# Tocilizumab

## THERAPY
## AND SAFETY MANAGEMENT

## Clinical tool guide

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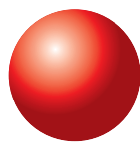
# Contents

The material presented in these fact sheets is classified into three groups according to the level of the underlying evidence, as follows:

| Evidence Based Medicine | Official recommendations | Expert opinion |

The level of evidence was based on a literature review and on the experts' personal experience with tocilizumab therapy.

Tocilizumab
# therapy and safety management

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# Abstract

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

**Objectives:**

To develop fact sheets about tocilizumab, in order to assist physicians in the management of patients with inflammatory joint disease.

**Methods:**

1. selection by a committee of rheumatology experts of the main topics of interest for which fact sheets were desirable;

2. identification and review of publications relevant to each topic;

3. development of fact sheets based on three levels of evidence: evidence-based medicine, official recommendations, and expert opinion. The 20 experts were rheumatologists and invited specialists in other fields, and they had extensive experience with the management of RA. They were members of the CRI (Club Rhumatismes et Inflammation), a section of the *Société Francaise de Rhumatologie*. Each fact sheet was revised by several experts and the overall process was coordinated by three experts.

**Results:**

Several topics of major interest were selected: contraindications of tocilizumab; the management of adverse effects and concomitant diseases that may develop during tocilizumab therapy ; and the management of everyday situations such as pregnancy, surgery, and immunizations. After a review of the literature and discussions among experts, a consensus was developed about the content of the fact sheets presented here. These fact sheets focus on several points:

1. in RA, initiation and monitoring of tocilizumab therapy, management of patients with specific past histories, and specific clinical situations such as pregnancy;

2. diseases other than RA, such as juvenile idiopathic arthritis;

3. models of letters for informing the rheumatologist and general practitioner;
4. and patient information.

**Conclusion:**

These tocilizumab fact sheets built on evidence-based medicine and expert opinion will serve as a practical tool for assisting physicians who manage patients on tocilizumab therapy. They will be available continuously at www.cri-net.com and updated at appropriate intervals.

# Introduction

| Evidence Based Medicine | Official recommendations | Expert opinion |

For each new biotherapy, a panel of experts working under the aegis of the CRI (Club Rhumatismes et Inflammation) develops and validates a set of fact sheets.

CRI fact sheets are available for TNF-α antagonists [1], rituximab [2], and abatacept [3].

The new fact sheets presented here are about tocilizumab (RoActemra®), the first interleukin-6 inhibitor. Tocilizumab is indicated in combination with methotrexate in adults with rheumatoid arthritis (RA) who have a history of inadequate effectiveness or intolerance during treatment with one or more disease-modifying antirheumatic drugs (DMARDs) or TNF antagonists. In these patients, tocilizumab can also be used alone when methotrexate is poorly tolerated or when further methotrexate therapy would be inappropriate.

As with previous fact sheets, and thanks to a panel of experts that has continued to expand, we have given pride of place to pragmatism by providing answers to the questions that arise most commonly in everyday practice before, during, and after tocilizumab therapy. To build our fact sheets on a solid foundation, we obtained advice from highly competent endocrinologists, hepatologists, and immunologists. These discussions were fascinating, and we are delighted to be able to share their benefits with you under the form of these fact sheets.

As previously, we have used a colour code to ensure ready differentiation of material supported by evidence from the literature, official recommendations, and expert opinion.

These fact sheets will help us to improve our everyday clinical practice. Further benefits will be obtained from the nationwide registry of patients on tocilizumab (for any reason) set up under the aegis of the CRI and French Society for Rheumatology (SFR). Your contribution to this registry will be invaluable.

Our deepest gratitude goes to the experts who have expended enormous amounts of energy to develop these fact sheets. The fact sheets are published in this special issue of Joint Bone Spine, to whose editorial board we extend our warmest thanks for their close collaboration; and they will be available on the CRI site (http://www.cri-net.com).

Please feel free to send us your comments and requests about these fact sheets. Your input will help to improve future updates.

Xavier Mariette, Thao Pham and Jean Sibilia, who were the expert panel coordinators; and all the experts on the panel.
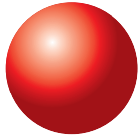
# Initial
# pre-treatment workup

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

This checklist is designed to help you conduct a systematic search for the main contraindications to tocilizumab and to determine whether special precautions are in order. It does not include the evaluations needed to assess the activity and severity of the disease treated with tocilizumab.

**When interviewing the patient, ask about a history of any of the following:**
➤ Severe, chronic, and/or recurrent infections (bacterial or viral)
➤ Tuberculosis (contact of the patient or family with tuberculosis cases)
➤ Cancer
➤ Diverticulitis

Determine whether the patient is taking any drugs metabolized by the CYP450 enzymes, whose dosage may need to be adjusted upon tocilizumab initiation or discontinuation. The most widely used medications metabolised by CYP450 are listed in Table 1. The full list is available online at http://medicine.iupui.edu/clinpharm/ddis.

**When conducting the physical examination, check the absence of the following:**
➤ Fever
➤ Active infection
➤ Lymphadenopathy
➤ Signs suggesting a malignant disease
➤ Hypertension
➤ Abdominal pain

**Vaccinations:**
➤ Updates should be offered. The interval between vaccine administration and tocilizumab initiation should be at least 2 weeks; with live vaccines, the ideal interval is 4 weeks
➤ The pneumococcal vaccine should be recommended

**Investigations that should be obtained routinely at the first evaluation:**
➤ Blood cell counts
➤ Transaminases
➤ Serum lipid profile including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides
➤ Serum protein electrophoresis
➤ Chest radiograph
➤ 5 IU intradermal tuberculin test (Tubertest®) or QuantiFERON Gold® *in vitro* test or T-Spot-TB® (under evaluation in France)
    • If prophylactic anti-tuberculous treatment was given based on the results of previous screening tests, further screening is unnecessary
    • If previous screening tests performed more than 1 year earlier were negative, they should be repeated

- In patients who have never had screening tests, AFSSAPS recommendations about screening for latent tuberculosis should be followed
➤ Serological tests for hepatitis B and C, even if performed previously
➤ Serological test for HIV infection, with the consent of the patient; if test results obtained within the last 5 years are available, further testing is unnecessary unless the patient has risk factors for HIV infection
➤ Detection of risk factors for malignancy and early malignancy detection in accordance with good practice guidelines
➤ and immunoglobulin assays by weight in patients previously treated with rituximab.

## Contraindications and precautions

**Contraindications to tocilizumab therapy:**
➤ Hypersensitivity to tocilizumab or to any of the excipients
➤ Severe uncontrolled infections such as sepsis and opportunistic infections.

**Diseases that warrant special precautions when using tocilizumab:**
➤ Diverticulitis
➤ Active liver disease and liver failure
➤ Neutropenia and thrombocytopenia
➤ Dyslipidaemia
➤ History of cardiovascular disease
➤ Demyelinating disease
➤ Malignancy within the last 5 years, other than non-melanoma skin cancer that was removed completely with disease-free margins

# Monitoring tocilizumab therapy

| Evidence Based Medicine | Official recommendations | Expert opinion |

Clinical and laboratory parameters should be monitored to assess the effectiveness and safety of tocilizumab therapy.

Treatment monitoring is easy to perform during the monthly intravenous infusions (see the model information letters for the usual rheumatologist and primary-care physician). European recommendations advise a dosage of 8 mg/kg every 4 weeks.

In the short-term, patients should be monitored for infusion-related reactions (see the sheet on "Infusion-related reactions").

● Clinical parameters are monitored to evaluate the treatment response, based on the number of joints with synovitis and the DAS 28. Given the mechanism of action of tocilizumab, markers for inflammation may improve in the absence of clinical improvements. In theory, the objective of tocilizumab therapy is to achieve a remission or, at least, a low level of disease activity (DAS28 <3.2).

➤ If the DAS 28 score has not fallen by at least 0.6 point after 12 weeks, further treatment with tocilizumab is not recommended.

➤ Subsequently, the treatment response should be monitored every 3 months by performing a basic evaluation of clinical disease activity and laboratory evidence of inflammation (ESR and/or CRP) (see the model letter for the usual rheumatologist in the appendices).

➤ Radiographs of the hands and feet should be obtained once a year to monitor progression of the structural damage.

➤ Safety should be monitored at each tocilizumab infusion and whenever an unexpected event occurs. As with all biotherapies, tocilizumab requires a high level of alertness to bacterial and viral infections and to symptoms that might indicate cancer or a haematological malignancy (see the fact sheets entitled "Bacterial and viral infections" and "Solid cancer or haematological malignancy").

The data from the OPTION, TOWARD, LITHE, AMBITION, SAMURAI, and RADIATE trials have been used to assess the tocilizumab response profile over at least 6 months. In patients who had responded inadequately to TNF antagonists, tocilizumab therapy produced significant decreases in disease activity. A significant decrease of at least 1.2 in the DAS 28 score was found as early as the first treatment month.

The response occurred promptly (week 2) and increased in magnitude with continued treatment. The optimal time for assessing the effectiveness of tocilizumab therapy is 3 to 6 months after treatment initiation.

## ● **Laboratory tests for treatment monitoring**

Specific laboratory tests are required to monitor tocilizumab therapy, in addition to the inflammation marker assays needed to determine the DAS 28 score and to the laboratory tests required by concomitant treatments (e.g., methotrexate).

The following tests should be obtained before each tocilizumab infusion:

➤ **Serum transaminases (ALAT and ASAT):** During the clinical trials of tocilizumab, many patients had mild to moderate elevations in serum liver transaminase levels, which were either transient or intermittent, in the absence of clinical liver impairment. If the tests done during the first 3 treatment months show no evidence of liver toxicity, subsequent testing at 3-month intervals is appropriate. If they show transaminase elevation, in contrast, the methotrexate dosage should be adjusted if needed. The CRI expert panel developed two algorithms for managing patients with persistent transaminase elevation (see the sheet entitled "Management of patients with past or present hepatic abnormalities", Figures 1 and 2).

➤ **Blood cell counts:** Decreases in neutrophil and platelet counts have been noted after tocilizumab therapy in a dosage of 8 mg/kg in combination with methotrexate. The risk of neutropenia may be increased in patients who have a history of TNF antagonist therapy. Table 2 describes the management strategy for patients in whom neutropenia or thrombocytopenia develops during follow-up.

A **serum lipid profile before** the third tocilizumab infusion, including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides: Increases in these lipid parameters have been reported in patients taking tocilizumab, with no increases in the atherogenicity indices. Total cholesterol elevation responded to statin therapy.

● In women of childbearing potential, contraception should be used throughout tocilizumab therapy and for the first 12 weeks following the last infusion. The tocilizumab elimination half-life suggests 3 months as a reasonable interval between the last infusion and conception (as 97.5% of the drug is eliminated in 3 months) (see the sheet entitled "Management of patients who are pregnant"). The potential effects of tocilizumab on spermatogenesis are unknown. Therefore, men should follow the same precautions as women (3-month wait between the last infusion and conception).

● Monitoring potential drug-drug interactions: Tocilizumab therapy may diminish the effectiveness of drugs that are metabolized by the CYP450 isoenzymes such as benzodiazepines, warfarin, atorvastatin, calcium channel inhibitors, and theophylline. Therefore, the dosages of these drugs should be adjusted upon tocilizumab initiation and discontinuation, while bearing in mind the possible persistence of tocilizumab-induced effects on CYP450 isoenzymes for several weeks after the drug is stopped. The most widely used medications that are metabolized by CYP450 are listed in Table 1.

A number of clinical situations (pregnancy, vaccination, travel, surgery, and drug-drug interactions) are discussed in specific fact sheets.

## 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.

❶ 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.

❷ 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.

❸ 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.

❹ In patients who experience acute coronary events, preventive therapy should be instituted immediately after the event.

❺ 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].
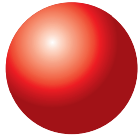
Management of Patients with Past or Present
# Haematological Abnormalities

| Evidence Based Medicine | Official recommendations | Expert opinion |
| --- | --- | --- |

## Can tocilizumab therapy cause blood cell count abnormalities?

Patients on tocilizumab therapy should be monitored for the following blood cell count abnormalities:

➤ neutrophil count decline to less than 2000/mm$^3$

➤ and platelet count decline to less than 100,000/mm$^3$.

### ● Neutropenia

In controlled trials and open-label extensions, neutropenia <2000/mm$^3$ occurred in 16% to 39% of patients receiving tocilizumab 8 mg/kg. Both proportions were significantly higher than in the control groups (Table 6).

Most cases of neutropenia were mild (grade 1 or 2) and therefore were not associated with a substantial risk of infection. Grade 3 neutropenia (<1000 neutrophils/mm$^3$) was less common and grade 4 neutropenia (<500/mm$^3$) was exceedingly rare except in the RADIATE study of patients having failed TNF antagonist therapy (1.5% of patients) (Table 6).

Neutropenia developed within 4 to 8 weeks of treatment initiation or, in some cases, earlier (as early as day 5) and was generally short lived. The neutropenia occurrence rate seemed unrelated to the concomitant use of methotrexate or other disease-modifying antirheumatic drugs.

Neutropenia was not found to affect the risk of serious infection [4], probably because of its short duration.

The cause of neutropenia during tocilizumab therapy is unknown. Some studies suggest neutrophil margination rather than marrow stem cell impairment [28].

### ● Thrombocytopenia

Platelet count declines to less than 100,000/mm$^3$ were more common in the tocilizumab groups (1.7% vs. 1% in the control groups) of therapeutic trials. No bleeding events were reported in the patients with thrombocytopenia.

## Course of action before tocilizumab therapy in patients with blood cell count abnormalities

Before starting tocilizumab therapy, blood cell counts must be obtained routinely.

The strategy recommended by the EMA [4] is described below:

| | | |
|---|---|---|
| Neutrophils: | 500-2,000/mm³ | No contraindication |
| or platelets: | 50,000-100,000/mm³ | Use tocilizumab with caution |
| Neutrophils: | < 500/mm³ | The use of tocilizumab is not recommended |
| or platelets: | < 50,000/mm³ | |

## What warning signs deserve special attention in patients receiving tocilizumab?

A fever or signs of infection should suggest neutropenia.
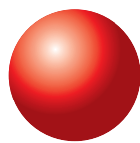
Purpura, gingival bleeding, or a hematoma developing in the absence of trauma should suggest thrombocytopenia.

In both situations, blood cell counts should be obtained.

Declines in all three cell lines should prompt investigations for macrophage activation syndrome related to an infection.

## In practice, what is the course of action when neutropenia or thrombocytopenia develops during tocilizumab therapy?

In light of the recommendations issued by the EMA [4], the CRI experts advocate the following strategy in patients with neutropenia (<2,000/mm³) or thrombocytopenia (<150,000/mm³) (Table 2)

Management of Patients with Past or Present
# Hepatic Abnormalities

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

## Course of action before tocilizumab therapy in patients with a history of liver disease

Tocilizumab therapy, particularly when combined with methotrexate, may be associated with hepatic transaminase elevation. No studies specifically designed to assess the effects of liver failure on tocilizumab pharmacokinetics are available [4]. Consequently, the Summary of Product Characteristics [4] indicates that caution should be exercised when considering tocilizumab therapy in patients with active liver disease or liver function impairment, as the safety of tocilizumab in these patients has not been evaluated.

**In practice:**

- In patients who have liver disease with alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) levels >1.5 x upper limit of normal (ULN) but <5 x ULN, tocilizumab therapy initiation can be considered [4] but requires special caution. Before starting tocilizumab, the advice of a hepatologist should be sought to determine the cause and severity of the underlying liver disease. To facilitate the conduct of tocilizumab therapy, treatment directed at the cause of the pre-existing liver disease (metabolic, alcohol-related, viral, haemochromatosis...) should be given if possible. Depending on the severity of the liver disease evaluated using non-invasive tests for fibrosis (biochemical tests and elastometry), the tocilizumab dosage may need to be adjusted. If tocilizumab therapy is initiated in a patient with pre-existing liver disease, the transaminase levels should be monitored routinely, at intervals no longer than 15 days for the first 3 months and no longer than 3 months subsequently.

- Tocilizumab therapy is not recommended in patients with ALAT or ASAT levels >5 x ULN (SPC).

- In patients with chronic viral hepatitis B or C with or without transaminase elevation, tocilizumab therapy initiation can be considered, although special caution is in order. The advice of a hepatologist should be obtained before considering the initiation of tocilizumab therapy, in particular to determine whether pre-emptive treatment with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) [39] is in order to prevent viral reactivation (see also the Additional Information section).

## What are the warning signs of liver disease?

The development of clinical manifestations of hepatitis or hepatocellular insufficiency has not been reported in patients receiving tocilizumab therapy. In most cases, the hepatic abnormalities were discovered fortuitously by routine laboratory tests [4, 40].

## When and how should the transaminase levels be monitored and what should be done in the event of transaminase elevation?

In clinical trials, transient or intermittent mild-to-moderate elevations of the transaminase levels were common in patients receiving tocilizumab, in the absence of clinical liver injury [4]. The use of concomitant medications with potential hepatotoxic effects (e.g., methotrexate) was associated with an increased rate of transaminase elevation [4, 29, 30, 32, 35-37, 39-42].

### ● Monitoring transaminase levels

The Summary of Product Characteristics [4] recommends that ALAT and ASAT levels be monitored every 4 to 8 weeks for the first 6 months of treatment and every 12 weeks thereafter [4].

The recommendations issued in Japan [43], where tocilizumab is usually given as monotherapy, do not mention a need for monitoring the transaminase levels.

**In practice, the transaminases (ALAT and ASAT) should be assayed before each infusion during the first 3 treatment months (four infusions) and the result checked before starting the infusion. Thereafter, the interval between the transaminase assays can be extended to 3 months.**

In patients with underlying viral hepatitis, if tocilizumab therapy is started, the transaminase levels must be monitored routinely, at an interval no longer than 15 days for the first 3 months and no longer than 3 months thereafter.

### ● Course of action in patients with transaminase elevation

In practice, the first step consists in adjusting the methotrexate dosage if needed. The CRI experts developed two algorithms for managing patients with persistent transaminase elevation (Figures 1 and 2).

## Other liver test abnormalities

Total bilirubin elevation to less than 3 times the ULN was noted in 0.1% to 11% of patients given tocilizumab alone or with a disease-modifying antirheumatic drug [4, 33, 35, 37]. In the clinical studies, transaminase elevation was not associated with clinically significant elevations in the conjugated bilirubin levels, the classic marker for severe hepatotoxicity [4]. An increase in the total bilirubin level (with a parallel increase in unconjugated bilirubin) does not require special monitoring tests or specific treatment.

The recommendations on tocilizumab therapy do not indicate a need for monitoring the serum levels of bilirubin, γGT, or alkaline phosphatase [4]. In the LITHE study [38], however, tocilizumab therapy was discontinued in patients with indirect bilirubin elevation to more than twice the ULN (evidence-based medicine).

