B.PHARMACY
8TH SEMESTER
PHARMACOLOGY-IV(BPHM-804)
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MODULE 8TH

1.Joint and Connective tissue disorders- Rheumatoid arthritis

Arthritic disease is one of the commonest chronic inflammatory conditions in developed countries, and rheumatoid arthritis is a common cause of disability. One in three patients with rheumatoid arthritis is likely to become severely disabled. The joint changes, which are probably driven by an autoimmune reaction, involve inflammation, proliferation of the synovium and erosion of cartilage and bone. The primary inflammatory cytokines, IL-1 and TNF- α, have a major role in pathogenesis. The pathogenesis of rheumatoid arthritis, and the action of therapeutic drugs, are summarised in Figure 26.4.

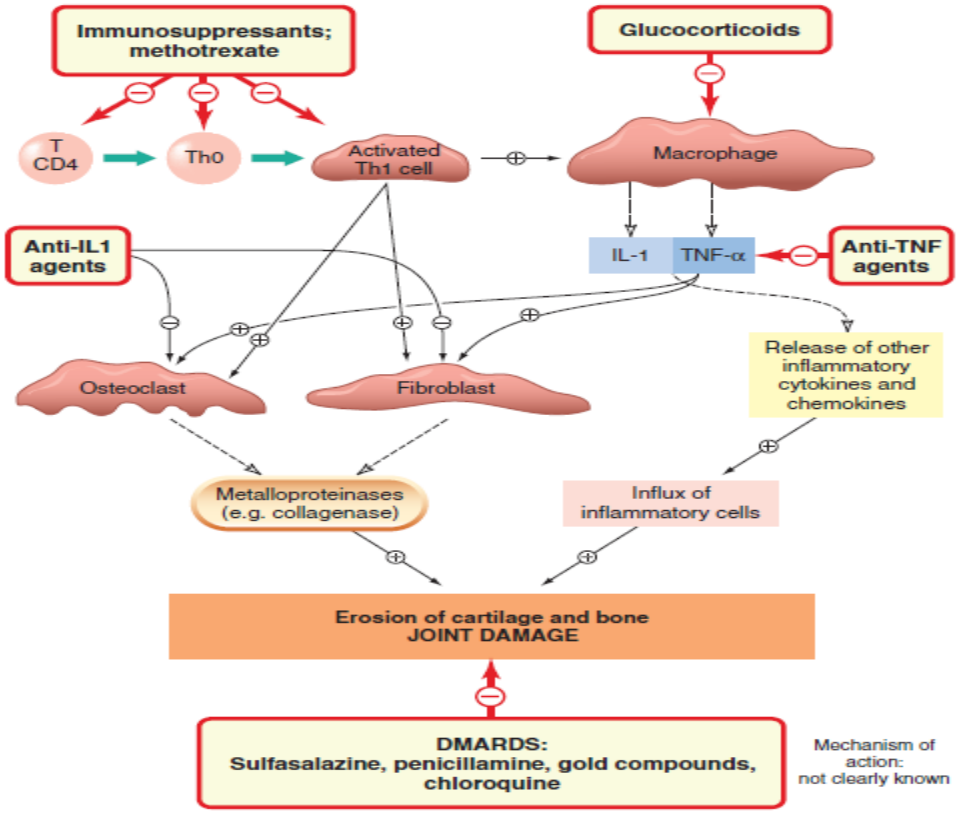


Fig. 26.4 A schematic diagram of the cells and mediators involved in the pathogenesis of rheumatoid joint damage, indicating the sites of action of antirheumatoid drugs. DMARD, disease-modifying antirheumatic drug. For details of the anti-TNF, IL-1 and IL-2 receptor agents, see Table 26.3

TREATMENT

The drugs most frequently used in initial therapy are the 'disease-modifying antirheumatic drugs' (DMARDs) and the NSAIDs. Unlike the NSAIDs, which reduce the symptoms but not the progress of the disease, the former group may halt or reverse the underlying disease itself. Although such claims may be optimistic, these drugs are nevertheless useful in the treatment of discrete groups of patients, and Rau (2005) has argued for their continuing use even when the newer anticytokine agents are available. Some immunosuppressants (e.g. **azathioprine**, **ciclosporin**) are also used, as are the glucocorticoids.

DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

The term 'DMARD' is a latex concept that can be stretched to cover a heterologous group of agents with unrelated chemical structures and different mechanisms of action. Included in this category are **methotrexate**, **sulfasalazine**, **gold** compounds, **penicillamine** and **chloroquine** and other antimalarials and various immunosuppressant drugs.

The antirheumatoid action of most of these agents was usually discovered through a mixture of serendipity and clinical intuition.

When the drugs were introduced, nothing was known about their mechanism of action and decades of in vitro experiments have generally resulted in further bewilderment rather than understanding. DMARDs generally improve symptoms and can reduce disease activity in rheumatoid arthritis, as measured by reduction in the number of swollen and tender joints, pain score, disability score, X-ray appearance and serum concentration of acute-phase proteins and of rheumatoid factor (an immunoglobulin [Ig] M antibody against host IgG).

The DMARDs were often referred to as *second-line drugs*, with the implication that they are only resorted to when other therapies (e.g. NSAIDs) failed. Today, however, DMARD therapy may be initiated as soon as a definite diagnosis has been reached. Their clinical effects are usually slow (months) in onset, and it is usual to provide NSAID 'cover' during this induction phase. If therapy is successful (and the success rate is not invariably high), concomitant NSAID (or glucocorticoid) therapy can generally be dramatically reduced. Some DMARDs have a place in the treatment of other chronic inflammatory diseases, whereas others (e.g. penicillamine) are not thought to have a general anti-inflammatory action.

METHOTREXATE

Methotrexate is a folic acid antagonist with cytotoxic and immunosuppressant activity and potent antirheumatoid action. It is a common firstchoice drug. It has a more rapid onset of action than other DMARDs, but treatment must be closely monitored because of potential blood dyscrasias (some fatal) and liver cirrhosis. It is, however, superior to most other DMARDs in terms of efficacy and unwanted effects, and is often given in conjunction with the anticytokine drugs.

SULFASALAZINE

Sulfasalazine, a common first-choice DMARD in the UK, produces remission in active rheumatoid arthritis and is also used for chronic inflammatory bowel disease. It may act by scavenging the toxic oxygen metabolites produced by neutrophils. The drug is a complex of a sulfonamide (**sulfapyridine**) and salicylate. It is split **5-aminosalicylic** acid being the putative radical scavenger.

It is poorly absorbed after oral administration. The common side effects include gastrointestinal disturbances, malaise and headache. Skin reactions and leucopenia can occur but are reversible on stopping the drug. The absorption of folic acid is sometimes impaired; this can be countered by giving folic acid supplements. A reversible decrease in sperm count has also been reported.

PENICILLAMINE

Penicillamine is dimethylcysteine; it is produced by hydrolysis of **penicillin** and appears in the urine after treatment with that drug. The D-isomer is used in the therapy of rheumatoid disease. About 75% of patients with rheumatoid arthritis respond to penicillamine. In responders, therapeutic effects are seen within weeks but do not reach a plateau for several months. Penicillamine is thought to modify rheumatoid disease partly by decreasing the immune response, IL-1 generation and/or partly by an effect on collagen synthesis, preventing the maturation of newly synthesised collagen. However, the precise mechanism of action is still a matter of conjecture. The drug has a highly reactive thiol group and also has metal-chelating properties, which are put to good use in the treatment of ***Wilson's disease*** (pathological copper deposition causing neurodegeneration) or heavy metal poisoning. Penicillamine is given orally, and only half the dose administered is absorbed. It reaches peak plasma concentrations in 1–2 h and is excreted in the urine. Dosage is started low and increased only gradually to minimize unwanted effects. Unwanted effects occur in about 40% of patients treated and may necessitate cessation of therapy. Rashes and stomatitis are the most common unwanted effects but may resolve if the dosage is lowered. Anorexia, fever, nausea and vomiting, and disturbances of taste (the last related to the chelation of zinc) are seen, but often disappear with continued treatment. Proteinuria occurs in 20% of patients and should be monitored. Hematological monitoring is also required when treatment is initiated. Thrombocytopenia may require lowering the dose. Leucopenia or aplastic anaemia are absolute contraindications, as are the various autoimmune conditions (e.g. thyroiditis, myasthenia gravis) that sometimes supervene. Because penicillamine is a metal chelator, it should not be given with gold compounds.

GOLD COMPOUNDS

Gold is administered in the form of organic complexes; **sodium aurothiomalate** and **auranofin** are the two most common preparations. The effect of gold compounds develops slowly over 3–4 months. Pain and joint swelling subside, and the progression of bone and joint damage diminishes. The mechanism of action is not clear, but auranofin, although not aurothiomalate, inhibits the induction of IL-1 and TNF-α. Sodium aurothiomalate is given by deep intramuscular injection; auranofin is given orally. The compounds gradually become concentrated in the tissues, not only in synovial cells in joints but also in liver cells, kidney tubules, the adrenal cortex and macrophages throughout the body. The gold complexes remain in the tissues for some time after treatment is stopped. Excretion is mostly renal, but some is eliminated in the gastrointestinal tract. The half-life is 7 days initially but increases with treatment, so the drug is usually given first at weekly, then at monthly intervals. Unwanted effects with aurothiomalate are seen in about one-third of patients treated, and serious toxic effects in about 1 patient in 10. Unwanted effects with auranofin are less frequent and less severe. Important unwanted effects include skin rashes (which can be severe), mouth ulcers, non-specific flu-like symptoms, proteinuria, thrombocytopenia and blood dyscrasias. Encephalopathy, peripheral neuropathy and hepatitis can occur. If therapy is stopped when the early symptoms appear, the incidence of serious toxic effects is relatively low.

ANTIMALARIAL DRUGS

Hydroxychloroquine and **chloroquine** are 4-amino- quinoline drugs used mainly in the prevention and treatment of malaria (Ch. 53), but they are also used as DMARDs. Chloroquine is usually reserved for cases where other treatments have failed. They are also used to treat another autoimmune disease, *lupus erythematosus*, but are contraindicated in patients with *psoriatic arthropathy* because they make the skin lesions worse. The related compound, **mepacrine**, is also sometimes used for discoid lupus. The antirheumatic effects do not appear until a month or more after the drug is started, and only about half the patients treated respond.

IMMUNOSUPPRESSANT DRUGS

Immunosuppressants are used in the therapy of autoimmune disease and also to prevent and/or treat transplant rejection. Because they impair immune responses, they carry the hazard of a decreased response to infections and may facilitate the emergence of malignant cell lines. However, the relationship between these adverse effects and potency in preventing graft rejection varies with different drugs. The clinical use of immunosuppresants is summarised in the clinical box. Most of these drugs act during the induction phase of the immunological response, reducing lymphocyte proliferation, although others also inhibit aspects of the effector phase. They can be roughly characterised as:

• drugs that inhibit IL-2 production or action (e.g. **ciclosporin**, **tacrolimus**)
• drugs that inhibit cytokine gene expression (e.g. the corticosteroids)
• drugs that inhibit purine or pyrimidine synthesis (e.g. **azathioprine**, **mycophenolate mofetil**).

