Le terapie biologiche nell'anziano

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Autoimmune Diseases

- ✓ Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunological tolerance to self-antigens and represent a heterogeneous group of disorders that afflict specific target organs or multiple organ systems.

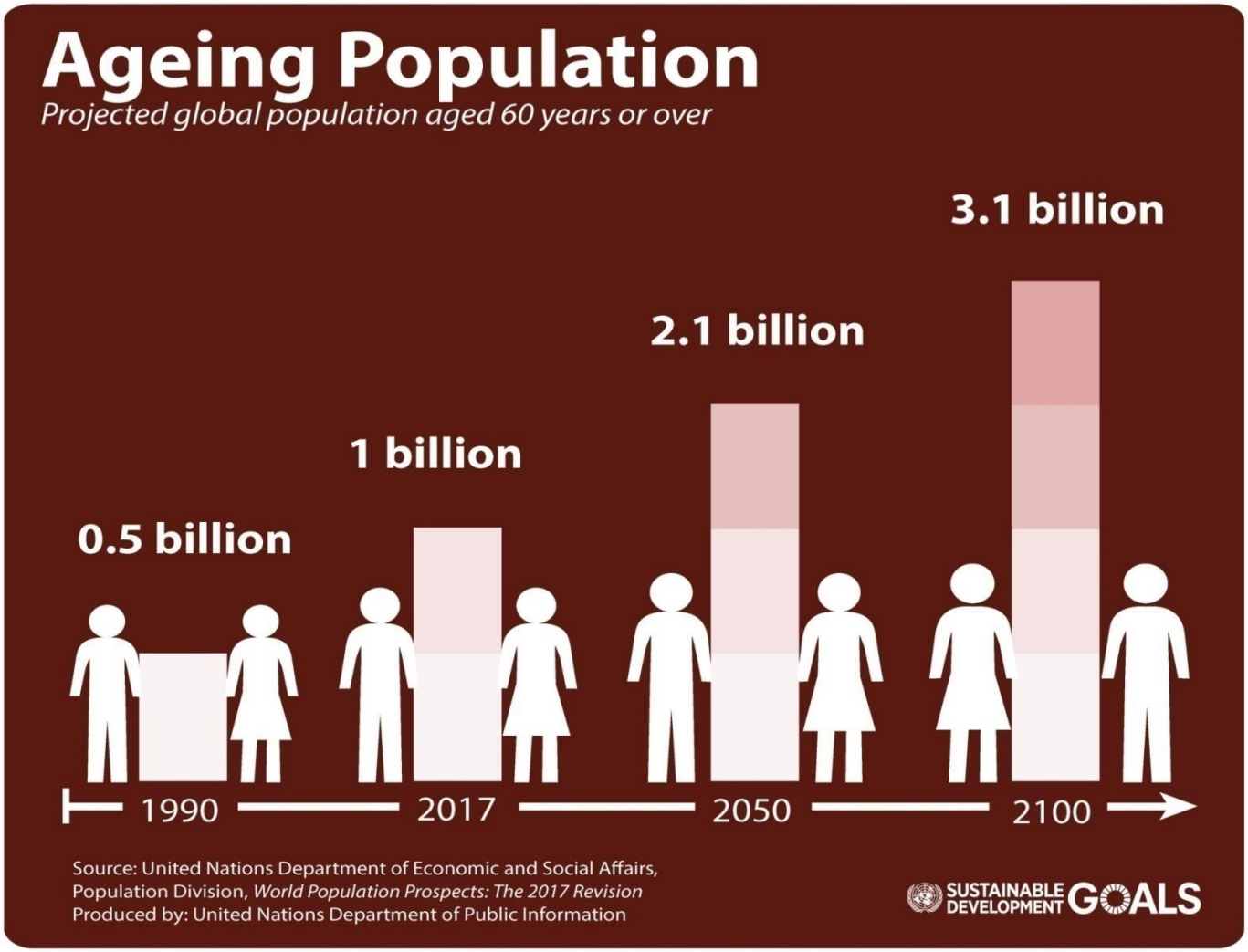
- ✓ Autoimmune diseases are heterogeneous with regard to prevalence, manifestations, and pathogenesis.

- ✓ It has been identified 81 autoimmune diseases. Forty-five autoimmune diseases have been associated with well-defined autoantigens (36 autoantigens are tissue specific).

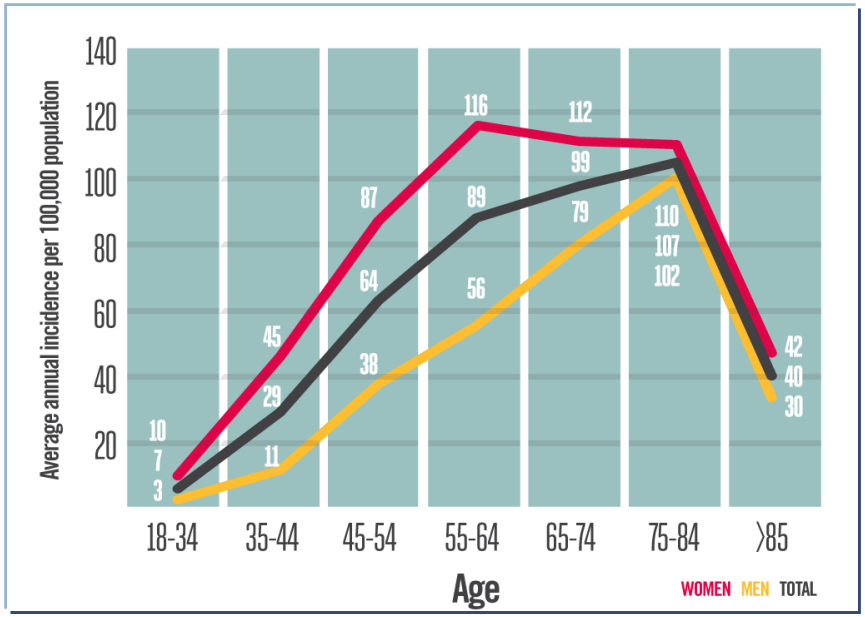
Autoimmune Diseases - Heterogeneity

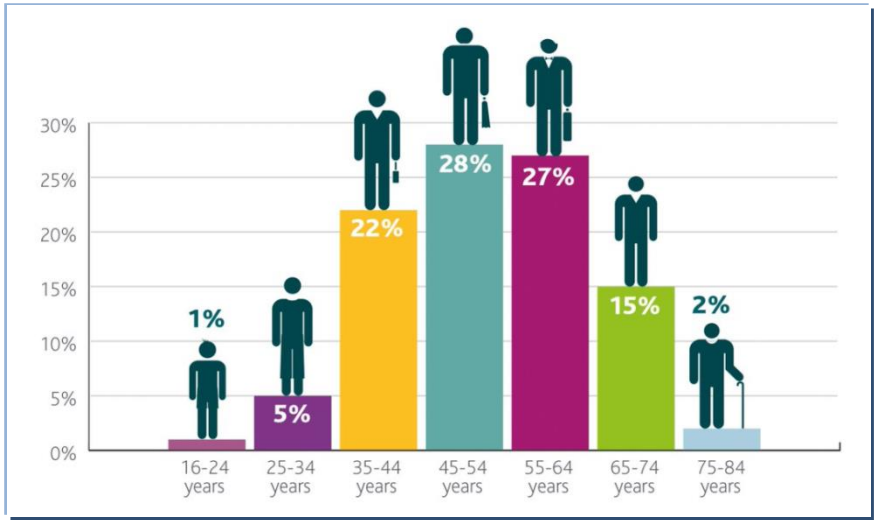
- ✓ Almost 5% of the world population develops AD. Of this 5% approximately 80% are women and it is considered the fourth leading cause of disability for them.
- ✓ Considering all diseases in the class, the most common mean age-of-onset was 40–50 years.

The aging of the population is a defining characteristic of the western world



Rheumatoid arthritis
Is the Incidence Rising?





- ✓ The concept of rheumatoid arthritis, a chronic progressive inflammatory disease of the synovial joints, as a disorder of middle age is changing to include patients outside the range of 40 to 60 years.
- ✓ Cause age is one of the major determinants in clinical decision-making, there are distinct considerations for treatment strategies and clinical outcomes for elderly patients with RA.

PLoS One. 2018 Oct 16;13(10):e0205651

EORA means Elderly-Onset Rheumatoid Arthritis

RA is categorized into three clinical subsets:

YORA I (16-40 years), YORA II (41-60 years) and EORA >60 year

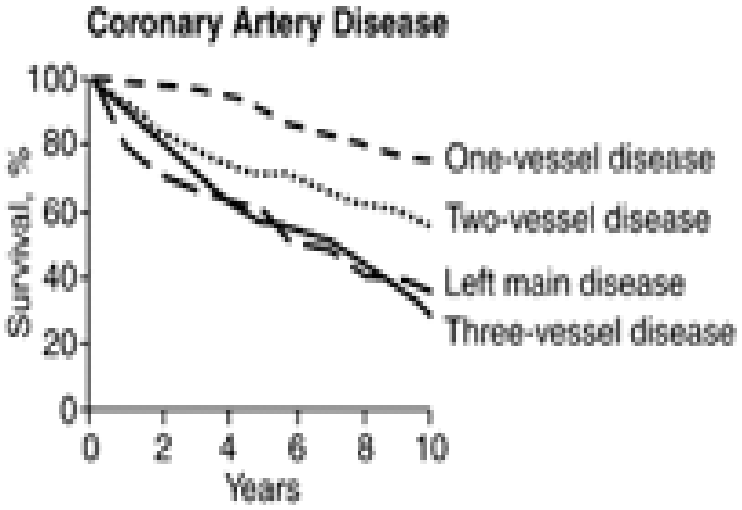
Both large and small joints are affected more frequently initially at onset, serological tests show equal or slightly lower percentage of positivity of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody in individuals with EORA.

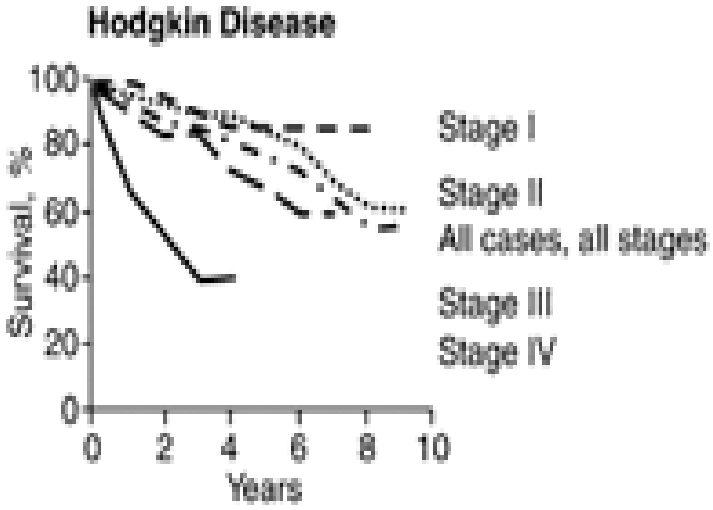
Individuals with EORA have higher disease activity scores, erythrocyte sedimentation rates, and C-reactive protein levels.

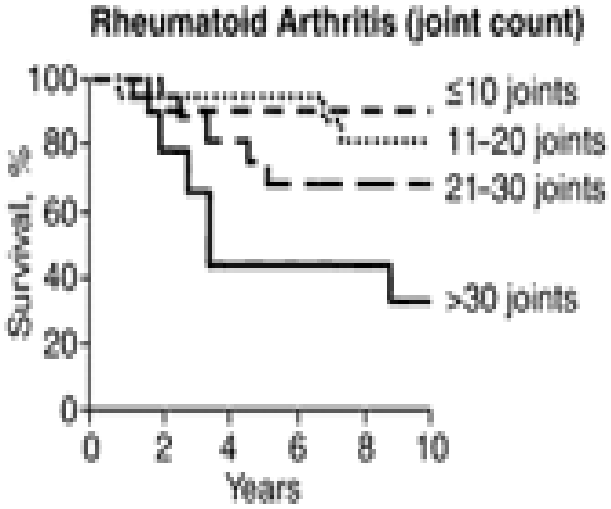
An explosive onset of shoulder arthritis, resembling polymyalgia rheumatica (PMR) is observed in 13–23 % of patients with EORA.

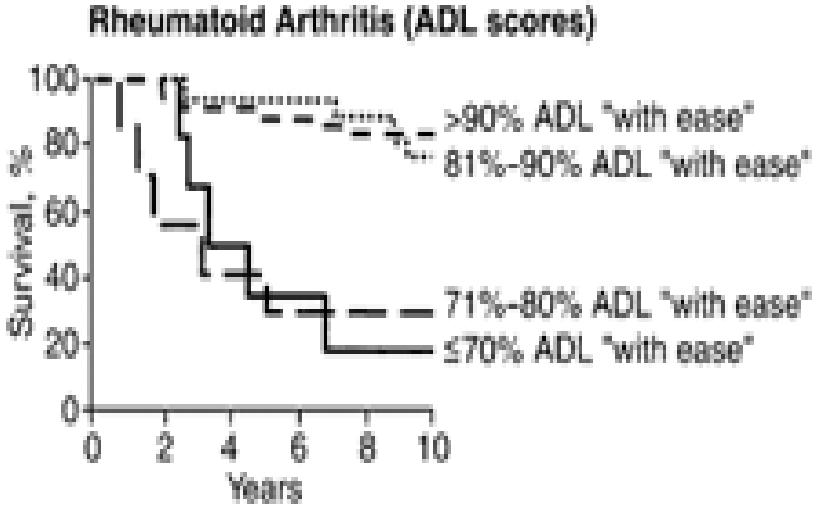
Drugs Aging 2016 33:97–107

RA is an Aggressive Disease





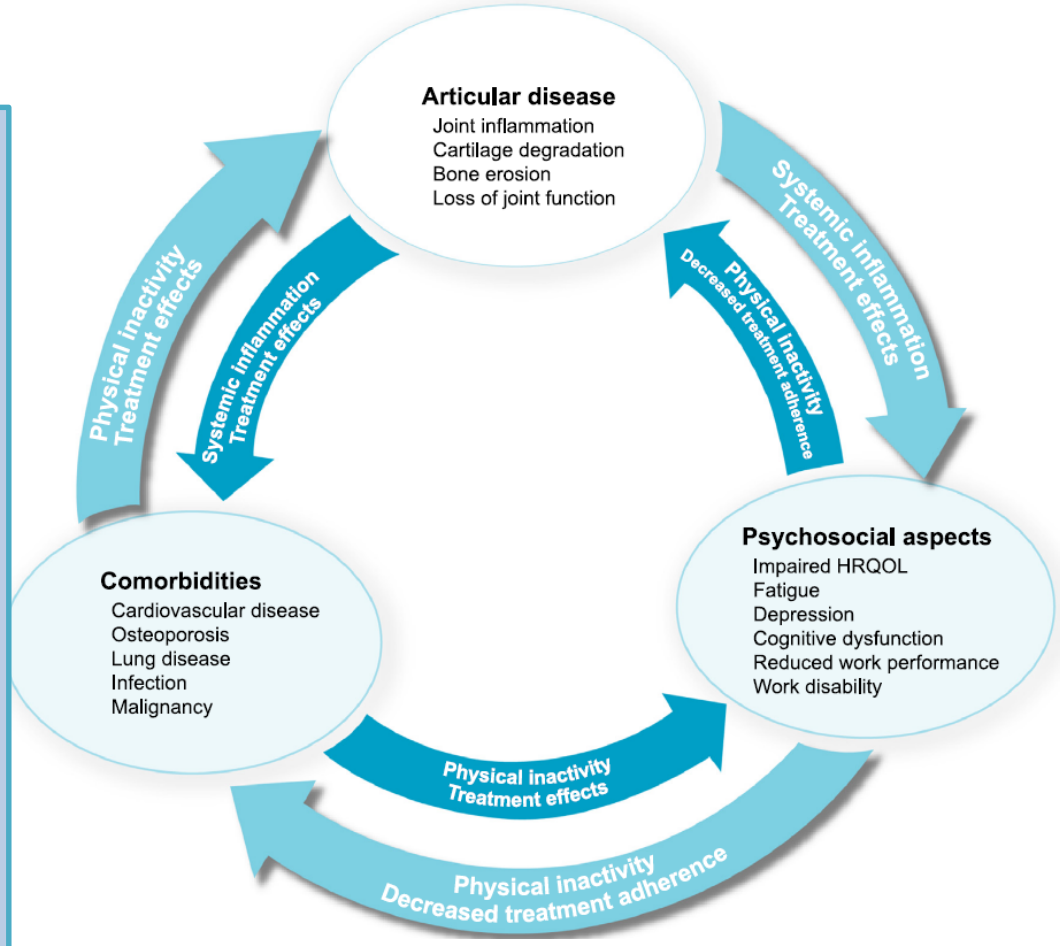




Pincus T. et al. J. Rheumatol. 1986;13:841-5

Nevertheless, it is important to recognize that RA is a systemic disease and other disease manifestations may still be present eventhough joint damage has been controlled.

Although in the past, the clinical understanding of disease burden emphasized destruction of the joints, now it must also focus on the systemic manifestations associated with RA, including comorbidities, psychosocial aspects, and health-related quality of life (HRQOL) impairments.



M. Cutolo et al. / Seminars in Arthritis and Rheumatism 43 (2014) 479–488

General Therapeutic Principle for Established RA

- ✓ *Remission of symptoms*
- ✓ *Return to full function*
- ✓ *Maintenance of remission*

Preliminary Criteria for Clinical remission in Rheumatoid Arthritis

Table 4. Proposed criteria* for complete clinical remission in rheumatoid arthritis†

Five or more of the following requirements‡ must be fulfilled for at least 2 consecutive months:§

1. Duration of morning stiffness not exceeding 15 minutes
2. No fatigue
3. No joint pain (by history)
4. No joint tenderness or pain on motion
5. No soft tissue swelling in joints or tendon sheaths
6. Erythrocyte sedimentation rate (Westergren method) less than 30 mm/hour for a female or 20 mm/hour for a male

* These criteria are intended to describe either spontaneous remission or a state of drug-induced disease suppression, which simulates spontaneous remission.

