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Dipartimento di Scienze Cliniche e di Comunità,
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UOC Reumatologia Clinica e DH
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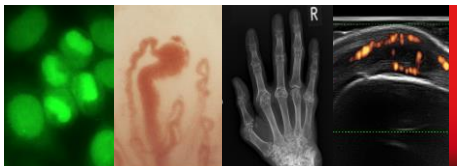
meccanismi d'azione e principi di utilizzo dei farmaci biologici *(in reumatologia)*

RECAP_RD
Research Center for Adult & Pediatric Rheumatic Diseases

Centro Specialistico Ortopedico Traumatologico
Gaetano Pini-CTO
– Sistema Socio Sanitario
Regione Lombardia

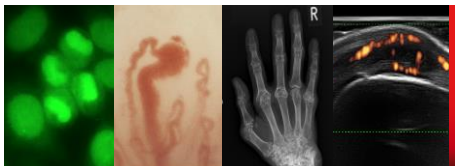


UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE CLINICHE E DI COMUNITÀ

DISCLOSURES

Speaker's fee and consultation fee from

- Abbvie
- Amgen
- BMS
- Celltrion
- Gilead/Galapagos
- Fresenius-Kabi
- Lilly
- MSD
- Pfizer
- Roche
- Sanofi
- Samsung-Bioepis
- UCB



RHEUMATOLOGY

Rheumatology 2018;57:vii5–vii10
doi:10.1093/rheumatology/key059

20 years of experience with tumour necrosis factor inhibitors: what have we learned?

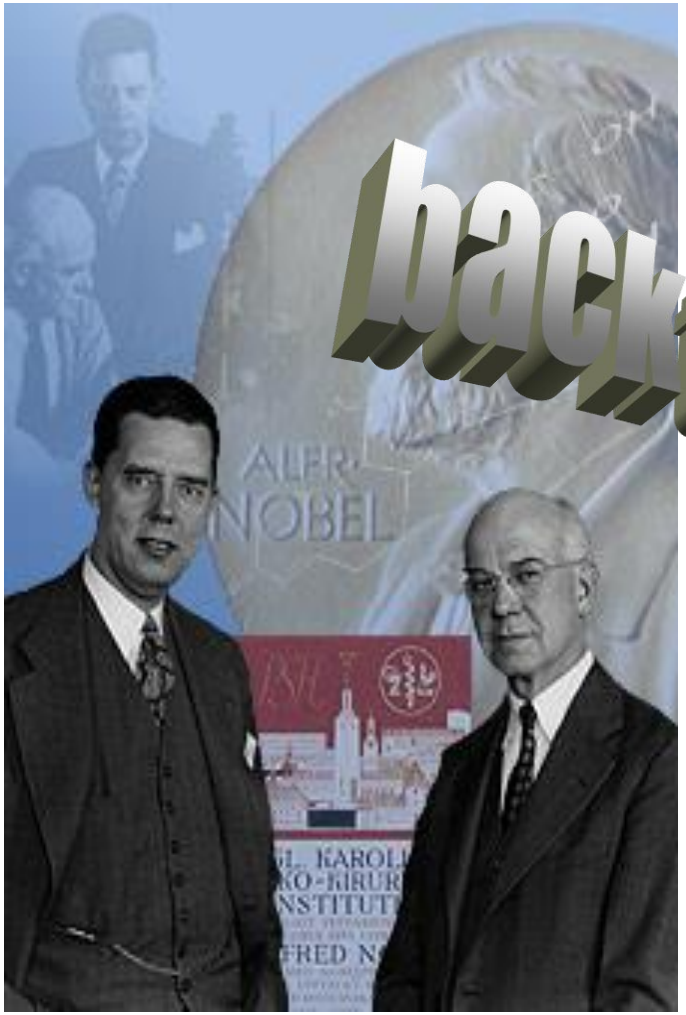
Roberto Caporali[1], Gloria Crepaldi[2], Veronica Codullo[1], Francesca Benaglio[1], Sara Monti[1], Monica Todoerti[1] and Carlomaurizio Montecucco[1]

Rheumatology key messages

- Biologics have revolutionized the way we treat RA.
- TNF inhibitors were the first biologics used both in randomized controlled trials and in clinical practice.
- TNF inhibitors are effective and safe and represent a valid option for RA.

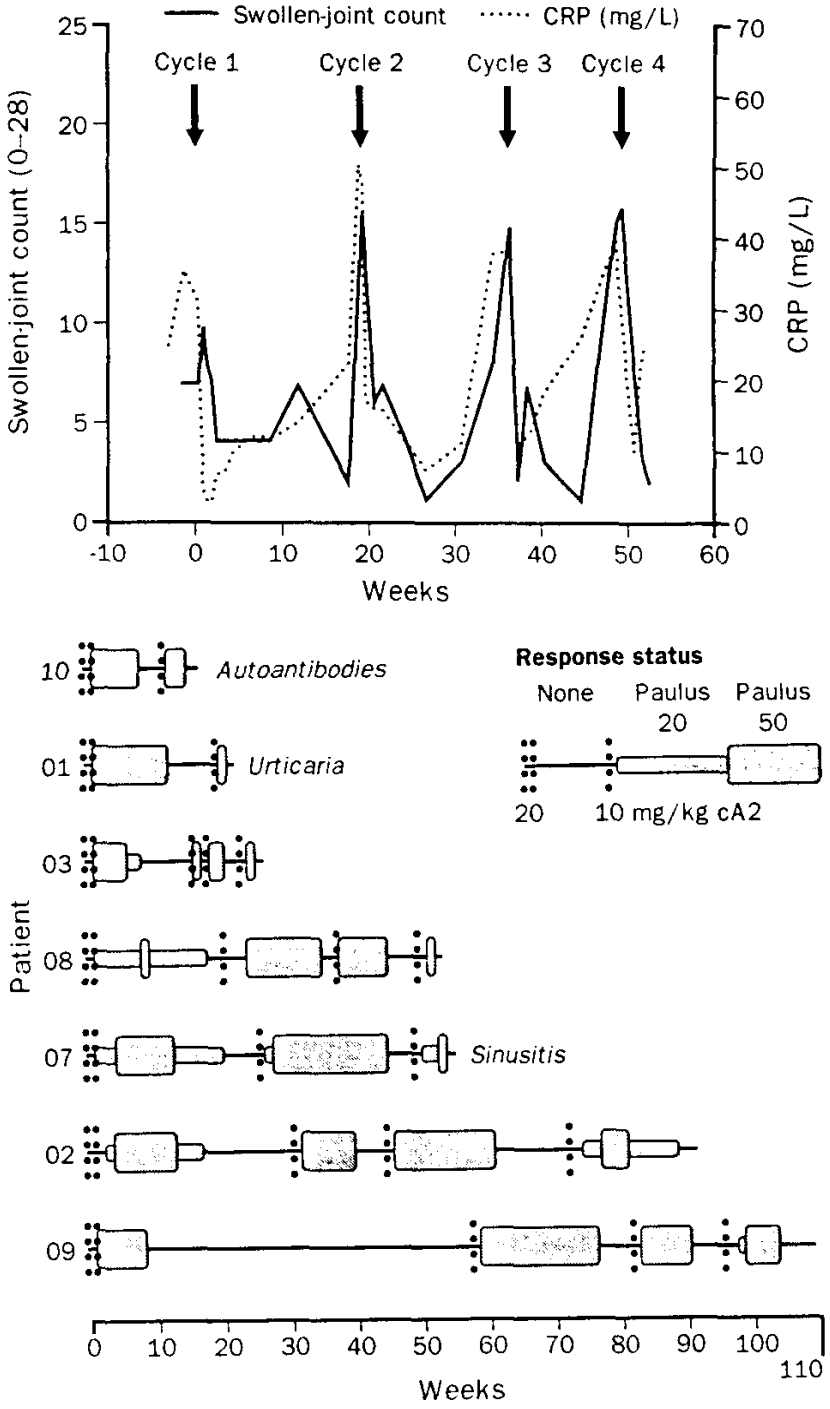
1949 Albert Lasker Award for Clinical Medical Research 2003

back to the future



Philip Hench & Edward Kendall

Marc Feldmann & Ravinder Maini

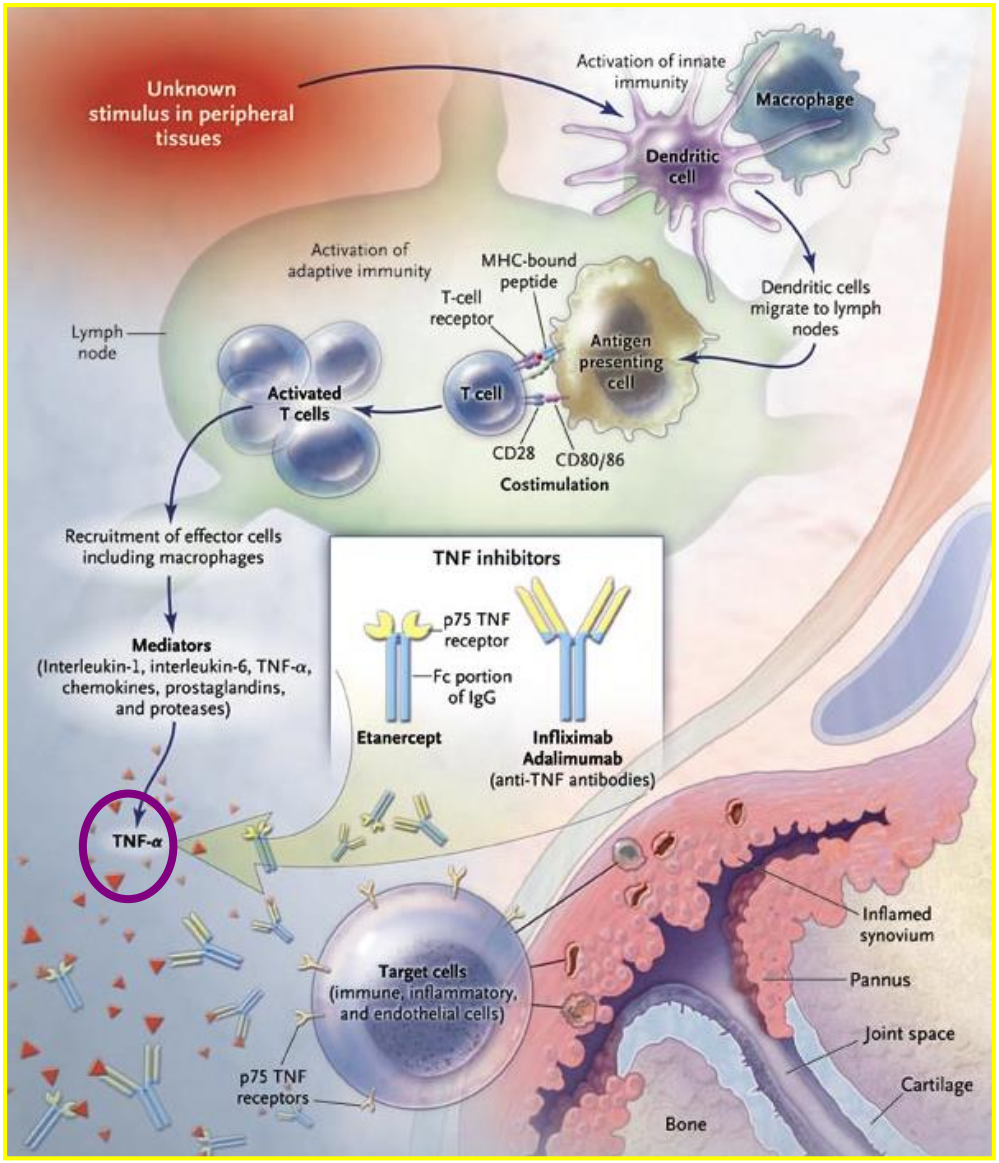


Articles

Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis

Michael J Elliott, Ravinder N Maini, Marc Feldmann, Joachim R Kalden, Christian Antoni, Josef S Smolen, Burkhard Leeb, Ferdinand C Breedveld, John D Macfarlane, hanny Bijl, James N. Woody

Lancet 1994;344:1105-10



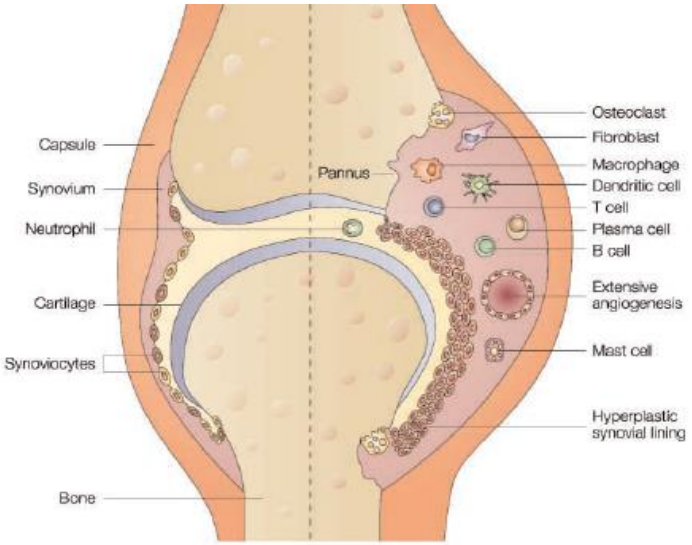
Scott & Kingsley. N Engl J Med 2006

TNFα is a proinflammatory cytokine that plays a critical role in mediation of the inflammatory synovitis, articular matrix degradation, and bony erosions in RA and is an important molecular target for directed biologic interventionis.

