Clinical and Experimental Rheumatology 2023; 41: 744-746.

Switching from intravenous tocilizumab to subcutaneous administration during the COVID-19 pandemic: impact on treatment efficacy and patient satisfaction

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Received on March 16, 2022; accepted in revised form on July 1, 2022.

Key words: intravenous tocilizumab, subcutaneous tocilizumab, switching, COVID19

Competing interests: none declared.

ABSTRACT

Objective. *We aimed to assess the efficacy and patient satisfaction of subcutaneous tocilizumab (SC TCZ) in patients previously treated with intravenous tocilizumab (IV TCZ) during the COVID-19 pandemic.*

Methods. *We conducted a single-centre retrospective study at the Rheumatology Day Care at the Rheumatology Institute, Rambam Health Care Campus, Israel. Clinical and laboratory data of IV TCZ treated patients who switched to SC TCZ were retracted and analysed. Data were collected from the last two visits before switching to SC treatment and two visits afterwards. A telephone call conversation was conducted for all patients who continued SC treatment and did not come to follow-up visits.*

Results. *Forty patients (age 53.03 (± 15.7)) treated with IV TCZ were switched to SC TCZ in April-May 2020. Three patients were excluded from the study. Most of the patients were treated with TCZ for 6.35 (±2.89) years and had low disease activity. 26/37 (70%) patients discontinued SC TCZ therapy and switched back to IV TCZ. The majority of discontinuations were due to flare up of the underlying disease reflected by increased number of tender and/or swollen joints, prolongation of morning stiffness or increased pain VAS score. Two patients were hospitalised for IV glucocorticoids and 1 patient underwent knee arthrocentesis. 11/37 (30%) patients continued SC TCZ treatment. 3/11 (27%) expressed less satisfaction with SC TCZ therapy.*

Conclusion. *More than half of the patients who switched from IV TCZ to SC TCZ showed signs of flare of their underlying disease or were less satisfied with SC treatment.*

Introduction

Tocilizumab (TCZ) is a humanised monoclonal antibody targeting both the soluble and membrane bound forms of the IL-6 receptor (IL-6R). By binding to IL-6R, TCZ blocks receptor signalling and subsequent pro inflammatory cascade with consequent broad antagonism of both innate and adaptive immunity. TCZ is approved for the treatment of patients with rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, giant cell arteritis, and severe/life-threatening cytokine storm also known as cytokine release syndrome secondary to the use of CAR-T cell therapy (1).

TCZ is administered by intravenous (IV) or subcutaneous (SC) route and has demonstrated efficacy with a similar safety profile as IV TCZ in two head-to-head studies (2, 4).

The Phase III SUMMACTA study evaluated the efficacy and safety of TCZ-SC in combination with disease-modifying anti-rheumatic drugs (DMARDs) in patient with moderate to severe RA and achieved non-inferiority of TCZ-SC 162 mg weekly to TCV-IV 8 mg/kg every 4 weeks with regard to the American College of Rheumatology 20 (ACR20) and safety profile at week 24 (4). Long-term efficacy and safety were assessed up to week 97 through the open-label phase III SUMMACTA extention trial. TCZ-SC had comparable safety profile to TCZ-IV, except that injection site reactions (ISRs) were more common with TCZ-SC (5).

MUSASHI trial had comparable results as the SUMMACTA trial in Japanese patients with RA (3).

At the beginning of the COVID-19 pandemic, following reports of efficacy of TCZ in preventing cytokine-storm in patients with severe Covid-19 (6, 7), TCZ became part of the protocol treatment for severe COVID-19 disease. Due to the worldwide shortage of IV TCZ, the Israeli Ministry of Health ordered a mandatory switch of all IV TCZ-treated patients to SC TCZ.

The present study aimed to assess the efficacy and satisfaction of patients previously treated with IV TCZ who switched to SC.

Patients and methods

The current study is a single-centre retrospective study at the Rheumatology Institute, Rambam Health Care Campus, Israel. Eligible patients were >18 years and who were treated monthly with TCZ IV for at least 6 months and had low disease activity. Treatments with DMARDs were allowed. Exclusion criteria included active infectious disease.

