University Hospital Southampton NHS
NHS Foundation Trust

MRC Lifecourse Epidemiology Unit

UNIVERSITY OF Southampton

Biologics and Inflammatory Arthritis

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Disclosures

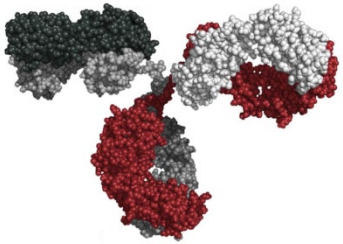
- I have received speakers fees from BMS, Pfizer, Lily, Abbvie and Roche/ Chugai and Celtrion
- I have attended advisory boards for Abbvie, UCB, BMS, Janssen, Napp and Novartis
- I have received funding to attend meetings by Abbvie, UCB, Chugai/ Roche, Celgene, BMS and Pfizer

Introduction

- Biologics first licensed for RA in late 1990s
- Revolutionised management of many rheumatic diseases
- Licensed (with NICE approval) across a range of rheumatic conditions

  - RA, AS, PsA
  - Vasculitis, GCA
  - JIA
  - SLE
  - Periodic fever syndromes

What is a biologic?



- “Any medicinal product manufactured in or extracted from biological sources (distinct from chemically synthesized pharmaceuticals)”

- Either extracted from living systems, or produced by recombinant DNA; 3 main types:

  - Substances that are (nearly) identical to the body's own key signalling proteins - erythropoetin, growth hormone or biosynthetic human insulin and its analogues

  - Monoclonal antibodies - "custom-designed“ antibodies

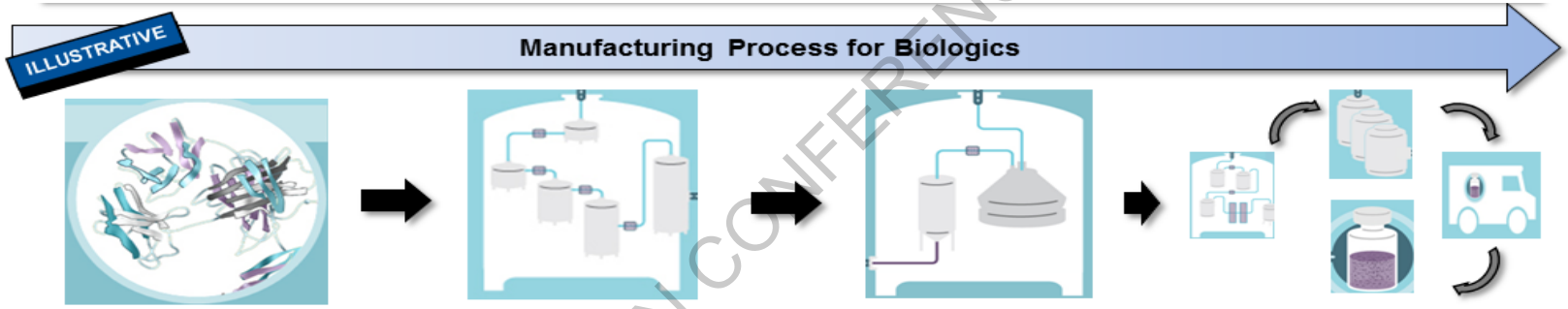
  - Receptor constructs (fusion proteins) - based on a naturally-occurring receptor linked to immunoglobulin frame

Families of biological medications for rheumatic diseases

- Anti-cytokine therapies
  - Block pro-inflammatory cytokines from binding their receptors
  - Anti-TNF, anti-IL6, anti-IL1, anti-IL 12/23, anti-IL 17

- Cell-oriented therapies
  - Removal of or prevent activation and/or proliferation of cells implicated in disease
  - Rituximab (B-cells), abatacept (T-cells)

Biologics are very large, complex structures. Most are produced using recombinant DNA technology



Step 1: Genetic development
Biologic protein developed through DNA engineering

- Biologic medicines are derived from living organisms; DNA is inserted into living cells, (known as the 'cell line')
- Cell lines are unique to each manufacturer and source of all future biologic medicine

Step 2: Cell Culture
Frozen cells from most effective, unique cell line selected for expansion

- Cells are initially placed in seed bioreactors for cell expansion
- Cells are then transferred from a seed bioreactor to a production bioreactor

Step 3: Recovery
Isolation and purification of biologic protein

- Cells are harvested and separated through filtration or centrifugation, depending on the cell type
- Biologic protein produced by cells is then transferred to a collection tank for purification

Step 4: Purification and Finish
Biologic is prepared for patient use

- The therapeutic protein undergoes extensive purification, including primary purification, viral inactivation, chromatography, ultrafiltration, bulk filtration and sterile filtration
- The formulated biologic drug is then finished for storage, transport and patient use

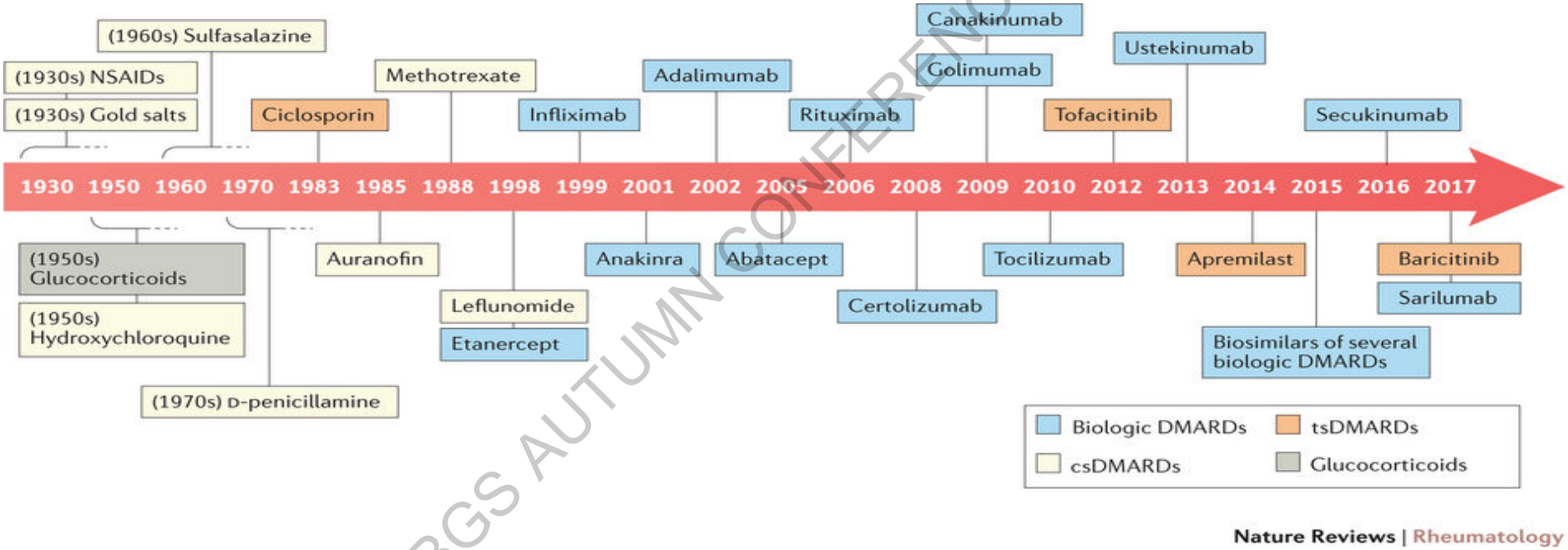
What is inflammatory arthritis?

"Inflammatory arthritis is a group of diseases characterized by inflammation of the joints and often other tissues"

Worldwide prevalence of 3%

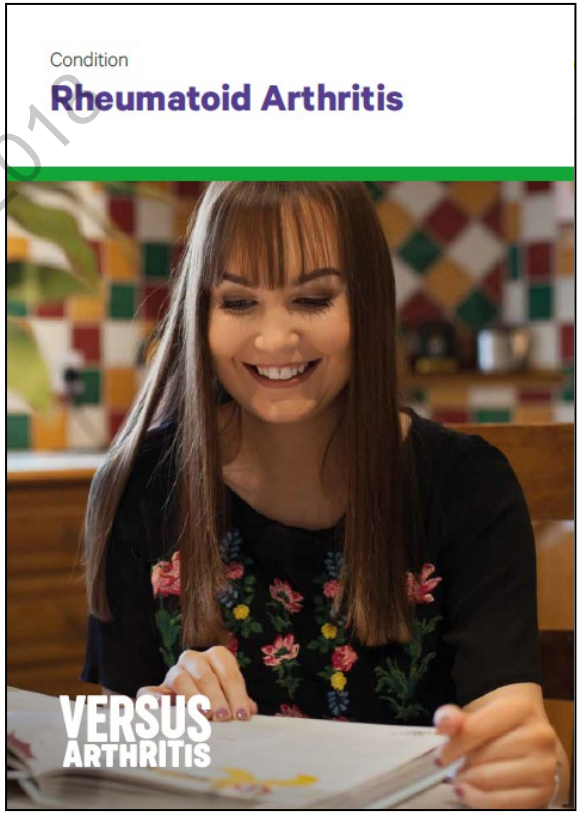
Most common types are RA, PsA, spondyloarthritis / ankylosing spondylitis

How far have we come? Therapies



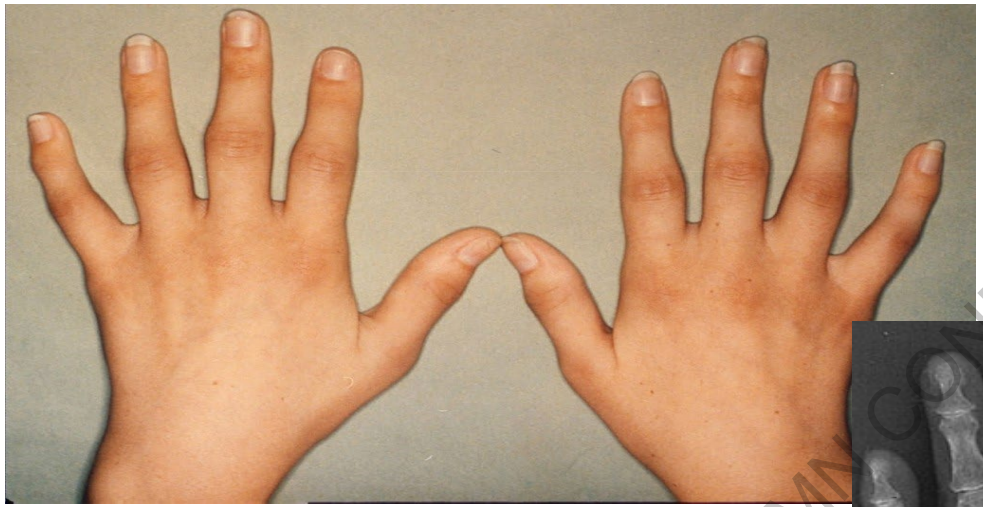
Gerd R. Burmester, Johannes W. J. Bijlsma, Maurizio Cutolo & Iain B. McInnes
Nature Reviews Rheumatology **volume 13**, pages 443–448(2017)

