Pharmacotherapy in Systemic Rheumatic Diseases

4

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4.1 Introduction

Over the past two decades, better understanding of the immunopathophysiologic basis of various rheumatic diseases led to the discovery of variety of drugs that are now approved and widely used in clinical practice. These drugs are categorized into the following categories: nonsteroidal anti-inflammatory drugs (NSAIDs), synthetic disease-modifying anti-rheumatic drugs (sDMARDs), biological disease-modifying anti-rheumatic drugs (bDMARDs), corticosteroids and drugs used in crystal-induced arthritis. Few other drugs are also used by rheumatologists. These include anti-resorptive drugs and symptom-specific drugs.

- Explain the mechanism of action, dosages, indications, adverse effects, cautions, contraindications and pregnancy category of each drug

4.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory, antipyretic and analgesic drugs. Although they differ widely in their chemical class, they share the property of blocking the production of prostaglandins (PGs). This is achieved by inhibiting the activity of the enzyme prostaglandin G/H synthase (PGHS), also called *cyclooxygenase* (COX).

There are two different COX isoforms, COX-1 and COX-2. Inhibition of COX-2 by NSAIDs blocks PG production at sites of inflammation, while inhibition of COX-1 in certain other tissues, most importantly platelets and the gastroduodenal mucosa, can lead to common adverse effects of NSAIDs such as bleeding, bruising and gastrointestinal ulceration [1].

In addition to their use in rheumatoid arthritis and osteoarthritis, NSAIDs are widely used in the symptomatic management of other rheumatic diseases characterized by chronic musculoskeletal pain and diverse forms of acute pain.

4.2 Learning Objectives

By the end of this chapter, you should be able to:

- Recall the main drug categories used in the treatment of systemic rheumatic diseases

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NSAIDs are associated with elevated cardiovascular disease risk and risk for gastrointestinal bleeding and ulceration [2, 3]. For that, it is important to identify patients with these risks, and if present, avoiding NSAIDs or using intermittent, low-dose and short half-life drugs is advisable. It is also important to know that use of NSAIDs together with aspirin, which is an NSAID too, can increase gastrointestinal toxicity and lead to aspirin resistance [4].

Patients who take regular doses of NSAIDs should undergo periodic assessment of blood pressure, haemoglobin level, electrolytes and renal and liver function tests.

Complete details about different NSAIDs are shown in Table 4.1

4.4 Synthetic Disease-Modifying Anti-Rheumatic Drugs (sDMARDs)

This category consists of drugs that have been used as first-line therapies in the majority of systemic rheumatic diseases. Although their precise mechanism of action is still incompletely understood, they have both anti-inflammatory and immunomodulatory effects.

Generally, the choice of a sDMARD therapy should be decided for each patient individually. This should also give attention to patient's age, fertility plans, comorbid conditions and other concomitant drugs. Adverse effects from sDMARDs may cause significant morbidity and mortality. So, appropriate dosing and monitoring for toxicity are required.

4.4.1 Methotrexate

Over the past 25 years, methotrexate has become the sDMARD of choice in the treatment of rheumatoid arthritis and is used in many other rheumatic diseases as well (psoriasis, psoriatic

arthritis, polymyositis, dermatomyositis, granulomatosis with polyangiitis, giant cell arteritis, subacute lupus erythematosus, scleroderma and vasculitis).

Methotrexate increases the concentration of adenosine, which is a potent inhibitor of inflammation. It also inhibits the enzyme dihydrofolic acid reductase [5].

The effects of methotrexate can be enhanced by using the subcutaneous form instead of the oral form or by splitting the oral dose (within 12-h window) when doses greater than 15 mg weekly are given [6]. Doses should be adjusted based on renal and hepatic function.

A weekly oral dose of folic acid 5–10 mg given 48–72 h post methotrexate dose protects against mucosal ulceration and keeps folic acid levels optimum [7].

4.4.2 Leflunomide

Leflunomide is approved for the treatment of rheumatoid arthritis. It has both anti-inflammatory and immunomodulatory effects. It inhibits the enzyme dihydroorotate dehydrogenase and pyrimidine synthesis [8].

Loading doses are not used in clinical practice due to gastrointestinal toxicity. Leflunomide is found to have a very long half-life because of its enterohepatic recirculation [9]. It is absolutely contraindicated in pregnancy.

4.4.3 Azathioprine

It is an imidazolyl derivative of mercaptopurine. It antagonizes purine metabolism and may inhibit the synthesis of DNA, RNA and proteins. It also inhibits cellular metabolism [10].

Azathioprine can be effective as a glucocorticoid-sparing agent in remission maintenance therapy, particularly in systemic lupus erythematosus and necrotizing vasculitis.