## Additional information on the risk of hepatic abnormalities during tocilizumab therapy

### ● Hepatotoxicity of medications in general

All medications have the potential to induce hepatotoxicity. Nevertheless, hepatotoxicity is uncommon, with a rate of 1% to 1/100,000 depending on the drug and mechanism involved (direct toxicity or immunoallergic response). Prior liver disease, which must be detected before starting tocilizumab therapy, may increase the risk of hepatotoxicity with synergistic or additive effects. Therefore, closer monitoring is needed in these patients. With the exception of severe liver cirrhosis, liver disease is not considered a definite contraindication to the use of hepatotoxic drugs, provided the patient is appropriately monitored.

### ● Viral hepatitis and pre-emptive treatment

For the hepatitis C virus, apart from pre-existing fibrosis of the liver associated with chronic infection, there is no definite contraindication a priori to the use of tocilizumab.

For the hepatitis B virus, a positive test for HBs does not contraindicate tocilizumab therapy, particularly when the liver tests fail to suggest significant fibrosis; however, HBs-positive patients should receive pre-emptive antiviral therapy with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) [39] to prevent viral reactivation, which can have severe consequences [41]. This strategy applies to all immunosuppressive drugs, including tocilizumab. The pre-emptive treatment should be continued as long as the immunosuppressive medication is used, if warranted by the hepatic status, in compliance with standard recommendations [42], and for 6 to 12 months after the immunosuppressive medication is stopped. Finally, in patients with underlying viral hepatitis who are started on tocilizumab therapy, the transaminase levels should be monitored routinely, at intervals no longer than 15 days for the first 3 months and no longer than 3 months thereafter.

### ● Transaminase elevation in therapeutic trials

According to the Summary of Product Characteristics [4], 3778 patients in all received at least one dose of tocilizumab 4 mg/kg or 8 mg/kg. The long-term open-label extension studies included 2562 patients who received tocilizumab 8 mg/kg with or without DMARDs. Exposure duration was usually less than 6 months. Total exposure in the long-term safety analysis was 3685 patient-years [4].

In the clinical trials, ALAT elevation was noted in 1% to 16% of patients given tocilizumab alone or with DMARDs [4, 38].

Transient ALAT and ASAT elevation >3 x ULN was noted in 2.1% of patients given tocilizumab 8 mg/kg compared to 4.9% of patients on methotrexate, 6.5% of patients on tocilizumab 8 mg/kg plus DMARD, and 1.5% of patients on placebo plus DMARD.

The concomitant use of potentially hepatotoxic medications (e.g., methotrexate) was associated with an increased rate of transaminase elevation compared to patients on tocilizumab monotherapy. ALAT and ASAT elevation >5 x ULN was

noted in 0.7% of patients on tocilizumab monotherapy and 1.4% of those on tocilizumab plus DMARD [4]. Most of these patients were taken off tocilizumab permanently.

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE [32, 35-37] in RA patients, including 2562 patients exposed to tocilizumab for a mean of 1.5 years showed that transaminase elevation was common but usually resolved in the absence of any changes in the treatment regimen [44]. In the pooled analysis, the rate of transaminase elevation to 1-3 x ULN on two consecutive assays was 54.5% on tocilizumab 8 mg/kg + DMARD *versus* 39.5% on methotrexate alone [44]. In the same analysis, the rate of transaminase elevation to >3 x ULN was 2% (ALAT) to 6.5% (ASAT) on tocilizumab 8 mg/kg + DMARD *versus* 2.1-4.9% on methotrexate alone [45].

In the OPTION and TOWARD studies [32, 35], transaminase elevation required temporary tocilizumab discontinuation (values >3 x ULN) in 1.9% to 3.4% of patients and permanent tocilizumab discontinuation (for values >5 x ULN or >3 x ULN persistently) in 0.8% to 3.4% of patients [35]. Transaminase levels >3 x ULN returned to normal despite tocilizumab continuation in over one-third of cases in these trials [35]. A few patients who had prolonged liver test abnormalities underwent liver biopsy, which showed no evidence of aggressive hepatitis [46].

### ● Bilirubin elevation in therapeutic trials

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE (32, 35-37) in RA patients, including 2,562 patients exposed to tocilizumab for a mean of 1.5 years showed a rate of bilirubin elevation of 9.1% with tocilizumab 8 mg/kg + DMARD *versus* 8.7% with tocilizumab 8 mg/kg alone and 1.8% with methotrexate alone [45]. Bilirubin elevation above 3x ULN was extremely rare [45]. An increase in the unconjugated bilirubin level does not require tocilizumab discontinuation.

### ● Liver data during long-term tocilizumab therapy

In the STREAM 12-week randomized controlled trial followed by a 12-week open-label extension phase [30], patients given tocilizumab 8 mg/kg as monotherapy were monitored for up to 5 years [30]. ASAT and ALAT elevations of grade 2 or higher occurred during the study in 6.3% (n=9/143) and 9.8% (n=14/143) of patients. Transaminase elevation was usually transient; of the 143 initial patients, 2 had transaminase elevations categorized as serious adverse events. No cases of clinical hepatitis were observed [30].

The Food and Drug Administration [47] determined that the risk was not higher in patients who received long-term tocilizumab therapy. The risk of liver test abnormalities was about 1% in patients monitored after participating in controlled trials, and 8% of patients experienced at least one episode of transaminase elevation >2 x ULN. Bilirubin elevation to >2 x ULN occurred in 1% of patients.

● **Hepatic abnormalities recorded in registries**

To date, no cases of hepatic abnormalities have been reported in the registries.

## Conclusion

In sum, tocilizumab is not associated with severe hepatotoxicity. Hepatic disease is not a definite contraindication to tocilizumab therapy, except for severe hepatocellular failure, which limits the use of all drugs and requires pharmacokinetic and pharmacodynamic evaluations to define the modalities of use, if any.

However, as with all recently introduced medications, the use of tocilizumab requires regular monitoring by laboratory tests followed by dosage adjustments as indicated by the results. Patients with pre-existing hepatic risk factors require non-invasive tests for fibrosis and, in some cases, a pre-treatment liver biopsy to enable appropriate dosage adjustment and intensification of the monitoring program. Finally, as with all immunosuppressive drugs, patients considered for tocilizumab therapy should be screened for hepatitis B and C virus infections.

Management of Patients with Past or Present
# Bacterial and/or Viral Infections

| Evidence Based Medicine | Official recommendations | Expert opinion |

## Steps to be taken before tocilizumab initiation to prevent infections

### ● Bacterial infections

➤ Evaluate the overall risk by looking for predisposing factors: co-morbidities (diabetes, diverticulitis, respiratory disease, and chronic wounds), foreign material in the body (prosthesis, indwelling catheter), a past or present history of treatment with immunosuppressive agents or glucocorticoids, and evidence by patient interview and/or physical examination of an overt or latent focus of infection.

➤ Check the immunisation record: always check that all vaccines are up to date. Consider administering the pneumococcal vaccine if possible at least 2 weeks before tocilizumab initiation, as with all biotherapies used in rheumatoid arthritis.

➤ Rule out contraindications to tocilizumab therapy: tocilizumab is contraindicated in patients with severe uncontrolled infections (septicaemia, opportunistic infections) or a high risk of bacterial infection (recent infection of a prosthesis, indwelling catheter) [4].

➤ In patients with diverticulitis: see, in particular, the sheet entitled "Management of patients with a past or present history of ileocolonic disease".

➤ Obtain screening tests for latent tuberculosis if not done in the past 2 years. As with other biotherapies, patients should be screened for latent tuberculosis before starting tocilizumab therapy [4], in keeping with AFSSAPS recommendations [48]: 5 U Tubertest® or in vitro QuantiFERON Gold® test or T-Spot-TB® test (which are being evaluated in France) and chest radiograph. Patients with latent tuberculosis should receive prophylactic anti-tuberculous therapy (isoniazid for 9 months or isoniazid plus rifampin for 3 months) and tocilizumab should be postponed for at least 3 weeks after initiation of the anti-tuberculous regimen.

### ● Viral infections

The results of serological tests for the hepatitis B and C viruses and the HIV should be available before starting tocilizumab therapy.

A positive serological test for the hepatitis C virus in the absence of pre-existing fibrosis related to chronic HCV infection does not a priori constitute a definite contraindication to tocilizumab therapy.

Positive serological test for the hepatitis B virus: a positive test for HBs, particularly when the liver tests show no evidence of significant fibrosis, does not contraindicate tocilizumab therapy; however, as with other immunosuppressive drugs, patients with a positive HBs test should receive

pre-emptive treatment with nucleoside analogues (lamivudine, entecavir) or nucleotide analogues (tenofovir) (see the sheet entitled "Management of patients with a past or present history of hepatic abnormalities").

Positive test for the HIV: tocilizumab therapy can be considered in the event of highly refractory and incapacitating rheumatoid arthritis, provided the plasma viral load is monitored closely throughout the treatment period.

The advice of specialists (hepatologist, infectiologist) should be obtained before choosing the treatment strategy.

## What are the warning signs of infection in patients on tocilizumab?

In patients on tocilizumab, many warning signs may develop:
➤ a fever
➤ chills
➤ asthenia
➤ abdominal pain
➤ a cough
➤ dyspnea
➤ a skin rash
➤ a burning sensation during urination
➤ sudden recurrence of joint pain, highly inflammatory monoarthritis or oligoarthritis
➤ depending on the site of infection: low back pain in pyelonephritis or discitis, abdominal pain in diverticulitis
➤ re-ascent of the laboratory markers for inflammation
➤ leukocytosis.

**Special vigilance for the detection of infections is in order in patients receiving tocilizumab therapy, as IL-6 inhibition, similar to TNF inhibition, may blunt the signs and symptoms of acute inflammation associated with infection: thus, IL-6 inhibition may result in the absence of fever, leukocytosis, and CRP elevation (and of elevations in other acute-phase reactants).**

## Course of action in the event of infection during tocilizumab therapy

As with all biotherapies, the development of an infection requires the discontinuation of tocilizumab therapy, an evaluation of the severity of the infection, the collection of microbiological specimens whenever possible and, without waiting for the results, the prompt initiation of anti-infectious therapy, whose effectiveness should be evaluated and monitored.

Special vigilance for the detection of infections is in order in patients receiving tocilizumab therapy, as IL-6 inhibition, similar to TNF inhibition, may blunt the signs and symptoms of acute inflammation associated with infection: thus, IL-6 inhibition may result in the absence of fever, leukocytosis, and CRP

elevation (and of elevations in other acute-phase reactants). In this situation, other biological markers may be useful, such as CD64 [49].

**At the slightest suspicion of infection, tocilizumab therapy should be discontinued until the infection is either ruled out or, if not severe, controlled and resolved. Severe infection contraindicates tocilizumab therapy (see above) [4].**

Serious infections (defined as infections requiring hospital admission or intravenous antimicrobial therapy) should be reported to the pharmacovigilance centre.

## When can tocilizumab therapy be re-started?

Once the patient is fully recovered from the infection, the appropriateness of re-starting tocilizumab therapy should be evaluated based on the risk/benefit ratio. The tocilizumab re-start date depends on the severity and site of the infection but should always occur at a distance from discontinuation of the antibiotics.

Close monitoring is in order when re-starting tocilizumab therapy. Prompt recurrence of the manifestations of infection should prompt an assessment of the appropriateness of permanent tocilizumab discontinuation.

## Additional information on current knowledge

### ● Role for IL-6 in defence mechanims againts infection

IL-6 activates the macrophages and neutrophils and upregulates the expression of adhesion molecules, the chemokine profile, and antibody production. Therefore, IL-6 plays a role in defence mechanisms against infection. IL-6 decreases HBV replication [48] and IL-6-deficient mice are at increased risk for a number of infections (listeriosis, toxoplasmosis, candidiasis) [50]. IL-6 inhibition by tocilizumab may interfere with these antibacterial defence mechanisms, thereby promoting the development or reactivation of infections. The role for IL-6 in defence mechanisms against mycobacterial infections is probably ancillary, but IL-6 contributes to macrophage activation.

The precautions aimed at minimising the risk of infection are those recommended for all biotherapies.

### ● Risk of bacterial and viral infections during tocilizumab therapy

In controlled studies, the infection rate in patients receiving tocilizumab (8 mg/kg) + DMARD was 127/100 patient-years compared to 112/100 patient-years in the placebo + DMARD groups. In the long-term open-label extension studies, the infection rate in patients receiving tocilizumab + DMARD was 116/100 patient-years [4].

### Serious infections

In controlled studies (LITHE, OPTION, TOWARD, and RADIATE), the rate of serious infections in patients receiving tocilizumab 8 mg/kg + DMARD (n=1,582) was 5.2/100 patient-years (95% CI, 3.7-7.1) compared to 3.8/100 patient-years (95% CI, 2.3-5.9) in the placebo + DMARD group (n=1170) [51]. With tocilizumab monotherapy (AMBITION), the rate of serious infections was 2.9/100 patient-years in the tocilizumab group (95% CI, 0.8-7.3), compared to 1.5/100 patient-years (95% CI, 0.2-5.4) in the methotrexate group [37].

The following serious infections were reported: pneumonia, cellulitis, herpes zoster, gastroenteritis, diverticulitis, septicaemia, and bacterial arthritis.

Van Vollenhoven et al. [40] reported that the serious infection rate in long-term studies (n=4009; mean follow-up, 2.4 years) was 4.7/100 patient-years and showed no increase with increasing exposure time.

A pooled analysis of the extension phases of four phase III trials (AMBITION, OPTION, TOWARD, and RADIATE [30, 45, 52, 53] in RA patients, including 2,562 patients exposed to tocilizumab for a mean of 1.5 years showed that the serious infection rate was 3.9/100 patient-years (95% CI, 3.3-4.6). Statistically significant associations were found between the risk of serious infection and diabetes, age older than 65 years, a past history of infection, and systemic glucocorticoid therapy; whereas no association was found with neutropenia [45].

In Japan, the 5-year open-label extension phase of a phase II trial (STREAM) included 143 patients, of whom 66% took tocilizumab for 5 years. The rate of serious infections during the resulting 612 patient-years of tocilizumab monotherapy was 5.7/100 patient-years [30].

Tuberculosis seems uncommon [52], with 6 cases during 10,552 patient-years of tocilizumab therapy, including 2 cases in patients who did not undergo tuberculosis screening before treatment initiation.

It is worth noting that active chronic EBV infection may be exacerbated by treatment with anti-IL-6 antibodies [53] and that no exacerbation of hepatitis occurred in a patient with chronic hepatitis B who took tocilizumab for 5 years in combination with an antiviral agent [54].

A very small number of cases of acute infection related to reactivation of herpes viruses (EBV, CMV) and complicated by macrophage activation syndrome have been reported [29, 55].

## Management of Patients with Past or Present
# Solid Cancer or
#                Haematological Malignancy

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

When evaluating a new immunomodulating agent, the potential for increasing the risk of malignant disease should always receive close attention, particularly when the drug interferes with the cytokines involved in innate immunity such as TNF-α or interleukin-6 (IL-6).

The preclinical development program for tocilizumab found no evidence suggesting an increased risk of malignancy. During the clinical development program (phase II and III studies), a very limited number of patients were diagnosed with cancer, the prevalence being comparable to that seen in the methotrexate-treated control groups of monotherapy trials and in the groups given conventional DMARDS and a placebo in the combination trials [46] (Table 7).

In the LITHE trial, after 2 years of follow-up, the rate of cancer was higher in the group given tocilizumab 4 mg/kg plus methotrexate compared to the other groups: 0.4/100 patient-years (1/284.81 patient-years) with the placebo, 1.9/100 patient-years (10/521.9 patient-years) with tocilizumab 4 mg/kg, and 0.9/100 patient-years (12/1,320.41 patient-years) with tocilizumab 8 mg/kg [46]. Given the current state of knowledge, the observed differences are not relevant but warrant continued surveillance.

An analysis of the Roche database including all patients who participated in randomized trials showed no cancer risk increase with tocilizumab 8 mg/kg compared to the control groups Only four haematological malignancies were recorded (two non-Hodgkin lymphomas, one Hodgkin lymphoma with pre-existing manifestations, and one gammapathy, also with pre-existing manifestations). There was no excess of non-melanoma skin cancers [11]. In this database, the risk of developing malignant disease does not increase with the duration of tocilizumab exposure (Table 8).

This meta-analysis of controlled randomised trials produces a control group of patients selected at random, which enables a valid risk analysis. However, the limited number of patients and fairly short period of double-blind therapy does not provide information on the risk of delayed events that may develop after prolonged exposure. In addition, the patients included in the trials were selected; more specifically, patients with solid cancer diagnosed within 5 years before study initiation were not eligible. These restrictions should be borne in mind when comparing the solid cancer and lymphoma rates in tocilizumab-exposed patients to those expected in the general population or observed in historical cohorts of rheumatoid arthritis patients treated with non-biological or biological agents.

## What steps should be taken before tocilizumab therapy in patients with a history of solid cancer or haematological malignancy?

No studies have evaluated the advantages or risks of tocilizumab therapy in patients with cancer or lymphoproliferative disease, or a recent history of these diseases.

Given the absence of data, prudence dictates that tocilizumab not be used in patients with a history of solid cancer or haematological malignancy in the past 5 years, except for basal or squamous cell epithelioma removed with tumour-free margins. Nevertheless, in patients with localized cancer that was completely removed (no risk of metastasis), the use of tocilizumab may be discussed with the oncologist on a case-by-case basis.

In patients with myeloma (or a past history of myeloma) or monoclonal gammopathy of undetermined significance, the use of tocilizumab may be considered according to the risk/benefit ratio in the individual patient. Tocilizumab therapy can be considered, as sound preclinical and clinical data suggest a beneficial effect of IL-6 inhibition in this situation.

In patients with a history of lymphoma, given the absence of data, the initiation of tocilizumab therapy is not indicated. Nevertheless, when all other treatment strategies including rituximab fail, the appropriateness of tocilizumab therapy may be discussed with the haematologist after an analysis of the risk/benefit ratio. Theoretical considerations suggest that IL-6 inhibition might have beneficial effects on non-Hodgkin B-cell lymphoma. In contrast, in patients with EBV-induced lymphoproliferative disease, tocilizumab therapy is not recommended.

No data are available on the risk of malignancy in patients with risk factors (smoking, HPV infection, exposures to toxic agents such as asbestos). Although these risk factors do not contraindicate tocilizumab therapy, the risk/benefit ratio should first be assessed carefully in conjunction with the oncologist or other relevant specialist.

## What are the warning signs during tocilizumab therapy?

During tocilizumab therapy, the development of several clinical signs may suggest a malignancy, particularly the following:
➤ unexplained fever
➤ decline in general health
➤ weight loss
➤ asthenia
➤ suspicion of lymphoma: peripheral lymphadenopathy, hepatomegaly, splenomegaly, recurrent infections, diaphoresis, pruritus
➤ suspicion of solid cancer: local signs depending on the organ involved.

## Course of action in patients with solid cancer or haematological malignancy during tocilizumab therapy

When a solid cancer or haematological malignancy is found in a patient on tocilizumab therapy, the steps listed below should be taken.

➤ Perform investigations to confirm the diagnosis and assess the stage of the disease.

➤ Discontinue tocilizumab therapy (i.e., do not administer the next scheduled injection).

➤ Adjust the maintenance RA treatment regimen and determine whether concomitant immunomodulators (methotrexate, leflunomide...) should be stopped, at least during the treatment for the malignancy.

➤ Report the case to the pharmacovigilance centre and start appropriate treatment if the diagnosis is confirmed.

