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Christchurch

Saturday, August 10, 2019

(Room 8)

7:00 - 7:55 AbbVie Breakfast Session - Biologics in Rheumatology

Biologics in rheumatology – tips for a busy GP

Marina Sew Hoy
Rheumatology Associates
Christchurch
10 August 2019

Disclosures & Disclaimer

- This presentation is sponsored by Abbvie.

- Pfizer
- Novartis
- Janssen-Cilag
- ACC

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Biologic DMARDs funded in NZ for rheumatic diseases

Agent	Class	Target	Structure
adalimumab (Humira)	cytokine inhibitor	TNF-α	human monoclonal antibody
etanercept (Enbrel)	cytokine inhibitor	TNF-α	TNF-α receptor – Fc fusion protein
infliximab (Remicade)	cytokine inhibitor	TNF-α	chimeric monoclonal antibody
tocilizumab (Actemra)	cytokine inhibitor	IL-6 receptor	humanised monoclonal antibody
ritixumab (Mabthera)	cell-depleting agent	CD20	chimeric monoclonal antibody

Iain B McInnes & Georg Schett The Lancet Jun 2017

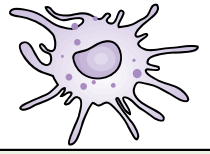
Rheumatoid Arthritis

Genetic factors
(eg, HLA-DR4, PTPN22)

Environmental triggers
- Smoking
- Periodonitis
- Dust exposure
- Microbiome alterations

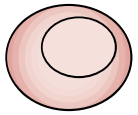
Protein modifications
- Citrullination
- Carbamylation
- Acetylation

Antigen presentation



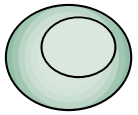
T-cell activation

T cell



B-cell activation

B cell



Smoke cessation

PAD inhibitor

Tolergenic dendritic cells

Abatacept

Rituximab

First hit: break of tolerance

JAK inhibitor

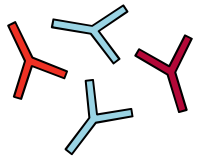
Btk inhibitor

Treg

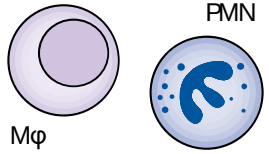
Syk inhibitor

Second hit: joint homing

Autoantibodies
- AMPA
- Rheumatoid factor



Synovial inflammation
- TNF, interleukin 6



Abatacept

Rituximab

Interleukin 23 inhibitors (early disease?)

TNF inhibitors

Interleukin-6 ligand and receptor inhibitors

JAK inhibitor

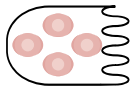
GM-CSF inhibitors

Local

Synovial hyperplasia

Cadherin 11, synoviolin, Tyro3

Osteoclasts and bone erosion



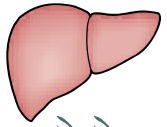
RANKL, M-CSF
TNF, interleukin 6, interleukin 1β

