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 and/or platelets	> 1 000/mm^3 > 100 000/mm^3	Continue tocilizumab therapy. Monitor blood cell counts at 15-day intervals until stable.
Neutrophils and/or platelets	500-1000/mm^3 50,000-100,000/mm^3	Discontinue tocilizumab. 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 and/or platelets	< 500/mm^3 < 50,000/mm^3	Discontinue tocilizumab. 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].

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

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).

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].

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)

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

* Proteinuria >300 mg/24 h or creatinine clearance estimated using the Cockcroft-Gault equation at <60 ml/min (Cockcroft-Gault equation: creatinine clearance $= \frac{(140 - \text{age in years}) \times \text{weight (kg)} \times K, \text{ in ml/min/1.73 m}^2}{\text{serum creatinine in } \mu\text{mol/L}}$ (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		Consequences
			Pbo	TCZ	
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 - 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 - 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 - 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 - 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% 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% 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 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 -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

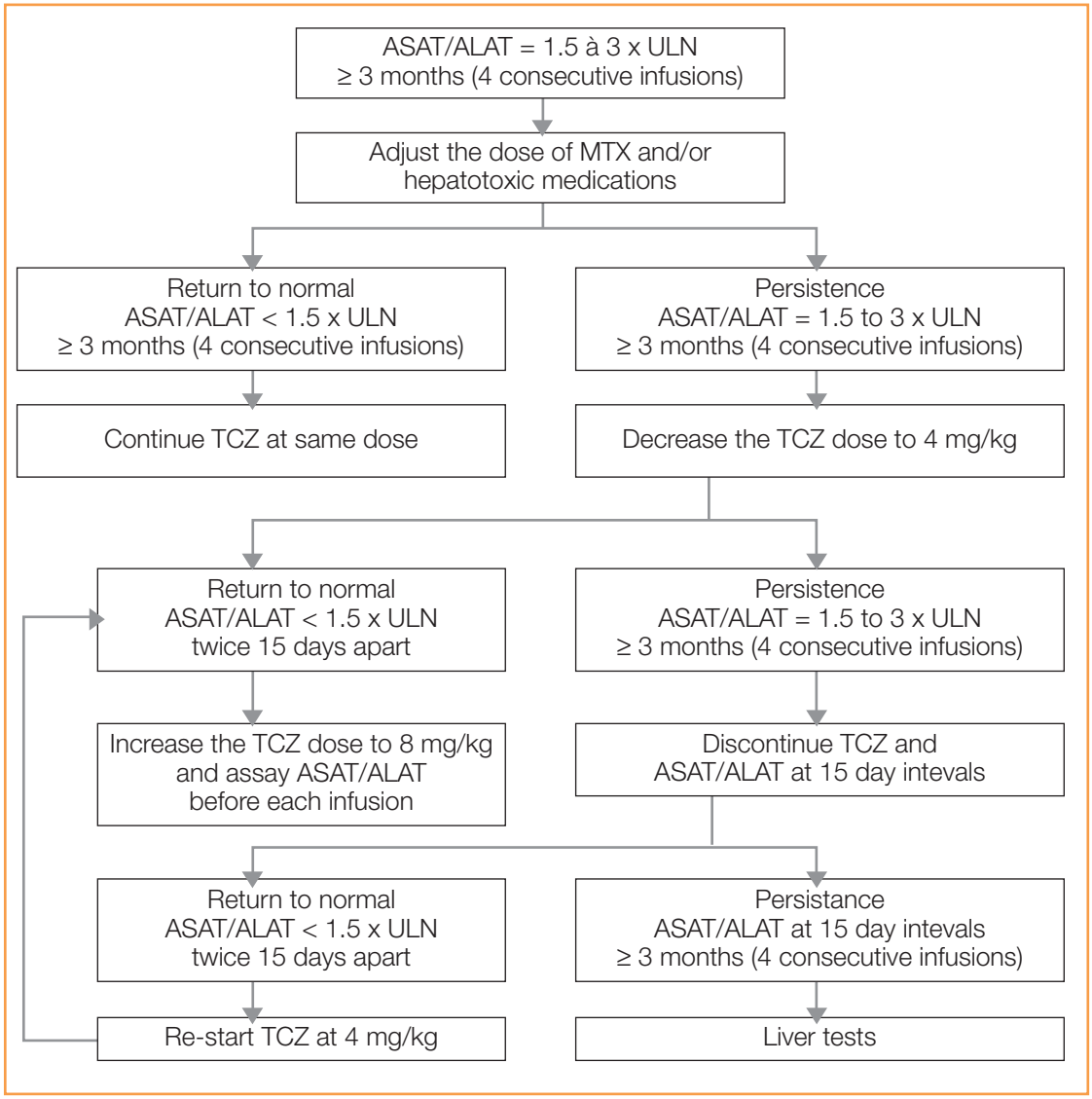
[a] OL, open-label study; LI, lead-in phase; DB, double blind; R, randomised; Pbo, placebo-controlled; [b] Pts: Patients ; [c] MTX, methotrexate; CsA, cyclosporine A; NSAID, nonsteroidal antiinflammatory drug; [d] ACRPedi30, at least 30% improvement from baseline in at least three of the six following 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]; [d] systemic score, fever, rash, lymphadenopathy, hepatosplenomegaly, serositis [92]; [e] UAW, upper airways; [†]: 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).