

Biologics in Inflammatory Rheumatic Diseases

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Disclosures

- Advisory Boards and speaker at meetings: Abbott, Roche, Pfizer/Wyeth, MSD, Novartis and Quintiles CRO.
- Investigator in clinical trials for: Boehringer Ingelheim, MSD, UCB, Medi-Immune, Centocor, Roche, Abbott and Pfizer.



“It’s a great time to be a Rheumatologist ... It’s an even better time to be a patient”

Prof. Ed Keystone, Toronto, Canada

“Few, if any, areas of medical therapeutics have witnessed such dramatic changes as those that have occurred in the therapy of RA during the past two decades. Improvements in clinical trials, methodologies, introduction of 9 biologics and development of better strategies have all contributed to the new age in RA therapeutics”

Prof. Ronald van Vollenhoven, Stockholm, Sweden



Take Home Message:

Rapid referral to a Rheumatologist of all inflammatory arthritis or when RA is suspected is crucial to the prognosis of the patient.

This may be supported by the presence of any of the following:

- ≥ 3 swollen joints
- MTP/MCP involvement
- morning stiffness of ≥ 30 minutes.

P Emery et al. ARD 2002;61:290-7



NB: No blood tests in the alarm signals for early referral for potential RA

- Don't delay referral because of test results:

	% of negative tests
X-rays of hands and feet	80
CRP	50
RF and anti-CCP antibodies	40

Why early referral?

- Window of opportunity of up to six months to reset immunology of RA so Rheumatologists need to see patients within 12 weeks of onset of arthritis
- If achieved clinical remission within six months of onset of disease, can stop treatment in up to 80% of undifferentiated inflammatory arthritis



The Treat-to-Target initiative

- An international initiative to define treatment targets in RA (similar to glycated haemoglobin targets in diabetes or BP in hypertension)
- Target is clinical remission



Definition of clinical remission

- A DAS 28 score of
 - <3.2 = low disease activity.
 - <2.6 = remission
- Disease activity score which is a composite score based on:
 - Tender joint count
 - Swollen joint count
 - Patient global assessment
 - ESR or CRP



To achieve remission:

- (i) Initiation of treatment early in disease process
- (ii) Vigilant monitoring with prompt adjustment of therapy for flares (“tight control”) and for medication toxicity
- (iii) Combination DMARDs
- (iv) Biologics



Historic milestones in therapy of RA

- Pre-historic Opium for pain/rheumatism
- 1763 Willow bark for rheumatism
- 1876 Salicylic acid
- 1897 Synthetic aspirin
- 1929 Gold salts
- 1941 Recognition of RA as a distinct entity by American Rheumatism Association
- 1949 First Glucocorticoid used in arthritis
- 1955 Prednisone for RA (Nobel Prize for Phillip Hench)



- 1960s NSAIDs,
Chloroquine/hydroxychloroquine
- 1980s DMARDs: Sulphasalazine, oral gold
Azathioprine, cyclosporine,
penicillamine, methotrexate
- 1998 Leflunomide, etanercept
- 1999 COX-2 inhibitors, infliximab
- 2001 Anakinra
- 2002 Adalimumab
- 2005 Abatacept
- 2006 Rituximab
- 2009 Tocilizumab, Certolizumab, Golimumab



Tumour Necrosis Factor Alpha

- Major mediator of immune responses and inflammatory reactions
- Functions as a soluble messenger protein to act on target cells
- Involved in the pathogenesis of many human diseases, including autoimmune diseases, such as RA



Key Actions Attributed to TNF-alpha

Macrophages	<u>↑pro-inflammatory cytokines</u> <u>↑chemokines</u> →	Increased inflammation
Endothelium	<u>↑adhesion molecules</u> → <u>↑vascular endothelial growth factor (VEGF)</u> →	Increased cell infiltration Increased angiogenesis
Hepatocytes	<u>↑acute phase response</u> →	Increased CRP in serum
Synoviocytes	<u>↑metalloproteinase synthesis</u> →	Articular cartilage degradation



TNF-alpha Inhibitors

5 Commercially Available:

Infliximab (Remicade) - IV

Etanercept (Enbrel) - SC

Adalimumab (Humira) - SC

Certolizumab Pegol (Cimzia) - SC

Golimumab, humanized form of Infliximab
(Simponi) - SC and IV



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The skin was moist and dry.

Occasional, constant infrequent headaches.

Patient was alert and unresponsive.



PHARMAC'S 7 Criteria for Adalimumab (Humira) since 1.1.2006

1. Adjunct to Methotrexate or monotherapy if intolerant to Methotrexate.
2. No response to at least three months of 20 mg weekly of Methotrexate or maximum tolerated dose.
3. No response to at least three months of Methotrexate in combination with at least two of the following (triple therapy): sulphasalazine, prednisone ≥ 7.5 mg/day, azathioprine, IM Gold or Hydrochloroquine (at maximum tolerated doses).
4. Severe and active erosive RA for ≥ 6 months.