Systemic

Atherogenesis

Interleukin 6, VCAM1

Metabolism
Liver function

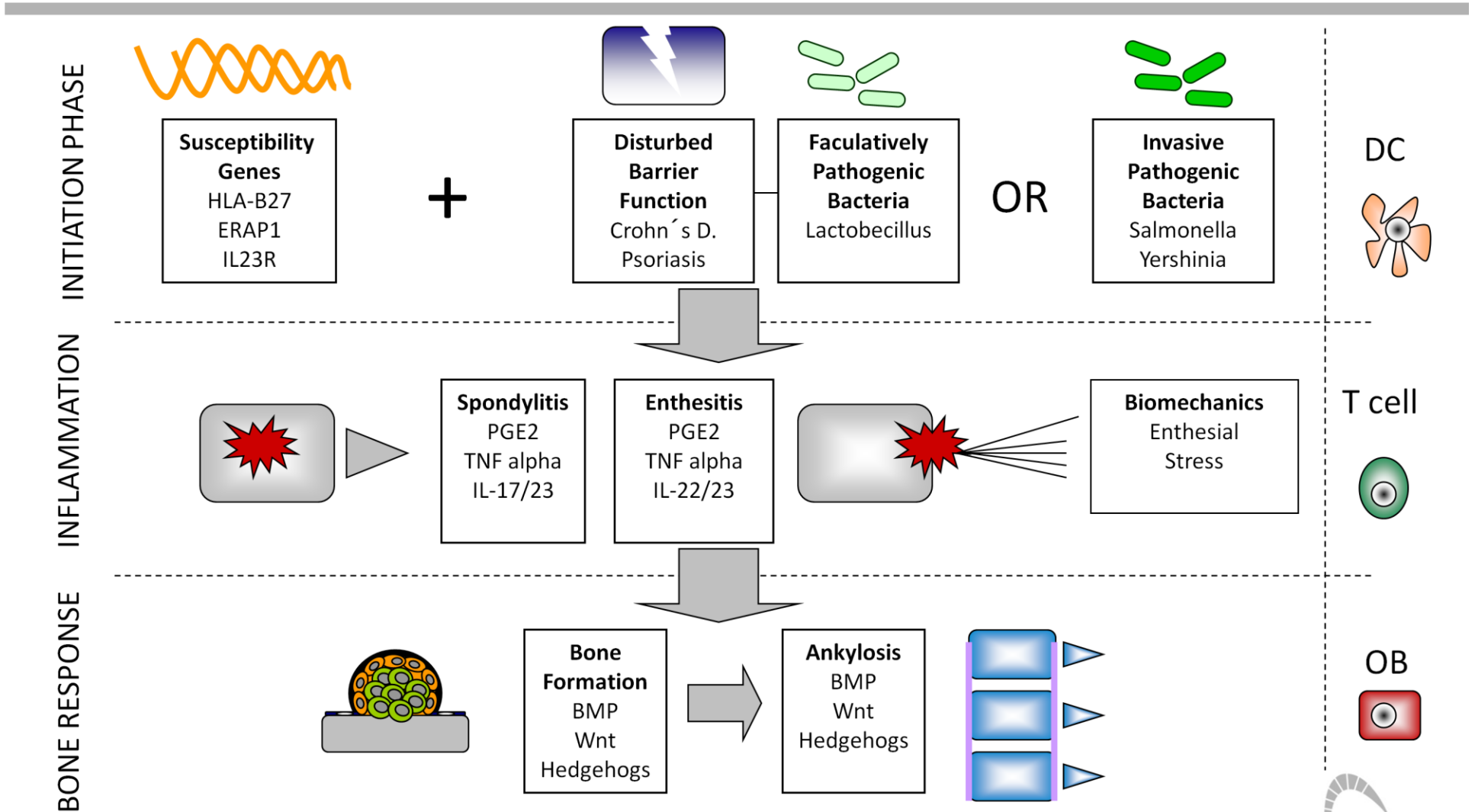


C-reactive protein, LDL, HDL, hepcidin, interleukin 6

CNS pain and depression

TNF, interleukin 1β, interleukin 6

Proposed Interaction between Inflammation and New Bone Formation in Spondyloarthritis



BMP – bone morphogenetic protein, DC – dendritic cell, ERAP1 – endoplasmic reticulum aminopeptidase 1, OB – osteoblast, PGE2 – prostaglandin E2, TNF alpha – tumor necrosis factor alpha.

