The cytochrome P450s (CYPs) are members of a superfamily of oxidative enzymes, which represent the major system for the oxidative metabolism of therapeutic substances. Sequencing of the human genome has revealed 58 different human CYP genes, which encode various CYP isoenzymes. The most important enzyme for most dermatological drugs is CYP3A.

*Inducers* are drugs that increase the levels of CYP3A, leading to increased metabolism and decrease of effectiveness of other drugs; Rifampin is one example of drugs used in dermatology that are inducers.

*Inhibitors* block CYP3A and lead to decreased metabolism and increased effectiveness; examples of systemic dermatological medication include antifungals (Itraconazole, Ketoconazole) and antibiotics (Erythromycin, Clarithromycin).

*The substrate drugs* are primarily metabolized by CYP3A and are the most influenced; examples: immunosuppressive agents (Cyclosporine, Tacrolimus), macrolides (Erythromycin, Clarithromycin); some drugs are both inhibitors and substrates [1].

The cardiovascular toxicity of the medication used in current practice is important to be considered by any prescribing physician. Mladěnka et al. identified in their 2017 review of the cardiovascular toxicity of drugs and related agents several types of cardiovascular insults: disturbances in cardiac rhythm, functional and
structural heart impairment, arterial and venous thrombo-embolism, effects on blood pressure [2].

In the last decades more and more systemic agents are being used alone, or combined with topical therapy.

Some of the most frequently used classes of systemic drugs that are in the daily armamentarium of dermatologists, together with information on the mechanism of action, cardiovascular effects and interactions with cardiovascular drugs are shown in Annex (Table 22.1).

**Dapsone**

Dapsone is an aniline derivative; it combines both antimicrobial/antiprotozoal properties and anti-inflammatory effects resembling those of non-steroidal anti-inflammatory drugs. As an antimicrobial agent, dapsone is bacteriostatic in action [17]. Dapsone is a competitive antagonist of Para-AminoBenzoic Acid (PABA) interfering with normal synthesis of folic acid by bacteria.

Dapsone is effective in dermatoses with abnormal neutrophil accumulation, through many potential mechanisms. Dapsone interferes with neutrophil chemotactic migration and β2 integrin (CD11b/CD18)—mediated adherence of human neutrophils in vitro. Dapsone interferes with the activation or function of the G-protein that initiates the signal transduction cascade common to chemotactic stimuli. This inhibition suppresses neutrophil recruitment and local production of toxic respiratory and secretory products of neutrophils [18].

The well-established indications are leprosy and dermatitis herpetiformis. It is also indicated for linear IgA dermatosis, bullous lupus, erythema elevatum et diutinum as well as other autoimmune bullous dermatoses, vasculitis, neutrophilic dermatoses (Sweet syndrome, pyoderma gangrenosum, Behçet syndrome) and other dermatoses [133].

**Cardiovascular side effects:** hypersensitivity myocarditis has been associated with Dapsone at therapeutic doses [19] [20]. Dapsone-induced DRESS, with fever, maculo-papular eruptions that progresses to exfoliative dermatitis, cervical lymphadenopathy, transaminitis, and cardiac involvement has been described in just a few cases [20]. The cardiac involvement in DRESS syndrome is represented by hypersensitivity myocarditis that can occur in two forms: hypersensitivity myocarditis (also known as acute eosinophilic myocarditis) and acute necrotizing eosinophilic myocarditis. Hypersensitivity myocarditis is usually self-limited, with a good prognosis once the offending agent is discontinued and the hypersensitivity reaction is suppressed by immunotherapy. ECG evaluation often shows nonspecific ST segment or T-wave abnormalities, conduction delay, or sinus tachycardia. Acute necrotizing eosinophilic myocarditis is a much more severe form of hypersensitivity myocarditis that presents with chest pain, ST segment elevation, elevated cardiac enzymes, and normal coronary arteries. The prognosis is poor and the mortality rate associated with this type of myocarditis is greater than 50% [21].
**Antimalarial Agents**

Chloroquine (CQ) and hydroxy-chloroquine (HCQ) have immunomodulatory, anti-inflammatory, and antiproliferative properties; they alleviate UV-induced inflammation, inhibit thrombocyte aggregation, enhance glucose tolerance, and cause increased porphyrin excretion [40]. They act by inhibition of antigen processing and presentation, inhibition of cytokine release, inhibition of stimulation of toll-like receptors that participate in immune response. Antimalarials decrease the activity of natural killer cells, inhibit the activity of cytotoxic T lymphocytes, regulate apoptosis; they competitively inhibit anti-DNA antibodies and decrease prostaglandin and leukotriene levels and they block superoxide radicals [40].

Antimalarials are effective for the treatment of the specific skin lesions of cutaneous lupus erythematosus whether acute, subacute, or chronic. Off-label indications include photosensitivity dermatoses (porphyria cutanea tarda, polymorphous light eruption, solar urticaria, dermatomyositis), granulomatous dermatoses (sarcoidosis, granuloma annulare), lymphocytic infiltrates, panniculitis and other dermatoses [41].

**Cardiovascular side effects:** At normal dosages, CQ/HCQ have no negative effects on the heart. There are case reports, however, on conduction disorders, cardiomyopathy, and even death [40].

