T2T Vodič za ciljano lečenje reumatoidnog artritisa

Ivica Jeremić

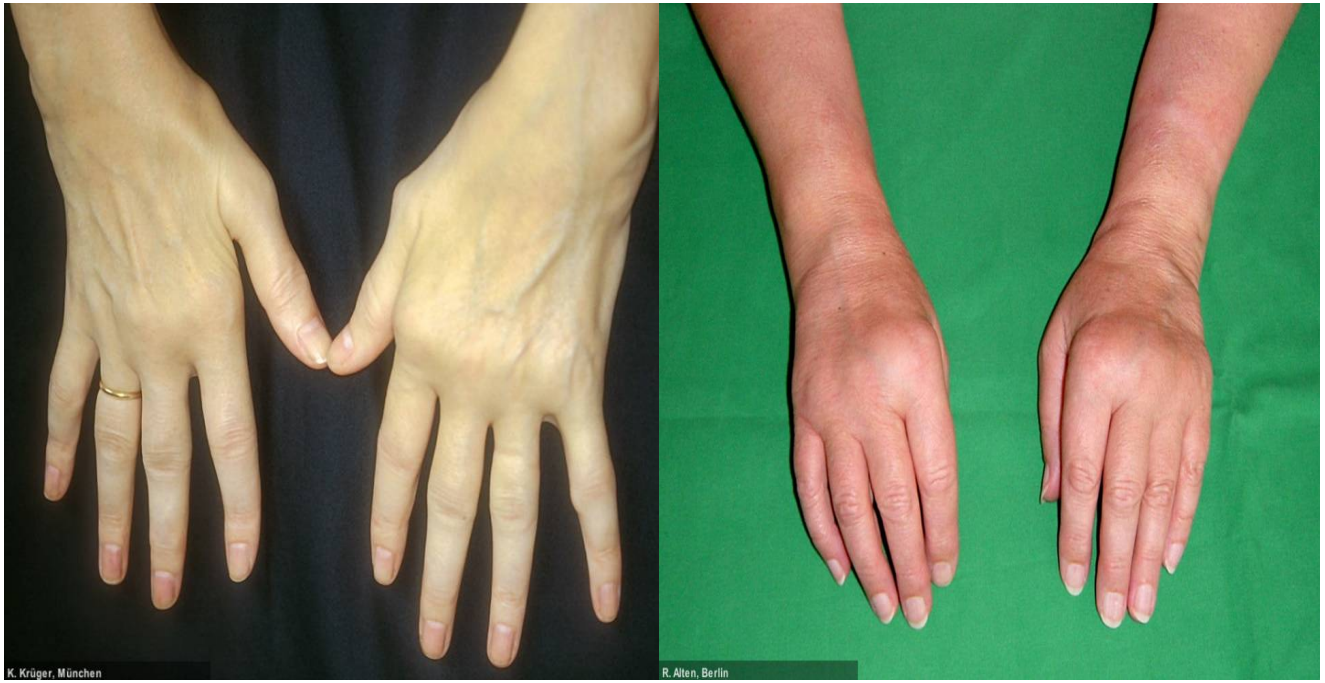
Reumatoidni artritis

Najčešća vrsta autoimunskog artritisa kod odraslih

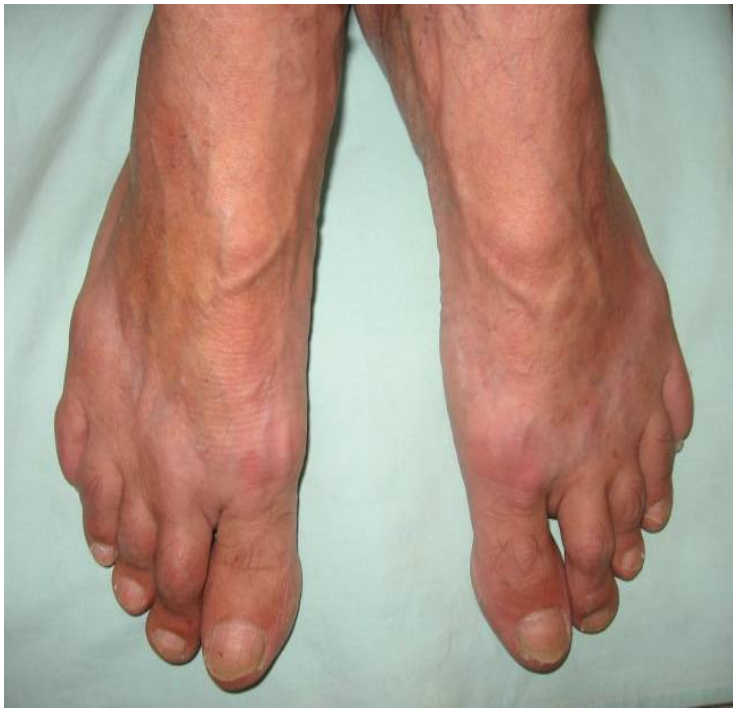
- Početak je postepen i često nespecifičan
- Incidenca ~40 na 100,000
- Prevalenca je ~1% kod bele rase ali varira od 0.1% do ~5% (kod Pima i Chippewa indijanaca)
- Žene boluju 2-3 puta češće u odnosu na muškarce
- Može se javiti u bilo kojem životnom dobu

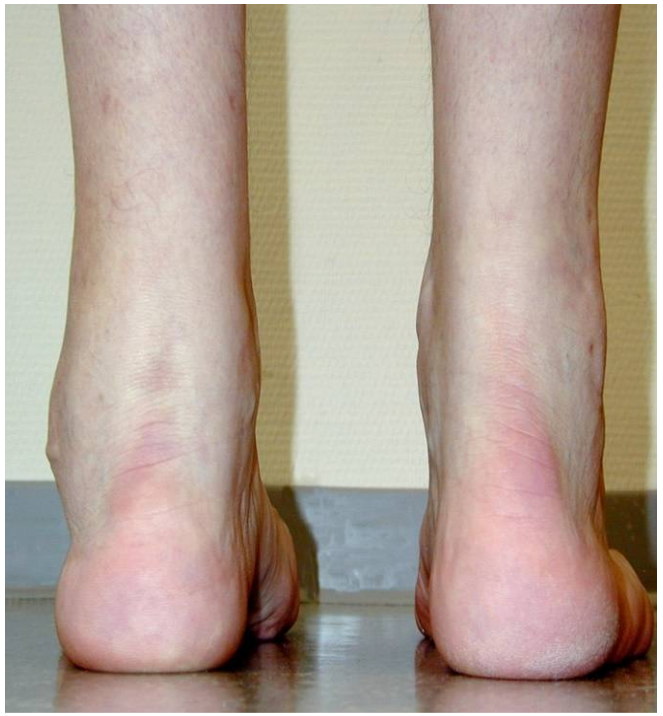
Smolen JS, et al. *Nat Rev Dis Primers*. 2018;4:18001;
Cross M, et al. *Ann Rheum Dis*. 2014;73:1316-1322;
McDougall C, et al. *Semin Arthritis Rheum*. 2017;46:675-686.

