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Methylprednisolone pulses are associated with faster remission in Giant Cell Arteritis: a multicentre inception cohort study

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Abstract

Background Despite being the cornerstone of induction therapy in Giant Cell Arteritis (GCA), glucocorticoids (GCs) often fail to achieve sustained disease control and are associated with substantial morbidity, while evidence supporting the broader use of intravenous methylprednisolone (MP) pulses beyond high-risk patients remains limited and conflicting. We aimed to evaluate the effectiveness and safety of MP as induction therapy in newly diagnosed GCA.

Methods Retrospective, observational, multicentre study of patients with newly diagnosed GCA according to the 2022 ACR/EULAR classification criteria, comparing induction treatment with either MP or oral GCs. The primary outcome was time to remission. The effect of MP on time to remission was estimated using inverse probability weighted regression adjustment (IPWRA).

Results A total of 206 patients were included; 116 (56.3%) received MP. Patients in the MP group more frequently had ischemic symptoms at onset. Overall, 196 patients (95.1%) achieved remission with a median time of 8.6 weeks ($p = 0.287$). IPWRA analysis showed that MP was associated with a shorter time to remission (average treatment effect, ATE: −14.2 weeks; 95% CI − 20.5 to − 7.8, $p < 0.001$). In adjusted Weibull regression, MP was associated with a higher hazard of remission (HR 2.44; 95% CI 1.66–3.59, $p < 0.001$). Patients treated with MP had a significantly lower median cumulative prednisone dose (733 vs. 1,902 mg; $p < 0.001$) and lower average daily prednisone dose until remission (13.6 vs. 30 mg; $p < 0.001$). At 3 months, the MP group required lower daily and cumulative prednisone doses and had fewer cases of diabetes mellitus and osteoporosis.

Conclusions In this real-world multicentre cohort, MP during induction were associated with faster remission and significant glucocorticoid sparing without increased short-term toxicity. These findings support reconsideration of the role of MP beyond patients with ischemic manifestations and warrant prospective confirmation.

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Keywords Giant cell arteritis, Methylprednisolone pulses, Induction therapy, Time to remission, Cumulative prednisone dose, Glucocorticoid-sparing effect, Real-world data

Introduction

Giant Cell Arteritis (GCA) is a chronic granulomatous vasculitis of large vessels that primarily affects older adults [1, 2]. Beyond its systemic manifestations—such as fever, weight loss, or polymyalgia rheumatica—the disease is characterized by vascular inflammation leading to luminal occlusion and ischemic complications, including irreversible visual loss and stroke [3, 4]. In recent years, increasing recognition of distinct clinical phenotypes—cranial, large-vessel and systemic—has highlighted the heterogeneity of GCA and the variability in clinical course, prognosis and therapeutic response [5, 6].

Given its autoimmune and inflammatory nature, current treatment of GCA relies on glucocorticoids (GCs), typically initiated at 40–60 mg/day of oral prednisone or prednisolone, which are considered effective in rapidly controlling inflammation and preventing vision loss [7–9]. However, relapse rates remain high, and a substantial proportion of patients experience persistent disease activity after one year of treatment [10–13]. In parallel, cumulative GC exposure is associated with a considerable burden of toxicity, including osteoporosis, diabetes, cardiovascular complications, infection and neuropsychiatric effects, even at relatively low doses or during short treatment courses [9, 14]. Accordingly, current guidelines from the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR) and British Society for Rheumatology emphasize the need to minimize long-term GC use and to implement steroid-sparing strategies [8, 15, 16].

Two conceptually distinct but complementary strategies have therefore emerged to optimize outcomes while reducing GC toxicity. First, intravenous methylprednisolone pulses (MP) exert rapid anti-inflammatory effects, allowing for earlier tapering and reduced cumulative glucocorticoid exposure [17]. Although current recommendations reserve MP for patients with visual involvement or high ischemic risk [8, 15, 16], broader application may be clinically justified, as suggested by experience in other systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and inflammatory myopathies, where pulse GC regimens are routinely employed as induction strategies [18–22]. However, evidence supporting their use and safety in GCA remains limited and conflicting, and current data do not yet allow for a uniform recommendation for their use in all patients, despite the intrinsic severity and potential complications of the disease [3, 23–26].

Second, steroid-sparing immunosuppressive agents, including methotrexate (MTX) and biologic therapies such as tocilizumab (TCZ), have been shown to reduce relapse rates and cumulative GC exposure [10, 13, 24, 27, 28]. More recently, the JAK inhibitor upadacitinib has demonstrated promise in lowering rates of active disease and steroid dependence [12].

Nevertheless, although some long-term studies have shown that disease control can be maintained with low doses of glucocorticoids through these two strategies, clinical guidelines still relegate the use of MP to patients with ischemic complications and leave the choice of immunosuppressive regimen to physician discretion, as no direct comparative studies have established the optimal induction or maintenance strategy [8, 11, 13, 15, 16, 24, 26, 29]. This remains a crucial issue given the severity of the vasculitis and the profile of affected patients—elderly individuals with a high burden of comorbidities and an increased risk of steroid-related complications [4, 9, 14, 25, 30, 31].

Taken together, these uncertainties underscore the need for further evaluation of induction strategies in GCA, particularly in real-world settings that reflect the heterogeneity and complexity of clinical practice. Drawing on experience from other autoimmune diseases, we hypothesized that MP may accelerate clinical remission while reducing cumulative oral GC exposure and its associated toxicity, ultimately improving short-term outcomes in patients with newly diagnosed GCA. We therefore aimed to evaluate the effect of MP on time to remission, glucocorticoid exposure and early safety outcomes in a large, multicentre real-world inception cohort.

Materials and methods

Study design and population

We designed this study based on the Giant Cell Arteritis-Comunidad Autónoma de Madrid (GCA-CAM) inception cohort, which included patients with newly diagnosed GCA according to the 2022 ACR/EULAR classification criteria under GC or immunosuppressant treatment [2]. This retrospective observational cohort comprises patients from several Autoimmune Diseases Units from hospitals across the Comunidad Autónoma de Madrid, in Spain, included from 2008 to 2025. In the GCA-CAM database, patients are followed for up to 36 months. The epidemiological and clinical variables collected at baseline, as described below, were recorded at fixed time points (3, 12, 24, and 36 months, and at the last visit if follow-up is discontinued), as well as at the time of flares or medication changes due to inefficacy, adverse events, or dose adjustment. For the present study, we focused on the induction phase and restricted the

analysis to the first 3 months after diagnosis. This study was reported in accordance with the STROBE guidelines for observational research.

