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Sarilumab in the management of Graves orbitopathy with low clinical activity scores

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Sarilumab in the management of Graves Orbitopathy with low clinical activity scores

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Key Messages

What is known

- Graves Orbitopathy has a profound impact on the quality of life of affected patients. This impact is measured using validated questionnaires (GO-QOL).
- Anti-IL-6 inhibitors, such as Tocilizumab, have been shown to be safe and effective in the treatment of active Graves Orbitopathy (GO).

What is new

- Our results suggest that Sarilumab is effective and safe in the treatment of Graves Orbitopathy with low clinical activity scores. We observed a significant reduction in the Clinical Activity Score (CAS) and TSH-receptor-stimulating immunoglobulin (TSI) levels.
- Graves orbitopathy patients with mild activity are not routinely treated. In our study we demonstrated the impact in the quality of life of patients with CAS 1 to 3 before and after treatment, using GO-QOL,

suggesting that treatment should be offered to patients with low CAS GO when quality of life is impaired.

Abstract

We aim to investigate the efficacy and safety of Sarilumab 150 mg and 200 mg administered subcutaneously in the treatment of cases of patients with Graves Orbitopathy (GO) with low clinical activity scores and a reported impaired quality of life. We performed a retrospective, longitudinal study of patients diagnosed with GO and EUGOGO's clinical activity score (CAS) 1 to 3 out of 10 treated with Sarilumab at a single center, Centro Oftalmologico Moreiras. Inclusion between January 2019 and January 2024. Main primary outcomes included reduction in the CAS and Thyroid stimulating immunoglobulin (TSI) blood levels. The GO-QOL questionnaire was used to evaluate the quality-of-life impairment. Sixty-two patients (mean age 44.23 years, 80.6% female) met the inclusion criteria. The mean number of Sarilumab sessions was 3.42. After treatment we observed a significant reduction from an initial mean CAS of 2.22 to a final mean CAS of 0.05. TSI levels were significantly reduced after treatment, from an initial mean TSI of 38.70 U/L to a final mean of 10.53 U/L. The GO-QOL baseline mean total score was 64.72%, which significantly improved to 96.38% after treatment. No major adverse events were registered. Our findings suggest that Sarilumab is an effective and safe option for the treatment of low CAS GO.

Key words: Graves orbitopathy, Thyroid eye disease, sarilumab

Statements and Declarations

The authors have no relevant financial or non-financial interests to disclose.

Introduction

Graves' orbitopathy (GO) is the main extra-thyroidal manifestation of Graves' disease, with an estimated incidence of 0.54–0.9 cases/100 000/year in men and 2.67–3.3 cases/100 000/year in women.[1] GO incidence in Graves' disease is reported to be 50%, with the majority of cases presenting subclinically and only 3-5% manifesting severe forms of GO.[2] GO has a significant impact on patients' quality of life, even within mild forms of the disease. In 2021, the European Thyroid Association (ETA) and European Group on GO (EUGOGO) published an updated version of the treatment guidelines, focusing on medical management of GO. [1] The study group considered that most patients diagnosed with GO and a Clinical Activity Score (CAS) equal or under 2, will present spontaneous resolution of ophthalmological manifestations and therefore no targeted medical treatment was recommended for this subgroup of GO patients in the

mentioned guidelines, besides support measures. EUGOGO considers that mild cases should be managed with a watchful strategy and that only oral selenium supplementation should be considered in most cases. According to EUGOGO, low-dose immunomodulation may be reserved for a minority of patients with mild GO that report a profound impact on quality of life. However, our group defends that any sign of ocular activity reflects the inflammation (activity) of a systemic disease and therefore the medical treatment of these patients should be considered in order to achieve better control of the disease from a holistic perspective, especially when the quality of life is impaired.

GO physiopathology is not yet well established. There is evidence that thyrotropin receptor and insulin-like growth factor 1 receptor are expressed in the orbital fibroblasts of GO patients and act by stimulating adipogenesis and hyaluronic acid synthesis. Thyrotropin receptor antibodies (TRAbs) seem to play a central role in the pathogenesis of GO. Classical TRAb measurements were limited by the inability to discriminate between thyroid-stimulating and thyroid-blocking antibodies. The thyrotropin receptor-stimulating immunoglobulin (TSI) assay measures cyclic adenosine monophosphate production after Thyroid-stimulating antibodies bind to thyrotropin receptor, enabling a more specific result.[2]

In the active phase of GO, there is a predominant production of pro-inflammatory cytokines such as interleukin-6 (IL-6), which is increased in Graves' disease patients with active GO compared with those patients with inactive or absent GO. IL-6 might play a role in the pathogenesis of GO by stimulating thyrotropin receptor expression within the orbit, and therefore it has been considered a good target for treatment of active GO.[3, 4]

Sarilumab is a human monoclonal antibody with a selective action against IL-6 receptors and is available in two different injectable doses, 150 mg and 200 mg. It is approved by the US FDA and EMA for the treatment of rheumatoid arthritis since 2017. Tocilizumab, another human monoclonal antibody against IL-6, has been used as a treatment for severe glucocorticoid-resistant GO, in Santiago de Compostela, Spain, since 2010,[5] reflecting the efficacy of anti-IL-6 inhibitors in the treatment of GO. Comparing to tocilizumab in in vitro experiments, sarilumab was found to bind to IL-6Ra with a 15 to 22-fold higher affinity, suggesting it would be a suitable clinical option for the management of GO.[6]