Rani RA

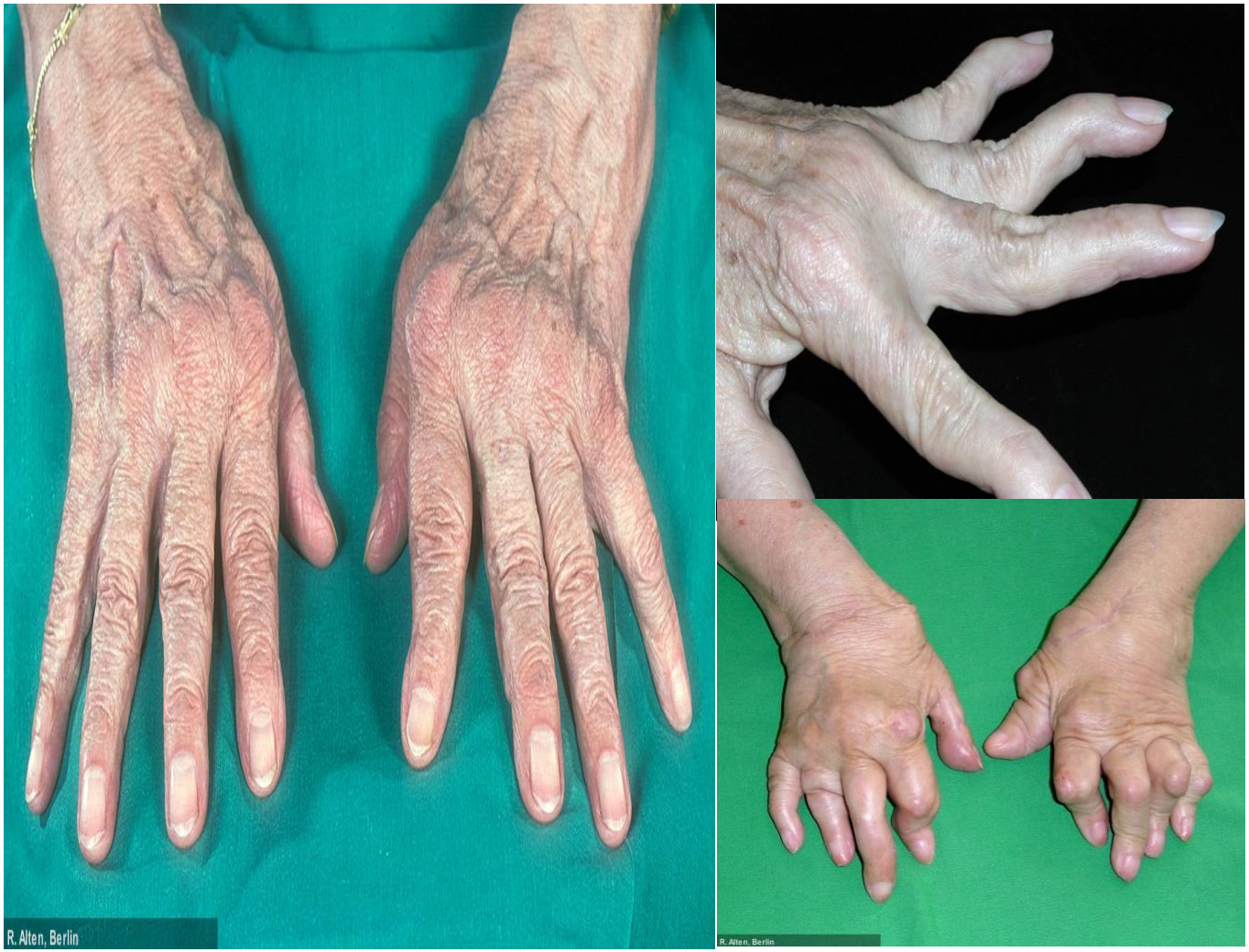


Rani RA





Dugotrajni (loše lečen) RA



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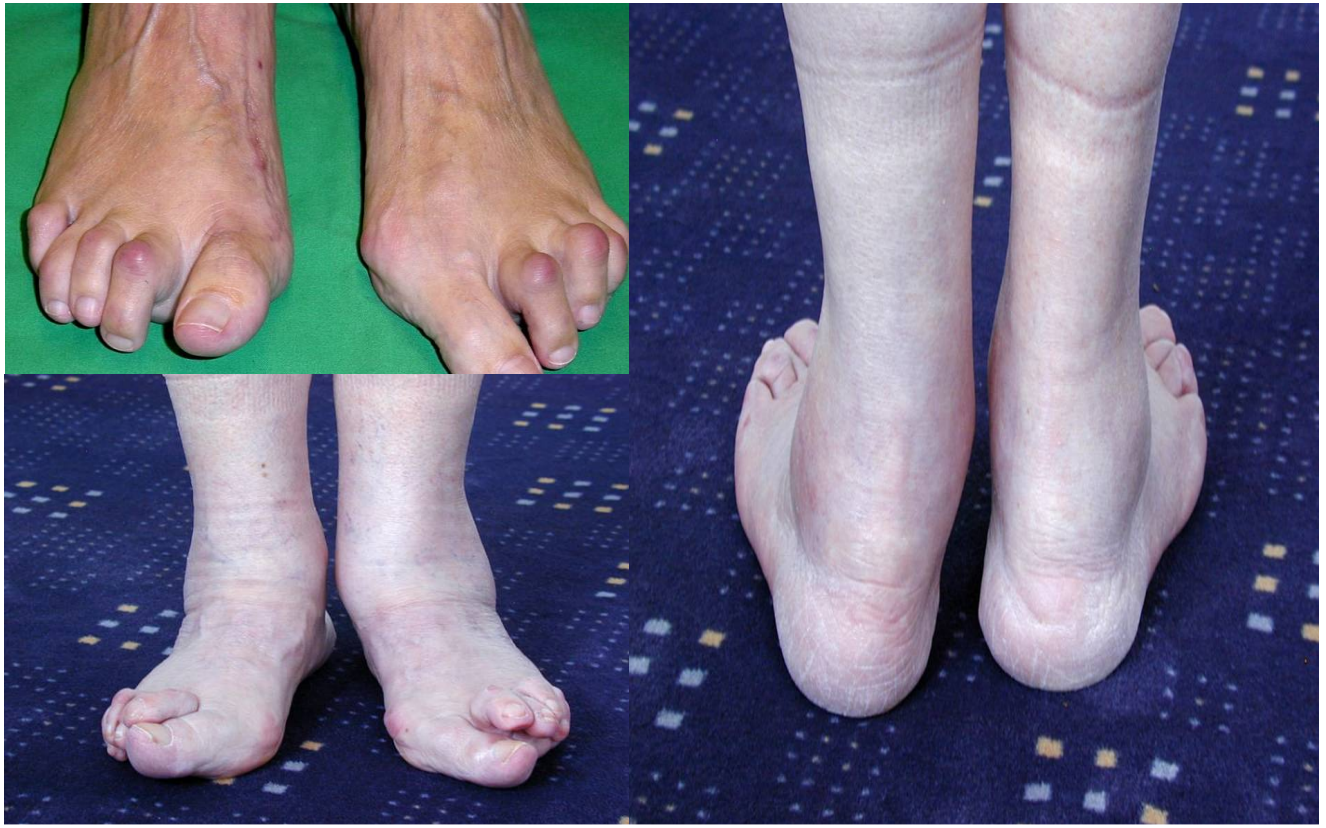

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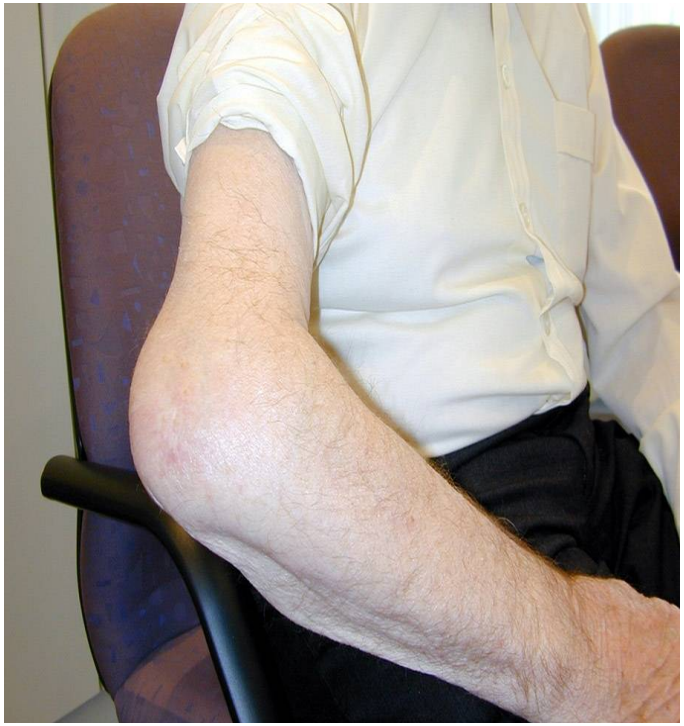
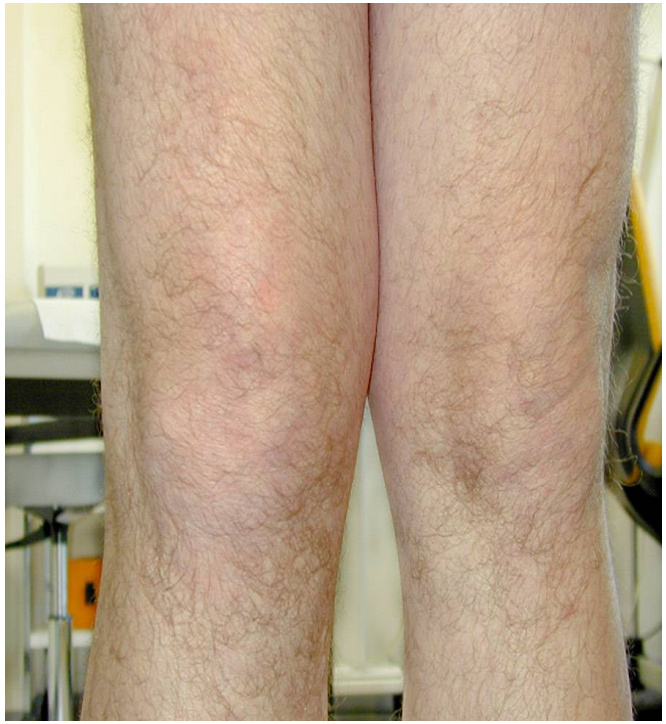
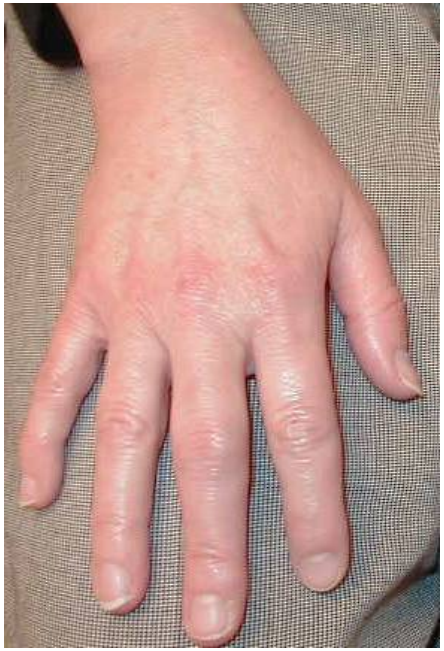