TACROLIMUS

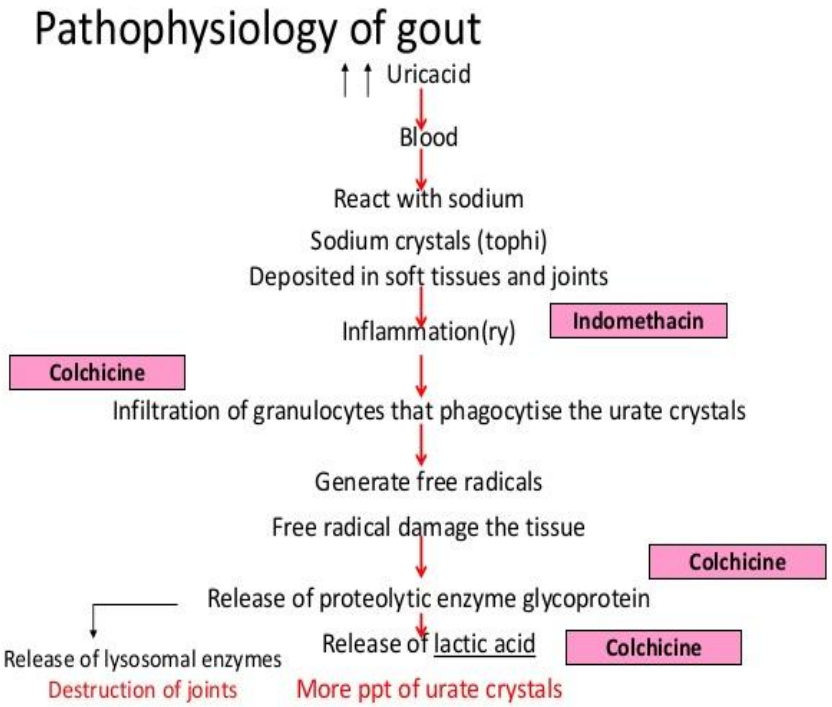
Tacrolimus is a macrolide antibiotic of fungal origin with a very similar mechanism of action to ciclosporin, but higher potency. The main difference is that the internal receptor for this drug is not cyclophilin but a different immunophilin termed *FKBP* (FK-binding protein, so-called because tacrolimus was initially termed FK506). The tacrolimus–FKBP complex inhibits calcineurin with the effects described above. It is mainly used in organ transplantation and severe atopic eczema. **Pimecrolimus** (used topically for atopic eczema) acts in a similar way. **Sirolimus** (used to prevent organ rejection after transplantation, and also in coating on stents to prevent restenosis) also combines with an immunophilin, but activates a protein kinase to produce its immunosuppressant effect. Tacrolimus can be given orally, by intravenous injection or as an ointment for topical use in inflammatory disease of the skin. It is 99% metabolised by the liver and has a half-life of approximately 7 h.

AZATHIOPRINE

Azathioprine interferes with purine synthesis and is cytotoxic. It is widely used for immunosuppression, particularly for control of autoimmune diseases such as rheumatoid arthritis and to prevent tissue rejection in transplant surgery. This drug is metabolised to give mercaptopurine, a purine analogue that inhibits DNA synthesis. Both cell-mediated and antibody-mediated immune reactions are depressed by this drug, because it inhibits clonal proliferation during the induction phase of the immune response through a cytotoxic action on dividing cells. As is the case with mercaptopurine itself, the main unwanted effect is depression of the bone marrow. Other toxic effects are nausea and vomiting, skin eruptions and a mild hepatotoxicity.

2. GOUT AND HYPERURICEMIA

Gout is a metabolic disease in which plasma urate concentration is raised. Sometimes this is linked to overindulgence in alcoholic beverages, especially beer, or purine-rich foods such as offal. Increased cell turnover in haematological malignancies, particularly after treatment with cytotoxic drugs, or impaired excretion of uric acid are other causes. It is characterised by very painful intermittent attacks of acute arthritis produced by the deposition of crystals of sodium urate (a product of purine metabolism) in the synovial tissue of joints and elsewhere. An inflammatory response is evoked, involving activation of the kinin, complement and plasmin systems, generation of lipoxygenase products such as leukotriene B4, and local accumulation of neutrophil granulocytes. These engulf the crystals by phagocytosis, releasing tissue-damaging toxic oxygen metabolites and subsequently causing lysis of the cells with release of proteolytic enzymes. Urate crystals also induce the production of IL-1 and possibly other cytokines.



TREATMENT OF GOUT

Drugs used to treat gout act in the following ways:

• By inhibiting uric acid synthesis (**allopurinol**, the main prophylactic drug).
• By increasing uric acid excretion (uricosuric agents: **probenecid**, **sulfinpyrazone**).
• By inhibiting leukocyte migration into the joint (**colchicine**).
• By a general anti-inflammatory and analgesic effect (NSAIDs and occasionally glucocorticoids).

Their clinical uses are summarised in the clinical box, below.

ALLOPURINOL

Allopurinol is an analogue of hypoxanthine that reduces the synthesis of uric acid by competitive inhibition of *xanthine oxidase*. It is first converted to alloxanthine by xanthine oxidase, and this metabolite, which remains in the tissue for a considerable time, is an effective noncompetitive inhibitor of the enzyme. Some inhibition of de novo purine synthesis also occurs. Allopurinol reduces the concentration of the relatively insoluble urates and uric acid in tissues, plasma and urine, while increasing the concentration of their more soluble precursors, the xanthines and hypoxanthines. The deposition of urate crystals in tissues (*tophi*) is reversed, and the formation of renal stones is inhibited. Allopurinol is the drug of choice in the long-term treatment of gout, but it is ineffective in the treatment of an acute attack and may even exacerbate the inflammation

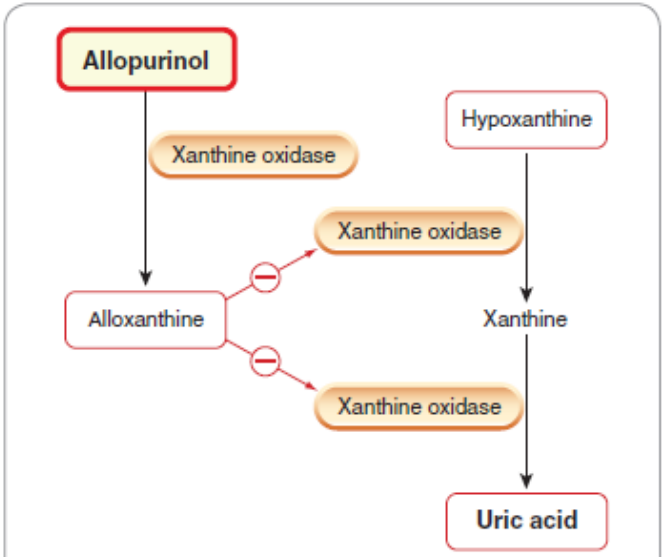


Fig. 26.5 Inhibition of uric acid synthesis by allopurinol

Allopurinol is given orally and is well absorbed. Its halflife is 2–3 h: its active metabolite alloxanthine (Fig. 26.5) has a half-life of 18–30 h. Renal excretion is a balance between glomerular filtration and probenecid-sensitive tubular reabsorption. Unwanted effects are few. Gastrointestinal disturbances, allergic reactions (mainly rashes) and some blood problems can occur but usually disappear if the drug is stopped.Potentially fatal skin diseases such as **Stevens–Johnson syndrome** are rare—but devastating. Re-challenge under these circumstances is never justified. Acute attacks of gout occur commonly during the early stages of therapy (possibly as a result of physicochemical changes in the surfaces of urate crystals as these start to re-dissolve), so treatment with allopurinol is never initiated during an acute attack and is usually combined with an NSAID initially.

URICOSURIC AGENTS

Uricosuric drugs increase uric acid excretion by a direct action on the renal tubule. Common drugs used are **probenecid** and **sulfinpyrazone**. **Benzbromarone** is also available on a named patient basis for treatment of patients with renal impairment. They remain useful as prophylaxis for patients with severe recurrent gout who have severe adverse reactions to allopurinol. Sulfinpyrazone also has NSAID activity. Treatment with uricosuric drugs is initiated with an NSAID, as for allopurinol. Aspirin and salicylates antagonise the action of uricosuric drugs and should not be used concurrently. Although not strictly speaking in this group, **rasburicase**, a preparation containing the enzyme *uric acid oxidase*, is sometimes used for aggressive treatment. It oxidises uric acid in the blood to allantoin, which is more soluble and thus more readily excreted.

COLCHICINE

Colchicine is an alkaloid extracted from the autumn crocus. It has a specific effect in gouty arthritis and can be used both to prevent and to relieve acute attacks. It prevents migration of neutrophils into the joint by binding to *tubulin*, resulting in the depolymerisation of the microtubules and reduced cell motility. Colchicine-treated neutrophils develop a ‘drunken walk’. Colchicine may also prevent the production of a putative inflammatory glycoprotein by neutrophils that have phagocytosed urate crystals, and other mechanisms may also be important in bringing about its effects. Colchicine is given orally, and is excreted partly in the gastrointestinal tract and partly in the urine. The acute unwanted effects of colchicine are largely gastrointestinal and include nausea, vomiting and abdominal pain. Severe diarrhoea may be a problem, and with large doses may be associated with gastrointestinal haemorrhage and kidney damage. Prolonged treatment can, rarely, cause blood dyscrasias, rashes or peripheral neuropathy.

3. ACUTE LEUKEMIA

These are aggressive tumors, composed of immature lymphocytes (lymphoblasts), which occur predominantly in children and young adults. The various lymphoblastic tumors are morphologically indistinguishable and often cause similar signs and symptoms. Because precursor B- and T-cell neoplasms have overlapping features, we will consider them together.

Just as B-cell precursors normally develop within the bone marrow, pre-B-lymphoblastic tumors characteristically appear in bone marrow and peripheral blood as leukemias. Similarly, pre-T-lymphoblastic tumors commonly present as masses involving the thymus, which is the site of early stages of normal T-cell differentiation. However, pre-T-cell "lymphomas" often progress rapidly to a leukemic phase, and other pre-T-cell tumors seem to involve only the marrow at presentation. Hence, *both pre-B- and pre-T-lymphoblastic tumors usually take on the clinical appearance of an acute lymphoblastic leukemia (ALL) at some time during their course.* As a group, ALLs constitute 80% of childhood leukemia, peaking in incidence at age 4, with most of the cases being of pre-B-cell origin. The pre-T-cell tumors are most common in adolescent males of between 15 and 20 years of age.
The pathophysiology, laboratory findings, and clinical features of ALL closely resemble those of acute myelogenous leukemia (AML), the other major type of acute leukemia. Because of these similarities, we will first step back to review the features common to the acute leukemias before discussing those that are specific to ALL.

Pathophysiology of Acute Leukemias

Although acute leukemias are rapidly growing tumors, normal bone marrow progenitors grow at an even more rapid rate. *The principal pathogenetic problem in acute leukemia is a block in differentiation.* This leads to the accumulation of immature leukemic blasts in the bone marrow, which suppress the function of normal hematopoietic stem cells by physical displacement and other poorly understood mechanisms. Eventually bone marrow failure results, which accounts for the major clinical manifestations of acute leukemia. Thus, the therapeutic goal is to reduce the leukemic clone sufficiently to allow normal hematopoiesis to resume.
Clinical Features of Acute Leukemias
The acute leukemias have the following characteristics:

Abrupt stormy onset. Most patients present within 3 months of the onset of symptoms.*Symptoms related to depression of normal marrow function.* These include fatigue (due mainly to anemia), fever (reflecting infections resulting from the absence of mature leukocytes), and bleeding (petechiae, ecchymoses, epistaxis, gum bleeding) secondary to thrombocytopenia.*Bone pain and tenderness.* These result from marrow expansion and infiltration of the subperiosteum.*Generalized lymphadenopathy, splenomegaly, and hepatomegaly.* These reflect dissemination of the leukemic cells, and are more pronounced in ALL than in AML.*Central nervous system manifestations.* These include headache, vomiting, and nerve palsies resulting from meningeal

spread; these features are more common in children than in adults and are more common in ALL than AML.

Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia

These two disorders are morphologically, phenotypically, and genotypically identical, differing only in the extent of peripheral blood involvement. Arbitrarily, if the peripheral blood lymphocytosis exceeds 4000 cells/mm^3, the patient is diagnosed with chronic lymphocytic leukemia (CLL); if not, a diagnosis of small lymphocytic lymphoma (SLL) is made. Most patients fit the criteria for CLL, which is the most common leukemia of adults in the western world. In contrast, SLL constitutes only 4% of NHLs. For unclear reasons, both CLL and SLL are much less common in Asia.

Pathophysiology

The neoplastic B cells, through mechanisms that are not understood, suppress normal B-cell function, often resulting in hypogammaglobulinemia. Paradoxically, approximately 15% of patients have autoantibodies against autologous red cells; other autoantibodies can also be detected. When present, these autoantibodies are made by nontumor B cells, indicating that there is a general breakdown in immune regulation. As time passes the tumor cells tend to displace the normal marrow elements, leading to anemia, neutropenia, and eventual thromobocytopenia.

There are a number of different medical approaches to the treatment of leukemia. Treatment will typically depend upon the type of leukemia, the patient's age and health status, as well as whether or not the leukemia cells have spread to the cerebrospinal fluid. The genetic changes or specific characteristics of the leukemia cells as determined in the laboratory can also determine the type of treatment that may be most appropriate.

Watchful waiting may be an option for some people with a chronic leukemia who do not have symptoms. This involves close monitoring of the disease so that treatment can begin when symptoms develop. Watchful waiting allows the patient to avoid or postpone the side effects of treatment. The risk of waiting is that it may eliminate the possibility of controlling the leukemia before it worsens.

Treatments for leukemia include chemotherapy (major treatment modality for leukemia), radiation therapy, biological therapy, targeted therapy, and stem cell transplant. Combinations of these treatments may be used. Surgical removal of the spleen can be a part of treatment if the spleen is enlarged.

Acute leukemia needs to be treated when it is diagnosed, with the goal of inducing a remission (absence of leukemia cells in the body). After remission is achieved, therapy may be given to prevent a relapse of the leukemia. This is called consolidation or maintenance therapy. Acute leukemias can often be cured with treatment.

Chronic leukemias are unlikely to be cured with treatment, but treatments are often able to control the cancer and manage symptoms. Some people with chronic leukemia may be candidates for stem cell transplantation, which does offer a chance for cure.

Many patients opt to receive a second opinion before beginning treatment for leukemia. In most cases, there is time to receive a second opinion and consider treatment options without making the treatment less effective. However, in rare cases of very aggressive leukemias, treatment must begin immediately. One should discuss with a doctor the possibility of obtaining a second opinion and any potential delays in treatment. Most doctors welcome the possibility of a second opinion and should not be offended by a patient's wish to obtain one.

Chemotherapy

Chemotherapy is the administration of drugs that kill rapidly dividing cells such as leukemia or other cancer cells. Chemotherapy may be taken orally in pill or tablet form, or it may be delivered via a catheter or intravenous line directly into the bloodstream. Combination chemotherapy is usually given, which involves a combination of more than one drug. The drugs are given in cycles with rest periods in between.

Sometimes, chemotherapy drugs for leukemia are delivered directly to the cerebrospinal fluid (known as intrathecal chemotherapy). Intrathecal chemotherapy is given in addition to other types of chemotherapy and can be used to treat leukemia in the brain or spinal cord or, in some cases, to prevent spread of leukemia to the brain and spinal cord. An Ommaya reservoir is a special catheter placed under the scalp for the delivery of chemotherapy medications. This is used for children and some adult patients as a way to avoid injections into the cerebrospinal fluid.

Side effects of chemotherapy depend on the particular drugs taken and the dosage or regimen. Some side effects from chemotherapy drugs include hair loss, nausea, vomiting, mouth sores, loss of appetite, tiredness, easy bruising or bleeding, and an increased chance of infection due to the destruction of white blood cells. There are medications available to help manage the side effects of chemotherapy.

Some adult men and women who receive chemotherapy sustain damage to the ovaries or testes, resulting in infertility. Most children who receive chemotherapy for leukemia will have normal fertility as adults, but depending on the drugs and dosages used, some may have infertility as adults.

Biological therapy

Biological therapy is any treatment that uses living organisms, substances that come from living organisms, or synthetic versions of these substances to treat cancer. These treatments help the immune system recognize abnormal cells and then attack them. Biological therapies for various types of cancer can include antibodies, tumor vaccines, or cytokines (substances that are produced within the body to control the immune system). Monoclonal antibodies are antibodies that react against a specific target that are used in the treatment of many kinds of cancer. An example of a monoclonal antibody used in the treatment of leukemia is alemtuzumab, which targets the CD52 antigen, a protein found on B-cell chronic lymphocytic leukemia (CLL) cells. Interferons are cell signaling chemicals that have been used in the treatment of leukemia.

Side effects of biological therapies tend to be less severe than those of chemotherapy and can include rash or swelling at the injection site for IV infusions of the therapeutic agents. Other side effects can include headache, muscle aches, fever, or tiredness.

Targeted therapy

Targeted therapies are drugs that interfere with one specific property or function of a cancer cell, rather than acting to kill all rapidly growing cells indiscriminately. This means there is less damage to normal cells with targeted therapy than with chemotherapy. Targeted therapies may cause the target cell to cease growing rather than to die, and they interfere with specific molecules that promote growth or spread of cancers. Targeted cancer therapies are also referred to as molecularly targeted drugs, molecularly targeted therapies, or precision medicines.

Monoclonal antibodies (described above in the section on biologic therapy) are also considered to be targeted therapies since they specifically interfere and interact with a specific target protein on the surface of cancer cells. Imatinib (Gleevec) and dasatinib (Sprycel) are examples of targeted therapies that are used to treat CML, some cases of ALL, and some other cancers. These drugs target the cancer-promoting protein that is formed by the BCR-ABL gene translocation.

Targeted therapies are given in pill form or by injection. Side effects can include swelling, bloating, and sudden weight gain. Other side effects can include nausea, vomiting, diarrhea, muscle cramps, or rash.

Radiation therapy

Radiation therapy uses high energy radiation to target cancer cells. Radiation therapy may be used in the treatment of leukemia that has spread to the brain, or it may be used to target the spleen or other areas where leukemia cells have accumulated.

Radiation therapy also causes side effects, but they are not likely to be permanent. Side effects depend on the location of the body that is irradiated. For example, radiation to the abdomen can cause nausea, vomiting, and diarrhea. With any radiation therapy, the skin in the area being treated may become red, dry, and tender. Generalized tiredness is also common while undergoing radiation therapy.

Stem cell transplant

In stem cell transplantation, high doses of chemotherapy and/or radiation are given to destroy leukemia cells along with normal bone marrow. Then, transplant stem cells are delivered by an intravenous infusion. The stem cells travel to the bone marrow and begin producing new blood cells. Stem cells may come from the patient or from a donor.

Autologous stem cell transplantation refers to the situation in which the patient's own stem cells are removed and treated to destroy leukemia cells. They are then returned to the body after the bone marrow and leukemia cells have been destroyed.

An allogeneic stem cells transplant refers to stem cells transplanted from a donor. These may be from a relative or an unrelated donor. A syngeneic stem cell transplant uses stem cells taken from a healthy identical twin of the patient.

Stem cells may be removed (harvested) in different ways. Typically, they are taken from the blood. They can also be harvested from the bone marrow or from umbilical cord blood.

Stem cell transplantation is done in a hospital, and it is necessary to remain in the hospital for several weeks. Risks of the procedure include infections and bleeding due to the depletion of normal blood cells. A risk of stem cell transplant with donor cells is known as graft-versus-host disease (GVHD). In GVHD, the donor white blood cells react against the patient's normal tissues. GVHD can be mild or very severe, and often affects the liver, skin, or digestive tract. GVHD can occur at any time after the transplant, even years later. Steroids or medications that suppress the immune response may be used to treat this complication.

Chimeric antigen receptor (CAR) T-cell treatment

Chimeric antigen receptor (CAR) T-cell treatment is a new form of treatment in which a patient's own normal T lymphocytes are re-engineered in a laboratory to attack the leukemia cells and are then reintroduced into the patient's bloodstream. This treatment has been used for people with B-cell lymphomas that have relapsed or are refractory to treatment. It is also an approved treatment option for certain cases of leukemia. The U.S. FDA approved tisagenlecleucel (Kymriah) in 2018 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

CAR-T therapy is also available in clinical trials. Cytokine-release syndrome (CRS) is a potentially serious side effect frequently associated with CAR T-cell therapy. Cytokines are chemical messengers produced when the CAR T-cells multiply in the body and kill cancer cells. CRS may cause a range of symptoms from mild flu-like symptoms to more serious symptoms including fast heart rate, low blood pressure, and heart problems. Other side effects can include nerve damage, suppressed immune function, and a condition known as tumor lysis syndrome that results when cancer cells are rapidly destroyed.

Because CAR T-cell therapy is so new, the patients who have had this treatment have not been followed over the long term. Studies are under way to determine whether CAR-T treatment may be useful in other types of leukemia.

Supportive treatments

Because many of the treatments for leukemia deplete normal blood cells, increasing the risk for bleeding and infection, supportive treatments may be needed to help prevent these complications of treatment. Supportive treatments may also be needed to help minimize and manage unpleasant side effects of medical or radiation therapy.

Types of supportive and preventive treatments that can be used for patients undergoing treatment for leukemia include the following:

- Vaccines against the flu or pneumonia
- Blood or platelet transfusions
- Anti-nausea medications
- Antibiotics or antiviral medications to treat or prevent infections
- White blood cell growth factors to stimulate white blood cell production (such as granulocyte-colony stimulating factor [G-

CSF], made up of filgrastim [Neupogen] and pegfilgrastim [Neulasta] and granulocyte macrophage-colony stimulating growth factor [GM-CSF], made up of sargramostim [Leukine])
- Red cell growth factors to stimulate red blood cell production (darbepoetin alfa [Aranesp] or epoetin alfa [Procrit])
- Intravenous injections of immunoglobulins to help fight infection

What are complications of leukemia?

Many of the challenges of leukemia relate to the depletion of normal blood cells as well as the side effects of treatments as described in the previous section, such as frequent infections, bleeding, and GVHD in recipients of stem cell transplants. Weight loss and anemia are further complications of leukemia and its treatment. Complications of any leukemia also include a relapse or a progression of the disease after a remission has been achieved with treatment.

Other complications of leukemia relate to the specific type of leukemia. For example, in 3% to 5% of cases of CLL, the cells change characteristics and transform into an aggressive lymphoma. This is known as a Richter transformation. Autoimmune hemolytic anemic, in the body attacks and destroys red blood cells, is another potential complication of CLL. People with CLL are also more likely to develop second cancers and other blood disorders and blood cancers.

Tumor lysis syndrome is a condition caused by the rapid death of cancer cells during acute treatment. It can occur in almost any type of cancer, and it is seen with some cases of leukemia, particularly when large numbers of leukemia cells are present such as with AML or ALL. The rapid destruction of the leukemia cells leads to the release of large amounts of phosphate, which further causes metabolic abnormalities and can lead to kidney failure.

Children who receive therapy for ALL may experience late adverse effects including central nervous system (CNS) impairment, slowing of growth, infertility, cataracts, and an increased risk for other cancers. The incidence of these late effects varies depending upon the age at treatment and the type and strength of therapies.

What is the prognosis of leukemia?

The prognosis of leukemia depends upon the type of leukemia that is present and the age and health status of the patient. Mortality (death) rates for leukemia are higher in the elderly than in younger adults and children. In many cases, leukemia can be managed or cured with treatments available today. In particular, childhood ALL has a very high 5-year survival rate.

Modern treatments have led to a greater than fourfold increase since 1960 in five-year survival rates for leukemia. Five-year survival

rates for different types of leukemia from 2007-2013 are approximately:

CML: 68%

CLL: 86%

AML: 27% overall, 66% for children and teens younger than 15

ALL: 71% overall, over 90% for children

How often does leukemia recur?