5. No response to at least three months of either:
Cyclosporin alone or in combination with another agent, Leflunomide alone or in combination with another agent.
6. Either:
 - 6.1: persistent symptoms of poorly controlled and active disease in at least 20 active, swollen joints; or
 - 6.2: at least four active joints from the following: wrist, elbow, knee, ankle and either shoulder or hip.
7. Either:
 - 7.1: CRP \geq 15 mg/l measured no more than prior to application; or
 - 7.2: CRP not measured as patient is receiving Prednisone $>$ 5 mg/day and has done for $>$ three months.




Renewal criteria

1. Applicant is a Rheumatologist or a practitioner with evidence that a Rheumatologist has confirmed continuing treatment with Adalimumab
2. Adjunct to Methotrexate or monotherapy where use of Methotrexate is limited by toxicity or intolerance
3. Following 4 months of initial treatment, 50% decrease in active joint count from baseline and clinically significant response in the opinion of the physician OR subsequent reapplications patient demonstrates at least 30% improvement in active joint count from baseline and clinically significant response in the opinion of physician
4. No greater than 40 mg every 14 days OR can't take MTX and requires Adalimumab > 40mg every 14 days

Psoriatic Arthritis

Pharmac's five criteria for Adalimumab (Humira) since 01.08.2009 for PsA

1. Severe active psoriatic arthritis for ≥ 6 months
 2. No response to at least 3 months of 20mg weekly of Methotrexate or maximum tolerated dose
 3. Tried and not responded to Sulphasalazine of at least 2gm daily or Leflunomide 20mg daily or maximum tolerated doses
 4.
 - a. Patient has 20 active, swollen, tender joints or
 - b. at least 4 active joints in the following: wrist, elbow, knee, ankle and either shoulder or hip
 5.
 - a. CRP > 15 or
 - b. ESR > 25 or
 - c. ESR and CRP not measured as patient taking Prednisone ≥ 5 mg daily and has done so for > 3 months
- 

PsA renewal criteria

1. Applicant is a Rheumatologist or on recommendation from a Rheumatologist
2.
 - a. Following 4 months of initial treatment at least 50% decrease in active joint count from baseline and clinically significant response
 - b. Patient demonstrates at least 50% improvement in active joint count from baseline and clinically significant response
3. Adalimumab no greater than 40 mg every 14 days



Pharmac's 7 criteria for Adalimumab (Humira) for Ankylosing Spondylitis since 01.08.2009

1. Confirmed diagnosis of AS \geq 6 months
2. Low back pain and stiffness relieved by exercise and not by rest
3. Bilateral sacroiliitis demonstrated by plain x-rays, CT or MRI scan
4. Inadequate response to 2 or more NSAIDs, in combination with anti-ulcer therapy, if indicated, while patient undergoing at least 3 months of exercise regimen supervised by physiotherapist



5. a. Limitation of lumbar spine in sagittal and frontal planes by score of at least 1 on lumbar flexion and side flexion of the BASMI (Bath Ankylosing Spondylitis Metrology Index) measurements OR
 - b. Limitation of chest expansion by at least 2.5cm below average normal values corrected for age and gender
6. BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) of at least 6 on a 0 to 10 scale
7. ESR of >25 or CRP >15



BASMI 3-point answer scale

	0	1	2
	Mild	Moderate	Severe
Lateral lumbar flexion (cm)	>10cm	5-10cm	<5cm
Lumbar flexion (modified Schober)	>4cm	2-4cm	<2cm

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

All questions refer to last week

1. How would you describe the overall level of fatigue/tightness you have experienced?
2. How would you describe the level of AS neck, back or hip pain you have had?
3. How would you describe the overall level of pain, swelling and joints other than neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of morning stiffness you have from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?



Renewal criteria for AS

1. Applicant is a rheumatologist or on recommendation of a rheumatologist
2. After 12/52, BASDAI improved by ≥ 4 or 50% whichever is greater
3. ESR or CRP within normal range
4. Physician considers patient has benefitted and treatment is appropriate
5. Adalimumab 40 mg no greater than 14 days



