PARE – Web-meeting december 2017

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UMC Utrecht

ITEMS TO DISCUSS

- NEW GUIDELINES 2016
- Q & A
- NEW BIOLOGICALS / BIOSIMILARS
- Q & A
- NEWS ON GLUCOCORTICOIDS
- Q & A
- JAK-inhibitors
- Q & A

ITEMS TO DISCUSS

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Process of recommendations

- Proposal to EULAR by convenor and epidemiologist
- Selection of the group (15–20): rheumatologists, epidemiologist, research fellow(s), health professional(s), patients, others as deemed relevant. Different European countries
- First meeting: presentation by fellow(s) of recent literature, discussion on present status; formulation of research questions / formulation of recommendations (Delphi method).
- Evaluation of research questions, again back to literature

Process of recommendations

- Second meeting: evidence on research questions presented; recommendations confirmed / adapted; explaining text formulated.
- Grading categories of evidence and of recommendations (Oxford Centre for Evidence Based Medicin)

- LoE = Level of Evidence (1-5)
- LoA = Level of Agreement (1-10)
- SoR = Strength of Recommendation (A – D)

Process of recommendations

Level of evidence	Study type
1a	Meta-analysis of RCT (homogeneity)
1b	RCT (with narrow confidence interval)
2a	Meta-analysis of cohort studies (homogeneity)
2b	Cohort study or low quality RCT
3	Case control studie(s)
4	Case series or poor quality cohort and case control studies
5	Expert opinion

2016 EULAR recommendations for management of early arthritis

Overarching principles

A] Management of early arthritis should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

B] Rheumatologists are the specialists that should primarily care for patients with early arthritis

C] A definitive diagnosis in a patient with early arthritis should only be made after a careful history taking and clinical examination which should also guide laboratory testing and additional procedures.

2016 EULAR recommendations for management of early arthritis

1. Patients presenting with arthritis (any joint swelling, associated with pain or stiffness) should be referred to, and seen by, a rheumatologist, within six weeks after the onset of symptoms. Ib B 9,4

2. Clinical examination is the method of choice for detecting arthritis, which may be confirmed by ultrasonography. IIb C 9,5

2016 EULAR recommendations for management of early arthritis

3. If a definite diagnosis cannot be reached and the patient has early undifferentiated arthritis, risk factors for persistent and/or erosive disease, including number of swollen joints, acute phase reactants, rheumatoid factor, ACPA and imaging should be considered in management decisions. IIb C 9,8

4. Patients at risk of persistent arthritis should be started on DMARDs as early as possible (ideally within 3 months), even if they do not fulfill classification criteria for an inflammatory rheumatological disease.

Ia A 9,4

2016 update recommendations treatment of RA with DMARDs

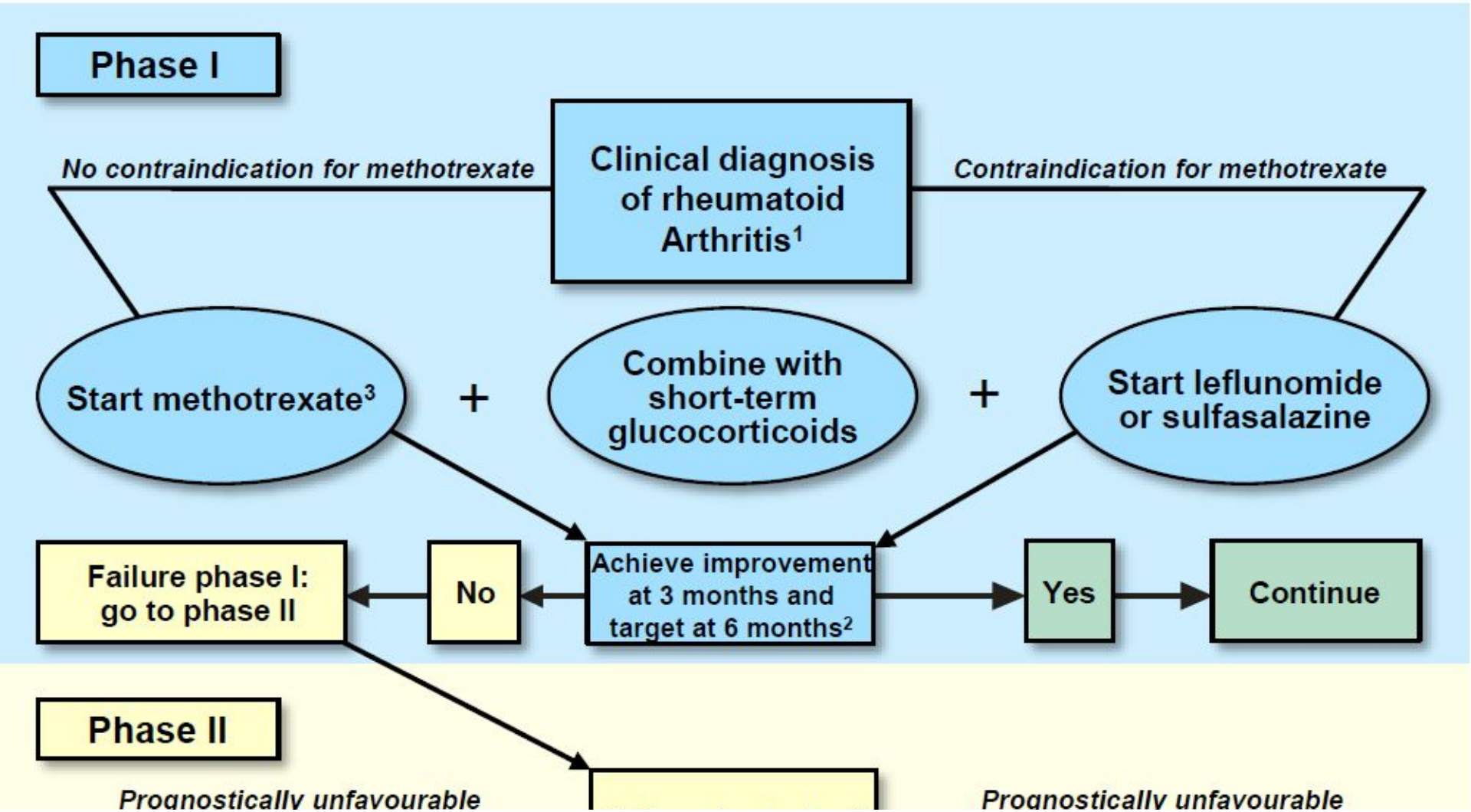
EULAR GUIDELINES UPDATE 2016:
Overarching principles

A	Treatment of RA patients 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 and other patient factors, such as progression of structural damage, comorbidities and safety issues.

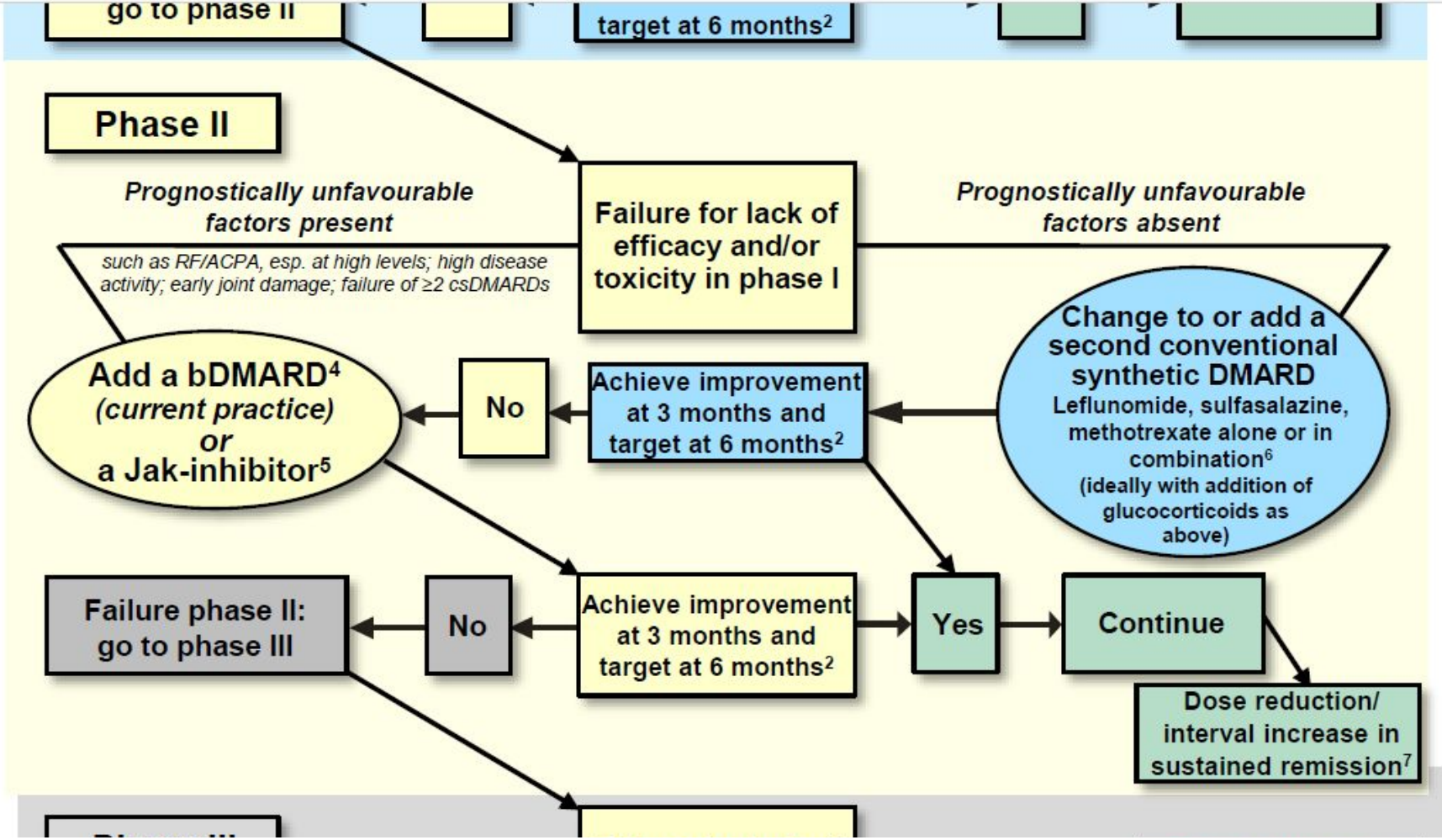
EULAR GUIDELINES UPDATE 2016: Overarching principles

C	Rheumatologists are the specialists who should primarily care for RA patients.
D	RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

