Rheumatoid Arthritis

BIOM30002 Biomedicine: Molecule to Malady

Introduction to Rheumatoid Arthritis

Approximately three million Australians have arthritis.

The prevalence of arthritis in Australia is increasing.

The prevalence of arthritis in indigenous Australians is higher than the prevalence of arthritis in non-indigenous Australians.

The vast majority of cases of arthritis involve osteoarthritis, rheumatoid arthritis, or gout.

Rheumatoid arthritis is a chronic inflammatory autoimmune disease with unknown aetiology.

Rheumatoid arthritis is associated with articular manifestations, systemic complications, progressive disability, and a reduced life expectancy.

Epidemiology

The incidence of rheumatoid arthritis in adult Caucasian populations is between ten and one hundred cases per one hundred thousand people per annum.

The prevalence of rheumatoid arthritis in adult Caucasian populations is one per cent.

Rheumatoid arthritis is more common in females than it is in males.

The mean age of onset of rheumatoid arthritis is forty.

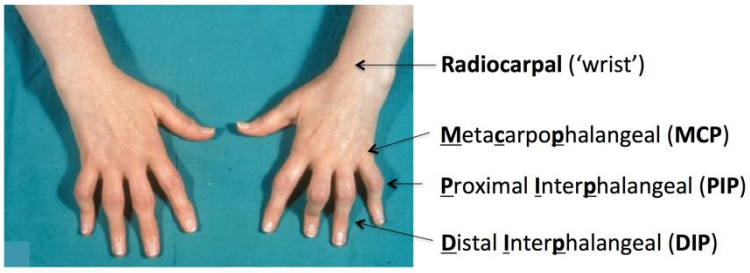
Disease Manifestations

Articular

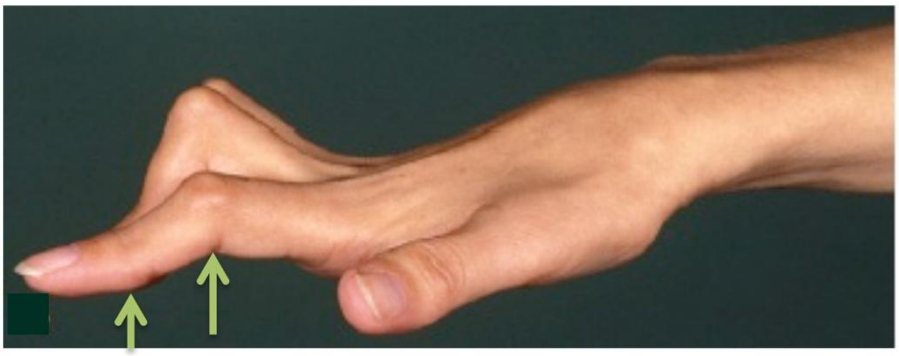
Articular manifestations of rheumatoid arthritis typically have an insidious onset, and can have an acute onset.

Articular manifestations of rheumatoid arthritis are symmetrical, and include morning stiffness, pain, and swelling.

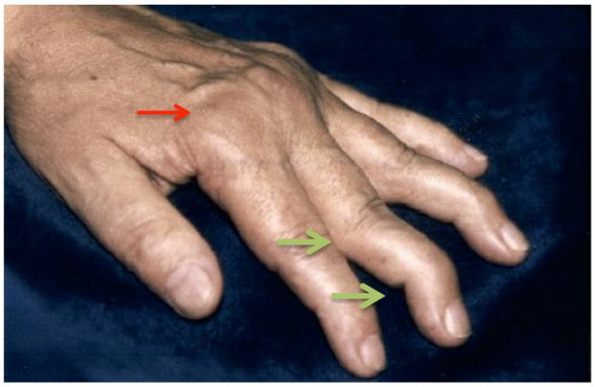
Rheumatoid arthritis commonly affects joints of the hand, joints of the wrist, the knees, the shoulders, joints of the ankle, and joints of the foot.



Joints of the hand and wrist.

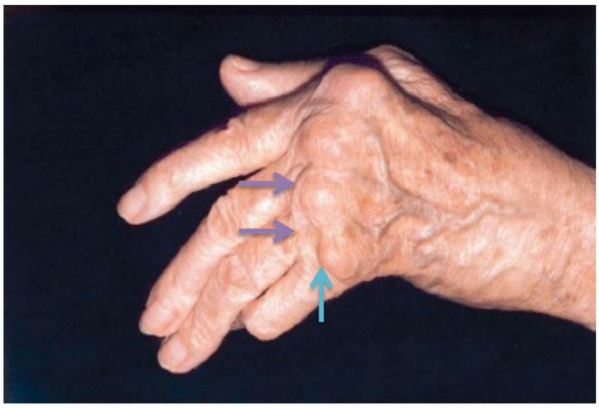


The boutonniere deformity involves the fixed flexion of the proximal interphalangeal joint and the fixed hyperextension of the distal interphalangeal joint of a digit, and is caused by the rupturing of the extensor tendon of the digit.



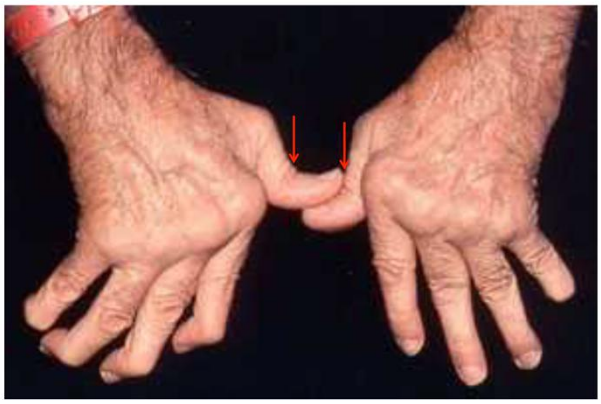
MCP swelling, Swan neck deformity

Swelling of the metacarpophalangeal joint and the swan neck deformity. The swan neck deformity involves the fixed hyperextension of the proximal interphalangeal joint and the fixed flexion of the distal interphalangeal joint of a digit, and is caused by the rupturing of the flexor tendon of the digit.