Ronneberger M et al. Curr Rheumatol Rep 2011;13:416-20

Infection and Immunity

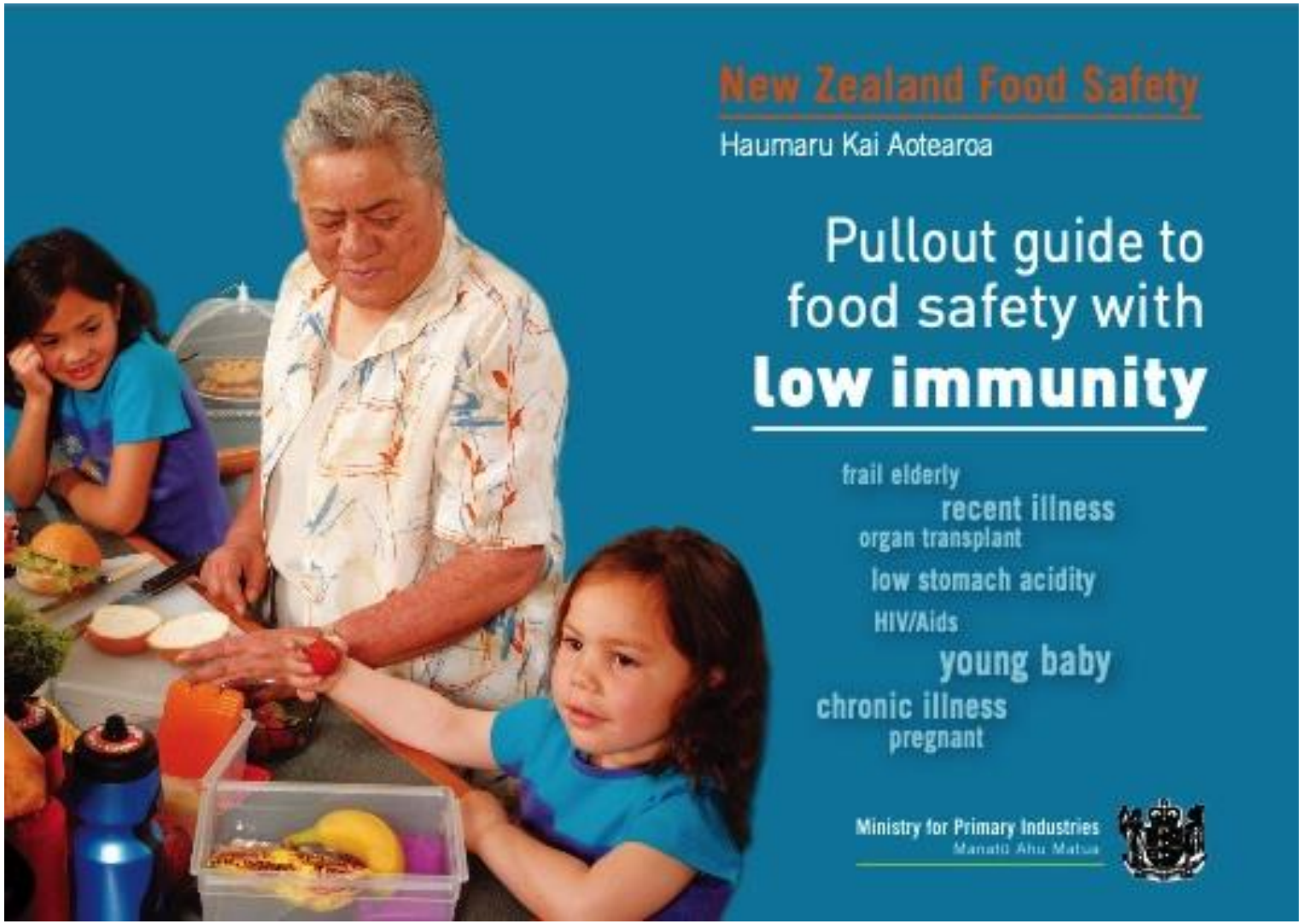
- TNFa : control and containment of intracellular pathogens; stimulates recruitment of inflammatory cells toward the infection; stimulates formation & maintenance of granulomas to contain infection; activates macrophages (phagocytose pathogens)
- IL6 : mediator of fever and acute phase response; production of neutrophils; supports B cells
- B cells : production of antibodies (humoral immunity); antigen-presentation

Biologics and Risky Activities
Adoption of Safer Lifestyle Practices

Adoption of Safer Lifestyle Practices

- Smoking cessation / avoidance
    - treatment inefficacy
- Reducing infection risk
    - Listeriosis
    - Legionnaires disease
- Sun-protection against Skin cancer

Avoid exposure to Listeria



Protection from Legionella

Be SunSmart

Being SunSmart is about protecting skin and eyes from damaging UV radiation – especially when outdoors from September to April.

Slip on a shirt

Slip on a shirt with long sleeves. Fabrics with a tighter weave and darker colours will give you better protection from the sun.

Slip into the shade

Slip into the shade of an umbrella or a leafy tree. Plan your outdoor activities for early or later in the day when the sun's UV levels are lower.

Slop on sunscreen

Slop on plenty of broad spectrum sunscreen of at least SPF 30. Apply 20 minutes before going outside and reapply every two hours and especially after being in water or sweating.

Slap on a hat

With a wide brim or a cap with flaps. More people are sunburnt on the face and neck than any other part of the body.

Wrap on sunglasses

Choose close fitting, wrap around style sunglasses. Not all sunglasses protect against UV radiation, so always check the label for sun protection rating.