Bertolini DR et al. Nature 1986
Brennan FM et al. Lancet 1989

Normal joint

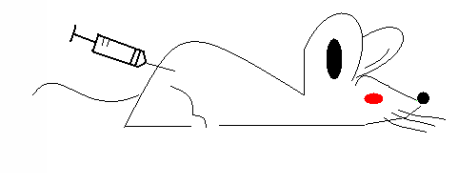
RA joint



Patients with RA

TNF INCREASED IN SYNOVIAL MEMBRANE AND SYNOVIAL FLUID

Mouse models

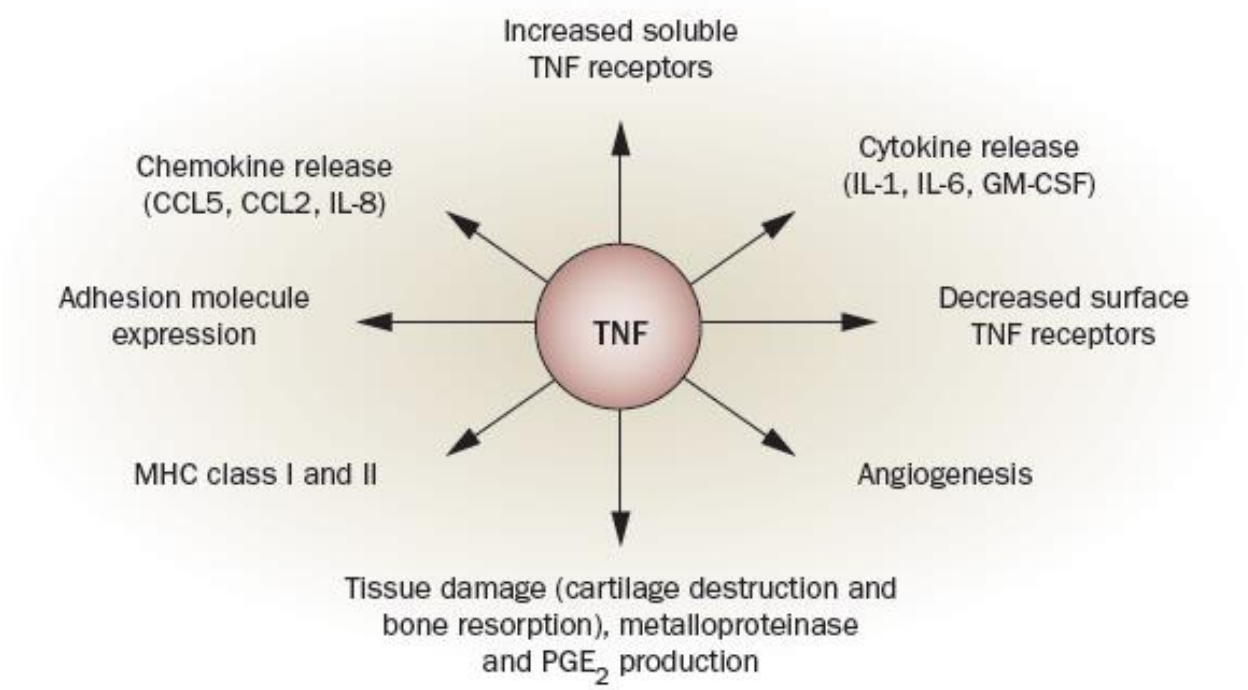


TRANSGENIC MICE FOR HUMAN TNF DEVELOP EROSIVE POLYARTHRITIS

ANTI-TNF TREATMENT IMPROVES IN VIVO COLLAGEN INDUCED ARTHRITIS

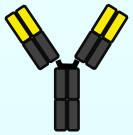
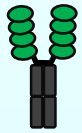
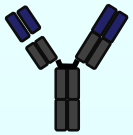
Keffer J et al. EMBO J 1991
Feldmann M et al. Ann Rev Immunol 2001

The biologic actions of TNF in the pathogenesis of RA



Taylor & Feldmann. Nat Rev Rheumatol 2009

Physical and Pharmacological Properties of originator anti-TNFalpha agents

	Infliximab	Etanercept	Adalimumab	Golimumab	Certolizumab
Design	human/murine chimeric mAb	human TNF-receptor/ Fc fusion protein	recombinant human mAb	recombinant human mAb	recombinant human antibody
Isotype	IgG_1	IgG_1 ($no\ CH_1$ domain)	IgG_1	IgG_1	Fab Pegylated fragment
bb					
Origin	Murine myeloma cells	Chinese hamster ovary cells	Chinese hamster ovary cells	Murine myeloma cells	Manufactured in E. coli and conjugation to PEG
Formulation	Lyophilized powder 100 mg for infusion	Solution, 0,5/1 ml 25 mg or 50 mg Pre-filled syringe or pen	Solution, 0,8 ml 40 mg Pre-filled syringe or pen	Solution, 0,5 ml 50 mg Pre-filled syringe or pen	Solution, 1 ml 200 mg Prefilled syringe
Specificity	TNFα	TNFα/LT	TNFα	TNFα	TNFα
Frequency of administration	1 x/6–8 weeks (maintenance therapy)	1-2 x/week	1 x/2 weeks	1 x/month	1x/2 weeks (maintenance therapy)
Half-life	8–10 days	ca. 3 days	ca. 2 weeks	ca. 12 days	ca. 2 weeks

TNF inhibitors in RA

A key argument in favor of TNF inhibitors is their **outstanding efficacy** that has revolutionized the treatment of the inflammatory arthropaties leading to novel treatment paradigms.

Combination therapy - RA

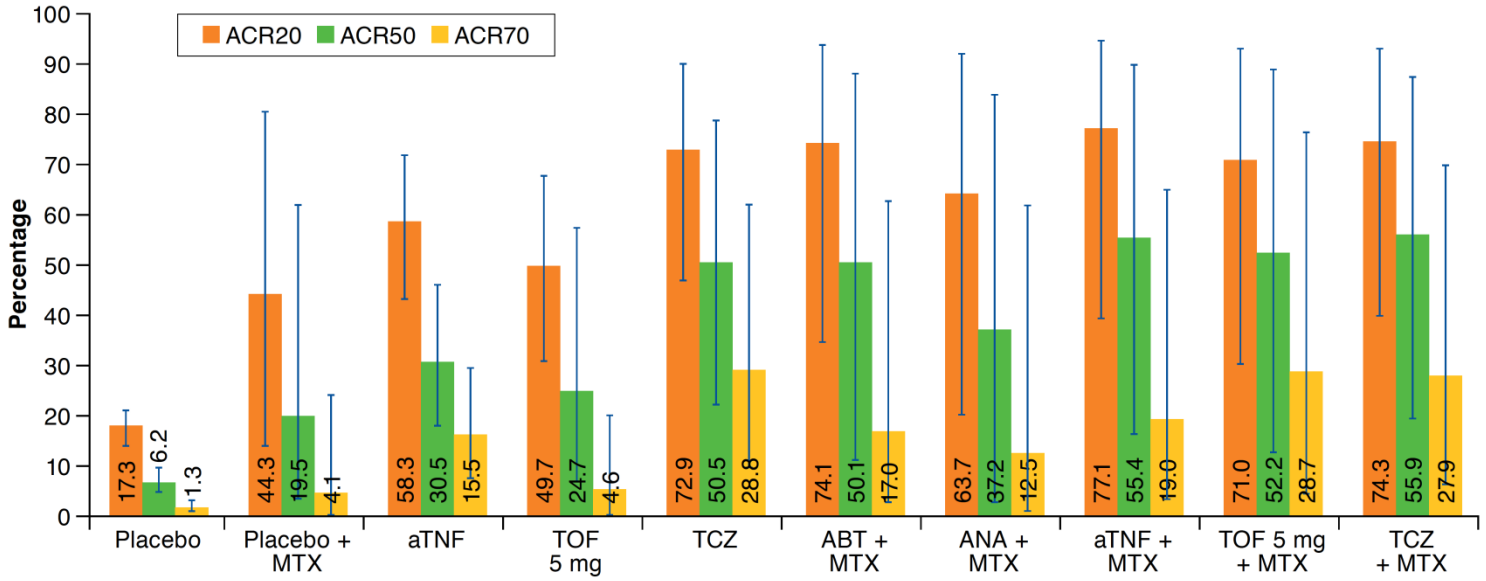
Combination therapy of biologics with MTX achieves better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs in MTX-naïve subjects or those not recently on MTX

Comparative Efficacy of Novel DMARDs as Monotherapy and in Combination with Methotrexate in Rheumatoid Arthritis Patients with Inadequate Response to Conventional DMARDs: A Network Meta-Analysis

J Manag Care Spec Pharm. 2015

Felicity Buckley, MA; Axel Finckh, MD, PhD; Tom W. J. Huizinga, MD, PhD; Fred Dejonckheere, MD, MSc; and Jeroen P. Jansen, PhD

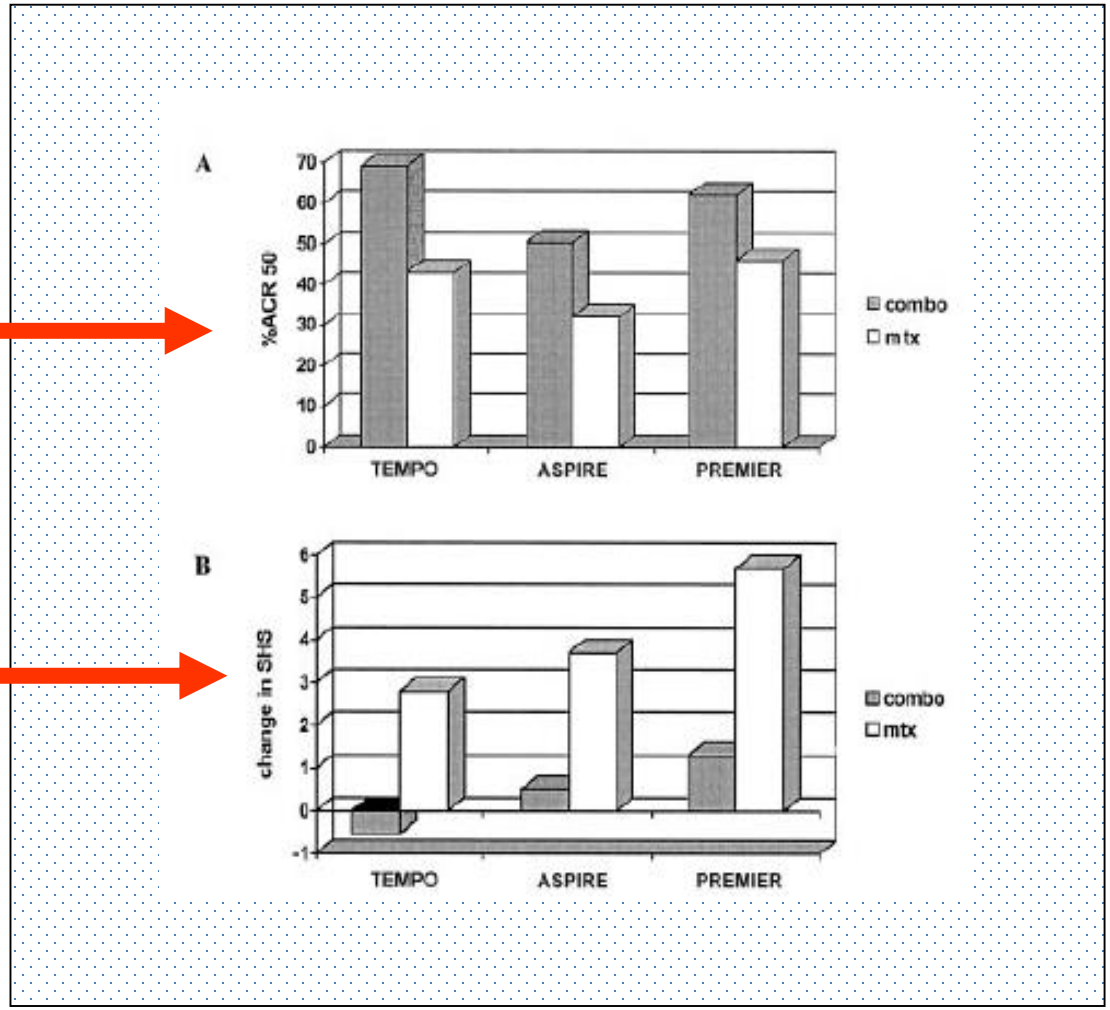
Probability of ACR20/50/70 response with 95% CrI in RA



Anti-TNF-alpha therapy:
early rheumatoid arthritis

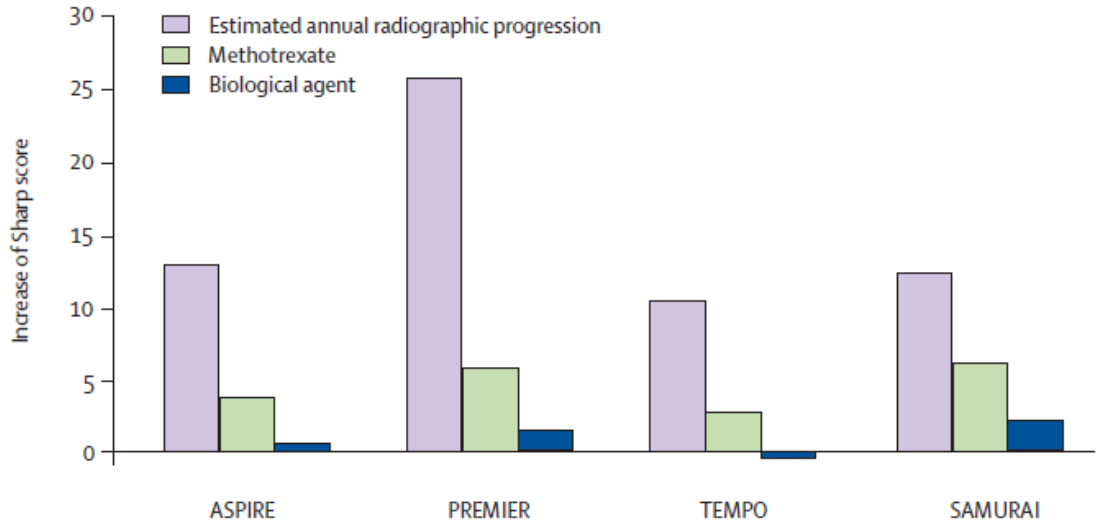
clinical

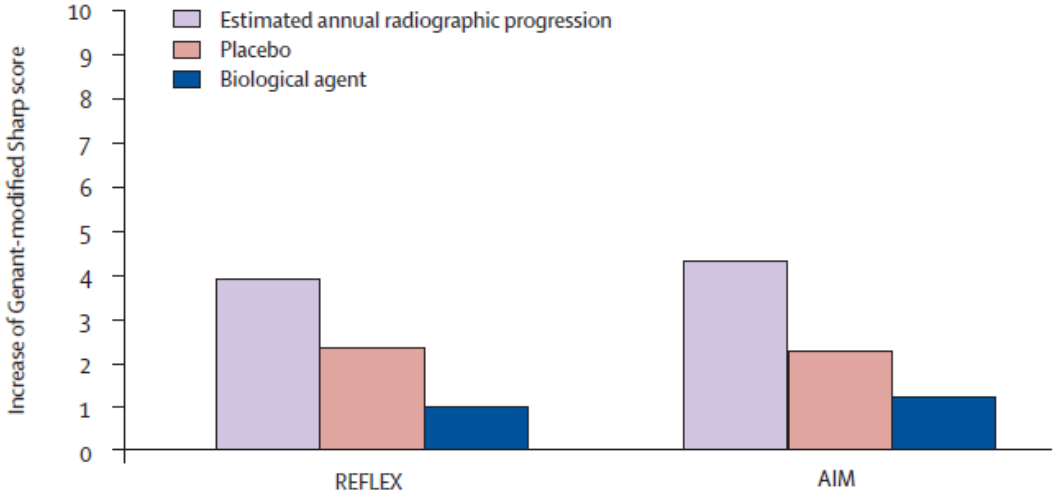
RX !!!!



