Mass Switch From Intravenous to Subcutaneous Tocilizumab in Rheumatic Diseases During the SARS-COV-2 Pandemic

Vicente Aldasoro Cáceres, MD,* María Laiño Piñeiro, MD,* Berta Ibáñez-Beróiz, PhD,†‡ and Mónica Enguita-Germán, PhD†‡

BACKGROUND: With the arrival of the SARS-CoV-2 pandemic in 2020, it was proposed to make the change from intravenous (IV) tocilizumab (TCZ) to its subcutaneous formulation, in order to avoid rheumatological patients having to go to the day hospital and guarantee enough IV TCZ for those critical patients with COVID who needed it. The aim of this study was to describe the rate and reasons for switching back to IV TCZ from subcutaneous TCZ.

METHODS: We included patients from the rheumatology service that were on treatment with IV TCZ in February 2020 and were followed up until March 2021. Patients that remained on subcutaneous TCZ were compared with those who switched back to IV TCZ (switch-back group). A subgroup analysis according to rheumatic disease was performed.

RESULTS: Fifty-five patients switched to subcutaneous TCZ. 28 rheumatoid arthritis, 19 giant cell arteritis, 4 polymyalgia rheumatica, 2 juvenile idiopathic arthritis, and 2 systemic sclerosis. Seventeen patients switched back to IV TCZ, due to ineffectiveness (n = 8), patient preference (n = 4), adverse events (n = 4), and difficulty with the SC administration route (n = 1). In the analysis by disease, 4 of 23 patients switched back to IV TCZ in giant cell arteritis/polymyalgia rheumatica group due to ineffectiveness (n = 2), injection site reaction (n = 1), or patient preference (n = 1). In rheumatoid arthritis group, 11 of 28 patients switched back to IV TCZ: ineffectiveness (n = 5), patient preference (n = 3), headache (n = 1), injection site reaction (n = 1), and due to difficulty with the SC administration route (n = 1).

CONCLUSIONS: Mass switch from IV to subcutaneous TCZ during the SARS-CoV-2 pandemic has been safe, effective, and well tolerated after 1 year of follow-up.

Key Words: intravenous tocilizumab, subcutaneous tocilizumab, rheumatic diseases, switch, COVID

In March 2020, the first glimmer of hope was observed in the treatment of patients with severe coronavirus disease 2019 (COVID-19) with intravenous (IV) tocilizumab (TCZ). In fact, currently, TCZ is the standard treatment for COVID-19 in adults on systemic corticosteroids that require supplementary oxygen or mechanical ventilation.

Given the potential use of this drug in the treatment of critically ill patients, various strategies and protocols were established to facilitate the management of COVID-19 patients. These included the proposal of switching patients on TCZ from an IV to a subcutaneous (SC) form, seeking to avoid them needing to attend the day hospital and ensuring the availability of IV TCZ for critically ill COVID-19 patients requiring this treatment.

The aim of this study was to describe, in patients with rheumatic diseases treated with IV TCZ, the rate and reasons of returning back to their initial treatment with IV TCZ after switching to SC TCZ, to assess demographic and/or clinical factors associated with the need for this change, and to search for potential predictive factors of a poor response to switching.

METHODS

In this observational study, we invited patients from the rheumatology service of the Navarre Health System who were receiving treatment with IV TCZ in February 2020 to switch to the SC route and be followed up until March 2021. Verbal consent was sought by the telephone before switching from IV TCZ to SC TCZ. The baseline characteristics of all patients treated with IV TCZ were recorded: sex, age, body weight, height, body mass index (BMI), the duration of treatment with IV TCZ that was computed as the time difference between the moment since TCZ was started because of uncontrolled disease and February 2020 (in months), and treatment with TCZ as monotherapy. The primary outcome was whether patients continued with TCZ or switched back to IV TCZ. These in- teractions and protocols were established with the aim of managing critically ill patients, various strategies and protocols were established to facilitate the management of COVID-19 patients. These included the proposal of switching patients on TCZ from an IV to a subcutaneous (SC) form, seeking to avoid them needing to attend the day hospital and ensuring the availability of IV TCZ for critically ill COVID-19 patients requiring this treatment.

The primary outcome was whether patients continued with SC TCZ or switched back to IV TCZ during the follow-up. Patients who continued on SC TCZ (adherent group) were compared with patients who switched back to IV TCZ (switch-back group) to evaluate whether switching back was associated with any of the recorded baseline characteristics.

We performed a subgroup analysis in patients diagnosed with giant cell arteritis (GCA) or polymyalgia rheumatica (PMR) and in patients with rheumatoid arthritis (RA).

The characteristics of the sample were described using descriptive statistics such as mean and standard deviation or median and interquartile range for continuous variables, depending on their nature, and using frequencies and percentages for categorical variables. Comparisons between the adherent group and the switch back group in the total sample as well as in the 2 subgroups were performed using the Student t test or Mann-Whitney U test for continuous variables and using the χ² test or Fisher test for categorical variables. Data analysis was performed using R version 4.0.4 and IBM SPSS Statistics 24.