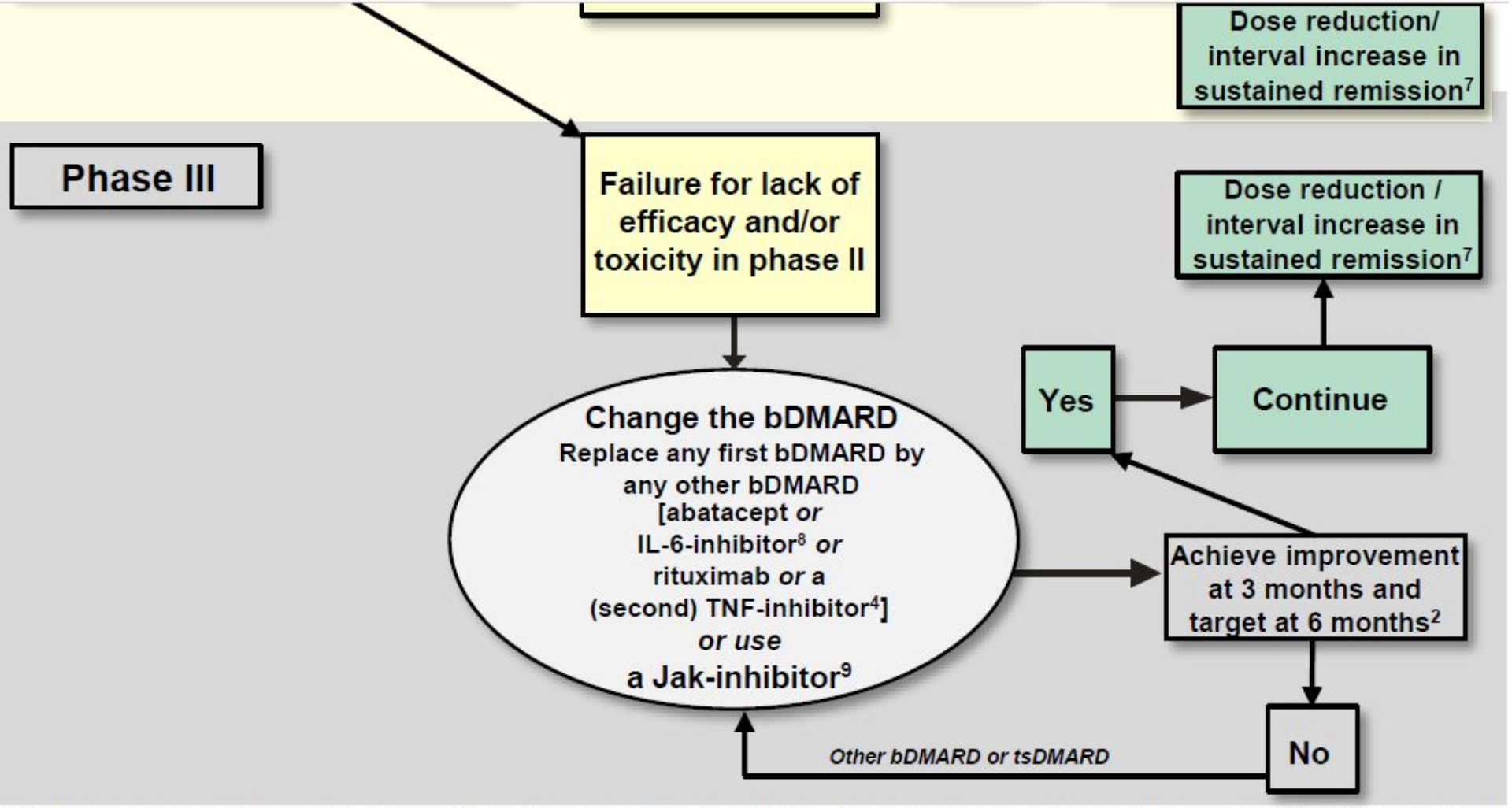
Algorithm phase I



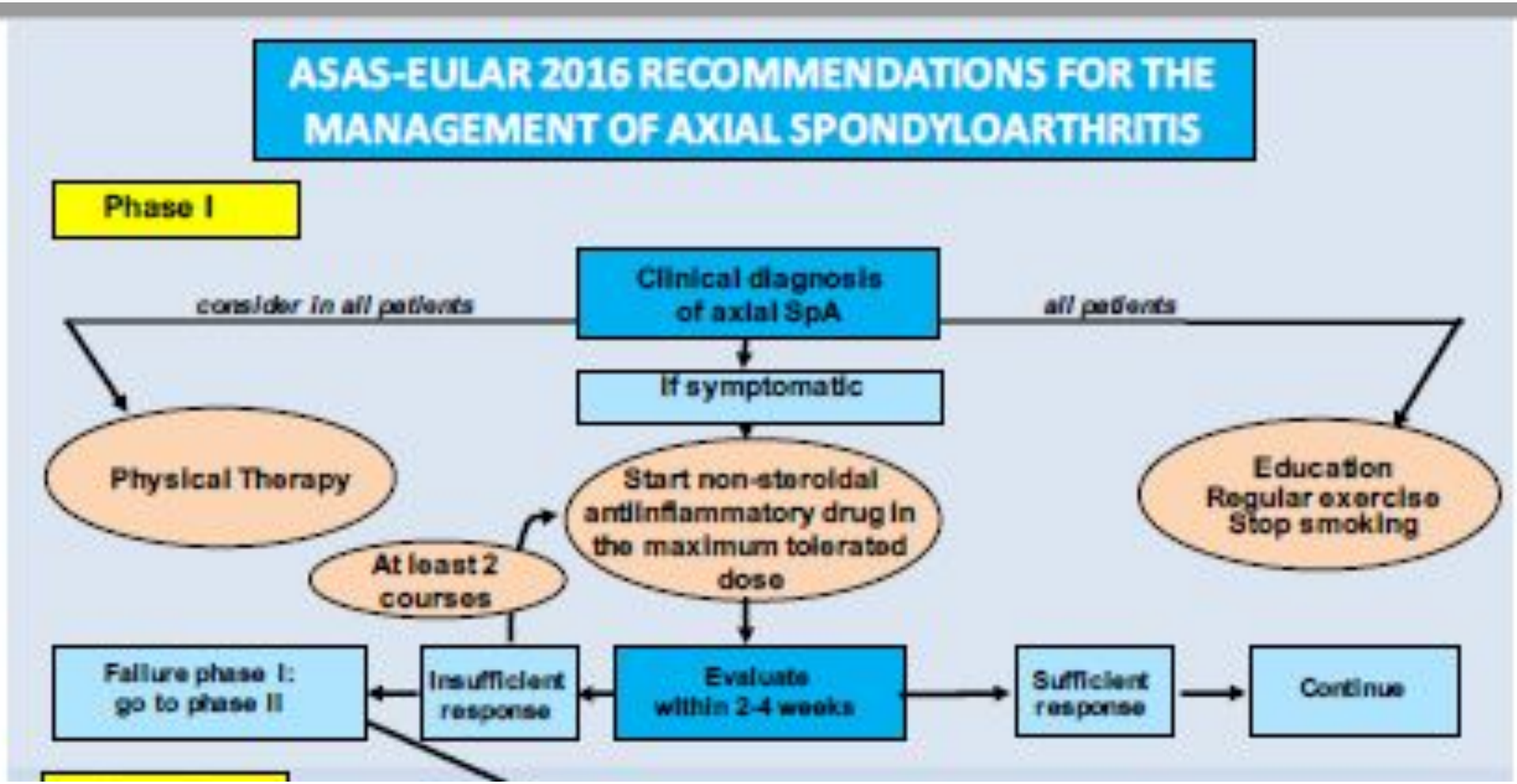
Algorithm phase II

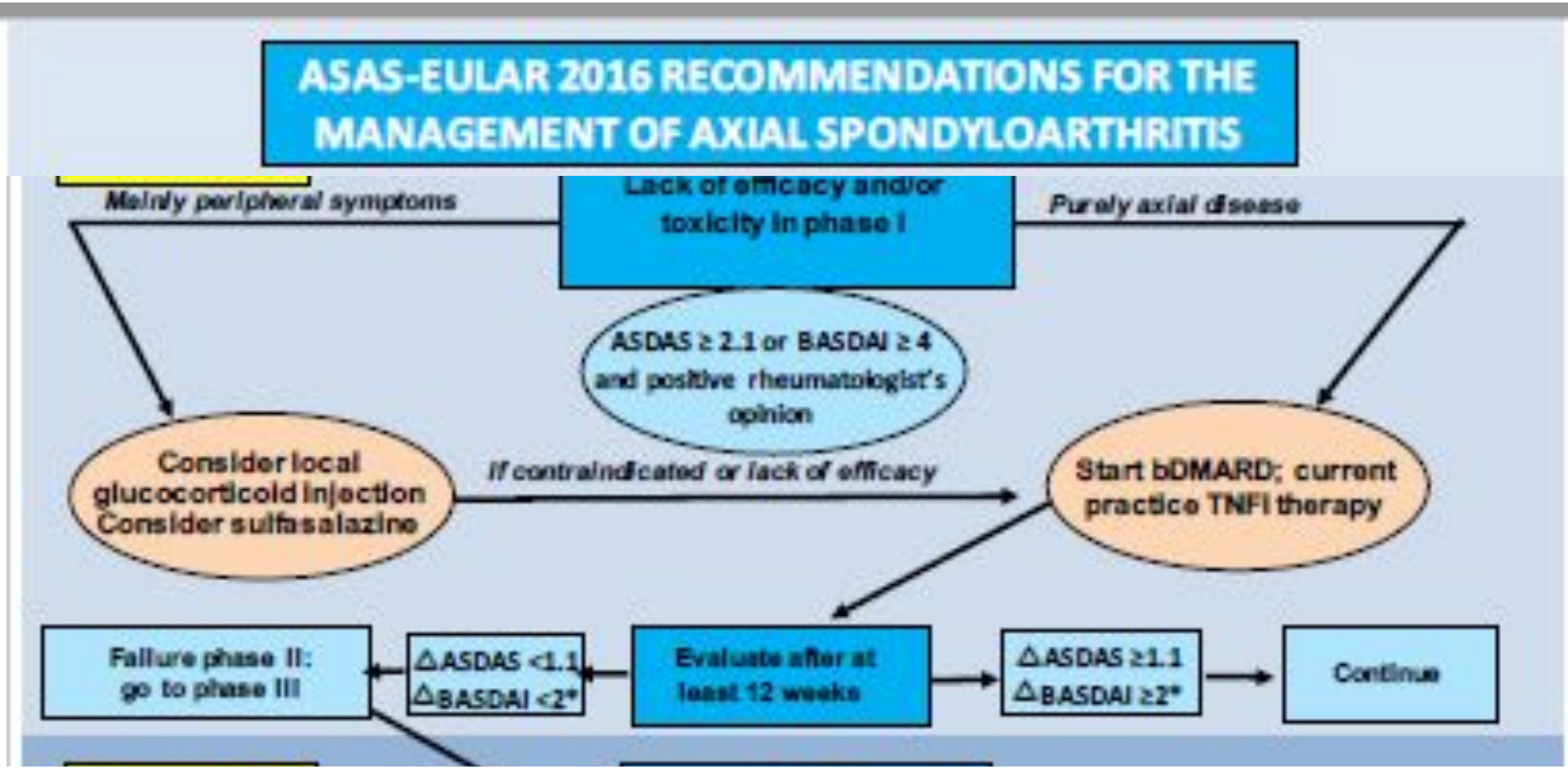


Algorithm phase III

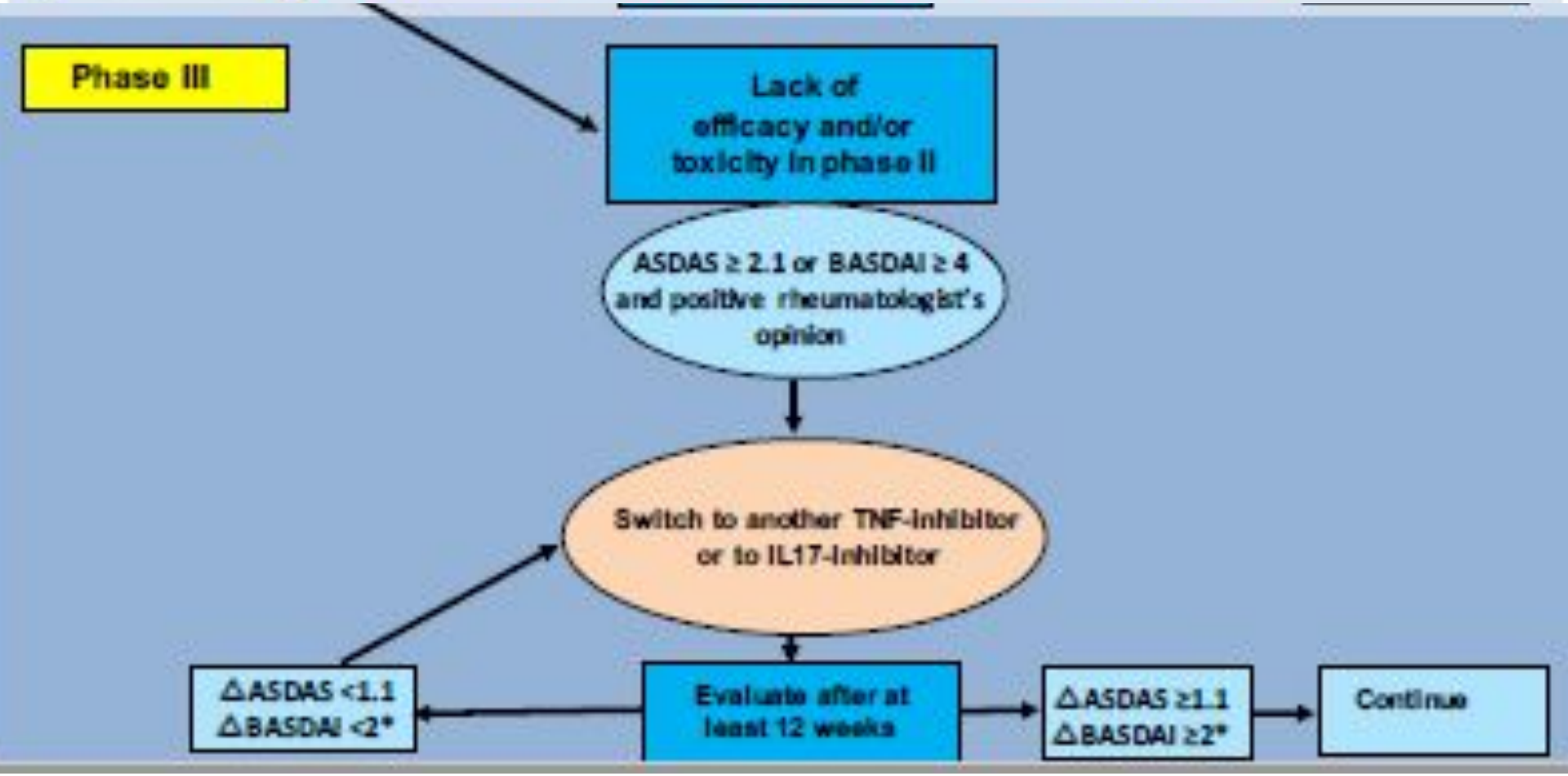


2016 update ASAS/EULAR recommendations on the management of axSpA


ASAS-EULAR 2016 RECOMMENDATIONS FOR THE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS
Phase I
Clinical diagnosis of axial SpA
consider in all patients
all patients
If symptomatic
Physical Therapy
Start non-steroidal antiinflammatory drug in the maximum tolerated dose
Education
Regular exercise
Stop smoking
At least 2 courses
Failure phase I: go to phase II
Insufficient response
Evaluate within 2-4 weeks
Sufficient response
Continue


ASAS-EULAR 2016 RECOMMENDATIONS FOR THE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS
Mainly peripheral symptoms
Lack of efficacy and/or toxicity in phase I
Purely axial disease
ASDAS ≥ 2.1 or BASDAI ≥ 4 and positive rheumatologist's opinion
Consider local glucocorticoid injection
Consider sulfasalazine
If contraindicated or lack of efficacy
Start bDMARD; current practice TNFi therapy
Failure phase II: go to phase III
ΔASDAS <1.1
ΔBASDAI <2*
Evaluate after at least 12 weeks
ΔASDAS ≥1.1
ΔBASDAI ≥2*
Continue

ASAS-EULAR 2016 RECOMMENDATIONS FOR THE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS



Recommendation 9: biological therapy

- bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (box 1); current practice is to start with TNFi therapy.

