Université de Poitiers
Faculté de Médecine et Pharmacie

ANNEE 2021

THESE

POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE

(décret du 25 novembre 2016)

présentée et soutenue publiquement
le 28 avril 2021 à Poitiers
par Florent BROCA

Complications infectieuses du Tocilizumab au cours des maladies systémiques hors rhumatismes inflammatoires chroniques : série multicentrique rétrospective de 37 patients

COMPOSITION DU JURY

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REMERCIEMENTS :

A Professeur Pascal ROBLOT, je vous remercie de votre présence en tant que président du jury pour évaluer ce travail de thèse. Merci également pour votre soutien dans mes projets et dans l'encadrement de mon internat en médecine interne.

A Docteur Odile SOUCHAUD-DEBOUVERIE, merci d'avoir participé avec moi à la réalisation de ce travail. Merci mille fois de ta présence, de ton soutien et de ton écoute attentive que ce soit pour la réalisation de cette thèse mais aussi pour l'aide apportée contre toutes les difficultés que l'on peut rencontrer en tant qu'interne. C'est une fierté d'avoir pu travailler avec toi, y compris dans le service de médecine interne et une chance de t'avoir eu comme tutrice pendant ces années d'internat, en espérant que tes conseils m'aideront à devenir un aussi bon médecin que tu ne l'es. Merci encore.

A Docteur Mickaël MARTIN, je te remercie d'avoir accepté de faire partie de ce jury pour m'aider à conclure ce parcours universitaire. Ton assistance et ton soutien sont toujours très appréciés.

A Docteur Mélanie CATROUX, un immense merci d'avoir accepté d'être membre de ce jury de thèse pour évaluer ce travail et ainsi d'apporter un regard connaisseur et instructif sur ce sujet.

A Docteur Evelyne LIUU, je te remercie infiniment du temps passé, des conseils et de l'aide consciencieuse apportée à la réalisation des statistiques de ce travail sans quoi la tâche se serait avérée bien plus difficile.

A tous les médecins et personnes ayant participé à l'inclusion et au recueil des données : Pr Françoise Debiais, Dr Rachel Brault, Pauline Lazaro, Dr Aurélie Grados, Victoire Delbee, Dr Bruno Gombert, Dr Lydia Faba, Dr Elisabeth Brottier-Mancini, Dr Florence Berthelemy, Dr Guillaume Denis, Agnes Tran, Dr Antoine Brigaud, Dr Elisabetta Lanciano, Dr Quentin Bodard.

A Mr Jeffrey Arsham, je vous remercie d'avoir participé à la relecture et à la correction de l'anglais de ce travail.

A tous les médecins du service de médecine interne du CHU de Poitiers, je vous remercie pour les capacités acquises à vos côtés, en espérant pouvoir revenir prochainement exercer et développer un peu plus mes compétences à vos côtés notamment pendant mes stages de Dr Junior.

A toutes les équipes médicales et paramédicales qui m'ont accompagné pendant mon internat et ont contribué à ma formation : dans le service de maladies infectieuses du Dr SUNDER (CH de Niort), dans le service de médecine interne et rhumatologie des Dr CHANEL et GOMBERT (CH de La Rochelle), dans le service d'hématologie du Pr LELEU (CHU de Poitiers), dans le service de médecine intensive et réanimation du Pr THILLE (CHU de Poitiers), dans le service de néphrologie du Dr PUJO (CH d'Angoulême) et dans le service de médecine gériatrique du Pr PACCALIN (CHU de Poitiers). Ce fut un plaisir et un honneur d'apprendre et de travailler à vos côtés.

A mes parents. Maman, je te remercie pour ton soutien inconditionnel y compris pendant ces longues et parfois difficiles études, de ma PACES et de l'exploit que tu as accompli pour m'encourager à réussir ce concours ; pendant toute la durée de ma formation, à Bordeaux comme à Poitiers, jusqu'à ce jour si important de ma thèse. Merci pour tout l'amour que tu m'apportes et tous ces bons moments passés avec toi que je n'oublierai jamais. Papa, je te remercie pour ta présence, y compris depuis le début de médecine, des premiers jours du concours jusqu'à ce jour de thèse et de tous les instants passés avec toi. Ta résilience, ta force, ton sourire malgré les difficultés que tu peux rencontrer sont pour moi un modèle infini de courage. Bastien, malgré la distance, je te remercie de ton soutien et de ta présence fraternelle. Tu as des qualités exceptionnelles et j'espère que tu réussiras pleinement à le réaliser et à t'épanouir dans ta vie future. Je vous aime fort et ne vous remercierai jamais assez de votre présence à mes côtés.

A mes grands-parents, Mamie Gisou et Papi Jeannot. Je vous remercie pour votre tendresse, votre amour et votre soutien infaillible. J'espère vous rendre fier. Je vous aime fort. Une grande pensée à mamie Paulette à qui cela aurait été une grande fierté de voir que je suis enfin devenu Docteur.

A toute ma famille, tantes, oncles et cousins qui m'ont toujours apporté amour et soutien. Merci de tout cœur.

A ma Lulu, ma chérie depuis deux ans et demi, merci pour ta douceur, ta délicatesse, ton soutien, ta simplicité, ton amour. Depuis que nous nous sommes rencontrés, je vis un véritable bonheur à tes côtés et j'espère pour encore de nombreuses années. Je t'aime très fort.

A mes amis les plus proches.

Alex, mon plus vieux copain d'enfance. 17 ans que l'on se connait. Merci pour ces moments et délires incroyables que j'ai pu passer avec toi, ces heures passées au téléphone et le temps à déconner entre « kaves ».