Govoni M, Caporali R.
Predicting and managing the progression of structural damage in rheumatoid arthritis: where do we stand?
Clin Exp Rheumatol 2012; 30: 459

BIOLOGICS: change of joint damage



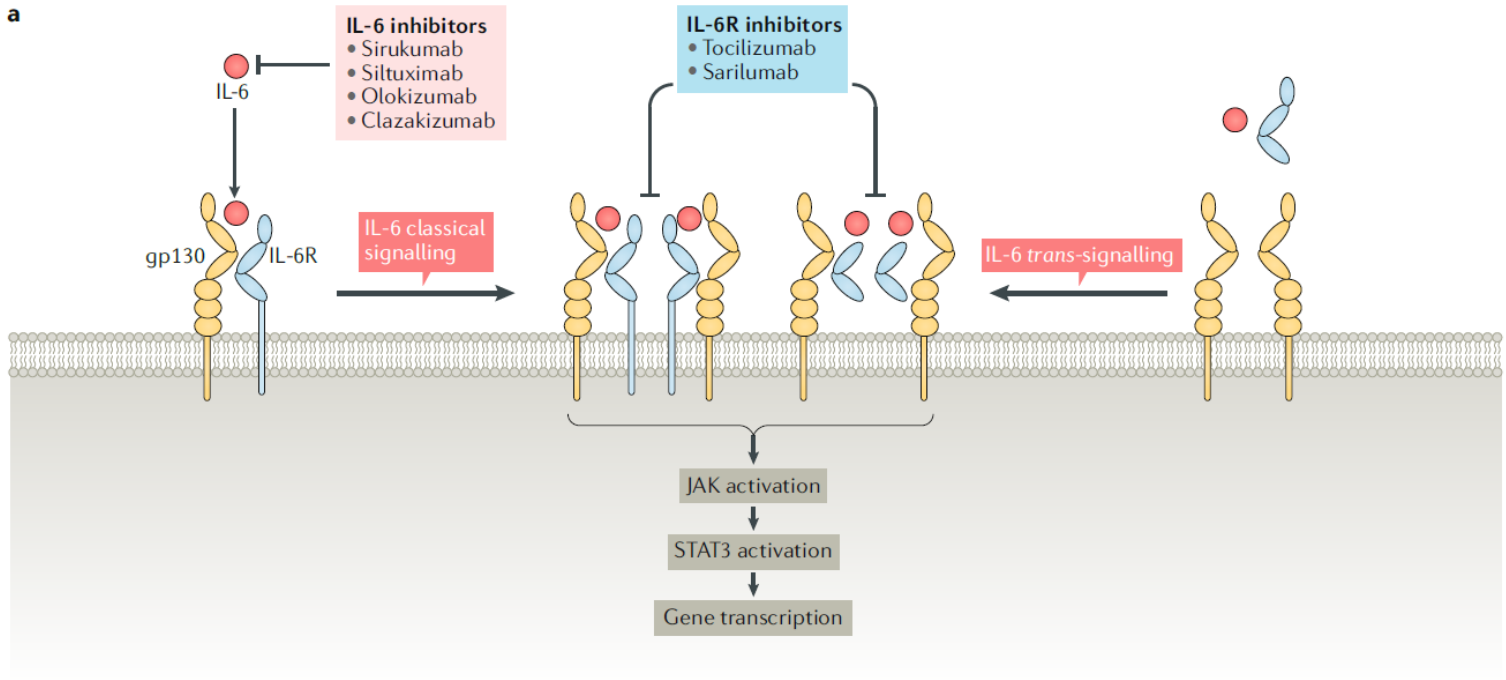


Smolen JS et al. Lancet 2007

Translating IL-6 biology into effective treatments

NATURE REVIEWS | RHEUMATOLOGY

Ernest H. Choy, Fabrizio De Benedetti, Tsutomu Takeuchi, Misato Hashizume, Markus R. John and Tadamitsu Kishimoto



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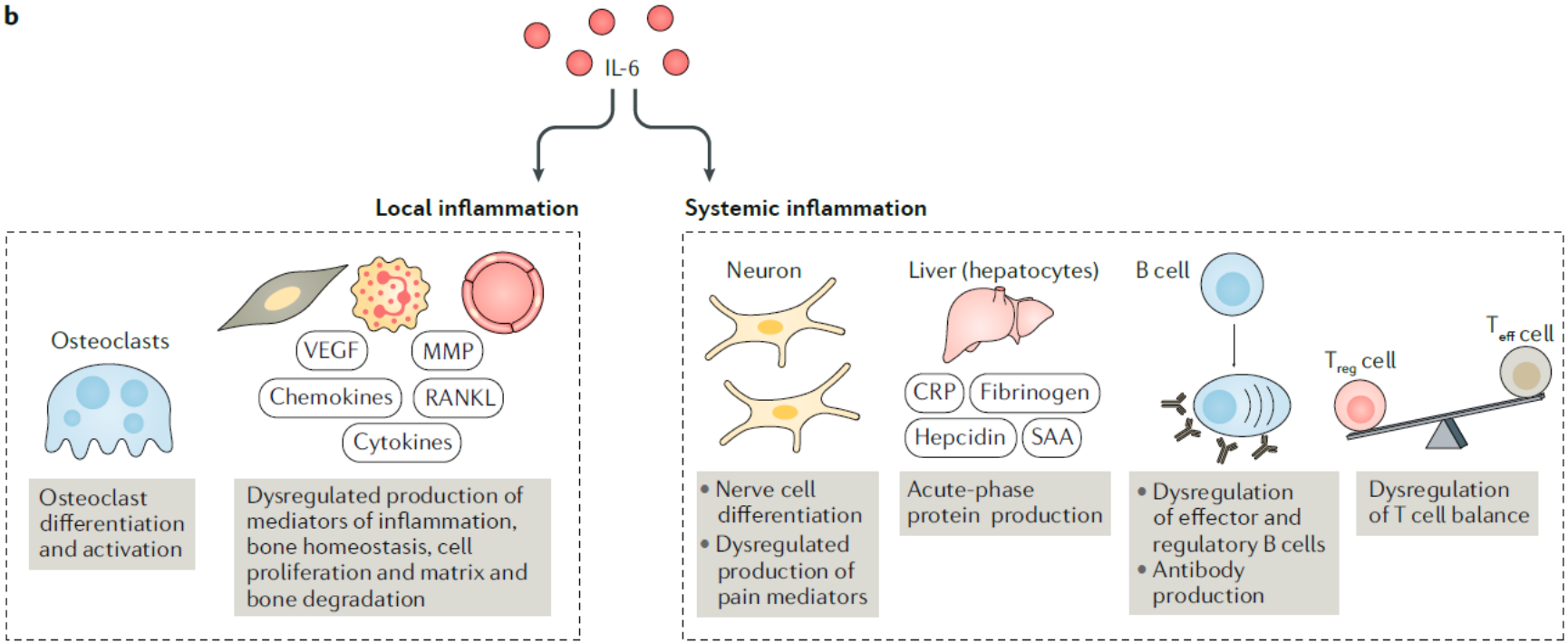

Translating IL-6 biology into effective treatments

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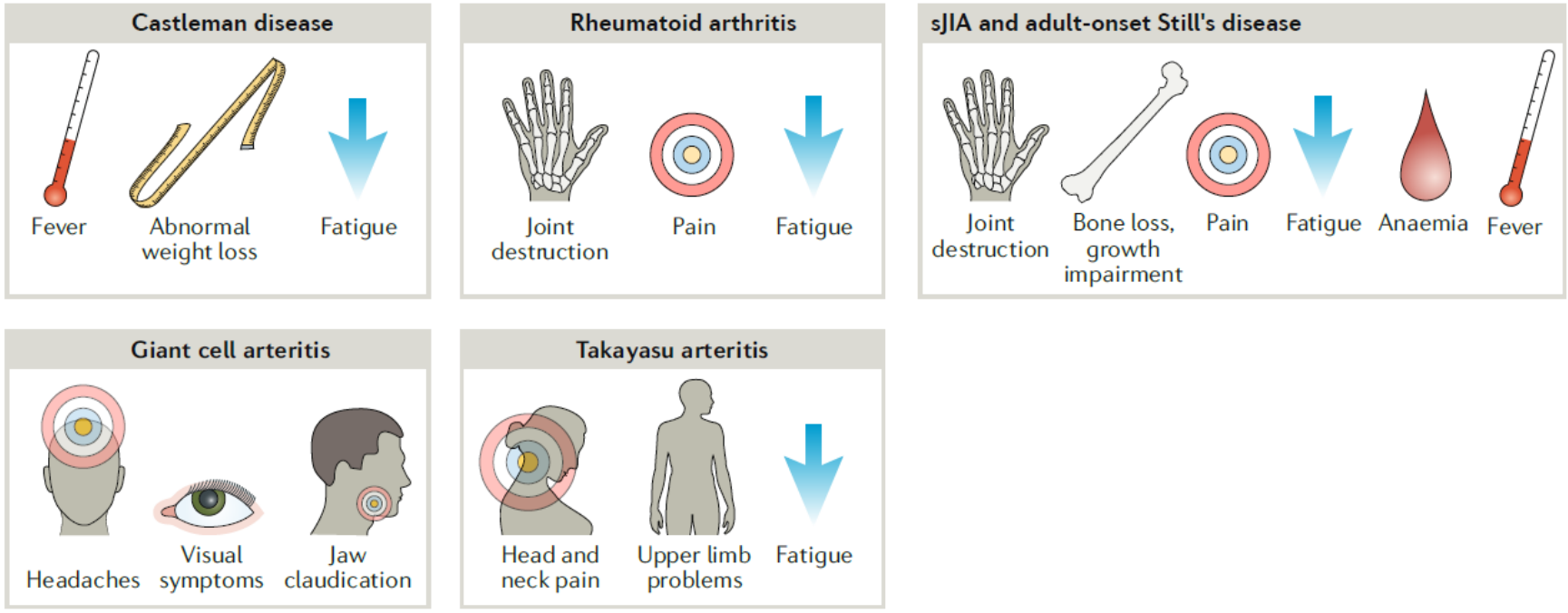
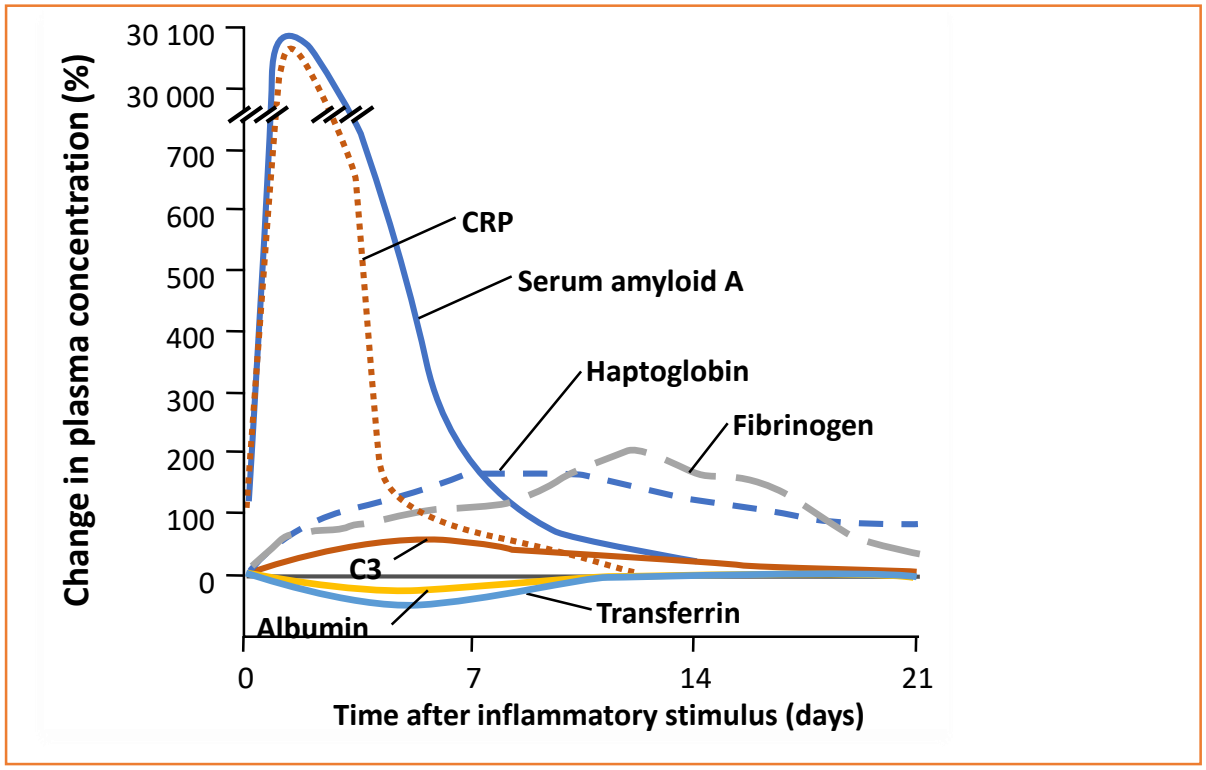
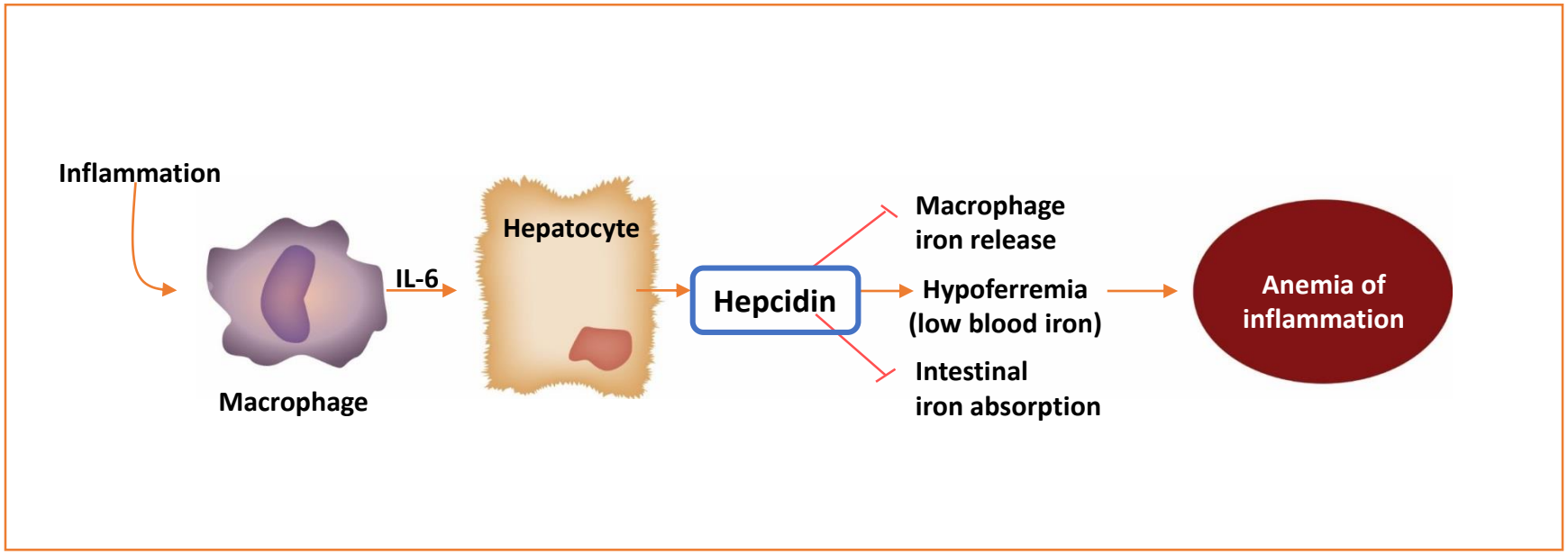