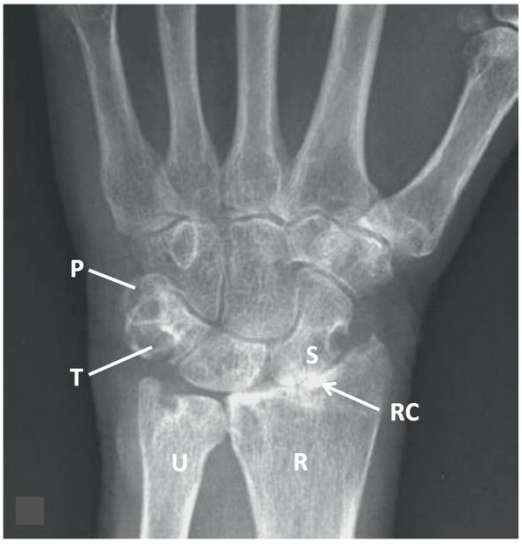
MCP subluxation, ulnar deviation

Subluxation of the metacarpophalangeal joint and ulnar deviation of the metacarpophalangeal joint.

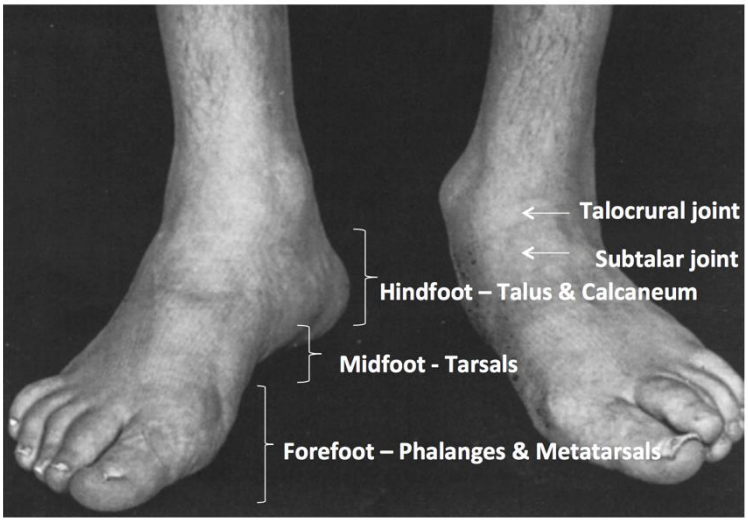


The Z deformity of the thumb involves the fixed flexion of the metacarpophalangeal joint, the subluxation of the metacarpophalangeal joint, and the fixed hyperextension of the interphalangeal joint of the thumb.

Radial deviation of the wrist is a common articular manifestation of rheumatoid arthritis.



Typical sites in the wrist of osseous erosion in rheumatoid arthritis.



Bones and joints of the foot.

Valgus talocrural and subtalar joints, midfoot pronation, and forefoot valgus are common articular manifestations of rheumatoid arthritis.

Ultrasound imaging can show synovial hyperaemia, which is associated with inflammation.

Magnetic resonance imaging can show synovitis.

Atlantoaxial instability is a rare articular manifestation of rheumatoid arthritis.

Systemic

Systemic manifestations of rheumatoid arthritis include subcutaneous nodules, pulmonary nodules, cardiac nodules, fibrosing alveolitis, episcleritis, scleritis, vasculitis, pyoderma gangrenosum, lung cancer, and lymphoma.

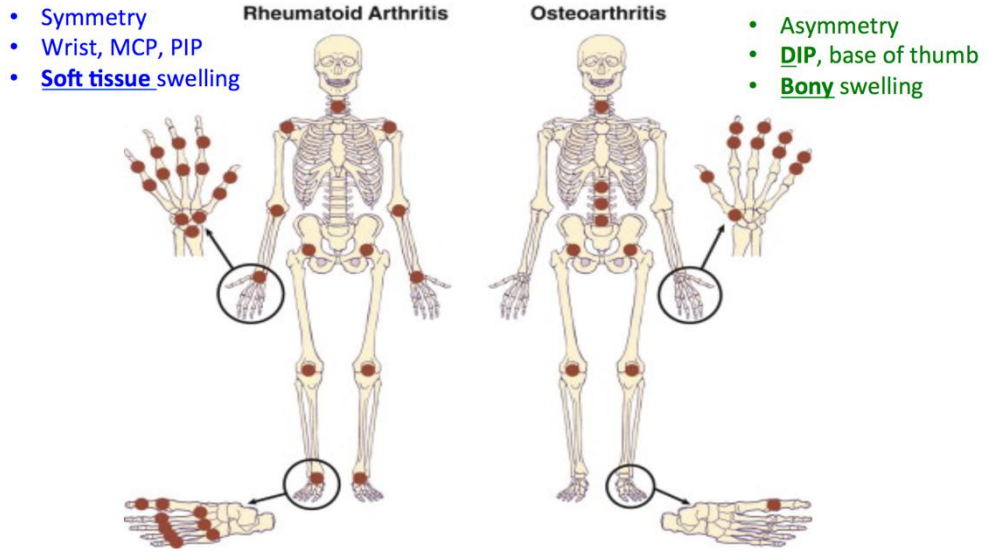
Felty's syndrome and amyloidosis are systemic manifestations of rheumatoid arthritis that are very rare when rheumatoid arthritis is effectively treated.

Differentiating Rheumatoid Arthritis from Osteoarthritis

Morning stiffness in rheumatoid arthritis lasts considerably longer than morning stiffness in osteoarthritis.

Joint pain in rheumatoid arthritis decreases throughout the day as the joints are used.

Joint pain in osteoarthritis increases throughout the day as the joints are used.



The distribution of commonly affected joints in rheumatoid arthritis and osteoarthritis.

Synovium in Health and Disease

Synovium in Health

Synovia consist of an intima layer, which consists of a few layers of synoviocytes, and a subintima layer, which consists of connective tissue that contains blood vessels, lymphatic vessels, and nerves.

Synovia facilitate movement between non-deformable structures within joints, contribute to the formation of synovial fluid, and provide nutrition to chondrocytes via synovial fluid.

Synovia provide hyaluronan, which is a polysaccharide lubricant that acts as a shock absorber, and provide lubricin, which is a proteoglycan lubricant that protects cartilage surfaces from protein deposition and cell adhesion, and inhibits synovial cell overgrowth.

