RA in the older

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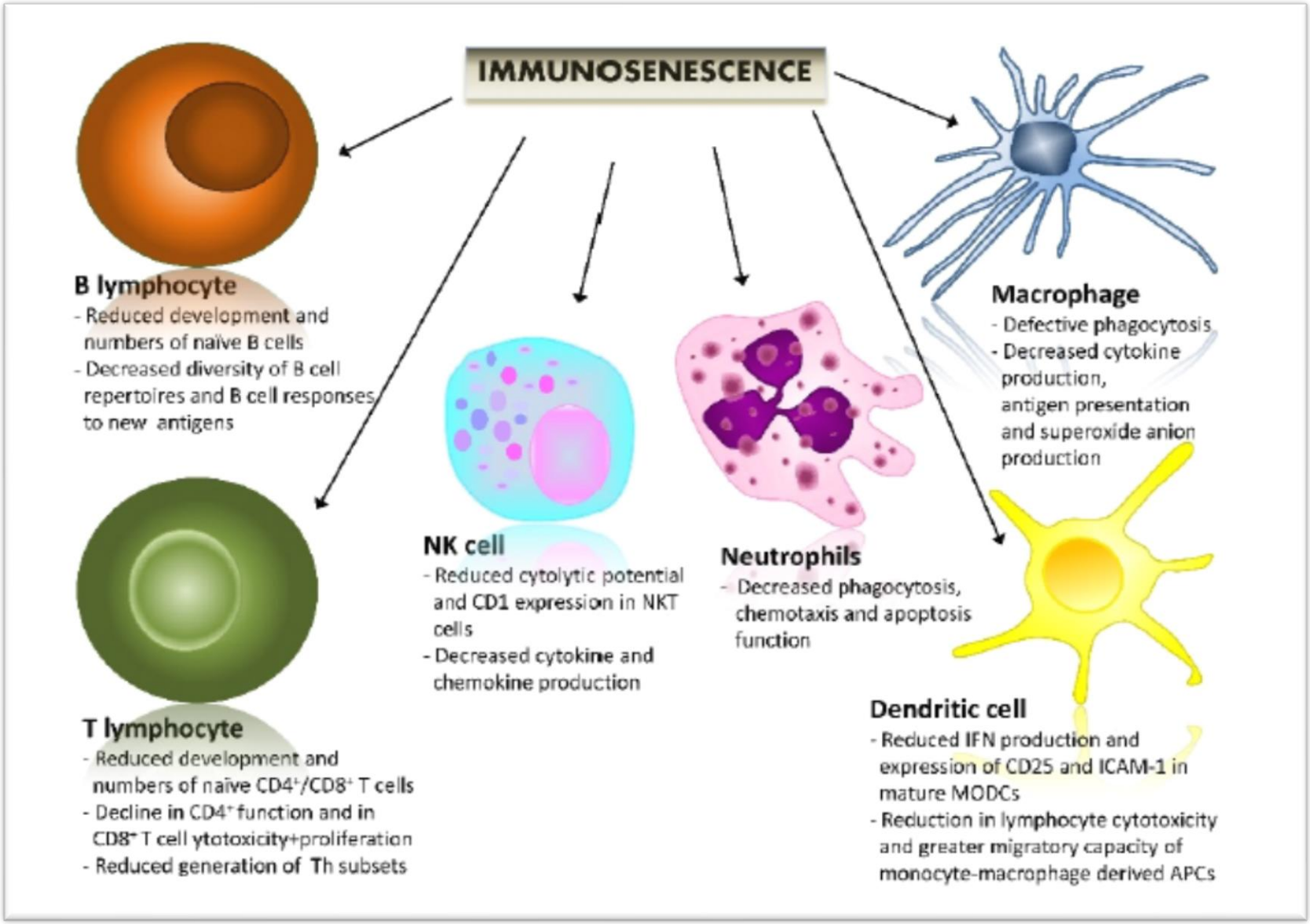
Outline

- Immunosenescence
- Epidemiology
- RA in the older

(clinics, mimics, prognosis, therapeutics)

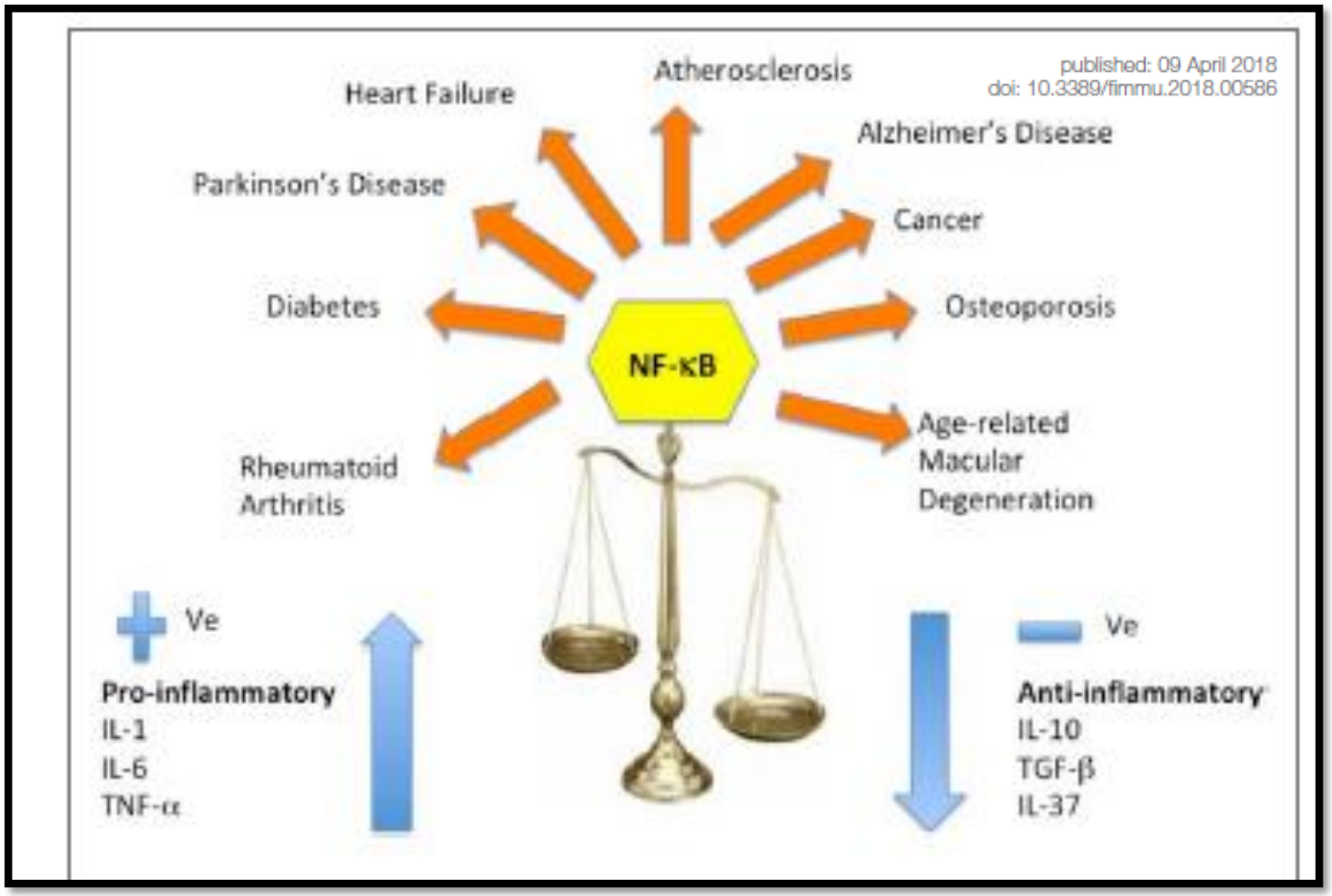
- Limits
- Conclusions



Cancers **2018**, *10*, 211; doi:10.3390/cancers10070211

Along with age increasing, the immune system undergoes a gradual process of remodeling

Inflamm-aging



With aging, innate immune cells are in a state of sustained activation > increase of homeostatic cytokine production

Epidemiology

EORA definition: ≥60 years, but heterogeneity across studies

Global RA prevalence 0.5% and 1%
Prevalence among persons aged >60 years of ~2%.

Mean age at RA onset has increased by 10 years over the past two decades.