Data collected and definitions

At baseline, epidemiological data, cardiovascular risk factors and baseline conditions, disease-related symptoms and signs, and laboratory parameters — including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and haemoglobin — were recorded. Units were reviewed and harmonized across centers. Imaging assessments such as ultrasonography, magnetic resonance imaging (MRI), positron emission tomography–computed tomography (PET–CT), and temporal artery biopsy were also collected, as well as the vascular territories involved. Following the recent phenotypic distinction of the disease and according to the 2022 ACR/EULAR classification criteria, GCA was categorized into three non-mutually exclusive clinical phenotypes based on the affected territories and systemic features: cranial GCA (involving temporal, facial, maxillary, lingual, occipital, and ophthalmic arteries), large-vessel GCA (involving the thoracic and abdominal aorta, brachiocephalic trunk, subclavian, axillary, carotid, vertebral, iliac, femoral, and popliteal arteries), and systemic GCA (characterized by fever > 38.3 °C, constitutional symptoms, weight loss, and inflammatory anaemia) [2, 5, 6]. The induction period was defined as the time between the initiation of GC therapy—either oral or intravenous—and the achievement of remission. Remission was defined, according to the 2018 EULAR recommendations, as the absence of clinical signs and symptoms of active GCA and normalization of acute-phase reactants at the same time point [8]. Given that the ESR is influenced by age and sex, reference limits were adjusted as follows: ESR below age/2 for men and ESR below (age + 10) /2 for women [32, 33]. The doses and routes of administration of GCs, MTX and TCZ, as well as treatment withdrawal and its cause during the induction phase, were recorded. Decisions regarding glucocorticoid dose adjustments, tapering strategies and the initiation of immunosuppressive therapy followed routine clinical practice and local protocols.

Outcomes

The present study was designed to evaluate the effectiveness and safety of MP during induction therapy in patients with newly diagnosed GCA, compared with standard oral GC regimens. The primary outcome was time to remission, defined as the interval in weeks between the start date of induction therapy and the remission date. Patients who did not achieve remission by the end of follow-up were censored at their last study visit.

Secondary outcomes included cumulative prednisone dose at remission (mg) and average daily prednisone dose until remission (mg per day), as well as remission rate at 3 months, clinical remission rate at 3 months (defined as the absence of clinical signs and symptoms irrespective of laboratory parameters), prednisone dose at 3 months (mg), cumulative prednisone dose at 3 months (mg), and average daily prednisone dose over the first 3 months (mg per day). Additional secondary outcomes included GC-related adverse effects and treatment-related complications associated with immunosuppressants (methotrexate or tocilizumab) at 3 months.

Average daily prednisone dose until remission and over the first 3 months was calculated as cumulative prednisone dose divided by time to remission and by 90 days, respectively. MP dose was not included in cumulative prednisone calculations, as pulse therapy predominantly activates non-genomic pathways and represents a pharmacodynamically distinct exposure [17].

GC-related adverse effects were defined as either the worsening of pre-existing conditions or new-onset hypertension, diabetes mellitus (DM), dyslipidemia, or osteoporosis requiring initiation or intensification of treatment, as well as Cushing syndrome and changes in mood, cognition, or sleep. Any dose escalation or modification of baseline therapy attributed to GC toxicity was also considered an adverse effect. Treatment-related complications associated with immunosuppressants included myelotoxicity and cytopenias, digestive adverse effects, allergic reactions, local injection-site adverse effects, and pharmacological interactions, among others.

Statistical analysis

Descriptive analyses were conducted using absolute and relative frequencies for categorical variables and means with standard deviations or medians with 25th and 75th percentiles for numerical variables, depending on the distribution of the data. Median time to remission was estimated using the Kaplan-Meier method and compared between the treatment arms through the log-rank test.

We estimated the effect of treatment on time to remission using inverse probability weighted regression adjustment (IPWRA). The outcome model used a Weibull distribution and included age, sex, TCZ use, MTX use and average daily prednisone dose until remission. The treatment model included the exposure (MP or oral GC) and the following baseline covariates: center, age, sex, hypertension, diabetes, dyslipidemia, obesity, osteoporosis, clinical phenotypes (cranial, large-vessel, and systemic GCA), ischemic symptoms at onset, and baseline inflammatory markers (ESR and CRP). The model was designed and specified according to a directed acyclic graph (DAG) framework (Supplementary Appendix Fig. 1). The average treatment effect (ATE) was estimated

along with the corresponding 95% confidence interval. The ATE is the population average contrasted in outcomes when everyone gets the treatment and when no one gets the treatment. Covariate balance after weighting was assessed using standardized differences and variance ratios, and the joint specification of treatment and outcome models was evaluated using the overidentification test. To evaluate whether sufficient common support exists across treatment groups, the overlap assumption was examined graphically. The IPWRA estimator provides doubly robust causal effect estimates when either the treatment or the outcome model is correctly specified.

In addition, we fitted a crude Weibull regression model only with MP/oral GC during induction treatment and a multivariable Weibull model adjusted for the covariates included in the IPWRA models. These models were used to obtain hazard ratios (HRs) and 95% confidence intervals (95% CI) as complementary effect measures.

The analyses were performed using Stata v.18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.) and the significance level was set at 0.05.

Ethics

The study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Puerta de Hierro University Hospital (PI 16/24), as well as by the local Institutional Review Boards of the participating centers. In accordance with Spanish law and the exemption granted by the Ethics Committee, informed consent was not required for this study.

Results

Study population

A total of 206 patients fulfilling the 2022 ACR/EULAR GCA criteria were included (Fig. 1; Table 1). Overall, 126 (61.2%) were female and 198 (96.1%) were Caucasian, with a mean age of 74.4 years. Fifty patients (24.3%) presented with ischemic symptoms at onset, including amaurosis fugax in 9 (4.4%), anterior ischemic optic neuropathy (AION) in 34 (16.5%), transient ischemic attack in 5 (2.4%) and stroke in 7 (3.4%). Only 52 patients (54.7% of the 95 biopsies performed) had a positive biopsy. Regarding clinical phenotypes, 135 patients (65.6%) were classified as cranial GCA, 42 (20.4%) as large-vessel GCA and 80 (38.8%) as systemic GCA.

