Farmaci Biologici nelle Malattie Autoimmuni

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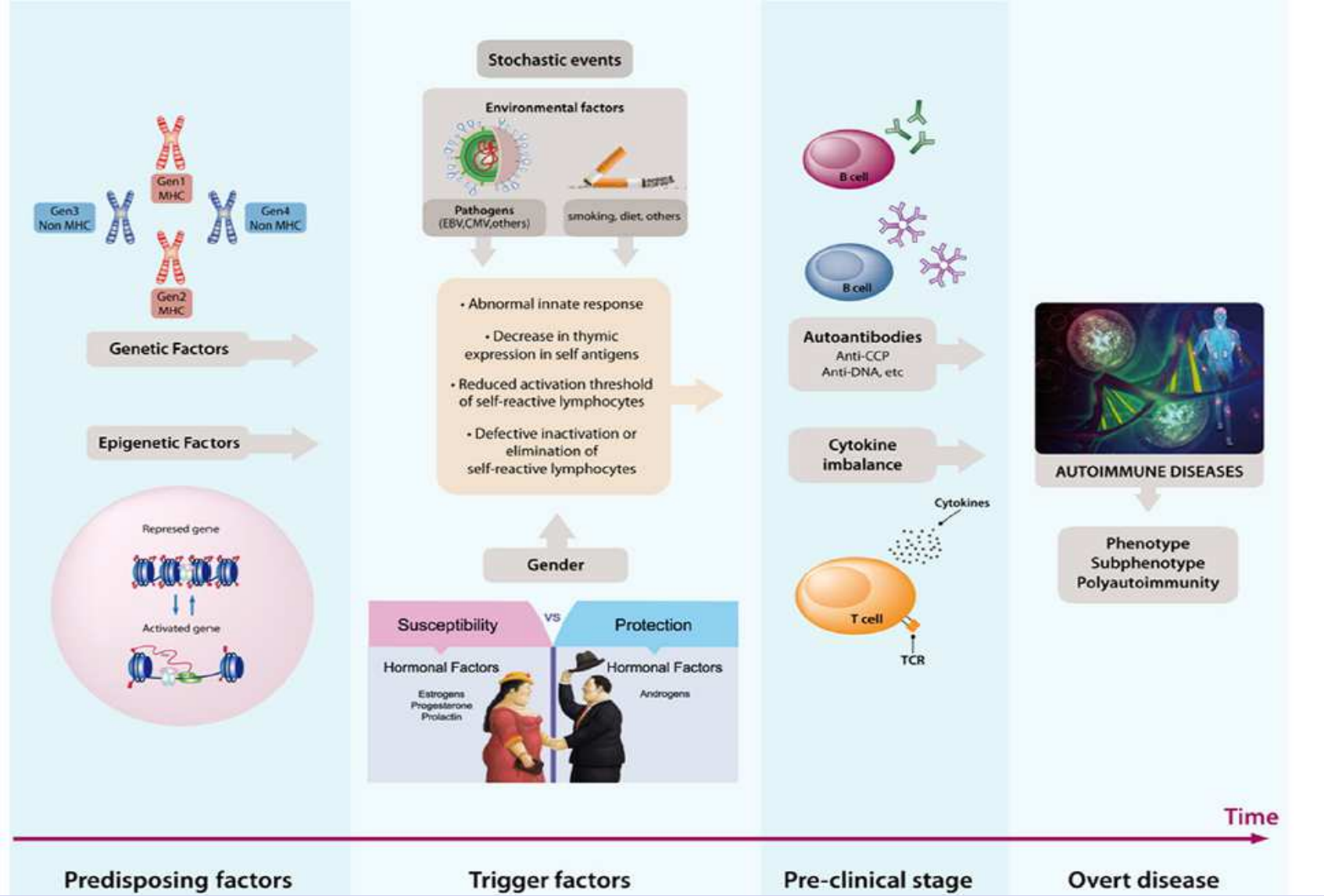
Autoimmune Diseases

- ✓ 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.

- ✓ 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.

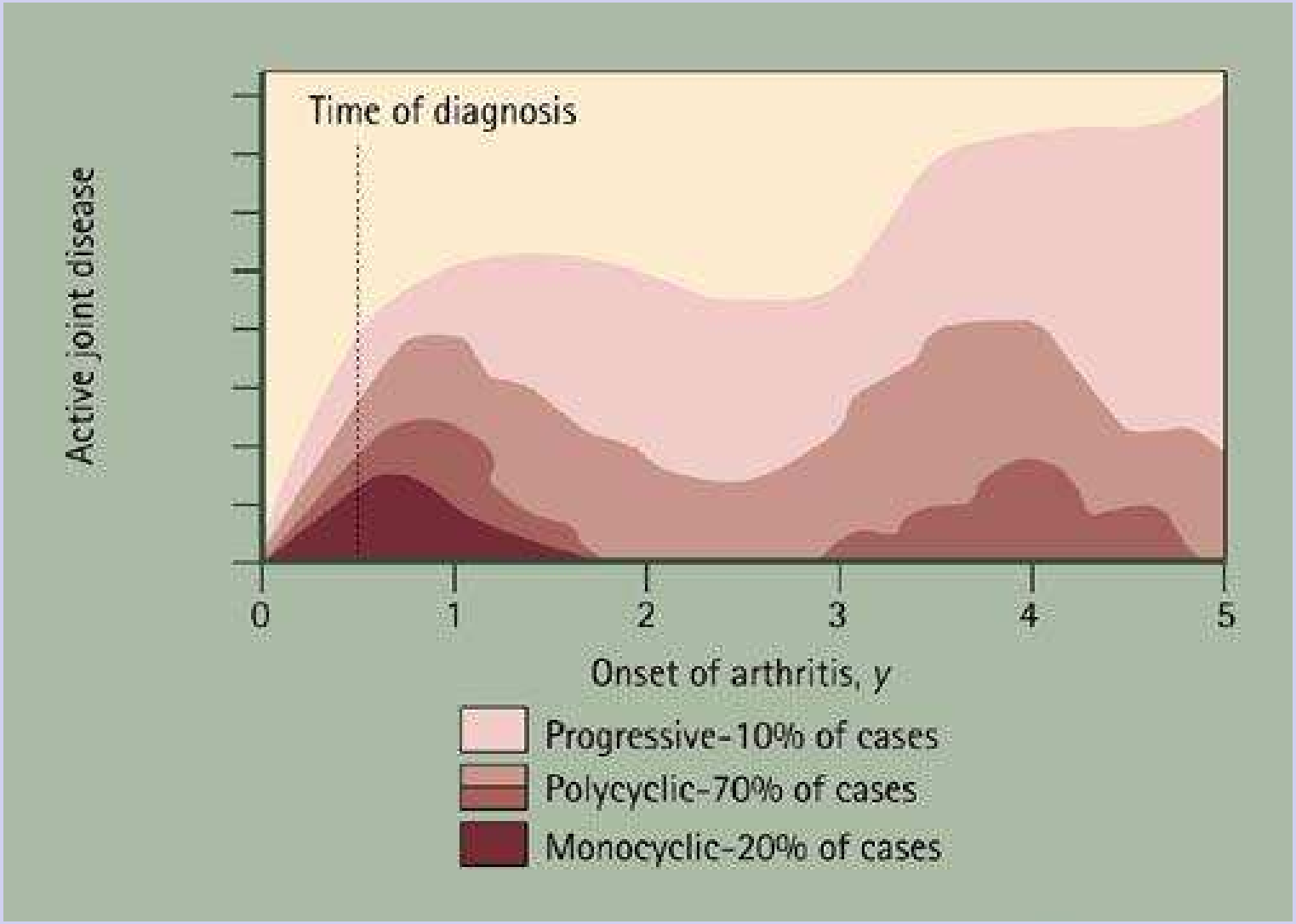
Common Mechanisms of Autoimmune Diseases



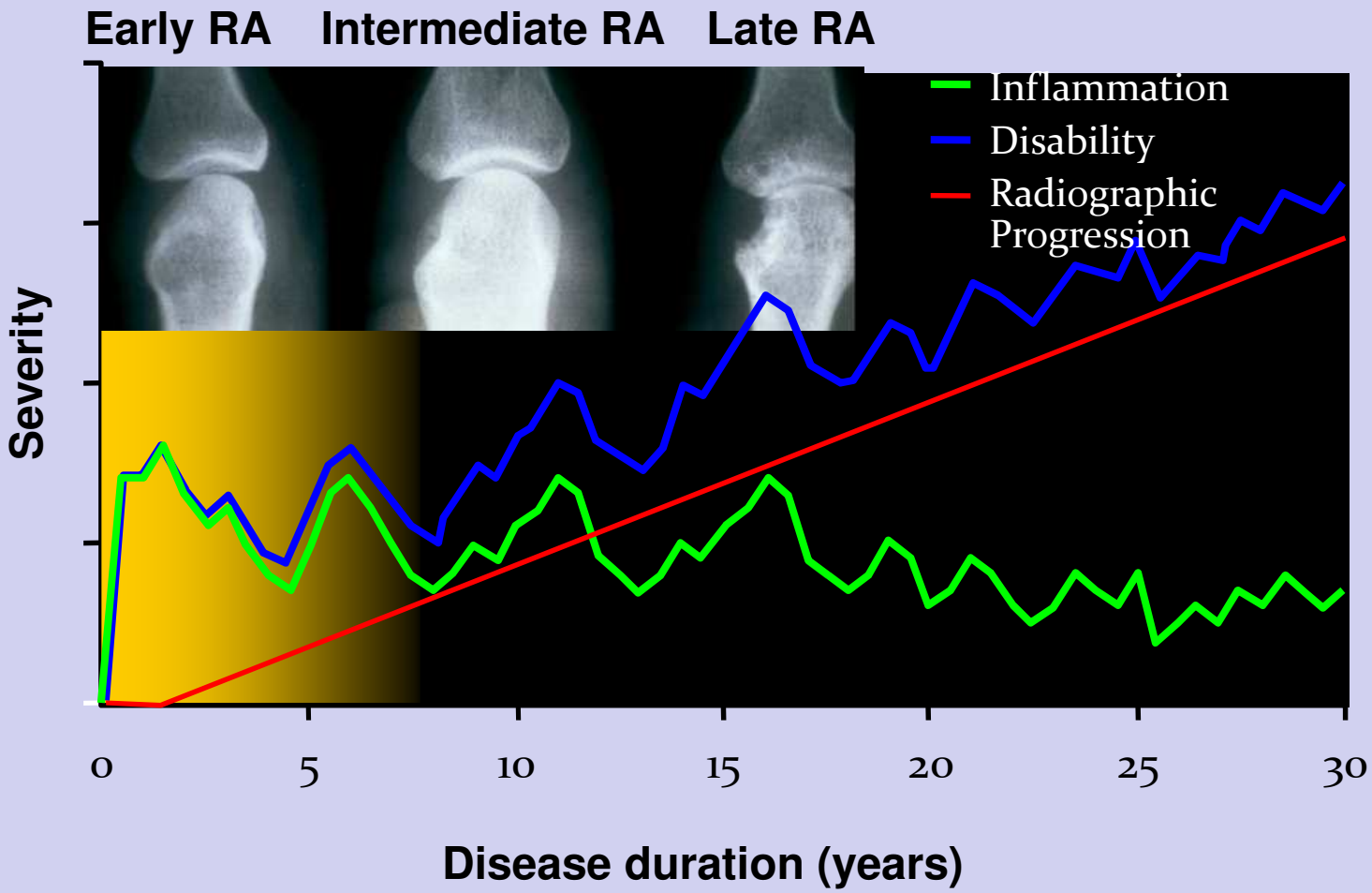
Heterogeneity of AD

- ✓ 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).

Heterogeneity of Rheumatoid Arthritis



Natural History of Rheumatoid Arthritis

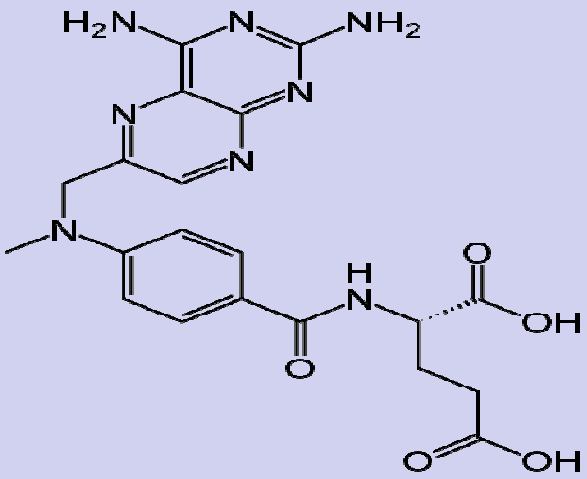


Graph: Adapted from Kirwan JR. J Rheumatol. 2001;28:881-886.
Photo: Copyright © American College of Rheumatology

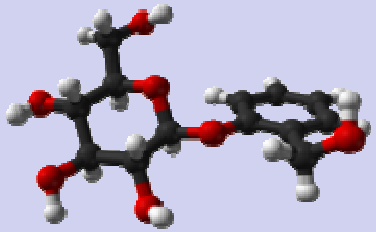
Long History of Conventional Drug Development…

Willow (Salix)

