

Real-World Effectiveness and Safety of Secukinumab in Giant Cell Arteritis: An Italian Multicenter Cohort Study

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Objective. The objective of this study was to evaluate the real-world effectiveness and safety of secukinumab in patients with giant cell arteritis (GCA).

Methods. This multicenter retrospective study included patients with GCA who received secukinumab at 14 Italian centers with at least six months of follow-up. Outcomes included clinical, complete, and glucocorticoid (GC)-free remission, GC dose reduction, drug retention rate, and adverse events.

Results. Thirty-six patients were included (66.7% women); median age at secukinumab initiation was 74 (interquartile range [IQR] 70–80) years. Overall, 32 of 36 patients (88.9%) had previously relapsed and 26 of 36 (72.2%) had received tocilizumab. Clinical remission was observed in 85.2%, 80.6%, and 83.3% at 3, 6, and 12 months, respectively. Complete remission occurred in 55.6%, 52.8%, and 63.3%, whereas GC-free remission increased progressively, reaching 14.8%, 27.8%, and 40.0% at 3, 6, and 12 months, respectively ($P = 0.012$). Median daily GC dose decreased from 8.7 (IQR 4.0–21.2) mg at baseline to 0 (0–5.0) mg at 12 months ($P < 0.001$); GCs were discontinued in 12 of 28 patients (42.9%). The 12-month retention rate was 77.0%. Adverse events occurred in 20 of 36 patients (55.6%); infections occurred in 18 of 36 patients (50.0%), accounting for 21 infectious episodes.

Conclusion. In this multicenter, real-world cohort of patients with GCA, including those with relapsing disease and previous biologic exposure, secukinumab was associated with high observed remission rates, progressive GC dose reduction, and increasing GC-free remission. Although the phase III GCaptAIN trial did not meet its primary endpoint, these findings suggest that interleukin-17A inhibition may warrant further evaluation in patients with GCA.

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SIGNIFICANCE & INNOVATIONS

- This multicenter study provides real-world evidence on secukinumab in patients with giant cell arteritis, including many with relapsing disease and previous biologic exposure, particularly tocilizumab.
- More than 80% of patients were in clinical remission at each follow-up time point, with progressive glucocorticoid dose reduction, increasing glucocorticoid-free remission, and an estimated 12-month treatment retention rate of 77.0%.
- No unexpected safety signals were observed, although adverse events were common, with infections representing the most frequently reported events.

INTRODUCTION

Giant cell arteritis (GCA) is a large vessel vasculitis and the most frequent primary systemic vasculitis in individuals aged 50 years and older.^{1,2} Although glucocorticoids (GCs) remain the cornerstone of treatment, prolonged GC exposure is associated with considerable toxicity.^{3,4} GC-related adverse events include cardiovascular complications, diabetes, osteoporosis, cataracts, and an increased risk of serious infections, all of which may significantly impair quality of life.^{3,5} A substantial proportion of patients experience relapses during GC tapering or after treatment discontinuation, requiring GC dose escalation or re-initiation of GC therapy and thereby substantially increasing cumulative GC exposure over time.^{3,6} Consequently, GC-sparing strategies are needed and have been incorporated into recommendations for the management of GCA.^{2-4,7}

Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, has marked a major advance in the management of GCA, substantially increasing rates of GC-free remission even when accelerated tapering regimens are used.⁸ However, up to 40% of patients receiving tocilizumab discontinue treatment because of inadequate response or adverse events,^{9,10} highlighting the need for alternative therapeutic strategies. Moreover, more than 40% of patients who initially respond to tocilizumab relapse after treatment discontinuation.⁹⁻¹¹

The cytokine IL-17A has been implicated in GCA pathogenesis, with evidence suggesting that IL-17A-producing T-helper 17 cells contribute to vascular inflammation.¹² This has provided a strong rationale for investigating IL-17A inhibition as a potential therapeutic strategy in GCA.¹² The phase II TitAIN trial showed that secukinumab, a monoclonal antibody targeting IL-17A, was associated with higher rates of sustained remission during a protocol-defined GC taper.¹³ Sustained remission at week 28 was achieved in 70% (95% confidence interval [CI] 52–85) of patients treated with secukinumab compared with 20% (95% CI 12–30) in the placebo group,¹³ providing preliminary clinical evidence for IL-17A inhibition in GCA. However, the subsequent phase III GCaptAIN trial did not meet its primary endpoint of

sustained remission at week 52, although favorable results were observed for cumulative GC exposure and GC-related toxicity.¹⁴

In this study, we aimed to evaluate the real-world effectiveness and safety of secukinumab and its association with GC dose reduction in a multicenter Italian cohort of patients with GCA, including individuals previously treated with biologic therapies, a population that remains underrepresented in clinical trials.