One hundred and sixteen patients (56.3%) received MP, and the remaining 90 patients (43.7%) received oral GC. Compared with the oral GC group, patients in the MP group had a lower proportion of females (54.3% vs. 70%, $p = 0.022$) and a higher frequency of ischemic symptoms at onset (33.6% vs. 12.2%, $p < 0.001$), including amaurosis fugax (6.9% vs. 1.1%, $p = 0.044$) and AION (24.1% vs. 6.7%, $p = 0.001$). Notably, PET-CT was performed in a higher proportion of MP- treated patients than in the oral GC group (65.5% vs. 37.8%, $p < 0.001$), although its diagnostic yield was similar (56.6% vs. 55.9%, $p = 0.920$). No significant differences were observed in baseline comorbidities, clinical manifestations of GCA, or serum inflammatory markers.

Induction treatment and primary outcome

Induction treatment, as well as primary and secondary outcomes, are shown in Table 2. The median MP dose was 250 mg (P25, P75:125, 500) for a median duration of 3 days (3, 3). The median oral prednisone dose after MP was lower than the initial prednisone dose in the oral GC group (30 mg vs. 50 mg, $p < 0.001$) (Fig. 2). In parallel,

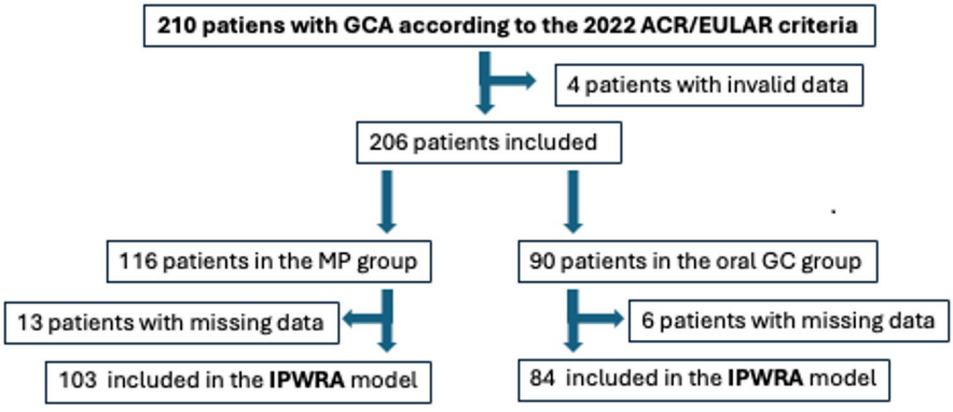

Fig. 1 Flow diagram of patient selection and inclusion in the IPWRA analysis. Flow diagram showing selection of patients with giant cell arteritis according to the 2022 ACR/EULAR classification criteria, exclusions due to invalid data during follow-up, and final inclusion in the inverse probability weighted regression adjustment (IPWRA) model. Patients were stratified by induction strategy into the intravenous methylprednisolone pulses group and the oral glucocorticoids group

Table 1 Baseline characteristics of patients with giant cell arteritis according to treatment group

	All patients (*n* = 206)	MP (*n* = 116)	Oral GC (*n* = 90)	*p*-value
Age at disease onset (years) (mean, SD)	74.4 (12.5)	74.2 (13.1)	74.7 (11.8)	0.765
Female (n, %)	126 (61.2)	63 (54.3)	63 (70)	0.022
Caucasian (n, %)	198 (96.1)	112 (96.6)	86 (95.6)	0.523
Baseline conditions (n, %)				
Hypertension	133 (64.6)	76 (65.5)	57 (63.3)	0.745
Diabetes mellitus	48 (23.3)	27 (23.3)	21 (23.3)	0.992
Dyslipidemia	93 (45.1)	54 (46.6)	39 (43.3)	0.645
Obesity	20 (9.7)	13 (11.2)	7 (7.8)	0.410
Tobacco	18 (8.7)	10 (8.6)	8 (8.9)	0.961
Osteoporosis	30 (14.6)	14 (12.1)	16 (17.8)	0.235
Giant cell arteritis signs and symptoms (n, %)				
Headache	116 (56.3)	69 (59.5)	47 (52.2)	0.297
Jaw claudication	60 (29.1)	36 (31)	24 (26.7)	0.494
Constitutional syndrome	117 (56.8)	60 (51.7)	57 (63.3)	0.095
Fever	71 (34.5)	40 (34.5)	31 (34.4)	0.995
PMR	78 (37.9)	38 (32.8)	40 (44.4)	0.086
Scalp tenderness	40 (19.4)	23 (19.8)	17 (18.9)	0.866
Stroke/ischemic	50 (24.3)	39 (33.6)	11 (12.2)	< 0.001
Amaurosis fugax	9 (4.4)	8 (6.9)	1 (1.1)	0.044
AION	34 (16.5)	28 (24.1)	6 (6.7)	< 0.001
TIA	5 (2.4)	2 (1.7)	3 (3.3)	0.457
Stroke	7 (3.4)	5 (4.3)	2 (2.2)	0.412
Abnormal temporal examination	38 (18.4)	20 (17.2)	18 (20)	0.613
Diagnostic procedures (n, %)				
Ultrasonography	136 (66)	81 (69.8)	55 (61)	0.190
Halo sign	75 (55.1)	44 (54.3)	31 (56.4)	0.800
MRI	21 (10.2)	16 (13.8)	5 (5.6)	0.052
Diagnostic	2 (9.5)	1 (6.3)	1 (20)	0.450
PET-CT	110 (53.4)	76 (65.5)	34 (37.8)	< 0.001
Diagnostic	62 (56.4)	43 (56.6)	19 (55.9)	0.920
Biopsy	95 (46.1)	48 (41.4)	47 (52.2)	0.120
Diagnostic	52 (54.7)	25 (52.1)	27 (57.4)	0.600
Clinical phenotype (n, %)				
Cranial	136 (65.5)	82 (70.7)	53 (58.9)	0.077
Large-vessel	42 (20.4)	25 (21.6)	17 (18.9)	0.638
Systemic	80 (38.8)	43 (37.1)	37 (41.1)	0.555
Serum markers (median, p25-p75)				
CRP (mg/L)	58.2 (13.4-150.5)	60 (18.2-162.8)	56.7 (9.7-140.1)	0.355
ESR (mm)	74 (50-100.5)	73 (50.5–100)	75 (49-101.5)	0.721
Ferritin (ng/ml)	357.5 (164.3-645.5)	371 (150.5–745)	340 (186–492)	0.184
Haemoglobin (g/dL)	12 (10.7–13)	12 (10.6–13)	11.9 (11.8–13)	0.724

