Tocilizumab and mesenteric arterial thrombosis: drug-drug interaction with anticoagulants metabolized by CYP 450 and/or by P-glycoprotein

B. Clarivet, P. Robin, Y. Pers, R. Ferreira, J. Lebrun, C. Jorgensen, D. Hillaire-Buys, V. Brés, Jean-Luc Faillie

Tocilizumab and mesenteric arterial thrombosis: drug-drug interaction with anticoagulants metabolized by CYP 450 and/or by P-glycoprotein

B. Clarivet[1], P. Robin[1], YM. Pers[2], R. Ferreira[2], J. Lebrun[1], C. Jorgensen[2], D. Hillaire-Buys[1], V Brés[1], J L. Faillie[1].

[1]*Pharmacovigilance Regional Centre, Department of Medical Pharmacology and Toxicology, CHU Montpellier University Hospital, Montpellier, France.*

[2]*Clinical Immunology and Osteoarticular Diseases Therapeutic Unit, CHU Montpellier University Hospital, Montpellier, France.*

CORRESPONDING AUTHOR

Dr Béatrice Clarivet

Centre Régional de Pharmacovigilance du Languedoc-Rousillon- Hôpital Lapeyronie 371, Avenue du Doyen Gaston Giraud 34295 Montpellier cedex 5 France

E-mail : b-clarivet@chu-montpellier.fr

RUNNING HEAD

Tocilizumab and anticoagulants: drug-drug interaction

KEY WORDS

Tocilizumab, Acute mesenteric arterial thrombosis, Drug interaction, Anticoagulant drugs, Rheumatoid arthritis

WORD COUNT

797 (including references)

TABLES AND FIGURES

0

SUMMARY

AIM

Based on a case report, we analyze the potential drug-drug interactions for tocilizumab and anticoagulant treatments.

METHOD

We report a case of mesenteric arterial thrombosis (MAT) associated with tocilizumab. We searched for other case reports in the WHO global individual case safety report (ICSR) database, VigiBase (high-level terms = Gastrointestinal vascular occlusion and infarction, according to MedDRA).

RESULTS

A 52 year-old woman with RA, obesity, hypertension, hyperlipidemia and atrial fibrillation (AF) presented with abdominal pain. She was included 10 months before the event in a clinical trial evaluating subcutaneous tocilizumab 162 mg weekly. A mesenteric ischemia with superior MAT was diagnosed and an urgent surgical treatment was done. The patient died the following day from a refractory cardiogenic shock. We identified two other reports of MAT with tocilizumab in the VigiBase, both associated with an anticoagulant treatment (warfarine or rivaroxaban). Ten other cases were identified, for which anticoagulant treatment was not specified.

CONCLUSION

Among 13 cases of gastrointestinal vascular events with tocilizumab, three were associated with a previous anticoagulant treatment. Considering the rarity of MAT, the question arises of a possible interaction tocilizumab-anticoagulant. IL-6 inhibits expression of CYP450 and treatment with tocilizumab can restore CYP450 metabolism. Our case, occurring with dabigatran, suggests a possible interaction with P-gp. Therefore a specific attention is necessary when TCZ is introduced in patients under anticoagulant treatments not only for those metabolized by CYP450 but also for those whose absorption/excretion involves P-gp.

Tocilizumab (TCZ) is a humanized monoclonal antibody directed against the interleukin-6 (IL-6) receptor. We herein report one case of mesenteric arterial thrombosis (MAT), in a rheumatoid arthritis (RA) patient receiving TCZ. In August 2015, a 52 year-old woman presented to emergency room with acute epigastric pain.. Her medical history included RA (diagnosed in 2013), obesity, smoking, hypertension, hyperlipidemia, recurrent bronchitis and atrial fibrillation (AF). RA was initially treated by methotrexate, then by leflunomide and oral steroids. In October 2014, she initiated subcutaneous TCZ 162 mg weekly. The last injection was performed in July 2015. Three days before the event, she consulted for pulmonary symptomatology and was prescribed empiric amoxicillin. Other medications included dabigatran, flecainide (stopped two weeks earlier), telmisartan/hydrochlorothiazide, atenolol, furosemide and budesonide/formoterol. On the day of admission, she was afebrile, blood pressure was 241/137 mmHg, the electrocardiogram found a depressed ST segment, and blood tests revealed a moderate hepatic cytolysis and an increased high-sensitivity troponin T. A treatment by nicardipine, enoxaparin, and isosorbide dinitrate was initiated. The day after, the abdominal pain worsened. CT scan revealed a superior MAT with bowel injury. An urgent surgical treatment was performed but the patient died few hours after.