PATIENTS AND METHODS

Patients and inclusion and exclusion criteria. We conducted a multicenter retrospective observational cohort study within the Italian Society of Rheumatology Vasculitis Study Group (the Steering Committee members of the Italian Society of Rheumatology Vasculitis Study Group are listed in Appendix A). We included adult patients (≥18 years) with a clinical diagnosis of GCA, fulfilling the 2022 American College of Rheumatology/EULAR classification criteria,¹⁵ who were treated with secukinumab across 14 Italian centers between 2022 and 2026. Patients with other forms of large vessel vasculitis were excluded. In order to be eligible, patients were required to have at least six months of follow-up after secukinumab initiation. One additional patient had initiated secukinumab but did not meet the at least six-month follow-up criterion because the patient died from pneumonia before completing the secukinumab loading regimen; this patient was therefore excluded from the study cohort. At diagnosis, patients were classified as having predominant cranial GCA, predominant large vessel GCA, or balanced phenotype based on available clinical and imaging information.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Territoriale Area Centro-Est Veneto (protocol no. 6329/EST/25). Secukinumab was prescribed at the discretion of the treating rheumatologist. According to Italian standards of care for off-label treatment, all patients provided informed consent, and prior authorization from the relevant health authorities was obtained. Factors contributing to the decision to initiate secukinumab included relapsing disease, GC-sparing intent, imaging progression, persistent elevation of acute-phase reactants, and intolerance or contraindications to other therapies. Given the retrospective, real-world nature of the study, no predefined protocols were used for secukinumab dosing or GC tapering after treatment initiation. GC escalation around secukinumab initiation was defined as an increase in prednisone-equivalent dose immediately before or at secukinumab initiation.

Data collection and assessment. Patient data were retrieved from electronic medical records, collected using a predefined case report form (CRF), and entered into a dedicated central database. The CRF included demographic characteristics,

disease features, laboratory parameters, imaging findings, concomitant medications, clinical outcomes, adverse events, and reasons for treatment discontinuation. All entries were double-checked for accuracy.

Demographic characteristics, comorbidities, vasculitis history, and prior treatments were collected at the time of secukinumab initiation (baseline). Clinical data, laboratory parameters, treatment exposure, and adverse events were recorded at baseline and at 3, 6, and 12 months, as well as at the last follow-up visit within 12 months of follow-up (whenever it occurred up to May 2026).

Outcomes. The primary effectiveness outcome was the proportion of patients achieving clinical remission at 3, 6, and 12 months.

Secondary outcomes included complete remission and GC-free remission at each time point. Clinical remission was defined as the absence of signs and symptoms attributable to GCA.¹ Complete remission was defined as a composite of clinical remission and normalization of acute-phase reactants, namely C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), in accordance with EULAR definitions.^{4,6} GC-free remission was defined as complete remission in the absence of ongoing GC therapy.⁴

Additional outcomes evaluated were GC dose reduction, retention rate, and occurrence of adverse events. Relapse was defined as recurrence of active disease according to the treating physician, including cranial, systemic, polymyalgia, or ischemic manifestations; imaging evidence of active vascular inflammation; or otherwise unexplained elevation of acute-phase reactants.¹ Relapse was further classified as minor or major relapse according to EULAR definitions.⁴ Data collection on adverse events included the number and type of adverse events, particularly infections, hospitalizations, and death.

Data analysis. Categorical variables were summarized as counts and percentages, whereas continuous variables were reported as medians and interquartile ranges (IQRs). Descriptive proportions at each time point were calculated using available-case denominators. For longitudinal statistical comparisons, only patients with paired data across the evaluated time points were included. The normality of continuous variable distributions was assessed using the Shapiro–Wilk test. As most continuous variables were not normally distributed, nonparametric tests were used.

For primary outcomes, exact 95% CIs for proportions were calculated using the Clopper–Pearson method. Changes over time of categorical variables were compared using the Cochran Q test for repeated measures from months 0 to 12 (only patients with available paired data across the evaluated time points were compared). When the overall Cochran Q test was statistically significant ($P < 0.050$), post hoc comparison between each follow-

up time point with baseline was performed using the McNemar test, with an additional Bonferroni correction for multiple comparisons. A P value of 0.005 was considered statistically significant. Changes of continuous variables over time were assessed using the Friedman test for repeated measures from month 0 to month 12, including only patients with paired data available at all evaluated time points. In case this overall test was significant ($P < 0.050$), post hoc comparisons between each follow-up time point and baseline were performed using the Wilcoxon signed-rank test, with Bonferroni correction for multiple testing. A P value of 0.004 was considered statistically significant.

Between group comparisons at a given time point were performed using the χ^2 test, Fisher's exact test, the Mann-Whitney test, and the Kruskal-Wallis test, as appropriate. Kaplan-Meier survival analysis was used to assess the cumulative retention rate of secukinumab. Patients who remained on secukinumab were censored at last available follow-up. Discontinuation due to inefficacy, relapse, or adverse events was considered an event.

No formal sample size calculation was performed; all eligible patients treated during the study period were included. All statistical tests were two-sided, and no imputation of missing data was performed.

To explore whether GC-free remission and GC dose reduction were influenced by baseline GC dose or previous tocilizumab exposure, exploratory regression analyses were performed among patients with available 12-month data. Logistic regression was used for GC-free remission at 12 months, and linear regression was used for prednisone-equivalent GC dose at 12 months. Models included baseline prednisone-equivalent GC dose and previous tocilizumab exposure as covariates. An additional exploratory analysis was performed for the mutually exclusive primary-indication group (clinically relapsing or persistently active disease, imaging-driven progression, adverse events or contraindications to previous or alternative therapies, or GC-sparing intent); retention between subgroups was compared using the log-rank test.

