

SUSTAINED DRUG-FREE REMISSION IN GIANT CELL ARTERITIS: RESULTS FROM THE SPANISH ARTESER REGISTRY

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BACKGROUND

The duration of glucocorticoid (GC) therapy in giant cell arteritis (GCA) varies significantly. It is commonly assumed that GC treatment in GCA lasts about 2 to 3 years, with only a minority of patients requiring long-term treatment with low doses of GC. However, the average duration of GC treatment in real-life practice remains unclear. Identifying predictors of long-term remission without GC treatment could help optimize therapeutic strategies, reducing exposure to GC and thus minimizing GC-related side effects.

OBJECTIVE

To evaluate the frequency and timing of sustained drug-free remission (SDFR) in a Spanish cohort of patients with giant cell arteritis (GCA) and to identify potential predictive factors for this outcome.

METHODS

We conducted a retrospective review of all patients included in the large Spanish multicenter registry for GCA (ARTESER) from June 1st, 2013, to March 29th, 2019. SDFR was defined as the absence of typical signs, symptoms, or other features of active GCA for at least 12 months after discontinuing treatment. A generalized estimating equation (GEE) logistic regression model was used to identify risk factors for SDFR.

RESULTS

3.1. Study population.

During the study period, 1675 patients were diagnosed with GCA. Of these, 1284 patients were followed-up for at least one year and included in the study. Table 1 summarises the main clinical features, laboratory data, and treatments received by the patients. Of the total, 316 (24.6%) patients were treated with intravenous (IV) methylprednisolone (MP) boluses (at doses of 125 mg to 1 g per day for three days) due to severe ischemic complications (visual manifestations or stroke), and 535 (41.6%) patients received TCZ and/or immunosuppressants (mainly MTX) plus concomitant oral GC.

3.2. Sustained drug-free remission

The median duration of follow-up was 24 months (IQR 25<sup>th</sup>-75<sup>th</sup>: 12 – 36). The pooled proportions of patients achieving SDFR at 2, 3, and 4 years were 6.3% (55/872), 20.5% (109/532), and 25%, respectively. The initial dose of prednisone was comparable between patients who did and did not achieve long-term remission (50.5±16.2 mg/day vs. 48.8±16.7 mg/day; p=0.216). Notably, patients who reached SDFR were able to decrease their prednisone dosage to 10 mg/day and 5 mg/day more rapidly than those who did not achieve remission (p=0.131 and p<0.001, respectively). The cumulative doses of prednisone at 1 year (637.4±964.5 vs. 774±1209.6 gr; p<0.001) were significantly lower in patients who attained SDFR (637.4±964.5 g vs. 774±1209.6 g; p<0.001). Disease flare-ups were less common among patients with SDFR compared to those without (21% vs. 27%; p=0.114).

3.3. Predictors of sustained drug-free remission

Table 2 compares demographic, clinical and laboratory findings at diagnosis, treatments received, and relapses between patients with and without SDFR. Patients achieving SDFR were notably older (p=0.002) and had a higher frequency of fever > 38° C (p=0.036). They presented with lower hemoglobin levels (p=0.04) and had a reduced incidence of coexisting PMR (p=0.036) at the time of diagnosis.

Regarding treatment approaches, patients failing to achieve SDFR more frequently required initial IV MP boluses (p=0.002). There were no significant differences between groups in the usage or necessity for TCZ or immunosuppressants. The rate of relapses was numerically higher among those who did not achieve SDFR. Multivariate analysis (Table 3) revealed that only the presence of relapses (OR: 0.485, 95% CI 0.351 to 0.670; p<0.001) and the necessity for IV methylprednisolone (MP) boluses at diagnosis (OR: 0.560, 95% CI 0.389 to 0.806; p=0.002) were significantly associated with a decreased likelihood of achieving SDFR. Neither the coexistence of PMR nor the severity of the inflammatory response at diagnosis reached statistical significance

3.4.- Recurrences.

The median follow-up time for patients who achieved SDFR was 48 months (IQR 25th-75th: 36 – 48 months). Only 5 patients experienced a recurrence, occurring at a median of 19 months post-SDFR, (IQR 14 – 35 months).