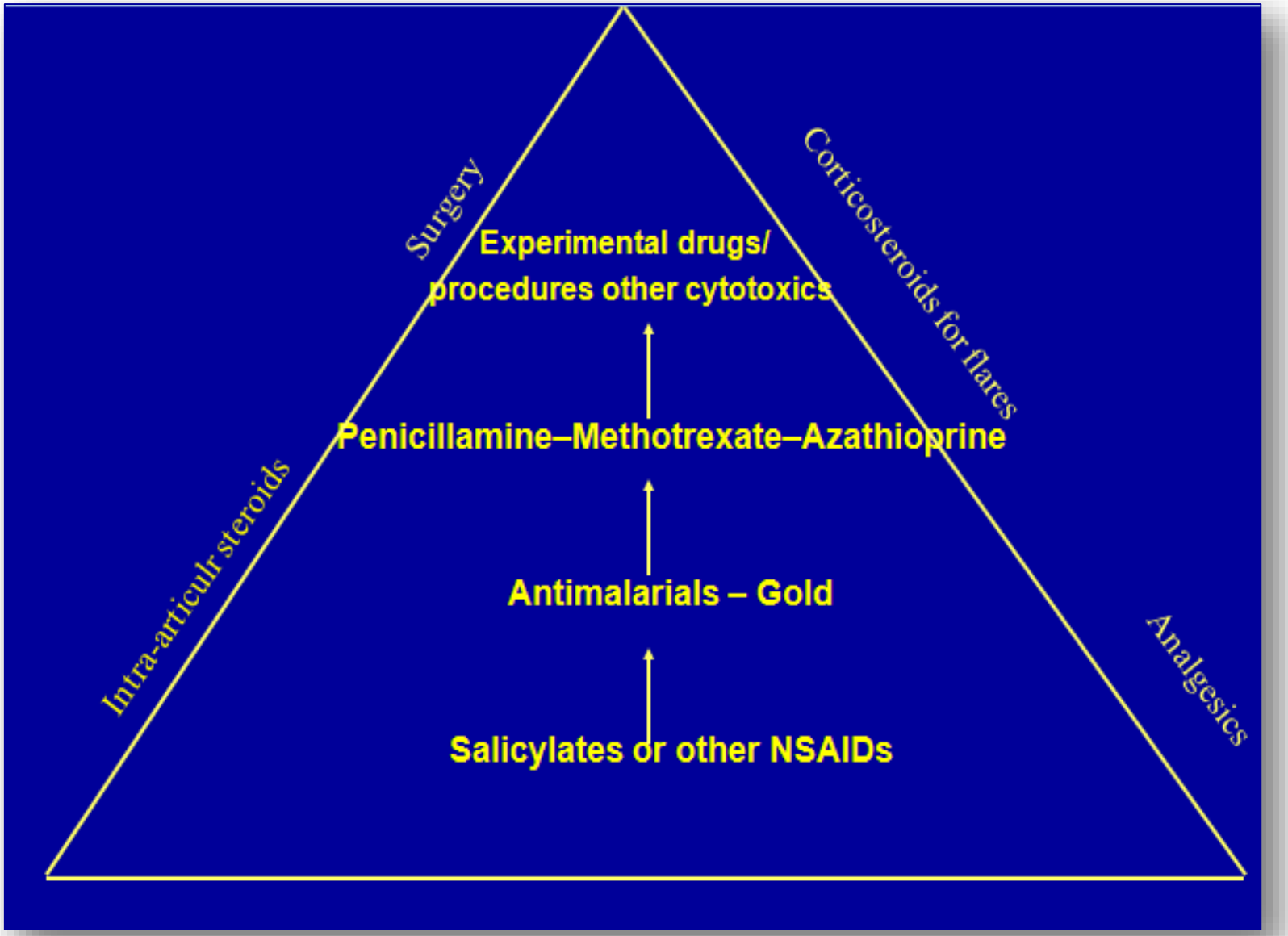
† To be considered for this designation a patient must have met the ARA criteria for definite or classic rheumatoid arthritis at some time in the past.

‡ No alternative explanations may be invoked to account for the failure to meet a particular requirement. For instance, in the presence of knee pain, which might be related to degenerative arthritis, a point for "no joint pain" may not be awarded.

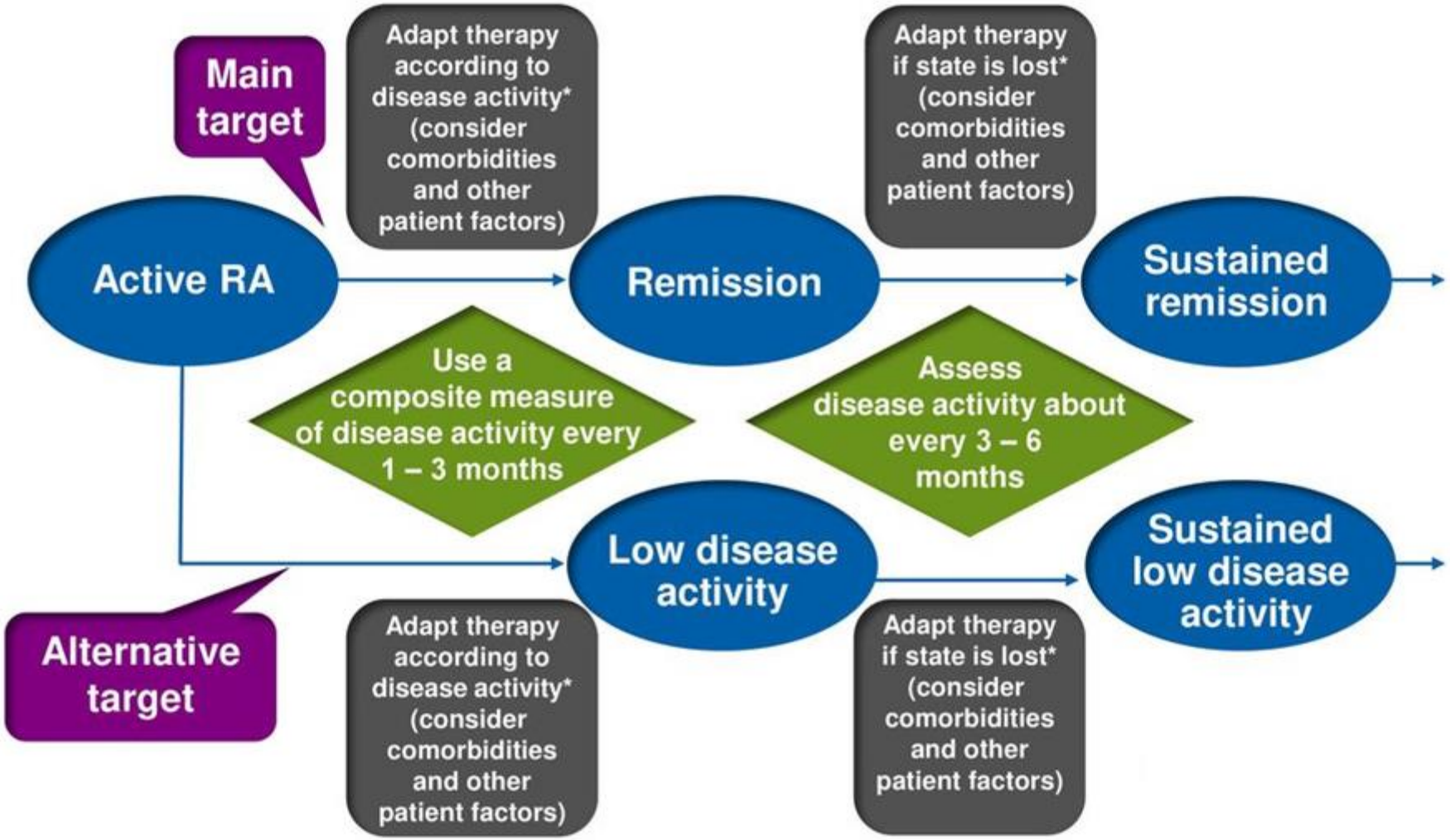
§ Exclusions: Clinical manifestations of active vasculitis, pericarditis, pleuritis or myositis, and unexplained recent weight loss or fever attributable to rheumatoid arthritis will prohibit a designation of complete clinical remission.

Pinals RS 1981, Arthitis and Rheumatism 24:1308

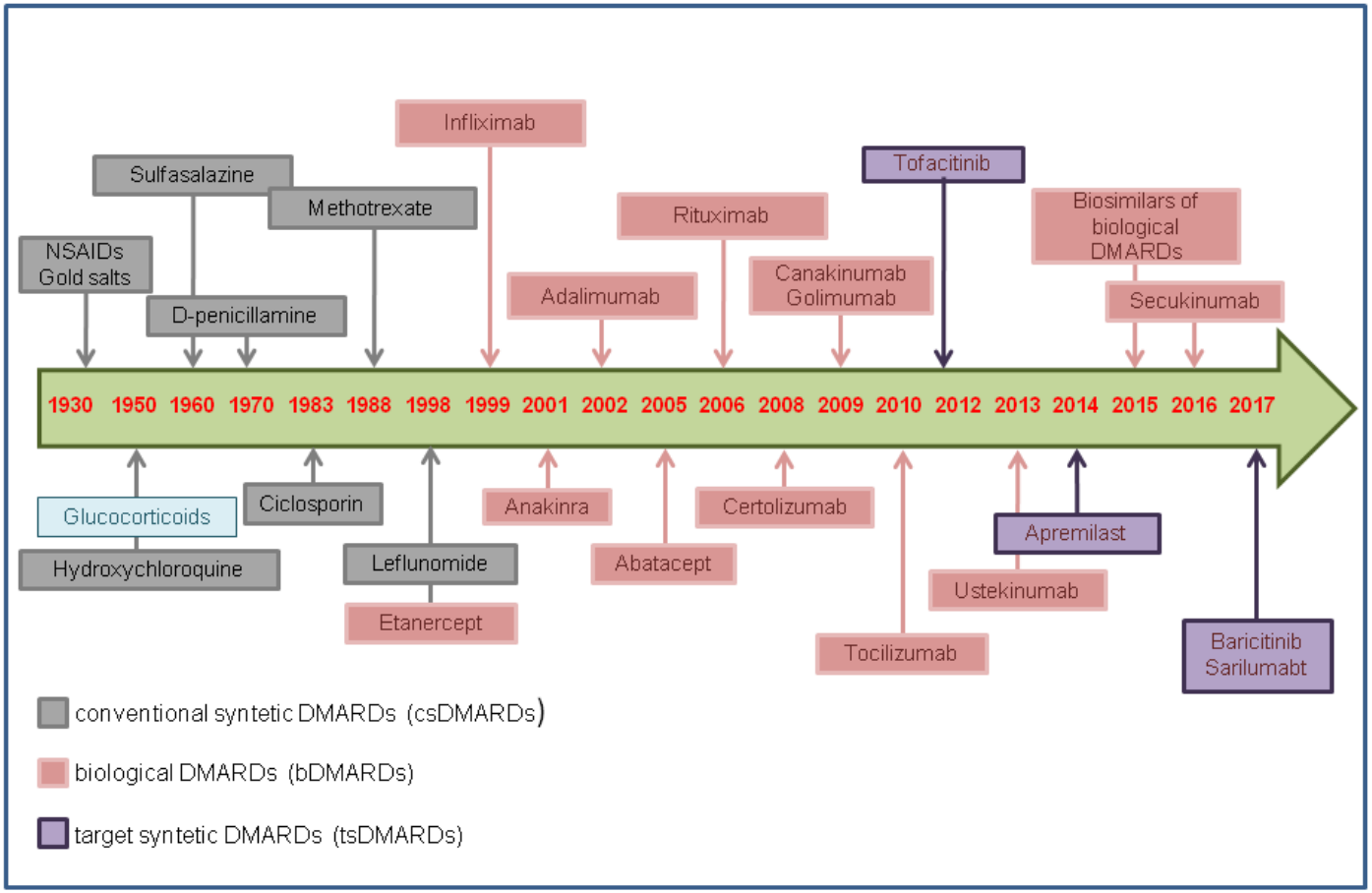
Traditional Pyramid Model Treatment



Algorithm for treating rheumatoid arthritis (RA)



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



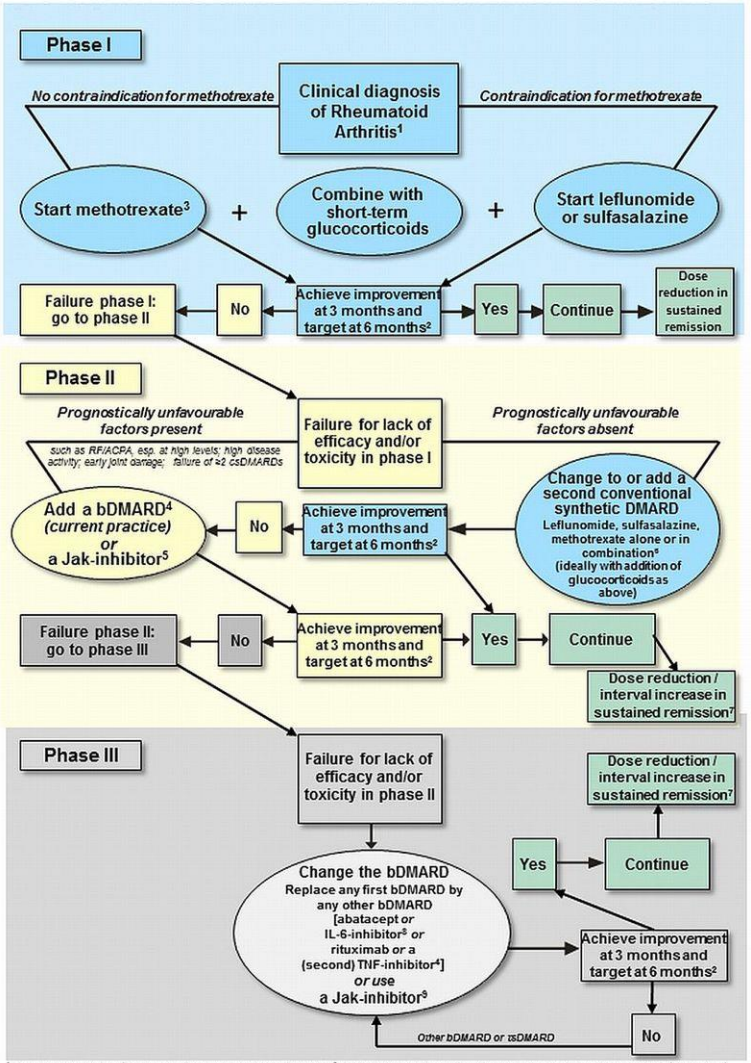
The mechanistic immune classification has implications for understanding the compexity of RA and for thinking about therapy in an **immune-centric way**.

antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		**Biological DMARDs (bDMARDs)**	
Conventional synthetic DMARDs (csDMARDs)	Targeted synthetic DMARDs (tsDMARDs)	Biological originator DMARDs (boDMARDs)	Biosimilar DMARDs (bsDMARDs)

F.W. Rossi et al 2018

Algorithm based on the 2016 European League Against Rheumatism (EULAR) recommendations on rheumatoid arthritis (RA) management



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Josef S Smolen et al. Ann Rheum Dis 2017;76:960-977

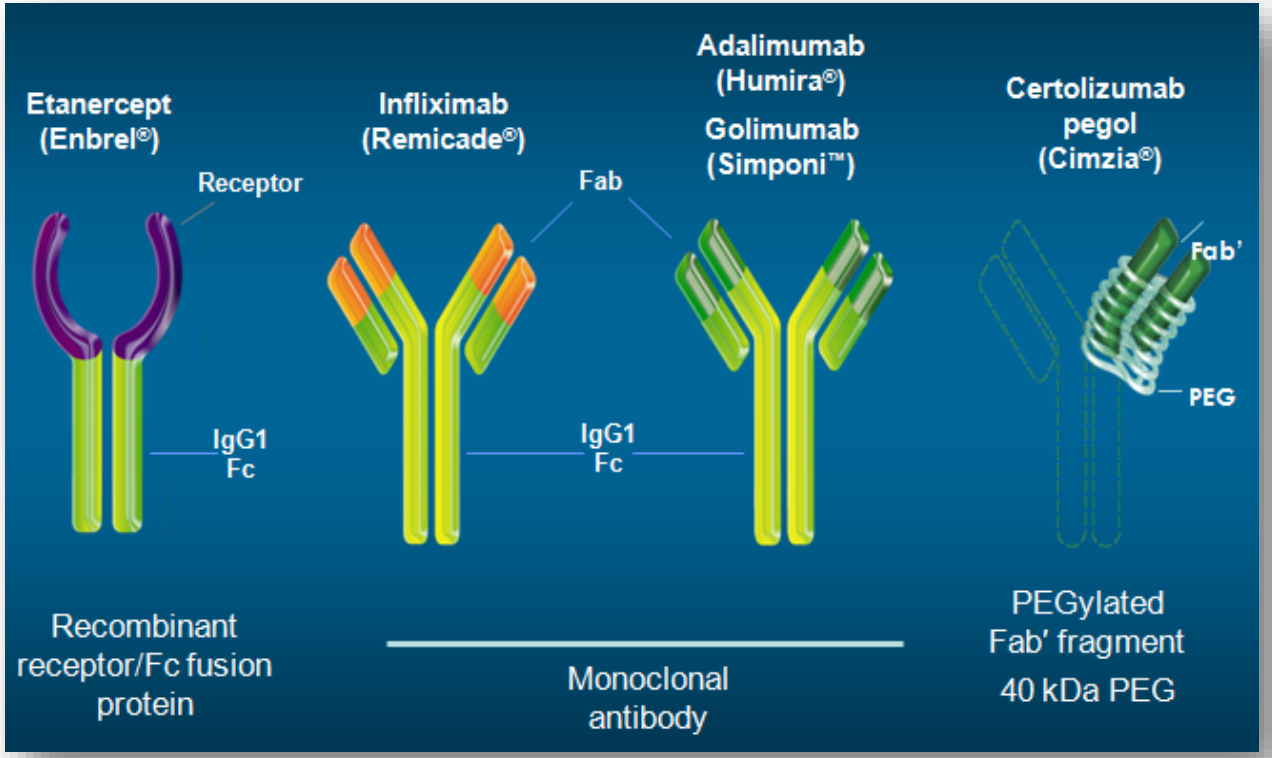
Obstacles to the use of biologic therapies

✓Related not only to prescribers but also to patients.

✓The two main reasons for resisting changes in RA therapy were fear of loss of disease control (OR 6.8) and fear of side effects (OR 4.4), reported by two-thirds of patients.

✓Physician opinion on the current treatment (OR1.9) and fear of high costs (OR 1.3) lagged far behind.

Ann Rheum Dis 2006;65: 1226–9
Rheumatology 2009;48: 906–10
Ann Rheum Dis 2006;65: 1226–9
Arthritis Rheum 2007;56:2135–42



Patients with RA treated with anti-TNFs constitute an ideal group for assessing the benefits and risks of biologic treatment in the elderly.

Anti-TNFs are among the oldest biologics and are still by far the most widely used and have the longest follow-up in RA.

Data on the other biologics and other inflammatory diseases are less robust.

CONCISE REPORT

Do patients with older-onset rheumatoid arthritis receive less aggressive treatment?

Z Tutuncu, G Reed, J Kremer, A Kavanaugh

Ann Rheum Dis 2006;**65**:1226–1229. doi: 10.1136/ard.2005.051144

Table 2 Characteristics of patients by comorbidities

	Age at onset of RA						
	⩾60 years			40–60 years			
	%	Freq	n	%	Freq	n	p Value
Sex (female)	69.3	1440	2077	71.9	1506	2094	0.072
Use of methotrexate	63.9	1342	2101	59.6	1253	2101	0.005
Use of biological agent	25.0	525	2101	33.1	696	2101	0.000
Use of >1 DMARD	30.9	649	2101	40.5	851	2101	0.000
Use of prednisone	41.0	837	2039	37.64	778	2067	0.025
Hx of peptic ulcer disease	6.4	135	2101	5.6	118	2101	0.299
Hx of CAD	8.9	187	2101	3.7	77	2101	0.000
Hx of GERD	16.8	353	2101	16.7	352	2101	1.000
Hx of MI	5.9	125	2101	3.0	63	2101	0.000
Hx of hypertension	41.4	870	2101	27.4	575	2101	0.000
Hx of stroke	3.8	79	2101	1.4	30	2101	0.000
Hx of CVD*	14.4	303	2101	6.6	138	2101	0.000

CAD, coronary artery disease; CVD, cardiovascular disease; DMARD, disease-modifying antirheumatic drug; Freq, frequency; GERD, gastroesophageal reflux disease; Hx, history; MI, myocardial infarction; RA, rheumatoid arthritis.
*CAD, MI, stroke combined.