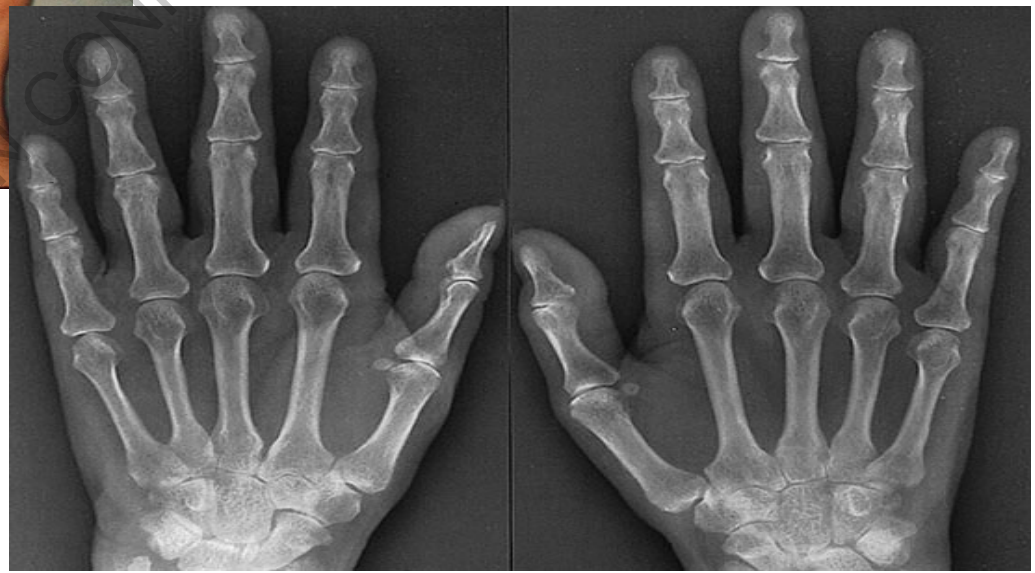
Rheumatoid arthritis



- Autoimmune Inflammatory arthritis
- ~400,000 people in UK affected
- Prevalence in UK 0.5-1%
- 3 x more common in women
- In UK approx.: 12,000 people per year develop RA
- Peak incidence 4th – 6th decades – can occur at any age
- Cost to UK economy: £3.8-4.75 billion per year

At presentation:





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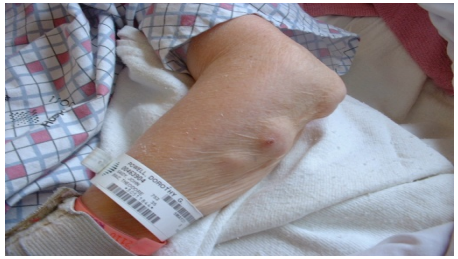

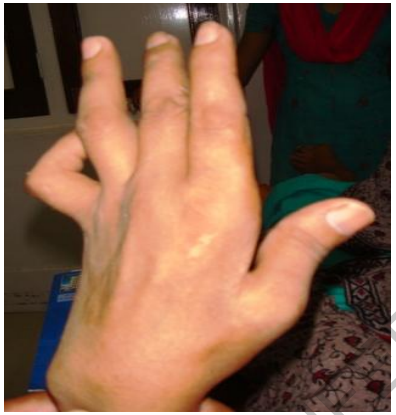

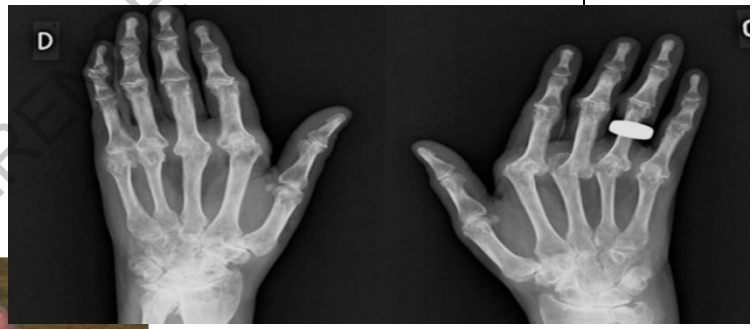

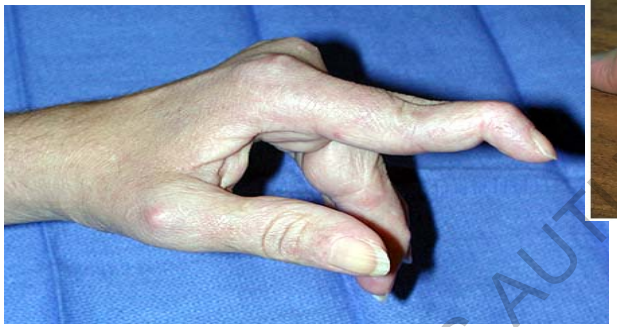

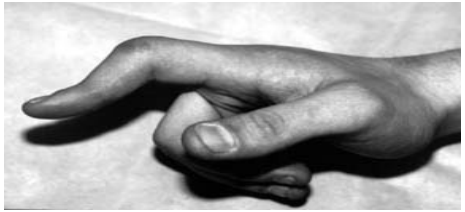

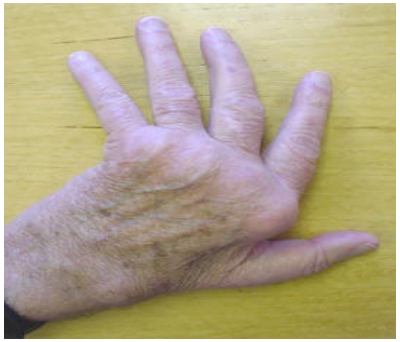

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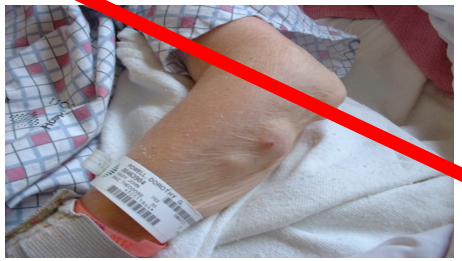
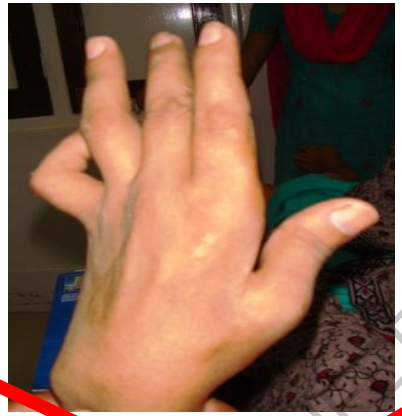
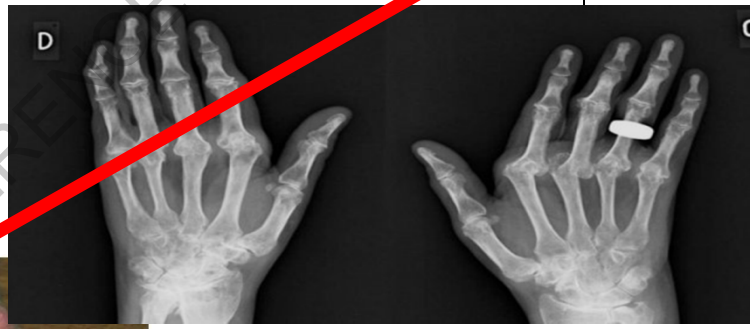
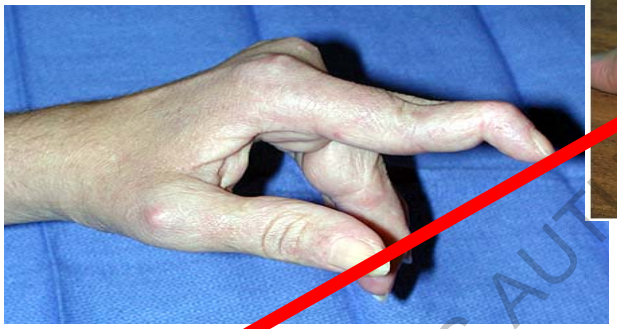
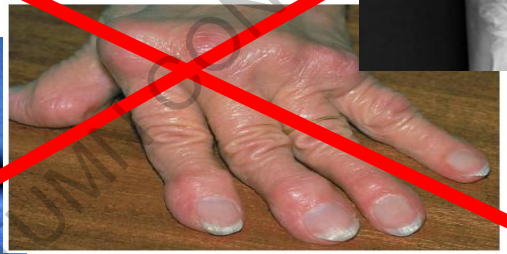
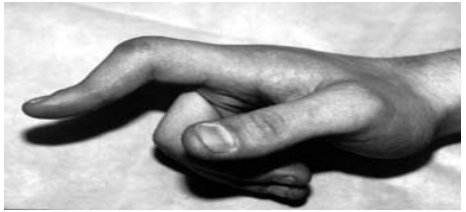


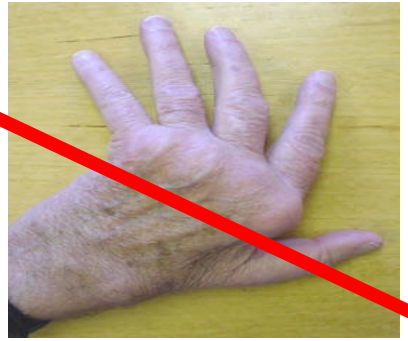






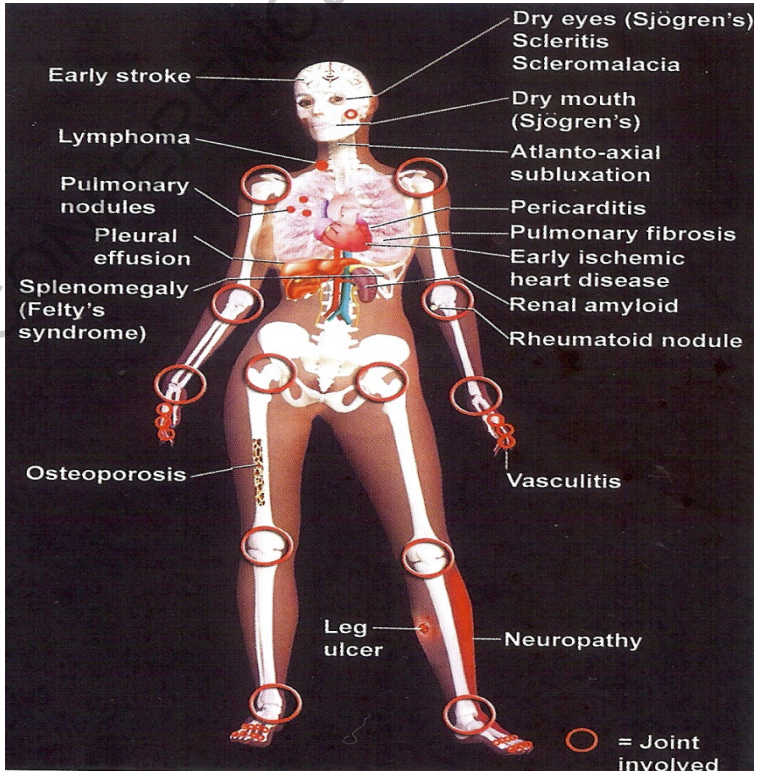




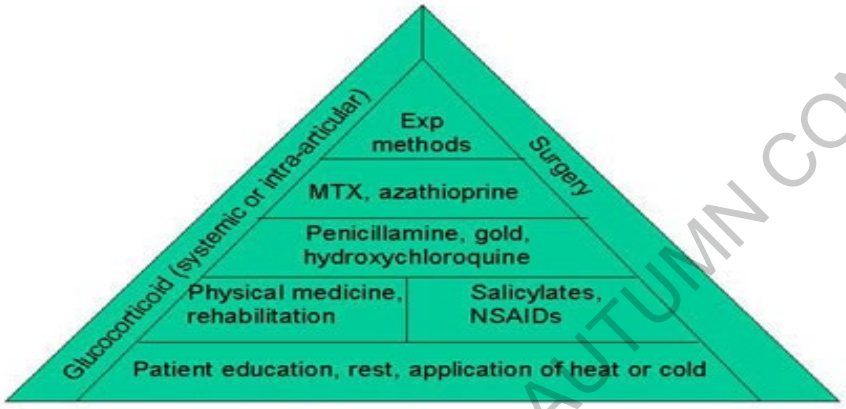


Extra-articular manifestations

- Interstitial Lung Disease
- Vasculitis
- Felty's Syndrome
- Ocular Disease
- Secondary Amyloid
- Osteoporosis