Table 4.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Inhibit COX-1 and COX-2 isoenzymes, thus inhibiting prostaglandin synthesis and release of inflammatory mediators	Ibuprofen Pain: 300–800 mg PO q6hrs Fever: 100–200 mg PO q4–6hrs PRN Inflammatory diseases: 400–800 mg PO q6–8hrs Osteoarthritis: 300 mg, 400 mg, 600 mg or 800 mg PO q6–8hrs; not to exceed 3.2 g/day Rheumatoid arthritis: 300–800 mg PO q6–8hrs; not to exceed 3.2 g/day	May cause elevated creatinine or liver enzymes in patients with active SLE. Gastrointestinal complaints like erosion, ulceration or bleeding Hepatotoxicity, asthma, rashes, itchiness, tinnitus, dizziness, headache and aseptic meningitis (particularly in patients with systemic lupus erythematosus)	Ibuprofen Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excreted into breast milk, use not recommended
	Naproxen Pain: 500 mg PO initially followed by 250 mg PO q6–8hrs PRN; alternatively, 500 mg q12hr. Not to exceed 1250 mg/day PO Rheumatoid arthritis, ankylosing spondylitis or osteoarthritis: 500–1000 mg PO divided q12hrs. Not to exceed 1500 mg/day PO	Fluid retention and renal toxicity occur less frequently Drug interactions: 1. Concomitant administration with aspirin will antagonize the irreversible platelet inhibition induced by aspirin 2. Reduce the natriuretic effect of furosemide and thiazides in some patients 3. May also increase lithium plasma levels due to decreased renal clearance 4. Use of NSAIDs with ACE inhibitors may potentiate renal disease states 5. Concomitant administration with prednisone may increase the risk of GIT ulceration	Naproxen Pregnancy category: B or D if used for prolonged periods or near term Lactation: Excreted into breast milk, use should be carefully evaluated
	Meloxicam Rheumatoid arthritis, osteoarthritis or ankylosing spondylitis: 7.5–15 mg PO daily; not to exceed 15 mg/day		Meloxicam Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excretion into breast milk is unknown, use not recommended
Inhibits COX-2 isoenzymes (does not affect COX-1), thus inhibiting synthesis of prostaglandin and release of the inflammatory mediators	Celecoxib Rheumatoid arthritis, osteoarthritis or ankylosing spondylitis: 200 mg PO once daily or divided Q12hr	Headache, hypertension, abdominal pain, nausea and vomiting Fluid retention and renal toxicity occur less frequently Increased risk of cardiovascular events and gastrointestinal toxicity	Celecoxib Pregnancy category: C or D at 30 weeks of gestation or more May cause premature closure of ductus arteriosus Lactation: Excreted into breast milk, use should be carefully evaluated

It can induce severe myelosuppression in patients with low or absent thiopurine methyltransferase (TPMT) activity that is affected by a polymorphism that can be identified by genetic screening [11]. Severe myelosuppression can also occur in patients with normal TPMT activity, and regular monitoring of white blood cell counts is recommended.

Azathioprine interacts with allopurinol and this can lead to fatal myelosuppression. Concomitant use of these two drugs should be avoided.

4.4.4 Hydroxychloroquine

It is an anti-malarial drug and a well-tolerated sDMARD that is now used as a cornerstone therapy in patients with systemic lupus erythematosus and in combination therapy regimens for rheumatoid arthritis [12].

Hydroxychloroquine is more commonly used than chloroquine. It has a very long half-life, attributed to its affinity for melanin-containing cells in the skin. Doses of hydroxychloroquine should not exceed 6.5 mg/kg/day in chronic therapy to minimize the risk of retinal toxicity [13]. Although routine laboratory monitoring is not required, ophthalmologic screening is an essential component of toxicity monitoring.

Diabetic patients initiating hydroxychloroquine should be instructed to follow blood sugars closely because of the hypoglycaemic effects of the drug.

Hydroxychloroquine is considered safe in pregnancy; it is recommended that most pregnant patients with SLE remain on the drug to improve pregnancy outcomes.

4.4.5 Sulfasalazine

It is a sDMARD that has both antimicrobial and anti-inflammatory properties. The exact mechanism of action is unknown. However, it is a 5-aminocyclic acid derivative that inhibits leukotriene synthesis [14].

Sulfasalazine is commonly used as part of combination therapy for rheumatoid arthritis. Its dose should be increased gradually with regular laboratory monitoring to minimize the risk of adverse effects and drug intolerance.

Gastrointestinal intolerance and rash are common side effects. Monitoring complete blood counts, liver transaminases and creatinine levels should be done periodically during therapy [15].

4.4.6 Mycophenolate Mofetil

It is a powerful inhibitor of lymphocyte proliferation that has a potential glucocorticoid-sparing effect. It is used for the treatment of patients with various rheumatic diseases. It inhibits inosine monophosphate dehydrogenase enzyme which decreases T- and B-cell proliferation and antibody production [16].

Mycophenolate mofetil can be used as a remission induction agent in lupus nephritis and is now increasingly used for remission maintenance treatment of systemic lupus erythematosus and necrotizing vasculitis [17].

It is generally well tolerated, although diarrhoea and leucopenia may necessitate its discontinuation. Complete blood counts should be performed within the first 2 weeks of therapy and then once every 6–8 weeks thereafter if no cytopenia is noted [18].

4.4.7 Cyclophosphamide

It is an alkylating agent and one of the most potent immunosuppressive therapies available. It is a pro-drug which prevents and inhibits cell division [19].

The indications for its use include induction of remission in lupus nephritis. It is also used to treat rheumatoid vasculitis, interstitial lung disease associated with connective tissue diseases and many types of systemic vasculitides.

Although very effective, it has the potential for devastating toxicity both in the short and long term. Its toxicities include myelosuppression, infection, ovarian failure, haemorrhagic cystitis and malignancy including bladder cancer, especially with high cumulative doses.

The intermittent intravenous doses given every 3–4 weeks are associated with less bladder toxicity compared to oral daily doses [20]. To further minimize bladder toxicity, intravenous fluids, anti-emetics and MESNA (2-mercaptoethanesulfonic acid) may be used.

4.4.8 Tofacitinib

Tofacitinib is a targeted sDMARD that is now approved for the treatment of rheumatoid arthritis. It inhibits the enzymes janus kinase 1 (JAK1) and janus kinase 3 (JAK 3) and thus prevents the phosphorylation and activation of signal transducers and activators of transcription (STATs), which transmit extracellular information into the cell nucleus, influencing DNA transcription [21].

The most commonly reported adverse effects which occur in less than 5% of patients treated with tofacitinib are upper respiratory tract infec-

tions, headache, diarrhoea and nasopharyngitis. Neutropenia and lymphopenia are also reported in less than 1% of patients and laboratory monitoring is recommended.