Julien et Emilie, ce sont toujours des moments et soirées inoubliables que l'on passe avec vous. Merci pour votre soutien, votre amitié fidèle et pour les délires passés avec vous. Merci aussi à tous les autres copains de Bordeaux avec qui je passe toujours des moments exceptionnels et que je n'oublie pas : James, Lilie, Alex, Elvyna, Cyril, Mathieu, Héloïse et toute la clique.

Les amis de l'enjaillement : Damien, mon premier pote de fac qui me manque quand même pas mal depuis son départ à la Réunion ; Rodolphe dont j'ai eu l'honneur et le privilège d'avoir été le témoin de mariage ; Simon, Justine, Louise, Axelle, Auranne, Elisa, Anne-Sophie, Clotilde, Marion, Mickael, Gaelle. Des voyages, week-ends et moments passés avec vous que je n'oublierai jamais. Je vous kiffe les amis.

Les copains de la colloc de feu : Clément le bro depuis le 1er jour d'internat (sans oublier Ondine & Bababook), Antoine le VP danse ou Dr Mazout, Francesca, Constance, c'est un plaisir de vous avoir rencontré, de vous compter parmi mes amis depuis le début de l'internat à LR city et d'avoir partagé cette colloc avec vous. Merci encore.

A la BPIIE (<3) : Mylène (MDDP) et Jojo de #onaéchangénoscollocs, Phiphi et Agathe pour avoir été la meilleure promo d'internistes-infectiologues que j'ai jamais vu.

A tous mes autres amis que je n'oublie pas : Roland, Emilie, Alice, Toto et toute l'équipe du tutorat d'Anatomie de Bordeaux, Titi, Mélanie, Pauline, Mathilde, Camille.

A tous mes co-internes : Paul, Marie, Manon, Anaïs, Phiphi, JPouille, Faustine, Adeline, Amandine, Clément le Bro, Maumone, Nils, Arthur, Agathe, Clémence, Laly, Niels, Laura, Louis, François, Claire, Karine, Guillaume, Alice, Jonathan, Dara, Sylvain, Marie, Mymy, Colline, Victor, Camille, Benjamin, Anna, Sébastien, Benjamin, Paul, Céline, Alexandre, Agnès, Audrey. Aux autres copains de médecine interne pour ces soirées de congrès de folie : Axel, Gaëtan, Maryam, Jérémie.

TABLE DES MATIERES

ABBREVIATIONS :

TCZ: Tocilizumab.

CRP: C-Reactive Protein.

IL-6: Interleukin 6.

RA: Rheumatoid Arthritis.

GCA: Giant Cell Arteritis.

TNF: Tumor Necrosis Factor.

DMARDS: Disease-modifying antirheumatic drugs.

IV: Intravenous infusion.

SC: Subcutaneous infusion.

CART-Cell: Chimeric-Antigen Receptor T Cells.

CTC: Corticosteroids.

AZA: Azathioprine.

DIS: Disulone.

MTX: Methotrexate.

ANA: Anakinra.

NA: Non available.

HBV: Hepatitis B virus.

HCV: Hepatitis C virus.

ORIGINAL ARTICLE :

Complications infectieuses du Tocilizumab au cours des maladies systémiques hors rhumatismes inflammatoires chroniques : série multicentrique rétrospective de 37 patients

Infectious complications of Tocilizumab during systemic diseases excluding chronic inflammatory rheumatisms: a retrospective multicenter observational real-world study of 37 patients:

Authors: Florent Broca[1], Odile Souchaud-Debouverie[1], Evelyne Liuu[2], Mélanie Catroux[3], Pascal Roblot[1], Mickael Martin[1].

[1]: Service de Médecine Interne, CHU la Milétrie, Poitiers, France.

[2]: Service de Médecine Gériatrique, CHU la Milétrie, Poitiers, France.

[3]: Service de Maladies Infectieuses et Tropicales, CHU la Milétrie, Poitiers, France.

Correspondence:

F. BROCA

Service de Médecine Interne – CHU de Poitiers ; 2 rue de la Milétrie BP 577 ; 86021 Poitiers. France. Tel: 05.49.44.44.44

Fax : 05.49.44.40.47.

E-mail : florent.broca@orange.fr

ABSTRACT & KEY MESSAGES:

Objective: To describe infectious complications occurring in systemic diseases treated with Tocilizumab (TCZ).

Methods: Among patients treated with TCZ for systemic diseases in five hospitals and meeting inclusion criteria: demographic, pre-therapeutic and infectious complications data were collected from medical record by investigator with descriptive analyses. Chronic inflammatory rheumatisms were excluded to avoid the possible biases highlighted in studies in Rheumatoid Arthritis (RA).

Results: Thirty-seven patients were analyzed, mainly suffering from Giant Cell Arteritis. Twenty-five patients (68%) had at least one infectious event. Fifteen severe infections occurred in 6 patients (3.2/100 patient-years), mainly with respiratory and skin infections. Severe bacterial infections were associated with a marked biological inflammatory syndrome, even under a usual cycle of administration of TCZ. Two severe zonas and one diverticulitis with digestive perforation occurred. No tuberculosis or viral hepatitis reactivation was observed.

Conclusion: The incidence of severe infections was lower than in RA studies, probably due to lower use of immunosuppressants, although the co-prescription of corticosteroids remains an important bias. Contrary to the data reported in some clinical cases, severe bacterial infections may be associated with a marked biological inflammatory syndrome. Age over 65 years, history of infection including under corticosteroid therapy, and other causes of immunosuppression seemed to be associated with an increased risk of severe infections. The occurrence of digestive perforation remains rare but should be known. The occurrence of severe zonas leading to disabling post-zosterian pain may suggest the possible interest of prophylaxis. A larger study should be performed to confirm these results.