At the time of writing, several potential treatments for treating Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 were under investigation. Some candidate drugs may cause PR prolongation (e.g. lopinavir/ritonavir) and/or QT prolongation (chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, and others). The expectedly short treatment duration for COVID-19 (5−10 days) mitigates the drugs’ cardiac risks to an extent [134].

Antimalarials induced cardiomyopathy is a rare, probably under-recognized, complication of prolonged treatment with antimalarials. It presents as hypertrophic, restrictive cardiomyopathy with or without conduction abnormalities [42].

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**Retinoids**

Retinoids are small-molecule hormones that exert their effects on target cells by binding and activating nuclear retinoid receptors [43–45]. For several decades, systemic retinoids have been used to treat psoriasis and disorders of keratinization [135]. FDA approved systemic retinoid use in three dermatoses: Acitretin is indicated for psoriasis, Isotretinoin for acne vulgaris and Bexarotene for selected cases of mycosis fungoides. Other indications for dermatologic disorders include: follicular disorders (acne-related conditions, hidradenitis suppurativa, dissecting cellulitis of the scalp), disorders of keratinization (Darier’s disease, pityriasis rubra pilaris, ichthyosis, keratodermas), rosacea, chemoprevention of malignancies (syndromes with increased risk of cutaneous malignancy, xeroderma pigmentosum, Kaposi’s sarcoma) and other inflammatory dermatoses [43].

**Cardiovascular side effects:** There are limited reports on the adverse cardiac effects of isotretinoin in literature. According to case reports, systemic isotretinoin
therapy can cause cardiac side effects, like atrial tachycardia, congenital heart disease, cardiac remodeling and sinus tachycardia [46, 47]. Premature ventricular contractions were also reported to be associated with isotretinoin use [47, 48].

Regarding isotretinoin it is stipulated that a major mechanism of teratogenesis is a deleterious effect on cephalic neural-crest cell activity that results in craniofacial, cardiac, thymic malformations. The cardiac malformations included conotruncal heart defects and aortic-arch abnormalities [136].

The most common laboratory abnormality observed in patients taking systemic retinoids is elevation in serum lipids. Patients with obesity, diabetes or excessive alcohol intake are at increased risk. Triglycerides levels are affected to a greater degree than cholesterol levels. The magnitude of this effect, in terms of both percentage of patients affected and severity of elevation, is much greater with bexarotene than with other systemic retinoids [43].

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**Corticosteroids**

Glucocorticoids are primary stress hormones that regulate a variety of physiological processes and are essential for life. Systemic glucocorticoids are one of the most important dermatological medication due to their anti-inflammatory, immunosuppressive and antiproliferative role.

The actions of glucocorticoids are predominantly mediated through the classic glucocorticoid receptor.

Oral administration of steroids is particularly useful in acute hypersensitivity diseases, connective tissue diseases, immunological blistering diseases, and the commoner dermatoses when they are very severe and widespread [49].

Dermatological indications include: severe dermatitis, erythrodermas, bullous dermatoses, vasculitis (cutaneous and systemic), collagen vascular diseases, neutrophilic dermatoses and others (sarcoidosis, panniculitis, urticaria) [50].

**Cardiovascular side effects:** the cardiovascular effects of systemic corticosteroids are vasoconstriction, sodium retention and increases renin levels. These factors will lead to hypertension; the fluid retention can determine or exacerbate heart failure [51].

Another major adverse effect of glucocorticoids on the cardiovascular system is dyslipidemia. Glucocorticoids may predispose treated patients to coronary artery disease if high doses and prolonged courses are used. Accordingly, they should be employed carefully in patients with other risk factors for cardiovascular disease [52].

Atrial fibrillation and cardiac sudden death have been reported as risks of pulse iv corticosteroids. To date there has been no study prospectively monitoring for cardiac effects in dermatologic patients. White et al. recommend that monitoring of dermatologic patients during pulse iv corticosteroids should be titrated according to the individual patient’s active and past medical problems, concomitant drug therapy, and any previous reactions to pulse iv corticosteroids. Continuous cardiac monitoring is clearly indicated for patients with cardiac or renal disease who receive systemic corticosteroids [53].
Immunosuppressive Agents

*Azathioprine* is an immunosuppressive agent that acts as an antagonist of purine metabolism, resulting in the inhibition of DNA, RNA, and protein synthesis. It is an approved agent for the prevention of organ transplant rejection and severe rheumatoid arthritis. In dermatology it is indicated for autoimmune bullous disorders, lupus erythematosus, dermatomyositis and polymyositis and other inflammatory skin diseases such as eczema, psoriasis and vasculitis [54].

*Interactions with cardiovascular drugs* The use of angiotensin-converting enzyme inhibitors to control hypertension in patients on azathioprine has been reported to induce anemia and severe leukopenia; azathioprine may inhibit the anticoagulant effect of warfarin [54–56].

*Cyclophosphamide* is a precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that is metabolized primarily in the liver to aldophosphamide that will be converted to active metabolites.

Its specific mechanism used in treating autoimmune diseases is not well understood, but has been postulated to include apoptosis, decreased immunoglobulin G production due to B-cell suppression and decreased production of adhesion molecules and cytokines [57]. Dermatologic indications: mycosis fungoides, systemic vasculitis, bullous dermatoses, neutrophilic dermatoses, autoimmune connective tissue disease, neoplasms.