The need for permanently discontinuing tocilizumab therapy should be assessed on a case-by-case basis according to the nature of the malignancy.

➤ In patients with generalized cancer or cancer having a high risk of metastatic dissemination (e.g., breast cancer), the reintroduction of tocilizumab therapy is not recommended in the absence of additional data suggesting that there is no risk in this situation.

➤ In patients with localized tumours that were removed completely during surgery, tocilizumab therapy should be stopped until the end of the evaluation and surgical treatment. Subsequently, the appropriateness of re-starting tocilizumab therapy may be discussed with the oncologist on a case-by-case basis depending on the risk/benefit ratio.

➤ In patients with myeloma or lymphoma, tocilizumab therapy should be stopped until the anticancer treatment is completed. Then, in the event of a partial remission of the malignancy, and *a fortiori* of a complete remission, tocilizumab therapy re-initiation may be discussed with the oncologist based on the risk/benefit ratio.

Any malignancy occurring during tocilizumab therapy must be reported to the pharmacovigilance centre.

## Additional information on the role for IL-6 in carcinogenesis

The role for IL-6 in carcinogenesis has been extensively investigated.

➤ IL-6 was investigated in vitro using cell lines and in vivo using animal models (mice) lacking IL-6 (IL-6 -/-) or treated with dominant negative IL-6 inhibitors. In these models, the behaviour of induced tumours was investigated. Overall, these studies showed a pro-tumour effect of IL-6. Thus, IL-6 facilitated cancer-cell survival (by inhibiting the apoptosis) and proliferation, and also promoted metastatic dissemination by stimulating cellular adhesion and angiogenesis. IL-6 can also act by interfering with hormonal or enzymatic factors, for instance by increasing the production of aromatase (which may promote breast cancer). IL-6 also promotes the development of chemoresistance. The effect of IL-6 on the immunological response against tumours is more controversial [56, 57]. These overall pro-carcinogenic

effects of IL-6 are mediated by activation not only of the JAK-STAT (STAT3) pathway, but also of the MAPkinases pathway. Only a few studies in in vitro and in vivo models, all relatively old, suggest a possible anti-tumour role for IL-6 [58, 59]. Thus, overall, IL-6 is considered a pro-tumoural factor in lymphoproliferative syndromes (myeloma, lymphoma, Castleman's disease) and in several solid cancers (breast, ovary, prostate, lung, kidney, colon, glioma, melanoma...).

➤ The role for IL-6 in various malignant diseases in humans has been investigated

- Studies have shown that the -174G/C polymorphism of the IL-6 promoter (associated with high serum IL-6 levels) correlates with the development of lymphoproliferative syndromes (lymphoma, myeloma) and solid cancers (colon, breast)[60, 61]. Data reported about other cancers (e.g., head and neck cancers and gastric cancer) are more controversial.

- IL-6 serum and tissue levels in patients with various types of cancer have been assessed in nearly 200 studies [62]. Overall, serum IL-6 levels seemed elevated in patients with cancer. However, no prospective studies are available to establish a causal link between IL-6 production and the development of cancer.

- Pathophysiologic studies in a number of cancers strongly support a pro-tumour effect of IL-6.
  - In patients with myeloma, lymphoma, or Castleman's disease, IL-6 is considered a marker of adverse prognostic significance. IL-6 may be produced not only by the malignant cells (B cells or plasma cells), but also by the tumour environment (stromal cells). This autocrine and paracrine IL-6 production acts on the tumour cells, which express the IL-6 receptor. The role for IL-6 is particularly prominent in Castleman's disease. In Castleman's disease induced by human herpes virus 8, this virus can produce an IL-6 analogue that induces tumour proliferation.
  - In hepatocarcinoma, IL-6 has been shown to play a key role in the malignant transformation of hepatocytes subjected to a viral, toxic, or immunological insult. Elegant studies in a model of diethylnitrosamine-induced hepatocarcinoma confirmed the major importance of IL-6 in hepatocarcinoma development [63-65].

- Thus, in most of the malignancies seen in humans, IL-6 is believed to contribute to carcinogenesis and metastatic dissemination. Among the few controversial data, those obtained in studies of melanoma deserve to be mentioned. In vitro, on cell lines, IL-6 can inhibit melanoma, whereas in a murine melanoma model, IL-6 increases the risk of metastatic disease [66]. Serum IL-6 levels are elevated in humans with metastatic melanoma and correlate with tumour proliferation [67].

Taken in concert, this body of evidence pointing toward a pro-tumour effect of IL-6 prompted studies of various IL-6 inhibitors in several tumours [56]. The main malignancies studied to date are myeloma and Castleman's disease, although IL-6 inhibition has also been evaluated for the treatment of lymphoma and other disseminated cancers, most notably renal cancer, with conflicting results [68, 69].

## Management of Patients with Past or Present
# History of Ileocolonic Disease

| Evidence Based Medicine | Official recommendations | Expert opinion |

As with other biotherapies, the risk of infection is increased during tocilizumab therapy. Diverticulitis was one of the infectious events seen during tocilizumab therapy, albeit at a far lower rate than upper respiratory tract infections. Thus, diverticulitis is classified among the "uncommon" adverse events, i.e., those having rates of occurrence lower than 1/1000 but greater than 1/100.

Based on the clinical development program for tocilizumab, the FDA estimated the incidence of lower intestinal tract perforation at 0.15/100 patient-years. In the two North-American databases of RA patients who had not received tocilizumab therapy *(United Health Care Database and Marketscan Database)*, the incidences were 0.16 and 0.14 events/100 patient-years, respectively [70]. Lower intestinal tract perforation occurred only in the tocilizumab groups. However, all patients with lower gastrointestinal tract perforation had a history of bowel disease or current treatment with NSAIDs and/or glucocorticoids [40].

An even smaller number of patients experienced complications of diverticulitis, some of which were fatal. These complications consisted of generalized suppurative peritonitis, bowel perforation (usually of the colon), fistulas, and abscesses.

It should be borne in mind that NSAID therapy increases the risk of such complications in the general population [71]. More specifically, in RA patients the widespread use of NSAIDs and glucocorticoid therapy in combination is associated with an increased risk of these complications [72-76].

### What steps should be taken before tocilizumab therapy in patients with a history of ileocolonic disease?

➤ Routinely ask the patient about a known history of diverticular disease, particularly with episodes of diverticulitis, or of perforation or ulcers.

➤ Routinely inform the patient about the risk of ileocolonic complications and ask the patient to seek medical help promptly in the event of abdominal pain, bleeding, or a change in bowel habits, particularly if there is also a fever; the patient should immediately inform the physician that he/she is on tocilizumab therapy.

➤ Inform the patient's primary-care physician via the guide for physicians and pharmacists, which can be communicated via the patient or another means. This guide draws attention to the risk of diverticulitis and other complications, to the possibility that tocilizumab may mask classic signs of infection (fever and CRP elevation), and to the potentially devastating impact on patient outcomes of any delay in initiating appropriate treatment.

➤ In patients with a history of diverticulitis:

- reappraise the risk/benefit ratio; in this situation, a discussion with the gastroenterologist and primary-care physician may be helpful;
- to the extent possible, correct any other risk factors for superinfection or perforation such as poorly controlled diabetes, glucocorticoid therapy, or NSAID therapy;
- in patients who have had a prior episode of diverticular sigmoiditis, consider sigmoid colon resection surgery. Although surgery is generally indicated only in the event of a second episode, prophylactic surgery after the first episode should be considered in patients who are scheduled to receive treatment with tocilizumab (or another immunosuppressive agent).
- careful attention should be directed to informing and educating the patient and primary-care physician, as described above.

## What are the warning signs of ileocolonic disease?

Before each tocilizumab infusion, the absence of abdominal symptoms or signs should be checked. It should be borne in mind that the classic signs of infection (fever, CRP elevation) may be missing in patients on tocilizumab therapy, and the slightest suspicion should lead to the infusion being postponed until the patient is evaluated by a specialist.

## Course of action when ileocolonic disease is diagnosed

➤ If abdominal symptoms develop, discontinue tocilizumab therapy and refer the patient to a gastroenterologist; evaluation by a gastroenterologist should be obtained very promptly in patients with a fever, bleeding, or abnormal abdominal physical findings;

➤ The initial diagnostic and therapeutic strategy should be developed by the gastroenterologist based on national recommendations [77] then by the primary-care physician if there are no complications.

## When can tocilizumab therapy be re-started?

In patients who experience diverticulitis while on tocilizumab therapy, the available data are inadequate to recommend re-starting the drug.

Prophylactic surgical resection should be considered.

## Management of Patients with
# Infusion-Related Reactions

| Evidence Based Medicine | Official recommendations | Expert opinion |
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## Infusion-Related Reactions

Infusion-related reactions (defined as events occurring during or within 24 hours after an infusion) have been reported with tocilizumab. In clinical trials, infusion-related reactions were somewhat more common with tocilizumab than with the placebo (6.9% with tocilizumab 8 mg/kg + methotrexate *versus* 5.1% with the placebo + methotrexate)[4].

The manifestations reported to date are listed below.

➤ In most cases, the manifestations were minor and required no change in the treatment:

- hypertension (usually during the infusion); and headaches, rash, and urticaria (chiefly after the infusion)[4].

➤ More rarely, severe allergic reactions requiring treatment discontinuation occurred. Thus, hypersensitivity reactions (severe allergic reactions):

- occurred in 0.3% of patients in the clinical trials and open-label extensions,
- usually between the second and fifth infusion.
- Severe anaphylactic reactions
    - occurred in 0.2% of patients in clinical trials,
    - and were more common with 4 mg/kg than with 8 mg/kg[4].

## Frequency of immunisation against tocilizumab

An immune response to tocilizumab seems uncommon. In the clinical trials, anti-tocilizumab antibodies were found in only 1.6% of patients.

Most of the patients with hypersensitivity reactions had detectable anti-tocilizumab antibodies[4].

Whether anti-tocilizumab antibodies may play a role in potential escape phenomenon (decrease in effectiveness) is unknown.

## Should premedication be given?

The extremely low rate of infusion-related reactions does not warrant routine premedication.

## Course of action in the event of an infusion-related reaction

The management depends on the severity of the reaction.

Severe reaction (anaphylaxis, rapid development of a rash):

➤ Stop the infusion immediately.

➤ The other measures depend on the severity of the symptoms:
- antihistamines for moderate reactions,
- intravenous glucocorticoid therapy
- resuscitation in the most severe forms.

Mild reaction (moderate blood pressure elevation, headaches):

➤ decrease the infusion rate,

➤ or stop the infusion for a few minutes then re-start at a slower rate.

## Course of action in the event of a delayed reaction

An urticarial skin rash may develop 24 to 72 hours after the infusion.

Patients with severe symptoms should be admitted. In moderate forms, the treatment may consist in glucocorticoid therapy (or a transient increase in the previous glucocorticoid dosage), if needed combined with an antihistamine agent.

## When can tocilizumab therapy be re-started?

A severe allergic reaction is a definite contraindication to further tocilizumab therapy.

After a moderate reaction, tocilizumab therapy may be re-started, although caution is in order and the infusion should be started at a slower rate.

After a mild skin rash, premedication with an antihistamine agent and a glucocorticoid may be in order.

## Management of Patients
# Receiving Concomitant Medications

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

The initiation of tocilizumab treatment in combination with conventional DMARDs or after other biological agents raises many questions about the potential of concomitant medications for maintaining or even increasing the effectiveness of tocilizumab and, more importantly, about potential drug-drug interactions that may lead to adverse events. The results of the therapeutic trials have led to the recommendation that tocilizumab be used in combination with methotrexate. However, tocilizumab may be used alone in patients who cannot tolerate methotrexate or in whom further methotrexate therapy would be inappropriate.

In practice, when considering tocilizumab therapy in combination with a DMARD other than methotrexate, the TOWARD study [35] is of interest: the results suggest that such combinations may raise no specific safety concerns and may produce a similar level of therapeutic efficacy.

Tocilizumab therapy can be considered in a patient already treated with another biological agent, provided this last agent is discontinued and a suitable wash-out period is allowed to elapse. The duration of the wash-out period depends on the nature and half-life of the agent. Finally, pharmacokinetic data indicate that methotrexate, NSAIDs, and glucocorticoids have no effect on the clearance of tocilizumab.

In contrast, medications that are metabolized by the cytochrome P450 enzymes require individual dosage adjustment to maintain effectiveness.

### Tocilizumab combined with, or given after, another biologic agent

See table 9.

In the RADIATE study [36], treatment with tocilizumab or a placebo combined with methotrexate was offered to patients who had intolerance or an inadequate therapeutic response to TNF antagonists. The interval between TNF antagonist discontinuation and tocilizumab initiation was at least 5 times the half-life of the TNF antagonist. Tocilizumab was more effective than the placebo. The most common adverse events in the tocilizumab group were infections, gastrointestinal symptoms, and headaches.

## Tocilizumab in combination with conventional disease-modifying antirheumatic drugs

The OPTION trial [32] established the efficacy and safety of tocilizumab in combination with methotrexate in a mean dosage of 15 mg/week. In patients with intolerance or contraindications to methotrexate, the efficacy and safety of using another DMARD are key concerns. In the TOWARD trial [35], patients received either tocilizumab or a placebo, and they continued their previous DMARDs. The analysis of subgroups based on the nature of the DMARD (methotrexate, antimalarials, sulfasalazine, leflunomide, gold, or azathioprine) showed that, overall, the tocilizumab/DMARD combination was more effective than the DMARD alone and that the various DMARDs used with tocilizumab were fairly well tolerated. In this trial, no noticeable differences in adverse event rates were found across the DMARDs used with tocilizumab.

The most common adverse events in the tocilizumab/DMARD group were headaches, hypertension, neutropenia, cytolysis, and hypercholesterolemia (Table 10). It is unclear whether the tocilizumab/DMARD combination is associated with a higher adverse event rate than tocilizumab alone, as there are no published studies comparing a group of patients given tocilizumab alone to another group given tocilizumab plus a DMARD. However, in 5 patients who experienced neutropenia, decreasing the DMARD dosage significantly improved the neutrophil count.

The ongoing Act-Ray trial is comparing the efficacy and safety of tocilizumab alone or with methotrexate.

### Recommendations

Methotrexate is the recommended concomitant medication for patients on tocilizumab. However, in patients with intolerance or contraindications to methotrexate, another conventional DMARD may be used in combination with tocilizumab, and preference should then be given to DMARDs with proven structural effects.

In the event of neutropenia or cytolysis (<3 x ULN), refer to the sheets entitled "Monitoring tocilizumab therapy" and "Management of patients with past or present hepatic abnormalities".

## Tocilizumab monotherapy

In patients who cannot tolerate any of the conventional DMARDs or who are unwilling to continue DMARD therapy, tocilizumab monotherapy may be considered.

➤ In the AMBITION trial [37], patients with RA and no history of failing methotrexate or biological therapy received either methotrexate or tocilizumab monotherapy. Tocilizumab monotherapy was more effective than methotrexate, and safety was fairly similar except for higher rates in the tocilizumab group of grade 3 neutropenia (500-1,000/mm$^3$; 3.1% *vs*. 0.4%), dyslipidaemia (13.2% *vs*. 0.4%), and severe infection (1.4% *vs*. 0.7%).

➤ The efficacy and safety of tocilizumab were also assessed comparatively to methotrexate in two studies, the SATORI study [33] and the SAMURAI study 31).

• The SATORI study was a multicentre randomised controlled trial in which 125 patients who had failed low-dose methotrexate therapy were given either tocilizumab 8 mg/kg once monthly + placebo or continued low-dose methotrexate (8 mg/kg/week). The proportion of patients who had an ACR20 response after 24 weeks was 80.3% in the tocilizumab group and 25.0% in the methotrexate group (p<0.001). A DAS remission was achieved in 43.1% of the tocilizumab patients and in 1.6% of the controls [33]. Serious adverse events were reported in 6.6% of the patients on tocilizumab and 4.7% of those on methotrexate; these events had favourable outcomes with appropriate treatment [34].

• The SAMURAI trial was a multicentre, randomised, controlled, open-label trial in RA patients who had failed at least one DMARD. Tocilizumab 8 mg/kg once monthly (n=158) was compared to DMARDs (including methotrexate, in a mean dosage of 8 mg/week) (n=148). The change in the total Sharp score between baseline and week 52 (primary criterion) was significantly smaller in the tocilizumab group than in the DMARD group (p<0.001) and significant differences in favour of tocilizumab were also found for the ACR20, ACR50, and ACR70 response rates (p<0.001 for all comparisons). At week 52, a DAS remission was noted in 59.1% of the patients given tocilizumab compared to 3% of those given a DMARD (p<0.001). Serious adverse events were reported in 18% of patients given tocilizumab *versus* 13% of those given DMARDs; they consisted chiefly of infections [34].

## Tocilizumab combined with an anti-inflammatory or analgesic agent

Population pharmacokinetics studies found no evidence that methotrexate, NSAIDs, or glucocorticoids affected the clearance of tocilizumab [4].

There are no published data indicating increased intolerance to tocilizumab in patients receiving concomitant treatment with a glucocorticoid, an NSAID, or an analgesic.

## Tocilizumab combined with other treatments

*In vitro* vitro studies of cultured human hepatocytes have shown that IL-6 downregulates the expression of the isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP3A4. Tocilizumab therapy normalizes the expression of these enzymes. Given the fairly long elimination half-life of tocilizumab (t1/2=8 to 14 days), the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after tocilizumab discontinuation.

When initiating or discontinuing tocilizumab therapy in patients who are also taking medications that are metabolized by the CYP3A4, 1A2, 2C9, or 2C19 isoenzymes (e.g., atorvastatin, calcium channel inhibitors, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) (Table 1) and that require individual dosage adjustment, monitoring is in order, as the dosages may need to be adjusted to maintain the treatment effect :
- at tocilizumab initiation -> increase in the dosage of the concomitant drug
- 1 to 2 weeks after tocilizumab discontinuation -> decrease in the dosage of the concomitant drug.

# Management of Patients Who
# Require Surgery or Dental Care

| Evidence Based Medicine | Official recommendations | Expert opinion |

Surgery in patients receiving tocilizumab therapy may, in theory, lead to infectious complications and/or delayed healing [78, 79]. However, these risks have not been evaluated in detail in published studies (no clear recommendation in the Summary of Product Characteristics). Therefore, the advice given here is based on the opinions of experts, who considered, among other factors, the risk of infection associated with the surgical procedure.

## Pharmacokinetic data [47]

The half-life of tocilizumab varies with the concentration of the drug. At the steady state, after a dose of 8 mg/kg every 4 weeks, the effective half-life decreases from 14 to 8 days as the concentrations decline over the interval between infusions.

## Anti-IL-6 treatment: data from the literature

No specific data are available on the risk of postoperative infection in patients treated with tocilizumab. The only available study is a retrospective study designed to investigate changes in parameters suggesting infection (fever, CRP level, leukocyte count, neutrophil count, and lymphocyte count) for 2 weeks after surgery in 22 patients receiving tocilizumab (8 mg/kg every 4 weeks) and 22 patients receiving conventional maintenance treatment (including 10 on methotrexate and 17 on glucocorticoids) matched on age, sex, and type of surgical procedure [80].