RA: Traditional Treatment Paradigm

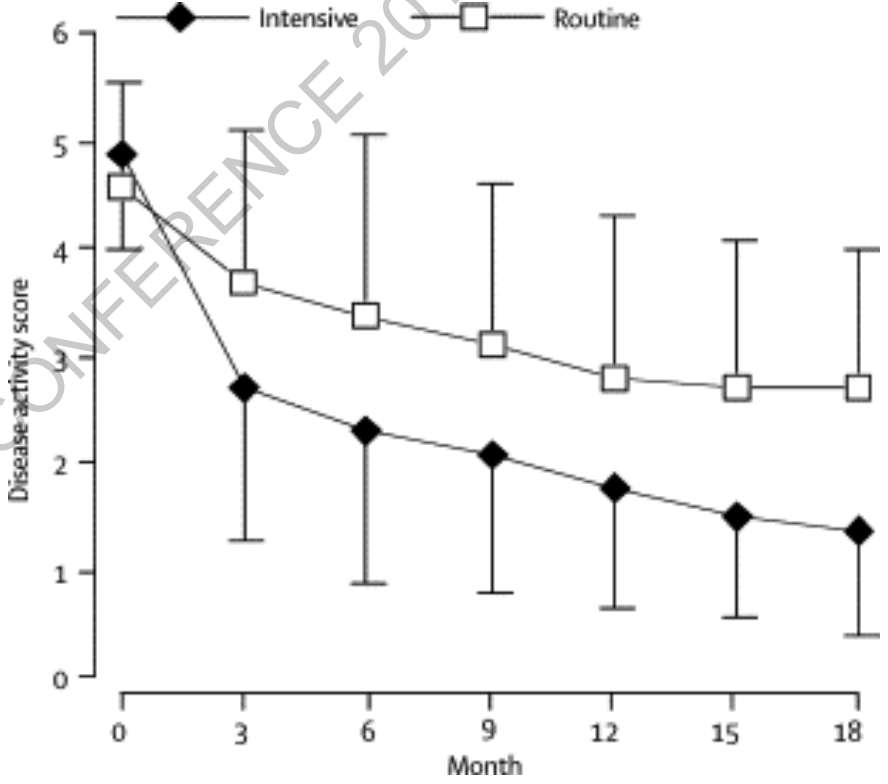


Pyramid of therapy

- Start conservatively
- Gradually ascend the pyramid in order of potency and toxicity of therapy
- Only the most severely affected patients receive immuno-suppressive, DMARDs
- DMARD therapy begun only after period of significant delay

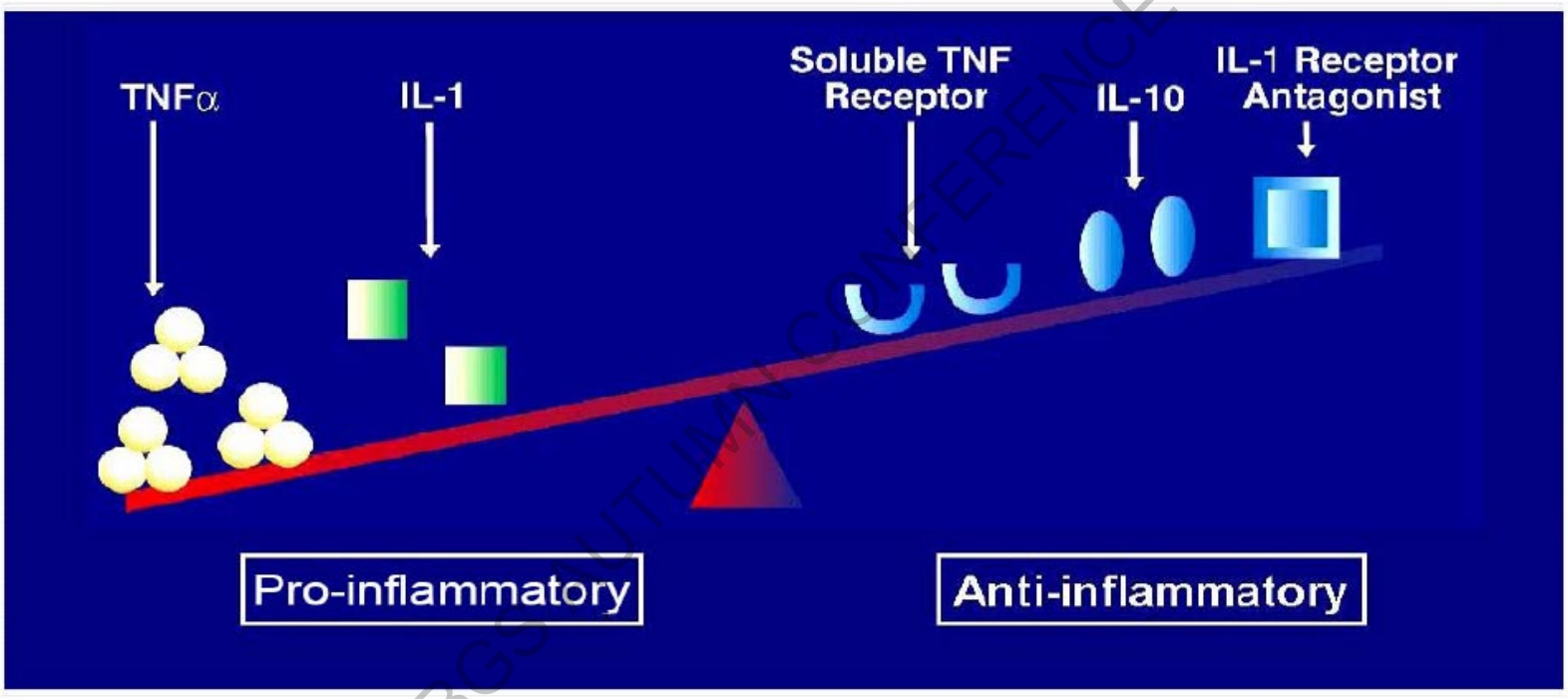
TICORA study

A strategy of intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.



Grigor C et al. Lancet 2004; 364:263-269

Disequilibrium of Cytokines in Joints of Patients with Rheumatoid Arthritis

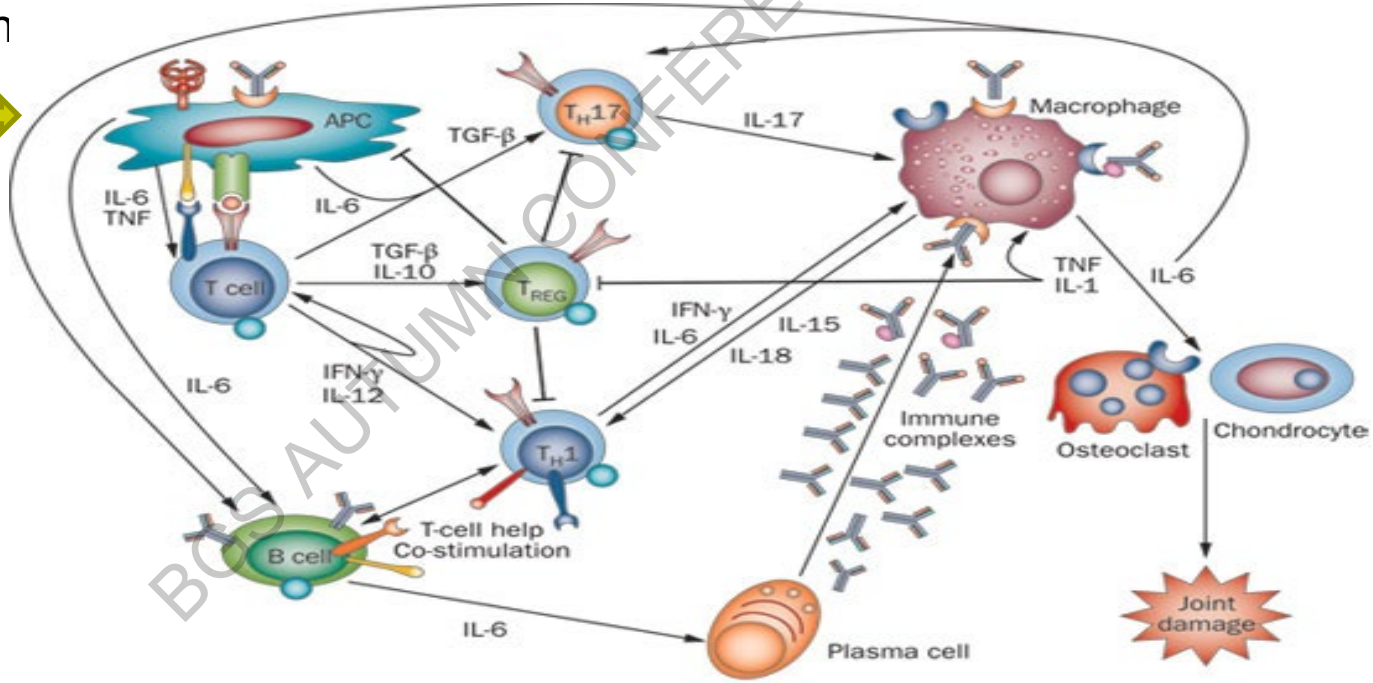


Feldman M, et al. *Rheum Arthritis.* 1996;85:307-310.