*Cardiovascular side effects:* Cardiotoxicity is an uncommon complication in high-dose chemotherapy regimens. The cardiovascular side effects can present as a syndrome of congestive heart failure, myocarditis or both, and can be fatal [57].

The precise mechanism of cyclophosphamide cardiotoxicity is not known, but it is thought that it may cause endothelial injury with outpouring of toxic metabolites that result in damage to the cardiomyocytes [58].

Clinical manifestations of cardiotoxicity range from asymptomatic pericardial effusions to heart failure and myopericarditis. The risk of cardiotoxicity appears to be dose related and occurs within 1 to 10 days after the administration of the first dose of cyclophosphamide [59, 60].

*Cyclosporine* is a potent immunomodulatory agent that blocks the transcription of cytokine genes in activated T cells; in particular, cyclosporine inhibits the transcription of interleukin 2. Although cyclosporine's major actions are on T cells, there is some evidence that it produces direct effects on other cell types [137, 138]. While indicated only for the treatment of moderate to severe psoriasis, cyclosporine has also been used as an off-label drug for the treatment of various inflammatory skin conditions, including atopic dermatitis, blistering disorders, connective tissue diseases, neutrophilic dermatosis, neoplastic disorders, alopecia and granulomatous dermatoses [62, 139, 140, 141].

*Cardiovascular side effects:* Hypertension is the most important cardiovascular side effect. The risk of developing hypertension increases with the dose and duration of therapy. Potential mechanisms for cyclosporine-induced hypertension are: activation of neurohormonal vasoconstrictors, alterations in vascular reactivity, renal tubular reabsorption of sodium in association with volume expansion, alterations in regulation of intracellular calcium ions, excess production of vasoconstrictors (prostaglandins, thromboxane, endothelin), decreased production of vasodilatory prostaglandins, stimulation of the renin-angiotensin system [61].
Methotrexate competitively and reversibly binds to dihydrofolate reductase preventing the conversion of dihydrofolate to tetrahydrofolate. Methotrexate is indicated in proliferative dermatoses, immuno-bullous dermatoses, autoimmune connective tissue diseases, vasculitis and neutrophilic dermatoses [67].

**Cardiovascular side effect:** Methotrexate may have a cardio-protective effect for patients with early onset rheumatoid arthritis [142], as well as for patients with psoriasis. Meta-analysis data from studies that involved patients with psoriasis showed that patients treated with methotrexate had fewer cardiovascular incidents compared to patients not treated with methotrexate [63, 64].

There is some in vitro and in vivo proof that methotrexate might have a combination of anti-inflammatory, blood pressure lowering, and vasculoprotective effects. Some mechanisms were proposed for the potential antiatherosclerotic, blood pressure lowering, and vasculoprotective effects of methotrexate, particularly cytokine modulation, adenosine accumulation, and activation of 5′ adenosine monophosphate-activated protein kinase [65]. However, Ridker et al. concluded in a recent publication that among patients with stable atherosclerosis, low-dose methotrexate (at a target dose of 15 to 20 mg weekly) did not reduce levels of interleukin-1β, interleukin-6, or C-reactive protein and did not result in fewer cardiovascular events than placebo [66].

**Interactions with cardiovascular drugs:** Methotrexate may decrease serum levels of inotropic cardiac drugs and of digoxin [67].

**Mycophenolate mofetil** (MMF) is a lymphocyte selective immunosuppressive agent that inhibits de novo purine synthesis via its active metabolite, mycophenolic acid. Mycophenolic acid depletes guanosine nucleotides by noncompetitively, selectively, and reversibly inhibiting inosine monophosphate dehydrogenase. Off-label dermatological indications of MMF include inflammatory skin conditions, psoriasis, autoimmune blistering disorders, connective tissue disorders and neutrophilic dermatosis (e.g. refractory pyoderma gangrenosum) [143, 144].

**Cardiovascular side effects:** MMF is very well tolerated. The most common side effects are gastrointestinal but there are reports about MMF improving hypertension [68, 69].

**Antiandrogens**

**Spironolactone** is an aldosterone antagonist with weak antiandrogen effect; by blocking the androgen receptor spironolactone inhibits the effects of androgens in the body. Off label dermatological indications are: hirsutism, acne, androgenetic alopecia and hidradenitis suppurativa. The main cardiovascular side effect is venous thrombosis [70].

**Cyproterone acetate** is available in European countries and is used off label for hirsutism. Cyproterone acetate, as one of the components of the combined oral contraceptive (COC) use has been associated with venous thrombosis (VT) (i.e., deep venous thrombosis and pulmonary embolism). Risk of venous thrombosis for combined oral contraceptives with 30-35 μg ethinylestradiol and gestodene, desogestrel, cyproterone acetate and drospirenone were similar [70].

A case of cerebral vascular accident associated with cyproterone acetate–ethinyl estradiol has been reported [71], as well as cases of increased plasma apolipoprotein A-I and HDL-phospholipid levels in women with polycystic ovary syndrome treated with cyproterone acetate [72].
Biologic Therapeutics

Biologic therapeutics are used in several chronic dermatoses (e.g. psoriasis, atopic dermatitis) and other skin conditions (e.g. hydradenitis suppurativa). Various cardiovascular adverse events have been associated with biological therapies. Heart failure is one of the most important adverse reactions reported in the medical literature. Arrhythmias were also reported in patients receiving infliximab. Data regarding the effect of biological therapies on the vascular system is contradictory. Some authors considered that TNF blockers etanercept and adalimumab might have a favorable effect on the lipid profile and reduce the rate of cardiovascular events while others consider that long-time treatment with infliximab could be pro-therogenic [145].