The statistical analyses were performed using the jamovi (version 2.4.11, jamovi project) and IBM SPSS Statistics (version 26, IBM Corp., Armonk, NY, USA) software. Graphics were generated using GraphPad Prism (version 10.1.1, GraphPad Software).

Data availability statement. De-identified data from this study are available from the corresponding author upon reasonable request.

RESULTS

Study population. Thirty-six patients were included, of whom 24 (66.7%) were female. Patient demographic and clinical characteristics at GCA diagnosis are listed in Supplementary Table S1. At diagnosis, the median age was 70 (IQR 66–77)

years, and 30.6% of patients had predominant cranial GCA, 22.2% had predominant large vessel GCA, and 47.2% had a balanced phenotype. Visual manifestations were reported in 36.1% of patients, of whom 38.5% (5 of 13) had permanent vision loss.

Patient demographic and clinical characteristics at secukinumab initiation are listed in Table 1. At secukinumab initiation, the median age was 74 (IQR 70–80) years, and the median disease duration was 24 (12–52) months. Secukinumab was administered at a dose of 300 mg in 31 of 36 patients (86.1%) and at 150 mg in 5 of 36 patients (13.9%). Both regimens included weekly loading doses at weeks 0, 1, 2, 3, and 4, followed by

Table 1. Demographic and clinical characteristics of participants at secukinumab initiation*

	GCA cohort (N = 36)
Demographics	
Age at secukinumab initiation, years	74 [70–80]
Disease duration at secukinumab initiation, months	24 [12–52]
Signs and symptoms	
Cranial signs and symptoms	16 (44.4)
Ocular signs and symptoms	6 (16.7)
PMR signs and symptoms	8 (22.2)
Constitutional symptoms	12 (33.3)
Laboratory parameters	
CRP, mg/L	1.8 [0.5–13.3]
Elevated CRP	15 of 35 (42.9)
ESR, mm/h	7 [2–27]
Elevated ESR	6 of 26 (23.1)
Elevated CRP and/or ESR	15 of 35 (42.9)
Hb, g/L	134 [120–140]
Platelet count, $\times 10^9/L$	241 [202–295]
Imaging	
^{18}F -FDG-PET performed	11 (30.6)
Positive	11 of 11 (100)
Ultrasound performed	16 (44.4)
Positive	9 of 16 (56.3)
Previous treatment	
GC discontinuation before secukinumab initiation	20 of 35 (57.1)
At least 1 relapse before secukinumab initiation	32 (88.9)
2 or more relapses before secukinumab initiation	19 (52.8)
Patients receiving previous csDMARDs, bDMARDs, and/or tsDMARDs	33 (91.7)
Patients receiving previous csDMARDs (MTX or AZA)	19 (52.8)
Patients receiving previous bDMARDs or tsDMARDs	26 (72.2)
TCZ	26 of 26 (100)
Other (baricitinib, ustekinumab, abatacept)	3 of 26 (11.5)

* Data are expressed as median [IQR] or absolute numbers (%). AZA, azathioprine; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; ^{18}F -FDG-PET, ^{18}F -fluorodeoxyglucose positron emission tomography; GC, glucocorticoid; GCA, giant cell arteritis; Hb, hemoglobin; IQR, interquartile range; MTX, methotrexate; PMR, polymyalgia rheumatica; TCZ, tocilizumab; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

maintenance dosing every four weeks. At treatment initiation, manifestations of active disease included persistent cranial symptoms in 16 of 36 patients (44.4%), persistent ocular signs and/or symptoms in 6 of 36 (16.7%), polymyalgia symptoms in 8 of 36 (22.2%), constitutional symptoms in 12 of 36 (33.3%), isolated elevation of CRP and/or ESR without clinical manifestations in 5 of 36 (13.9%), and new vascular lesions or worsening on ultrasound and/or ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) findings in 19 of 36 (52.8%). These manifestations were not mutually exclusive. In addition, adverse events related to prior therapies contributed to the decision to initiate secukinumab as a maintenance strategy in 2 of 36 patients (5.6%), whereas contraindications to tocilizumab were the main reason for secukinumab initiation in 2 of 36 additional patients (5.6%). On review of the primary-indication for secukinumab initiation, 16 of 36 (44.4%) patients were treated for clinically relapsing or persistently active disease, 15 of 36 (41.7%) for imaging-driven progression, 3 of 36 (8.3%) because of adverse events or contraindications to previous or alternative therapies, and 2 of 36 (5.6%) primarily for GC-sparing intent.

When secukinumab was started, 28 of 36 patients (77.8%) were receiving oral GCs, with a median prednisone-equivalent dose of 8.7 (IQR 4.0–21.2) mg/day, and 10 of 36 patients (27.8%) were already receiving methotrexate. Moreover, among 31 patients with active disease (clinical or imaging-driven) at secukinumab initiation, 18 (58.1%) underwent GC dose escalation around treatment initiation, whereas 13 (41.9%) started secukinumab without increasing GC dose.

