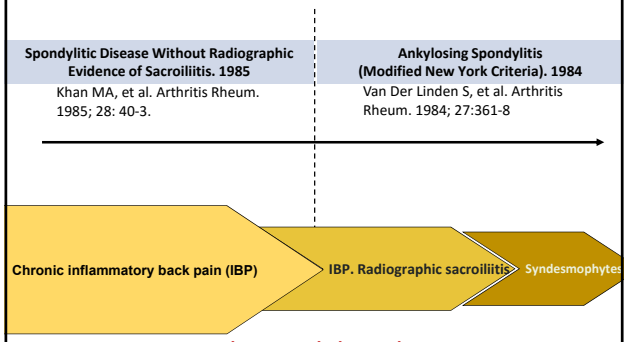
Chronic inflammatory back pain (IBP) IBP. Radiographic sacroiliitis Syndesmophytes

1993: **ASsessment in Ankylosing Spondylitis**

ASAS

www.asas-group.org

Assessment in SpondyloArthritis international Society



Axial Spondyloarthritis

Rudwaleit M, Khan MA, Sieper J. The challenge of Diagnosis and classification of early AS. Do we need new criteria? Arthritis Rheum 2005 Apr;52(4):1000-8

From: Khan MA. Clinical features. Axial SpA book (in press)

Parameters (Red Flags) that Suggest Axial SpA and Point to its Early Diagnosis

❖ **Clinical Features:**

1. Inflammatory back pain
2. Enthesitis (heel)
3. Peripheral arthritis (often asymmetric & in LE)
4. Dactylitis
5. Acute anterior uveitis
6. Family history for SpA
7. Psoriasis
8. Crohn's disease or ulcerative colitis
9. Good symptomatic response to NSAIDs

❖ **Lab tests / MRI:**

- Elevated CRP
- Presence of HLA-B27
- MRI

Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. Ann Rheum Dis 2004;63:535-543

Inflammatory Back Pain according to ASAS experts

- ❖ **Insidious onset**
- ❖ **Pain at night** (with improvement upon getting up) (OR = 20.4)
- ❖ **Age at onset <40 years**
- ❖ **Improvement with exercise** (OR = 23.1)
- ❖ **No improvement with rest**

Best trade-off if ≥ 4 of the above 5 parameters are fulfilled

Sensitivity 79.6% & Specificity 72.4%
(Against expert clinical judgement from ASAS validation cohort; n = 648)

Positive Likelihood Ratio (+LR) = 79.6 / 27.6 = 2.9

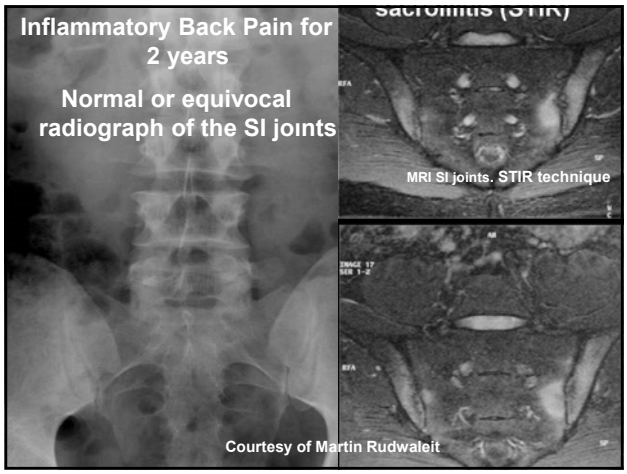
Sieper J, et al. *Ann Rheum Dis*. 2009; 68(6):784-8. Rudwaleit M, et al. *ARD*. 2009; 68(6):777-783.
Ozgocmen S, Akgul O, Khan MA. Mnemonic for ASAS criteria. *J Rheumatol*. 2010 Sep;37(9):1978-9.

Clinical utility of the Clinical Features ("Red Flags")

	Sensitivity	Specificity	+LR
Inflammatory back pain (*updated information*)	80%	72%	2.9
Enthesitis (heel pain)	37 %	89%	3.4
Peripheral arthritis	40	90	4.0
Dactylitis	18	96	4.5
Acute anterior uveitis	22	97	7.3
Positive family history for AS, AAU, IBD, ReA	32	95	6.4
Psoriasis	10	96	2.5
Inflammatory bowel disease	4	99	4.0
Good response to NSAIDs	77	85	5.1
↑acute phase reactants	50	80	2.5

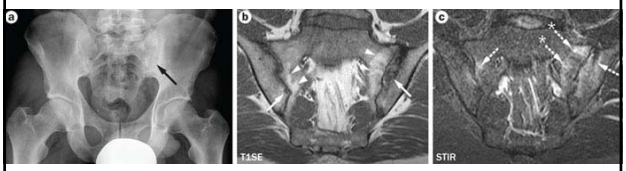
Rudwaleit M, van der Heijde D, Khan MA, Braun J,Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis 2004;63:535-43*

Positive Likelihood Ratio = **2.9 x 6.4 x 5.1 = 97.7**



Sacroiliitis in a patient with axSpA

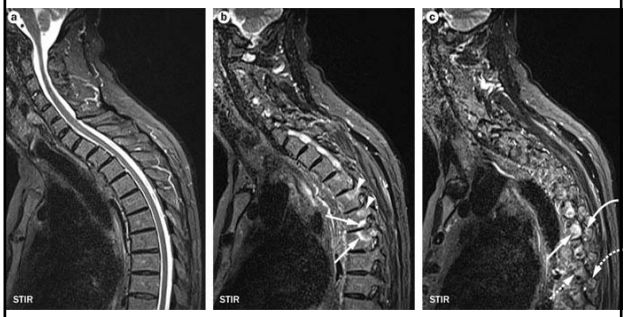
T1 and STIR MRI images are complementary



NOTE: No need for Gadolinium enhancement

van Tubergen, A. & Weber, U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat. Rev. Rheumatol.* 2012. doi:10.1038/nrrheum.2012.33

Spinal MRI can identify Axial SpA-associated inflammation



van Tubergen, A. & Weber, U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2012.33

Posterior elements (including pedicles and facet joints) and postero-lateral articulations (costovertebral and costotranverse joints)

Spondyloarthritis (SpA)

In patients with ≥3 months back pain and age at onset <45 years

Sacroiliitis on imaging plus ≥1 SpA feature OR **HLA-B27** plus ≥2 other SpA features

SpA features
- inflammatory back pain (IBP)
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

Sensitivity: 79.5%, Specificity: 83.3%; n=975

In patients with peripheral symptoms ONLY

Arthritis or enthesitis or dactylitis plus

≥1 SpA feature
- uveitis
- psoriasis
- Crohn's/colitis
- preceding infection
- HLA-B27
- sacroiliitis on imaging

OR

≥2 other SpA features
- arthritis
- enthesitis
- dactylitis
- IBP ever
- family history for SpA

Rudwaleit M et al. Ann Rheum Dis 2011;70:25-31 (with permission)

Need for improvement of the ASAS Criteria for AxSpA:

Akkoc N, Khan MA. ***Curr Rheumatol Report***. 2015 Jun;17(6):515.
van der Linden S, et al. ***Curr Rheumatol Report***. 2015 Sep;17(9):535.

Early Recognition of Axial SpA

Berlin Referral Model for PCP

Chronic LBP (> 3 months), onset at age ≤ 45 yrs

Inflammatory type
- Morning stiffness > 30 minutes
- Pain at night or early morning
- Improvement with exercise

or

HLA-B27(+)

Sacroiliitis on imaging (only if imaging is available)

Refer to rheumatologist for further evaluation

Rudwaleit, M. & Sieper, J. Referral strategies for early diagnosis of axial spondyloarthritis *Nat. Rev. Rheumatol.* 2012. doi:10.1038/nrrheum.2012.39

Early Recognition of Axial SpA

Dutch Referral Model for PCP

Pre-selection for referral in primary care setting should be based on the following 4 components:

- ❑Inflammatory back pain
- ❑Good response to NSAIDs
- ❑Family history of SpA
- ❑Symptom duration

Sensitivity 83% and Specificity 59%. +LR = 83/41 = 2

The above conclusion was based on assessment of 364 CLBP (median duration 9 years) patients ages 20–45 years (mean age 36) identified from PCPs records. The assessment clinical H & PE, ASAS questionnaire for IBP, HLA–B27, CRP, X-ray and MRI, and 24% of them were found to meet the ASAS Classification Criteria for Axial SpA.

van Hoeven L, et al. *Arthritis Care and Research*. 2014; 66; 3: 446–453.

Management of AS/axSpA

Patient Education

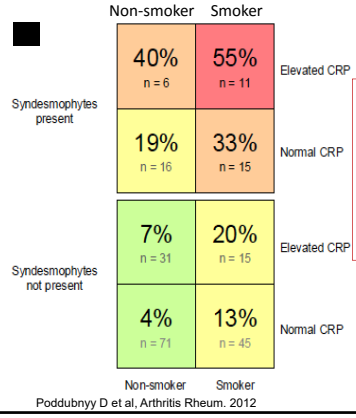
Physical therapy and rehabilitation training

Lifelong exercise program

Lifestyle and employment modification

Complete avoidance of smoking

Patients demonstrating at least 2 mSASSS units progression after 2 years



Poddubnyy D et al, Arthritis Rheum. 2012

Smoking: An environmental risk factor for worse disease

Disease activity in male smokers has a >10-fold amplified effect on radiographic damage in comparison with female non-smokers in AS.

Ramiro S, et al. Ann Rheum Dis 2014;73:212-213. EULAR 2014: Scientific Abstract THU0103.

Radiographic Progression

Strongly dependent on the following risk factors:

- ❖ **Genetics (HLA-B27)**
- ❖ **Gender (more in males vs females)**
- ❖ **Environmental (smoking)**
- ❖ **Inflammatory (MRI positivity)**
- ❖ **Syndesmophytes at baseline**
- ❖ **Hip joint involvement**
- ❖ **Elevated CRP &/or ESR**

Poddubnyy D, et al. *Ann Rheum Dis*. 213, 72:143.
Poddubnyy D, Sieper J. *Curr Opin Rheumatol*. 2012 Apr 5.
Jang JH, et al. *Radiology*. 2011Jan;258(1):192-8.
Stolwijk C, et al. ACR 2013 Meeting Poster. (In smokers 5-fold worsening; 13.5 fold in males vs females)
Ramiro S, et al. Ann Rheum Dis 2014;73:212-213. EULAR 2014: Scientific Abstract THU0103

Management of AS/axSpA

Patient self-help groups and associations

Spondylitis.org
Spondylitis.ca
NASS.co.uk
Bechterew.ch/en/
ASIF.info/en
ASAS-group.org
Spondyloarthritis.com
HLAB27.com

Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of AS patient advocacy groups. *Curr Opin Rheumatol*. 2000 Jul;12(4):239-47.

Management of AS/axSpA

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HLAB27.com

Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of AS patient advocacy groups. *Curr Opin Rheumatol*. 2000 Jul;12(4):239-47.

Dr. Google & the iSNAKE Oil

2010 ASAS/EULAR Recommendations for the Management of AS

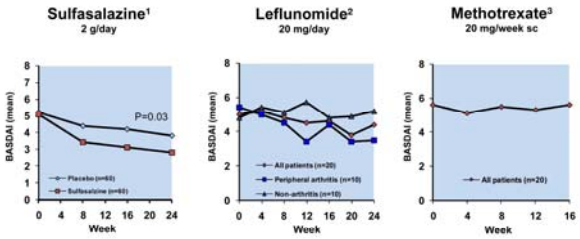
Patient Education

NSAIDs

- ❑ High to moderate quality evidence indicates that both traditional and COX-2 NSAIDs are efficacious.
- ❑ Moderate to low quality evidence indicates harms may not differ from placebo in the short term.
- ❑ Various NSAIDs are equally effective. Etoricoxib > Naproxen
- ❑ Continuous NSAID use may reduce radiographic spinal progression, but this requires confirmation.

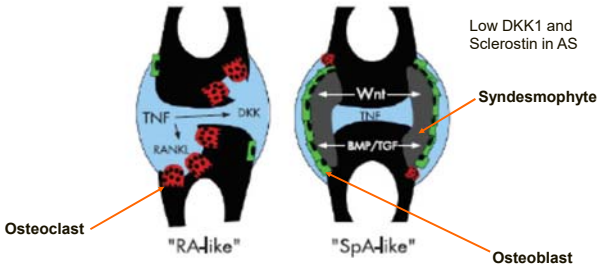
Kroon FP, et al. NSAIDs) for axial SpA (AS and nr-axSpA). ***Cochrane Database Syst Rev***. 2015 Jul 17;7:CD010952. [Epub ahead of print]

Conventional DMARDs Are Largely Not Effective for the Treatment of Patients with AS



1. Braun J et al. Ann Rheum Dis 2006;65:1147-53
2. Haibel H et al. Ann Rheum Dis 2005;64:296-8
3. Haibel H et al. Arthritis Rheum 2006;54:678-81

Structural damage in SpA has to be seen differently from that observed in RA



RANKL = RANK ligand; **DKK1** = Dickkopf proteins; **BMP** = bone morphogenetic proteins; **TGF** = transforming growth factor beta; **Wnt** = Wingless proteins.