More balanced Male to Female ratio (1:2)

RA incidence (NOAR register) :
steeply rises with age in men,
increases up to age 45 years, plateaus until age 75 years, afterwards declines in women

Drugs Aging 2009; 26 (9): 739-750

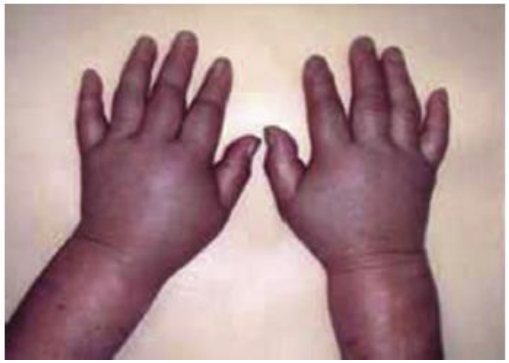
Clinical features

EORA is a heterogeneous disease characterized by three distinct clinical patterns

Most common clinical form (70%) =
RA-like, RF positivity, joint erosions and worse prognosis than YORA

Second form (25%) =
PMR-like, usually RF negative, acute onset,
no joint erosions, good prognosis

Third form=
RS3PE-like syndrome



Drugs Aging 2009; 26 (9): 739-750

Distinctive features: EORA vs YORA

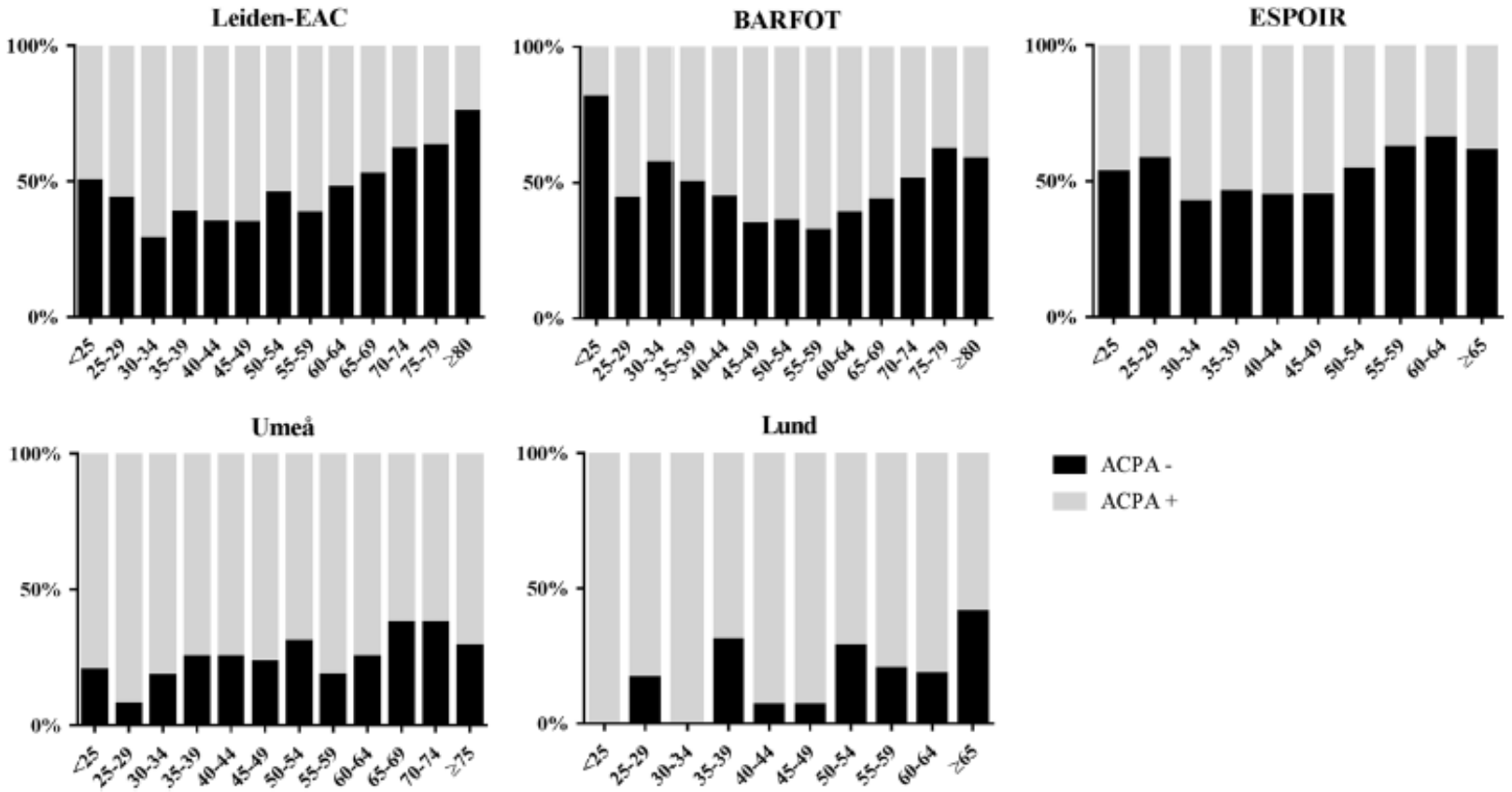
Clinical	Lab	X-Ray
Simultaneous small and large joint involvement Acute onset pattern Marked constitutional symptoms Less common deformities, Sjogren's syndrome, lung involvement More frequent spontaneous remission	Higher ESR and/or CRP More frequent chronic disease anemia RF and anti-CCP+ at similar/lower rates	Radiological narrowing of the joint space An aggressive, destructive EORA form reported

Ther Adv Musculoskel Dis
2018, Vol. 10(1) 3–11

The prevalence of ACPA is lower in rheumatoid arthritis patients with an older age of onset but the composition of the ACPA response appears identical

Boeters *et al. Arthritis Research & Therapy* (2017) 19:115

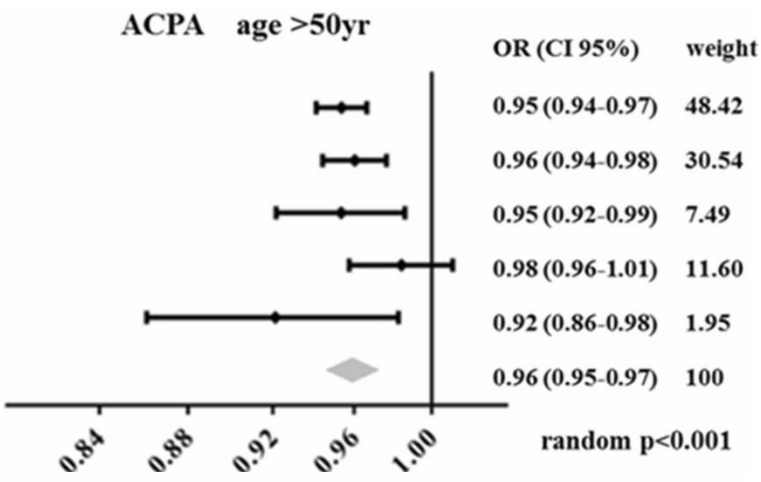
3321 RA patients from 5 cohorts (older ≥50 years)