IL-6 is the major inducer of the acute-phase response



Gabay C, et al. N Engl J Med 1999;340:448–54;

Role of IL-6 in anemia

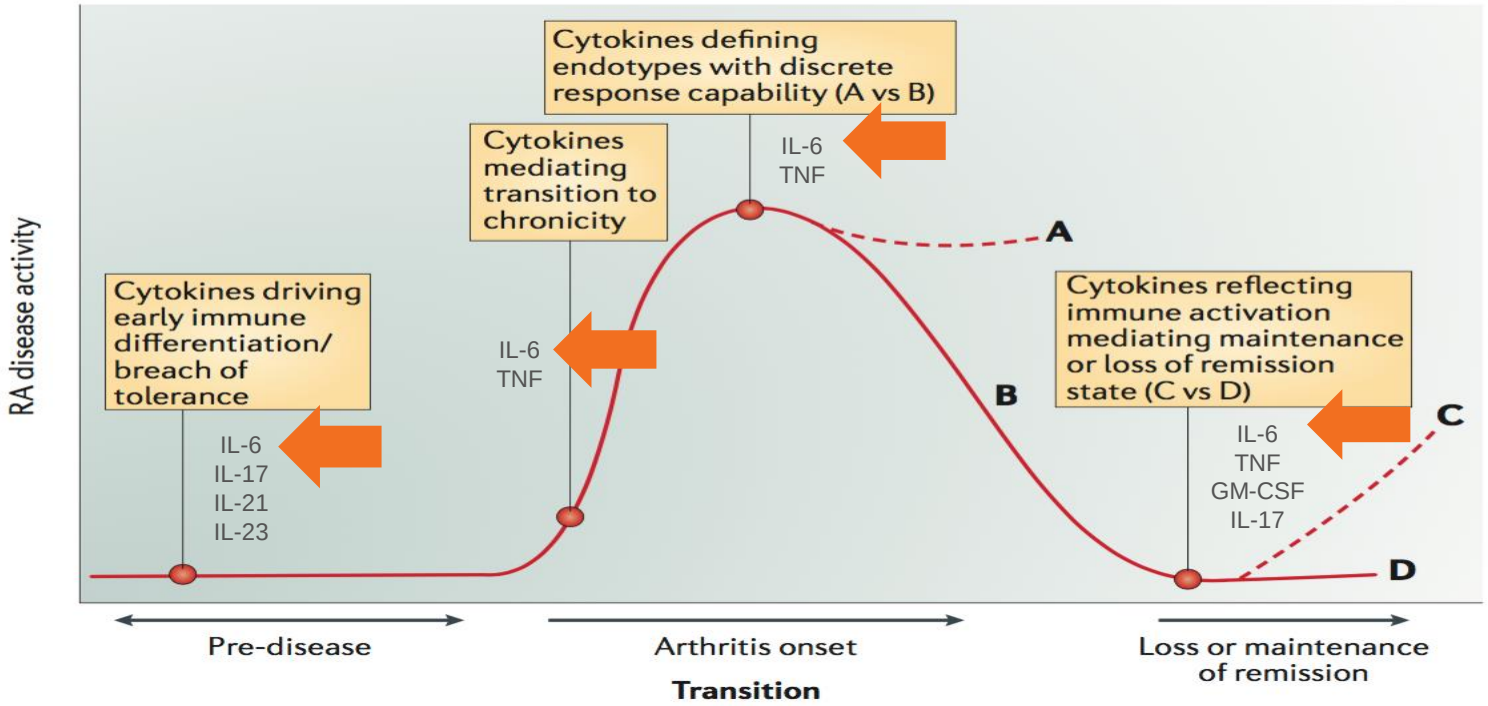


Moreland LW, et al. Semin Arthritis Rheum 2009;39:132–43;

Cytokines in rheumatoid arthritis —shaping the immunological landscape

Iain B. McInnes, Christopher D. Buckley and John D. Isaacs

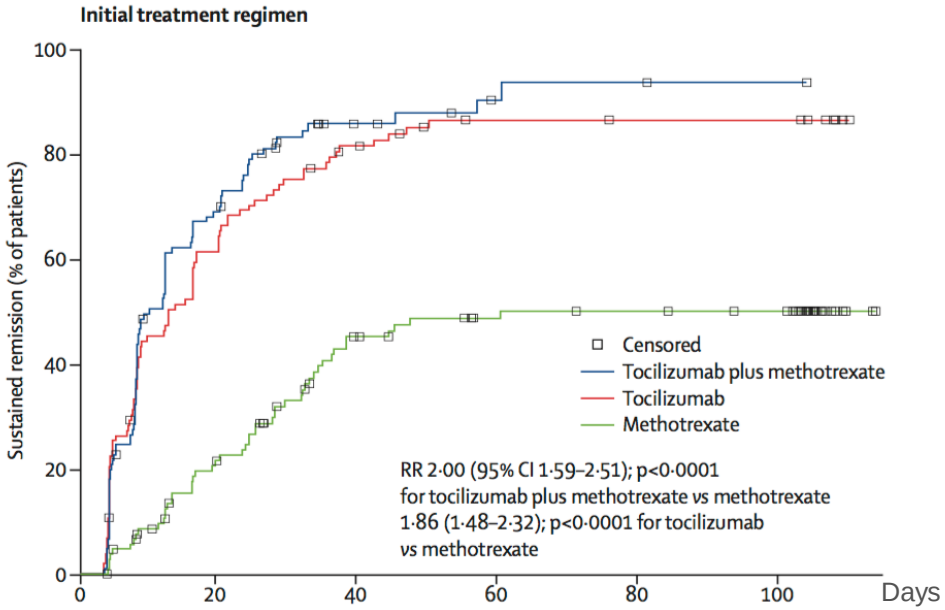
Nat Rev Rheumatol 2016

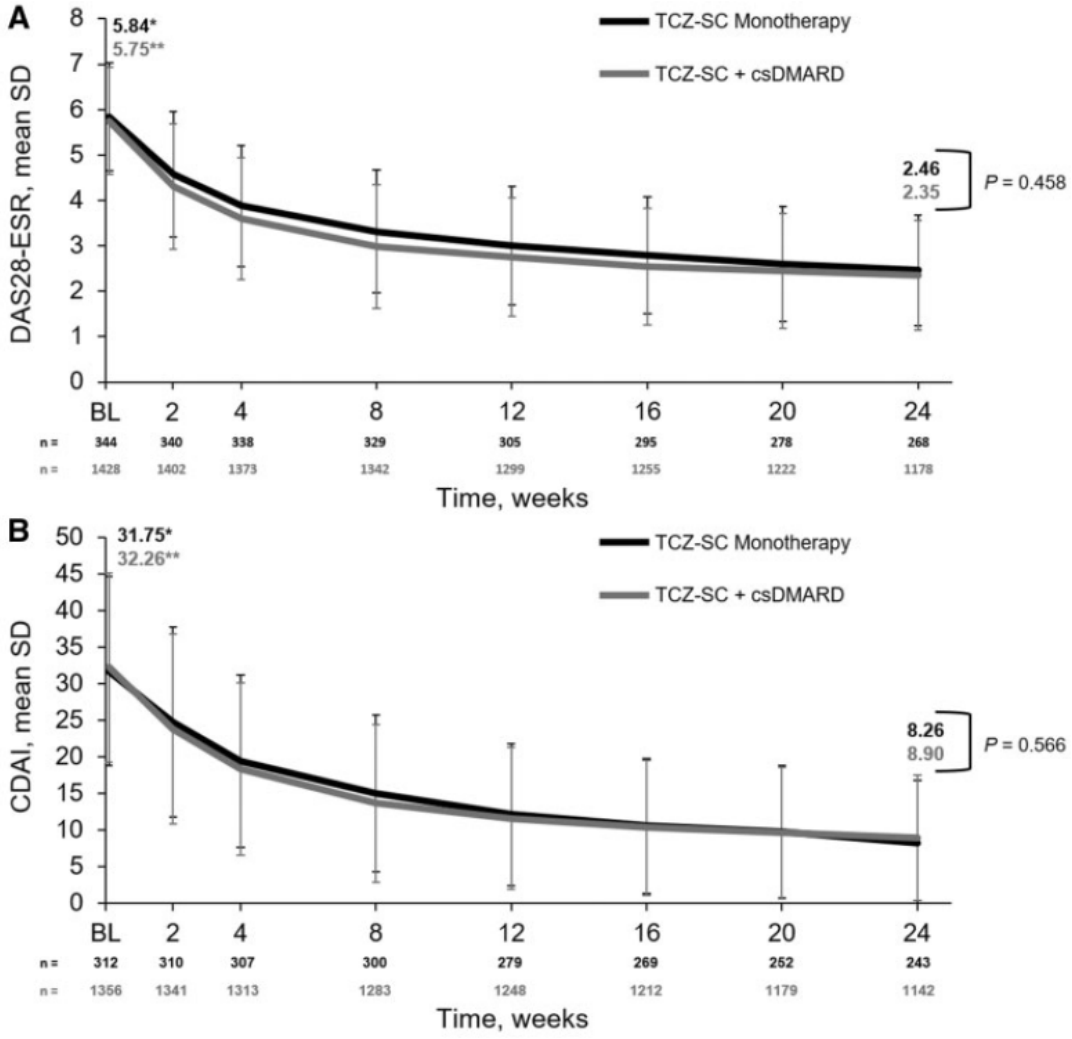


Lancet 2016

Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial

Johannes W J Bijlsma, Paco M J Welsing, Thasia G Woodworth, Leonie M Middelink, Attila Pethö-Schramm, Corrado Bernasconi, Michelle E A Borm, Cornelis H Wortel, Evert Jan ter Borg, Z Nazira Jahangier, Willemijn H van der Laan, George A W Bruyn, Paul Baudoin, Siska Wijngaarden, Petra A J M Vos, Reinhard Bos, Mirian J F Starmans, Eduard N Griep, Joanna R M Griep-Wentink, Cornelia F Allaart, Anton H M Heurkens, Xavier M Teitsma, Janneke Tekstra, Anne Carien A Marijnissen, Floris P J Lafeber, Johannes W G Jacobs



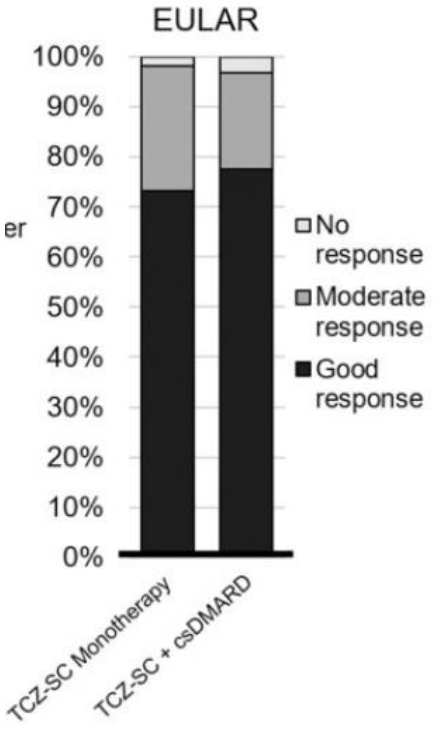


RHEUMATOLOGY
Rheumatology 2018;57:499–507
doi:10.1093/rheumatology/kex443
Advance Access publication 13 December 2017

Original article

Subcutaneous tocilizumab in rheumatoid arthritis: findings from the common-framework phase 4 study programme TOZURA conducted in 22 countries

Ernest Choy[1], Roberto Caporali[2], Ricardo Xavier[3], Bruno Fautrel[4], Raimón Sanmarti[5], Min Bao[6], Corrado Bernasconi[7] and Attila Pethö-Schramm[7]



Patterns of tocilizumab use, effectiveness and safety in patients with rheumatoid arthritis: core data results from a set of multinational observational studies