The likelihood that leukemia will recur (come back after successful treatment) depends upon the type of leukemia including the specific molecular characteristics of the cancer cells and the patient's response to initial treatment. Some acute leukemias are successfully treated, and the patient never experiences a recurrence. In chronic leukemias, such as CML, ongoing symptoms and recurrences are common, and treatments may be directed at keeping the leukemia under control.

Most people who develop leukemia do not have a known risk factor, and it is generally not possible to prevent leukemia. Certain risk factors, such as exposure to radiation or benzene, may be minimized, but this does not guarantee prevention of leukemia.

Leukemia is an active area of biomedical research. Ongoing studies are examining the risk factors and causes of leukemia, as well as examining new and improved treatment options.

4. Hodgkin Lymphoma

Hodgkin lymphoma encompasses a distinctive group of neoplasms that arise almost invariably in a single lymph node or chain of lymph nodes and spread characteristically in a stepwise fashion to the anatomically contiguous nodes. It is separated from the non-Hodgkin lymphomas for several reasons. First, it is *characterized morphologically by the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells*, which are admixed with reactive, nonmalignant inflammatory cells. Second, it is often associated with somewhat distinctive clinical features, including systemic manifestations such as fever. Third, its stereotypical pattern of spread allows it to be treated differently than most other lymphoid neoplasms. Despite these distinguishing features, molecular studies have shown that it is a tumor of B-cell origin.

Classification

Five subtypes of Hodgkin lymphoma are recognized: (1) nodular sclerosis,
(2) mixed cellularity,
(3) lymphocyte predominance,
(4) lymphocyte rich, and
(5) lymphocyte depletion.

The latter two subtypes are uncommon and will not be mentioned further. Before delineating the remaining three, however, we should describe the common denominator among all-RS cells and variants thereof-and the staging system used to characterize the extent of the disease in an individual

Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas

Hodgkin Lymphoma	**Non-Hodgkin Lymphoma**
More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal involvement uncommon	Extranodal involvement common

Treatment options

The main treatments for Hodgkin lymphoma are chemotherapy alone, or chemotherapy followed by radiotherapy. In a few cases, chemotherapy may be combined with steroid medication.

Surgery isn't generally used to treat the condition, except for the biopsy used to diagnose it.

Overall, treatment for Hodgkin lymphoma is highly effective and most people with the condition are eventually cured.

Chemotherapy

Chemotherapy is a type of cancer treatment where medicine is used to kill cancer cells. This medication can be given in a number of different ways, depending on the stage of your cancer.

If doctors think your cancer is curable, you'll normally receive chemotherapy through a drip directly into a vein (intravenous chemotherapy). If a cure is unlikely, you may only need to take chemotherapy tablets to help relieve your symptoms.

Chemotherapy is usually given over a period of a few months on an outpatient basis, which means you shouldn't have to stay in hospital overnight. However, there may be times when your symptoms or the side effects of treatment become particularly troublesome and a longer hospital stay may be needed.

Chemotherapy can have several side effects, the most significant of which is potential damage to your bone marrow. This can interfere with the production of healthy blood cells and cause the following problems:

- fatigue
- breathlessness
- increased vulnerability to infection
- bleeding and bruising more easily

If you experience these problems, treatment may need to be delayed so you can produce more healthy blood cells. Growth factor medicines can also stimulate the production of blood cells.

Other possible side effects of chemotherapy include:

- nausea and vomiting
- diarrhoea
- loss of appetite
- mouth ulcers
- tiredness
- skin rashes
- hair loss
- infertility, which may be temporary or permanent (see complications of Hodgkin lymphoma for more information)

Most side effects should pass once your treatment has finished. Tell your care team if the side effects become particularly troublesome, as there are treatments that can help.

Read more about the side effects of chemotherapy.

If regular chemotherapy is unsuccessful or Hodgkin lymphoma returns after treatment, you may have a course of chemotherapy at a higher dose.

However, this intensive chemotherapy destroys your bone marrow, leading to the problems mentioned above. You'll need a stem cell or bone marrow transplant to replace the damaged bone marrow.

Radiotherapy

Radiotherapy is most often used to treat early-stage Hodgkin lymphoma, where the cancer is only in 1 part of the body.

Treatment is normally given in short daily sessions, Monday to Friday, over several weeks. You shouldn't have to stay in hospital between appointments.

Radiotherapy itself is painless, but it can have some significant side effects. These can vary and will be directly related to the part of your body being treated. For example, treatment to your throat can lead to a sore throat, while treatment to the head can lead to hair loss.

Other common side effects include:

- tiredness
- nausea and vomiting
- dry mouth
- loss of appetite

Most side effects are temporary, but there's a risk of long-term problems, including infertility and permanently darkened skin in the treatment area.

Steroid medication

Steroid medication is sometimes used in combination with chemotherapy as a more intensive treatment for advanced cases of Hodgkin lymphoma, or if initial treatment hasn't worked.

The steroid medication is given intravenously, usually at the same time as your chemotherapy.

Common side effects of steroid medication include:

- increased appetite, which can lead to weight gain
- indigestion
- problems sleeping

- feeling agitated

The side effects of steroid medication usually start to improve once treatment finishes.

Rituximab

If you're diagnosed with a rare type of Hodgkin lymphoma called lymphocyte-predominant Hodgkin lymphoma, you may have chemotherapy in combination with a medication called rituximab.

Rituximab is a type of biological therapy called a monoclonal antibody. It attaches itself to the surface of cancerous cells and stimulates the immune system to attack and kill the cell.

It's given through a drip directly into a vein over the course of a few hours.

Side effects of the drug can include:

- flu-like symptoms, such as headaches, fever and muscle pain
- tiredness
- nausea
- diarrhoea

You may be given additional medication to prevent or reduce side effects. Any side effects should improve over time as your body gets used to the medication.

Brentuximab vedotin

Brentuximab vedotin is a relatively new drug used to treat a particular type of Hodgkin lymphoma.

It is available on the NHS for people with CD30-positive Hodgkin lymphoma who:

- have already had a stem cell transplant using their own cells or cannot have chemotherapy

- cannot have a stem cell transplant using their own cells, but have already had at least 2 other treatments

It is given in the same way as rituximab, but the treatment session takes around 30 minutes.

Side effects of brentuximab vedotin include:

- skin rash
- shortness of breath
- cough
- fever
- back pain
- chills
- headache
- feeling sick (nausea) or being sick (vomiting)

5. Ankylosing spondylitis:

Spondyloarthropathy (SpA) refers to a heterogeneous group of rheumatic diseases that present common clinical and genetic features, which are classified as peripheral or axial (axSpA) based on what parts of the body are predominantly affected. Ankylosing spondylitis (AS), a type of SpA, is an autoimmune disease that mainly involves spine joints, sacroiliac joints (SIJs) and their adjacent soft tissues, such as tendons and ligaments. In more advanced cases, this inflammation can lead to fibrosis and calcification, resulting in the loss of flexibility and the fusion of the spine, resembling "bamboo" with an immobile position. The main clinical manifestations include back pain and progressive spinal rigidity as well as inflammation of the hips, shoulders, peripheral joints and fingers/toes. In addition, there are extra-articular manifestations, such as acute anterior uveitis and inflammatory bowel disease (IBD). However, these extra-articular manifestations differ between East Asian and Caucasian populations. In a study involving 988 patients with ankylosing spondylitis in east Asia, only 0.4% developed inflammatory bowel disease However, in some analyses performed in Western countries, ~5%–10% of patients with AS present with inflammatory bowel disease

The prevalence of AS has a clear correlation with the human leukocyte antigen (HLA)-B27 positive rate in specific populations. Studies have revealed that in HLA-B27-positive populations, the prevalence rate of AS is ~5%–6%. In a 2009 national survey in the United States, the prevalence of HLA-B27-positive populations varied in different ethnic communities, with 7.5%, 4.6%, and 1.1% in non-Hispanic whites, Mexican-Americans, and non-Hispanic blacks, respectively.5 In the literature, males reportedly account for the vast majority of cases of AS, while the incidence among men and women is similar in nonradiographic axial spondyloarthropathy (nr-axSpA), which refers to individuals meeting clinical criteria for axSpA without radiological evidence of sacroiliitis. A meta-analysis including eight studies including 2 236 patients with AS and 1 242 patients with nr-axSpA revealed that males accounted for 70.4% of AS patients and 46.5% of patients with nr-axSpA.Genetic susceptibility results have shown the following recurrent risk factors in different generations of relatives: monozygotic (MZ) twins, 63% (17/27); first-generation relatives, 8.2% (441/5 390); second-generation relatives, 1.0% (8/834); and third-generation relatives, 0.7% (7/997).

The confusion in diagnosis and lack of disease-modifying therapeutics, including anti-TNF-α and anti-IL-17 treatment of AS, are largely due to the limited knowledge of the pathogenesis, which may involve immunity, heredity and other factors. In this paper, we reviewed the etiology of AS, current investigations of its pathogenesis and available treatments.

Etiology

As an autoimmune disease, AS develops through complex interactions between genetic background and environmental factors. Although significant progress has been achieved in the past decades, the etiology of AS remains unclear to some extent. To date, studies have revealed some factors that may be related to the occurrence of AS, including genetic background, immune reaction, microbial infection, and endocrinal abnormity.

Genetic background

Genetic factors have been acknowledged as crucial in the genesis of AS. The correlation between AS and genetics has been a perpetual topic since hereditary factors of AS were first confirmed within families in 1961. Twin studies have revealed significantly higher concordance between monozygotic twins (63%) than between dizygotic twins (23%). Genetic effects have been identified as pathogenic factors that contribute to over 90% of the population variance for AS manifestations. One of the most important genetic factors is major histocompatibility complex (MHC) class I allele HLA-B27, which was discovered in 1973. Despite the unclear pathomechanism, HLA-B27 has been associated with the prevalence of AS in different populations around the world. Studies have shown that 90%–95% of AS patients are HLA-B27 positive, while 1%–2% of HLA-B27-positive populations develop AS. This number increased to 15%–20% for those with an affected first-degree relative. The familial tendency of AS was remarkable with relative risks of 94, 25, and 4 for first-, second-, and third-degree relatives, respectively. In addition to the association with the genesis of AS, HLA-B27-positive patients showed a significantly lower average onset age and a higher prevalence of acute anterior uveitis than did HLA-B27-negative patients. HLA-B27 has a high degree of polymorphism. Over 100 subtypes have been identified thus far, with differing prevalence rates among different ethnicities, especially between those of East Asian and Caucasian descent. As reported, the most prevalent subtypes in AS are HLA-B2705 (Caucasian populations), HLA-B2704 (Chinese populations), and HLA-B2702 (Mediterranean populations). By contrast, two subtypes, HLA-B2706 and HLA-B2709, seem unrelated to AS. In addition, genetic influence is not alone in the development of AS. HLA-B27-transgenic rat studies on β2 microglobulin (β2m), a noncovalent part of the MHC-I complex, has proven that additional β2m reduces HLA-B27 misfolding and promotes arthritis and spondylitis, implying that B27 misfolding is associated with intestinal inflammation. This result suggested that abnormal β2m can coordinate with HLA-B27 in AS development, which may be explained by protein misfolding theories and will be discussed later in the pathogenesis section.

Immunological and microbial factors

AS is related to a series of autoimmune diseases, including IBD, anterior uveitis and psoriasis, which suggests that they may share a genetic basis and some common immunological processes. The differences observed in immune cells and cytokines in AS suggest the role of immunological effects in AS pathogenesis. In the peripheral blood of AS patients and healthy HLA-B27-positive controls, the

levels of T cells secreting tumor necrosis factor (TNF)-α and interferon (IFN)-γ were reportedly lower. CD8+ T cells in AS patients tended to secrete more IL-10. Other findings have also demonstrated immunological influences in AS development, which is discussed in the following section.