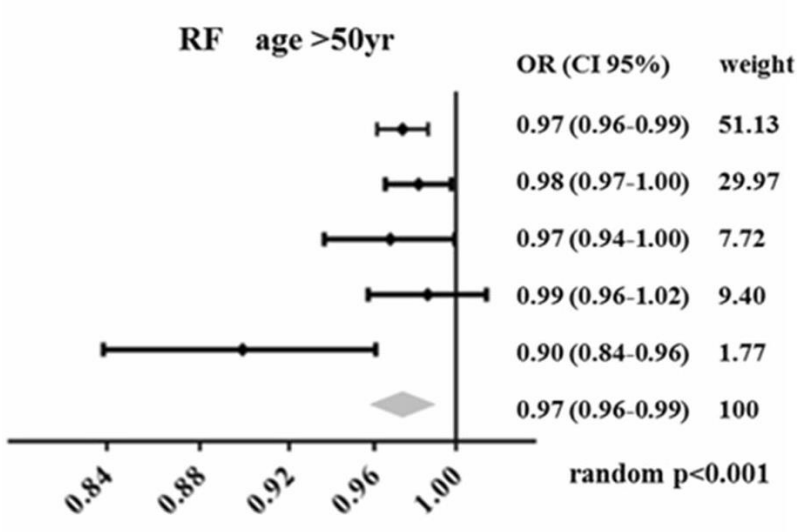


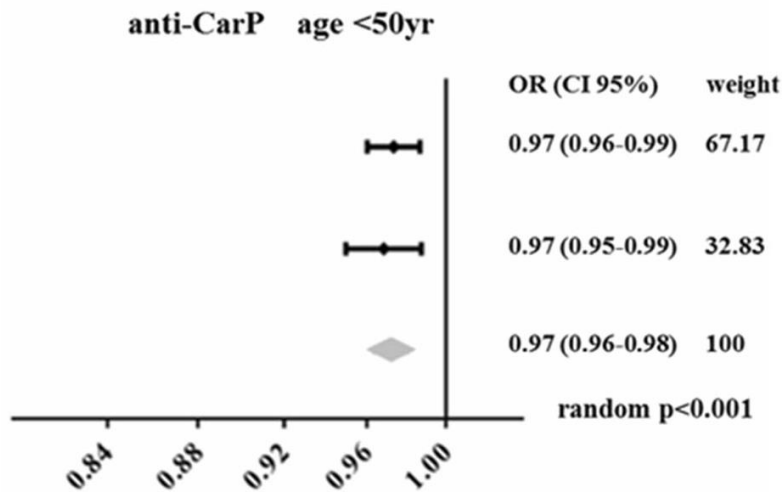
The proportion of ACPA-positive patients seemed to decrease after age of onset of 50 years across all cohorts.

The prevalence of ACPA is lower in rheumatoid arthritis patients with an older age of onset but the composition of the ACPA response appears identical

Boeters *et al. Arthritis Research & Therapy* (2017) 19:115

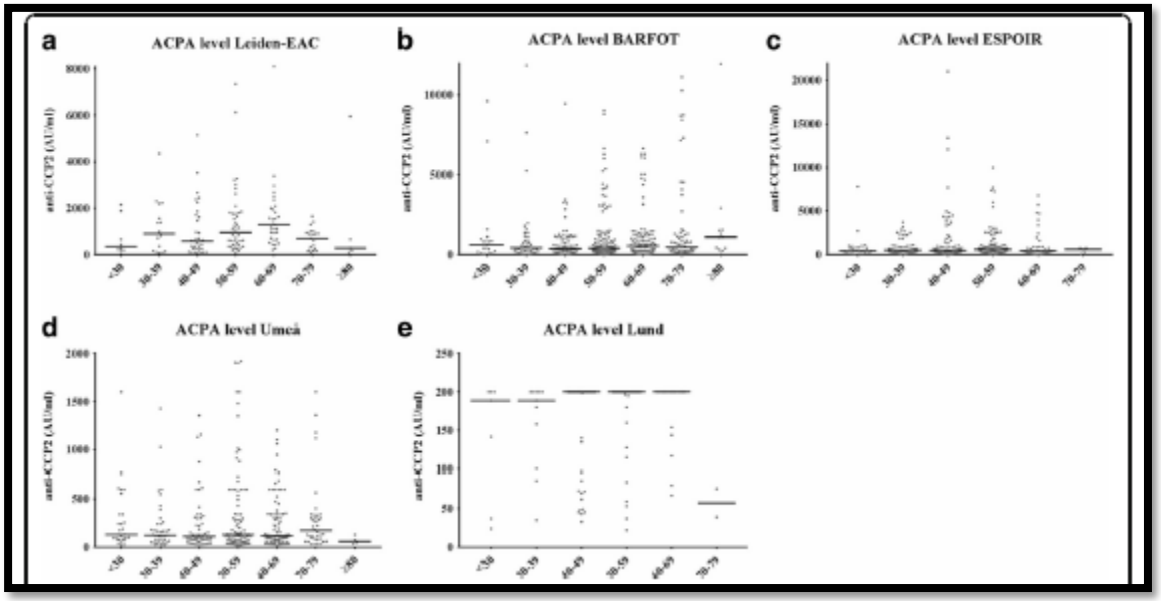


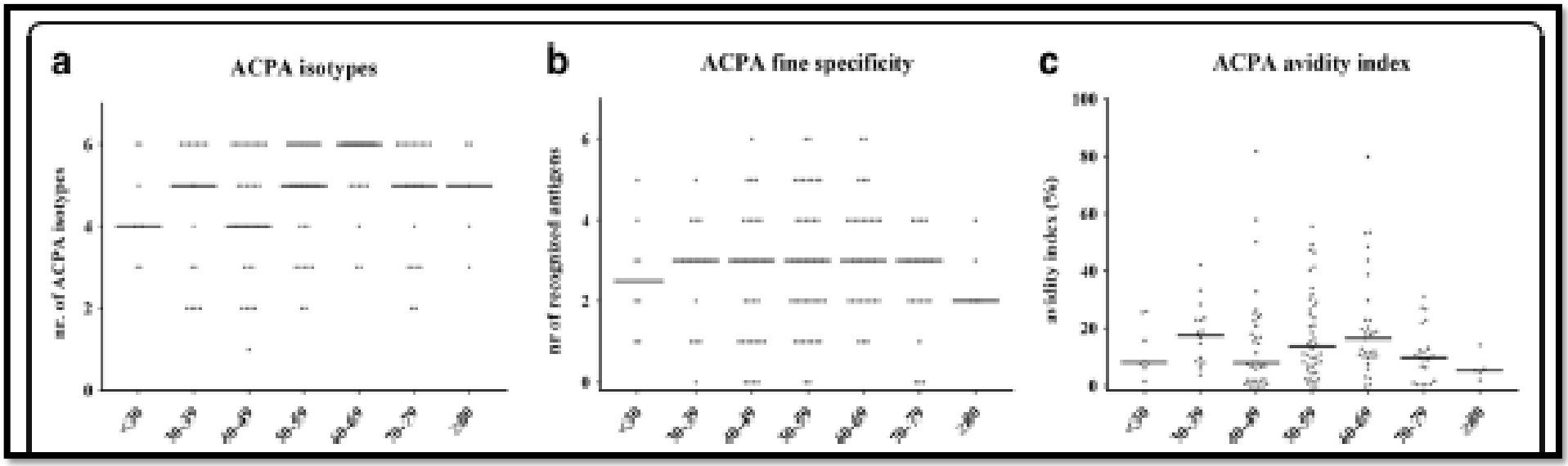




Age of onset >50 years was associated with a significantly lower frequency of ACPA positivity

Similar results were observed for RF and anti-CarP





The composition of the ACPA response did not change with increasing age of onset with respect to titer, isotype distribution, fine specificity and avidity index.

EORA: mimics

Table 1. Differential diagnosis of elderly-onset rheumatoid arthritis.

Osteoarthritis
Polymyalgia rheumatica
Crystal arthritis (gout, pseudogout or chronic pyrophosphate arthropathy)
Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE syndrome)
Spondyloarthropathy
Connective tissue disease
Systemic vasculitis
Paraneoplastic syndrome
Hypertrophic osteoarthropathy
Sarcoidosis
Infectious arthritis (viral and bacterial infections)

Delay in diagnosis

Mis-diagnosis

Missed-diagnosis

Ther Adv Musculoskel Dis

2018, Vol. 10(1) 3–11

PMR and EORA: to the mirror

- Clinical findings
- Immunological findings
- Serological findings
- Cytokine/hormonal findings
- Genetic findings
- Imaging findings
- Hystological findings
- Therapuetic findings

Peripheral arthritis had poor PPV
Caporali R, ARD 2001

Proliferative synovitis of the shoulder bursae is a key feature for discriminating EORA-PMR from PMR.
Suzuki T, AMD 2017

FOLLOW UP MIGHT GIVE US THE ANSWER!

Prognosis

- **Prognostic factors in EORA patients**

RF and ACPA+ > higher SJC, more radiological damage

Acute onset > good prognosis (response to therapy)

Pitting oedema > less structural damage (erosions)

- **EORA as a prognostic factor (versus YORA)**

- lower remission rates

- more radiographic progression

- higher HAQ scores

Drugs Aging 2009; 26 (9): 739-750

Therapy

The ‘age bias’ =
disparities in the prescription of treatment by doctors based on patient age due to a greater risk of AEs.