Schett et al. *Ann Rheum Dis*. 2007;66:709-711.
(This figure is from the cover of the *ARD* July 2007 issue.)

2010 ASAS/EULAR Recommendations for the Management of AS

Patient Education

Exercise
Physical therapy
Rehabilitation,

Patient associations & self-help groups

NSAIDs

Axial disease

Peripheral disease

Analgesics

Surgery

One DMARD, preferably SSZ

Local C/S injection

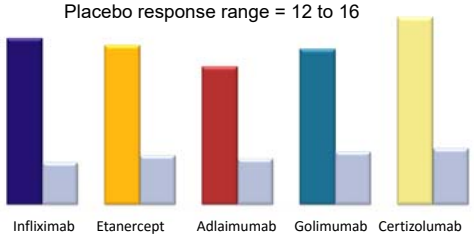
TNF antagonists

Zochling J et al. *Ann Rheum Dis.* 2006;65:442-52. Braun J et al. *Ann Rheum Dis.* 2011;70:896-904.

ASAS 40 Response by AS Patients after 24 Weeks of Treatment with TNFi

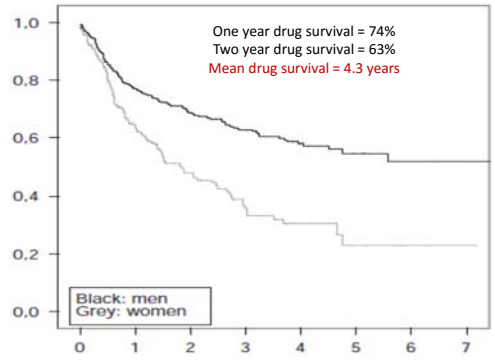
TNFi response range = 39 to 53

Placebo response range = 12 to 16



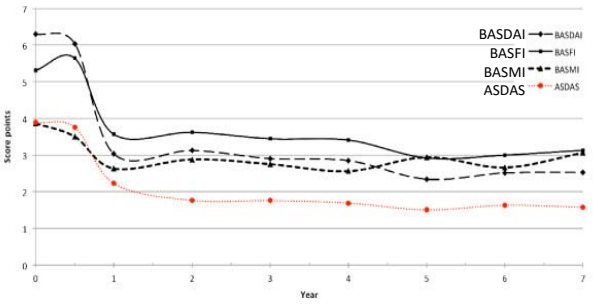
Davis , et al. *Arthritis Rheum 2003; 48:3230-6.*
van der Heijde, et al. Arthritis Rheum. 2005; 52:582-91
van der Heijde, et al. Arthritis Rheum 2006; 54: 2136-46
Inman, et al. Arthritis Rheum 2008; 58 3402-12

Drug Survival (Rate of Discontinuation) of Treatment with TNF-blockers in 842 Patients with AS



Glintborg B, et al. Ann Rheum Dis. 2010 Nov;69(11):2002-8.

Long-term outcome of patients with active AS with etanercept: Sustained efficacy and safety after 7 years



Baraliakos X, et al. Long-term outcome of patients with active AS with etanercept-sustained efficacy and safety after seven years. *Arthritis Res Ther*. 2013; 15(3): R67

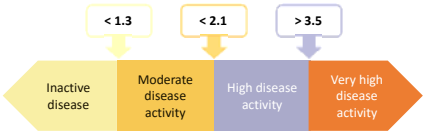
Song IH, et al. Consistently good clinical response in patients with early axial SpA after 3 years of continuous treatment with etanercept: Longterm data of the ESTHER trial. *J Rheumatol*. 2014 Jul 15. pii: jrheum.140056. [Epub ahead of print]

ASDAS (Ankylosing Spondylitis Disease Activity Score)

Parameters used for calculation of the ASDAS

1. Total back pain (BASDAI question 2)
2. Patient global
3. Peripheral pain/swelling (BASDAI question 3)
4. Duration of morning stiffness (BASDAI question 6)
5. CRP in mg/l (or ESR)

Need for a Treat to Target (T2T) Approach



A free app available from www.asas-group.org

Ramiro et al. Ann Rheum Dis 2014;73:1455–1461
Lukas et al. Ann Rheum Dis. 2009;68:18-24.
Machado et al. Ann Rheum Dis. 2011;70:47-53.
van der Heijde et al. Ann Rheum Dis. 2009;68:1811-1818.

Clinically important improvement = Delta > 1.1
Major improvement = Delta > 2.0

There is no approved use of biological agents other than TNF-inhibitor in AS

Rituximab (anti-CD20 monoclonal antibody): Some response in TNF-inhibitor naïve patients with active AS, but not in those who failed TNF-inhibitors
(Possible mild efficacy in PsA in a open-label study of 9 patients)

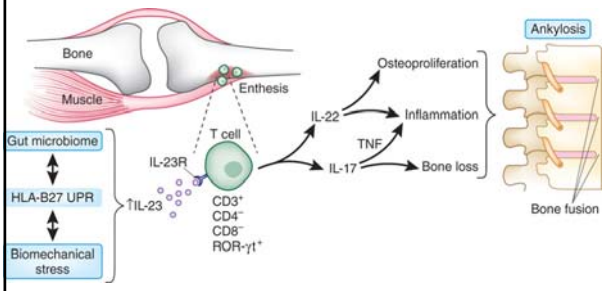
Abatacept: Not effective in AS in an open-label study
(Modest efficacy in PsA in a phase 2 trial)

Tocilizumab & **Sarilumab** (IL-6R antagonists):
Not effective in AS

Anakinra (anti-IL-1):
Not effective in AS

Song IH, et al. Arthritis Rheum. 2010; 62:1290-7 (Rituximab)
Song IH, et al. Ann Rheum Dis. 2013; 71:1868-71. (Rituximab)
Wendling D, et al. J Rheumatol. 2012; 39:2327-31. (Rituximab)
Jimenez-Boj E, et al. Ann Rheum Dis. 2012; 72:305-6. (Rituximab)
Song IH, et al. Ann Rheum Dis. 2011; 70:1108-10 (Abatacept)
Mease P, et al. Arthritis Rheum. 2011; 63:939-48 (Abatacept)
Sieper J, et al. Ann Rheum Dis. 2012;71 (Suppl 3):110 (Tocilizumab)
Sieper J, et al. Ann Rheum Dis. 2012 (Suppl 3):111. 2014; Feb 18 (Sarilumab)

IL-23 and entheseal-resident T cells in the pathogenesis of spondyloarthritis

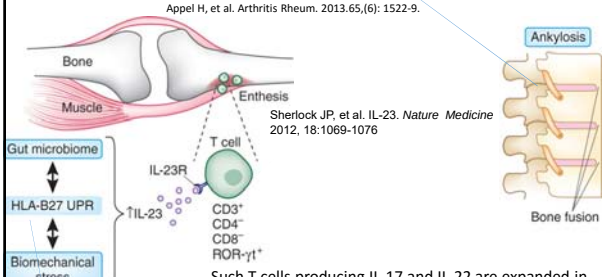


Enthesis (the junction between tendon and bone) has been suggested to be a key target in SpA. This zone is now shown to contain a unique population of resident T cells, which, when activated by the cytokine IL-23, can promote pathogenesis that is characteristic of SpA.

Lories RJ , McInnes IB. Primed for inflammation: enthesis resident T-cells. Nature Medicine 2012; 18: 1018–1019
Sherlock JP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. ***Nature Medicine*** **2012, 18:1069-1076**

IL-23 is expressed in the facet joints of AS patients in the subchondral bone marrow and fibrous tissue replacing bone marrow

Appel H, et al. Arthritis Rheum. 2013.65,(6): 1522-9.



Sherlock JP, et al. IL-23. *Nature Medicine* 2012, 18:1069-1076

Such T cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid and the bone marrow of AS patients..

Ann Rheum Dis. 2015;74:1739-47

HLA-B27 misfolding occurs in the gut of AS patients and is accompanied by activation of autophagy (rather than an UPR) in the gut that is associated with increase in IL-23.
Ann Rheum Dis. 2015;73:1566-74

Genetic Associations and AS Treatment

Genetic studies implicate IL-23 receptor signaling in the development of AS & IBD

GENETIC ASSOCIATIONS WITH AS	TARGET MOLECULES	TREATMENTS & THERAPEUTIC TRIALS IN AS
TNFR1	TNF	Etanercept, infliximab, adalimumab, golimumab, certolizumab
IL12B, IL23R	IL-17A	**Secukinumab** (Cosentyx)
IL12B, IL23R	P40 subunit of IL-12 & IL-23	**Ustekinumab** (Stelara)
PTGER4	Prostaglandins	NSAIDs

Cortes A, et al. *Nat Genet.* 2013 July; 45(7): 730–

Secukinumab Efficacy in AS at Wk 16

[MEASURE 1]

	Secu 75 mg§ (N=124)	Secu 150 mg§ (N=125)	Placebo (N=122)	p Value
ASAS 20%‖	59.7%*	60.8%*	28.7%	p<0.01 p<0.0001
ASAS 40%	33.1%*	41.6%*	13.1%	p<0.01 p<0.001

*all patients received 10mg/kg IV loading dose before SC maintenance dosing
‖Primary endpoint
*statistically significant vs. placebo

For comparison:

ASAS 40 response to TNFi vs Placebo at Wk 24

TNFi response range = 39 to 53%

Placebo response range = 12 to 16%

❑ Baeten D, et al. Secukinumab in Rx of AS: a randomized, DB, PC Phase 2 trial. Lancet. 2013 Nov 23;382(9906):1705-13.
❑ Baeten D. L. et al. Secukinumab, Results of a 52-week Phase 3 Randomized PCTrial with IV Loading and S/C Maintenance Dosing; (Abst 819). ACR Annual Meeting. Nov. 17, 2014, Boston, MA.
❑ Clinicaltrials.gov: 16 Week Efficacy and 2 Year Long Term Safety and Efficacy of Secukinumab in Patients With Active AS (MEASURE 1) https://clinicaltrials.gov/ct2/show/NCT01358175?term=NCT01358175&rank=1

Secukinumab Efficacy in AS at Week 16 [MEASURE 2][3]

	Secu 150 mg§ (N=72)	Placebo (N=74)	p Value
ASAS20‖	61.1%*	27.0%	p<0.001[1]
ASAS20			
TNF-naïve	68.9%*	31.1%	p<0.05[1]
TNF-IR	48.1%*	20.7%	
ASAS40			
TNF-naïve	44.4%*	17.8%	p<0.05[1]
TNF-IR	22.2%*	0%	

(Secukinumab 75mg (N=73) provided numerically greater response than PBO at wk 16, but these did not reach statistical significance for any of the pre-specified primary or secondary endpoints)

UPDATE: 52 week data[2,3] – 73.8% of patients achieved ASAS20 response at 52 weeks with associated improvements in physical function and health-related quality of life.

§all patients received weekly subcutaneous dosing for 4 weeks followed by dosing every 4 weeks
‖Primary endpoint
* statistically significant vs. placebo

1. Sieper J., et al. Secukinumab significantly improves Signs and Symptoms of Active AS; Results of a Phase 3 Randomized Placebo-Controlled Trial with S/C Loading &Maintenance Dosing; (Abstract 536). ACR Annual Meeting. 2014, Boston, MA.
2. Novartis Press Release: Novartis announces new one-year results demonstrating sustained secukinumab efficacy in AS patients. [Published 10 June 2015; Accessed 2015 Sept 14]. https://www.novartis.com/news/media-releases/novartis-announces-new-one-year-results-demonstrating-sustained-secukinumab
3. Sieper et al. Secukinumab Significantly Improves Signs & Symptoms of Active Ankylosing Spondylitis: 52-week data from MEASURE 2, A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial with Subcutaneous Loading and Maintenance Dosing; (Abstract 168, Oral Presentation). EULAR Annual Meeting; 2015, Rome, Italy.

