ATLAS 2024

QUESTIONI APERTE NELLA CURA DELLA FIBROMIALGIA

Dolore residuo nelle malattie infiammatorie articolari: è sempre dolore nociplastico?

Contro

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Speaker Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Lilly	x	x						
BMS	x	x						
Pfizer	x	x						
Alfasigma	x	x						
Novartis	x	x						
Colinfarma	x	x						
Celltrion	x	x						
Galapagos	x	x						
UCB	x	x						

Pain in arthritis: a universal reality

Those reporting **moderate arthritis impairment or symptoms** are not doing as well as people in the general population. Numbers in this range (5 to 7) are a cause for concern, requiring appropriate resources and support.

Patients with **severe impairment or symptoms** are not doing nearly as well as the general population. Numbers in this range (8 to 10) are alarming, and appropriate resources and support are urgently needed.

100%

of survey respondents reported pain over the past 7 days.

15%

felt pain at 8 or higher, described as intense, excruciating or unbearable.

Editorial Lancet Rheumatol 2021

For the **Live Yes! INSIGHTS survey report** see https://www.arthritis.org/getmedia/34e83e02-8932-47ce-8225-20c62bbfb52b/How-It-Hurts-Report.pdf

Pain in arthritis: a universal reality

Pain Is Extremely Prevalent

Chronic arthritis pain can't be ignored. It is an intense and constant presence that impairs physical function, disturbs sleep and causes debilitating fatigue. Compounding the pain and disability are the hardships, isolation and marginalization people with arthritis often encounter. Since our last report, scores have worsened, indicating what an even more challenging year it was for arthritis patients.

5.4

Average Pain Score on a 10-point scale

66%

report a pain level of 5 or higher, indicating moderately strong pain approaching distress.

Editorial Lancet Rheumatol 2021

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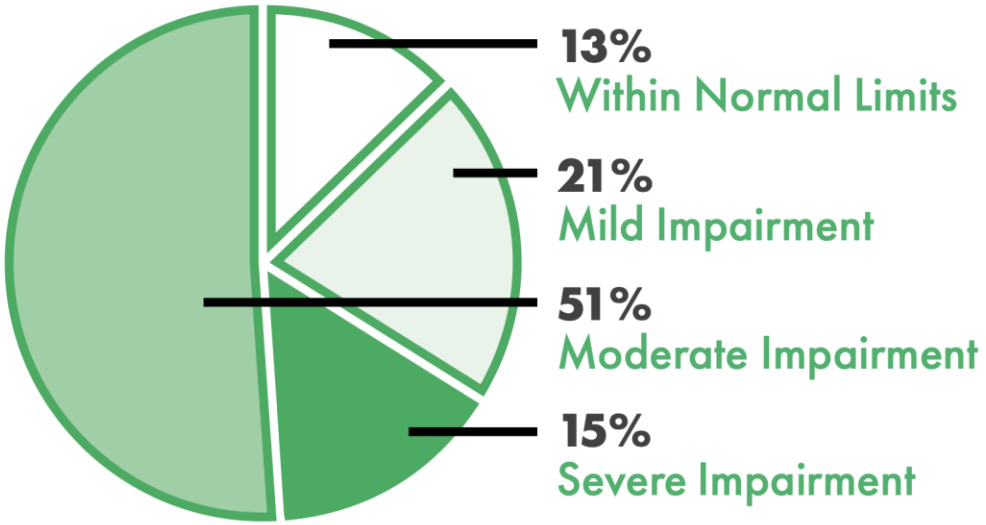
Pain in arthritis: a universal reality

Daily Life and Activities

Almost 90% of arthritis patients surveyed have pain that interferes with their daily lives and activities.



75%

reported that pain interfered somewhat, quite a bit or very much with their day-to-day activities.

- 66% reported that pain interfered somewhat, quite a bit or very much with their ability to participate in social activities.

Editorial Lancet Rheumatol 2021

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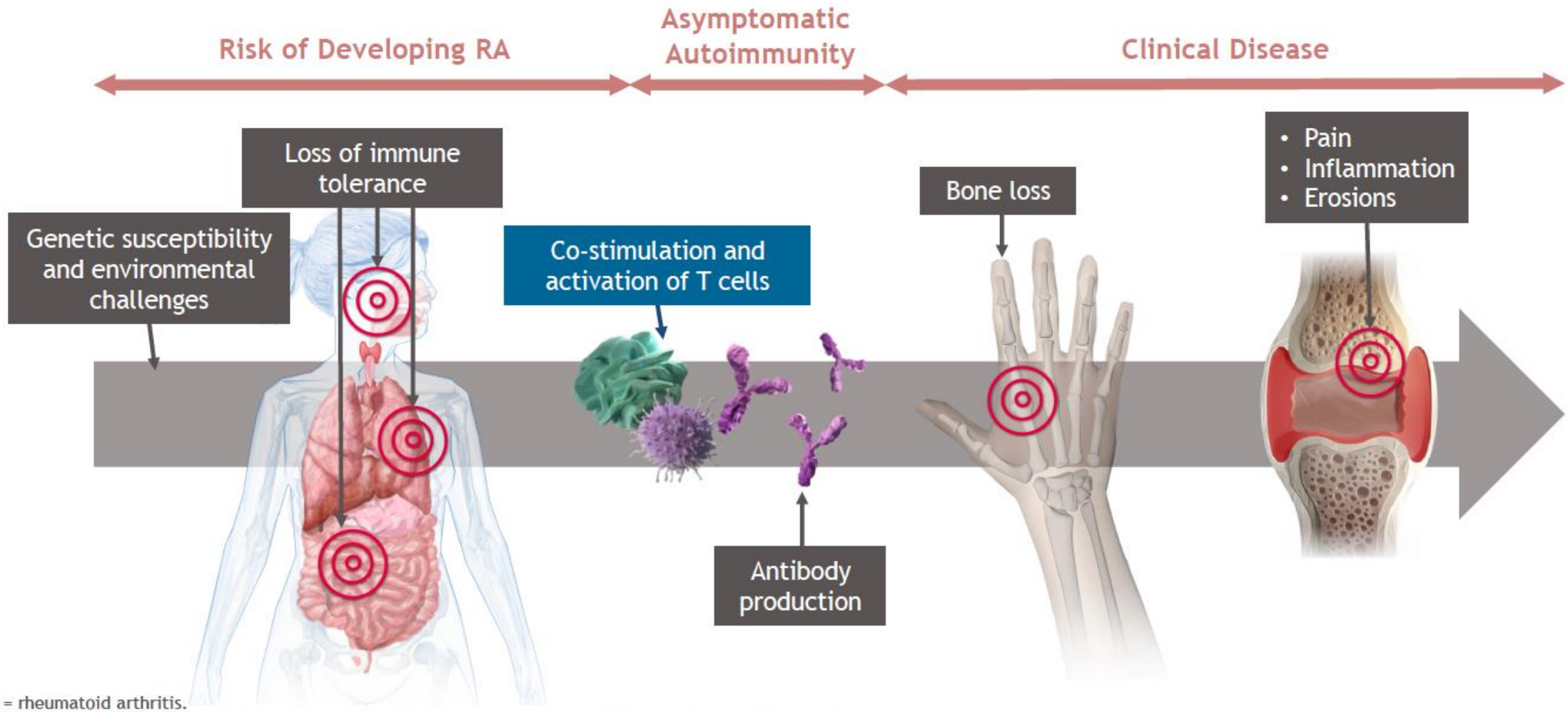
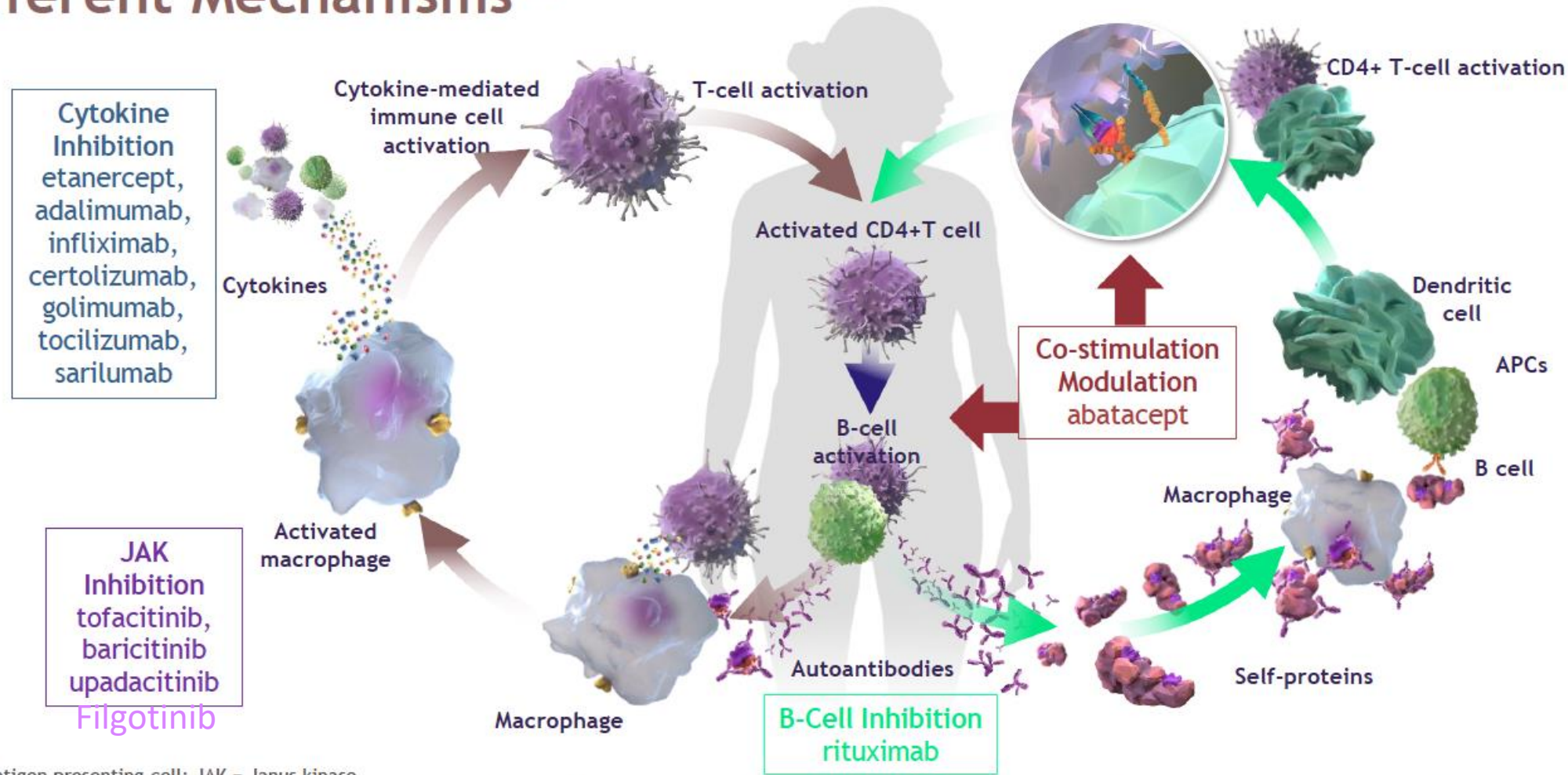
RA Is a Progressive and Heterogenous Disease[1,2]



RA = rheumatoid arthritis.

1. Catrina AI, et al. *Nat Rev Rheumatol*. 2017;13:79-86; 2. Smolen JS, et al. *Nat Rev Dis Prim*. 2018;46:18001.

Current RA Treatments Target the Autoimmune Cycle via Different Mechanisms[1-3]

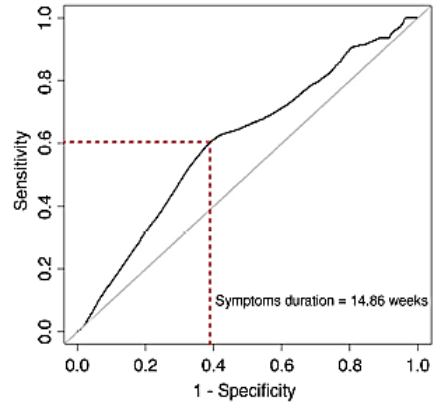


APC = antigen presenting cell; JAK = Janus kinase.

1. Murphy K, Weaver C, eds. *Janeway's Immunobiology*. 2017; 2. Mosser DM, Edwards JP. *Nat Rev Immunol*. 2008;8:958-969; 3. Smolen JS, et al. *Nat Rev Dis Prim*. 2018;4:18001.

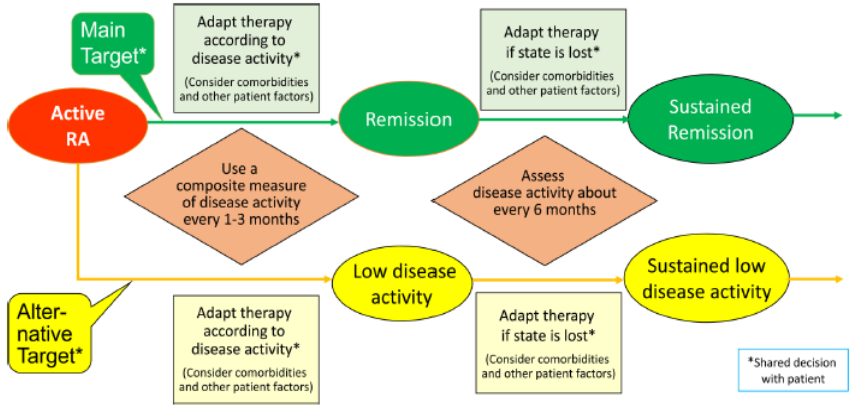
The outcomes of RA have changed

❶ treat early



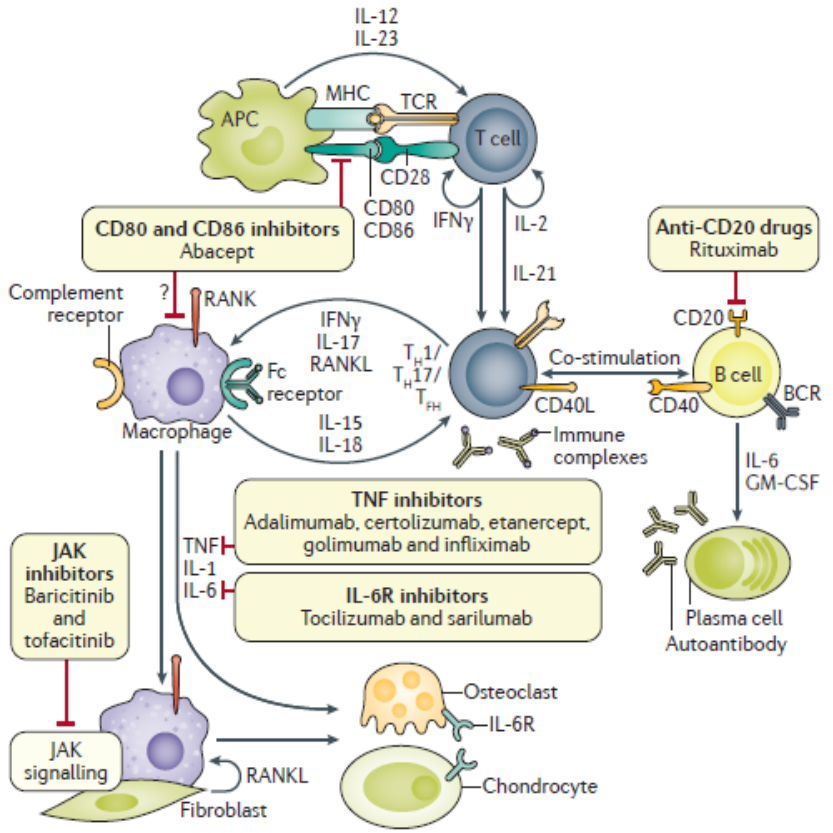
Van Nies JA et al. Ann Rheum Dis 2015;74:806-12.