Psoriasis, Crohn’s colitis, rheumatoid arthritis, and a variety of spondyloarthropathies benefit from using the biological agents [78, 79].

Monoclonal antibodies (e.g. Adalimumab, Avelumab, Brodalumab, Dupilumab, Ixekizumab, Nivolumab) are molecules that alter the normal cellular immune response, pathways of cell signaling, activation and cytokine production [78–80].

Anti-TNFα agents (e.g. Infliximab, Adalimumab) reduce inflammation and can stop inflammatory disease progression.

Cardiovascular side effects: Although TNF has been shown to have negative inotropic effects on the myocardium and may further contribute to left ventricular dysfunction and cardiomyopathy, the anti TNFα agents etanercept and infliximab did not show anticipated protective cardiovascular effect in clinical trials. While no benefit was seen, several patients did experience adverse cardiac outcomes and worsening of congestive cardiac failure with TNFα blockers are reported to occur [78–81, 54].

Rituximab is an anti-CD20 monoclonal antibody with considerable potential in dermatology due to an increase in off-label indications [146].

Cardiovascular side effects: Fatal infusion reactions include myocardial infarction, ventricular fibrillation, and cardiogenic shock [83]. In patients with a history of cardiorespiratory disease can cause exacerbations of angina, arrhythmias and heart failure [84].

Cardiovascular toxicity in the form of cardiac dysrhythmias has been reported in 8% of patients treated with rituximab. These include monomorphic ventricular tachycardia, supraventricular tachycardia, trigeminy and irregular pulse, and an isolated case of a fatal infusion secondary to myocardial infarction [84].

Ustekinumab is a human monoclonal antibody that binds to the p40 subunit common to both interleukin (IL)-12 and IL-23 [147].

Cardiovascular side effects: the totality of the available clinical data suggests neither a detrimental nor a beneficial effect of ustekinumab on serious CV events [86]. Other reports accrue exacerbation or new onset of congestive heart failure [87].

Omalizumab is a recombinant humanized monoclonal antibody targeting the high-affinity Fc receptor of IgE, registered for the treatment of chronic spontaneous urticaria and severe allergic asthma [148]; off label it has been used in atopic dermatitis [149].

Cardiovascular side effects: Omalizumab has been linked to higher incidence rate of cardiovascular or cerebrovascular events such as transient ischemic attack, myocardial infarction, pulmonary hypertension, pulmonary embolism or venous thrombosis and unstable angina [89].
**Dupilumab** is an interleukin 4 (IL-4) receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit used in atopic dermatitis [150].

*Cardiovascular side effects:* Cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes) were reported in clinical trials as associated with a small percentage of patients receiving dupilumab [92].

Chronic inflammatory diseases are characterized by an increased cardiovascular risk. IL-17A has a defined role in both aspects [151].

**Secukinumab** is a fully human anti-IL-17A monoclonal antibody, ixekizumab is a humanized IgG4 monoclonal antibody that neutralizes IL-17 and brodalumab is a human, anti-IL17RA monoclonal antibody which blocks the activity of IL17RA, 17A/F and 17E.

Several pre-clinical data indicate that IL-17 inhibitors may be effective in multiple mucocutaneous disorders beyond psoriasis. The possible targets for IL-17 inhibitors include oral lichen planus, alopecia areata, pyoderma gangrenosum, palmo-plantar pustulosis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, pemphigus vulgaris, pemphigoid, dermatitis herpetiformis, atopic dermatitis and chronic periodontitis [96].

*Cardiovascular side effects:* It is too early to conclude if IL-17 targeting will show protective CV effects in patients with chronic inflammatory diseases with Ixekizumab having a neutral impact on cardiovascular-related parameters in patients with psoriasis [95].

Still, from the clinical trials come reports of cardiac death due to cardiac arrest and cardiomyopathy linked to brodalumab [96].

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**Fusion Antibody Proteins**

Fusion antibody proteins (e.g. Etanercept, Alefacept, Abatacept, Onercept), also known as chimeric proteins, are proteins which are created by the fusion of the receptor domain of a human protein with the constant region of human IgG.

*Cardiovascular side effects:* etanercept can cause congestive heart failure [98] as well as silent ischaemic heart disease and diastolic dysfunction.

Less data exists on the association of anakinra, abatacept with cardiovascular adverse effects [80].

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**Recombinant Human Cytokines and Growth Factors**

Recombinant Human Cytokines and Growth Factors can be grouped as follows:

(a) Interferons: Interferon α (IFNα), Interferon γ (IFNγ)

Interferon therapy for HCV infection is cardiac safe in patients who have structurally normal heart. Female patients have a propensity of adverse events like severe diastolic dysfunction and mild pericardial effusion [105].

(b) Granulocyte macrophage colony stimulating factor (GM-CSF)
GM-CSF may have multiple direct and indirect beneficial cardiovascular effects including neovascularization of ischemic myocardium and reducing the extent of myocardial damage after infarction [106].