- LoE:
  - TNFi: 1a
  - IL–17: 1b

Treatment of axSpA patients with bDMARDs

- Rheumatologist's diagnosis of axial SpA

And

- Elevated CRP and/or positive MRI and/or radiographic sacroiliitis

And

- **Failure of standard treatment:**

  All patients

  At least 2 NSAIDs over 4 weeks (in total)

  Patients with predominant peripheral manifestation

  One local steroid injection if appropriate

  Normally a therapeutic trial of sulfasalazine

And

- High disease activity: ASDAS ≥ 2.1 or BASDAI ≥ 4

And

- Positive rheumatologist opinion

Continuation of bDMARDs

- Consider to continue bDMARDs if after at least 12 weeks of treatment:

- ASDAS improvement ≥ 1.1

or

- BASDAI improvement ≥ 2 (0-10)

and

- Positive rheumatologist's opinion to continue

Recommendation 10: TNFi failure

- If TNFi therapy fails, switching to another TNFi or IL17i therapy should be considered

- LoE:
  - Switch to another TNFi: 2
  - Switch to IL-17: 1b


discover
how?
where?
why
challenge
who?
QUESTIONS
clues
ask
who?
what?
when?
investigation
?
clues
how
why?
ask
knowing

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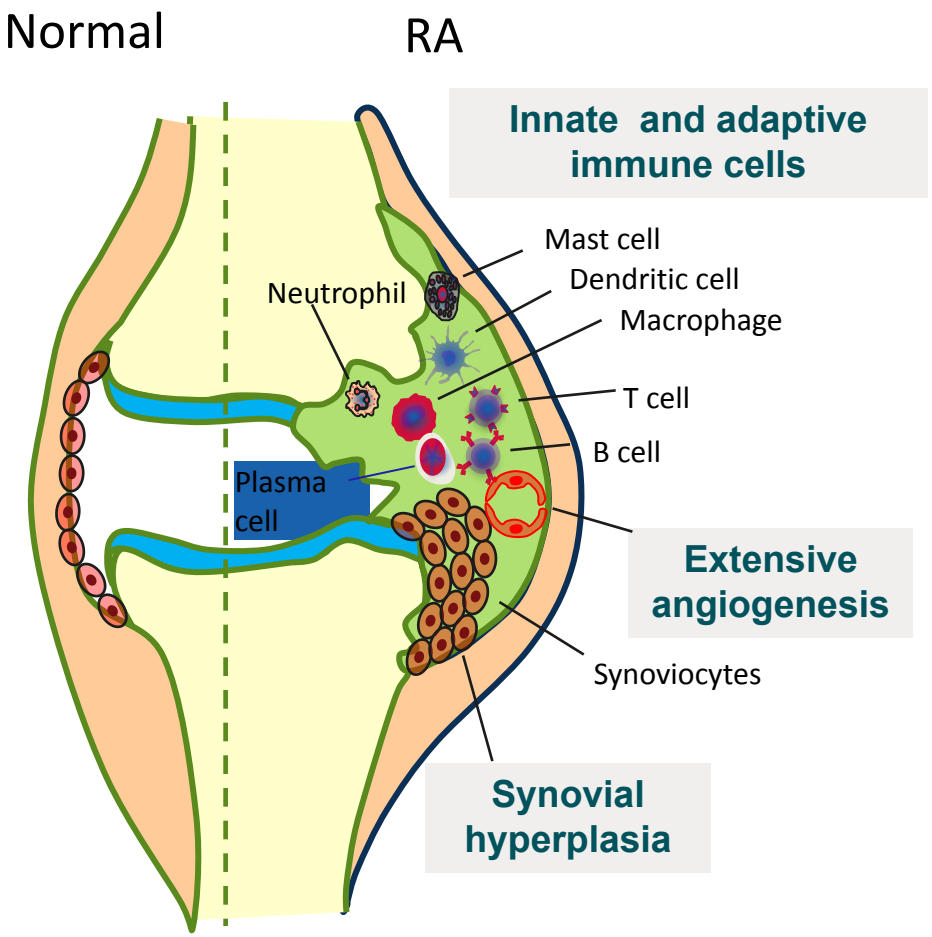
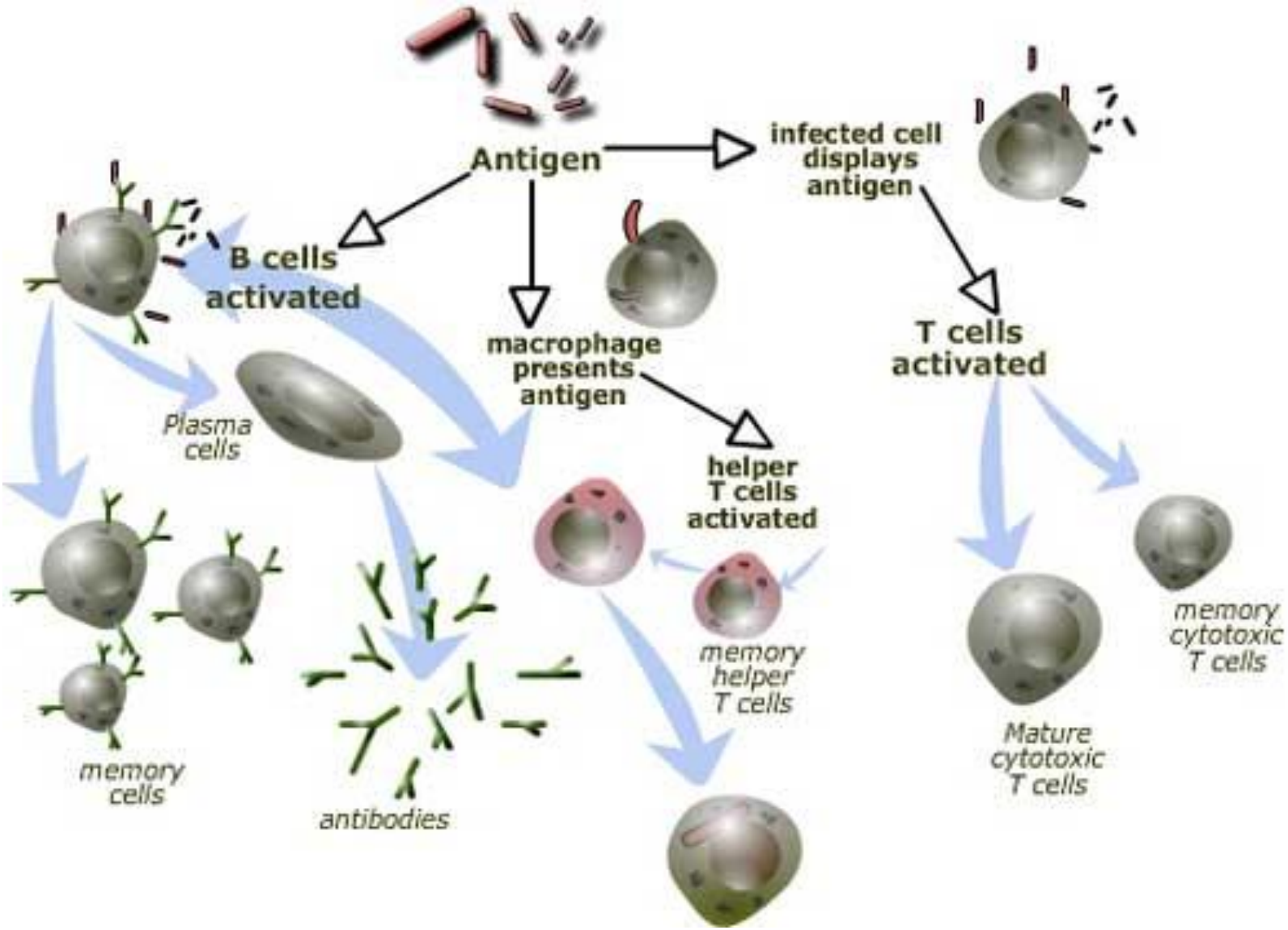
RA: Immune and Inflammatory Responses



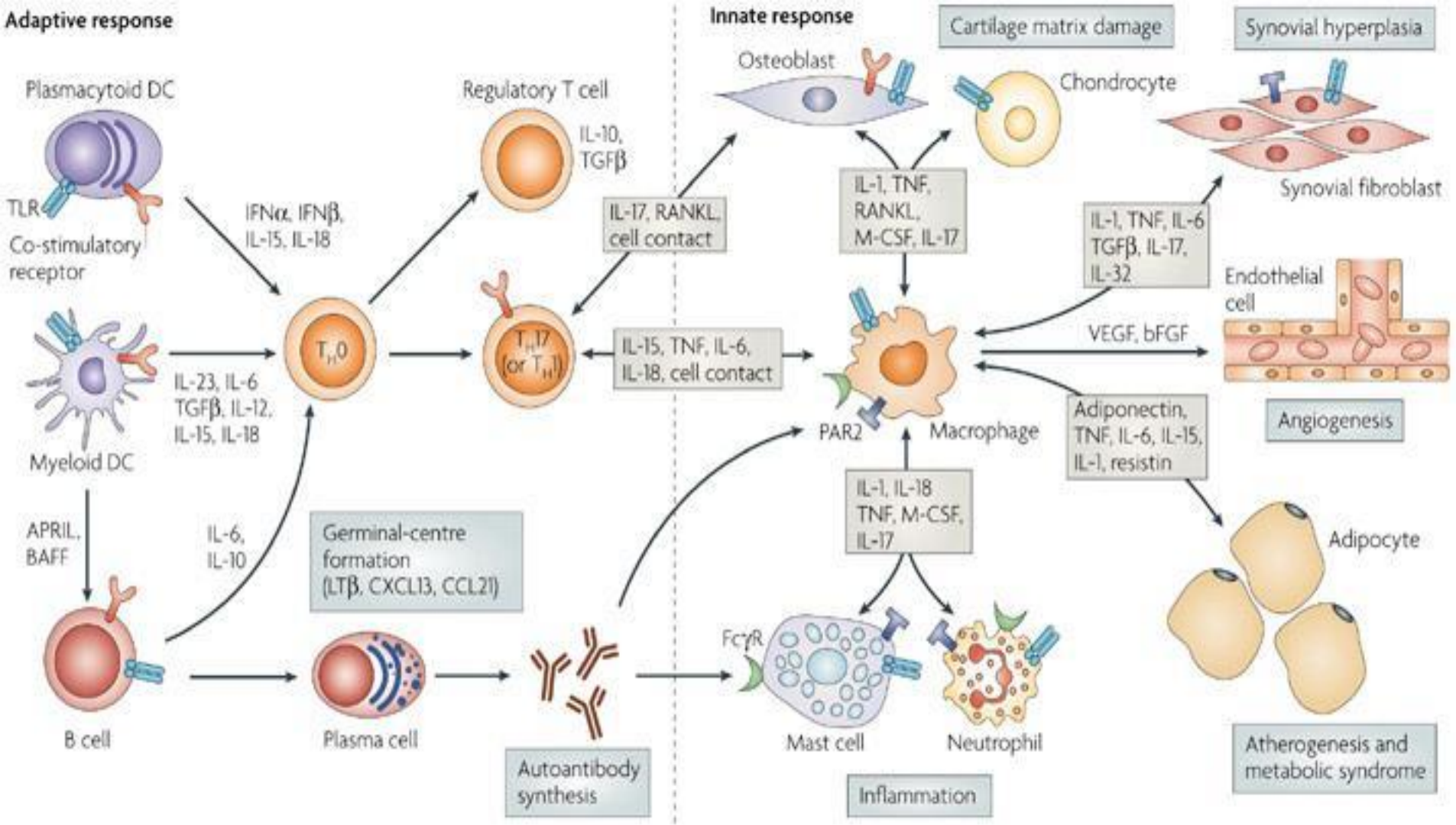
- Synovitis: inflammation of the synovial membrane that invades and destroys adjacent cartilage and bone[1]
- Characterized by[2]:
  - enhanced influx of immune cells
  - increased angiogenesis
  - synovial hyperplasia

1. Otero M, et al. *Arthritis Res Ther.* 2007:9;220; 2. Schett G, et al. *Arthritis Rheum.* 2008;58:2936-2948.
Figure adapted from Strand V, et al. *Nat Rev Drug Disc.* 2007;6:75-92.