RESULTS

Sixty-one patients on treatment with IV TCZ were asked to switch to the SC route and 55 agreed to this switch. Among the
55 patients, 28 had RA, 23 had GCA/PMR, 2 had juvenile idiopathic arthritis, and 2 had systemic sclerosis. A total of 17 patients switched back to IV TCZ, which implies an incidence of 30.9% (95% confidence interval, 19.5–44.9).

The baseline characteristics of the patients who continued SC TCZ and those who switched back to IV TCZ are summarized in Table 1. Seventeen patients switched back to IV TCZ: 2 patients with GCA, 2 with PMR, 2 with juvenile idiopathic arthritis, and 11 with RA. The reasons for switching back to IV TCZ were ineffectiveness in 8 cases, patient preference in 4, adverse events in 4 (1 case of headache and 3 cases of injection-site reaction), and difficulty with the SC administration route in 1 case. Patients who

### Table 1. Comparison of Baseline Characteristics Between “SC TCZ Adherent Group” and “Switched Back IV TCZ Group”

|                         | Adherent | Switch Back | Total | p value |
|-------------------------|----------|-------------|-------|---------|
| Total, n (%)            | 38 (69.1)| 17 (30.9)   | 55 (100)|         |
| Sex (women, %)          | 33 (68.8)| 15 (31.2)   | 48 (87.3)| 1.000   |
| Age, y                  | 74.5 (17.8)| 76.0 (23.0)| 75.0 (18.0)| 0.548   |
| Weight, kg              | 67.0 (13.3)| 66.6 (13.6)| 66.8 (13.3)| 0.927   |
| Body mass index, kg/m²  | 26.2 (4.6)| 26.8 (4.9) | 26.4 (4.7)| 0.669   |
| Diagnosis, %            |          |             |        |         |
| Rheumatoid arthritis    | 17 (60.7)| 11 (39.3)   | 28 (50.9)|         |
| Giant cell arteritis     | 15 (88.2)| 2 (11.8)    | 17 (30.9)|         |
| Polymyalgia rheumatica  | 4 (66.7)| 2 (33.3)    | 6 (10.9)|         |
| Systemic sclerosis      | 1 (100.0)| 0 (0.0)     | 1 (1.8)|         |
| Still disease           | 1 (100.0)| 0 (0.0)     | 1 (1.8)|         |
| Juvenile idiopathic arthritis | 0 (0.0) | 1 (100.0) | 1 (1.8)|         |
| Duration of IV TCZ treatment, mo | 25.4 (49.8)| 47.7 (81.8)| 28.4 (56.2)| 0.023   |

### Table 2. Comparison of Baseline Characteristics Between “SC TCZ Adherent Group” and “Switched Back IV TCZ Group” Stratified by Disease Type

|                         | Adherent | Switch Back | Total | p value |
|-------------------------|----------|-------------|-------|---------|
| GCA/PMR group           |          |             |       |         |
| Total, n (%)            | 19 (82.6)| 4 (17.4)    | 23 (100)|         |
| Sex (women, %)          | 17 (81.0)| 4 (19.0)    | 21 (91.3)| 1.000   |
| Age, y                  | 82.0 (12.0)| 80.0 (6.2)| 82.0 (10.5)| 1.000   |
| Weight, kg              | 65.6 (11.6)| 76.9 (11.8)| 67.5 (12.2)| 0.090   |
| Height, cm              | 157.3 (7.1)| 154.2 (0.5)| 156.7 (6.5)| 0.414   |
| Body mass index, kg/m²  | 26.4 (4.0)| 32.3 (5.0) | 27.5 (4.7)| 0.052   |
| Monotherapy, %          | 16 (84.2)| 3 (15.8)    | 19 (82.6)| 1.000   |
| Duration of IV TCZ treatment, mo | 11.7 (21.6)| 34.0 (20.6)| 20.3 (28.2)| 0.372   |
| Rheumatoid arthritis group |        |             |       |         |
| Total, n (%)            | 17 (60.7)| 11 (39.3)   | 28 (100)|         |
| Sex (women, %)          | 14 (60.9)| 9 (39.1)    | 23 (82.1)| 1.000   |
| Age, y                  | 65.0 (20.0)| 76.0 (27.5)| 66.5 (21.2)| 0.888   |
| Weight, kg              | 69.2 (15.8)| 66.5 (9.5)| 68.1 (13.5)| 0.613   |
| Height, cm              | 162.8 (8.4)| 161.7 (8.7)| 162.4 (8.3)| 0.755   |
| Body mass index, kg/m²  | 26.1 (5.6)| 25.4 (3.2)| 25.9 (4.7)| 0.722   |
| Monotherapy, %          | 8 (44.4)| 10 (55.6)   | 18 (64.3)| 0.041   |
| Duration of IV TCZ treatment, mo | 48.1 (67.5)| 65.6 (78.9)| 56.0 (71.8)| 0.230   |
| Rheumatoid factor positive, % | 12 (60.0)| 8 (40.0)    | 20 (71.4)| 1.000   |
| Anticyclic citrullinated peptide positive, % | 14 (66.7)| 7 (33.3) | 21 (75)| 0.381   |
| Previous biologies, %   |          |             |       |         |
| None                    | 1 (100.0)| 0 (0.0)     | 1 (3.6)|         |
| 1                       | 3 (75.0)| 1 (25.0)    | 4 (14.3)|         |
| 2                       | 4 (80.0)| 1 (20.0)    | 5 (17.9)|         |
| ≥3                      | 9 (50.0)| 9 (50.0)    | 18 (64.3)|         |