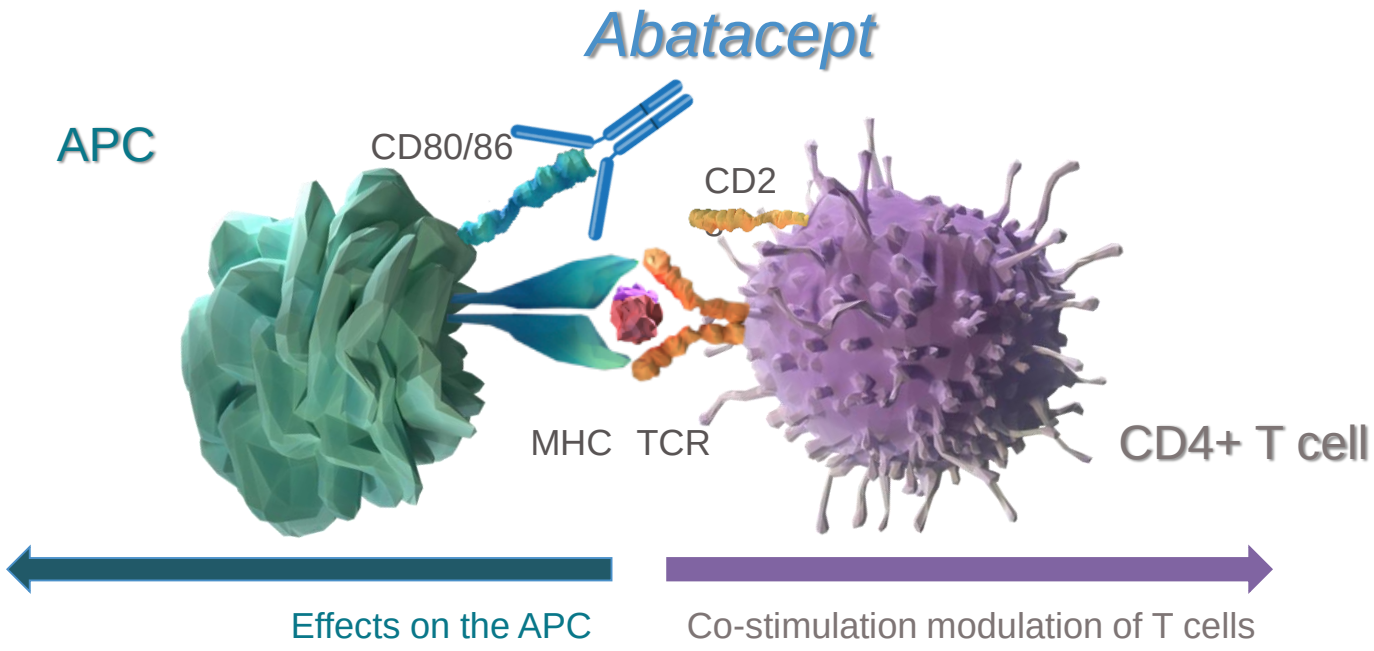
B. Haraoui[1], G. Casado[2], L. Czirják[3], A. Taylor[4], C. Bernasconi[5], W. Reiss[5], R. Caporali[6]

Country	All patients, n (%)*
Argentina	50 (3.7)
Australia	37 (2.8)
Belgium	68 (5.1)
Canada	198 (14.8)
Estonia	23 (1.7)
Finland	29 (2.2)
Greece	60 (4.5)
Hungary	290 (21.7)
Indonesia	43 (3.2)
Israel	184 (13.8)
Italy	151 (11.3)
Peru	16 (1.2)
Serbia	80 (6.0)
Sweden†	107 (8.0)
Total, n	1336

Monotherapy: 37.9%

Clinical and Experimental Rheumatology 2017; **35**: 899-906.

Abatacept Selectively Modulates the Co-stimulatory Signal Required For T-Cell Activation[1,2]

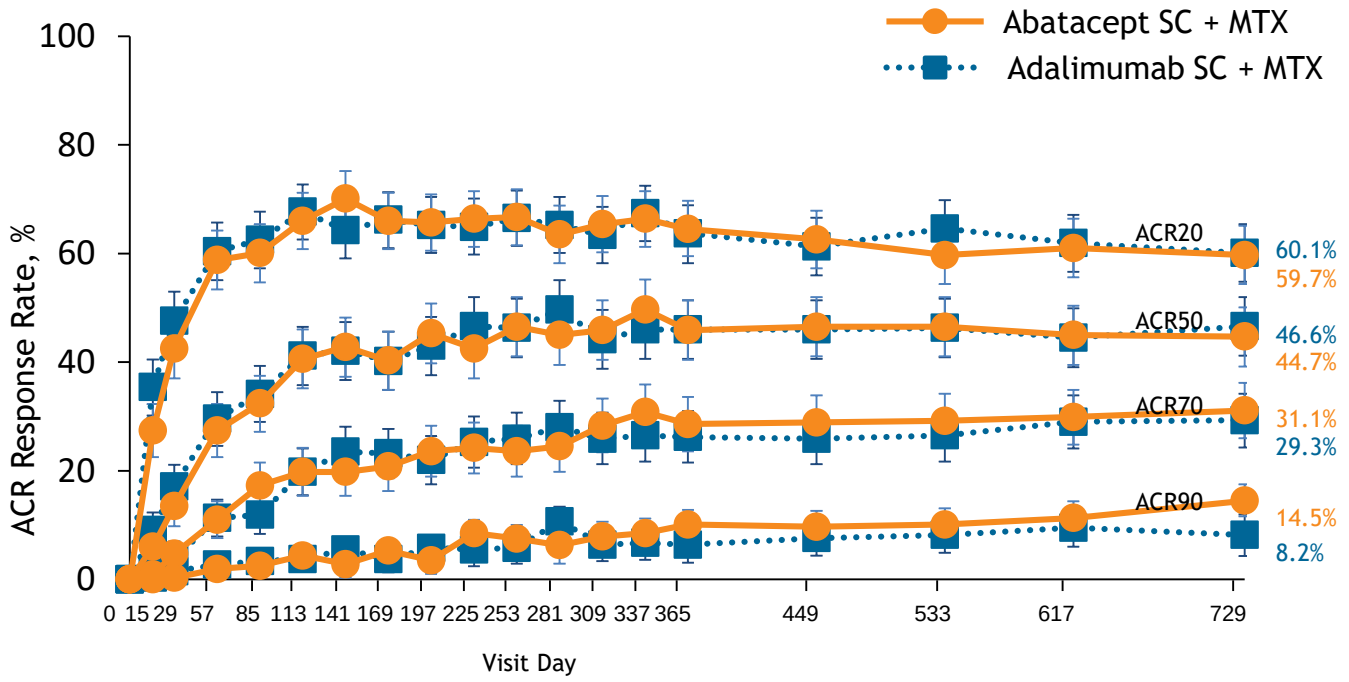


APC = antigen-presenting cell; CD = cluster of differentiation; MHC = major histocompatibility complex; TCR = T-cell receptor

1. Westhovens R. *Future Rheumatol*. 2006;1:15-22; 2. ORENCIA (abatacept) Prescribing Information. 2019.

Abatacept Is Noninferior to Adalimumab in RA

AMPLE PhIIIb N=646

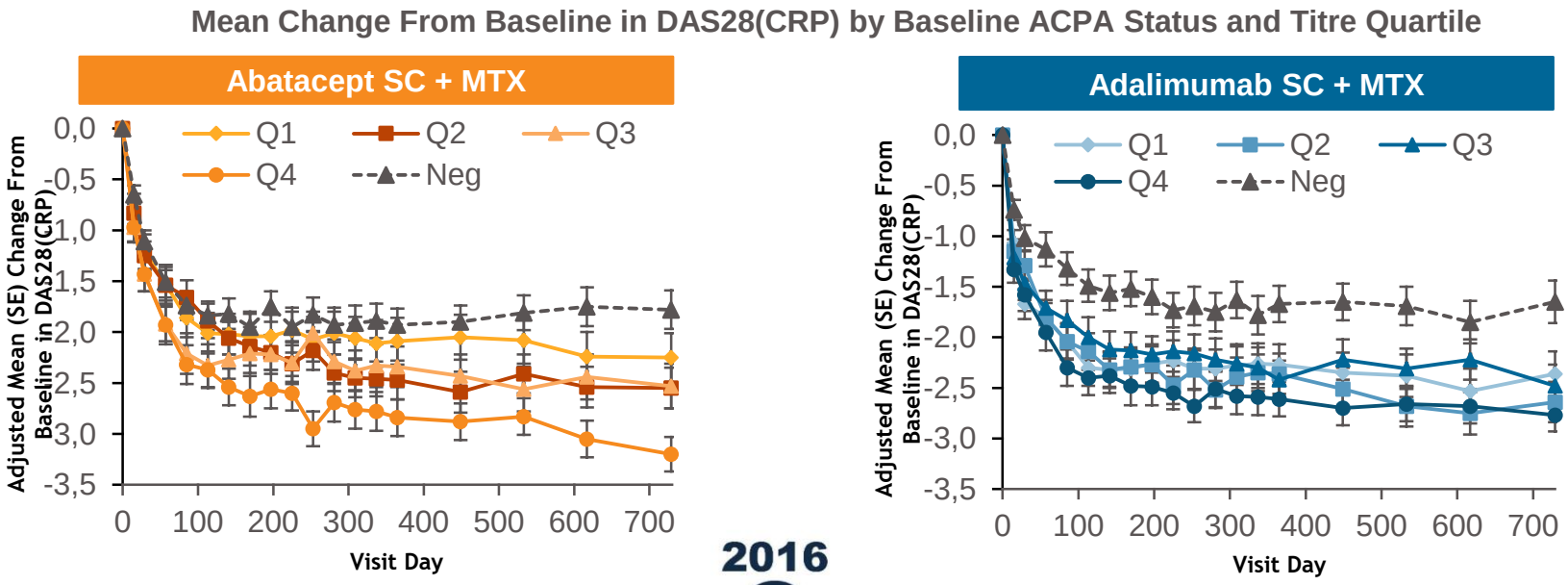


2013

Weinblatt ME, et al. *Arthritis Rheum*. 2013;65:28-38; Schiff M, et al. *Ann Rheum Dis*. 2014;73:86-94.

Abatacept Treatment Showed Differential Efficacy in Patients With Higher ACPA Titres

AMPLE Post-hoc N=508

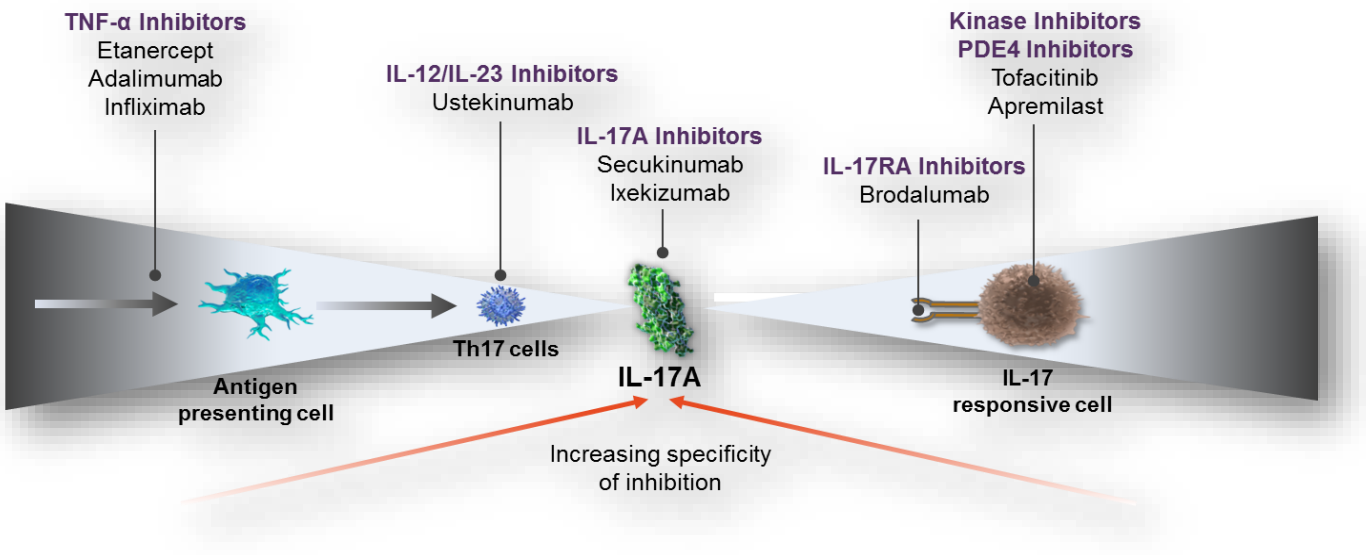


2016

ACPA = anti-citrullinated protein antibody; AMPLE = Abatacept versus adaliMumab comParison in bioLogic-naïvE rheumatoid arthritis (RA) subjects with background methotrexate; DAS28(CRP) = Disease Activity Score in 28 joints-C-reactive protein; MTX = methotrexate; Neg = ACPA negative; Q = quartile; SC = subcutaneous; SE = standard error.