(c) Platelet derived growth factor (PDGF)

PDGFs drive pathological mesenchymal responses in vascular disorders such as atherosclerosis, restenosis, pulmonary hypertension and cardiac fibrosis [107].

**Intravenous Immunoglobulin**

Immunoglobulin infusion adverse reactions include arrhythmia occurring during or after (supraventricular tachycardia and bradycardia), stroke, myocardial infarction, and pulmonary embolism [112].

**Immune Checkpoint Inhibitors: Anti PD-1**

The development of immune checkpoint inhibitors has revolutionized the treatment of melanoma. However, immunotherapy is not without side effects. Cardiotoxicity is an under-recognized and potentially life-threatening complication of targeted immune checkpoint therapy [152].

(a) Ipilimumab. The first case of cardiotoxicity induced by ipilimumab was reported in 2013, which presented as myocardial fibrosis within a retrospective study among 752 ipilimumab-treated patients for melanoma [117]. Other cardiac reported side effects induced by ipilimumab: cardiac arrest [118], myocarditis, myocardial fibrosis [117] congestive heart failure [119], left ventricular dysfunction, reduction in ejection fraction, paroxysmal atrial fibrillation, ischemia [120], pericarditis, pericardial effusion [121] and biventricular failure [122].

The overall incidence of cardiac adverse events in the published literature was rare, occurring in approximately 1% of treated cases. However, the cardiovascular-specific mortality rate was 42% in patients who developed cardiotoxicity while on the drug [118, 153].

(b) Nivolumab and Ipilimumab. Myocarditis occurred with greater severity in patients who received combination therapy of ipilimumab and nivolumab [153]. They can determine as well immune-induced myocarditis and cardiomyopathy [119] or lymphocytic myocarditis [125].

(c) Pembrolizumab. In the published pembrolizumab monotherapy cohorts, the rates of adverse cardiac events were higher, occurring in approximately 1.2% of treated patients.

The published articles revealed during the treatment with pembrolizumab autoimmune cardiomyopathy (grade 3 CTCAE) and myocarditis [128], ventricular arrhythmia, left ventricular systolic dysfunction, myocarditis with cardiomyopathy, cardiac atrial flutter, hypertension, sinus tachycardia, stable angina pectoris [129], congestive cardiac failure [127], myocardial infarction [130, 131].

**Annex**
| Class                  | Drug          | Mechanism of action                                                                 | Cardiovascular contraindications/side effects | Interactions with cardiovascular drugs                                                                 |
|-----------------------|---------------|-------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------|
| **Antiviral Agents**  |               |                                                                                     |                                               |                                                                                                           |
|                       | Acyclovir     | Blocks viral DNA polymerase [3,4]                                                   | N/A                                           | Antiviral agents may increase the serum levels and potential toxicity of inotropic agents (digoxin) [4] |
|                       | Valacyclovir  | Prodrug of acyclovir; converted in first pass through the gastrointestinal tract and liver to acyclovir [4] |                                               |                                                                                                           |
|                       | Famciclovir   | The oral prodrug of penciclovir [3,4]                                               |                                               |                                                                                                           |
|                       | Brivudine     | Blocks viral DNA synthesis by interacting with deoxythymidine kinase and DNA polymerase [5,6] |                                               |                                                                                                           |
| **Antibacterial Agents** |               |                                                                                     |                                               |                                                                                                           |
| **β-lactam antibacterial agents** | Penicillins | The β-lactam antibacterial agents bind to penicillin-binding-proteins in the bacterial cell membrane and | Vasospasm seen with parenteral or intramuscular formulations | Penicillins may elevate serum levels or potentiate the therapeutic effects of anticoagulants and may prolong prothrombin times [15] |
| Class               | Example Drugs                                      | Mechanism of Action                                                                 | Cardiovascular Side Effects                                                                 |
|---------------------|----------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| **Cephalosporins**  |                                                    | bacterial cell wall peptidoglycan synthesis.                                          | Cefotetan and cefoperazone (containing N-methylthiotetrazole ring) may determine hypoprothrombinemia [16] |
| **Macrolides**      | Erythromycin, Azithromycin, Clarithromycin         | Bind reversibly to the bacterial ribosome, inhibiting RNA-dependent protein synthesis; they also possess anti-inflammatory effect [7] | Cardiac conduction abnormalities; in utero exposure to erythromycin was linked by some authors to cardiovascular malformation [11], while others dispute this association [12] Erythromycin inhibits CYP leading to decreased metabolic clearance of digoxin and warfarin Erythromycin and clarithromycin may alter the metabolism of drugs known to influence cardiac conduction ex terfenadine and their combination is contraindicated [7] |
| **Fluoroquinolones**| Ciprofloxacin, Gatifloxacin, Gemifloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin | Interfere with bacterial DNA replication by inhibition of DNA gyrase and topoisomerase IV [8] Gatifloxacin and moxifloxacin are associated with QTc interval prolongation [8] Gatifloxacin, moxifloxacin, and levofloxacin had a higher risk of serious arrhythmias [13] Fluoroquinolones increase serum levels for antiarrhythmic agents (ex. mexiletine); in combination with warfarin may increase the risk of hemorrhage [8] Gatifloxacin and moxifloxacin increase the risk of QT interval prolongation in combination with antiarrhythmic agents (ex amiodarone, bepridil, disopyra mide, dofetilide, ibutilide, procainamide, quinidine) and beta blockers (especially sotalol) [8] | |
| **Tetracyclines**   | Tetracycline, Doxycycline, Minocycline              | Are bacteriostatic and inhibit bacterial protein synthesis by binding to the 30S subunit of the bacterial ribosome. Tetracyclines also have anti-inflammatory and anti-collagenolytic effects [9] | Protective effect on the murine myocardium [14] Tetracyclines may increase the serum levels of oral anticoagulants [9] |