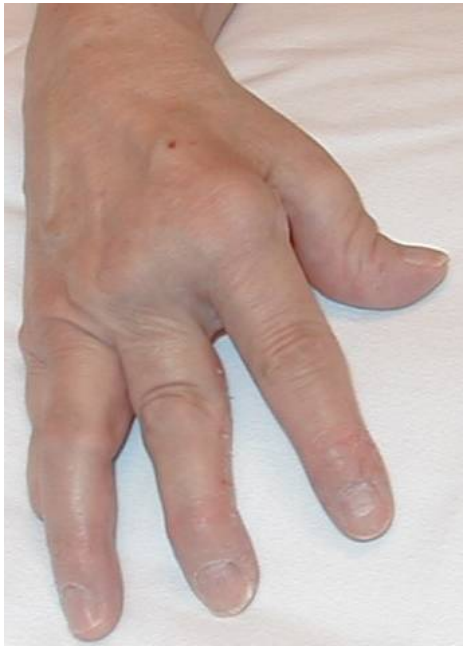


Klinički tok RA

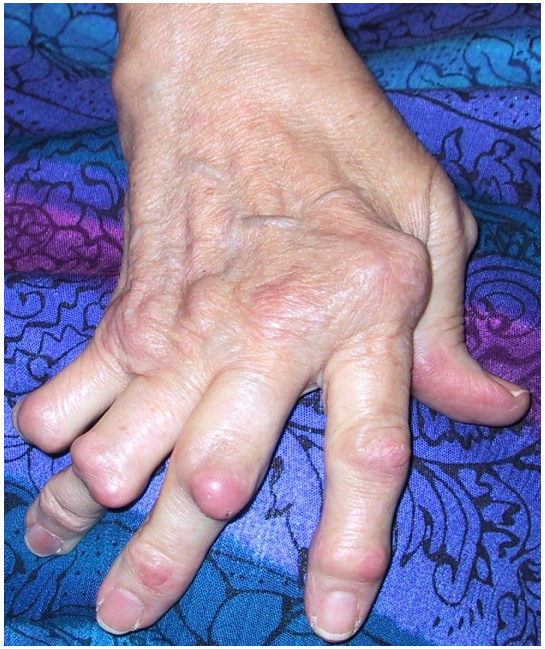
Rani RA



RA srednjeg trajanja



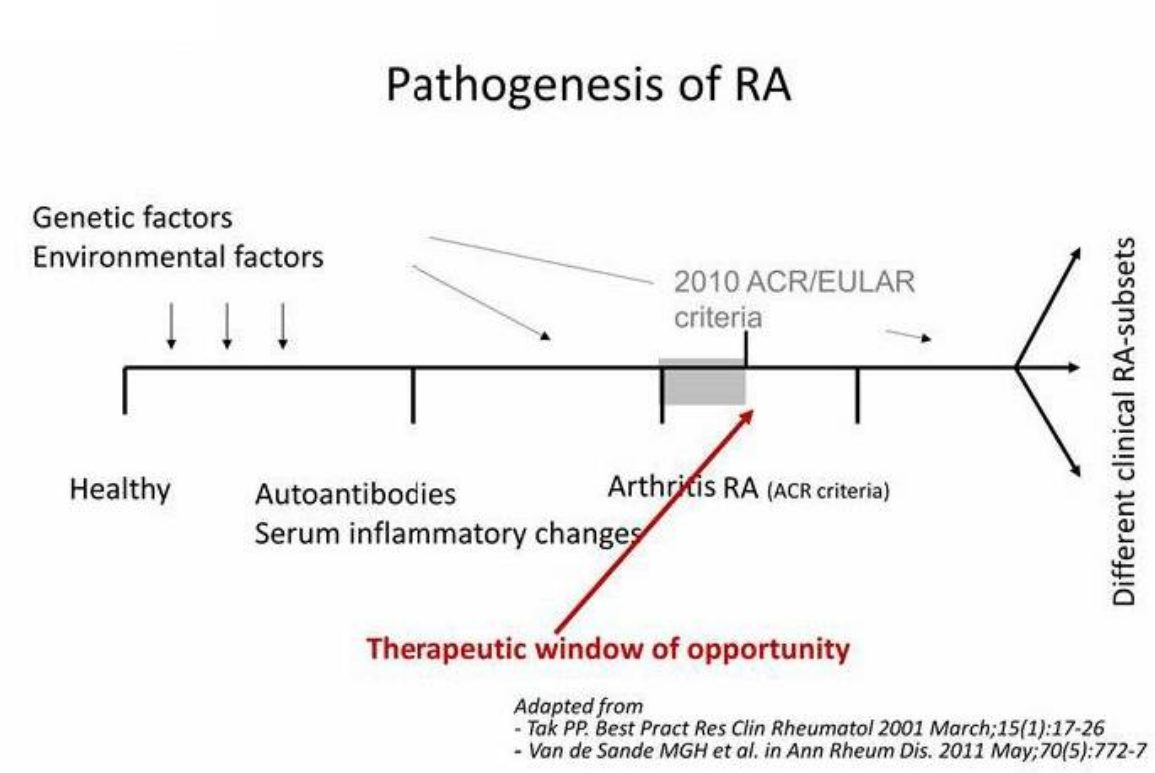
Težak RA



Photos courtesy of J. Cush, 2002.

Zašto moramo rano da lečimo RA?

- Dijagnoza
- Prognoza
- Lečenje: ,,window of opportunity,,



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Kako određujemo metu?