Of 36 patients, 32 (88.9%) had experienced at least one relapse, and 19 of 36 patients (52.8%) had two or more relapses. Before secukinumab initiation, 19 of 36 patients (52.8%) had received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and 26 of 36 patients (72.2%) had received tocilizumab. Among the 26 patients previously treated with tocilizumab, treatment had been discontinued because of lack of efficacy in 12 patients (primary failure, $n = 1$; secondary failure, $n = 11$), adverse events in 11 patients, intolerance in 2 patients, and prolonged remission in 1 patient. Adverse events leading to discontinuation included hepatotoxicity ($n = 2$), diverticulitis ($n = 3$), neutropenia ($n = 3$), diffuse cutaneous rash ($n = 1$), and severe infections ($n = 2$).

Primary and secondary outcomes. Data on primary and secondary outcomes are summarized in Table 2, Figure 1, and Figure 2. The proportion of patients in clinical remission increased from 25.0% at baseline to 85.2% (95% CI 66.3–95.8) at 3 months, 80.6% (95% CI 64.0–91.8) at 6 months, and 83.3% (95% CI 65.3–94.4) at 12 months. Additionally, clinical remission was observed in 13 of 15 patients (86.7%) who underwent GC escalation and 10 of 12 (83.3%) who did not ($P = 0.809$). The proportion of patients in complete remission increased from 16.7% at baseline to 55.6% (95% CI 35.3–74.5) at 3 months

Table 2. Longitudinal efficacy data of the cohort (36 patients) treated with secukinumab*

	T0 (N = 36)	T3 (n = 27)	P value (T3 vs baseline)	T6 (N = 36)	P value (T6 vs baseline)	T12 (n = 30)	P value (T12 vs baseline)	P value overall
Clinical remission	9 (25.0)	23 (85.2)	<0.001	29 of 36 (80.6)	<0.001	25 (83.3)	<0.001	<0.001
Complete remission	6 (16.7)	15 (55.6)	<0.001	19 (52.8)	<0.001	19 (63.3)	<0.001	<0.001
GC-free remission	3 (8.3)	4 (14.8)	0.500	10 (27.8)	0.016	12 (40.0)	<0.002	0.012
Elevated CRP	15 of 35 (42.9)	10 (37.0)	— ^a	9 of 35 (25.7)	— ^a	8 (26.7)	— ^a	0.179
CRP, mg/L	1.8 [0.5–13.3]	2.8 [1.2–8.3]	— ^a	3.3 [1.2–6.2]	— ^a	4.0 [1.7–6.2]	— ^a	0.318
Elevated ESR	6 of 26 (23.1)	2 of 20 (10.0)	— ^a	5 of 27 (18.5)	— ^a	6 of 24 (25.0)	— ^a	0.392
ESR, mm/h	7 [2–27]	22 [13–28]	— ^a	13 [3–30]	— ^a	20 [8–33]	— ^a	0.787
Ongoing GC	28 (77.8)	20 (74.1)	1.000	20 (55.6)	0.021	14 (46.7)	0.003	0.004
GC, mg/day	8.7 [4.0–21.2]	5.0 [1.8–7.5]	0.002	1.2 [0–5.0]	<0.001	0 [0–5.0]	<0.001	<0.001

* Data are expressed as median [IQR] or absolute numbers (%) unless otherwise indicated. Column headings indicate the number of patients with available clinical follow-up data at each time point. Outcome-specific denominators are shown in individual rows when data were missing for a given variable. Percentages were calculated using the available-case denominator for each outcome. Each follow-up time point (months 3, 6, and 12) was compared with baseline. Repeated-measures analyses were performed only in patients with paired data across the evaluated time points. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; IQR, interquartile range.

^a Friedman or Cochran Q test not significant; therefore, pairwise comparisons were not performed.

and remained high at 6 months (52.8%; 95% CI 35.5–69.6) and 12 months (63.3%; 95% CI 43.9–80.1). The proportion of patients in GC-free remission increased progressively from 8.3% at baseline to 14.8% (95% CI 4.2–33.7) at 3 months, 27.8% (95% CI 14.2–45.2) at 6 months, and 40.0% (95% CI 22.7–59.4) at 12 months. Outcomes by primary indications are reported in Supplementary Table S2.

At baseline, elevated CRP and ESR levels were observed in 15 of 35 patients (42.9%) and 6 of 26 patients (23.1%), respectively. No significant changes in CRP or ESR levels were observed during follow-up (overall $P = 0.318$ and $P = 0.787$, respectively).

The median daily GC dose decreased from 8.7 (IQR 4.0–21.2) mg/day at baseline to 5.0 (IQR 1.8–7.5) mg/day at 3 months, 1.2 (IQR 0–5.0) mg/day at 6 months, and 0 (IQR 0–5.0) mg/day at 12 months. At baseline, 28 of 36 patients (77.8%) were receiving GC therapy, whereas 8 of 36 patients (22.2%) were GC-free. Among the 28 patients receiving GC at baseline, 12 (42.9%) discontinued GC during follow-up. At 12 months, 14 of 30 patients

(46.7%) were receiving GCs. Among the 10 patients receiving concomitant methotrexate at baseline, 2 patients (20.0%) discontinued it during follow-up.