4.4.9 Apremilast

This sDMARD is now approved for the treatment of psoriatic arthritis and psoriasis. It is a small molecule inhibitor of phosphodiesterase-4 (PDE4), which breaks down cyclic adenosine monophosphate (cAMP) in inflammatory cells. This results in down-regulation of the expression of a number of the pro-inflammatory factors like tumour necrosis factor alpha (TNF α), interleukin-17, interleukin-23 and many others and up-regulation of the anti-inflammatory interleukin-10.

Headache, back pain, nausea, diarrhoea, fatigue, nasopharyngitis, upper respiratory tract infections and weight loss are common adverse effects and are reported in up to 10% of patients taking apremilast [22].

Complete details about different sDMARDs are shown in Table 4.2.

4.5 Biological Disease-Modifying Anti-Rheumatic Drugs (bDMARDs)

The bDMARDs target specific components of the immune response that are dysregulated and are thought to be the cause of the disease process. These components are called pro-inflammatory cytokines. Tumour necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and others

Table 4.2 Synthetic disease-modifying anti-rheumatic drugs (sDMARDs)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Methotrexate (Trexall)	Inhibits the enzyme dihydrofolic acid reductase	<p>Rheumatoid arthritis: 10–25 mg weekly in single PO dose, not to exceed 30 mg</p> <p>15–25 mg SC weekly if tablets are not tolerable</p> <p>Juvenile rheumatoid arthritis: 10 mg/m² PO/IM weekly, then 5–15 mg/m² weekly in single dose or in 3 divided doses given q12hrs</p> <p>Dosing modifications: Renal impairment 1. CrCl 61–80 mL/min: Give 75% of dose 2. CrCl 51–60 mL/min: Give 70% of dose 3. CrCl 10–50 mL/min: Give 30–50% of dose at normal dosing interval 4. CrCl <10 mL/min: Avoid use</p> <p>Hepatic impairment 1. Bilirubin 3.1–5.0 mg/dL or AST >180 international units/L: Give 75% of dose 2. Bilirubin >5.0 mg/dL: Avoid use</p>	<p>Most commonly ulcerative stomatitis, leucopenia, nausea and abdominal distress</p> <p>A weekly dose of folic acid 5–10 mg given 48–72 h post methotrexate dose protects against mucosal ulceration and keeps folic acid levels optimum</p> <p>High doses can cause severe haematologic and gastrointestinal toxicity</p> <p>Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently, but cirrhosis is rare (< 1%)</p> <p>A rare “hypersensitivity” lung reaction with acute shortness of breath</p> <p>Drug interactions: NSAIDs and salicylate administered concomitantly with lower doses of methotrexate, reduce the tubular secretion of methotrexate and may enhance its toxicity</p> <p>Trimethoprim antibiotic may increase the toxicity of methotrexate</p>	<p>Pregnancy category: X</p> <p>Lactation: Excreted into breast milk, do not nurse</p> <p>Methotrexate toxicity</p> <p>Leucovorin is an antidote that restores folate and displaces intracellular methotrexate</p> <p>Oral, IV, or IM</p> <p>15 mg (approximately 10 mg/m²) every 6 h until methotrexate concentration declines to <0.005 mcg/mL (0.01 µM)</p> <p>If 24-h S_{cr} increases 50% over baseline, 24-h methotrexate concentration is >2.27 mcg/mL (5 µM, or 48-h methotrexate concentration is >0.409 mcg/mL (0.9 µM); increase leucovorin dosage immediately to 150 mg (approximately 100 mg/m²) IV every 3 h until methotrexate concentration declines to <0.005 mcg/mL (0.01 µM)</p>
Leflunomide (Arava)	Reversibly inhibits pyrimidine synthesis	<p>Rheumatoid arthritis: 10–20 mg PO daily</p> <p>Dosing modifications: Can be used safely in renal impairment</p> <p>Cholestyramine 8 g PO TID for 11 days to wash out drug's active metabolite prior to conceive</p>	<p>Diarrhoea, respiratory infections, alopecia, hypertension, skin rash, gastrointestinal symptoms and liver injury are common</p> <p>Contraindicated in: 1. Active liver disease (ALT is double) 2. Active infections 3. Myelosuppressive diseases</p>	<p>Pregnancy category: X</p> <p>Lactation: Excretion into breast milk is unknown; do not nurse</p>