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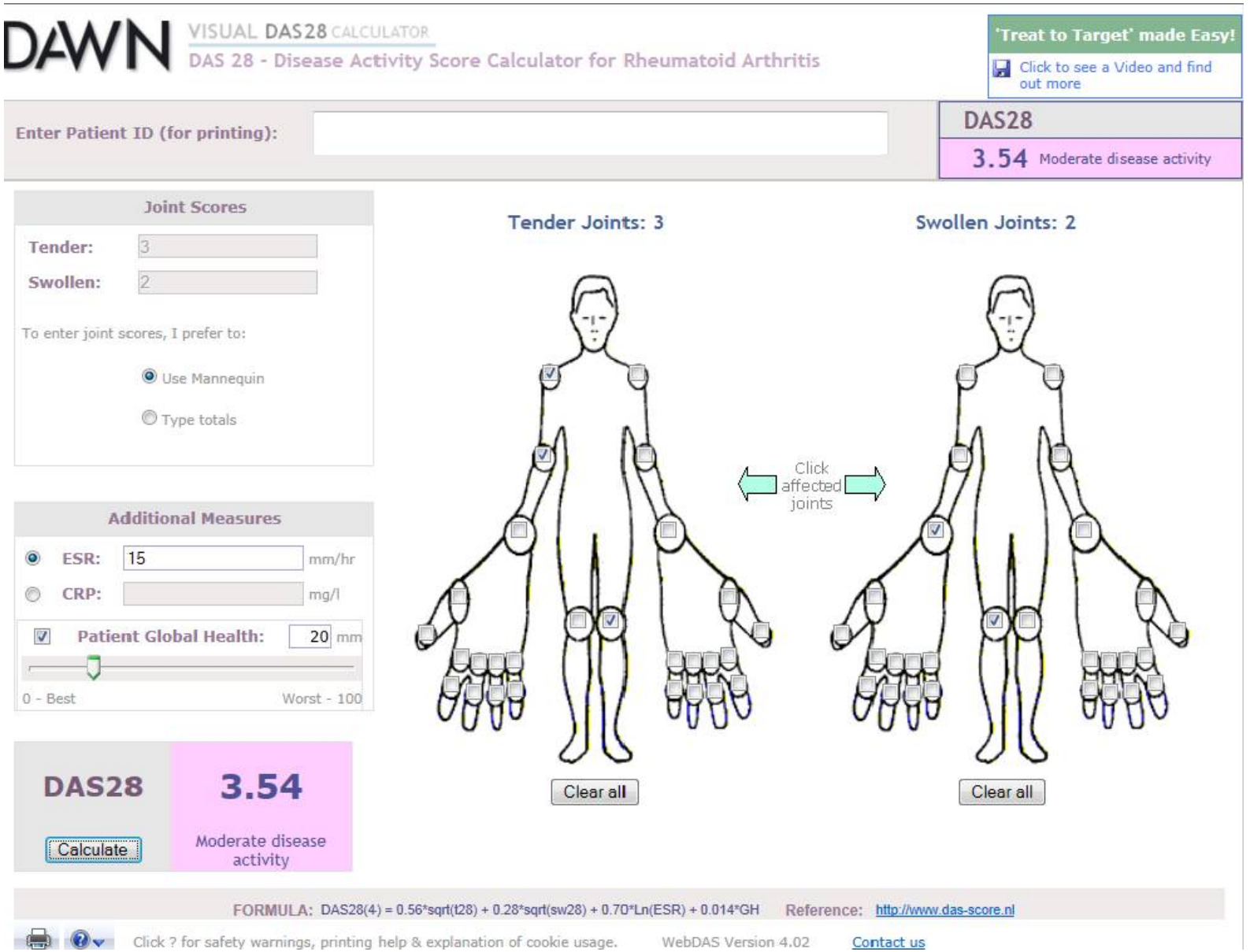

DAWN
VISUAL DAS28 CALCULATOR
DAS 28 - Disease Activity Score Calculator for Rheumatoid Arthritis
'Treat to Target' made Easy!
Click to see a Video and find out more
Enter Patient ID (for printing):
DAS28
3.54 Moderate disease activity
Joint Scores
Tender: 3
Swollen: 2
To enter joint scores, I prefer to:
Use Mannequin
Type totals
Additional Measures
ESR: 15 mm/hr
CRP: mg/l
Patient Global Health: 20 mm
0 - Best
Worst - 100
DAS28
3.54
Calculate
Moderate disease activity
Tender Joints: 3
Swollen Joints: 2
Click affected joints
Clear all
Clear all
FORMULA: DAS28(4) = 0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR) + 0.014*GH
Reference: http://www.das-score.nl
Click ? for safety warnings, printing help & explanation of cookie usage.
WebDAS Version 4.02
Contact us

DAS28

Aktivnost bolesti	DAS28 skor
Viska	> 5.1
Umerena	3.2–5.1
Niska	2.6–3.2
Remisija	< 2.6

- Promena DAS28:
  - < 1.2 = bez odgovora
  - ≥ 1.2 = umereni odgovor
  - ≥ 1.2 < 3.2 = dobar odgovor

KaKo procenjujemo aktivnost RA?

Instrumenti za merenje aktivnosti i procenu remisije

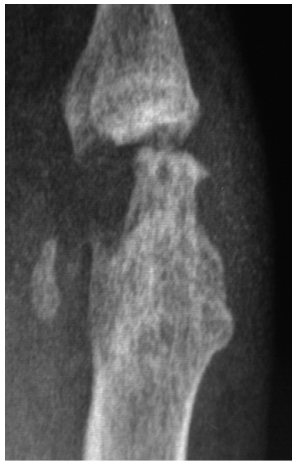
Instrument	Thresholds of Disease Activity
Disease Activity Score 28 (DAS28) ESR (range 0–9.4)	Remisija: <2.6
	Niska aktivnost: ≥2.6 do <3.2
	Umerena aktivnost: ≥3.2 to ≤5.1
	Visoka aktivnost: >5.1
Simplified Disease Activity Index (SDAI) (range 0–10)	Remisija: ≤3.3
	Niska aktivnost: >3.3 to ≤11.0
	Umerena aktivnost: >11.0 to ≤26
	Visoka aktivnost: >26

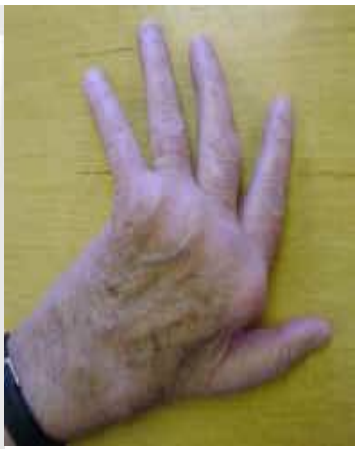
Singh JA, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Vreme je Važno
u RA!!!