Retention rate. The Kaplan-Meier test estimated the 12-month retention rate was 77.0% (Figure 3). Overall, 8 of 36 patients (22.2%) discontinued secukinumab during follow-up, after a median treatment duration of 10 (IQR 8–11) months. Reasons for discontinuation included relapses ($n = 5$), infections ($n = 2$), and malignancy ($n = 1$). All relapses observed during follow-up led to secukinumab discontinuation. Among patients who discontinued secukinumab because of relapse, one experienced a major relapse characterized by visual symptoms, increased acute-phase reactant levels, and worsening metabolic activity on ^{18}F -FDG-PET. The remaining four patients experienced minor relapses, characterized by worsening imaging findings on temporal artery ultrasound or ^{18}F -FDG-PET, with concomitant increases in acute-phase reactant levels in three

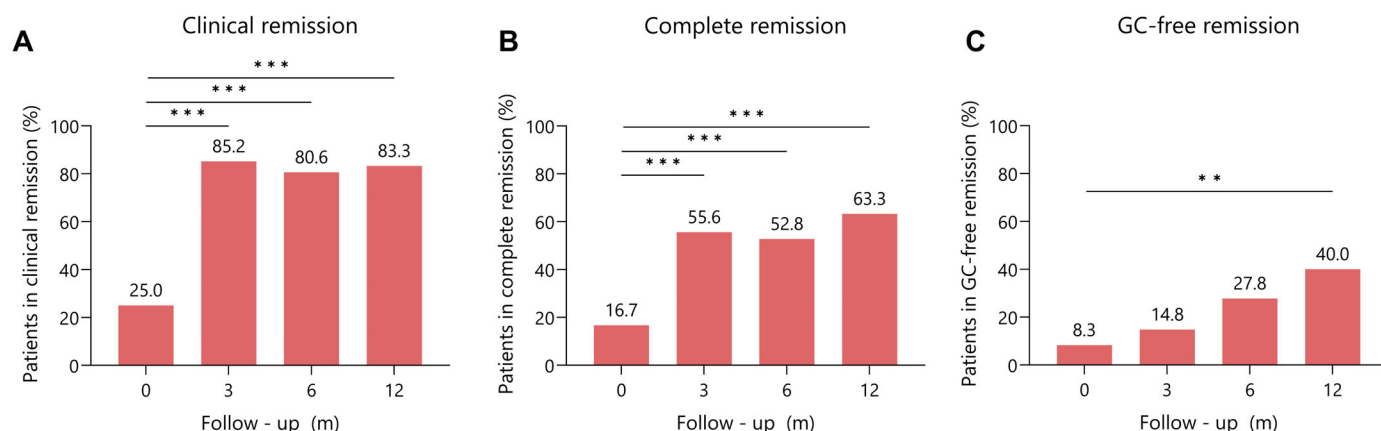


Figure 1. Remission rate following secukinumab treatment. Proportions of patients achieving (A) clinical remission, (B) complete remission, and (C) GC-free remission at baseline and months 3, 6, and 12. Complete remission required clinical remission and normalization of C-reactive protein and erythrocyte sedimentation rate; GC-free remission required complete remission without GC treatment. Percentages were calculated using available-case denominators. Paired comparisons with baseline were performed using the McNemar test with Bonferroni correction. ** $P < 0.005$, *** $P < 0.001$. GC, glucocorticoid.

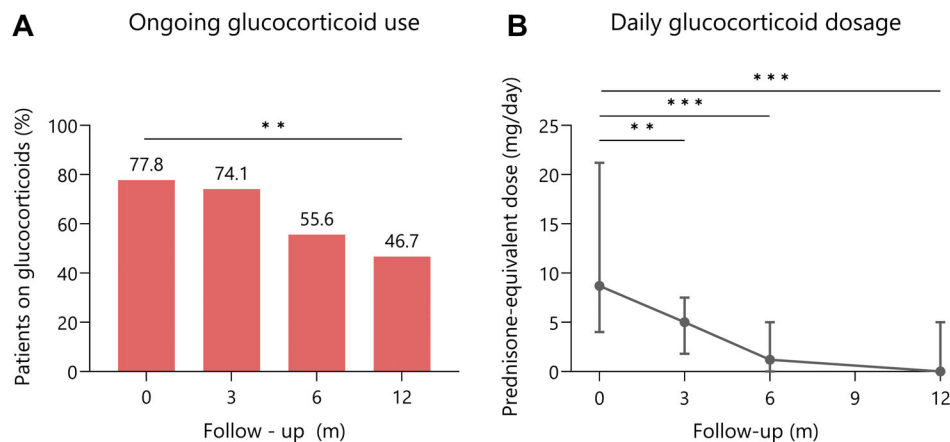


Figure 2. Glucocorticoid use and dose during secukinumab treatment. (A) Proportion of patients receiving oral glucocorticoids and (B) median daily prednisone-equivalent dose with interquartile range at baseline and months 3, 6, and 12. A dose of 0 mg/day was assigned to patients not receiving glucocorticoids. Paired comparisons with baseline were performed using the McNemar test for glucocorticoid use and the Wilcoxon signed-rank test for daily dose, with Bonferroni correction. $**P < 0.005$ for glucocorticoid use (A) and $P < 0.004$ for glucocorticoid dose (B), $***P < 0.001$.

patients. At relapse, the median prednisone-equivalent GC dose was 0 (IQR 0–0) mg/day; four of five patients were GC-free, whereas one patient was receiving 5 mg/day.