Azathioprine (Imuran)	A 6-mercaptopurine derivative, inhibits the synthesis of both DNA and RNA Also inhibits cellular metabolism	Rheumatoid arthritis: Initial: 1 mg/kg IV/PO daily or divided BID, may increase as follows: 1. By 0.5 mg/kg/day after 6–8 weeks 2. By 0.5 mg/kg/day q4Weeks, no more than 2.5 mg/kg/day 3. Maintenance: Reduce dose by 0.5 mg/kg q4Weeks until lowest effective dose reached Lupus nephritis: Induction and maintenance therapy: 2 mg/kg/day PO with or without low-dose corticosteroids	Bone marrow suppression, anaemia, skin rashes, fever, nausea, diarrhoea and some increase in infection risk Rarely, fever, rash and hepatotoxicity signal acute allergic reactions Drug interactions: Allopurinol will decrease the metabolism of azathioprine	Pregnancy category: D Lactation: Excreted into breast milk at low levels, use not recommended
Hydroxychloroquine (Plaquenil)	Suppresses response of T lymphocyte mitogens Decreases WBC chemotaxis Stabilizes lysosomal enzymes Inhibits DNA and RNA synthesis. Traps free radicals	Rheumatoid arthritis and systemic lupus erythematosus: 200–400 mg daily. Not to exceed 6.5 mg/kg/day	Dizziness, nightmares, rash, itching, aplastic anaemia, leucopenia, alopecia, thrombocytopenia, nausea, vomiting, diarrhoea and abdominal cramps Corneal changes or deposits and retinal damage with long-term use Skin and musculoskeletal pigmentation	Pregnancy category: C Lactation: Compatible with nursing
Cyclosporine (Neoral)	Calcineurin inhibitor that suppresses both cellular and humoral immunities	Rheumatoid arthritis: 3–5 mg/kg/day divided into two doses	Nephrotoxicity. Drugs that inhibit CYP3A like diltiazem and potassium-sparing diuretics increase nephrotoxicity. So, serum creatinine should be closely monitored Other toxicities include hypertension, hyperglycaemia, gum hyperplasia, gingival hyperplasia, hyperkalaemia, hepatotoxicity and hirsutism	Pregnancy category: C Lactation: Excreted into breast milk, use not recommended
Sulfasalazine (Azulfidine)	5-Aminocyclic acid derivative inhibits leukotriene synthesis	Rheumatoid arthritis: Enteric coated: 2–3 g/day divided into 3 doses. Dose should be increased gradually	Tinnitus, hearing loss, hepatotoxicity and gastrointestinal complaints like erosion, ulceration or bleeding and drug rash	Pregnancy category: B or D if used for prolonged periods or near term. Increases kernicterus risk Lactation: Excreted into breast milk, used with care

(continued)

Table 4.2 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Mycophenolate (Cellcept)	Inhibits inosine monophosphate dehydrogenase Inhibits T and B-cell proliferation and antibody production	Class III/IV lupus nephritis: Induction: 1 g PO q12hrs for 6 months Maintenance: 0.5–3 g/day or 1 g PO BID Administer with initial IV corticosteroid pulse for 3 days and then prednisone 0.5–1 mg/kg/day PO; after a few weeks, taper prednisone to lowest effect dose	Hyperglycaemia, hyperkalaemia, increased urea, hypertension, various infections, hypocalcaemia, hypercholesterolaemia and hypomagnesaemia Vomiting and diarrhoea are common Hepatic toxicities are infrequent but must be monitored	Pregnancy category: D Lactation: Excretion into breast milk is unknown, use not recommended
Cyclophosphamide (Cytosan)	Immunosuppressive, a pro-drug which prevents and inhibits cell division	Juvenile idiopathic arthritis/vasculitis: 10 mg/kg IV every 2 weeks Lupus nephritis: Induction therapy is by one of the following: 1. Low dose: 500 mg IV every 2 weeks for 6 doses plus corticosteroids, then maintenance with mycophenolate mofetil or azathioprine 2. High dose: 500–1000 mg/m ² IV monthly for 6 doses plus corticosteroids Dosing modifications: Hepatic impairment: Give 75% of normal dose if transaminase levels are >3 times upper limit of normal or bilirubin is 3.1–5 mg/dL Renal impairment: CrCl<10 mL/min, give 75% of normal dose; CrCl>10 mL/min, give full dose	Can cause significant dose-related infertility in both men and women Nausea and vomiting, bone marrow suppression, alopecia, haemorrhagic cystitis and, rarely, bladder carcinoma	Pregnancy category: D Lactation: Excreted into breast milk, use not recommended

Tofacitinib (Xeljanz)	Inhibits the JAK-STAT signalling pathway	<p>Rheumatoid arthritis: 5 mg PO Q12hrs or 11 mg of the extended-release tablet daily</p> <p>Dosing modifications: Co-administration with cytochrome P450 3A4 inhibitors: Not to exceed 5 mg daily Moderate renal or hepatic impairment: Reduce dose to less than 5 mg daily It has not been studied in patients with severe hepatic impairment or in patients with CrCl <40 mL/min</p>	Upper respiratory tract infections, headache, diarrhoea, nasopharyngitis, neutropenia and lymphopenia No contraindications have been listed	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Apremilast (Otezla)	Small molecule inhibitor of PDE-4	<p>Active psoriatic arthritis or plaque psoriasis (moderate to severe): Day 1: 10 mg PO in AM Day 2: 10 mg AM and PM Day 3: 10 mg AM and 20 mg PM Day 4: 20 mg AM and PM Day 5: 20 mg AM and 30 mg PM Day 6 and thereafter: 30 mg BID</p> <p>Dosing modifications: Mild to moderate renal or hepatic impairment, no adjustment required CrCl <30 mL/min: Reduce dose to 30 mg daily</p>	Headache, back pain, nausea, diarrhoea, fatigue, nasopharyngitis, upper respiratory tract infections and weight loss Worsening depression, suicidal thoughts and other mood changes may also occur Concurrent use of strong cytochrome P450 enzyme inducers can result in loss of apremilast efficacy	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended

are the pro-inflammatory cytokines found in the rheumatoid synovium. Few other bDMARDs target B and T cells. These agents have considerable efficacy in the treatment of patients with rheumatoid arthritis and other systemic inflammatory disorders.

4.5.1 TNF- α Blockers

Five TNF- α inhibitors are approved for the treatment of selected rheumatic disease by the United States Food and Drug Administration. These are adalimumab, etanercept, infliximab, golimumab and certolizumab.

A 2008 systematic review of synthetic and biologic DMARD therapy for rheumatoid arthritis concluded that anti-TNF monotherapy was similar in efficacy to treatment with methotrexate alone, while the combination of an anti-TNF agent with methotrexate reduced disease activity more and slowed radiographic progression to a greater extent than did anti-TNF monotherapy or methotrexate alone [23].

