Management of Patients with Past or Present Cardiovascular Disease

Evidence Based Medicine | Official recommendations | Expert opinion

To date, there are no recommendations focusing specifically on the prevention of cardiovascular disease or dyslipidaemia during tocilizumab therapy for RA [4].

However, the following recommendations are available:

- recommendations developed by healthcare authorities about the therapeutic management of patients with dyslipidaemia [5], hypertension [6], or type 2 diabetes [7];
- and recommendations developed by experts about the evaluation and management of cardiovascular risk factors in RA patients in everyday clinical practice [8].

These recommendations can assist in defining a strategy for preventing cardiovascular disease and managing dyslipidaemia in patients receiving tocilizumab therapy for RA.

Steps to be taken before tocilizumab initiation in patients with a history of cardiovascular disease or dyslipidaemia

Risk factor management

The Summary of Product Characteristics lists no contraindications to tocilizumab therapy in patients with a history of cardiovascular disease or dyslipidaemia. The section on precautions for use indicates that "RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care" [4].

Regarding the specific management of dyslipidaemia in patients at high cardiovascular risk, for secondary prevention or an equivalent risk level, the recommendations are listed below.

- Lipid-lowering drug treatment should be initiated as promptly as possible (Grade B), in combination with dietary treatment and interventions to correct other risk factors (e.g., inactive lifestyle, smoking, overweight).
- In principle, the nature and dosage of the lipid-lowering drug should reflect the treatments that proved effective in vast interventional studies. Standard practice consists in starting with a low dosage and increasing the dosage subsequently based on effectiveness and safety data. A decision to use high dosages or combinations of lipid-lowering drugs may be taken on a case-by-case basis. However, this decision should not jeopardize tolerance or treatment adherence.
- No conclusive evidence is available for defining a treatment objective. Consequently, the objective should be determined on a case-by-case basis (tolerance of the treatment and baseline cholesterol levels). In general, keeping the LDL-cholesterol level lower than <1 g/L (2.6 mmol/L) is desirable [5].

Attention should be given to potential drug-drug interactions

Expression of the hepatic CYP 450 isoenzymes (CYP1A2, CYP 2C9, CYP2C19, and CYP3A4) is diminished by IL-6 and may be restored by tocilizumab therapy [4]. When starting or stopping tocilizumab therapy, close monitoring is in order in patients who take medications metabolized by the CYP450 isoenzymes (e.g., atorvastatin, calcium channel inhibitors, warfarin, theophylline, phenytoin, cyclosporine, and benzodiazepines), as maintaining the therapeutic effect of these medications may require a dosage increase or decrease (if TCZ stopped) [4] (See Table 1). Tocilizumab has a fairly long half-life and may therefore continue to affect the activity of the CYP450 isoenzymes for several weeks after treatment discontinuation [4].

Steps to be taken before tocilizumab initiation in patients who have no history of cardiovascular disease (primary prevention)

Screening for dyslipidaemia

The first-line evaluation should include assays for total cholesterol, triglycerides, and HDL-cholesterol with computation of the LDL-cholesterol level, in serum from a blood sample drawn after a 12-hour fast [5].

In patients with no cardiovascular risk factors other than RA, the cut-offs used to define normal serum lipid levels are as follows: LDL-cholesterol <1.60 g/L (4.1 mmol/L), triglycerides <1.50 g/L (1.7 mmol/L), and HDL-cholesterol >0.40 g/L (1 mmol/L). Values above these cut-offs define dyslipidaemia [5].

In RA patients scheduled for tocilizumab therapy, serum lipid assays should be obtained before treatment initiation and before the third tocilizumab infusion (before week 8) [4].

Evaluation of the cardiovascular risk

To date, no tool for objectively evaluating the cardiovascular risk has been validated in France. Until such a tool is available, simply counting the risk factors in each individual patient (Table 3) is appropriate in everyday clinical practice (consensus of experts) [5].