Sokolove J, et al. *Ann Rheum Dis*. 2016;75:709-714.

seronegative spondyloarthritis

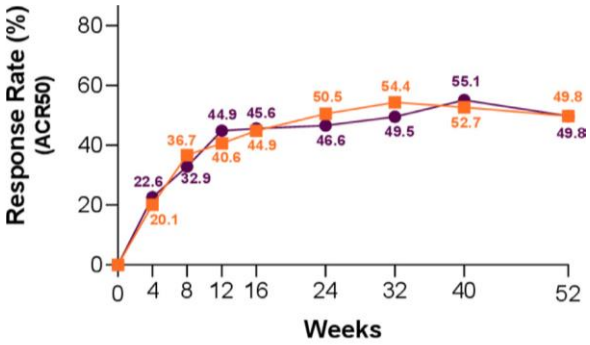


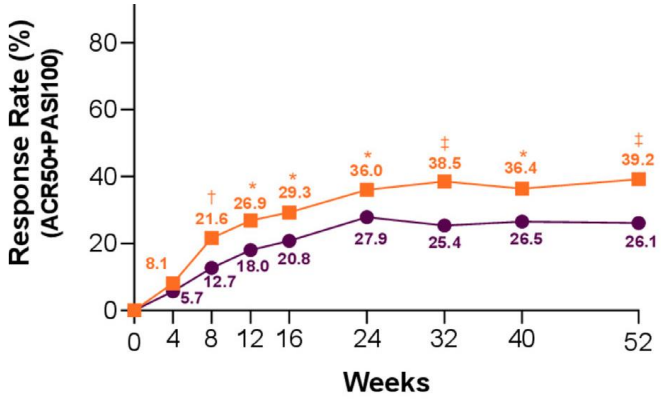
OPEN ACCESS

CLINICAL SCIENCE

Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52

Josef S Smolen,[1] Philip Mease,[2,3] Hasan Tahir,[4] Hendrik Schulze-Koops ,[5] Inmaculada de la Torre,[6] Lingnan Li,[6] Maja Hojnik,[6] Christophe Sapin,[6] Masato Okada,[7] Roberto Caporali,[8] Jordi Gratacós,[9] Philippe Goupille,[10] Soyi Liu Leage,[6] Sreekumar Pillai,[6] Peter Nash [11]





B

Smolen JS, *et al*. *Ann Rheum Dis* 2020;**79**:1310–1319. doi:10.1136/annrheumdis-2020-217372

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Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52

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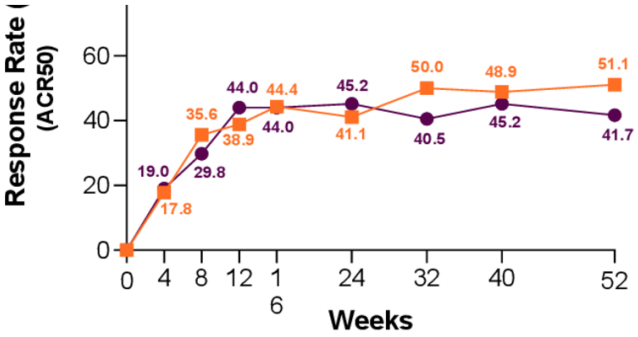
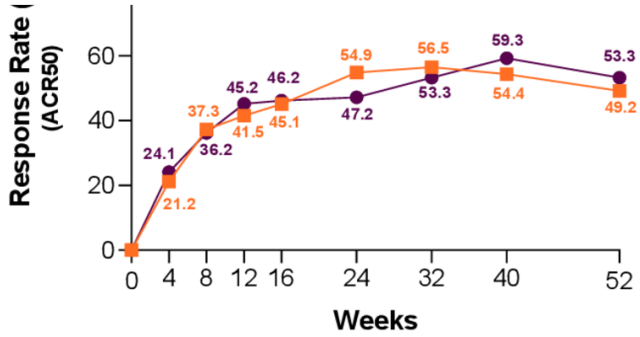




Smolen JS, *et al*. *Ann Rheum Dis* 2020;**79**:1310–1319. doi:10.1136/annrheumdis-2020-217372

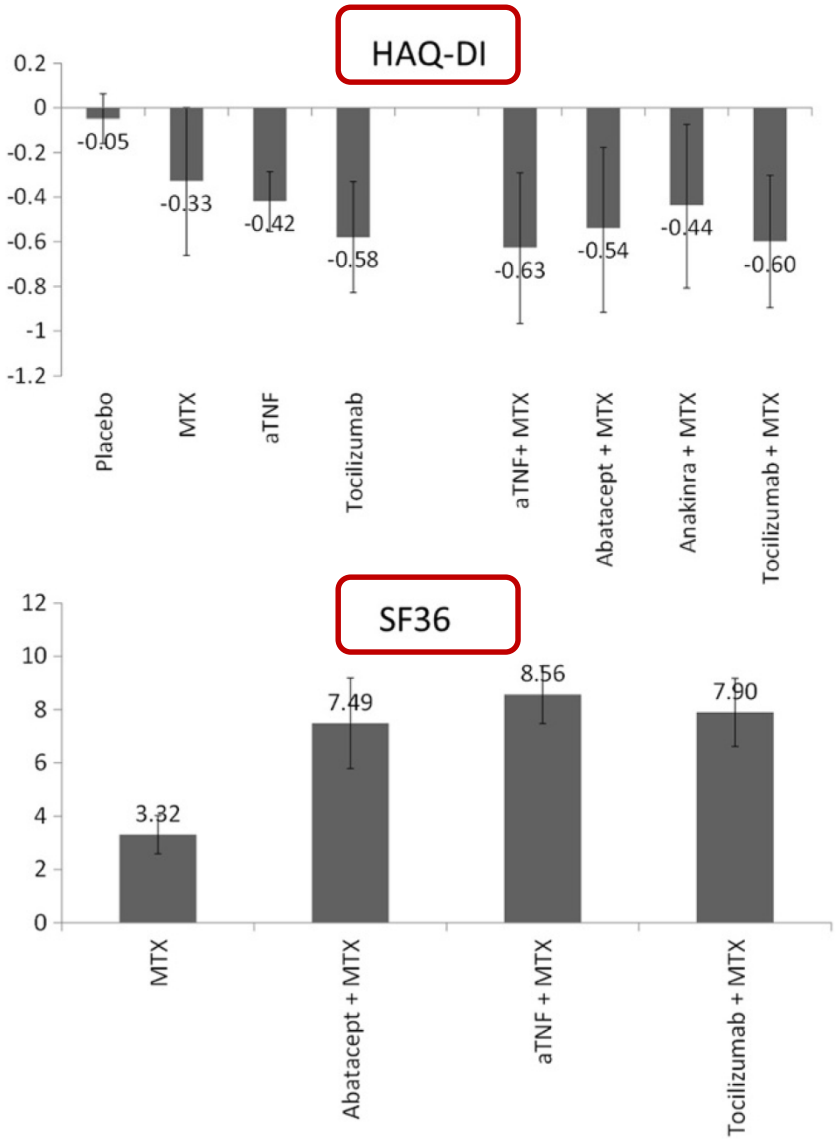
Biologics improve HRQoL in RA

Health and Quality of Life Outcomes 2014

Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs – a systematic review and network meta-analysis

Jeroen P Jansen[1,2], Felicity Buckley[3*], Fred Dejonckheere[4] and Sarika Ogale[5]

Change in HAQ-DI and SF36 for different classes of biologic treatments with and without MTX



Biologics improve HRQoL in RA

Improvements in SF-36 PCS and HAQ-DI scores in patients with RA are associated with:

- improved work productivity,
- reduced long-term disability,
- reduced health care utilization and costs,
- reduced mortality.

Singh JA et al. Semin Arthritis Rheum 2005
Hazes JM et al. Rheumatology 2010
Lekander I et al. Eur J Health Econ 2013
Morgan CL et al. Rheumatology 2014

Impact of one-year treatment with biotechnological drugs on work ability in patients with rheumatoid arthritis in Italy: a prospective real-life study

M. Manara[1], R. Caporali[2,3], C. Lomater[4], R. Gorla[5], E. Fusaro[6], P. Sarzi-Puttini[7], P. Stobbione[8], S. Capri[9], L. Sinigaglia[1]

Table III. Number of days of activity impairment and rate of arthritis interference with work productivity according to WPS-RA questionnaire, at baseline, 6 months and 12 months.

	Baseline [mean (SD)]	6 months [mean (SD)]	12 months [mean (SD)]
Employed	(n=55)	(n=45)	(n=37)
Q2: Number of days of work missed (absenteeism)	2.6 (4.8)	0.8 (3.2)*	0.6 (1.5)*
Q3: Number of days of reduced productivity (presenteeism)	5.5 (7.7)	0.9 (2.3)*	0.7 (1.5)*
Q4: Rate of arthritis interference with work productivity (0-10 points scale)	4.3 (2.8)	1.4 (2.4)*	1.1 (1.9)*
All patients	(n=99)	(n=82)	(n=75)
Q5: Number of days of household work missed	6.7 (8.5)	3.4 (7.3)*	2.7 (5.2)*
Q6: Number of days of reduced productivity in household work	9.1 (9.9)	2.8 (5.1)*	2.7 (5.2)*
Q7: Number of days with social activities missed	6.2 (8.9)	2.1 (5.3)*	1.9 (4.8)*
Q8: Number of days with outside help	5.7 (8.4)	1.9 (5.1)*	1.5 (4.6)*
Q9: Rate of arthritis interference with household work productivity (0-10 points scale)	6.1 (2.7)	2.8 (2.9)*	2.9 (2.9)*

*$p<0.05$ compared to baseline; *t*-test for paired data. SD: standard deviation; n: number.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

Josef S Smolen ,[1] Robert B M Landewé,[2,3] Johannes W J Bijlsma,[4] Gerd R Burmester,[5] Maxime Dougados,[6] Andreas Kerschbaumer ,[1] Iain B McInnes,[7] Alexandre Sepriano ,[8] Ronald F van Vollenhoven,[9] Maarten de Wit ,[10] Daniel Aletaha,[1] Martin Aringer ,[11] John Askling,[12] Alejandro Balsa,[13] Maarten Boers,[14] Alfons A den Broeder,[15] Maya H Buch ,[16] Frank Buttgereit,[5] Roberto Caporali,[17] Mario Humberto Cardiel,[18] Diederik De Cock,[19] Catalin Codreanu,[20] Maurizio Cutolo ,[21] Christopher John Edwards,[22] Yvonne van Eijk-Hustings ,[23] Paul Emery ,[24] Axel Finckh,[25] Laure Gossec ,[26] Jacques-Eric Gottenberg,[27] Merete Lund Hetland,[28] Tom W J Huizinga ,[29] Marios Koloumas,[30,31] Zhanguo Li,[32] Xavier Mariette,[33] Ulf Müller-Ladner,[34] Eduardo F Mysler,[35] Jose A P da Silva ,[36] Gyula Poór,[37] Janet E Pope ,[38] Andrea Rubbert-Roth ,[39] Adeline Ruyssen-Witrand,[40] Kenneth G Saag,[41] Anja Strangfeld,[42] Tsutomu Takeuchi,[43] Marieke Voshaar,[44] René Westhovens,[19] Désirée van der Heijde [29]

Smolen JS, *et al*. *Ann Rheum Dis* 2020;**0**:1–15. doi:10.1136/annrheumdis-2019-216655

	Recommendations			
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	1a	A	9.8
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*	1a	A	9.7
3.	Monitoring should be frequent in active disease (every 1–3 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.	2b	B	9.3
4.	MTX should be part of the first treatment strategy.	1a	A	9.4
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9.0
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.	1a	A	8.9
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors*, other csDMARDs should be considered.	5	D	8.4
8.	If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors* are present, a bDMARD† or a tsDMARD‡ should be added.	1a	A	9.3
9.	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.	1a	A	8.9
10.	If a bDMARD[#] or tsDMARD[##] has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	[#]1b [##]5	A D	8.9
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.	1b	A	9.2
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

	Recommendations			
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10.	If a bDMARD[#] or tsDMARD[##] has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	[#]1b [##]5	A D	8.9
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.	1b	A	9.2
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

If the treatment target is not achieved with with the first csDMARDs strategy, when poor prognostic factors are present, a bDMARD or a tsDMARD should be added.

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Poor prognostic factors	► Persistently moderate or high disease activity despite conventional synthetic DMARD (csDMARD) therapy according to composite measures including joint counts ► High acute phase reactant levels ► High swollen joint count ► Presence of RF and/or ACPA, especially at high levels ► Presence of early erosions ► Failure of two or more csDMARDs

	Recommendations			
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2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.*	1a	A	9.7
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4.	MTX should be part of the first treatment strategy.	1a	A	9.4
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7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors*, other csDMARDs should be considered.	5	D	8.4
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12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

bDMARDs and tsDMARDs should be combined with a csDMARDs (MTX). In patients who cannot use csDMARDs… IL-6..and tsDMARDs may have some advantages….

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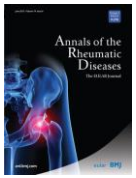
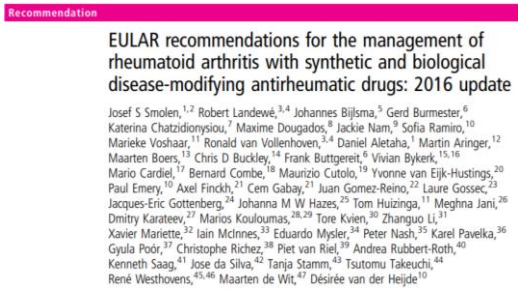


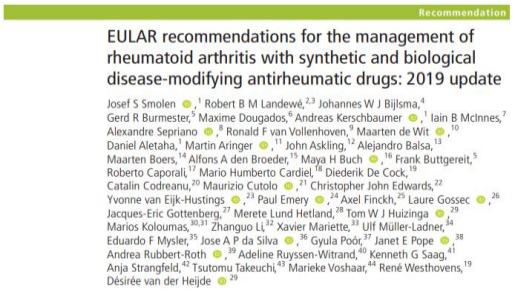
APPARENTLY, SMALL FORMAL DIFFERENCES…



Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Josef S Smolen,[1,2] Robert Landewé,[3,4] Johannes Bijlsma,[5] Gerd Burmester,[6] Katerina Chatzidionysiou,[7] Maxime Dougados,[8] Jackie Nam,[9] Sofia Ramiro,[10] Marieke Voshaar,[11] Ronald van Vollenhoven,[3,4] Daniel Aletaha,[1] Martin Aringer,[12] Maarten Boers,[13] Chris D Buckley,[14] Frank Buttgereit,[6] Vivian Bykerk,[15,16] Mario Cardiel,[17] Bernard Combe,[18] Maurizio Cutolo,[19] Yvonne van Eijk-Hustings,[20] Paul Emery,[10] Axel Finckh,[21] Cem Gabay,[21] Juan Gomez-Reino,[22] Laure Gossec,[23] Jacques-Eric Gottenberg,[24] Johanna M W Hazes,[25] Tom Huizinga,[11] Meghna Jani,[26] Dmitry Karateev,[27] Marios Kouloumas,[28,29] Tore Kvien,[30] Zhanguo Li,[31] Xavier Mariette,[32] Iain McInnes,[33] Eduardo Mysler,[34] Peter Nash,[35] Karel Pavelka,[36] Gyula Poór,[37] Christophe Richez,[38] Piet van Riel,[39] Andrea Rubbert-Roth,[40] Kenneth Saag,[41] Jose da Silva,[42] Tanja Stamm,[43] Tsutomu Takeuchi,[44] René Westhovens,[45,46] Maarten de Wit,[47] Désirée van der Heijde[10]



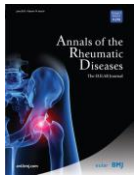
Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update

Josef S Smolen,[1] Robert B M Landewé,[2,3] Johannes W J Bijlsma,[4] Gerd R Burmester,[5] Maxime Dougados,[6] Andreas Kerschbaumer,[1] Iain B McInnes,[7] Alexandre Sepriano,[8] Ronald F van Vollenhoven,[9] Maarten de Wit,[10] Daniel Aletaha,[1] Martin Aringer,[11] John Askling,[12] Alejandro Balsa,[13] Maarten Boers,[14] Alfons A den Broeder,[15] Maya H Buch,[16] Frank Buttgereit,[5] Roberto Caporali,[17] Mario Humberto Cardiel,[18] Diederik De Cock,[19] Catalin Codreanu,[20] Maurizio Cutolo,[21] Christopher John Edwards,[22] Yvonne van Eijk-Hustings,[23] Paul Emery,[24] Axel Finckh,[25] Laure Gossec,[26] Jacques-Eric Gottenberg,[27] Merete Lund Hetland,[28] Tom W J Huizinga,[29] Marios Koloumas,[30,31] Zhanguo Li,[32] Xavier Mariette,[33] Ulf Müller-Ladner,[34] Eduardo F Mysler,[35] Jose A P da Silva,[36] Gyula Poór,[37] Janet E Pope,[38] Andrea Rubbert-Roth,[39] Adeline Ruyssen-Witrand,[40] Kenneth G Saag,[41] Anja Strangfeld,[42] Tsutomu Takeuchi,[43] Marieke Voshaar,[44] René Westhovens,[19] Désirée van der Heijde[29]

10) If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action.