Key words: Tocilizumab, Interleukin-6 inhibitors, systemic diseases, infectious adverse events, infections.

Key messages:

- Severe infections seemed to be less frequent than in Rheumatoid Arthritis studies (3.2/100 patient-years).
- A significant elevation of CRP was observed in the majority of severe bacterial infections.
- The occurrence of severe zonas suggests the possible interest of prophylaxis.

INTRODUCTION:

Interleukin 6 (IL-6) is a pleiotropic cytokine produced in reaction to a cellular aggression that stimulates the hepatic production of acute inflammatory proteins (C-reactive protein (CRP), Serum Amyloid A protein, Haptoglobin, Fibrinogen…), lowers interleukin-1 (IL-1) production and stimulates the production of molecules implicated in tissue repair, proliferation and differentiation of B and T-cells.

Tocilizumab (TCZ) (RoActemra®) is a humanized IgG1 monoclonal antibody that selectively neutralizes both the soluble and membrane-bound forms of interleukin 6 receptor. It was first approved (in combination with Methotrexate or alone) for treatment of Rheumatoid Arthritis (RA) in 2009 and for Polyarticular and Systemic Juvenile Idiopathic Arthritis in 2013. Later on, starting in 2017, TCZ was approved for patients with Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica relapsing under corticosteroids or with unacceptable side effects (1). It has also been studied and is now used in several other systemic diseases such as Castleman disease (2), Polychondritis (3), Systemic sclerosis (4), Still disease (5) and Behcet disease (6). In adults, the drug is administered as intravenous infusion of 4 or 8 mg/kg at 4-week interval, or subcutaneously at a dose of 162 mg weekly or biweekly (depending on patient weight and clinical response).

Tocilizumab shows a rapid onset of action leading to reduction of inflammatory markers, particularly CRP levels, within the first 2 weeks of treatment. This has been linked in some case reports with the description of serious and life-threatening bacterial infections with minimal clinical (fever) and low biological inflammatory markers (7,8). Several studies have evaluated infectious adverse events occurring in patients treated with TCZ for RA, in both randomized clinical trials and real-world experience studies (9–11). It has been suggested that this treatment increases the risk of opportunistic and serious bacterial infection to an extent similar to other biological DMARDs, while also targeting pro-inflammatory cytokines, such as anti-TNFa agents (12). But some confounding factors can also be associated with infectious adverse events occurring in RA such as age, past infectious diseases, comorbidities (diabetes, undernutrition), the disease itself (activity, intensity of inflammatory response, duration of treatment), use of proton pomp inhibitors and, predominantly, the use of other Disease-modifying antirheumatic drugs (DMARDS) (especially Leflunomide and corticosteroids or biotherapies like Rituximab and anti-TNFa) (13,14). Nevertheless, TCZ is frequently used in second-line treatment or after the failure of other immunosuppressive agents in RA.

To our knowledge, up until now, no study has specifically evaluated the infectious adverse events occurring in systemic diseases treated with TCZ other than chronic inflammatory rheumatisms.

The main objective of this observational, retrospective, multicentric, real-world experience study is to assess and describe the infectious complications occurring in these patients and to avoid the possible biases related to the use of other biotherapies and confounding factors highlighted in studies evaluating patients with RA.

METHODS:

Patients: We included any patient treated with TCZ as part of a systemic disease between January 1st, 2012 and July 1st, 2020 in the former region Poitou-Charentes in France, including one university hospital (Poitiers) and four secondary hospital centers (Niort, Angouleme, Rochefort and La Rochelle). The list of each patient treated with TCZ in this period was collected with the pharmacy of each hospital regardless of the form used (intravenous or subcutaneous infusion). The exclusion criteria were age under 18 years, use of TCZ for rheumatologic indication (RA and, by extension, the other destructive rheumatisms using the same therapeutic regimens as Psoriatic Rheumatism, Spondylarthritis, Polyarticular and Systemic Juvenile Idiopathic Arthritis) or for a non-systemic disorder (Devic's Neuromyelitis, Graves' orbitopathy), or major lack of data. The indication of TCZ for the treatment of Cytokine Release Syndrome associated with Chimeric-Antigen Receptor T Cells (CAR T Cells) or for severe Covid-19 disease was also an exclusion criterion since a single injection was generally performed and therefore did not allow assessment of the risk of infectious adverse events. The patients were informed with a booklet on TCZ administration, systematically given upon arrival in hospital and orally expressed non-opposition to data collection. This study was approved by the CNIL (Commission Nationale de l'Informatique et des Libertés).

Collecting data: Data were collected by the investigator in the patients' medical records on the computer software specific to each hospital (Telemaque, Crossway) with biometrical, clinical, and biological data. The cumulative dose of TCZ (with the protocol used) and of each immunosuppressive agent (corticosteroids, Methotrexate, Azathioprine, Cyclophosphamide, biotherapies and other DMARDS) used in the evolution of the disease was calculated. Pretherapeutic assessment was also checked for each patient. Any infectious adverse event occurring during the disease follow-up and until January 1st, 2021 was recorded with data concerning the severity, the delay in relation to the first infusion of TCZ, the biologic inflammatory markers during infection (if available), the eventual treatment (antibiotics...), duration of treatment and its evolution. CRP was considered increased if greater than 5 mg/l. Moreover, for purposes of comparison, each infectious complication occurring before the initiation of TCZ was also collected when another immunosuppressive treatment was administered. For purposes of perspective, data were collected up to at least 6 months after the first injection of TCZ. An infection was defined as serious if it resulted in death or was life-threatening, required hospitalization (initial or prolonged), necessitated intravenous treatment or was responsible for disability or permanent damage in accordance with the US Food & Drug Administration's definition of serious adverse events (15).