Based on the number of risk factors, three levels of risk can be defined:

- low risk: no cardiovascular risk factors other than dyslipidaemia
- intermediate risk: at least one risk factor in addition to dyslipidaemia
- high risk: history of documented coronary artery disease and/or disease of other arteries; type 2 diabetes with a high cardiovascular risk; 10-year cardiovascular risk ≥20% (Table 4) [5].

At present, estimation of the 10-year cardiovascular risk relies on equations such as the Framingham, SCORE, and QRISK equations. None of these equations has been validated in France or in a population of RA patients [9].

Importantly, RA should be considered an independent risk factor and added to the risk factors selected by the AFSSAPS for estimating the cardiovascular risk. The latest algorithm from the QRISK study (QRISK2) includes RA among the variables used to estimate the cardiovascular risk, alongside other variables such as age, sex, body mass index, smoking, treated hypertension, systolic blood pressure, the ratio of total cholesterol over HDL-cholesterol, type 2 diabetes, and a family history of premature coronary artery disease [10].

● Management of dyslipidaemia

Objectives of dyslipidaemia management

Depending on the number of risk factors in addition to dyslipidaemia, determined by adding RA to the AFSSAP-listed risk factors present in the patient, these objectives are as follows (consensus of experts):

- no risk factors: LDL-cholesterol <2.20 g/L (5.7 mmol/L);
- one risk factor: LDL-cholesterol <1.90 g/L (4.9 mmol/L);
- two risk factors: LDL-cholesterol <1.60 g/L (4.1 mmol/L);
- more than two risk factors: LDL-cholesterol <1.30 g/L (3.4 mmol/L);
- documented cardiovascular disease or equivalent risk level: LDL–cholesterol <1 g/L (2.6 mmol/l) [5].

Overall strategy for dyslipidaemia management

General rules

- Dietary intervention is in order in patients with LDL-cholesterol levels >1.60 g/L (4.1 mmol/L) and in patients with at least one cardiovascular risk factor, regardless of the LDL-cholesterol level.
- Dietary intervention should always be combined with advice about regular physical activity such as a brisk 30-minute walk every day.
- Interventions should be instituted to manage any other risk factors such as smoking, type 2 diabetes, or hypertension [5].

Rules for primary prevention in patients with dyslipidaemia

- Dietary intervention should be used alone for at least 3 months.
- The diet should be continued even if the treatment objective is reached.
- If the treatment objective is not reached after 3 months of an appropriate diet, pharmacological treatment designed to further lower the LDL-cholesterol level should be added to the diet [5].

● Screening and management for other risk factors

Patients should be screened and managed for other risk factors (e.g., smoking, type 2 diabetes, and hypertension) in accordance with available recommendations, which will not be discussed here [6, 7].

Signs that should alert to the possibility of developing cardiovascular disease in patients on tocilizumab therapy

Although there are no specific signs, several clinical signs may suggest the development of cardiovascular disease:

- dyspnea upon exertion, at rest, or when recumbent
- chest pain or tightness of the chest
- palpitations
- tachycardia upon auscultation of the heart
- crepitant rales upon auscultation of the lungs
- and oedema of the lower limbs.

When starting tocilizumab therapy in a patient with RA, the serum lipid profile should be determined before treatment initiation and before the third tocilizumab infusion (before week 8) [4].

Management of patients who develop cardiovascular events or dyslipidaemia while on tocilizumab therapy

Cardiovascular event during tocilizumab therapy

The safety data from the clinical development program for tocilizumab in RA were updated on February 6, 2009. At that time, 4009 patients had received at least one tocilizumab dose during phase I clinical trials, phase III clinical trials (OPTION, AMBITION, RADIATE, TOWARD, and LITHE), or open-label extensions (GROWTH95 and GROWTH96) (9414 patient-years of exposure and 2.4 years of mean follow-up).