❷ treat intensively: T2T & tight control



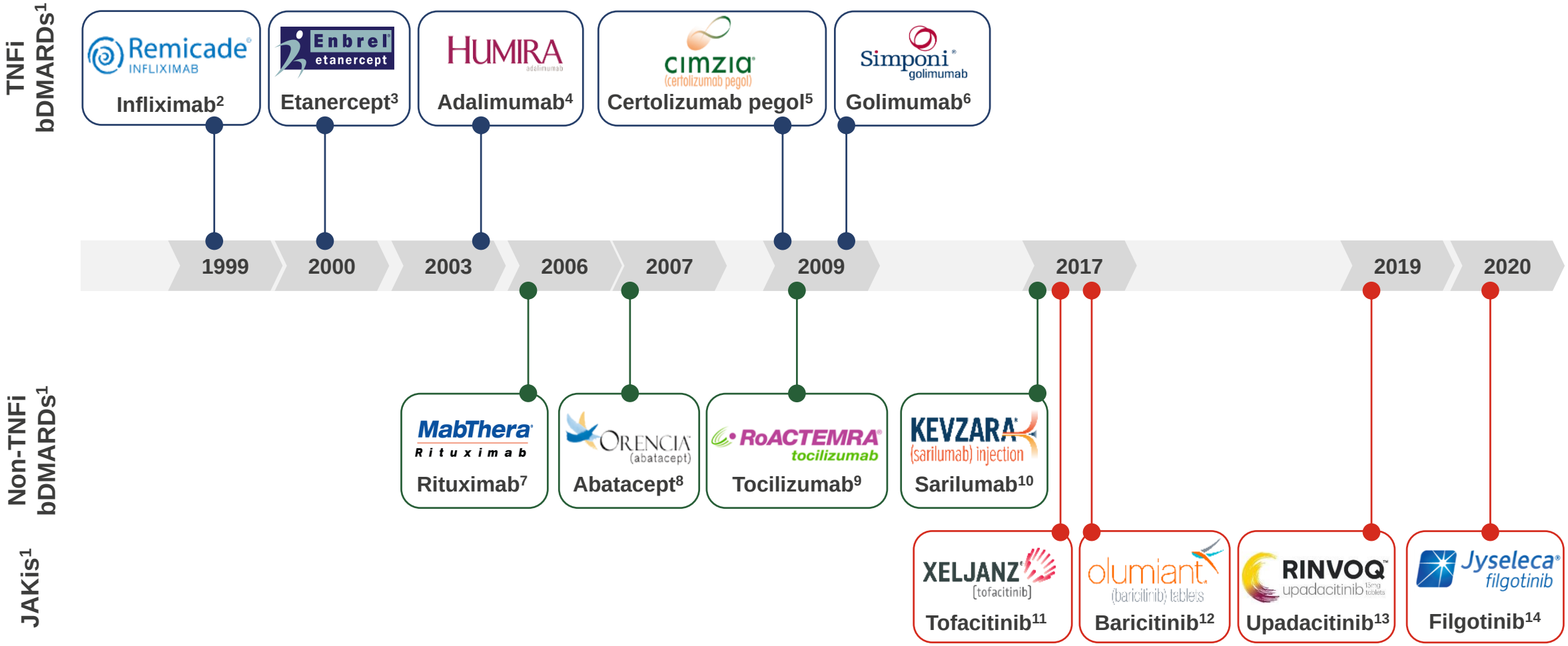
Smolen JS et al. Ann Rheum Dis 2016;75:3-15.

❸ targeted therapies



Smolen JS et al. Nat Rev Dis Primers 2018;4:18001.

DMARDs Approved for RA by the EMA in the Last 23 Years



bDMARD=biologic disease-modifying antirheumatic drug; DMARD=disease-modifying antirheumatic drug; EMA=European Medicines Agency; JAKi=Janus kinase inhibitor; RA=rheumatoid arthritis; TNFi=tumor necrosis factor inhibitor.
See speaker notes for references.

Achievement of Key RA Treatment Goals with DMARDs

40-50% of patients reach LDA or remission after **first-line therapy** with MTX in combination with GCs

Up to 40% of patients achieve LDA with **second-line therapy** using bDMARDs or tsDMARDs

Using sequential application of therapies, **approximately 75%** of patients can **achieve remission or LDA**

bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoid; LDA: low disease activity; MTX: methotrexate; RA: rheumatoid arthritis; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

1. Aletaha D, et al. *JAMA* 2018;320.

Achieving and Maintaining Disease Control Can Be Challenging

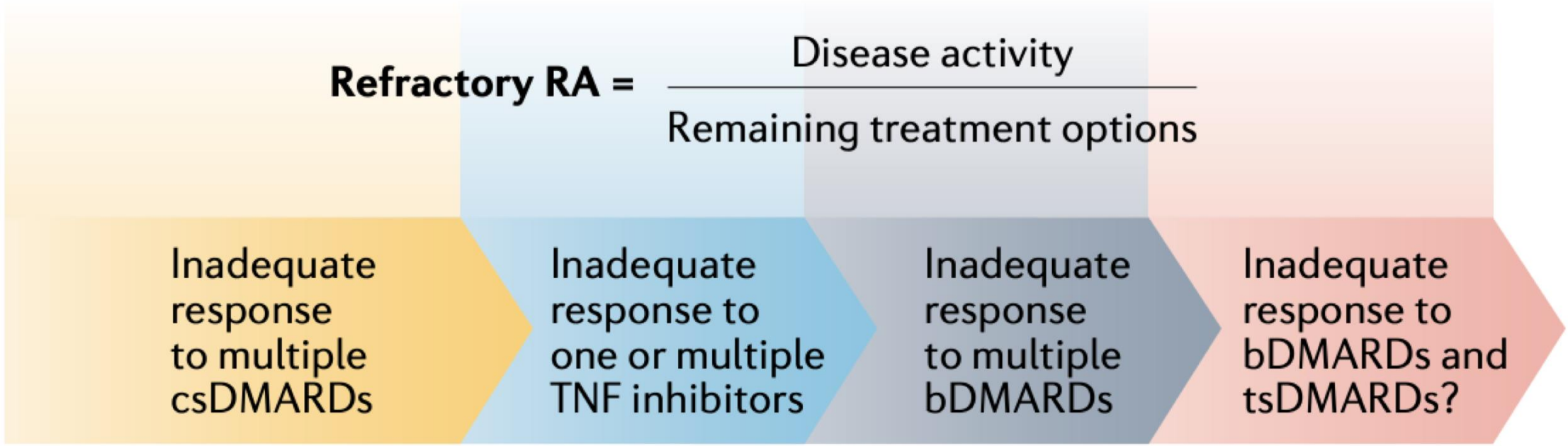
- **Despite availability of multiple agents, some patients fail to achieve LDA or remission** due to[1-5]:
  - Failure to respond to initial DMARD course[3]
  - Intolerance of MTX monotherapy treatment[4]
  - Loss of treatment response over time[5]
- **Further barriers to disease control include**[3,5,6]:
  - **Pain, including noninflammatory pain, fatigue**
  - Treatment safety
  - Comorbidities
  - Quality-of-life limitations
  - Discordance between patient and physician
- Many patients struggle to maintain disease control and relapse following tapering or withdrawal of bDMARDs or tsDMARDs[3]

At least 25% of patients with RA do not achieve remission or LDA[3]

Up to 75% relapse with rates varying widely and depending on many factors[7]

bDMARD: biologic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; LDA: low disease activity; MTX: methotrexate; RA: rheumatoid arthritis; tsDMARD: targeted synthetic disease-modifying antirheumatic drug. 1. Taylor PC, et al. *Rheumatol Int*. 2016;36(5):685-695. 2. Montag K, et al. *Intern Med J*. 2011;41(6):450-455. 3. Aletaha D, Smolen JS. *JAMA*. 2018;320:1360-1372. 4. Bello AE, et al. *Open Access Rheumatol.* 2017;9:67-69. 5. Rubbert-Roth A, et al. *Arthritis Res Ther*. 2009;11:S1. 6. Tymms K, et al. *Arthritis Care Res.* 2014;66(2):190-196. 7 Schett G, et al. *Ann Rheum Dis*. 2016;75(8):1428-1437.

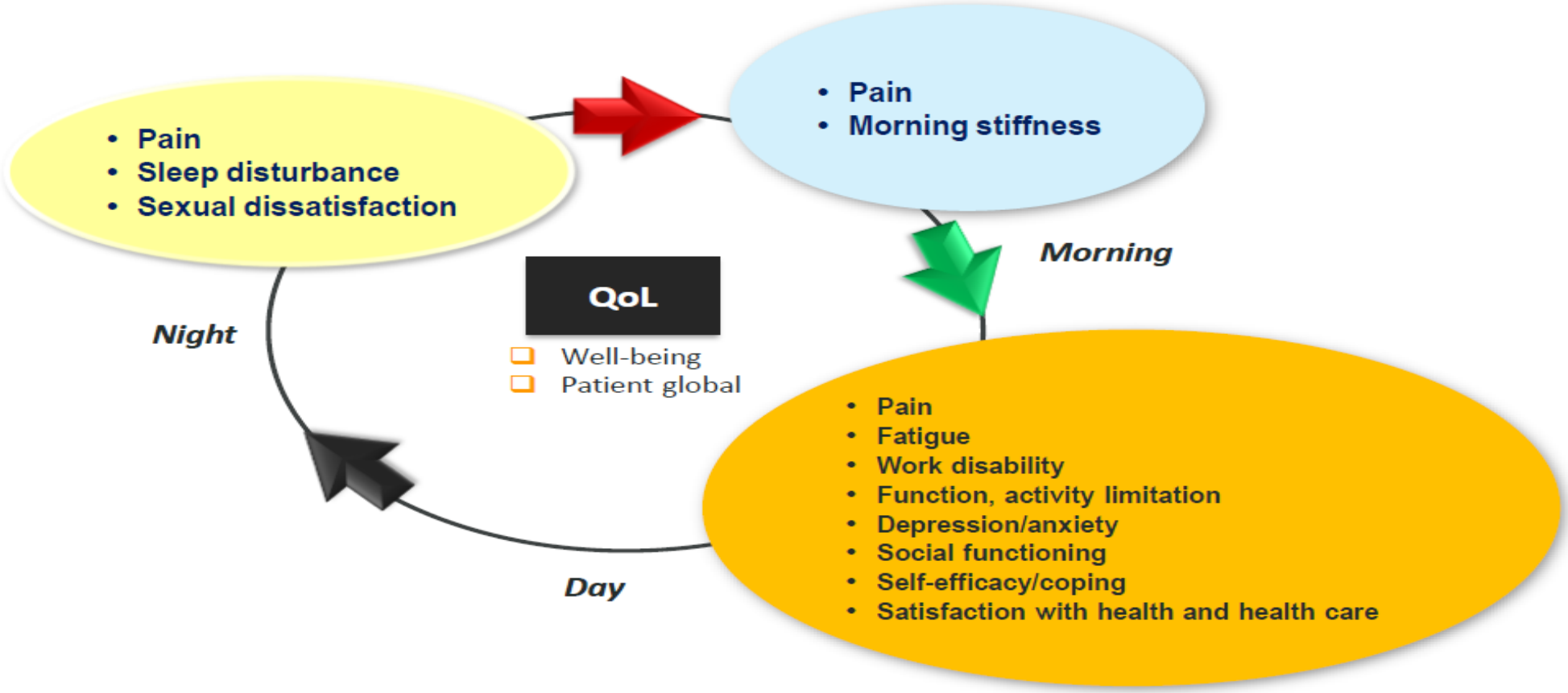
The true definition of refractory RA



Persistent disease activity resistant to multiple treatments

Buch M, et al. Nature Rev Rheumatol 2020

The patient's perspective may differ from the physician's



There is a cycle between fatigue-sleep-depression-pain that affects the patient's quality of life

Gomez-Reino et al. Arthritis Res Ther 2006

Still the patient remains unsatisfied

- **<u>Pain and fatigue control are not always fully achieved</u>**
- Many patients with RA still experience pain and fatigue despite receiving intensive treatment[1]
- Leiden Early Arthritis Clinic (EAC) cohort: while patients with RA over time presented with shorter symptom duration and less inflammatory findings, PROs worsened[2]

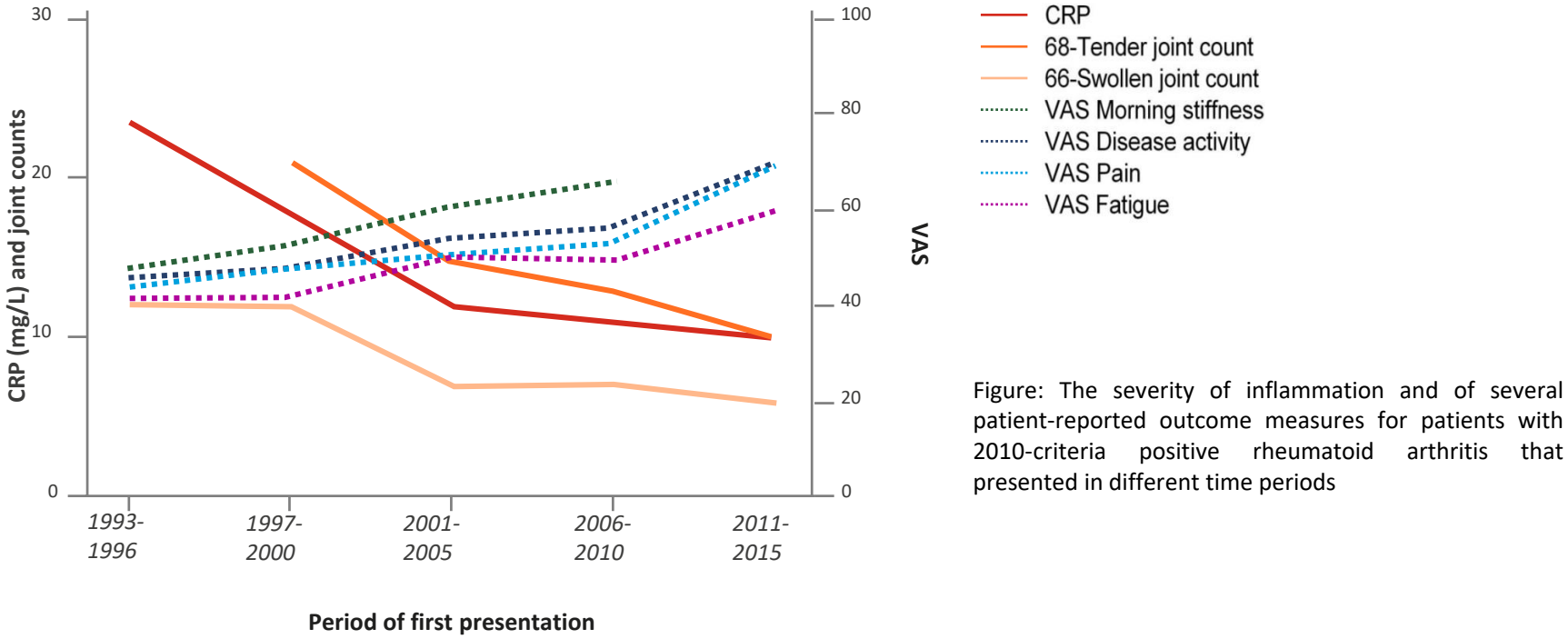


Figure: The severity of inflammation and of several patient-reported outcome measures for patients with 2010-criteria positive rheumatoid arthritis that presented in different time periods