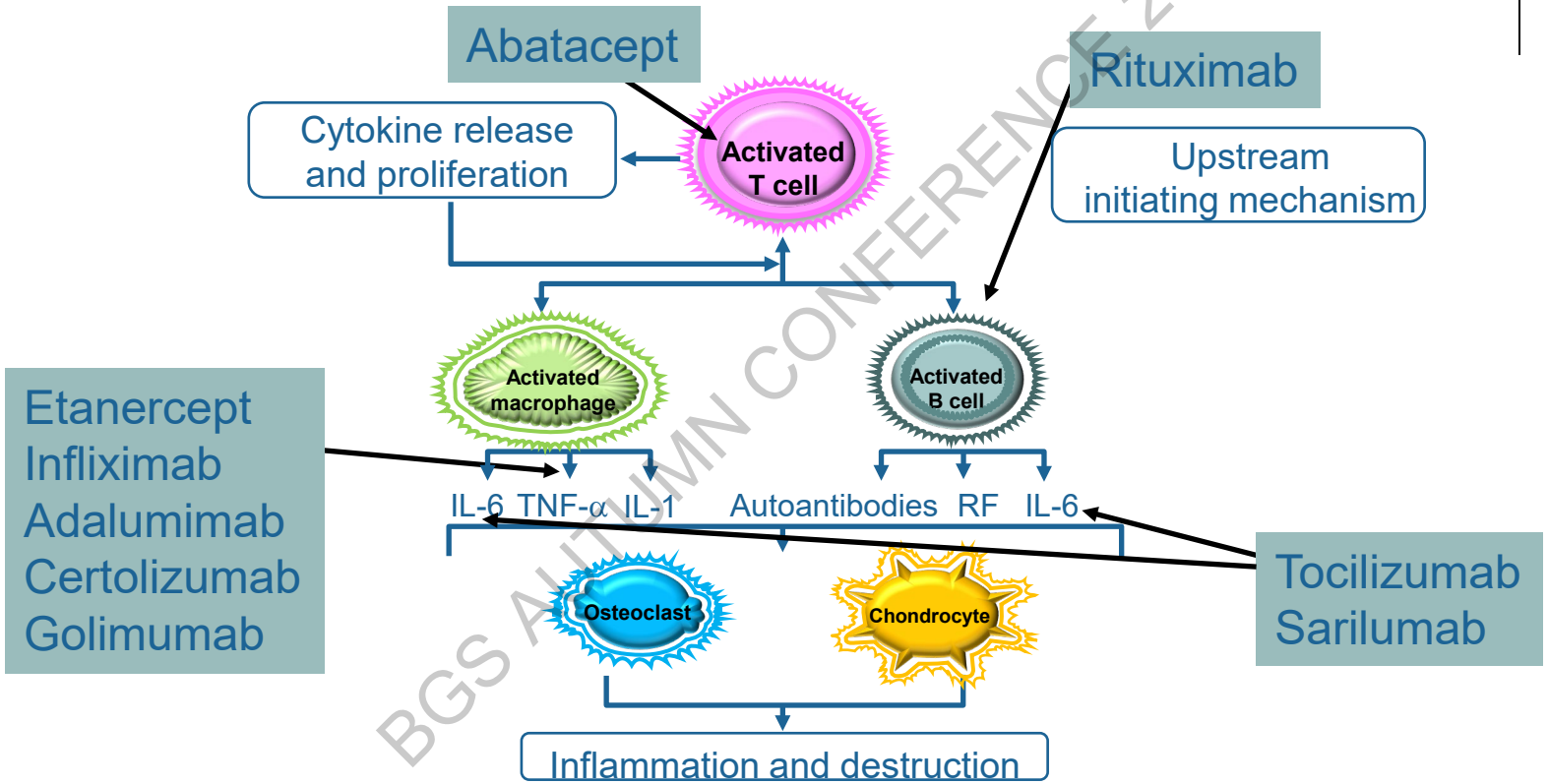
Pathogenesis

- Immunopathology of RA is complex and not fully elucidated
  - Arthritogenic antigens stimulate T-cell-initiated inflammatory response
  - Increased production of autoantibodies, e.g. rheumatoid factor (RF) and cyclic citrullin

Arthritogenic antigen



Biological therapies for RA

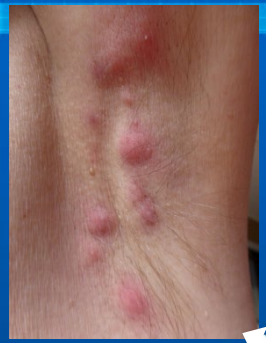


IL=interleukin; RF=rheumatoid factor.

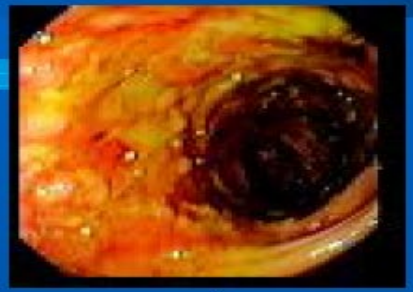
Genovese MC, et al. N Engl J Med 2005. Adapted from Smolen JS. Nature Rev Drug Dis 2003

Ankylosing Spondylitis

Hydradenitis Suppurativa

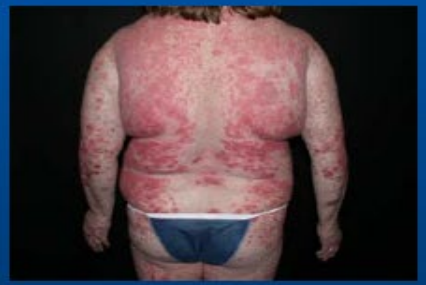


Crohn's disease



Rheumatoid Arthritis

Psoriasis

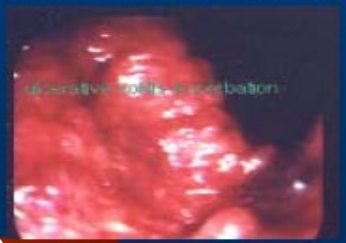


TNFα

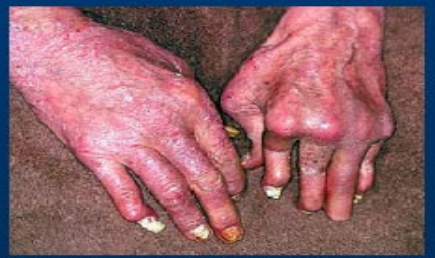
Juvenile Rheumatoid Arthritis

Non-infectious Uveitis

Ulcerative Colitis



Psoriatic Arthritis



TNF-α

- Pro-inflammatory cytokine
- Over-expressed in RA (majority)
- Primarily expressed by activated macrophages, T and B cells

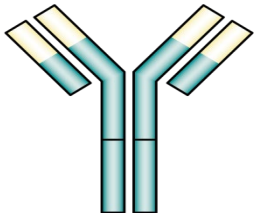
- Important biological effects:
  - Essential in control and containment of intracellular pathogens
  - Integral to granuloma formation and maintenance
  - Activates macrophages to phagocytose and kill mycobacterium and other pathogens
- Mice deficient in TNF more susceptible
  - TB, *Histoplasma*, *Listeria*, *Klebsiella*, *S. pneumoniae*

History of Anti TNF- α

- Early experiments associated TNF function with pathogenesis of bacterial sepsis
- First preclinical studies showed that anti-TNF antibodies protected mice from sepsis.
- Subsequent clinical trials in sepsis patients showed no significant benefit with anti-TNF treatment.
- 1991: causal role of TNF in the development of polyarthritis and theory that anti-TNF treatments could be effective against human arthritides
- 1992: first of a series of successful clinical trials in RA was performed at Kennedy Institute, Charing Cross Hospital, UK using infliximab. Further clinical trials followed
- 1998: Etanercept licensed for treatment of RA in USA

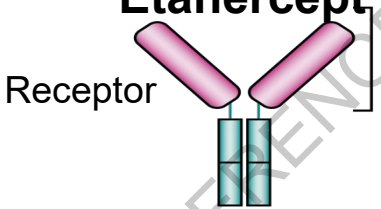
Anti-TNF agents

Infliximab



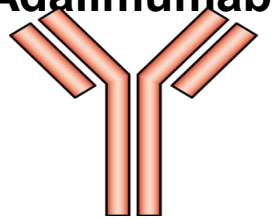
Monoclonal antibody
Chimeric mouse/human
IV
6-8 weekly
½ life 10.5 days

Etanercept



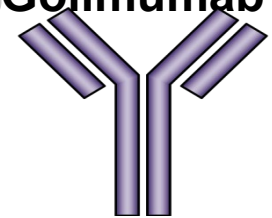
Fusion protein
Decoy receptor
s/c
weekly
½ life 3 days

Adalimumab



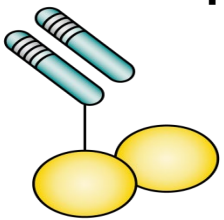
Monoclonal antibody
human
s/c
fortnightly
½ life 10-20 days
World's largest selling drug

Golimumab



Monoclonal antibody
human
s/c
monthly
½ life 14 days

Certolizumab pegol

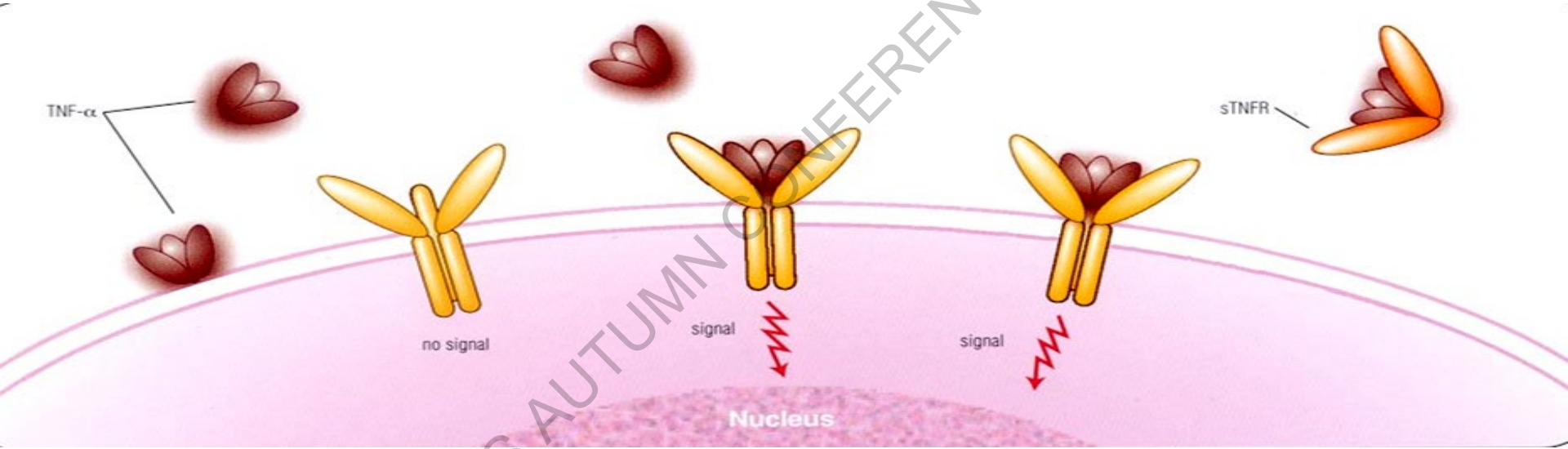


Monoclonal antibody
Humanized (from mouse)
s/c
fortnightly
½ life 14 days
Pegylated Fab fragment

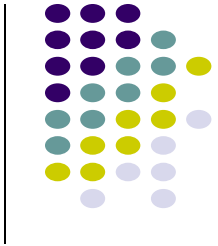
All approved by NICE for treatment of severe RA

Adapted from van Vollenhoven RH. *Nat Rev Rheumatol* 2011;7:205–215.