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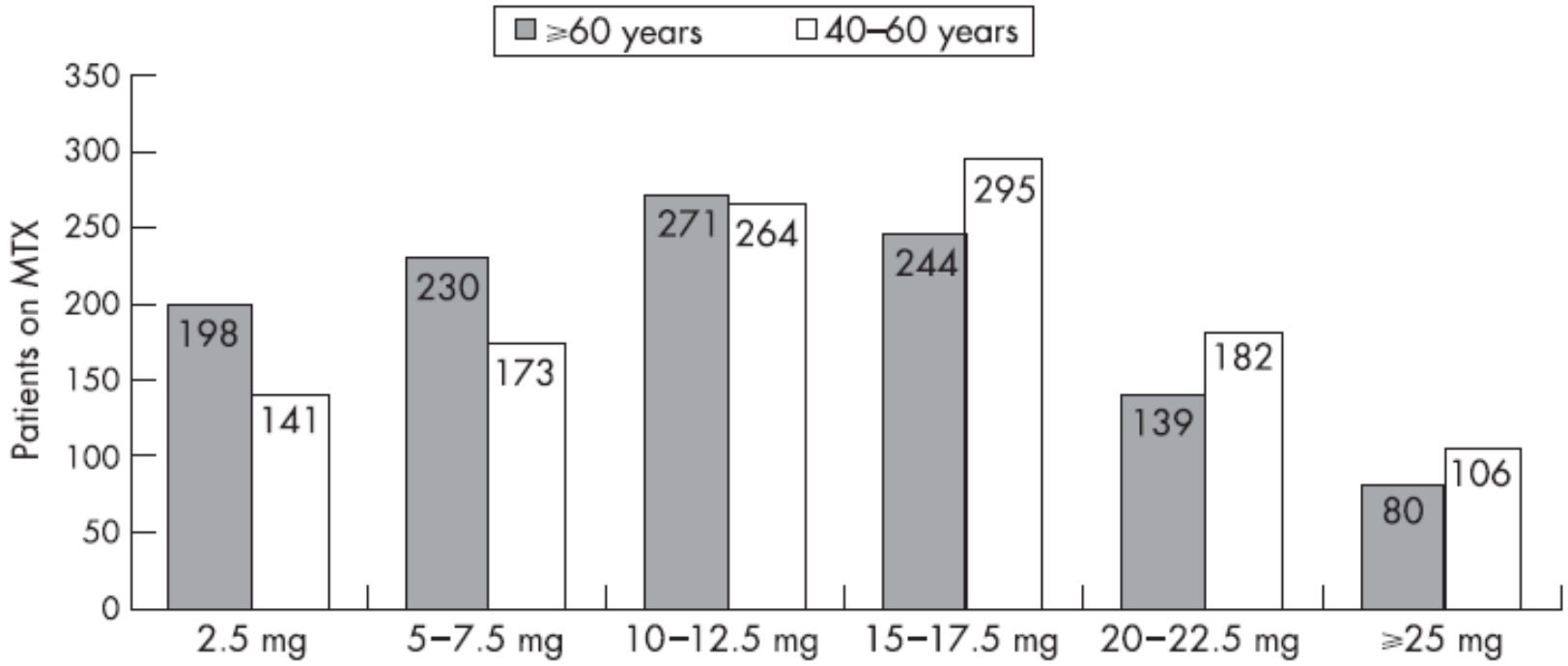


Rheumatology 2009;48:906–910
Advance Access publication 28 May 2009
doi:10.1093/rheumatology/kep129

Missed opportunities in the treatment of elderly patients with rheumatoid arthritis

Beáta J. Radovits[1], Jaap Fransen[1], Agnes Eijsbouts[2], Piet L. C. M. van Riel[1] and Roland F. J. M. Laan[1]

Rheumatology key messages

- Elderly RA patients are less likely to receive anti-TNF-α treatment compared with younger patients.
- Elderly patients require significantly higher disease activity in order to receive anti-TNF-α treatment.

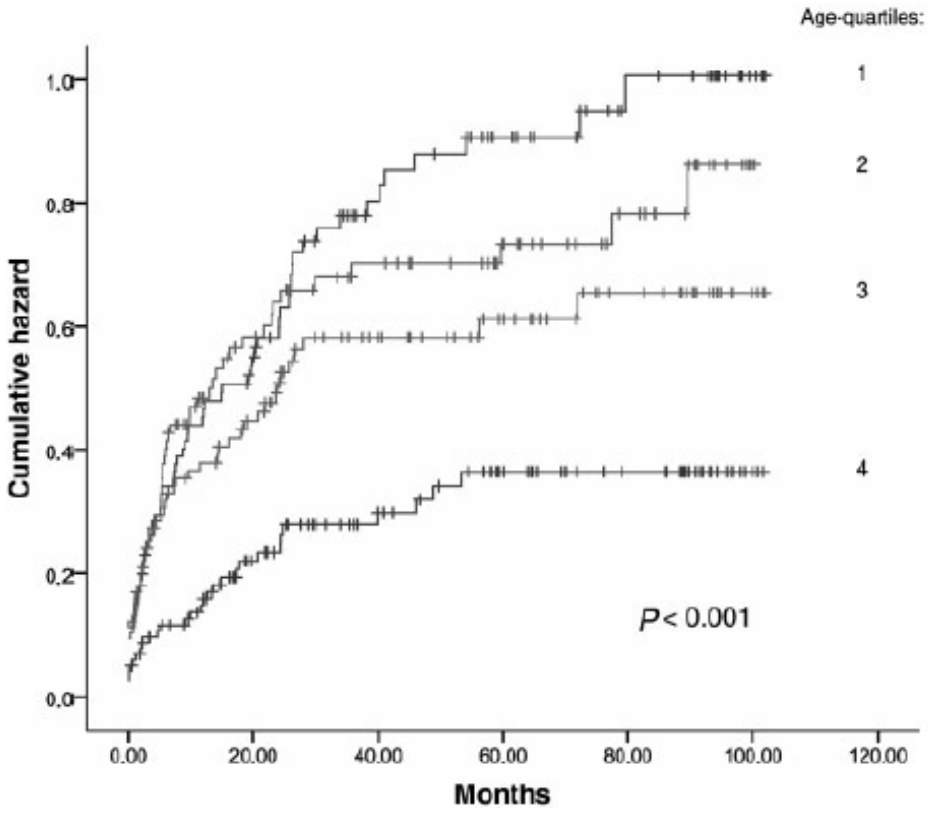


FIG. 2. Cumulative hazards in four age quartiles (Kaplan–Meier method). Age quartiles: 1 = <49.0 years; 2 = 49.0–58.9 years; 3 = 58.9–68.3 years; 4 = >68.3 years. Hazard is interpreted as the chance of receiving anti-TNF-α treatment within an equal period of time compared with the eldest age group.

Table 1
Clinical trials and registries assessing the effects of aging on efficacy and/or safety of anti-TNFs in RA patients.

Study	Design	Efficacy	Tolerance
Bathon et al., 2006 [19]	Subset analysis (age ≥ 65 yrs vs. age < 65 yrs) of 4 randomized controlled clinical studies (n = 1353) or 2 long-term extensions (n = 1049) studying ETA in DMARD-resistant or late stage RA	Elderly subjects tended to have somewhat less robust ACR responses to treatment than younger subjects. A similar slowing in radiographic progression after one year of ETA was observed in both age groups	Rates of SAE tended to be higher in the elderly than in younger subjects, but are equivalent to elderly placebo- or MTX-treated subjects
Hyrich et al., 2006 [23]	Register of RA patients starting ETA (1267) or INF (1612) (Mean age: 55 years)	Age did not predict EULAR response or remission with either drug at 6 months	No assessment
Setoguchi et al., 2006 [48]	Cohort (mean age: 70 years) comparing 1152 patients on boDMARDs with 7306 patients on MTX	No assessment	boDMARDs patients showed no difference in hematologic malignancies or solid tumor incidence compared to MTX users
Tutuncu et al., 2006 [14]	Register; 2101 patients with EORA (after	No assessment	Toxicities related to treatment with ETA,
Ge			were identical s significantly RA (7.1%
Sch			s among y was itiators (RR 1.0
Ask			r risk was , regardless of 51–74,
Köl			
McDonald et al., 2009 [44]	Cohort of 20,357 veterans with RA, including 3661 patients treated with boDMARDS (mean age: 59.3 years)	No assessment	Unlike use of anti-TNF, increased age was an independent risk factor for herpes zoster
Radovits et al., 2009 [24]	Register of 730 RA patients, categorized into three age groups (< 45, 45–65 and > 65 years) at initiation of anti-TNF. Longitudinal analysis of DAS28 during the first year of treatment	Elderly patients had fewer EULAR good responses and remission and less improvement in disease activity and physical functioning than younger patients	Drug survival, co-medication use and tolerance were comparable between the three age groups
Filippini et al., 2010 [25]	Observational cohort involving 1114 RA patients treated with anti-TNF therapy (311 age ≥ 65 and 803 age < 65 years) and followed up to 3 years	Decrease in DAS28 and ESR was comparable, but EULAR response was somewhat lower in the elderly group. HAQ scores were higher at baseline and showed less improvement after treatment in elderly patients	Anti-TNFα therapy was discontinued by 42% of the elderly and 36.6% of the younger patients. SAEs, infection and overall cancer were higher in the elderly patients
Hetland et al., 2010 [26]	Register of 2326 RA patients beginning boDMARDs (median age; 57 years). Treatment responses were assessed after 6 months and 12 months	Older age and initial low functional status were negative predictors of a clinical response and remission during anti-TNF treatment of RA	No assessment
Amari et al., 2011 [51]	Cohort of 20,648 veterans with RA (mean age: 63 years), including 4088 patients treated with anti-TNFs	No assessment	Age (per decade, HR 1.23; 95% CI: 1.09–1.38), as anti-TNF use (compared to csDMARDs, HR 1.42; 95% CI: 1.24–1.63) were risk factors for developing NMSC
Galloway et al., 2011 [32]	Prospective observational study assessing the risk of severe infection between 11,798 and 3598 csDMARDs-treated RA patients, stratified by age (< 55, 55–64, 65–74 and > 75 years)	No assessment	The crude rate of infection increased markedly with age. The increased risk of SI associated with anti-TNF therapy (+20% compared to csDMARDs) is equivalent in elderly and younger patients
Lane et al., 2011 [33]	Cohort of 20,814 veterans (mean age: 63 years) with RA, including 3796 anti-TNF-treated patients. Rate of hospitalization for SI was compared with csDMARD-users (mean follow-up: 2.7 years)	No assessment	In multivariate analysis, unlike csDMARD use, anti-TNF use was associated with hospitalization for infection (HR, 1.24; 95% CI: 1.02–1.50)
Curtis et al., 2012 [34]	Prospective cohort of 11,657 RA patients (mean age: 61.9 years) initiating anti-TNF therapy. The observed 1-year rates of infection were compared to a predicted infection risk score estimated in the absence of anti-TNF exposure	No assessment	The rate of SI for anti-TNF agents was incrementally increased by a fixed absolute difference irrespective of age (above vs. below 65 years)
Herrinton et al., 2012 [30]	Cohort of 46,424 patients with selected autoimmune diseases. Mortality was compared between new anti-TNF users and similar new csDMARDs users	No assessment	Anti-TNF therapy was associated with a reduction in mortality among RA patients with ≥ 2 comorbid conditions (aHR, 0.87; 95% CI: 0.77–0.99), or, though not significant, age ≥ 75 years (aHR, 0.89; 95% CI: 0.76–1.03)
Toh et al., 2012 [35]	Retrospective study of 3485 RA patients (mean age: 57.9 years) who initiated INF or ETA. Rate of SI or opportunistic infections during the first year was compared between infliximab initiators and etanercept initiators	No assessment	Rate of SI per 100 person-years was 5.4 (95% CI: 3.8–7.5) in patients < 5 years and 16.0 (95% CI: 10.4–23.4) in patients ≥ 65 years during the first 3 months following treatment initiation. The increased risk of SI associated with infliximab compared to etanercept in young subjects disappeared in patients above age 65
Dreyer et al., 2013 [49]	Register of RA patients (mean age 58 years). The incidence of cancer in patients treated with (3347) or without TNF inhibitors (3812) was evaluated over a mean follow-up of 2.5 years	No assessment	TNF antagonist-treated patients showed no increased risk for overall cancer (HR 1.02; 95% CI: 0.80–1.30) compared to non-treated patients, even > 65 years (HR 1.10; 95% CI: 0.80–1.50)

ADA: Adalimumab; aHR: adjusted Hazard Ratio; boDMARDs: Biological Originator DMARDs; csDMARDs: Conventional Synthetic DMARDs; EORA: Elderly-Onset Rheumatoid Arthritis; ETA: Etanercept; HAQ: Health Assessment Questionnaire; HR: Hazard Ratio; INF: Infliximab; KIN: Kineret; MTX: Methotrexate; NMSC: Non-Melanoma Skin Cancer; RA: Rheumatoid Arthritis; SAE: Serious Adverse Event; SI: Severe Infection; YORA: Younger-Onset Rheumatoid Arthritis.

There is much evidence that anti-TNF-agents do not cause a significantly higher incidence of adverse events in elderly compared with younger RA patients

Cho et al. BMC Musculoskeletal Disorders (2016) 17:333
DOI 10.1186/s12891-016-1185-6

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Drug retention and safety of TNF inhibitors in elderly patients with rheumatoid arthritis

Soo-Kyung Cho[1,2], Yoon-Kyoung Sung[1,2], Dam Kim[1,2], Soyoung Won[2], Chan-Bum Choi[1,2], Tae-Hwan Kim[1], Jae-Bum Jun[1], Dae-Hyun Yoo[1] and Sang-Cheol Bae[1,2*]

The concerns about the development of adverse events (AEs) in elderly RA patients as a result of age-related changes in drug metabolism and the presence of comorbid illnesses are emphasizing due to increasing prevalence of rheumatoid arthritis (RA) in old age.

However, they tend to be inadequately represented in RA clinical trials because of the exclusion criteria that are commonly applied.

The retention rate of TNF in the elderly was comparable with that in younger patients

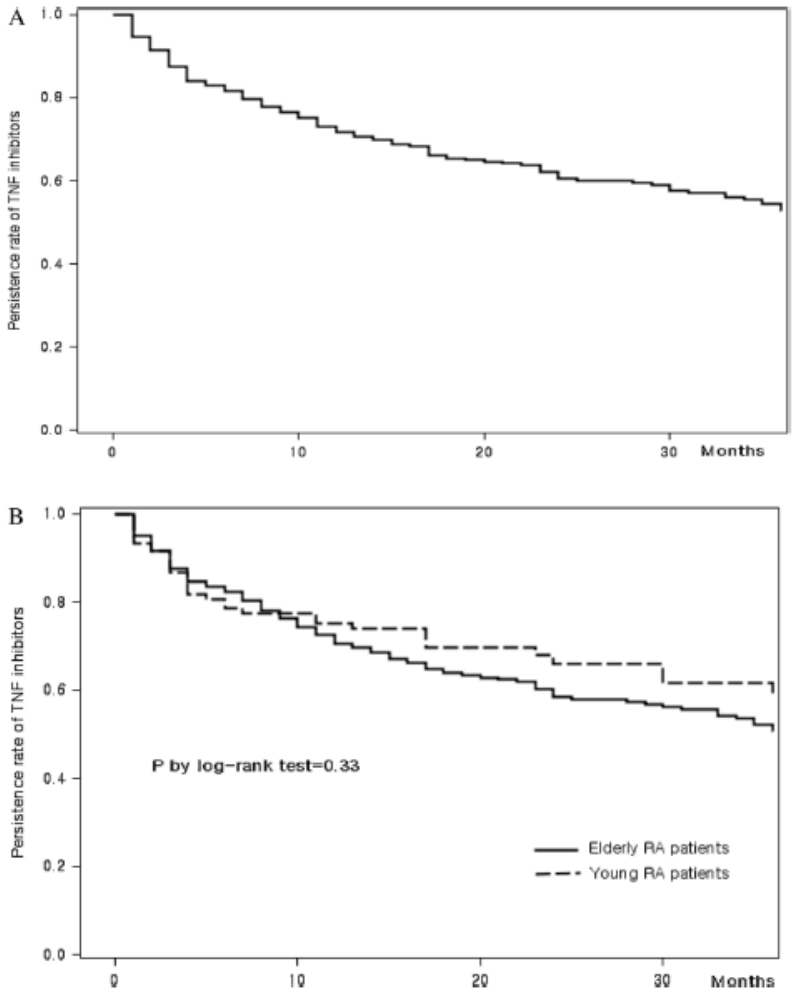


Fig. 1 Persistence rate of TNF inhibitors. **a** Persistence rate of TNF inhibitors in total patients. **b** Comparison of TNF inhibitor persistence rate between elderly patients and younger patients

Discontinuation in the elderly patients

	Total ($n = 429$)	Elderly patients ($n = 107$)	Younger patients ($n = 322$)	p value
Number of discontinuations	167 (38.9)	35 (32.7)	132 (41.0)	0.16
Reason for discontinuation				0.43
Adverse effect	**44 (26.4)**	**12 (34.3)**	**32 (24.2)**	
Ineffectiveness	**64 (38.3)**	**9 (25.7)**	**55 (41.7)**	
Patient need	37 (22.2)	9 (25.7)	28 (21.2)	
Good effectiveness	7 (4.2)	2 (5.7)	5 (3.8)	
Economic problem	3 (1.8)	1 (2.9)	2 (1.5)	
Operation or hospitalization	4 (2.4)	1 (2.9)	3 (2.3)	
Other[a]	3 (1.8)	1 (2.9)	2 (1.5)	
Unknown	5 (3.0)	-	5 (3.8)	

[a]Other reasons include mobility impaired, preparation for pregnancy, and dental treatment
Bold means statistical significant at the $p < 0.05$

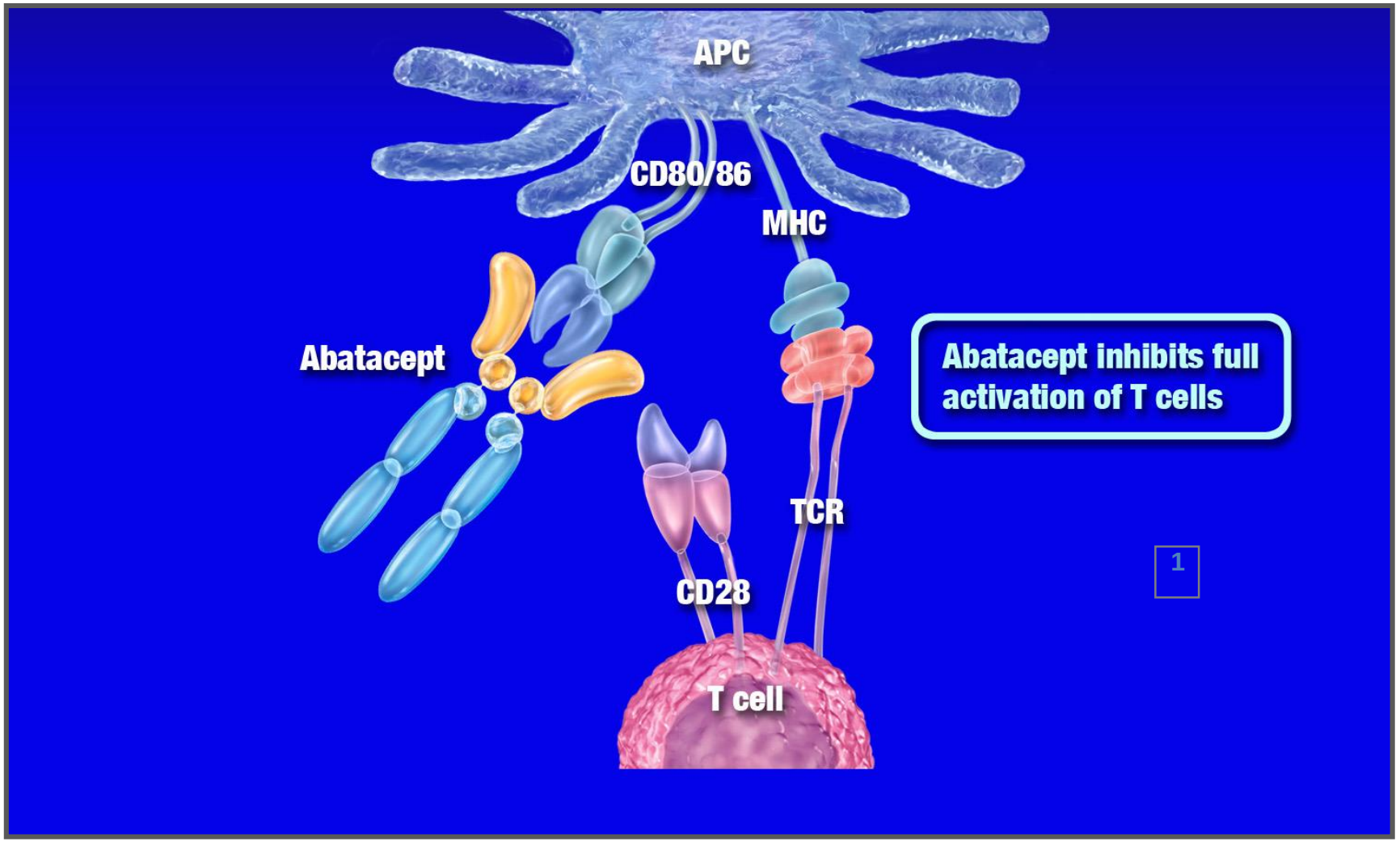
The major cause of discontinuation in the elderly patients was AEs, while it was drug ineffectiveness in younger patients.