- Changing in pharmacokinetics and pharmacodynamics
- Impaired health literacy
- Polypharmacy (drug-to-drug interactions)
- Comorbidities

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

Cross-sectional study from CORRONA register

Table 2 Characteristics of patients by comorbidities

	Age at onset of RA ≥60 years			Age at onset of RA 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

Mean MTX dose among the YORA group was higher than that in the EORA group.

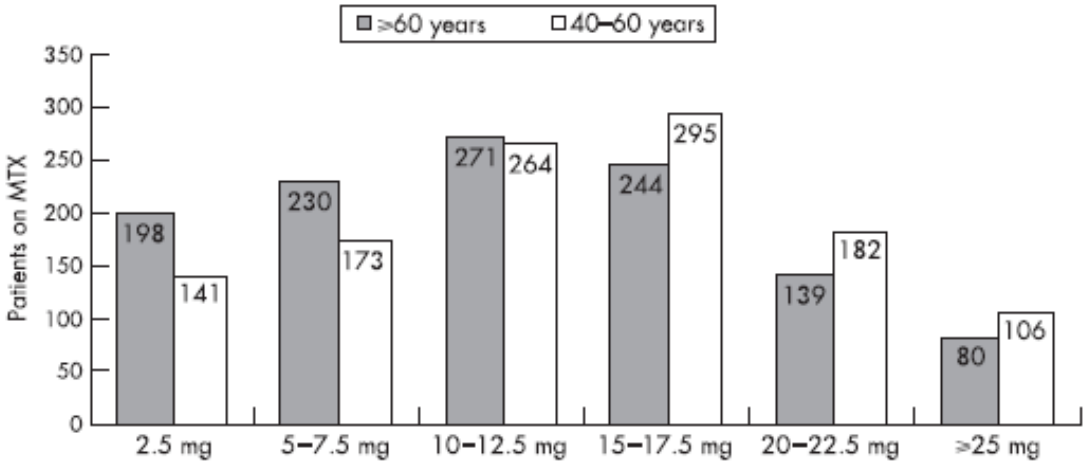


Figure 1 Distribution of methotrexate (MTX) dose.

The challenging interplay between rheumatoid arthritis, ageing and comorbidities

van Onna and Boonen *BMC Musculoskeletal Disorders* (2016) 17:184

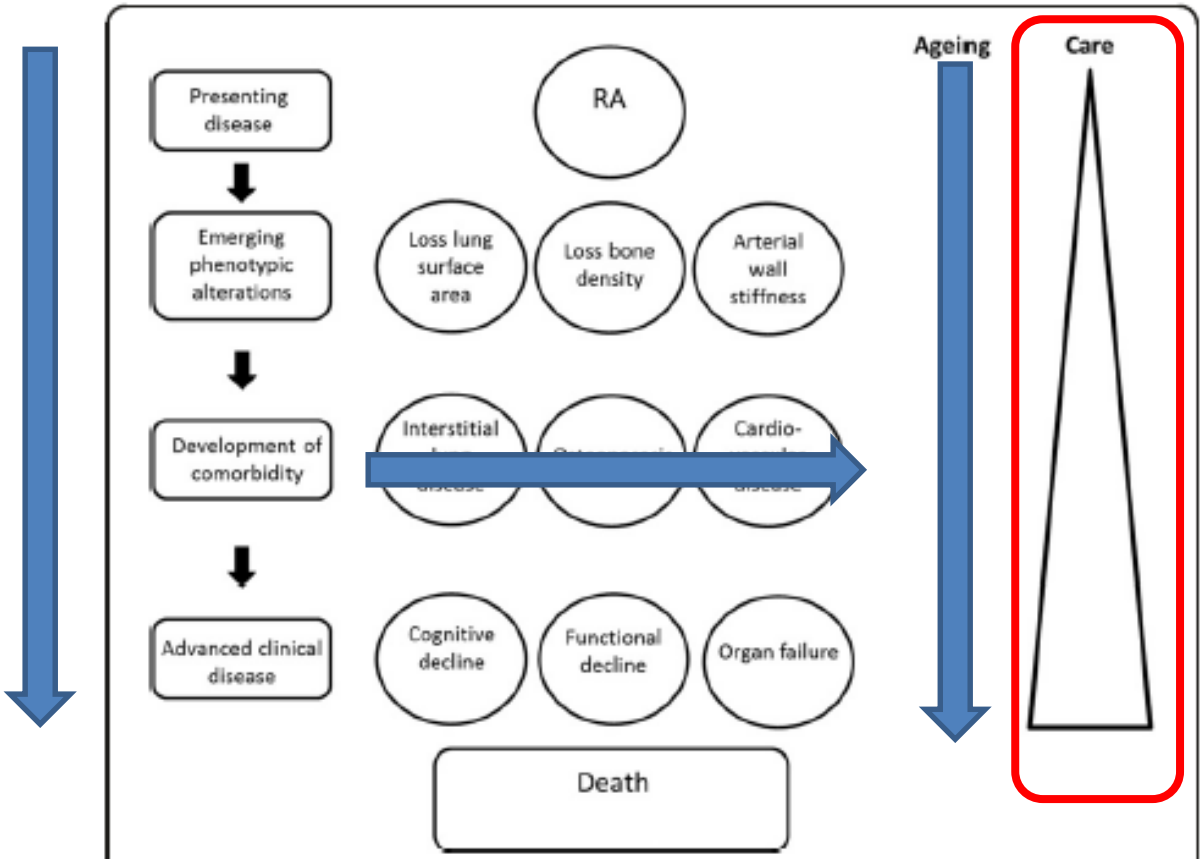


Fig. 1 Conceptual model for the effects of ageing and development of comorbidity in patients with RA. Abbreviation: RA, rheumatoid arthritis

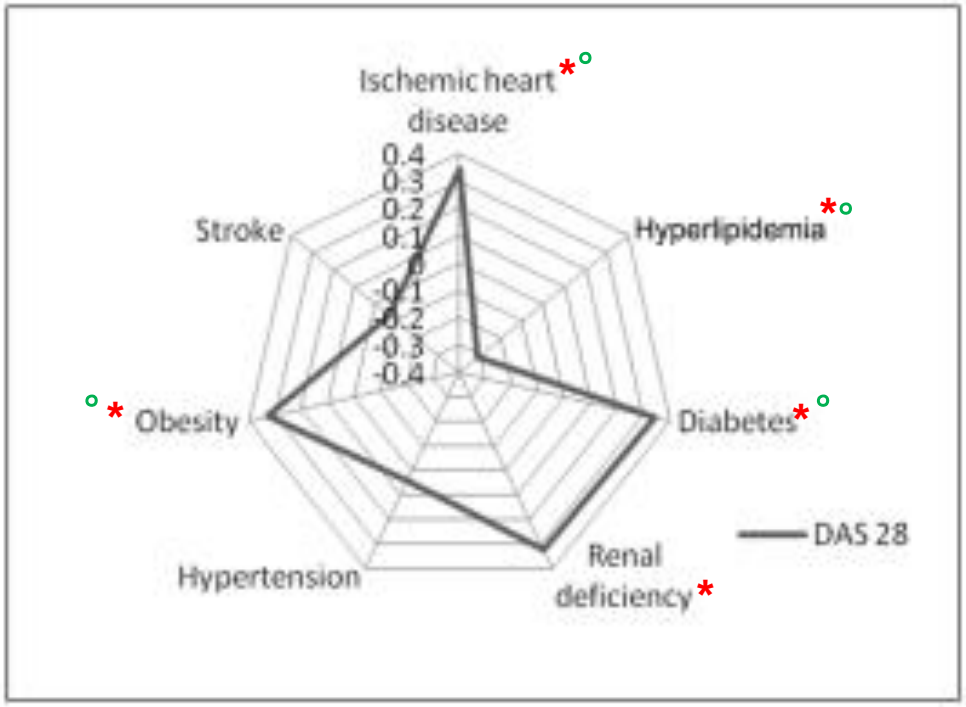
Cardiovascular Comorbidities Relate More than Others with Disease Activity in Rheumatoid Arthritis

Gloria Crepaldi[1], Carlo Alberto Scirè[2], Greta Carrara[2], Garifallia Sakellariou[1], Roberto Caporali[1]*, Ihsane Hmamouchi[3], Maxime Dougados[4], Carlomaurizio Montecucco[1]

PLOS ONE | DOI:10.1371/journal.pone.0146991

Association between CDV comorbidities and disease activity (DAS28)

AIM: to explore the relation between comorbidities and disease activity in 3920 RA patients included in the cross-sectional observational multicenter international study COMORA.