10) If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD should be considered; if one TNFi therapy has failed, patients may receive an agent with another MOA or a second TNFi.



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3.	Monitoring should be frequent in active disease (every 1–3 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.	2b	B	9.3
4.	MTX should be part of the first treatment strategy.	1a	A	9.4
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.	1a	A	9.0
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible.	1a	A	8.9
7.	If the treatment target is not achieved with the first csDMARD strategy, in the absence of poor prognostic factors*, other csDMARDs should be considered.	5	D	8.4
8.	If the treatment target is not achieved with the first csDMARD strategy, when and poor prognostic factors* are present, a bDMARD† or a tsDMARD‡ should be added.	1a	A	9.3
9.	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other bDMARDs.	1a	A	8.9
10.	If a bDMARD[#] or tsDMARD[##] has failed, treatment with another bDMARD† or a tsDMARD‡ should be considered; if one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.	[#]1b [##]5	A D	8.9
11.	If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs or tsDMARDs, especially if this treatment is combined with a csDMARD.	1b	A	9.2
12.	If a patient is in persistent remission, tapering the csDMARD could be considered.	2b	B	9.0

If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering DMARDs

Smolen JS, *et al*. *Ann Rheum Dis* 2020;**0**:1–15. doi:10.1136/annrheumdis-2019-216655

Recommendation

OPEN ACCESS

EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update

Laure Gossec ,[1,2] Xenofon Baraliakos,[3] Andreas Kerschbaumer ,[4] Maarten de Wit ,[5] Iain McInnes,[6] Maxime Dougados,[7] Jette Primdahl ,[8,9] Dennis G McGonagle,[10,11] Daniel Aletaha,[12] Andra Balanescu,[13] Peter V Balint,[14] Heidi Bertheussen,[15] Wolf-Henning Boehncke,[16] Gerd R Burmester,[17] Juan D Canete ,[18] Nemanja S Damjanov,[19] Tue Wenzel Kragstrup,[20,21] Tore K Kvien,[22] Robert B M Landewé,[23,24] Rik Jozef Urbain Lories,[25,26] Helena Marzo-Ortega,[10,11] Denis Poddubnyy ,[27,28] Santiago Andres Rodrigues Manica ,[29,30] Georg Schett ,[31] Douglas J Veale ,[32] Filip E Van den Bosch,[33] Désirée van der Heijde ,[22,34] Josef S Smolen[35,36]

Gossec L, *et al*. *Ann Rheum Dis* 2020;**79**:700–712. doi:10.1136/annrheumdis-2020-217159

	Recommendations	Level of evidence	Grade of recommendation	Level of agreement, mean (SD)
1	Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy.	1b	A	9.4 (1.0)
2	Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A	9.6 (0.8)
3	Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis*; systemic glucocorticoids may be used with caution at the lowest effective dose†.	3b* 4†	C	9.5 (1.1)
4	In patients with polyarthritis, a csDMARD should be initiated* rapidly†, with methotrexate preferred in those with relevant skin involvement*.	1b* 5†	B	9.5 (0.8)
5	In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered.	4	C	9.3 (1.0)
6	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.	1b	B	9.4 (1.1)
7	In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered.	1b	B	9.2 (1.3)
8	In patients with mild disease* and an inadequate response to at least one csDMARD†, in whom neither a bDMARD nor a JAK inhibitor is appropriate*, a PDE4 inhibitor may be considered.	5* 1b†	B	8.5 (1.9)
9	In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.	1b	B	9.3 (0.9)
10	In patients with predominantly axial disease which is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor; when there is relevant skin involvement, IL-17 inhibitor may be preferred.	1b	B	9.7 (0.6)
11	In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered*, including one switch within a class†.	1b* 4†	C	9.5 (1.2)
12	In patients in sustained remission, cautious tapering of DMARDs may be considered.	4	C	9.5 (0.9)

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5	In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered.	4	C	9.3 (1.0)
6	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.	1b	B	9.4 (1.1)
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Gossec L, *et al*. *Ann Rheum Dis* 2020;**79**:700–712. doi:10.1136/annrheumdis-2020-217159

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9	In patients with unequivocal enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.	1b	B	9.3 (0.9)
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11	In patients who fail to respond adequately to, or are intolerant of a bDMARD, switching to another bDMARD or tsDMARD should be considered*, including one switch within a class†.	1b* 4†	C	9.5 (1.2)
12	In patients in sustained remission, cautious tapering of DMARDs may be considered.	4	C	9.5 (0.9)

Gossec L, *et al*. *Ann Rheum Dis* 2020;**79**:700–712. doi:10.1136/annrheumdis-2020-217159

	Recommendations	Level of evidence	Grade of recommendation	Level of agreement, mean (SD)
1	Treatment should be aimed at reaching the target of remission or, alternatively, low disease activity, by regular disease activity assessment and appropriate adjustment of therapy.	1b	A	9.4 (1.0)
2	Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.	1b	A	9.6 (0.8)
3	Local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis*; systemic glucocorticoids may be used with caution at the lowest effective dose†.	3b* 4†	C	9.5 (1.1)
4	In patients with polyarthritis, a csDMARD should be initiated* rapidly†, with methotrexate preferred in those with relevant skin involvement*.	1b* 5†	B	9.5 (0.8)
5	In patients with monoarthritis or oligoarthritis, particularly with poor prognostic factors such as structural damage, high erythrocyte sedimentation rate/C reactive protein, dactylitis or nail involvement, a csDMARD should be considered.	4	C	9.3 (1.0)
6	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced; when there is relevant skin involvement, an IL-17 inhibitor or IL-12/23 inhibitor may be preferred.	1b	B	9.4 (1.1)
7	In patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate, a JAK inhibitor may be considered.	1b	B	9.2 (1.3)
8	In patients with mild disease* and an inadequate response to at least one csDMARD†, in whom neither a bDMARD nor a JAK inhibitor is appropriate*, a PDE4 inhibitor may be considered.	5* 1b†	B	8.5 (1.9)
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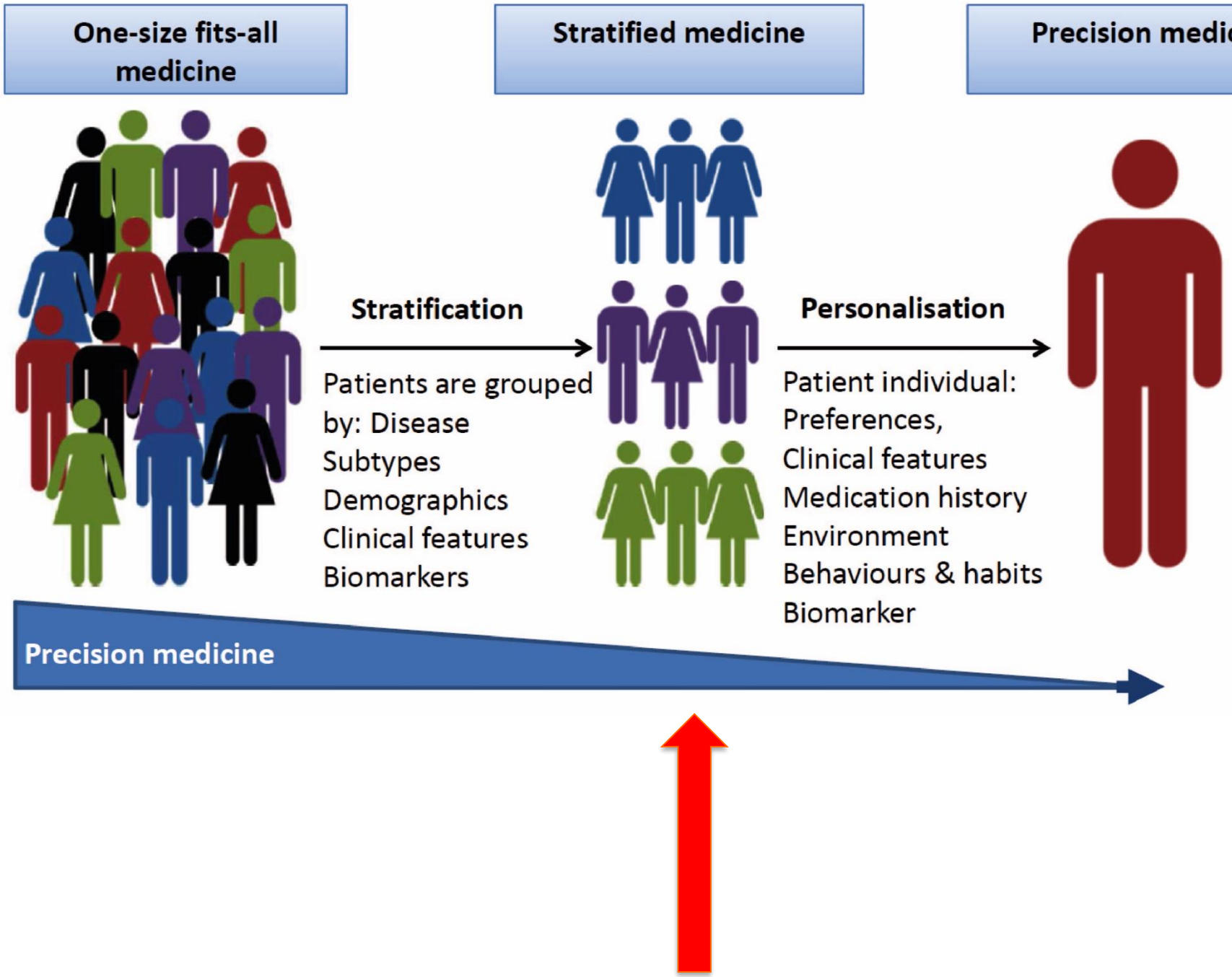
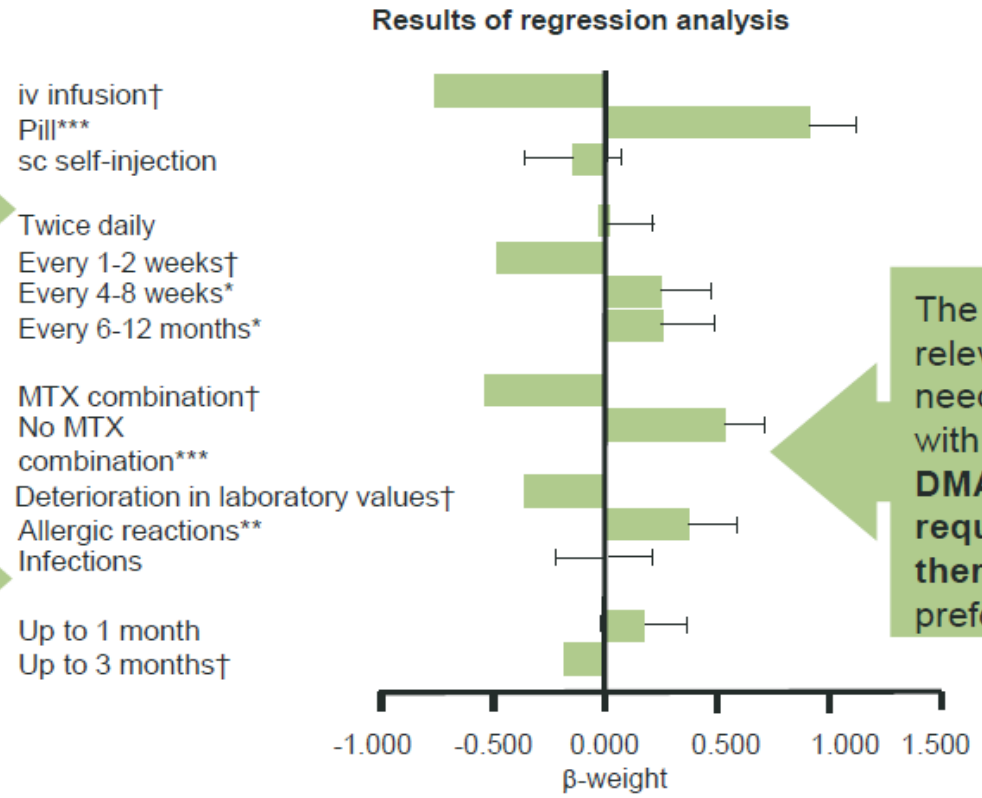

One-size fits-all medicine
Stratified medicine
Precision medicine
Stratification
Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers
Personalisation
Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker
Precision medicine

…..But patient preference is about more than just route of administration

When asked to choose the most- and least-preferred drug among hypothetical treatment options '**Mode of administration**' was the most important attribute associated with the preferred treatment