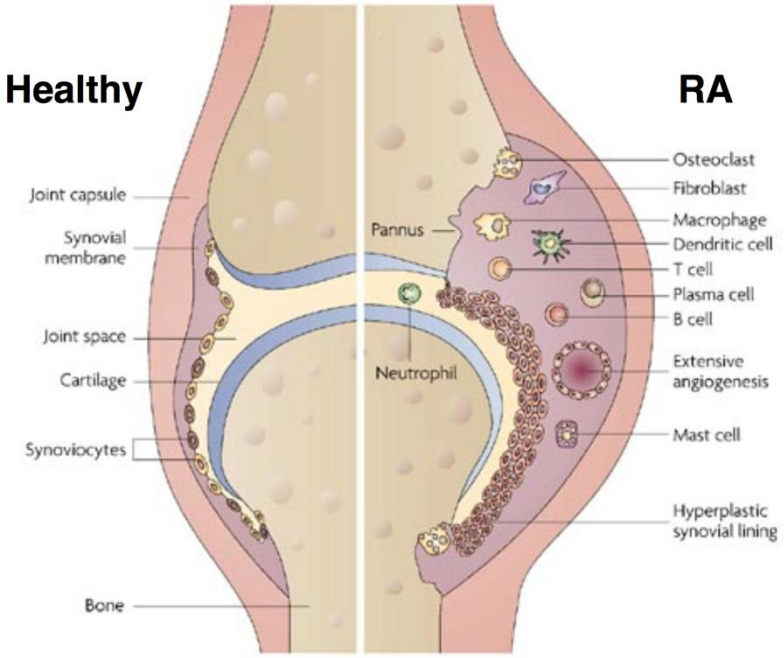
Twenty per cent of the cells of the intima layer of synovia are macrophage-like synoviocytes, which are also known as type A synoviocytes.

Macrophage-like synoviocytes are phagocytic cells, remove debris, and express receptors that bind the Fc domains of IgG antibodies.

Eighty per cent of the cells of the intima layer of synovia are fibroblast-like synoviocytes, which are also known as type B synoviocytes.

Fibroblast-like synoviocytes produce hyaluronan, lubricin, collagen, and fibronectin.

Synovium in Disease



A healthy joint and a joint affected by rheumatoid arthritis.

Synovial inflammation caused by rheumatoid arthritis involves hyperplasia of the intima layer, the infiltration of inflammatory cells into the subintima, angiogenesis, ectopic lymphoid neogenesis, and the deposition of fibrin.

The pannus of synovia affected by rheumatoid arthritis has many fibroblast-like synoviocytes, and contains fewer immune cells than 'peripheral' synovia, and is hypoxic.

Cells of the pannus of synovia affected by rheumatoid arthritis release factors that destroy cartilage and bone.

Cells

The macrophage-like synoviocytes in synovia affected by rheumatoid arthritis outnumber fibroblast-like synoviocytes, are activated, and may trans-differentiate to osteoclasts.

Activated macrophage-like synoviocytes express phagocytic markers, have an increased expression of MHC class II molecules, produce inflammatory cytokines, including TNF-alpha, IL-1, and IL-6, and produce chemokines.

Fibroblast-like synoviocytes respond to inflammation by producing inflammatory cytokines, including TNF-alpha, IL-1, and IL-6, by producing chemokines, by producing enzymes that destroy cartilage, including metalloproteinases, by producing factors that promote bone destruction, including TNF-alpha and RANKL, and by producing factors that inhibit bone formation, including TNF-alpha, DKKs, and sFRPs.

CD4+ T cells, including TH17 cells, and regulatory T cells, are prevalent in synovia affected by rheumatoid arthritis.

TH17 cells are recruited by IL-6, express IL-17, which is an inflammatory cytokine, and express RANKL.

Regulatory T cells, which act to suppress inflammation, are non-functional in synovia affected by rheumatoid arthritis.

The concentration of B cells in synovia affected by rheumatoid arthritis is variable.

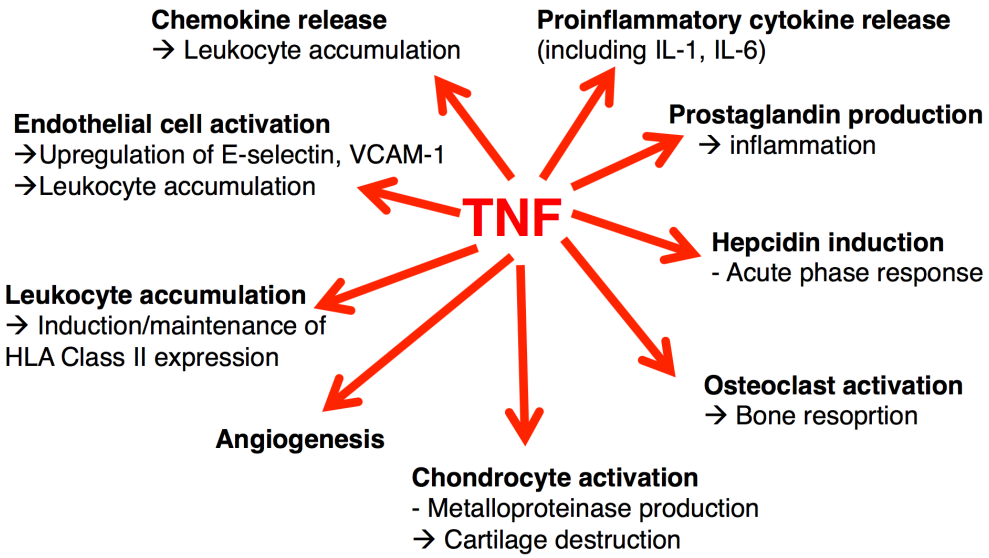
B cells in synovia affected by rheumatoid arthritis are activated by T cells that have been activated by antigen-presenting cells, produce autoantibodies, including rheumatoid factor, anti-citrulline containing peptide antibodies, and anti-collagen type II antibodies, present antigens to CD4+ T cells, and produce factors that promote bone destruction, including RANKL.

Molecules

TNF-alpha converting enzyme cleaves membrane-bound TNF-alpha, which is active, to soluble TNF-alpha, which is active.

TNF receptor 1 is expressed constitutively.

The expression of TNF receptor 2 is regulated.



TNF-alpha has many roles in synovia affected by rheumatoid arthritis.

IL-1-alpha and IL-1-beta are isoforms of IL-1.

IL-1-alpha is found in the cytoplasm of some cells.

IL-1-beta is secreted and then cleaved into its active form by IL-1 converting enzyme.

IL-1 activity is regulated by soluble IL-1 decoy receptors, and by IL-1 receptor antagonist.

IL-1 in synovia affected by rheumatoid arthritis activates leukocytes, activates endothelial cells, activates fibroblast-like synoviocytes, induces the expression of cytokines, induces the expression of chemokines, induces the expression of metalloproteinase, and induces the expression of RANKL.

IL-6 receptors can be membrane-bound or soluble.

IL-6 produces its effects by binding to homodimers of gp130 while bound to an IL-6 receptor.

IL-6 contributes to systemic inflammation, induces antibody production, promotes the differentiation of TH17 cells, induces the expression of cytokines, and induces the expression of RANKL.