*set of analysis adjusting for demographics, disease-related variables, and treatment variables.

° set of analysis adjusting also for other comorbidities.

EORA: which therapy?

✓Acute systemic and articular involvement

✓ Lab features (severe inflammation)

✓Comorbidities (mood/fatigue)

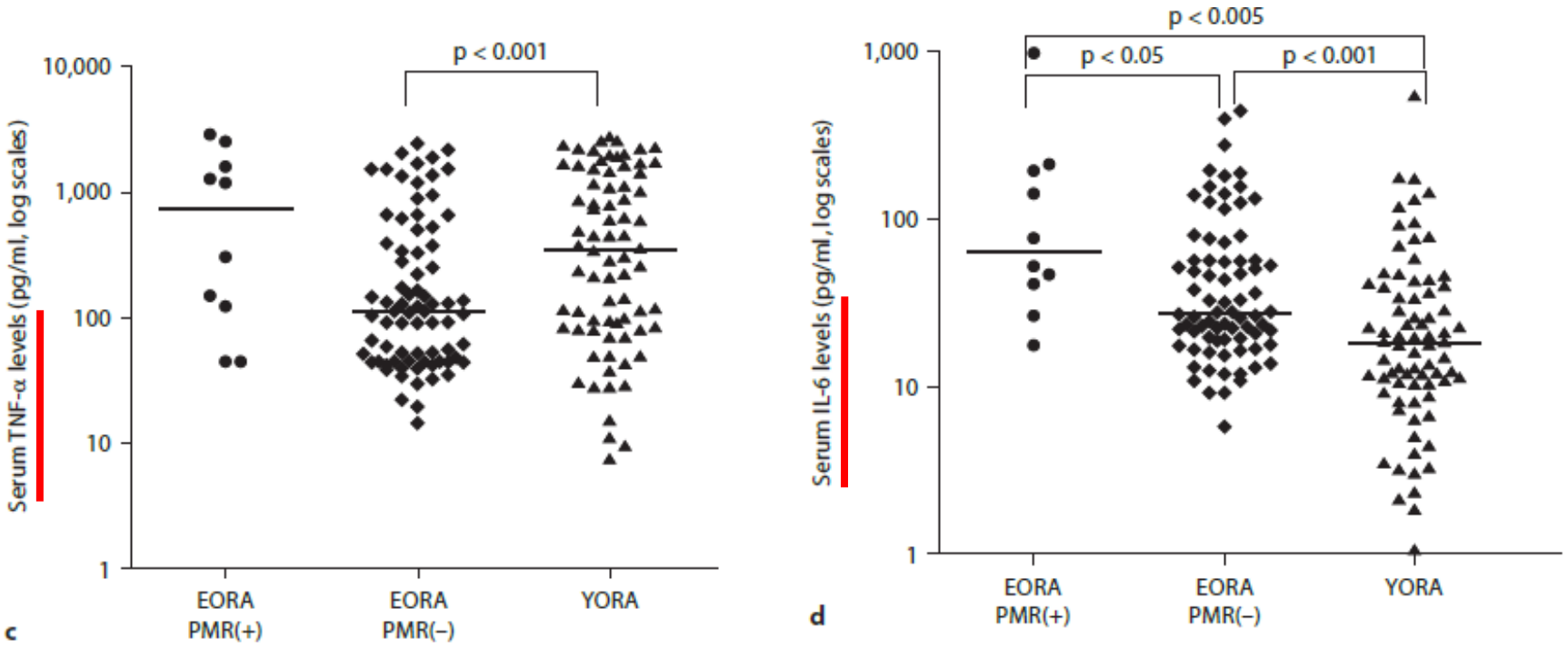
✓Safety

EORA profiling?

Proinflammatory Cytokine Profiles of Patients with Elderly-Onset Rheumatoid Arthritis: A Comparison with Younger-Onset Disease

Gerontology 2009;55:250–258

Comparison of serum inflammatory cytokines in 86 active EORA (>60) vs 76 active YORA

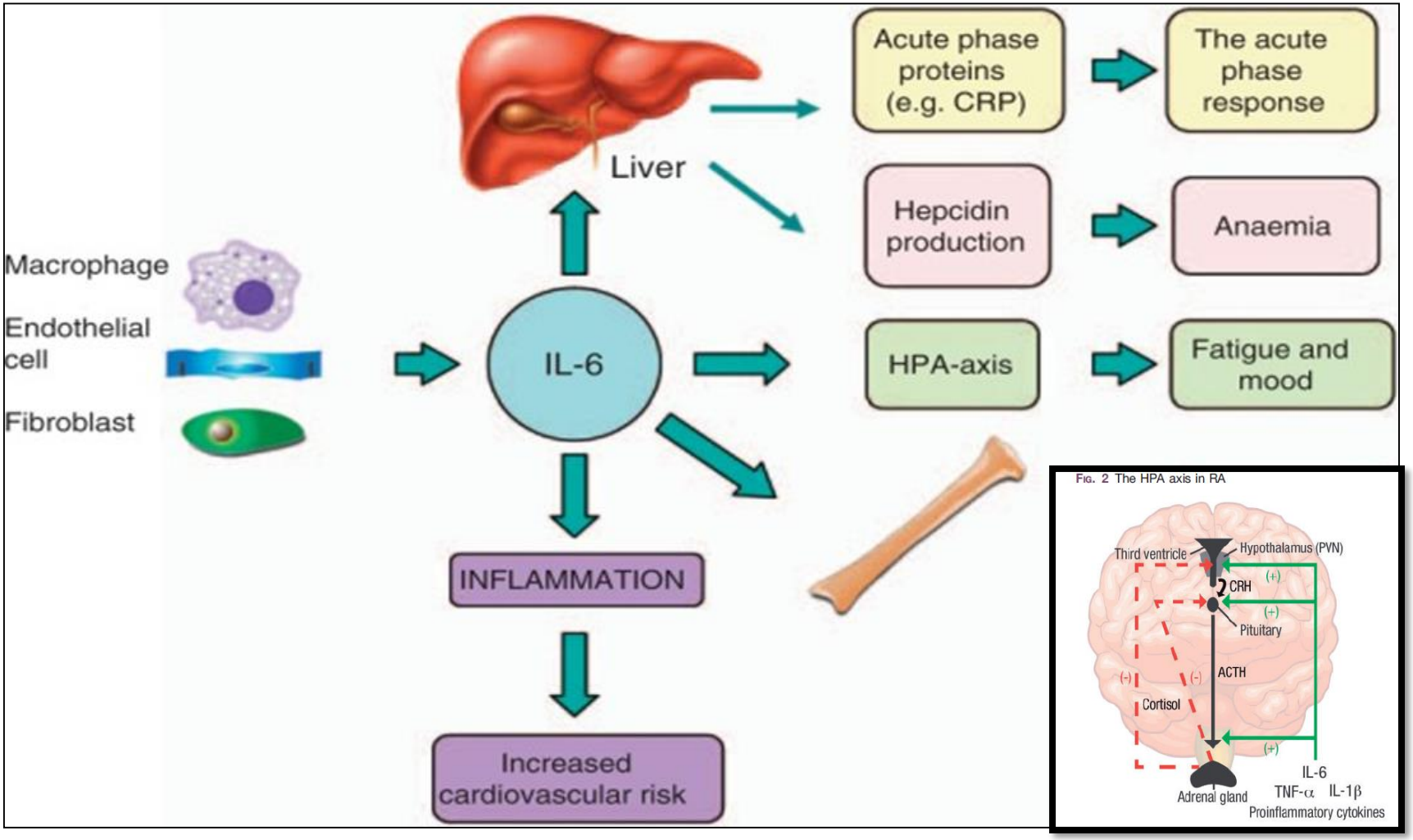


Significantly higher IL-6 and lower TNF- levels in EORA vs YORA patients.

Higher levels of serum IL-6 in EORA patients with PMR-like symptoms than in those without

No differences for levels of IL1, IL8, INF among groups

Is IL6 the key?



Srirangan S, et al. Ther Adv Musculoskelet Dis. 2010 Oct; 2(5): 247–256.