Most patients with rheumatoid arthritis respond to treatment with TNF inhibitors, with significant improvements in signs and symptoms of disease, significant decrease in radiographic damage and significant improvement in quality of life and functional status.

They have also proved to be highly effective in treating patients with ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and juvenile idiopathic arthritis. However, they were ineffective in patients with scleroderma or vasculitis.

4.5.2 Rituximab

Rituximab is a chimeric monoclonal antibody that binds to CD20 antigen and leads to B-cell inhibition [24]. It is an effective biologic therapy

for rheumatoid arthritis with a greatest benefit in seropositive patients. If given as two infusions of 1 gram each, it slows the radiographic progression in rheumatoid arthritis.

Rituximab is considered as a safe drug in rheumatoid arthritis, but infusion reactions can occur; most are mild to moderate. Pre-medication with methylprednisolone, diphenhydramine and acetaminophen can reduce these reactions.

Rituximab therapy carries a risk of hepatitis B reactivation amongst patients who have positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). All patients should be screened for HBsAg and anti-HBc prior to starting treatment [25].

4.5.3 Abatacept

It is a fully human fusion protein that inhibits co-stimulation (an essential step in the induction of adaptive immune responses) and inhibits T-cell activity [26].

Abatacept can be used when sDMARDs and/or other biologic drugs have failed to control inflammatory arthritis. Infection risk with abatacept is higher compared to other biologics [26].

It is administered as a 30-min intravenous infusion that is usually achieved without complications. Subcutaneous administration is equally effective and is now approved.

Abatacept is used to treat rheumatoid arthritis and polyarticular juvenile idiopathic arthritis. Clinical trials on abatacept in psoriatic arthritis and scleroderma have shown promising results [27].

4.5.4 Tocilizumab

It is a humanized monoclonal antibody that antagonizes the cytokinetic effect of IL-6. It has been approved for treatment of rheumatoid arthritis

tis [28] and systemic onset juvenile idiopathic arthritis. It was recently granted a breakthrough designation status by the United States Food and Drug Association for giant cell arteritis based on positive results from a phase 3 clinical trial [29].

A dose of 4 mg/kg is started initially and then increased to 8 mg/kg based on clinical response. It is administered intravenously every 4 weeks. Administration through the subcutaneous route is also available. It may cause dyslipidemia but is generally well tolerated. Periodic monitoring of lipid profile along with other routine investigation is required.

4.5.5 Ustekinumab

Ustekinumab is a humanized monoclonal antibody that binds to and interferes with the biological effects of IL-12 and IL-23. It is approved for the treatment of psoriatic arthritis and moderate to severe plaque psoriasis [30].

It is administered at a dose of 45 mg subcutaneously at week zero, followed by a second dose at week 4 and then every 12 weeks. Nasopharyngitis, upper respiratory tract infections and nausea are common side effects.

4.5.6 Secukinumab

Secukinumab is a humanized IgG1 monoclonal antibody that selectively binds to IL-17A and inhibits its pro-inflammatory action. It is approved for the treatment of active ankylosing spondylitis, psoriatic arthritis and moderate to severe plaque psoriasis [31].

Nasopharyngitis, upper respiratory tract infections and diarrhoea are common side effects. If

administered with a loading dose, 150 mg subcutaneously is given at weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks. Without a loading dose, 150 mg subcutaneously is administered every 4 weeks.

Complete details about different bDMARDs are shown in Table 4.3.

4.6 Glucocorticoids

Glucocorticoids exert both anti-inflammatory and immunosuppressive effects. They inhibit prostaglandin and leukotriene synthesis, reduce macrophage phagocytosis and inhibit the release of collagenase and lysosomal enzymes [32].

Generally, five types of glucocorticoids are used in rheumatology daily practice. These are hydrocortisone, prednisolone, methylprednisolone, triamcinolone and dexamethasone. They differ considerably in potency and biologic half-life as shown in Table 4.4. They are used in the majority of systemic rheumatic diseases.

The chronic use of low-dose glucocorticoids can cause multiple adverse events [33]. For that, the dose of glucocorticoids should be tapered as quickly as possible to the lowest effective dose when chronic use is anticipated. Serum glucose, lipid profile and bone mineral density to prevent glucocorticoid-induced osteoporosis should be performed to monitor toxicity. Patients should also be screened frequently for polydipsia, oedema and shortness of breath, visual changes, weight gain and changes in blood pressure during therapy.

Complete details about different glucocorticoids are shown in Table 4.4.

Table 4.3 Biological disease-modifying anti-rheumatic drugs (bDMARDs)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Infliximab (Remicade)	Chimeric monoclonal antibody against TNF- α	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: Initially: IV infusion at a dose of 5 mg/kg at weeks 0, 2 and 6 Maintenance: 5 mg/kg IV infusions every 8 weeks. Dose may be increased to 10 mg/kg	Common: Infusion reactions (itching, hives, rash, nausea, headache) and upper respiratory infections (colds, sinusitis, bronchitis, etc.) Rare and serious: Serious bacterial infections, unusual infections (tuberculosis and fungal), worsening of CHF, hepatitis B reactivation,	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Adalimumab (Humira)	Humanized monoclonal antibody against TNF- α	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: 40 mg SC once every other week	hepatotoxicity, possible malignancies, haematologic and neurologic events, lupus-like syndrome	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Etanercept (Enbrel)	TNF receptor fusion protein	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: 50 mg SC once weekly or 25 mg SC twice weekly		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Certolizumab (Cimzia)	Humanized monoclonal antibody against TNF- α	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: Initially: 400 mg SC at weeks 0, 2 and 4 Maintenance: 200 mg SC every other week		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Golimumab (Simponi)	Humanized monoclonal antibody against TNF- α	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: 50 mg SC once monthly		Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Rituximab (MabThera)	Monoclonal antibody, binds to CD20 antigen B-cell inhibitor	Rheumatoid arthritis: 1000 mg IV infusion for 2 doses 2 weeks apart (one cycle) Repeat cycle every 24 weeks or based on clinical evaluation Systemic lupus erythematosus, granulomatosis with polyangitis and Microscopic polyangitis: 375 mg/m ² IV every week for 4 weeks	Common toxicity: Infusion reactions, nausea, upper respiratory tract infections, hypertension, arthralgias, pruritus and pyrexia Rare and serious: Fatal infusion reactions Severe mucocutaneous reactions Progressive multifocal leucoencephalopathy Hepatitis B reactivation with fulminant hepatitis Neurologic events Lupus-like syndrome	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended

Table 4.3 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Abatacept (Orencia)	Human fusion protein, inhibits co-stimulation T-cell inhibitor	Rheumatoid arthritis: According to body weight: < 60 kg = 500 mg IV 60–100 kg = 750 mg IV > 100 kg = 1000 mg IV At weeks 0, 2 and 4 Then repeated every 4 weeks thereafter or may be given as weight-based IV loading dose, then 125 mg SC once weekly	Common: Infusion reactions, headaches, upper respiratory tract infections, nausea and nasopharyngitis Rare and serious: Serious bacterial infections Possible malignancies COPD exacerbation	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Tocilizumab (Actemra)	Interleukin-6 (IL-6) antagonist	Rheumatoid arthritis: 4 mg/kg IV every 4 weeks initially, may be increased to 8 mg/kg IV every 4 weeks based on clinical response SC: 162 mg every week	Common: Infusion reactions, dyslipidemia, headaches, upper respiratory tract infections, nausea and nasopharyngitis Rare and serious: Serious bacterial infections	Pregnancy category: C Lactation: Excretion into breast milk is unknown, use not recommended
Ustekinumab (Stelara)	Interleukin-12 and 23 (IL-12, IL-23) antagonist	Psoriatic arthritis: 45 mg SC at weeks 0 and 4, then every 12 weeks	Common: Infusion reactions, upper respiratory tract infections, nausea and nasopharyngitis Rare and serious: Serious infections and malignancies	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended
Secukinumab (Cosentyx)	Interleukin-17A (IL-17A) antagonist	Psoriatic arthritis and ankylosing spondylitis: With a loading dose: 150 mg SC at weeks 0, 1, 2, 3 and 4 followed by 150 mg every 4 weeks Without a loading dose: 150 mg SC every 4 weeks	Nasopharyngitis, upper respiratory tract infections and diarrhoea	Pregnancy category: B Lactation: Excretion into breast milk is unknown, use not recommended

Table 4.4 Glucocorticoids

Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Anti-inflammatory and immunosuppressive drugs	<p>Methylprednisolone: Used as a pulse dose in various severe systemic rheumatic diseases: Severe lupus nephritis, severe vasculitis: 1 g IV over 1 h $\times$3 days</p> <p>Prednisolone: Used as a high dose (1 mg/kg/day) for some active severe forms of vasculitis and then tapered slowly. Or initial dose can be started and then increased or decreased based on clinical response. Dose must be tapered slowly</p> <p>Hydrocortisone: Used as pre-medication or during the perioperative period</p>	<p>Fat redistribution on the face (moon face), oedema, fluid retention, hypokalaemia, hypertension, aggravation of diabetes, muscular atrophies and weakness, fatigability, menstrual cycle disturbances, peptic ulcer and increase in the risk of infections</p> <p>Adrenal insufficiency at rapid withdrawal of the treatment</p> <p>Bone disorders: Glucocorticoid-induced osteoporosis</p> <p>Neuropsychiatric disorders, nervousness, insomnia, depression, aggravation of epilepsy, increase in intracranial pressure in children</p> <p>Ocular disorders: Glaucoma, cataract</p> <p>Haematological effects: Leucocytosis and thrombocytosis, decrease of T-cell lymphocytes</p>	<p>Pregnancy category: C</p> <p>Lactation: Compatible with nursing but use with caution</p>
Drug name	Duration of action	Anti-inflammatory potency	Equivalent dose
Hydrocortisone	Short acting	Potency is 1 for a 20 mg dose	20 mg oral dose
Prednisolone	Intermediate acting	4 times more potent than hydrocortisone	5 mg oral dose is equivalent to 20 mg hydrocortisone
Methylprednisolone	Intermediate acting	5 times more potent than hydrocortisone	4 mg oral dose is equivalent to 20 mg hydrocortisone
Triamcinolone	Intermediate acting	5 times more potent than hydrocortisone	4 mg oral dose is equivalent to 20 mg hydrocortisone
Dexamethasone	Long acting	30 times more potent than hydrocortisone	1 mg oral dose is equivalent to 20 mg hydrocortisone

4.7 Anti-Resorptive Drugs

4.7.1 Bisphosphonates

Alendronate, risedronate, ibandronate and zoledronic acid are effective for the treat-

ment of osteoporosis. These drugs inhibit bone resorption, increase bone mass and reduce the incidence of fractures. They are considered as first-line therapy for osteoporosis in post-menopausal women and men because of their efficacy, favourable cost and the availability of

safety data. For those who cannot tolerate oral bisphosphonates; who have difficulty with dosing requirements, including the inability to sit upright for 30–60 min; or who have relative contraindications to bisphosphonates (achalasia, scleroderma oesophagus, oesophageal strictures), intravenous zoledronic acid is the choice of therapy. Bisphosphonates should be avoided in renal impairment. They are also avoided in women of childbearing age due to foetal risk. Bisphosphonates cross the placenta and accumulate in the foetal bones [34].