Risk factors

	Total RA		Elderly patients		Young RA	
	Adjusted HR (95 % CI)	*p*	Adjusted HR (95 % CI)	*p*	Adjusted HR (95 % CI)	*p*
Age at start of biologics	1.00 (0.99 – 1.02)	0.66	**1.09 (1.02 – 1.16)**	<0.01	1.00 (0.99 – 1.02)	0.64
Sex, female	1.06 (0.65 – 1.74)	0.81	1.81 (0.64 – 5.12)	0.27	0.84 (0.47 – 1.49)	0.55
Switcher vs. first user	**0.55 (0.35 – 0.86)**	<0.01	0.43 (0.16 – 1.22)	0.11	**0.57 (0.34 – 0.94)**	0.03
Disease duration, per year	**0.97 (0.95 – 0.997)**	0.03	0.96 (0.91 – 1.00)	0.05	**0.97 (0.94 – 0.997)**	0.03
Biologics						
Etanercept	1.00		1.00		1.00	
Infliximab	1.44 (0.92 – 2.27)	0.11	0.43 (0.10 – 1.97)	0.28	**1.81 (1.11 – 2.95)**	0.02
Adalimumab	0.88 (0.59 – 1.32)	0.54	0.72 (0.30 – 1.74)	0.46	0.86 (0.54 – 1.37)	0.53
Concomitant use of methotrexate	0.72 (0.51 – 1.01)	0.06	**0.44 (0.21 – 0.91)**	0.03	0.91 (0.62 – 1.35)	0.64
Concomitant glucocorticoid dosage						
<5 mg/day	1.00		1.00		1.00	
≥5 mg/day	1.05 (0.76 – 1.46)	0.75	1.18 (0.53 – 2.62)	0.68	0.97 (0.67 – 1.41)	0.89
Comorbidity[a]	0.91 (0.64 – 1.29)	0.59	**0.37 (0.15 – 0.91)**	0.03	1.04 (0.71 – 1.52)	0.83

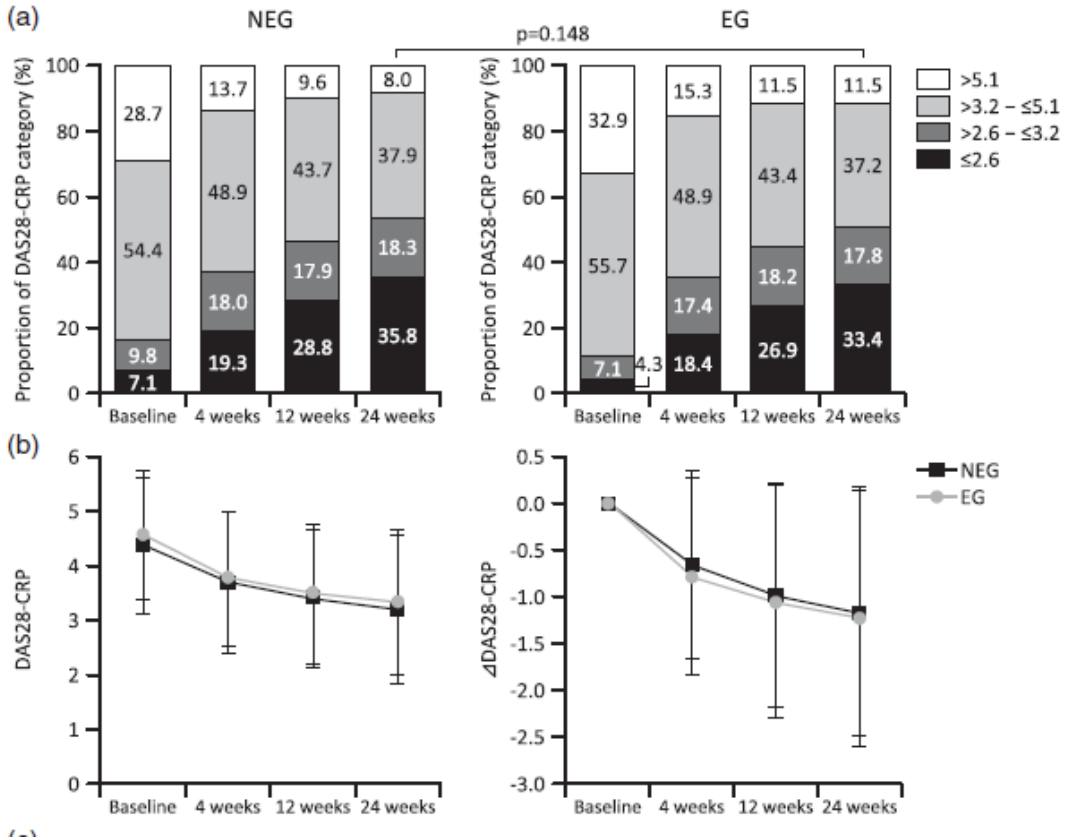
TNF tumor necrosis factor, *HR* hazard ratio, *CI* confidence interval, *RA* rheumatoid arthritis
[a]Comorbidity: the presence of a comorbid condition
Bold means statistical significant at the $p < 0.05$

Biologic Therapies: Targeting T Cells

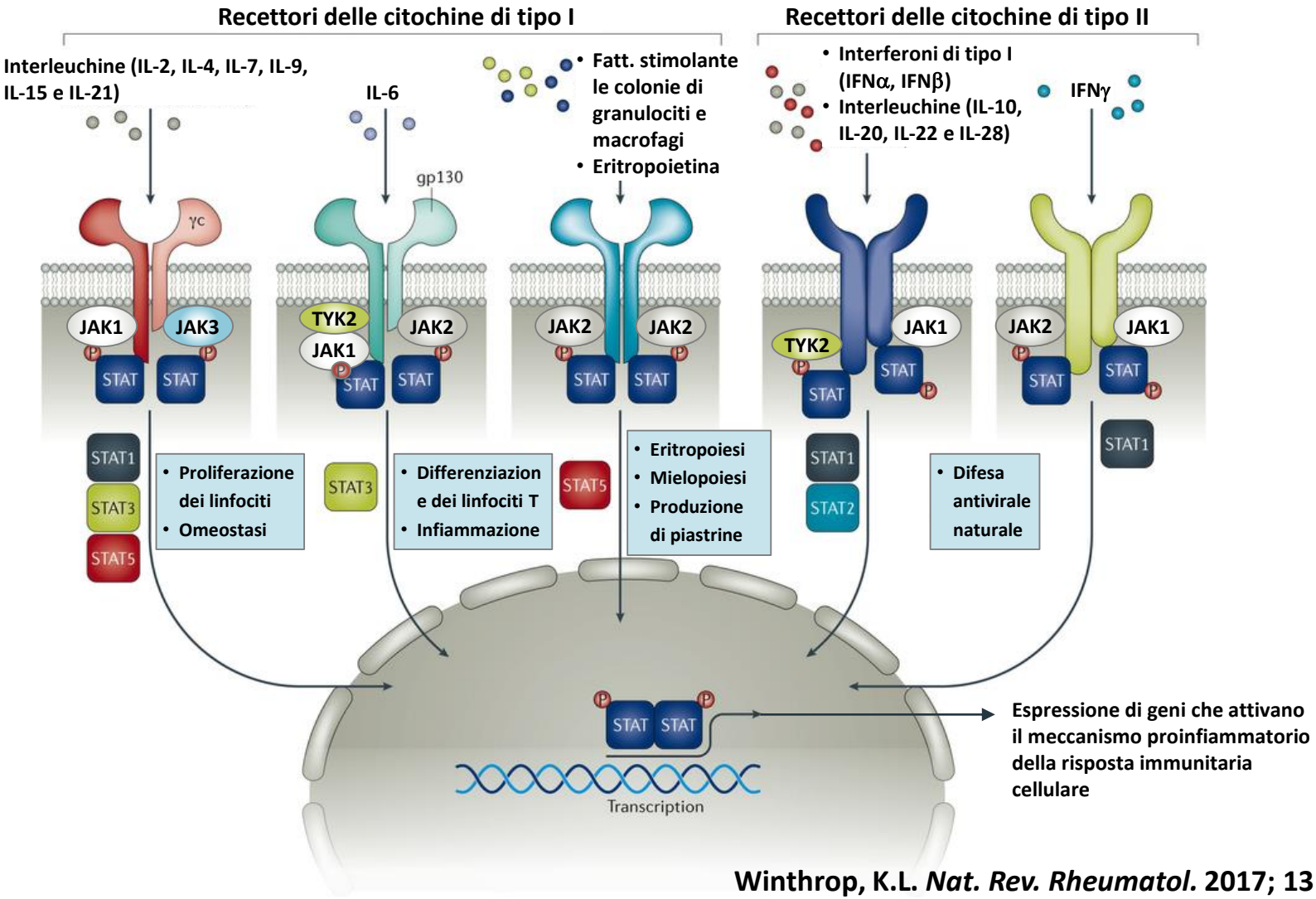


Safety and effectiveness of abatacept in Japanese non-elderly and elderly patients with rheumatoid arthritis in an all-cases post-marketing surveillance

Masayoshi Harigai[a], Naoki Ishiguro[b], Shigeko Inokuma[c], Tsuneyo Mimori[d], Junnosuke Ryu[e], Syuji Takei[f], Tsutomu Takeuchi[g], Yoshiya Tanaka[h], Yoshinari Takasaki[i], Hisashi Yamanaka[a], Yuri Yoshizawa[j], Ichino Chinen[j], Toru Nakao[j] and Takao Koike[k]



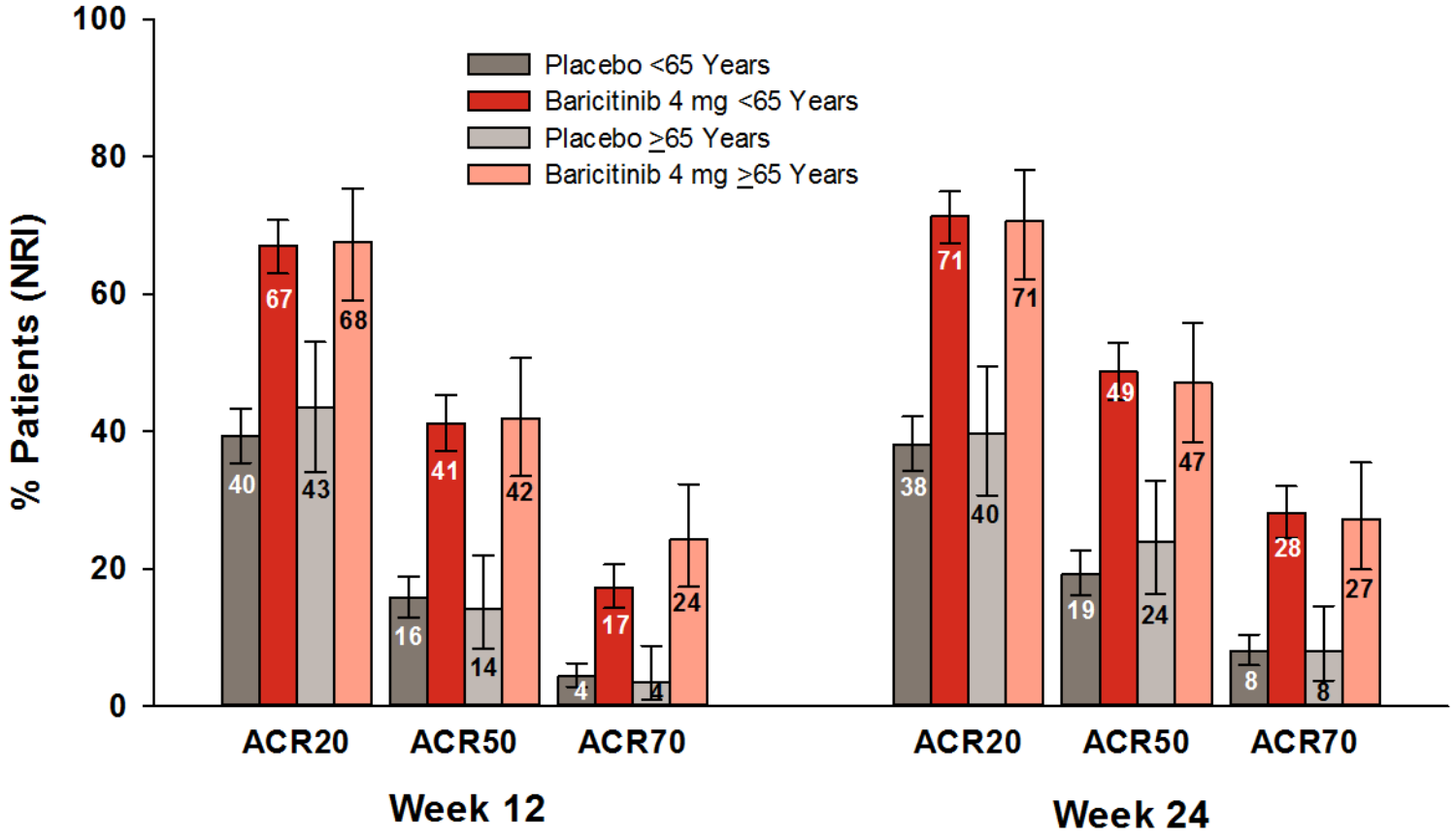
Cytokine Receptors and JAK/STAT Signaling



Winthrop, K.L. *Nat. Rev. Rheumatol.* 2017; 13:234.

Bariticitinib:

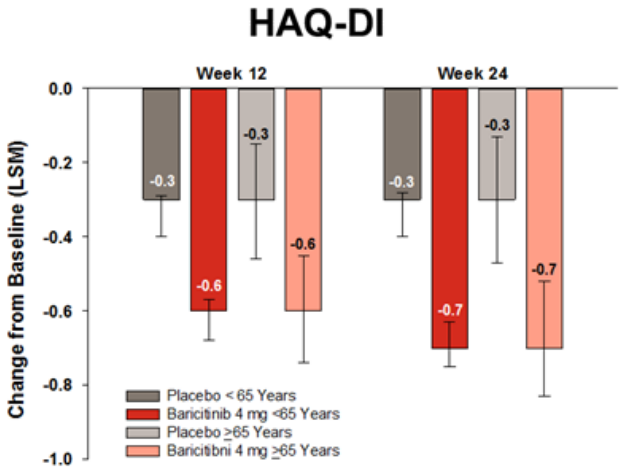
ACR Outcomes in Patients ≥65 Years vs Patients <65 Years



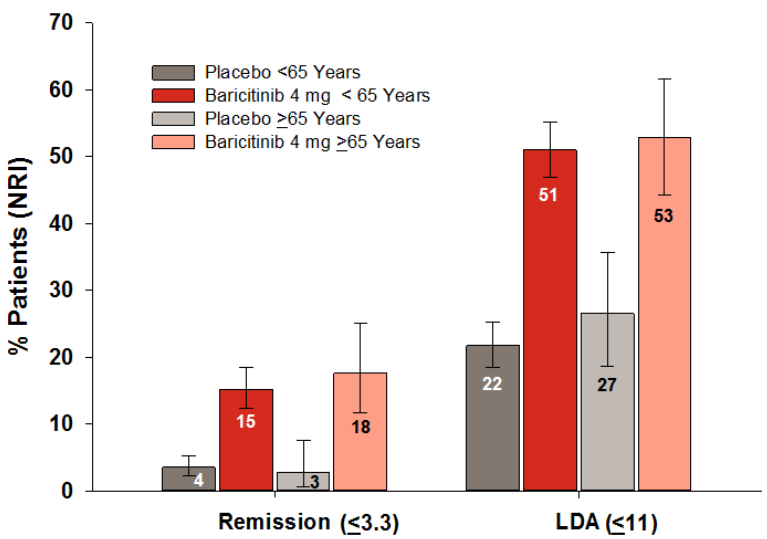
Error bars represent 95% confidence interval
Abbreviations: ACR=American College of Rheumatology; NRI=non-responder imputation.

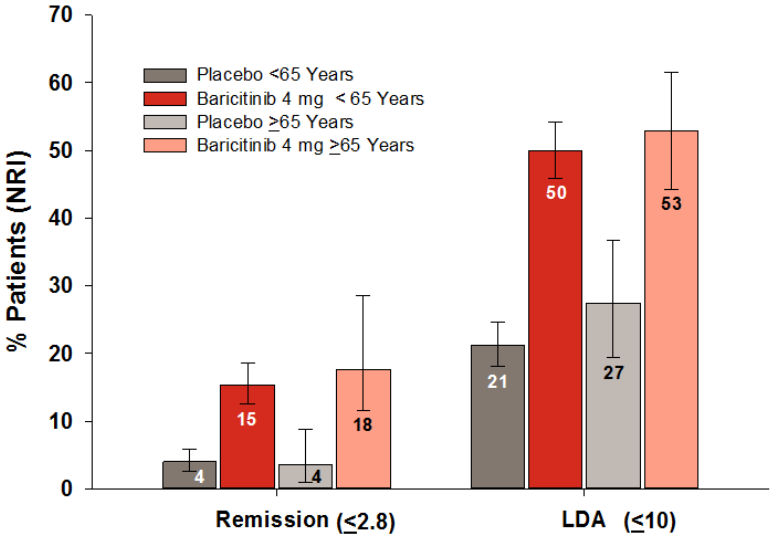
Fleischmann R et al. presented at American College of Rheumatology/ARHP 2016

Efficacy Outcomes in Patients ≥65 Years vs Patients <65 Years



Percent Patients Achieving Remission and LDA





Fleischmann R et al. presented at American College of Rheumatology/ARHP 2016

Safety at Week 24

	<65 Years		≥65 Years	
	Placebo (N=603)	Baricitinib 4 mg (N=578)	Placebo (N=113)	Baricitinib 4 mg (N=136)
Patients with ≥1 adverse event	538 (89.2)	525 (90.8)	111 (98.2)	135 (99.3)
Discontinuation from study due to adverse event or death	20 (3.3)[a]	24 (4.2)[b]	7 (6.2)[c]	12 (8.8)[d]
Death	2 (0.3)	1 (0.2)	0	1 (0.7)
Serious adverse event	21 (3.5)	23 (4.0)	12 (10.6)	12 (8.8)
Serious infections	9 (1.5)	5 (0.9)	2 (1.8)	4 (2.9)
Herpes zoster	0	0	0	4 (2.9)
Cardiac disorders[e]	2 (0.3)	2 (0.3)	2 (1.8)	2 (1.5)

Data presented as n (%).

[a] AEs were subarachnoid hemorrhage, myocardial infarction, pregnancy, myopathy, lung cyst, renal failure, suicidal ideation, depression, diarrhea, herpes zoster (n=2), dermatitis allergic, skin necrosis, RA aggravated (n=2), lymphocyte counts decreased, cancer (breast, ovarian), upper respiratory tract infection, abnormal liver function test.

[b] AEs were urinary tract infection (n=2), pneumonia, interstitial lung disease, disseminated tuberculosis, herpes zoster (n=6), increase blood triglycerides, cholecystitis acute, amenorrhea, drug-induced liver injury, circulatory collapse, alanine aminotransferase increased (n=2), interstitial lung disease, hepatitis B DNA assay positive, lung squamous cell carcinoma stage III, lymphocytosis, drug intolerance, dermatitis allergic.

[c] AEs were gastrointestinal hemorrhage, mood altered, decreased glomerular filtration rate, acute pancreatitis, renal impairment, squamous cell carcinoma skin, kidney infection.

[d] AEs were hypersensitivity, decreased lymphocyte count, pneumonia, breast cancer, cardiac failure, herpes zoster (n=3), asthenia, gastric ulcer, nasopharyngitis, thrombocytosis.