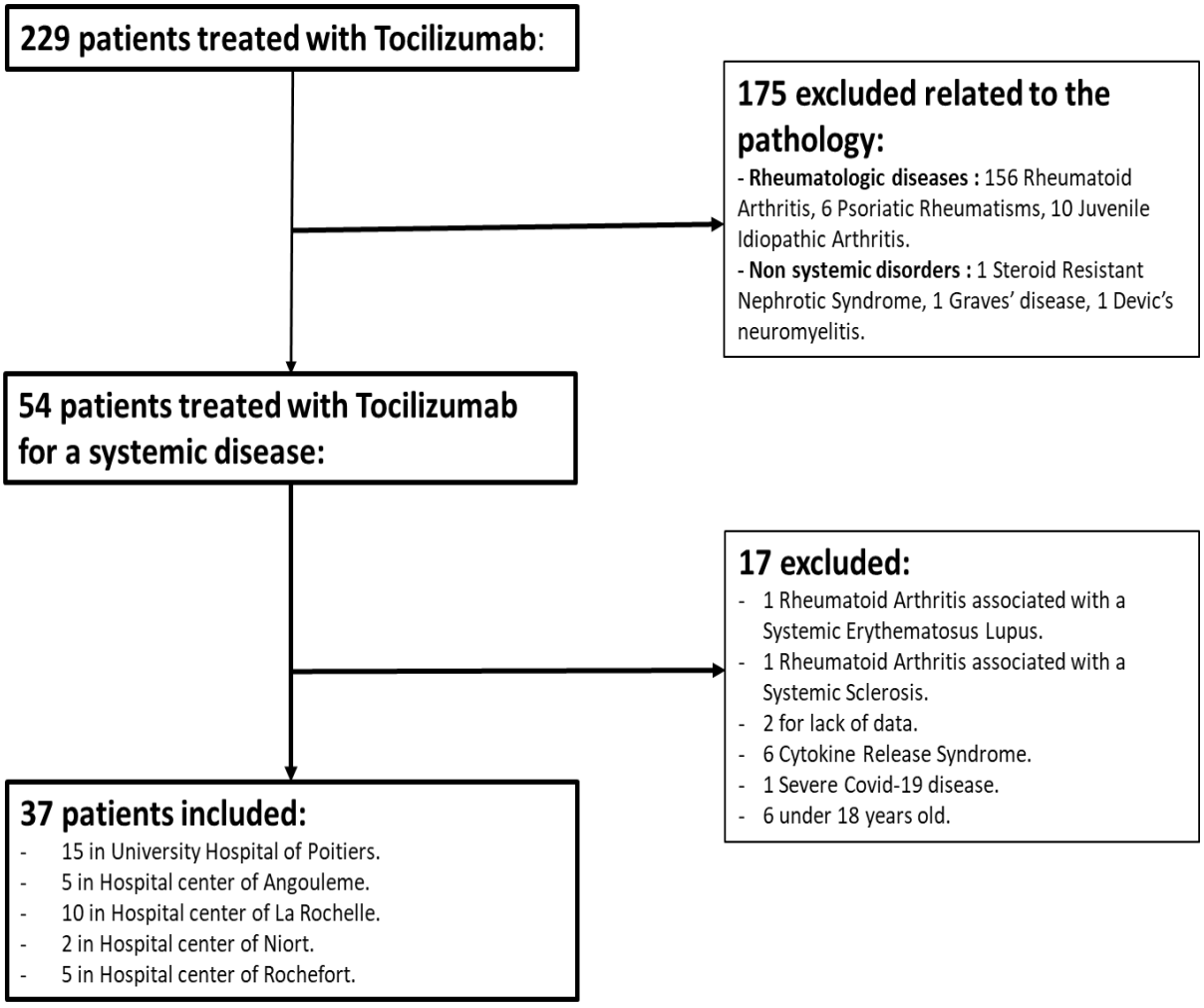
Statistical analysis: Demographic data, pre-therapeutic data and infectious adverse events were analyzed by standardized methods of descriptive analysis using the Statview software to determine the mean and standard deviations or the median and interquartile value of the variable studied. No univariate or multivariate analysis could be performed because of the small number of individuals in this sample.

Fundings and conflicts of interest: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article. Authors declare that they have no conflict of interest in the writing of this article.

RESULTS:

Population study: Two hundred and twenty-nine patients were treated with TCZ between 2012 and July 1st, 2020. One hundred and ninety-two patients were excluded. Finally, 37 patients were included in the study and received a first infusion of TCZ between January 1st, 2015 and July 1st, 2020 (*Figure 1*).