GP Vigilance

- Women – up to date with routine cervical smears
- Early presentation for infection assessment, closer monitor & treatment
    - tocilizumab normalises C reactive protein
- Vaccinations

Vaccination

- Safety of vaccination
  - Live vaccines contraindicated with all biologics
  - Live vaccines and Steroids, Non-biologic DMARD
    - » Contraindicated with prednisone 20mg or more daily
    - » Contraindicated with leflunomide
    - » Safe with Methotrexate - inflammatory disease doses
- DMARD impact on vaccination response
- Annual flu vaccination
- HPV for up to 26 year olds
- pneumococcal vaccination

Treatments when Live Vaccines may be contraindicated

Diseases and medications when live vaccines may be contraindicated (Immune system dysfunction and live attenuated viral vaccines)

The Immunisation Advisory Centre

Table 2. Immunosuppressive or immunostimulatory treatment – alphabetical list by generic name

Generic name	Safe dose*	Vaccination BEFORE treatment initiation	Vaccination AFTER treatment cessation*
5-ASA/Mesalazine	Any dose	Any time before, during or after treatment	
6-Mercaptopurine	≤1.5 mg/kg/day	1 month before	3 months after
Abatacept	NONE	1 month before	12 months after
Adalimumab	NONE	1 month before	12 months after
Anakinra	NONE	1 month before	12 months after
Atezolizumab	May or may not have a safe dose	1 month before	6 months after
Azathioprine	≤3.0 mg/kg/day	1 month before	3 months after
Chemotherapy – traditional cancer alkylating agents, plant alkaloids, antitumour antibiotics, antimetabolites, topoisomerase inhibitors, other antineoplastics	NONE	1 month before	6 months after
Ciclosporine	NONE	1 month before	3 months after
Cyclophosphamide	NONE	1 month before	3 months after

https://www.immune.org.nz/sites/default/files/resources/Written%20Resources/AdministrationImmunecompLiveVac20180507V02Final.pdf

What are the Live Attenuated Vaccines (LAV)?

- Measles, Mumps, Rubella MMR
- Zoster vaccine Zostavax and chickenpox/Varicella vaccine
    - N.B. recombinant (non-live) zoster vaccine Shingrix is unavailable in NZ
- Rotavirus
- Travel vaccines
    - yellow fever, oral typhoid, BCG, oral polio, Japanese encephalitis virus

Biologics and Travel

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Vaccination

- Safety of vaccination
- DMARD impact on vaccination response
  - Methotrexate (uncertain)
  - TNF inhibitors, tocilizumab (none)
  - Rituximab (major – vaccinate 2-3 weeks before start or 6 months after dose & 4 weeks before the next)
- Annual flu vaccination
- HPV for up to 26 year olds
- Pneumococcal vaccination (not funded)

Vaccination

- Safety of vaccination
- DMARD impact on vaccination response
- Annual flu vaccination
    - Two week methotrexate holiday after flu vax
- HPV for up to 26 year olds (over 26y?)
- Pneumococcal vaccination (not funded)
    - Prevenar 13 then Pneumovax 23 minimum of 8 weeks later and booster after minimum of 5 years, 3rd dose after 65 years
    - https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

Blood Test monitoring

2015 American College of Rheumatology Treatment Guidelines

Table 3. Recommendations for optimal followup laboratory monitoring intervals for complete blood cell count, liver transaminase levels, and serum creatinine levels for patients with rheumatoid arthritis receiving disease-modifying antirheumatic drugs*

	Monitoring interval based on duration of therapy‡		
Therapeutic agents†	<3 months	3–6 months	>6 months
Hydroxychloroquine	None after baseline§	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

* More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose, and the outer bound of the monitoring interval is recommended beyond 6 months of therapy. Adapted from ref. 6.
† Listed alphabetically.
‡ The panel indicated that patients with comorbidities, abnormal laboratory results, and/or multiple therapies may require more frequent laboratory testing than what is generally recommended laboratory monitoring for disease-modifying antirheumatic drugs as shown in the table.