TNFα and it's Receptor



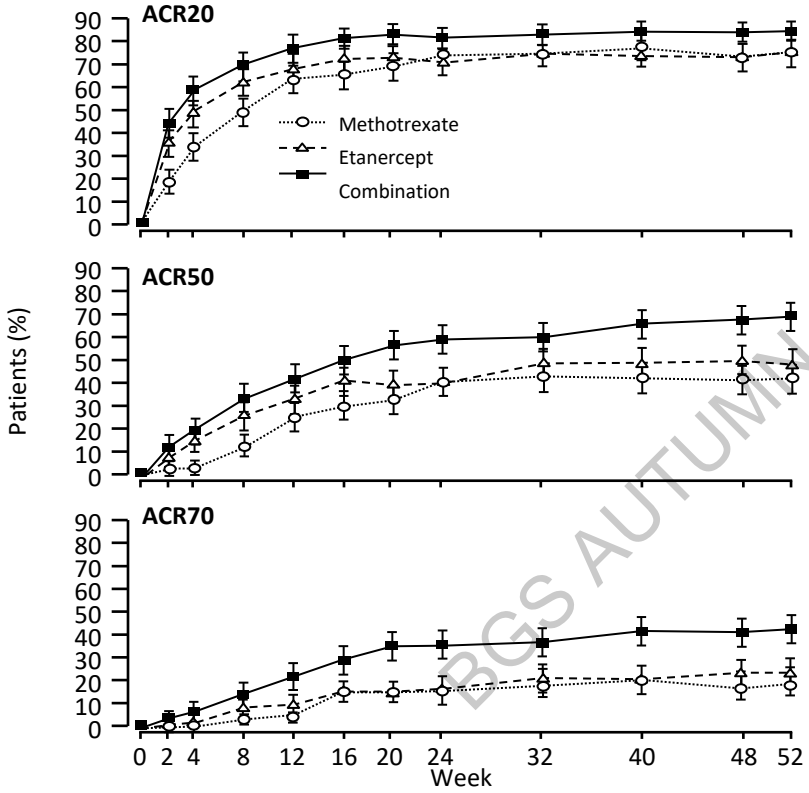
Efficacy

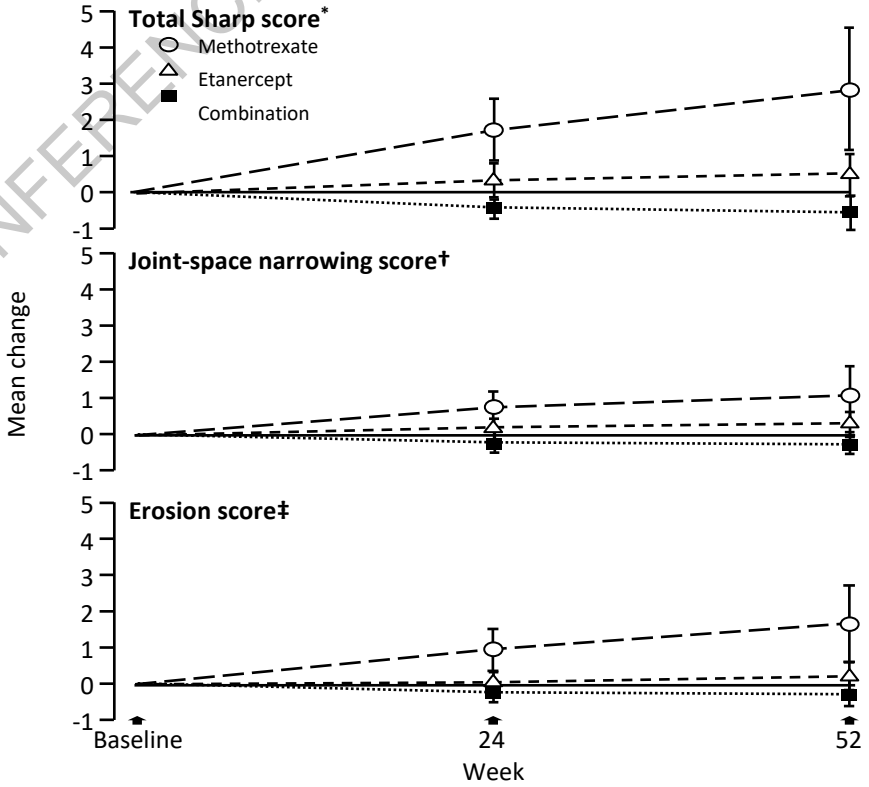


- Clinical trials have consistently demonstrated:
  - significant improvement in clinical response (ACR/ DAS response)
  - Increased rates of remission and low disease activity
  - Reduction in radiographic progression
  - Improvement in quality of life

  - NB – anti-TNF efficacy as a monotherapy is similar to that of MTX in terms of clinical response. Combination of MTX and biologic gives greater clinical response

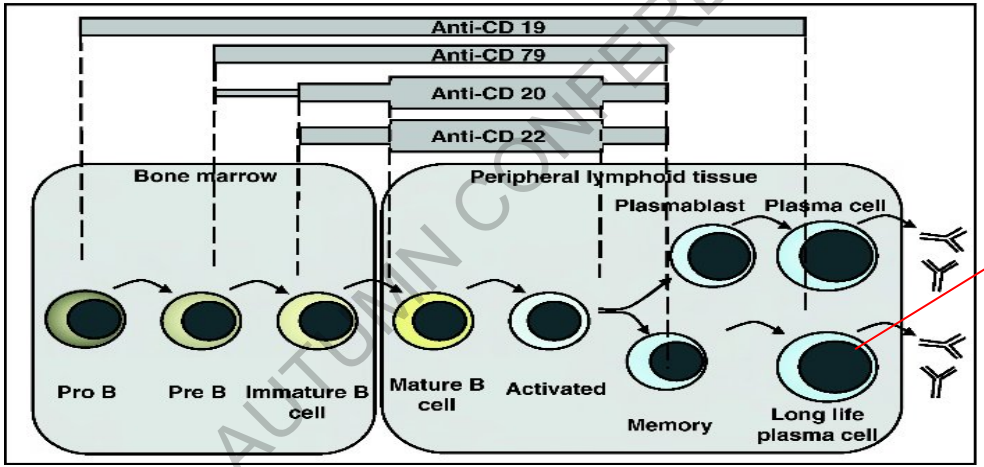
Anti-TNF agents should be given in combination with MTX





Rituximab

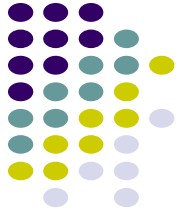
- Chimeric monoclonal antibody (mouse/human) binds to protein CD20 found on surface of B cells; leads to cell death



Does not affect Pro-B, plasmablasts or plasma cells as they do not possess CD20

- First licensed for tx of resistant B cell non-Hodgkin lymphoma 1997; approved by EMA in 2006 for tx of RA

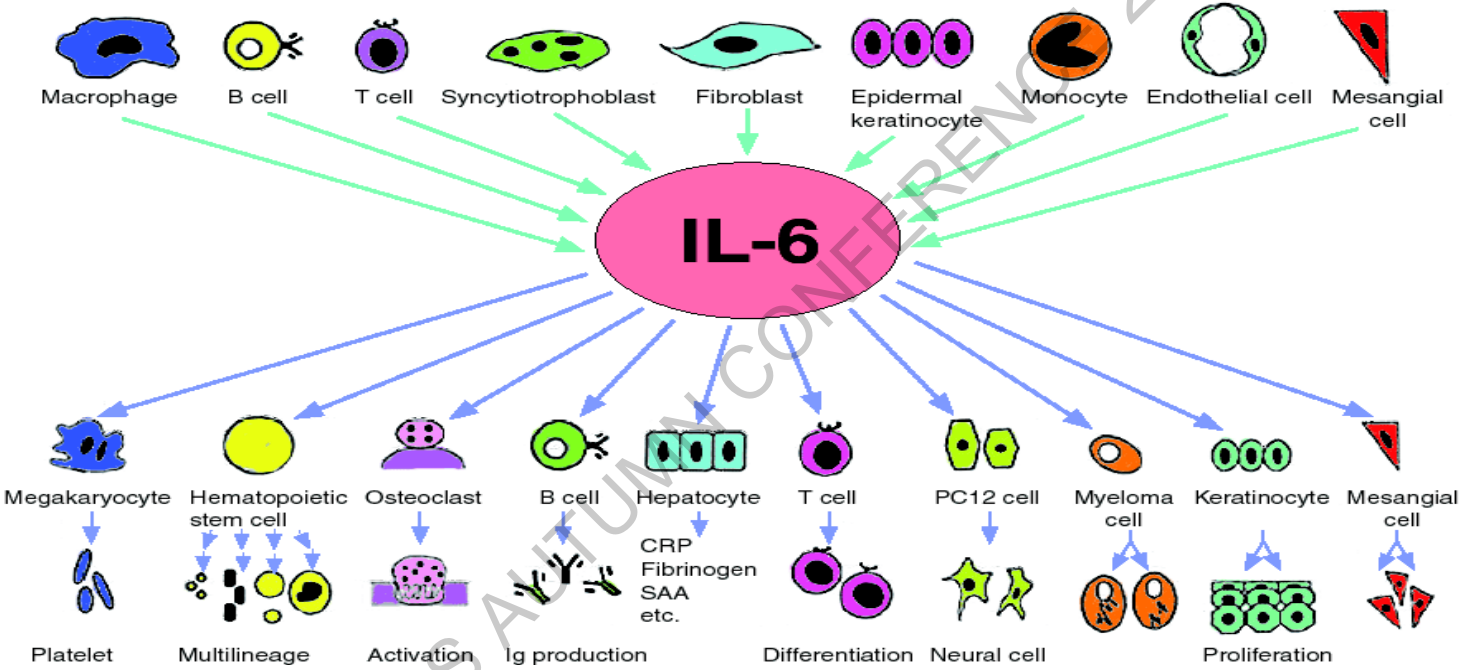
B-Cell Depletion Therapy in RA



- Rituximab given IV – max every 6/12

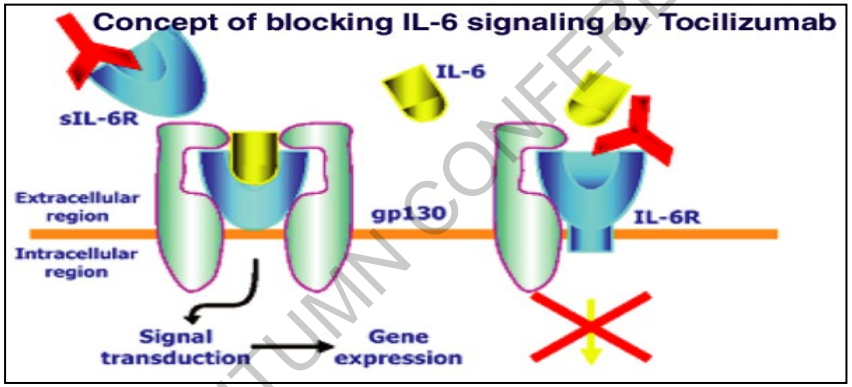
- How does B-Cell Depletion work?
  - B-Cells cannot act as APC to activate T-Cells
  - B-Cells cannot produce Rheumatoid Factor
  - B-Cells cannot release cytokines

  More effective in patients who are sero-positive and in those taking concomitant MTX