In the World Health Organization global individual case safety report database, VigiBase™, we identified two other reports of MAT with TCZ, associated with an anticoagulant treatment (rivaroxaban and warfarin, respectively). Ten other cases of TCZ-associated intestinal infarction or ischemia (without more details) were not associated with ananticoagulant treatment. All these 12 cases were women, mean age was 53 years. Time to onset (stated in only four cases) varied from 15 days to 21 months; it was 15 days for the case with rivaroxaban and was not specified for the case with warfarin. Seven fatal outcomes were reported.

In total, we identified three cases of TCZ-associated MAT with a previous anticoagulant treatment (one for AF, one for deep vein thrombosis and one for an unknown reason). We suspect a drug-drug interaction which adds to the potential thrombogenic effect of the RA disease and/or RA treatments. It has been demonstrated that IL-6 reduces the activity of

cytochrome P450 isozymes (1). Therefore, the use of TCZ, by decreasing the IL-6-mediated inhibition of CYP450, can act as an inducer and increases the metabolism of drugs. Rivaroxaban is a substrate of CYP3A4 and Pgp and warfarine is a substrate of CYP2B6, CYP2C9, CYP2C19 and CYP3A4. Concomitant use of TCZ could have resulted in decreased concentration of anticoagulant and favored the occurrence of thrombosis. Dabigatran etexilate is known for its poor biodisponibility (6.5%) and is a P-glycoprotein (P-gp) substrate. P-gp affects drug pharmacokinetics by limiting oral absorption and promoting excretion. In our case, a possible interaction with P-gp is suggested. The observed ratio of dabigatran $AUC_{0\rightarrow\infty}$ (AUCR) and C_{max} in presence or absence of the P-gP inducer rifampicine was 0.33 and 0.34, respectively (2). Since IL-6-treated mice displayed a 70% reduction in protein expression and a 40–70% reduction in the mRNA levels of all P-gp *mdr* isoforms (3), we can hypothesize that, TCZ's inhibition of IL-6 activity could restore normal P-gp functions and reduce bioavailability of dabigatran etexilate, as observed with a P-gp inducer.

In conclusion, we can reasonably assume that, in our patient, co-administration of tocilizumab with dabigatran had induced a progressively decreased anticoagulant effect of dabigatran etexilate, favouring thrombosis. Attention must be reinforced when TCZ is introduced in patients under anticoagulant treatments not only for those metabolized by CYP450 but also for those whose absorption/excretion involves P-gp.

REFERENCES

1. Mimura H., Kobayashi K., Xu L., et al., 2015. Effects of cytokines on CYP3A4 expression and reversal of the effects by anti-cytokine agents in the three-dimensionally cultured human hepatoma cell line FLC-4. Drug. Metab. Pharmacokinet. 30, 105-10.
2. Hartter S., Koenen-Bergmann M., Sharma A., et al., 2012. Decrease in the oral bioavailability of dabigatran etexilate after co-medication with rifampicin. Br. J. Clin. Pharmacol. 74, 490-500.
3. Hartmann G., Kim H., Piquette-Miller M., 2001. Regulation of the hepatic multidrug resistance gene expression by endotoxin and inflammatory cytokines in mice. Int. Immunopharmacol. 1, 189-99.

ACKNOWLEDGMENTS

Vigibase data were provided by the Uppsala Monitoring Centre, but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, national pharmacovigilance centres, or WHO.