The overall incidence of serious adverse events was 14.9/100 patient-years. The incidence of death was 0.53/100 patient-years. Myocardial infarction occurred with an incidence of 0.25/100 patient-years (13.6/100 patient-years with 4 mg/kg and 14.5/100 patient-years with 8 mg/kg) and stroke with an incidence of 0.19/100 patient-years. The incidence of serious cardiovascular adverse events remained stable during follow-up and did not seem greater than expected in a comparable population of RA patients. The serum concentrations of LDL-cholesterol, HDL-cholesterol, and triglycerides increased within the first 6 weeks and subsequently showed little change over time. Most of the 313 (7.8%) patients in whom lipid-lowering agents were started during tocilizumab therapy responded to these agents and experienced no complications [11].

Although no increase in the rate of serious cardiovascular adverse events was noted during the clinical development program, tocilizumab therapy is best interrupted at the acute phase of coronary artery events or ischemic stroke, until the cardiovascular parameters are stable.

Dyslipidaemia during tocilizumab therapy

The data from the clinical development program for tocilizumab in RA were used to evaluate changes in serum lipids and inflammation markers between the baseline and the week-24 visit in patients receiving tocilizumab (8 mg/kg) combined with a non-biological disease-modifying antirheumatic drug (in OPTION, TOWARD, LITHE, and RADIATE [n=1582]) or tocilizumab (8 mg/kg) alone (in AMBITION [n = 288]), comparatively to patients receiving a placebo and any non-biological disease-modifying antirheumatic drug (in OPTION, TOWARD, LITHE, and RADIATE [n=1170]) or methotrexate (in AMBITION [n=284]) (Table 5). In patients receiving tocilizumab either with a non-biological disease-modifying antirheumatic drug or alone, the serum cholesterol and triglyceride levels increased noticeably within the first 6 treatment weeks and remained stable thereafter, while the inflammation markers decreased substantially, as detailed in table 5 [12].

Thus, about 24% of the patients receiving tocilizumab during these clinical trials had prolonged total cholesterol elevation ≥2.4 g/L (≥6.2 mmol/L) and 15% had prolonged LDL-cholesterol elevation ≥1.6 g/L (≥4.1 mmol/L) [4].

In the 195 patients who were on statin therapy before tocilizumab initiation, the LDL-cholesterol increase was smaller than in the overall population of 2644 tocilizumab-treated patients (+0.12 g/L vs. +0.19 g/L). In the 37 patients who were started on statin therapy after tocilizumab initiation, the introduction of a statin was associated with a decrease in the LDL-cholesterol level (-0.31 g/L) by week 24, despite an increase in LDL-cholesterol at week 6 (+0.33 g/L), compared to the pre-tocilizumab LDL-cholesterol level [13].

Thus, the decreases in inflammation markers induced by tocilizumab therapy occur concomitantly with increases in serum lipid concentrations. To date, given the number of patients and follow-up duration, it remains unclear whether these changes in inflammation markers and serum lipids affect the incidence of cardiovascular events in patients with RA.

Management of dyslipidaemia developed during tocilizumab therapy

- **tocilizumab therapy should not be interrupted;**
- **screening tests should be performed to look for other cardiovascular risk factors, whose number should then be used to determine the target LDL-cholesterol level;**
- **in patients with no history of cardiovascular disease (primary prevention), an appropriate diet should be prescribed** alone for 3 months, after which the serum lipid assays should be repeated and statin therapy started if the results show persistent dyslipidaemia;
- **in patients with a history of cardiovascular disease (secondary prevention), statin therapy should be started** as promptly as possible, in conjunction with a diet and interventions to correct any other risk factors (e.g., inactive lifestyle, smoking, overweight).
  - **statin therapy should be started in a low dosage to optimise tolerance and adherence;**
  - **fluvastatin, pravastatin, and rosuvastatin are not metabolised by the hepatic CYP450 isoenzymes, whose activity is diminished by IL–6;**
- **the serum lipid assays should be repeated 1 month after statin therapy initiation.** If the LDL-cholesterol target is not reached, the statin dosage should be increased and the serum lipid assays repeated 1 month later. If the LDL-cholesterol target is reached, the serum lipid assays should be repeated after 3 months then every 6 months.