Figure 1. Flow chart



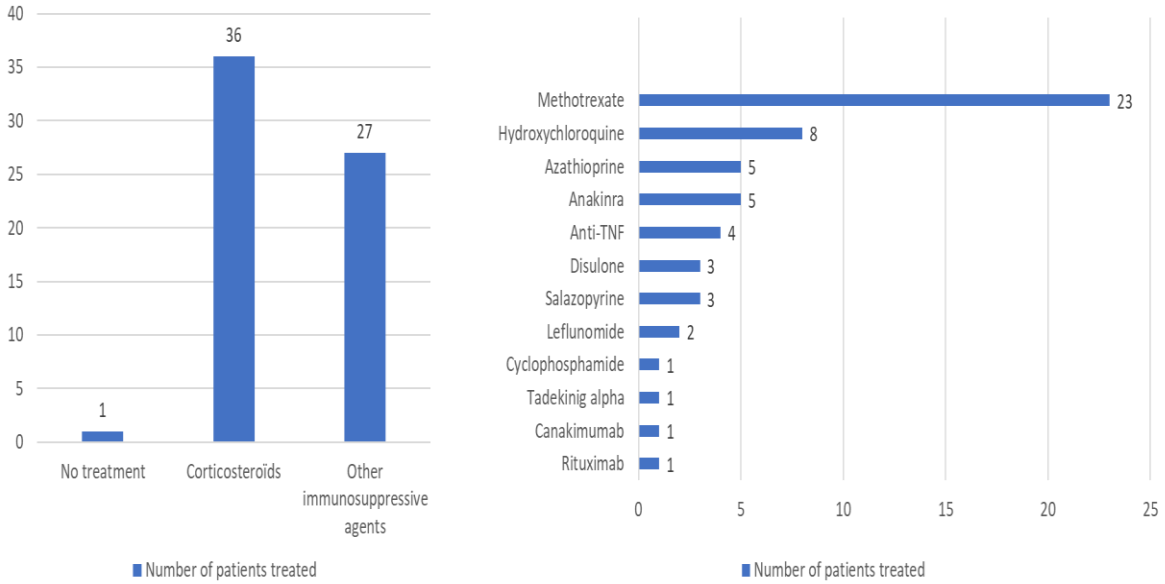
Median age was 66 years [61-74] and 11 patients were under 65 years of age. The majority (n=26) were women (70%). Eleven patients (30%) had a history of infection before any immunosuppressive therapy including two primary tuberculosis infections, two recurrent urinary tract infections, C hepatitis that had been treated with Ribavirin and interferon and considered as cured, a herpes zoster ear infection, bacterial dermohypodermatitis, infectious mononucleosis and a bacterial meningitis (*Table 1*). Twenty-seven patients received vaccines before the first TCZ infusion, most of them against *Streptococcus pneumoniae* (n = 24).

Table 1 . Demographics and characteristics of population study (n=37)

Population		
Age at diagnosis (years)		66 [61-74]
Female sex		26 (70%)
Body Mass Index (kg/m²)		25,5 ± 5
Diabetes		6 (16%)
Chronic Renal Failure		3 (8%)
Previous infectious diseases		11 (30%)
History medical of cancer		11 (30%)
Known diverticulosis		7 (19%)
Disease		
Duration before Tocilizumab infusion (years)		2 [1-5]
Age at first Tocilizumab injection (years)		67 ±15
Protocole used	Intravenous (IV)	32 (89%)
	Subcutaneous (SC)	12 (33%)
Treatments before Tocilizumab		
Vaccinations		27 (73%)
Median dose of Prednisone at Tocilizumab initiation (mg/j)		17,5 [8-30]
Using of other DMARDS		27 (73%)
Follow up		
Death		4 (11%)
Duration of follow up post-treatment (months)		33 ± 19
Remission with Tocilizumab		35 (95%)
Total Cumulative dose of Tocilizumab (g)		9.2 ± 5.9
Total cumulative dose of Prednisone (g)		14.6 [8.0-42.1]

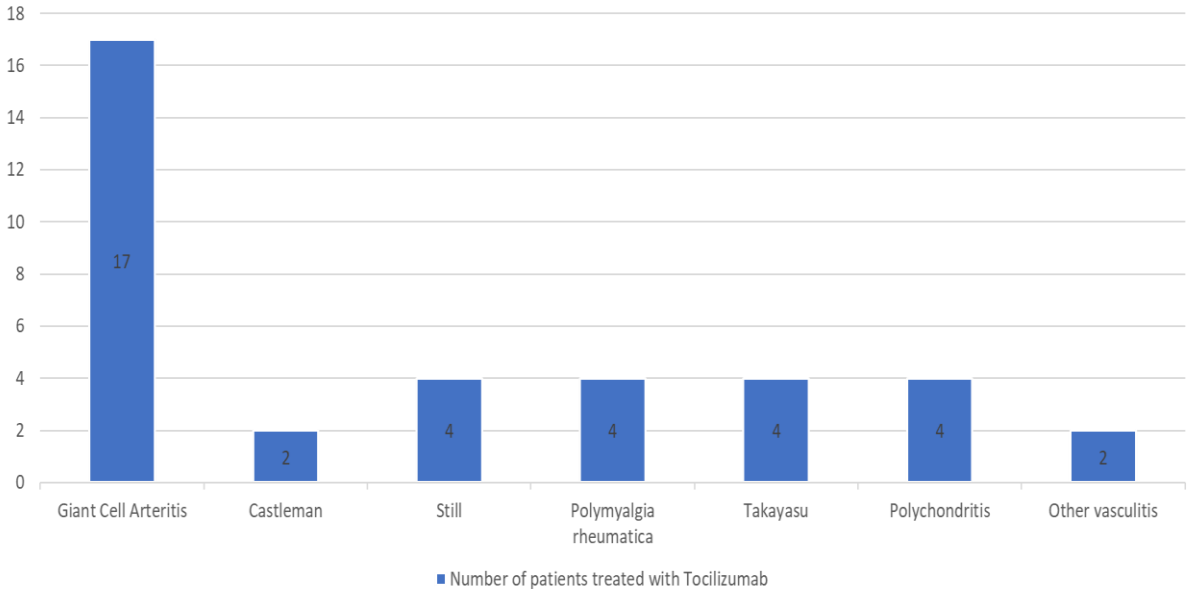
Treatments: Only one patient did not receive any therapy before TCZ initiation. Thirty-six patients were treated with corticosteroids (95%) and 27 with other immunosuppressive molecules (73%), mostly with Methotrexate for 23 patients (62%) (*Figure 2*). The median cumulative dose of corticosteroids at TCZ initiation was 13.7 g [6.4-34.4] and the average cumulative dose of TCZ was 9.2g (+/- 5.9g). The median time to initiation of TCZ was 2 years [1-5] after the diagnosis, at an average age of 67 years (+/- 15 years) (*Table 1*).