Image reused with permission

CRP=C-reactive protein; EAC=Early Arthritis Clinic; PRO=patient-reported outcome; RA=rheumatoid arthritis; VAS=visual analog scale

1. Taylor PC et al. Rheumatol Int 2016;36(5):685-95; 2. Nieuwenhuis WP, et al. Ann Rheum Dis 2016;75:2054-6; 3. Emery P. Presented at EULAR Symposium 2017

Pain, functional disability and fatigue are important health domains to RA patients

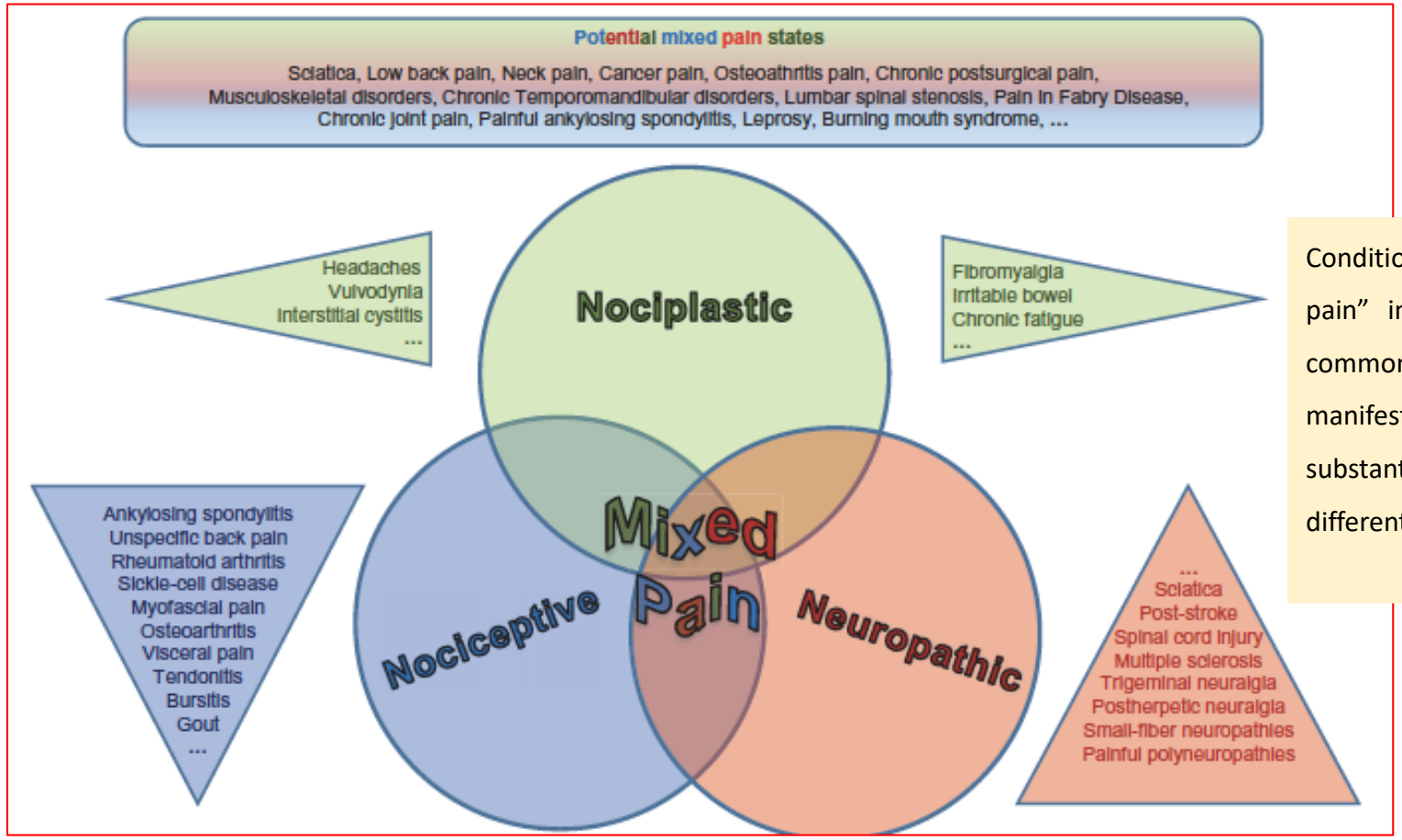
- 96 patients from 10 European countries ranked importance of 17 PRO domains

	Median rank	Order by medians	% Rank 1 to 7	% Rank 1 to 3
Pain	**2**	**1**	**78.1**	**59.4**
Functional disability	**5.5**	**2**	**64.6**	**30.2**
Fatigue	**6**	**3**	**61.4**	**26.0**
Physical well-being	9	5	44.8	24.0
Coping	9	5	41.7	16.7
Sleep	8	4	45.8	13.5
Emotional well-being	9	5	33.3	8.3
Being a burden to others	9.5	9	40.6	15.6
Family life	10	11	38.5	20.8

PRO=patient reported outcome; RA=rheumatoid arthritis

Gossec L et al. Ann Rheum Dis 2009;68:1680-5; 2. Emery P. Presented at EULAR Symposium 2017

The three different types of pain defined by the IASP give rise to overlap which can be acknowledged as “mixed pain”.



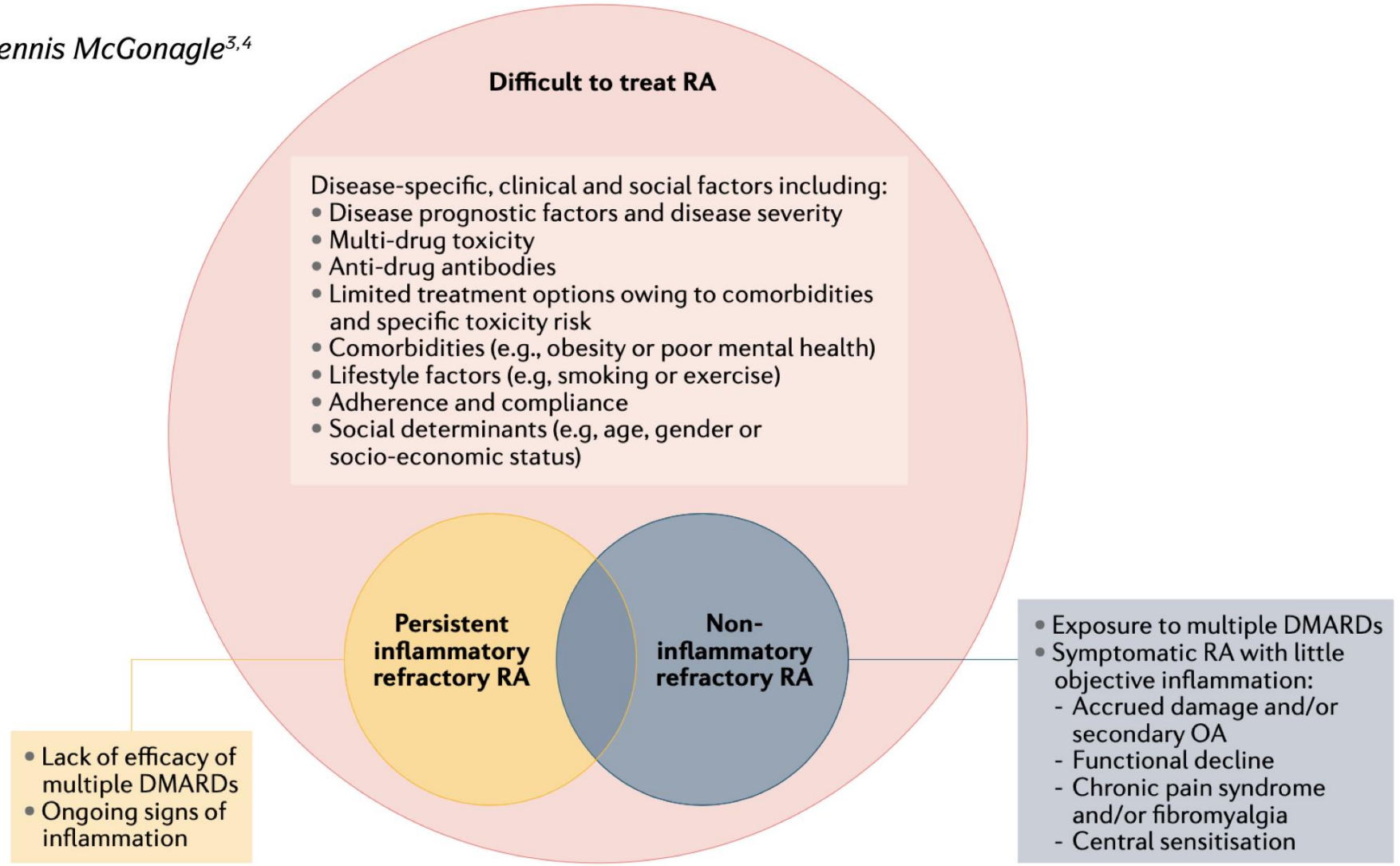
Conditions described as “mixed pain” in the literature share a common characterization of manifesting clinically with a substantial overlap of the different known pain types.

Freynhagen R, et al.. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin. 2019 Jun;35(6):1011-1018.

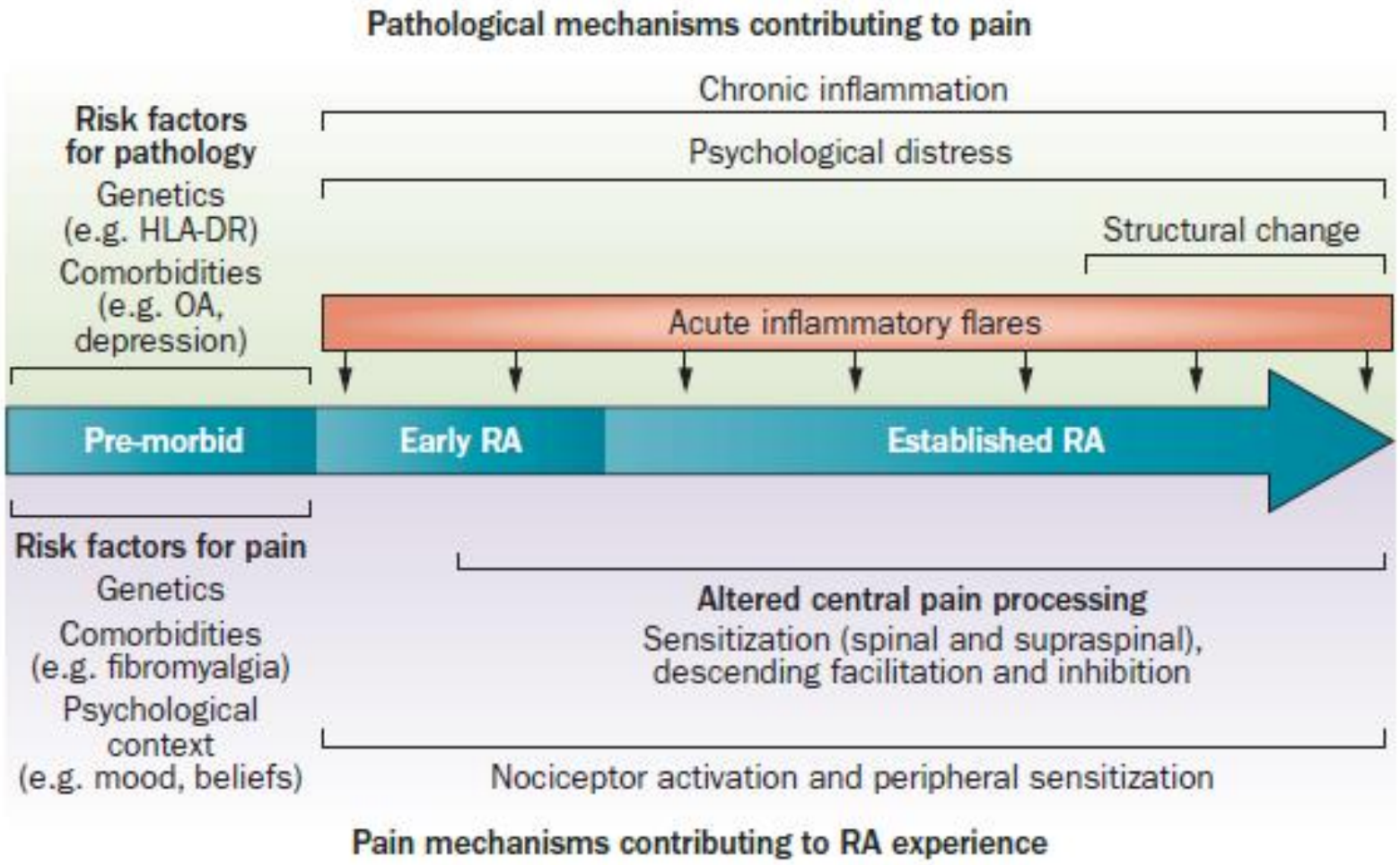
Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis

Maya H. Buch[1,2,3]✉, *Stephen Eyre*[1,2] *and Dennis McGonagle*[3,4]

Nature Rev Rheumatol
2020



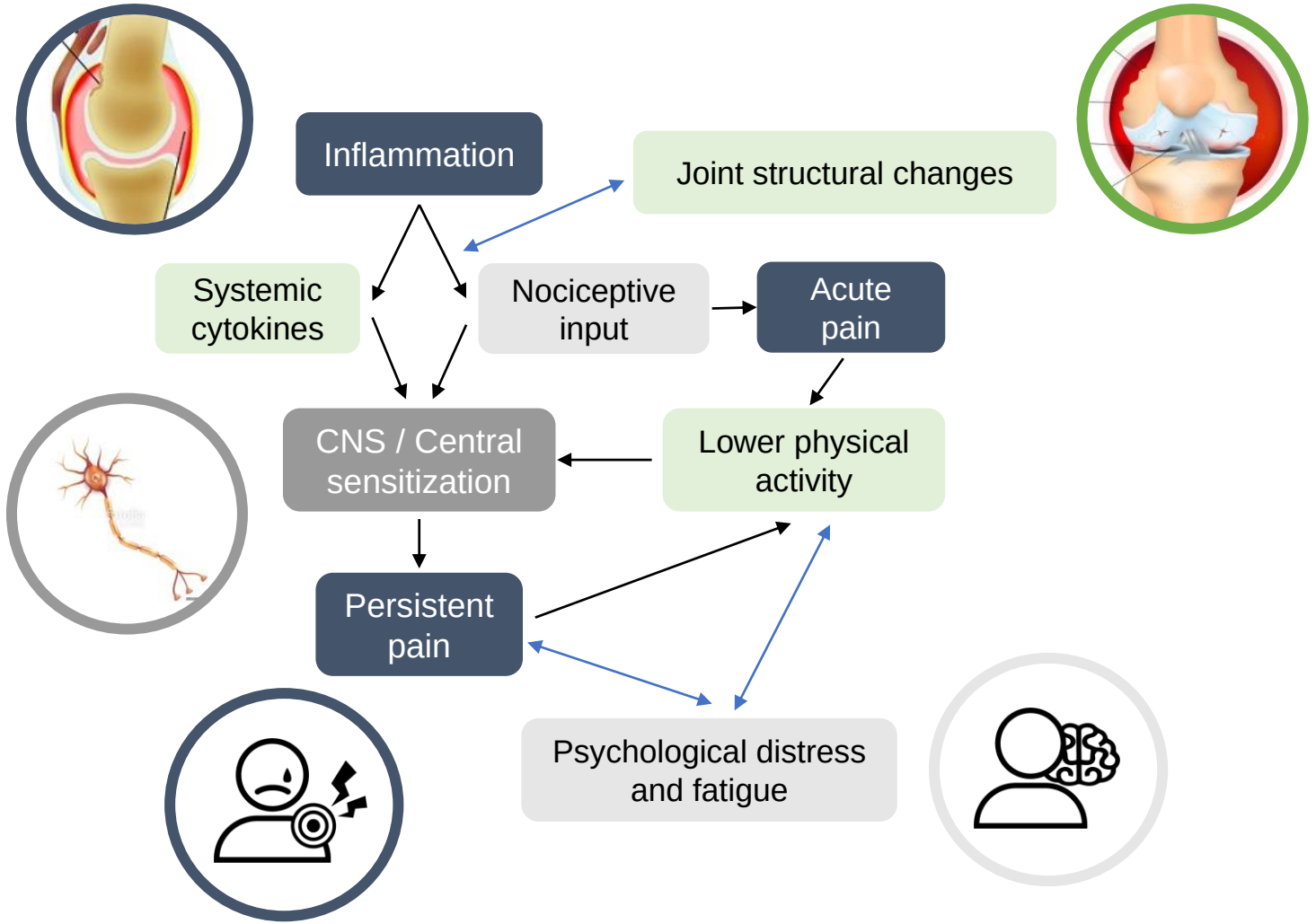
The complex pathogenesis of pain in RA



Walsh DA et al. Nat Rev Rheumatol 2014 ;10:581-92.