When should tocilizumab be re-started?

At the end of the acute phase of a coronary artery event or ischemic stroke, tocilizumab can be re-started in the previous dosage. Before re-starting tocilizumab, screening tests for cardiovascular risk factors should be performed and appropriate interventions initiated. To this end, the patient should be referred to a cardiologist or neurologist for initial advice followed by regular follow-up.

The Summary of Product Characteristics does not list NYHA class III/IV heart failure as a contraindication to re-starting tocilizumab therapy [4]. However, given the available experimental data on the role for IL-6 in the development, maintenance, and protection of the myocardium [14], appropriate heart failure treatment should be given. To this end, the patient should be referred to a cardiologist for initial advice followed by regular follow-up.

Additional information

Background information on cardiovascular disease and its prevention

Cardiovascular disease is the leading cause of death and disability in industrialized countries. Although the age-specific prevalence of cardiovascular disease has decreased, the aging of the population has translated into a stable or increasing overall prevalence. In France and throughout the world, cardiovascular disease is a major public health concern.

Cardiovascular disease classically manifests as coronary artery disease, ischemic stroke, and/or peripheral occlusive arterial disease. These events are all complications of atherosclerosis and often develop at a late stage of the disease. Atherosclerosis is a chronic inflammatory arterial disease process that is initiated and perpetuated by cardiovascular risk factors. Major cardiovascular risk factors play a causative role in atherosclerosis. They include LDL-cholesterol elevation, hypertension, diabetes, and smoking. The AFSSAPS has issued specific recommendations about the management of major cardiovascular risk factors.

There is general agreement that cardiovascular risk factors are highly amenable to preventive measures. Prevention may be instituted at two levels:

- primary prevention, in patients with a negative history of cardiovascular disease;
- and secondary prevention in patients who have cardiovascular disease [5].

The results of vast interventional studies have provided five new insights about cardiovascular prevention via lipid-lowering medications.

1. Secondary prevention is in order not only in patients with coronary artery disease, but also in those with documented atheromatous lesions at other sites manifesting as stroke or transient ischemic attacks and/or as peripheral occlusive arterial disease.
2. The benefits of lipid-lowering pharmacotherapy used for cardiovascular prevention are not confined to the coronary arteries. In high-risk patients with no previous history of stroke, a decrease in the risk of stroke has been demonstrated. The benefits extend to all cardiovascular events.
3. Cardiovascular prevention has been proved effective in new patient subgroups including patients aged 70 to 80 years, postmenopausal women, patients with hypertension, patients with type 2 diabetes, and patients with a history of vascular disease.
4. In patients who experience acute coronary events, preventive therapy should be instituted immediately after the event.
5. The cardiovascular risk decrease is dependent on the LDL-cholesterol decrease. The cardiovascular risk diminishes even in high-risk patients whose baseline LDL-cholesterol concentrations are close to those seen in the general population [5].

The decrease in serum LDL-cholesterol is the best marker for assessing the effectiveness of cardiovascular prevention via lipid-lowering pharmacotherapy (grade A). This readily available parameter was therefore selected to develop recommendations for dyslipidaemia screening and management.

Nevertheless, other lipid parameters such as HDL-cholesterol and triglycerides deserve attention also, and the results of ongoing prevention trials may lead to changes in the current prevention strategy [5].

The therapeutic management of patients with dyslipidaemia should include interventions to correct all cardiovascular risk factors (Table 3). Its goal is to delay the development (primary prevention) or recurrence (secondary prevention) of clinical events related to atherosclerosis (grade A) [5].

Role for IL-6 in the pathogenesis of cardiovascular disease

IL-6 overexpression is associated with many disease states characterized by low-grade inflammation such as obesity, insulin resistance, type 2 diabetes, coronary artery disease, and congestive heart failure [14, 15].

In cohorts of coronary artery disease patients, serum IL-6 levels correlate positively with age, smoking, systolic blood pressure, body mass index, serum triglyceride level, fasting blood glucose level, and various pro-inflammatory markers such as CRP. In contrast, serum IL-6 levels are inversely correlated with the total cholesterol level [15].