IL6 inhibition and anemia

AIM: impact of TCZ, TOFA, obDMARDs, onbDMARS on anaemia markers in American RA patients

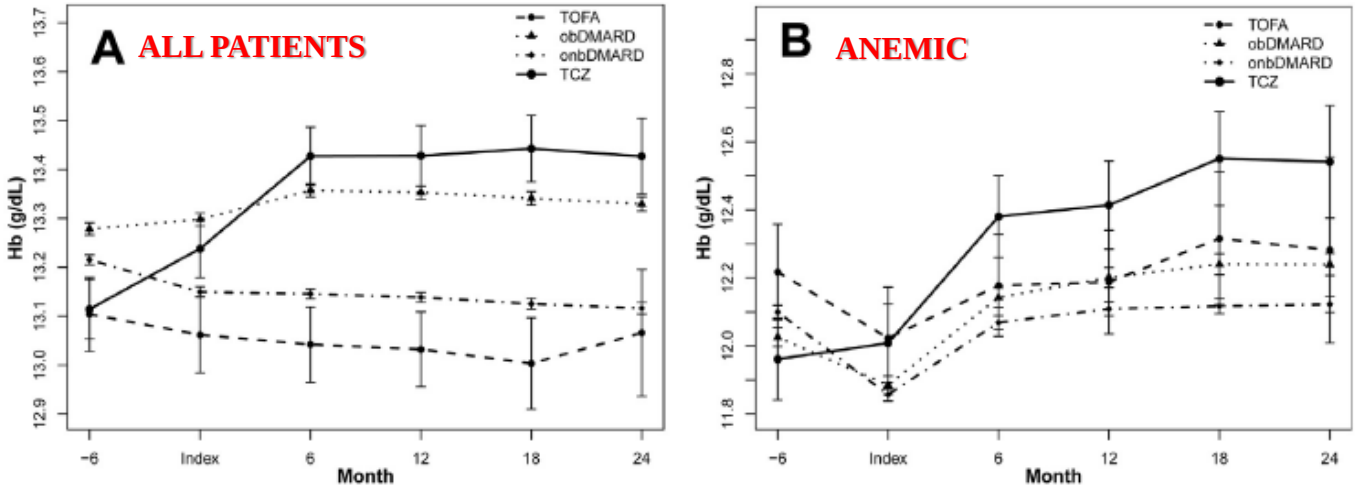


Table 2
Change in haemoglobin at 6, 12, and 24 months from index date. Treatment groups balanced on sex and baseline measures. Analysis was adjusted for age, sex, and duration of RA, history of CVD, CKD, cancer, and diabetes prior to index date

	Mean (95% CI) (g/dL) index date		Changes at 6 months (g/dL) mean (95% CI)		Changes at 12 months (g/dL) mean (95% CI)		Changes at 24 months (g/dL) mean (95% CI)	
	All	Anaemic at index date	All	Anaemic at index date	All	Anaemic at index date	All	Anaemic at index date
TCZ	13.26 (13.22, 13.3)	12.06 (11.98, 12.14)	0.22 (0.14, 0.30)	0.40 (0.24, 0.56)	0.24 (0.13, 0.36)	0.55 (0.32, 0.78)	0.23 (0.14, 0.42)	0.72 (0.36, 1.08)
TOFA	13.04 (12.99, 13.09)	11.89 (11.81, 11.97)	0.00 (−0.11, 0.11)	0.40 (0.22, 0.58)	0.06 (−0.07, 0.18)	0.46 (0.15, 0.76)	0.04 (−0.34, 0.43)	0.58 (0.05, 1.11)
obDMARD	13.27 (13.26, 13.29)	11.90 (11.87, 11.92)	0.06 (0.04, 0.07)	0.20 (0.16, 0.24)	0.07 (0.04, 0.09)	0.25 (0.21, 0.30)	0.04 (0.02, 0.07)	0.35 (0.29, 0.41)
onbDMARD	13.14 (13.14, 13.15)	11.86 (11.84, 11.88)	−0.06 (−0.10, −0.02)	0.17 (0.14, 0.19)	−0.05 (−0.09, −0.02)	0.21 (0.18, 0.24)	−0.08 (−0.1, −0.06)	0.26 (0.22, 0.30)

IL6 inhibition and PROs

Drug	Study	Treatment	*n*	Pain (VAS) Baseline	Pain (VAS) Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	60.7 (21.0)	−25.0**	NR
		8 mg/kg q4w + MTX qw	205	59.9 (22.4)	−29.8*	
		Placebo q4w + MTX qw	204	57.3 (22.2)	−14.0	
					Week 24	
	AMBITION [51]	8 mg/kg q4w	268	58.7 (22.9)	−31.9	NR
		MTX qw	262	61.5 (20.6)	−29.9	
					Week 4	Week 24
	TAMARA [50]	8 mg/kg q4w + DMARD	286[b]	60.4 (21.5)	36.0 (26.7)	23.6 (26.3)
					Week 52	Week 104[c]
	LITHE [48, 49]	4 mg/kg q4w + MTX qw	399	NR	−23.1***	−26.6 (25.4)
		8 mg/kg q4w + MTX qw	398		−26.2*	−28.9 (25.5)
		Placebo q4w + MTX qw	393		−15.1	−25.6 (24.4)
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	65.4 (21.4)	−28.5 (1.4)*	−32.7 (1.4)*
		200 mg q2w + MTX qw	399	66.7 (21.4)	−31.8 (1.3)*	−33.1 (1.4)*
		Placebo q2w + MTX qw	398	63.7 (19.9)	−15.4 (1.4)	−19.3 (1.6)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	71.0 (19.3)	−26.9 (1.9)*	−31.9 (2.1)**
		200 mg q2w + csDMARDs	184	74.9 (18.4)	−30.6 (1.9)*	−33.7 (2.0)*
		Placebo q2w + csDMARDs	181	71.6 (18.2)	−15.1 (1.9)	−21.3 (2.3)
					Week 24	
	MONARCH [54]	200 mg q2w	184	70.9 (18.8)	−36.2 (1.8)**	NR
		Adalimumab 40 mg q2w	185	70.3 (19.3)	−27.4 (1.8)	

Drug	Study	Treatment	*n*	Fatigue (FACIT-F) Baseline	Fatigue (FACIT-F) Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	27.0 (11.5)	7.3**	NR
		8 mg/kg q4w + MTX qw	205	27.7 (10.6)	8.6*	
		Placebo q4w + MTX qw	204	26.7 (11.1)	4.0	
					Week 24	
	ADACTA [74]	8 mg/kg q4w	163	NR	11.4	NR
		Adalimumab 40 mg q2w	162		8.9	
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	26.3 (9.8)	8.6 (0.5)*	9.1 (0.5)*
		200 mg q2w + MTX qw	399	25.9 (10.4)	9.2 (0.5)*	9.2 (0.5)*
		Placebo q2w + MTX qw	398	27.2 (10.4)	5.8 (0.5)	6.1 (0.5)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	23.5 (10.6)	8.0 (0.7)***	9.9 (0.8)***
		200 mg q2w + csDMARDs	184	23.1 (10.8)	9.5 (0.7)*	10.1 (0.8)***
		Placebo q2w + csDMARDs	181	23.7 (10.8)	5.6 (0.7)	6.8 (0.9)
					Week 24	
	MONARCH [54]	200 mg q2w	184	23.6 (8.9)	10.2 (0.7)	NR
		Adalimumab 40 mg q2w	185	24.4 (10.3)	8.4 (0.7)	

