L'ALLEANZA CLINICO-FARMACISTA NELLA GESTIONE DELLA CRONICITÀ: IL CASE STUDY ARTRITE REUMATOIDE NAPOLI, 15 novembre 2018

Le linee Guida Internazionali

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ARTRITE REUMATOIDE

- **Sindrome caratterizzata da**

  - **Poliartrite simmetrica erosiva**
  - **Manifestazioni extraarticolari**

ARTRITE REUMATOIDE “case definition”

Poliartrite simmetrica con interessamento di polsi e metacarpofalangee ed associata a rigidità mattutina di durata > 30 minuti

F Wolfe 1992

SUBSET DI ARTRITE REUMATOIDE

SUBSET	SIEROPOSITIVA RF e/o ACPA positiva	SIERONEGATIVA
Erosioni	+++	+/-
Disabilità	+++	+
Mortalità	++	+/-

Misure di Outcome nell'Artrite Reumatoide

Standard aurei di outcome

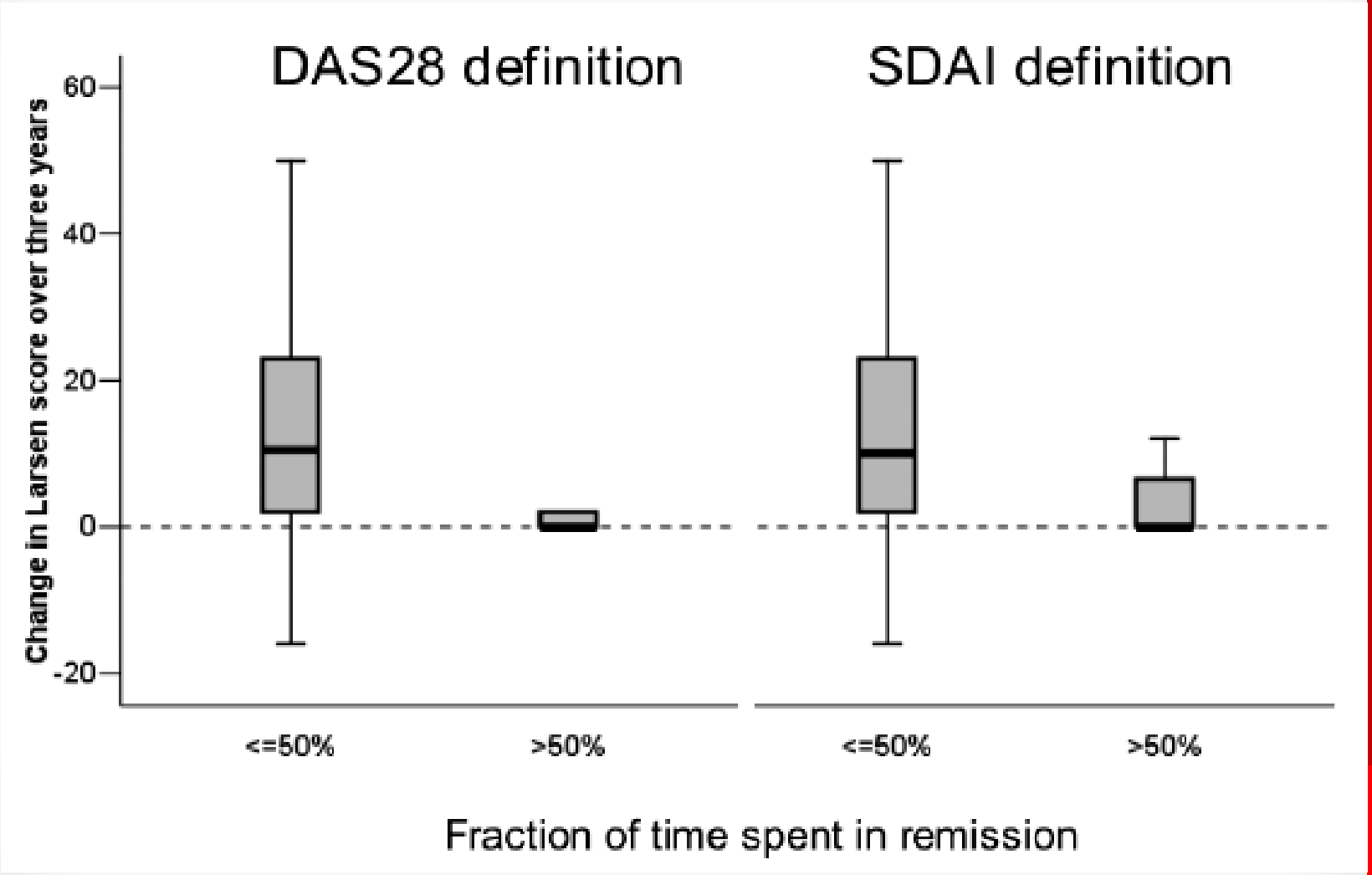
- Morte
- Disabilità
- Interventi chirurgici di protesizzazione
- Perdita del lavoro