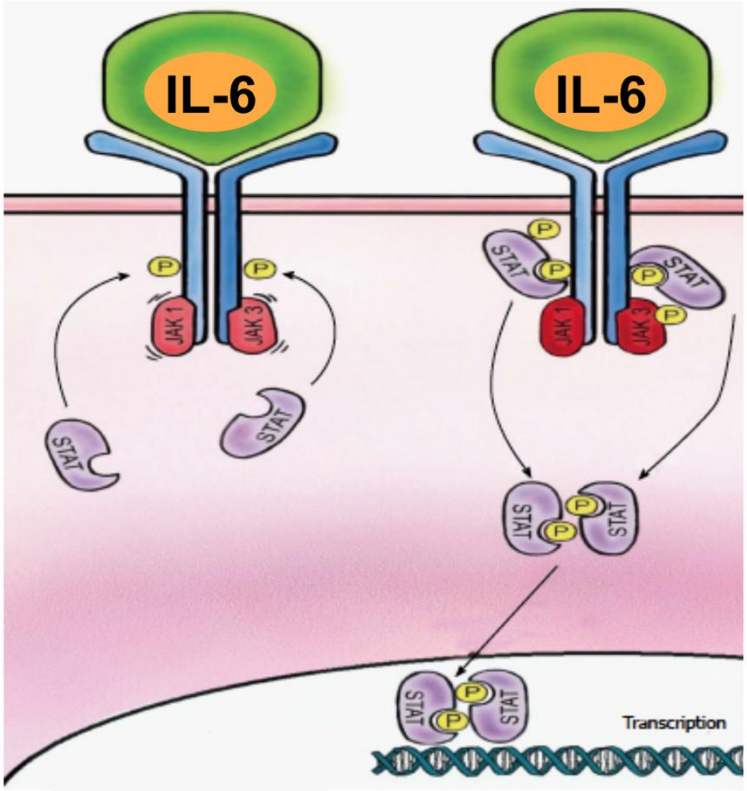
JAK-STAT Signalling

JAK1, JAK2, JAK3, and TYK2 are JAK proteins.

There are six STAT proteins.

Many cytokines signal via JAK-STAT.

The phosphorylation of STAT3 is increased in cells in synovia affected by rheumatoid arthritis, promotes cytokine expression, suppresses the apoptosis of fibroblast-like synoviocytes, promotes T cell survival, promotes antibody production, and promotes RANKL expression.



IL-6 JAK-STAT signalling, which involves the binding of IL-6 that is bound to an IL-6 receptor to a homodimer of gp130.

Models of Rheumatoid Arthritis

The Collagen-Induced Arthritis Model

The collagen-induced arthritis model is the most commonly used model for screening potential therapeutic compounds, and is produced by the injection of foreign type II collagen and Freund's complete adjuvant into the tail of susceptible mice.

The collagen-induced arthritis model produces symmetrical arthritis, is dependent on T cells and B cells, involves the increased expression of inflammatory cytokines, and involves the production of rheumatoid factor.

The collagen-induced arthritis model can only be produced with some mice strains, requires a large sample size due to the variable disease severity, involves the production of antibodies to collagen, and is dependent on IL-1 expression.

The hTNF.Tg Mouse Model

The hTNF.Tg mouse model is a genetic model, involves the overexpression of TNF-alpha, and involves the spontaneous production of arthritis.

The hTNF.Tg mouse model is a reliable model of rheumatoid arthritis, and can demonstrate the effectiveness of TNF-alpha antibodies.

The hTNF.Tg mouse model is dependent on IL-1 expression, and is not dependent on T cells and B cells.

TNF-Alpha as a Therapeutic Target

In the 1980s, the TNF-alpha gene was cloned, and TNF-alpha was found in synovia affected by rheumatoid arthritis.

In the 1990s, a neutralising TNF-alpha antibody was found to reduce the expression of inflammatory cytokines *in vitro* and was found to reduce synovitis in the collagen-induced arthritis model.

Bone in Health and Disease

Bone in Health

Cortical bone, which is hard, surrounds trabecular bone.

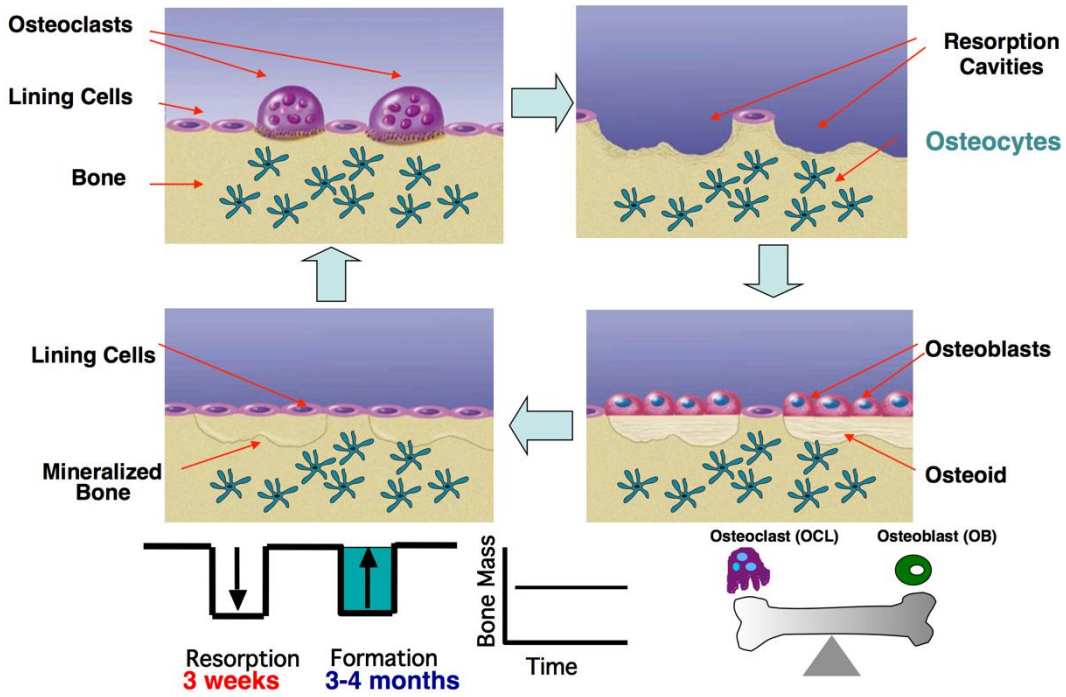
Ten per cent of adult bone mass is collagen.

Sixty-five per cent of adult bone mass is hydroxyapatite, which is an insoluble salt of calcium and phosphorus.

Twenty-five per cent of adult bone mass is water.

Approximately ten per cent of adult bone is replaced each year.

Bone remodelling maintains mineral ion homeostasis, maintains structural integrity, and allows for the shape of bone to be adapted.