4.7.2 Raloxifene

It is a selective oestrogen receptor modulator that inhibits bone resorption and reduces the risk of vertebral fracture. It is suggested for those who cannot tolerate or are not candidates for bisphosphonate therapy [35]. It is also usually chosen for osteoporosis when there is an independent need for breast cancer prophylaxis.

4.7.3 Teriparatide

It is a recombinant formulation of endogenous parathyroid hormone. It stimulates osteoblast function, increases gastrointestinal calcium absorption and increases renal tubular reabsorption of calcium. In postmenopausal women, teriparatide has been shown to decrease osteoporosis-related fractures. This drug is also suggested for those who cannot tolerate or are not candidates for bisphosphonates therapy [36].

4.7.4 Denosumab

It is a fully human monoclonal antibody that specifically binds to receptor activator of nuclear factor kappa B ligand (RANKL). It reduces the formation, function and survival of osteoclasts, which results in decreased bone resorption and increased bone density. It is suggested for those who cannot tolerate or are not candidates for bisphosphonate therapy [37].

Complete details about different anti-resorptive drugs are shown in Table 4.5.

Table 4.5 Anti-resorptive drugs

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Alendronate (Fosamax)	Bisphosphonate, inhibits resorption of bones Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis: 70 mg PO once weekly If CrCl is <35, not recommended Reduces hip and spinal fracture risk by 50%	Hypocalcaemia, hypophosphataemia, abdominal pain, nausea, diarrhoea, acid regurgitation, esophagitis and bony pain Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min. Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; use caution

(continued)

Table 4.5 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Ibandronate (Boniva)	Bisphosphonate, inhibits resorption of bones Increases density of bones	Osteoporosis in postmenopausal women (treatment and prevention): 150 mg PO every month. Or 3 mg IV every 3 months If CrCl is <30, not recommended No efficacy in non-vertebral fractures	Upper respiratory infections, back pain, dyspepsia, esophagitis and bony pain Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min. Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; use caution
Risedronate (Actonel)	Bisphosphonate, inhibits resorption of bones Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis: 5 mg PO once daily, or 35 mg PO once weekly, or 150 mg PO once monthly If CrCl is <30, not recommended Reduces vertebral fracture risk by 41% and non-vertebral fracture risk by 39% over 3 years	Bony pain, diarrhoea, headache, abdominal pain, esophagitis and dysphagia Must be taken at early morning with plain water on empty stomach. Then must stay in upright position for 30 min Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Excretion into breast milk is unknown; avoid using
Zoledronic acid (Aclasta)	Bisphosphonate, inhibits resorption of bones Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis: 5 mg IV every year for treatment and every 2 years for prevention If CrCl is <30, not recommended Reduces hip fracture risk by 41%, spinal fracture risk by 71% and non-vertebral fracture risk by 25% over 3 years	Bony pain, diarrhoea, headache, abdominal pain, nausea, fever, fatigue and anaemia Ensure adequate use of calcium and vitamin D	Pregnancy category: D Lactation: Excretion into breast milk is unknown; avoid using

Table 4.5 (continued)

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Teriparatide (Forteo)	Recombinant parathyroid hormone stimulates osteoblasts Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men, glucocorticoid-induced osteoporosis: 20 mg SC once daily into thigh or abdominal wall Reduces spinal fracture risk by 65% and non-spinal fracture risk by 54%	Hypercalcaemia, bony pain, flulike illness, nausea and orthostatic hypotension Ensure adequate use of calcium and vitamin D	Pregnancy category: C Lactation: Safe
Raloxifene (Evista)	Selective oestrogen receptor modulator Increases density of bones	Osteoporosis in postmenopausal women: 60 mg PO once daily Reduces spinal fracture risk by 30–55%	Hot flashes, headache, flu syndrome, sinusitis, arthralgias and infection Increased risk of thrombosis and embolism. Thus, contraindicated in patients with history of thrombosis	Pregnancy category: X Lactation: Contraindicated
Denosumab (Prolia)	Monoclonal antibody, inhibits resorption of bones Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men: 60 mg SC every 6 months	Bony pain, hypercholesterolaemia, cystitis, upper respiratory infections, sciatica and hypocalcaemia Ensure adequate use of calcium and vitamin D	Pregnancy category: X Lactation: Excretion into breast milk is unknown; avoid using
Strontium ranelate	Musculoskeletal agent Increases density of bones	Osteoporosis (treatment and prevention), osteoporosis in men: 2 g/day dissolved in water, prior to bedtime, 2 h after eating (preferably) If CrCl is <30, not recommended	Diarrhoea, nausea, headache, dermatitis and eczema	Pregnancy category: NA Lactation: Excretion into breast milk is unknown; avoid using

4.8 Drugs Used in Crystal Arthropathy

4.8.1 Colchicine

It is a uricosuric agent that prevents activation, degranulation and migration of neutrophils associated with mediating some gout symptoms. It can be used for both acute flare and prophylaxis against recurrent attacks of gouty arthritis [38].

Common adverse effects of colchicine may include diarrhoea and abdominal cramping. It is

contraindicated in severe renal or hepatic impairment. Colchicine treatment may also benefit patients with acute episodes of pseudogout and arthritis due to other crystals.