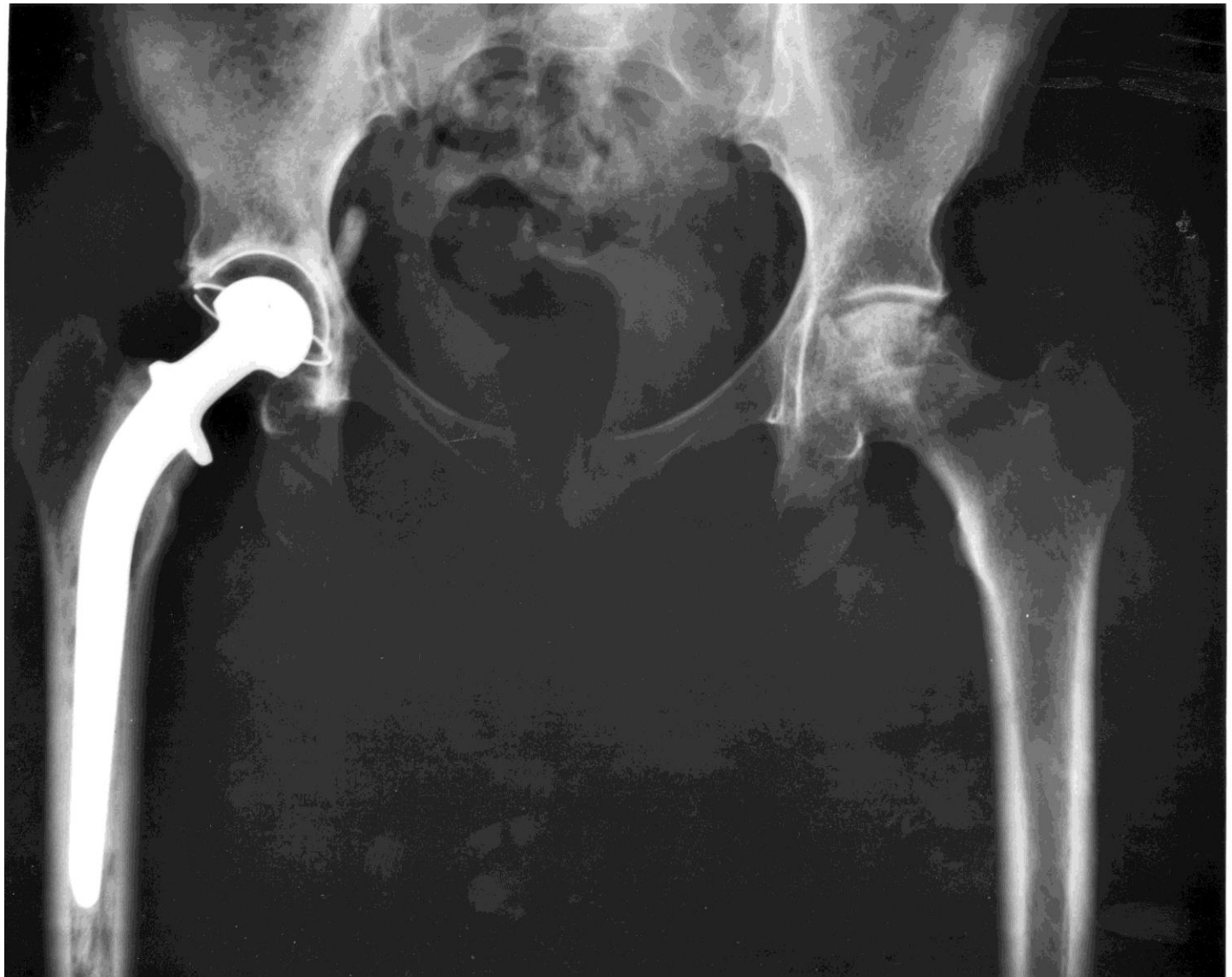
SHARING OF RESULTS OVERSIGHT

Specific monitoring for biologics

- TNF inhibitors
  - dictated by concomitant traditional DMARD or 3 – 6 monthly
  - annual skin cancer check (for psoriatic patients)
- tocilizumab – annual lipids
- For intravenous treatments, frequency determined by infuser (before each infusion)
    - infliximab – CBC, creatinine, LFT
    - tocilizumab – CBC, LFT
    - rituximab – CBC, serum immunoglobulins

BSR Guidelines 2019; ACR Guidelines 2016

Biologics and Surgery



Surgery & Biologics

2019 British Society for Rheumatology Safety Guidelines

TABLE 7 Dosing intervals, recommendations for timing of surgery and half-lives of biologic therapies

Drug	Dosing interval	Period in which surgery should be scheduled (relative to last biologic dose administered)	One half-life, days	Five half-lives, days
Adalimumab	Every 2 weeks	Week 3	14	70
Etanercept	Weekly or twice weekly	Week 2	3	15
Golimumab	Every 4 weeks	Week 5	14	70
Infliximab	Every 4, 6 or 8 weeks	Week 5, 7 or 9	9	45
Rituximab	Two doses 2 weeks apart, no more frequent than every 6 months	Months 4–7	18	90
Tocilizumab i.v.	Every 4 weeks	Week 5		
4mg/kg			11	55
8mg/kg			13	65

Mothers and Babies and Biologics

Pregnancy & Lactation

- Infants of mothers on TNF inhibitors exposed in utero particularly in the 3rd trimester
    - No live vaccines for 6 months – there may be detectable drug in serum (e.g. rotavirus, BCG)
- Rituximab normally infant is not exposed to agent.
- Tocilizumab – a large molecule; little if any is transferred through the placenta before 12 weeks gestation.
- The large size of molecule therefore no significant transfer into breast milk.