Bone remodelling by osteoclasts and osteoblasts. Osteoblasts become osteocytes when they are surrounded by bone.

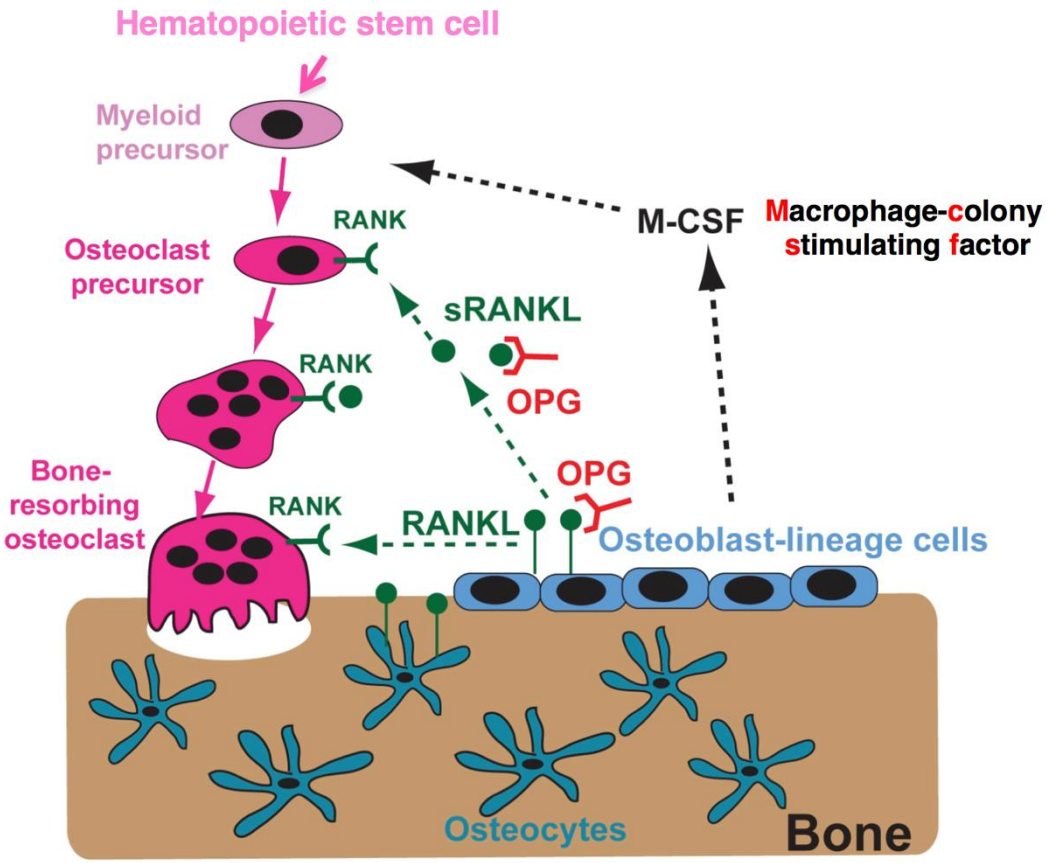
Osteoporosis occurs when the rate of bone resorption is faster than the rate of bone formation.

Osteopetrosis occurs when the rate of bone resorption is slower than the rate of bone formation.

Osteoclasts

Osteoclasts are large multinucleated bone resorbing cells, and have many mitochondria.

Osteoclasts resorb bone by forming an integrin-mediated sealing zone, degrading the mineral component of bone with acid, degrading the organic component of bone with collagenases and other enzymes, and absorbing and secreting the bone degradation products.



The differentiation of osteoclasts. RANKL is a member of the TNF family of ligands, is cleaved into its soluble form, is necessary and sufficient for osteoclast differentiation, and is produced by osteoblasts and osteocytes. Osteoprotegerin is structurally distinct from RANK, is a decoy receptor of RANKL, and is produced by osteoblasts.

Osteoclast differentiation is regulated by the ratio of RANKL to OPG.

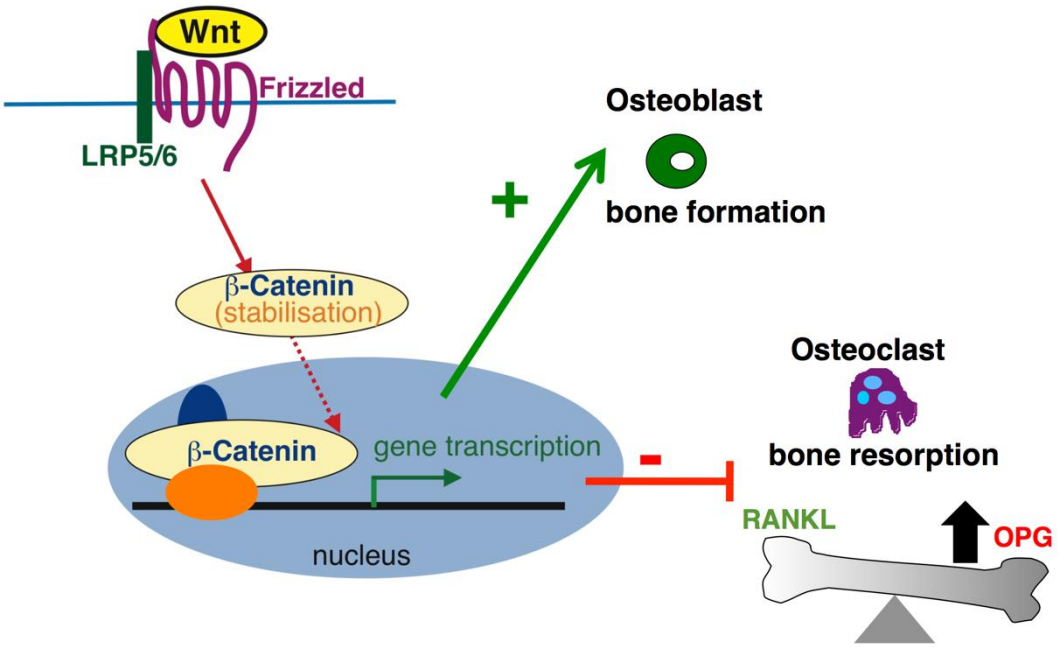
Osteoblasts

Osteoblasts are bone forming cells, share a common precursor with muscle cells and adipocytes, can become osteocytes, can become lining cells, and can undergo apoptosis.