[e] Any serious adverse event based on the MedDRA dictionary system organ class.

Severe adverse drug reactions to biological disease-modifying anti-rheumatic drugs in elderly patients with rheumatoid arthritis in clinical practice

L. Leon[1,2], A. Gomez[3], C. Vadillo[3], E. Pato[3], L. Rodriguez-Rodriguez[1], J.A. Jover[3,4], L. Abasolo[1]

Table II. Characteristics of the severe adverse drug reactions (ADRs). Results are expressed as number (n) and percentage (%).

	Severe ADR
bDMARDs	
- ETN	**6 (9.68)**
- GOLI	1 (1.61)
- CERTO	0
- IFX	**28 (45.16)**
- ADA	**15 (24.19)**
- RTX	**11 (17.74)**
- ABT	1 (1.61)
- TOCI	0
Causes of severe ADR	
- Cancer	4 (6.45)
- Ischaemic cardiopathy	3 (4.84)
- General	1 (1.61)
- Congestive heart failure	5 (8.06)
- Infection	**32 (51.61)**
- Mucocutaneous	1 (1.61)
- Exitus	**16 (25.81)**

Table III. Incidence rate (IR) of severe ADRs in eldery RA patients with bDMARDs, by sex, diagnostic period, and therapy.

ADR	Patient-years	Severe ADR		
		n	IR	95% CI
	604	62	10.2	7.9-13.1
By sex				
Women	505	51	10.08	7.6-13.2
Men	94	11	11.6	6.4-21.1
By Calendar time				
2000-2001	32.48	8	7.54	3.7-15
2002-2003	278	6	13.3	5.9-29.6
2004-2005	455.2	9	11.5	5.9-22.1
2006-2007	378.1	10	7.9	4.2-14.8
2008-2009	172.4	16	13.03	7.9-21.2
2010-2011	161.4	8	8.9	4.4-17.4
2012-2013	99.7	5	13.3	5.5-32.8
By bDMARDs:				
Infliximab	176.7	28	15.8	10.9-22.9
Adalimumab	185.4	15	8.08	4.8-13.4
Etanercept	117.1	6	5.12	2.3-11.3
Rituximab	91.6	11	12	6.6-21.6
Other TNF-α	33.4	2	3.2	1.4-23.9

n: events; IR: incidence rate per 100; CI 95%: confidence interval.

Clinical and Experimental Rheumatology 2018; **36**: 29-35.

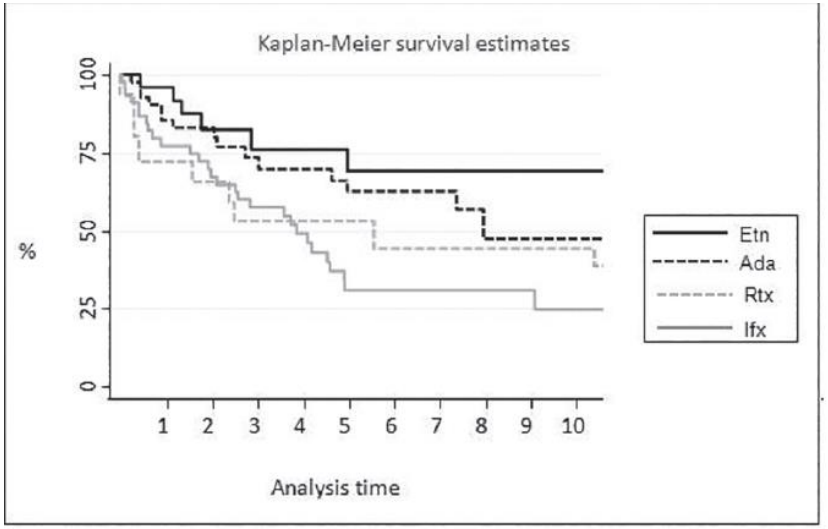


Fig. 1. Incident rates for etanercept, adalimumab, rituximab and infliximab.

Table V. bDMARD discontinuation due to severe adverse drug reactions (ADR): multivariate analysis.

	Severe ADRs		
	HR	95%CI	*p*-value
Gender, male	1.5	0.6-3.8	0.34
Age at first bDMARD, years	1.07	1.01-1.14	0.01
Calendar time: 2000-2013	1.2	1.03-1.4	0.01
Comorbid conditions:			
Congestive heart failure	1.96	0.98-4.1	0.07
Liver disease	4.3	1.6-11.3	0.003
Cardiovascular disease	2.3	1.12-4.9	0.02
Concomitant corticosteroids	3.8	1.6-8.8	0.001
Positive ACPAs	2.45	0.87-6.8	0.08
bDMARDs:			
Etanercept	1	-	-
Infliximab	5.5	1.7-17.7	0.004
Adalimumab	2.7	0.7-9.9	0.1
Rituximab	4.1	1.4-12.3	0.01
Other bDMARDs	1.6	0.4-7.3	0.5

The incidence of discontinuation due to severe ADR estimated was 10.2 (events/ 100 patient-years).

The most frequent cause of severe ADRs was infections.

Interestingly, the IR of severe ADRs in the whole cohorts of RA, is superior in elderly compared to younger patients reflecting the complexity of RA management in old, comorbid patients.

Regarding the incidence in the different treatment regimens studied, for the severe ADRs, IFX had the highest risk of ADR development compared to other bDMARDs, and ETN the lowest.

Challenge in Treatment Targeting LDA in patients with EORA

Cardiovascular disease

Atherosclerosis is a common age-related comorbidity and an important RA-related comorbidity among patients with RA.

Various studies have demonstrated the risk of cardiovascular disease in RA populations.

The risk for myocardial infarction was reduced in middle-aged patients with RA who responded well to TNF inhibitors.

Patients with RA related comorbidities such as cardiovascular disease may undergo intensive treatment.

This may be the case with EORA.

ILD

ILD is associated with mortality. Existence of ILD should be examined before treating patients with EORA, as the age at the time of diagnosis of RA was a risk factor for the development of ILD.

However, chronic lung diseases including ILD is a well-established risk factor of infection in patients with RA.

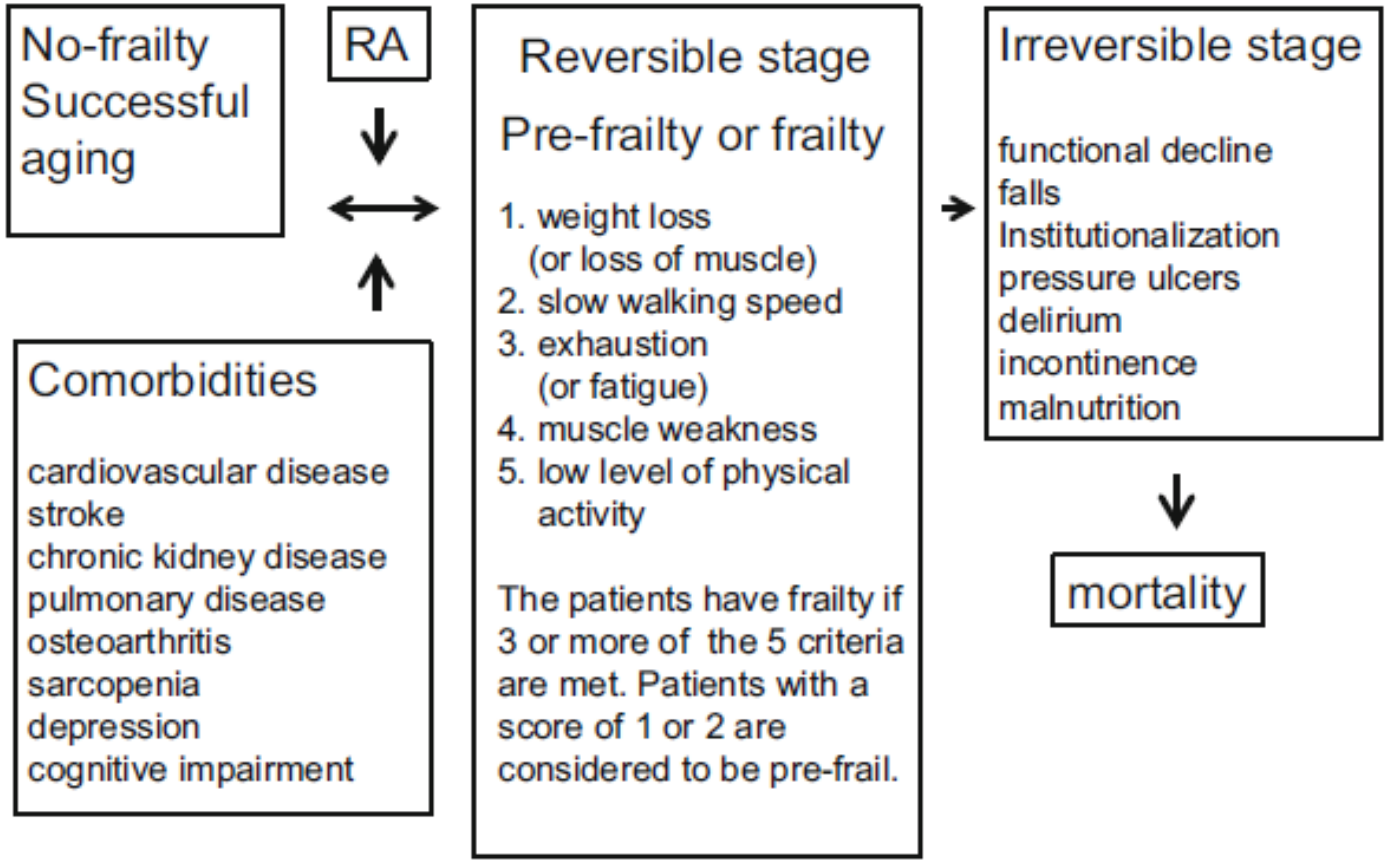
Rheumatologists sometimes hesitate to use MTX in patients with RA with ILD, and treatment with glucocorticoids is commenced.

Coexistence of chronic lung diseases, older age, and concomitant use of glucocorticoids can further increase risk for infection or serious infection.

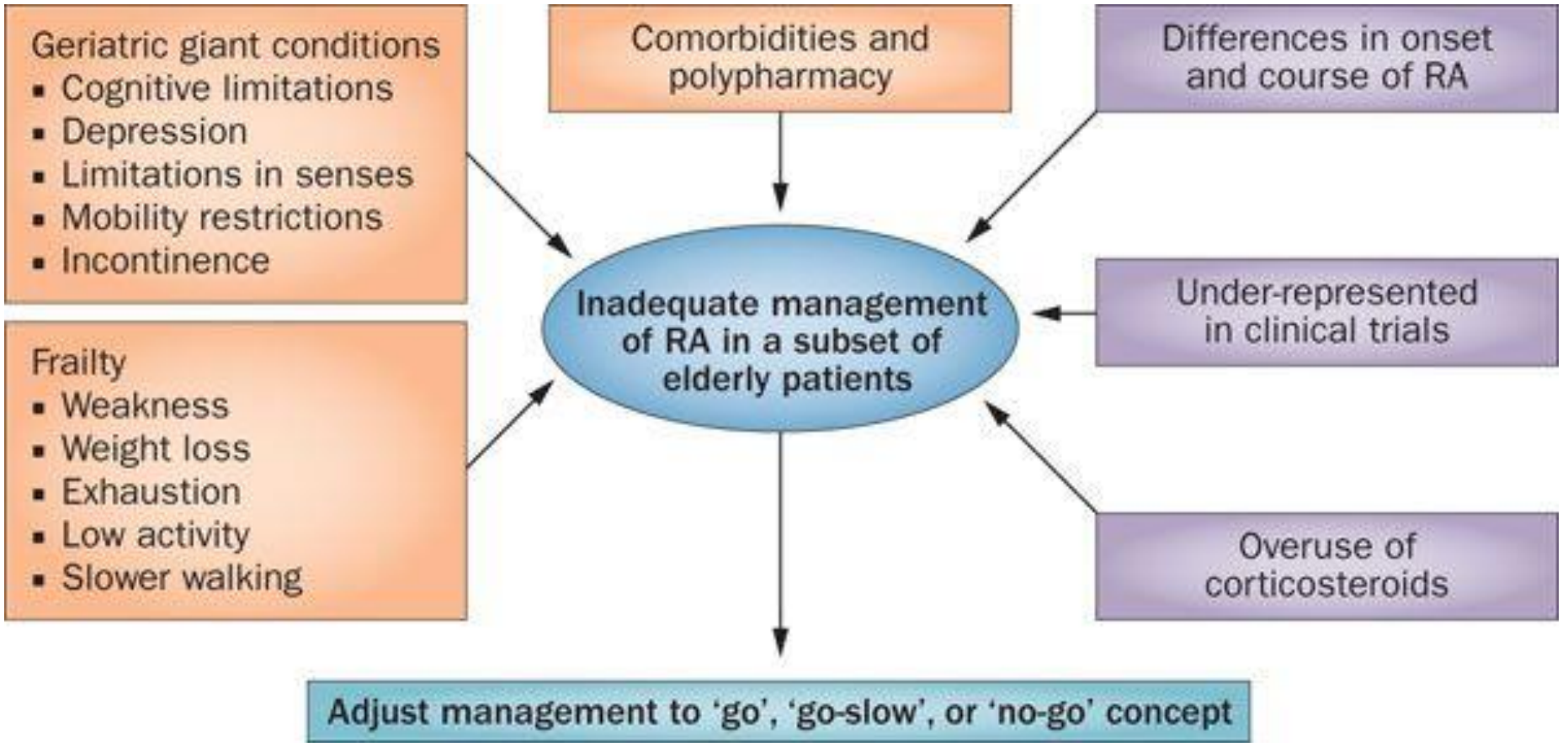
Treatment with bDMARDs in RA patients with ILD is challenging. In patients with RA-associated ILD, mortality following treatment with anti-TNF therapy is not higher than that with traditional DMARDs.

Hence, the benefit/risk balance of bDMARDs in patients with ILD should be evaluated carefully before starting treatment.

Conclusion (I)
RA is a risk factor of frailty



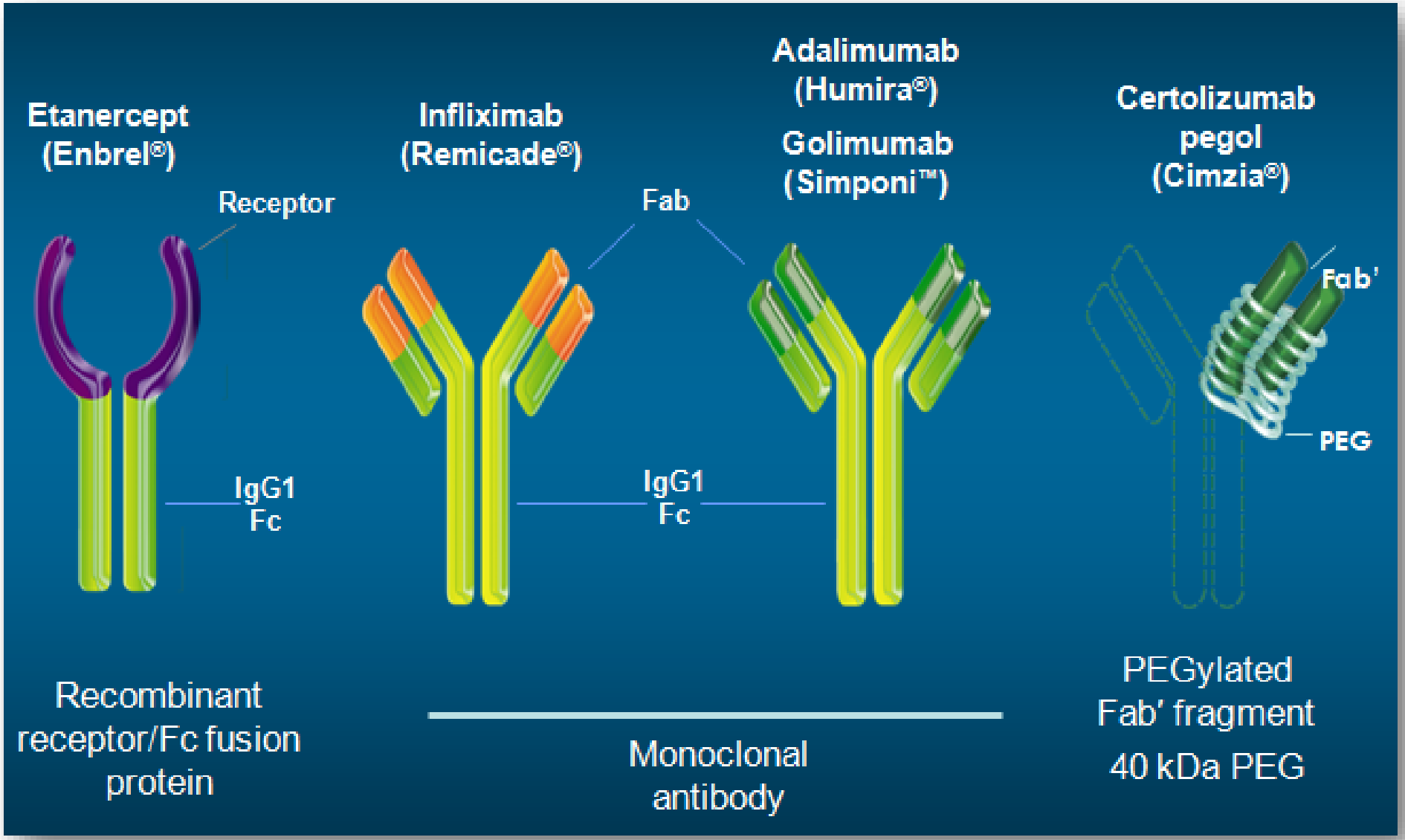
Conclusion (II)
Key points



Data suggest that elderly individuals with RA are undertreated and inadequately managed, despite DMARDs and biologic therapies being effective and seemingly well tolerated in this population

Nature Reviews Rheumatology **9**, pages604–613 , 2013

Structure of Biologic Drugs



Weir N, Athwal D, et al. Therapy. 2006;3:535-45

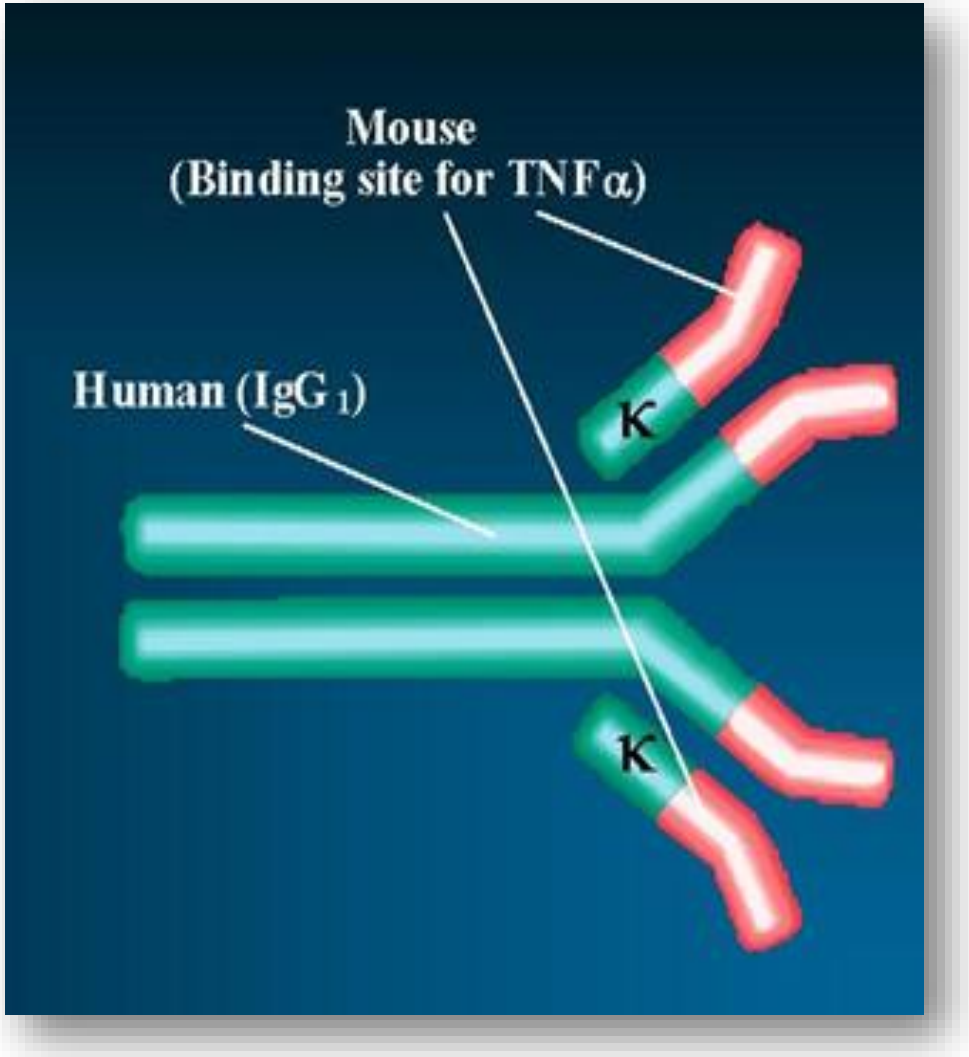
Eular recommendations 2017

- Pharmacotherapies are started at the time of RA diagnosis, with the goal of achieving clinical remission or, if that is not possible, low disease activity.
- Specific treatment choices are guided by disease activity and prognostic features.
- With this therapeutic approach, most patients can be treated effectively, and bone and cartilage destruction can largely be prevented.