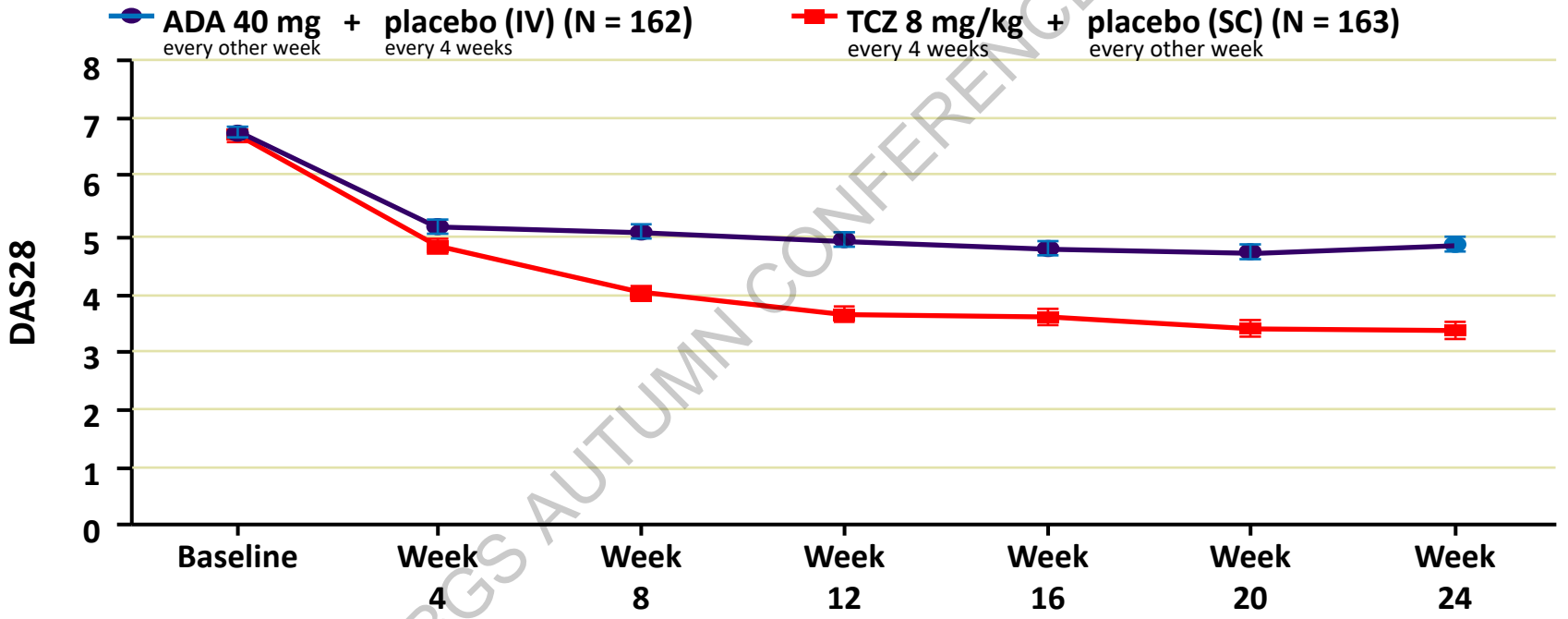
Tocilizumab

- Humanized monoclonal antibody against IL-6 receptor
- Binds to soluble and membrane bound IL-6R



- Approved for use in severe RA by EMA in 2009
- Initially monthly IV; 2014 s/c weekly preparation launched
- CRP/ ESR usually normal in patients receiving this therapy (even in presence of infection)

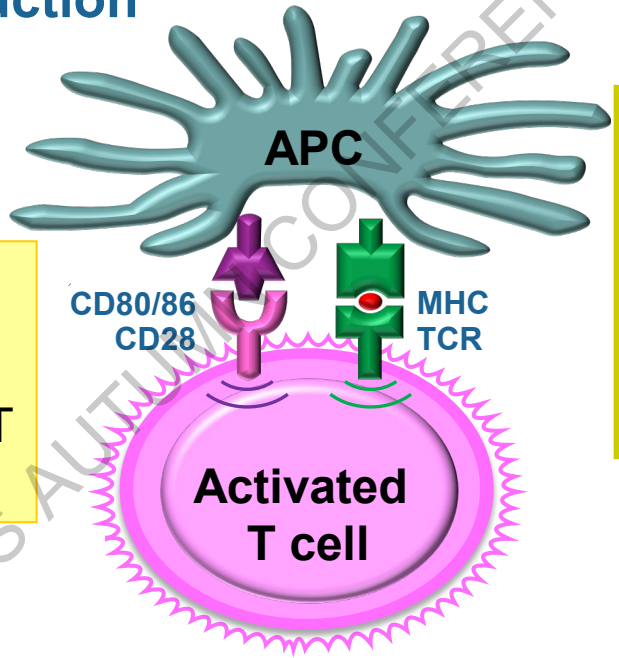
DAS28 ESR: Mean (±SE) over time



Gabay C. ADACTA study. Lancet 2013;381:1541-1550.

T Cell Activation

- **2 signals needed for full T cell activation, proliferation, survival and cytokine production**



Signal 1

APC binds antigen to MHC molecule and presents it to T cell receptor

Signal 2

APC presents either CD80/86 to CD28 on T cell

APC=antigen-presenting cell; MHC=major histocompatibility complex; TCR=T-cell receptor.
Chambers CA, et al. *Cold Spring Harb Symp Quant Biol* 1999;64:303–12.

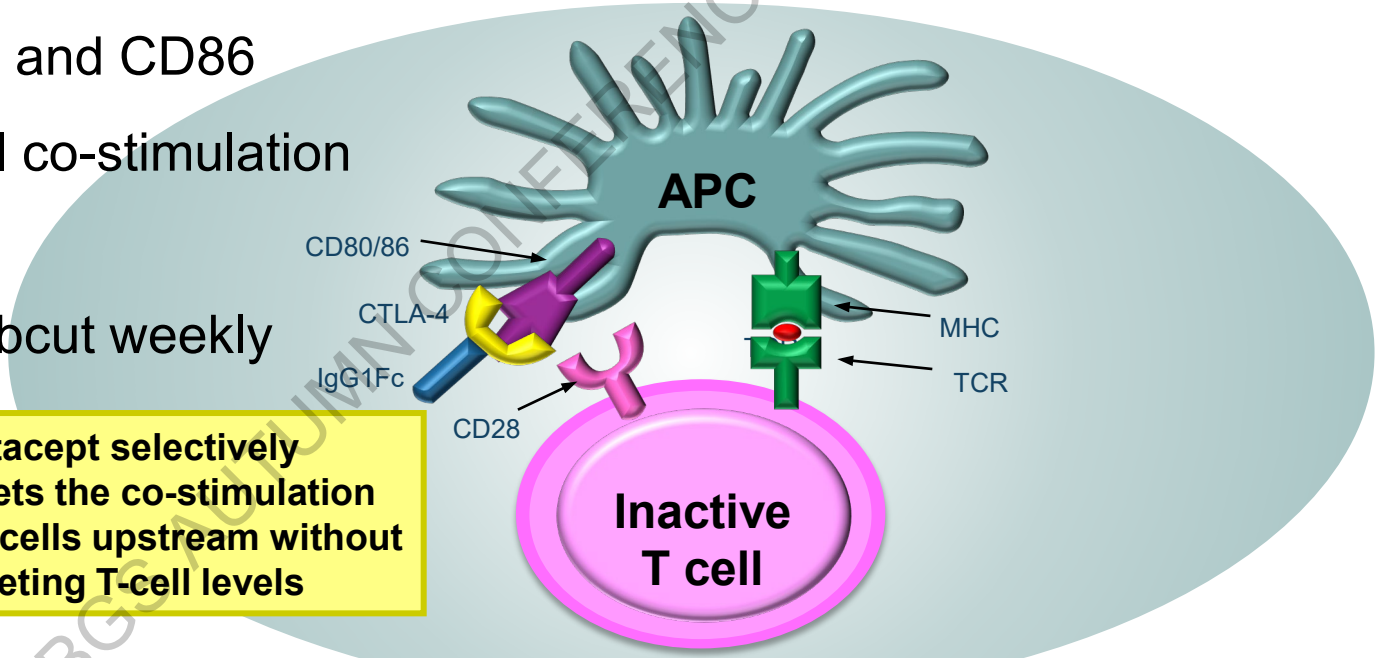
Abatacept

Fusion protein of CTLA-4 and IgG

Binds to CD80 and CD86

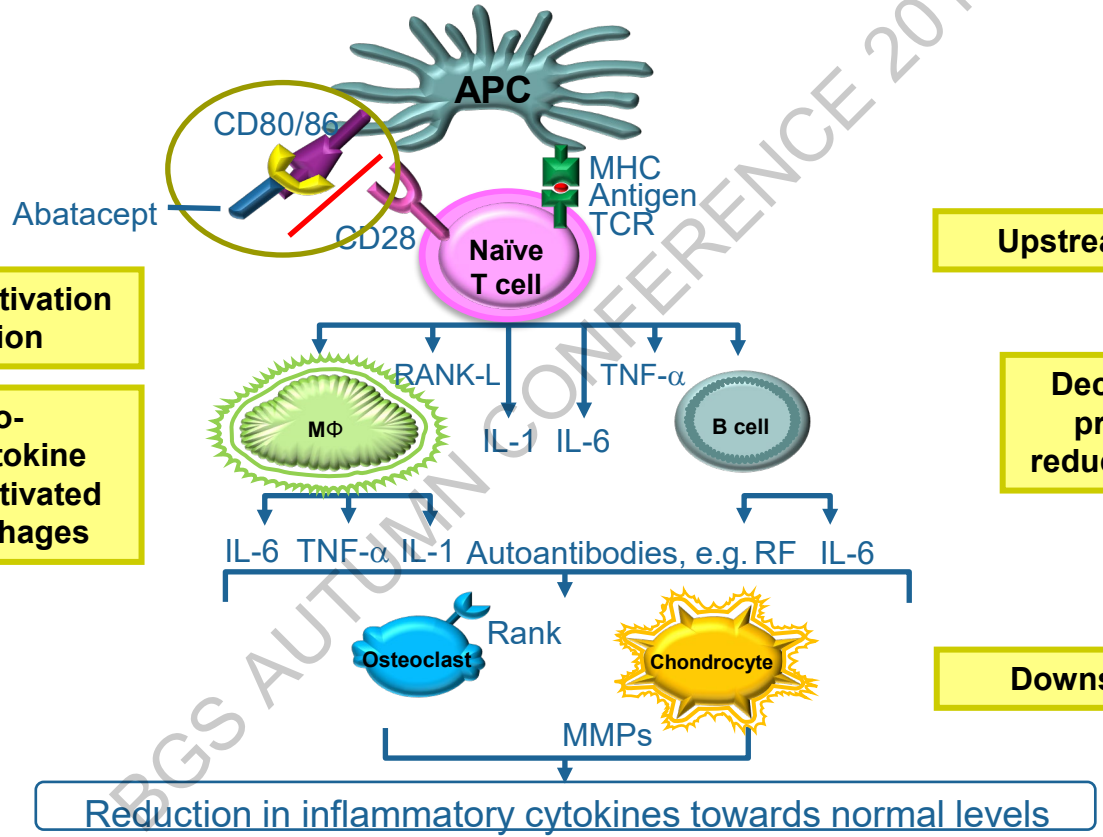
Prevents T cell co-stimulation

IV monthly/ subcut weekly



Abatacept selectively targets the co-stimulation of T cells upstream without depleting T-cell levels

APC=antigen-presenting cell; CTLA=cytotoxic T-lymphocyte antigen; Ig=immunoglobulin; MHC=major histocompatibility complex; TCR=T-cell receptor.
Adapted from Linsley PS, et al. *J Exp Med* 1991;174:561–9.