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Novartis (Basel)	**Secukinumab (Cosentyx)** Human	IL-17A	• Approved for PsO (2015) • Phase 3 completed in PsA • Phase 3 completed in AS • AS & PsA regulatory filing 2015 • CD terminated
Janssen (New Jersey)	**Ustekinumab (Stelara)** Human	IL-12/23 p40	• Approved: Mod-severe PsO (2009) • Approved: Active PsA (2013) • Phase 2 completed in AS • Phase 2 published, Phase 3 completed in CD
AbbVie (Chicago)	**Briakinumab** Humanized	IL-12/23 p40	• Phase 3 completed in PsO • CD terminated

Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol. 2015 Jul;11(7):415-29.
Ratner M. *Nature Biotechnology*. 2014; 35:505-7
Reich K, et al. A 52-Week Trial Comparing Briakinumab with Methotrexate in Patients with Psoriasis. N Engl J Med 2011; 365:1586-96.

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Merck/Sun Pharma (New Jersey)	**Tildrakizumab** (MK-322)	IL-23 p19	• Phase 2 completed in PsO • Phase 3 in PsO
Janssen (New Jersey)	**Guselkumab**	IL-23 p19	• Phase 2 in PsO completed • Phase 3 in PsO ongoing
Boehringer Ingelheim (Connecticut)	**BI-655066**	IL-23 p19	• Phase 2 ongoing in AS • Phase 2 ongoing in CD • Phase 2 completed in PsO
Amgen/ MedImmune (California/Maryland)	**AMG-139**	IL-23 p19	• Phase 1 completed in PsO • Phase 1 ongoing in CD

❑ Gordon K.B., et al. *N Engl J Med* Jul 9;373(2):136-44.
❑ Ratner M., *Nat Biotechnol* 2014 Jun;32(6):505-7. doi: 10.1038/nbt0614-505.
❑ Papp K et al. *Br J Dermatol*. 2015 Jun 3. doi: 10.1111/bjd.13932. [Epub ahead of print
❑ A Study to Evaluate the Efficacy and Safety/Tolerability of S/C Tildrakizumab (SCH 900222/MK-3222) in Participants With Moderate-to-Severe Chronic Plaque Psoriasis Followed by a Long-term Extension Study (MK-3222-011) https://clinicaltrials.gov/ct2/show/record/NCT01729754
❑ Clinicaltrials.gov: BI 655066 Proof of Concept Dose Finding Study in AS; https://clinicaltrials.gov/ct2/show/NCT02047110
❑ Clinicaltrials.gov: BI 655066 Dose Ranging in Psoriasis, Active Comparator Ustekinumab; https://clinicaltrials.gov/ct2/show/study/NCT02054481

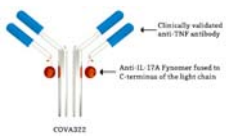
Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Lilly (Indianapolis)	**Ixekizumab** Humanized	IL-17A	• Phase 3 completed in PsO filing planned 2Q2015 • Phase 3 in PsA • Deferred in AS
AstraZeneca/ Valeant (London/Canada)	**Brodalumab** Humanized	IL-17RA	• Phase 3 in PsO; filing planned 4Q2015 • Phase 3 in PsA • Withdrawn in AS

❑ Clinicaltrials.gov: UNCOVER-1 - https://clinicaltrials.gov/ct2/show/NCT01474512; UNCOVER-2 - https://clinicaltrials.gov/ct2/show/NCT01597245; UNCOVER-3: https://clinicaltrials.gov/ct2/show/NCT01646177
❑ Clinicaltrials.gov: Study of Ixekizumab in Participants With Active AS (SPIRIT A1) https://clinicaltrials.gov/ct2/show/NCT01870284
❑ A Study of Ixekizumab (LY2439821) in Participants With Active Psoriatic Arthritis (SPIRIT-P2) https://clinicaltrials.gov/ct2/show/NCT02349295
❑ Clinicaltrials.gov: Study of Efficacy and Safety of Brodalumab Compared With Placebo in Subjects With Axial Spondyloarthritis; https://clinicaltrials.gov/ct2/show/NCT02429882
❑ Ratner M., *Nat Biotechnol* 2014 Jun;32(6):505-7.

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Janssen/ Covagen (New Jersey/Switzerland)	**COVA322** Fully Humanized, Bispecific	TNF/IL-17A	• Phase 1/2 in PsO • Preclinical in PsA • Preclinical in AS
AbbVie (Chicago)	**ABT-122** Fully Humanized, Bispecific	TNF/IL-17A	• Phase 1 completed in RA • Phase 2 in PsA



❑ Gaffen S.L., et al. *Nature Reviews Immunology*. 2014 Sep;14(9):585-600.
❑ Covagen.com: COVA322 overview - http://covagen.com/pipeline/cova322
❑ Clinicaltrials.gov: A Phase 2 Study to Investigate the Safety, Tolerability and Efficacy of ABT-122 in Subjects With Active PsA Who Have an Inadequate Response to MTX; https://clinicaltrials.gov/ct2/show/NCT02349451
❑ Clinicaltrials.gov: Dose Ranging Study Comparing the Efficacy, Safety and Pharmacokinetics of Intravenous Infusions of ABT-874 vs Placebo in Subjects With Active Crohn's Disease https://clinicaltrials.gov/ct2/show/NCT00562887

Newer Treatments Being Developed for SpA

Company	Drug	Drug target	US status
Pfizer (New York)	**Tofacitinib** (Xeljanz)	JAK3	• Phase 3 in PsO completed: FDA approval est. October 2015 • Phase 3 in PsA • Phase 2 completed in AS
Celgene (New Jersey)	**Apremilast** (Otezla)	PDE4	• Approved for PsO • Approved for PsA • Phase 2 AS published; Phase 3 AS ongoing
Bristol-Myers Squibb (New York)	**Abatacept** (Orencia)	Prevents T-cell activation	• Phase 2 published in PsA • Phase 3 in PsA • Ineffective in AS
Alder (Washington State)	**Clazakizumab**	IL-6	• Phase 2 in PsA

- Ratner M., *Nat Biotechnol* 2014 Jun;32(6):505-7. doi: 10.1038/nbt0614-505.
- Song I.H., et al *Ann Rheum Dis.* 2011 Jun;70(6):1108-10.
- Mease P., et al. *Arthritis Rheum.* 2011 Apr;63(4):939-48.
- FitzGerald O. SpA: Apremilast: welcome advance in Rx of PsA. *Nat Rev Rheumatol.* 2014 Jul;10(7):385-6.
- Pathan E. *Ann Rheum Dis.* 2013 Sep 1;72(9):1475-80.
- Clinicaltrials.gov: Efficacy and Safety of Subcutaneous Abatacept in Adults With Active Psoriatic Arthritis (ASTRAEA); https://clinicaltrials.gov/ct2/show/NCT01860976
- Clinicaltrials.gov: Dose-Ranging Study Of Tofacitinib In Adults With Active Ankylosing Spondylitis; https://clinicaltrials.gov/ct2/show/NCT01786668
- Clinicaltrials.gov: Efficacy And Safety Of Tofacitinib In Psoriatic Arthritis: Comparator Study (OPAL BROADEN); https://clinicaltrials.gov/ct2/show/NCT01877668
- Clinicaltrials.gov: Study of Apremilast to Treat Subjects With Active Ankylosing Spondylitis (POSTURE); https://clinicaltrials.gov/ct2/show/NCT01583374
- Alder.com: Pipeline - http://www.alderbio.com/therapeutics/pipeline/

AS / Axial SpA: Associated Manifestations/Comorbidities

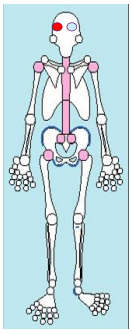
Axial disease
Enthesitis
Peripheral arthritis
Dactylitis

Aberrant Ossification Juxtaposed with Osteopenia/Osteoporosis
19 to 62 %

Acute Anterior Uveitis
25 – 45 %

Skin
Psoriasis & Nail Changes
5 – 16 %

Gut
UC & Crohn 5 – 8 %
(Microscopic lesion 22 – 69 %)



Lung
Restrictive Lung Disease
Apical Fibrocystic Disease 1 – 2%
Obstructive sleep apnea

Heart
Aortic Insufficiency / Heart Block 2 – 3 %
Increased risk CAD as a result of chronic inflammation and inactivity
Hypertension
NSAID induced risks

Kidneys
IgA nephropathy 1 to 2 %
Renal amyloidosis 0.3– 1.2 %
NSAID induced nephropathy

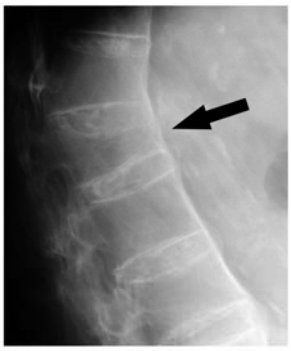
Cauda equina syndrome 0.5 %
Atlantoaxial subluxation

Spinal ankylosis

- *Compression fractures of vertebrae*
- *High risk of post-traumatic **spinal fractures**, even after trivial injury*

Khan MA. Clinical features. Axial SpA book (in press)

Vertebral Fracture (arrow) in Advanced Ankylosis of the Spine with Fusion of the Facet Joints

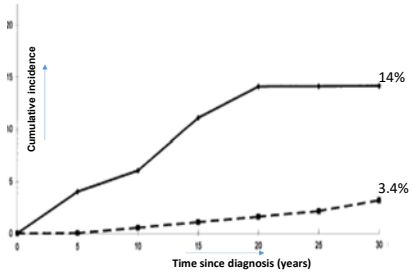


ASAS handbook, Ann Rheum Dis 2009; 68 (Suppl II) (with permission)

Vertebral Compression Fractures

Cumulative incidence over a 30 year period since diagnosis

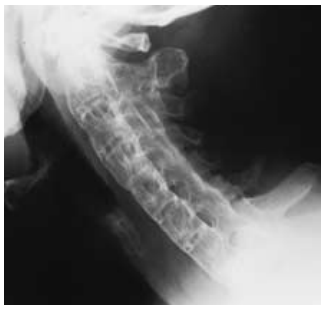
Anterior vertebral wedge compression fractures worsen spinal kyphosis. Occurred in 14% of AS patients versus 3.4% in controls



Bessant R et al. J Rheumatol. 2002; 29(7):1511-9.

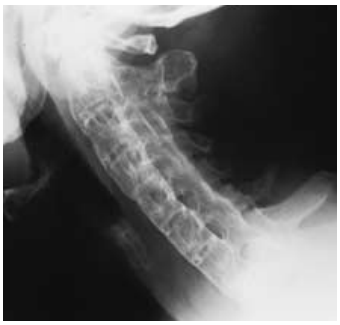
Osteopenia and Osteoporosis Juxtaposed with Osteoproliferation

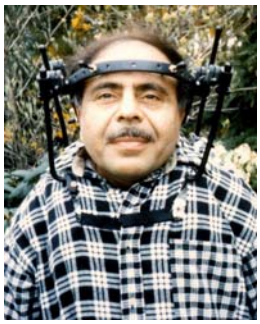
- ❖ Osteopenia or osteoporosis of the spine and hip but not peripheral skeleton.
- ❖ DEXA overestimates bone mineral density when syndesmophytes are present
- ❖ High risk of post-traumatic spinal fractures, even after trivial injury



Magrey M, Khan MA. Osteoporosis in AS. *Curr Rheumatol Report.* 2010; 12: 332-6

Khan MA: Spondyloarthropathies. In: Hunder G (Ed.). ***ATLAS OF RHEUMATOLOGY***. 3rd Edition. Philadelphia, PA: Current Medicine **2002**, pp.141–167.





Khan MA: Spondyloarthropathies. In: Hunder G (Ed.). ***ATLAS OF RHEUMATOLOGY***. 3rd Edition. Philadelphia, PA: Current Medicine **2002**, pp.141–167.

THNAK YOU

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Identify the Key Components in the Pathogenesis of Knee Osteoarthritis: Current Clinical Data and Outcome Associated with the Use of Chondroitin Sulfate and Glucosamine

Marc C. Hochberg, MD

Osteoarthritis: Update 2015

Marc C. Hochberg, MD, MPH
Professor of Medicine and Epidemiology and Public Health, Head, Division of Rheumatology and Clinical Immunology, Vice Chair, Department of Medicine
Baltimore, MD

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

Disclosures

- I receive research support from the National Institutes of Health.
- I serve as a consultant to the following commercial entities:
  - Bioiberica S.A., EMD Serono International S.A., Iroko Pharmaceuticals, Novartis Pharma AG, Pfizer Inc., Rottapharm Biotech, Samumed LLC and Strategic Sciences and Technology.
- I have stock ownership in and serve on the Medical Advisory Board of
  - Theralogix LLC

"Degenerative Joint Disease"

Definition of Osteoarthritis: OARSI Definition (2011)

- OA is a progressive disease representing the failed repair of joint damage that, in the preponderance of cases, has been triggered by abnormal intra-articular stress.
- All of the tissues of the joint are involved, including the articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles and peripheral nerves.
- OA may be initiated by an abnormality in any of these tissues. Thus, OA is not a disease merely of cartilage but is a failure of the synovial joint.