Oral administration being most preferred and iv infusion being least preferred

Frequency and **safety** are also important considerations

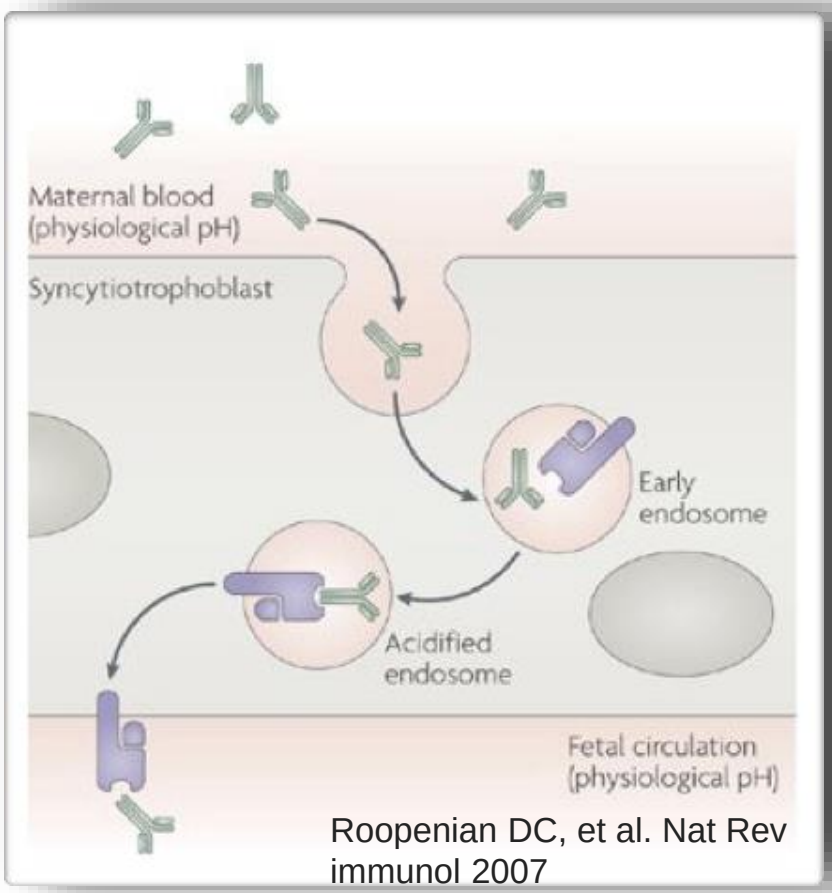


The second most relevant factor was need for combination with MTX, with **DMARDs not requiring combination therapy** being the most preferred option

Frequency, safety and monotherapy are also important considerations for RA patients

Kruger et al. Presented at EULAR 2015

Biologic agents and placental transfer



Roopenian DC, et al. Nat Rev immunol 2007

- All biological agents containing the fragment crystallizable region (Fc) part of IgG are actively transferred through the placenta by Fc receptors on the trophoblast [1]
- In constrast to a whole IgG anti-TNF antibody, certolizumab pegol demontrated in animal models a minimal fetal exposure because of no placental transfer [2]

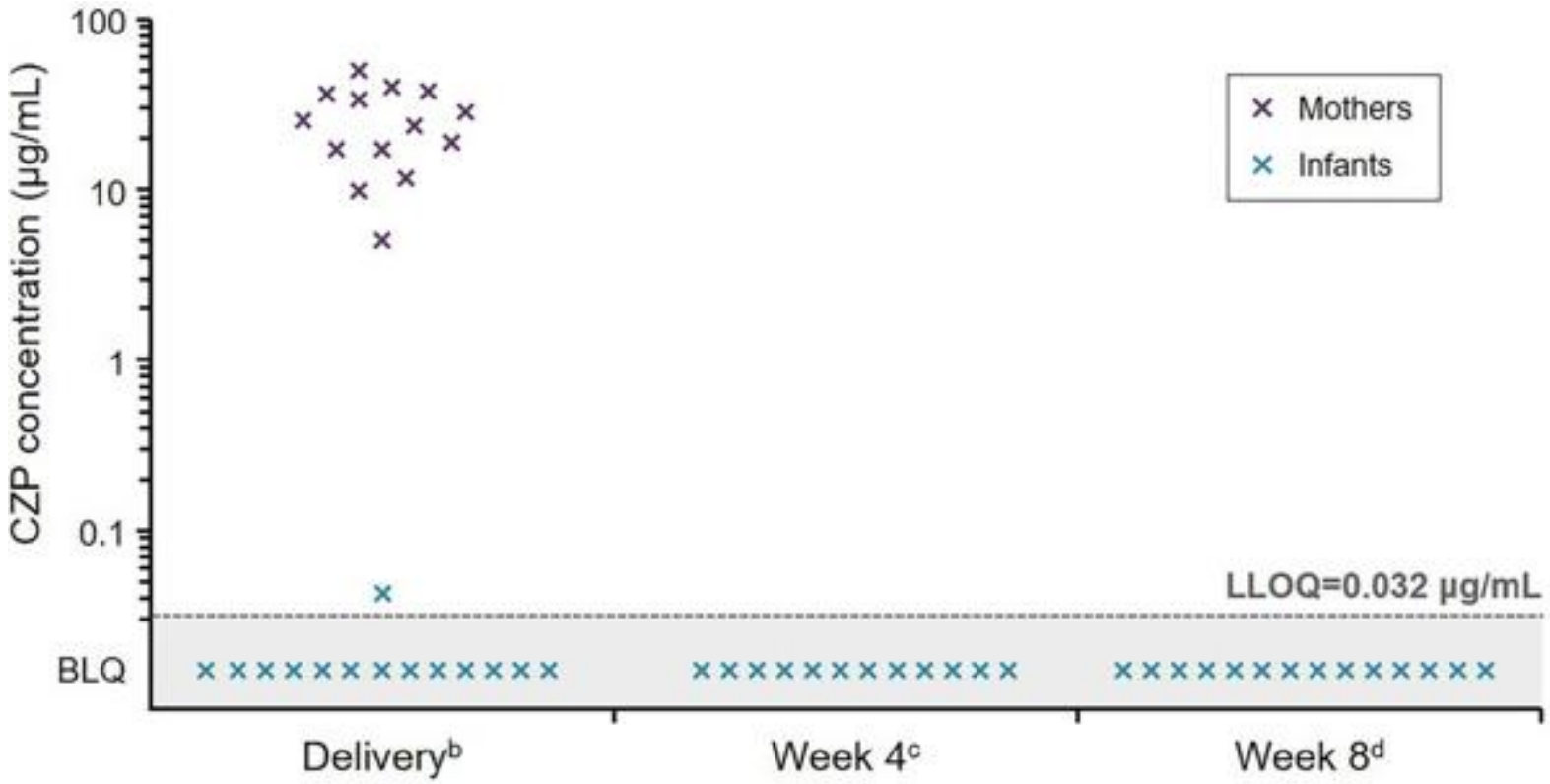
[1] Kane SV, et al. Am J Gastroenterol 2009

[2] Wakefield I, et al. Toxicol Sci 2011

Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study

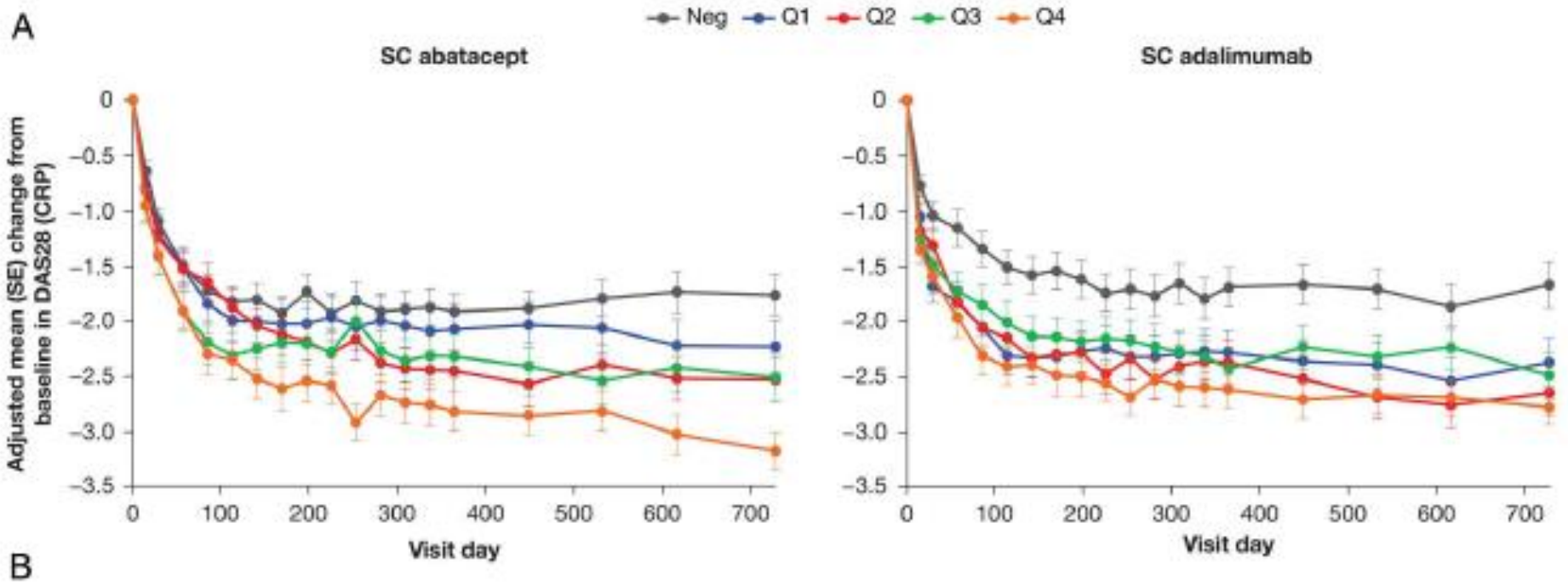
Xavier Mariette,[1] Frauke Förger,[2] Bincy Abraham,[3] Ann D Flynn,[4] Anna Moltó,[5] René-Marc Flipo,[6] Astrid van Tubergen,[7] Laura Shaughnessy,[8] Jeff Simpson,[8] Marie Teil,[9] Eric Helmer,[10] Maggie Wang,[8] Eliza F Chakravarty[11]

Ann Rheum Dis 2017



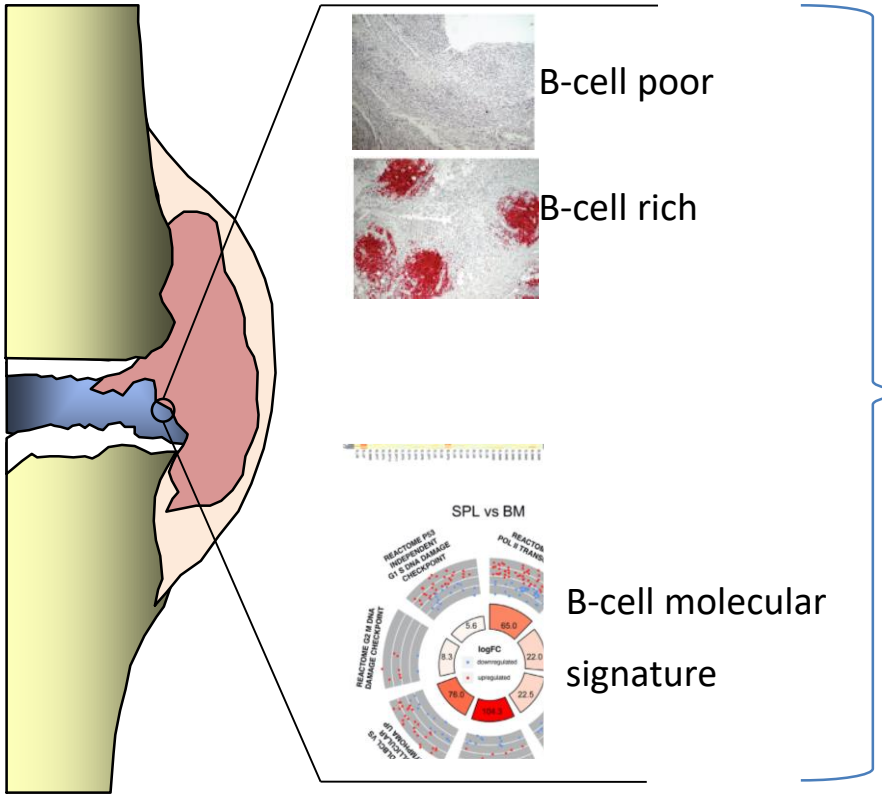
EG Favalli, Gaetano
Pipi Institute

Impact of baseline ACPA concentration: the Ample trial



Sokolove J et al. Ann Rheum Dis 2016:75:709-14.

R4RA study



Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial

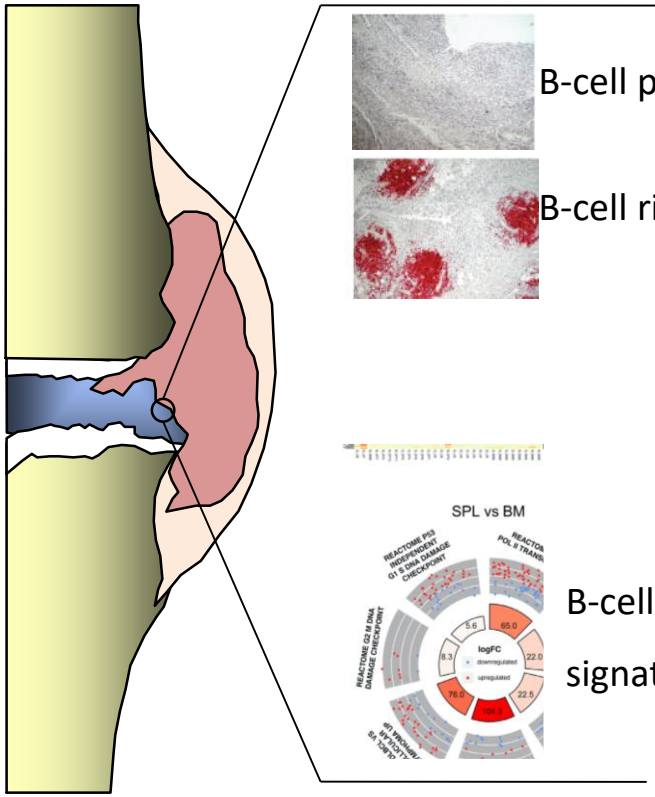
Frances Humby, Patrick Durez, Maya H Buch, Myles J Lewis, Hasan Rizvi, Felice Rivellese, Alessandra Nerviani, Giovanni Giorli, Arti Mahto, Carlomaurizio Montecucco, Bernard Lauwerys, Nora Ng, Pauline Ho, Michele Bombardieri, Vasco C Romão, Patrick Verschueren, Stephen Kelly, Pier Paolo Sainaghi, Nagui Gendi, Bhaskar Dasgupta, Alberto Cauli, Piero Reynolds, Juan D Cañete, Robert Moots, Peter C Taylor, Christopher J Edwards, John Isaacs, Peter Sasieni, Ernest Choy, Costantino Pitzalis, on behalf of the R4RA collaborative group

Lancet 2021; 397: 305–17

- 164 RA patients TNF-IR
- Rituximab (83)
- Tocilizumab (81)

→ 50% CDAI improvement

R4RA study



B-cell molecular signature

→ No difference

→ Tocilizumab better than rituximab in patients Classified as B-cell poor with RNA sequencing

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Personalized medicine in rheumatoid arthritis: is the glass half full or half empty

Huizinga TW. J Intern med 2014 (Oct 14)