Given the small size of the other indication groups, exploratory retention comparisons were restricted to patients treated for clinically relapsing or persistently active disease and those treated for imaging-driven progression. Discontinuation occurred in 2 of 16 (12.5%) and 5 of 15 (33.3%) patients, respectively ($P = 0.166$), with estimated 12-month retention rates of 87.5% and 66.7%, respectively (log-rank $P = 0.244$).

Safety. Overall, adverse events were reported in 20 of 36 patients (55.6%). Infections were the most frequent events, occurring in 18 of 36 patients (50.0%), for a total of 21 infectious

episodes. Of these, 6 (28.6%) occurred during concomitant GC treatment and 3 (14.3%) during concomitant methotrexate treatment. Infection events included respiratory tract infections (pneumonia, $n = 3$; bronchitis, $n = 2$; COVID-19, $n = 1$; upper respiratory tract infection, $n = 1$; and progression of pre-existing lung abscesses, $n = 1$), influenza ($n = 1$), urinary tract infections (cystitis, $n = 4$), viral gastroenteritis ($n = 2$), herpes zoster ($n = 1$), and skin and soft tissue infections ($n = 3$), including cutaneous fungal infection ($n = 1$). Two other or unspecified infections were also recorded. Hospitalizations occurred in 3 of 36 patients (8.3%) and included pneumonia ($n = 1$), hemoptysis associated with suspected fungal or bacterial infection and progression of pre-existing lung abscesses ($n = 1$), and diagnosis of anorectal cancer leading to secukinumab discontinuation ($n = 1$). No injection-site reactions were reported. No deaths occurred among the 36 patients included in the study cohort. No statistically significant differences were observed between patients who developed infections and those who did not in terms of age, sex, disease duration at secukinumab initiation, previous tocilizumab exposure, baseline GC dose, ongoing GC therapy at secukinumab initiation, or concomitant methotrexate use at baseline (all $P > 0.050$; Supplementary Table S3).

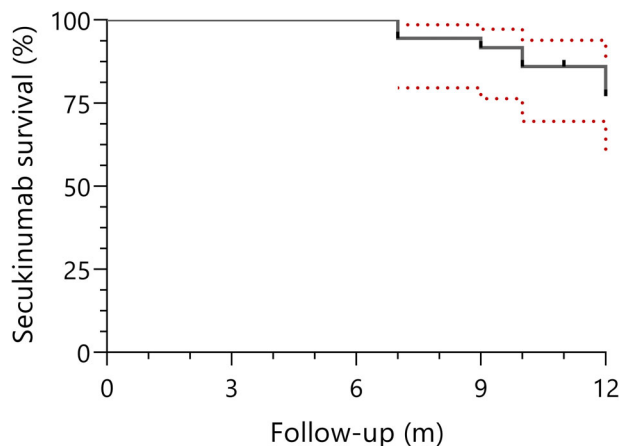


Figure 3. Kaplan-Meier curve of secukinumab retention over 12 months. The solid line indicates the estimated retention probability, dotted lines indicate 95% confidence intervals, and tick marks indicate censored observations.

Exploratory subgroup analyses. Exploratory subgroup analyses were performed among patients with available 12-month follow-up data. At 12 months, no statistically significant differences in remission outcomes were observed between patients receiving secukinumab as their first biologic DMARD ($n = 10$), namely biologic-naïve, and those previously exposed to tocilizumab ($n = 20$). At 12 months, the two groups yielded comparable rates of clinical remission (9 of 10, 90.0% vs 16 of

20, 80.0%; $P = 0.488$), complete remission (8 of 10, 80.0% vs 11 of 20, 55.0%; $P = 0.180$), and GC-free remission (3 of 10, 30.0% vs 9 of 20, 45.0%; $P = 0.429$). Discontinuation occurred in 1 of 10 biologic-naïve patients (10%) and in 7 of 26 patients (26.9%) previously exposed to tocilizumab ($P = 0.274$). The 12-month retention rate did not differ significantly between groups (log-rank $P = 0.318$). At baseline, patients previously exposed to tocilizumab had lower CRP levels (median 0.7 [IQR 0.5–3.0] vs median 13.2 [IQR 7.8–38.4] mg/L, $P = 0.010$), consistent with prior IL-6 blockade. Before secukinumab initiation, patients previously exposed to tocilizumab had lower GC doses than biologic-naïve patients (5 [0–10] vs 17.5 [12.5–25.0] mg/day, $P = 0.014$). At secukinumab initiation, the corresponding GC doses were 5 (0–10) and 12.5 (5.6–19.7) mg/day, respectively ($P = 0.042$). At 12 months, CRP levels did not differ significantly between groups (2.4 [0.9–6.0] vs 4.0 [2.8–4.5] mg/L, $P = 0.708$). At 12 months, median GC dose was 0 (0–5) mg/day in the prior-tocilizumab group and 2.5 (0–5) mg/day in biologic-naïve patients ($P = 0.389$); the corresponding median GC dose reductions from baseline were 1.8 (0–7.3) and 8.7 (5–17.8) mg/day ($P = 0.052$). Additional baseline and treatment characteristics are reported in Supplementary Table S4.