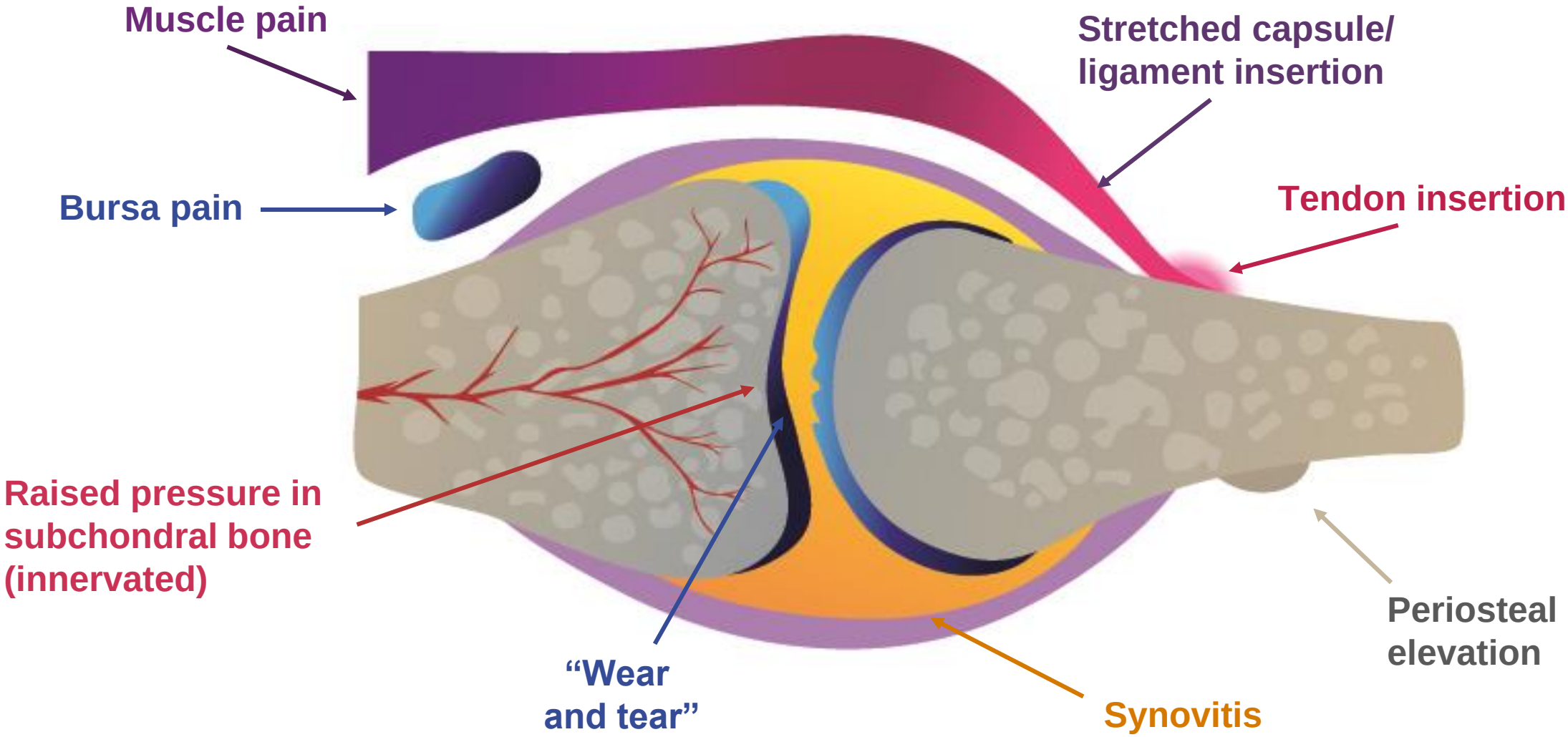
Pain in RA is driven by multiple mechanisms

Pain results from interplay between joint pathology and processing of pain signals by peripheral nerves, spinal and supraspinal pain pathways



Walsh DA, McWilliams DF. *Nat Rev Rheumatol.* 2014;10:581-592; McWilliams DF, Walsh DA. *Clin Exp Rheumatol.* 2017;35(Suppl. 107):S94-S101; Boyden SD et al. *Curr Rheumatol Rep.* 2016;18:30.

Anatomical origin of arthritis pain is complex

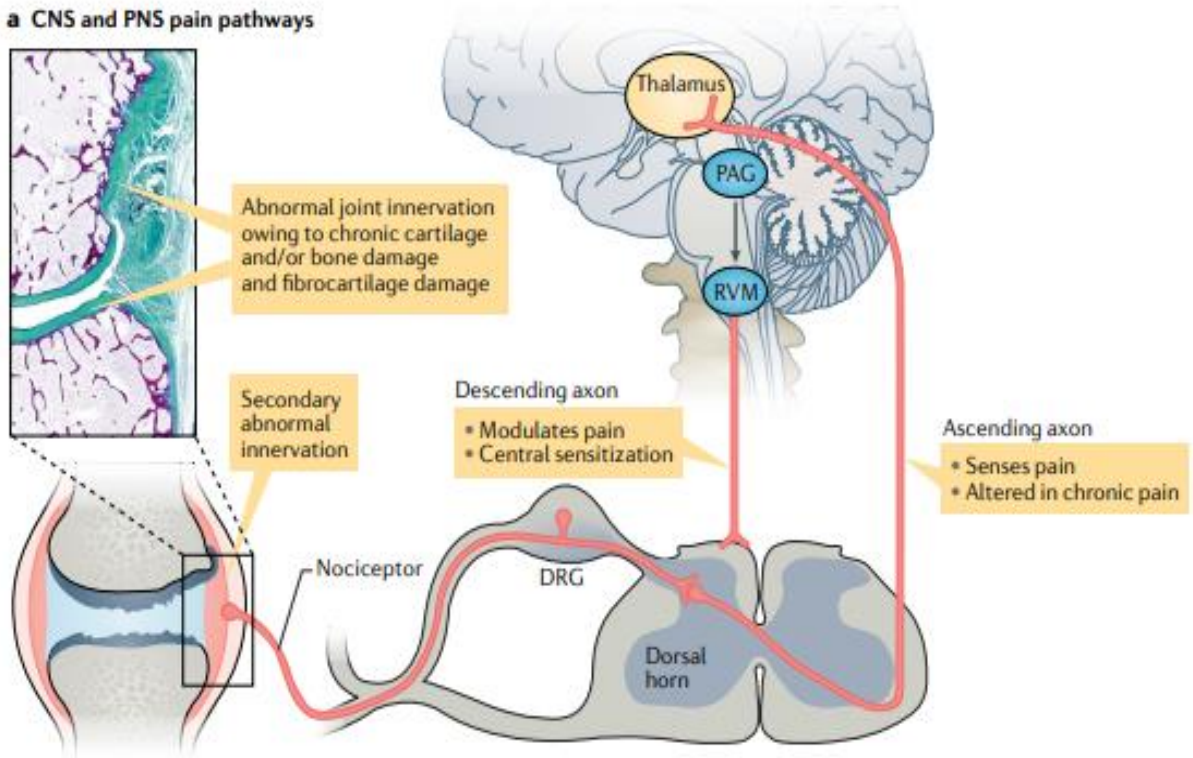


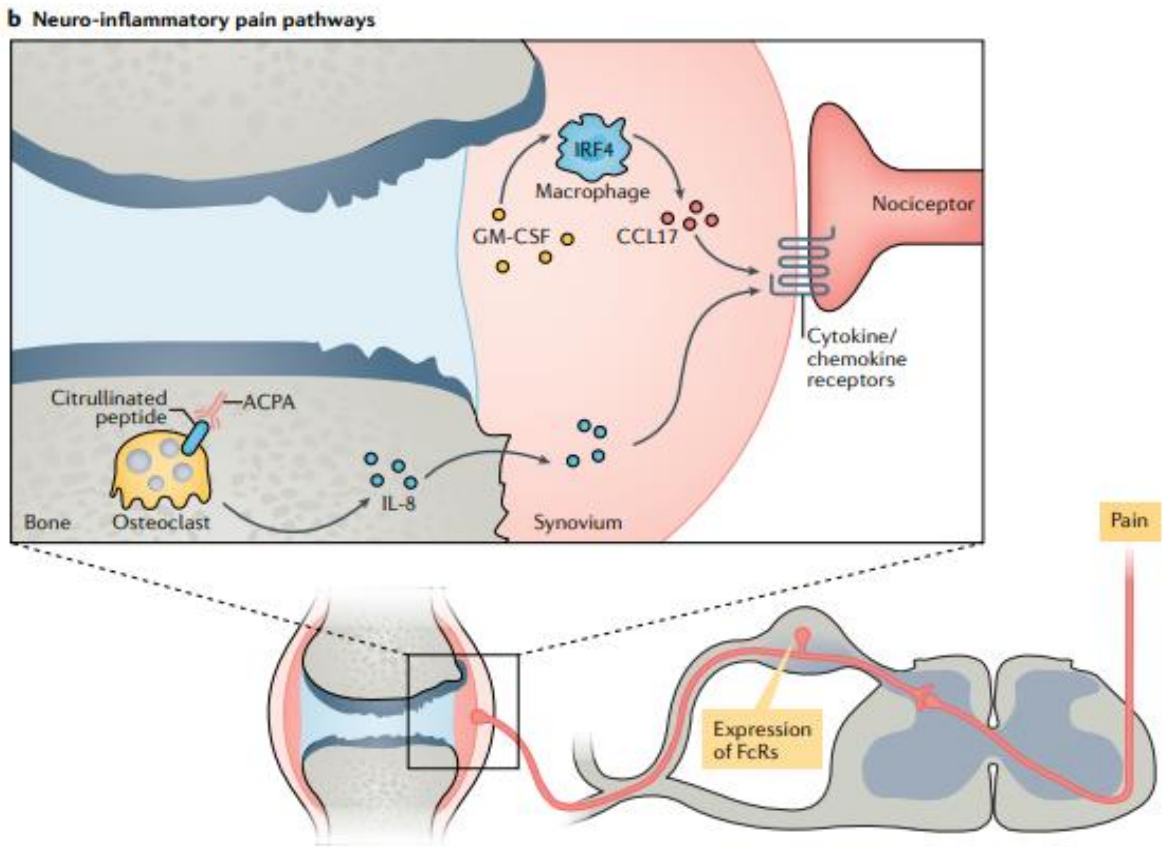
Pain in RA: peripheral and central mechanisms

Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis

Maya H. Buch[1,2,3]✉, *Stephen Eyre*[1,2] *and Dennis McGonagle*[3,4]