Tocilizumab therapy was not stopped. The mean time from the last tocilizumab infusion to surgery was 16.0±9.5 days (3-27 days). Nevertheless, no cases of postoperative infection or delayed healing were recorded in the tocilizumab group. Tocilizumab therapy was associated with significantly less body temperature elevation (0.45° *vs* 0.78°C) and with complete absence of the CRP elevation usually seen after surgery: thus, of the 22 tocilizumab patients, 18 had normal CRP values and 4 had increases by 1 to 10 mg/L; whereas CRP levels were elevated in all the controls (55 mg/L on day 1, 29 mg/L after 1 week, and 22 mg/L after 2 weeks). Finally, the leukocyte counts did not change substantially in either group.

The only available recommendations are those found in the practical guide to tocilizumab use issued in 2009 by the Japan College of Rheumatology [43]. Given that tocilizumab may delay healing and can blunt signs of postoperative infection (no fever, normal CRP), the authors recommend that surgery be postponed until at least 14 days have elapsed since the last tocilizumab infusion.

## Elective surgery

**Given the half-life of tocilizumab and the persistence of active drug levels 4 weeks after the infusion, in this situation where postponing surgery is feasible, the experts recommend stopping tocilizumab therapy at least 4 weeks before the surgical procedure.**

This washout period may be adjusted and modified on a case-by-case basis depending on the factors listed below.

➤ nature of the surgical procedure, as the risk of infection may vary across procedures: "sterile environment" (e.g., cataract surgery), septic environment (e.g., sigmoiditis), or environment at risk for sepsis (e.g., joint replacement surgery);

➤ co-morbidities and other patient-related factors: history of infection, joint prostheses, diabetes, concomitant corticosteroid therapy;

➤ severity of the joint disease and degree of control achieved by treatment (a longer wash-out period, which probably decreases the risk of postoperative infection, does not necessarily carry a risk of RA exacerbation).

In every case, tocilizumab therapy should be re-started only when healing is complete and provided there is no infection.

## Emergent surgery

For patients who require immediate surgery, the experts suggest the following recommendations.

➤ Stop tocilizumab therapy.

➤ Consider prophylactic antimicrobial therapy if the procedure is associated with a high risk of infection (e.g., peritonitis) [81].

➤ Provide very close postoperative monitoring: special attention should be directed to the local operative site findings and to the presence of pain, as patients on tocilizumab therapy may have no fever or CRP elevation.

➤ Re-treat with tocilizumab only after complete healing is achieved (and any antibiotics are discontinued), in the absence of infection.

## Dental care

Regular oral hygiene and visits to the dentist are recommended. Appropriate dental care should be provided before initiating tocilizumab therapy.

● **Routine dental care (cavities, scaling):**

Although there are no data suggesting a need to discontinue tocilizumab therapy, prophylactic antimicrobial therapy can be suggested.

● **Dental procedures associated with a risk of infection (e.g., extraction, apical granuloma, or abscess):**

Tocilizumab should be stopped at least 4 weeks before the procedure and prophylactic antimicrobial therapy should be suggested [82].

● **Implants :**

There is no definite indication to stop tocilizumab, although a high level of vigilance for potential infection is in order.
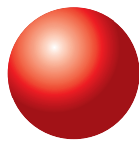
## Management of Patients
# Who Are or Want to Become Pregnant

| Evidence Based Medicine | Official recommendations | Expert opinion |

Given the absence of adequate data, tocilizumab is contraindicated in pregnant women. Therefore, effective contraceptive methods must be used as soon as tocilizumab therapy is initiated.

## Pharmacokinetic data [4]

The half-life of tocilizumab varies with the concentration of the drug. At the steady state, after a dose of 8 mg/kg every 4 weeks, the effective half-life decreases from 14 to 8 days as the concentrations decline over the interval between infusions.

## Data from the literature [4]

None of the preclinical data suggests any effect of tocilizumab on fertility. No effect on the endocrine glands or reproductive system was identified during a toxicity study in cynomolgus monkeys, and neither was reproductive capability altered in mice lacking IL-6. Tocilizumab given to cynomolgus monkeys during early pregnancy had no direct or indirect deleterious effects on the pregnancy or the embryonic or foetal development. However, small increases in abortion, embryonic mortality, and foetal mortality rates were noted after systemic exposure to high doses (more than 100-fold the exposure in humans) in a group receiving a high dose of tocilizumab (50 mg/kg/jour) comparatively to the placebo group and to the groups receiving lower doses.

## In women who want to become pregnant

### ● Before tocilizumab therapy

During the tocilizumab initiation visit, women of child-bearing potential should be asked whether they want to become pregnant.

In women who plan to initiate a pregnancy within the next few months, tocilizumab initiation is not recommended.

However, the severity of the disease should be evaluated. When tocilizumab therapy is deemed crucial to preserve function, the option of postponing plans for a pregnancy should be suggested to the patient (as a means of achieving disease control and subsequently stopping tocilizumab and initiating the pregnancy under better conditions; see "During tocilizumab therapy").

● **During tocilizumab therapy**

**Regarding methotrexate therapy, if used in combination with tocilizumab:**

Women who are already receiving tocilizumab and who plan to initiate a pregnancy should discontinue tocilizumab therapy. The first step consists in stopping methotrexate therapy. The CRAT recommends stopping methotrexate at least 15 days before attempting conception [80]. **The CRI experts recommend waiting for at least one menstrual cycle (4 weeks) after methotrexate discontinuation before attempting conception.**

**In male patients, methotrexate therapy should be stopped and at least one full spermatogenesis cycle (71 days) should be allowed to elapse prior to attempted conception.**

**Regarding tocilizumab therapy:**

The Summary of Product Characteristics (4) recommends that effective contraception be used throughout tocilizumab therapy and for 6 months after the end of the treatment.

This suggested 6-month waiting period is not based on scientific data. It reflects the precautionary principle and should be assessed in the light of the product half-life.

Assuming that the waiting period should be equal to 5 times the half-life (the estimated time needed to eliminate 97.5% of the drug from the body), and using the highest reported half-life times (i.e., 5 times 14 days, 70 days) to obtain a conservative estimate, it may be reasonable to initiate a pregnancy 3 months after the end of tocilizumab therapy.

The factors listed below should also be considered:

➤ The long time to attempted conception recommended in the SPC may lead to challenging clinical situations (exacerbation of the joint disease), particularly as achieving a pregnancy may take time.

➤ The potential effects of tocilizumab on spermatogenesis are unknown. Therefore, the precautions recommended for women apply also to men (3-month wait between the last tocilizumab infusion and attempted conception).

**All these considerations suggest that waiting 3 months between the last tocilizumab infusion and attempts to initiate a pregnancy is reasonable in both women and men.**

## Course of action in the event of a pregnancy during tocilizumab therapy

At present, occurrence of a pregnancy during tocilizumab therapy requires the measures listed below.

➤ immediate discontinuation of tocilizumab therapy (and of methotrexate therapy if not yet stopped);

➤ sonographic foetal monitoring;

➤ and report to the pharmacovigilance centre.

Thus, in the event of a pregnancy in a woman who has not discontinued tocilizumab therapy, a recommendation to continue the pregnancy can be made provided the obstetrical evaluation yields normal results.

In the event the pregnancy is continued, prenatal screening tests focusing on the birth defects described to date should be performed; the healthcare professionals who manage the neonate should be informed of the treatments taken by the mother [83].

## Conception by a male patient taking tocilizumab therapy

At present, conception by a male patient on tocilizumab therapy requires the measures listed below.

➤ sonographic foetal monitoring;

➤ and report to the pharmacovigilance centre.

If the obstetrical evaluation shows no abnormalities, a recommendation can be made to continue the pregnancy.

## Lactation

No data on potential tocilizumab excretion in human breast milk are available, and no studies have been performed in animals.

In patients who want to breast-feed, tocilizumab therapy should not be re-started until the baby is fully weaned.

If the joint disease flares after delivery (a fairly common event in rheumatoid arthritis), the appropriateness of re-starting tocilizumab therapy and, therefore, of weaning the baby should be discussed on a case-by-case basis.

# Vaccinations
## and Tocilizumab Therapy

| Evidence Based Medicine | Official recommendations | Expert opinion |

Rheumatoid arthritis (RA) does not contraindicate vaccinations and, in the absence of immunosuppressive therapy, the response to vaccines is adequate[84]. If a potentially immunosuppressive agent is used, potential safety issues raised by vaccines should be discussed.

As with all biological therapies, the immunisation history of patients given tocilizumab therapy should be checked at several points in time, as indicated below.

➤ before tocilizumab therapy initiation (more specifically, routinely check whether the **mandatory immunisations**, are up to date, particularly those against tetanus and poliomyelitis, and whether the **recommended immunisations** have been performed as appropriate given the patient's characteristics);

➤ when changing from one biological agent to another;

➤ every year in late summer;

➤ and in the event of travel abroad.

## Vaccines that should be recommended prior to tocilizumab initiation

Always check that the mandatory immunisations (particularly those against tetanus and poliomyelitis) are up to date and that recommended immunisations have been performed as appropriate given the patient's characteristics. The appropriate vaccines should be administered if needed (according to the modalities described in "Vaccination with a live attenuated vaccine" and "Vaccination with an inactivated vaccine").

In the fall, when tocilizumab therapy is considered, the influenza vaccine is recommended.

Administration of the pneumococcal vaccine is recommended every 3 to 5 years, particularly in patients with risk factors for lung infections. Pneumococcal vaccination is not contraindicated in patients who have a history of confirmed or unconfirmed pneumococcal infection. The pneumococcal vaccine can be administered at the same time as the influenza vaccine (if appropriate), at a different injection site.

## Which immunisations should be performed in patients who are switched from another biological agent to tocilizumab?

The recommendations about immunisations are similar across biological agents. Therefore, the immunisation strategy used when continuing the same biological agent applies also to switching from one biological agent to another.

## Which immunisations should be performed in patients on long-term tocilizumab therapy?

Check regularly that the mandatory immunisations (particularly those against tetanus and poliomyelitis) are up to date, as well as the immunisations that are appropriate to the patient's history.

Administration of the influenza vaccine should be recommended in the fall and of the pneumococcal vaccine every 3-5 years.

## Should immunisations be offered to close contacts of the patient?

Immunisation of close contacts (children and grandchildren) may be considered (particularly the influenza vaccine) to diminish the risk of contamination of the patient on tocilizumab therapy.

## Immunisation with live attenuated vaccines

The live attenuated vaccines are listed below.
➤ BCG
➤ Yellow fever
➤ Measles-Mumps-Rubella (MMR)
➤ Oral polio (reserved for outbreaks)
➤ Varicella

● **Modalities of immunisation with live attenuated vaccines before tocilizumab initiation**

Live attenuated vaccines that need to be administered prior to tocilizumab therapy initiation should be given at a time when the patient has no immune deficiency (i.e., is no longer under the effect of any prior biological treatments). The immunisation should be performed **at least 2 weeks, and ideally 4 weeks,** before tocilizumab initiation.

In practice, the issue of greatest concern is yellow fever immunisation. Always ask the patient about trips to areas of yellow fever endemicity, before and during tocilizumab therapy. In patients who are likely to travel in the near- or mid-term

to countries where yellow fever immunisation is mandatory, the vaccine (which is effective for 10 years) should be given after the immunosuppressive effects of any prior treatments have worn off, **at least 2 weeks, and ideally 4 weeks,** before starting tocilizumab therapy.

If the patient is taking methotrexate therapy, the yellow fever vaccine can be given provided the CD4+ cell count is higher than 250/mm3. Otherwise, methotrexate therapy should be discontinued before administering the vaccine.

### ● Can live attenuated vaccines be given to patients on tocilizumab therapy?

Both the safety and the efficacy of live attenuated vaccines are of concern in patients who are receiving biological agents.

As with other biotherapies, live attenuated vaccines are contraindicated in tocilizumab-treated patients, given the risk of treatment-related loss of attenuation of the vaccine micro-organism, which warrants the utmost caution.

Live attenuated vaccines should not be given concomitantly with tocilizumab therapy, as no clinical safety data are available for this combination. There are no available data on secondary transmission of the vaccine microorganism from patients immunised with live attenuated vaccines to tocilizumab-treated patients. Neither are any reliable data available about potential effects of tocilizumab on viraemia levels or reactions to live vaccines. Antibody production in response to prophylactic immunisation may be altered. However, any effects on antibody production do not seem greater with tocilizumab than with conventional DMARDs or TNF antagonists [85, 86].

### ● What are the modalities for administering live attenuated vaccines in tocilizumab-treated patients?

When a live attenuated vaccine is required in a tocilizumab-treated patient, **the treatment should be stopped at least 70 days (5 times the half-life) before administration of the vaccine.** The recommended interval **from vaccine administration to tocilizumab re-treatment is 2 weeks at least and 4 weeks ideally.**

## Immunisation with inactivated vaccines

The main inactivated and component vaccines are listed below.

➤ Influenza
➤ Pneumococcus
➤ Meningococcus
➤ Haemophilus influenza
➤ Hepatitis A and hepatitis B
➤ Combined Diphtheria-Tetanus-Polio-Pertussis-*Haemophilus influenza* b,
➤ Typhoid fever
➤ Injectable polio

● **What are the modalities for administering inactivated vaccines in tocilizumab-treated patients?**

The concern with inactivated vaccines is effectiveness. Therefore, inactivated vaccines and component vaccines can be administered during tocilizumab therapy (the worst-case scenario is a decrease in vaccine effectiveness).

**When an inactivated vaccine is required in a tocilizumab-treated patient (e.g., the influenza vaccine in the fall), the vaccine can be given at any time, and there is no need to postpone the next tocilizumab infusion.**

Although the effectiveness of inactivated vaccines in tocilizumab-treated patients is somewhat uncertain, studies with other biological agents have established that these vaccines can induce an immune response. Thus, the risk/benefit ratio is in favour of administering inactivated vaccines if needed.

# Management of Patients Who
# Plan to Travel

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## Can tocilizumab-treated patients travel?

Tocilizumab-treated patients can travel. The Summary of Product Characteristics [4] contains no specific recommendations about travelling and, therefore, the advice given here is based on the opinions of experts. Precautions are in order, and trips to high-risk countries are not recommended.

## What immunisations should be recommended before starting tocilizumab? (see the sheet entitled "Immunisations")

Depending on the country of travel, specific immunisations are required. Planning ahead is crucial in this situation.

**When a live attenuated vaccine must be administered** to a tocilizumab-treated patient, the treatment must be stopped at least **70 days (5 times the half-life) before the immunisation.** The recommended interval **from vaccine administration to tocilizumab re-treatment is 2 weeks at least and 4 weeks ideally.**

In practice, yellow fever is the main concern. Before and during tocilizumab therapy, patients should be asked routinely about plans to travel to areas of yellow fever endemicity.

**When an inactivated vaccine (hepatitis A or B, typhoid fever) must be given** to a tocilizumab-treated patient, the vaccine can be given at any time, and there is no need to postpone the next tocilizumab infusion.

Although the effectiveness of inactivated vaccines in tocilizumab-treated patients is somewhat uncertain, studies with other biological agents have established that these vaccines can induce an immune response. Thus, the risk/benefit ratio is in favour of administering inactivated vaccines if needed.

## Can tocilizumab-treated patients take antimalarial prophylaxis?

Antimalarial prophylaxis is not contraindicated. Concomitant treatment with chloroquine or its derivates (which are antimalarials) does not affect tocilizumab pharmacokinetics.

## What other measures should be taken?

Patients should be advised to carry written information (in English if possible) about their treatment (dose and date), for use in the event of health problems during their stay abroad.

During their stay, they should follow the usual precautions regarding hygiene, food and beverages, and insects. Medical advice should be obtained promptly in the event of a fever or symptoms of infection.

Patients travelling to remote areas where medical help is unavailable should carry antibiotics for use in the event of infectious symptoms (e.g., amoxicillin + clavulanic acid and a quinolone, a combination that is effective in common infections of the lower respiratory tract and urinary tract).

Use of tocilizumab in
# Juvenile Idiopathic Arthritis

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

The data generated by clinical trials of tocilizumab in adults with rheumatoid arthritis or Still's disease cannot be directly extended to paediatric patients.

Some subgroups of juvenile idiopathic arthritis (JIA) have no equivalent in adults (oligoarticular JIA with chronic anterior uveitis) and others exist in adults but may present with different initial clinical manifestations (psoriatic arthritis, enthesitis-related arthritis). Furthermore, the distribution of clinical patterns differs between JIA and chronic inflammatory joint disease in adults (for example, juvenile RA <5% of JIA cases).

IL-6 directly and indirectly inhibits the growing bone, from birth to puberty, an effect not relevant to adults.

The same drug may have different safety profiles in paediatric patients and adults, as both the immune system and the drug clearance pathways are at different stages of maturation; and the environment, most notably in terms of exposure to infectious agents, also differs.

The low prevalence of JIA has limited the number of high-quality randomised controlled trials, as well as the number of patients included in each trial. Furthermore, no sufficiently powered long-term trial in paediatric patients is available. Consequently, although effects in adults with RA cannot be extended to paediatric patients, thorough familiarity with the clinical trials in adults is crucial to a sound evaluation of the risks and benefits of a biological agent in JIA [87].

## In what indications has tocilizumab been used in paediatric patients with joint disease?

Depending on the country of travel, specific immunisations are required. Planning ahead is crucial in this situation.

● **Systemic juvenile idiopathic arthritis (systemic JIA or childhood-onset Still's disease)**

Systemic JIA is characterised by an unexplained spiking fever for at least 2 weeks, arthritis, and extra-articular manifestations (rash, hepatosplenomegaly, lymphadenopathy, and serositis) in a patient younger than 16 years of age [88, 89].

This clinical pattern contributes 10% of all cases of JIA. Systemic JIA is a serious disease with a 10-year remission rate of only 37% [90].

Furthermore, among JIA patterns, systemic JIA has the highest mortality rate. The main causes of death are macrophage activation syndrome, infections, and AA amyloidosis.

To achieve disease control, in most cases, high doses of glucocorticoids must be used. These high doses jeopardise the long-term outcome by inducing adverse effects (arrest in statural growth, osteoporosis with fractures) [91].

The results of therapeutic trials indicate that tocilizumab is among the most promising treatments for systemic JIA [92-95], a disease that is often steroid-dependent (50%) and refractory to multiple conventional maintenance drugs (methotrexate, cyclosporine A, intravenous immunoglobulins...) [96, 97] and sometimes also to biological agents against TNF and IL-1 [98, 99]. Furthermore, tocilizumab may prevent the development of long-term complications of systemic JIA (amyloidosis, statural growth delay, and osteoporosis) [100-102].

### ● Polyarticular-course juvenile idiopathic arthritis

Two open-label studies conducted in Japan and presented at the October 2006 ACR meeting and June 2009 EULAR meeting indicate a high level of effectiveness of tocilizumab in children with polyarticular-course JIA, with a suggestion of structural lesion improvement during treatment [88, 89, 103, 104].

### ● Amyloidosis in a patient with extended oligoarticular JIA

Systemic amyloidosis complicating extended oligoarthritis in a 14-year-old girl was successfully treated with tocilizumab. This case-report deserves careful attention, as no effective treatment for AA amyloidosis is currently available [105].