Microbial infection acts as a triggering factor of the host innate immune system and AS development. HLA-B27 transgenic rats failed to develop features of SpA in a germ-free environment, which changed when commensal bacteria were introduced into the germ-free models, suggesting possible interactions between HLA-B27 and the microbiome. The gut microbiome, including *Lachnospiraceae*, *Veillonellaceae*, *Prevotellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*, showed significant differences in AS patients compared with that in healthy controls. *Klebsiella pneumoniae* acts as an opportunistic pathogen in the normal human gut, and studies have suggested that it may be an exacerbating agent in the autoimmune process of AS. Controversial results exist regarding the relationship between the fecal microbiome load, such as *Klebsiella pneumoniae*, and AS activity. Some scientists hypothesized that *Klebsiella pneumoniae* influences AS development indirectly through interplay with HLA-B27. In addition, gut microbiome infection is partly due to the relative deficiency of immune components, leading to immune responses of a higher intensity and longer duration.

Other factors

Early in 1973, an etiological association between endocrine factors and AS was hypothesized because the presence of HLA-B27 and AS differed with sex. A study of 22 patients with AS detected testicular function and found a diminished testicular testosterone (T) reserve, elevated luteinizing hormone (LH) level, estradiol/testosterone ratio (E2:T) inversion and slightly increased estradiol (E2) level. The results in studies of ovarian function have also indicated sex hormone differences in menstruating and menopausal AS patients compared with those in matched healthy controls. It is reported that estradiol levels in patients with active AS are significantly lower than those in patients with inactive AS in the menstruation period. More observational results, such as male predominance, peak onset at young age and increased number of first manifestations after pregnancy, imply that sex hormones play a role in AS. Low levels of sex hormones, especially dehydroepiandrosterone sulfate (DHEAS), may also contribute to bone loss in patients with AS. Meta-analyses have suggested that vitamin D deficiency may be related to AS development. Vitamin D may play a protective role in AS based on a positive correlation between the serum vitamin D level and disease severity. There is a significant negative correlation between the vitamin D level and disease activity indicated by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. However, there are conflicts regarding the relationship between the vitamin D level and AS disease activity. The cause of low vitamin D levels in patients with AS is also largely unclear.

Pathogenesis

MHC genetics

The human MHC, also called the HLA complex, belongs to the cell-surface proteins acting in the process of acquired immunity. There are three subgroups in the MHC gene family: class I, II, and III. MHC class I encodes HLA-A, HLA-B, and HLA-C and is present on all nucleated human cells and platelets, presenting epitopes to T cell receptors (TCRs) on the surface of cytotoxic T lymphocytes (CTLs).57 The heterodimer MHC class I subgroup consists of a polymorphic heavy chain. The chain contains three domains, i.e., α1, α2, and α3. The α1 domain links noncovalently with the non-MHC molecule β2m, while α3 spans the plasma membrane and interacts with the CD8 coreceptor of T cells.58,59 The MHC class I complex can link to peptides of 8–10 amino acids in length via one cleft spaced by both α1 and α2, leading to the initiation and propagation of immune responses.59,60 A stable MHC molecule needs to be properly packaged and then folded in the cell organelle endoplasmic reticulum (ER) under guidance of chaperones (calreticulin and tapasin).57 Although the classic MHC class I contains one heavy chain, there are three different structures of MHC-I, comprising cell-surface HLA-B27 homodimers and intracellular and exosomal MHC-I dimers. These components may function in distinct pathophysiological processes.

HLA-B27

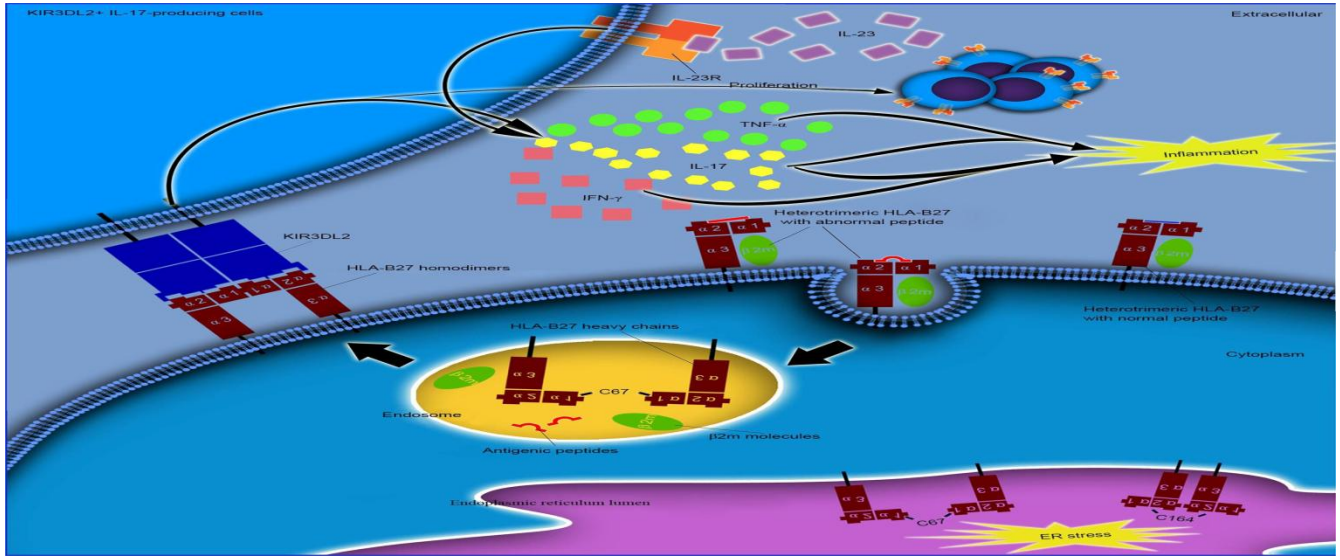
HLA-B27, basically belonging to the MHC-I surface protein encoded by the MHC B gene on chromosome 6, is the most essential gene that predisposes an individual to AS. HLA-B27 presents peptide antigens to T immunocytes of the human body defense process and is considered to be significantly linked to AS and associated inflammatory diseases. A study reviewed over 7500 endogenous peptides presented by the eight most frequent HLA–B27 allotypes (HLA–B2702 to HLA–B2709), suggesting that consensus-binding and selection motifs showed significant similarities and differences between various HLA–B27 allotypes. The connection between HLA-B27 and AS has not yet been fully elucidated, although it is widely accepted that the entire intracellular process of HLA-B27 formation needs to be considered. There are some prevailing theories regarding the mechanism, including the hypothesis of arthritogenic peptide, misfolding hypothesis, the hypothesis of molecular mimicry, as well as the hypothesis of the cell-surface HLA-B27 homodimer.

Founded on the antigenic peptide presentation role of HLA class I molecules, the arthritogenic peptide hypothesis postulates that structurally exclusive peptide-MHC complexes can directly initiate HLA-B27-specific autoimmune responses by relying on the primary structure of antigen peptides. Some microbial peptides are similar to self-peptides in body tissues and can activate the response of certain HLA-B27-specific CD8+ T lymphocytes. The T lymphocytes react with these HLA-B27-peptide complexes, leading to autoreactivity and autoimmune disease. It has been suggested that cartilage, particularly the proteoglycan aggrecan,66 is the basic immunological target in SpA; however, currently, studies on such peptides have obtained inconsistent results. In addition, rats with HLA-B27-specific CD8- T lymphocytes still have AS, which means that more peptide mechanisms remain

unelucidated. Additionally, a spectrometry study reviewed a large quantity of HLA-B27 subtypes and indicated that it is quantitative instead of qualitative changes in the peptide repertoire that may be more relevant to AS initiation and progression,62 further challenging the arthritogenic peptide hypothesis. The molecular mimicry hypothesis posits that the antigenic components of infectious bacterial pathogens partially resembling or cross-reacting with HLA molecules can stimulate CD8+ T lymphocytes, followed by responding to one HLA-B27 relevant self-peptide or the peptides directly produced by HLA-B27. This hypothesis is largely based on previously identified amino acid structures of homologous origin between the HLA structure and specific sequences and previous results depicting cross-reactions among the HLA and some bacterial antigens. *K. pneumoniae* is a highlighted microorganism thought to participate in the pathogenesis of AS as a triggering and/or perpetuating factor. Some components in *K. pneumoniae* share structural likenesses with specific genetic or somatic sequences in humans and exhibit molecular mimicry in AS and other diseases. Similarly, molecular modeling suggested that a HLA-B27-derived dodecamer, a natural ligand of disease-associated B27 subtypes, was strikingly homologous to protein sequences from arthritogenic bacteria, particularly *Chlamydia trachomatis*, demonstrating the process of molecular mimicry of Chlamydial proteins. PulD-secreted pullulanase can cross-react with HLA-B27 and myosin, while pulA components can cross-react with type I, III, and IV collagens, proving the reasonability of the molecular mimicry hypothesis. These cross-reactions give rise to an amount of antibacterial antibodies that link to HLA molecules on immunocytes, chondrocytes and fibroblasts, further triggering a cascade of inflammatory reactions with the amount of cytokines, complement proteins, proteinases and the like produced. These sequential reactions lead to the genesis of arthritis and extra-articular or even systemic symptoms and signs of AS.

The mature HLA-B27 complex is a quaternary structure with three important components. The proper assembly and folding of HLA-B27 in the ER is essential for its function. After being synthesized as free heavy chains, HLA-B27 is then noncovalently linked and folded with β2m and antigenic peptide, followed by transport to the cell surface as a trimolecular complex. Nevertheless, HLA-B27 exhibits a predisposition to misfolding and creating dimers and even multimers these characteristic changes may originate in its structure, which includes cysteine (C) at sites 67 (C67), 101 (C101), 164 (C164), and 325 (C325). Without correct folding, HLA-B27 would be produced and transmitted to the cell surface merely as homodimers consisting of heavy chains. The disease-related structures of HLA-B27, including HLA-B2705, HLA-B2704, and HLA-B2702, have been found to exhibit a relatively lower rate of correct folding procedures compared with those of HLA-B2706 and HLA-B2709, which are generally not considered associated with AS. Due to cysteine residue C67 and other reasons, HLA-B27 tends to fold slower than other HLA alleles, and without proper folding, these defective HLA-B27 proteins continually gather in the ER. Improperly folded HLA-B27 proteins accumulate in the ER and activate autophagy and the interleukin (IL)-23/IL-17 pathway. Moreover, these misfolded molecules can interfere with ER function, leading to ER stress and even triggering the pro-inflammatory endoplasmic reticulum unfolded protein response (ERUPR), which further activates the IL-23/IL-17 pathway. However, conflicts also exist regarding whether the HLA-B27-activated ERUPR occurs in AS patients. The increased production of IL-23 without significant ERUPR induction occurs in macrophages in AS. The disease-related polymorphisms of the ERAP1 or HLA-B27 locus would not change the ER stress intensities of AS, which also

remained controversial in other studies conducted later. One possibility is that HLA-B27 misfolding results in autophagy and triggers the IL-23/IL-17 pathway instead of ERUPR. Further research is required for illumination of the connection of ERUPR and HLA-B27 during the development of AS.