Clinical and laboratory data of IV TCZ treated patients who switched to SC TCZ were retracted and analysed. The parameters included: physical examination (tender and swollen joints), morning stiffness, pain VAS, blood tests (complete blood count, liver and kidney functional blood count, C-reactive protein and erythrocyte sedimentation rate), corticosteroids treatment and non-steroidal anti-inflammatory drugs, the adherence to treatment and the need for arthrocentesis or hospitalisation due to active inflammatory disease.

Data were collected from the last two visits before switching to SC treatment and two visits afterwards. A telephone call conversation was conducted for all patients who continued SC treatment and did not come to follow-up visits.

Results

Forty patients (mean (SD) age 53.03 (±15.7)) treated with IV TCZ 8 mg/kg monthly, at the Rheumatology Day Care were switched to SC TCZ 162 mg every 2 weeks in April-May 2020. Following the order to perform the mandatory switch to SC, all the patients were summoned to our Rheumatology Day Care, where they received the first injection of SC TCZ and were monitored for adverse events. They were further instructed how to inject by themselves. Patients who were reluctant to self-inject were referred to the HMO facilities for the injections. All patients continued to be routinely followed at our clinic. Adherence to treatment was assessed at their routine visit. Three patients were excluded from the study: one suffered from an intercurrent illness, one was treated <6 months with TCZ and one had an active disease under IV TCZ. Most of the patients were treated with IV TCZ for prolonged periods of time (mean (SD) 6.35 (±2.89) years) and had low disease activity.

Group I

Twenty-six out of thirty-seven (70%) patients discontinued SC TCZ therapy and switched back to IV TCZ within 3–4 months. Most of the patients were treated with TCZ as a monotherapy (28 patients (76%)), 14/37 (38%) received concomitant prednisone 5–10 mg a day (Fig. 1). All patients received SC TCZ for at least 2–3 months.

The majority of the discontinuations were due to flare up of the underlying disease reflected by an increased number of tender joints (more than 50%) and/or an increased number of swollen joints (at least one swollen joint), prolongation of the morning stiffness or increased articular pain, (according to patient VAS pain score) (Table II).

Skin reactions were observed in 5 patients, and elevated liver function tests in 1 patient. Two patients were hospitalised for IV glucocorticoids treatment and 1 patient underwent knee arthrocentesis.

Group II

Eleven out of 37 (30%) patients continued SC TCZ treatment, 3/11 (27%) expressed less satisfaction with the treatment and 3/11 (27%) experienced worsening pain with SC TCZ therapy.

Here are some examples of unsuccessful switches:

1. A 52-year-old male patient had rheumatoid arthritis for almost 13 years and had failed treatment with methotrexate and abatacept. Thereafter, he started IV TCZ treatment. He was on remission for more than 3 years. Two to three months after the mandatory switch to SC TCZ during the Covid-19 pandemic, during the routine follow-up clinic, he com-

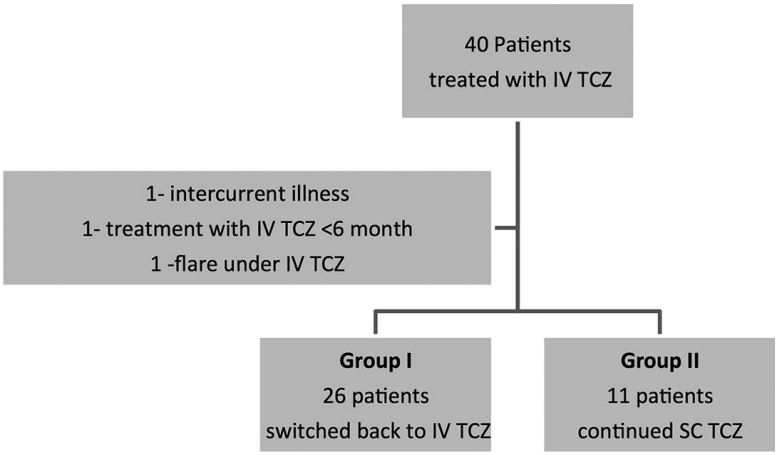

Fig. 1.

Table I. Demographic and characteristics at baseline.