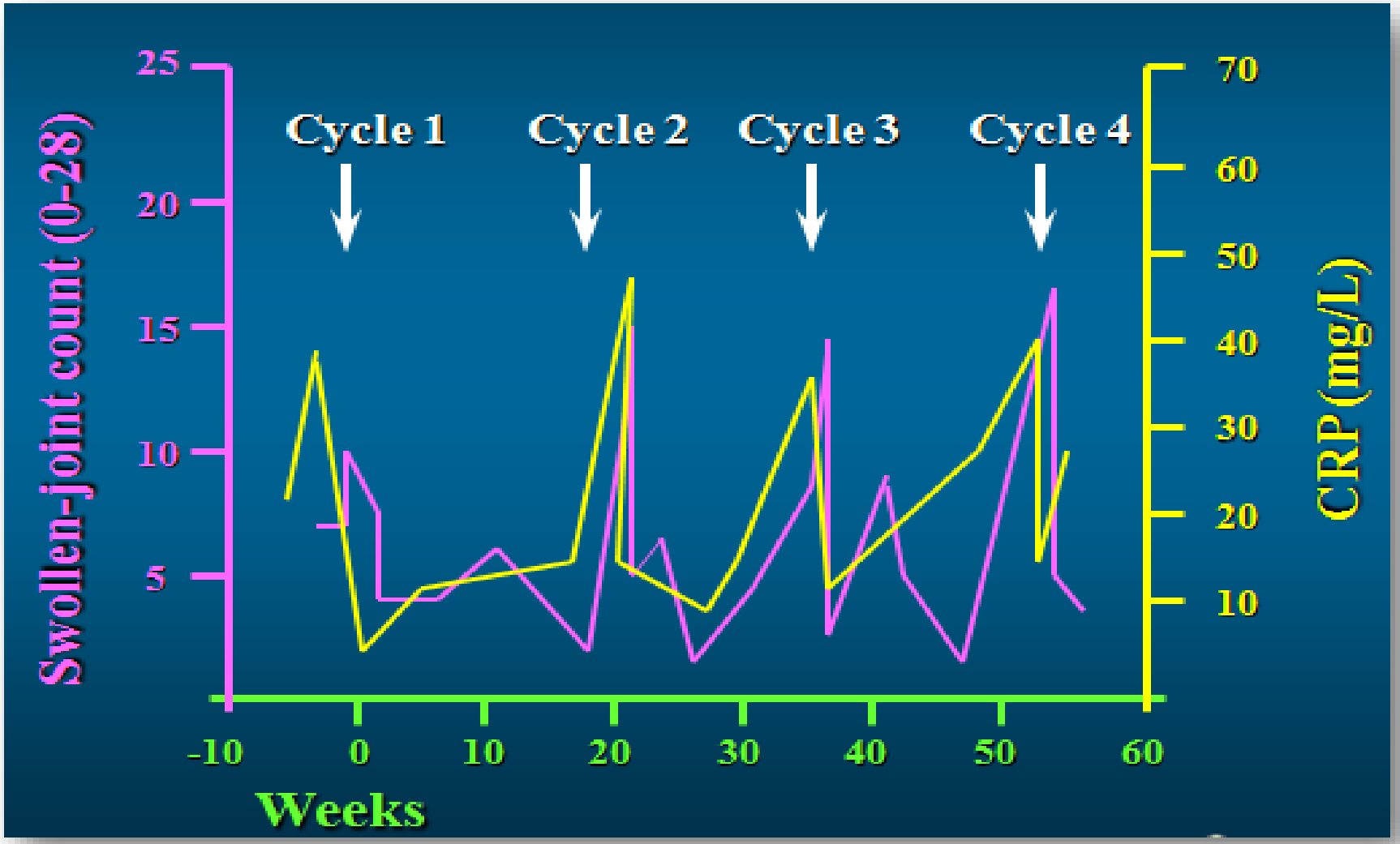
Ann Rheum Dis. 2017 Jun;76(6):960-977

Structure of Infliximab (cA2)

- ✓ Chimeric (mouse/human) IgG_1 monoclonal antibody
- ✓ Binds to TNFα with high affinity and specificiy



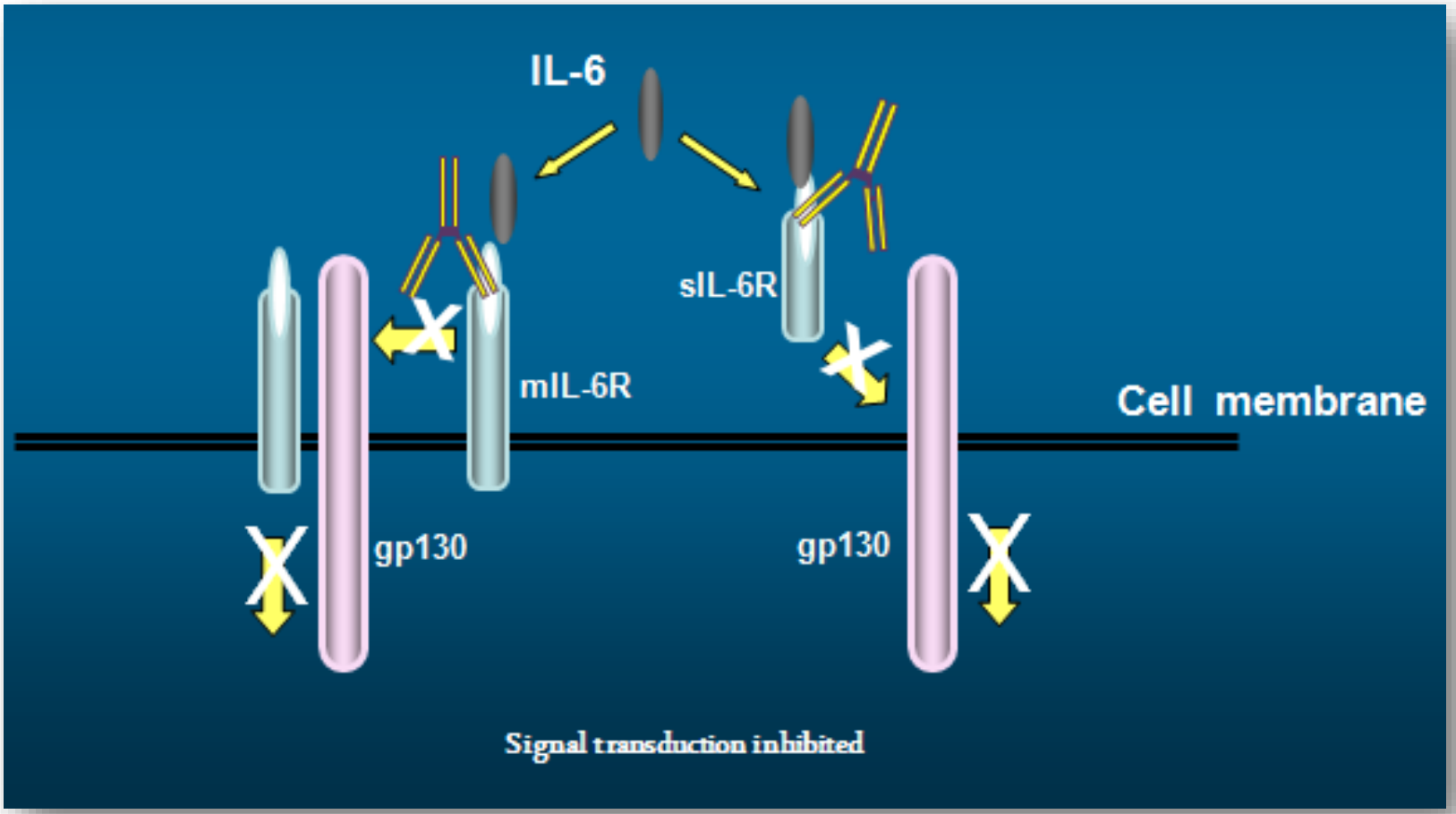
RA Therapy with Monoclonal Antibody to TNF-α

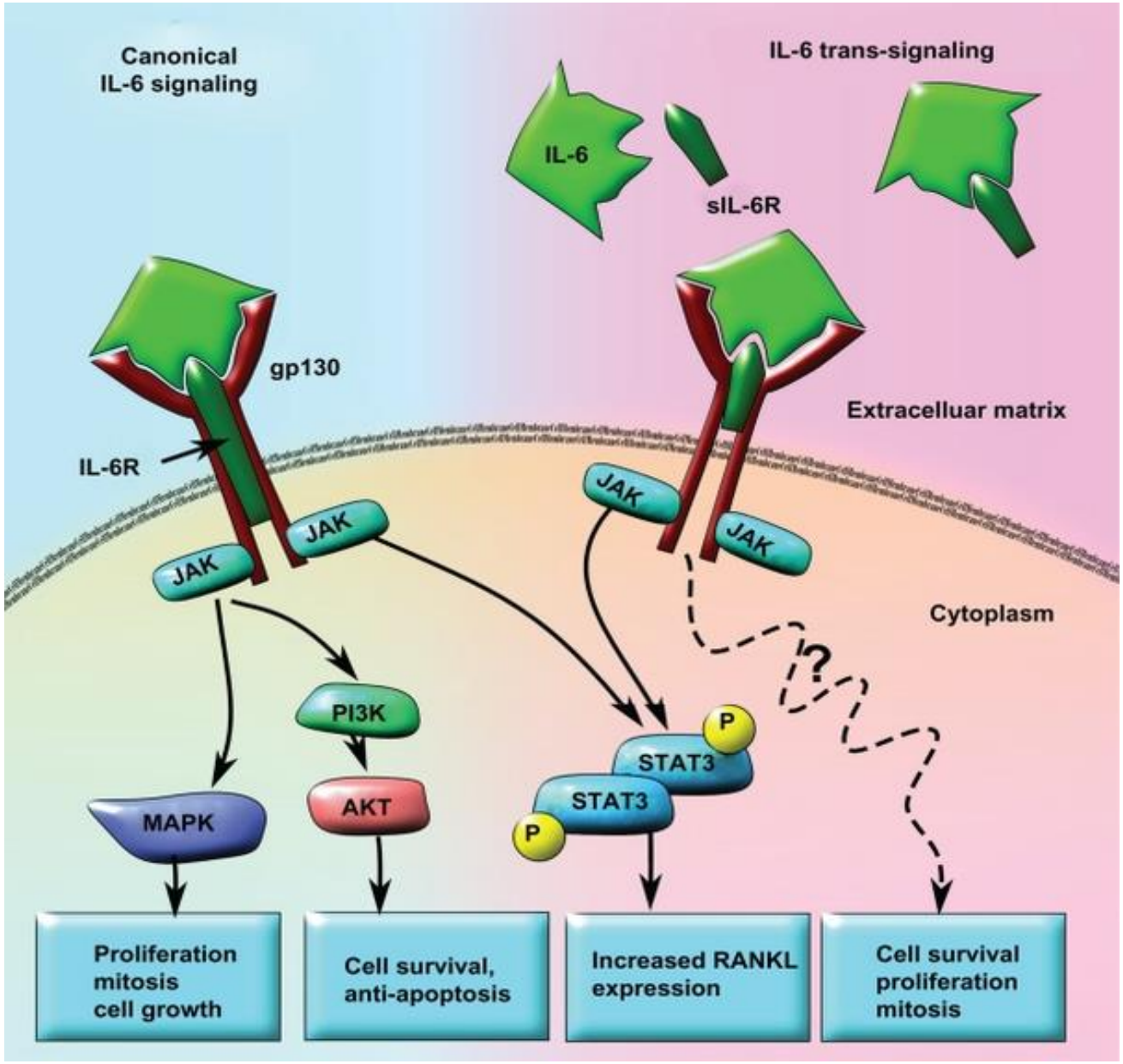


Elliot et al. Lancet 344: 1125, 1994

Tocilizumab:
Humanized anti-IL-6R monoclonal antibody

Tocilizumab binds to both the mIL-6R and the sIL-6R, preventing binding of IL-6 and association with the gp130β chain and thus IL-6-mediated signaling




Canonical
IL-6 signaling
IL-6 trans-signaling
IL-6
sIL-6R
gp130
IL-6R
Extracelluar matrix
JAK
JAK
JAK
JAK
Cytoplasm
?
PI3K
AKT
MAPK
STAT3
STAT3
P
P
Proliferation
mitosis
cell growth
Cell survival,
anti-apoptosis
Increased RANKL
expression
Cell survival
proliferation
mitosis

Rheumatology 1999;38:1150–1152

Case Report

Remission of inflammatory arthropathy in association with anti-CD20 therapy for non-Hodgkin's lymphoma

A. Protheroe, J. C. W. Edwards[1], A. Simmons, K. Maclennan and P. Selby

ICRF Cancer Medicine Research Unit, St James' University Hospital, Leeds and [1]Centre for Rheumatology, University College London, UK

blood 2001 98: 952-957
doi:10.1182/blood.V98.4.952

Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura

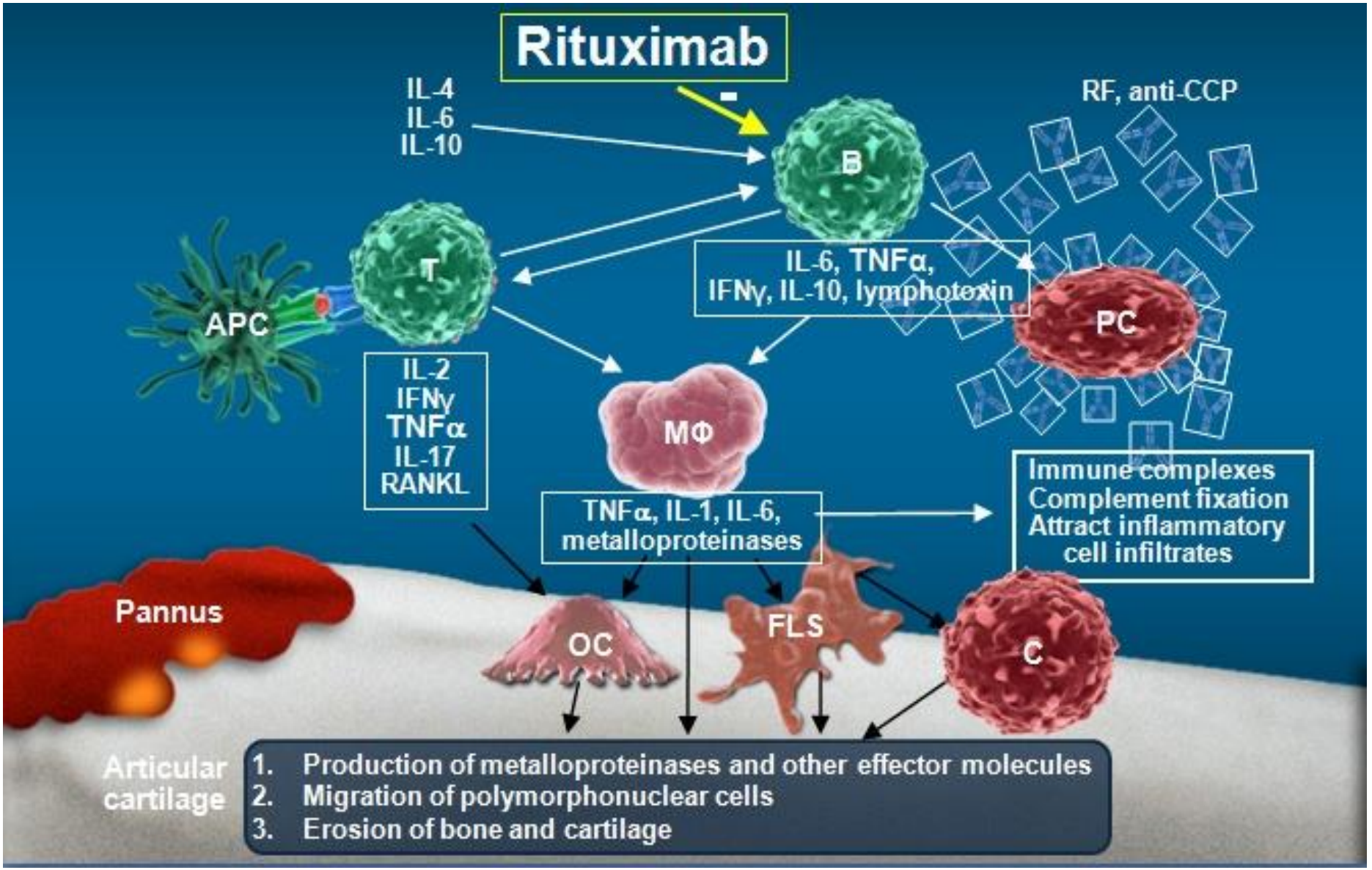
Roberto Stasi, Adalberto Pagano, Elisa Stipa and Sergio Amadori

Rheumatology 2001;40:205–211

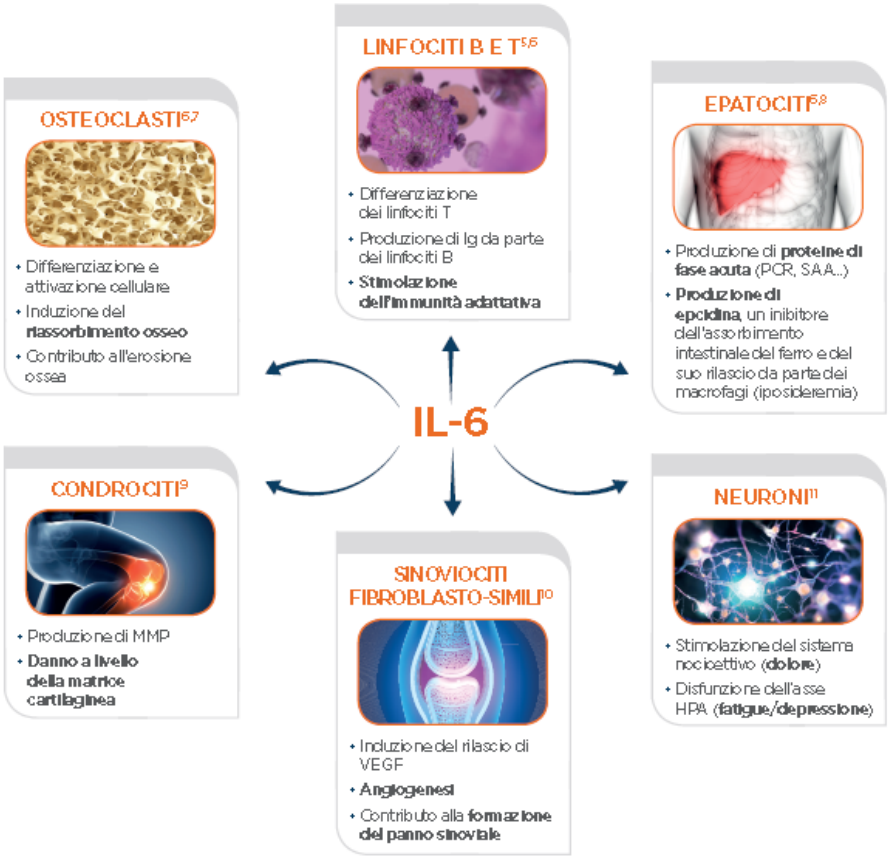
Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes

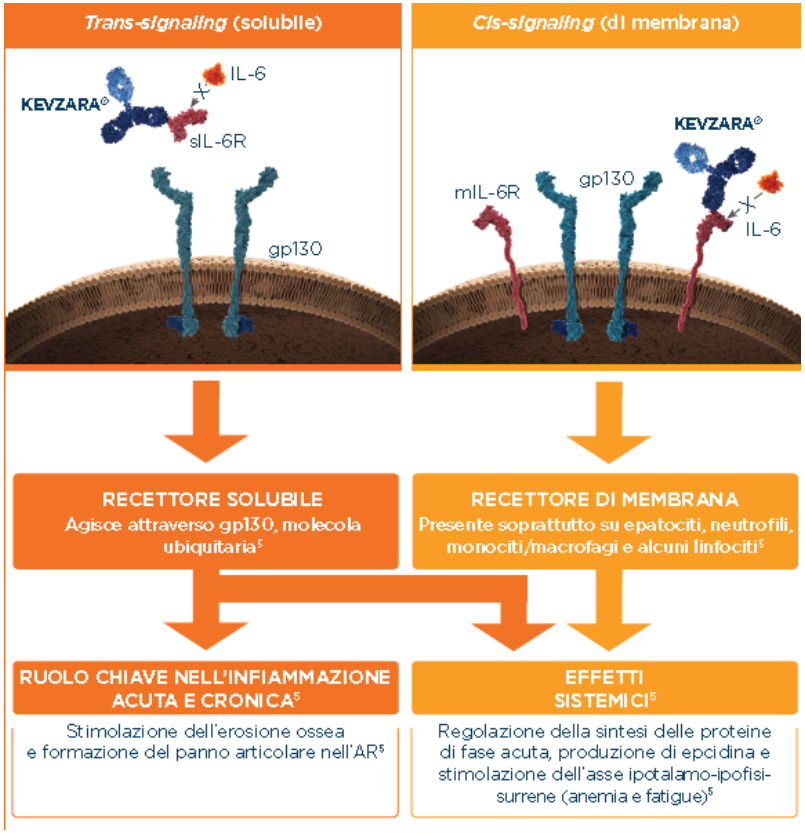
J. C. W. Edwards and G. Cambridge

University College London Centre for Rheumatology, London, UK

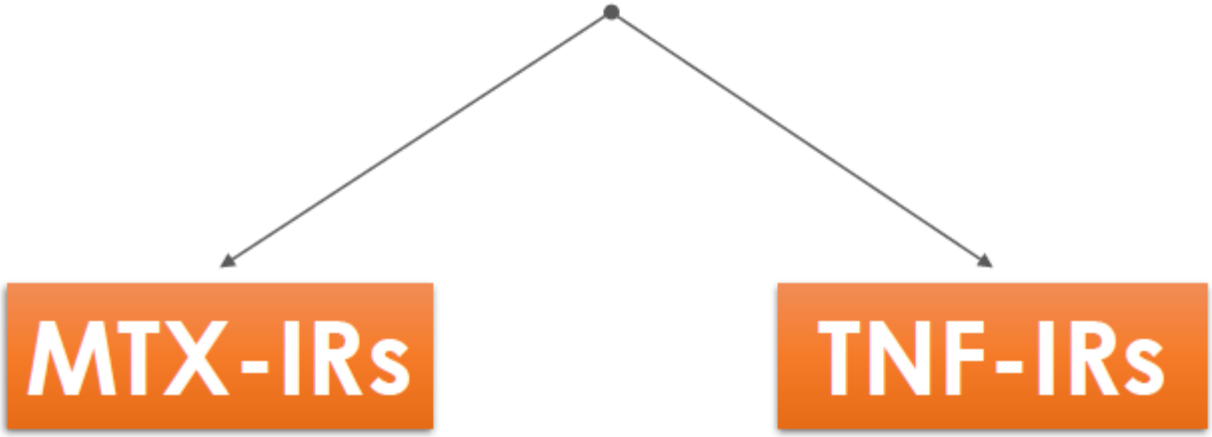

Rituximab
IL-4
IL-6
IL-10
B
RF, anti-CCP
T
APC
IL-6, TNFα,
IFNγ, IL-10, lymphotoxin
PC
IL-2
IFNγ
TNFα
IL-17
RANKL
MΦ
Immune complexes
Complement fixation
Attract inflammatory
cell infiltrates
TNFα, IL-1, IL-6,
metalloproteinases
Pannus
OC
FLS
C
Articular
cartilage
1. Production of metalloproteinases and other effector molecules
2. Migration of polymorphonuclear cells
3. Erosion of bone and cartilage

Perché ancora anti-IL-6?
Sarilumab





EULAR Recommends JAK-Inhibitors



alternative to bDMARD

Recommendations of T2T

10 recommendations on treating rheumatoid arthritis to target based on both evidence and expert opinion:

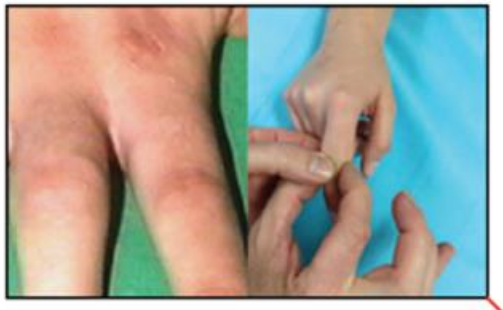
(1) The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
(2) Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
(3) While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
(4) Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
(5) Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
(6) The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
(7) Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
(8) The desired treatment target should be maintained throughout the remaining course of the disease.
(9) The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
(10) The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

Smolen J, et al. Ann Rheum Dis 2010;69:631-7

A

Diagnostic procedures

Clinical signs



Joint swelling

Laboratory

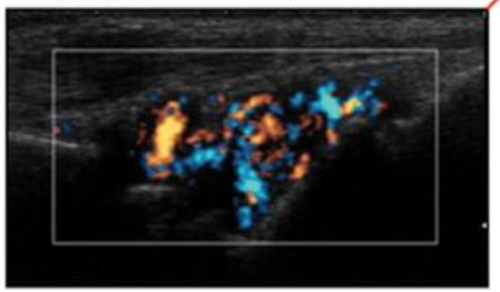
Acute phase reactants

- Erythrocyte sedimentation rate
- C-reactive protein

Autoantibodies

- Rheumatoid factors
- Anti-citrullinated protein antibodies

Imaging (if available)



ie, ultrasound, (grey scale, power doppler)

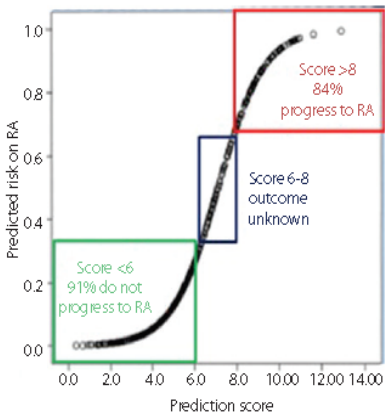
Diagnosis established

Rheumatoid arthritis

- Patient education
- Shared decision
- Search for comorbidities

A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis

Variables		Score
Age (years)		X 0.02
Female		1
Joint distribution	Small joints of hand/feet	0.5
	Symmetry	0.5
	Upper limb	1.0
	Upper&lower limb	1.5
Morning stiffness (on 100 mm VAS)	26-90 mm	1.0
	>90 mm	2.0
Tender joints (n)	4-10	0.5
	>10	1.0
Swollen joints	4-10	0.5
	>10	1.0
CRP (mg/L)	5-50	0.5
	>50	1.5
RF positivity		1
ACPA positivity		2



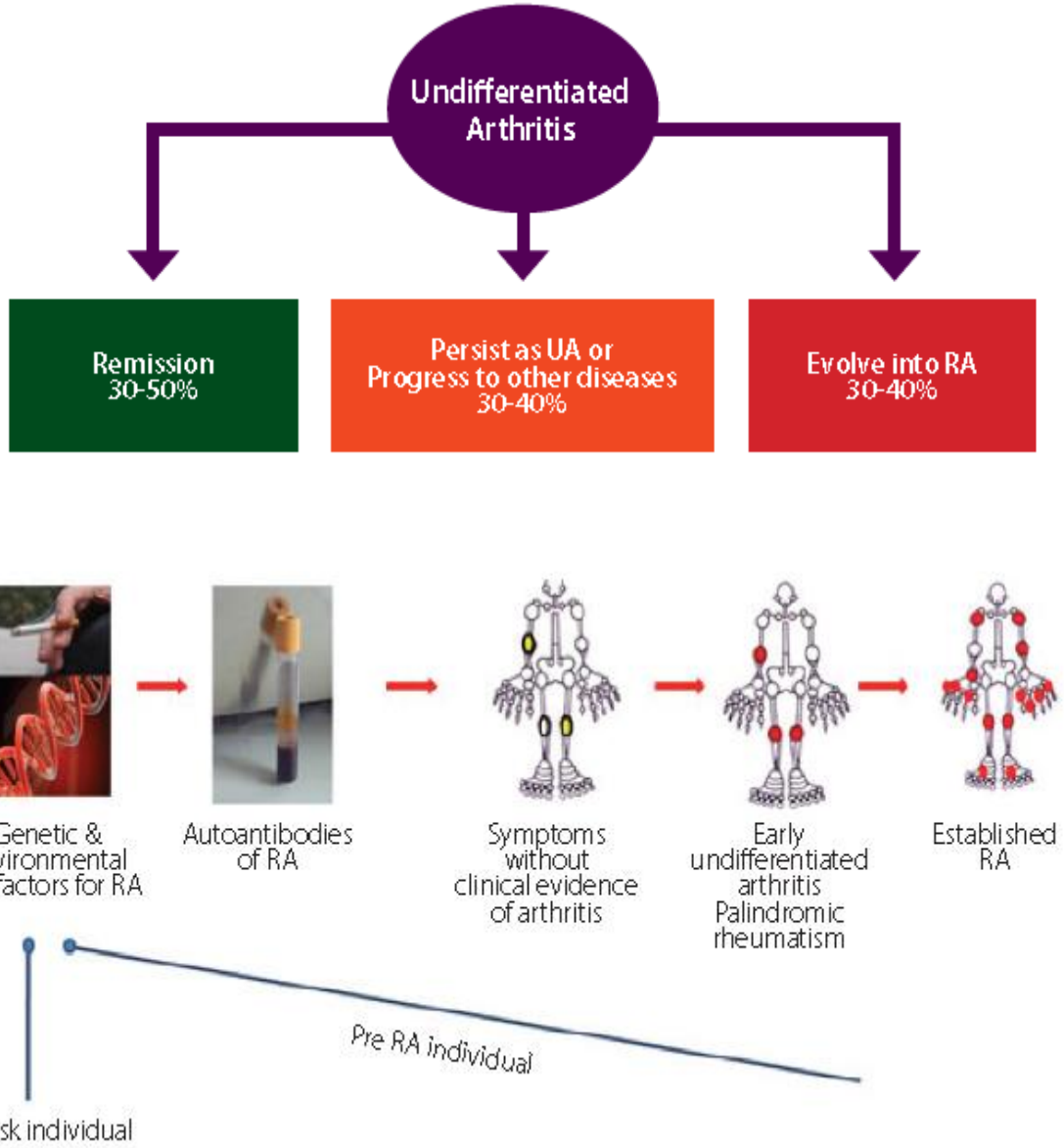


Table 1. Pre-RA

a. Genetic risk factors for R

b. Environmental risk factor

c. Systemic autoimmunity a

d. Symptoms without clinic

e. Early undifferentiated ar t

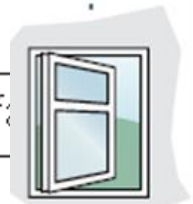
RA: rheumatoid arthritis

Table 2. Modifying risk f

- Avoid/Quit smoking
- Good dental hygiene: T
- Balanced diet containi
- Avoid excess coffee an
- Optimizing body weig
- Prevent infection

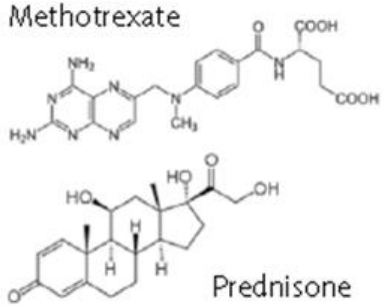
Immediate treatment

Safety screening
Liver, kidney, blood counts, hepatitis B and C serology, evidence of lung disease, liver disease, alcohol use, pregnancy



Window of opportunity of about 4 months

Methotrexate



Prednisone

Remission*?
Yes/No

Alternative treatments for patients who are intolerant to methotrexate: leflunomide, sulfasalazine

Asymptomatic

Symptomatic

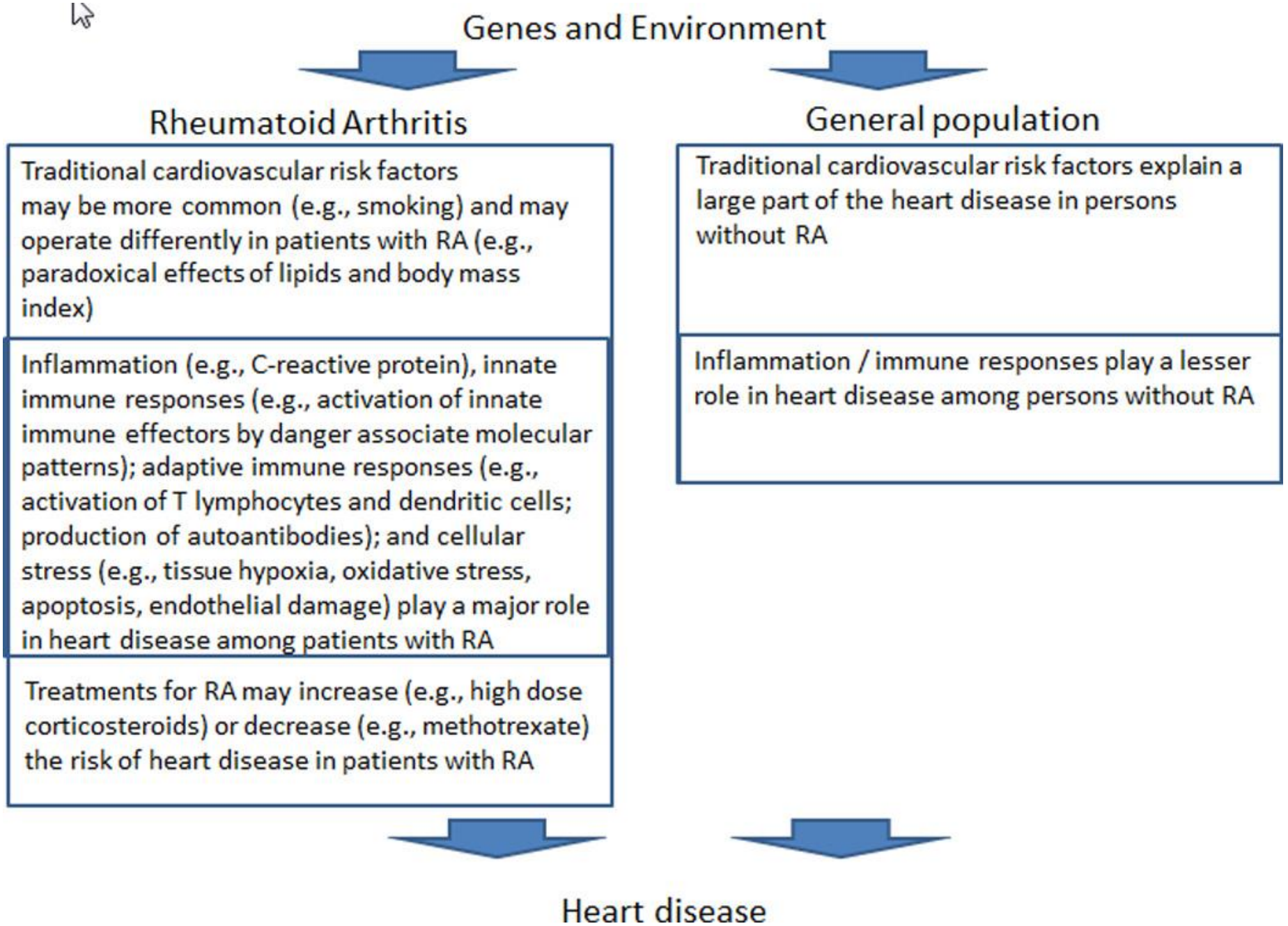
How RA Inflammation Affects Your Heart

An increased cardiovascular morbidity and mortality, including the risk of sudden cardiac death (SCD), has been shown in patients with rheumatoid arthritis (RA).

Abnormalities in autonomic markers such as heart rate variability and ventricular repolarization parameters, such as QTc interval and QT dispersion, have been associated with sudden death in patients with RA. T

he interplay between these parameters and inflammation that is known to exist with RA is of growing interest.

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis
Clinical features	Female/ male: 3/1 Onset in 4th–6th decades	Male/female: 3/1 Onset variable, usually <30 years	Slight predominance in men Onset variable, frequently 40–55 years
	Arthritis of ≥ 3 joints, usually symmetrical with involvement of hands and feet	Inflammatory back pain, inflammation of joints of the spine. Sacroiliitis	Asymmetrical arthritis of large and small joints; in hands: DIPs > PIPs Psoriasis in 85–90%
Laboratory	APR increased > 90% RF and ACPA (+) in 70–80%	APR increased in 50% HLA-B27 (+) in 70–90% RF and ACPA typically negative	APR increased > 50–60% RF and ACPA normally negative
Radiology	Bone erosions and typical deformities in hands/ft	Spinal ankylosis; syndesmophyt-es sacroiliitis (seen by MRI in early stages)	Erosions, periostitis in DIP joints of hands and feet, deformities in hands/feet
Traditional CVRF	Smoking; DM; HT; DL; overweight; usually underdiagnose-d; physical activity ↓	Smoking; DM; HT; DL; physical activity ↓	Smoking; DM; HT; DL; frequent obesity; typical MetS features; physical activity ↓
CV risk & mortality	Twofold increased mortality rate (~DM2) (SMR 1.3–2.3) CV main cause death Sudden death ↑ (HR 2.36; 1.30, 4.27) CHF responsible 1/8 deaths	Increased mortality rate (SMR 1.6–1.9) CV main cause of death MI risk ↑ (OR 1.60; 1.32, 1.93)	Increased mortality rate (SMR 0.8–1.6) CV important cause of death MI risk ↑ (SPR 2.57; 1.73, 3.80)


Genes and Environment
Rheumatoid Arthritis
General population
Traditional cardiovascular risk factors may be more common (e.g., smoking) and may operate differently in patients with RA (e.g., paradoxical effects of lipids and body mass index)
Traditional cardiovascular risk factors explain a large part of the heart disease in persons without RA
Inflammation (e.g., C-reactive protein), innate immune responses (e.g., activation of innate immune effectors by danger associate molecular patterns); adaptive immune responses (e.g., activation of T lymphocytes and dendritic cells; production of autoantibodies); and cellular stress (e.g., tissue hypoxia, oxidative stress, apoptosis, endothelial damage) play a major role in heart disease among patients with RA
Inflammation / immune responses play a lesser role in heart disease among persons without RA
Treatments for RA may increase (e.g., high dose corticosteroids) or decrease (e.g., methotrexate) the risk of heart disease in patients with RA
Heart disease

Pulmonary involvement and rheumatic diseases

Table 1: Spectrum and relative prevalence of lung involvements in rheumatic diseases.