## Why use tocilizumab in systemic JIA?

### ● Systemic JIA and IL-6

– Systemic effects

Patients with systemic JIA have very high serum IL-6 levels that fluctuate in lockstep with the daily fever spikes that characterize the disease. The high serum IL-6 levels contribute also to the profound asthenia and anorexia seen in patients with systemic JIA. IL-6 promotes the development of amyloidosis in systemic JIA by inducing the production of Serum Amyloid A (SAA), the precursor of amyloid protein. IL-6 also promotes the development of macrophage activation syndrome by exacerbating the responses to infectious stimuli. Biologically, IL-6 is the main positive regulator of liver synthesis of acute-phase proteins (CRP, SAA, fibrinogen), whose levels are consistently elevated during flares of systemic JIA. Finally, IL-6 induces thrombocytosis and severe microcytic anaemia (via increased release of hepcidin, an iron metabolism regulator), which is a common finding in refractory systemic JIA [106-108].

– Osteoarticular effects

Serum IL-6 levels correlate with the extent and severity of joint involvement in patients with systemic JIA [108]. IL-6 may play a direct role in joint destruction and osteoporosis, as it promotes osteoclast differentiation.

Serum IL-6 elevation in children with systemic JIA correlates with decreases in growth velocity. This effect is related to at least two mechanisms: IL-6 decreases the growth-promoting effects of serum IGF1 and locally inhibits the early stages of chondrogenesis [109, 110].

## ● Systemic JIA and tocilizumab

How can the effectiveness of treatment be evaluated in systemic JIA?

The effectiveness of treatment in patients with JIA is evaluated using the ACRPedi scale based on six variables (1/ global VAS assessment by the physician, 2/ global VAS assessment by the patient or parent, 3/ C-HAQ, 4/ number of joints with active arthritis, 5/ number of joints with limited range of motion, and, 6/ ESR). ACRPedi30 is an at least 30% improvement in at least three of the six variables, without a 30% or greater worsening of more than one of the six variables [111].

In studies of systemic JIA, the ACRPedi scale was modified to take the systemic manifestations into account. In some studies, the CRP level had to remain below a threshold, which varied across studies. In other studies, a more comprehensive tool was used, such as the systemic score developed by Woo et al. and based on the presence of a fever, peripheral lymphadenopathy, hepatosplenomegaly, serositis (pericarditis, pleuritis, or peritonitis), and a rash [92]. To date, no systemic score has been validated.

It has been suggested that the steroid-sparing effect of the study treatment may deserve to be evaluated.

Results of therapeutic trials of tocilizumab in systemic JIA

➤ Tocilizumab has been proven effective in improving both the systemic and the articular manifestations of systemic JIA refractory to conventional DMARDs or to biologics against TNF or IL-1 [92-94] (Table 11).

➤ Two phase II studies have been published, one from the UK and the other from Japan [92, 93].

- The study from the UK included 18 patients with systemic JIA, who were allocated at random to tocilizumab in a fixed dose of 2, 4, or 8 mg/kg [in systemics, the doses are given every 2 weeks, and the trial attributed in a random manner 3 fixed doses], with follow-up for 4, 6, and 8 weeks, respectively [92] (Table 11). In addition to steroid therapy, 12 patients also received fixed-dose methotrexate (< 20 mg/m$^2$/week). Three patients were excluded because of protocol violations (rescue by increasing the steroid dosage). The proportions of patients with an ACRPedi30 response at week 1 were 75% with 2 mg/kg (n=4), 83% with 4 mg/kg (n=6), and 60% with 8 mg/kg (n=5); corresponding proportions at week 6 were 0%, 67%, and 40%, respectively; and at week 8 0%, 0%, and 20%, respectively. The systemic score (cervical, axillary, and inguinal lymphadenopathy; hepatomegaly and splenomegaly; fever; rash; and clinical serositis [pericarditis, pleuritis, or peritonitis]) and the laboratory markers for inflammation showed marked improvements as early as 1 week after the infusion. This study showed that the efficacy of the 4 and 8 mg/kg dosages was greater and longer lasting in patients with systemic JIA

• The Japanese study was done in 11 patients with systemic JIA who received escalating tocilizumab dosages (2, 4, and 8 mg/kg/ 2 weeks) depending on the serum CRP level measured 15 days after the infusion [93] (Table 11). Two weeks after the third fixed-dose tocilizumab infusion, the proportions of patients with an ACRPedi30 response were 64% with 2 mg/kg (n=11), 87% with 4 mg/kg (n=8), and 100% with 8 mg/kg (n=3); in these three groups, an ACRPedi70 response was obtained in 9%, 50%, and 100% of patients, respectively. As early as the first treatment week, 6 of the 11 patients were apyretic. Abrupt CRP elevations were noted between the second and fourth treatment weeks until an adequate serum tocilizumab level was achieved; these elevations coincided with systemic symptom recurrences. The authors concluded that tocilizumab produced a highly significant decrease in the activity of systemic JIA, with a marked dose-effect.

➤ The only published Phase III study was done in Japan in 56 patients with refractory systemic JIA that was inadequately controlled by steroid therapy [94] (Table 11). Conventional DMARDs were not allowed during the trial. After a 6-week open-label lead-in phase during which all patents received tocilizumab (8 mg/kg/2 weeks), patients with an ACRPedi30 response and a CRP level <5 mg/L were allocated at random to double-blind treatment with tocilizumab or a placebo for 12 weeks. A 48-week open-label extension was then conducted. During the double-blind phase, patients in the placebo group who relapsed (i.e., who did not maintain an ACRPedi30 response and/or had CRP levels >15 mg/L) were transferred to the open-label extension phase.

At the end of the open-label lead-in phase, the proportions of patients with ACRPedi30, 50, and 70 responses were 91%, 86%, and 68%, respectively. Among the 43 randomised patients, 17% [4/23] of the placebo patients and 80% [16/20] of the tocilizumab patients maintained an ACRPedi30 response and CRP levels <15 mg/L (p<0.001). At the end of the open-label extension phase (n=48), the proportions of patients with ACRPedi30, 50, and 70 responses were 100%, 95%, and 90%, respectively. These data confirm that IL-6 blockade significantly improves the health status of patients with systemic JIA.

➤ An international Phase III study in patients with systemic JIA is under way to generate further efficacy and safety data in this indication and to identify the optimal tocilizumab dosage, particularly in children weighing less than 30 kg, in whom the Phase II Japanese trial showed decreased efficacy related to pharmacokinetic differences (ClinicalTrials.gov identifier: NCT00642460).

➤ The beneficial effects of tocilizumab 8 mg/kg/2 weeks in patients with systemic JIA were maintained in the long term. A single long-term study is available; it was conducted in patients entered into open-label extension phases of Phase II and III studies and in 61 additional patients with systemic JIA, for a total of 128 patients with a median follow-up of 9 years [94] (Table 11). The median steroid dosage was 0.5 mg/kg/d before tocilizumab initiation and the median duration of tocilizumab treatment was 78 weeks. At week 48 (n=78), the proportions of patients with ACRPedi30, 50, and 70 responses were 94%, 88%, and 81%, respectively; corresponding proportions at week 96 (n=58) were 100%, 98%, and 93%; and at week 144 (n=41) 100%, 100%, and 90%.

➤ Tocilizumab may also be able to slow structural disease progression. The first report of the effects of tocilizumab therapy (8 mg/kg/2 weeks) on radiological lesions in patients with systemic JIA was presented at the June 2009 EULAR meeting [95]. The 20 patients underwent radiographs of all large joints before and during tocilizumab therapy. Mean treatment duration was 41 months. Marked improvements were noted not only in the periarticular osteoporosis and swelling, but also in the joint space narrowing and joint erosions. All 20 patients achieved a clinical and biological response. The structural effects of tocilizumab therapy deserve to be investigated in larger cohorts.

➤ Finally, tocilizumab therapy improves the extra-articular manifestations of systemic JIA. More specifically, a highly significant improvement in statural growth was observed, as well as a decrease in osteoporosis and effective prevention of systemic amyloidosis [93, 101, 102].

## Why use tocilizumab in polyarticular-course JIA?

### ● Polyarticular-course JIA and IL-6

As with systemic JIA, significant correlations are found in extended oligoarticular and polyarticular JIA between serum IL-6 levels and both CRP and ESR values [112], and 95% of joint fluids from patients with extended oligoarticular or polyarticular JIA contain high IL-6 levels [112, 113]. These data, together with the results of studies in adults, indicate that IL-6 blockade is a worthwhile treatment objective in polyarticular-course JIA (see the fact sheets for adults).

### ● Polyarticular-course JIA and tocilizumab

➤ The effects of tocilizumab in polyarticular-course JIA were reported at the ACR meeting held in October 2006 [103] (Table 11). In 19 patients aged 3 to 19 years and having extended oligoarticular or polyarticular JIA, open-label tocilizumab monotherapy was given in a dosage of 8 mg/kg every 4 weeks for 12 weeks. At week 12, the proportions of patients with ACRPedi30, 50, and 70 responses were 95%, 95%, and 58%, respectively. These highly promising preliminary findings may warrant the use of tocilizumab in international Phase III therapeutic trials in patients with polyarticular-course JIA.

➤ Finally, the first prospective data on the effects of tocilizumab on structural disease progression in polyarticular-course JIA were presented at the June 2009 EULAR meeting [104]. Tocilizumab 8 mg/kg/2 weeks was given to 3 patients with JIA (6-19 years) for 24 to 31 months. There was an excellent response in terms of the swollen and tender joint counts and laboratory markers for inflammation. Furthermore, the joint space narrowing decreased in over half the affected joints. Thus, IL-6 blockade in patients with polyarticular-course JIA may decrease or reverse radiographic joint lesion progression.

## What adverse effects have been reported in tocilizumab-treated paediatric patients with systemic or polyarticular-course JIA?

Table 11 reports the adverse events (AEs) and serious adverse events (SAEs) in the Phase II and III studies and long-term study of systemic JIA and in the only open-label study in polyarticular-course JIA [92-94].

### ● Systemic JIA

➤ In brief, in systemic JIA, the most common adverse events were nasopharyngitis (59%), upper airway infections (34%), and gastroenteritis (29%), as well as moderate and transient transaminase elevations (20-30%), particularly in patients receiving concomitant methotrexate therapy.

Mild-to-moderate infusion-related reactions occurred in 18% of patients. Elevations in total cholesterol levels seem moderate and within the normal range in patients with systemic JIA.

Potential effects of tocilizumab on immunity, such as immunogenicity (production of IgE antibodies to tocilizumab) and a decrease in lymphocyte counts should be carefully looked for and monitored in these patients who often have severe immunodeficiency, related to the many years spent with a markedly steroid-dependent disease.

➤ To date, no cases of tuberculosis, opportunistic infections, cancer, or autoimmune disease have been reported in paediatric patients treated with tocilizumab.

➤ The main SAEs in patients with systemic JIA were severe infections (14.5/100 patient-years), which chiefly affected the gastrointestinal tract and lungs. The rate of serious infections may be ascribable in part to the low level of clinical and biological inflammation during infections in tocilizumab-treated patients, which contributes to delay the diagnosis. Other reported SAEs consist of 1 case each of transient pancytopenia, macrophage activation syndrome, gastrointestinal bleeding, anaphylaxis, and cardiac amyloidosis. Finally, 2 children with systemic JIA died during tocilizumab treatment, one from macrophage activation syndrome and the other from cardiac amyloidosis; of these two complications, only macrophage activation syndrome may be related to tocilizumab treatment [94].

### ● Polyarticular-course JIA

The experience acquired with tocilizumab in polyarticular-course JIA (extended oligoarticular and polyarticular forms) is consistent with the results in children with systemic JIA. Thus, the most common adverse events were commonplace upper respiratory tract infections and modest elevations in serum transaminases and lipids [103].

## Selecting patients with systemic or extended oligoarticular/polyarticular JIA for tocilizumab therapy

➤ Tocilizumab was granted a marketing licence (AMM) in 2009 in France for rheumatoid arthritis in adults; to date, this drug is not approved for use in paediatric patients in Europe in any indication.

In Japan, tocilizumab was granted a marketing licence for systemic JIA and polyarticular-course JIA in April 2008. Tocilizumab is delivered only after inclusion of the patient in the Japanese nationwide registry.

➤ The analysis of the data on JIA rests on both valid scientific evidence and expert opinion.

- Tocilizumab is a treatment alternative in patients with systemic JIA refractory to appropriate steroid therapy. An international study in patients with systemic JIA is ongoing to determine the optimal tocilizumab dosage, particularly in children weighing less than 30 kg, and to validate the efficacy and safety data reported by the Japanese groups. This study will also determine whether tocilizumab has a steroid-sparing effect.

  The youngest age for using tocilizumab therapy in systemic JIA was 2 to 3 years, depending on the trial (Table 11).

  The optimal dosage used in the trials was 8 mg/kg and the interval between intravenous infusions in patients with systemic JIA was 2 weeks. An international randomised double-blind placebo-controlled trial in this indication has allready started. The results will show whether the efficacy and safety data presented at rheumatology meetings are confirmed.

  According to the therapeutic trials, the lowest age at which tocilizumab can be prescribed in polyarticular-course JIA is 2 years (Table 11).

  The optimal dosage used in the trials was 8 mg/kg and the interval between intravenous infusions in patients with polyarticular-course JIA was 4 weeks.

- Tocilizumab is a treatment alternative in patients with polyarticular-course JIA refractory to one or more DMARDs or anti TNF therapy.

## Work-up before initiating tocilizumab therapy in a paediatric patient

This workup is separate from the assessment of disease activity and severity.

➤ Look for contraindications to tocilizumab (hypersensitivity and severe uncontrolled infections such as sepsis and opportunistic infections) and/or conditions requiring special precautions (active liver disease, neutropenia and thrombocytopenia, dyslipidaemia, malignancy within the last 5 years).

➤ Identify and eradicate any active foci of acute, chronic, or recurring infection.

➤ Look for active or latent tuberculosis (symptoms, history, contact, suggestive clinical signs): Tubertest 5IU, read between the 48th and 72nd hour and considered positive (i) if induration >5 mm in children not immunized with the BCG vaccine or having severe immunosuppression, (ii) if induration >10 mm in children immunized

with the BCG or having mild immunodepression. Even the slightest doubt about the Tubertest result, most notably in BCG-immunized children, should prompt testing with Quantiferon or TB-Spot (which may raise problems with health insurance reimbursement) and a chest radiograph.

➤ Look for concomitant medications that interact with tocilizumab (see the fact sheet on drug-drug interactions)

➤ In teenagers, a discussion of birth control is crucial.

The pre-treatment blood tests should include the following:

➤ Blood cell counts, ESR, CRP

➤ ASAT and ALAT

➤ Total cholesterol, LDL and HDL cholesterol, triglycerides

➤ Urea, serum creatinine, urine dipstick test

➤ Serological tests for hepatitis B and C and, with the parents' consent, HIV infection.

Immunisations should be up to date. Tocilizumab therapy does not place any restrictions on the administration of inactivated vaccines (hexavalent vaccines to diphtheria, tetanus, polio, pertussis, haemophilus, and pneumococcus; pneumococcal vaccines; influenza vaccines; vaccines against typhoid fever, hepatitis A, hepatitis B, and papilloma virus, etc.), which are best given during periods of lesser disease activity.

At present, tocilizumab therapy contraindicates all live attenuated vaccines (MMR, varicella, BCG, yellow fever, and oral polio) for as long as tocilizumab is given. If allowed by the patient's status and the treatment regimen, a useful measure may consist in administering live attenuated vaccines at least 3 weeks before starting tocilizumab therapy (particularly in children who have a negative history for varicella).

## Evaluating the safety and effectiveness of tocilizumab therapy in paediatric patients: how and how often?

➤ Before each tocilizumab infusion, a physical examination should be performed to look for evidence suggesting an infection, cancer, autoimmune disease, or demyelination. The parents should be informed of the risk of infection associated with tocilizumab therapy. Any symptoms that suggest an infection in a tocilizumab-treated patient should lead routinely to prompt evaluation by a physician and to appropriate treatment. It should always be borne in mind that tocilizumab therapy blunts or abolishes the acute-phase inflammatory response. The risk of demyelination in paediatric patients treated with tocilizumab is unknown. Neither are any data available on the risk of cancer in this population.

➤ Before the tocilizumab infusion, the following laboratory tests should be obtained.

   • Blood cell counts, a platelet count, and transaminase levels every 15 days for the first 3 months to look for cytopenia (neutropenia, lymphopenia, and thrombocytopenia) and transaminase elevation,

which may contraindicate further tocilizumab therapy (transaminase elevation may be more common in patients on concomitant methotrexate therapy, and the risk of neutropenia may be increased in patients with a history of TNF antagonist therapy). Subsequently, the laboratory tests may be performed monthly for 6 months then every 3 months as long as the results remain normal. In patients with cytopenia or transaminase elevation, given the absence of paediatric data, the tocilizumab dosage should be adjusted based on current practice in adults with RA and on normal ranges for paediatric individuals, which vary across age groups.

- Serum lipid assays should be obtained 4 to 8 weeks after tocilizumab initiation. The patients should be monitored in compliance with clinical practice guidelines for the management of dyslipidaemia. No cardiovascular abnormalities related to tocilizumab-induced dyslipidaemia have been reported in paediatric patients.

- CRP monitoring should prove helpful for tocilizumab dosage adjustment, as CRP is a marker for complete inhibition of IL-6 effects.

➤ During the tocilizumab infusion and for 2 hours after the end of the infusion, the patient should be monitored in the hospital for evidence of intolerance and for skin reactions.

**Evaluation of the effectiveness of tocilizumab in JIA relies chiefly on the ACRPedi criteria [108] and on resolution of the clinical and laboratory evidence of systemic inflammation, which should be checked at least once every 3 months as long as the treatment proceeds uneventfully.**
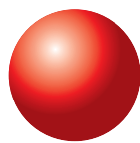
# Use of Tocilizumab in
# Castleman's Disease

| Evidence Based Medicine | Official recommendations | Expert opinion |

Castleman's disease, also known as angiofollicular hyperplasia, is a rare lymphoproliferative disease first described in 1956. It is characterised by benign lymphovascular hyperplasia with polyclonal lymphoplasmacytic proliferation either in a single lymph node (unicentric form, the most common) or in multiple lymph nodes. The main sites of involvement are the mediastinum and retroperitoneal space. Progression is slow and may lead to lymphoma. The HHV8 has been implicated as an initiating factor, and cases of Castleman's disease have been reported in patients with HTLV1 infection.

## Rationale for targeting IL-6 in Castleman's disease

Tocilizumab was licensed in Japan in April 2005 [114] for the treatment of Castleman's disease (angiofollicular hyperplasia) based on its ability to specifically block IL-6.

The clinical manifestations are related to IL-6 overproduction by the affected lymph nodes. This "syndrome of inappropriate IL-6 secretion" explains the full range of manifestations, which include constitutional symptoms (fever, weight loss, lymphadenopathy, splenomegaly...) and laboratory test abnormalities (anaemia, systemic inflammation, hypergammaglobulinaemia, autoantibodies, cold agglutinins...). Patients may experience complications such as haemolytic anaemia, amyloidosis, cardiac involvement, or interstitial lung disease [102].