MP Methylprednisolone pulses, *GC* Glucocorticoids, *SD* Standard deviation, *PMR* Polymyalgia rheumatica, *AION* Anterior ischemic optic neuropathy, *TIA* Transient ischemic attack, *MRI* Magnetic resonance imaging, *PET-CT* Positron emission tomography–computed tomography, *CRP* C reactive protein, *ESR* Erythrocyte sedimentation rate

patients in the MP group received MTX (42.2% vs. 14.4%, $p < 0.001$) and TCZ (17.4% vs. 6.7%, $p = 0.022$) more frequently during induction therapy, although the median duration of drug exposure was similar in both groups ($p > 0.05$).

Overall, 196 patients (95.1%) achieved remission: 109 (94%) in the MP group and 87 (96.7%) in the oral GC group ($p = 0.371$). The median time to remission was 8.6 weeks (95%CI 6.4; 10.1), with no difference between groups (7.6 weeks in the MP group vs. 8.9 weeks in the oral GC group, log-rank $p = 0.287$).

IPWRA analysis

The IPWRA estimator achieved adequate covariate balance after weighting, as shown by standardized differences similar to zero and variance ratio similar to one across all variables (Supplementary Appendix Table 1). The overidentification test did not indicate model misspecification ($p = 0.638$), and the overlap assessment confirmed sufficient common support in the propensity-score distributions (Supplementary Appendix Fig. 2).

The average treatment effect showed that patients treated with intravenous MP had a shorter time to remission compared with those receiving oral steroids (ATE: -14.2 weeks; 95% CI: -20.5 to -7.8; $p < 0.001$) with a potential mean outcome over the oral GC group of 25.1 weeks (95%CI 19.3; 30.9).

Weibull regression models

In the unadjusted Weibull model, MP was associated with a HR of 1.18 (95% CI: 0.88–1.57) for time to remission (Fig. 3). After adjustment by baseline covariates included in the IPWRA model, the association yielded an adjusted HR of 2.44 (95% CI: 1.66–3.59).

Overall, the results from the IPWRA estimator and Weibull models analyses were consistent, indicating that intravenous pulses were associated with a faster time to remission.

Secondary outcomes

In addition to the aforementioned differences regarding time to remission, both the median cumulative prednisone dose at remission (733 mg vs. 1,902 mg) and the median average daily prednisone dose until remission (13.6 mg vs. 30 mg) were lower in patients who received MP ($p < 0.001$ for both comparisons) (Fig. 2).

Regarding secondary outcomes 3 months after treatment initiation, 133 patients (64.6%) were in remission and 152 (73.8%) were in clinical remission, with similar proportions in both groups ($p > 0.05$). Overall, 192 patients (99%) remained on steroid treatment, but MP-treated patients were receiving lower daily doses at 3 months (7.5 mg vs. 15 mg, $p < 0.001$), had a lower cumulative prednisone dose at 3 months (675 mg vs. 1,110 mg,

Table 2 Induction treatment, primary and secondary outcomes in patients with giant cell arteritis according to treatment group

	General (*n* = 206)	MP (*n* = 116)	Oral GC (*n* = 90)	*p*-value
Time to treatment initiation (days),(median, p25-p75)	26.5 (8–66)	23 (8–63)	30.5 (7.3–66)	0.925
Initial prednisone dose (mg) (median, p25-p75)	30 (20–60)	30 (20–30)	50 (30–60)	< 0.001
Methotrexate (n, %)	62 (30.1)	49 (42.2)	13 (14.4)	< 0.001
Weeks (median, p25-p75)	8.9 (41-18.9)	6.9 (3.5–16.6)	30.8 (5.3–79.1)	0.066
Tocilizumab (n, %)	26 (12.6)	20 (17.4)	6 (6.7)	0.022
Weeks (median, p25-p75)	5.6 (3.5–12.2)	4.4 (2.8–11.6)	9.3 (5.5–40.3)	0.317
Acetyl-salicylic acid (n, %)	82 (39.8)	50 (43.1)	32 (35.6)	0.535
Primary outcomes				
Time to remission (weeks) (median, 95% CI)	8.6 (6.4–10.1)	7.6 (5.6–10.9)	8.9 (6-10.7)	0.287
Remission-cumulative prednisone* dose (mg) (median, p25-p75)	1,183 (495-2,134)	733 (354-1,473)	1,902 (903-3,398)	< 0.001
Remission-average daily prednisone* dose (mg) (median, p25-p75)	18.6 (11.3–30.7)	13.6 (9.3–20.8)	30 (15–48)	< 0.001
Secondary outcomes 3 months after treatment initiation				
Remission (n, %)	133 (64.6)	78 (67.2)	55 (61.1)	0.362
Clinical remission (n, %)	152 (73.8)	89 (76.7)	63 (70)	0.276
Steroid (n, %)	192 (99)	107 (100)	85 (97.7)	0.115
Prednisone dose at 3 months* (mg) (median, p25-p75)	10 (5–20)	7.5 (5–10)	15 (10–30)	< 0.001
Cumulative prednisone dose over the first 3 months* (mg) (median, p25-p75)	900 (410-1,519)	675 (350-1,274)	1,110 (618-2,650)	0.006
Average daily prednisone dose* (mg) (median, p25-p75)	10 (4.6–16.9)	7.5 (3.9–14.2)	12.3 (6.9–29.4)	0.006
GC- related adverse effects (n, %)	60 (29.1)	30 (25.9)	30 (33.3)	0.240
Hypertension	16 (7.8)	8 (6.9)	8 (3.9)	0.596
Diabetes mellitus	20 (9.7)	5 (4.3)	15 (16.7)	0.003
Dyslipidemia	10 (4.9)	5 (4.3)	5 (5.6)	0.680
Osteoporosis	9 (4.4)	2 (1.7)	7 (7.8)	0.035
Others	24 (11.7)	16 (13.8)	8 (8.9)	0.277
Infectious complications (n, %)	15 (7.6)	9 (8.2)	6 (6.9)	0.736
Treatment-related complications (n, %)	13 (6.6)	8 (7.3)	5 (5.7)	0.641