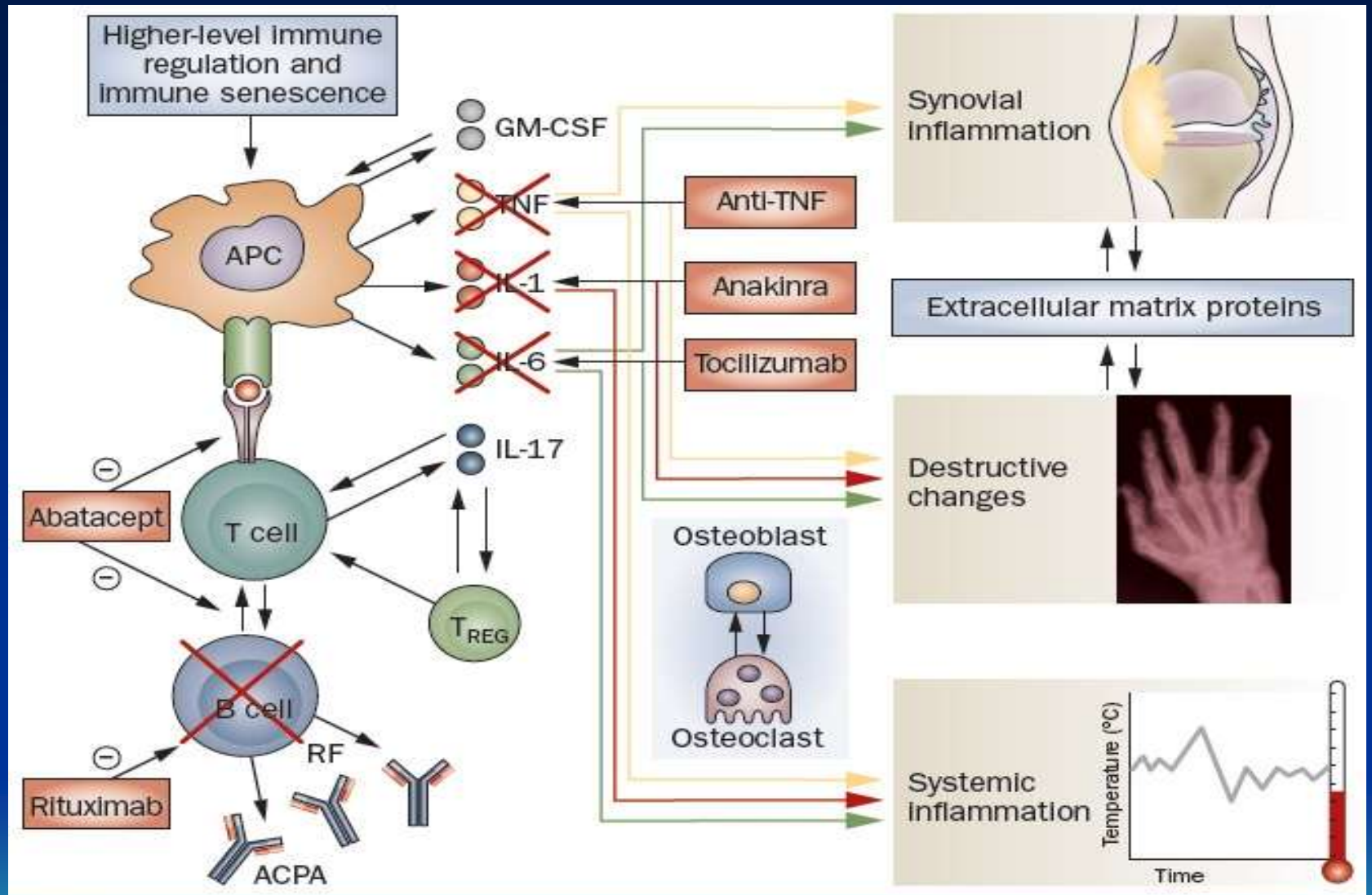
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Rectal examination revealed a normal sized thyroid.

She stated that she had been constipated for most of her life until she got a divorce.

Patient has two teenage children, but no other abnormalities.





The Unmet Need in RA Therapy 2010

- Many patients are partial responders
- True remission is achieved by only a minority
- 'Cure' remains an elusive goal
- Toxicities and adverse effects
- Destructive process cannot be halted in all patients
- Repair of previous damage remains elusive



Future therapies

- More biologics
- Better biomarkers to identify more accurately severe cases and give the most appropriate treatment ('personalised medicines')
- Small molecule inhibitors
 - Oral administration, so much cheaper
 - Small molecules inhibit cellular kinases (eg. P38 JAK or SyK) that mediate signalling and transcription of pro-inflammatory genes (biologics inhibit extracellular pro-inflammatory cytokines or cell function)
 - Tascocitinib, an orally active, highly selective inhibitor of Janus Kinase (JAK) family of kinases, including JAK1 and JAK3 in phase III studies



Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation

V.P. van Halm et. al. ARD 2009; 68: 1395-1400

Conclusion:

The prevalence of CVD in RA is increased to an extent that is at least comparable to that of Type II diabetes mellitus. This should have implications for primary cardiovascular prevention strategies in RA.



H.K. Choi et. al. Lancet 2002; 359:
1173-7

Suppressing inflammation reduces the risk of CVD, and Methotrexate has been demonstrated to have protective effects against CVD in RA.



Typed by medical secretaries in NHS Greater Glasgow

Both breasts are equal and reactive to light and accommodation.

Examination of genitalia reveals that he is circus sized.

The lab test indicated abnormal lover function.