## IL-6 antagonist therapy in Castleman's disease: data from the literature

The conventional treatment rests on surgical removal of focal lesions and on glucocorticoid and antimitotic therapy in patients with diffuse lesions.

In the seminal study of tocilizumab [114], 28 patients with Castleman's disease refractory to all other treatments (including surgery and long-term glucocorticoid therapy) received tocilizumab 8mg/kg every 15 days for 4 months. The main clinical and biological abnormalities improved [114]. The lymphadenopathy resolved, as well as the clinical and laboratory evidence of inflammation. Furthermore, gradual improvements occurred in the anaemia, hypoalbuminaemia, total cholesterol, and body mass index. All patients reported significant alleviation of fatigue [115, 116].

In 28% of patients, a decrease in the tocilizumab dosage was possible (down to 4 mg/kg/month), as well as an increase in the interval between infusions (up to 1 month). In 73% of patients, the glucocorticoid treatment was decreased or stopped [114].

In the open-label extension phase, whose mean duration was 1191 days, the safety and efficacy of tocilizumab therapy were maintained [114, 116, 117]. The main adverse events were nasopharyngitis (88.6%), rashes (31.4%), pruritus (28.6%), and neutropenia (25.7%). Overall safety was good. The optimal treatment duration remains to be determined [115, 117].
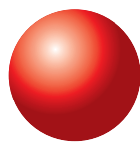
Use of Tocilizumab in
# Adult-Onset Still's Disease

| Evidence Based Medicine | Official recommendations | Expert opinion |

## Rationale for targeting IL-6 in Still's disease

In patients with adult-onset Still's disease, serum IL-6 levels increase during the flares and correlate with disease activity [121-125]. IL-6 overproduction may explain the main symptoms, as IL-6 can induce a fever, leukocytosis, thrombocytosis, elevations in protein markers for inflammation, and bone resorption.

A prospective controlled study has established that tocilizumab is effective in systemic juvenile idiopathic arthritis [94].

## IL-6 antagonist therapy in adult-onset Still's disease: data from the literature

The only published data on tocilizumab therapy for adult-onset Still's disease come from anecdotal case-reports [55, 118-120] and a French retrospective study of 10 patients with adult-onset Still's disease refractory to conventional treatments including methotrexate, anakinra, and TNF antagonists.

No dose-finding studies in patients with adult-onset Still's disease are available and, consequently, the modalities of tocilizumab administration in this indication remain to be determined.

In the French retrospective study, half the 14 patients given tocilizumab 8 mg/kg monthly had a good EULAR joint response within 3 months and a joint remission (EULAR criteria) within 6 months [121] with resolution of the systemic signs in the vast majority of patients. In some patients, however, the joint manifestations failed to improve. The rate of improvement in the systemic manifestations was even higher. Escape phenomenon affecting both the joint and the systemic manifestations occurred in some patients. These results were obtained in patients with refractory adult-onset Still's disease who failed methotrexate, anakinra, and at least two TNF antagonists.

Tocilizumab has been used in a dosage of 4 to 8 mg/kg every 15 days from the outset in some patients with adult-onset Still's disease [55, 118-120], although no proof has been obtained that twice monthly infusions confer additional benefits. Increasing the interval between the infusions was successful in some patients [55, 119] but led to a relapse of the joint and systemic manifestations in others [55, 118].

The safety profile of tocilizumab in adult-onset Still's disease seems similar to that described in rheumatoid arthritis or systemic juvenile idiopathic arthritis. A case of macrophage activation syndrome, a well-known complication of Still's disease, occurred during cytomegalovirus infection in a tocilizumab-treated patient, although there is no proof of a causal link with the drug [55]. Bolus methylprednisolone therapy combined with cyclosporine ensured a favourable outcome, and re-treatment with tocilizumab in the same dosage

produced a good therapeutic effect with no relapse of the macrophage activation syndrome [55].

The optimal duration of tocilizumab therapy remains to be determined. Tocilizumab therapy seems to suspend the symptoms in the overwhelming majority of cases. Nevertheless, a prolonged remission (up to 7 years without treatment) was reported after 18 months of tocilizumab therapy in one patient with adult-onset Still's disease [118, 120].

Use of Tocilizumab in
# Spondyloarthropathies

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Spondyloarthropathies may constitute potential candidates for treatments directed against interleukin-6 (IL-6).

## Rationale for targeting IL-6 in spondyloarthropathies

Although to date no case-reports or prospective studies of tocilizumab in spondyloarthropathies are available, several findings provide a rationale for targeting IL-6 in these diseases.

Several studies showed serum IL-6 elevation in patients with ankylosing spondylitis (over 85% of the patients studied by Tutuncu [125], compared to controls (Table 12).

However, there is no evidence that serum IL-6 levels predict disease progression over the following year [133].

In a study of 4 patients with ankylosing spondylitis, François et al. [134] consistently found evidence of IL-6 expression in the sacroiliac joints, with higher expression levels in early active lesions.

No association was found between ankylosing spondylitis and the polymorphism of the IL-6 gene promoter [135].

## IL-6 antagonist therapy in spondyloarthropathy: data from the literature

To date, a single case has been published. The patient had severe undifferentiated spondyloarthropathy that responded to a murine monoclonal antibody against IL-6 (different from tocilizumab) combined with a monoclonal antibody against CD4 [133].

## Selecting patients for IL-6 blockade

A discussion of patient selection would be premature, as the efficacy of tocilizumab has not been evaluated in patients with spondyloarthropathy. In patients with axial disease that is inadequately controlled by NSAID therapy, TNF antagonists are the only available biotherapies.

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**Annex 1:** Model Information Letter for the
# Office-Based Rheumatologist

| Evidence Based Medicine | Official recommendations | Expert opinion |

..........................,  ........................

Dear Colleague,

Thank you for referring your patient,

M. (Ms) .................................................................

born on ..................................... for treatment with tocilizumab (RoActemra®).

You are following this patient for rheumatoid arthritis with unresponsiveness, contraindications, or intolerance to conventional maintenance drugs or to TNF antagonists.

**The following data were evaluated before starting tocilizumab therapy.**

❏ Evaluation of the patient before the first tocilizumab injection:

- DAS 28 *(Disease Activity Score)*:          ❏ obtained on........
- HAQ *(Health Assessment Questionnary)*: ❏ obtained on........ ❏ not obtained
- ESR/CRP:                                          ❏ obtained on........ ❏ not obtained
- ASAT/ALAT :                                       ❏ obtained on........ ❏ not obtained
- Blood cell counts:                              ❏ obtained on........ ❏ not obtained
- Total cholesterol/LDL-Ch/Triglycerides: ❏ obtained on........ ❏ not obtained
- Intradermal tuberculin test:                  ❏ obtained on........ ❏ not obtained
- Chest radiograph:                              ❏ obtained on........ ❏ not obtained
- Radiographs of the hands and feet:       ❏ obtained on........ ❏ not obtained
- Erosions:                                          ❏ obtained on........ ❏ not obtained
- Chondrolysis:                                    ❏ obtained on........ ❏ not obtained

❏ The patient stopped any prior TNF antagonist therapy or other biotherapies (with or without a wash-out period) for the following reason:

.........................................................................................
.........................................................................................
.........................................................................................
.........................................................................................
.........................................................................................
.........................................................................................

❏ The patient has no contraindications to tocilizumab therapy (allergy, active infection, premalignant or malignant lesions diagnosed within the past 5 years).

❏ We checked whether the patient was taking drugs having potential interactions with tocilizumab and possibly requiring dosage adjustment at tocilizumab initiation or discontinuation.

- The patient is not receiving any drug likely to interact with tocilizumab.

- The patient is taking the following drug(s) (.....................................................) and we have

|  | yes | no |
|---|---|---|
| - no dosage adjustment | ❏ | ❏ |
| - dosage adjustment | ❏ | ❏ |

If yes, new dosage(s): ........................................................

❏ We have checked the immunisation status of the patient (particularly vaccines against tetanus, polio, influenza, and pneumococcal infections).

Inactivated or component vaccines, particularly those against seasonal infections, can be given safely after the tocilizumab infusion. Although perhaps less effective in this situation, yearly influenza immunisation is recommended.

Live attenuated vaccines (yellow fever, varicella-zoster, oral poliomyelitis, MMR, and BCG) are contraindicated in tocilizumab-treated patients. If a live attenuated vaccine must be administered, the tocilizumab treatment must be stopped at least 70 days before the immunisation. The recommended interval from vaccine administration to tocilizumab re-treatment is 2 weeks at least and 4 weeks ideally.

❏ We performed the following:

❏  No immunisations

❏ The following immunisations: ...................................... ❏on ...../...../........
...................................... ❏on ...../...../........
......................................❏on ...../...../........

❏ We checked that the patient was screened for latent tuberculosis (history, chest radiograph, and Tubertest©).

In your patient, the pre-treatment status was as follows:

| | | | |
|---|---|---|---|
| – Contact with a TB case | ❏yes, on ........ | ❏no | ❏ not assessed |
| – Chest radiograph abnormality | ❏yes, on ........ | ❏no | ❏ not assessed |
| – Tubertest® | ❏yes, on ........ | ❏no | ❏ not assessed |
| – QuantiFERON Gold® or T-Spot-TB® | ❏yes, on ........ | ❏no | ❏ not assessed |
| – Prior anti-TB prophylaxis | ❏yes, on ........ | ❏no | ❏ not assessed |

Date on D1 : ...................

1) If the screen done before TNF antagonist therapy was positive, the patient received prophylactic treatment against tuberculosis.

If the patient adhered to this treatment, and in the absence of contact with a tuberculous patient since then, tocilizumab therapy can be started with no other specific precautions.

2) If the screen done before TNF antagonist therapy was negative and dates back more than 1 year, a new screen in recommended. These precautions are recommended although there is no proof that tocilizumab therapy increases the risk of tuberculosis. This risk cannot be evaluated accurately, because the patients who participated in the early studies underwent screening and, based on the results, were either excluded or received prophylactic anti-tuberculous therapy. Should the screen be positive, the patient should receive the anti-tuberculous regimen recommended for TNF antagonist therapy (AFSSAPS 2005). The first tocilizumab infusion can be given after 3 weeks of anti-tuberculous therapy, which should be continued for 3 months in all (if it consists of isoniazid (Rimifon®) + rifampin).

❏ We evaluated the factors listed below.

1) The risk of infection, based on classic factors (age, diabetes, glucocorticoid therapy, co-morbidities...) and iatrogenic factors related to prior biological therapy. In patients previously treated with rituximab, the serum immunoglobulin level and the circulating B-cell count will be taken into account when evaluating the risk of infection.

2) The risk of malignancy, which depends on pre-existing premalignant or malignant lesions, personal risk factors, and familial risk factors.

The findings that are important in your patient are listed below.

❏ Risk factors for infection        ❏yes ❏no

If yes, specify which ones ..................................................................................

❏ Risk factors for malignancy     ❏yes ❏no

If yes, specify which ones ..................................................................................

❏ No risk factors for infection or malignancy

**How was the treatment conducted?**

❏ Tocilizumab treatment was started in a dosage of ................... mg/kg with no premedication

❏ was given with methotrexate or, in the event of a contraindication, in combination with the following treatment ..................................................

❏ or was given as monotherapy.

## The tocilizumab infusion

❏  was uneventful, with no infusion-related reaction

❏  was complicated by the following event: ....................................................

Intolerance (reaction to the molecule) may develop during or after the infusion. This event is rare and, more importantly, very rarely severe (0.3%).

Although infusion-related reactions are not serious, they warrant symptomatic treatment. The patient should be admitted on an emergency basis if any of the following develops: constitutional symptoms, respiratory manifestations, cardiovascular manifestations, or diffuse skin lesions.

The tocilizumab infusions will be given once a month, in the same dosage, except in the event of transaminase elevation or neutropenia.

## Evaluating the clinical and biological response to tocilizumab

The monthly infusion provides an opportunity for regular monitoring, with an evaluation before each infusion. However, as his/her usual rheumatologist, you will evaluate the patient. Your objective is to evaluate the treatment response and to monitor the patient in conjunction with the primary-care physician.

The therapeutic objectives are as follows:

➤ response by week 12, with an at least 0.6-point decrease in the DAS 28

➤ and response by week 24, with an at least 1.2-point decrease in the DAS 28 and ideally a DAS 28 ≤ 3.2.

To monitor the response to tocilizumab, the following should be evaluated at least every 3 months: clinical disease activity (DAS 28 or SDAI), quality of life, and laboratory tests for inflammation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]). The effect of tocilizumab on structural disease progression will be assessed by obtaining radiographs of the hands and feet about 1 year after the first infusion.

## Evaluating the safety of tocilizumab

During tocilizumab therapy, the only laboratory tests required are as follows:

➤ blood cell counts (risk of neutropenia, which is uncommon and usually transient)

➤ liver function tests (transaminases, of which elevations are uncommon and usually moderate)

➤ and serum lipid levels (total cholesterol, LDL cholesterol, and triglycerides, as the LDL-cholesterol level may increase, which infrequently requires the introduction of a lipid-lowering medication), every 3 months initially.

When selecting laboratory tests for treatment monitoring, it is important to consider concomitant drugs, most notably methotrexate. There are no routinely available immunological tests for monitoring and assessing the effectiveness of tocilizumab therapy.

## Risks associated with tocilizumab therapy

Infections may occur in tocilizumab-treated patients. Pneumonia and bronchitis are the most common forms, although cellulitis, pyelonephritis, and diverticulitis have also been reported. These infections require prompt management with appropriate antimicrobials.

In tocilizumab-treated patients, infections may fail to elevate the levels of CRP, other inflammation markers, or neutrophils. Elevations in other biological markers (e.g., overexpression of the membrane marker CD64 by neutrophils detected by flow cytometry) may suggest a diagnosis of infection in a tocilizumab-treated patient.

Therefore, infections should be looked for by obtaining specimens for microbiological studies and by performing appropriate imaging studies. In patients with a strong clinical suspicion of infection, promptly initiate treatment with appropriate antibiotics or, if warranted, antiviral, antifungal, or antiparasitic agents.

Other adverse events have been reported such as blood pressure changes (hypertension, hypotension), hepatic cytolysis (without severe hepatitis), neutropenia (reversible), hypercholesterolemia, and headaches.

There is no evidence that tocilizumab can induce the development of autoimmune disease. However, there have been reports of demyelination, for which no causal link with tocilizumab therapy has been demonstrated.

Available data do not suggest an increased risk of malignancy in association with tocilizumab therapy for RA. However, close monitoring is warranted.

## Further tocilizumab treatment

If after 12 weeks there is no treatment response (less than 0.6-point improvement in the DAS 28), further tocilizumab therapy is not recommended.

If there is a partial response by week 12, with a DAS 28 improvement of at least 0.6 (but of less than 1.2), the treatment can be continued until week 24.

If the DAS 28 improvement is less than 1.2 by week 24, the treatment strategy should be reappraised.

In patients who have a response (DAS 28 improvement >1.2 by week 24) with residual disease activity (DAS 28 >3.2), the treatment strategy should be reappraised in the light of available alternative treatments.

## Modalities of follow-up in everyday practice

Several situations such as vaccinations, surgery, travel, pregnancy, and lactation are discussed in fact sheets available from us on request or from the CRI site (www.cri.net.com). We have given the patient a written document that describes tocilizumab and the treatment modalities.

We will be happy to provide you with any additional information you may need.

Sincerely,

***Physician in charge:***

Dr..................................................................

Telephone:.....................................................

Stamp:

**Annex 2:** Model Information Letter for the
# Primary-Care Physician

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

.........................., .........................

Dear Colleague,

You will soon receive a visit from your patient M (Ms) .........................................

born on......................................... in whom we recently started tocilizumab (RoActemra®) treatment for rheumatoid arthritis.

## What is tocilizumab?

Tocilizumab is a monoclonal antibody that inhibits the receptor for interleukin-6. Tocilizumab has been proven effective in improving the symptoms and structural disease progression in patients with rheumatoid arthritis (RA).

Based on this evidence of efficacy, tocilizumab was granted a marketing licence in 2009 for active moderate-to-severe RA in patients having failed one or more DMARDs or TNF antagonists, as add-on treatment to methotrexate or as monotherapy in the event of intolerance to methotrexate or when further methotrexate therapy would be inappropriate.

The first tocilizumab infusion was given intravenously in a dosage of ...................................................................................................................

in the department of ...................................................................................
(Dr ...............................................................), on ...........................

An infusion will be given once monthly, in the same dosage, in the absence of pregnancy, infection, surgery, or adverse events.

A DMARD was prescribed in combination with tocilizumab.

❏ YES (specify the nature and dosage of the DMARD) ...............................
❏ NO (tocilizumab monotherapy)

## Effectiveness of tocilizumab therapy

The effect of tocilizumab therapy on the signs and symptoms of RA usually becomes apparent gradually over the first few treatment months.

The final evaluation of the effectiveness of tocilizumab therapy is usually performed after 6 months of treatment.

## What are the risks associated with tocilizumab therapy?

Intolerance (a reaction) to the molecule during the infusion or within the next few

hours is very rare. In most cases, simple symptomatic measures suffice. However, admission on an emergency basis is required in patients with constitutional symptoms, respiratory manifestations, cardiovascular manifestations, or diffuse skin lesions.

Infections may occur in tocilizumab-treated patients. Pneumonia and bronchitis are the most common forms, although cellulitis, pyelonephritis, and diverticulitis have been reported also. In tocilizumab-treated patients, infections may fail to elevate the levels of CRP, other markers for inflammation, or leukocytes.

In the absence of signs of a serious infection, prompt initiation of appropriate antimicrobial therapy is warranted. Patients with constitutional symptoms or complications should be admitted on an emergency basis.

Other adverse events have been reported such as blood pressure changes (hypertension, hypotension), hepatic cytolysis (without severe hepatitis), neutropenia (reversible), hypercholesterolemia, and headaches.

Despite this non-exhaustive list of adverse events, it should be borne in mind that the overall safety record of tocilizumab so far is very good.

Interactions may occur between tocilizumab and drugs metabolized via the cytochrome P450 enzymes such as some of the statins (atorvastatin, simvastatin), calcium channel inhibitors, theophylline, warfarin, cyclosporine, benzodiazepines, and phenytoin. These interactions may require dosage adjustment at tocilizumab initiation or discontinuation (dosage increase at tocilizumab initiation and dosage decrease 1 to 2 weeks after tocilizumab discontinuation).

## Practical considerations

➤ The infusions will be given once every 4 weeks during brief hospital stays (1 hour to a few hours).

➤ The effectiveness and safety of tocilizumab therapy will be monitored during a rheumatologist visit at least 3 months after the initiation of tocilizumab therapy, but the patient may ask to see you in the event of unusual symptoms, whose possible link to tocilizumab will have to be evaluated.

Please contact one of the members of our team if you are unsure about anything.

➤ The rheumatologist must evaluate the patient at least once every 3 months to assess the clinical effectiveness of tocilizumab therapy (based on the DAS (Disease Activity Score) and the effect on laboratory tests (ESR-CRP)).

➤ We provide most of the monitoring required to assess safety. The only laboratory tests required by tocilizumab therapy are blood cell counts, serum transaminase assays, and serum lipid assays, at 3-month intervals. Additional tests should be performed as indicated by the concomitant medications (e.g., methotrexate and corticosteroids).