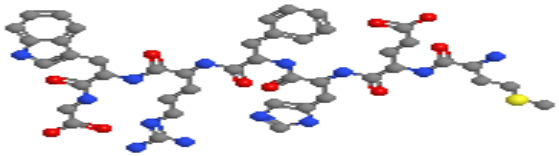
Johann Andreas Buchner



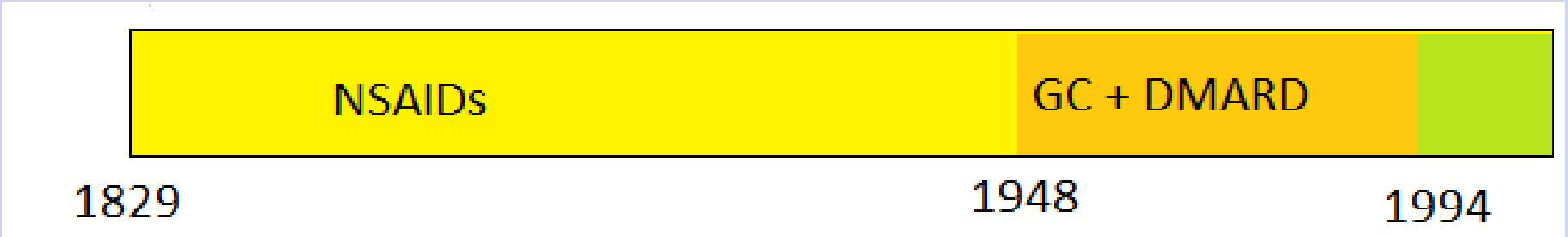
MTX



SALICIN

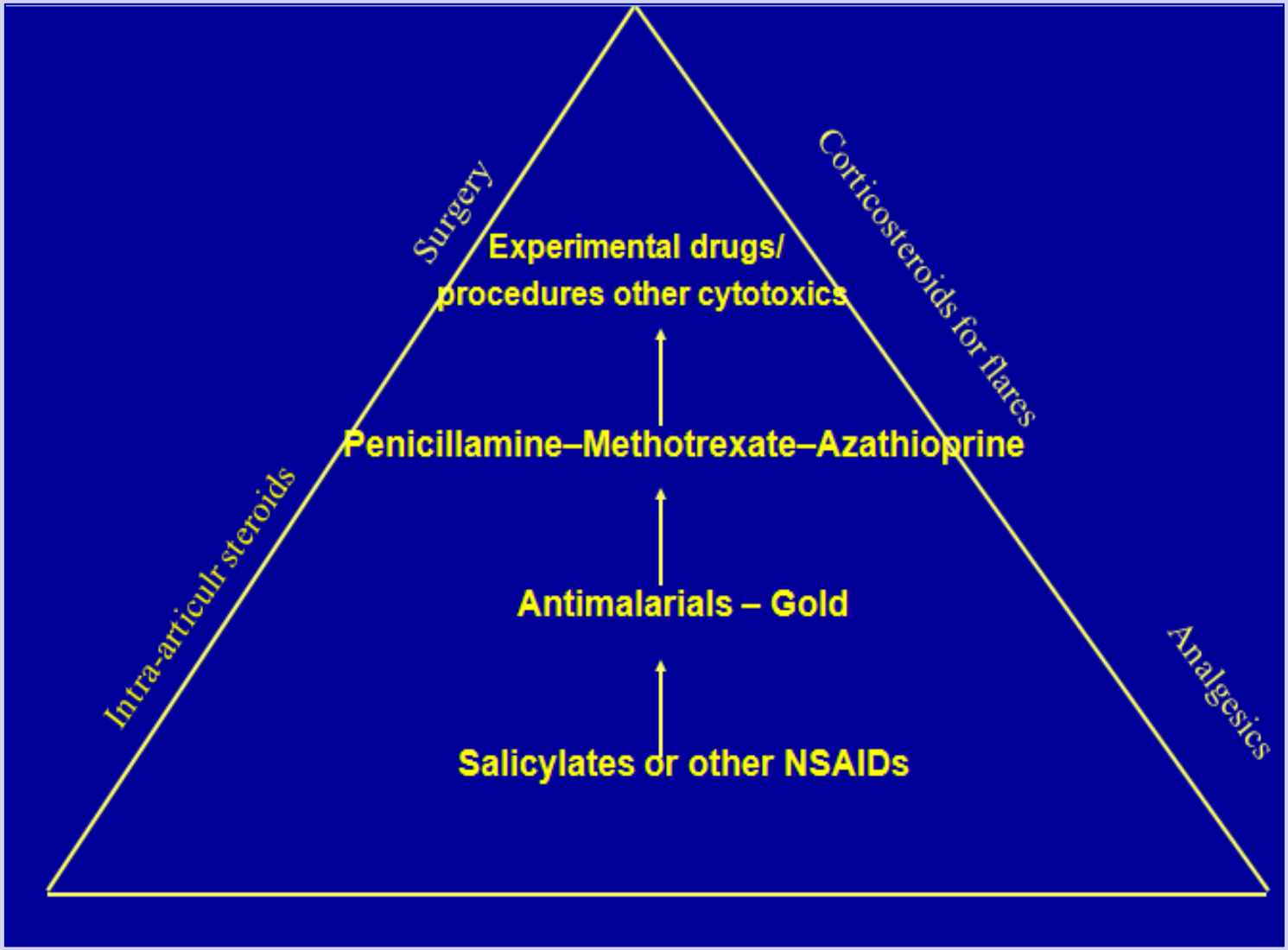


ACTH

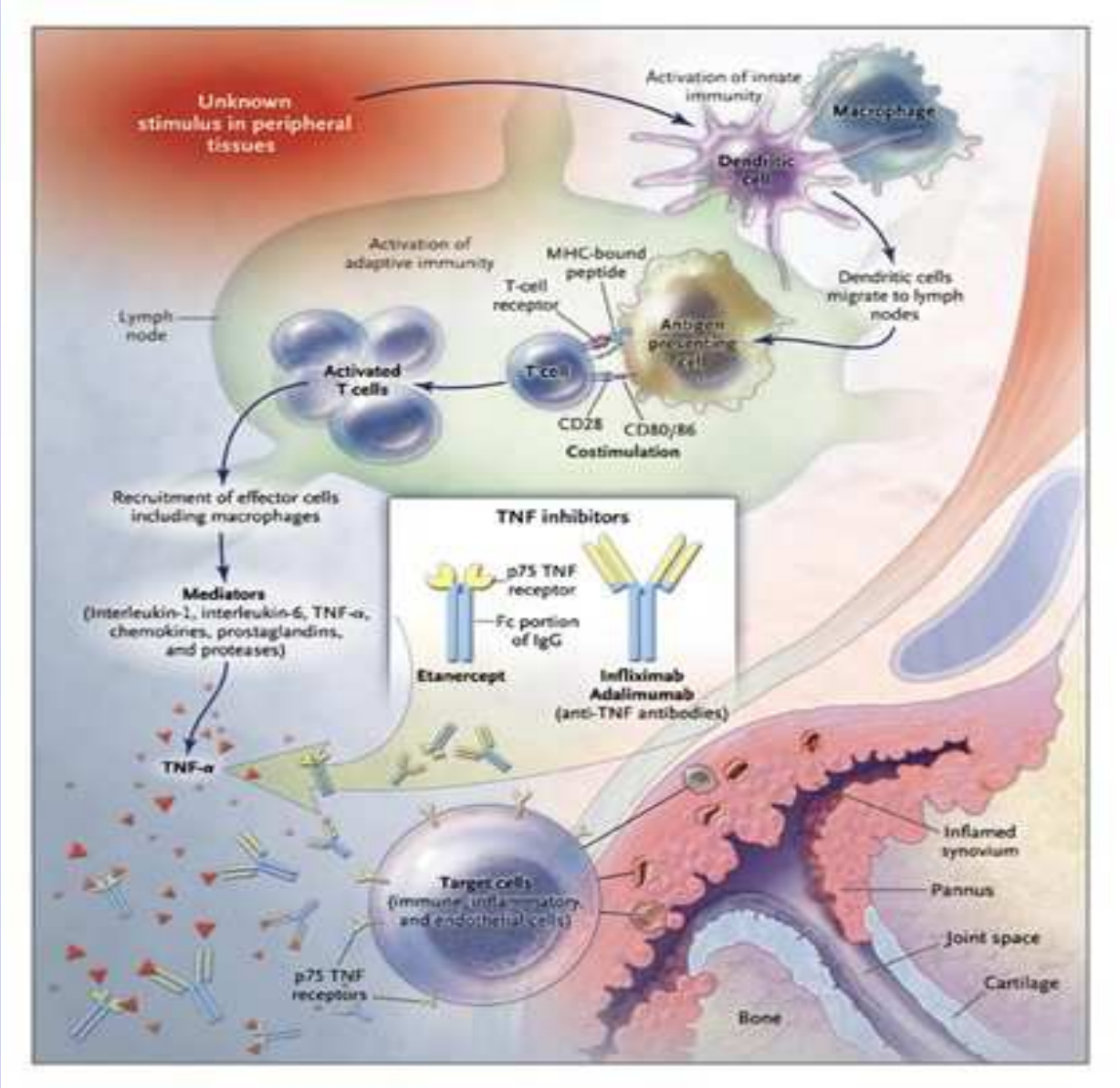


Traditional Pyramid Model Treatment

Start low, go slow….

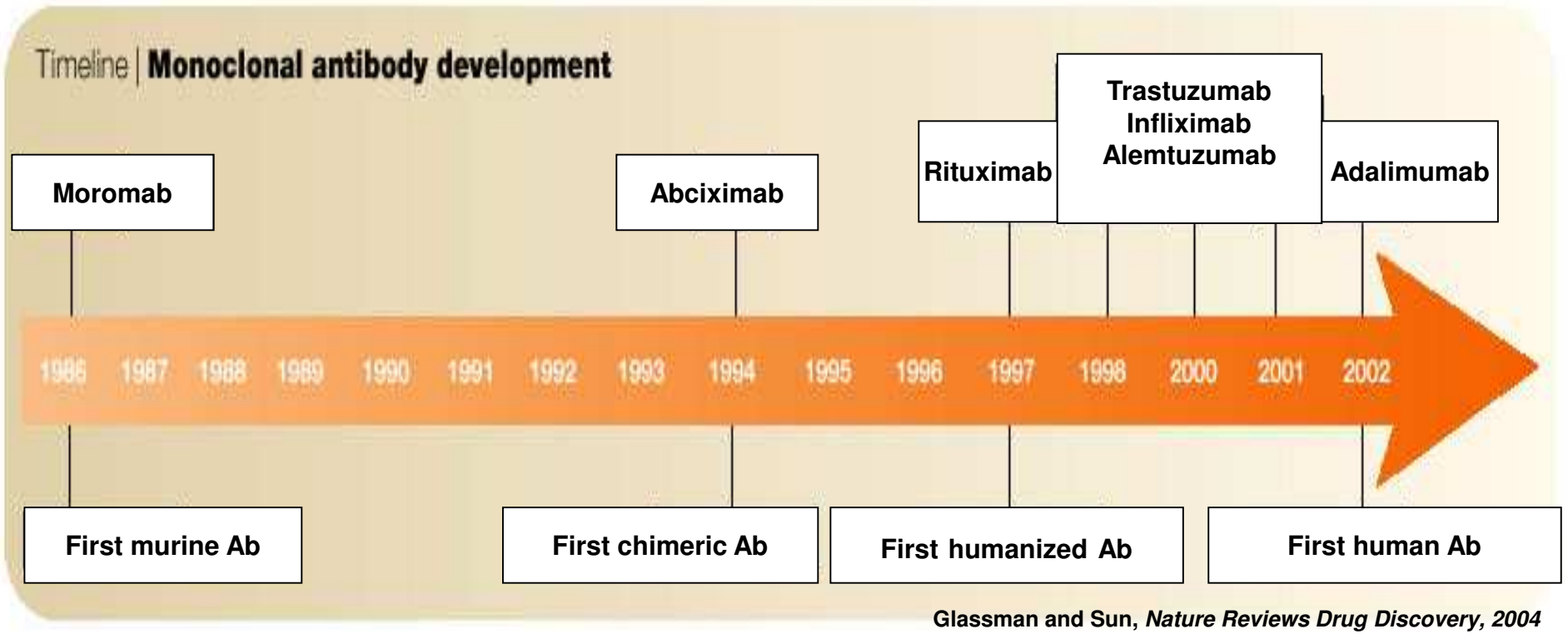


Pathogenesis of RA



Monoclonal antibodies

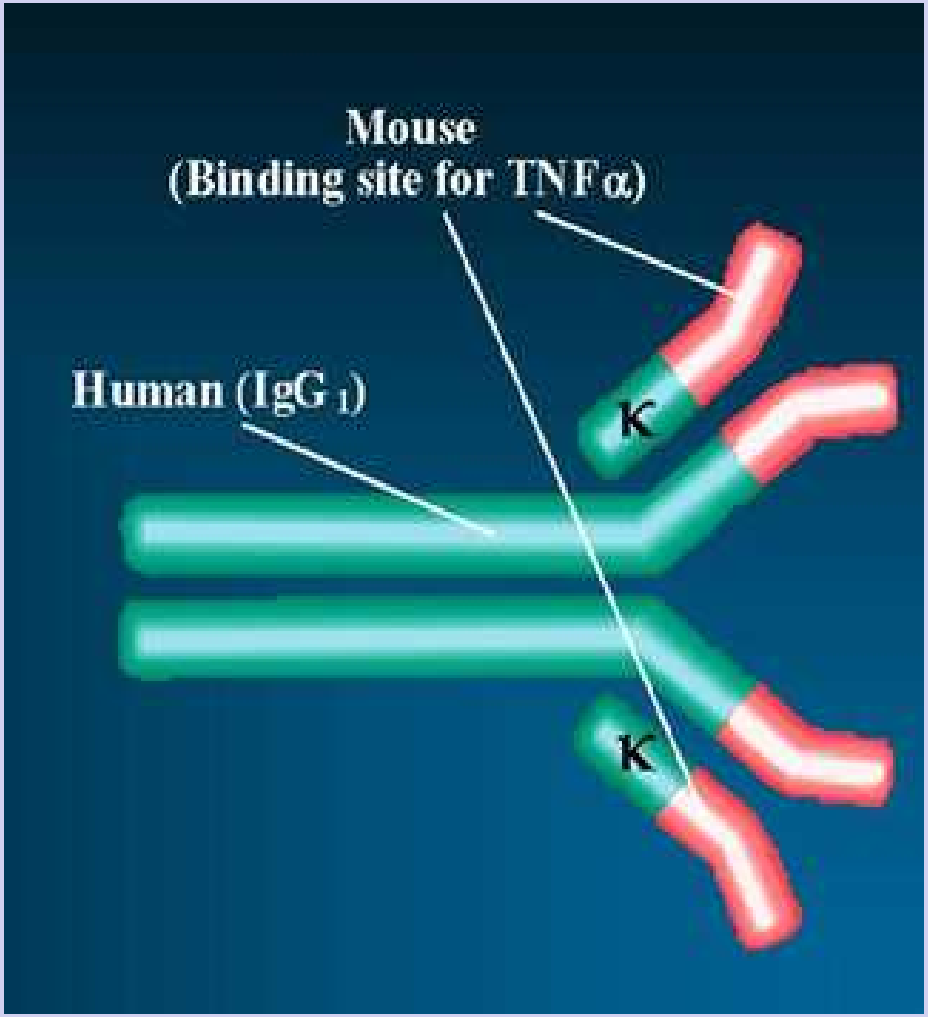
1975 - Cesar Milstein e Georges Kohler (Nobel prize for Medicine in 1984)