HLA-B27 heavy chains tend to form homodimers without β2m via the disulfide bonds of the cysteine at C67. The dimeric HLA-B27 complexes, mostly found in the gut and synovium of patients, may contribute to the genesis of AS and some other SpAs. These HLA-B27 dimers could occur on antigen-presenting cells, thus stimulating IL-23 receptor + T lymphocytes to produce IL-17. The hypothesis of cell-surface HLA-B27 homodimer formation suggests that HLA-B27 dimers might contribute to the development of AS. HLA-B27 homodimers have been linked to receptors expressed on natural killer (NK) immunocytes, myelomonocytes and lymphocytes. The binding is realized via killer cell immunoglobulin-like receptors (KIRs) and leucocyte immunoglobulin-like receptors (LILRs), thus acting in the processes related to autoimmune disorders. The 3 immunoglobulin domains and the long cytoplasmic tail 2 (KIR3DL2) receptor expressed by certain increased immune cells, including NK cells and Th17 cells, can recognize cell-surface HLA-B27 homodimers via a greater affinity than that with the classic HLA-B27 heterotrimers. The binding of KIR3DL2 with HLA-B27 homodimers was revealed to stimulate the survival and differentiation of KIR3DL2+CD4+ T lymphocytes in patients

with SpA. Compared to KIR3DL2− lymphocytes, these T cells significantly increase cytokine output, including IL-17, TNF-α and INF-γ. These findings suggest that the aberrant HLA-B27 homodimers function in AS pathogenesis.

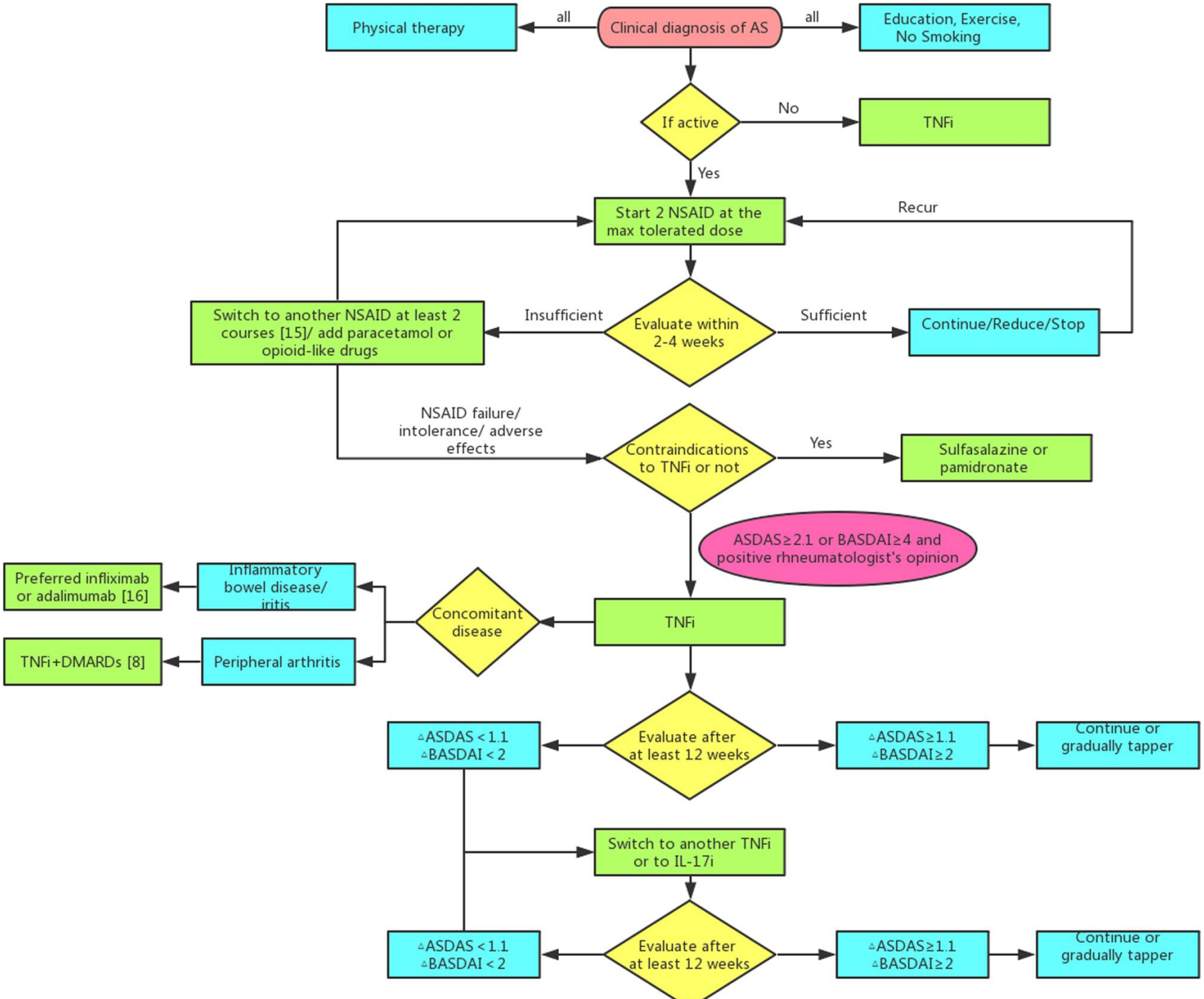
Treatments for AS

Pharmacological treatments

The aims of treating AS are to improve and maintain spinal flexibility and normal posture, relieve symptoms, decrease functional limitations, and reduce complications. The mainstays of pharmacological treatment involve nonsteroidal anti-inflammatory medications (NSAIDs) and TNF-α inhibitors (TNFis). Additional treatments include non-TNFi biologics (secukinumab), methotrexate, and sulfasalazine. Furthermore, the oral small molecule JAK inhibitors tofacitinib and filgotinib appear promising in clinical trials and may soon be approved for AS. For all AS patients, regardless of whether the disease is active or stable, physical therapy, exercise and abstaining from smokingare universally advised. NSAIDs, especially selective inhibitors of cyclooxygenase 2, are first-line treatments for patients with active AS. The determination of active disease is founded on laboratory (CRP/ESR), clinical and imaging (magnetic resonance imaging, MRI) findings. Compared with on-demand treatment, continuous NSAID treatment has shown no benefits in any clinical aspect, while hypertension and depression are more common among individuals undergoing continuous NSAID treatment. However, continuous use should be advised if symptom recurrence occurs after stopping or reducing the dose of NSAID drug. In adults with active AS, an appropriate trial consists of at least 2 kinds of NSAIDs, each administered over a minimum of 2 weeks at the maximum tolerated dosage, unless contraindicated. Nevertheless, the 'lowest effective dose' of NSAIDs has also been recommended in the National Institute for Health and Care Excellence (NICE) guidelines. No NSAID is recommended in terms of preferred efficacy. NSAID treatment should be chosen based on the patient's history of NSAID application, comorbidities, and risk factors for adverse effects. Good responses to NSAIDs include a reduction in inflammatory back pain and functional improvement. An insufficient response to NSAID therapy is identified as active disease despite the administration of at least two different NSAIDs at the maximum anti-inflammatory dose and duration (at least two weeks for each). Intolerance or adverse effects are also involved. Analgesics, especially opioid-like drugs, may be added when NSAID treatment is unsuccessful or contraindicated.16

When AS patients fail to respond to the first TNFi, treatment with a second biologic should be advised. The different biologics can be an IL-17 inhibitor (IL-17i) or a different TNFi. The treatment should be changed if no significant improvement occurs after application for 3 months. If a 6-month trial results in no clinical remission or decrease in disease severity, the treatment must be changed. After failure treatment of the first TNFi, a second TNFi with a lower efficacy can also be effective. However, before switching the treatment, it is essential to reconsider the indications of the first TNFi. Given the circumstances of a primary lack of efficacy, primary failure might be due to an incorrect diagnosis rather than drug resistance. Furthermore, the symptoms and signs may

result from either a different or concomitant condition. Biologics may fail in AS patients with concomitant vertebral fracture or degenerative disc disease. In patients with persistent remission, the tapering of TNFi or IL-17i treatment can be considered. The period


Physical therapy
all
Clinical diagnosis of AS
all
Education, Exercise, No Smoking
If active
No
TNFi
Yes
Start 2 NSAID at the max tolerated dose
Recur
Switch to another NSAID at least 2 courses [15]/ add paracetamol or opioid-like drugs
Insufficient
Evaluate within 2-4 weeks
Sufficient
Continue/Reduce/Stop
NSAID failure/ intolerance/ adverse effects
Contraindications to TNFi or not
Yes
Sulfasalazine or pamidronate
ASDAS≥2.1 or BASDAI≥4 and positive rhneumatologist's opinion
Preferred infliximab or adalimumab [16]
Inflammatory bowel disease/ iritis
Concomitant disease
TNFi
TNFi+DMARDs [8]
Peripheral arthritis
▵ASDAS < 1.1
▵BASDAI < 2
Evaluate after at least 12 weeks
▵ASDAS≥1.1
▵BASDAI≥2
Continue or gradually tapper
Switch to another TNFi or to IL-17i
▵ASDAS < 1.1
▵BASDAI < 2
Evaluate after at least 12 weeks
▵ASDAS≥1.1
▵BASDAI≥2
Continue or gradually tapper

of remission should be at least 6 months. Ideally, tapering can be continued to zero (withdrawal). However, tapering only very slowly and allowing sufficient time for remission are suggested before the next step in the tapering process.

Local injections of glucocorticoids seem to be an option for treating enthesopathy and arthritis. Glucocorticoid injections into involved peripheral joints, sacroiliac joints, or entheses could provide immediate symptom relief. Previous studies have shown that partly because of the increased risks of osteoporosis, hyperlipidemia and insulin resistance, long-term treatment with systemic glucocorticoids is relatively contraindicated. A recent study reported that AS patients achieved relief from signs and symptoms after short-term treatment with high doses of glucocorticoids (50 mg/day). In patients with peripheral arthritis as a comorbidity, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, leflunomide, and sulfasalazine, should be considered but not in those with isolated axSpA or enthesitis. Methotrexate treatment has not been proven effective in AS patients without peripheral arthritis, regardless of administration of a TNFi.

Other biologics include rituximab (a monoclonal antibody against CD20+ B cells), ustekinumab (a monoclonal antibody against IL-12/23) and secukinumab (a monoclonal antibody against IL-17). If TNFi fails to treat AS, rituximab may be an alternative approach. In AS patients with concomitant moderate to severe psoriasis, ustekinumab treatment reportedly achieved safe and significant improvements. Ustekinumab can also reduce arthritis, enthesitis, dactylitis, and skin lesions and improve function. In a prospective clinical trial, ustekinumab was associated with a reduction in signs and symptoms in active AS and was well tolerated. However, a recent study did not demonstrate the efficacy of ustekinumab (anti-IL12p40) and risankizumab (anti-IL23p19) in the treatment of axial SpA. At the moment, the mechanism of blocking IL-23, which does not play a role in SpA treatment, remains uncovered. IL-17A and IL-22 could be suppressed in anti-IL23R in prophylactic experiments and were comparable to those after therapeutic anti-IL23R treatment. Thus, the initiation instead of the persistence of experimental SpA may depend on IL-23 signaling. Secukinumab targets IL-17 and is effective in patients with TNFi failure. In a phase 3 trial, secukinumab showed salient efficacy in AS patients with an insufficient response or contraindications to TNFis. In another phase 3 trial, secukinumab was verified to provide sustained efficacy in signs, symptoms and physical function in subjects with AS over 3 years. A study cohort of Taiwanese patients indicated that secukinumab was also well tolerated in Asian patients, with a safety profile consistent with that reported in the overall study population.[1]

In patients with stable AS, using NSAID treatment on-demand is recommended. Continuing treatment with TNFi alone is suggested rather than treatment with TNFi and NSAID or DMARD. The continued use of NSAIDs or DMARDs has uncertain therapeutic effects with increased risks of gastrointestinal, cardiovascular, renal and hematological toxicity.

Surgical treatments

Untreated AS can cause spinal deformity, with more than 30% of AS patients suffering from thoracolumbar kyphosis. Corrective osteotomy and stabilization are very common in surgical procedures and are recommended under certain conditions, such as adult patients suffering severe kyphosis or advanced hip arthritis. This procedure has a perioperative mortality rate of 4% and permanent neurologic sequelae rate of 5%.202 This surgery is confirmed to contribute to preventing the natural processes of progressive deformity, reducing pain caused by muscle fatigue, improving disability, restoring the global balance and horizontal axis of view, and improving respiratory and digestion function.