MP Methylprednisolone pulses, *GC* Glucocorticoid, *SD* Standard deviation

* Methylprednisolone dose was not included in cumulative prednisone calculations, as pulse therapy predominantly activates non-genomic pathways and represents a pharmacodynamically distinct exposure

$p = 0.006$) and lower average daily prednisone over the first 3 months (7.5 mg vs. 12.3 mg, $p = 0.006$) (Fig. 4). Although no differences were identified in the composite of GC-related adverse effects (25.9% vs. 33.3%, $p = 0.240$), these lower GC doses were associated with lower rates of worsening or new-onset of DM (4.3% vs. 16.7%, $p = 0.003$) and osteoporosis (1.7% vs. 7.8%, $p = 0.035$) (Fig. 5). The incidence of infectious complications (7.8% vs. 6.7%) and treatment-related complications (6.9% vs. 5.6%) was similar between the two groups.

Discussion

Our multicentre retrospective inception cohort study based on real-world, newly diagnosed patients with GCA provides evidence supporting both the effectiveness and safety of MP as induction treatment. Considering the intrinsic severity of the disease, as well as the elevated risk of complications from ischemic occlusion and high-dose GC exposure in patients with GCA, this therapy may be considered a first-line option for all patients, even in the absence of major ischemic complications [3, 9, 31].

Classically, treatment of the disease has been based on long-term, high-dose oral GC regimens [7–9]. However, given the suboptimal response to these therapeutic schemes and the higher rate of GC-related complications, the impact of MP on remission has been investigated in the literature for almost 30 years [23, 24, 26, 34–36]. Nevertheless, results have been conflicting, and to date, the benefit and safety of MP pulses have not yet been robustly confirmed.

On the one hand, in the classical study by Chevalet *et al.*, which included 164 patients, MP pulses did not result in lower cumulative GC doses or fewer GC-related adverse effects after one year of treatment, nor did

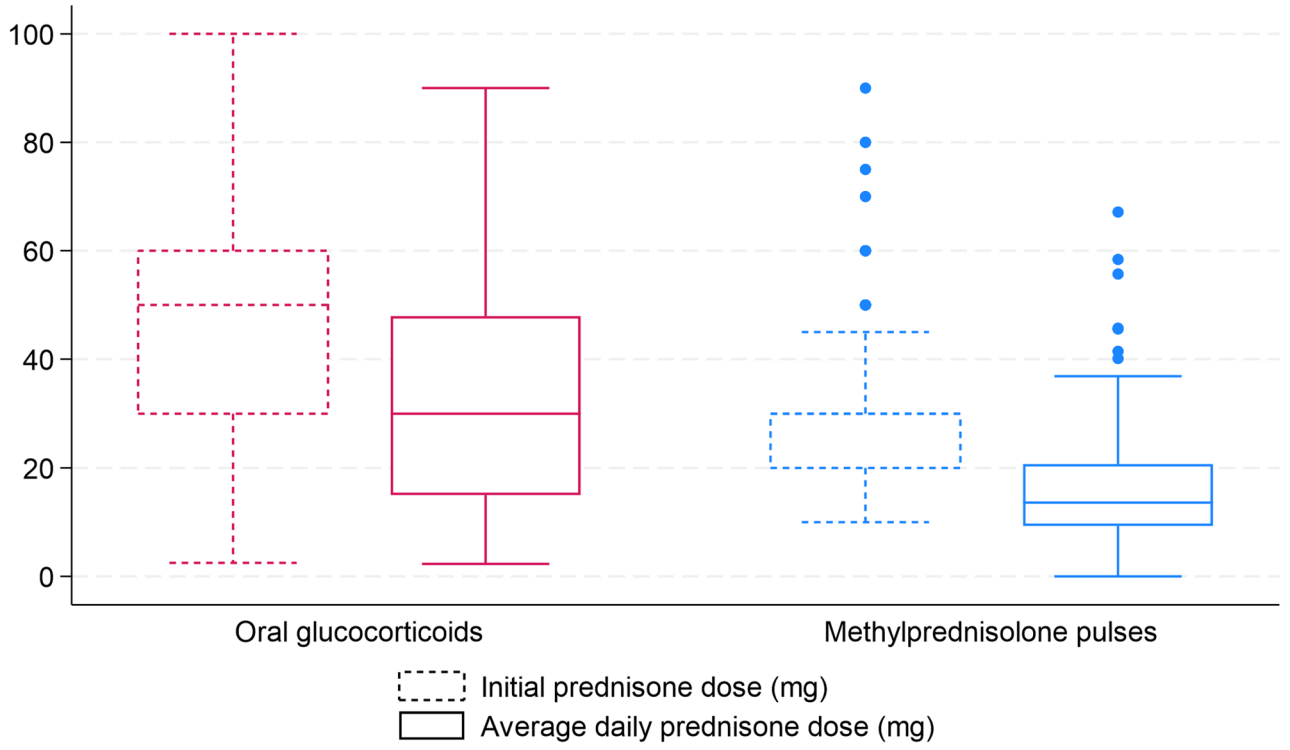

Fig. 2 Initial oral prednisone induction dose and average daily prednisone dose until remission according to treatment group. Boxplots showing the distribution of initial oral prednisone dose and average daily prednisone dose until remission according to induction strategy in patients treated with intravenous methylprednisolone pulses (MP group) and those treated with oral glucocorticoids alone (oral GC group). Boxes represent the median and interquartile range, and whiskers indicate the full range. Individual points represent outliers

they shorten the time to CRP normalization [26]. More recently, the BOB-ACG study found that MP pulses were associated with more GC-related complications during the first month and did not prevent bilateral ophthalmologic damage once unilateral visual ischemia had occurred, compared with the classical mg/kg per day GC regimen [23]. Finally, the largest study to our knowledge evaluating MP in GCA again used visual acuity as the primary outcome and included more than 90% of patients with visual and ischemic manifestations in the MP arm [34]. After adjustment, it failed to demonstrate an improved visual prognosis compared with oral GC alone.