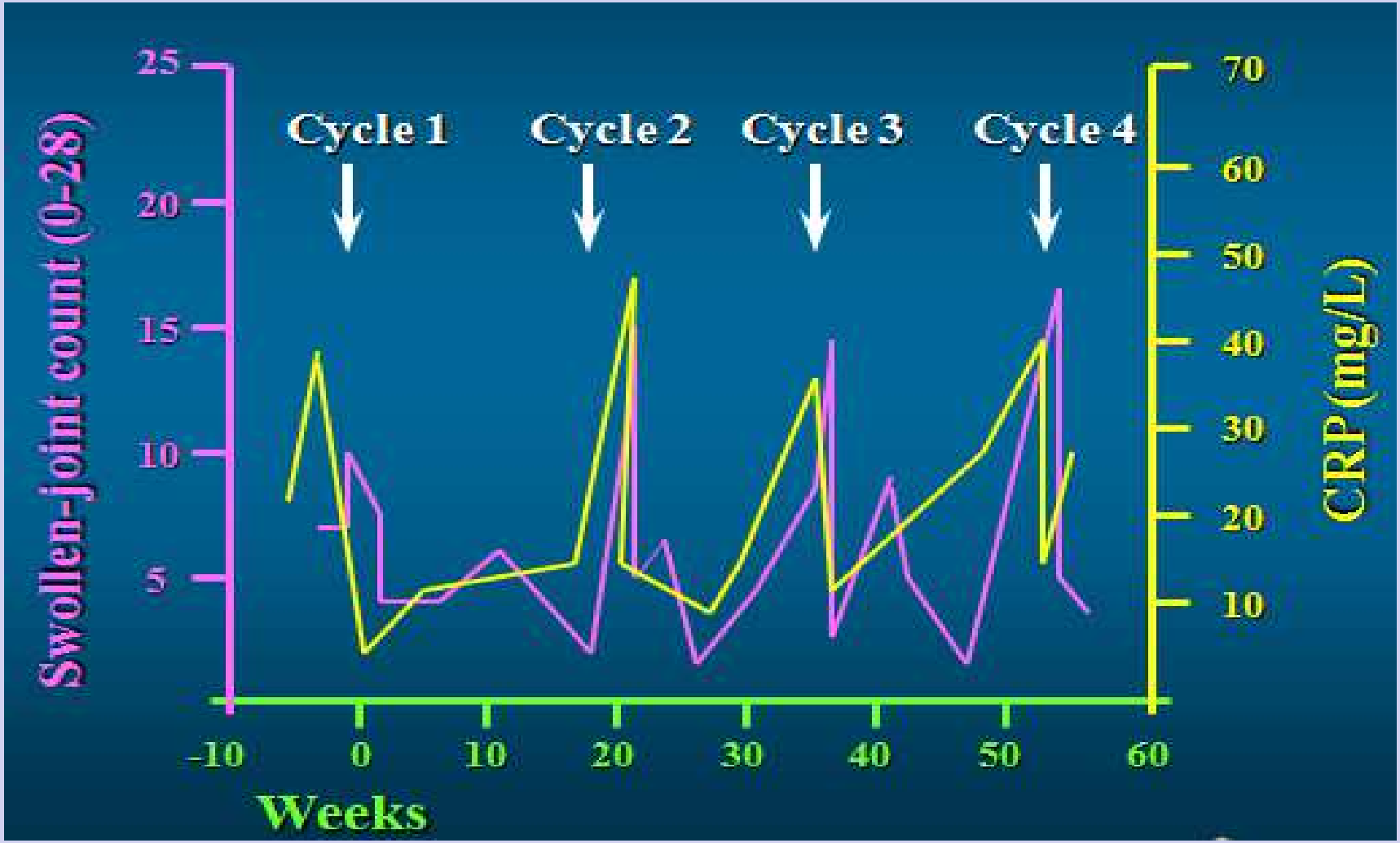
Glassman and Sun, *Nature Reviews Drug Discovery, 2004*

Structure of Infliximab (cA2)