Lane N et al: Osteoarthritis Cart 2011; 19:478-82.

Definition of Osteoarthritis: OARSI Definition (2015)

- Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.

http://oarsi.org/research/standardization-osteoarthritis-definitions.

Construct of OA

- Disease
  - Structural abnormalities visualized on plain radiographs and magnetic resonance images
- Illness
  - Symptom complex including pain (aching, discomfort), stiffness, fatigue and sleep disturbance that results in functional limitation, physical disability and reduced health related quality of life

Lane N et al: Osteoarthritis Cart 2011; 19:478-82.

OA: The Big Picture

- The most common form of arthritis
- Accounts for more functional limitation, work loss and physical disability than any other chronic disease
- Most common indication for total joint arthroplasty
- Costs range from 1-3% of GNP in developed countries
- Associated with increased risk of all-cause and CV-related mortality

OA: Pathophysiology

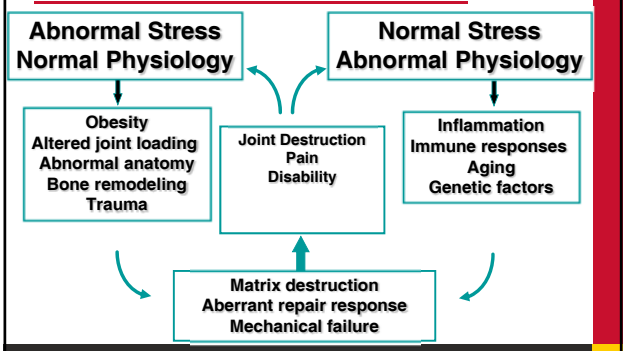
- The etiopathogenesis is complex
  - Changes in bone and cartilage are integral components of the OA process
  - Inflammation plays an important role in the production of symptoms and signs as well as the progression of disease

Pathogenesis

- "OA can be thought of as a mechanically driven but chemically mediated active disease process of joints in which attempted (or aberrant) repair is one of the dominant aspects of the process."
- OA affects all of the tissues of the joint.

Dieppe P. Stepping Away from OA. 1999 NIH Conference

Pathways to Osteoarthritis



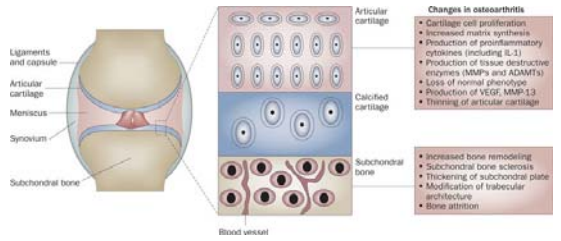
Chondrocytes

- Synthesize and secrete matrix components
  - Collagens (Types II, VI, IX, X, XI)
  - Proteoglycan aggregates
    - Hyaluronan, link and core proteins, KS, CS
  - Other macromolecules
    - COMP, Leucine Rich Repeat Proteins

Chondrocytes

- Synthesize and secrete the substances that degrade the matrix
  - Matrix metalloproteases
    - Aggrecanase, collagenase, stromelysin, gelatinase, etc.
  - Cytokines and other inflammatory mediators
    - IL-1, TNF, COX and LOX products
    - Reactive N and O species

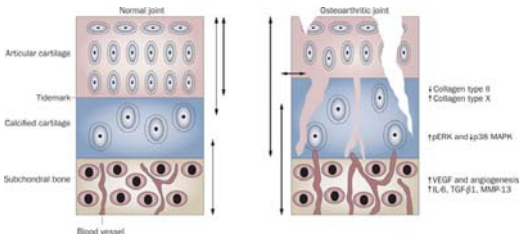
Figure 2 The bone–cartilage unit is at the center of joint function and disease



Lories, R. J. & Luyten, F. P. (2010) The bone–cartilage unit in osteoarthritis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2010.197

nature REVIEWS RHEUMATOLOGY

Figure 3 Complex changes in the bone–cartilage unit increase the flow of fluid and solutes in osteoarthritic joints



Lories, R. J. & Luyten, F. P. (2010) The bone–cartilage unit in osteoarthritis
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2010.197

nature REVIEWS RHEUMATOLOGY

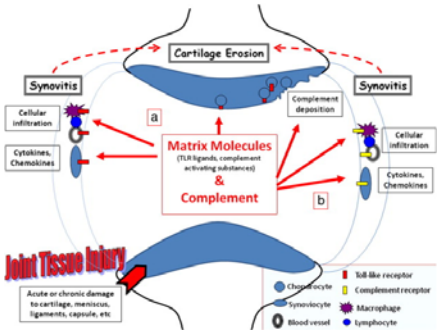
Evidence for Inflammation in OA

- Arthroscopic synovitis near cartilage defects
  - Synovial hyperplasia, increased lining cells
  - Increased expression of IL-1, TNF, COX-2, MMPs
- Synovitis predicts OA progression
- Elevated CRP in progressive OA
- Elevated proinflammatory genes in cartilage and PBMC from patients with OA

Immune-mediated inflammation in OA

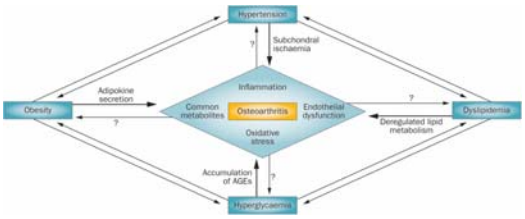
- Innate immune system
  - Toll-like receptors (TLR-2, 4) on chondrocytes
  - Bind fibronectin fragments, crystals, etc.
  - Activation of alternative complement pathway

Immune-mediated inflammation in OA



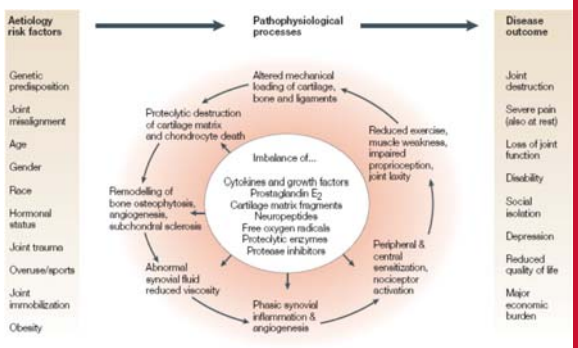
Scanzello CR, Goldring SR: Bone 2012;51:249-57.

Relationship of OA to Metabolic Syndrome



Zhuo Q, et al: Nat Rev Rheumatol 2012 Dec;8(12):729-37.

Many Facets of Osteoarthritis



Wieland HA, et al. *Nat Rev Drug Dis*. 2005;4:331–344

OA: Management 2015

- There is no known cure for OA
- Current treatment goals are focused on
  - Reducing pain
  - Maintaining or improving joint mobility
  - Limiting functional impairment
  - Improving health-related quality of life
- Future treatment goals include development of targeted therapies to prevent structural progression
- Total joint arthroplasty is cost-effective for patients with end-stage hip or knee OA

Management of OA

- "If there is an illness for which people offer many remedies, you may be sure that particular illness is incurable, …"
  - Leonid Andreevich Gayev, The Cherry Orchard, Anton Checkov

Multidisciplinary Approach

- Nonpharmacologic
  - Self-management programs
  - Referral to PT
  - Regular exercise
    - Aerobic, aquatic, resistance
  - Weight loss, if overweight
  - Walking aids
  - Thermal modalities
  - Patellar taping
  - Tai Chi
  - Bracing
  - Appropriate footwear
  - TENS/TESA
  - Acupuncture
- Pharmacologic
  - Acetaminophen
  - Nutriceuticals
  - NSAIDs, including COX-2 selective inhibitors
  - Topical agents
    - Capsaicin, lidocaine and NSAIDs
  - Intra-articular therapies
    - Glucocorticoids
    - Hyaluronates
    - PRP (unapproved)
  - Centrally acting agents
    - Duloxetine
  - Opioid analgesics
    - Tramadol

Chronic OA Management Initiative (COAMI) of US BJI

- Objective: To critically review existing OA management guidelines
- Methods: Systematic review of MEDLINE and AHRQ Clearinghouse from 1/1/2000 – 4/1/2013
- Results: 188 articles reviewed of which 16 were included in final review
- Conclusions: Relative agreement on many OA management recommendations across organizations

Nelson AE, et al: Semin Arthritis Rheum 2014;43(6):701-12.

Major Areas of Controversy

- SySADOAs (Nutraceuticals)
  - Glucosamine hydrochloride or sulfate
  - Chondroitin sulfate
- NSAIDs and COX-2 selective inhibitors
  - Absolute vs relative contraindications
- Intra-articular hyaluronate injections
- Acupuncture
- Disease modifying OA drugs (DMOADs)

Glucosamine and Chondroitin SO_4

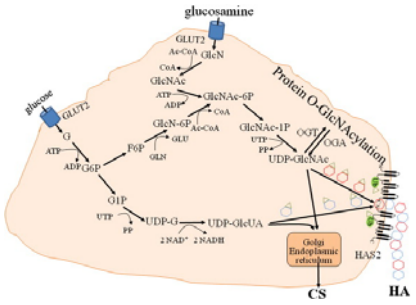
ACR	Conditionally not recommended as these are only available as non-FDA approved "nutriceuticals" in the U.S.
EULAR (2003)	There is growing evidence to support the use of both of these agents for their symptomatic effects
OARSI	Uncertain for symptomatic relief; not appropriate for structure modification
NICE	Do not offer glucosamine or chondroitin products

Glucosamine and Chondroitin Sulfate: Mechanisms of Action

- Anti-inflammatory effects via inhibition of NF-κB nuclear translocation
- Increase in HA synthesis via upregulation of HA synthase

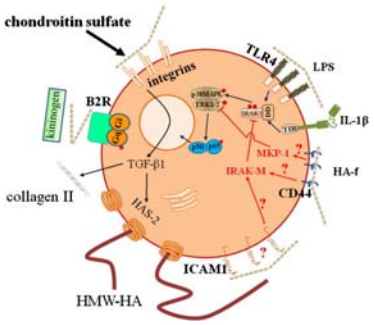
Du Souich P: Pharmacol Ther 2014;142:362-74.

Transmembrane transport of Glucosamine



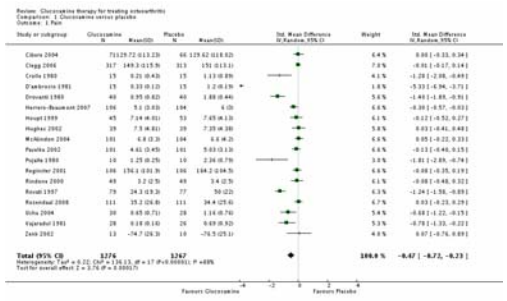
Du Souich P: Pharmacol Ther 2014;142:362-74.

CS: Proposed Mechanism of Action



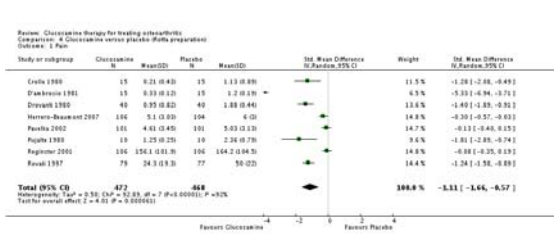
Du Souich P: Pharmacol Ther 2014;142:362-74.

Glucosamine for OA: Cochrane Review



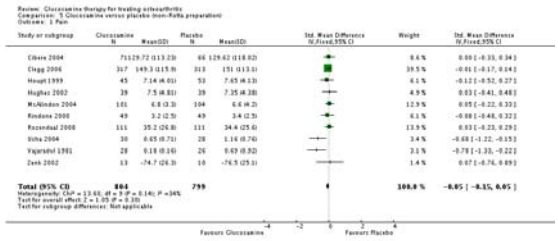
Towheed T, et al: Cochrane Database Syst Rev 2005;2:CD002946.

Glucosamine for OA: Crystalline Glucosamine SO_4



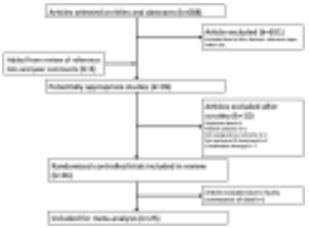
Towheed T, et al: Cochrane Database Syst Rev 2005;2:CD002946.