(continued)
| **Rifamycins** | Rifampin | Rifamycins inhibit RNA synthesis by inhibiting DNA-dependent RNA polymerase [10] | Rifamycins decrease the drug level of cardiovascular drugs as: digoxin, mexiletine, propafenone, quinidine, warfarin (risk of thrombosis), carvedilol, all calcium channel blockers [10] |
| --- | --- | --- | --- |
| | Rifabutin | | |

**Dapsone**

| | Competitive antagonist of PABA interfering with normal synthesis of folic acid by bacteria; antineutrophil action [17, 18] | Contraindications: severe cardiovascular disease Side effects: may determine hypersensitivity myocarditis [19,20] Dapsone-induced DRESS [20,21] | |

**Antifungal Agents**

| | Oral antifungals interfere with the enzymes involved in producing ergosterol, a key component of fungal cell walls [22] | | |
| --- | --- | --- | --- |
| Griseofulvin | Is incorporated into keratin; it interferes with microtubule formation [23] | Impairs action of coumarin antiarrhythmic drugs and calcium channel blockers [22] | |

**Allylamines**

| | Inhibits sterol biosynthesis by blocking squalene peroxidase causing accumulation of squalene and cell death [24, 25] | Impairs action of coumarin; enhances the effect of antiarrhythmic drugs and beta blockers [22] | |
| Terbinafine | | | |

**Azoles**

| | Ketoconazol | Ketokonazol use has been limited due to serious liver damage and harmful interactions [28, 29] | |

Ketoconazol |
| **Triazoles** | Itraconazole, fluconazole: | Itraconazol, fluconazol: QT interval prolongation torsades de pointes risk of sudden death [30] Itraconazol: cardiac contractility reduction, dilated cardiomyopathy in animal models [31]; hypertension premature ventricular contractions, ventricular fibrillation, heart failure [32, 33] | As inhibitors of CYP450 enzymes, triazoles can impair metabolism of coadministered drugs, increasing the risk of toxicity [26] Itraconazole and fluconazole can enhance coumarin effect and the risk of hemorrhagic complications Enhance the effect of antiarrhythmic drugs and calcium channel blockers. Coadministration of azole drugs with cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol is contraindicated. These combinations may cause severe cardiac events including ventricular tachycardia, torsades de pointes, cardiac arrest and/or sudden death [22] |
| — | Triazoles impair synthesis of ergosterol by inhibiting C14-sterol demethylase [26, 27] | |

| **Antihistamins** | Block the action of histamine by competing for receptor sites [34] | |

| **Sedating H1** | Diphenhydramine Clemastine Tripelennamine Hydroxyzine Chlorpheneramine Promethazine Cyproheptadine | Dose-related sinus tachycardia, reflex tachycardia supraventricular arrhythmias, dose related prolongation of the QT interval, ventricular arrhythmias [35] | H1 antihistamins may enhance CYP 2D6 substrates as antiarrhythmic agents and beta blockers [36] |
| Ethanolamine Ethylenediamine Piperazine Alkylamine Phenothiazine Piperidine | |

| **Non Sedating H1** | Azelastine Cetirizine Levocetirizine Ebastine Fexofenadine Loratadine Desloratadine | Poorly lipophilic; do not cross the blood-brain barrier; highly selective action; little or no anticholinergic activity [36] | Terfenadine: life threatening cardiac arrhythmias (no longer available) [36] Fexofenadine- no effect on QTc interval [37] Loratadine: no clinical effect upon the potassium |
| — | — | |