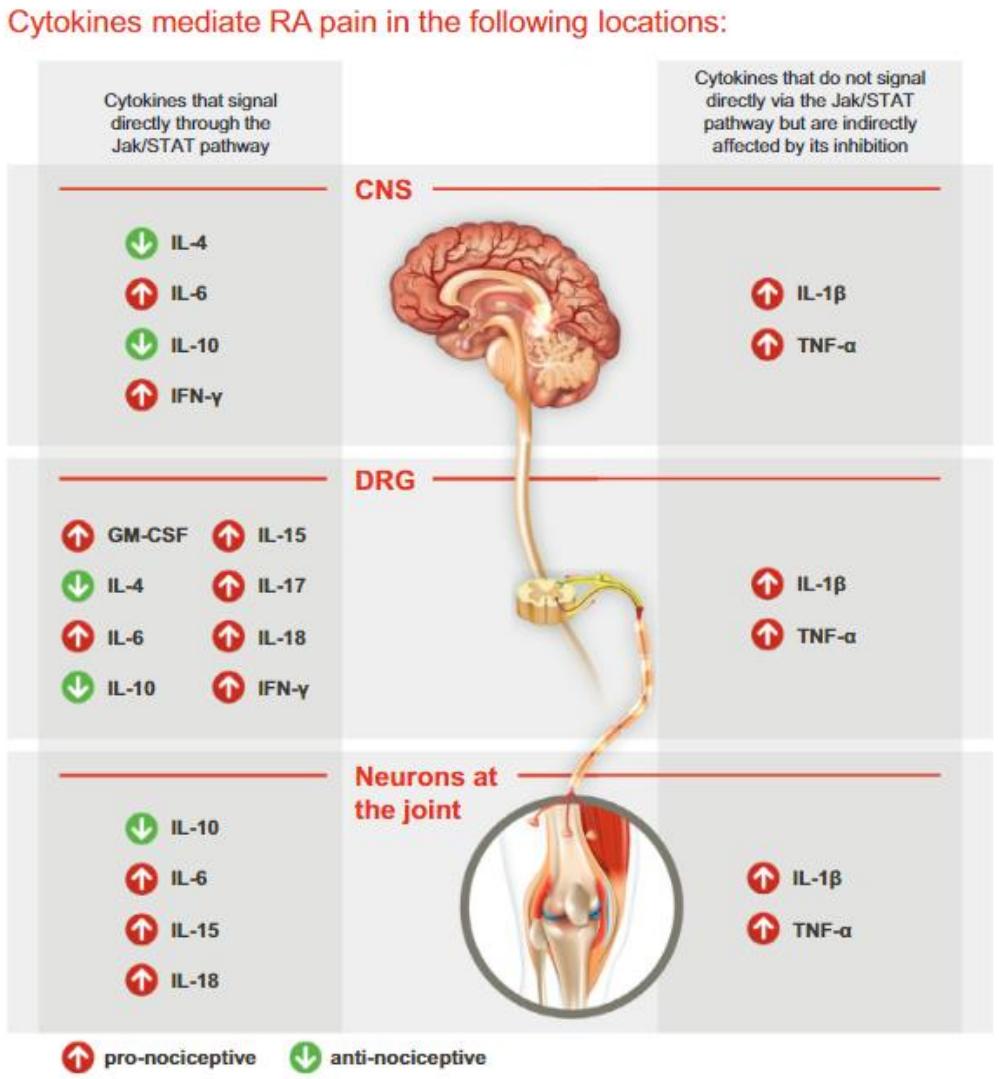
Nat. Rev. Rheumat. 2021

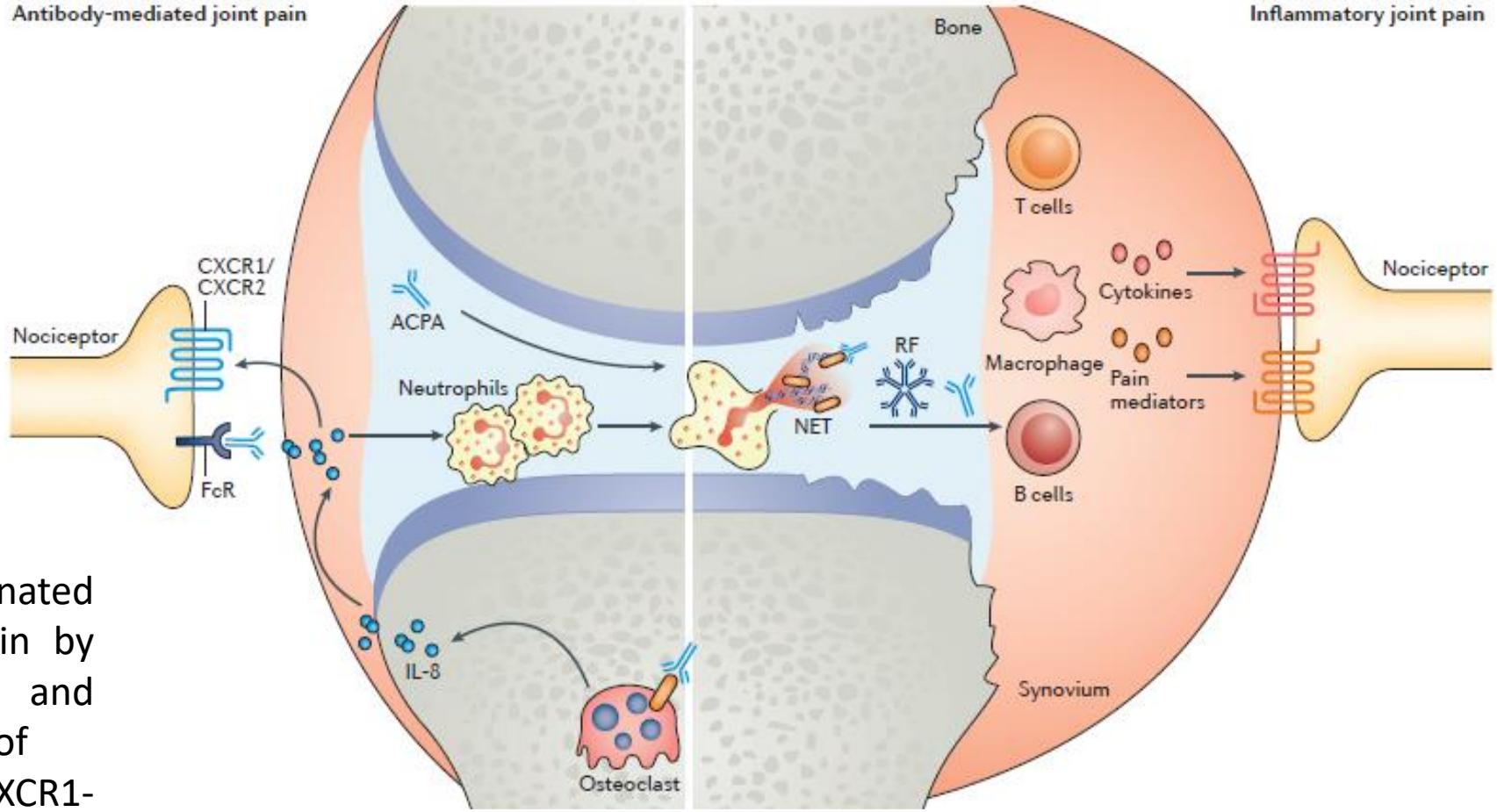




The Jak/STAT pathway: a focus on pain in rheumatoid arthritis

L.S. Simon et al. / Seminars in Arthritis and Rheumatism 51 (2021) 278–284





Antibodies to citrullinated proteins can induce pain by binding to osteoclasts and inducing the production of IL-8 this through the CXCR1-CXCR2 receptors sensitizes peripheral nociceptors, APCAs can also have a direct effect mediated by an Fc receptor expressed on dorsal root ganglion

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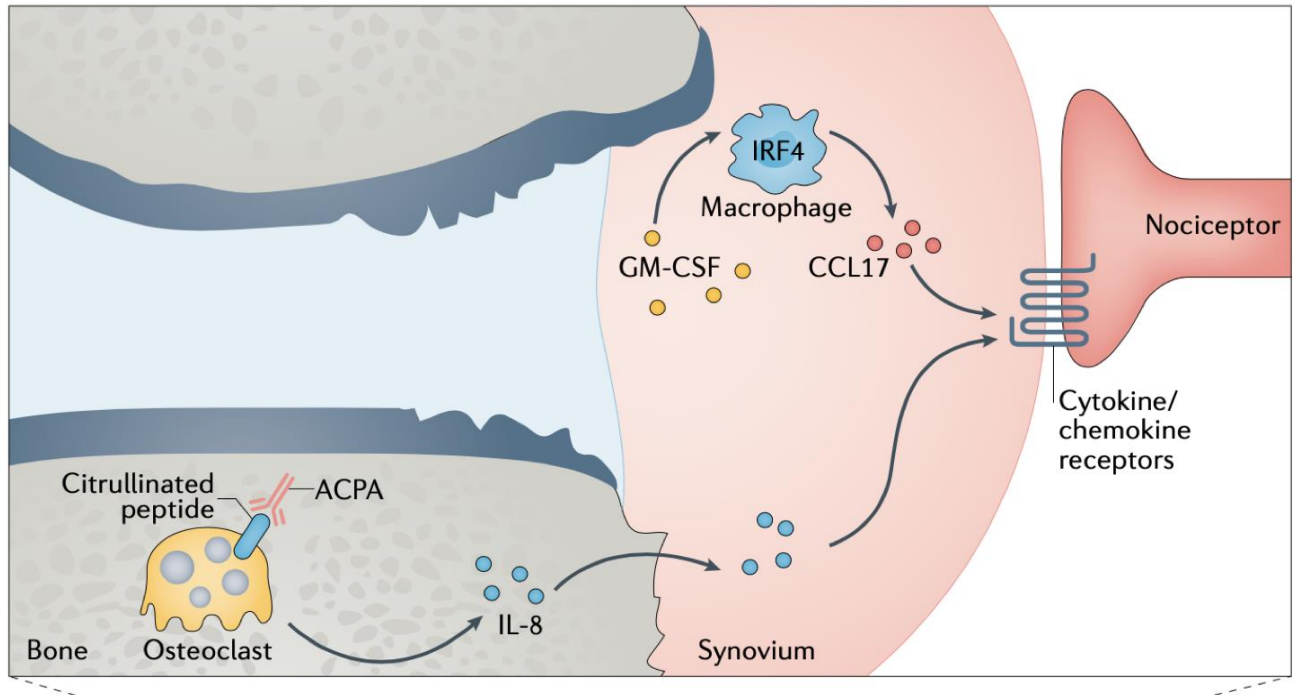
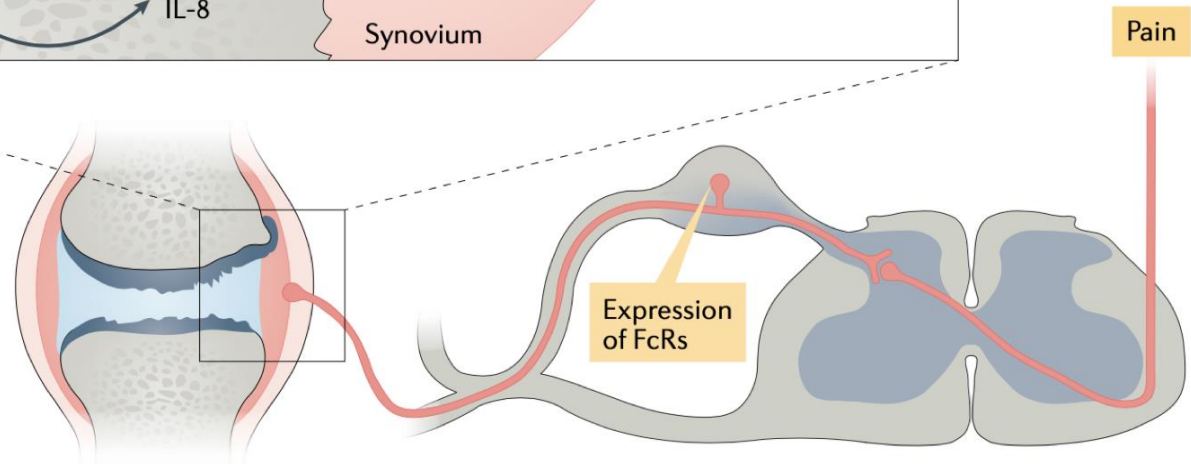
Neuro-inflammatory pain pathways





Inflammatory mediators such as Chemokine Ligand-17 (CCL17) and GM-CSF pathway, mediated by Interferon Regulatory Factor-4 has been demonstrated in experimental model of arthritis

Can pain and /or fibromyalgia go unrecognised in the era of T2T?

Prevalence of FM in CRD

Tabella IV. Prevalenza della FM in pazienti affetti da spondiloartriti (SpA)

Autore (anno)	Numero di pazienti con SpA	Prevalenza della FM nelle SPA (%)
Artrite psoriasica (AP)		
• Magrey et al (2012)	34	22,0
• Salaffi et al. (2014)	191	17,2
• Brikman et al (2016)	73	17,8
• Salaffi et al. (2016)	144	18,7
Spondilite anchilosante (SA)		
• Almodovar et al. (2010)	462	4,1
• Azevedo et al. (2010	71	15,0
• Salaffi et al. (2014)	211	12,7
• Hallioglu et al. (2014)	119	10,1
• Bello et al (2016)	196	21,4
• Sahli et al	100	20.0

Tabella V. Prevalenza della FM in pazienti affetti da artrite reumatoide (AR)

Autore (anno)	Numero di pazienti con AR	Prevalenza della FM nell'AR (%)
• Naranjo et al. (2002)	57	14,8
• Wolfe et al (2004)	11.866	17,1
• Dhir et al. (2009)	200	15,0
• Ranzolin et al (2009)	270	13,4
• Wolfe et al. (2011)	9.739	7,4
• Kaapor et al. (2011)	285	15,0
• Hallioglu et al. (2014)	197	6,6
• Abbasi et al. (2014)	120	25,8
• Fan et al. (2017)	325	7,7
• Perrot et al. (2017)	172	22,1
• Gist et al. (2018)	117	33,3
• Provan et al. (2019)	502	30,0

Nell' ARTRITE REUMATOIDE la FM è stata osservata nel 6,6-33.3% dei pazienti

Nelle SPONDILOARTRITI la FM è stata osservata nel 17.2-22% dei pazienti

Salaffi, F., Farah, S
https://www.rheumalab.it/site/fibromialgia/

Prevalence of FM in CRD

Tabella II. Prevalenza della FM in pazienti affetti da lupus eritematoso sistemico (LES)

Autore (anno)	Numero di pazienti con LES	Prevalenza della FM nel LES (%)
• Middleton et al. (1994)	102	22,0
• Morand et al. (1994)	87	25,3
• Gladman et al. (1997)	119	22,0
• Wallace et al. (1997)	102	23,0
• Handa R et al .(1998)	158	8,2
• Lopez-Osa et al. (1999)	90	10,0
• Karaaslan et al. (1999)	56	25,0
• Friedman et al. (2003)	266	5,0
• Valencia-Flores et al. (2004)	187	9,5
• Akkasilpa et al. (2005)	173	17,3
• Wolfe et al. (2009)	834	22,1
• Torrente Segorra et al. (2010)	84	35,7
• Iannuccelli et al. (2012)	50	32,0
• Haliloglu et al. (2014)	67	13,4
• Torrente Segorra et al. (2016)	3.591	6,2

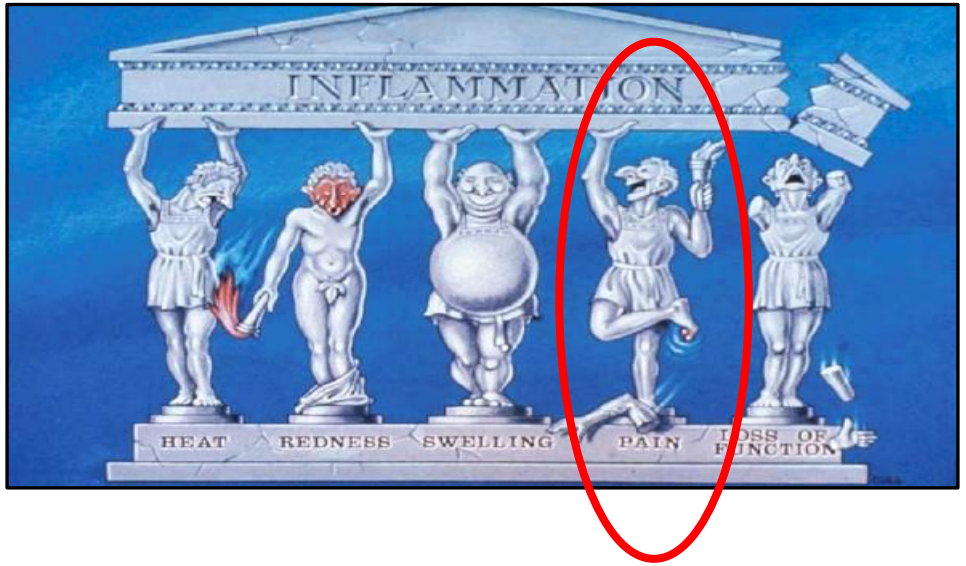
Nel LUPUS ERITEMATOSO SISTEMICO la FM è stata osservata nel 5-35,7% dei pazienti

Tabella III. Prevalenza della FM in pazienti affetti da sindrome di Sjögren.