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

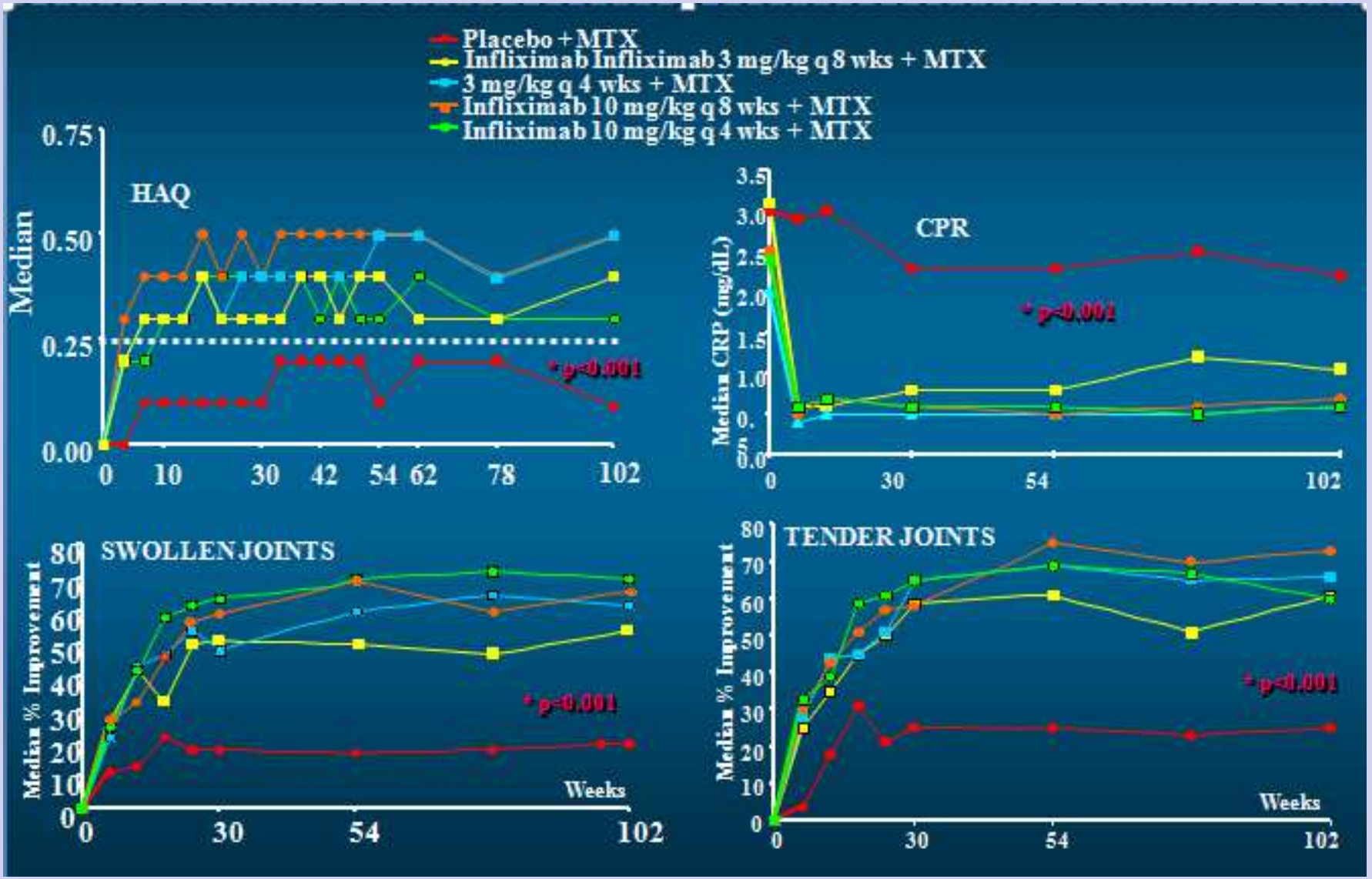


RA Therapy with Monoclonal Antibody to TNF-α



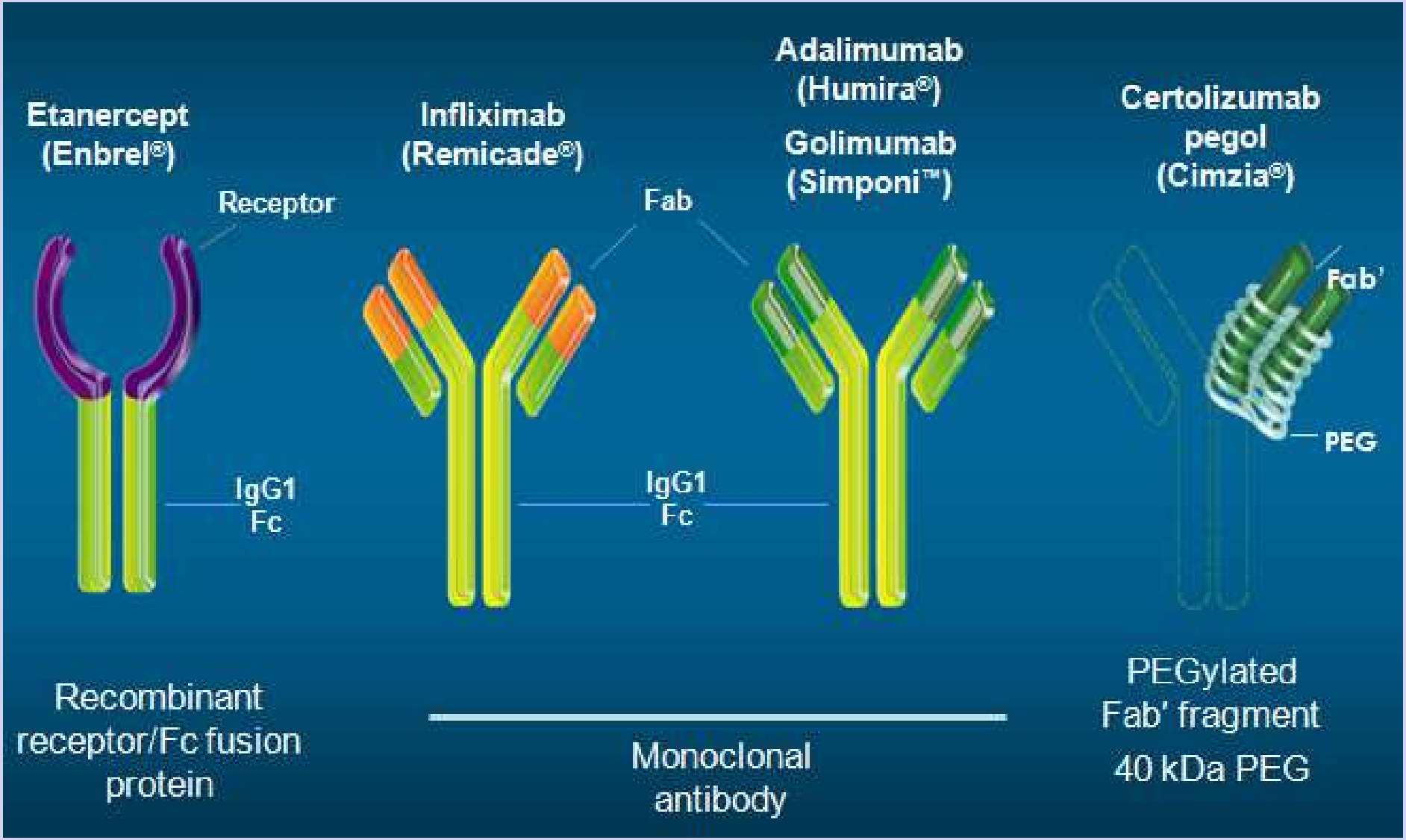
Elliot et al. Lancet 344: 1125, 1994

ATTRACT STUDY – 102 ws



Maini R et al. Lancet 354:1932; 1999

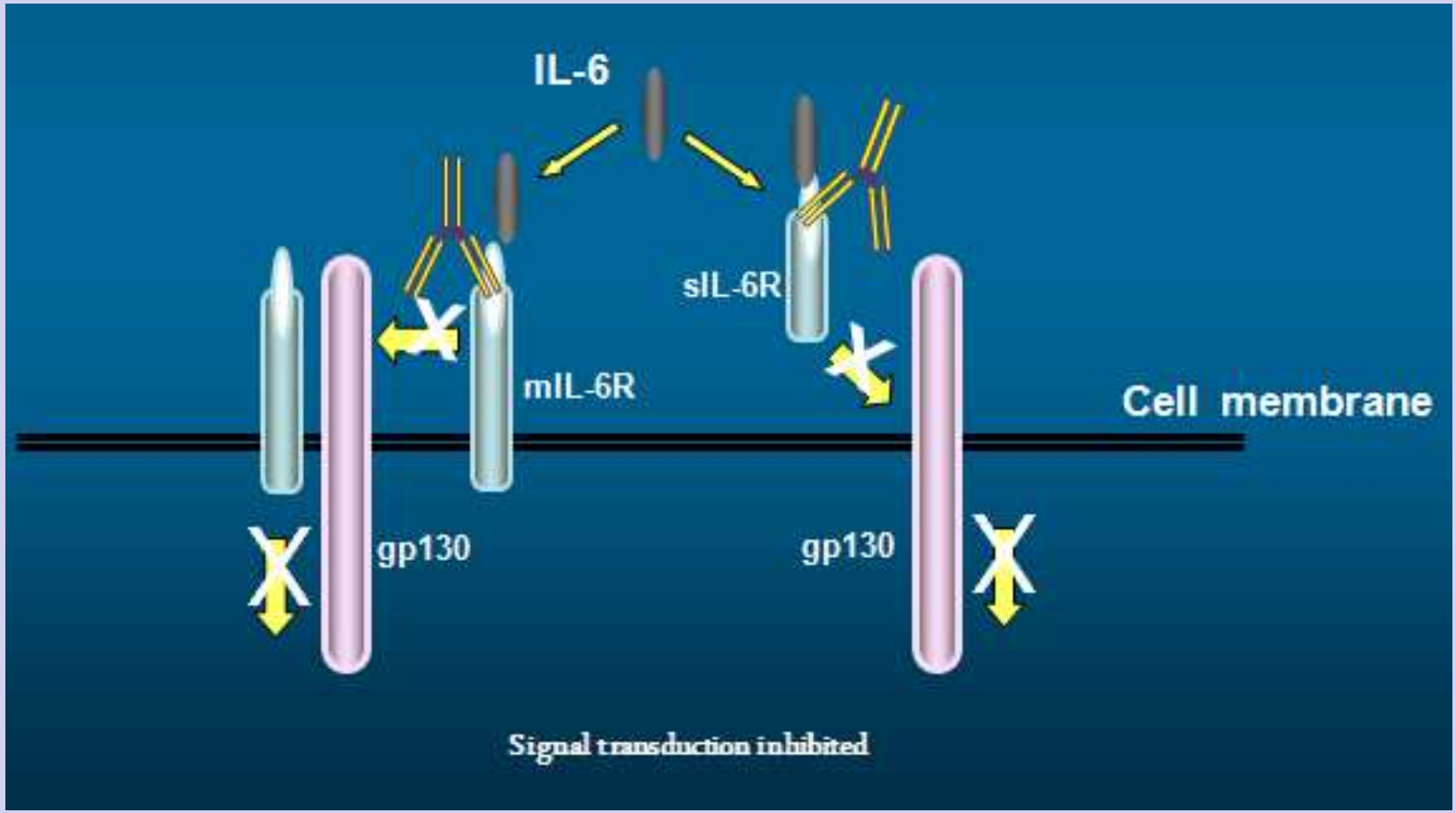
Structure of Biologic Drugs



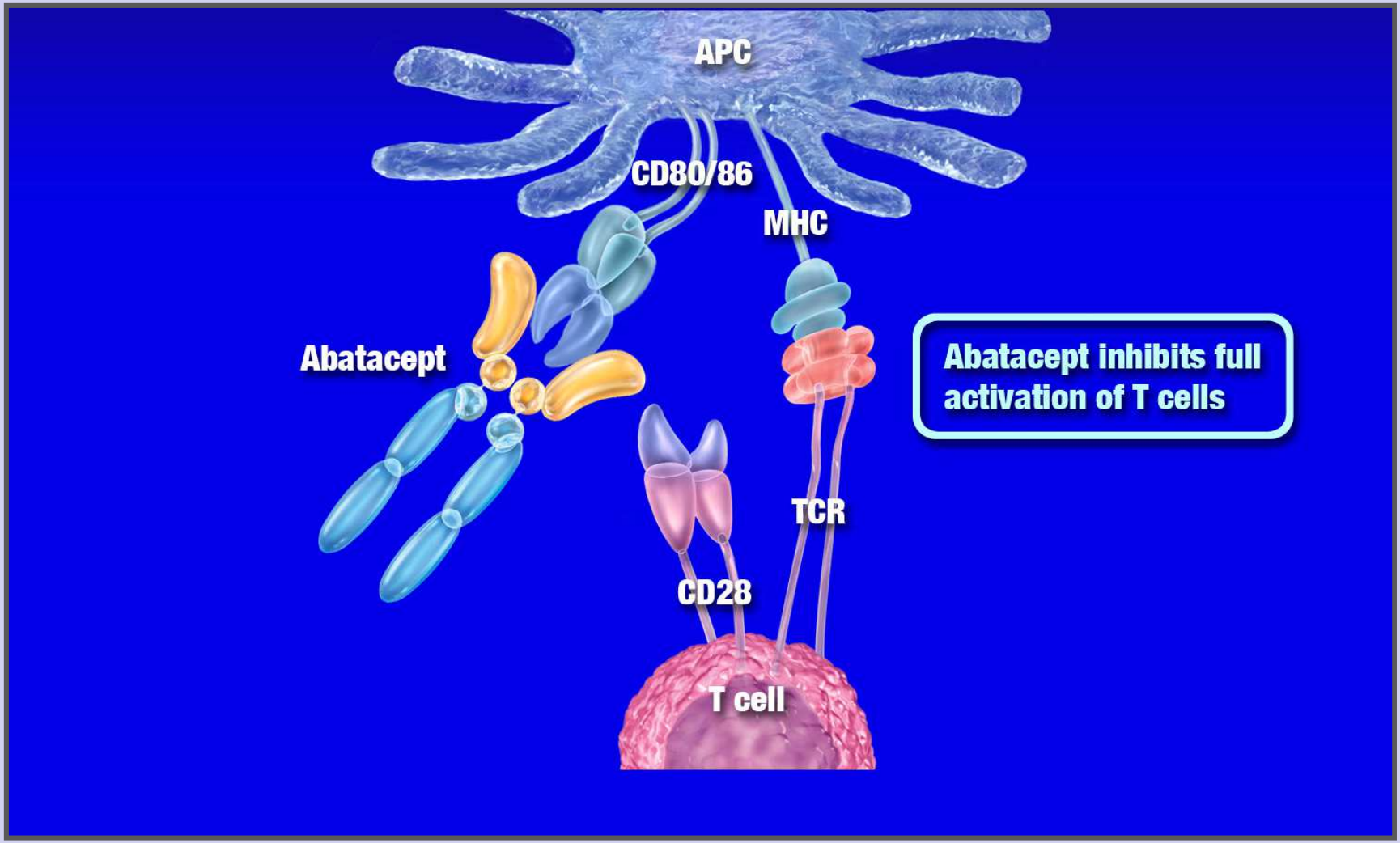
Weir N, Athwal D, et al. Therapy. 2006;3:535-45