Misure di Outcome nell'Artrite Reumatoide

Surrogati di Outcome

- Criteri di risposta EULAR
- Criteri di risposta ACR 20, 50, 70, 90, N
- **Criteri di remissione e di bassa attività di malattia**
- Estensione del danno radiologico

Radiographic Progression in Remission

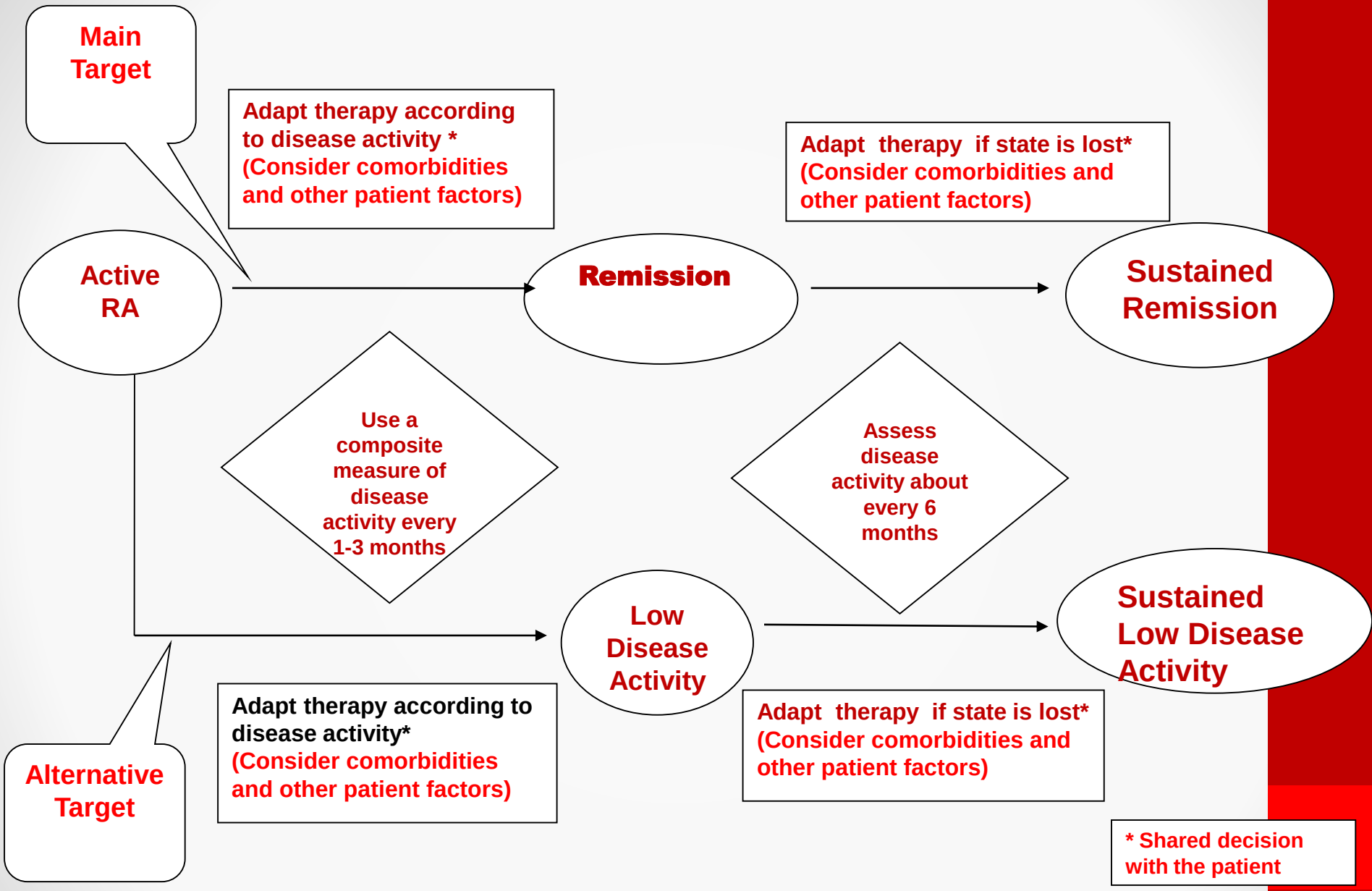


D. Aletaha et al. Clin Exp Rheumatol. 2006; 24: S-45-51.

ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS DISEASE ACTIVITY, FUNCTIONAL LIMITATION AND LONG-TERM RISK OF ORTHOPAEDIC SURGERY

- 2045 patients from 2 early arthritis inception cohorts
- 27986 person-years follow-up
- Significantly increased cumulative incidence of major surgery in patients with high and moderate disease activity
- No HAQ-DI progression in patients in remission
- Significant relationship between rising disease activity and HAQ progression in patients from Low to High Disease Activity