Glucosamine for OA: Glucosamine HCl



Towheed T, et al: Cochrane Database Syst Rev 2005;2:CD002946.

Glucosamine for OA: Meta-analysis



- Systematic review of PBO-controlled RCTs
  - 2 reviewers evaluated reports individually; disagreements resolved by consensus
- Stratified meta-analysis
  - Glucosamine brand
  - Overall risk of bias
  - Chemical structure
  - Industry funding

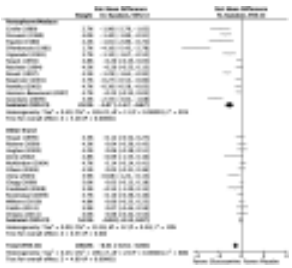
Eriksen P, et al: Arthritis Care Res 2014;66:1844-55.

Glucosamine for OA: Potential Risk of Bias

- Overall effect
  - Fixed Effect 0.23 (0.17, 0.30)
  - Random Effect 0.51 (0.30, 0.73)
- Asymmetry of funnel plot suggests potential for bias due to poor quality small studies

Eriksen P, et al: Arthritis Care Res 2014;66:1844-55.

Glucosamine for OA: Meta-analysis stratified on brand



- 25 studies included 3,458 patients
- 12 studies used $GluSO_4$
  - 11 affiliated with or funded by Rottapharm
- Overall risk of bias
  - High 10
  - Low 8
  - Unclear 7

Eriksen P, et al: Arthritis Care Res 2014;66:1844-55.

Glucosamine for OA: Results of Stratified Meta-regression

Variable	Trials (No.)	Effect Size	95% CI	P value
Overall	25	0.58	0.26, 0.90	
Brand				0.0003
Rottapharm	12	1.05	0.68, 1.43	
Other	13	0.11	-0.24, 0.46	
Risk of bias				0.004
Low	8	0.09	-0.36, 0.54	
Unclear	7	0.39	-0.12, 0.90	
High	10	1.14	0.69, 1.59	
Analysis of low-bias studies				0.0023
Rottapharm	3	0.27	0.12, 0.43	
Other	5	-0.02	-0.12, 0.08	

Eriksen P, et al: Arthritis Care Res 2014;66:1844-55.

Glucosamine for OA

- Glucosamine produced an overall statistically significant reduction of pain in RCTs
  - Overall effect size moderate (0.51)
  - Large heterogeneity predominantly due to product used (41% of heterogeneity) and risk of bias (32% of heterogeneity)
- Small significant effect of Rottapharm product in sensitivity analysis of low risk of bias studies
  - Single daily dose of 1500 mg

Eriksen P, et al: Arthritis Care Res 2014;66:1844-55.

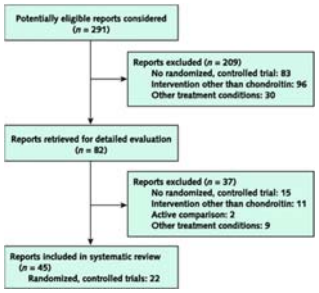
Glucosamine: Summary

- Preponderance of evidence indicates that crystalline glucosamine sulfate manufactured by Rottapharm is associated with significant efficacy compared to placebo in patients with knee OA
- Incidence of adverse events is similar to that seen with placebo and significantly lower than with NSAIDs
- Results support role in ESCEO algorithm for treatment of patients with knee OA

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Meta-analysis: Chondroitin for Osteoarthritis of the Knee or Hip

Ann Intern Med. 2007;146(8):580-590. doi:10.7326/0003-4819-146-8-200704170-00009



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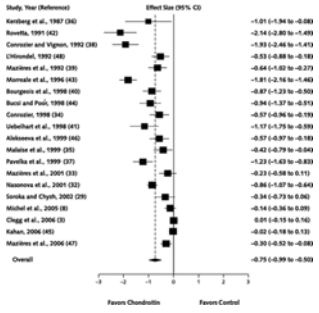
From: Meta-analysis: Chondroitin for Osteoarthritis of the Knee or Hip

Forest plot of 20 trials comparing chondroitin with control. I^2 = 92% (P < 0.001). The size of the boxes is proportional to the random-effects weights used in the meta-analysis.

Ann Intern Med. 2007;146(8):580-590. doi:10.7326/0003-4819-146-8-200704170-00009



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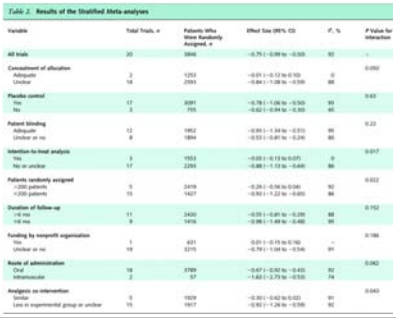
Results of the Stratified Meta-analyses

Ann Intern Med. 2007;146(8):580-590. doi:10.7326/0003-4819-146-8-200704170-00009



Chondroitin SO_4: Summary

- Preponderance of evidence indicates that chondroitin SO_4 alone is not associated with significant efficacy compared to placebo in patients with knee OA; however, fixed-dose combination with glucosamine is of benefit in patients with moderate-to-severe pain.
- Incidence of adverse events is similar to that seen with placebo and significantly lower than with NSAIDs.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Analgesic, anti-inflammatory and antipyretic agents that act by inhibiting prostaglandin H synthase (aka cyclo-oxygenase [COX]-1 and COX-2 enzymes)
- Two broad categories
  - Traditional, non-selective NSAIDs
  - COX-2 selective inhibitors

Day RO & Graham GG: BMJ 2013;346:f3195.

FDA Approved Indications

- Acute pain and dysmenorrhea
- Acute gout
- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Chronic low back pain
- Juvenile rheumatoid arthritis

Adverse Events

- Common
  - Gastrointestinal
  - Cardiovascular
  - Renovascular
  - Aspirin-induced asthma
- Rare
  - Hepatotoxicity
  - Aseptic meningitis
  - Stevens-Johnson syndrome
  - Pregnancy-related
    - 1st trimester abortion
    - Premature closure of PDA

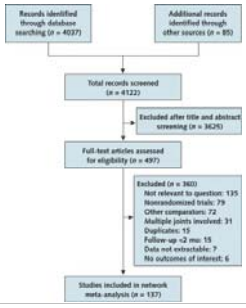
NSAID Utilization
June 2014-May 2015 (IMS Health)

Drug	New Prescriptions (millions)	Total Prescriptions (millions)
Ibuprofen	29.01	36.41
Meloxicam	14.92	27.26
Naproxen	14.15	19.32
Celecoxib	4.35	8.68
Diclofenac	4.89	8.13

Annals of Internal Medicine

Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis:

A Systematic Review and Network Meta-analysis

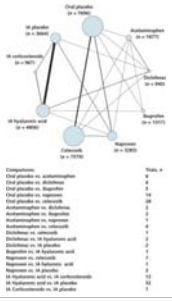


Bannuru RR, et al: Ann Intern Med 2015;162:46-54.

Annals of Internal Medicine

Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis:

A Systematic Review and Network Meta-analysis



Bannuru RR, et al: Ann Intern Med 2015;162:46-54.

Results

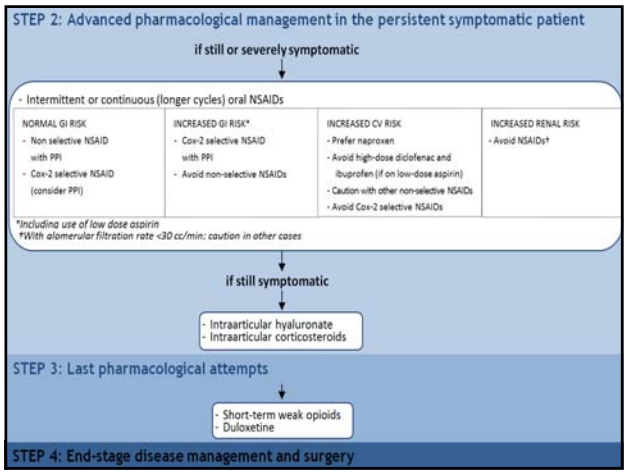
- 129 RCTs contributed to analysis of pain-related outcomes
- All interventions significantly better than oral placebo
- All interventions except celecoxib significantly better than ACT
- Similar results for function and stiffness

Treatment	ES (95% CI)
Acetaminophen	0.18 (0.04, 0.33)
IA Placebo	0.29 (0.04, 0.54)
Celecoxib	0.33 (0.25, 0.42)
Naproxen	0.38 (0.27, 0.49)
Ibuprofen	0.44 (0.25, 0.63)
Diclofenac	0.52 (0.34, 0.69)
IA Corticosteroids	0.61 (0.32, 0.89)
IA Hyaluronates	0.63 (0.39, 0.88)

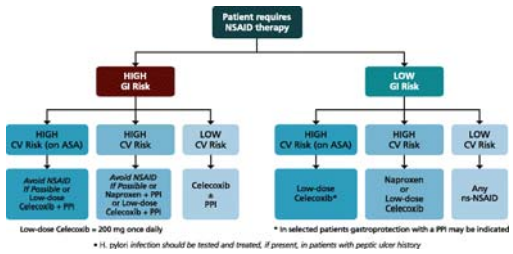
Bannuru RR, et al: Ann Intern Med 2015;162:46-54.

Clinical Decision Making

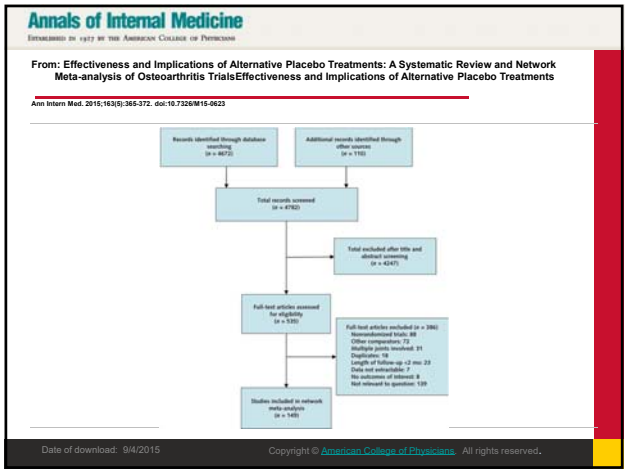
- Patient's underlying risk of CV and GI events
  - Type of arthritis, prevalent CV and GID, risk factors for CV and GID, use of LDA or other antiplatelet agents and/or glucocorticoids
- Type and dose of NSAID to be used
  - Coxib vs. nonselective NSAID
- Level of evidence
  - Beyond a reasonable doubt
  - Preponderance of the evidence



Consensus algorithm for Long-term NSAID Use in Patients with OA



Scarpignato C, et al: BMC Medicine 2015;13:55.



Annals of Internal Medicine

From: Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis TrialsEffectiveness and Implications of Alternative Placebo Treatments

Ann Intern Med. 2015;163(5):365-372. doi:10.7326/M15-0623

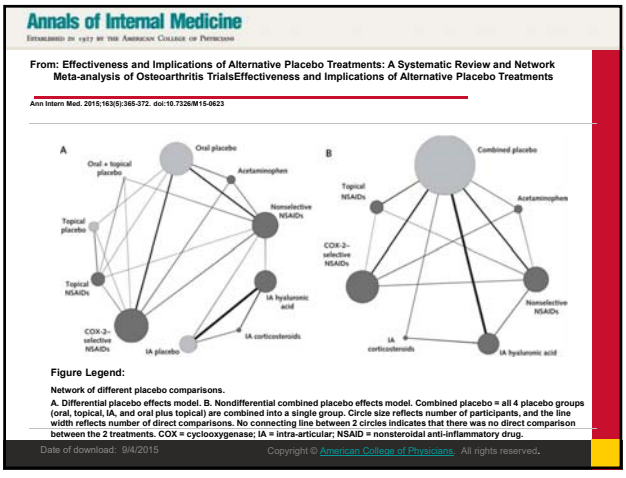


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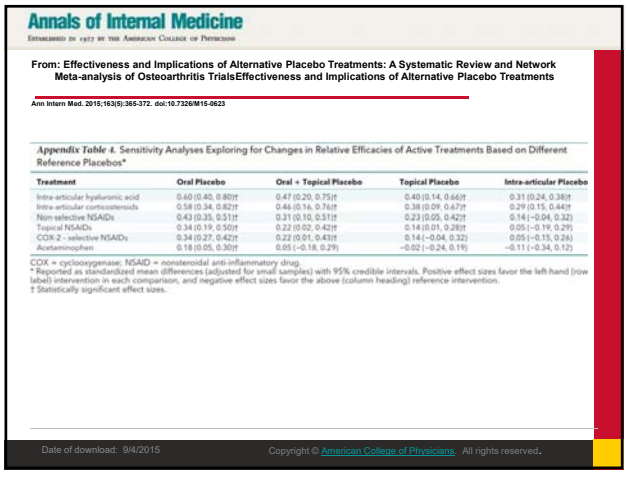
Figure Legend:

Network of different placebo comparisons.