In an exploratory regression analysis restricted to patients with available 12-month data, GC-free remission at 12 months was not clearly associated with baseline prednisone-equivalent GC dose (odds ratio [OR] per 5 mg/day increase 0.76, 95% CI 0.46–1.27, $P = 0.293$) or previous tocilizumab exposure (OR 1.36, 95% CI 0.23–8.14, $P = 0.734$). Similarly, in an exploratory linear regression model, 12-month prednisone-equivalent GC dose was not clearly associated with baseline GC dose (β +0.48 mg/day per 5 mg/day increase, 95% CI –0.89 to 1.85, $P = 0.493$) or previous tocilizumab exposure (β +0.58 mg/day, 95% CI –3.42 to 4.59, $P = 0.775$). In stratified analyses, 12-month GC-free remission was observed in 6 of 15 patients (40.0%) with baseline GC dose ≤ 7.5 mg/day and in 6 of 15 patients (40.0%) with baseline GC dose > 7.5 mg/day. Similarly, GC-free remission at 12 months was observed in 3 of 10 biologic-naïve patients (30.0%) and 9 of 20 patients previously exposed to tocilizumab (45.0%). Other exploratory subgroup analyses according to concomitant polymyalgia rheumatica symptoms at baseline and concomitant methotrexate

use are summarized in Table 3. No clear differences in remission outcomes were shown across subgroups.

DISCUSSION

In this multicenter retrospective cohort, secukinumab treatment was associated with high observed remission rates and progressive GC reduction in a highly treatment-experienced population with GCA. Clinical remission was observed in more than 80% of evaluable patients at each follow-up time point, whereas complete remission was achieved in approximately half of patients at early follow-up and increased to nearly two-thirds of those with available 12-month data. These findings were observed in a population characterized by long-standing disease, a high relapse burden, and substantial previous exposure to biologic therapies, particularly tocilizumab. In addition, GC dose decreased progressively over time, and GC-free remission increased during follow-up. The progressive reduction of GC exposure remains clinically relevant given the well-known toxicity associated with long-term GC use in GCA.^{16,17} The increase in complete remission may largely reflect resolution of clinical activity in patients with already normal or near-normal markers of inflammation at secukinumab initiation, a situation particularly relevant among those previously exposed to tocilizumab. Early clinical improvement may also have been influenced by concomitant GC escalation, although remission was also observed in patients without GC escalation. Moreover, the nonstandardized GC taper limits causal attribution of the observed GC reduction to secukinumab.

Our findings should be interpreted in the context of the available clinical trial evidence. In the phase II TitAIN trial, secukinumab, combined with a protocol-defined 26-week GC taper, was associated with a higher Bayesian median sustained remission rate until week 28 than placebo (70% vs 20%).¹³ However, the subsequent phase III GCaptAIN trial did not meet its primary endpoint, which required remission by week 12 and its maintenance through week 52 without clinical relapse. Nevertheless, numerically favorable outcomes were observed for sustained remission, cumulative GC exposure, and GC-related toxicity.¹⁴ Interpretation of GCaptAIN is further complicated by a protocol amendment introduced during recruitment, which added the secukinumab 150 mg arm and modified randomization.¹⁴ Direct comparisons

Table 3. Exploratory 12-month subgroup analyses*

	Concomitant PMR symptoms (n = 6)	No concomitant PMR symptoms (n = 24)	Secukinumab monotherapy (n = 22)	Concomitant methotrexate (n = 8)	Biologic-naïve (n = 10)	Previous tocilizumab therapy (n = 20)
Clinical remission	5 (83.3)	20 (83.3)	17 (77.3)	8 (100)	9 (90.0)	16 (80.0)
Complete remission	4 (66.7)	15 (62.5)	14 (63.6)	5 (62.5)	8 (80.0)	11 (55.0)
GC-free remission	2 (33.3)	10 (41.7)	10 (45.5)	2 (25.0)	3 (30.0)	9 (45.0)
Ongoing GC treatment	3 (50.0)	11 (45.8)	8 (36.4)	6 (75.0)	6 (60.0)	8 (40.0)

* Data are presented as absolute numbers (%). Percentages were calculated using available-case denominators among patients with available 12-month follow-up data. GC, glucocorticoid; PMR, polymyalgia rheumatica.

between these trials and our cohort should be interpreted with caution because of substantial differences in study design, outcome definitions, treatment protocols, and patient populations. Notably, TitAIN and GCaptAIN enrolled mixed populations of patients with new-onset or relapsing active GCA, among whom new-onset disease accounted for approximately 81% and 66% of participants, respectively.^{13,14} Moreover, TitAIN and GCaptAIN mainly enrolled treatment-naïve or less refractory patients, whereas most patients in our cohort had relapsing disease and 72.2% had previously received tocilizumab. Thus, our study reflects a clinically relevant, real-world population that remains underrepresented in randomized controlled trials and warrants further investigations. Our findings should be considered hypothesis generating, as the retrospective, uncontrolled design, lack of a standardized GC taper, absence of blinded outcome assessment, and potential expectation and ascertainment biases limit causal inference.