4.8.2 Allopurinol

It is a xanthine oxidase inhibitor that inhibits its conversion to uric acid. It is considered as the first-line urate-lowering agent for the treatment of chronic gout. The dose of allopurinol should

Table 4.6 Drugs used in crystal arthropathy

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Colchicine	Uricosuric agent, prevents activation and migration of neutrophils	Acute gout flare: 1.2 mg PO at first sign of flare, then 0.6 mg PO 1 h later. Do not exceed 1.8 mg in 1-h period Gout prophylaxis: 0.6 mg PO once or twice daily. Do not exceed 1.2 mg/day	Gastrointestinal symptoms, fatigue and headache	Pregnancy category: C Lactation: Excreted into breast milk, use caution
Allopurinol	Xanthine oxidase inhibitor, inhibits its conversion to uric acid	Chronic gout: 100 mg/day initially, increase weekly to reach 200–300 mg/day. Do not exceed 600 mg/day in severe cases If CrCl is <40, 150 mg/day If CrCl is <20, 100 mg/day If CrCl is <10, 100 mg/2 days	Nausea, rash, vomiting, arthralgias and rarely Steven-Johnson syndrome	Pregnancy category: C Lactation: Excreted into breast milk, use caution
Febuxostat	Xanthine oxidase inhibitor, inhibits its conversion to uric acid	Chronic gout: Initial: 40 mg PO once daily. Maintenance: 40–80 mg PO once daily	Nausea, rash, vomiting, arthralgias and liver function abnormalities	Pregnancy category: C Lactation: Excretion into breast milk is unknown

be adjusted based on the stage of renal disease. Febuxostat is another urate-lowering agent that can be used if allopurinol is to be avoided [39]. Allopurinol decreases the metabolism of azathioprine.

Complete details about different drugs used in crystal arthropathy are shown in Table 4.6.

4.9 Symptom-Specific Drugs

Systemic rheumatic diseases are multi-system diseases that can affect different body organs. These disease cause symptoms that can be

either due to the immunopathologic changes or adverse effects from the DMARD therapy. Most of these rheumatic symptoms are effectively treated with different DMARDs. However, few other symptoms require additional specific drugs. For example, Raynaud's phenomenon, fatigue, generalized aches and pains and acid reflux are common symptoms that patients describe to their rheumatologists. Table 4.7 provides a list of common symptom-specific medications that rheumatologists prescribe during their daily clinical practice. Table 4.8 defines the pregnancy categories for pharmacological agents.

Table 4.7 Common symptom-specific drugs

Drug name	Mechanism of action	Indication and doses	Adverse effects and caution	Pregnancy and lactation
Dihydropyridine calcium channel blockers	Inhibit influx of extracellular calcium ions across myocardial and vascular smooth muscle cell membranes, resulting in vasodilation of main coronary and systemic arteries	Raynaud's phenomenon: Nifedipine: 30–120 mg (extended release) PO daily Amlodipine: 5–10 mg PO daily	Peripheral oedema, dizziness, flushing and headache	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Sildenafil	Inhibits phosphodiesterase-5, thus increasing cyclic guanosine monophosphate to allow smooth muscle relaxation and vasodilation	Raynaud's phenomenon: 5 or 20 mg PO 3 times daily	Dizziness, flushing, headache and epistaxis	Pregnancy category: B Lactation: Excretion into breast milk is unknown
Pilocarpine	Cholinergic parasympathomimetic with muscarinic action, increases secretion of exocrine glands	Xerostomia associated with Sjogren's syndrome: 5 mg PO up to 4 times daily	Sweating, headache, flushing, dizziness, nausea, urinary frequency and diaphoresis	Pregnancy category: C. Lactation: Excretion into breast milk is unknown.
Amitriptyline	Anticholinergic, serotonin and norepinephrine reuptake inhibitor.	Fibromyalgia: 10–50 mg PO at bedtime, dose can be escalated up to 200 mg daily.	Dizziness, headache and dry mouth	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Duloxetine	Serotonin and norepinephrine reuptake inhibitor	Fibromyalgia: 30 mg PO daily initially for 1 week, then increase to 60 mg daily	Dizziness, headache, dry mouth and somnolence	Pregnancy category: C Lactation: Excreted into breast milk, discontinue drug or refrain from nursing
Proton pump inhibitors	Bind to hydrogen-potassium-exchanging adenosine triphosphatase in gastric parietal cells, resulting in suppression of acid secretion	Heart burn or gastritis: Omeprazole: 20–40 mg PO daily Esomeprazole: 20–40 mg PO daily	Headache, flatulence, indigestion, nausea and abdominal pain	Pregnancy category: C Lactation: Excretion into breast milk is unknown, discontinue drug or refrain from nursing

Table 4.8 Pregnancy category definitions

Category	Definition
A	Generally acceptable. Controlled studies in pregnant women show no evidence of foetal risk
B	May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human done and showed no risk
C	Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done
D	Use in life-threatening emergencies when no safer drug is available. Positive evidence of human foetal risk
X	Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternative exists
NA	Information not available

Abbreviations

ACEIs	Angiotensin-converting enzyme inhibitors
ALT	Alanine amino transferase
Anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
BID	Two times a day
cAMP	Cyclic adenosine monophosphate
COX	Cyclooxygenase
CrCl	Creatinine clearance
DMARDs	Disease-modifying anti-rheumatic drugs
HBsAg	Hepatitis B surface antigen
IL	Interleukin
IM	Intramuscular
IV	Intravenous
MESNA	2-Mercaptoethanesulfonic acid
NSAIDs	Nonsteroidal anti-inflammatory drugs
PDE-4	Phosphodiesterase-4
PGHS	Prostaglandin G/H synthase
PGs	Prostaglandins
PO	Orally (by mouth)
PRN	As needed (pro re nata)

q6hrs	Every 6 hours
QID	Four times a day
RANKL	Receptor activator of nuclear factor kappa B ligand
SC	Subcutaneous
SLE	Systemic lupus erythematosus
STATs	Signal transducers and activators of transcription
TID	Three times a day
TNF	Tumour necrosis factor
TPMT	Thiopurine methyltransferase

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