Before the first tocilizumab infusion, we checked your patient's immunisation records.

❏ Immunisation against ................................. was performed on ...../...../........

❏ No immunisations were deemed necessary.

If immunisation or re-immunisation with an inactivated vaccine (e.g., influenza) is required, it may be performed during tocilizumab treatment. Administration of the influenza vaccine is recommended once a year.

In contrast, live vaccines (oral poliomyelitis, MMR, varicella-zoster, yellow fever, and BCG) are contraindicated during tocilizumab therapy and during the first 70 days after treatment discontinuation.

➤ In the current state of our knowledge, pregnancy is contraindicated during and until 3 months after tocilizumab therapy. No data are available on potential effects of tocilizumab therapy on the foetus.

➤ In patients who require elective surgery, the recommended interval between the last tocilizumab infusion and the surgical procedure is 4 weeks at least. This interval may be modulated depending on the nature of the surgical procedure (as the risk of postoperative infection varies across procedures), any co-morbidities and patient-related factors, the severity of the joint disease, and the extent of disease control.

If emergency care is required, the appropriateness of prophylactic antibiotics should be discussed on a case-by-case basis.

➤ When routine dental care is needed (cavities, scaling), prophylactic antimicrobial therapy can be suggested, with no change in the treatment regimen for the joint disease.

When dental procedures that carry a risk of infection are required (extraction, apical granuloma, abscess...), the tocilizumab infusion should be postponed as with surgical procedures and prophylactic antimicrobial therapy should be offered.

➤ The patient may travel provided no live vaccines (e.g., yellow fever) are required, as live vaccines can be given only after discontinuing tocilizumab therapy. As with all travellers, measures aimed at preventing infections should be followed scrupulously. Standard antimalarial prophylaxis can be used.

An information sheet explaining all these points was given to the patient before the tocilizumab infusion.

Sincerely,

**Physician in charge:**

Dr..............................................................

Telephone:...............................................

Stamp:
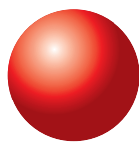
**Annex 3:** Patient information document. Use of
# Tocilizumab to Treat Rheumatoid Arthritis

| Evidence Based Medicine | Official recommendations | Expert opinion |

To give you a good understanding of the benefits and specificities of tocilizumab treatment, this document supplies you with practical answers to ten questions.

Tocilizumab therapy may require changes in the dosage of other medications. When you receive your first tocilizumab injection, and when you stop tocilizumab therapy, remember to give your doctor the full list of medications you are taking. Your doctor will be able to determine whether you need adjustments in the doses.

## What is tocilizumab?

Tocilizumab is a medication that treats rheumatoid arthritis by regulating your immune system in order to alleviate your symptoms such as joint pain and swelling. This medication may also improve your ability to go about your daily activities. The objective of tocilizumab therapy is to halt the progression of your disease by diminishing your risk of experiencing further joint damage (joint space narrowing and bone erosions).

## Why did your rheumatologist suggest tocilizumab treatment?

Your rheumatologist suggested tocilizumab because this medication has been proven effective in patients with rheumatoid arthritis. Tocilizumab is used in adults who have active moderate-to-severe rheumatoid arthritis and who did not respond adequately to earlier treatments. Tocilizumab was granted a marketing licence (AMM) in 2009 in France. You and your rheumatologist have decided together to use tocilizumab to treat your disease, based on the features of your disease and on your own characteristics (past medical history, infections, allergies …).

## How does tocilizumab work?

Tocilizumab is one of the "biotherapies" or "biologics". These names mean that tocilizumab specifically acts to prevent the stimulation of a biological component of your immune system. More specifically, tocilizumab is a monoclonal antibody that blocks the effects of a specific protein (a cytokine) called interleukin-6. This protein is involved in the inflammatory processes that take place in the body, and blocking it is an effective way of combating inflammation.

## What are the risks of tocilizumab therapy?

The main risk is the occurrence of infections that may develop because tocilizumab blunts the immune responses of the body. The most common infections affect the lungs, lower airways, and urinary tract. Most of them are non-serious infections that are easy to treat.

Tocilizumab may induce complications that can be diagnosed only by blood tests (decrease in the number of white blood cells in blood, known as neutropenia or leukopenia; decrease in the number of platelets, known as thrombocytopenia; increase in the cholesterol level; and abnormalities in liver function tests known as cytolysis). For this reason, your doctor will monitor you during and after the treatment, and you will have blood samples drawn. You must inform your doctor of any symptoms you may experience.

## How is tocilizumab used?

Tocilizumab can only be given in hospitals. Your doctor will refer you to a hospital department where the specialists have acquired experience with tocilizumab and are accredited to use it. Tocilizumab must be given as an intravenous infusion once every 4 weeks. The infusion contains only tocilizumab and requires 1 hour to administer on a day-hospital basis.

You will continue your other treatments for rheumatoid arthritis. In particular, methotrexate is useful, as it increases the effectiveness of tocilizumab. Do not change your treatment without first talking to your doctor. In some cases, however, tocilizumab may be used alone, if your doctor feels that methotrexate therapy is not appropriate.

## What will happen before the first tocilizumab infusion?

Your doctor will ask questions about several important points.

➤ You must be aware of all the medications that you take, as their effectiveness may in some cases be affected by the addition of tocilizumab. Therefore, it is important that you give your doctor the full list of all the medications you use so that he/she can adjust their dosages if needed.

➤ You must have detailed information on your medical history. In particular, it is important to know whether you have a history of

- infections
- viral hepatitis (B or C)
- tuberculosis
- diverticulitis or intestinal ulcers. The symptoms may consist of abdominal pain and of an unexplained change in bowel habits with a fever.
- heart disease, hypertension, or too much cholesterol
- lung disease or any other chronic disease
- allergies to medications or foods

➤ You must check that you are properly immunised against tetanus and polio, and your doctor may recommend that you receive vaccines against influenza and pneumococcal disease. If your immunisations are not up to date, you will have to receive new shots.

➤ If you are a woman, you must make sure that you are not pregnant, and if you have just had a baby, you will not be able to breast-feed, since the effects of tocilizumab during pregnancy and breast-feeding are not known.

➤ Whether you are a woman or a man, you must use effective contraception throughout the treatment with tocilizumab. If you want a baby, you must discuss your plans with your doctor before stopping your contraception.

If you have any questions before the first tocilizumab infusion, feel free to discuss them with your doctor.

## What will happen during the rituximab infusion?

You will be expected at the hospital early in the morning. The infusion will last about 1 hour. You can eat breakfast before leaving home except if you are scheduled to have blood drawn for a cholesterol test. Remember to bring the things you might need (such as books, drinks, your phone…).

If you have an infection of any kind (even a simple cold) on the day your infusion is scheduled, the infusion can be postponed until you feel better. Feel free to contact your doctor or the day-hospital nurse before the infusion to tell them about the infection.

You will be comfortable during the infusion. You will be able to read, listen to music, or watch television.

During the infusion, pay attention to any abnormal symptoms that might indicate a reaction to the medication. Such reactions are rare with tocilizumab.

These symptoms may consist of trouble breathing, swelling of your tongue or lips, a headache, a feeling of warmth and/or shivering, redness or itching of the skin, nausea and/or vomiting, itchiness inside your nose and/or sneezing, itchiness in your throat, pain in your chest, and/or an abnormally fast heartbeat.

You must report all your symptoms to the nurse in charge of monitoring you. If you experience symptoms of any kind, the nurse will stop or slow the infusion and call the doctor working in the hospital department. If your symptoms resolve rapidly, the doctor may decide to continue the infusion. Severe reactions that require permanent discontinuation of the infusion are very rare.

If you experience any symptoms during the infusion, you will be monitored at the hospital for at least 2 hours before going home.

## What will happen after the infusion?

If the infusion went well, you will return home. You may leave with a family member or friend or ask us to help you find an appropriate means of transportation.

Between the infusions, you will go on with your life normally.

Pay attention to any possible symptoms during the first few hours and days following the infusion, although delayed allergic reactions are exceedingly rare.

Until the next infusion, pay attention to any symptoms that may indicate an infection. These symptoms may consist of a fever, chills, a sore throat or bad cold, an unusual cough and/or trouble breathing, a burning sensation during urination, back pain, weight loss, spots on your skin (redness, swelling, blisters) or breaks in your skin, or marked weakness.

Patients who are taking tocilizumab may experience a form of abdominal infection known as diverticulitis, although this is uncommon. Obtain advice from a doctor immediately if you have stomach pains or abdominal cramps or if you pass blood through your rectum.

Feel free to contact your rheumatologist if you notice anything that is unusual, or talk to your primary doctor if needed. It is better to ask questions right away than to wait. Do not take any medications without first talking to your doctor.

## How and when will you notice the effects of the treatment?

Tocilizumab has been proven effective in rheumatoid arthritis. Tocilizumab improves not only the pain and fatigue, but also the joint swelling. You should be aware, however, that the full effect often requires several weeks to develop. You will objectively document your improvements with your doctor, who will perform a physical examination and order blood tests to evaluate the degree of inflammation (based on the erythrocyte sedimentation rate [ESR] and/or C-reactive protein [CRP] level). The longer-term effectiveness of the treatment will be assessed by obtaining radiographs of your hands and feet about 1 year after the first infusion.

## How long should tocilizumab be used?

Tocilizumab therapy may induce a remission, but the disease relapses if the treatment is stopped. Therefore, if tocilizumab is effective and well tolerated, it should be continued. The maximum treatment duration is unknown, but some patients will require tocilizumab for several years at least.

Your rheumatologist will see you at least once every 6 months to perform a physical examination, ask questions, and order blood tests for monitoring the degree of inflammation. You will discuss further tocilizumab therapy with your rheumatologist.

In the intervals between rheumatologist visits, you will see your primary doctor if needed, according to the course of your joint disease and to whether you have other health problems that require attention, such as infections that may be precipitated by the treatment.

We hope this information was helpful.

**If you have any questions, feel free to discuss them with your doctor or the other healthcare professionals.**

# Tables

| Evidence Based Medicine | Official recommendations | Expert opinion |
|---|---|---|

## Table 1:

Examples of drugs that are metabolized by the cytochrome P450 isoenzymes

The full list is available online at http://medicine.iupui.edu/clinpharm/ddis.

| Main interactions | INN |
|---|---|
| CYP 1A2 | Theophylline |
| CYP 2C9 | Phenytoin |
|  | Warfarin |
| CYP 2C19 | Benzodiazepines (alprazolam, diazepam, midazolam, prazepam, tetrazepam, chlorazepate…) |
| CYP 3A4 | Cyclosporine |
|  | Atorvastatin, simvastatin |
|  | Calcium channel inhibitors (amlodipine, diltiazem, nifedipine, felodipine, isradipine, nicardipine, nitrendipine, bépridil, bépridil, verapamil…) |

## Table 2:

Management of patients with neutropenia ($<2000/mm^3$) or thrombocytopenia ($<150\,000/mm^3$) during tocilizumab therapy for rheumatoid arthritis, depending on the neutrophil or platelet count

| Neutrophils | $> 1\,000/mm^3$ | Continue tocilizumab therapy. |
|---|---|---|
| and/or platelets | $> 100\,000/mm^3$ | Monitor blood cell counts at 15-day intervals until stable. |
| Neutrophils | $500\text{-}1000/mm^3$ | Discontinue tocilizumab. |
| and/or platelets | $50,000\text{-}100,000/mm^3$ | Discontinue tocilizumab. Monitor blood cell counts at 15-day intervals. Re-start tocilizumab at 4 mg/kg when -the neutrophils are above $1000/mm^3$ -the platelets are above $100,000/mm^3$. Tocilizumab can be restarted in a dosage of 8 mg/kg after 2 months with neutrophils above $1,000/mm^3$ and platelets above $100,000/mm^3$ |
| Neutrophils | $< 500/mm^3$ | Discontinue tocilizumab. |
| and/or platelets | $< 50,000/mm^3$ | Monitor blood cell counts at least once a week. Tocilizumab re-treatment at 4 mg/kg under close blood cell count monitoring can be considered when the neutrophils are above $1,000/mm^3$ and the platelets above $100,000/mm^3$. Tocilizumab can be restarted in a dosage of 8 mg/kg after 2 months with neutrophils above $1,000/mm^3$ and platelets above $100,000/mm^3$. |

### Table 3:

Cardiovascular risk factors that should be taken into account when determining the target LDL-cholesterol level [5].

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**Risk Factors**
- Age :          - male aged 50 years or older
                    - female aged 60 years or older
- Family history of premature coronary artery disease
         - myocardial infarction or sudden death before 55 years of age in the father or another first-degree male relative
         - myocardial infarction or sudden death before 65 years of age in the mother or another first-degree female relative
- Current smoker or smoking cessation within the last 3 years
- Treated or untreated permanent hypertension (see specific recommendations)
- Type 2 diabetes or other type of diabetes (see specific recommendations)
- HDL-cholesterol <0.40 g/L (1.0 mmol/L) in a male or female patient

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**Protective factor**
- HDL-cholesterol ≥0.60 g/L (1.5 mmol/L): subtract one risk factor from the cardiovascular risk score

(Example: a 60-year-old female with an HDL-cholesterol level of 0.70 g/L (1.8 mmol/L) is considered free of risk factors).

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### Table 4:

The three categories of high-cardiovascular-risk patients in whom the serum LDL-cholesterol level should be kept below 1 g/L [5].

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**1/ Patients with a history of**
       - documented coronary artery disease (stable or instable angina, revascularisation, myocardial infarction, documented silent myocardial infarction)
       - documented vascular disease at other sites (ischemic stroke or peripheral occlusive arterial disease stage II or higher)

---

**2/ Patients with type 2 diabetes and no history of cardiovascular disease but a high cardiovascular risk defined as**
     - renal involvement*
     - or at least two of the following risk factors:
         - age :   - male aged 50 years or older
                   - female aged 60 years or older
         - family history of premature coronary artery disease:
            - myocardial infarction or sudden death before 55 years of age in the father or another male first-degree relative
            - myocardial infarction or sudden death before 65 years of age in the mother or another female first-degree relative
         - current smoking or smoking cessation within the last 3 years
         - treated or untreated permanent hypertension (see the specific recommendations)
         - HDL-cholesterol <0.40 g/L (1.0 mmol/L) in a male or female patient
         - microalbuminuria (> 30 mg/24 hours)

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**3/ Patients whose 10-year coronary event risk (estimated using a risk equation) is greater than 20% ***

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\* Proteinuria >300 mg/24 h or creatinine clearance estimated using the Cockcroft-Gault

equation at <60 ml/min (Cockcroft-Gault equation: creatinine clearance $= \frac{(140 - age\ in\ years) \times weight\ (kg) \times K}{serum\ creatinine\ in\ \mu mol/L}$, in ml/min/1.73 m$^2$ (K =1.23 in males and 1.04 in females).

\*\*See ANAES: Recommendations on methods for evaluating the overall cardiovascular risk.

## Table 5:

Lipid parameters measured in patients enrolled in studies of tocilizumab therapy.

| Mean change [± SD] from baseline to week 24 | Tocilizumab in combination with other drugs | | Tocilizumab alone | |
|---|---|---|---|---|
| | TCZ 8mg/kg + DMARD (n=1582) | Placebo + DMARD (n=1170) | TCZ 8mg/kg + placebo (n=288) | Methotrexate (n=284) |
| Total cholesterol (g/L) | 0.30 [±0.35] | 0.04 [±0.26] | 0.37 [±0.40] | 0.07 [±0.35] |
| LDL-cholesterol (g/L) | 0.20 [±0,30] | 0.02 [±0.22] | 0.26 [±0.34] | 0.05 [±0.28] |
| HDL-cholesterol (g/L) | 0.05 [±0.12] | 0.01 [±0,10] | 0.04 [±0.12] | 0.03 [±0.11] |
| Triglycerides (g/L) | 0.28 [±0.77] | 0.02 [±0.49] | 0.39 [±0.90] | -0.04 [±0.46] |
| Apolipoprotein A1 (g/L) | 0.20 [±0.27] | 0.00 [±0.26] | 0.20 [±0.30] | 0.10 [±0.26] |
| Apolipoprotein B (g/L) | 0.10 [±0.26] | 0.00 [±0.19] | 0.20 [±0.28] | 0.00 [±0.23] |
| CRP (mg/L) | -23 [±29] | -4 [±25] | -27 [±34] | -19 [±33] |
| SAA (ng/ml) | -58,479 [±84,929] | -7,017 [±71,535] | -67,857 [±90,304] | -47,623 [±87,819] |
| Lipoprotein A  (mg/L) | -124 [±181] | -1 [±114] | -135 [±172] | -51 [±97] |

## Table 6:

Rates of neutropenia during studies of tocilizumab in rheumatoid arthritis

| Study | Design | Arms | Rate of neutropenia Pbo | TCZ | Consequences |
|---|---|---|---|---|---|
| **Nishimoto, 2004** [29] | DMARD-IR 12 weeks N = 164 | DMARD + Pbo DMARD + TCZ | Any grade 0% including G4 0% | Any grade 16% including G4 0% | TCZ discontinued in 1 pt No serious infections |
| **STREAM** [30] | Open-label extension (Nishimoto) N = 143 | MTX + TCZ | - - | G1 0% G2 12% G3 6% G4 0% | No serious infections |
| **CHARISMA** [31] | MTX-IR 16 weeks N = 359 | MTX + Pbo Pbo + TCZ MTX + TCZ | Any grade 0% including G4 0% | Any grade 5-14% (dose dep.) including G4 0% | No serious infections no impact of MTX |
| **OPTION** [32] | MTX-IR 24 weeks N = 623 | MTX + Pbo MTX + TCZ | Any grade 2% | Any grade 17-33% (dose dep.) | No serious infections |
| **SATORI** [33] | MTX-IR 24 weeks N = 125 | MTX + Pbo MTX + TCZ | - | - | None mentioned dans la publication |
| **SAMURAI** [34] | DMARD-IR 52 weeks N = 306 | DMARD + Pbo DMARD + TCZ | - | - | Aucune mention in the article |
| **TOWARD** [35] | DMARD-IR 24 semaines N = 1220 (2 :1) | DMARD + Pbo DMARD + TCZ | G1 4% G2 <1% G3 0% G4 0% | G1 19% G2 12% G3 4% G4 0% | TCZ discontinued in 3 pts Dose reduction in 5 pts No serious infections |
| **RADIATE** [36] | AntiTNF-IR 24 weeks N = 499 | MTX + Pbo MTX + TCZ | Any grade <1% including G4 0% | Any grade 20-28% (dose dep.) (G4 : 1.5%) | TCZ discontinued in 5 pts No serious infections |
| **AMBITION** [37] | MTX naïve 24 weeks N = 673 | MTX + Pbo Pbo + TCZ | G1 8% G2 2% G3 <1% G4 0% | G1 18% G2 10% G3 3% G4 0% | TCZ discontinued in 2 pts No serious infections |
| **LITHE** [38] | MTX-IR 52 weeks N = 1190 | MTX + Pbo MTX + TCZ | G1 3,1% G2 1.3% G3 0% G4 0% | TCZ 4 mg/kg G1 10.8% G2 8,5% G3 1.8% G4 <1% TCZ 8 mg/kg G1 22.1% G2 14.5% G3 4.3% G4 <1% | TCZ discontinued in3 pts No serious infections |

IR, inadequate responder; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; Pbo, placebo; TCZ, tocilizumab; G, neutropenia grade

Neutropenia grades (WHO): G1, 1,500 to 2,000/mm$^3$; G2, 1500 to 1,000/mm$^3$; G3, 1000 to 500/mm$^3$; G4, <500/mm$^3$

### Table 7:

Prevalence of cancers and lymphomas in randomised controlled studies of tocilizumab as monotherapy *versus* methotrexate or as combination therapy *versus* placebo, with a mean treatment duration of 2.4 years[11].

| | Initial randomized population (n=4,199) | | | All exposed individuals (n=4,009) |
|---|---|---|---|---|
| | Contrôles n=1,555 | TCZ 4 mg/kg + DMARDs* n=774 | TCZ 8 mg/kg + DMARDs* n=1,870 | |
| **Exposure duration (patient-years)** | 825 | 565 | 1,194 | 9,414 |
| **Rate/100 patient-years (number of events)** | | | | |
| **All cancers** | 0.7 (6) | 1.6 (9) | 0.7 (8) | 11 (105) |
| **Non-myeloma skin cancers** | 0.4 (3) | 0.5 (3) | 0.3 (4) | 0.4 (37) |
| **Solid cancers** | 0.4 (3) | 0.9 (5) | 0.3 (4) | 0.6 (61) |
| **Lymphomas** | 0 | 0 | 0 | 0;0 (4) |
| **Other cancers [a]** | 0 | 0.2 (1) | 0 | 0.0 (3) |

[a]: other cancers in which the primary was not identified.