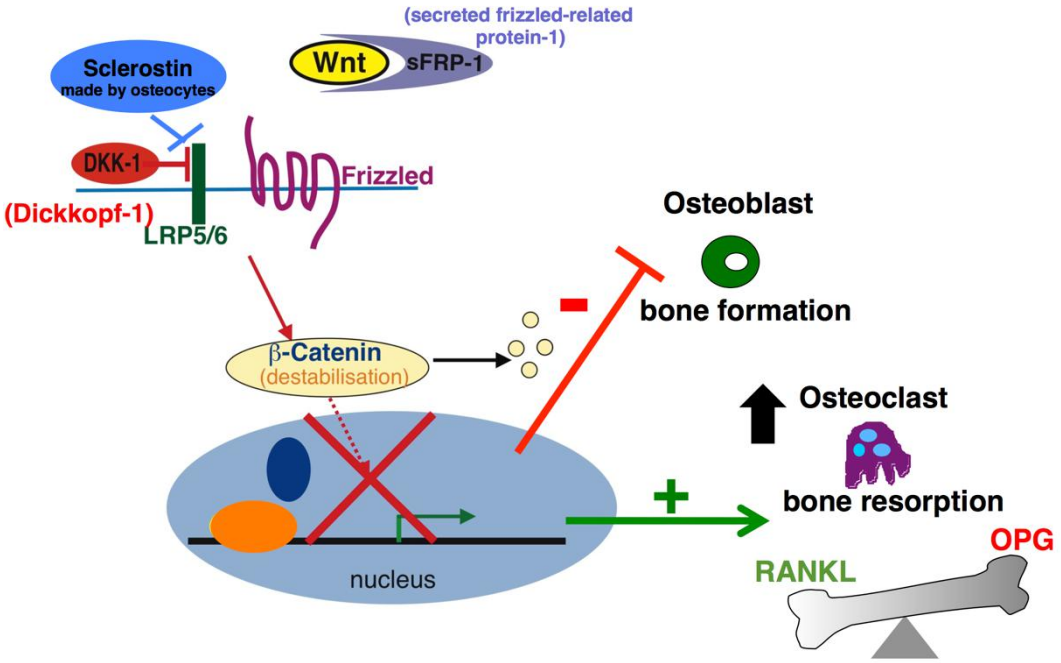
Preosteoblasts produce RANKL.

Mature osteoblasts produce OPG.

Osteoblasts form bone by secreting extracellular matrix proteins, including collagen, bone sialoprotein, and osteocalcin, and expressing alkaline phosphatase, which enables mineral deposition.



Wnt signalling in osteoblasts and osteoblast precursor cells promotes bone formation, and inhibits bone resorption by increasing the expression of OPG.



The inhibition of Wnt signalling in osteoblasts and osteoblast precursor cells inhibits bone formation and promotes bone resorption.

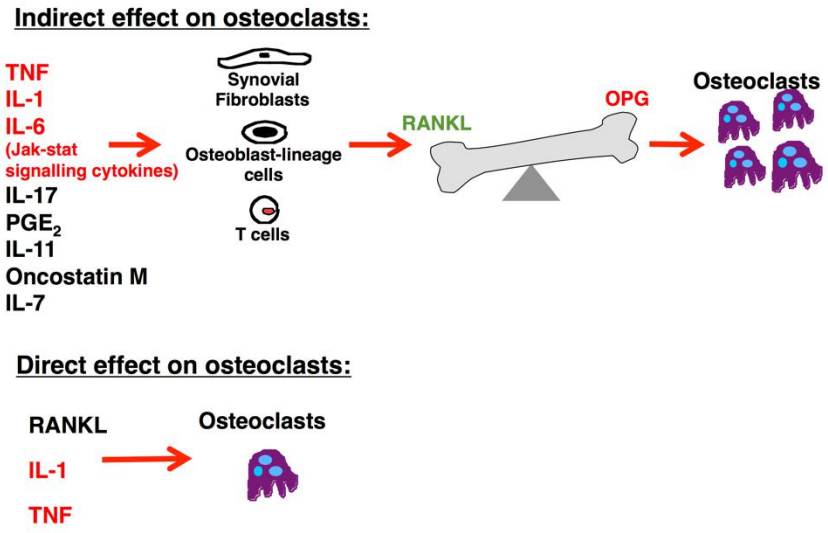
Bone in Disease

Rheumatoid arthritis causes periarticular osteopenia of trabecular bone, causes focal bone erosion of cortical bone, and causes systemic osteoporosis of trabecular bone and cortical bone.

The healing of focal bone erosions is rare in patients in remission.

Osteoclasts

Sources of RANKL in synovia affected by rheumatoid arthritis include osteoblast-lineage cells, fibroblast-like synoviocytes, and T cells.



Indirect and direct effects of cytokines and factors on osteoclasts.

TNF-alpha increases the expression of RANK on osteoclast precursor cells, and promotes the proliferation of osteoclast precursor cells.

IL-1 promotes the cell fusion of mononuclear osteoclast precursor cell, and promotes the cell survival of osteoclasts.

Osteoblasts

Osteoblasts in synovia affected by rheumatoid arthritis are immature.

The expression of DKKs and sFRPs is increased in synovia affected by rheumatoid arthritis.

TNF-alpha increases the expression of DKKs by fibroblast-like synoviocytes, increases the expression of RANKL by osteoblasts, and impairs the differentiation and function of osteoblasts.

TNF-Alpha as a Therapeutic Target

TNF-alpha antibodies reduce focal bone erosion in the collagen-induced arthritis model.

Risk Factors, Diagnosis, and Assessing Disease Activity

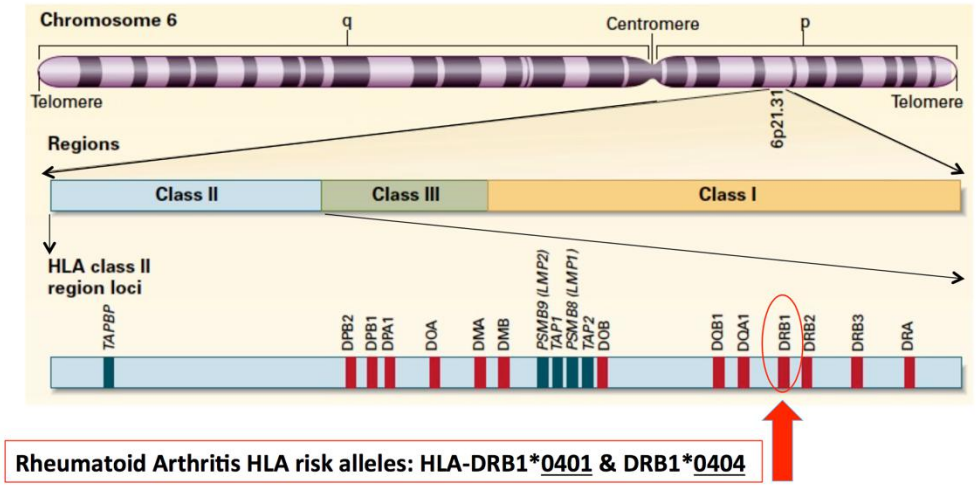
Risk Factors

An odds ratio is a measure of the association between an exposure and an outcome.

