CARDIOVASCULAR SIDE EFFECTS OF DRUGS USED FOR TREATMENT OF AUTOIMMUNE DISEASES

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Treatment of autoimmune diseases and cardiovascular system

- In spite of the unfavorable influence of autoimmune diseases, AD treatment has also a significant impact on the CV system.
- The pharmaceutical treatment of autoimmune diseases takes a toll on the CV system, creating a broad array of side effects.

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- The most common drugs used in AD pharmacotherapy are non-steroidal anti--inflammatory drugs (NSAIDs), glucocorticoids, and so-called disease-modifying antirheumatic drugs (DMARDs) like methotrexate, sulfasalazine or chloroquine. Cyclophosphamide, cyclosporine, and biological treatment are also used.

In general, the cardiovascular complications of autoimmune diseases therapy can be divided into seven main categories:

1. Myocardial dysfunction and heart failure (HF).
2. Coronary artery disease (CAD).
3. Arrhythmias, especially those induced by QT-prolonging drugs.
4. Arterial hypertension.
5. Thromboembolic disease.
6. Peripheral vascular disease and stroke .
7. Pericardial complications .

NSAIDs

NSAIDs therapy increases the risk of:

- MI.
- Cerebrovascular accident.
- The cyclooxygenase-2 (COX-2) inhibitors may create a pro-thrombotic/coagulation imbalance on the endothelial surface, with thrombus formation and potentially fatal embolization.
- Congestive HF especially in the elderly, as they may exacerbate pre-existing HF due to renal dysfunction .
- NSAIDs therapy is associated with sodium and water retention, with double the hospitalizations due to congestive HF .

NSAIDs

- Systemic hypertension with higher elevations in hypertensive patients.
- NSAIDs interfere with the anti-hypertensive effects of several classes of CV drugs, including: diuretics, angiotensin-converting enzyme inhibitors and beta-blockers.
- Sustained use of non-selective NSAIDs and selective COX-2 inhibitors results in an extremely increased hazard ratio for ischemic stroke, 1.7 and 4.5, respectively.

Glucocorticoids

Are associated with :

- Hypertension(62%),
- Diabetes (18%).
- Dyslipidemia (66%) .
- Thromboembolic complications.
- They alter kidney function inducing fluid and electrolyte disorders, resulting in congestive HF and hypertension.
- Glucocorticoids are generally considered to increase the CV risk.
- Recent studies in SLE and RA have suggested that corticosteroids have a potential to reduce CV risk probably by lowering the autoimmune activity and the severity of inflammation

Sulfasalazine and Leflunomid

- Patients being treated with sulfasalazine and leflunomid may develop pericarditis and hypertension, respectively

Chloroquine

- Widening of the QRS complex.
- QT interval prolongation.
- T wave changes .
- in rare cases complete heart block, necessitating pacemaker implantation.
- Cardiomyopathy and ensuing congestive HF resulting from long-term chloroquine therapy.

Methotrexate

- A huge QUEST-RA study (2005–2006) recruiting over 4000 patients from 15 countries proved that one year treatment with methotrexate was associated with:
  - 15% decreases of risk for all CV events
  - 18% decreases MI
  - 11% decreases stroke .
  - Methotrexate has been of some benefit to the CV system as it has been reported to reduce atherosclerotic lesions in coronary arteries .

Methotrexate

Methotrexate may cause

- Pericarditis or pericardial effusions .
- Pulmonary fibrosis
- Congestive HF.
- Increase the risk of hypotension, diabetes and thromboembolic events (arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolization).

Cyclosporine

Patients treated with cyclosporine may experience

- Hypertension.
- Hyperlipidemia.
- Chest pain.
- Cardiac arrhythmias.
- The most severe complication of cyclosporine therapy is renal failure resulting in hypertension, fluid and electrolytes imbalance (hyperkalemia, hypomagnesemia) and imminent congestive HF

Cyclophosphamide

- Generally well tolerated in terms of cardiovascular toxicity.
- However, high-dose rapid administration may induce lethal acute pericarditis and hemorrhagic myocarditis.
- Although the etiology of this complication is not fully understood, direct oxidative cardiac injury has been implicated

Infliximab

- Increases the frequency of arrhythmias.
- Hypertension .
- HF.
- In rare cases may cause episodes of hypotension.
- However, the large population QUEST-RA study revealed lowered risk for all CV events in patients with a long history of TNF-alpha blockers treatment .