Characteristics	Baseline n=37 (± SD)	
Age, years	53.03 (± 15.7)	
Female, Male	24, 13 (65, 35)	
Background disease	RA	30 (81)
	sJIA	4 (11)
	Takayasu	2 (5)
	Overlap	1 (3)
Disease duration, years	14.24 (±7.25)	
TCZ IV duration, years	6.35 (±2.89)	
DMARDs	9 (24)	
Glucocorticoids	Prednisone 5-10 mg,	14 (38)

Data are presented as n (%) or mean ± SD.
RA: rheumatoid arthritis; JIA: systemic juvenile idiopathic arthritis; DMARDS: disease-modifying anti-rheumatic drugs.

Table II. Group I

	TCZ IV	TCZ SC	*p*-value
SJC	2.25 (± 4.78)	9 (± 7.49)	$p<0.005$
TJC	0.25 (± 0.85)	1.63 (±2.26)	$p<0.005$
VAS patient	3.04 (±2.65)	5.46 (±2.6)	$p<0.005$

*Values are the mean ± SD. SJC: swollen joint count; TJC: tender joint count.

Table III. Disease flare

	TCZ SC, n=26 (%)
Morning stiffness	11 (42%)
Adverse events	6 (23%)
Patients' dissatisfaction	5 (19%)

Table IV.

	Group I n=26 (%)	Group II n=11(%)	
Male, Female n (%)	17.9 (65, 35)	7.4(64, 36)	
Disease type n (%)	RA 21 (81) JIA 3 (12) Takayasu 1 (3.5) Overlap 1 (3.5)	RA 9 (81.2) JIA 1 (9.4) Takayasu 1 (9.4)	
Disease duration, mean ± SD years	14.11	14.55	p=0.87
TCZ IV duration, mean (SD) years	6.19	6.73	p=0.61

* RA: rheumatoid arthritis; sJIA: systemic juvenile idiopathic arthritis.

plained of severe arthralgia. The musculoskeletal examination revealed 6 tender joints and 3 swollen joints, indicating a worsening of the underlying condition.

2. A 72-year-old male patient with long-term seropositive rheumatoid arthritis received IV TCZ for more than 10 years and had a low disease activity disease status. Following switching to SC TCZ treatment, he complained of prolonged morning stiffness, arthralgia and of substantial weakness and fatigue the day after injection.

3. A 65-year-old female patient who had been on IV TCZ for nine years switched to SC TCZ. Three months later she was admitted at the rheumatology department with exacerbation of the arthritis, requiring methylprednisolone IV therapy.

There were no statistically significant differences between the groups, regarding sex, type of disease, disease duration and TCZ treatment duration in patients who switched back to IV TCZ (group I) and patients who continued SC TCZ (group II) (Table IV).

Discussion

This study was conducted to assess the efficacy and patient satisfaction of SC TCZ in patients previously treated with IV TCZ during COVID 19 pandemic. More than half of the patients switched from IV TCZ to SC TCZ showed signs of flare of their underlying disease or were less satisfied with SC treatment.The safety profile of SC TCZ was similar to IV TCZ except for skin reactions, however, all events were mild and manageable.

It is important to mention that the majority of the study patients were previously on IV TCZ for prolonged periods of time and some of them were after failure of other biological therapies. This treatment led to stable disease or low disease activity status. Mandatory switching of long-term IV treatment to SC TCZ may be difficult in some of the patients. Furthermore, the transition of therapy provided under medical supervision with professional nurses and physicians to self- provided home therapy might be challenging. We believe that switching from IV to SC treatment should be performed only in patients who are willing to do it, are highly compliant with the treatment and are not reluctant to make the weekly self-injections. The self-satisfaction of patients from treatment plays an important role in treatment efficacy.

The main limitations of our study are the relatively small number of patients and of being a retrospective single-centre study. Nevertheless, although our study is retrospective, it is based on a prospective well-maintained database.

Conclusion

A significant proportion of patients who were previously treated with IV TCZ for long periods of time and were mandatorily switched to SC TCZ preferred to return to IV treatment due to disease flare-up or dissatisfaction with treatment. We believe that some of the patients were reluctant to switch monthly intravenous treatment, administered under the supervision of well-trained nurses and experienced rheumatologists, to weekly self-administered injections at home. Besides the "psychological" difficulties, there were also objective flare ups, suggesting that there may be other causes, for example, differences in pharmacological properties that affect efficacy and differences of levels of drug concentration in blood, that should be investigated further.

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