A. Differential placebo effects model. B. Nondifferential combined placebo effects model. Combined placebo = all 4 placebo groups (oral, topical, IA, and oral plus topical) are combined into a single group. Circle size reflects number of participants, and the line width reflects number of direct comparisons. No connecting line between 2 circles indicates that there was no direct comparison between the 2 treatments. COX = cyclooxygenase; IA = intra-articular; NSAID = nonsteroidal anti-inflammatory drug.



Annals of Internal Medicine

From: Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis TrialsEffectiveness and Implications of Alternative Placebo Treatments

Ann Intern Med. 2015;163(5):365-372. doi:10.7326/M15-0623

Appendix Table 4. Sensitivity Analyses Exploring for Changes in Relative Efficacies of Active Treatments Based on Different Reference Placebos*

Treatment	Oral Placebo	Oral + Topical Placebo	Topical Placebo	Intra-articular Placebo
Intra-articular hyaluronic acid	0.60 (0.40, 0.80)†	0.47 (0.20, 0.75)†	0.40 (0.14, 0.66)†	0.31 (0.24, 0.38)†
Intra-articular corticosteroids	0.58 (0.34, 0.82)†	0.46 (0.16, 0.76)†	0.38 (0.09, 0.67)†	0.29 (0.15, 0.44)†
Non-selective NSAIDs	0.43 (0.35, 0.51)†	0.31 (0.10, 0.51)†	0.23 (0.05, 0.42)†	0.14 (−0.04, 0.32)
Topical NSAIDs	0.34 (0.19, 0.50)†	0.22 (0.02, 0.42)†	0.14 (0.01, 0.28)†	0.05 (−0.19, 0.29)
COX-2 - selective NSAIDs	0.34 (0.27, 0.42)†	0.22 (0.01, 0.43)†	0.14 (−0.04, 0.32)	0.05 (−0.15, 0.26)
Acetaminophen	0.18 (0.05, 0.30)†	0.05 (−0.18, 0.29)	−0.02 (−0.24, 0.19)	−0.11 (−0.34, 0.12)

COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug.
* Reported as standardized mean differences (adjusted for small samples) with 95% credible intervals. Positive effect sizes favor the left-hand (row label) intervention in each comparison, and negative effect sizes favor the above (column heading) reference intervention.
† Statistically significant effect sizes.

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Established in 1927 by the American College of Physicians

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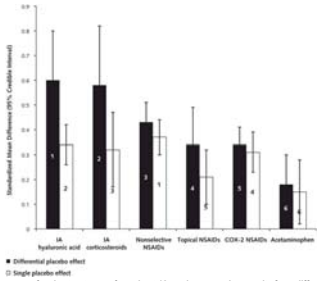


Standardized mean differences of active treatments for pain at 12 weeks comparing results from differential and nondifferential placebo effect network models.
COX = cyclooxygenase; IA = intra-articular; NSAID = nonsteroidal anti-inflammatory drug.

Thank you for your attention

Neurobiology of Central Sensitization in Conditions Such as Rheumatoid arthritis, Osteoarthritis and Ankylosing Spondylitis – How it Influences Standard Outcome Measures?

Philip J. Mease, MD

The Role of Central Sensitization in Chronic Rheumatic Diseases and How it May Influence Assessment of Disease Severity

Philip Mease MD
Director, Rheumatology Research, Swedish Medical Center
Clinical Professor, University of Washington School of Medicine
Seattle, WA

Disclosures/Acknowledgements

- Research grants, consultation, and/or speaking
  - Abbvie, Amgen, BMS, Celgene, Cresendo Bioscience, Genentech, Lilly, Merck, Novartis, Pfizer, UCB
- Acknowledgements for Concept Develolpment
  - Dan Clauw, Roland Staud, Don Goldenberg

What pain (and fatigue, dyscognition, sleep and mood disorder) are we treating when we treat rheumatic diseases?

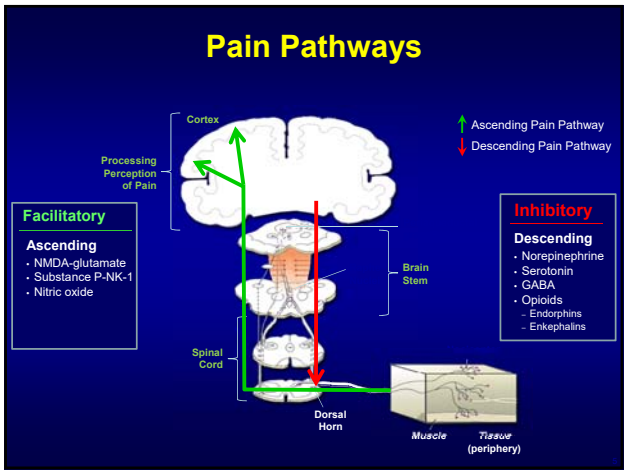
- **If centrally acting pharmacologic agents, devices, or non-pharmaceutical methods are effective in improving pain, function, and patient global in conditions such as OA, CLBP, RA, SLE, AS/AxSpA etc. are we treating**
  - **Primary disease generated central pain?**
  - **Primary disease + FM centrally generated pain?**
  - **Primary disease + FM + mood disorder centrally generated pain?**
- **Is it appropriate to move beyond the "F" word and instead use terminology such as "central pain" or "central sensitization syndrome"?**

"Central Sensitization" (aka Fibromyalgia) as a Co-Morbid Condition in Rheumatic Disease

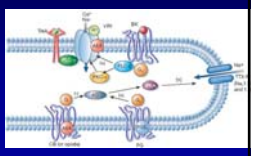
Comorbid Condition	Author	Prevalence of Fibromyalgia (%)
SLE	Ostuni, et al Valencia-Flores, et al Grafe, et al Neumann, Buskila	1 10 30 65
RA	Wolfe, Michaud	17
Sjogren's	Bonafede, et al	50
OA	Wolfe, Cathey	6.7
Spondyloarthritis	Wallis D Aloush V	6 (AS) 14 (nr-AxSpA) 50 (Fem AS)

Weir PT, et al. *J Clin Rheumatol*. 2006;12:124-128.
Wallis D, et al. J Rheum. 2013. 40:2038-2041
Aloush V, et al. Rheumatol Int 2007; 27:865-8

Pain Pathways



Peripheral Pain Processing



Transduction
TPRV1, TRPV2, TRPV3, TRPM8
ASIC, DRASIC
MDEG, TREK-1
BK1, BK2
P2X3

Peripheral Sensitization
NGF, TrKA
TRPV1
Nav1.8
PKA, PKC, CaMK IV
Erk1/2, p38, JNK
IL-1, cPLA2, COX2, EP1, EP3, EP4

Membrane Excitability of Primary Afferents
Nav1.8, Nav1.9
K^+ channel

Synaptic Transmission
VGCC
Adenosine-R
mGlu-R

Slide courtesy of Roland Staud MD
Mease P. Neurobiology of Pain in Osteoarthritis. Oxford Textbook of Osteoarthritis. 2015

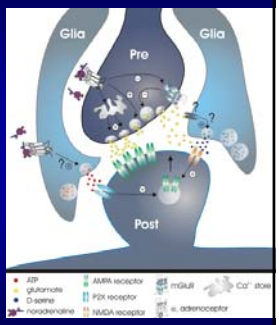
Central Pain Processing

Synaptic Transmission
AMPA/Kainate-R, NMDA-R, mGlu-R
NK1
Nav1.3
K^+ channels

Central Inhibition
GABA, $GABA_A$-R, $GABA_B$-R
Glycine-R
NE, 5-HT
Opioid receptors
CB1

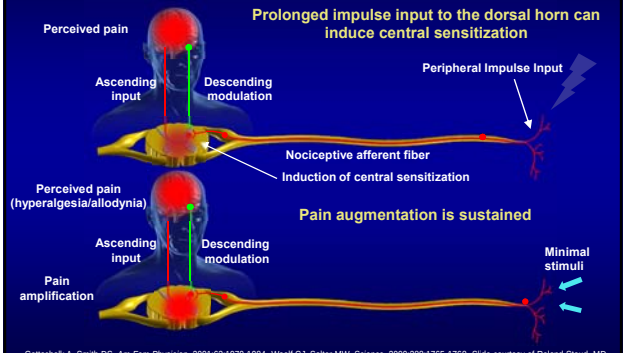
Signal Transduction
PKA, PKC isoforms
MAPK, p38, JNK

Gene Expression
cFos, cJun, CREB
DREAM, COMT alleles



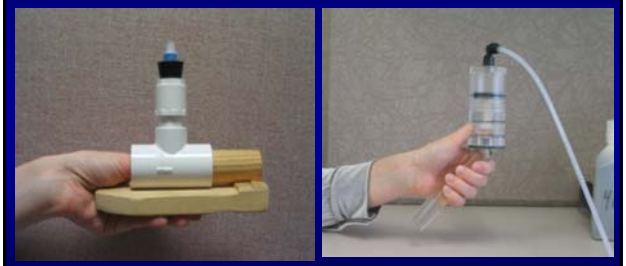
Slide courtesy of Roland Staud MD
Mease P. Neurobiology of Pain in Osteoarthritis. Oxford Textbook of Osteoarthritis. 2015

Mechanisms of Central Sensitization



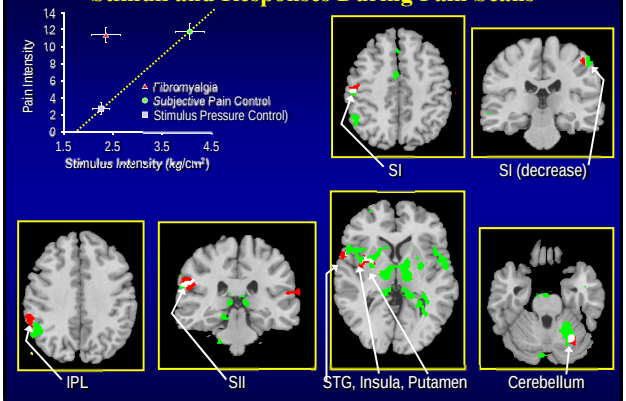
Gottschalk A, Smith DS. *Am Fam Physician*. 2001;63:1979-1984. Woolf CJ, Salter MW. *Science*. 2000;288:1765-1768. Slide courtesy of Roland Staud MD

Experimental Methodology: Induction of Pressure Stimuli



Gracely R, et al. *Arthritis Rheum*. 2002;46:1333-1343.

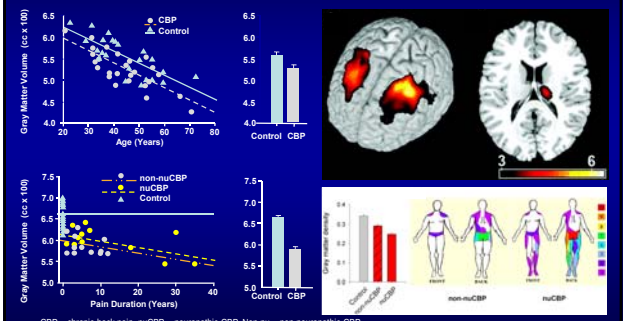
Stimuli and Responses During Pain Scans



STG=superior temporal gyri, SI=primary somatosensory cortex, SII=secondary somatosensory cortex, IPL=inferior parietal lobule.

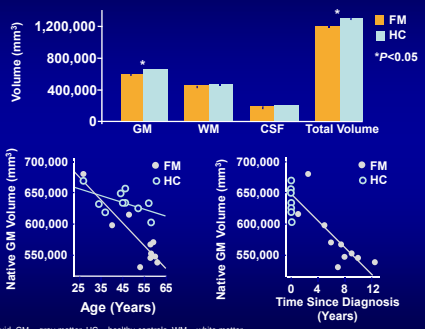
Gracely. *Arthritis Rheum*. 2002;46:1333-1343.

Gray Matter Volume After Long-term Back Pain



CBP = chronic back pain. nuCBP = neuropathic CBP. Non-nu = non-neuropathic CBP.
Apkarian AV, et al. *Eur J Pain*. 2005;9:463-484.