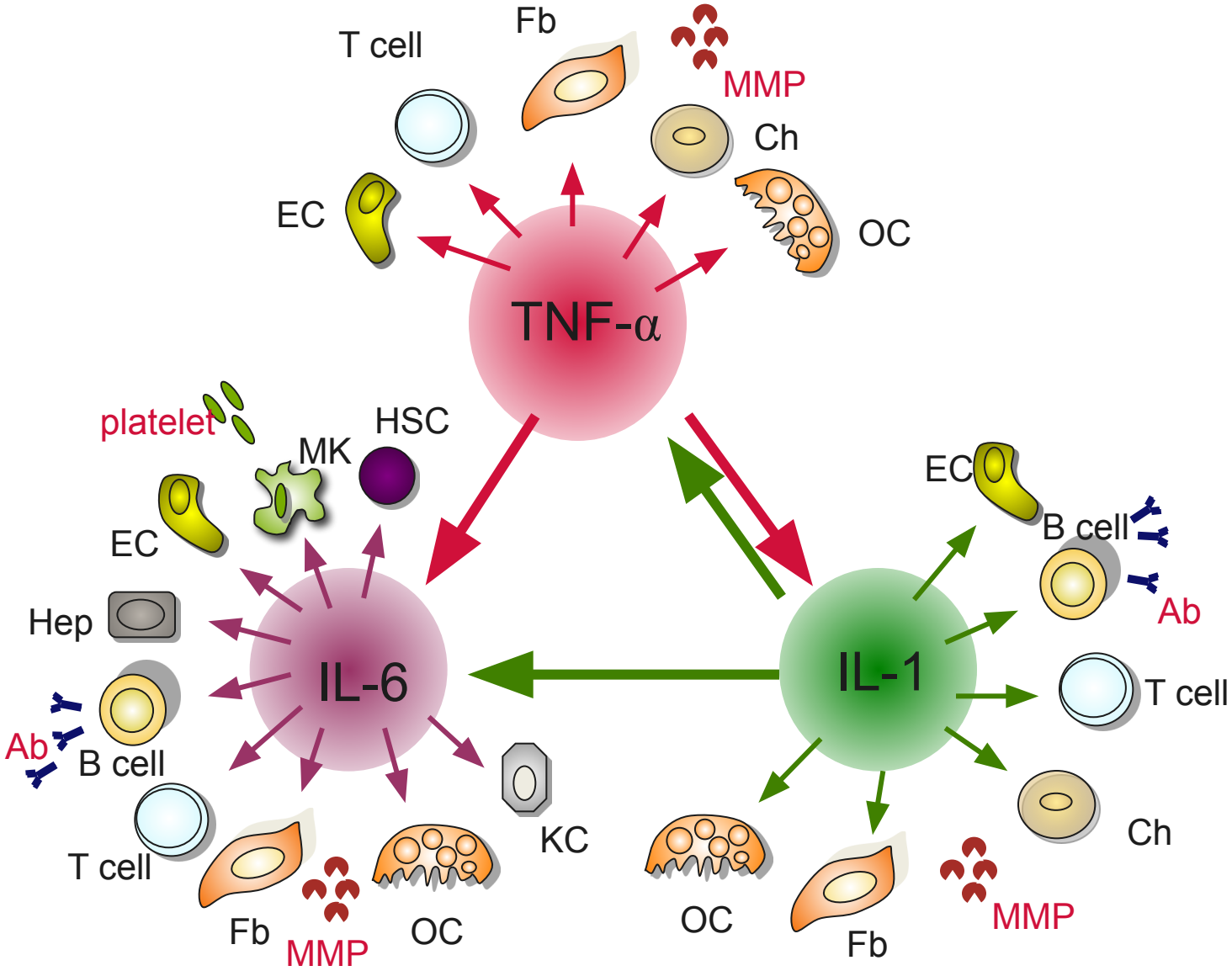
Different immune cells



Cytokine mediated synovial interaction



Proinflammatory cytokines



Cytokines implicated

Cytokine	Articular cell expression	Potential functions in the pathogenesis of rheumatoid arthritis
IL-1α and/or IL-1β	Monocytes, B cells, synovial fibroblasts, chondrocytes	↑Synovial fibroblast cytokine, chemokine, MMP, iNOS and PG release; ↑monocyte cytokine, ROI and PG release; ↑osteoclast activation; ↓GAG synthesis, ↑NO, ↑MMP and collagenase; endothelial-cell adhesion molecule expression
IL-18	Monocytes, PMNs, DCs, platelets, endothelial cells	T-cell differentiation (T_H1 cells with IL-12; T_H2 cells with IL-4); NK-cell activation, cytokine release and cytotoxicity; ↓chondrocyte GAG synthesis, iNOS expression; monocyte cytokine release and adhesion molecule expression; PMN activation, cytokine release and migration; pro-angiogenic for endothelial cells
TNF	Monocytes, T cells, B cells, NK cells, PMNs, mast cells, synovial fibroblasts, osteoblasts	↑Monocyte activation, cytokine and PG release; ↑PMN priming, apoptosis and oxidative burst; T-cell apoptosis, clonal regulation and TCR dysfunction; ↑endothelial-cell adhesion molecule expression, cytokine release; ↓synovial fibroblast proliferation and collagen synthesis, ↑MMP and cytokine release; ↑adipocyte FFA release; endocrine effects
LTα and/or LTβ	T cells, monocytes, synovial fibroblasts	Peripheral lymphoid organ development; otherwise similar bioactivities to TNF
RANKL	Stromal cells, osteoblasts, T cells	Stimulates bone resorption via osteoclast maturation and activation; modulates T-cell–DC interactions
BAFF	Monocytes, T cells, DCs	B-cell proliferation, antibody secretion, isotype switching and survival; T-cell co-stimulation
APRIL	Monocytes, T cells	B-cell proliferation
IL-17A	T_H17 cells, synovial fibroblasts	↑Synovial fibroblast cytokine and MMP release; osteoclastogenesis; haematopoiesis; ↓chondrocyte GAG synthesis; ↑leukocyte cytokine production
IL-12	Macrophages, DCs	T_H1-cell proliferation and maturation; T-cell and NK-cell cytotoxicity; B-cell activation
IL-23	Macrophages, DCs	T_H17-cell proliferation
IL-7	Synovial fibroblasts, monocytes?	T-cell expansion and survival; macrophage activation; haematopoietic regulation; thymic regulation; NK-cell maturation
IL-15	Monocytes, synovial fibroblasts, mast cells, B cells, PMNs, DCs	T-cell chemokinesis, activation and memory maintenance; B-cell differentiation and isotype switching; NK-cell activation and cytotoxicity; synovial fibroblast activation; macrophage activation/suppression (dose dependent); PMN activation, adhesion molecule expression and oxidative burst
IL-10	Monocytes, T cells, B cells DCs, epithelial cells	↑Macrophage cytokine release, iNOS and soluble receptor expression, ↓ROI; T-cell cytokine release, ↓MHC expression, anergy induction, T_{Reg}-cell maturation and effector function(?); ↓DC activation and cytokine release; ↓synovial fibroblast MMP and collagen release; ↑B-cell isotype switching
IL-6	Monocytes, synovial fibroblasts, B cells, T cells	B-cell proliferation and antibody production; haematopoiesis and thrombopoiesis; T-cell proliferation, differentiation and cytotoxicity; ↑hepatic acute-phase response; ↑neuroendocrine effects
Oncostatin M	Monocytes, activated T cells	Megakaryocyte differentiation; ↑synovial fibroblast TIMP and cytokine release, ↑acute-phase reactants, ↑protease inhibitors; ↓monocyte TNF release, ↓IL-1 effector function; ↑neuroendocrine effects and corticosteroid release; osteoblast modulation(?)
TGFβ	Synovial fibroblasts, monocytes, T cells, platelets	Wound repair, matrix maintenance and fibrosis; T_H17- and T_{Reg}-cell proliferation; ↓NK-cell proliferation and effector function; initial activation then suppression of inflammatory responses; ↑early phase leukocyte chemoattractant, gelatinase and integrin expression; early macrophage activation then suppression; ↓ iNOS expression
BMP family (BMP2–BMP15)	Epithelial cells, synovial fibroblasts, mesenchymal embryonic tissues	Regulate crucial chemotaxis, mitosis and differentiation processes during chondrogenesis and osteogenesis; tissue morphogenesis
PDGF	Platelets, macrophages, endothelial cells, synovial fibroblasts	Paracrine and/or autocrine growth factor for various lineages; wound healing
FGF family	Synovial fibroblasts, monocytes	Growth and differentiation of mesenchymal, epithelial and neuroectodermal cells
VEGF	Monocytes, endothelial cells, synovial fibroblasts	Angiogenesis
IL-32	Epithelial cells, monocytes(?), synovial fibroblasts(?)	Macrophage cytokine, PG and MMP release
MIF	Macrophages, activated T cells, synovial fibroblasts	↑Macrophage phagocytosis, cytokine and NO release; T-cell activation, DTH; fibroblast proliferation, COX expression, PLA_2 expression and intrinsic oxidoreductase activity ('cytozyme')
Type I IFNs	Widespread	Antiviral response; broad immunomodulatory effects; ↑MHC expression; macrophage activation; lymphocyte activation, differentiation, survival (antiproliferative) and cytoskeletal alterations

This table is adapted and updated from several tables contained in REF. 129. APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BMP, bone morphogenetic protein; COX, cyclooxygenase; DTH, delayed-type hypersensitivity; DC, dendritic cell; FFA, free fatty acid; FGF, fibroblast growth factor; GAG, glycosaminoglycans; IFN, interferon; IL, interleukin; iNOS, inducible nitric-oxide synthase; LT, lymphotoxin; MIF, macrophage migration-inhibitory factor; MMP, matrix metalloproteinase; NK, natural killer; PDGF, platelet-derived growth factor; PG, prostaglandin; PLA_2, phospholipase A_2; PMN, polymorphonuclear leukocyte; RANKL, receptor activator of nuclear factor-κB (RANK) ligand; ROI, reactive oxygen intermediate; TCR, T-cell receptor; TGFβ, transforming growth factor-β; T_H, T helper; TIMP, tissue inhibitor of MMPs; TNF, tumour-necrosis factor; T_{Reg}, regulatory T; VEGF, vascular endothelial growth factor.