Table 1. Demographic and clinical characteristics of the 1284 patients followed for 2.1 year in the ARTESER registry

Women / Men (Ratio)	905 / 379 (2.38)
Ethnic groups	Caucasian 1275 (99.3%) / African 9 (0.7%)
Age at diagnosis	76.5 ± 8
Positive TAB	621 (62.9%)
Clinical features at diagnosis	
Headache	1046 (81.8%)
Abnormal temporal artery	640 (53.7%)
Jaw claudication	473 (38.6%)
Visual manifestations	448 (35.7%)
Cerebrovascular accidents	71 (5.5%)
Limb claudication	121 (10.5%)
Arm claudication	407 (39.4%)
Legs claudication	119 (10.3%)
Polymyalgia rheumatica	537 (43.7%)
Malaise	666 (57.2%)
Anorexia	451 (39.4%)
Weight loss	407 (36%)
Fever	301 (26%)
Laboratory data at diagnosis	
ESR (mm/h)	76.5 ± 33.4
Hb (g/dl)	11.8 ± 1.61
Platelets (x10 <sup>9</sup> cells/mm3)	329 ± 189
Raised ALT/AST*	148 (11.4%)
Raised alkaline phosphatase*	147 (11.8%)
Treatment	
Intravenous methylprednisolone boluses (for 3 days) *	316 (24.6%)
125 mg	37 (2.9%)
250 mg	47 (3.6%)
500 mg	92 (7.2%)
1 g	160 (12.5%)
Total dose of prednisone at last follow-up, mg	751.5 ± 1173.8
GC + Tocilizumab	136 (10.6%)
GC + immunosuppressant*	487 (38.3%)
Methotrexate	467 (36.4%)
Leflunomide	18 (1.4%)
Azathioprine	27 (2.1%)
Others (CYC, MMF)	14 (1.1%)
Aspirin	456 (35.5%)

Results are presented as mean ± standard deviation (SD) or number of cases with frequencies.

\*Increased alkaline phosphatase and ALT/AST were considered if values at diagnosis were 1.5 times normal.

\*Some patients received a bolus more than once.

\*Some patients received more than one immunosuppressant.

ABBREVIATIONS

CYC: cyclophosphamide; ESR: erythrocyte sedimentation rate; GC: glucocorticoids; Hb: hemoglobin; MMF: mycophenolate mofetil; TAB: temporal artery biopsy.

Table 2. Comparative study between patients with and without sustained drug-free remission