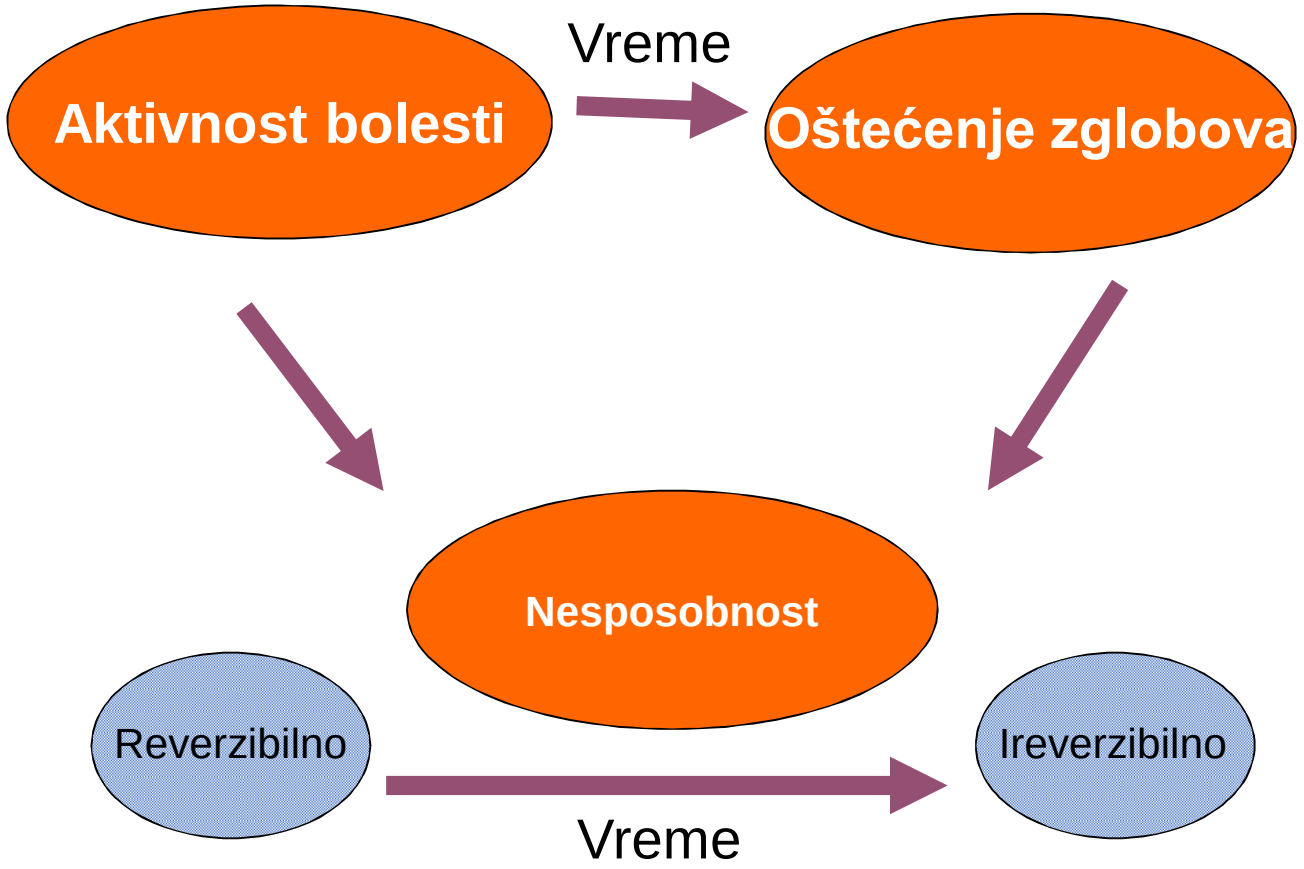
Posledice neadekvatno lečene bolesti





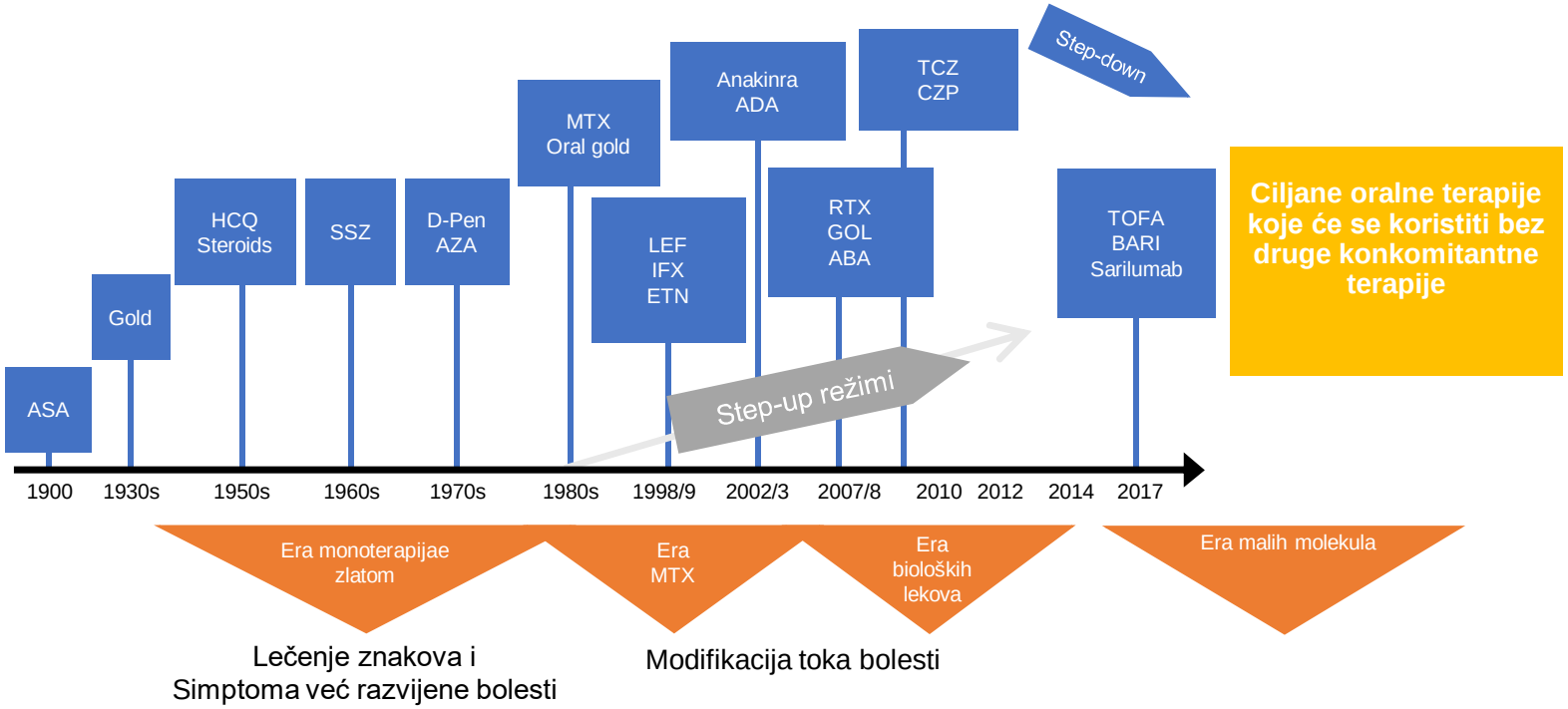



Evolucija Ra



Evolucija lEkova za Ra: Gde smo danas?

- Broj terapijskih opcija je dramatično porastao poslednjih godina što je dovelo do značajno boljeg ishoda pacijenata



ABA, abatacept; ADA, adalimumab; ASA, aspirin; AZA, azathioprine; BARI, baricitinib; CZP, certolizumab; D-Pen, D-penicillamine; ETN, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; IFX, infliximab; LEF, leflunomide; RA, rheumatoid arthritis; RTX, rituximab; SSZ, sulfasalazine; TCZ, tocilizumab; TOFA, tofacitinib

Smolen JS, et al. Ann Rheum Dis 2010;69:631–7;
Smolen JS, et al. Ann Rheum Dis 2016;75:3–15;
Smolen JS, et al. Ann Rheum Dis 2017;76:960–77;
Singh JA, et al. Arthritis Care Res 2016;68:1–25;
Upchurch KS, Kay J. Rheumatology 2012;51(Suppl. 6):vi28–36

Klasični lekovi koji modifikuju tok bolesti

- Metotreksat (MTX)
  - Oralni i subkutani
- Hidroksihlorokin (HCQ)
- Leflunomid (LEF)
- Sulfasalazin (SFZ)

Mogu da se daju kao mono, dvostruka, ili trostruka terapija

*Excludes azathioprine, cyclosporine, minocycline, and gold.

Singh JA, et al. *Arthritis Rheumatol*. 2016;68:1-26.

Tradicionalni lekovi

Lek	Doziranje	Neželjene reakcije	Napomena
Metotreksat	7.5 – 25 mg nedeljno	Stomatitis, mijelosupresija, hepatotoksičnost	• Trudnoća X • Obavezna folna kiselina
Leflunomid (Arava)	20mg dnevno	Mijelosupresija, hepatotoksičnost, hipertenzija	• Trudnoća X
Hydroksihlorokin (Plaquenil)	Max 5mg/kg	Retinopatija, nesanica, diskoloracija kože	• Oftalmološki predledi
Sulfasalazin (Salazopyrin)	2-3g dnevno	Mijelosupresija, hepatotoksičnost	• Promena boje urina

Biološki lekovi (TNF-I)

- **Etanercept (Enbrel)**
- **Adalimumab (Humira)**
- **Infliximab (Remicade)**
- **Golimumab (Simponi)**

Biološki lekovi drugog mehanizma

- **Rituximab (Mabthera)**
- **Tocilizumab (Actemra)**

Sintetički mali molekuli

- **Tofacitinib (Xeljanz)**
- **Baricitinib (Olumiant)**
- **Upadacitinib (Rinvoq)**