(continued)
| Table 22.1 (continued) |
|------------------------|
| **Mizolastine** | **channels without QT modification [38]** | **Tricyclic antidepressant** |
| Doxepin | Doxepin is a psychotropic agent with tricyclic antidepressant and anxiolytic properties | Dose-related CV adverse effects: hypotension, hypertension, tachycardia, palpitations [39] | Metabolized by CYP2D6; quinidine may increase risk of QTc prolongation. Antiarrhythmic agents (CYP 2C9 inhibition) and antiplatelet drugs (CYP 2C19) may increase serum levels and potential toxicity of doxepin [39] |
| **Other antiallergic agents** | **Cromolyn** | **Ketotifen** | **Rupatadine** |
| Mast cell stabilizer | H1 receptor antagonist and mast cell stabilizer | Dual histamine H1 receptor and platelet activating factor receptor antagonist[34] |  |
| **Antimalarials** | **Chloroquine** | **Hydroxychloroquine** | **Quinacrine** |
| Antimalarials stabilize membranes; downregulate expression of MHC molecules; interact with the complement system, inhibit prostaglandin synthesis [40, 41] |  |  | EKG abnormalities: depression of T wave, hypotension, cardiomyopathy [40-42] | Increase levels of digoxin and antiarrhythmic agents as propafenone [41] |
| **Retinoids** | **Tretinoin** | **Isotretinoin** | **Etretinate** | **Acitretin** | **Bexarotene** |
| Modulate the differentiation and keratinization of keratinocytes, alter fibroblast activity and modulate T-cell response [43-45] |  |  |  |  | Atrial tachycardia, congenital heart disease, cardiac remodeling, sinus tachycardia [46, 47], premature ventricular contractions [47, 48], increased lipid blood levels [43] |
| **Corticosteroids** | Hydrocortisone  
Prednisone  
Prednisolone  
Methylprednisolone  
Triamcinolone  
Dexamethasone | Immunosuppressive and anti-inflammatory effects | Hypertension  
Heart failure  
Coronary artery disease  
[49-52]  
For pulse iv:  
Cardiac dysrhythmias  
Risk of sudden death [53] | Increase renal clearance of aspirin  
Hypokalemia may lead to digitalis toxicity  
Enhances/impairs warfarin  
With other QT „prolongers“ (antiarrhythmic agents, macrolides, fluoroquinolones) may increase the risk of QT prolongation and torsades de pointes [49, 52] |
| **Immunosuppressive agents** | Azathioprine | Purine antagonist that interferes with NK, T  
and B cells [54] | Angiotensin-converting enzyme inhibitors may increase the risk of leukopenia and anemia [54, 55]  
Azathioprine may decrease the anticoagulant effect of warfarin [56] |
| | Cyclophosphamide | Alkylating agent, blocks DNA and RNA | Cardiotoxicity  
Congestive heart failure, myocarditis [57-59]  
Reduces absorption of digoxin  
Increases the anticoagulant effect of warfarin; may decrease the Gl absorption of digoxin [60] |
| | Cyclosporine | Inhibits helper T-cell function by blocking IL-2 function; also blocks the release of other lymphokines | Hypertension [61]  
Amiodarone increases cyclosporine levels  
Diltiazem and verapamil increase cyclosporine levels  
Cyclosporine increases the levels of digitalis [62] |
| | Methotrexate | Folic acid antagonist | Protective effect  
(Antiatherosclerotic, lowers blood pressure,  
vasculoprotective effect) [63-65]. Did not reduce levels of interleukin-1, interleukin-6, or C-reactive protein and did not result in fewer cardiovascular events than placebo[66]  
May decrease serum levels of inotropic cardiac drugs and of digoxin [67] |
| | Mycophenolate mofetil | Inhibits lymphocytic inosine monophosphate dehydrogenase; influences mast cell | Improves hypertension [68, 69] |
| **Antiandrogens** | Spironolactone | Aldosterone antagonist | Spironolactone together with angiotensin-converting enzyme inhibitors may decrease aldosterone and increase the risk of hyperkalemia. May give falsely elevated serum digoxin levels; enhances digoxin. [73, 74] |
|------------------|-----------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Cyproterone acetate | Progestin with antiandrogenic properties | Venous thrombosis [70] Cerebral vascular accident [71] Increased plasma apolipoprotein A-I and HDL -phospholipid levels in women with polycystic ovary syndrome [72] | Inhibitors and inducers of the cytochrome P450 enzyme CYP3A4 (ex: Amlodipine, Clopidogrel, Disopyramide, Lovastatin, Quinidine) may interact with Cyproterone acetate [74] |
| **Colchicine** | Inhibits microtubular system, interfering with cell division, migration, other neutrophil functions, collagen synthesis and deposition of amyloid [75] | May have cardiovascular benefits [76] | Colchicine is a substrate of Cytochrome P450 3A4 (CYP3A4) and concentrations may be increased by drugs that are inhibitors such as diltiazem, verapamil [77] |
| **Biologic therapeutics** | | | |
| **Monoclonal antibodies** | Anti- TNFα: Infliximab, Adalimumab, Certolizumab, Golimumab | Molecules that alter the normal cellular immune response, pathways of cell signaling, activation | Negative inotropic effects worsening of congestive cardiac failure [78-81] | It is worth stressing that TNF inhibitors very rarely cause drug interactions [82] |
| · Anti-CD20: Rituximab | The antibody labels B lymphocytes, which have the CD20 cell marker. These cells are then killed by 1 of 3 mechanisms: antibody-dependent cytotoxicity, complement-dependent cytotoxicity, or stimulation of apoptosis [83]. | Fatal infusion reactions include myocardial infarction, ventricular fibrillation, and cardiogenic shock [83]. In patients with a history of cardiorespiratory disease can cause exacerbations of angina, arrhythmias and heart failure [84]. | Clinically important, potentially hazardous interaction with Benazepril, Captopril, Clevidipine, Enalapril, Fosinopril, Irbesartan, Lisinopril, Omesartan, Quinapril, Ramipril [85] |
| | · Anti -IL-12 and anti -IL-23 monoclonal antibody: Ustekinumab | Binds with specificity to the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines. | Neither a detrimental nor a beneficial effect [86] Exacerbation or new onset of congestive heart failure [87] |
| · Anti-IgE: Omalizumab | Binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. | Unstable angina Myocardial infarction Venous thrombosis Pulmonary embolism [89] | Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions [90]. None noted [91]. |
| · Anti IL-4: Dupilumab | Inhibits signaling of IL-4 and IL-13, type 2 cytokines. | Cardiovascular deaths, non-fatal myocardial infarctions [92] | Dupilumab is not anticipated to directly interact with cytochrome P450 enzymes, thus no typical drug-drug interactions of dupilumab with other drugs via are expected [93]. |
| · Anti IL 17-A: Secukinumab/Ixekizumab | Interleukin-17A inhibitor | too early to conclude if IL -17 targeting will show protective CV effects in patients with chronic inflammatory diseases [94] Ixekizumab -neutral impact [95] | Drug interaction studies have not been conducted for secukinumab. The product labeling cautions that change in the metabolism of CYP -450 substrates, particularly those with a narrow therapeutic index, may be altered during initiation or discontinuation of secukinumab therapy [97]. |