E Nikiphorou et al. Ann Rheum Dis 2016; March 15

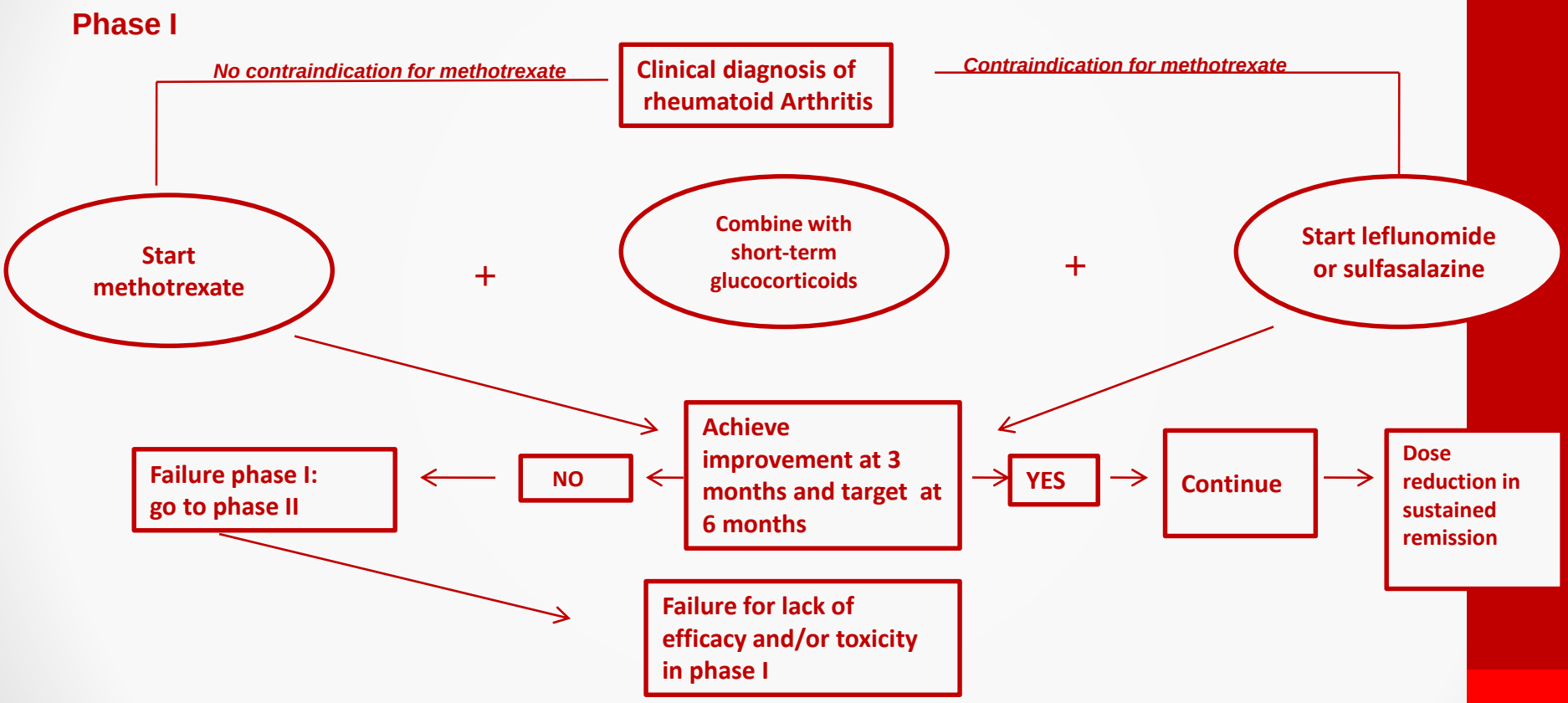


JS Smolen et al Ann Rheum Dis 2016;75: 3-15

FATTORI PROGNOSTICI NEGATIVI all'esordio

- Positività del FR e/o degli ACPA
- Alterazione degli indici di flogosi (PCR>1 mg/dl)
- N.art.tumefatte>6
- HAQ (Health Assessment Questionnaire) ≥ 1
- Presenza di danno articolare
- Sesso Femminile

Algorithm based on the 2016 European League Against Rheumatism Recommendations on rheumatoid arthritis management I



JS Smolen et al. Ann Rheum Dis 2017

CONTROINDICAZIONI ALL'USO DEL METOTREXATE

- Uso corrente di alcool (> 1 bicchiere di vino/settimana!)
- Gravidanza (o potenziale generazione di un figlio nei successivi 3 mesi)
- Infezione da HBV in assenza di profilassi antivirale
- Insufficienza renale con CrCl<10 ml/min