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



Biologic Therapies: Targeting T Cells



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

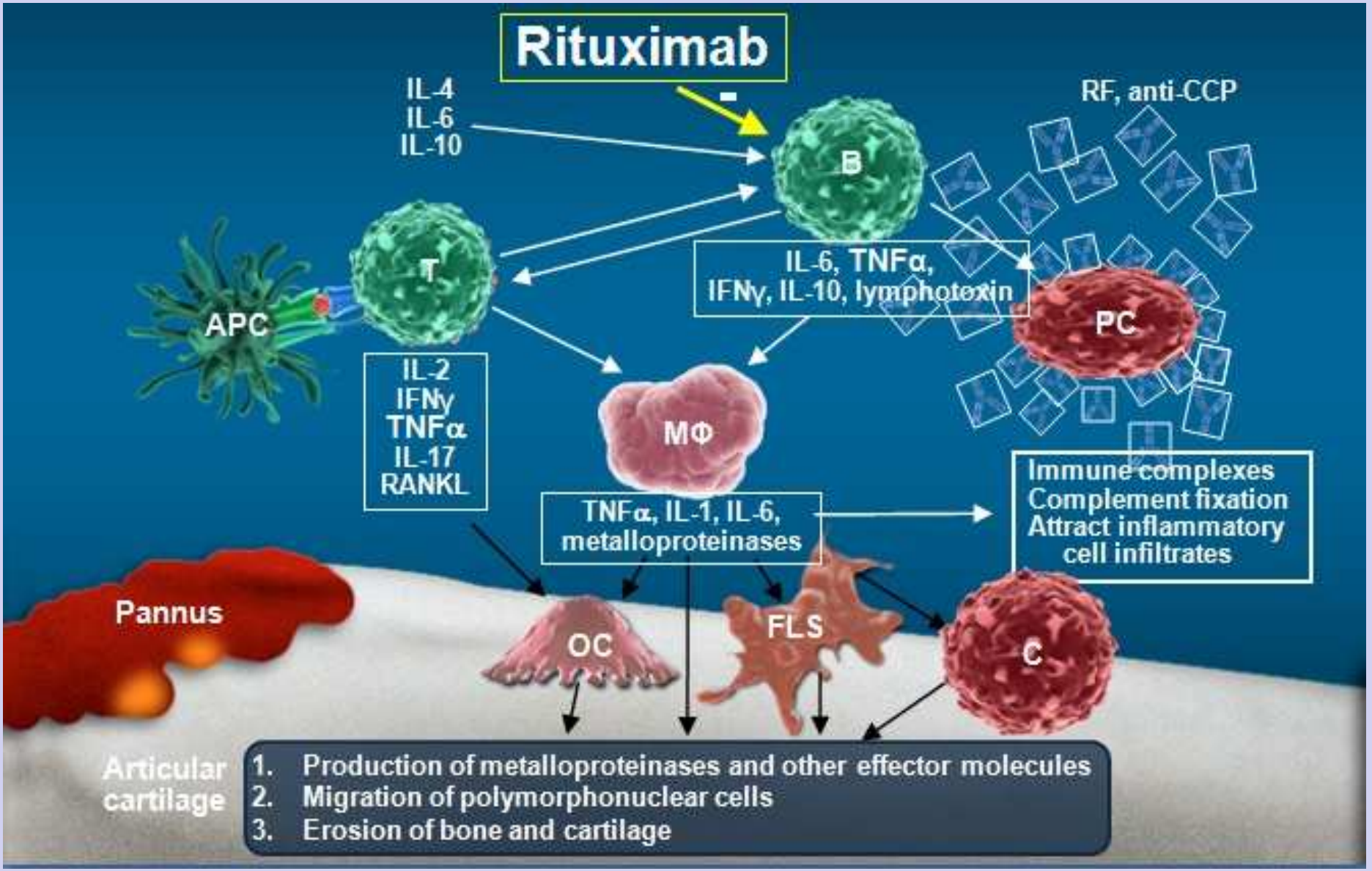
Rheumatology 2001;40:205–211

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

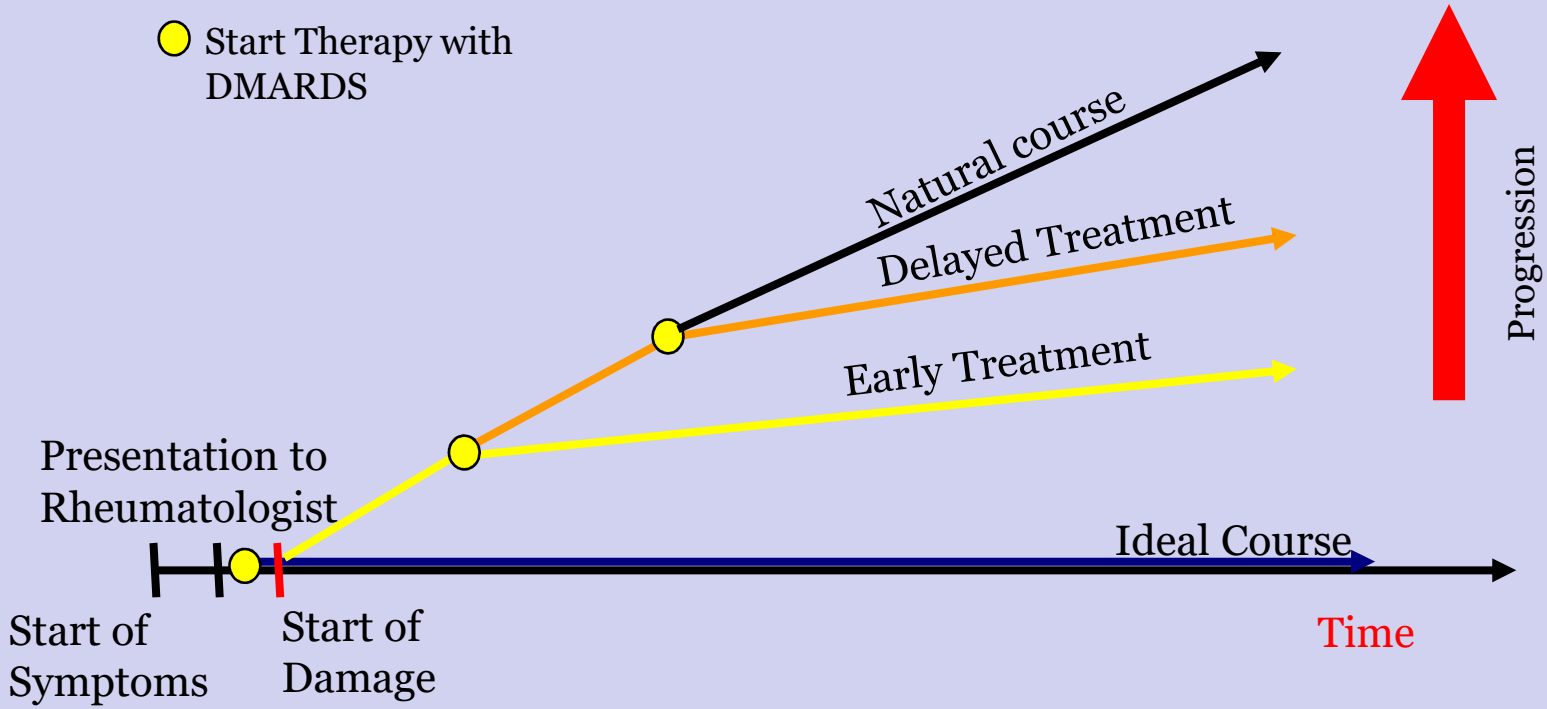
Biologic Therapies Targeting B Cells



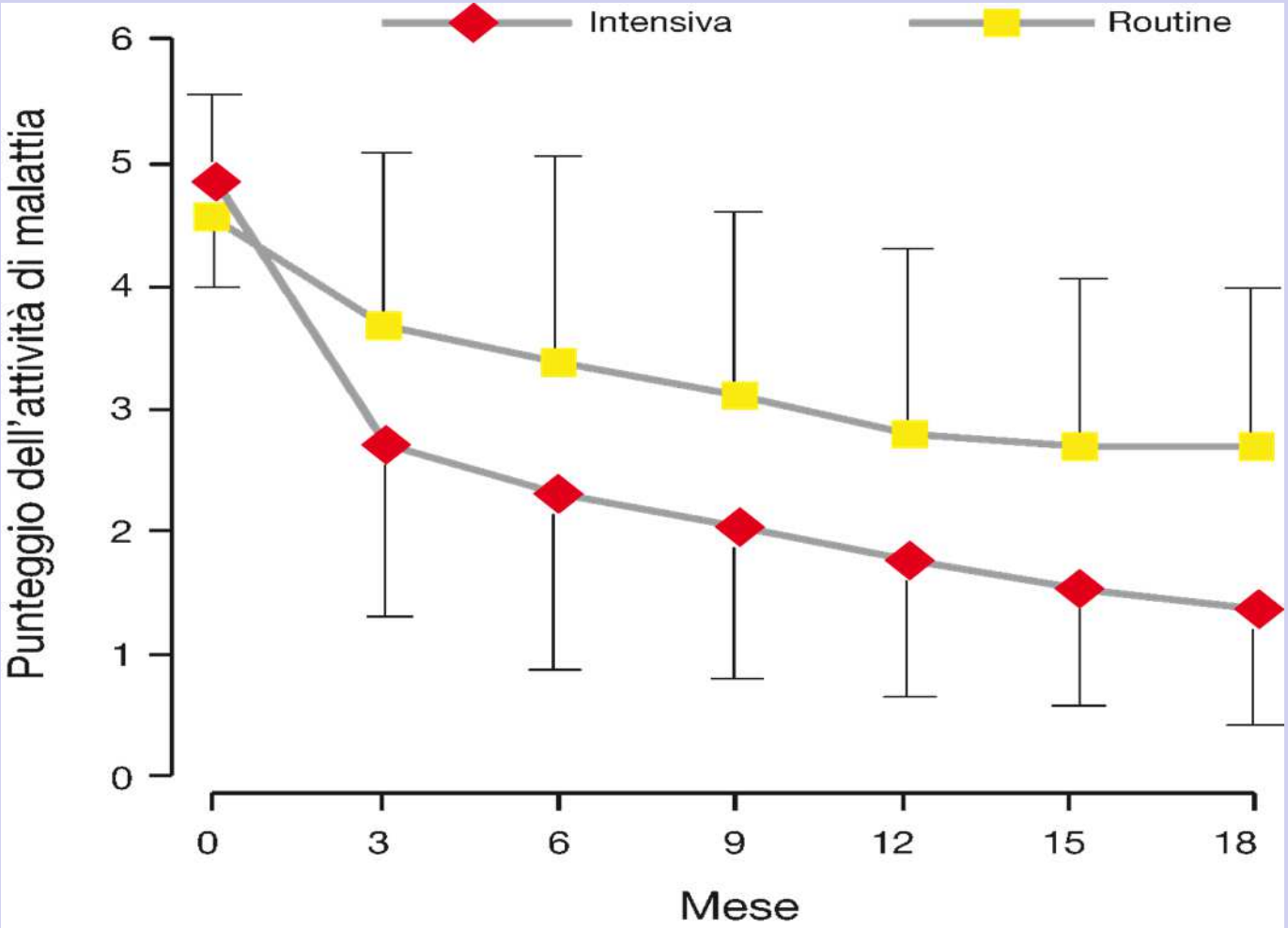
General Therapeutic Principle for Established RA

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

Change the Course of RA



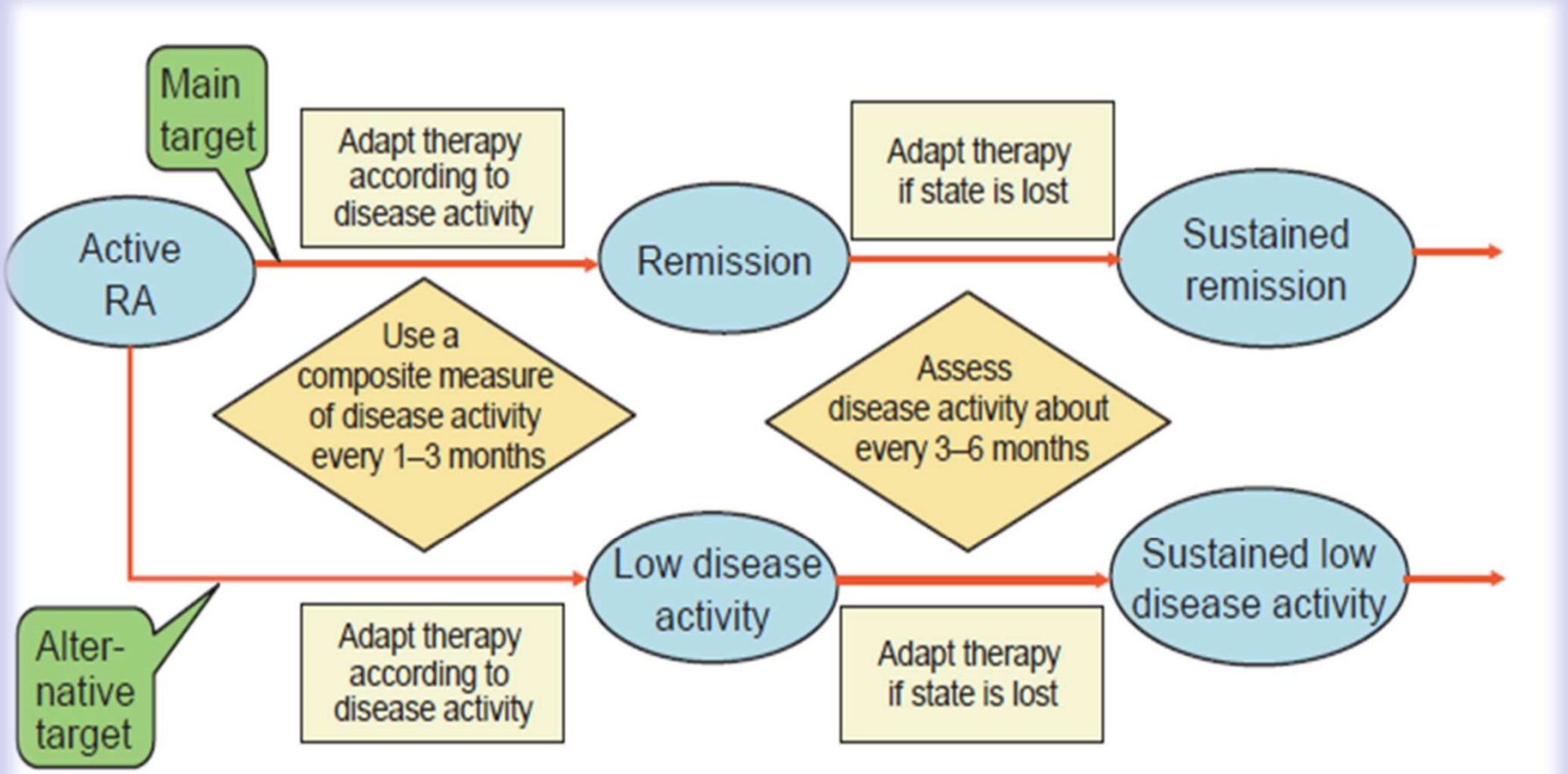
TIGHT CONTROL: TICORA STUDY



Mean scores of disease activity**.** T-Student Test. After 3 months, intensive vs routine p<0.0001

. Grigor et al. Lancet 2004; 364: 263-9.

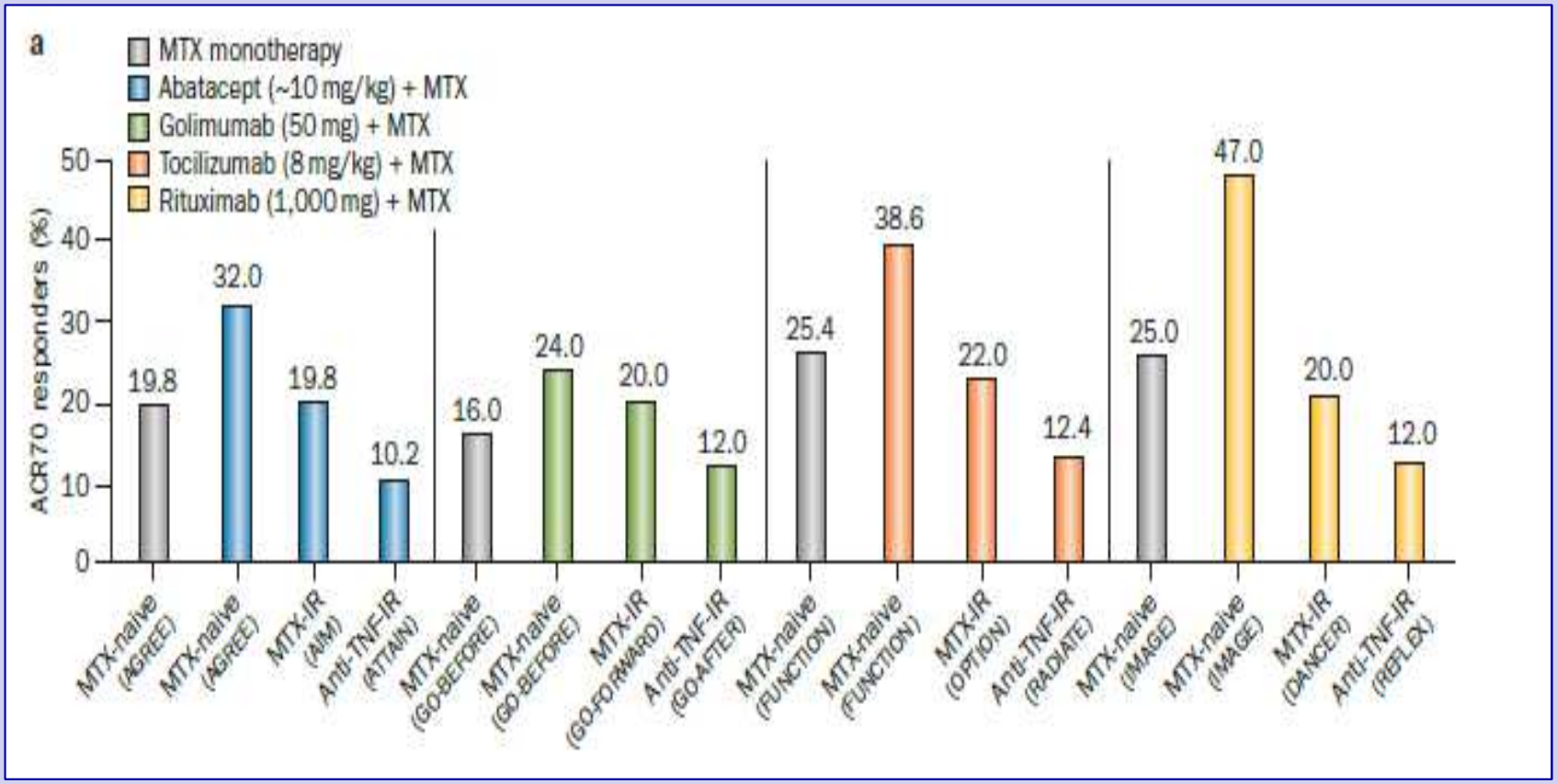
Algorithm for treating rheumatoid arthritis (RA)



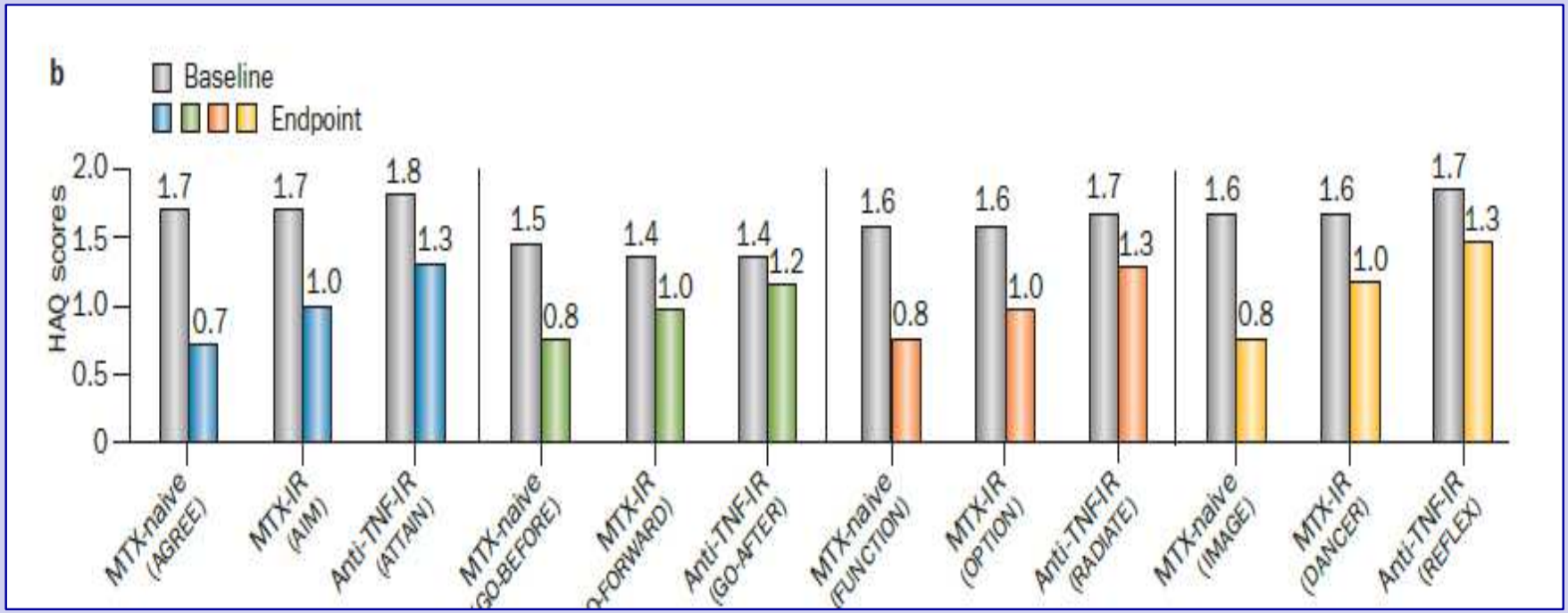
Indicated as separate threads are the main target (remission and sustained remission) and the alternative target (low disease activity in patients with long-term disease), but the approaches to attain the targets and sustain them are essentially identical