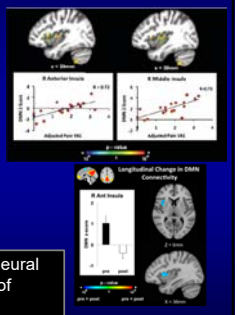
Brain Gray/White Matter in Fibromyalgia and Healthy Controls



CSF = cerebrospinal fluid. GM = gray matter. HC = healthy controls. WM = white matter.
Kuchinad A, et al. *J Neurosci*. 2007;27:4004-4007.

Intrinsic brain connectivity in FM associated with chronic pain intensity and decreases with effective treatment of pain

- Intrinsic, resting-state connectivity in default mode network (DMN) and executive attention network (EAN), and their connection to insula associated with increased spontaneous pain in fibromyalgia (FM) compared to controls
- Effective pain treatment in FM is associated with a decrease in connectivity in these networks compared to controls



Evidence of increased intrinsic, resting-state neural activity in key brain networks supports theory of increased central sensitization in FM

Napadow V, et al. Arthritis Rheum. 2011;62:2545-55.
Napadow V, et al. Arthritis Rheum. Jan 2012.

Terminology

"Central pain"
"Central sensitization syndrome"
"Central sensitivity syndrome"
"Chronic widespread pain"
"Fibromyalgia"

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain

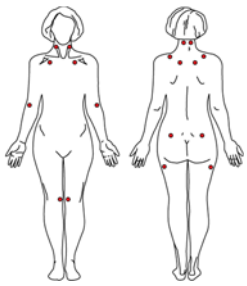
Peripheral ⟷ Centralized

Acute pain
Osteoarthritis
RA
Ehler's Danlos
Low back pain
IBS
Fibromyalgia
Tension HA

Slide courtesy of Dan Clauw

American College of Rheumatology (ACR) Classification Criteria for FM

- ACR criteria
  - History of chronic widespread pain ≥3 months
  - Patients must exhibit ≥11 of 18 tender points
- Inclusion of other symptoms did not improve the accuracy of the criteria
- No exclusions for other diseases, or abnormal laboratory / radiographic findings



ACR criteria are both sensitive (88.4%) and specific (81.1%)

Wolfe et al. *Arthritis Rheum.* 1990;33:160-172.

The Tender Point Exam

Photo courtesy of Rick Gracely and Dan Buskila

Arthritis Care & Research
Vol. 62, No. 5, May 2010, pp 600–610
DOI 10.1002/acr.20140
© 2010, American College of Rheumatology

ORIGINAL ARTICLE

The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity

FREDERICK WOLFE,[1] DANIEL J. CLAUW,[2] MARY-ANN FITZCHARLES,[3] DON L. GOLDENBERG,[4] ROBERT S. KATZ,[5] PHILIP MEASE,[6] ANTHONY S. RUSSELL,[7] I. JON RUSSELL,[8] JOHN B. WINFIELD,[9] AND MUHAMMAD B. YUNUS[10]

Wolfe F et al. *Arthritis Care Res.* 2010;62(5):600-610.

2010 ACR Preliminary FDC

FDC composed of

1) Widespread Pain Index (WPI)

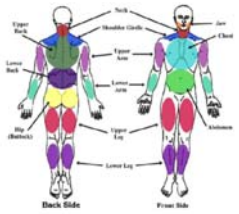
Establishes presence/absence of pain in up to 19 body areas

2) Symptom Severity Scale (SS)

Grading of 3 additional symptom domains: fatigue, sleep, and cognition. Grading of overall symptom burden of additional clinical features

1) Widespread pain index (WPI): note the number of areas in which the patient has had pain over the last week. Score 0-19

Shoulder girdle, left Shoulder girdle, right Upper arm, left Upper arm, right Lower arm, left Lower arm, right	Hip (buttock, trochanter), left Hip (buttock, trochanter), right Upper leg, left Upper leg, right Lower leg, left Lower leg, right	Jaw, left Jaw, right Chest Abdomen	Upper back Lower back Neck



Wolfe F, et al. Arth Care Res 2010;62:600-610

2010 ACR Preliminary FDC (cont)

2) Symptom severity (SS) scale:

3 items: Fatigue, waking unrefreshed, and cognitive dysfunction

Graded 0-3 in severity over past week

1 item: Somatic symptoms in general*

Graded 0-3 in number of symptoms present

Score 0-12

FM diagnostic criteria achieved if the following 3 conditions are met:

- Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.
- Symptoms have been present at a similar level for at least 3 months.
- The patient does not have other pain disorder which can explain chronic widespread pain (CWP) (nb. does not exclude other pain/rheumatic disorders which do not account for CWP)

*Muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Wolfe F, et al. Arth Care Res 2010;62:600-610

It's everywhere we look . . .

- Interstitial cystitis/chronic prostatitis
- Irritable bowel syndrome
- Post-deployment syndromes including mild traumatic brain injury
- Osteoarthritis
- Low back pain
- Chronic pelvic pain, endometriosis
- Temporomandibular joint disorder
- Perioperative setting
- Rheumatoid arthritis
- Lupus
- Spondyloarthritis
- Crohn's disease
- Hepatitis C
- Lyme disease
- Cancer pain
- Vulvodynia
- "Irritable Eye Syndrome"
- Sickle Cell Disease
- Ehler's Danlos Syndrome

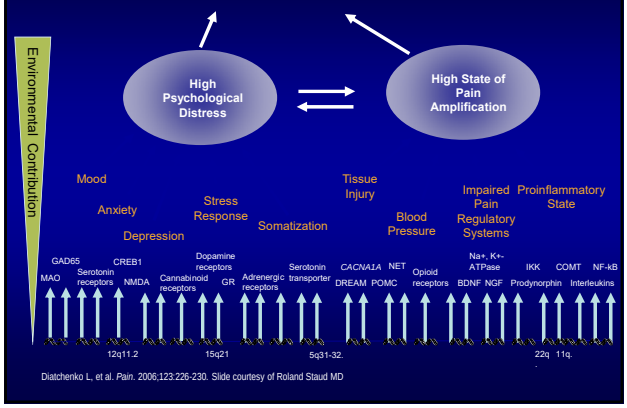
Slide courtesy of Dan Clauw

Fibromyalgia Pathophysiology: Multifactorial Origin

Mechanism	Description
Genetic factors[1,2,3,4]	• Strong familial predisposition: odds ratio (OR) for first-degree relatives to develop fibromyalgia: >8 • Genes that may be involved: Serotonin transporter, Dopamine D receptor, COMT (catecholamine o-methyl transferase)
Central pain amplification[5,6,7]	Due to: • Decreased descending analgesic activity • Central sensitization
Psychiatric comorbid conditions	May predispose to the development of FM: depression, anxiety, posttraumatic stress, and somatization
Other factors	• Role of neurohormones: dopamine, growth hormone deficiency • Sleep dysregulation

1. Arnold et al. Arthritis Rheum. 2004;50:944-952; 2.Offenbaecher et al. Arthritis Rheum. 1999;42:2482-2488; 3. Buskila et al. Mol Psychiatry. 2004;9:73; 4. Gursoy et al. Rheumatol Int. 2003;23:104-107; 5. Staud R. Arthritis Res Ther.2006;8:208; 6. Staud R. Rheum Dis Clin NA. 2009;35:263-274 ; 7. Ablin K, et al. Rheum Dis Clin NA. 2009;35:233-251

Persistent Pain Conditions



Diatchenko L, et al. Pain. 2006;123:226-230. Slide courtesy of Roland Staud MD

The Catecholamine-O-transferase (COMT) Story

- Breaks down catecholamines and is inducible by estrogen
- Met-val SNP first shown to be associated with human pain sensitivity in normals by Zubieta
- Maixner, Diatchenko did series of studies showing that COMT haplotype was associated with:
  - Risk of developing temporomandibular disorder
  - Sensitivity to experimental pain
- Has subsequently been shown to be associated with increased pain, especially in females, in:
  - Osteoarthritis
  - Dyspepsia
  - Shoulder pain
- Responsiveness of acute pain to opioids, depression to duloxetine, and beta-blockers to TMJD

Diatchenko et. al. HumMolGenet. 2005;14(1):135-43 Slide courtesy of Dan Clauw MD

Clinical Features Suggesting Development of Central Sensitization

- Distribution – nonanatomical
- Symptoms – not consistent with physical exam
- Investigations – do not explain pain
- Systemic symptoms
  - Sleep – nonrestorative
  - Psyche – mood disorder
  - Fatigue – unexplained
  - Cognitive – memory and concentration
  - Sensitivity – light, sound, perfumes, and cold
- Behavior – fear of activity
- History – migraine, IBS, depression, abuse
- Examination – hyperalgesia, allodynia

Rheumatoid Arthritis

Rheumatoid Arthritis and Chronic Widespread Pain

- RA patients with CWP incur $3580 more in healthcare costs than those without CWP[1]
- RA patients have lower pain thresholds than controls[2]
- RA patients manifesting similar disease activity have large differences in pain severity[3]
- There is often little correlation of CRP and ESR with pain[4]

CRP = c-reactive protein. ESR = erythrocyte sedimentation rate. RA = rheumatoid arthritis.
1. Wolfe F, Michaud K. *J Rheumatol*. 2004;31:695-700. 2. Leffler AS, et al. *Eur J Pain*. 2002;6:161-176. 3. Heiberg T, et al. *Ann Rheum Dis*. 2005;64:191-195. 4. Konttinen YT, et al. *J Rheumatol*. 1992;19:851-855.

Rheumatoid Arthritis and Allodynia

- In patients with RA <1 year and >5 years duration, allodynia was present over painful joint
  - But in patients with RA >5 years only, allodynia was present in nonpainful thigh, indicating altered central pain processing[1]
- Patients with RA injected with capsaicin had contralateral allodynia (as did controls);[2] related to RA symmetry?
- Patients with RA displayed general hyperalgesia to mechanical and thermal stimuli across several body sites
  - Patients with RA tended to show elevations in serum IL-6 and demonstrated enhanced pain reactivity of serum levels of TNF-α compared with the healthy controls ($P<0.05$)[3]

IL = interleukin. TNF-α = tumor necrosis factor-α.
1. Leffler AS, et al. *Eur J Pain*. 2002;6:161-176. 2. Shenker NG, et al. *Rheumatology (Oxford)*. 2008;47:1417-1421. 3. Edwards RR, et al. *Arthritis Res Ther*. 2009;11:R61.

Disease activity in RA and FM

Objective:
- Does FM impact disease activity indices in RA?

Methods:
- 120 RA pts assessed for FM using ACR 1990 criteria
- Evaluated RA disease activity and functional disability

Results:
- 25 (20.8%) had FM (RA/F)
- No difference in sociodemographics, inflammatory markers, RF, or ACPA
- TJC and Pt global health VAS contributed most to disease activity differences between RA and RA/F
- MD global health VAS also higher in pts with RA/F

Composite indices		
	RA/F n=25	RA n=90
DAS-28	5.35	3.67
SDAI	31.8	13.5
CDAI	29.6	11.8
HAQ	1.83	0.87

*P = 0.001 for all differences

In pts with both RA and FM, disease activity indices may be influenced by an individual patient's pain and negative global perception

Toms J, et al. EULAR 2012, Berlin, THU0344

BRASS

Vectra® DA Scores were Similar in RA Patients with or without Fibromyalgia

- DAS28-CRP and Patient Global Assessment were statistically significantly different between the RA + FM and RA alone groups

	RA + FM (N=25)	RA alone (N=173)	P-value
Vectra DA	**33**	**32**	0.65
DAS28-CRP	3.59	2.80	<0.01
Patient global assessment*	**50**	**15**	<0.001
TJC	6.6	4.0	0.06
SJC	3.8	2.5	0.32
CRP mg/dL*	0.2	0.16	0.83

*Values are means except for patient global assessment and CRP, which are medians. P-values were by t-test, except for patient global assessment and CRP, which were by Wilcoxon rank-sum test.