P Emery et al. Ann Rheum Dis 2013; 72:1897-904

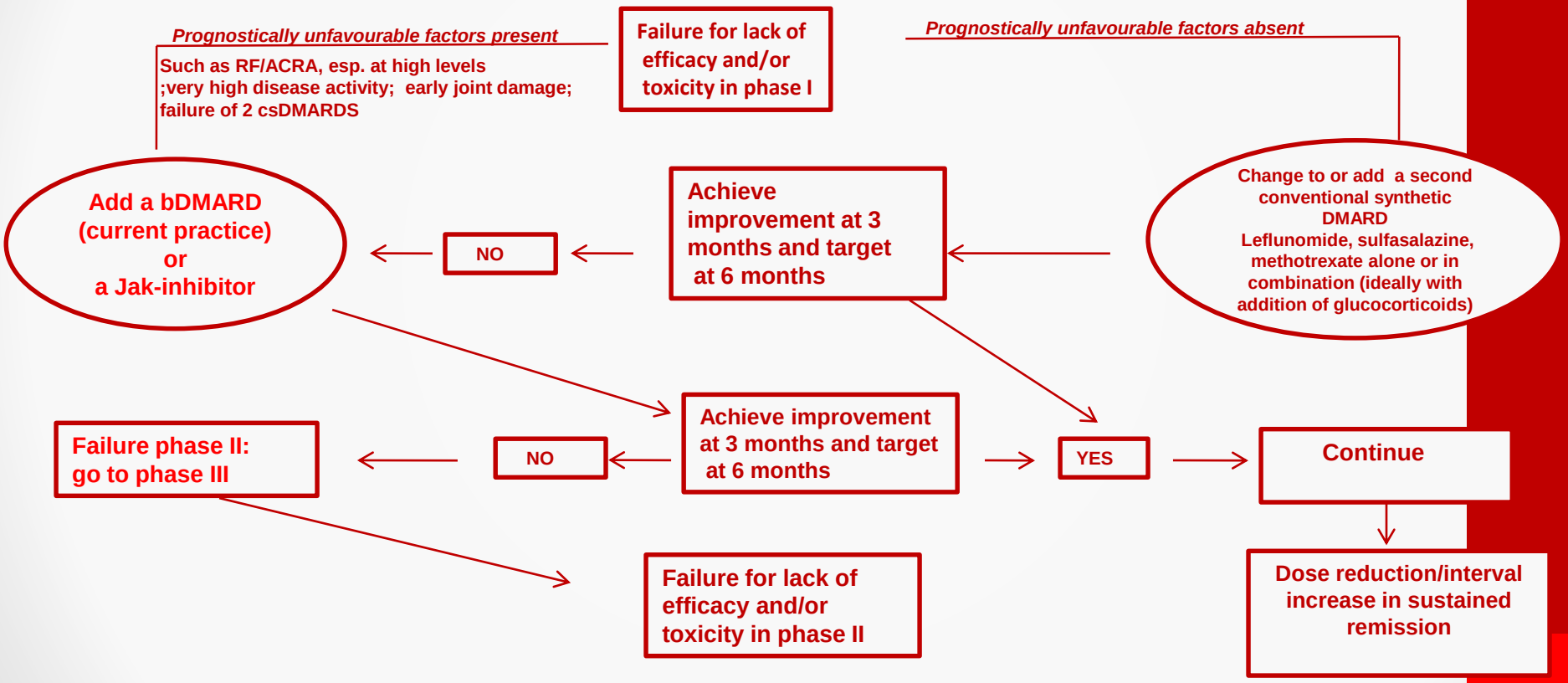
CONDIZIONI ASSOCIATE AD AUMENTATA INCIDENZA DI Ad Ev DA MTX

- **Insufficienza renale**
  (CrCl = 61-80 ml/min ↓25%; 51-60 ↓30%; 10-50 ↓50-80%)
- **Diabete Mellito**
- **Ipoalbuminemia**
- **Alterazioni radiologiche polmonari**
- **Epatite B e C attive**
- **Epatite alcoolica**
- **Obesità**

P Emery et al. Ann Rheum Dis 2013; 72:1897-904

Algorithm based on the 2016 European League Against Rheumatism recommendations on rheumatoid arthritis management II

Phase II



JS Smolen et al. Ann Rheum Dis 2017

DIMENSIONE DEL PROBLEMA

- **Il 40% dei pazienti di AR immessi in terapia con un primo farmaco biologico in RCT non soddisfa i criteri di risposta ACR20**

- **Il 50-60% dei pazienti immessi in terapia con un primo farmaco biologico in studi osservazionali e/o in registri sospende il farmaco entro i primi 5 anni**

EG Favalli et al. Autoimmunity Rev 2017

MOTIVI DEL FALLIMENTO

- Mancata risposta
- Risposta parziale non soddisfacente il raggiungimento del target
- Perdita di risposta dopo una risposta iniziale
- Comparsa di effetti collaterali

EG Favalli et al. Autoimmunity Rev 2017

OPTIONS TO BE CONSIDERED FOR THE MANAGEMENT OF THE FIRST Bio-DMARD

- *Optimization of csDMARD treatment (increasing dosage or changing route admin.)*
- *Addition of a csDMARD in patients undergoing bioDMARD monotherapy*
- *Changing the csDMARD (from MTX to LFN)*
- *Increasing bioDMARD dosage (infliximab)*

- **Switching to a second bioDMARD of the same class (cycling strategy)**
- **Swapping to a second bioDMARD of a different class**

EG Favalli et al. Autoimmunity Rev 2017