*Mean (SD).*

*Median (IQR).*
switched back to IV TCZ had been receiving this drug for a longer period (Table 1). None of the patients were active smokers.

In the analysis by disease, we identified 23 patients with GCA/PMR who were on IV TCZ at baseline and agreed to switch to SC TCZ (Table 2). Four patients switched from SC TCZ to IV TCZ: 2 due to ineffectiveness, 1 due to injection site reaction, and other due to patient preference. We did not observe statistically significant differences in the variables analyzed between the adherent and switch-back groups, although the BMI mean value in patients of the latter group was 5.9 kg/m² higher and had been treated with IV TCZ for a longer time (nearly 3 years vs 1 year).

There were 28 patients with RA on IV TCZ. Of these, 11 switched back from SC TCZ to IV TCZ: 5 because of ineffectiveness, 3 due to patient preference, 1 due to headache, 1 due to injection-site reaction, and the latter due to difficulty with the SC administration route. Patients in the switch back group were more likely to receive this treatment as monotherapy; they also tended to be older, had been treated with IV TCZ for a longer time, and had received a larger number of biological treatments previously (Table 2).

No serious adverse events were observed in any of the groups assessed. All patients who switched back to IV TCZ showed a good response in terms of clinical status and laboratory test results until the end of follow-up, as well as it happened in the SC TCZ group.

**DISCUSSION**

This is the first study providing data on switching from IV TCZ to SC TCZ over 12 months in different diseases in SARS-CoV-2 pandemic. Previous studies have had follow-up periods of 3 to 6 months and have focused on RA alone.3,4 Overall, excluding patients who switched back to IV TCZ due to patient preference, more than three quarters (76%) of patients continued with the SC route of administration with a good response in terms of clinical status and laboratory test results and without any findings of concern regarding safety. The proportion of patients who continued SC TCZ was higher in our study than in similar previous studies.5,6

In this study, we also present data on switching from IV to SC TCZ in patients with GCA/PMR with a rate of continuation of SC treatment of 87%, excluding the case in which the switch back to IV TCZ was based on patient request alone. This could be something logical because the only GCA-approved treatment is SC TCZ.7,8 However, there are clinical practice data which suggest that IV TCZ is also as effective as SC TCZ.8,9

Some of the variables that we assessed as potential predictors of switching back to IV TCZ were body weight and BMI, assuming that patients on IV TCZ might receive doses better adjusted to their weight than those in the SC TCZ group.

Nonetheless, we did not find significant differences in the overall analysis or disease, although in the stratified analysis, the GCA/PMR patients who switched back had a BMI mean value approximately 6 kg/m² higher than the group who continued SC TCZ. A clinical association between BMI and switching the formulation may be plausible but we cannot dismiss the possibility of this to be a type II error due to the reduced sample size.

On the other hand, we observed that patients in the switch back group had received treatment with IV TCZ for a longer time than in the adherent group. This is contrary to what we would expect, because a longer duration of treatment with IV TCZ might imply greater disease stability, meaning that these patients might easily remain on SC TCZ, something that was not observed in this study. Other plausible explanation to this finding could be that patients in IV TCZ were better responders than those in SC TCZ.

The limitations of this study are related to its nature (review of medical records) and small sample size. For example, this is reflected in the decision to group patients with GCA and PMR into a single group, as they share some clinical characteristics, in order to obtain a larger sample size and be able to make comparisons between groups.

In conclusion, in our hospital, the mass switch from IV to SC TCZ during the SARS-CoV-2 pandemic has been safe, effective, and well tolerated after 1 year of follow-up.

**KEY POINTS**

Because of the SARS-CoV-2 pandemic, many rheumatological patients changed from IV TCZ to SC TCZ.

Mass switch from IV to SC TCZ during the SARS-CoV-2 pandemic has been safe, effective, and well tolerated in GCA/PMR group; one third of RA patients failed to tolerate the switch. This study provides 1 year safety and efficacy data not only in RA but in GCA/PMR.

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