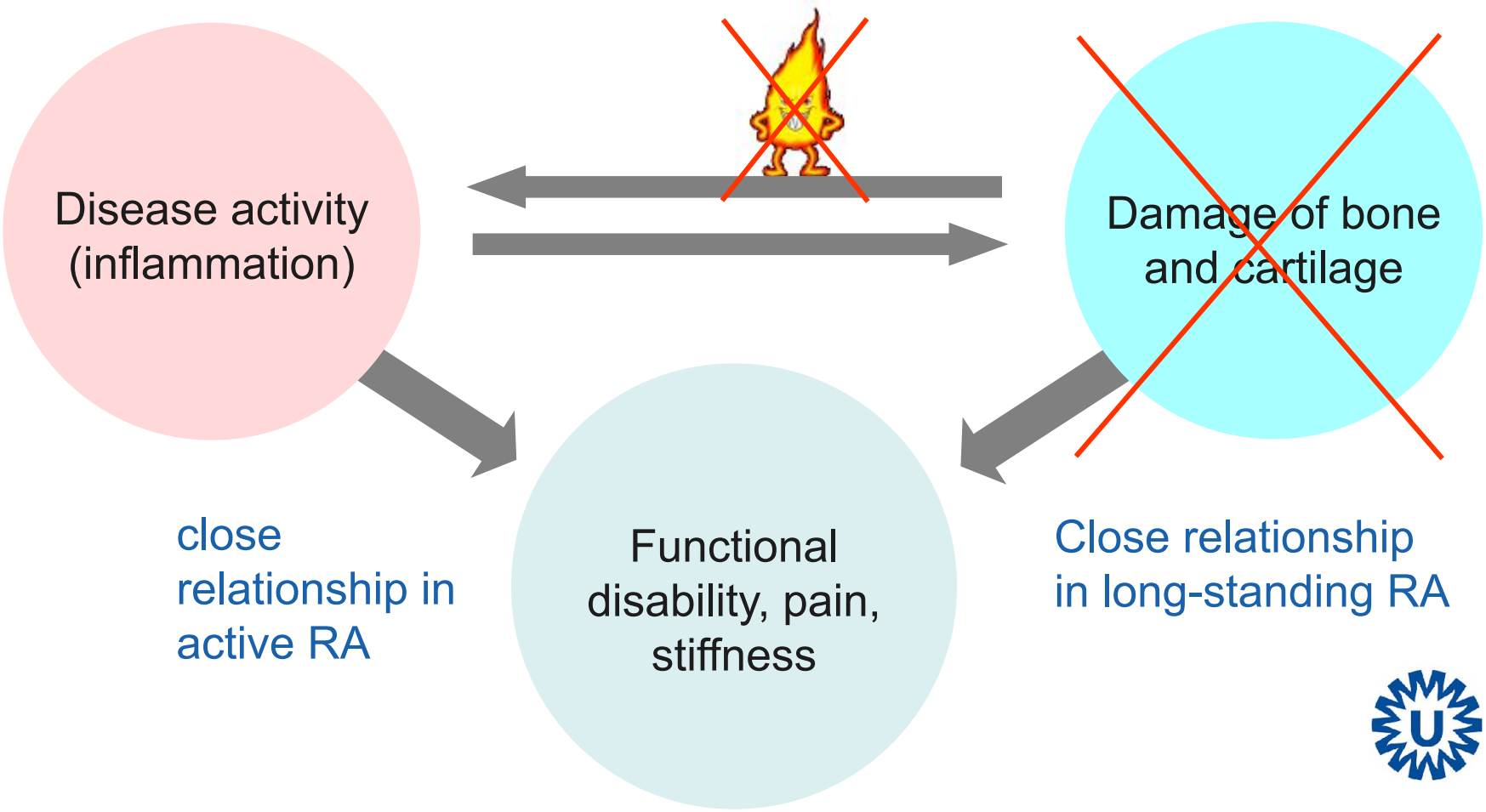
Therapeutic targets

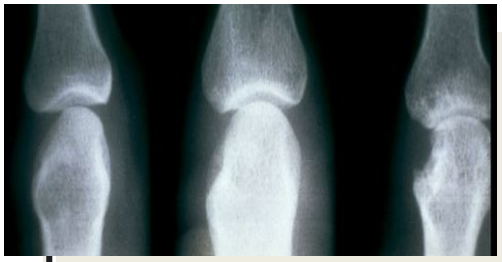
Cytokine	Advantages as a target	Disadvantages as a target	Development stage	Agent(s)
TNF	Plausible bioactivity *in vitro* and in models; validated clinical target; efficacy in approx 70% of recipients	Infection risk (such as tuberculosis); possible increased malignancy	Widespread clinical use	Infliximab*, adalimumab‡ (TNF-specific antibodies); etanercept§ (TNF receptor–Fc fusion protein)
IL-1	Plausible bioactivity *in vitro* and in models; particular role in matrix degradation	Limited efficacy in clinical trials; infection risk	Licensed for clinical use	Anakinra¶ (recombinant IL-1RA)
IL-6	Plausible bioactivity *in vitro* and in models; good efficacy so far in clinical trials	Essential role in host defence? Lipid and vascular modification?	Phase III clinical trials	Tocilizumab# (IL-6-receptor-specific antibody)
IL-12 or IL-23	Plausible bioactivity in models; role in T_H1- and/or T_H17-cell expansion; role in breach of tolerance?	Limited investigation in synovial biology; essential role in host defence?	Pre-clinical or proof of concept	Antibodies specific for p40, antibodies specific for p19
IL-15	Plausible bioactivity *in vitro* and in models; trends to efficacy in early clinical trials; role in breach of tolerance?	Essential role in host antiviral responses? Essential role in NK-cell biology?	Phase II clinical trials	AMG714**
GM-CSF	Plausible bioactivity *in vitro* and in models	Unclear hierarchical priority in rheumatoid arthritis	Pre-clinical or proof of concept	Antibody specific for cytokine or receptor
IL-17	Plausible bioactivity *in vitro* (synergy with TNF); key role in rodent models of autoimmunity	Human biology requires clarification; essential role in host defence?	Phase I clinical trials	Antibody specific for cytokine
IL-18	Plausible bioactivity *in vitro*	Ambiguous *in vivo* targeting; essential role in host defence?	Phase I clinical trials	Antibody specific for cytokine, IL-18-binding protein

*Remicade; Centocor. ‡Humira; Abbott Laboratories. §Enbrel; Amgen, Wyeth. ¶Kineret; Amgen. #Actemra; Chugai, Roche. **Amgen. GM-CSF, granulocyte/macrophage colony-stimulating factor; IL, interleukin; IL-1RA, IL-1 receptor antagonist; NK, natural killer; T_H, T helper; TNF, tumour-necrosis factor.

Window of opportunity

Therapy early in the course of RA may alter the disease process and outcome...





Disability
Radiographs
Inflammation
Severity (arbitrary units)
0
5
10
15
20
25
30

THE U-ACT-EARLY STRATEGY STUDY: RAPID AND SUSTAINED REMISSION IN EARLY RA, TREATED TO TARGET WITH TOCILIZUMAB, METHOTREXATE, OR COMBINATION

JWJ Bijlsma,[1] PMJ Welsing,[1] TG Woodworth,[2] LM Middelink,[3] C Bernasconi,[4] MEA Borm,[5] FPJ Lafeber,[1] JWG Jacobs[1]

[1]Universitair Medisch Centrum, Utrecht, Netherlands; [2]David Geffen School of Medicine, Los Angeles, United States; [3]Middelinc, Utrecht, Netherlands; [4]Roche, Basel, Switzerland; [5]Roche Nederland BV, Woerden, Netherlands

Lancet, on line

Study design:

- Multicenter, randomized, 3 parallel arms, double-blind, placebo-controlled, 2-year study

Primary Objective:

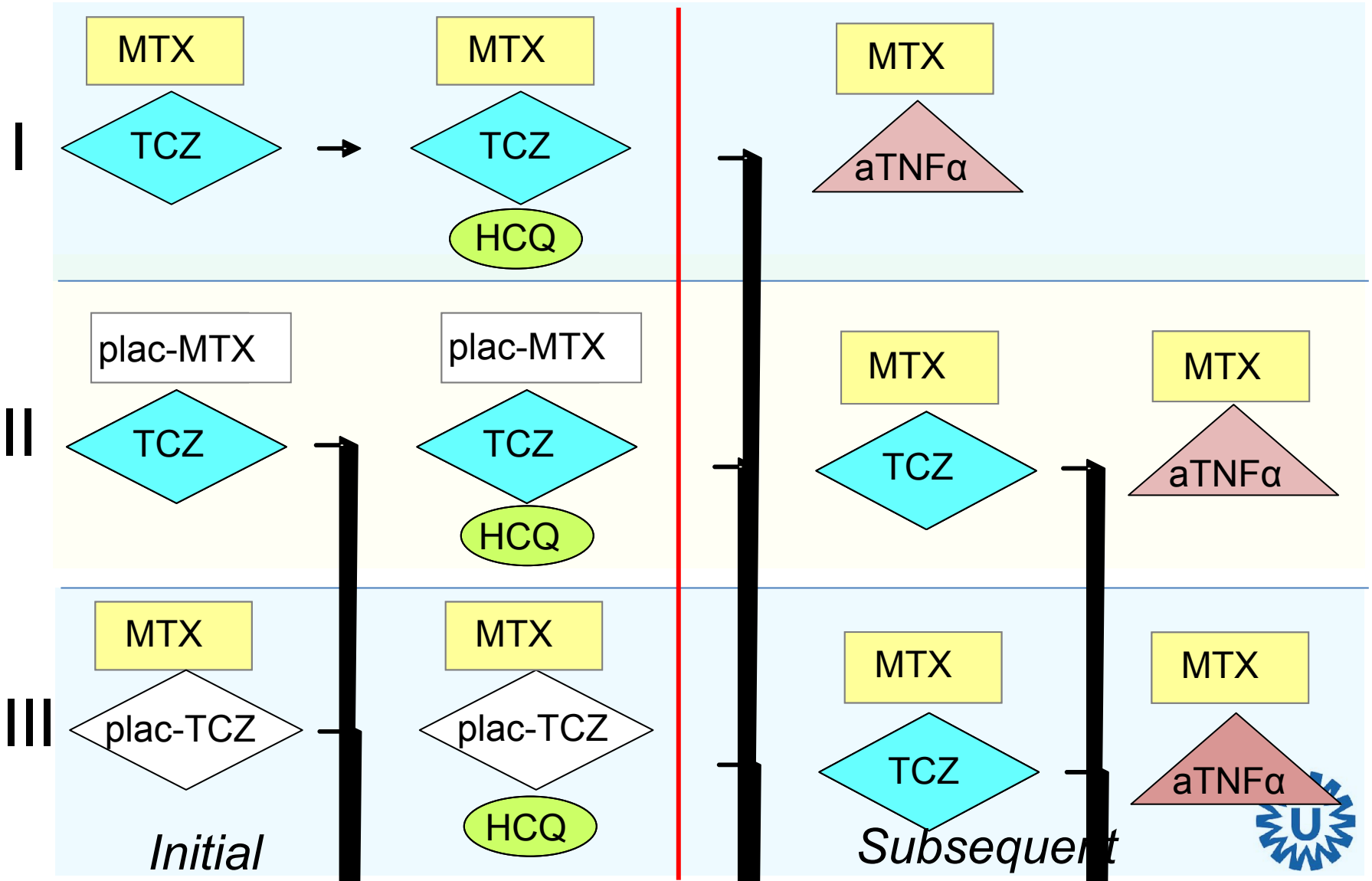
- To assess efficacy of TCZ + MTX and TCZ monotherapy versus MTX monotherapy in patients with early RA as measured by **sustained remission(SR)**, defined as a DAS28 <2.6 for ≥24 weeks and the number of swollen joints ≤ 4.

Secondary Objectives:

- To assess
  - DAS28/CDAI/SDAI and ACR20/50/70/90 scores over time
  - Functional disability (DC-HAQ), quality of life over time
  - Safety

Bijlsma JWJ et al, Lancet 2016

Treatment Strategies



Bijlsma JWJ et al. Lancet 2016

Tight control strategy: T2T

Initial regimen:

- MTX or placebo-MTX: start 10 mg once weekly; increased every four weeks by 5 mg up to max 30 mg/week until DAS28 remission or dose-limiting toxicity
  - Folic acid 5 mg twice a week to prevent MTX toxicity

- TCZ or placebo-TCZ intravenously every 4 weeks in a fixed dose of 8mg/kg (maximum of 800mg)

- Hydroxychloroquine 200 mg b.i.d added in case maximum MTX/placebo-MTX tolerated dose without DAS28 remission

Bijlsma JWJ et al, Lancet 2016

Step-down Therapy (when SR achieved)

- MTX/placebo-MTX reduced 5mg/wk every 4 wks down to 10mg/wk and then stopped 4 wks later as long as SR persisted

- If 4 weeks thereafter SR persisted:
- - TCZ and placebo-TCZ were decreased to 4mg/kg
- for 12 wks and stopped thereafter

Bijlsma JWJ et al, Lancet 2016

Baseline demographics

	TCZ+MTX N=106	TCZ+PBO N=103	MTX+PBO N=108
Females %	61	76	64
RF/ACPA pos. %	75	76	86
Mean age, years	53	55	52
Median disease duration, days	25	26	27
Mean DAS28	5.2	5.3	5.1
Median TJC 28	6	7	7
Median SJC 28	7	7	6
Median ESR mm/1hr	24	27	25
Mean VAS	58	58	56
Mean HAQ	1.1	1.3	1.1