IL-6 is the main cytokine that stimulates the production and release of CRP not only by the hepatocytes, but also by cells within inflammatory microenvironments such as the rheumatoid synovial membrane or the atherosclerotic arterial wall. CRP, similar to IL-6, is a pro-inflammatory factor capable of activating the immune cells locally, within inflamed tissues, as well as at remote sites such as the arterial wall, where it promotes endothelial dysfunction and the subsequent development of atherosclerosis [14, 15].

Risk of cardiovascular disease or dyslipidaemia in patients with rheumatoid arthritis

Mortality is increased in RA patients compared to the general population [17]. This excess mortality is largely ascribable to cardiovascular disease. Thus, the standardized mortality ratio (SMR) for cardiovascular disease was estimated at 1.5 (95% CI, 1.39-1.61) in a recent meta-analysis [18], indicating a 50% increase in cardiovascular mortality overall. The mortality risk increase was 59% for coronary artery disease and 52% for ischemic stroke [18].

Possible explanations to the excess mortality in RA may include an increased prevalence of cardiovascular risk factors, inadequate therapeutic management of cardiovascular risk factors, the chronic inflammation that characterizes RA, or a combination of these three factors [17].

Studies of cardiovascular risk factor prevalence in patients with RA showed an increased prevalence of smoking [19]. Smoking is associated with increased susceptibility to RA and with increased production of antibodies to cyclic citrullinated peptides, most notably in patients who have one or two HLA-DRB1

alleles encoding the shared epitope [17]. No increase in the prevalence of hypertension has been reported in RA patients [17, 19, 20]. It is difficult to draw definitive conclusions about type 2 diabetes, although a recent meta-analysis suggests an increased prevalence in RA patients [19]. An important point to bear in mind is that glucose regulation disorders in patients with RA may be due to glucocorticoid therapy [17]. Finally, RA is associated with dyslipidaemia, which is usually characterized by low HDL-cholesterol levels [17, 19, 20]; some studies also showed decreases in the total cholesterol level or even the LDL-cholesterol level, most notably in patients with active early-stage RA [17, 20]. Furthermore, in patients with chronic inflammatory diseases such as RA, lipoprotein metabolism disturbances may lead to functional HDL abnormalities with complete or partial loss of the normal anti-inflammatory and anti-oxidant properties of HDLs [21].

The management of co-morbidities often receives insufficient attention in patients with chronic diseases. Cardiovascular co-morbidities in RA patients are a case in point [17]. Thus, a recent study of the management of hypertension in RA patients showed that only 60% of hypertensive patients were receiving antihypertensive medications and that only 22% of these were optimally treated [22]. In addition to the inadequate management of cardiovascular co-morbidities, patients receive insufficient information and education about cardiovascular disease [23].

RA per se is an independent cardiovascular risk factor whose impact is similar to that of type 2 diabetes [24]. Conceivably, the chronic inflammation that characterizes RA may produce pro-inflammatory conditions in the arterial wall, which in turn may promote the development of atherosclerosis via shared cellular and intercellular factors such as mononuclear cells and pro-inflammatory cytokines [17]. Furthermore, glucocorticoids, which are widely used in RA, constitute a potentially major cardiovascular risk factor, particularly when used in high dosages and for long periods [25].

Impact of RA management

As pointed out above, RA is an independent cardiovascular risk factor [24].

Optimal RA treatment designed to promptly achieve a low level of disease activity or a remission, with a return to normal of CRP levels, may diminish the endothelial dysfunction, delay atherosclerosis progression, and ultimately decrease the excess mortality associated with RA [26, 27].

When selecting the best treatment strategy for achieving these objectives, physicians should ideally consider available data on the cardiovascular effects of the drugs used to treat RA. For instance, methotrexate and TNF antagonists may decrease the cardiovascular risk, whereas high-dose glucocorticoids may increase the cardiovascular risk [25].