EULAR preporuke za lečenje reumatoidnog artritisa

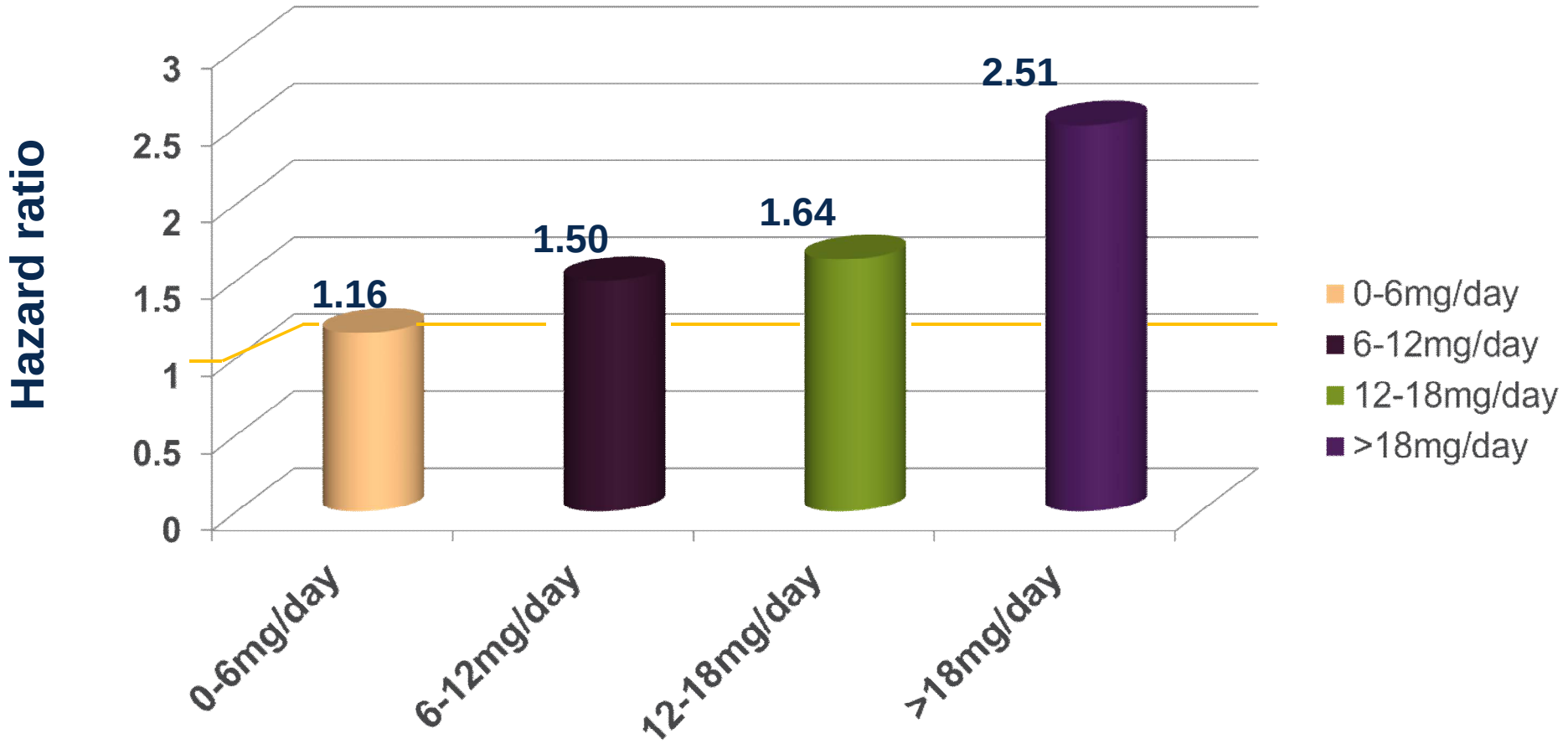
- Evropske preporuke za lečenje reumatoidnog artritisa preporučuju **smanjivanje doze glikokortikoida što je pre moguće**.
- Dugotrajnu upotrebu glikokortikoida, naročito u dozi iznad 5mg/dan trebalo bi izbegavati zbog brojnih potencijalnih rizika

6. *Short-term GC 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.* The added efficacy of GC when combined with csDMARDs is well established. Indeed, hitherto all trials com-

By stating '...tapered as rapidly as clinically feasible', the Task Force underlines that GC should be gradually reduced and ultimately stopped, usually within 3 months from treatment start and only exceptionally by 6 months. Long-term use of GC, especially at doses above 5 mg/day, should be avoided because of the many potential risks presented in the SLR.[50 52 57] While some of these risk associations may be due to confounding by indication in patients with high disease activity,[151] the evidence for increased overall and cardiovascular mortality at a dose above a threshold of 7.5 mg/day or a cumulative dose of 40 g is considerable.[152] Of note, applying GC as a sole therapeutic

Smolen JS, et al. Ann Rheum Dis 2014;

Doza GC – rizik od neželjenih pojava



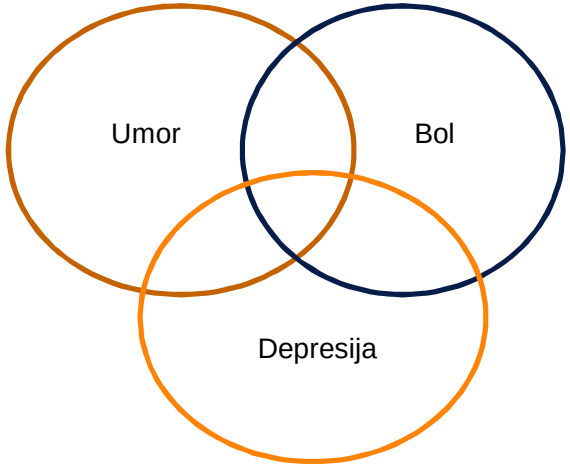
Thamer M, *et al*. J Rheumatol. 2009;36(3):560–4.

Nezadovoljene potrebe u reumatoidom artritisu

- Klinički ishod u RA je značajno bolji, ali bol, umor i psihosocijalni problem i dalje nisu rešeni kompletno

These unmet needs are linked[4–6]

- Podaci iz BSRBR registra pokazuju da 38.8% ima težak umor
- 61% pacijenata ima loš kvalitet sna



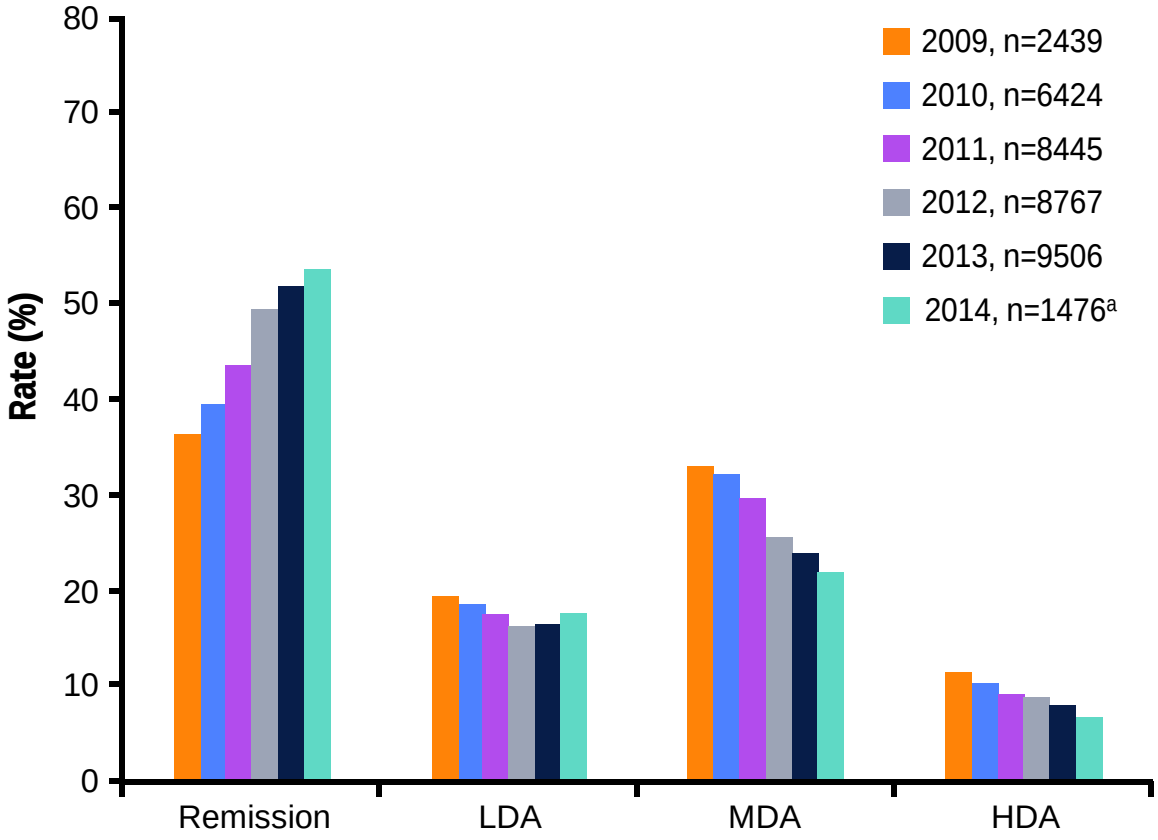
BSRBR, British Society for Rheumatology Biologics Register; RA, rheumatoid arthritis