Figure 2. Therapies used before Tocilizumab initiation



Disease: The main indication of TCZ was GCA with 17 patients (Figure 3). The other indications were Polymyalgia Rheumatica, Takayasu Arteritis, Still disease, Polychondritis, Castleman disease and other vasculitis (Behcet disease and unclassified vasculitis).

Figure 3. Tocilizumab indications



Infectious adverse events: During TCZ therapy, 25 patients (68%) presented at least one infectious adverse event with a total of 63 infections recorded. Fifteen serious infections were recorded in 6 patients (17%) with a ratio of 3.2 events/100 patient-years of exposure (*Table 2*).

Table 2 – Description of serious infectious adverse events

	Sex	Therapies used before TCZ	Infections before TCZ (n)	Delay of occuring (Months)	Age at infection (years)	Site	Documentation	CRP level	Treatment	Evolution
1	Male	CTC ANA MTX AZA DIS	3	16	82	ORL	No	140 mg/l	CEFTRIAXONE 1g x 3/day then AMOXICILLIN- CALVULANIC ACID 1g x 3/day during 7 days	Healing
				24	82	Urinary	*Escherichia Coli*	161 mg/l	OFLOXACIN 200 mg x 2/day during 15 days	Healing
				31	83	Pulmonary	No	331 mg/l	AMOXICILLIN- CLAVULANIC ACID 1g x 3/day + SPIRAMYCIN 3 MUI x 3/day during 14 days	Healing
				34	83	Skin	No	340 mg/l	AMOXICILLIN-CLAVULANIC ACID 1g x 3/day during 14 days	Healing
				37	83	Skin	No	187 mg/l	Surgery + AMOXICILLIN-CALVULANIC ACID 1g x 3/day during 14 days then LINEZOLID 600 mg x 2/day during 2 days then PIPERACILLIN-TAZOBACTAM during 7 days	Healing
2	Male	CTC ANA	0	5	75	Pulmonary	No	368 mg/l	CEFTRIAXONE 1g x 3/day during 14 days + METRONIDAZOLE 500 mg x 3/day during 7 days	Healing
3	Male	No	0	1	88	Digestive (Diverticulitis)	No	36 mg/l	CEFTRIAXONE 2g/day during 10 days	Healing
4	Female	CTC DIS MTX AZA	1	3	73	Skin	VZV	NA	VALACICLOVIR 1g x 2/day during 10 days	Post-zosterian pain
5	Female	CTC MTX	1	3	66	Digestive (oesophagitis)	*Candida sp*	1,6 mg/l	Mouthwashes of AMPHOTERICIN B and Sodium BICARBONATE + FLUCONAZOLE 100 mg/day during 3 months	Healing
				15	67	Skin	VZV	< 1 mg/l	VALACICLOVIR 1g x 2/day during 2 days then 10 mg/kg/8h during 7 days then PO 1g x 2/day during 3 months	Post-zosterian pain
6	Male	CTC MTX	3	1	65	Skin	*Enterobacter Cloacae*	NA	VAC therapy + surgery + AMOXICILLIN-CLAVULANIC ACID 1g x 3/day during 7 days then BACTRIM FORTE 1 pill x 2/day during 7 days.	Skin wound
				3	65	Skin (septic shock due to a necrotizing fasciitis)	*Escherichia Coli*	61 mg/l	PIPERACILLIN-TAZOBACTAM 4g x 4/day during 2 days + 1 dose of AMIKACIN 2400 mg then CEFOTAXIME 2g x 3/day during 15 days.	Skin wound
				3	65	Bacteriemia	*Pseudomonas aeruginosa*	NA	CEFEPIME 2g x 3/day during 10 days	Healing
				6	66	Pulmonary	VRS + *Enterobacter cloacae*	126 mg/l	AMOXICILLIN-CALVULANIC ACID 1g x 3/day during 6 days then BACTRIM 800 mg x 2/day during 10 days	Healing
				7	66	Skin	*Pseudomonas aeruginosa* + *Staphylococcus aureus* + *Streptococcus pyogenes*	47 mg/l	AMOXICILLIN-CALVULANIC ACID 1g x 3/day during 10 days	Healing

TCZ = Tocilizumab, CRP = C-Reactive Protein, NA = Non available, CTC = Corticosteroid therapy, ANA = Anakinra, MTX = Methotrexate, AZA = Azathioprine, DIS = Disulone.

Before TCZ introduction: two patients had presented at least one significant infectious episode before any treatment for their condition (n°2 and 4). Four patients had at least one infectious episode on therapy prior to initiation of TCZ (patients 1, 4, 5 and 6). Only one patient did not receive corticosteroid or any other immunosuppressive therapy before TCZ initiation (patient 3). The median cumulative dose of Prednisone was 22.8 g [9.4-77.8] at TCZ first infusion. Two patients had hypogammaglobulinemia of around 4g/l before TCZ initiation (patients 4 and 6).