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

Clinical Response to Biologic Agents in Patients with RA

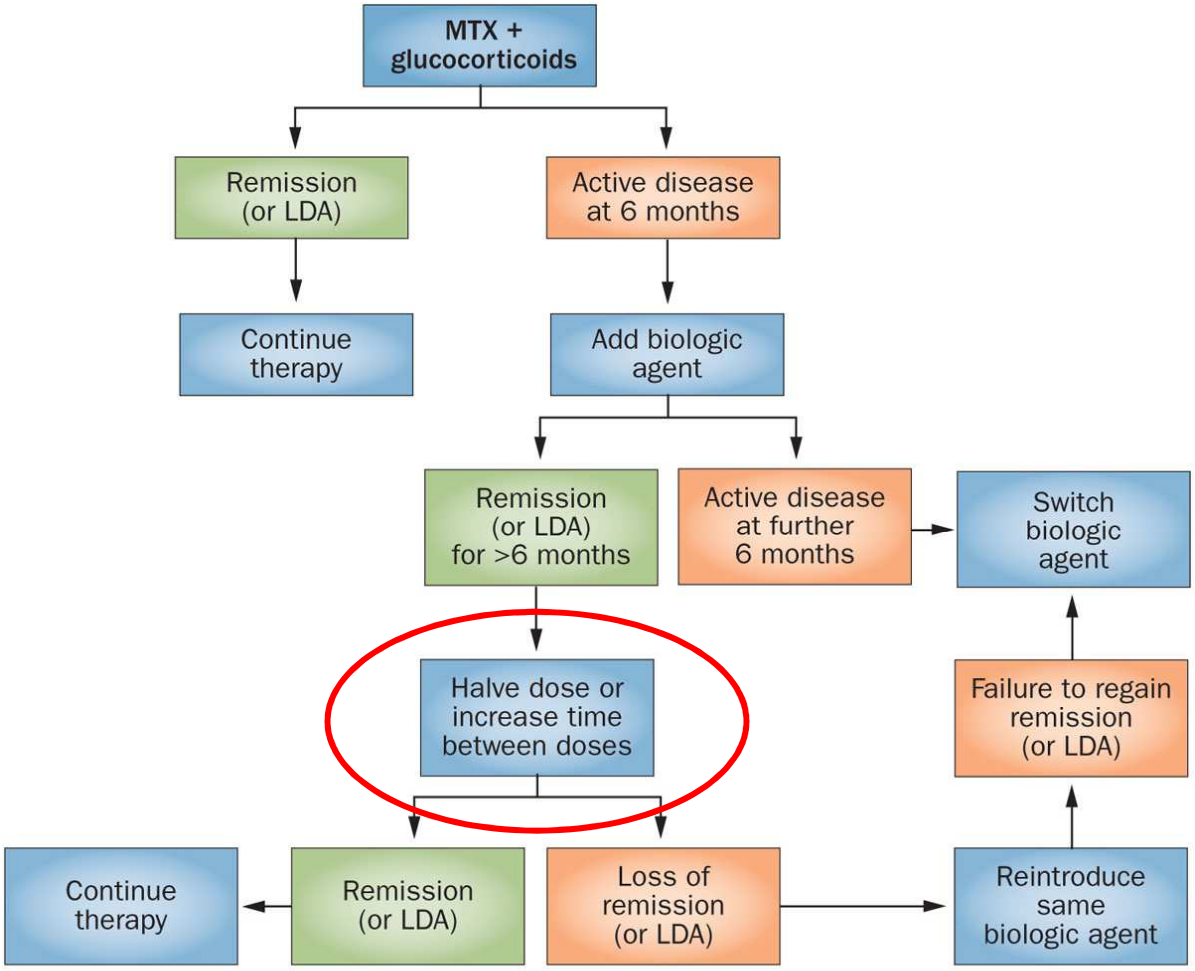


Functional Response to Biologic Agents in Patients with RA



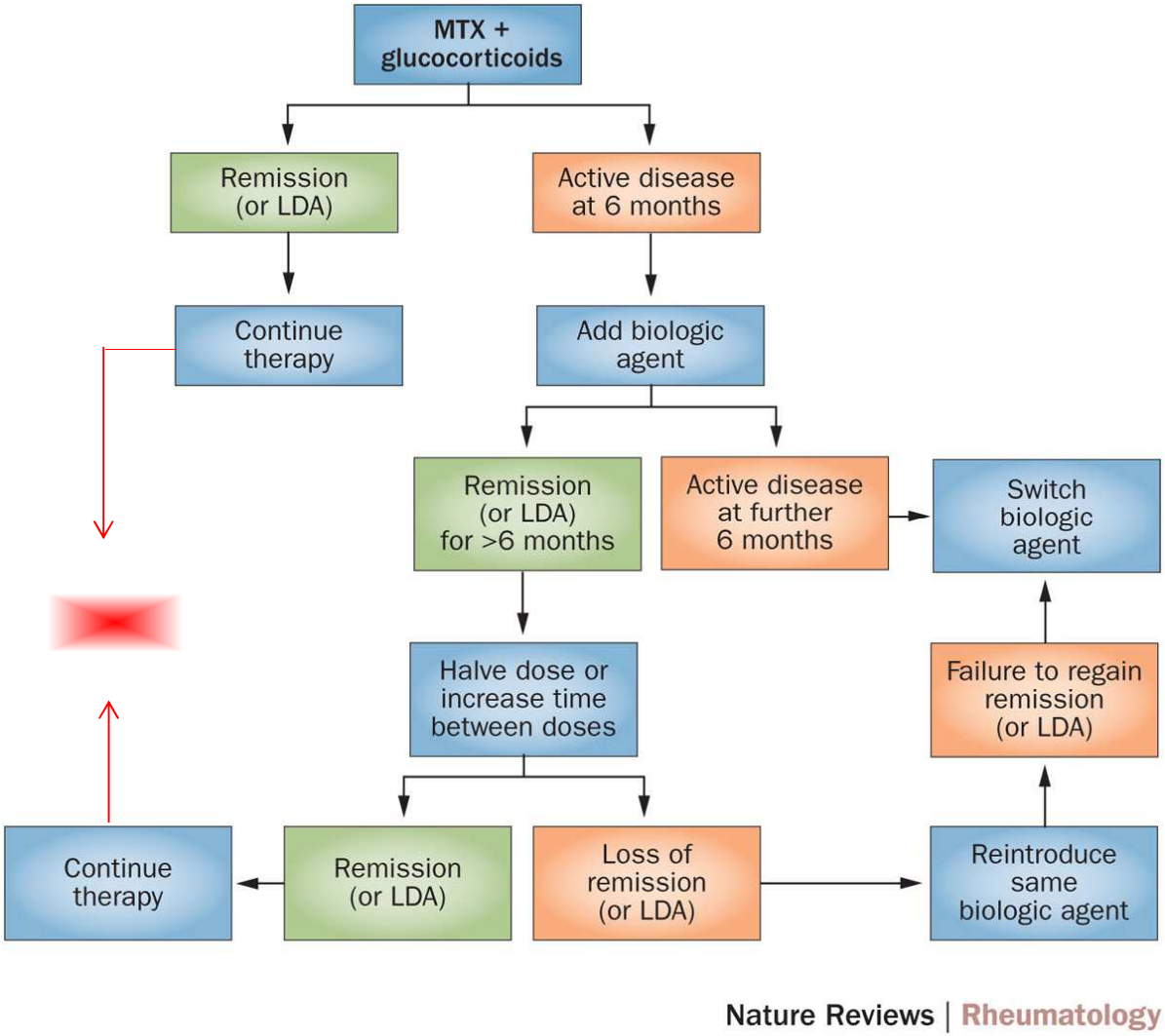
Smolen, J. S. & Aletaha, D. Nat. Rev. Rheumatol 11., 276–289 ;2015

Proposed algorithm for treatment in patients with active RA

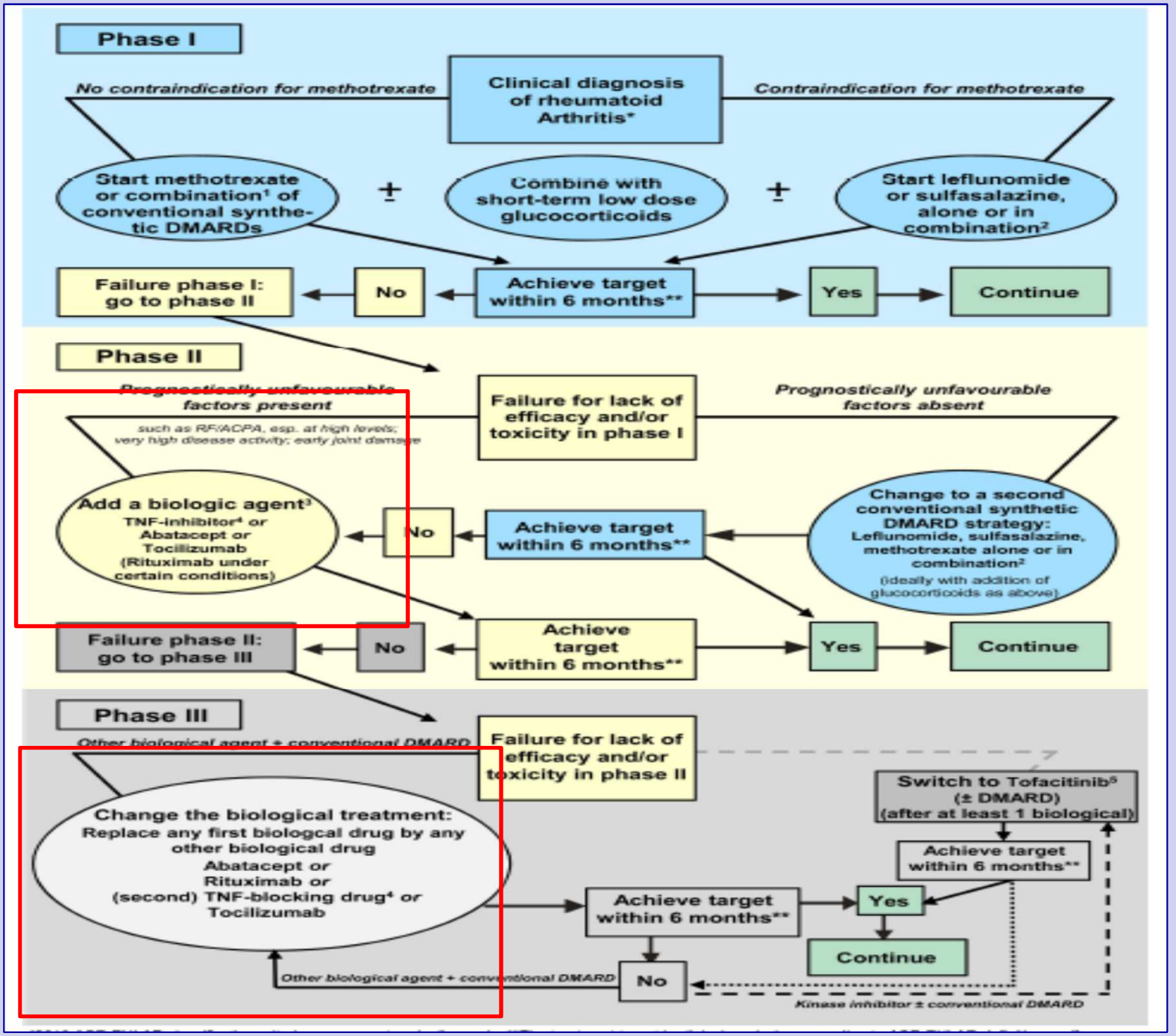


Smolen, J. S. & Aletaha, D. (2015) Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2015.8

Proposed algorithm for treatment in patients with active RA

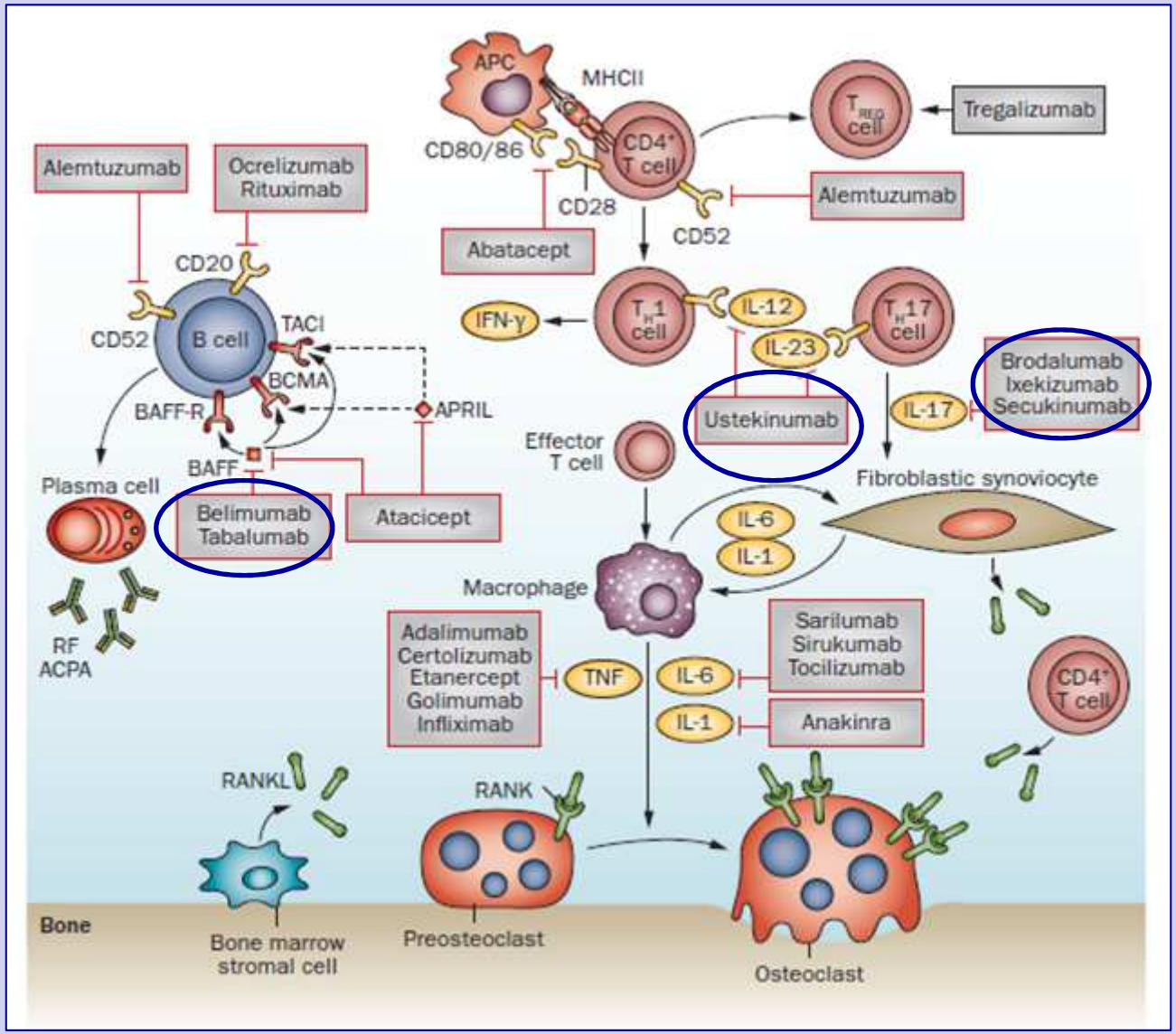


Smolen, J. S. & Aletaha, D. (2015) Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2015.8



Smolen JS, et al. Ann Rheum Dis 2014;73:492–509

Biological Therapies for Autoimmune Diseases



Smolen, J. S. Et al., Nat. Rev. Rheumatol 11,276–289;2015

The Advent of Biosimilar

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]

Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2012-203090)

For numbered affiliations see end of article.