* *DMARD : Disease-Modifying Anti-Rheumatic Drug*

### Table 8:

Prevalence (events per 100 patient-years (PY)) of cancers in randomised controlled studies of tocilizumab and their open-label extensions - F. Hoffmann-La Roche clinical study report: Original US Biologic License Application, summary of clinical safety

| Follow-up duration (months) | Tocilizumab (n = 4009) | | |
|---|---|---|---|
| | Exposure duration (patients/années (PA) | Number of events | Events/100 patient-years (95%CI) |
| 0-6 | 1.805 | 17 | 0.94 (0.55, 1.51) |
| 7-12 | 1,664 | 18 | 1.08 (0.64, 1.71) |
| 13-18 | 1,542 | 12 | 0.78 (0.40, 1.36) |
| 19-24 | 1,440 | 19 | 1.32 (0.79, 2.06) |
| 25-30 | 1,290 | 19 | 1.47 (0.89, 2.30) |
| 31-36 | 964 | 13 | 1.35 (0.72, 2.31) |
| 37-42 | 528 | 7 | 1.33 (0.53, 2.73) |

**Table 9:**

Tocilizumab and other biological agents

| Biotherapy | Data from the literature on combinations of TCZ and other biotherapies | Wash-out period duration | |
|---|---|---|---|
| | | Other biotherapy to TCZ | TCZ to other biotherapy |
| **TNF antagonist** | - no published studies<br>- not recommended | Anti-TNF to TCZ: except in very rare cases, TCZ can be started on the day of the next scheduled anti-TNF dose. In patients at high risk for infection, a wash-out period equal to 5 times the anti-TNF half-life may deserve discussion before TCZ initiation. | TCZ to anti-TNF: no published studies; anti-TNF initiation may be considered 4 weeks after the last TCZ infusion. |
| **Anakinra (ANA)** | - no published studies; 1 ongoing study<br>- not recommended | ANA to TCZ: despite the absence of scientific data, given the short half-life of ANA, TCZ can be started 1 week after ANA discontinuation. | TCZ to ANA: no published studies but ANA may be started 4 weeks after the last TCZ infusion |
| **Rituximab (RTX)** | - no published studies; 1 ongoing study<br>- not recommended | RTX to TCZ: a study (ACTEMAB) is evaluating the safety of TCZ given 1 month after RTX. | TCZ to RTX: no published studies; RTX initiation may be considered 4 weeks after the last TCZ infusion. |
| **Abatacept (ABA)** | - no published studies<br>- not recommended | ABA to TCZ: except in very rare cases, TCZ can be started on the day of the next scheduled ABA dose. | TCZ to ABA: except in very rare cases, ABA can be started on the day of the next scheduled TCZ dose. |

## Table 10:

The most common adverse events in patients receiving a disease-modifying antirheumatic drug combined with tocilizumab or a placebo in the TOWARD trial

|  | Tocilizumab + DMARD | DMARD + placebo |
|---|---|---|
| Headaches | 6% | 4% |
| Hypertension | 5% | 3% |
| Cytolysis: ALAT/ASAT ≤3N | 41.7% / 35.7% | 14.0% / 11.8% |
| Grade 3 neutropenia (500-1000 neutrophils/mm$^3$) | 3.7% | 0% |
| Cholesterol ≥240 mg/dl | 23.0% | 5.5% |

## Table 11:

Recapitulation of published studies of tocilizumab therapy in paediatric joint disease

| | 2005 | 2005 | 2008 | 2008 | 2006 |
|---|---|---|---|---|---|
| Authors | Yokota et al. [7] | Woo et al. [6] | Yokota et al. [8] | Yokota et al. [26] | Imagawa et al. [17] |
| Study design (OL, LI, DB, R, Pbo)[a] | OL (Phase II) Escalating doses | OL (Phase II) Fixed doses | LI, DB, R, Pbo (Phase II) | OL (extension Phases II and III) | OL |
| Duration | 14 weeks | 4-8 weeks | 4-5 months (6 wks LI+12 wks R) | 30 months (median) | 12 weeks |
| JIA category | systemic JIA | systemic JIA | systemic JIA | AJI systémique | polyarticular17 and extended oligoarticular2 JIA [2] |
| Number of patients [b] Age | 11 3-20 years | 18 2-18 years | 56 (LI), 43 (R) 2-19 years | 128 9 years (median) | 19 3-19 years |
| Tocilizumab dose | 2-4-8mg/kg/2wks | 2-4-8mg/kg/2wks | 8 mg/kg/2 wks | 8 mg/kg/2 wks | 8 mg/kg/4 wks |
| Concomitant drugs [c] | MTX, CsA, steroids, NSAIDs (fixed doses) | MTX (12/18 pts), steroids, NSAIDs (fixed doses) | Steroids, NSAIDs (fixed doses) | Steroids, NSAIDs (fixed doses) | NSAIDs, low-dose steroids (fixed doses) |
| Primary criterion | % pts ACRPedi30-50-70 2 wks after 3 fixed doses + lab* | % pts ACRPedi30-50-70 + systemic score at the end of each wk + lab* | % pts ACRPedi30 + lab* at the end of the DB period (wk 18) without rescue therapy | % pts ACRPedi30/3 months | % pts ACRPedi30 at wk 12 |
| Efficacy [d] | 11 pts: 2 mg/kg ACRPedi30: 64% ACRPedi50: 64% AcrPedi70: 9% 8 pts: 4 mg/kg ACRPedi30: 87% ACRPedi50: 87% AcrPedi70: 50% 3 pts: 8 mg/kg ACRPedi30: 100% ACRPedi50: 100% AcrPedi70: 100%<br><br>Rapid and stable ESR and CRP decreases | 15 pts (3 protocol violations) 4 pts: 2 mg/kg Wk1, ACRPedi30: 75% Wk6, ACRPedi30: 0% Wk8, ACRPedi30: 0% 6 pts: 4 mg/kg Wk1, ACRPedi30: 83% Wk6, ACRPedi30: 67% Wk8, ACRPedi30: 0% 5 pts: 8 mg/kg Wk1, ACRPedi30: 60% Wk6, ACRPedi30: 40% Wk8, ACRPedi30: 20%<br><br>Stable ESR and CRP decreases at Wk1 | ACRPedi30, 80% TCZ vs. 17% Pbo ACRPedi50, 80% TCZ vs. 17% Pbo ACRPedi70, 75% TCZ vs. 13% Pbo<br><br><br><br><br><br><br><br>Stable ESR and CRP decreases at Wk2 | N=78 pts at Wk48 ACRPedi30: 94% ACRPedi50: 88% AcrPedi70: 81% N=58 pts at Wk96 ACRPedi30: 100% ACRPedi50: 98% AcrPedi70: 93% N=41 pts at Wk144 ACRPedi30: 100% ACRPedi50: 100% AcrPedi70: 98% | ACRPedi30: 95% ACRPedi50: 95% AcrPedi70: 58% |
| Common adverse events [e] (in order of decreasing frequency) | -Moderate total cholesterol elevation (4/11) -Moderate decrease in γGb (4/11) -Pustules on hands and feet -Mild UAW infections -Moderate ALAT elevation (2/11) -Glycosuria (2/11) -Eczema -Anti-TCZ antibodies | -Infections -Gastrointestinal symptoms -Respiratory symptoms -Transient moderate ALAT elevation (3/15 with MTX) -Transient lymphopenia at Wk1-2 (15/15; 8 had lymphopenia before treatment) -Urticaria (1/15) | -Nasopharyngitis 59% -UAW infections 34% -Gastroenteritis 29% -Bronchitis 25% -Moderate ASAT elevation 21%, ALAT 29%, LDH 18% -Mild-to-moderate infusion-related reactions 18% -small total cholesterol increase within normal range -4/56 pts, anti-TCZ antibodies including 3 IgE -1 acute EBV infection (re-tt with TCZ at the extension phase) -1 gastrointestinal bleed | Common adverse events not detailed 5 pts anti-TCZ IgE | -UAW infections -Moderate ALAT/ASAT elevations -Moderate total cholesterol elevation |
| Serious adverse events | | -1 varicella -1 transient pancytopenia at Wk7 1 oral herpes simplex infection<br><br>-2 systemic JIA flares at Wh2 and Wk6 | 1 anaphylactoid reaction without anti-TCZ antibodies | -serious infection rate: 14.5/100 PY (mostly gastroenteritis and pneumonia) -1 MAS †6 -2 anaphylactoid reactions -1 duodenal perforation -1 gastric bleed -1 cardiac amyloidosis† -2 infusion-related reactions | -2 gastroenteritis 1 scalp dysaesthesia |

[a] OL, open-label study; LI, lead-in phase; DB, double blind; R, randomised; Pbo, placebo-controlled; [b] Pts: Patients ; [c] MTX, methotrexate; CsA, cyclosporine A; NSAID, nonsteroidal antiinflammatory drug; [d] ACRPedi30, at least 30% improvement from baseline in at least three of the six following variables: 1/ global VAS score by the physician 2/global VAS score by the patient or parent, 3/ CHAQ, 4/ number of joints with active arthritis, 5/number of joints with motion range limitation, 6/ESR; and no more than one of these 6 variables with 30% or greater deterioration [111]; [e] systemic score, fever, rash, lymphadenopathy, hepatosplenomegaly, serositis [92]; [e] UAW, upper airways; [f†]: death; * Lab: decrease in CRP and ESR values

**Table 12:**

Serum IL-6 levels in patients with ankylosing spondylitis. Data from the literature.

| Author | Correlations |
| --- | --- |
| Bal [127] | ESR, CRP, VAS pain score |
| Gratacos [128] | ESR, CRP, limited spinal motion |
| Park [129] | CRP, BASDAI, leptin, BMI |
| Claudepierre [130] | ESR, serum IL-6 x 5 if peripheral arthritis |
| Falkenbach [131] | Limited spinal motion |
| Wendling [132] | ICAM-1 |

**Figure 1:**
Course of action in the event of ASAT/ALAT elevation to 1.5-3 x ULN. (In the event of ASAT/ALAT elevation to 1.5-3 x ULN, monitor the transaminase levels at intervals no longer than 1 month).
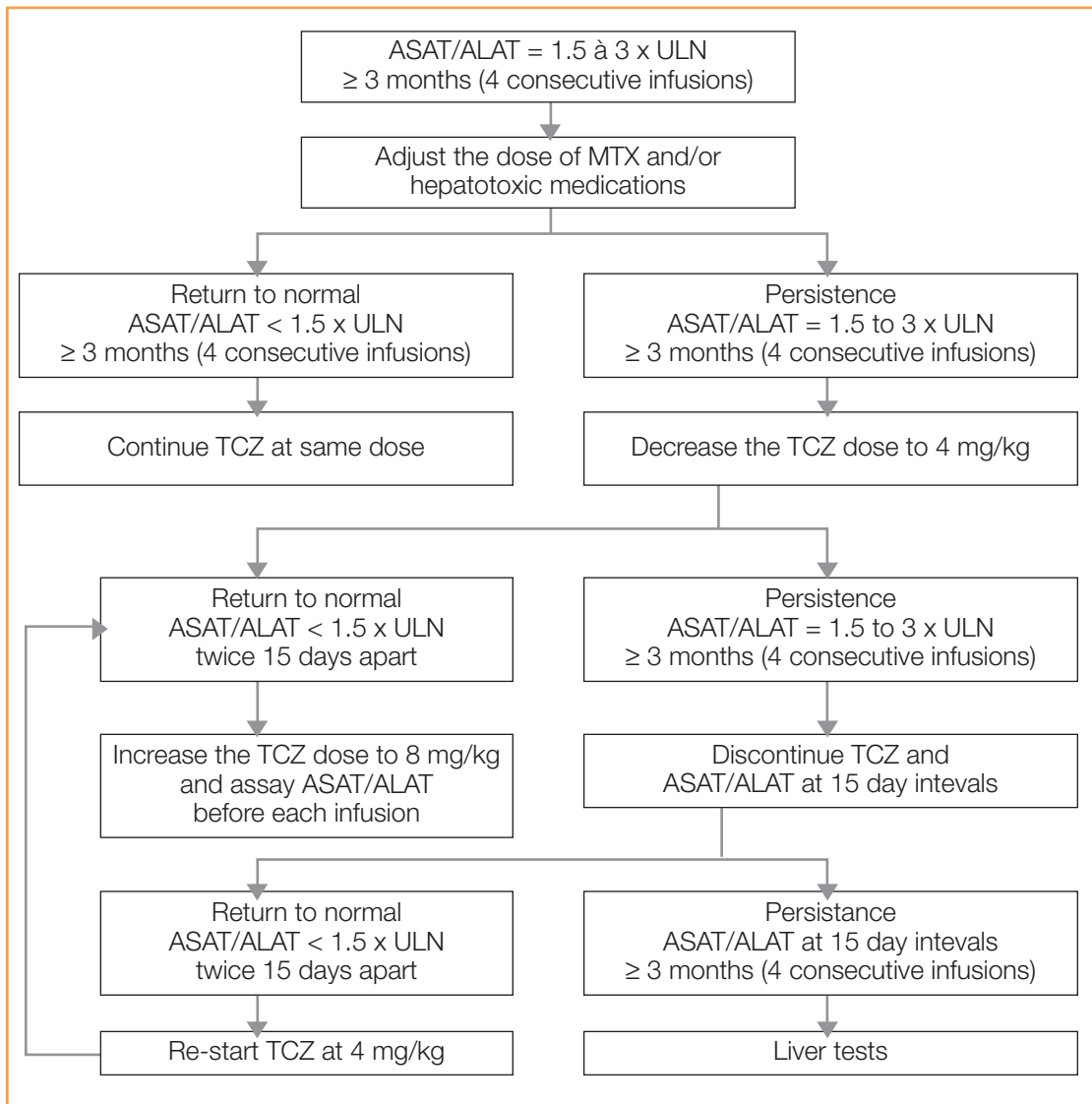


Note: Transaminase elevations should be interpreted not only relative to the normal values but also relative to the baseline values in the individual patient: caution should be exercised if the baseline value increases 3-fold (Ex: in a patient whose baseline transaminase level is 0.4 x ULN, a 3-fold increase will produce a value lower than 1.5 x ULN, which may therefore not be considered of concern).

**Figure 2 :**

Course of action in the event of ASAT/ALAT elevation to >3 x ULN. (In the event of ASAT/ALAT elevation to >3 x ULN, monitor the transaminase levels at intervals no longer than 15 days).

```
┌─────────────────────────────────────────────┐   ┌──────────────────────┐
│ ASAT/ALAT 3 to 5 x ULN twice, 15 days apart  │   │  ASAT/ALAT > 5 x ULN │
└─────────────────────────────────────────────┘   └──────────────────────┘
                    │                                          │
                    ▼                                          ▼
┌─────────────────────────────────────────────┐   ┌──────────────────────┐
│ Discontinue MTX and/or hepatotoxic medication│   │ Discontinue TCZ and  │
│       and repeat assays 15 days later        │   │ other hepatotoxic    │
└─────────────────────────────────────────────┘   │ medications          │
        │               │               │          │ Advice from          │
        ▼               ▼               ▼          │ hepatologist         │
┌──────────────┐ ┌──────────────┐ ┌──────────────┐ └──────────────────────┘
│ Return to    │ │ Improvement  │ │ Persistence  │
│ normal       │ │ in ASAT/ALAT │ │ of ASAT/ALAT │
│ ASAT/ALAT    │ │ to 1.5 et    │ │ at 3-5 x ULN │
│ < 1.5 x ULN  │ │ 3 x ULN      │ │ twice 15     │
│ twice 15     │ │ twice 15     │ │ days apart   │
│ days apart   │ │ days apart   │ │              │
└──────────────┘ └──────────────┘ └──────────────┘
        │               │               │
        ▼               ▼               ▼
┌──────────────┐ ┌──────────────┐ ┌──────────────┐
│ Continue TCZ │ │ Continue TCZ │ │ Discontinue  │
│ as           │ │ as           │ │ TCZ          │
│ monotherapy  │ │ monotherapy  │ │ Assay        │
│ and re-start │ │ and monitor  │ │ ASAT/ALAT    │
│ MTX and/or   │ │ ASAT/ALAT    │ │ at 15-day    │
│ other        │ │ (if          │ │ intervals    │
│ hepatotoxic  │ │ persistent   │ │              │
│ medications  │ │ elevation    │ └──────────────┘
│ if needed,   │ │ between 1.5  │
│ in the same  │ │ and 3 times  │
│ doses or     │ │ the ULN,     │
│ lower doses  │ │ see Figure 1)│
│ and monitor  │ │              │
│ ASAT/ALAT    │ │              │
└──────────────┘ └──────────────┘
                        │               │
        ┌───────────────┼───────────────┤
        ▼               ▼               ▼
┌──────────────┐ ┌──────────────┐ ┌──────────────┐
│ Return to    │ │ Improvement  │ │ Improvement  │
│ normal       │ │ of ASAT/ALAT │ │ of ASAT/ALAT │
│ ASAT/ALAT    │ │ at 1.5 et    │ │ at 3-5 x ULN │
│ < 1.5 x ULN  │ │ 3 x ULN      │ │ twice 15     │
│ twice 15     │ │ twice 15     │ │ days apart   │
│ days apart   │ │ days apart   │ │              │
└──────────────┘ └──────────────┘ └──────────────┘
        │               │               │
        ▼               ▼               ▼
┌─────────────────────────────────┐ ┌──────────────┐
│ Re-start TCZ at 4 mg/kg and      │ │ Liver tests  │
│ monitor ASAT/ALAT (see figure 1) │ │              │
└─────────────────────────────────┘ └──────────────┘
```