Autore (anno)	Numero di pazienti con SS	Prevalenza della FM nella SS (%)
• Vitali et al. (1989)	30	47,0
• Dohrenbush et al. (1996)	18	44,0
• Tishler et al. (1997)	65	55,0
• Giles et al. (2000)	75	12,0
• Ostuni R et al. (2002)	100	22,0
• Iannuccelli et al. (2012)	50	18,0
• Choi et al. (2014)	100	25,0
• Hallioglu et al. (2014)	25	12,0
• Choi et al. (2016)	100	31,0

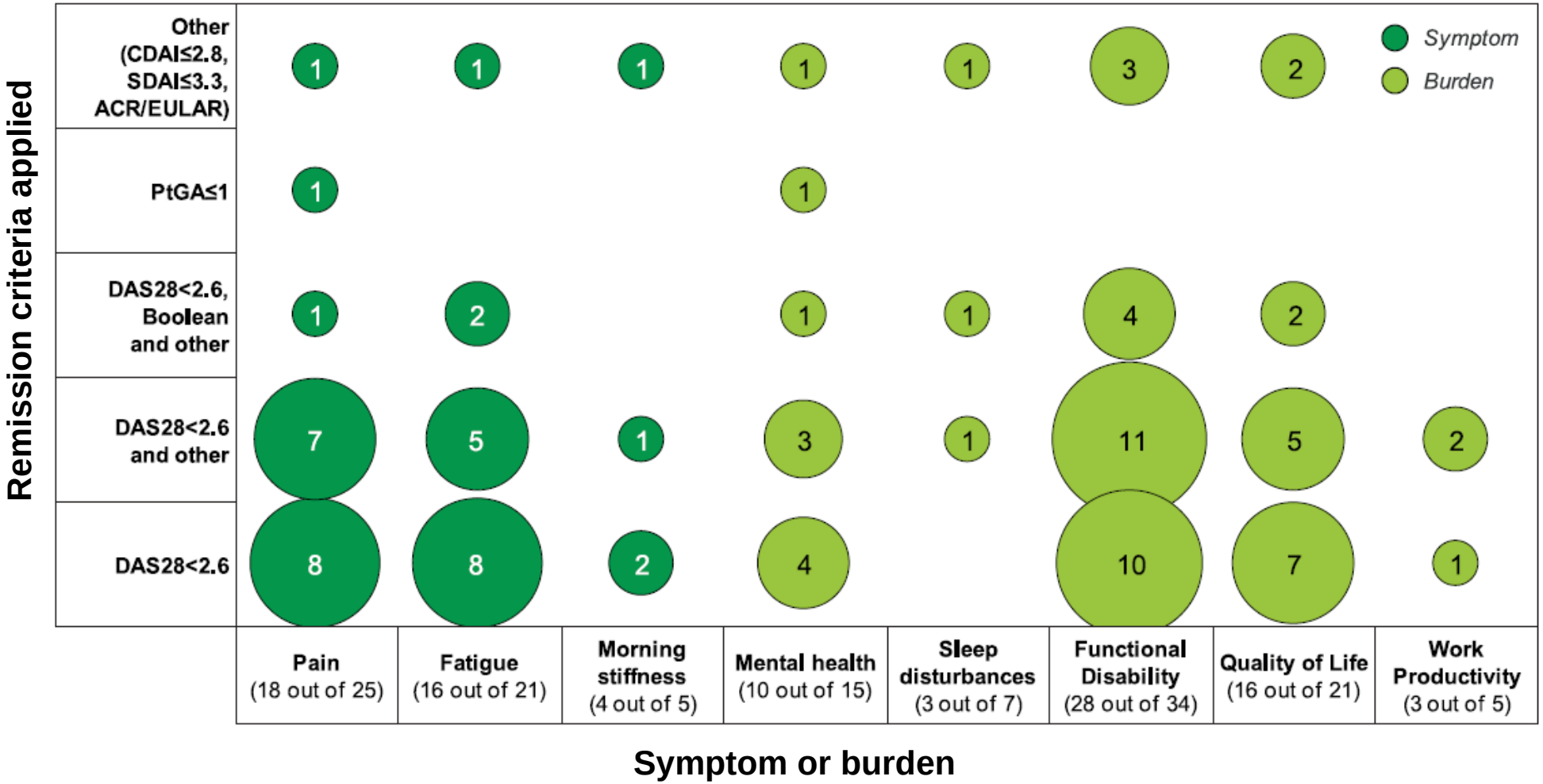
Nella SINDROME DI SJOGREN PRIMARIA la FM è stata osservata nel 12-55% dei pazienti

Salaffi, F., Farah, S
https://www.rheumalab.it/site/fibromialgia/



Has the appearance of biologics and jak-inhibitors solved the problem of pain and/or concomitant fibromyalgia in Rheumatoid Arthritis?

RA patients in clinical remission often have residual symptoms

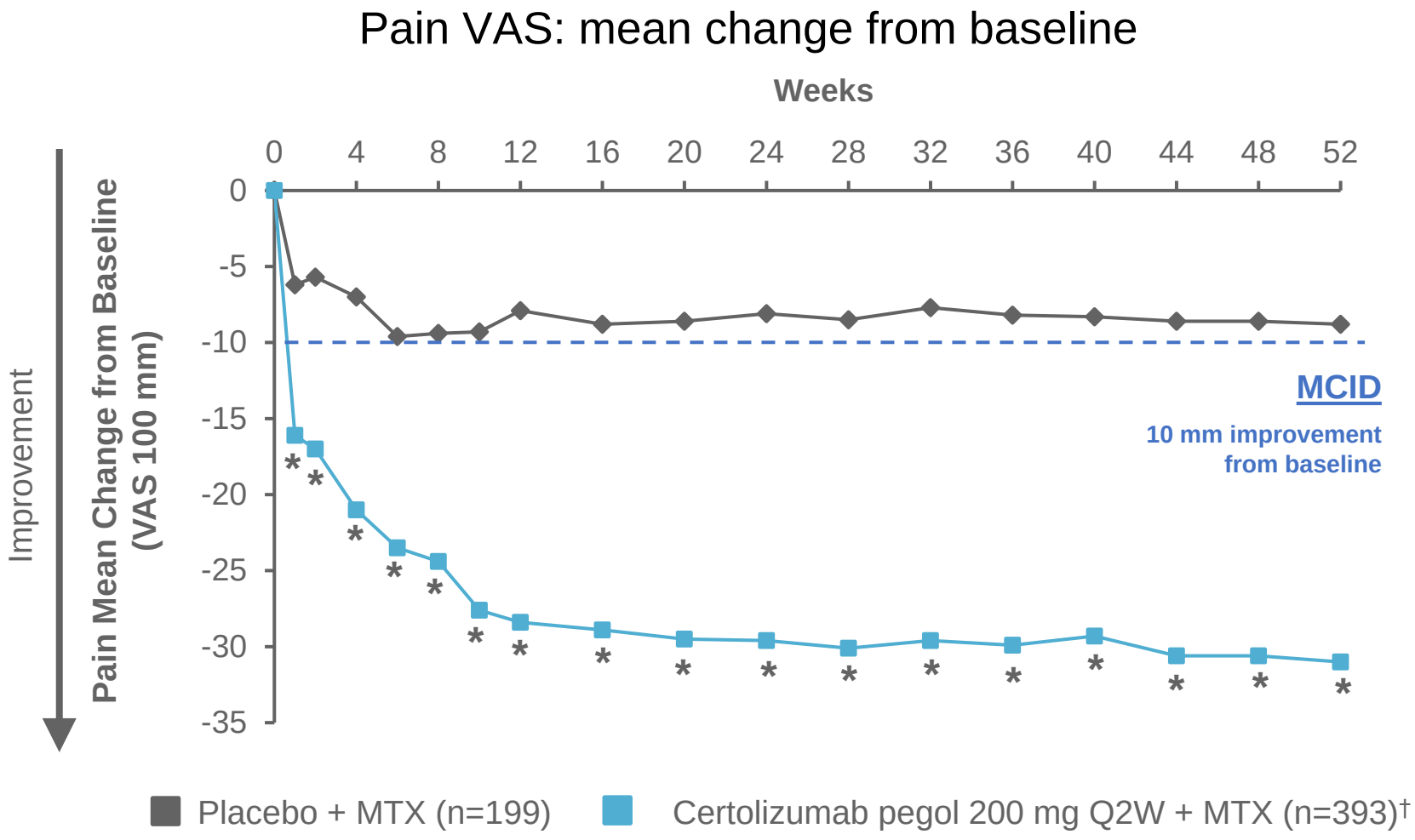


In an SLR, residual symptoms such as pain and fatigue were common in patients with RA who were in clinical remission (particularly DAS28 criteria)

Number of studies by definition of remission and symptom or burden Bubble size represents number of studies
SLR, systematic literature review

Ishida M, et al. Mod Rheumatol 2018;28:789–99

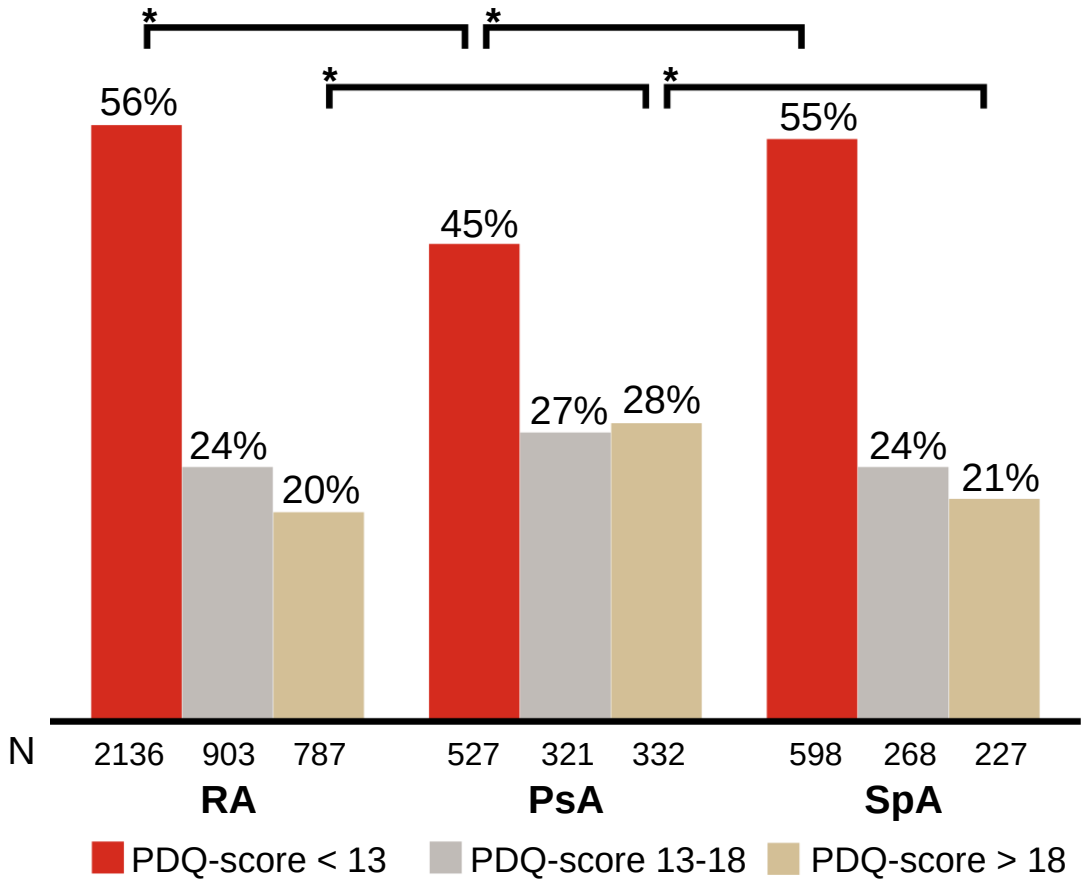
Impact of anti-TNFs on pain in established RA



LOCF (ITT population)
*P<0.001 vs. placebo. †Patients received a loading dose of certolizumab pegol 400 mg at Weeks 0, 2 and 4.

Strand V et al. *Arthritis Research & Therapy.* 2009 11:R170

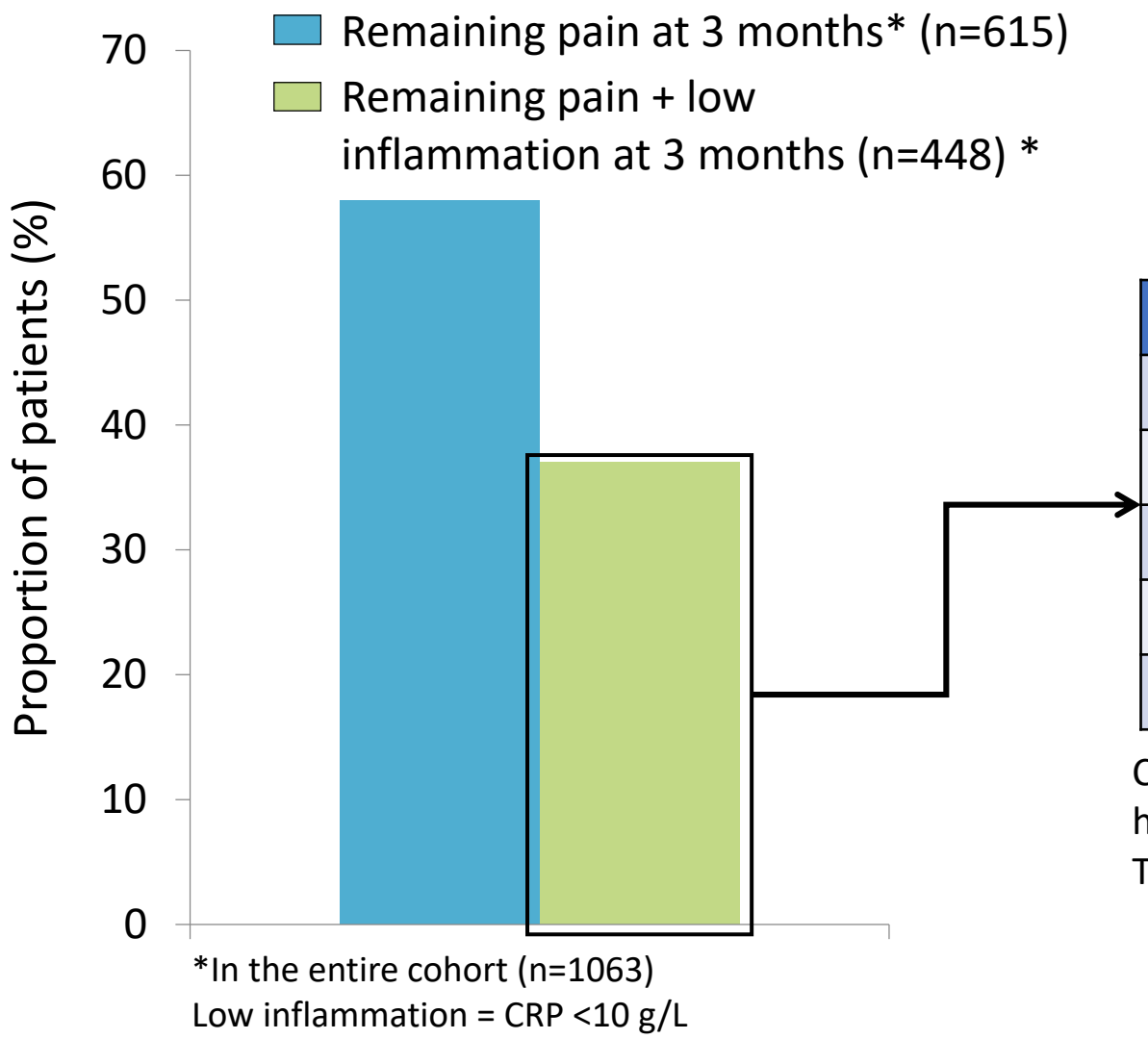
Inflammatory arthritis patients reported clinically significant pain despite anti-rheumatic therapy



PainDETECT questionnaire (PDQ) score was associated with composite disease activity and PROs but not with markers of inflammation (CRP and SJC)

*P<0.001.
N=15,978; Cross-sectional survey including patients registered in DANBIO, >90% of adults treated with biologics/DMARDs due to rheumatic disease.
CRP: C-reactive protein; PDQ: painDETECT questionnaire is a patient-administered screening questionnaire originally developed to identify neuropathic pain; PROs: patient reported outcomes; SJC: swollen joint count.
Rifbjerg-Madsen S, et al. *PLoS One*. 2017;12(7):e0180014.