1. Kievet W, et al. Rheumatology 2013;52:1500–8; 2. Druce KL, et al. Rheumatology 2015;54:964–71; 3. Løppenthin K, et al. Clin Rheumatol 2015;34:2029–39; 4. Katz P, et al. Arthritis Care Res 2016;68:81–90; 5. Matcham F, et al. Clin Psychol Rev 2015;39:16–29; 6. Louati K, et al. Arthritis Res Ther 2015;17:254; 7. Benka J, et al. Disabil Rehabil 2016;38:1172–9; 8. Connolly D, et al. Int J Environ Res Public Health 2015;12:13807–22

Remisija u realnom svetu

REMISSION-2 study

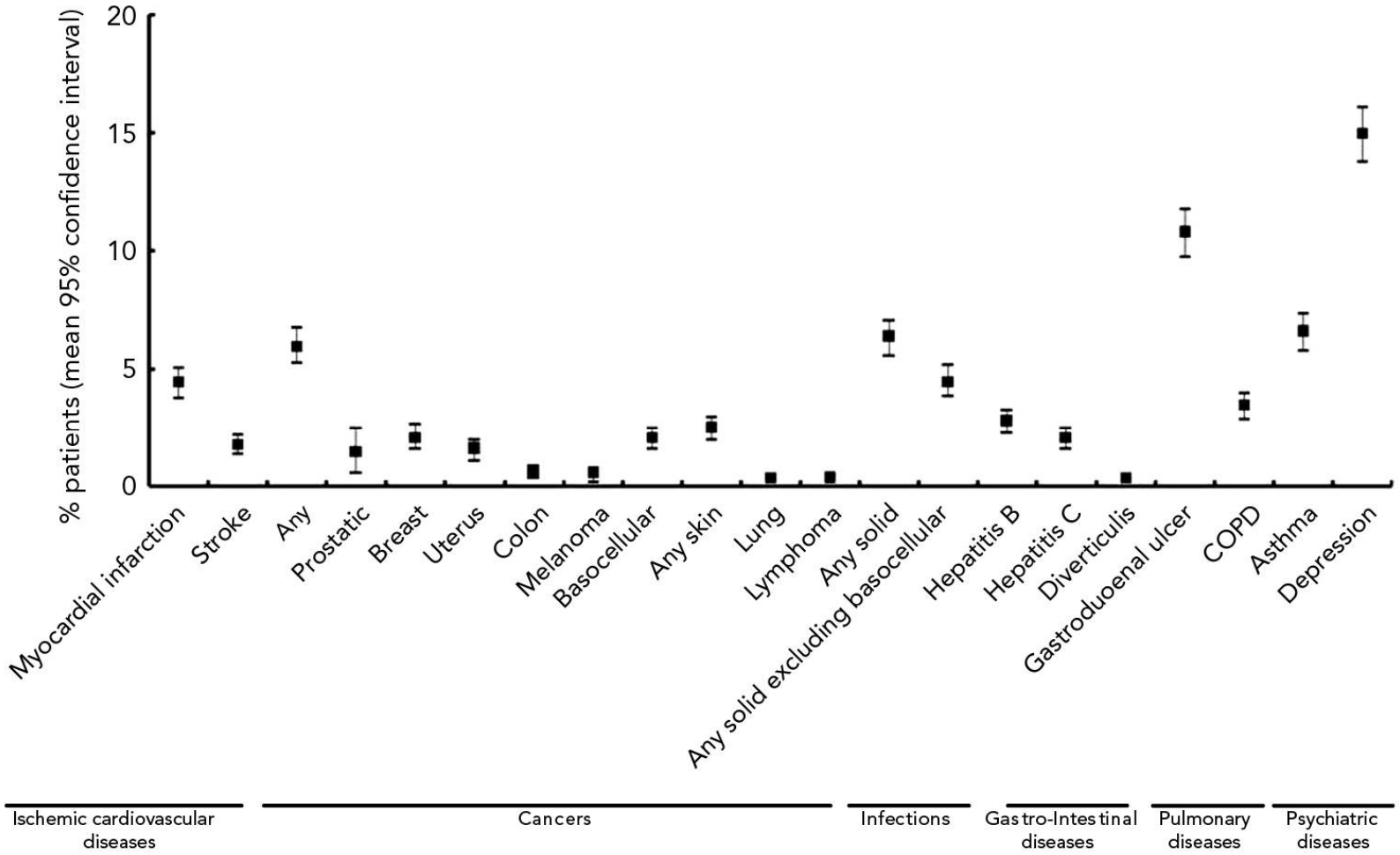
- Stopa remisije porasla sa 36.7% u 2009. na 53.5% u 2014.
- Pacijenti sa umerenom aktivnošu i visokom aktivnošću smanjili su se od 33% i 11% u 2009 na 22.2% i 6.8% u 2014
- Proporcija pacijenata na biološkoj terapji porasla je u svim grupama pacijenata



[a]Data available for January to March at time of analysis
DMARD, disease-modifying antirheumatic drug; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity

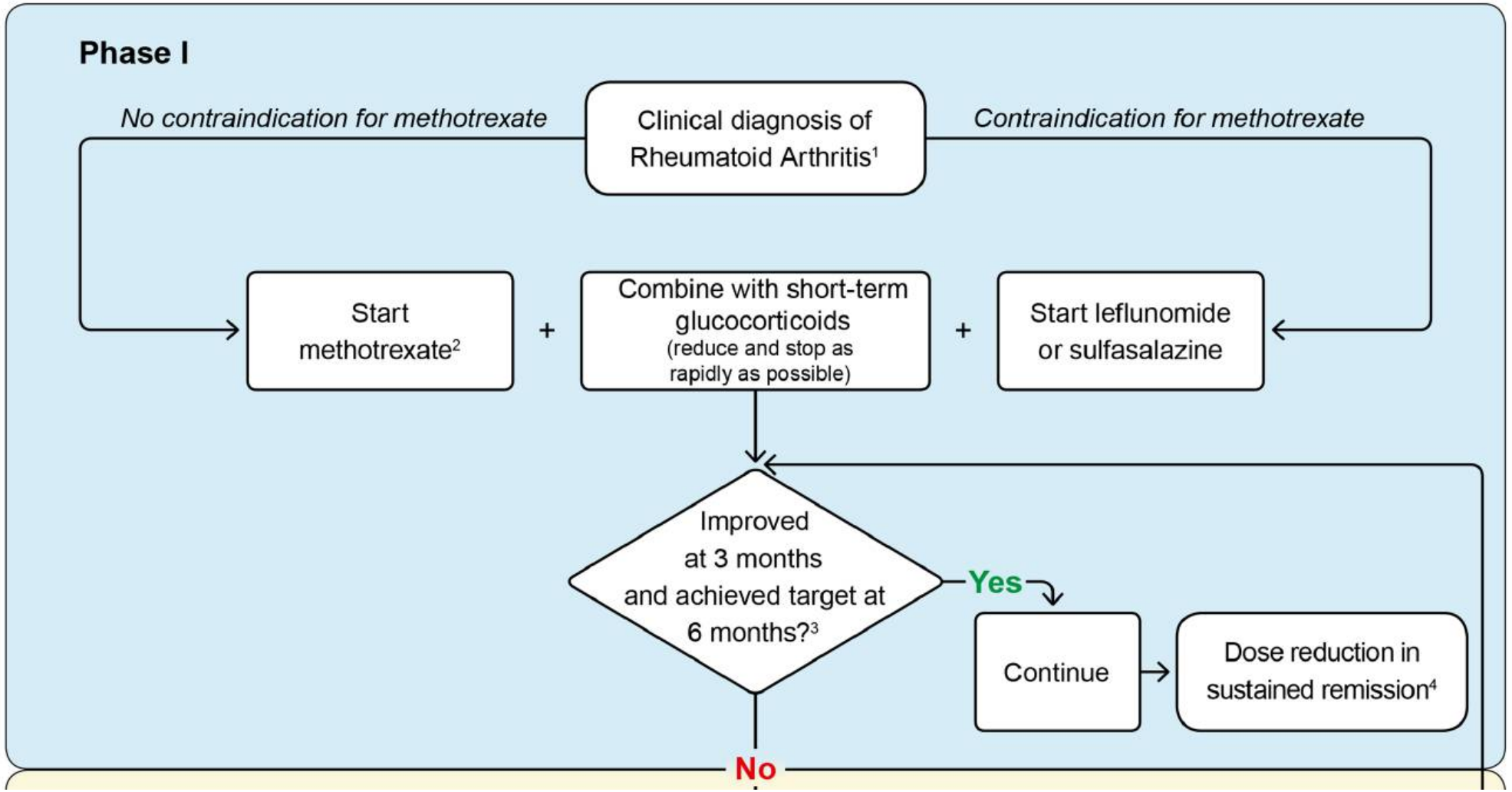
Littlejohn G, et al. J Rheumatol 2015;42:1603–9