	Parenchymal		Pleural	Vascular	
	ILD	Airways		PAH	DAH
Rheumatoid arthritis	++	++	++	+	–
Systemic sclerosis	+++	–	–	+++	–
Myositis	+++	–	–	+	–
Systemic lupus erythematosus	+	+	+++	+	++

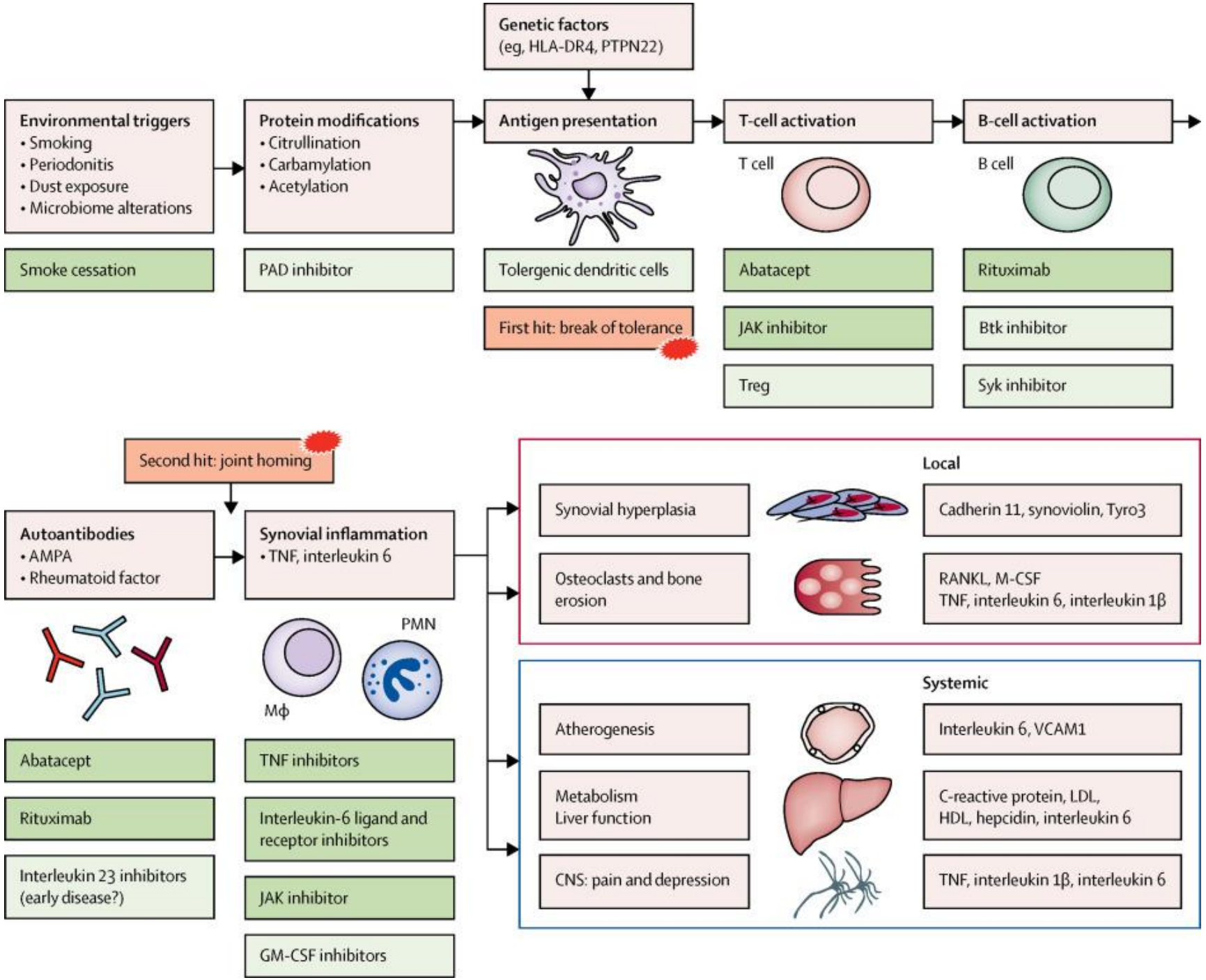
The signs show relative prevalence of each manifestation (none: –, low: +, medium: ++, and high: +++); ILD: interstitial lung disease; DAH: diffuse alveolar hemorrhage; PAH: pulmonary arterial hypertension (cited and modified from "Interstitial Lung Disease in Connective Tissue Disorders" by A. Fischer and R. du Bois. Lancet 2012; 380: 689–98).

TABLE 3] Options for Screening and Treatment of ILD for Specific Rheumatic Diseases

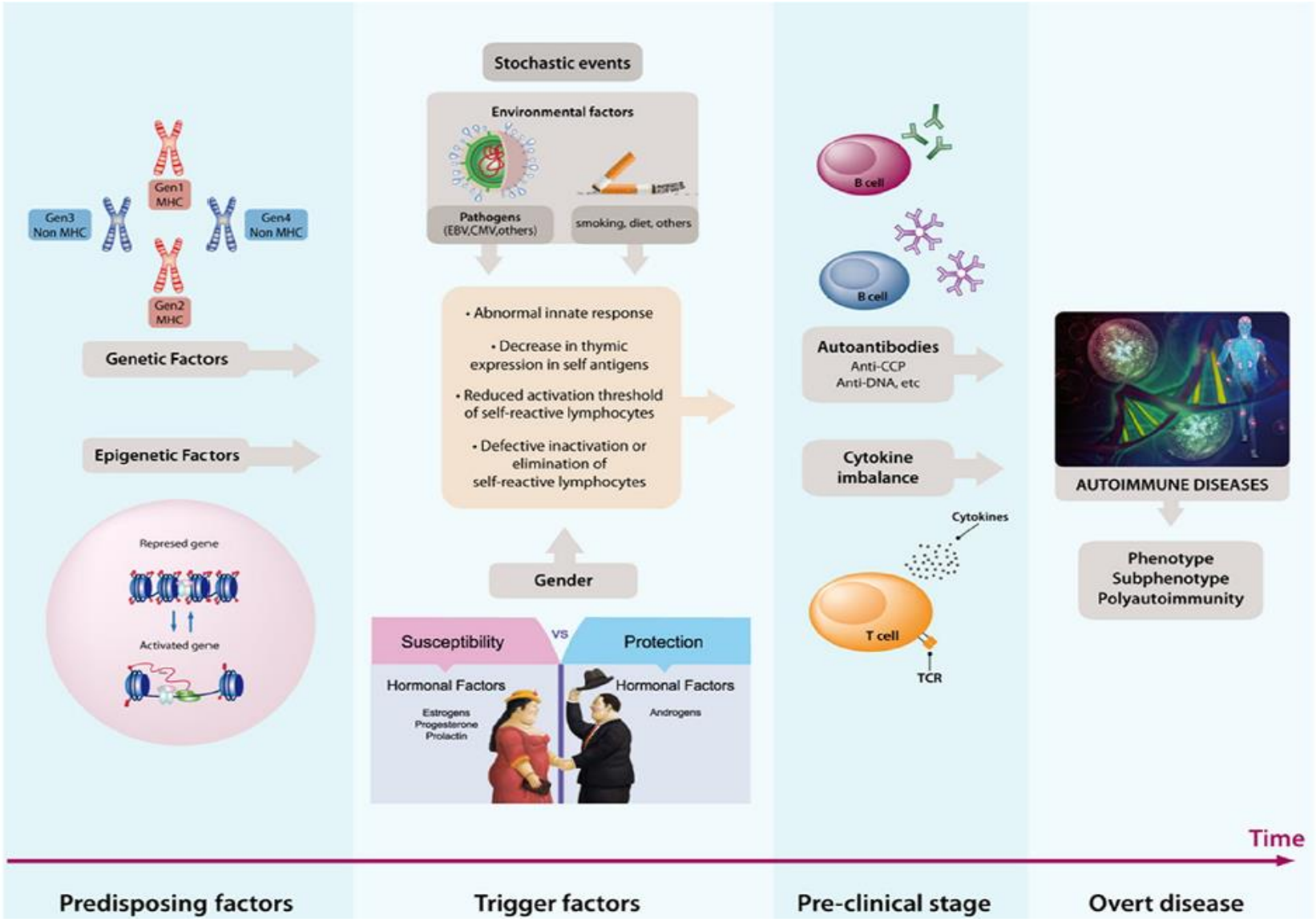
Rheumatic Disease	Screening	Treatment
SSc	Baseline PFTs, HRCT, and echocardiography for all patients; if normal, yearly PFTs. If there is a decline in FVC > 10% or D_{LCO} > 15% consider repeated CT imaging and echocardiography. Consider treatment in any patient with fibrotic lung disease > 20% on HRCT (extensive); if < 20%, PFTs every 3-6 mo.	MMF: Use up to 3 g/d CyC: An option for 6-9 mo with conversion to MMF or AZA In early rapidly progressive disease, consider suitability for stem cell transplantation at selected centers
AIM	Baseline PFTs and HRCT in all patients. If CT results are abnormal and patient is symptomatic with FVC < 70%, consider treatment. If patient is not symptomatic with FVC > 70%, PFTs every 3-6 mo.	For moderate disease: MMF, AZA, or tacrolimus with steroids Rituximab should be considered in antisynthetase syndrome In MDA5-ILD, aggressive therapy including high-dose glucocorticoids and at least 1 other steroid-sparing agents such as CyC, Rituxan or MMF should be used
Rheumatoid arthritis	Baseline PFTs in high-risk individuals (smokers, male sex, older age). If abnormal results, consider HRCT	If predominantly inflammatory disease, MMF or rituximab If predominantly fibrotic disease, consider antifibrotic agents pending results from ongoing trials

AZA azathioprine; CyC cyclophosphamide; D_{LCO} diffusion capacity for carbon monoxide; HRCT high-resolution CT; MDA5 melanoma differentiation-associated gene 5; MMF mycophenolate mofetil; PFTs pulmonary function tests. See Table 1 legend for expansion of other abbreviations.

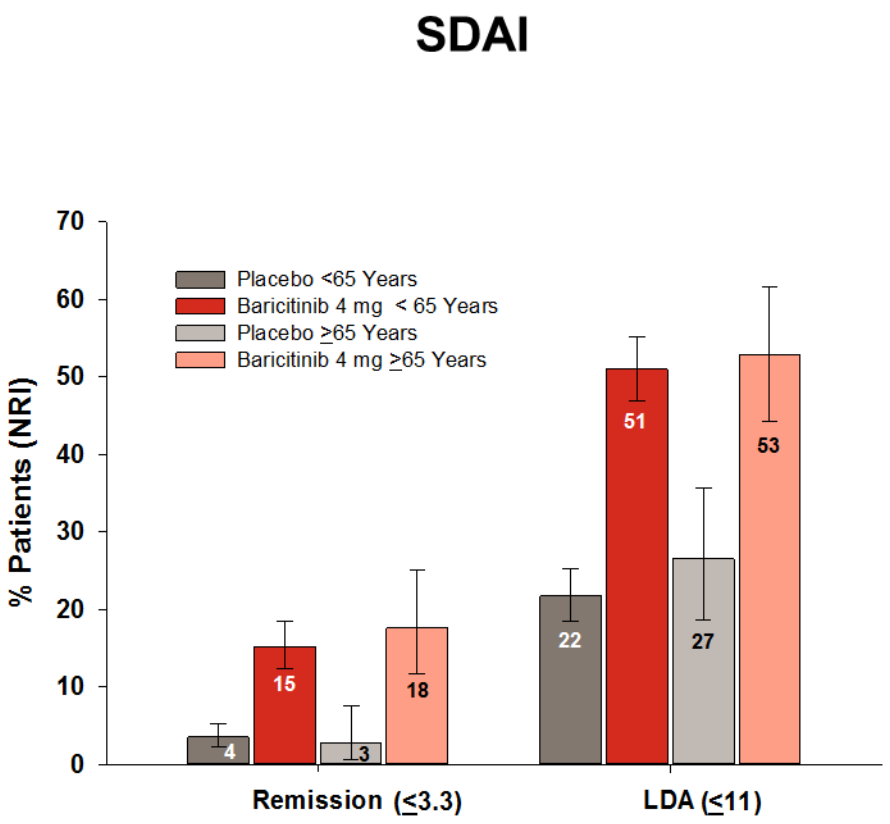
CHEST 2017; 152(6):1283-1295

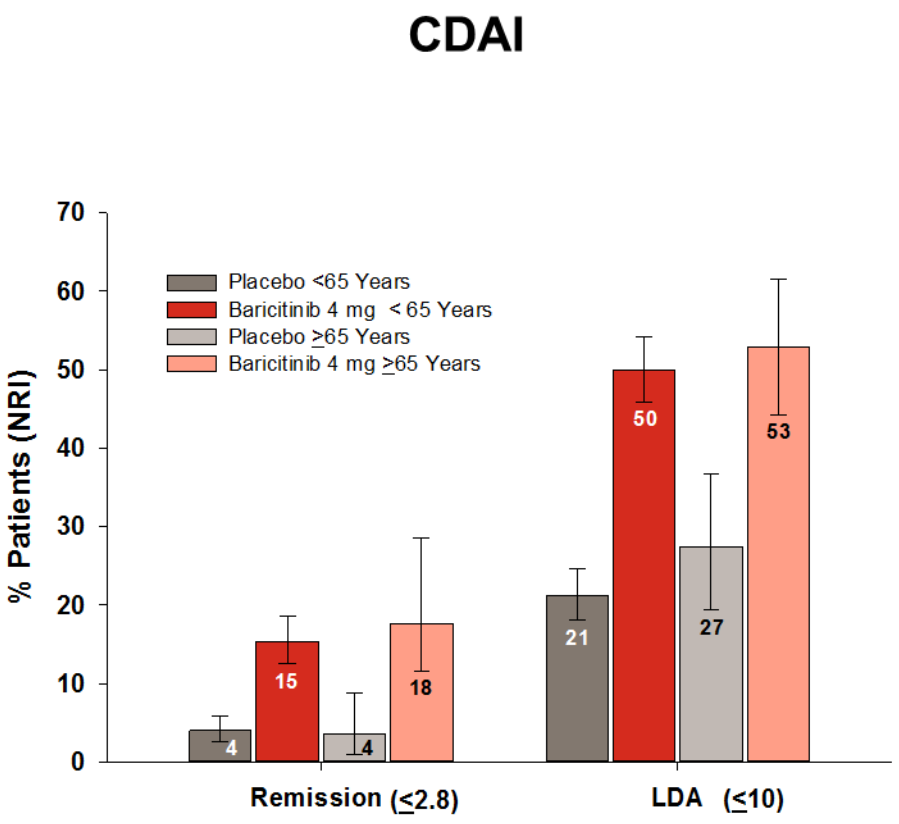

Genetic factors
(eg, HLA-DR4, PTPN22)
Environmental triggers
• Smoking
• Periodontitis
• Dust exposure
• Microbiome alterations
Protein modifications
• Citrullination
• Carbamylation
• Acetylation
Antigen presentation
T-cell activation
B-cell activation
T cell
B cell
Smoke cessation
PAD inhibitor
Tolergenic dendritic cells
Abatacept
Rituximab
First hit: break of tolerance
JAK inhibitor
Btk inhibitor
Treg
Syk inhibitor
Second hit: joint homing
Autoantibodies
• AMPA
• Rheumatoid factor
Synovial inflammation
• TNF, interleukin 6
PMN
Mϕ
Abatacept
Rituximab
Interleukin 23 inhibitors
(early disease?)
TNF inhibitors
Interleukin-6 ligand and
receptor inhibitors
JAK inhibitor
GM-CSF inhibitors
Local
Synovial hyperplasia
Cadherin 11, synoviolin, Tyro3
Osteoclasts and bone
erosion
RANKL, M-CSF
TNF, interleukin 6, interleukin 1β
Systemic
Atherogenesis
Interleukin 6, VCAM1
Metabolism
Liver function
C-reactive protein, LDL,
HDL, hepcidin, interleukin 6
CNS: pain and depression
TNF, interleukin 1β, interleukin 6

Common Mechanisms of Autoimmune Diseases



Percent Patients Achieving Remission and LDA

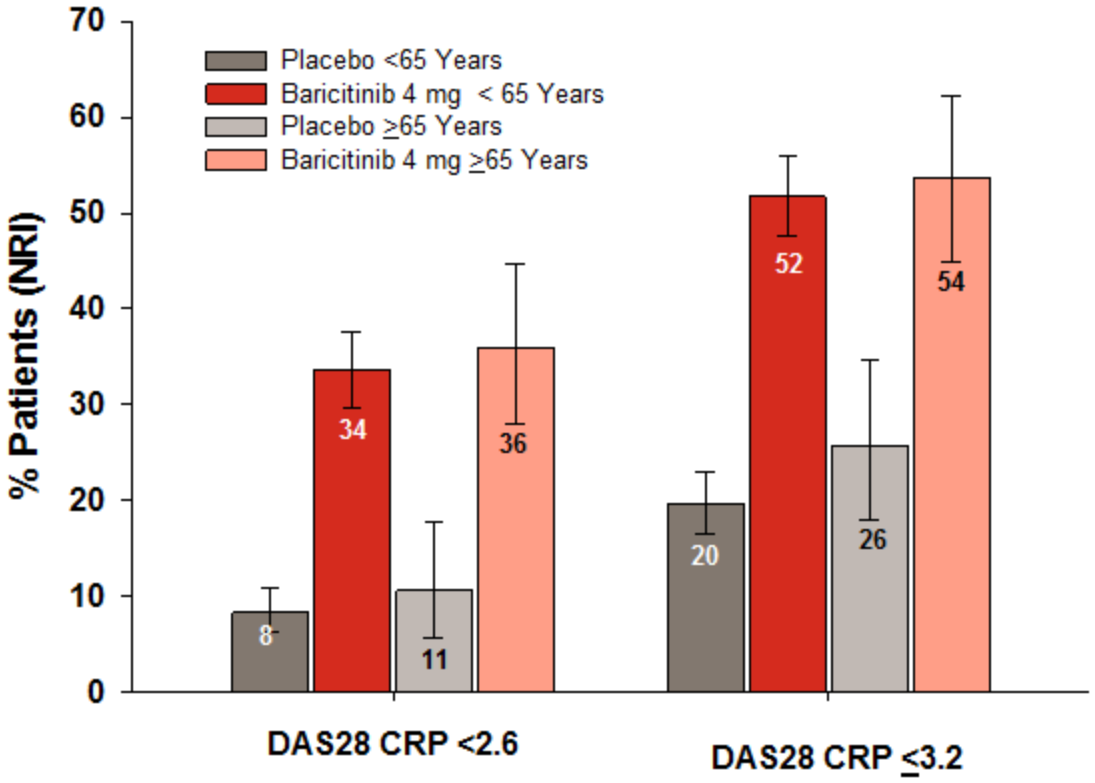




Error bars represent 95% confidence interval
Abbreviations: CDAI=Clinical Disease Activity Index; LDA=low disease activity; NRI=non-responder imputation; SDAI= Simplified Disease Activity Index.

Fleischmann R et al. presented at American College of Rheumatology/ARHP 2016

Figure 7. DAS28-CRP Disease Activity at Week 24 with 95% CI



Error bars represent 95% confidence interval
Abbreviations: DAS28=Disease Activity Score 28 joints; CRP=C-reactive protein; NRI=non-responder imputation.

Fleischmann R et al. presented at American College of Rheumatology/ARHP 2016

Is the Incidence of Rheumatoid Arthritis Rising?

The increase in RA among the elderly can be attributed to two main factors:

1) patients diagnosed with young-onset RA (YORA) are living longer due to better management;

2) increasing numbers of patients are being diagnosed with EORA. In a 2017 retrospective study from Japan, investigators reported that the mean age of onset had rapidly increased over the previous decade from 55.8 years in 2002-2003 to 59.9 years in 2012-2013, with a corresponding shift in peak age from 50-59 to 60-69 years during that same period of time.

Int J Rheum Dis. 2017;20(7):839-845