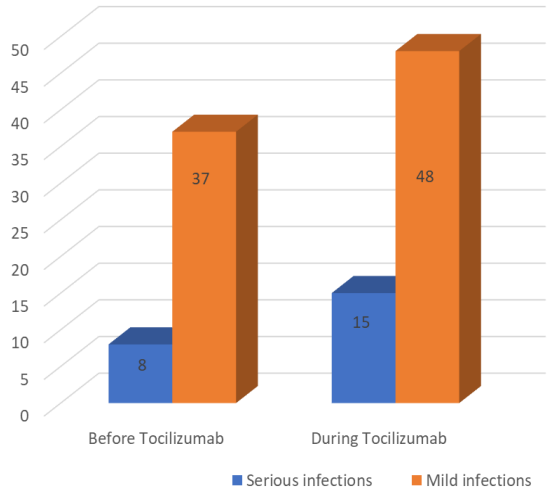
After TCZ initiation: five patients were treated with TCZ in association with Prednisone with a mean dose of 26 mg/day (+/- 17.8) and a median cumulative dose of 3.8 g [3-4.5] (patients 1, 2, 4, 5 and 6). None of them had another immunosuppressive agent associated. All were 65 years or more at TCZ initiation. Three patients were treated for GCA (patients 2, 5 and 6). Median duration of disease progression before introduction of TCZ was one year [1-2]. Median time to infection was six months [3-22] from the start of TCZ. Four infections resulted in permanent sequelae: two zonas resulted in disabling post-zosterian pain and two necrotizing fasciitis led to extensive skin wounds and scars. Most were documented or considered as bacterial infections (80%) leading to an increased biological inflammatory syndrome with a median value of CRP of 150 mg/l [61-331]. These serious adverse events occurred within the usual cycle of TCZ administration (4 weeks), as well as 3 that occurred up to 5 months after the last TCZ injection. Most were skin (n=7) or respiratory infections (n=3).

Two patients had several severe infections (patients 1 and 6), and both had a history of severe infection on immunosuppressive therapy prior to introduction of TCZ: one had a severe urinary tract infection, the other one contracted a chronic skin *Alternaria inflectora* infection that required prolonged antifungal treatment for almost 10 months. One of them (patient 6) also presented hypogammaglobulinemia with an IgG level below 4 g/l requiring an injection of polyvalent immunoglobulin.

None of these infections resulted in death. However, four patients died during follow-up, with no cause mentioned.

The ratio of moderate and severe infections was greater with TCZ compared to the number of infections collected before its introduction (Figure 4).

Figure 4 . Chronology of infectious adverse events



Forty-eight mild infections were recorded. Most of them were lower respiratory infections (31%) or upper respiratory infections (29%) but there were also skin infections (15%), urinary tract infections (15%), digestive infections (8%) or articular infections (2%). The presumed etiology was mainly bacterial (56%) or viral (36%) but most were not documented.

Seven patients had known sigmoidal diverticulosis during pre-therapeutic assessment and one case of diverticulitis occurred. Two patients had a positive QuantiFERON test before TCZ initiation: one patient had a history of atypical mycobacterial tenosynovitis that occurred under corticosteroid therapy and was treated, the other did not have significant history of exposure to any mycobacteria. Most patients had negative HBV serology or a history of immunization (natural or vaccine), only one patient had anti-Hbc antibody positivity before the introduction of TCZ. The only patient with a history of HCV had a negative viral load, all others were seronegative. No cases of tuberculosis or chronic viral hepatitis reactivation were reported during TCZ therapy.

DISCUSSION:

Tocilizumab (Roactemra®) is a targeted therapy that has been used for a long time in the treatment of chronic inflammatory rheumatic diseases, particularly RA. Several studies have evaluated the risk of infection in this indication. A systematic review of the literature found an estimated incidence of severe infectious events of 4.7 events per 100 patient-years of exposure and 3.6 events/100 patient-years of exposure when it was used in monotherapy (9). Many other studies found a roughly similar ratio of serious infections in RA (16–19). This risk is comparable to other biologic agents, although the risk of serious infection may be less than that incurred with TNF antagonists (11) or with Rituximab (20). But the most frequent cause of death in the all-exposed population remains serious infection (16). On the other hand, our study found a lower ratio of 3.2 serious infections/100 patient-years of exposure to TCZ. A comparative analysis of infectious adverse events in RA clinical trials and the GiACTA study revealed that the incidence ratios for serious infections and opportunistic infections were at least threefold greater in patients with GCA than in patients with RA, but the authors concluded that these results could be influenced by the disease itself and treatment with glucocorticoids more than TCZ treatment (21). Another national multicentric observational study of 134 patients treated for GCA with TCZ in Spain found serious infections in 16 patients (11.9%: 10.6/100 patient-years) but their patients were older, with a longer course of disease or a greater dose of Prednisone at TCZ initiation than ours (22).

In our study, severe infections occurred within 6 months to 2 years after initiation of TCZ and affected only people aged over 65 years. The number of infections was greater after initiation of TCZ than during the use of conventional immunosuppressive therapy. This result should be interpreted with caution because of the presence of biases related to other infectious risk factors that may be associated with the occurrence of such episodes after initiation of TCZ (older age, higher cumulative dose of immunosuppressive drugs, etc.). In contrast to the literature, these infections occurred in patients without long-standing disease. Infectious history, including under corticosteroid therapy alone, seems to be an important risk factor for the occurrence of severe infectious events, since 4 out of 6 patients had such a history, 2 of whom had recurrent severe infections. Other risk factors of immunodepression such as hypogammaglobulinemia or use of immunosuppressive agents also seemed to be associated with a high risk of serious infectious complication.

In agreement with the literature in RA, most infections were respiratory or skin infections (13,18,23).