Bijlsma JWJ et al, Lancet 2016

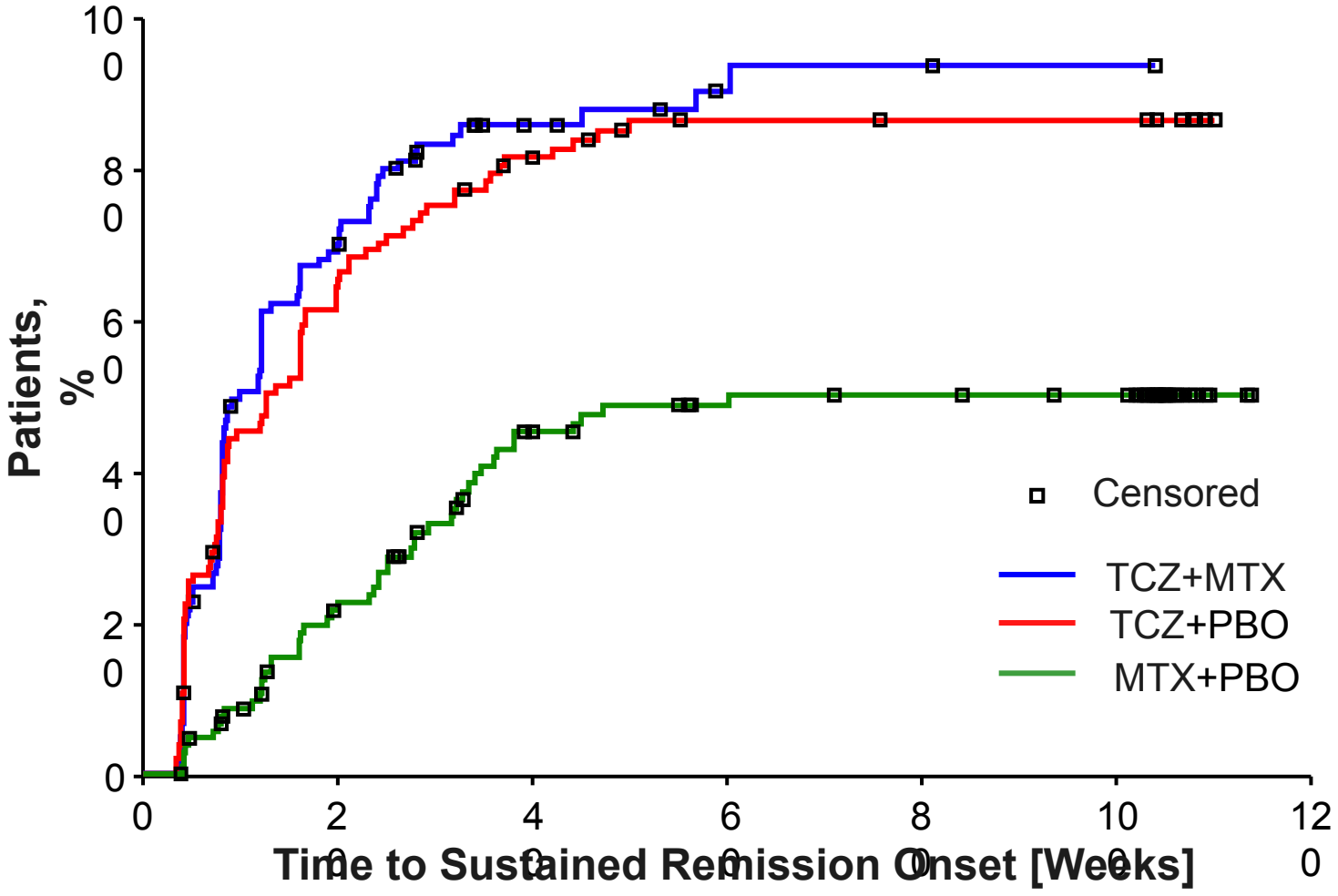
Primary Endpoint:
SR – initial regimen (ITT)

	TCZ+MTX	TCZ+PBO	MTX+PBO
Primary endpoint			
SRR_{inireg} , % (n/N)	**85.8** (91/106)	**83.5** (86/103)	**44.4** (48/108)

***Duration SR_{inireg} ,** *median wks (min, max)*	***60.9*** *(24.0,108.0)*	***64.5*** *(24.0,106.6)*	***48.6*** *(22.7,102.1)*
** End of sustained remission occurs in the treatment step-down phase of the study, with MTX being the first drug tapered*			

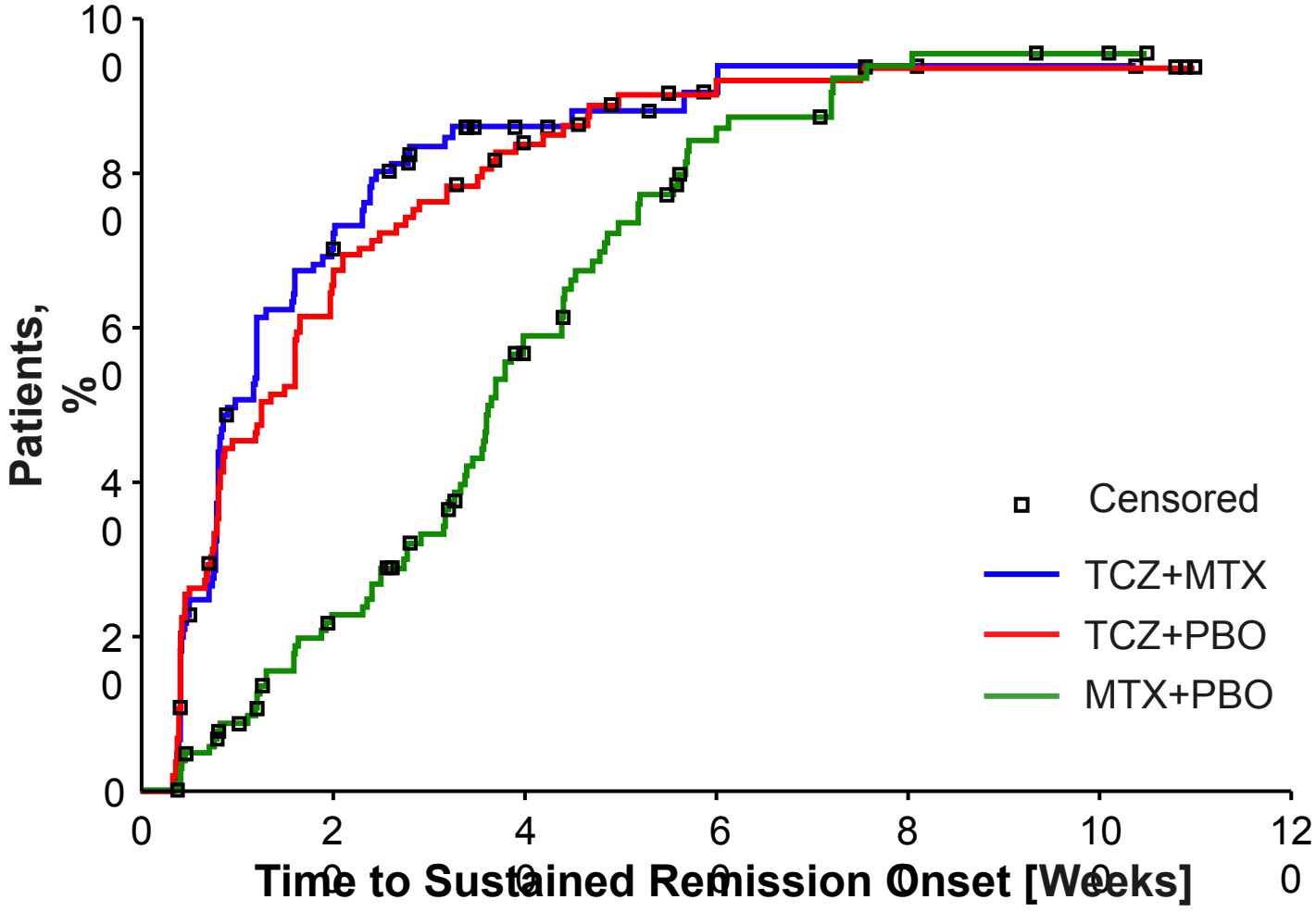
Bijlsma JWJ et al, Lancet 2016

Time to sustained remission: initial regimen



Bijlsma JWJ et al, Lancet 2016

Time to sustained remission: whole study



Bijlsma JWJ et al, Lancet 2016

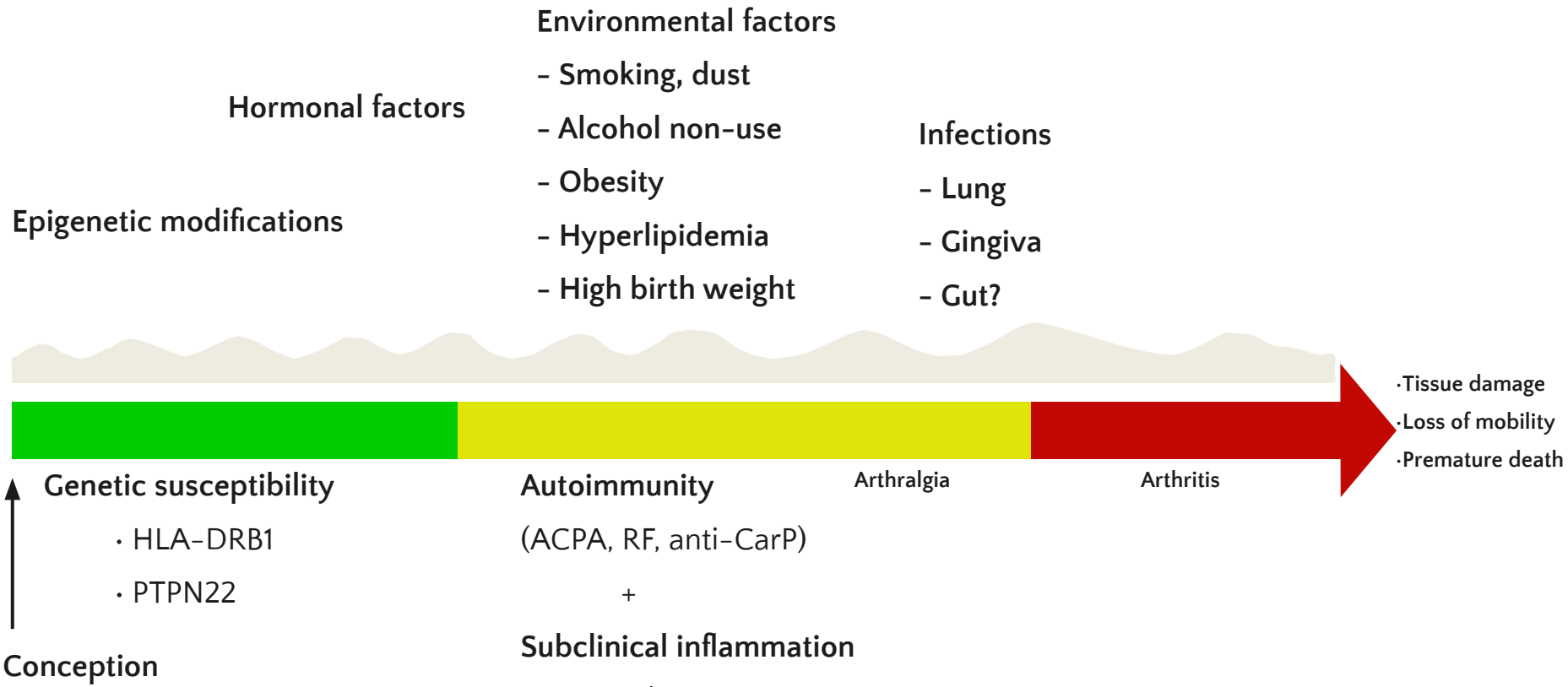
AEs of Particular Interest

Patients, n (%)	TCZ+MTX N = 106	TCZ+PBO N = 103	MTX+PBO N = 108
Serious infection	7 (6.6)	7 (6.8)	3 (2.8)
Myocardial infarction	1 (0.9)	1 (1.0)	0 (0.0)
GI-perforation/related event	2 (1.9)	0 (0.0)	2 (1.9)
Malignancy	1 (0.9)	1 (1.0)	1 (0.9)
Anaphylaxis/Hypersensitivity	0 (0.0)	1 (1.0)	0 (0.0)
Stroke	1 (0.9)	1 (1.0)	0 (0.0)
Laboratory values:			
ALT > 3 x ULN	14 (13.2)	5 (4.9)	12 (11.1)
AST > 3 x ULN	5 (4.7)	1 (1.0)	4 (3.7)
Absolute Neutrophil count < 1.0 x10^9/L	7 (6.6)	6 (5.8)	1 (0.9)
Platelets count < 100 x 10^9/L	4 (3.8)	3 (2.9)	1 (0.9)