By contrast, other studies have shown promising results in favor of MP pulses. Although it included only 27 patients with biopsy-proven GCA, the study by Mazlumzadeh *et al.* reported that MP pulses were associated with lower cumulative prednisone doses and a higher rate of sustained remission after GC withdrawal [35]. Similarly, the Cruces group demonstrated that MP pulses halved the time to clinical and biological remission while achieving ≤ 7.5 mg of daily prednisone [36]. Interestingly, this study also confirmed that MP pulses led to significantly lower cumulative prednisone doses at 6 months and fewer adverse effects. Finally, a recent study from our Spanish colleagues showed that a combined regimen of MP pulses plus early MTX during induction was equally effective in inducing remission and preventing relapses [24]. Although failing to achieve earlier remission compared with high-dose oral GC, this regimen again reduced cumulative prednisone doses and GC-related side effects.

Our work takes a step forward by demonstrating, in a multicentre study with a large population and a solid, well-balanced propensity score analysis, that MP might halve the time to remission in newly diagnosed GCA patients. This faster disease control is accompanied by a substantial reduction in initial prednisone doses, cumulative prednisone exposure and lower daily doses at remission and at 3 months, translating into fewer early glucocorticoid-related complications such as diabetes and osteoporosis. Thus, we believe that our work, on the one hand, evaluates a robust and validated outcome such as remission—according to the 2018 EULAR recommendations—as well as cumulative prednisone doses up to remission, whereas previous studies assessed outcomes related to visual prognosis or long-term glucocorticoid sparing alone [8, 23, 34]. In addition, our analysis—based on a heterogeneous yet well-balanced population—integrates key clinical variables, including clinical phenotype, disease severity and ischemic manifestations, as well as exposure to immunosuppressants (MTX and TCZ)

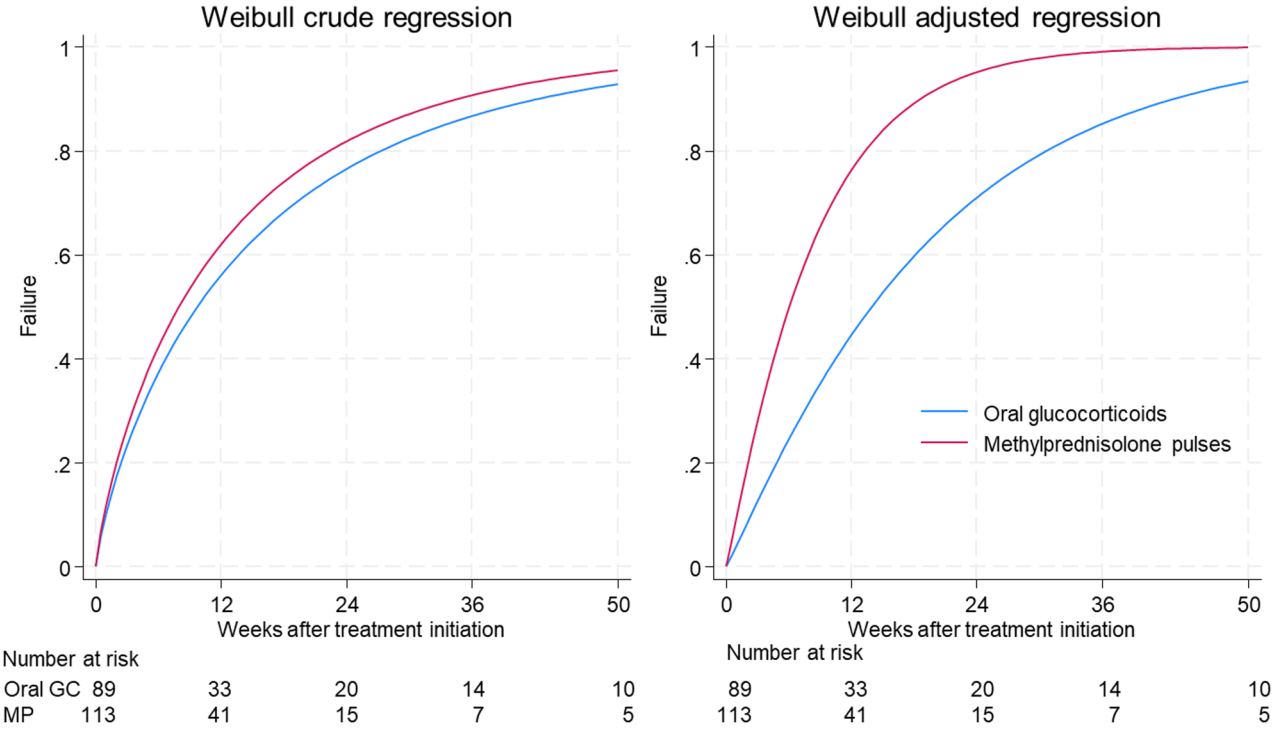

Fig. 3 Effect of methylprednisolone pulses on time to remission in unadjusted and adjusted models. Crude and adjusted Weibull failure curves comparing time to remission between patients treated with oral glucocorticoids and those receiving methylprednisolone pulses. The left panel shows unadjusted (crude) Weibull regression estimates, and the right panel shows adjusted estimates controlling for relevant clinical covariates. Numbers at risk at selected time points are displayed below each plot

during induction. In this way, we incorporate adjustment variables that have traditionally made it difficult to assess the role of MP pulses, such as their markedly higher use in ischemic patients in the previous studies, or the unequivocal use of MTX together with MP pulses in the work by Soto-Peleteiro *et al.* [23, 24, 34, 36]. In the same vein, the MP doses and duration (250 mg for 3 days) used in our study were fairly uniform, showing much less variability compared with other series. Finally, our study, in line with previous reports, confirms that MP use in patients with GCA is not only effective but also safe in the mid-term, as it is not associated with higher rates of related adverse effects or significant infections: if anything, the opposite [9, 24, 31, 35, 36].