JUVENILE RHEUMATOID ATHIRITIS

Introduction

Juvenile rheumatoid arthritis (JRA) is a generic term for arthritis that has an onset before the age of 16 and persists for more than 6 weeks. The JRA nomenclature represents an exclusion diagnosis that includes all forms of chronic childhood arthritis of unknown origin. JRA is the most common chronic rheumatic illness in children and is a significant cause of both short- and long-term disabilities. The heterogeneity of this disease suggests that different factors likely contribute to its pathogenesis. The current understanding of JRA indicates that it arises in a genetically susceptible individual due to environmental factors. Moreover, it has been proposed that an antigen-driven autoimmune process mediates the inflammatory pathology of some cases of arthritis (e.g., oligoarthritis, polyarthritis). In contrast, there are no signs of lymphocyte-mediated, antigen-specific immune responses in individuals with systemic onset disease. Recent investigations in the pathophysiology of systemic onset disease have indicated that this disorder is due to an uncontrolled activation of the innate immune system. Regardless of the differences in the underlying pathogenesis of the various types of JRA, proinflammatory cytokines are consistently overproduced and are related to the clinical manifestations in all types of JRA. Modulation of these cytokines results in improvement of clinical outcome, which strongly suggests that these cytokines play important roles in JRA.

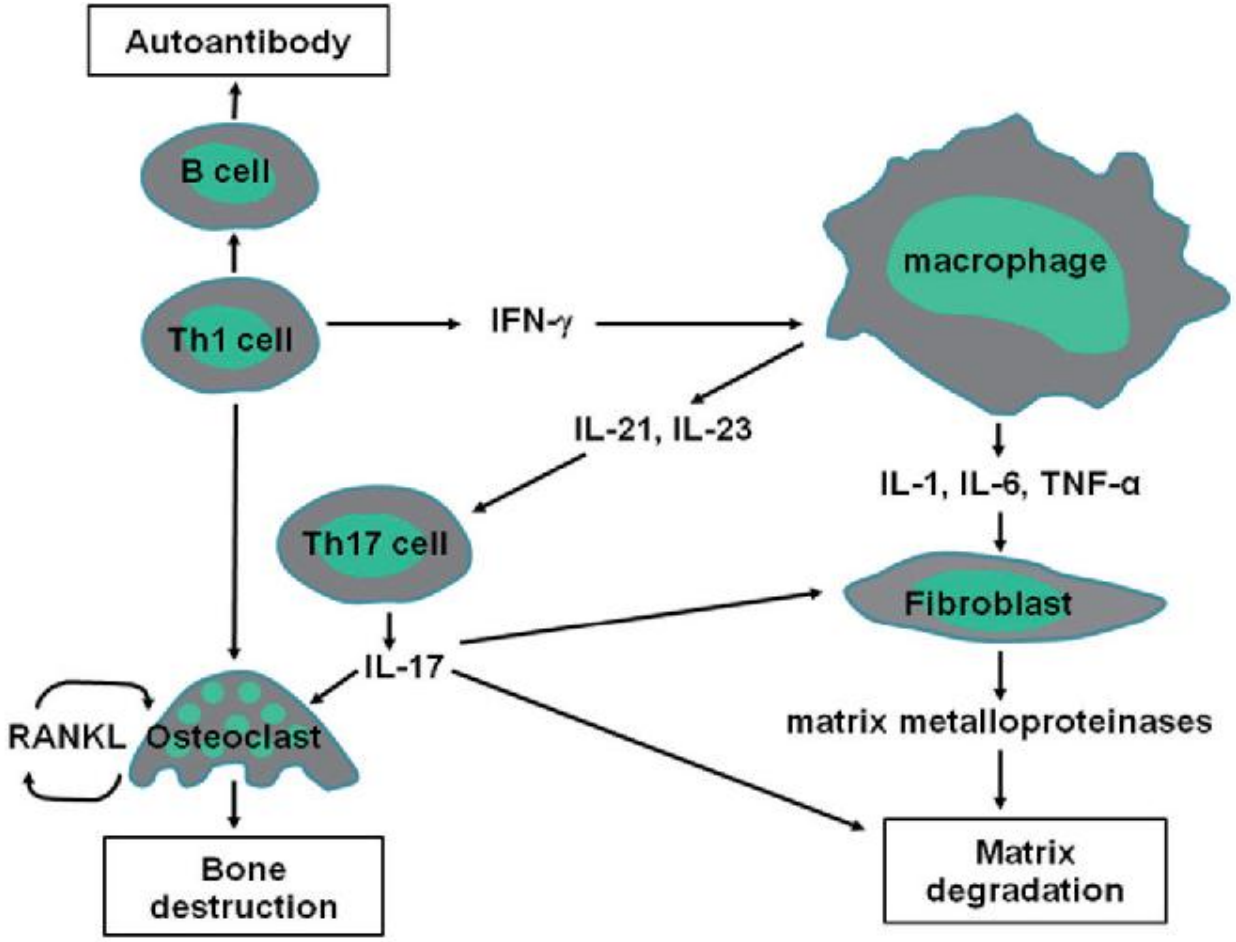


Fig. 1. Cytokine signaling pathways involved in JRA. Interactions among

Symptoms of juvenile rheumatoid arthritis

Symptoms are different among children. Typically, joints become swollen, stiff, painful and warm to the touch. They may start as early as 6 months of age. Your child may limp, especially in the morning when stiffness is the worse. He or she may have lower back

pain and avoid normal activities. Symptoms may come and go. They may be mild or intense. Symptoms can last for a short time or for years. There are four types of juvenile rheumatoid arthritis. Symptoms depend on the type.

- **Pauciarticular or "few joints."** This is the most common type. It affects 4 or fewer joints, usually the knee, leg, wrist or jaw. It also can cause inflammation in the eyes. This is called iritis and is common in girls younger than 7. It not treated properly, it can damage vision. Boys older than 8 who have this type of arthritis often have spine and hip problems. This type often goes away in about 50% of cases.
- **Polyarticular or "many joints."** This type of arthritis affects 5 or more small joints. This includes joints in the fingers and hands. Symptoms often appear in the same joints on both sides of the body. Other symptoms include a low fever, feeling tired and poor appetite. Your child may have a small rash on the lower torso and upper arms and legs. Some children with this disease have anemia (iron deficiency). In rare cases, this type can cause a child's organ, such as the liver or spleen, to swell. This type happens more often in girls than in boys. This type only goes away in fewer than half of children who have it.
- **Systemic or Still's disease.** This type is the least common. It can affect several areas of the body, including joints and organs. Early symptoms include a rash, chills and a high fever. Anemia is another common symptom. This type of arthritis is likely to cause long-term joint damage. About half of children who have this type recover. The rest have joint pain and stiffness for many years.
- **Spondyloarthritis.** This type affects the joints located between the bottom of the spine and pelvis. Symptoms resemble adult arthritis.

Approach to management

The aims of juvenile rheumatic arthritis (JRA) treatment are to control pain; to preserve range of motion (ROM), muscle strength, and function; to manage systemic complications; and to facilitate normal nutrition, growth, and physical and psychological development. Thus, the general aim of treatment is remission rather than improvement. Although the major focus of medical therapy for JRA is on the arthritis, other extra-articular complications (e.g., uveitis, serositis, growth retardation, and osteopenia) require consideration. In general, the treatment program for this disease should be family-centered, community-based, and well coordinated. An ideal approach involves a multidisciplinary team that consists of a pediatric rheumatologist, nurse clinician, social worker, physical therapist, occupational therapist, and psychologist. In addition, consultation with a physiatrist, psychiatrist, orthopedic surgeon, dentist, or nutritionist is often indicated. Moreover, regular ophthalmologic consultation is mandatory for JRA patients. Because this rheumatic disorder is characterized by chronic or recurrent inflammation of the joints and varying systemic manifestations, the child and his/her family should accept the need for long-term treatment and surveillance for effective management of the disease.

1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Most children with JRA are treated with one of the NSAIDs during the initial approach of therapy All of these drugs have antipyretic, analgesic, and anti-inflammatory actions, as well as a record of long-term safety. Most currently used NSAIDs inhibit the activity of cyclooxygenases 1 and 2 (COX-1 and COX-2, respectively). Therefore, these drugs have the potential to induce gastrointestinal (GI) irritationalthough this side effect is unusual in children, and ranitidine may ameliorate it. New selective COX-2 inhibitors are available, but have not generally been evaluated in childrenRecent observations in clinical trials involving older adults have suggested an increased risk of cardiovascular events secondary to nonsteroidal anti-inflammatory drugs (NSAIDs), but there are no comparable studies in children. Consideration should be given to continuation of an NSAID for at least 3 to 6 months after all evidence of active disease has disappeared. One might also consider a different mode of withdrawal, such as decreasing administration to every 2 weeks for a period of time before discontinuation

Naproxen has been shown effective in the management of joint inflammation in JRA at a dosage of 15 to 20 mg kg^{-1} d^{-1} given with food, and it only requires administration twice daily. Naproxen is typically well tolerated, although mild epigastric discomfort has been occasionally encountered. In addition, cutaneous pseudoporphyria is a side effect of this drug, and is characterized by a bullous eruption on the face, hands, or other sun-exposed areas, which often leaves an irregular, shallow scar on the affected individual.

Ibuprofen is a relatively mild anti-inflammatory agent and is typically well tolerated at a dosage of approximately 35 mg kg^{-1} d^{-1}, divided into 3 or 4 doses given with food. The suspension that is commonly administered to children consists of both S and R enantiomers and is not absorbed as well as the tabletsIt should therefore be given at a dosage of approximately 45 mg kg^{-1} d^{-1} divided into 3 or 4 doses.

Tolmetin, which is given with food in 3 divided dosages totaling 25-30 mg kg^{-1} d^{-1}, is equally effective as an anti-inflammatory drug.

Diclofenac may be useful in children who are unable to tolerable other NSAIDs because of gastric side effects. This drug is typically prescribed in 3 doses per day; a slow-acting preparation is also available.

Sulindac is an inactive prodrug that is converted *in vivo* to active sulfide, and therefore offers little theoretical exposure to the GI mucosa. It has also been suggested that this prodrug is less nephrotoxic than other NSAIDs.

Celecoxib and, more recently, analogues of the COX-2 inhibitors have been introduced for treatment of arthritis in adults. These drugs are reputedly less likely to cause gastric irritation and peptic ulcer disease than traditional NSAIDs

Indomethacin, typically at a dosage of 1-3 mg kg^{-1} d^{-1} but up to a maximum of 125 mg d^{-1}, is useful for treating fever and pericarditis associated with systemic disease. In many children, intermittent fever responds only to prednisone or indomethacin, the latter of which is a potent anti-inflammatory drug.

Piroxicam, which is only given once daily, may be particularly useful in older children and adolescents who are sometimes incompliant with taking prescribed medication.

Aspirin was previously the drug of choice in the initial management of inflammation, but has more recently been replaced by the NSAIDs. The reasons for this switch are related more to convenience of administration and relative freedom from side effects than to superior efficacy. In addition, aspirin likely resulted in more frequent instances of transaminasemia than the newer NSAIDs. Aspirin is typically started at 75-90 mg kg^{-1} d^{-1} in 4 doses given with food in order to minimize gastric irritation and to ensure therapeutic blood levels. It may be difficult to reach therapeutic levels in children with acute systemic disease, but care should be taken with increasing the dose beyond 130 mg kg^{-1} because this often results in salicylism. Of note, awakening children at night to administer aspirin is unnecessary because the serum half-life of salicylate is prolonged once therapeutic levels have been achieved. In terms of side effects, aspirin and other NSAIDs are associated with interstitial nephritis and renal papillary necrosis4).