Rheumatoid arthritis affects females more commonly than males.

Genetic

Genetic risk factors of rheumatoid arthritis account for fifty per cent of disease susceptibility.



*The HLA-DRB1*0401 and the HLA-DRB1*0404 alleles are associated with rheumatoid arthritis.*

HLA-DRB1 alleles that are associated with rheumatoid arthritis encode the shared epitope, which is a short sequence of amino acids that surrounds the peptide binding grove of MHC class II molecules.

HLA-DRB1 alleles that are associated with rheumatoid arthritis predict the production of anti-citrulline containing peptide antibodies, and may predict the severity of rheumatoid arthritis.

Citrullination is the post-translational conversion of arginine to citrulline by PADIs, and occurs at sites of inflammation.

Citrulline binds to the shared epitope more readily than arginine.

PADI2 and PADI4 are abundant in synovium affected by rheumatoid arthritis.

There are many non-HLA genetic risk factors of rheumatoid arthritis, including PTPN22 alleles, and PADI4 alleles.

Epigenetic

Epigenetic risk factors of rheumatoid arthritis involve post-translational histone modification, DNA methylation, and microRNAs.

Hormonal

Oestrogen is a hormonal risk factor of rheumatoid arthritis.

During pregnancy, the symptoms of rheumatoid arthritis improve.

Environmental

Rheumatoid arthritis was first described after the beginning of the industrial revolution.

Smoking causes inflammation that involves PADI2 expression, and is associated with rheumatoid arthritis.

Infections, including infections of aggregatibacter actinomycetemcomitans, are associated with rheumatoid arthritis.

Streptococcus activates toll-like receptor, which increases PADI expression.

Emerging Factors

Bacteria of the microbiome may cause rheumatoid arthritis in genetically predisposed individuals.

Stroke suffers can develop asymmetrical rheumatoid arthritis in their non-paralysed side.

The long-term altered microvasculature permeability caused by paralysation may prevent rheumatoid arthritis.

Diagnosis

A diagnosis of rheumatoid arthritis can be made by testing for rheumatoid factor and anti-citrulline containing peptide antibodies.

Rheumatoid factor and anti-citrulline containing peptide antibodies can be detected several years before the onset of symptoms of rheumatoid arthritis.

Sensitive tests produce few false negative results.

Specific tests produce few false positives results.

The positive likelihood ratio is the probability of a true positive result divided by the probability of a false positive result.

The negative likelihood ratio is the probability of a false negative result divided by the probability of a true negative result.

Rheumatoid factor tests are slightly more sensitive and significantly less specific than anti-citrulline containing peptide antibody tests.

Rheumatoid factor tests have a significantly lower positive likelihood ratio than anti-citrulline containing peptide antibody tests.

Rheumatoid factor tests have a similar positive likelihood ratio to anti-citrulline containing peptide antibody tests.

Rheumatoid factor seropositivity or anti-citrulline containing peptide antibody seropositivity is a predictor of disease severity.

Patients with at least one joint with definite clinical synovitis that is not better explained by another disease can be scored according to ACR/EULAR classification criteria.

Assessing Disease Activity

Rheumatoid factor tests and anti-citrulline containing peptide antibody tests cannot be used for assessing disease activity.

The assessment of disease activity can involve joint counts, a global assessment, a pain score, an ESR test, an CRP test, radiological tests, the consideration of morning stiffness, the consideration of disability, and the consideration of fatigue.

A DAS28-ESR score is commonly used to categorise disease activity.

Treatment of Rheumatoid Arthritis

Treatment Principles

Delays in treatment initiation result in increased joint damage.

The first three months following the onset of symptoms is known as the therapeutic window of opportunity.

The treatment of rheumatoid arthritis involves beginning treatment with disease-modifying drugs promptly after diagnosis, aiming for remission or low disease activity, and intensive treatment regimens.

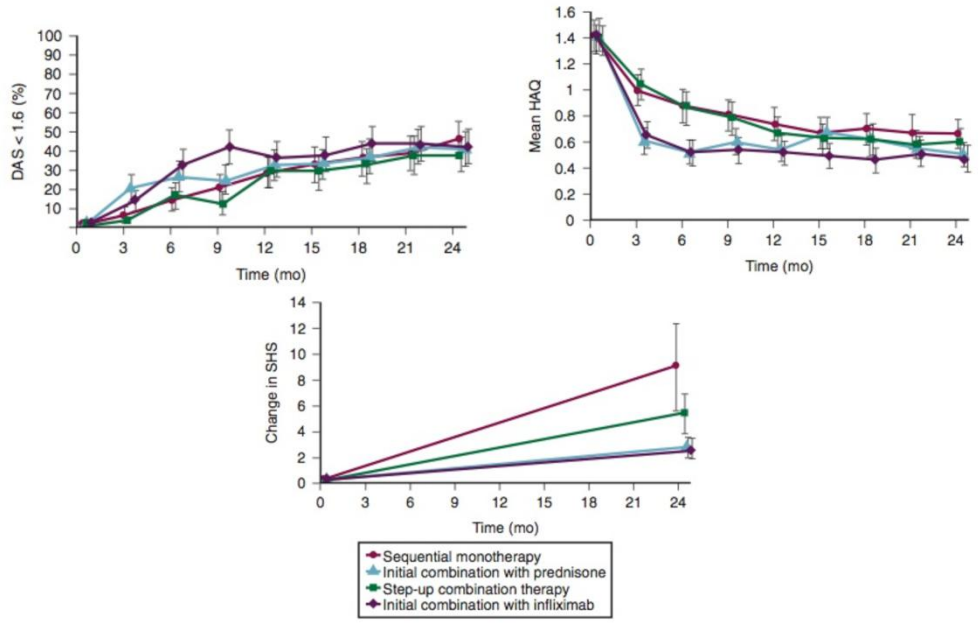
The TICORA trial found that an intensive treatment regimen is more effective than a routine treatment regimen.

Medications

Analgesics, NSAIDs, glucocorticoids, csDMARDs, and bDMARDs are used to treat rheumatoid arthritis.

Methotrexate is the most commonly used csDMARD.