The strategy of using MP in systemic autoimmune diseases is neither new nor unfamiliar. In fact, their use in systemic lupus erythematosus is clearly standardized and recommended in clinical practice guidelines [37]. Studies such as those from the Cruces–Bordeaux Inception Cohort, and later the AURORA trials, demonstrate that their use should be firmly established [18, 19, 38, 39]. Likewise, the PEXIVAS trial included MP pulses in all patients with ANCA-associated vasculitis, allowing for a significant reduction in the classical mg/kg dosing used in the treatment of the disease [40]. Despite all of the above—and probably due to the lack of solid studies confirming their efficacy and safety—current clinical practice guidelines for GCA do not support their widespread use [8, 15, 16]. Our work highlights that MP may represent and effective induction strategy in patients with GCA, as they significantly shorten the time to remission and allow for steroid sparing. Accordingly, they provide not only a favorable safety profile but also a reduction in certain steroid-related adverse effects. In this regard, the non-genomic effects of MP provide a clear benefit in a disease as severe and potentially complicated as GCA, and in a patient profile particularly vulnerable to the metabolic and infectious complications resulting from high and prolonged GC exposure [9, 17, 25, 31]. Finally, it is worth noting that our cohort, together with that of Soto-Peleteiro *et al.*, shows the highest remission rates reported, in contrast to classical series and to other studies that have even propose the use of ultrashort GC regimens in GCA [10, 12, 13, 24]. Therefore, MP, combined with a rapid prednisone taper and the early introduction of immunosuppressants, are likely to represent the most effective and safest treatment strategy for the disease.

Our study has several limitations. First, it is a retrospective, multicenter registry, with the inherent limitations and potential biases associated with this type of design. In addition, the study population is heterogeneous from clinical, diagnostic, and therapeutic

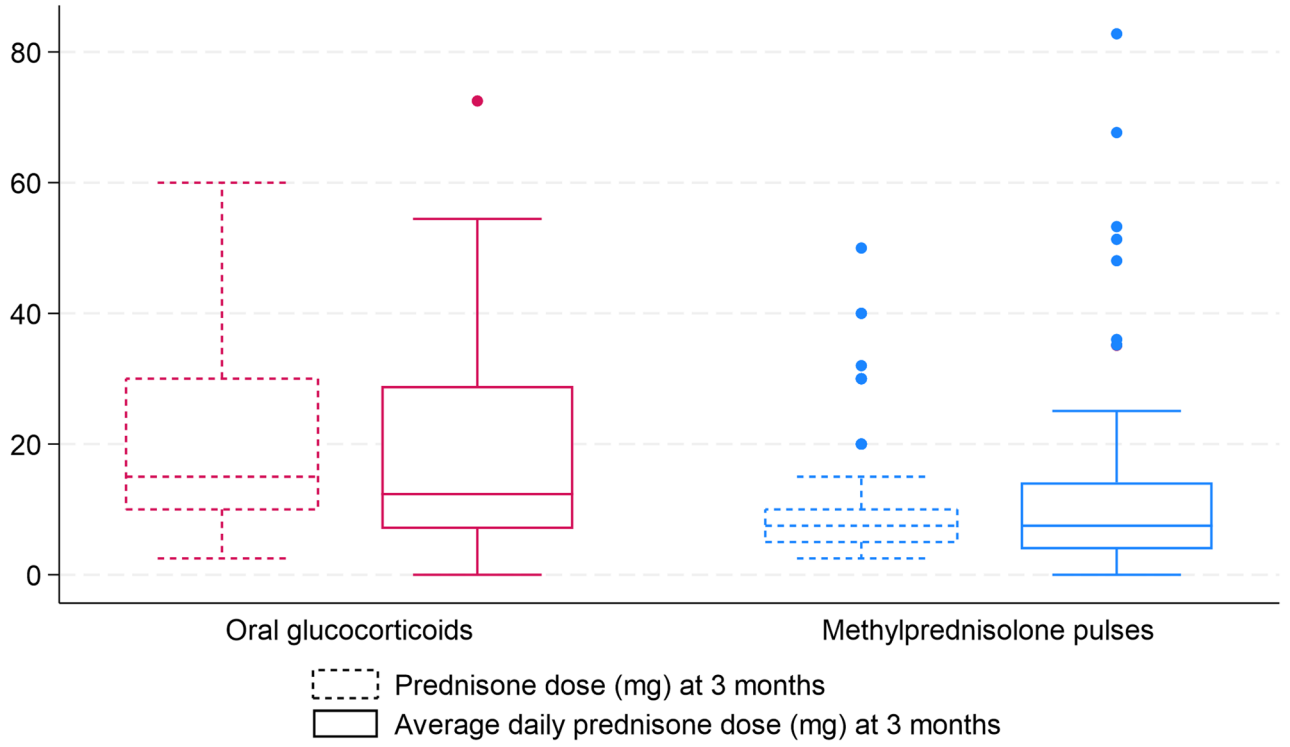

Fig. 4 Prednisone dose at 3 months and average daily prednisone dose over the first 3 months according to treatment group. Boxplots showing the distribution of oral prednisone dose at 3 months and average daily prednisone dose over the first 3 months according to induction strategy in patients treated with intravenous methylprednisolone pulses (MP group) and those treated with oral glucocorticoids alone (oral GC group). Boxes represent the median and interquartile range, and whiskers indicate the full range. Individual points represent outliers