(continued)
Table 22.1 (continued)

| Fusion antibody proteins | Brodalumab was linked to cardiac arrest and cardiomyopathy [96] |
|--------------------------|---------------------------------------------------------------|
| Etanercept, Alefacept, Abatacept, | Etanercept: TNF inhibitor  
Alefacept inhibits the activation of CD4+ and CD8+ T cells  
Abatacept prevents antigen-presenting cells from delivering the co-stimulatory signal.  
Silent ischemic diastolic dysfunction [98] |
| Absence of a pharmacokinetic interaction between Etanercept and Warfarin [94] or Digoxin [99].  
Alefacept may decrease the blood levels and effects of amiodarone, amlodipine, atorvastatin, felodipine, flecainide, lovastatin, nicardipine, nifedipine, procainamide, quinidine, warfarin [100].  
Concurrent therapy with Abatacept and TNF antagonists is not recommended (increased risk of serious infections) [101].  
Salicylates may be used during treatment with abatacept [102]. |
| Recombinant human cytokines and growth factors | |
| a) Interferons  
Interferon α (IFNα)  
Interferon γ (IFNγ) | Interferon alpha binds to interferon receptors which, upon dimerization, activate two Jak (Janus kinase) and Tyk2).  
Acts by stimulating stem cells to produce granulocytes, monocytes and macrophages [103] |
| b) Granulocyte macrophage colony stimulating factor (GM-CSF) | |
| c) Platelet derived growth factor (PDGF) | |
| **Intravenous immunoglobulin** |
|--------------------------------|
| PDGF is a dimeric glycoprotein which regulates and promotes granulation tissue formation, re-epithelialisation and wound angiogenesis [104]. |
| Atherosclerosis, restenosis, pulmonary hypertension and cardiac fibrosis [107]. |
| Arrhythmia (supraventricular tachycardia and bradycardia) occurring during or after immunoglobulin infusion Stroke, myocardial infarction, pulmonary embolism [112]. |
| Ig IV with other drugs and intravenous solutions have not been evaluated. It is recommended to be administered separately from other drugs or medications which the patient may be receiving [113]. |

| **Immune checkpoint inhibitors (anti-PD1)** |
|---------------------------------------------|
| Ipilimumab (cytotoxic T-lymphocyte antigen-4=CTLA -4) |
| The CTLA -4 is a cell surface molecule that regulates the adaptative immune response. The binding between CTLA -4 and B7 molecules on the antigen presenting cells, interrupts the stimulatory signal which in order blunts T-cell proliferation response [114]. Produce an exacerbated autoimmune [115]. |
| Myocarditis, myocardial fibrosis [117] Cardiac arrest [118] Congestive heart failure [119] Left ventricular dysfunction, reduction in ejection fraction, paroxysmal atrial fibrillation, ischemia [120] Pericarditis, pericardial effusion [121] Biventricular failure [122]. |
| Clinical pharmacology studies were not performed to evaluate the metabolism and the metabolic pathways of ipilimumab in humans, or to determine the potential for any drug-drug interactions of ipilimumab with other molecules. Ipilimumab is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes [123]. |

(continued)
### Table 22.1 (continued)

| Drug                          | Mechanism                                                                 | Side Effects                                                                 | Additional Information |
|-------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------|
| Nivolumab (CTLA-4 + PD-1 Inhibitor) | Block the activity of CTLA-4, thereby sustaining a potent T-cell response against tumor cells [116]. | Myocarditis [125] Immune-induced myocarditis and cardiomyopathy [119] Lymphocytic myocarditis [125] | No formal pharmacokinetic drug-drug interaction studies have been conducted with Nivolumab [126] |
| Pembrolizumab (PD-1 Inhibitor) | Nivolumab blocks the immune checkpoint PD-1. This mechanism is related to the reduction of the inhibitory signaling and to restore the patient's natural tumor-specific T-cell immune response [124] | Autoimmune cardiomyopathy (grade 3 CTCAE) and myocarditis [128] Ventricular arrhythmia, left ventricular systolic dysfunction, myocarditis with cardiomyopathy, cardiac atrial flutter, hypertension, sinus tachycardia, stable angina pectoris [129] Congestive cardiac failure [127] Myocardial infarction [130, 131] | No non-clinical or clinical dedicated pharmacodynamic drug-drug interactions studies with Pembrolizumab have been conducted [132]. |
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