Pain often persists in the absence of inflammation



Risk factors for remaining pain and low inflammation at 3 months

Baseline factor	OR†	95% CI
Disability (HAQ)	1.45	1.17 – 1.79
Inflammation (ESR)	0.86	0.81 – 0.91
PGA	1.1	1.05–1.16
CRP	0.83	0.79 – 0.88
28-TJC	1.04	1.01 – 1.06

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaires; PGA, patient global assessment; TJC, tender joint count. †Adjusted for age and gender.

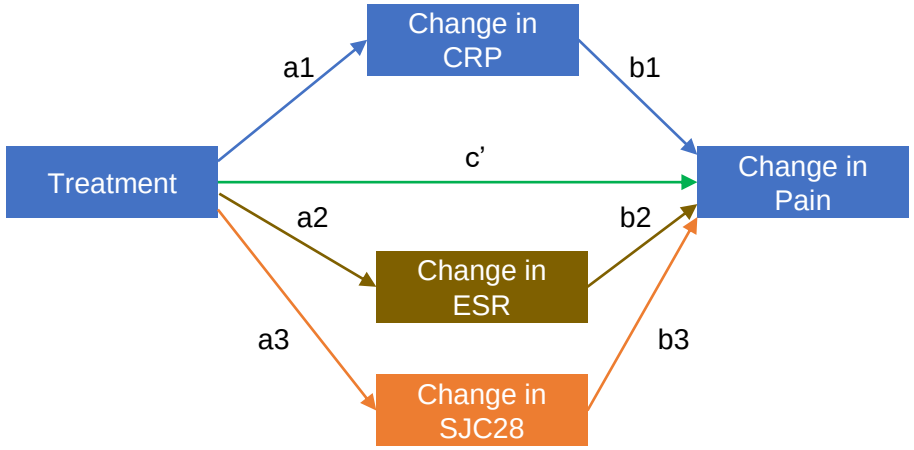
Altawil R et al. *Arthritis Care Res* 2016;68:1061-8.

Pain reduction and inflammation

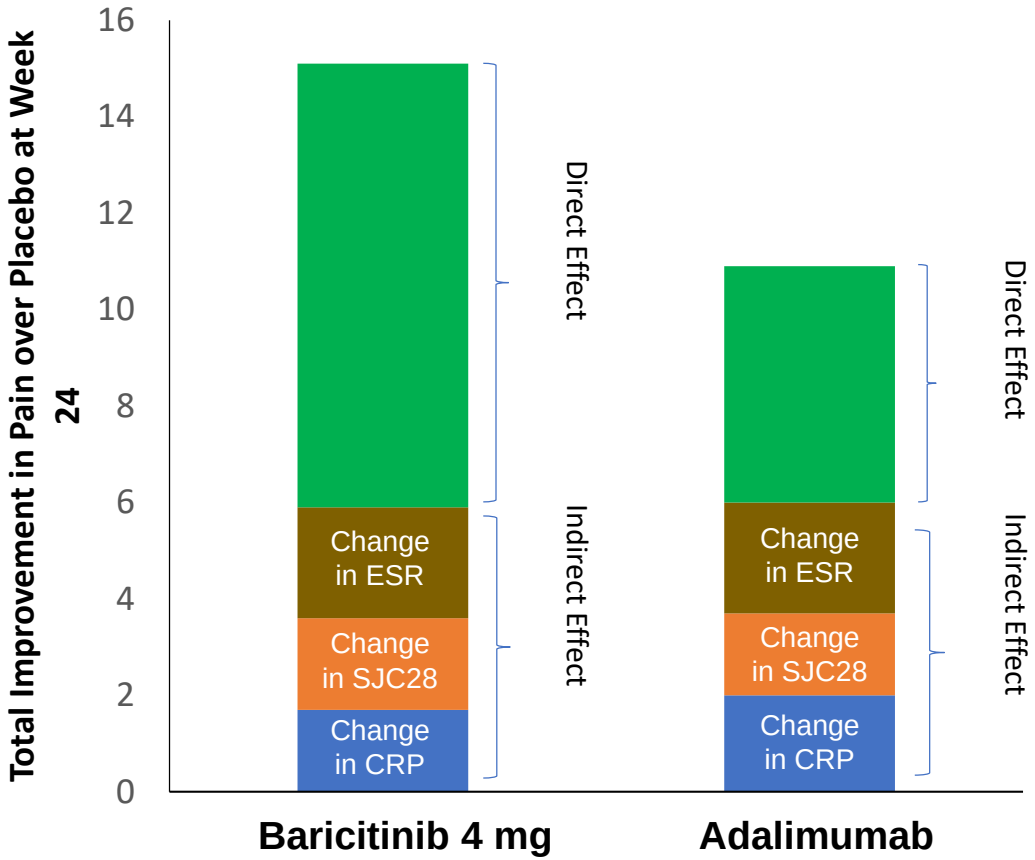
- Assessing the direct and indirect relationships between pain and inflammation with multiple mediation analysis

Indirect effect: Pain change attributable to inflammation change as assessed by objective markers (CRP/ESR/SJC)
Direct effect: Pain change that cannot be accounted for by change in CRP/ESR/SJC

CRP, ESR, and SJC as mediators on pain change by treatment

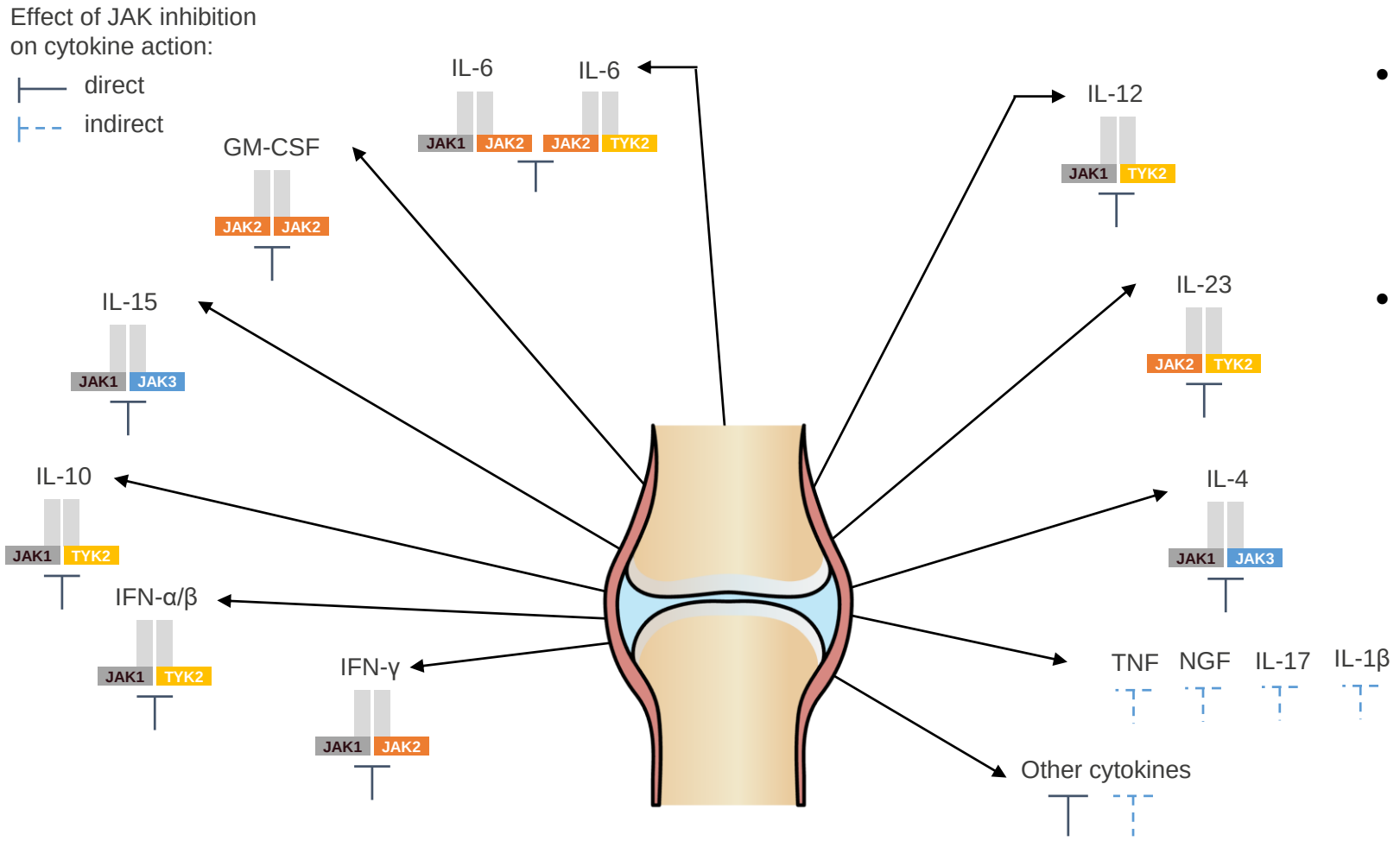


Direct effect: c'
Indirect effect: a1b1+a2b2+a3b3



Taylor PC et al. J Clin Medicine Jun 12;8(6). pii: E831

JAK Inhibitors May Directly or Indirectly Modulate Multiple Cytokines Involved in Inflammation and Pain

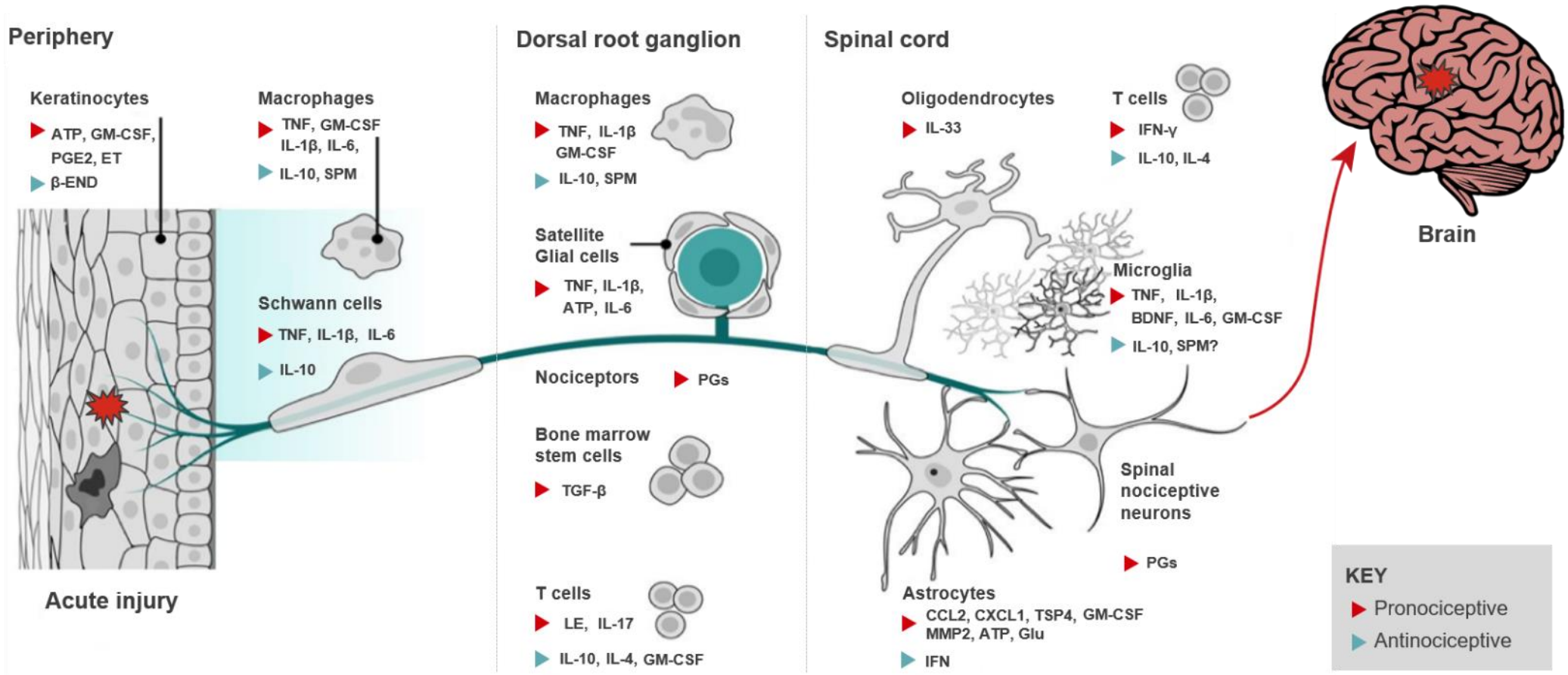


- Signaling of key cytokines implicated in **inflammation** and **pain** is blocked through direct inhibition of JAKs[1]
- Other cytokines signal independently of JAKs, but their expression is regulated by JAK-dependent cytokines and may be blocked indirectly by JAK inhibition[1]

GM-CSF: granulocyte-macrophage colony stimulating factor; IFN: interferon; IL: interleukin; JAK: Janus kinase; NGF: nerve growth factor; RA: rheumatoid arthritis; TYK: tyrosine kinase.

1. Veale DJ, et al. *Rheumatology (Oxford).* 2019;58(2):197-205. 2. O'Shea JJ, et al. *Annu Rev Med.* 2015;66:311-328. 3. O' Shea JJ, Plenge R. *Immunity.* 2012;36(4):542-550. 4. Salaffi F, et al. *Pain Res Manag*. 2018:8564215. 5. Nicol LSC, et al. *Pain.* 2018;159(3):550-559. 6. Kiu H, Nicholson SE. *Growth Factors.* 2012:30(2):88-106. 7. You T, et al. *Sci Rep*. 2017;7(1):1-15. 8. Murray PJ. *J Immunol*. 2007;178(5):2623-2629. 9. Raoof R, et al. *Rheumatology*. 2018;57(3):429-440. 10. Zhang A, Lee YC. *Curr Osteoporos Rep.* 2018;16(5):603-610.