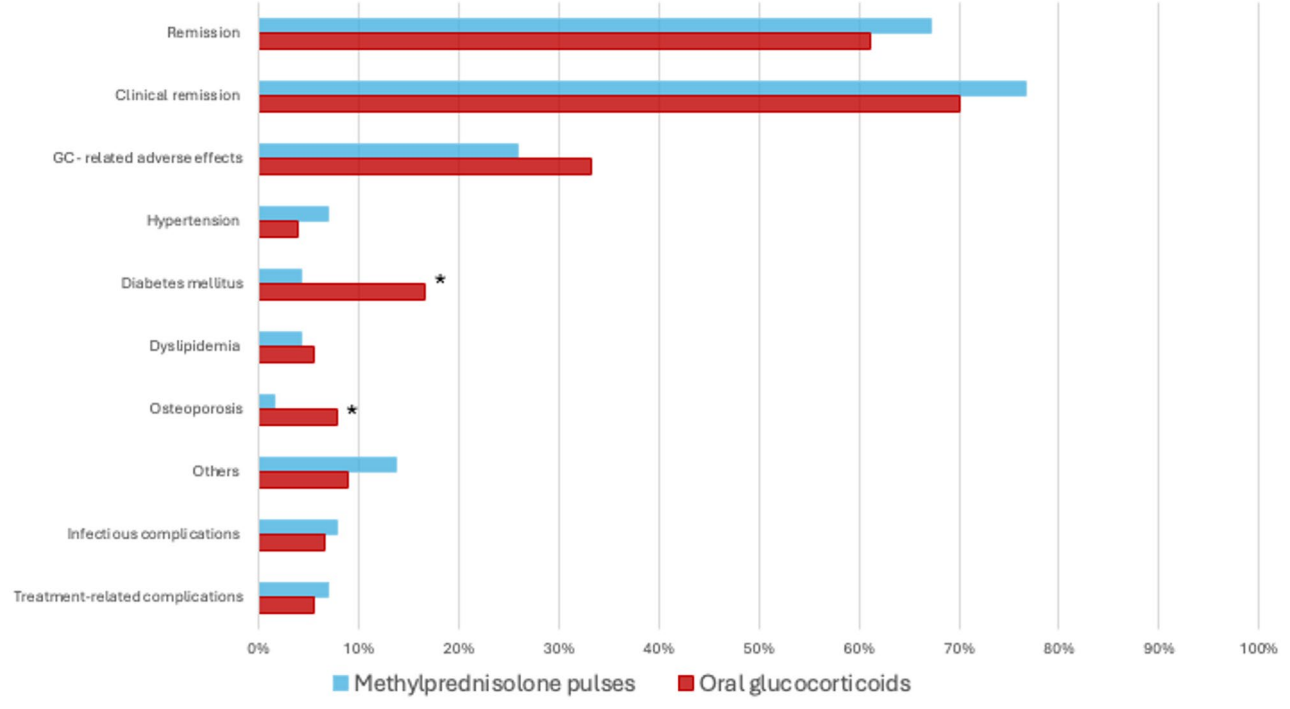

Fig. 5 Secondary outcomes at 3 months according to treatment group. Comparison of secondary outcomes at 3 months between patients treated with intravenous methylprednisolone pulses and those treated with oral glucocorticoids alone. The figure shows clinical remission and overall remission, glucocorticoid-related adverse effects (hypertension, diabetes mellitus, dyslipidemia, osteoporosis, and other events), as well as infectious and treatment-related complications. *An asterisk* (*) indicates a statistically significant difference between groups ($p < 0.05$)

perspectives, with substantial variability in treatment strategies. Consequently, there is considerable dispersion in prednisone induction doses, tapering regimens, and exposure to MTX or TCZ, among other factors. However, we used outcomes and variables with robust definitions, together with a solid, well-balanced propensity score analysis thoroughly evaluated according to a DAG framework, which we believe mitigates—or even eliminates—many of these limitations. Moreover, our data reflect the heterogeneity and real-world nature of routine clinical practice. The main limitation, however, is the relatively short follow-up period, given that our analysis was restricted to the induction phase. Although our primary outcomes focused on time to remission and cumulative prednisone doses up to remission, we did not evaluate the long-term efficacy and safety of MP pulses, including during the tapering or discontinuation phases. Our registry is actively incorporating follow-up data at 12, 24, and 36 months, as well as relapses and treatment withdrawals or changes. Nevertheless, we considered it appropriate to perform an initial analysis of the impact of MP during induction for two reasons: first, we believe these benefits should be communicated early; and second, a long-term assessment of efficacy and safety requires a larger sample size, given the complexity and interdependence of the variables influencing these outcomes. In a second phase, therefore, we will evaluate not only the role of MP pulses but also the impact of MTX and TCZ on remission, recurrences, cumulative steroid exposure, and treatment-related adverse events. In any case, we believe that—consistent with observations from other studies—MP pulses are associated with sustained remission and lower long-term GC requirements, in line with the benefits observed during the induction phase in our analysis [18–20, 24, 35, 38].

In conclusion, our multicenter real-world study provides evidence that MP pulses offer a potential meaningful therapeutic advantage in newly diagnosed GCA. By significantly shortening the time to remission, reducing cumulative prednisone exposure, and maintaining a favorable safety profile, MP pulses could address critical unmet needs in a disease characterized by high morbidity and substantial vulnerability to GC-related complications. Taken together, our findings support reconsideration of the role of MP beyond selected high-risk patients and warrant prospective studies to define the optimal induction strategy in GCA.

Abbreviations

ACR	American College of Rheumatology
AION	Anterior Ischemic Optic Neuropathy
ATE	Average Treatment Effect
CAM	Comunidad Autónoma de Madrid
CRP	C Reactive Protein
DAG	Directed Acyclic Graph
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
GC	Glucocorticoid
GCA	Giant Cell Arteritis
IPWRA	Inverse Probability Weighted Regression Adjustment
MP	Methylprednisolone
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
PET-CT	Positron Emission Tomography–Computed Tomography
TCZ	Tocilizumab

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

RFG: Conceptualization, Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing. AR: Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft. FTR: Data curation, Methodology, Validation, Visualization, Writing – review & editing. AGG, CAG, IPF, EGG, BM, EMR, TRS, MLG, DLL, RAH, DGG, LCT, SNJ, JMBF and IMC: Data curation, Methodology, Validation, Visualization, Writing – review & editing; VB: Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft. VMT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

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Data availability

De-identified participant data from this multicentre observational registry will be available to qualified researchers upon reasonable request to the corresponding author. Access will require a methodologically sound proposal and a data-sharing agreement. Data will be shared beginning 6 months after publication and for up to 5 years. The study protocol and data dictionary will also be available on request. Data sharing will comply with all applicable ethical approvals and data protection regulations.

Declarations

Ethics approval and consent to participate

The study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Puerta de Hierro University Hospital (PI 16/24), as well as by the local Institutional Review Boards of the participating centers. In accordance with Spanish law and the exemption granted by the Ethics Committee, informed consent was not required for this study.

Consent for publication

Not applicable.

Competing interests

AGG declares having received honoraria for lectures from Roche. The remaining authors declare they have no conflict of interest or personal relationship that could bias the findings reported in this paper.

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