Real-world evidence on secukinumab in GCA remains limited. The only previously published case series reported favorable outcomes in six patients treated after tocilizumab failure.¹⁸ Our study extends these observations in a larger multicenter cohort, including patients previously exposed to biologic therapies and treated for heterogeneous real-world indications such as relapsing and persistently active disease, imaging progression, GC-sparing intent, and intolerance or contraindications to previous therapies. In our exploratory subgroup analyses, clinical responses were observed both in biologic-naïve patients and in those previously treated with tocilizumab, with no statistically significant differences in 12-month remission outcomes between groups. However, these findings should be interpreted cautiously because of the small sample size and baseline differences between groups.

The overlap between GCA and polymyalgia rheumatica may also be relevant when interpreting these findings.¹⁹ The phase III REPLENISH trial demonstrated the efficacy of secukinumab 300 mg or 150 mg, combined with a 24-week GC taper, in relapsing polymyalgia rheumatica,²⁰ supporting the biologic and clinical relevance of IL-17A inhibition in these patients.²¹ Consistently, a post hoc analysis of the TitAIN trial suggested improved control of polymyalgia rheumatica symptoms among secukinumab-treated patients with GCA, whereas GCaptAIN included a prespecified exploratory subgroup analysis of patients with concomitant polymyalgia rheumatica.^{14,22}

The safety profile observed in our cohort was consistent with previous experience with secukinumab. Adverse events were reported in 55.6% of patients, with infections being the most frequent. Hospitalizations were uncommon, and no unexpected safety signals emerged. The patient with anorectal cancer had no known malignancy or premalignant condition at secukinumab initiation, and no causal relationship with secukinumab could be established. Nevertheless, the retrospective design and the lack of systematic adverse-event collection limit comparisons with clinical trial safety data.

The main strengths of our study include its multicenter design and the inclusion of a heterogeneous real-world population with relapsing disease and frequent prior biologic exposure. To our knowledge, this is the largest real-world cohort evaluating secukinumab in GCA. Some limitations should be acknowledged. The retrospective design introduces the risk of selection and information bias. In particular, the at least six-month follow-up eligibility criterion excluded one patient who died from pneumonia during the secukinumab loading phase, potentially favoring retention estimates and underestimating early safety events. Secukinumab dosing and GC tapering were not standardized, treatment decisions were physician-dependent, and previous tocilizumab exposure was nonrandom, with baseline GC dose differences between treatment subgroups potentially confounding GC-related outcomes. Imaging was performed in routine clinical practice without a predefined protocol or central adjudication, potentially introducing measurement variability or misclassification that may have affected retention estimates. Finally, the limited sample size hampers statistical power, particularly for subgroup and regression analyses, and the use of clinical remission as the primary outcome may have failed to capture subclinical vascular inflammation.

In this real-world multicenter study, secukinumab was associated with high observed rates of clinical remission, progressive GC dose reduction, and increasing rates of GC-free remission in patients with GCA, including those with relapsing disease and previous biologic exposure. Although these findings are hypothesis generating and should be interpreted in light of the phase III GCaptAIN results, they suggest that IL-17A inhibition may warrant further evaluation. Results from the phase III trial (NCT05380453, also known as the GigAINt trial) in new-onset GCA are awaited and may provide further insight into the potential place of secukinumab in the treatment pathway. More broadly, prospective registries are needed to systematically capture real-world effectiveness and safety data for novel targeted therapies in GCA, particularly in patient populations underrepresented in randomized trials.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Padoan confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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APPENDIX A: STEERING COMMITTEE MEMBERS OF THE ITALIAN SOCIETY OF RHEUMATOLOGY VASCULITIS STUDY GROUP

The Steering Committee members of the Italian Society of Rheumatology Vasculitis Study Group are: Luca Quartuccio (Udine), coordinator; Carlo Salvarani (Reggio Emilia); Roberto Caporali (Milan); Marco Amadeo Cimmino (Genoa); Christian Dejaco (Bolzano); Giacomo Emmi (Trieste); Pietro Leccese (Potenza); Roberto Padoan (Padua); Franco Schiavon (Padua); Sara Talarico (Pisa); Alvise Berti (Trento); Dario Camellino (Genoa); Corrado Campochiaro (Milan); Laura Coladonato (Bari); Giulio Forte (Naples); Sara Monti (Milan); Francesco Muratore (Reggio Emilia); and Elena Treppo (Udine).