Choy E., et al. Rheumatology 2017

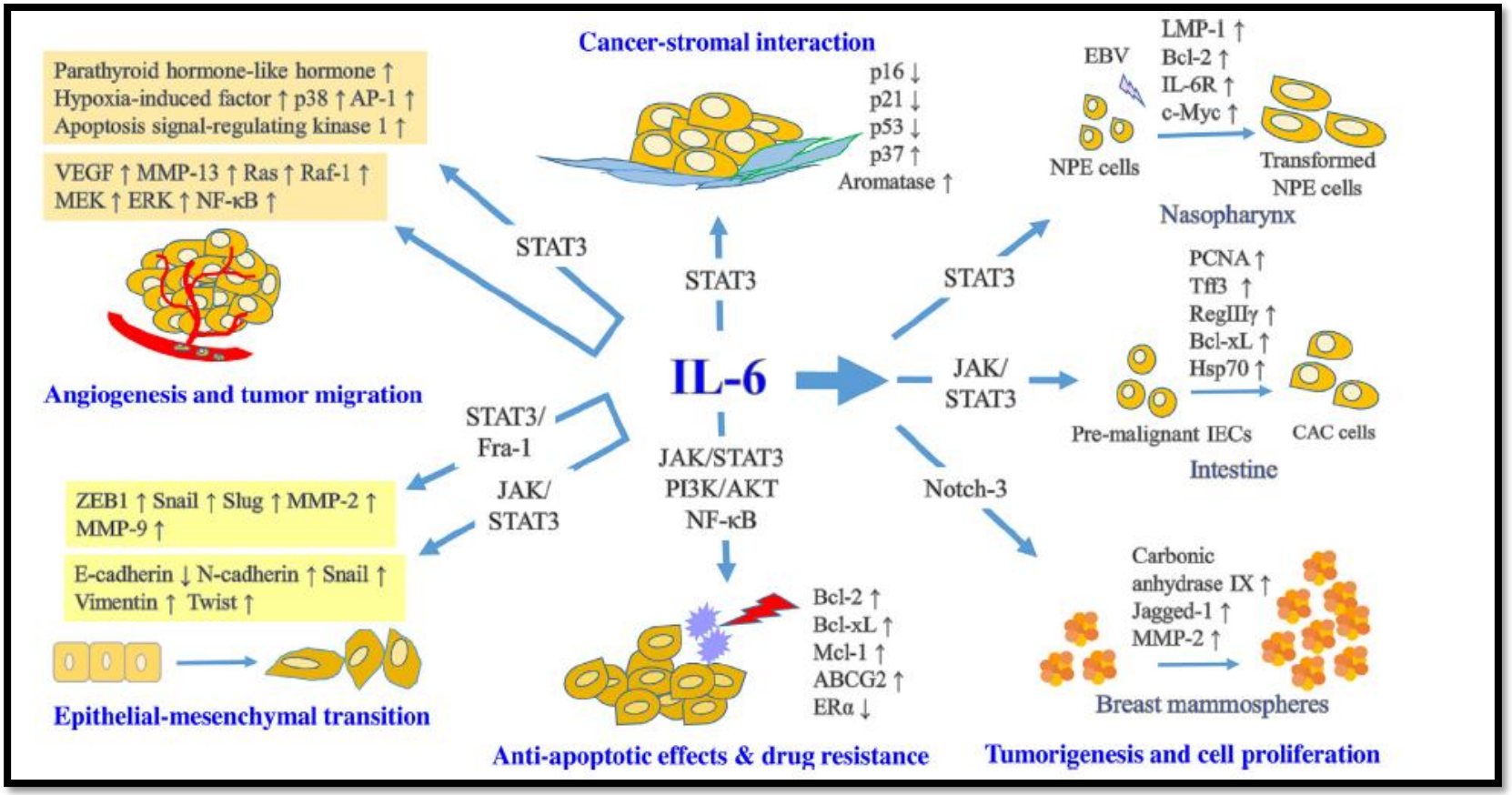
IL6 inhibition and mood

Drug	Study	Treatment	*n*	Mood (SF-36 MCS)		
				Baseline	Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	40.1 (11.8)	5.7****	NR
		8 mg/kg q4w + MTX qw	205	40.9 (10.6)	7.3***	
		Placebo q4w + MTX qw	204	39.1 (11.0)	2.7	
					Week 24	
	ADACTA [74]	8 mg/kg q4w	163	NR	7.9****	NR
		Adalimumab 40 mg q2w	162		5.0	
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	39.0 (11.3)	5.7 (0.6)****	7.1 (0.6)
		200 mg q2w + MTX qw	399	38.7 (12.0)	8.2 (0.6)*	8.4 (0.6)**
		Placebo q2w + MTX qw	398	38.9 (11.4)	3.9 (0.6)	5.5 (0.7)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	38.6 (11.4)	5.1 (0.8)	6.3 (0.8)
		200 mg q2w + csDMARDs	184	39.1 (11.4)	6.5 (0.7)****	6.8 (0.8)
		Placebo q2w + csDMARDs	181	38.5 (12.6)	3.5 (0.7)	4.7 (0.9)
					Week 24	
	MONARCH [54]	200 mg q2w	184	36.4 (10.4)	7.9 (0.8)	NR
		Adalimumab 40 mg q2w	185	36.9 (11.6)	6.8 (0.8)	
Sirukumab					Week 24	Week 52
	SIRROUND-T [55]	50 mg q4w	292	NR	3.9 (10.7)**	4.7 (10.1)
		100 mg q2w	292	NR	4.1 (9.3)**	4.9 (10.5)
		Placebo q2w	294	NR	1.1 (8.9)	

Values given as mean (S.D.). [a]Only phase 3 clinical trials reporting patient-reported mood were included in this table. $^{*}P \leqslant 0.0001$, $^{**}P < 0.001$, $^{***}P < 0.01$, $^{****}P < 0.05$. NR: not reported; qw: every week; q2w: every 2 weeks; q4w: every 4 weeks.

Choy E., et al. Rheumatology 2017

IL6 and cancer



L-J. Ho et al./Biochemical Pharmacology 97 (2015) 16–26

Efficacy and safety of biological agents in the older rheumatoid arthritis patients compared to Young: A systematic review and meta-analysis