- Differences not statistically significant

Bijlsma JWJ et al, Lancet 2016

Pathway to clinical RA



PREVENTION OF RHEUMATOID ARTHRITIS BY B CELL DIRECTED THERAPY IN THE EARLIEST PHASE OF THE DISEASE: THE PRAIRI STUDY

D. Gerlag et al for the Dutch PRAIRI investigators

„Pre-RA“: Arthralgia and antibodies (+CRP and/or subclinical MRI/US)

Arm 1: Rituximab ‚single shot‘ (1000mg)

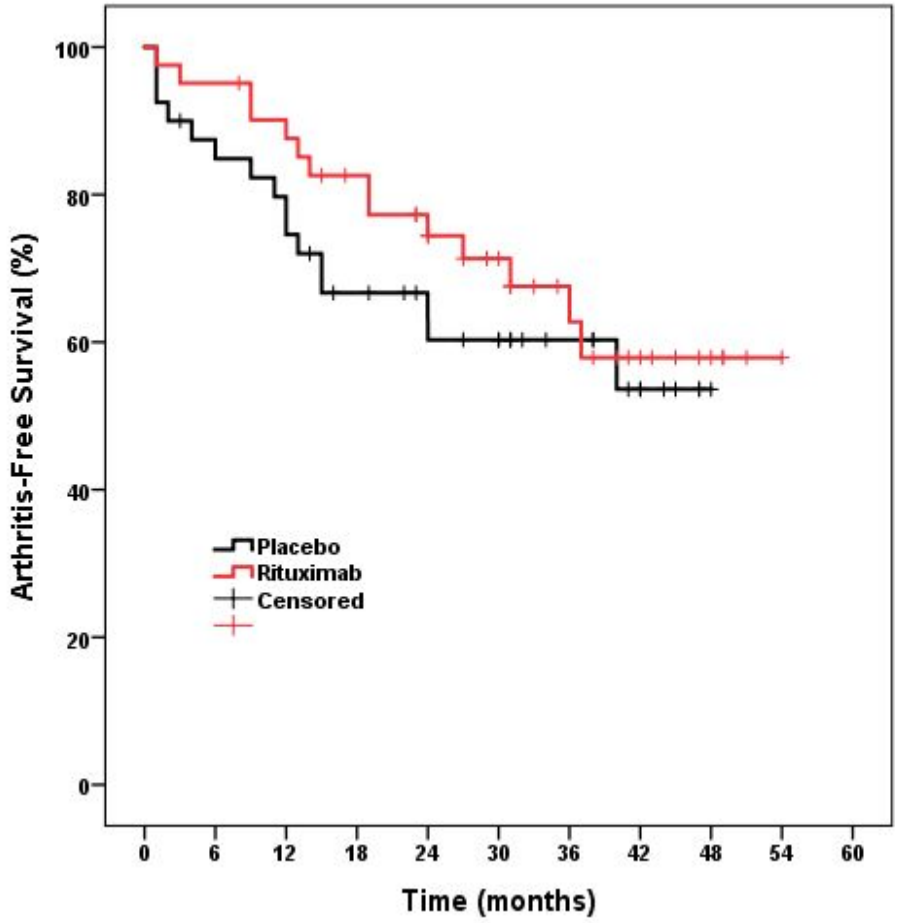
Arm 2: Placebo

QUESTION: Can one shot of Rituximab prevent the occurrence of arthritis?

PRAIRI

Prevention of RA by Rituximab

Time-to-clinically manifest arthritis



A single shot of rituximab in patients 'prone to develop RA':

- does NOT prevent arthritis
- but delays its occurrence

PRAIRI
Prevention of RA by Rituximab

Arthritis prevention in seropositive arthralgia
POINTS FOR DISCUSSION:

- Is 40 % chance on developing RA within 3 years enough to start early treatment ?
- Is decreasing the incidence of developing RA from 40 to 34 % enough to start early treatment ?
- Is delaying mean onset of RA with 5 months enough to start early treatment ?

However, it is proof of the concept !

PRAIRI
Prevention of RA by Rituximab

Rituximab is currently not approved for treatment of DMARD-naïve early RA patients

BIOSIMILARs

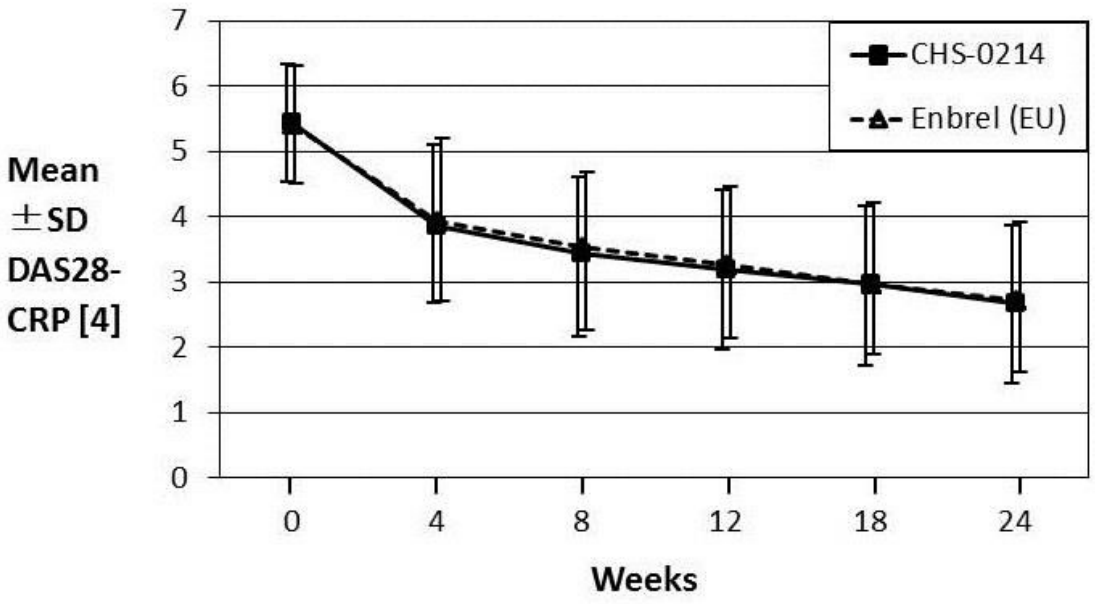
The Ethics of Biosimilarity

Will RCTs give resolution??

RANDOMIZED, DOUBLE-BLIND STUDY COMPARING CHS-0214 WITH ETANERCEPT IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS (RA) DESPITE METHOTREXATE (MTX) THERAPY

J. O'Dell et al for the Rapsody study group

Equivalence trial comparing CHS-0214 with etanercept in 644 pts

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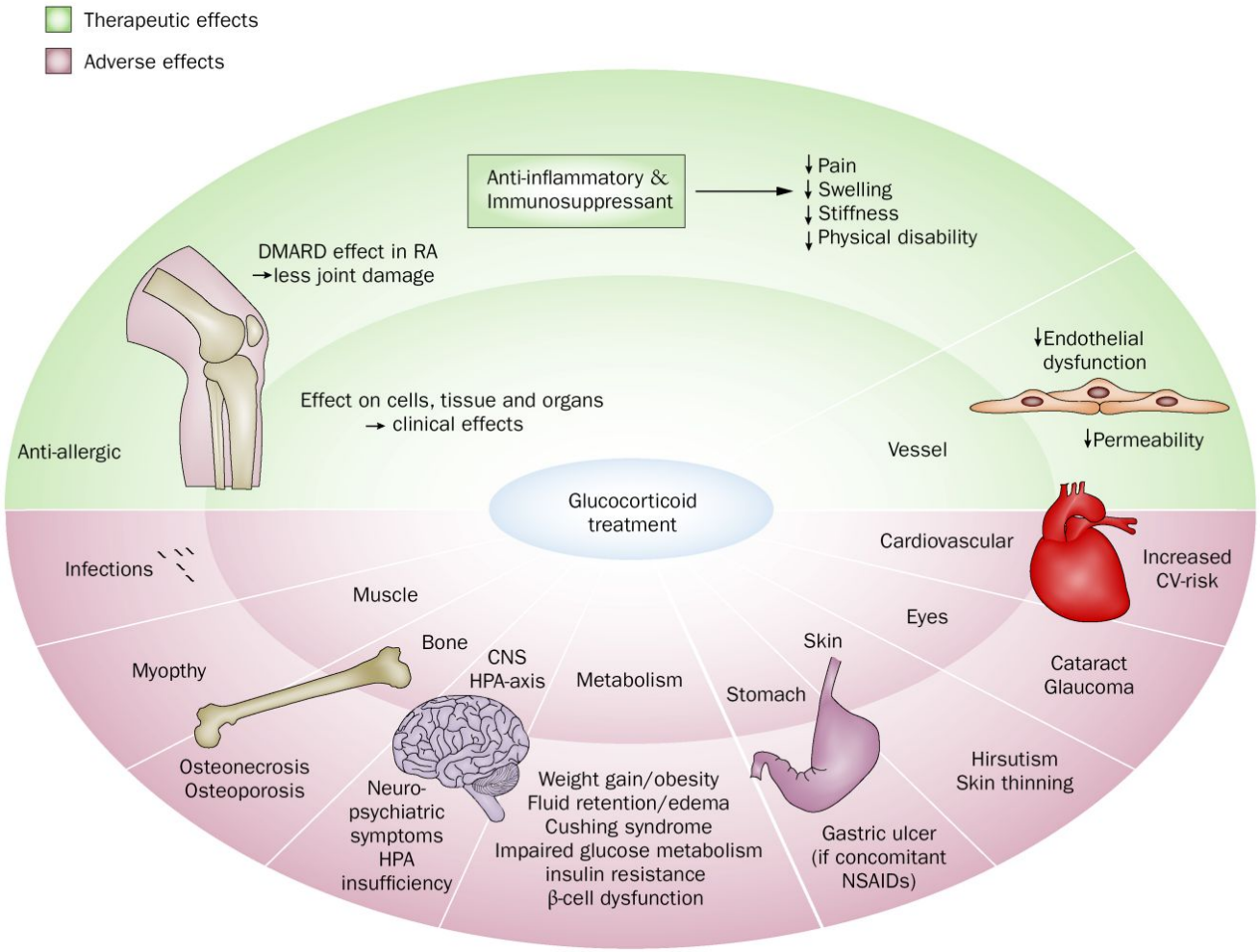
ITEMS TO DISCUSS

- NEW GUIDELINES 2016
- NEW BIOLOGICALS / BIOSIMILARS
- NEWS ON GLUCOCORTICOIDS
- JAK-inhibitors

Glucocorticoids: risks & benefits



Hoes, *Nature Rheumatology*, 2011.

EULAR Task Force

- Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: Viewpoints from an EULAR task force

  C. Strehl et al. ARD 2016; 75: 952-7

- *The risks of long-term glucocorticoid therapy are defined by both drug- (dose, duration) and patient-specific characteristics*

0 5 7.5 10 15 mg/d (prednisone equivalent)

benefits > risks in the majority* of patients

benefits < risks in the majority** of patients

The actual level of harm is patient-specific, i.e. it depends on the presence or absence of risk factors and/or preventive measures

shifting towards a lower level of harm

shifting towards an increased level of harm

* not true for high risk CV patients

** not true for patients with (partial) glucocorticoid resistance

The actual risk of harm is patient-specific, i.e. it depends on individual risk factors and/or preventive measures

Patient specific factors shifting towards a lower level of harm

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [20] [35]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[34] [37] [38] [39] [40]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[42] [48] [50]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[55] [56]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [57] [67] [72] [73] [74]

The actual risk of harm is patient-specific, i.e. it depends on individual risk factors and/or preventive measures