JAK/STAT PATHWAY IN PAIN

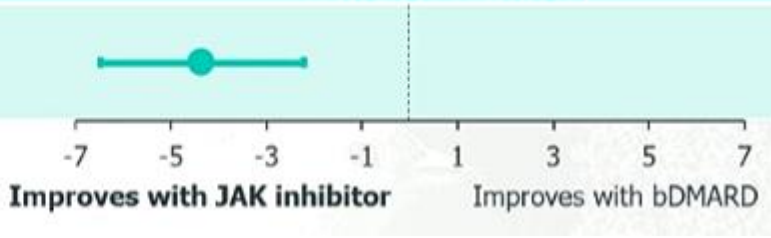


ATP=adenosine triphosphate; BDNF=brain-derived neurotrophic factor; CCL=C-C motif chemokine ligand; CXCL=C-X-C motif chemokine ligand; TSP=thrombospondin; END=endorphin; ET=endothelin; GM-CSF=granulocyte-macrophage colony-stimulating factor; Glu=glutamate; IFN=interferon; IL=interleukin; LE=leukocyte elastase; MMP=matrix metalloprotease; PGE2=prostaglandin E2; PGs=prostaglandins; SPM=specialized pro-resolution mediators; TGF=transforming growth factor; TNF=tumor necrosis factor

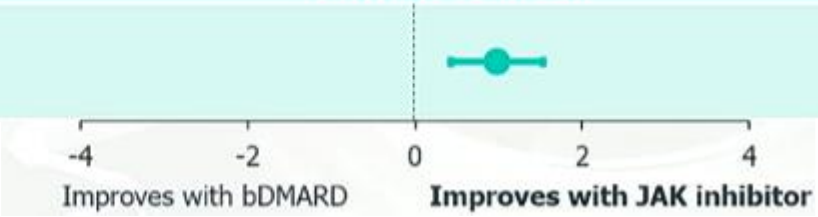
Figure adapted from Ji RR, et al. *Science.* 2016;354:572-577. Ji RR, et al. *Pain.* 2013;154(Suppl .1):S10-S28. Salaffi F, et al. *Pain Res Manag*. 2018;2018:8564215. Dominguez E, et al. *J Neurosci.* 2010:30;5754-66. Choy EHS, Calabrese LH. *Rheumatology (Oxford).* 2018;57:1885-1895.

Jak-inhibitors and pain

	JAK inhibitor	bDMARD	WMD (95% CI)
Pain (VAS 0–100 mm)	n=1264	n=915	

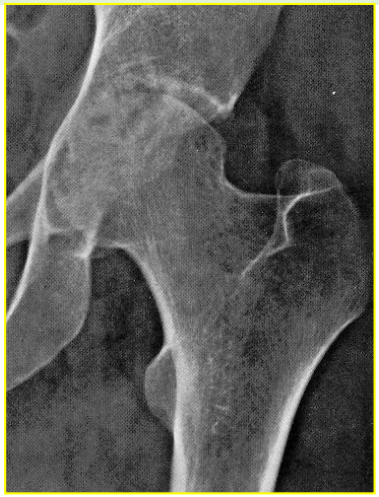


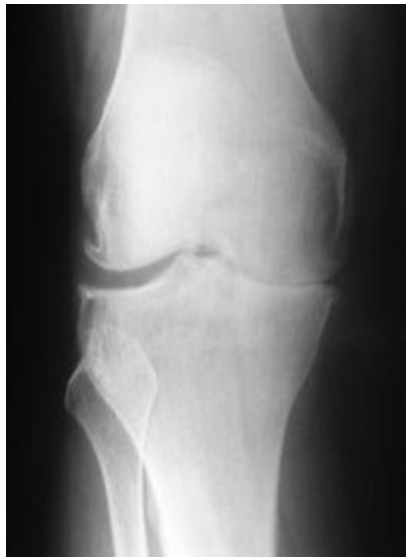
	JAK inhibitor	bDMARD	WMD (95% CI)
FACIT-F	n=3051	n=1794	



Toth et al. Int J Mol Sci. 2022 Jan 23;23(3):1246

Pain mechanisms in RA-secondary osteoathritis





- Furthermore, secondary osteoarthritis (OA) accompanies advanced disease.
- OA may be associated with abnormal sensory nerve growth into articular cartilage , and the inner two-thirds of the meniscus, possibly through the actions of NGF.
- These pathologic innervations could further aggravate pain during weight bearing or joint movement.

Suri S, Gill SE, Massena de Camin S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. Ann Rheum Dis. 2007;66:1423–8.

Pain mechanisms in RA-depression

- As with other chronic painful conditions, pain in RA is associated with important mood disturbance.
- The **prevalence of depression ranges from 13% to 20%** based on psychiatric assessments and considerably higher when based on self-report assessments
- Low mood may be a consequence of pain, but may also contribute to its distressing quality and impair facility to cope with pain.

Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res. 2006;60:469–76.

Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors

Tanya Covic[a,*], Graham Tyson[b], David Spencer[c], Graydon Howe[c]

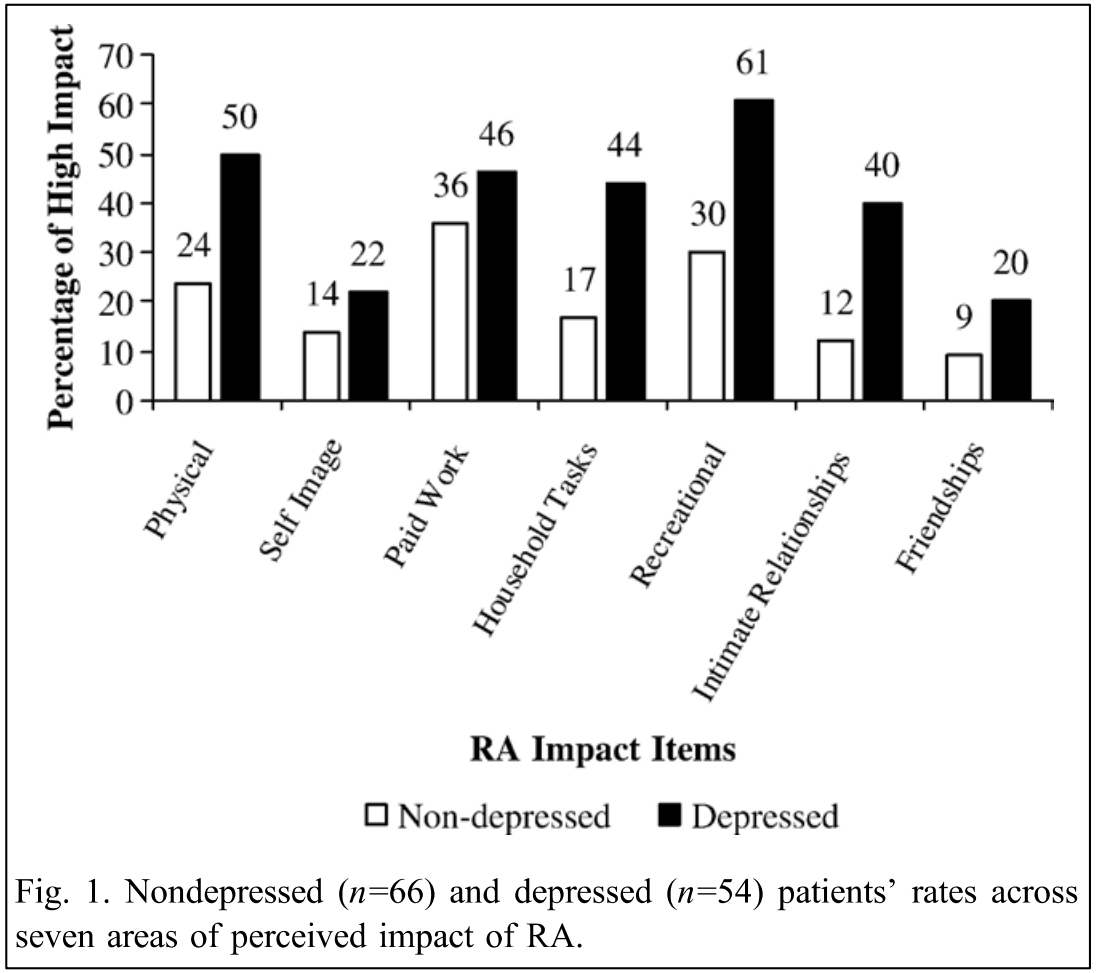


Fig. 1. Nondepressed (n=66) and depressed (n=54) patients' rates across seven areas of perceived impact of RA.

a seven-item scale developed to measure perceived impact of RA

Journal of Psychosomatic Research 60 (2006) 469–476J

Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors

Tanya Covic[a,*], Graham Tyson[b], David Spencer[c], Graydon Howe[c]

Discriminant loadings: contribution of each variable to the prediction of depressed ($n = 54$) and nondepressed ($n = 66$) participants

Independent variable—predictor	Discriminant loadings
AIMS—Tension	0.73**
RSE—Self-esteem	0.73**
RA Impact	0.58**
Fatigue	0.57**
AIMS—Pain	0.55**
CSQ—PC	0.47**
HAQ—Physical disability	0.44**
Medication effectiveness	−0.35**
BPCQ—Internal control	−0.30**
Medication side-effect concern	0.23*
Medication importance	−0.22*
BPCQ—Chance happening	0.19*

* $P < .05$.

** $P < .01$.

A discriminant analysis was performed with depression categories (depressed/nondepressed) as the dependent variable

Journal of Psychosomatic Research 60 (2006) 469–476J

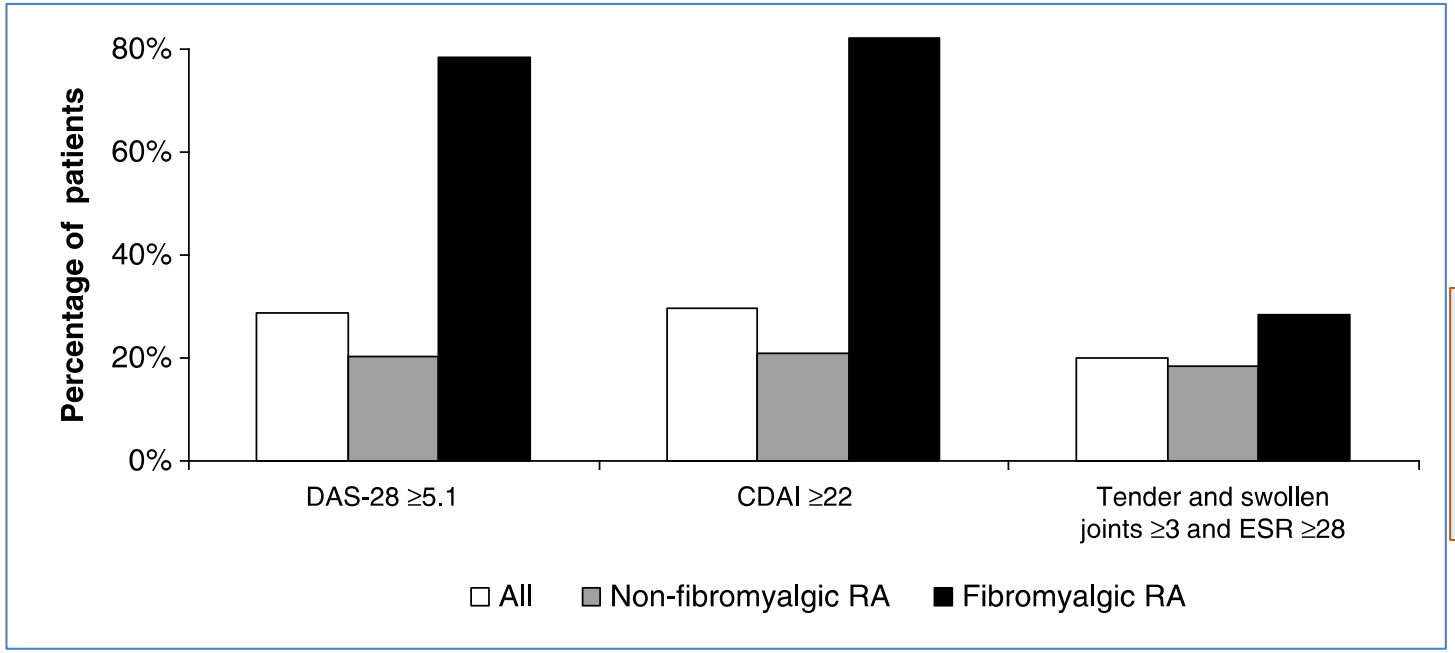
RHEUMATOLOGY

Rheumatology 2010;49:924–928
doi:10.1093/rheumatology/kep458
Advance Access publication 25 January 2010

Concise report

Fibromyalgic rheumatoid arthritis and disease assessment

Louise C. Pollard[1], Gabrielle H. Kingsley[1], Ernest H. Choy[1] and David L. Scott[1]



Impact of fibromyalgic RA on different assessments of active disease.

DAS-28 may overestimate the disease activity in patients with fibromyalgic RA.

Fibromyalgic RA patients can be identified by examining tender minus swollen joint counts.

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 61, No. 6, June 15, 2009, pp 794–800
DOI 10.1002/art.24430

ORIGINAL ARTICLE

Association of Concomitant Fibromyalgia With Worse Disease Activity Score in 28 Joints, Health Assessment Questionnaire, and Short Form 36 Scores in Patients With Rheumatoid Arthritis

ALINE RANZOLIN,[1] JOÃO CARLOS TAVARES BRENOL,[1] MARKUS BREDEMEIER,[1] JAIRO GUARIENTI,[1] MARCELE RIZZATTI,[1] DANIEL FELDMAN,[2] AND RICARDO MACHADO XAVIER[1]

Values of the DAS28 (and related variables), HAQ, patient pain VAS, and physician VAS in rheumatoid arthritis (RA) patients with and without fibromyalgia (FM)*

Evaluation measures of RA	RA (n = 238)	RA and FM (n = 32)	*P*†
DAS28, mean ± SD	4.03 ± 1.39	5.36 ± 0.99	< 0.001
ESR, mm/hour	25.0 (13.7–40.0)	29.0 (16.0–49.0)	0.343
Swollen joints	2.0 (0.0–5.0)	3.5 (1.0–5.0)	0.119
Tender joints	3.0 (0.0–8.0)	9.5 (4.5–16.0)	< 0.001
Disease activity VAS	32.0 (14.0–53.2)	56.5 (42.5–89.5)	< 0.001
Disease activity‡			0.001
High (DAS28 >5.1)	52 (21.8)	19 (59.4)	
Moderate (DAS28 >3.2 to ≤5.1)	111 (46.6)	12 (37.5)	
Low (DAS28 ≤3.2)	35 (14.7)	1 (3.1)	
Remission (DAS28 <2.6)	40 (16.8)	0 (0.0)	
HAQ score	1.12 (0.62–2.00)	2.00 (1.37–2.44)	< 0.001
Patient pain VAS	40.0 (16.0–66.0)	76.0 (52.0–87.2)	< 0.001
Physician VAS	23.5 (8.7–52.2)	53.5 (23.5–67.7)	0.001

* Values are the median (25th to 75th percentiles) unless otherwise indicated. DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; VAS = visual analog scale; ESR = erythrocyte sedimentation rate.
† Student's *t*-test, Fisher's exact test, or Mann-Whitney test according to the nature and distribution of the data.
‡ Absolute number (percentage).

Conclusions

- Despite the advent of biologic therapies for RA, pain is still one of the major issues for patients.
- The underlying pathophysiology of chronic pain is complex, involving peripheral and central neural conducting pathways.
- Pain may have multifactorial aetiologies including both inflammatory and/or non-inflammatory processes.
- With respect to inflammatory causes of pain, it is possible that different inflammatory pathways contribute differentially. In an era of targeted therapies, this possibility merits further research and could potentially refine future thinking regarding the treat-to-target paradigm.
- The substantial impact of chronic pain on patients' lives or a concomitant fibromyalgia may be under-represented in the formation of disease activity treatment goals to drive management decisions in the clinic.