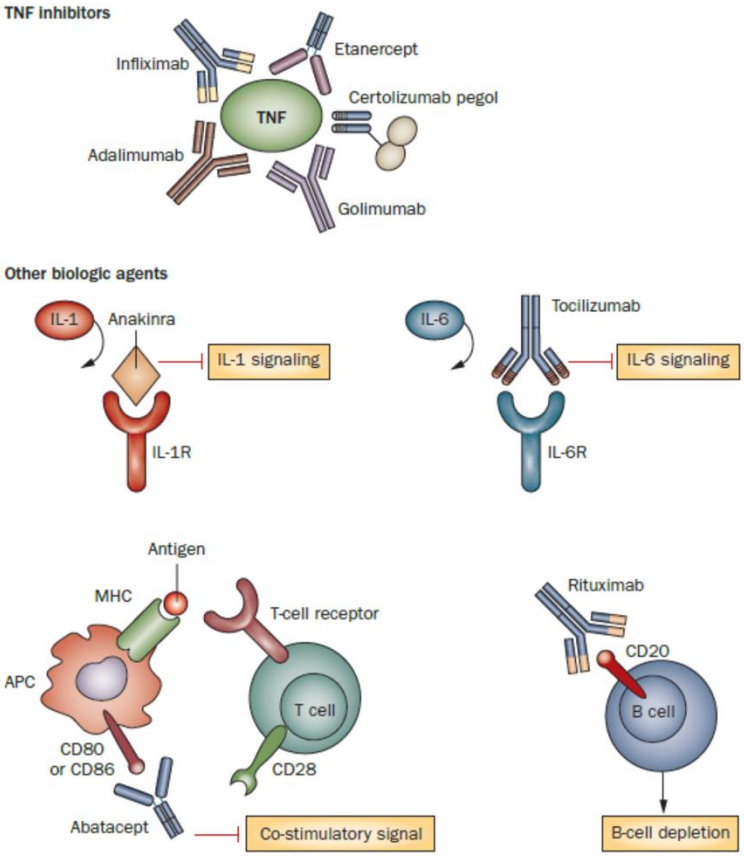
A triple therapy study found that triple DMARD therapy is more effective than dual DMARD therapy and DMARD monotherapy.



Results of the BeSt study. The DAS score is a measure of disease activity. The HAQ score is a measure of disability. The SHS score is a measure of bone erosion.

bDMARDs are used to treat patients that fail to respond to csDMARDs.

TNF-alpha inhibitors are the most commonly used bDMARDs.



bDMARDs.

The PBS has specific criteria for bDMARD eligibility.

TNF-Alpha Blockade

The first infliximab trial, which was the first human clinical trial of an anti-TNF-alpha antibody, found an improvement in symptoms, reduced signs of inflammation, and no alarming adverse events.

Anti-TNF-Alpha bDMARDs

Infliximab is a chimeric antibody that consists of human IgG constant regions and mouse antibody variable regions.

Etanercept is a fusion protein, which consists of TNF-alpha receptors and human IgG constant regions.

Adalimumab consists of human IgG constant regions and human antibody variable regions, and is the most commonly used bDMARD.

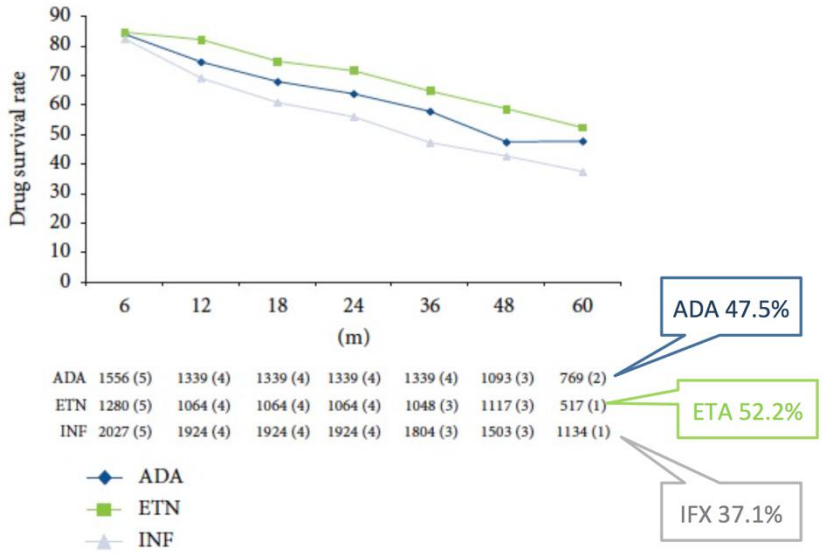
Certolizumab pegol consists of a human antigen-binding fragment and polyethylene glycol.

Golimumab is similar to adalimumab.

Treatment with golimumab requires less frequent injections than treatment with adalimumab.

Primary failure of anti-TNF-alpha antibodies occurs when TNF-alpha is not the principle molecule of disease.

Secondary failure of anti-TNF-alpha antibodies involves an immune response to the anti-TNF-alpha antibodies.



The survival rates of adalimumab, etanercept, and infliximab in patients on their first bDMARD.

Anti-TNF-alpha antibody treatments are associated with injection site reactions, cytopenia, neutropenia, infections, demyelinating disease, heart failure, non-melanoma skin cancer, lymphoma, psoriasis, and systemic lupus erythematosus.

Non-Anti-TNF-Alpha bDMARDs

Anakinra is an IL-1 receptor blocker, and is not as effective as anti-TNF-alpha bDMARDs.

Tocilizumab is a IL-6 receptor blocker.

Abatacept is a T cell costimulation blocker.

Rituximab depletes B cells by targeting CD20, which is a molecule found on B cells during many stages of their development.

Efficacy of bDMARDs

An ACR20 response involves an improvement in the American College of Rheumatology improvement criteria of at least twenty per cent.

A head-to-head trial of tocilizumab and adalimumab found that tocilizumab is superior to adalimumab, and that tocilizumab is associated with more adverse events than adalimumab.

A head-to-head trial of abatacept and adalimumab found that abatacept and adalimumab have comparable efficacy.

A head-to-head trial of rituximab and adalimumab or etanercept found that rituximab and adalimumab or etanercept have comparable efficacy.

A head-to-head trial of certolizumab pegol and adalimumab found that certolizumab pegol and adalimumab have comparable efficacy.

A head-to-head trial of sarilumab and adalimumab found that sarilumab is superior to adalimumab.

Targeted Synthetic Small Molecule Inhibitors

JAK signalling is involved in immune cell activation and the production of inflammatory cytokines.

Tofacitinib and baricitinib are JAK inhibitors.

Tofacitinib and adalimumab have comparable efficacy.

Baricitinib and adalimumab have comparable efficacy.

Tofacitinib cannot be used in combination with other bDMARDs, and can cause headaches, infections, and other adverse events.