Lee, YC. et al, EULAR 2013, poster # SAT0099

Spondyloarthritis

Observed Differences between Men and Women with Axial SpA

- Women tend to have a delayed diagnosis
- Evidence for increased symptom severity scores in women as compared to men
- Women generally with less radiographic damage and slower progression of damage in the axial skeleton compared to men, even with comparable (or higher) symptom severity scores.
- Women have lower inflammatory markers despite comparable (or higher) symptom severity scores.
- Differences between men and women have also been observed in regards to treatment response, with poorer response to treatment noted in women.
- Women with AxSpA may also have concomitant "fibromyalgia" (aka central pain) partially accounting for increased symptom severity

Van der Linden SM, et al. Arth&Rheum. 1984;27:241-249; Feldtkeller E, et al. Curr Opinion Rheum. 2000;12:239-47; Lee W, et al. Ann Rheum Dis. 2007. 66:633-638; Ortega CR, et al. Rheum Clin. 2013. 9:221-225; Rudwaleit M, et al. Arth Rheum. 2009. 60:717-727; Tournade A, et al. Arth Care & Research. 2013. 65:1482-1489; Roussou E, Sultana S. Clin Rheumatol 2011; 30: 121-127; Wu Q. Arth Rheum. 2013. 65:1494-1503; Aloush V, et al. Rheumatol Int 2007; 27:865-8; Wallis D. J Rheum. 2013. 40:2038-2041; Van der Horst-Bruinsma IE, et al. Ann Rheum Dis. 2013;72:1221-1224

The Role of Central Pain in AS

- 17 AS patients with mean painDETECT score of 15.1
  - 11 scored >12, corresponding to high probability of central pain
- These patients had areas of cortical thinning on MRI similar to that seen in other chronic pain condition studies
- painDETECT scores correlated with cortical thinning in select pain processing, sensorimotor, and mood brain areas

AS patients experience a central pain component similar to that in other chronic pain conditions

Wu Q. Arth Rheum. 2013. 65:1494-1503

AS and Fibromyalgia

- 2007 study from Tel Aviv: comparison of 18 women vs 18 men with *established* AS.
  - At baseline, both groups had equal bilateral SI joint involvement and equal amount of peripheral arthritis. They had similar ESR levels and similar proportions treated with NSAIDs and DMARDs.
  - Both groups had similar findings on exam of occiput-wall distance, chest expansion, lateral spinal flexion, cervical rotation, intermalleolar distance and Schober's.
  - The two groups differed in that women were older with longer duration of symptoms and delayed time to diagnosis (9.9 vs 4.1 years).
  - Women had more FM tender points and enthesitis.
- 50% of the women but none of the men had a concurrent diagnosis of FM.

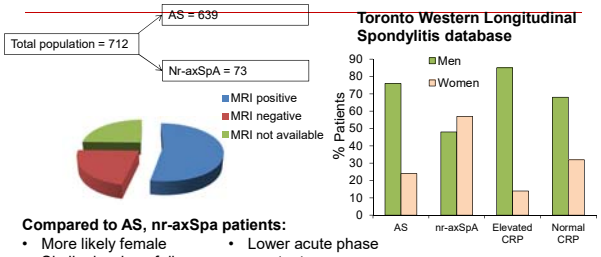
Aloush V, et al. Rheumatol Int 2007; 27:865-8

SpA and Fibromyalgia

- In this study 61% of men but only 5.5% of women were on a TNF agent, despite equivalent exam and imaging findings, and despite higher symptom scores in women.
  - Is there a prescribing bias related to women?
  - Were BASDAI and BASFI scores higher in women because of inadequate treatment or concurrent FM?
- Authors' conclusions: "The reliability of well-accepted assessment tools of AS, such as BASDAI and BASFI, in evaluating AS activity in women may be called into question due to a confounding effect by a coexisting FM."

Aloush V, et al. Rheumatol Int 2007; 27:865-8

Comparison of AS and nr-axSpA



Compared to AS, nr-axSpa patients:

- More likely female
- Similar burden of disease
- Similar biologic requirement
- Lower acute phase reactants
- More FM (13.7% in nr-AxSpA v. 6.1% in AS)

nr-axSpA pts have clinical features that differentiate them from AS pts

Inman R, et al. ACR 2013, San Diego, #2777; Wallis D. J Rheum. 2013. 40:2038-2041

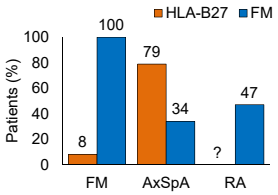
Differences Between Men and Women in Regards to Response to Treatment

- Retrospective study with pooled data from four clinical controlled trials including 1283 patients with AS (326 female and 957 male) treated with Enbrel, SSZ or placebo.
- Women had lower mean baseline CRP (13.1 vs 20.9 mg.l, p<0.001).
- Lower % of women were HLA B27 positive (76.3% vs 85.2%; p<0.001) compared with male patients
- Women had significantly (p<0.001) smaller differences in all week 12 efficacy assessments including ASDAS-CRP (0.87 vs −1.08), BASDAI (−19.22 vs −23.41) and BASFI (−13.89 vs −16.88) relative to men.
- "The number of those diagnosed with fibromyalgia during the trial period was low (4 men, 10 women). As all investigators and clinical trial sites were highly qualified AS centres, it is unlikely that the reduced response to treatment in women is due to an undiagnosed, concurrent condition such as fibromyalgia. However, through these observations we do acknowledge the need for formal fibromyalgia assessments in AS clinical trials."

Van der Horst-Bruinsma IE, et al. Ann Rheum Dis. 2013.72:1221-1224

Does Fibromyalgia Fulfill Classification Criteria for axSpA

- Concern:
  - FM patients fulfill ASAS clinical criteria, leading to over-diagnosis of axSpA
- Demographics:
  - Prospective study, 214 patients, rheumatology diagnosis, RA controls, and TNFi excluded
  - All had X-ray
  - MRI all axSpA and 20 FM



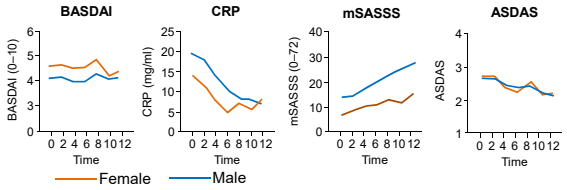
FM, 2010 FM criteria

No FM patient fulfilled ASAS classification criteria

Baraliakos X et al. EULAR 2015, Rome, #OP0038

Gender Differences in AS Outcomes

- Gender differences reported for AS outcomes, no previous longitudinal studies
- Prospective longitudinal study: 216 patients followed for mean 8.3 years
- Males better ASQoL and SF36 but higher MSASSS



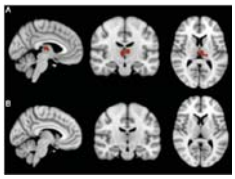
Males with AS show greater structural damage, higher CRP. Females with higher BASDAI and lower QOL despite less structural damage

Navarro-Compán V et al. EULAR 2015, Rome, #OP0042
Webers C et al. EULAR 2015, Rome, #SAT0238;

Osteoarthritis

Thalamic Atrophy Associated with Painful Hip OA is Reversible after Arthroplasty

- Chronic pain states are associated with regional gray matter volume changes by MRI voxel-based morphometry (VBM)
- 16 pts with primary hip OA showed decreased thalamic VBM volume; increased in cerebellum, insula and amygdala volume, compared to controls
- These changes reverted essentially to normal post hip athroplasty and were correlated with pain reduction and improved physical function
- These changes, associated with brain blood flow and metabolic changes, support the concept that some OA pain is central in origin, and related to central sensitization



As in other chronic pain states, pain from hip OA is associated with gray matter volume changes which reverses with corrective surgery

Gwilym, SE, et al. Arthritis Rheum. 2010; 62:2930-40.

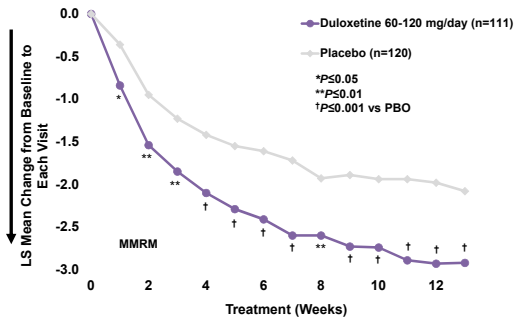
Osteoarthritis and Central Pain

- Historically classified as a peripheral pain disorder
- Poor relationship between structural abnormalities and symptoms[1]
  - 30-40% of individuals who have grade 3/4 Kellgren/Lawrence radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure[2]
- Subsets of patients with OA of the knee display hyperalgesia and attenuated DNIC[3]
- Knee OA pain improves with central neuromodulation[4,5]

DNIC = diffuse noxious inhibitory controls.
1. Creamer P, Hochberg MC. *Br J Rheumatol.* 1997;36:726-728. 2. Creamer P, Hochberg MC. *Arthritis Care Res.* 1998;11:60-65. 3. Kosek E, Ordeberg G. *Pain.* 2000;88:69-78. 4. Chappell AS, et al. Pain. 2009 5. Mease P, et al. J Rheum. 2011; 38: 1546-51.

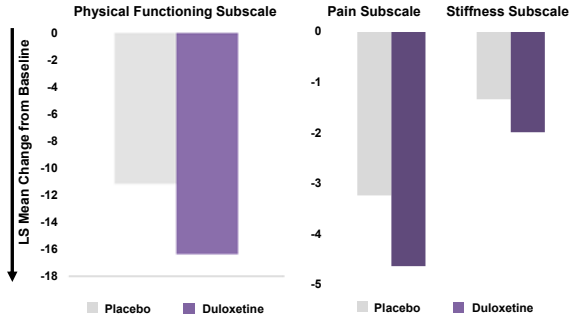
Duloxetine in Knee OA

Time Course of Change in Weekly Mean 24-hour Average Pain Scores



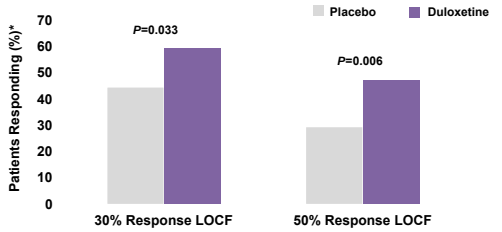
Chappell AS, et al. *Pain*. 2009].

Duloxetine in Knee OA: Change in WOMAC Subscales (LOCF)



WOMAC = Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index.
Chappell AS, et al. *Pain*. 2009.

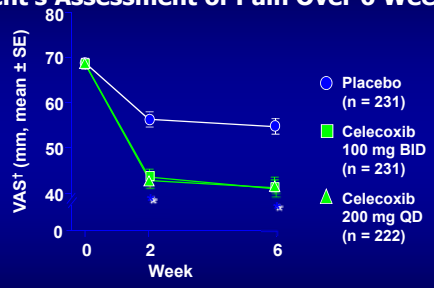
Duloxetine in Knee OA: Response Rates at Endpoint



*Response defined as at least a 30% or 50% reduction of weekly mean of the 24-hour average pain score from baseline.
Chappell AS, et al. *Pain*. 2009. [

6-Week OA Knee Trial: Celecoxib QD vs BID (Trial 060)

Patient's Assessment of Pain Over 6 Weeks



P = NS between active treatments
**P* < 0.001 for both doses of celecoxib vs placebo
†VAS = visual analog scale
Williams, et al. *J Clin Rheumatol*. 2000;6:65–74.

Rheumatologists Need To:

- Understand that the phenomenon of central sensitization may exist in parallel with the "primary" disease process they are treating, contributing to
  - Broadened symptomatology
  - Amplification of symptomatology, making PRO responses thought to be associated with the "primary" condition less reliable
  - Inability to achieve symptom-free states of remission or low disease activity – thus need to exercise careful judgment about adjustment of immunomodulatory treatment
  - Potential value of treating central pain, fatigue, sleep disturbance, mood disturbance with evidence-based therapies in parallel with primary immuno-inflammatory disorder

Treatment Lessons Learned from Fibromyalgia

- Evaluate all patients with rheumatic disease for chronic widespread pain/central sensitization, whether you call it FM or not
- Always evaluate sleep (poor sleep and depression are independently associated with pain)
- Antidepressants and anti-convulsants have an analgesic effect – "neuromodulatories"
- Cognitive behavioral therapy and exercise have efficacy for mood, function, and pain, as well as catastrophizing
- Improving peripheral pain may improve central pain
- Explain to patients the shared neurobiology of pain and depression
- Bundle the treatment of mood with physical symptoms carefully
- Utilize the model of dysregulation of central stress response

What Pain (and fatigue, dyscognition, sleep and mood disorder) are We Treating When We Treat Rheumatic Diseases?

- If centrally acting pharmacologic agents, devices, or non-pharmaceutical methods are effective in improving pain, function, and patient global in conditions such as OA, CLBP, RA, SLE, AS/AxSpA etc. are we treating
  - Primary disease generated central pain?
  - Primary disease + FM centrally generated pain?
  - Primary disease + FM + mood disorder centrally generated pain?
- Is it appropriate to move beyond the "F" word and instead use terminology such as "central pain" or "central sensitization syndrome"?

THANK YOU

The Role of Central Sensitization in Chronic Rheumatic Diseases and How it May Influence Assessment of Disease Severity

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