2. Methotrexate

Methotrexate is considered the initial second-line agent for treating most children with chronic arthritis, because of its relatively rapid onset of action, efficacy, and acceptable toxicity. The advantages of this medication are its efficacy at a relatively low dose, oral administration, once-a-week dosing, and apparent lack of oncogenicity and production of sterility9). Most patients respond to this drug by 3 months, although a child may occasionally require a longer period of treatment. Methotrexate therapy should likely be continued for 1 year or longer after remission has been achieved. The principal toxicities of this drug are directed at the bone marrow, liver, and very rarely the lung. However, cirrhosis of the liver is not an expected toxic effect in children on a weekly therapy10), although methotrexate-induced pneumonitis and effects on pulmonary function have been reported in children11). Folic acid, given at 1 mg d^{-1} during treatment with methotrexate, can reduce GI irritation and mucosal toxicity with no diminution in therapeutic effectiveness. Methotrexate is given as a single weekly dose on an empty stomach with clear liquids 45 minutes before breakfast; the minimum oral starting dose is 10 mg m^{-2} weekly. If a clinical response is inadequate or if oral administration is associated with nausea or vomiting, a trial of subcutaneous administration of the drug should be attempted. Methotrexate should be discontinued if no objective response is documented or if toxicity develops despite a reduction in dose.

3. Glucocorticoid drugs

Glucocorticoid medications are indicated for uncontrolled or life-threatening systemic disease, the treatment of chronic uveitis, and as an intra-articular agent. Systemic glucocorticoids should be administered to individuals with inflammation only with a well-considered therapeutic plan and a clear set of clinical objectives. Although the use of glucocorticoid drugs alone for suppression of joint inflammation is to be discouraged, low-dose or alternate-day prednisone is of benefit to children with severe polyarthritis that is unresponsive to other therapeutic programs. Moreover, low-dose prednisone can be used as a "bridging" agent in the initial treatment of moderately to severely affected children who are started on other slower-acting, anti-inflammatory drugs at the same time12). For severe uncontrolled systemic manifestations with marked disability, prednisone is often prescribed as a single daily morning dosage of 0.25-1.0 mg kg^{-1} d^{-1}, or in divided doses for more severe disease. Prolonged use of systemic glucocorticoids has been shown to lead to iatrogenic Cushing's syndrome, growth suppression, fractures, cataracts, and increased susceptibility to overwhelming infection. However, it often becomes difficult to reduce the dose of a glucocorticoid because of a child's adaptation to chronic steroid excess13). Moreover, steroid pseudorheumatism may complicate even slow withdrawal from the drug, particularly at lower dose levels.

Intravenous pulse glucocorticoid therapy offers an alternative approach to serious, unresponsive disease. The effect of this treatment is immediate and it is hoped that long-term toxicity is decreased5). Methylprednisolone is the drug of choice for this therapy, often at a dose of 10-30 mg kg^{-1} per pulse. Established protocols of this technique consist of single pulses spaced 1 month apart, 3 pulses given sequentially on 3 d each month, or 3 pulses administered on alternate days each month. This therapy should always be given with cardiovascular monitoring of the patient during the infusion and for a time thereafter, paying careful attention to electrolyte and fluid balance, and to the potential for cardiac arrhythmia or acute hypertension.

The protocol for intra-articular glucocorticoid administration is changing, but at the present time it is clearly indicated in the management of oligoarthritis that has not responded to an appropriate program of NSAIDs. Moreover, intra-articular glucocorticoid therapy should be considered in the management of polyarticular disease in which one or several target joints have not responded to NSAIDs or anti-inflammatory drugs. However, intra-articular injections should be given only a limited number of times per patient (3 times in a single joint during 1 year). Triamcinolone hexacetonide has been the drug of choice for large joints at a dose of 20-40 mg. Younger children, in addition to those individuals who are undergoing injection of a hip joint or several joints, may require conscious sedation or light general anesthesia prior to the treatment.

4. Biologic response modifiers

Recent therapeutic approaches for children with unremitting inflammatory disease include soluble TNF-α receptor (TNFR) p75 fusion protein (etanercept) and recombinant monoclonal human immunoglobulin G (IgG) antibody to TNF-α(infliximab and adalimumab). A

pivotal trial of adlimumab did prove its efficacy and ultimately resulted in the approval of the Food and Drug Administration (FDA). In addition, anti-interleukin (IL)-1 and anti-IL-6 therapies also look very promising, particularly for systemic disease patients. The costimulation modifier abatacept was also shown to be effective and relatively well tolerated according to a short-term analysis of patients, which also resulted in FDA approval. Continued FDA procedures for monitoring safety will improve the ability to identify short- and long-term toxicities of these new agents6).

Etanercept has become a standard therapy for arthritis that has not responded adequately to methotrexate. It is administered to patients at a minimum dose of 0.4 mg kg^{-1} subcutaneously twice a week with continuation of previous medications. However, this drug should not be started in any child with an infection or a history of recurrent infections. Furthermore, the risk of reactivation of tuberculosis or the development of granulomatous or fungal disease as a result of this drug must be recognized. The long-term safety profile of etanercept indicated the drug can be maintained up to 8 years of continuous use. Exposure-adjusted rates of serious adverse effects (SAEs) were not shown to increase over time, and the most common new SAEs reported beyond 4 years of drug exposure were a flare or worsening of disease7).

Adalimumab is a fully human, IgG, monoclonal anti-TNF antibody. The preliminary results of a multicenter, randomized, double-blinded, stratified study of this drug in polyarticular course JRA has previously been presented8). Based on the data in this trial, the United States FDA approved adalimumab as treatment to reduce the signs and symptoms of moderately to severely active polyarticular JRA in patients 4 years of age and older, in February 2008 (this was the first such approval for a biologic since 1999, when etanercept was approved)9).

Abatacept is a fully human, soluble fusion protein composed of the extracellular domain of the cytotoxic T lymphocyte-associated antigen cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the Fc component of IgG1, and selectively inhibits the costimulatory signal necessary for full T-cell activation19). This drug was investigated in an international, multicenter, prospective study with a design similar to the ones used in the pivotal etanercept and adalimumab trials in JRA. This trial showed abatacept was effective and generally well tolerated by patients, which ultimately resulted in FDA approval for treatment of polyarticular JRA in March 2008. Although it is difficult to compare results of separate trials, it appears that abatacept is as effective as anti-TNF agents, but its maximal effect may be achieved a few weeks later10).

Infliximab has not been approved for use in children. However, infliximab (either 3 or 6 mg kg^{-1}), in combination with methotrexate, has been shown to produce an important, rapid, and durable clinical effect in children with JRA at 1 year, but the primary efficacy endpoint of this study was not significantly different between the groups given infliximab or placebo at 14 weeks of treatment. Also of note, the lower dose (3 mg kg^{-1}) of infliximab was associated with a substantially higher risk of SAEs, infusion reactions, and the

development of antibodies to infliximab, ANAs, and anti-dsDNA compared with the corresponding measures in those individuals given the 6 mg kg^{-1} dose. Thus, the use of infliximab in children warrants further investigation11).

Recombinant interferon-γ has also been used experimentally. In one study, it was given to 10 children (6 systemic onset, 3 polyarthritis, 1 oligoarthritis), of whom 8 showed significant improvement, and 7 entered remission12).

Anakinra, which is a recombinant human IL-1 receptor antagonist (IL-1Ra), is currently undergoing therapeutic trials for treatment of chronic arthritis in children. There has been great interest in the role of IL-1 inhibition in the treatment of systemic JRA. Anakinra (1 mg kg^{-1}) administered as a subcutaneous injection once daily was previously well tolerated in pediatric patients with JRA. Moreover, infection rates of these patients were low, and no clinically significant abnormalities in laboratory data were observed. However, efficacy results from the previous study were not conclusive because of the small sample size. Pharmacokinetic assessments indicated that a daily dosage of 1 mg kg^{-1} administered subcutaneously provided adequate exposure for the treatment of JRA. Safety data from this study were consistent with results from larger studies in adults and indicated that anakinra was safe and well tolerated in JRA patients13).

Rilonacept, which is also called IL-1 trap, is a fusion protein composed of human cytokine receptor extracellular domains for both IL-1 type 1 receptor and the IL-1 accessory protein. Preliminary results of a phase II trial involving administration of this drug to systemic JRA patients have been presented and are published in abstract form14); 2 different doses (2.2 and 4.4 mg kg^{-1}) were studied. Marked improvements in fever, rash, and active joint counts were noted at both doses.

Tocilizumab is a monoclonal anti-IL-6 receptor antibody that inhibits IL-6 activity15). It has previously been reported to be effective in treating systemic JRA. Tocilizumab may also be useful for treatment of established amyloidosis.

Rituximab remains to be discussed in the context of JRA in the existing literature. That is, we were unable to find any published studies on rituximab for the treatment of JRA.

Thalidomide has been recommended for treatment of systemic onset arthritis16).

5. Modes of advanced therapy

Slow-acting antirheumatic drugs (SAARDs) or disease-modifying antirheumatic drugs (DMARDs) consist of cyclosporine, sulfasalazine, and antimalarials. Methotrexate has generally replaced the SAARDs in treating advanced cases of JRA. However,

SAARDs remain to be considered for children who have an incomplete response to various combinations of an NSAID, methotrexate, and a TNF-α blocker.

Cyclosporine is given at an oral dosage of 3-5 mg kg^{-1} d^{-1} in 2 divided doses exactly 12 hours apart. Blood pressure should be determined at home for 2 weeks during treatment with this drug and subsequently evaluated periodically with urinalyses and estimates of renal function. Of note, there may be a small long-term risk of developing lymphoma as a result of treatment. The role of this drug in the treatment of arthritis in children is uncertain, but it is likely critically important in treating reactive hemophagocytosis. Combined therapy of this drug with methotrexate has also been recommended in select children.

Hydroxchloroquine is a useful adjunctive agent for treating chronic arthritis in older children. The therapeutic effect of this drug is usually subtle and is rarely evident before 2 to 3 months of therapy. If this drug causes no improvement in a patient after 6 months of treatment, it should be discontinued. Hydroxychloroquine is never used alone, but is instead added to an NSAID regimen, usually at a dosage of 5-6 mg kg^{-1} d^{-1}. The medication should be taken with food because it can be a GI irritant. An ophthalmologic examination, including testing of color vision and visual fields, is usually performed before therapy is started and traditionally every 6 months thereafter. Hydroxychloroquine has not been recommended in children younger than 4 years of age, and sometimes in those younger than 7 years of age, because of the inability of young children to discern colors adequately for testing on grids or visual fields.

Sulfasalazine has been reported to have modest efficacy in some children with chronic arthritis, and it has the advantage of a more rapid onset of anti-inflammatory action than that which occurs with other SAARDs. This drug should not be used in children with known hypersensitivity to sulfa drugs or salicylate, impaired renal or hepatic function, or specific contraindications, such as porphyria or glucose-6-phosphate dehydrogenase deficiency. Moreover, severe side effects have been reported in children with systemic onset disease. Sulfasalazine is started at a dosage of 12.5 mg kg^{-1} d^{-1} given with food, and this dose is gradually increased until a dosage of 50 mg kg^{-1} d^{-1} is reached. The benefits of the drug are usually apparent within 4 to 8 weeks after initiation of therapy.

6. Autologous stem cell transplantation

Bone marrow transplantation has been initiated as an experimental treatment of severe autoimmune diseases including rheumatic diseases unresponsive to conventional therapy. Autologous stem cell transplantation (ASCT) is currently being evaluated, but only in a small number of children. This treatment approach is indicated only for children who are affected by severe active disease that fails to be controlled by conventional strategies, including anti-TNF therapy.