The main finding of our study is that although some clinical cases reported severe bacterial infectious episodes with few systemic and biological inflammatory manifestations, most of them can be associated with a marked biological inflammatory syndrome, even during a usual TCZ administration cycle. This could be helpful for the diagnosis of infectious adverse events. Another study in RA found that severe infections led to significant increases of CRP level in six out of eight patients (13). A larger study should be conducted to confirm this observation.

Our study found only one case of severe diverticulitis. In other studies, the crude incidence rate of lower intestinal perforation significantly increased in TCZ (2.7/100 patient-years) as compared with all other DMARDS treatments (0.2-0.6/1000 patient-years) (24). Two severe zonas occurred in our study resulting in disabling post-

zosterian pain, while no patient was on antiviral prophylaxis. This could lead to the consideration of preventive antiviral therapy with Valaciclovir under TCZ, even though other studies found a risk of herpes zoster infection similar to the risk found with other immunosuppressive agents such as TNF alpha inhibitors (19). No case of tuberculosis was found in our study. Only one study that screened every patient for latent tuberculosis found a ratio of 0.1 tuberculosis reactivation/100 patient-years of exposition in RA population (16). Other studies did not find any tuberculosis cases (9,11). Finally, no patient presented a reactivation of chronic viral hepatitis. This was in agreement with the literature on RA population (11,25).

The main limitation of our study is the sample size, which limits the interpretability of the results and the performance of statistical analysis. Another limitation is the retrospective nature of this study, which may have underestimated the number of infectious events, especially mild ones. Another possible bias for the evaluation of the infection risk of TCZ is the concomitant treatment with corticosteroids. A real-world database multicentric study found a statistically significant increased risk associated with each 1-g increase in cumulative glucocorticoid exposure for glucocorticoid-related serious infections and for infectious adverse events related to TCZ (26). A study with a larger population and greater power should be conducted to confirm these observations.

CONCLUSION:

This is the first study to specifically describe the infectious complications of TCZ in systemic diseases other than chronic inflammatory rheumatic diseases, particularly RA. The incidence of severe infections was 3.2/100 patient-years of exposure, which is lower than the results found in RA studies, probably related to the lower use of other immunosuppressive agents such as anti-TNFa. However, an important persistent bias is the co-prescription of corticosteroids, which remains a major risk factor for serious infections. One of our main observations is the persistence of a marked inflammatory syndrome during severe bacterial infectious events, including during a cycle of TCZ. The main infections represented were respiratory and skin infections, a finding consistent with known data in the literature. Therefore, particular attention must be paid to the risk of infection during TCZ therapy, mostly the occurrence of severe zonas or digestive perforations, especially in patients over 65 years of age, with a history of infection including during corticosteroid therapy, and in patients with other immunosuppression risk factors (hypogammaglobulinemia, use of other immunosuppressive agents, etc.). The occurrence of episodes of severe zonas suggests the possible interest of prophylaxis. A larger study should be carried out to confirm all these results.

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RESUME & MESSAGES CLES :

Objectif : Décrire les complications infectieuses survenant dans les maladies systémiques traitées par Tocilizumab (TCZ).

Méthodes : Parmi les patients traités par TCZ pour des maladies systémiques dans cinq hôpitaux et répondant aux critères d'inclusion : les données démographiques, pré-thérapeutiques et les complications infectieuses ont été collectées à partir du dossier médical par l'investigateur avec des analyses descriptives. Les rhumatismes inflammatoires chroniques ont été exclus pour éviter les biais possibles mis en évidence dans les études sur la Polyarthrite Rhumatoïde (PR).

Résultats : Trente-sept patients ont été analysés, principalement atteints d'Artérite à Cellules Géantes. Vingt-cinq patients (68 %) ont présenté au moins un événement infectieux. Quinze infections sévères sont survenues chez 6 patients (3,2/100 patients-années), principalement des infections respiratoires et cutanées. Les infections bactériennes sévères étaient associées à un syndrome inflammatoire biologique marqué, même dans le cadre d'un cycle habituel d'administration de TCZ. Deux zonas sévères et une diverticulite avec perforation digestive sont survenus. Aucune réactivation de tuberculose ou d'hépatite virale n'a été observée.

Conclusion : L'incidence des infections sévères était plus faible que dans les études sur la PR, probablement en raison d'une moindre utilisation des immunosuppresseurs, bien que la co-prescription de corticostéroïdes reste un biais important. Les infections bactériennes sévères peuvent être associées à un syndrome inflammatoire biologique marqué, contrairement aux données rapportées par certains cas cliniques. L'âge supérieur à 65 ans, les antécédents infectieux, y compris sous corticothérapie, et les autres causes d'immunosuppression semblent être associés à un risque accru d'infections sévères. La survenue d'une perforation digestive reste rare mais doit être connue. La survenue de zonas sévères entraînant des douleurs post-zostériennes invalidantes peut suggérer la nécessité d'une prophylaxie. Une étude de plus grande ampleur devrait être réalisée pour confirmer ces résultats.

Mots clés : Tocilizumab, inhibiteurs de l'interleukine-6, maladies systémiques, effets indésirables infectieux, infections.

<u>Messages clés :</u>

- Les infections graves semblent moins fréquentes que dans les études sur la polyarthrite rhumatoïde (3,2/100 patients-années).
- Une élévation significative de la CRP a été observée dans la majorité des infections bactériennes sévères.
- La survenue de zonas sévères suggère l'intérêt éventuel d'une prophylaxie.

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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- La survenue de zonas sévères suggère l'intérêt éventuel d'une prophylaxie.