	With SDFR N= 197	Without SDFR N= 1087	P
Women / Men (Ratio)	136 (69.04%) / 61 (30.96%)	769 (70.75%) / 318 (29.25%)	0.628
Ethnic groups	Caucasian 186 (99.49%) / African 1 (0.51%)	Caucasian 1079 (99.26%) / African 8 (0.74%)	0.724
Age at diagnosis	76.8 ± 8.1	74.9 ± 7.5	0.002
Positive TAB	99 (63.06%)	522 (62.89%)	0.969
Clinical features at diagnosis			
Headache	162 (82.65%)	884 (81.70%)	0.752
Abnormal temporal artery	106 (56.08%)	534 (53.29%)	0.480
Jaw claudication	72 (37.89%)	401 (38.78%)	0.818
Visual manifestations	58 (29.90%)	390 (36.79%)	0.065
Cerebrovascular accidents	16 (8.12%)	55 (5.06%)	0.084
Limb claudication			
Arm claudication	18 (10.23%)	103 (10.63%)	0.875
Legs claudication	16 (9.04%)	103 (10.62%)	0.526
Polymyalgia rheumatica	69 (36.70%)	468 (44.96%)	0.036
Malaise	96 (53.93%)	570 (57.75%)	0.343
Anorexia	79 (44.38%)	372 (38.51%)	0.141
Weight loss	84 (36.99%)	342 (35.84%)	0.771
Fever	37 (23.39%)	244 (24.87%)	0.036
Laboratory data at diagnosis			
ESR (mm/h)	77.1 ± 33.9	73.8 ± 30.5	0.206
Hb (g/dl)	11.8 ± 1.6	12.1 ± 1.8	0.041
Platelets (x10 <sup>9</sup> cells/mm3)	329.0 ± 194.2	329.2 ± 158.8	0.986
Raised ALT/AST*	28 (14.21%)	115 (10.86%)	0.172
Raised alkaline phosphatase*	24 (19.20%)	123 (17.60%)	0.666
Treatment			
Intravenous methylprednisolone boluses (for 3 days) *	31 (15.74%)	285 (26.22%)	
125 mg	1 (0.51%)	36 (3.31%)	
250 mg	3 (1.52%)	44 (4.05%)	
500 mg	13 (6.60%)	79 (7.27%)	
1 g	15 (7.61%)	145 (13.34%)	0.002
Initial prednisone dose, mean (SD) mg/day	50.5 ± 16.2	48.8 ± 16.7	0.216
Prednisone therapy duration, median (IQR) mo	22.0 ± 11.9	24.3 ± 15.2	0.048
Cumulative prednisone dose at1 year, mean (SD) mg	637.4 ± 96.5	774.0 ± 1209.6	<0.001
Total dose of prednisone at last follow-up, mean (SD) g	8.78 ± 17.59	10.23 ± 13.50	0.190
GC + Tocilizumab	22 (11.22%)	114 (10.99%)	0.793
GC + immunosuppressant*	81 (41.33%)	406 (37.73%)	0.341
Methotrexate	77 (39.29%)	390 (36.25%)	0.417
Leflunomide	2 (1.02%)	16 (1.49%)	0.611
Azathioprine	3 (1.53%)	24 (2.23%)	0.532
Others (CYC, MMF)	3 (1.53%)	11 (1.02%)	0.531
Aspirin	76 (38.97%)	380 (35.28%)	0.323
Relapses	42 (21.32%)	290 (26.68%)	0.114
Duration of follow-up, mo, median (IQR)	48 (36 - 48)	24 (12 - 36)	<0.001

Table 3. Predictive variables of sustained drug-free remission

	Odds ratio	95% Confidence interval	P
Age at diagnosis	0.985	0.970 - 1.001	0.059
Sex (Female)	0.918	0.701 - 1.202	0.534
Presence of cardiovascular risk factors* at diagnosis	0.909	0.610 - 1.073	0.141
Cranial manifestations at diagnosis	1.028	0.934 - 1.131	0.575
Severe ischemic complications** at diagnosis	0.970	0.696 - 1.351	0.855
Extracranial involvement at diagnosis	0.817	0.505 - 1.324	0.412
Limb claudication at diagnosis	1.829	0.814 - 4.109	0.144
Large vessel at diagnosis	0.963	0.690 - 1.343	0.823
Polymyalgia rheumatica	0.839	0.457 - 1.543	0.573
Malaise/anorexia/weight loss at diagnosis			
Fever at diagnosis	1.238	0.875 - 1.752	0.229
ESR at diagnosis	0.996	0.992 - 1.000	0.084
Anemia at diagnosis	0.498	0.123 - 2.021	0.329
Strong initial systemic inflammatory response*** at diagnosis	1.184	0.820 - 1.710	0.368
Treatment with methotrexate	0.924	0.702 - 1.215	0.570
Treatment with tocilizumab	1.394	0.923 - 2.104	0.114
Treatment with intravenous methylprednisolone boluses	0.560	0.389 - 0.806	0.002
Relapses	0.485	0.351 - 0.670	<0.001

\* Including arterial hypertension, dyslipidemia and diabetes mellitus.

\*\* Patients were considered to have severe ischemic complications if they suffered visual manifestations (i.e., transient visual loss including amaurosis fugax, permanent visual loss, or diplopia), cerebrovascular accidents (i.e., stroke and/or transient ischemic attacks), jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations (i.e., limb claudication) of recent onset.

\*\*\* Patients were considered to have a strong initial systemic inflammatory response if they had fever, weight loss, ESR ≥ 85 mm/h, and haemoglobin < 11 g/L.

ESR = erythrocyte sedimentation rate

CONCLUSION

Within 2-3 years of diagnosis, only one-quarter of patients with GCA successfully reach SDFR. Once SDFR is achieved, the likelihood of experiencing recurrences is notably low. Relapses and the requirement for GC boluses or MTX appear to be predictors of long-term GC need.