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Linked

► http://dx.doi.org/10.1136/annrheumdis-2012-203091
► http://dx.doi.org/10.1136/annrheumdis-2012-203198

To cite: Yoo DH, Hrycaj P, Miranda P, *et al*. *Ann Rheum Dis* 2013;**72**:1613–1620.

ABSTRACT

Objectives To compare the efficacy and safety of innovator infliximab (INX) and CT-P13, an INX biosimilar, in active rheumatoid arthritis patients with inadequate response to methotrexate (MTX) treatment.

Methods Phase III randomised, double-blind, multicentre, multinational, parallel-group study. Patients with active disease despite MTX (12.5–25 mg/week) were randomised to receive 3 mg/kg of CT-P13 (n=302) or INX (n=304) with MTX and folic acid. The primary endpoint was the American College of Rheumatology 20% (ACR20) response at week 30. Therapeutic equivalence of clinical response according to ACR20 criteria was concluded if the 95% CI for the treatment difference was within ±15%. Secondary endpoints included ACR response criteria, European League Against Rheumatism (EULAR) response criteria, change in Disease Activity Score 28 (DAS28), Medical Outcomes Study Short-Form Health Survey (SF-36), Simplified Disease Activity Index, Clinical Disease Activity Index, as well as pharmacokinetic (PK) and pharmacodynamic (PD) parameters, safety and immunogenicity.

Results At week 30, ACR20 responses were 60.9% for CT-P13 and 58.6% for INX (95% CI −6% to 10%) in the intention-to-treat population. The proportions in CT-P13 and INX groups achieving good or moderate EULAR responses (C reactive protein (CRP)) at week 30 were 85.8% and 87.1%, respectively. Low disease activity or remission according to DAS28–CRP, ACR–EULAR remission rates, ACR50/ACR70 responses and all other PK and PD endpoints were highly similar at week 30. Incidence of drug-related adverse events (35.2% vs 35.9%) and detection of antidrug antibodies (48.4% vs 48.2%) were highly similar for CT-P13 and INX, respectively.

Conclusions CT-P13 demonstrated equivalent efficacy to INX at week 30, with a comparable PK profile and immunogenicity. CT-P13 was well tolerated, with a safety profile comparable with that of INX.

ClinicalTrials.gov Identifier NCT01217086

INTRODUCTION

Innovator infliximab (INX), a chimeric monoclonal antibody to tumour necrosis factor-α (TNFα), with demonstrated beneficial effects in rheumatoid arthritis (RA) patients, was approved in 1999. The approval of INX was based on data from the ATTRACT study.[1]

The availability of targeted biological therapies has revolutionised the treatment of RA. However, the significant cost of these medications creates a major barrier that limits universal access to these effective therapeutic agents. This has led to interest in developing biosimilar products, which are highly similar, but not identical and not 'bioidentical', to approved 'reference' agents.[2]

CT-P13 is an immunoglobulin (Ig)G1 chimeric human–murine monoclonal antibody biosimilar to INX. CT-P13 is produced in the same type of cell-line (Sp2/0-Ag14—purchased from ATCC, Cat. CRL-1581) and has an identical amino acid sequence to INX. CT-P13 and INX have demonstrated comparable in vitro primary pharmacodynamics (PD) in a range of studies (CELLTRION, Inc unpublished data; see online supplementary appendix A). CT-P13 and INX showed comparable binding affinities to monomeric and trimeric forms of human TNFα (hTNFα), transgenic mouse hTNFα (tmhTNFα) expressed by Jurkat cells and to Fcγ receptors and FcRn. Comparable hTNFα neutralising activity against a TNFα-sensitive mouse sarcoma cell-line (WEHI-164) has also been demonstrated. CT-P13 and INX are also comparable in terms of: lack of binding activity with hTNFβ and TNFα from a range of different species known not to bind infliximab; relative binding affinities to complement protein C1q; complement dependent cytotoxicity effects and apoptotic effects against a Jurkat T cell-line expressing tmhTNFα. Comparable cytotoxic activities have been achieved as a result of antibody-dependent cellular cytotoxicity evaluation of human peripheral blood mononuclear cells against tmhTNFα–Jurkat T cells, demonstrating biosimilarity of CT-P13 and INX. Highly comparable human tissue cross-reactivity results have been observed for biotinylated CT-P13 and biotinylated INX. CT-P13 was also assessed for bioequivalence to INX in a phase 1 trial in ankylosing spondylitis (AS).[3]

Biosimilar in Development for the Treatment of Inflammatory Diseases

Table 1 | Biosimilars in development for the treatment of inflammatory diseases[2,58-67]

Reference drug	Biosimilar*	Manufacturer	Status as of July 2015
Adalimumab	ABP 501	Amgen Inc. (USA)	Clinical trials (phase III completed in RA and psoriasis
	BI695501	Boehringer Ingelheim Pharmaceuticals Inc. (Germany)	Clinical trials (phase III in RA)
	SB5	Samsung Bioepis (South Korea)	Clinical trials (phase III in RA)
	GP2017	Sandoz Pharmaceuticals AG (Switzerland)	Clinical trials (phase III in PsA)
	PF-06410293	Pfizer Inc. (USA)	Clinical trials (phase I completed; phase III planned in RA)
	CHS-1420	Coherus Biosciences Inc. (USA)	Clinical trials (phase III planned in psoriasis)
	ONS-3010	Oncobiologics Inc. (USA)/Viropro (USA)	Clinical trials (phase I completed)
	LBAL	LG Life Sciences Ltd (South Korea)/ Mochida Pharmaceutical Co., Ltd (Japan)	Clinical trials (phase I completed)
	BCD-057	Biocad (Russia)	Clinical trials (phase I)
	M923	Momenta Pharmaceuticals Inc. (USA)/ Baxter International Inc. (USA)	Clinical trial (phase I)
	BOW050	EPIRUS Biopharmaceuticals Inc. (USA)	Preclinical studies
	(N.D.)	AET BioTechnology Ltd (Germany)/ BioXpress Therapeutics SA (Switzerland)	Preclinical studies
Etanercept	SB4	Samsung Bioepis (South Korea)	Clinical trials (phase III in RA; completed)
	GP2015C	Sandoz Pharmaceuticals AG (Switzerland)	Clinical trials (phase III completed in psoriasis)
	CHS-0214	Coherus Biosciences Inc. (USA)/Baxter International Inc. (USA)/Daiichi Sankyo Co., Ltd (Japan)	Clinical trials (phase III in RA and psoriasis)
	TuNEX® (ENA11)	TSH Biopharm Co., Ltd (Taiwan)	Clinical trials (phase III in RA)
	LBEC0101	LG Life Sciences Ltd (South Korea)/ Mochida Pharmaceutical Co., Ltd (Japan)	Clinical trials (phase III in RA)
	DWP422	Daewoong Pharmaceutical Co., Ltd (South Korea)	Clinical trials (phase I)
	PRX-106	Protalix Biotherapeutics Inc. (Israel)	Clinical trials (phase I)
	Avent™	Avesthagen Ltd (India)	Preclinical studies
	BX2922	BioXpress Therapeutics SA (Switzerland)	Preclinical studies
Infliximab	SB2	Samsung Bioepis (South Korea)	Clinical trials (phase III in RA)
	PF-06438179	Pfizer Inc. (USA)	Clinical trials (phase III in RA)
	NI-071	Nichi-Iko Pharmaceutical Co., Ltd (Japan)	Clinical trials (phase III in RA)
	BCD-055	Biocad (Russia)	Clinical trials (phase I in AS)
	ABP 710	Amgen Inc. (USA)	Preclinical studies
Tocilizumab	BOW070	EPIRUS Biopharmaceuticals Inc. (USA)	Preclinical studies
	(N.D.)	BioXpress Therapeutics SA (Switzerland)	Preclinical studies
Rituximab	BCD-020	Biocad (Russia)	Clinical trials (phase III in RA)
	CTP10	Celltrion Inc. (South Korea)	Clinical trials (phase III in RA)
	SAIT101	Samsung Electronics Co. Ltd (South Korea)	Clinical trials (phase I/III in RA; prematurely ended)
	TL011	Teva Pharmaceutical Industries Ltd (Israel)	Clinical trials (phase III in RA; prematurely ended)
	PF-05280586	Pfizer Inc. (USA)	Clinical trials (phase I/II completed in RA)
	GP2013	Sandoz Biopharmaceuticals AG (Switzerland)	Clinical trials (phase I/II in RA)
	MK-8808	Merck Sharp & Dohme Co. (USA)	Clinical trials (phase I completed in RA)
	ABP 798	Amgen Inc. (USA)	Preclinical studies
	(N.D.)	iBio Inc. (USA)/GE Healthcare (USA)	Preclinical studies

Dörner. T, et al. Nat. Rev. Rheumatol. 11, 713–724;2015

Safety of Biologic Therapy

Table 1 | Nonimmediate adverse events caused by biologic agents used to treat rheumatic and immunologic disorders

Biologic agent	Major organs or systems affected					
	Skin	Cardiovascular and pulmonary system	Gastrointestinal system	Haematopoietic and immune system	Nervous system	Infections
Abatacept	Psoriasis (4 cases)	Cough, COPD exacerbation (increased by 20%), ILD exacerbation (>15 cases)	Elevated serum levels of aminotransferases	Leukopenia, thrombocytopenia (rare)	NA	Increased (intermediate) risk of reactivation of latent TB
Anakinra	Psoriasis (1 case)	NA	Elevated serum levels of aminotransferases	Leukopenia	NA	Increased risk of serious infection
Rituximab	Psoriasis (6 cases), cutaneous vasculitis (3 cases), TEN, SJS	ILD (0.3–1%, >175 cases)	NA	Thrombocytopenia (rare), progressive hypogammaglobulinaemia	Enhanced risk of PML with concomitant immunosuppressive therapy	Increased risk of liver failure with hepatitis B
TNF antagonists	Psoriasis (>200 cases); cutaneous vasculitis (>125 cases); cutaneous lupus; (neutrophilic) dermatoses	ILD (~1%, >120 cases), pulmonary vasculitis (3 cases), sarcoidosis (46 cases, 74% pulmonary, 29% cutaneous), heart failure (rare case reports)	Elevated serum levels of aminotransferases	Neutropenia, thrombocytopenia (0.1–2%), pancytopenia (2 cases with etanercept), aplastic anaemia (1 case with etanercept), increased risk of hepatosplenic lymphoma, thromboembolism (7 cases with adalimumab), inflammatory ocular disease (>90 cases), renal vasculitis (18 cases), autoimmune hepatitis (19 cases), inflammatory myopathy (5 cases), APS (30–40 cases), lupus-like syndrome (0.1–0.8%, >140 cases)	CNS vasculitis (6 cases), demyelinating disease, PNS vasculitis, relapse of multiple sclerosis, induction of optic neuritis, Guillain–Barré syndrome	Increased risk of reactivation of latent TB and opportunistic infections (high with anti-TNF monoclonal antibody therapy, intermediate with etanercept), increased risk of serious infections, increased risk of liver failure with hepatitis B
Tocilizumab	Psoriasis (1 case), erythroderma (1 case)	ILD (1%, >113 cases)	Intestinal perforation (0.3 per 100 patient-years), elevated serum levels of aminotransferases (~10%)	Neutropenia (4%), thrombocytopenia (1.7%)	NA	Increased risk of serious infections, increased (intermediate) risk of reactivation of latent TB

Woodrick et al. Nat. Rev. Rheumatol 11, 639-652 ;2015

Recommended Screening Before Initiation of Biologic Therapy

Table 3 | Recommended screening before initiation of biologic therapy

Screen	Agents and recommendations				
	TNF inhibitors	**Anakinra**	**Abatacept**	**Rituximab**	**Tocilizumab**
Complete Blood Count with differential	–	Recommended	–	–	Recommended
Congestive heart failure	Recommended	–	–	–	–
Diverticulitis	–	–	–	–	Recommended
Immunoglobulin levels	–	–	–	Recommended	–
Liver function tests	–	–	–	–	Recommended
Tuberculosis	Recommended	–	Recommended	–	Recommended
Viral hepatitis	Recommended	–	–	Recommended	Recommended
Lung disease	–	Recommended	–	–	–
Neurodegenerative conditions	Recommended	–	–	–	Recommended

Woodrick et al. Nat. Rev. Rheumatol 11, 639-652;2015

Summary of Drug Compatibility in Pregnancy and Breastfeeding

	Compatible peri-conception	Compatible with first trimester	Compatible with second/third trimester	Compatible with breastfeeding	Compatible with paternal exposure
Corticosteroids					
Prednisolone	Yes	Yes	Yes	Yes	Yes
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
Antimalarials					
HCQ	Yes	Yes	Yes	Yes	Yes[a]
DMARDs					
MTX <20 mg/week	Stop 3 months in advance	No	No	No	Yes[a]
SSZ (with 5 mg folic acid)	Yes	Yes	Yes	Yes[b]	Yes[c]
LEF	Cholestyramine washout, no	No	No	No data	Yes[a]
AZA <2 mg/kg/day	Yes	Yes	Yes	Yes	yes
CSA	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
Tacrolimus	Yes	Yes[d]	Yes[d]	Yes[a]	Yes[a]
CYC	No	No[e]	No[e]	No	No
MMF	Stop 6 weeks in advance	No	No	No	Yes[a]
IVIG	Yes	Yes	Yes	Yes	Yes[a]
Anti-TNF					
Infliximab	Yes	Yes	Stop at 16 weeks	Yes[a]	Yes[a]
Etanercept	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Adalimumab	Yes	Yes	Second but not third	Yes[a]	Yes[a]
Certolizumab	Yes	Yes	Yes[a]	Yes[a]	No data
Golimumab	No data	No data	No data	No data	No data
Other biologics					
Rituximab	Stop 6 months in advance	No[f]	No	No data	Yes[a]
Tocilizumab	Stop 3 months in advance	No[f]	No	No data	No data[g]
Anakinra	No	No[f]	No	No data	No data[g]
Abatacept	No	No[f]	No	No data	No data[g]
Belimumab	No	No[f]	No	No data	No data[g]