Efficacy of cycling strategy in RA patients with IR to a TNF inh

RCT

- **Golimumab (JS Smolen et al. 2009): at 14 wks ACR 20 in 35%**
- **Certolizumab (M Schiff et al. 2014): at 12 wks ACR 20 in 61.5%**
- **Certol.-Adalim. (primary non-r) (JS Smolen et al. 2016): LDA 58-62% at 12 wk**

Observational Studies and Registries

- **Metaanalysis-20 studies- 1st TNFinhIR (S Lloyd et al. 2010): EULAR resp. in 70**
- **Golimumab-1st+2nd TNFinhIR (M Manara et al. 2017): similar 2-year ret.rate**

Efficacy of bioDMARD swapping in RA patients with IR to a TNF inh

RCT

- **Abatacept (MC Genovese et al. 2005): at 24 wks ACR 20-50-70 in 50-20-10%**
- **Rituximab (SB Cohen et al. 2006): at 24 wks md-good EULAR response in 65%**
- **Tocilizumab (P Emery et al. 2008): at 24 wks ACR 20 in 50%; DAS rem. in 30%**

Observational studies and Registries

Indirect Comparison of the efficacy of biological antirheumatic drugs in RA in patients with IR to anti-TNF agent: a metaanalysis

The metanalysis of 18 trials and 1 abstract did not point out any significant difference in efficacy in TNF-in IR among Rituximab, tocilizumab, abatacept and golimumab

C Salliot et al. Ann Rheum Dis 2011

Comparative Efficacy and Safety in TNF ir as assessed by RCT indirect meta-analysis with pairwise comparison

- ✓ Indirect pairwise comparisons of abatacept, golimumab, rituximab and tolicilizumab showed no significant differences in ACR 50 and 70 at 24 weeks both after 1 and multiple TNFinh failures

- ✓ Golimumab had significantly fewer side effects

M Schoels et al. Ann Rheum Dis 2012

Comparative Efficacy and Safety of non TNF-targeted biologics vs a second anti-TNF* a 52-week RCT