Etanercept

An immunosuppressive agent with an extremely long half-life of 102 ± 30 h, is used to treat rheumatoid arthritis.

Etanercept has many side effects :

- Increased risk of coronary artery disease and MI.
- Chronic HF .
- Deep vein thrombosis .
- Hypertension.
- Fortunately, these side effects are relatively rare and observed in only 1.5% of patients receiving this treatment.

Anakinra

- Anakinra, a human interleukin-1 receptor antagonist, used in to treat autoimmune disease
- According to more recent reports, it also helps reduce myocardial ischemia in acute coronary syndromes.
- The exact mechanism of action is not fully known and requires further evaluation

Side effect of drugs used in autoimmune diseases of the cardiovascular system.

Drug	Side effects from the cardiovascular system
Glicocorticosteroids	Arterial hypertension, diabetes, thromboembolic complications, renal impairment, heart failure
Nonsteroidal anti-inflammatory drugs	Edema, arterial hypertension, worsening heart failure, acute coronary events
Sulfasalazine	Pericarditis
Leflunomid	Arterial hypertension
Chloroquine	Arterial hypotension, changes in the ECG: QRS prolongation, QT prolongation, T wave changes, cardiomyopathy, III degree atrioventricular block, heart failure, ventricular arrhythmias
Infliximab	Arrhythmias, arterial hypertension, heart failure aggravation, arterial hypotension
Etanercept	Coronary artery disease, myocardial infarction, heart failure, thrombosis, arterial hypertension
Cyclosporine	Chest pain, irregular heartbeat, kidney failure, arterial hypertension, heart failure
Metotrexate	Pericardial effusion, pulmonary fibrosis, asthma, pulmonary hypertension, heart failure, diabetes
	Beneficial effect of reducing atherosclerotic lesions in coronary arteries
Anakinra	Beneficial effect of reducing the area of ischemia in acute coronary syndromes

Diagnosis and monitoring

All patients being considered for immunosuppressive drugs should undergo a detailed cardiovascular evaluation.

Nevertheless only a subgroup of patients will develop cardiovascular complications.

Therefore early identification of high-risk patients should be a fundamental target for the cardiologist .

Early detection

- Patients should undergo a baseline electrocardiogram and should be evaluated for conduction block or repolarization abnormalities and calculation of QTc.
- Echocardiography measured LVEF is one of the most important predictors of prognosis

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- LVEF should be determined before and periodically during treatment for early detection of cardiac dysfunction in patients receiving potentially cardiotoxic immunosupressant
- The use of other indicators such as lipid profile and serum markers for monitoring cardiotoxicity is being investigated. A predictive role for biomarkers is not defined enough to include them as routine screening measurements.

Prevention

- Patients undergoing Immunosuppressant therapy should be encouraged to follow standard guidelines for reducing CV risk, such as blood pressure control, lipid level reduction, smoking cessation and lifestyle modifications

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- If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), ACE inhibitors (or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high risk of developing HF.

Prevention

- Patients with a history of QT prolongation, relevant cardiac disease, treated with QT-prolonging drugs, bradycardia, thyroid dysfunction or electrolyte abnormalities should be monitored by repeated 12-lead ECG.
- Consider treatment discontinuation or alternative regimens if the QTc is >500 ms, QTc prolongation is >60 ms or dysrhythmias are encountered.

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- Conditions known to provoke torsades de pointes, especially hypokalaemia and extreme bradycardia, should be avoided in patients with drug-induced QT prolongation.
- Exposure to other QT-prolonging drugs should be minimized in patients treated with potentially QT-prolonging drugs.

Treatment and follow up

Once cardiovascular side-effect occurs, the patients should be appropriately treated

- ACE inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.

Cont.

- Hypertension should be adequately treated according to the current standing clinical practice guidelines, and blood pressure should be monitored before initiating treatment and periodically during treatment, depending on the patient's characteristics and adequate blood pressure control
- For other severe cardiovascular complications, including severe hypertension, arrhythmias, and thromboembolism, it is important, in addition to stopping therapy, also considering intensive and appropriate treatments

Take home message

- Both autoimmune diseases and their management have a significant impact on the CV system, which results in decreased quality of life, higher mortality and increased cost of healthcare.
- Improving the quality of life, preventing CV adverse events, decreasing hospitalizations and mortality, all-the-while minimizing pharmacological side effects is the present goal of this multidisciplinary management of autoimmune disease.


THANK YOU