Patient specific factors shifting towards an increased level of harm

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[16] [26] [63]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[22] [33] [34] [35] [36]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high number of treatment failures, prior serious infections	[26] [41] [43] [45] [46] [47] [48] [49]
Carbohydrate metabolism	higher age, high body mass index, genetic predisposition, long disease duration	[52] [53]
Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positicomorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing´s syndrome)vity,	[27] [45] [62] [64] [69] [70] [71]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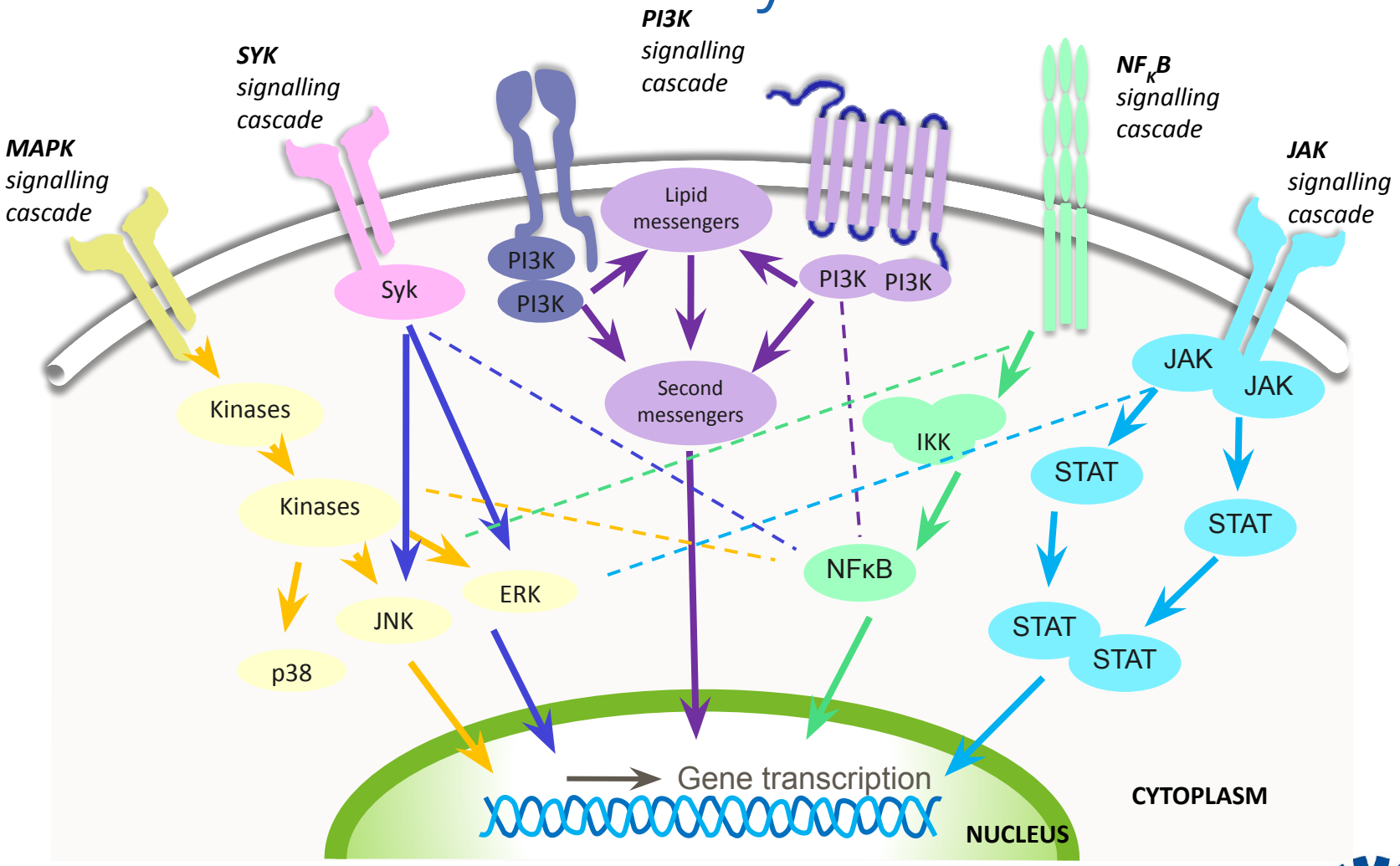
Cytokines Signal Through Different Intracellular Pathways



ERK=extracellular signal related kinases; IKK=inhibitor of kappaB kinase; JAK=Janus kinase; JNK=c-Jun N-terminal kinase; MAPK=mitogen-activated protein kinase; NFκB=nuclear factor kappa B; PI3K=Phosphoinositide 3-kinase; STAT=signal transducer and activator of transcription; Syk=Spleen tyrosine kinase.

Adapted from Mavers M, et al. *Curr Rheum Rep*. 2009;11:378-385 and Rommel C, et al. *Nat Rev Immunol.* 2007;7:191-201.

JAK Pathways

1. Cytokine binding to its cell surface receptor leads to receptor polymerization and autophosphorylation of associated JAKs

2. Activated JAKs phosphorylate the receptors that dock STATs

3. Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription

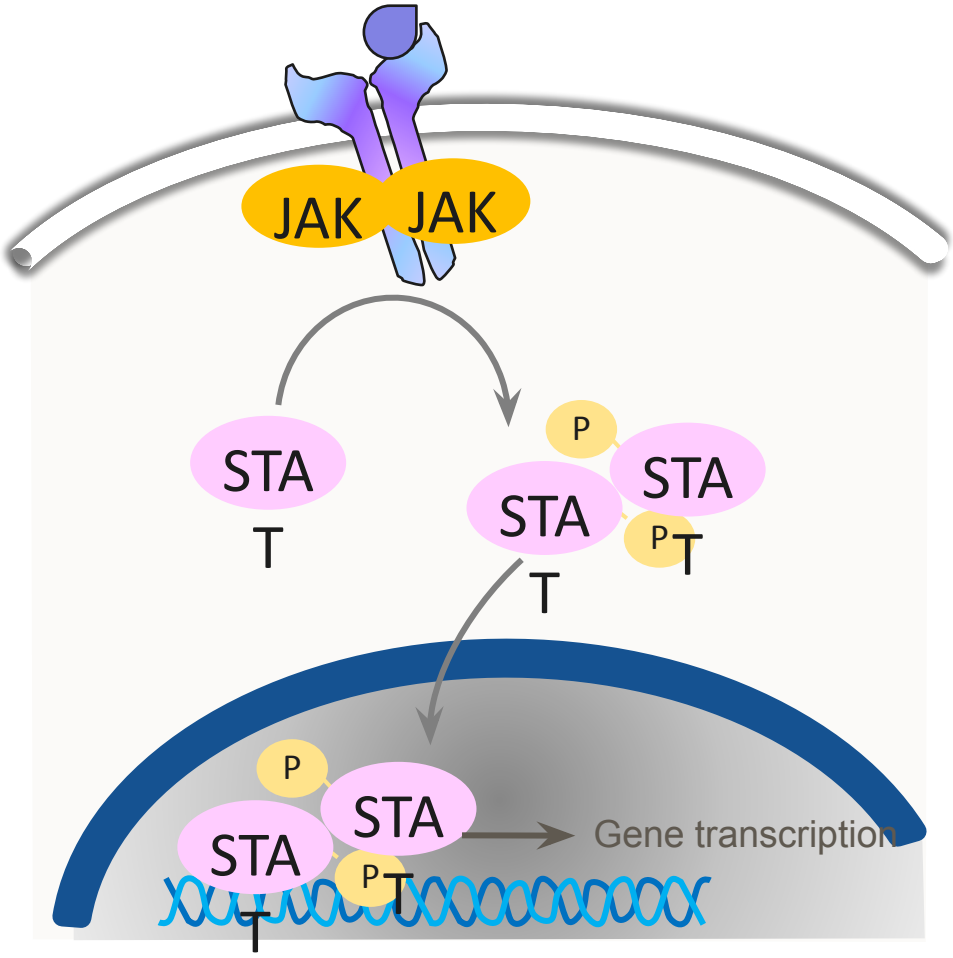


Figure adapted from Shuai K, et al. *Nat Rev Immunol*. 2003;3:900-911.

Oral JAK inhibitors for RA

Targeted Therapy	Type of Agent	Developer	Development Status
Tofacitinib[4] (CP-690,550)	JAK3/JAK1,2 inhibitor	Pfizer	FDA approved
Baricitinib[3] (LY3009104; INCB028050)	JAK1/JAK2 inhibitor	Incyte/Lilly	Phase 3
Fostamatinib[5] (R788)	SYK inhibitor	Rigel/ AstraZeneca	Development in RA halted
GLPG0634[1]	JAK1 inhibitor	Galapagos/ AbbVie	Phase 2
Decernotinib[2] (VX-509)	JAK3 inhibitor	Vertex	Phase 2/3

1. Tasset C, et al. *Arthritis Rheum.* 2013;65(suppl 10):S1018, abstract 2381; **2.** Strand V, et al. *Arthritis Rheum.* 2013;65(suppl 10):S1004, abstract 2350; **3.** Keystone E, et al. *Ann Rheum Dis.* 2012;71(suppl 3):152. Late-breaking abstract LB0005; **4.** Xeljanz [package insert]. New York, NY: Pfizer Inc; 2013; **5.** Weinblatt ME, et al. *Arthritis Rheum.* 2008;58:3309-3318.

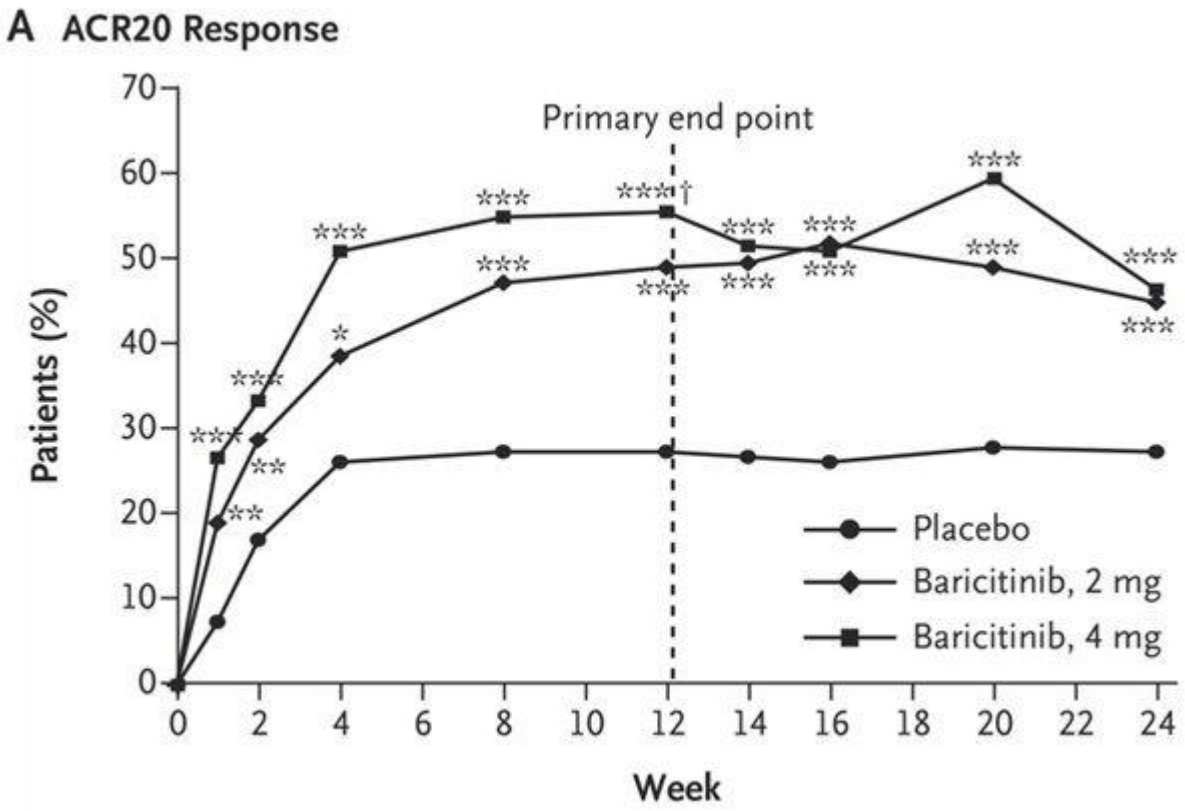
Clinical efficacy tofacitinib

Table 1. Efficacy Endpoints in 1044/Scan, 1046/Sync, and 1064/Standard Studies

EndPoint	1044/Scan			1046/Sync			1064/Standard			
	PBO	5 mg	10 mg	PBO	5 mg	10 mg	PBO	5 mg	10 mg	ADA
Primary										
ACR20 (%)	25.3	51.5	61.8	31.2	52.7	58.3	28.3	51.5	52.6	47.2
HAQ-DI†	0.15	0.40*	0.54	0.21	0.46	0.56	0.24	0.55	0.61	0.49
DAS28<2.6 (%)	1.6	7.2*	16.0	2.7	9.1	13.3	1.1	6.2	12.5	6.7
Mean ΔmTSS	0.47	0.12§	0.06	NA	NA	NA	NA	NA	NA	NA
Secondary										
ACR50 (%)	8.4	32.4	43.7	12.74	33.8	36.6	12.3	36.7	34.7	27.6
ACR70 (%)	1.3	14.6	22.3	3.2	13.2	16.2	1.9	19.9	21.9	9.1
No progression in mTSS (%)	77.7	88.8	86.9	NA	NA	NA	NA	NA	NA	NA

Statistically significant compared with placebo unless otherwise indicated
†Values expressed as decreases from baseline
*significance not declared due to step-down procedure
§Not statistically significant vs placebo
PBO=placebo, 5 mg=5 mg BID tofacitinib, 10 mg=10 mg BID tofacitinib, ADA =-adalimumab 40 mg SC every other week, NA=Not applicable

Clinical efficacy baricitinib

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PARE – Web-meeting december 2017

Thank you for your attention