Seminars in Arthritis and Rheumatism 000 (2018) 1–9

SR (April 2016): 32 studies (24 in ≥65 years patients), mainly for TNFis

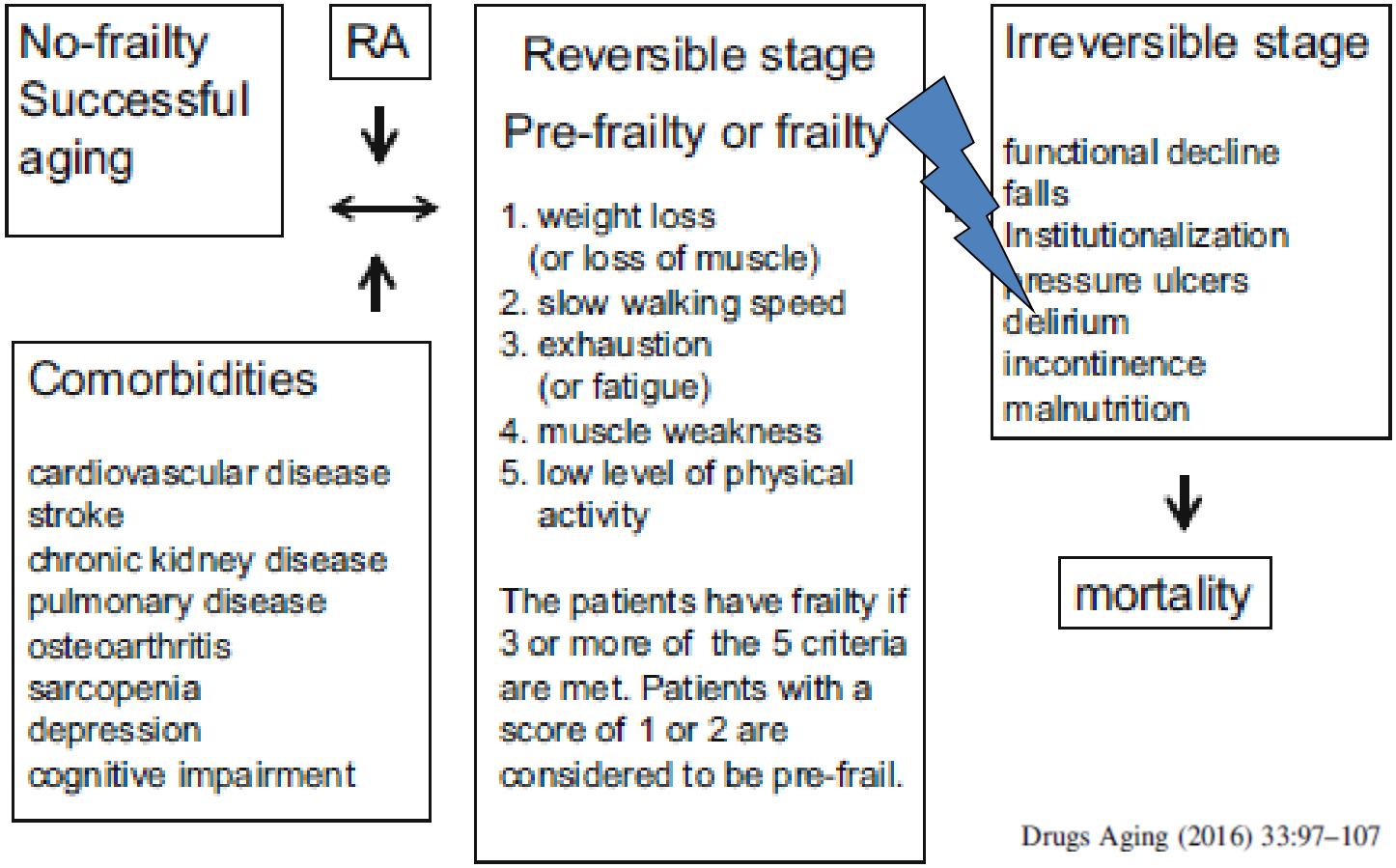
First author last name (year)	Country (ies)	Study type	Age cut off	Biologic(s) studied	Total sample size	Study's focus on elderly RA?	Efficacy	Safety	Baseline MTX use assessed by age
Studies using 60–65 years of age as cut-off for defining older RA									
Koike (2012) [60]	Japan	Observational	65	Anti-TNF	7099	No	x	x	
Fleischmann (2003) [43]	Multiple clinical trails	Post-hoc analysis of RCT	65	Anti-TNF	1128	Yes	x	x	
Genevay (2007) [55]	Switzerland	Observational	65	Anti-TNF	1565	Yes	x	x	Yes
Bathon (2006) [42]	Multiple clinical trials	Post-hoc analysis of RCT	65	Anti-TNF	1847	Yes	x	x	
Filipini (2010) [54]	Italy	Observational	65	Anti-TNF	1114	Yes	x	x	Yes
Koller (2009) [53]	USA & Europe	Post-hoc analysis of RCT	60	Anti-TNF	788	Yes	x		Yes
Radovits (2009) [56]	Netherlands	Observational	65	Anti-TNF	730	Yes	x		Yes
Schiff (2006) [44]	Multiple clinical trials	Post-hoc analysis of RCT	65	Anti-TNF	1847	Yes	x		
Burmester (2008) [67]	Germany, Italy, France, Spain	Observational	65	Anti-TNF	6610	No			
Askling (2007) [70]	Sweeden	Observational	65	Anti-TNF	4167	No			
van Dartel (2013) [71]	Netherlands	Observational	65	Anti-TNF	2044	No			
Takeuchi (2008) [72]	Japan	Observational	60	Anti-TNF	5000	No			
Lurati (2009) [58]	Italy	Observational	65	Anti-TNF	103	Yes			
Galloway (2011) [61]	UK	Observational	65	Anti-TNF	~~11,798~~	No			
Matsubara (2014) [57]	Japan	Observational	65	Anti-TNF	588	No			
Tutuncu (2006) [28]	USA	Observational	60	Anti-TNF	1221	Yes			
Lahaye (2016) [52]	France	Observational	65	Aba	1017	Yes			
Takahashi (2015) [68]	Japan	Observational	65	Aba	231	No			
Pers (2015) [46]	France	Observational	65	TCZ	222	Yes			
Koike (2014) [75]	Japan	Observational	65	TCZ	7901	No			
Koike (2011) [76]	Japan	Observational	65	TCZ	3881	No			
Payet (2014) [51]	France	Observational	65	Rituximab	1709	Yes	x	x	
Winthrop (2014) [48]	USA, Asia, Europe	Post-hoc analysis of RCT	60	Tofacitinib	4789	No		x	
Cohen (2014) [47]	Multiple clinical trials	Post-hoc analysis of RCT	65	Tofacitinib	4789	No		x	
Studies not using 60–65 years of age as cut-off for defining older RA									
Martin (2014) [59]	USA	Observational	55	Anti-TNF	1899	Yes	x	x	
Anecchino (2015) [65]	Italy	Observational	50	Anti-TNF	299	No	x		
Mancarella (2007) [66]	Italy	Observational	53	Anti-TNF	591	No	x		
Askling (2009) [69]	Sweeden	Observational	75	Anti-TNF	6604	No		x	
Nguyen-Khoa (2012) [73]	USA	Observational	70	Anti-TNF	~~16,045~~	No		x	
Chiang (2014) [74]	Taiwan	Observational	55	Anti-TNF	2144	No		x	
Perz (2014) [45]	France	Observational	55	TCZ	204	No	x		
Curtis (2014) [77]	USA	Observational	75	All biologics	3152	No		x	

Anti-TNF – anti tumor necrosis factor agents (etanercept, adalimumab, golimumab, infliximab, certolizumab), Aba – abatacept, TCZ – tocilizumab, RCT – randomized controlled trials.

Reduced benefit-to-risk ratio of bDMARDs in EORA vs YORA

Few informations of comorbidities

EORA: which target?



Drugs Aging (2016) 33:97–107

A different T2T strategy towards a benefit-to-risk ratio approach?

Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis

Rheumatology 2007;46:1020–1023

The majority (85%) of community population over age 50 among 1400 Finnish subjects did not meet criteria for remission or MDA in RA!

TABLE 1. ACR criteria for remission and OMERACT criteria for MDA

ACR criteria	OMERACT MDA criteria
1. No swollen joints	1. Swollen joint count (0–28) ≤1
2. No tender joints *on RADAI*[a]	2. Tender joint count (0–28) ≤1 (*≤1 tender joints on RADAI*)[a]
3. Normal ESR	3. ESR ≤20
4. Morning stiffness ≤15 min[a]	4. Pain (0–10) ≤2 (*pain ≤2/10*)[a]
5. No pain (*pain ≤1/10*)[a]	5. Patient global assessment of disease activity (0–10) ≤2 (*global ≤2/10*)[a]
6. No fatigue (*fatigue ≤1/10*)[a]	6. Physician global assessment of disease activity (0–10) ≤1.5
	7. Health assessment questionnaire (HAQ, 0–3) ≤0.5 *(HAQ ≤0.5)*[a]

Current criteria for disease control might not be accurate in the older

Limits

CLASSIFICATION/DIAGNOSIS

Definition of "older age" as a calendar state and not as a biological state might be inappropriate

Performance of ACR 1987 and ACR/EULAR criteria not specifically known in elderly population

Mis-diagnosis

CLINICAL MONITORING

Different performance of clinical composite scores in EORA vs YORA

TREATMENT

Older RA subset is under-represented in CTs

Different definitions of aged persons in RLD

Age-bias

T2T different approach

Disease and management beliefs of elderly patients with rheumatoid arthritis and comorbidity: a qualitative study

Clinical Rheumatology (2018) 37:2367–2372

Survey of 15 Dutch RA patients (mean age 67 years , range 51–83; mean disease duration 14 years)

Questions about RA and aging in general

What do you think about aging in general? What makes it difficult? Are there also advantages?

Are there joint complaints that you consider to be age-related? Are you able to differentiate these complaints from RA-related complaints? If so, how do you do that?

Questions about RA and comorbidity

Can you tell me about the other medical conditions you have, apart from RA?

How many doctors do you visit, apart from your GP?

Which medical condition takes most of your time? Why?

About which medical condition do you worry the most / the least? Why?

Is it possible for you to prioritize your medical conditions? Which condition is the most 'important' one, when you consider the impact on your health and daily functioning? Why? Which condition is the least 'important' one? Why?

Does comorbidity influence the medical treatment of your RA? If yes, can you give an example?

Questions about medication treatment for RA

Does it ever happen to you that you receive conflicting advice from different medical specialists? Can you give an example? When related to medication for a specific medical condition, which advice do you follow? Do you then prioritize the medication for RA or the comorbidity?

RESULTS:

Misconceptions: all physical complaints attributed to RA

Priority: comorbidities over RA.

AIMS:

Better understanding and informing of patients' beliefs on RA and comorbidity

Conclusions

- In the maxi-aging era, burden of chronic diseases in the elderly should be considered as an urgent need

- In aged persons, RA itself and prevalent/incident comorbidities might impact on disease presentation, management and prognosis

- Due to several reasons, EORA treatment is still an unmet need

- A benefit-to-risk ratio target might be suitable in the older to prevent/limit, while considering, a frailty state