Decrease T-cell activation and proliferation

Decrease pro-inflammatory cytokine secretion from activated synovial macrophages

Upstream modulation

Decrease autoantibody production (e.g. RF) reduces clonal expansion

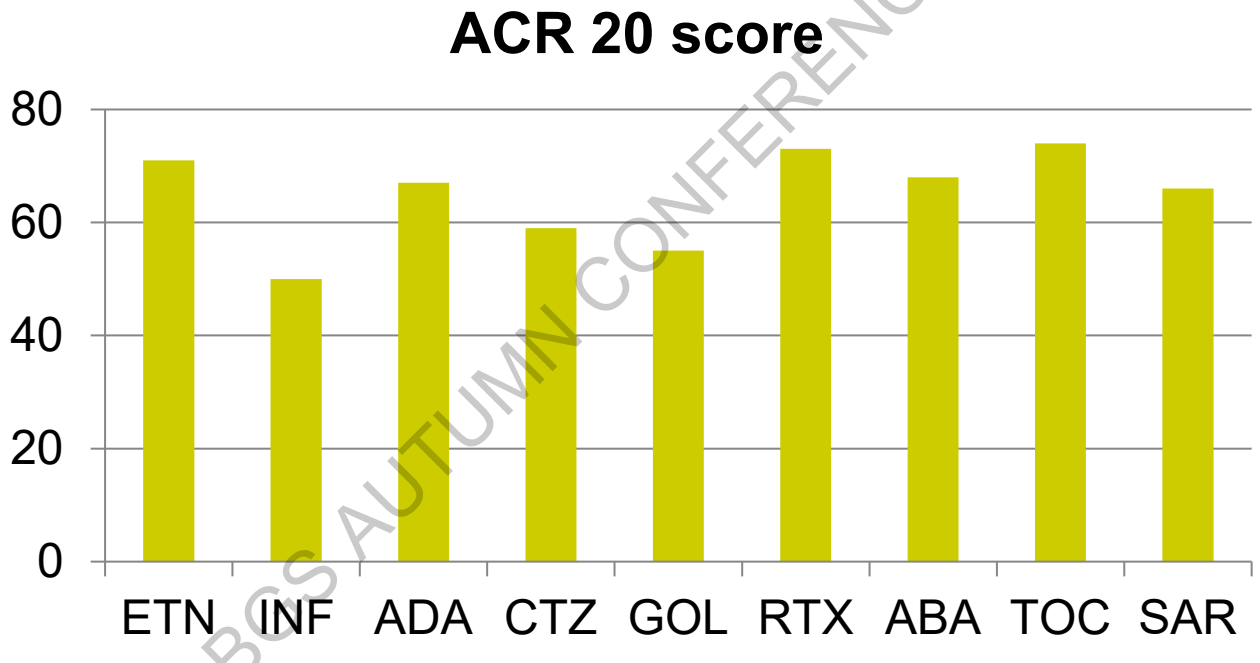
Downstream impact

APC=antigen-presenting cell; IL=interleukin; MHC=major histocompatability complex; MMP=matrix metalloproteinases; MΦ=macrophage; RF=rheumatoid factor; TCR=T-cell receptor.

Adapted from Choy EH, Panayi GS. *NEJM* 2001. Linsley PS, et al. *J Exp Med* 1991

Issues with biologics

Which biologic to choose?



ACR 20 scores from Phase III RCT; all biologics given with MTX

Which biologic to choose?

- Patient factors
  - RF positivity
  - Anti-CCP positivity
  - BMI
  - Infection risk
  - Compliance
  - Needle phobia
  - Past medical history – malignancy, CV disease
  - Extra-articular RA manifestations
  - Family history – MS
  - Patient preference – device, frequency of administration

Biologics are a big spend

- 6 of the top 10 medicines prescribed in hospitals by spend are biological products and are used to treat a range of conditions

Biologic	Condition	Spend in 2015/16 (£m)	Biosimilar estimated to be available
Adalimumab	Various including rheumatology, IBD, dermatology	£255	October 2018
Infliximab	Adult IBD, adult rheumatology conditions	£140	Since March 2015
Etanercept	Rheumatology conditions	£150	Since April 2016
Rituximab	Various including RA and cancer	£145	Since April 2017

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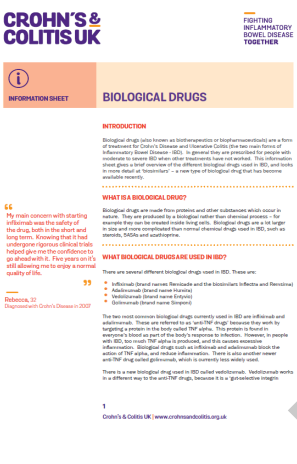
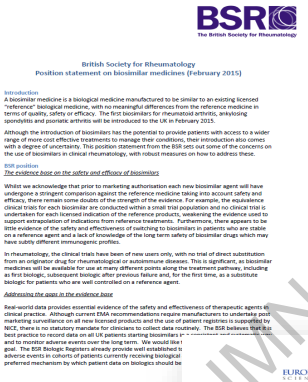
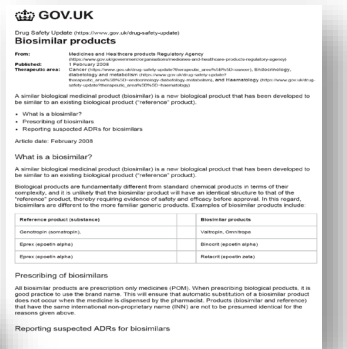
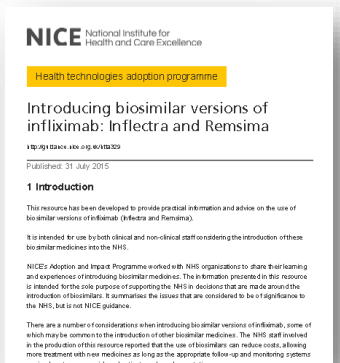
National Health Service. Commissioning framework for biological medicines (including biosimilar medicines). 2017. Available at: https://www.england.nhs.uk/wp-content/uploads/2017/09/biosimilar-medicines-commissioning-framework.pdf (accessed: July 2018)

Biosimilars









NHS England

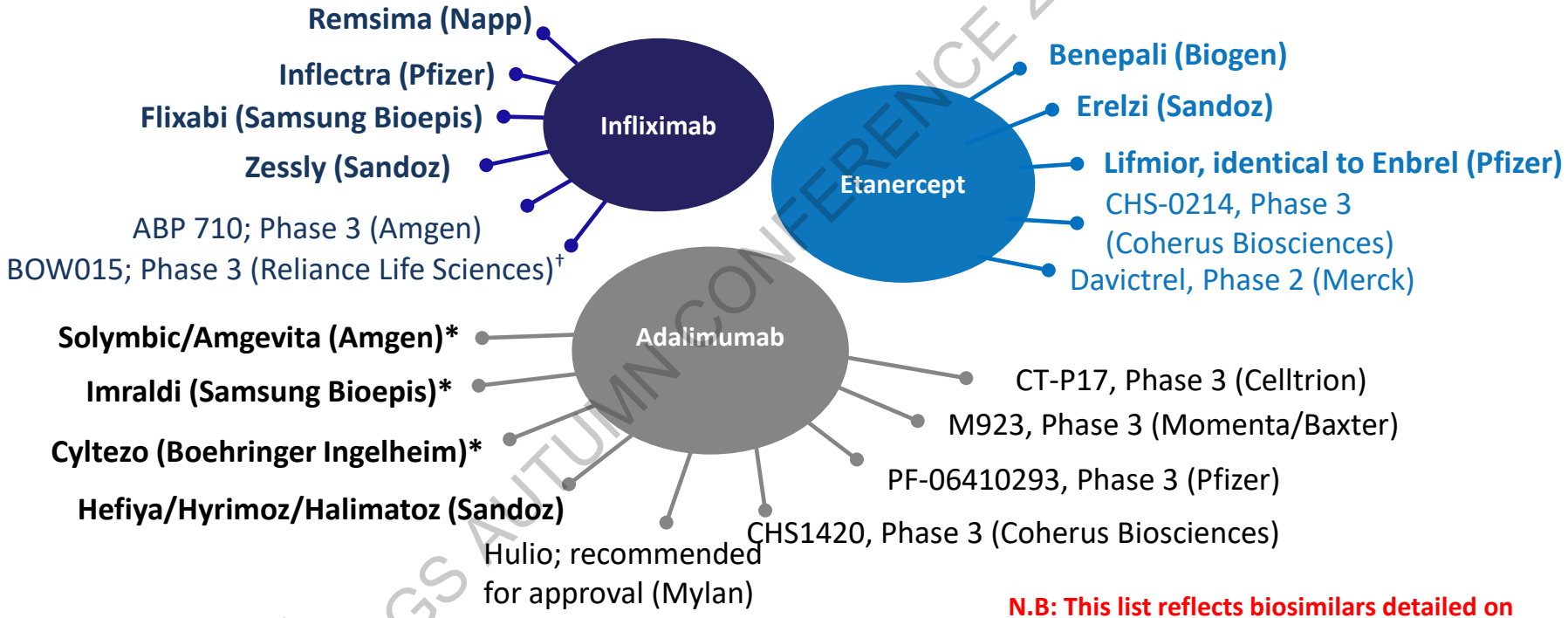
A biosimilar is an officially approved biological medicinal product which is highly similar to another biological medicinal product already in use

It is a biological medicine which has been shown not to have any clinically meaningful differences from the originator biological medicine in terms of quality, safety and efficacy

Biosimilar medicines are not considered generic equivalents to their originator biological medicine because the two products are similar but not identical. However, they will have met regulatory requirements in terms of comparative quality, safety and efficacy

10th September 2013: First anti-TNF biosimilar authorised

Bold: Licensed

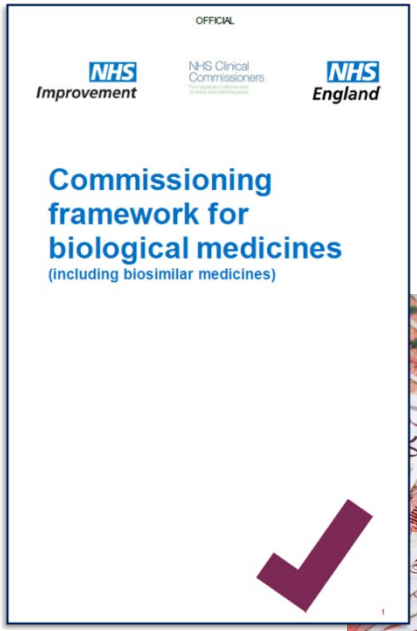


* Licensed, but not launched; †Phase 3 trials suspended, company looking for marketing partner.
Information collated from the NHS Specialist Pharmacy Service website:
https://www.sps.nhs.uk/medicines/infliximab/; https://www.sps.nhs.uk/medicines/adalimumab/;
https://www.sps.nhs.uk/medicines/etanercept/ (Accessed: August 2018).

N.B: This list reflects biosimilars detailed on the NHS Specialist Pharmacy Service website (August 2018) and is not exhaustive; other biosimilars are in development.

Cost savings

NHS England (Sept 2017)



"Our aim is that at least 90% of new patients will be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner, if possible"

Potential savings of **£200m–£300m/year** by 2020/21

Restrictions for use

NICE
National Institute for Health and Care Excellence

- Presently unable to follow European or US guidelines for biologics due to restrictions on use by NICE

- RA: DAS >5.1 (severe disease); tried 2 non-biological DMARDs
- PsA: TJC 3, SJC 3; tried 2 non-biological DMARDs
- AS: Severe disease, non responded to or cannot tolerate NSAIDs

- NICE guidelines may change as price of biologics fall??