- ✓ At week 24, 69% of non-TNF targeted vs 52% of second-TNF-inh treated patients exibited a good or moderate EULAR response (p= 0.004)

- ✓ At 52 weeks, 41% of non-TNF targeted vs 23% of second-TNF-inh** treated patients underwent a low disease activity state (p= 0.003)

JE Gottenberg et al. JAMA 2016

*The choise of the biologic was made by the treating physicians

** Golimumab was not a choise because of the period of enrollment

LIMITATIONS

- Salliot et al. Comparing data from different trials
  M Schoels et al. Enrollment independent from the cause of failure

- Gottenberg et al. Including all TNFinh in one category
  No patient received Golimumab
  16% only Certolizumab

- Both Enrollment in each arm independent from predictive and pathophysiologic factors

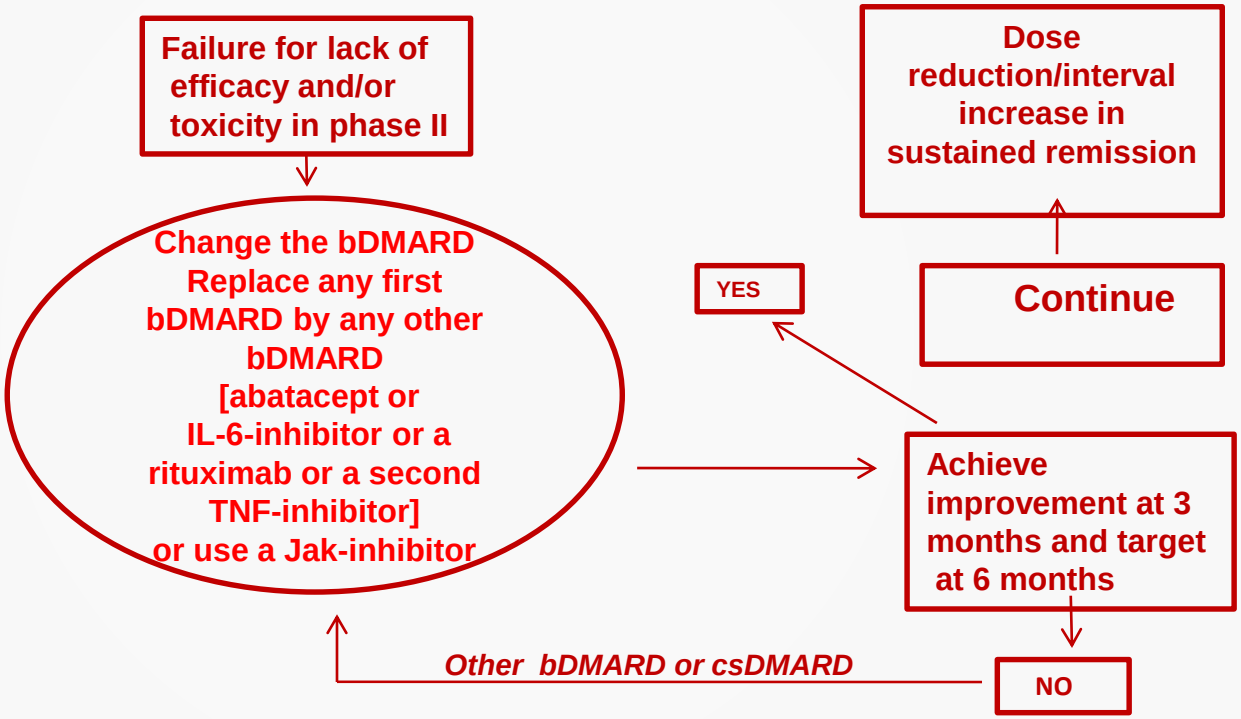
Efficacy of bioDMARD swapping in RA patients with IR to a non-TNF inh

- **S Das et al. 2014: Toci more effective than Abatacept in Rituximab IRs**

- **Pascart et al. 2016: Toci more effective in multiple non-TNFinh failures**

Algorithm based on the 2016 European league Against Rheumatism recommendations on rheumatoid arthritis management III