Flint j. Et al, BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding. Rheumatol. 2016

Trials of Withdrawal, Dose Reduction or Interval Spacing of TNF-Inhibitors in RA

Table 1 | Trials of withdrawal, dose reduction or interval spacing of TNF-inhibitors in RA

Study	Response threshold	Type of intervention	Brief summary of results
Early RA			
BeSt[142]	DAS44 ≤2.4	Withdrawal	Proportionally more frequent maintenance of remission in patients who immediately started with anti-TNF than those who received it after a delay, but reactivation occurred in about one-third, and overall more patients who immediately started with anti-TNF needed anti-TNF at 5 years than patients who started with conventional synthetic DMARDs
HIT HARD[143]	None, stopped at 24 weeks	Withdrawal	Maintenance of good outcome in >80% of patients upon adalimumab withdrawal; no control group
OPTIMA[113]	DAS28 <3.2	Withdrawal	Maintenance of good outcome in >80% of patients and only slightly more good outcomes upon anti-TNF continuation
PRIZE[144]	DAS28 <2.6	Withdrawal and dose-reduction	Half-dose etanercept had significantly better maintenance of good outcome than withdrawal of etanercept (no full-dose control arm)
Established RA			
CERTAIN[136]	CDAI ≤2.8	Withdrawal	Most patients experienced disease flare upon withdrawal of certolizumab pegol, but reintroduction of the drug re-established a good outcome in most patients
HONOR[131]	DAS28 <2.6	Withdrawal	>50% experienced flare upon adalimumab withdrawal; the lower the disease activity at time of withdrawal, the less likely was flare
PRESERVE[134]	DAS28 ≤3.2	Withdrawal and dose-reduction	Half-dose etanercept led to similar maintenance rates as full dose; withdrawal of etanercept led to flares in >50% of patients
RRR[130]	DAS28 <3.2	Withdrawal	Almost 50% flared upon withdrawal of infliximab
STRASS[139]	DAS28 ≤2.6 and no radiographic progression	Increased interval between doses	The interval between doses could be increased successfully in most patients, but the results were statistically worse than with maintenance of therapy

Abbreviations: CDAI, clinical disease activity index; DAS28, 28-joint disease activity score; DAS44, 44-joint disease activity score; RA, rheumatoid arthritis.

Smolen, J. S. & Aletaha, D. (2015)Nat. Rev. Rheumatol.

CONCLUSIONS

……We operate in the “window of opportunity” with early aggressive intervention, “aim at remission” for our patients and apply a “tight control” and “treat to target” strategies….

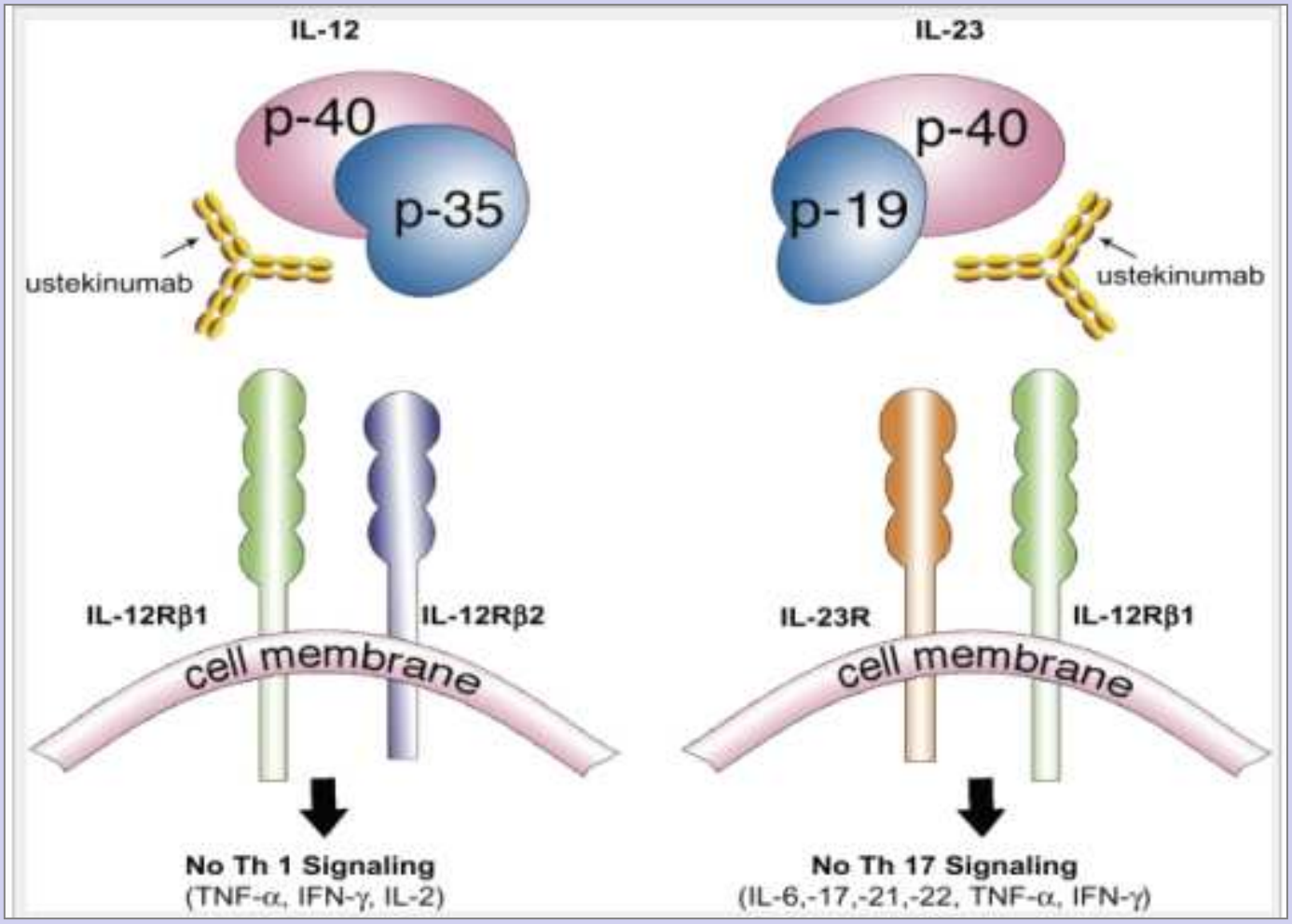
Withdrawal, Dose Reduction or Interval Spacing of TNF-Inhibitors in RA

Cessation of biological therapy will be followed by disease flares, whereas a reduction of dose or an increase in the interval between doses enables maintenance of treatment success.

Consideration before tapering:

- ✓ tapering plane,
- ✓ “target” prior to taper
- ✓ duration of disease
- ✓ disease activity prior to therapy initiation
- ✓ prior or concomitant treatment
- ✓ sequelae of flare, predictor of responses
- ✓ efficacy of retreatment.

Anti IL-12/23 Targeted Therapy in Psoriasis and PsA



Anti IL-17 Targeted Therapy in Psoriasis and PsA

Inhibitors of IL-17A

- A human anti-interleukin-17A monoclonal antibody.
- Selectively binds and neutralizes IL-17A, does not neutralize IL-17F.
- This specificity offers the potential of fewer off target effects.
- Achievement of almost clear to clear skin for the majority of patients (Mease et al. 2015)

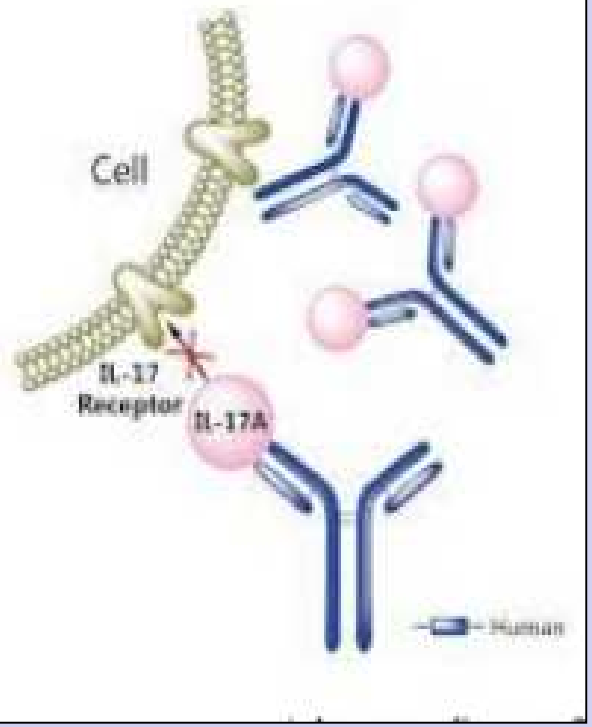
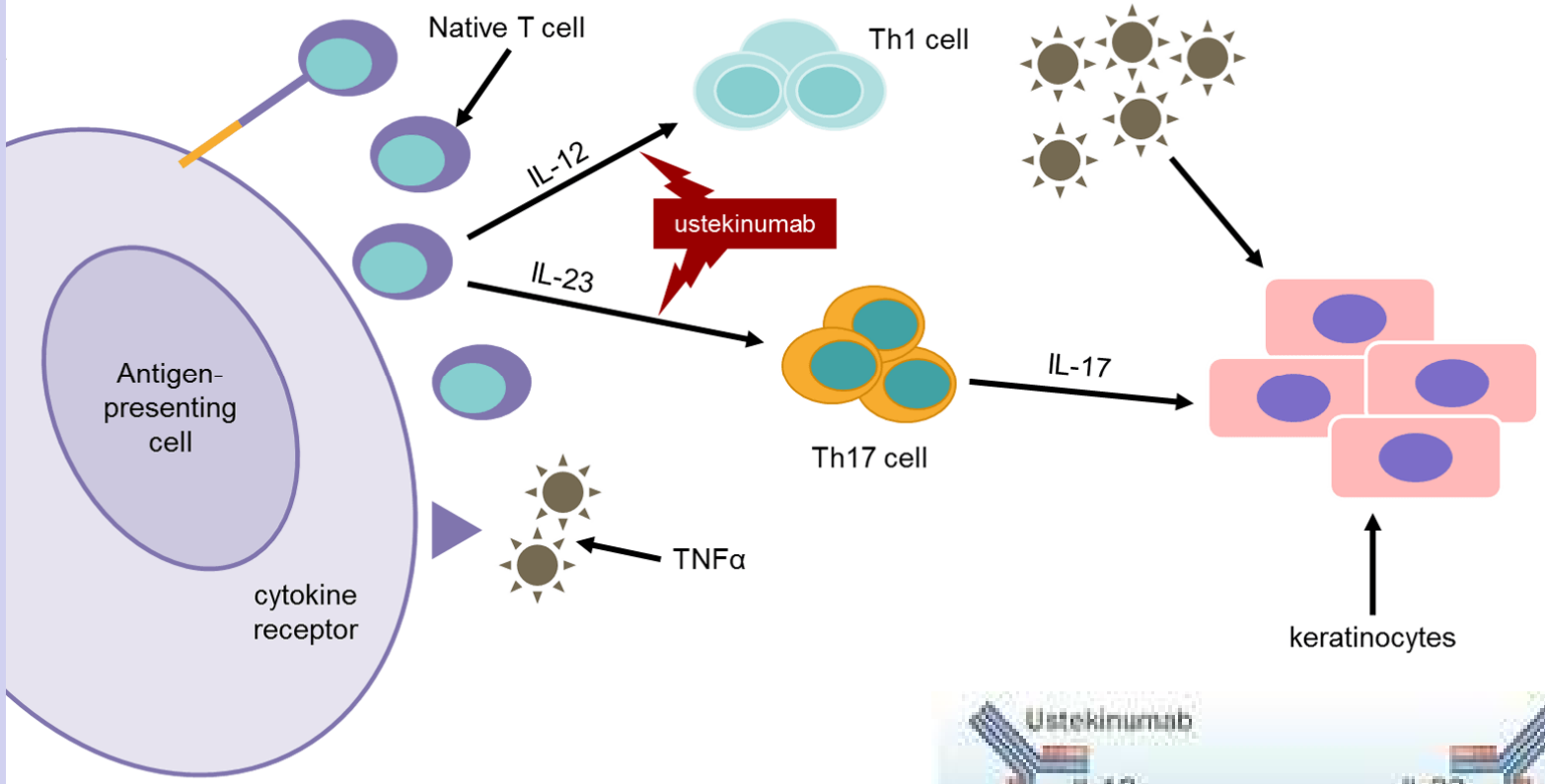
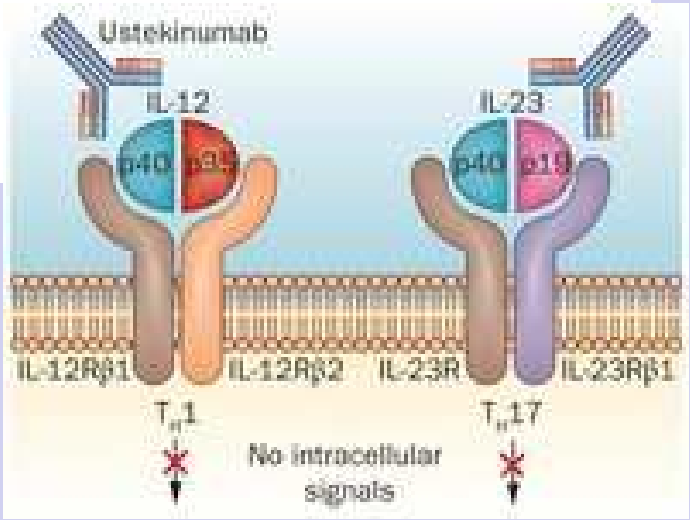


Figure 4. Anti-IL-12/IL-23–targeted Therapy in Psoriasis and PsA





Adapted from: Declercq SD, Pouliot R. *Scient World J.* 2014;2013:ID 980419.

Conclusions

- ✓ The therapeutic approach to RA has changed dramatically over the past two decade with the advent of biological drugs
- ✓ Irrispective of biological target, all effective therapies achieve similiar therapeutic effects in RA, with non of them able to induce remission in majority of patients.
- ✓ The efficacy of the varoius approaches seemingly differ by prior drug experience

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