Reumatoidni artritis-prevalence komorbiditeta

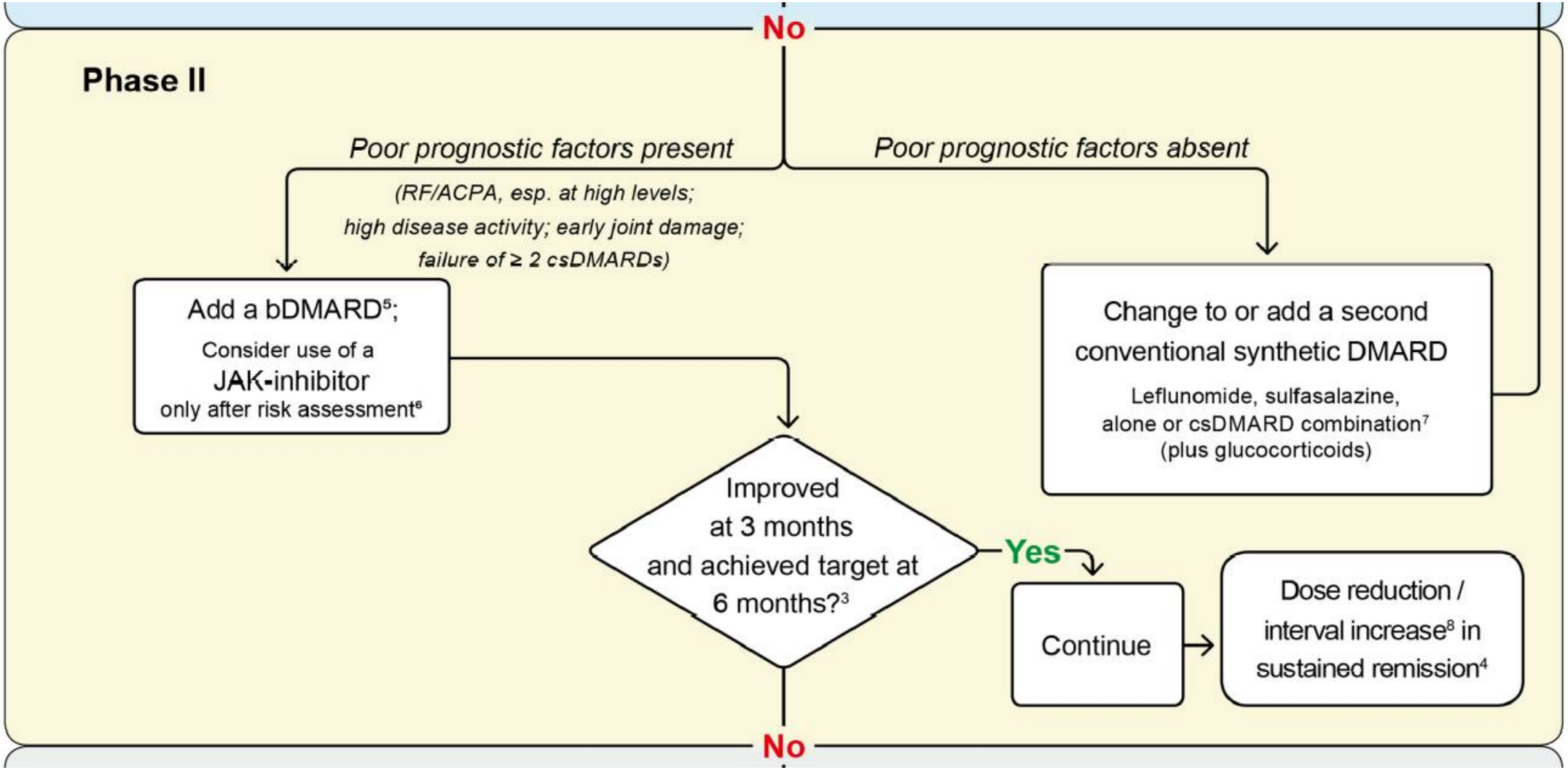


Dougados M, et al. *Ann Rheum Dis*. 2014;73:62-68.

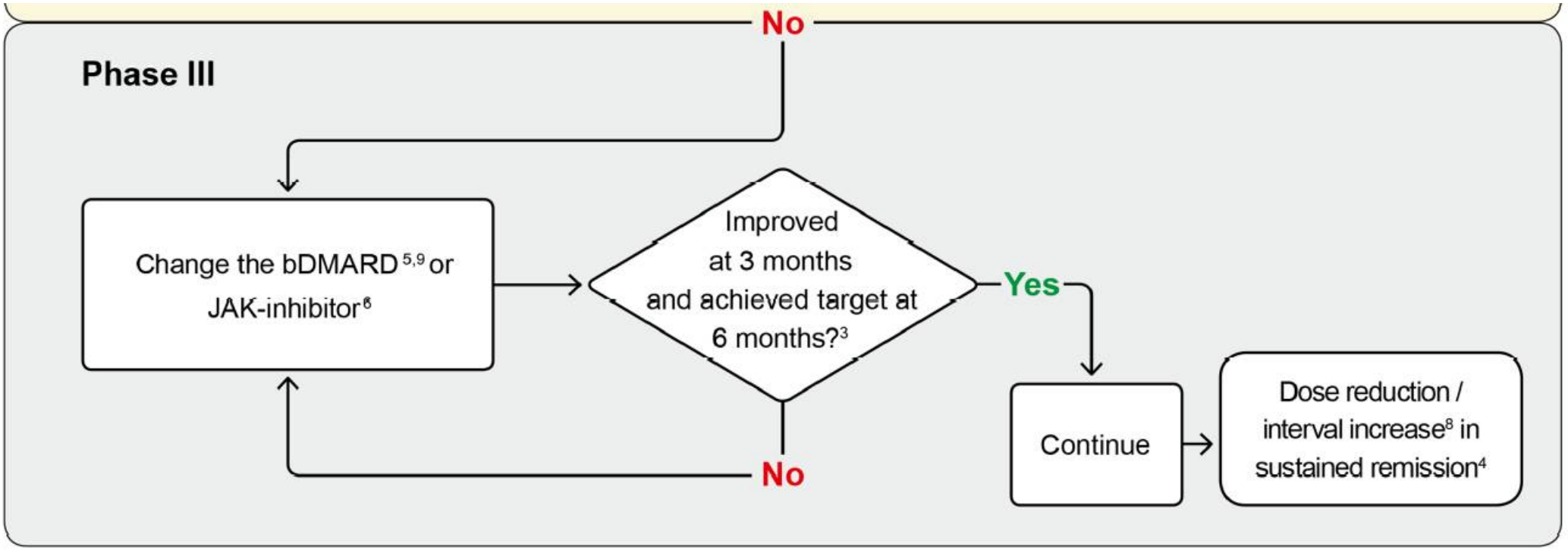
Algoritam lečenja RA-Faza I



Algoritam lečenja RA-Faza II



Algoritam lečenja RA-Faza III



EularovE preporuke

Table 2 EULAR RA management recommendations—2022 update

Overarching principles	
A.	Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
B.	Treatment decisions are based on disease activity, safety issues and other patient factors, such as comorbidities and progression of structural damage.
C.	Rheumatologists are the specialists who should primarily care for patients with RA.
D.	Patients require access to multiple drugs with different modes of action to address the heterogeneity of RA; they may require multiple successive therapies throughout life.
E.	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

EularovE preporuke

1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made.
2.	Treatment should be aimed at reaching a target of sustained remission or low disease activity in every patient.
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.
4.	MTX should be part of the first treatment strategy.
5.	In patients with a contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy.
6.	Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.
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.
8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account.
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.
10.	If a bDMARD or tsDMARD* has failed, treatment with another bDMARD or a tsDMARD*$^{+}$ should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor^{++}.
11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.

With so much choice, hoW to choose?