Phase III



JS Smolen et al. Ann Rheum Dis 2017

Settings of Efficacy of Baricitinib in Rheumatoid Arthritis

- MC Genovese et al. **Refractory Rheumatoid Arthritis** N Engl J Med 2016
- PC Taylor et al. **IR Response to Methotrexate vs Adalimumab**
  N Engl J Med 2017
- M Dougados et al. **IR or intolerance to csDMARDs**
  Ann Rheum Dis 2017
- R Fleischmann et al. **No or limited DMARD treatment**
  Arthritis Rheumatol 2017

Settings of Efficacy of Tofacitinib in Rheumatoid Arthritis

- R Fleischmann et al. **Very active-severe disease** N Engl J Med 2012
  Multiple previous drug failures
- GR Burmester et al. **Refractory Rheumatoid Arthritis** Lancet 2013
- J Kremer et al. **Inadequate csDMARD responders** Ann Int Med 2013
- EB Lee et al. **Metotrexate naive** N Engl J Med 2014
- SB Cohen et al. **Longterm extension study** Ann Rheum Dis 2017

Settings of Efficacy of Sarilumab in Rheumatoid Arthritis

- MC Genovese et al. **IR to Methotrexate** Arthritis Rheumatol 2015
- GR Burmester et al. **Sarilu. versus adalimu. Monotherapy**
  Ann Rheum Dis 2017
- R Fleischmann et al. **IR or intolerance to TNF inhs**
  Arthritis Rheumatol 2017

Updating

- **Baricitinib and Tofacitinib might (should*) be administered to patients with potentially severe rheumatoid arthritis and contraindications to MTX use**
- **Both can be used in refractory rheumatoid arthritis in association with MTX**
- **Sarilumab- a fully human MoAb antibody with a higher affinity for IL-6r than Tocilizumab- is to be considered in patients warranting IL-6 targeted treatment**

***Opinione Personale**

WHAT ABOUT JAKinhs FAILURE?

Biosimilari

- **Il biosimilare deve essere introdotto nel paziente naive e in quello in seconda linea in cui si sarebbe prescritto il corrispettivo originator**

- **"—Whilst prudent switching practices should be employed, growing safety experience accumulated thus far with CT-P13 and other biosimilars is favourable and *does not raise any specific concerns"***

J Braun, A Kudrin Biologicals 2016

SCELTA DEL BIOLOGICO
prima linea

Anti-TNFα	Abatacept	Tocilizumab	Rituximab
Pazienti sieronegativi con BMI < 25	ACPA+ Comorbidità s.c. o i.v. +MTX	RF+ Anemia refrattaria s.c. o i.v. monoterapia o + MTX	Storia di linfoma TBC latente Malattia demielinizzante i.v. +MTX
IFX i.v. + MTX Golimumab s.c. + MTX Adalimumab s.c. + MTX Etanercept s.c. + MTX o in monoterapia Certolizumab s.c. + MTX			

UOC Reumatologia- AOU Vanvitelli

SCELTA DEL BIOLOGICO
seconda o terza linea

Anti-TNFα	Abatacept	Tocilizumab	Rituximab
Anti-TNF con altro meccanismo d'azione Ab monoclonale→ Recettore o Fab Recettore o Fab→ Ab monoclonale Abatacept Tocilizumab Rituximab	Rituximab Tocilizumab Anti-TNF	Abatacept Rituximab Anti-TNF	Tocilizumab Abatacept Anti-TNF

Pz alg+ vs alg- generale

	ALG+ (38 pz)	ALG- (79 pz)	p
Risp.EULAR 3 mesi	34/38 pz (89.5%)	65/76 pz (85.5%)	**0,5**
Target a 6 mesi (R/LDA)	17/22 pz (77.3%)	45/67 pz (67.2%)	**0,37**
LDA/R 3 mesi	27/38 pz (71%)	51/76 pz (67%)	**0,6**

- Remission, R: SDAI<3.3
- Low disease activity, LDA: SDAI<11
- Risposta EULAR: miglioramento di 0.6 del DAS28CRP

26 pz alg+ vs alg- (appaiati)

	ALG+	ALG-	p
Risp.EULAR 3 mesi	25/26 pz (96.1%)	17/26 pz (65.4%)	**0,005**
Target a 6 mesi (R/LDA)	14/17 pz (82.3%)	13/25 pz (52%)	**0,05**
LDA/R 3 mesi	21/26 pz (80.8%)	12/26 pz (46.1%)	**0,01**

- Remission, R: SDAI<3.3
- Low disease activity, LDA: SDAI<11
- Risposta EULAR: miglioramento di 0.6 del DAS28CRP