Safety

RHEUMATOLOGY

Guidelines

doi:10.1093/rheumatology/key207

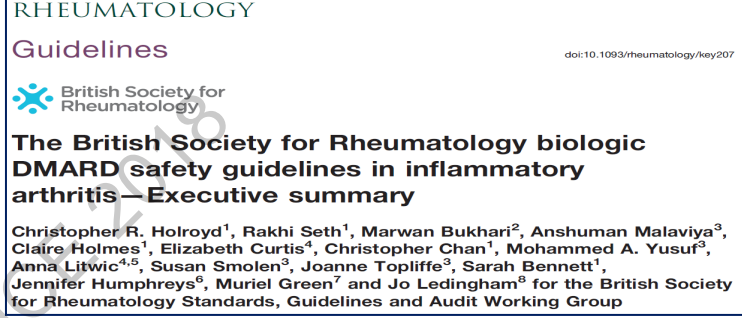
British Society for Rheumatology

The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis—Executive summary

Christopher R. Holroyd[1], Rakhi Seth[1], Marwan Bukhari[2], Anshuman Malaviya[3], Claire Holmes[1], Elizabeth Curtis[4], Christopher Chan[1], Mohammed A. Yusuf[3], Anna Litwic[4,5], Susan Smolen[3], Joanne Topliffe[3], Sarah Bennett[1], Jennifer Humphreys[6], Muriel Green[7] and Jo Ledingham[8] for the British Society for Rheumatology Standards, Guidelines and Audit Working Group

Holroyd C et al. Rheumatology 2018

Infection


RHEUMATOLOGY

Guidelines

doi:10.1093/rheumatology/key207

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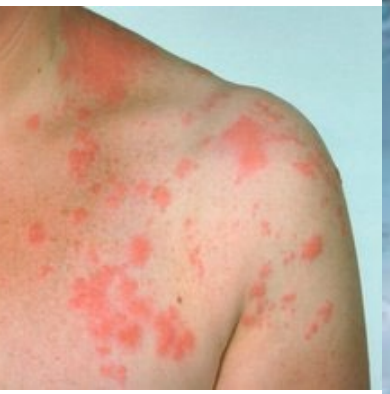
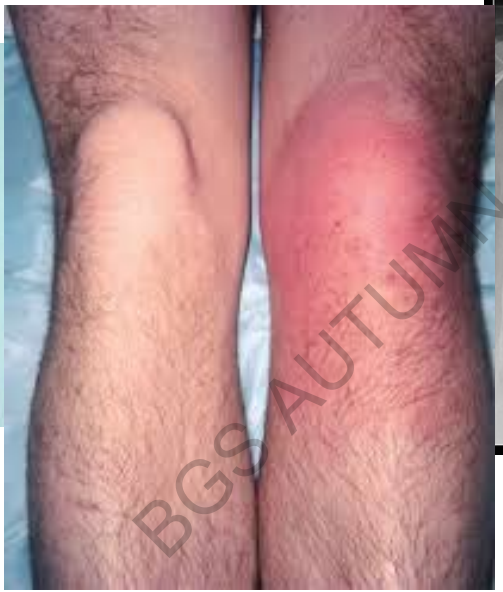
Evidence Base:

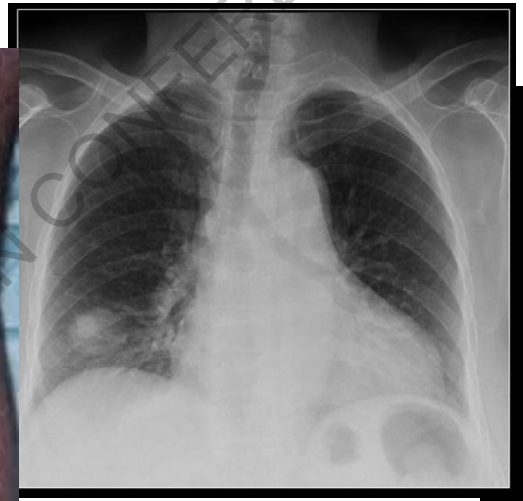
- Cochrane review of 106 controlled trials (42,330 RA patients; Singh 2015) OR=1.27 for serious infection compared to DMARD controls

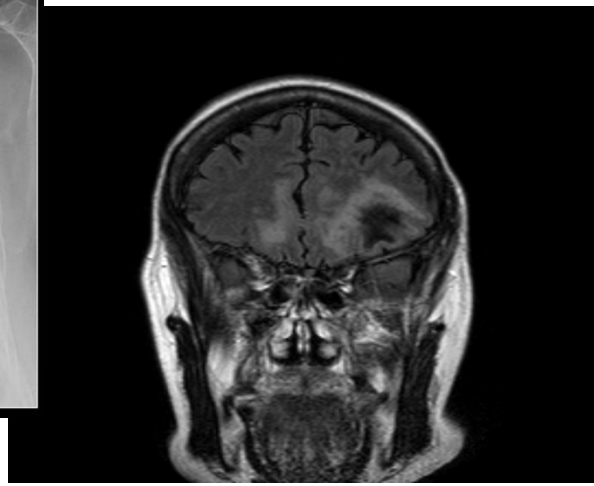
- Data from numerous registries: BSRBR (Galloway 2011), CORONNA (Greenburg 2010), BIOBADASER 2.0 (Cobo-Ibanez 2014) all show higher incidence of infection in RA patients receiving biologics compared to DMARD controls

Atypical infections









Infections in the elderly

RHEUMATOLOGY

Rheumatology 2011;50:124–131
doi:10.1093/rheumatology/keq242
Advance Access publication 31 July 2010

Original article

Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly

James B. Galloway[1], Kimme L. Hyrich[1], Louise K. Mercer[1], William G. Dixon[1], Bo Fu[1], Andrew P. Ustianowski[2], Kath D. Watson[1], Mark Lunt[1], BSRBR Control Centre Consortium* and Deborah P. M. Symmons[1] on behalf of the British Society for Rheumatology Biologics Register

Infections in the elderly

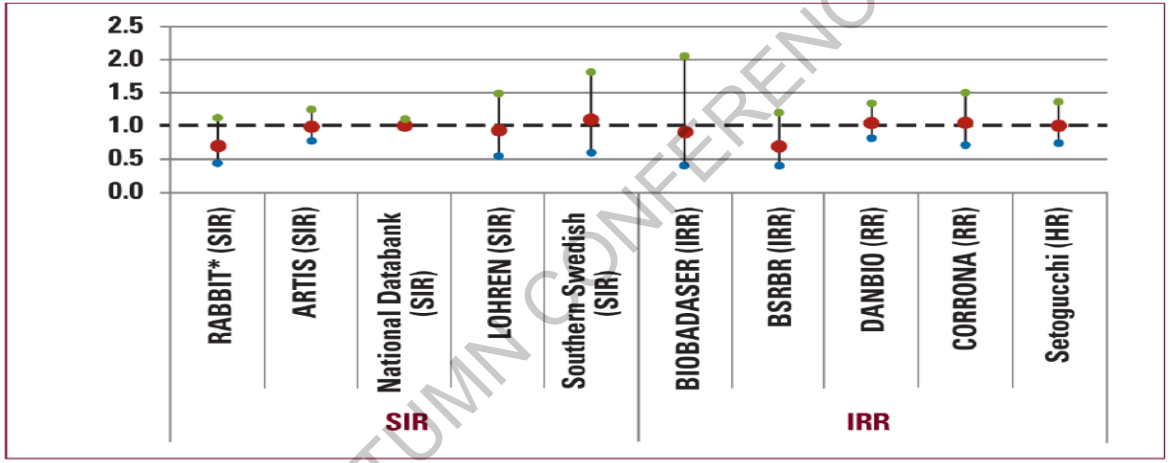
Age band, years	DMARD			Anti-TNF			
	Follow-up, pyrs	Infections (*n*)	Events/1000 pyrs (95% CI)	Follow-up, pyrs	Infections (*n*)	Events/1000 pyrs (95% CI)	AdjHR[a,b] (95% CI)
<55	2951	52	18 (13, 23)	17 100	477	28 (25, 31)	1.2 (0.8, 1.6)
55–64	2964	76	26 (20, 32)	11 608	533	46 (42, 50)	1.4 (1.1, 1.9)
65–74	2414	125	52 (43, 62)	6325	395	62 (56, 69)	0.9 (0.7, 1.2)
>75	931	43	46 (33, 62)	1198	99	83 (67, 101)	1.5 (0.9, 2.6)

[a]Adjusted for age, gender, COPD, diabetes, smoking, disease duration, DAS, HAQ, entry year, steroid use and MTX use. [b]Wald test for significance between groups confirms non-significance ($P = 0.210$). pyrs: patient-years.

Galloway J et al. Rheumatology 2011

Biologics and malignancy

- Registry data for biologics has been reassuring



Cush JJ, DSQ 2012

- Possible association between anti-TNF and skin malignancy (conflicting evidence)

- Rituximab considered safe in malignancy. Date for other biologics is lacking

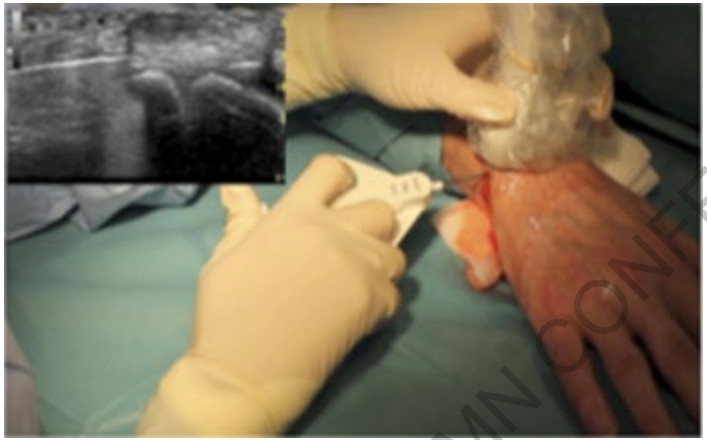
The Future

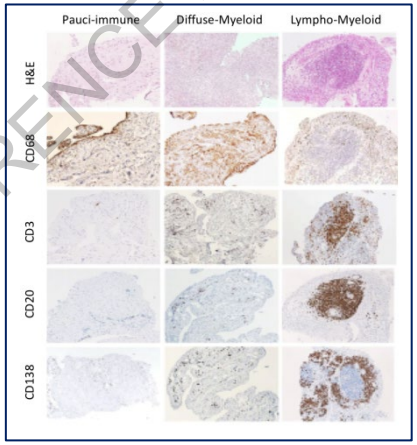
- More biologics in development
- New classes of drug: JAK kinase inhibitors
- Personalised medicine

Oral Small Molecules

- JAK kinase inhibitors
  - Inhibit the activity of ≥ 1 Janus Kinase enzymes (JAK1, JAK2, JAK 3, TYK2)
  - important tyrosine kinases for intracellular signal transduction of activated cytokine receptors
  - Tofacitinib (pan JAK inhibitor; blocks cytokines including IL-2, IL-4, IL-15 and IL-21)
    - FDA approved for mod-severe RA Nov 2012. Rejected by EMA in 2013 (HZ infection rates); approved 2017
  - Baricitinib (selective JAK1, JAK2), EMA approved 2017
  - Upadacitinib (selective JAK1), filgotinib (selective JAK1), peficitinib (JAK1 and JAK3 inhibitor), decernotinib (JAK3 inhibitor) AC-410 (JAK2 inhibitor)

Personalised medicine





Synovial Pathotype	RA ACPA + N= 90 (9 ungraded)	RA ACPA – N= 55 (12ungraded)	PSA N=41 (0 ungraded)	P value	P value ACPA+ VS ACPA-	P value ACPA+ VS PSA	P value ACPA- VS PSA
Pauci-immune	15 (16.6%)	17 (30.9%)	15 (36.5%)				
Diffuse-Myeloid	25 (27.7%)	14 (25.4%)	11 (26.8%)	0.01*	**0.03***	**0.005***	0.41
Lymphoid-Myeloid	**41 (45.55%)**	12 (21.81)	10 (24.3%)				

Slide courtesy of Dr Gloria Iliso-Ribero

University Hospital Southampton NHS
NHS Foundation Trust

MRC Lifecourse Epidemiology Unit

BSR The British Society for Rheumatology
Rheumatology
Best Practice Awards 2013
Best Practice Outstanding

Thank you