In the past, our group reported the efficacy and safety of Tocilizumab in the treatment of active steroid-resistant GO.[7–10] We retrospectively evaluated 50 patients with steroid-resistant GO treated with Tocilizumab. An absolute CAS response (CAS = 0 or 1) was achieved in 74% of the included patients after the fourth dose of tocilizumab (at week 16), with a TSI response being achieved in 55% (23/42) of patients. We concluded that at least 4 months of Tocilizumab monthly therapy provides a significant benefit to patients with active moderate-to-severe steroid-resistant GO. More recently, a multicenter study also reported the efficacy and safety of Tocilizumab as a therapeutic option in refractory GO.[11]

In this study, we aim to investigate the efficacy and safety of Sarilumab 150 mg and 200 mg administered subcutaneously in the treatment of incipient cases of GO defined as CAS between 1 and 3 in a scale out of 10, as defined by EUGOGO Classification system, and with a reported impaired quality of life, assessed using GO-QOL questionnaires.[1]

Methods

Study design and patients

A retrospective, longitudinal study was conducted on a cohort of patients diagnosed with low CAS GO se treated with Sarilumab (Sanofi Laboratories, France) at a single center, Moreiras' Ophthalmology and Orbit Center (Santiago de Compostela, Spain). Medical records between January 2019 and January 2024 were reviewed and demographic, clinical and laboratory data collected. The study protocol was conducted in conformity with the Helsinki Declaration and was approved by the Ethics Committee of Moreiras' Ophthalmology and Orbit Center. All participants provided written informed consent prior to enrollment, and in case of minors, informed consent was obtained from a parent or legal guardian. The patients were informed regarding the different treatment options available and the off-label use of sarilumab and the treatment costs were supported by the patients. An informed consent was obtained to publish the image (figure 5) in an online open-access publication.

Inclusion criteria (Figure 1) included age over 12 years; CAS between 1 and 3 on a 10-point scale in the more severely affected eye (1 point for each topic, as described by the EUGOGO severity classification)[1, 12, 13]; patients with self-reported impaired quality of life related to GO. Exclusion criteria were the following: any treatment during the previous 6 months, including radioactive iodine, corticosteroid infusions, surgery, or other immunosuppression drug; diagnosis of dysthyroid optic neuropathy; blood disorders (anemia, neutropenia, thrombocytopenia); neoplastic disease in the previous 5 years, cardiovascular or pulmonary disease, uncontrolled diabetes mellitus, positive history of hepatitis B or C, HIV, pregnancy and lactation.

Systemic and complete ophthalmological evaluation were performed at baseline and during the follow-up visits (scheduled during each treatment session and after treatment). The baseline evaluation included a first visit followed by a second visit to complete the CAS 10-point scale, during which the first sarilumab treatment was initiated. All participants were examined by the same orbital ophthalmologist (JPM). Prior to initiating Sarilumab, all patients underwent a complete laboratory evaluation (including complete blood count, thyroid function and auto-immunity [triiodothyronine, thyroxine, thyrotropin and TSI), lipid status, liver function and serology to rule out active infectious diseases (including hepatitis B and C, VIH and Tuberculosis). Laboratory evaluation was repeated every 40 days during treatment (after every two doses of sarilumab, that were spaced 20 days each). TRAb, as a heterogeneous antibody, can be classified into stimulatory

thyrotropin receptor antibodies (TSAb), blocking thyrotropin receptor antibodies (TBAb), and neutralizing antibodies. Among them, TSAb, also known as TSI, is considered to be the one that is closely associated with GD-related hyperthyroidism, and some findings suggest that TSI is also associated with the severity of the disease and extra-thyroidal manifestations, such as thyroid ophthalmopathy[14], and was therefore the analysis selected to evaluate our sample. Furthermore, participants were evaluated with orbital ultrasound (performed by JPM) and orbital magnetic resonance imaging (MRI) or computed tomography (CT), which were used as a supporting factor in the decision to treat patients with low CAS.

Sarilumab was administered in a subcutaneous injection of 150 mg or 200 mg, adjusted to patient's weight (patients with weight under 70 Kg were treated with 150 mg and patients with weight equal or above 70 Kg were treated with 200 mg). The injections were self performed in the abdomen every 20 days. No other medication for the treatment of orbitopathy was given alongside Sarilumab.

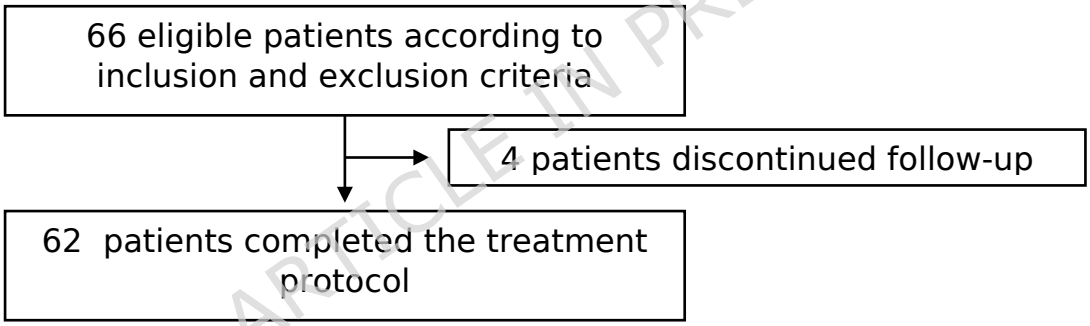

Figure 1. Patients enrollment in the study

Outcomes and assessments

Main primary outcomes included reduction in the CAS and TSI levels throughout the treatment period. The complete response to treatment was defined as a CAS 0 and TSI < 10U/l.

Secondary outcomes included reduction of proptosis, reduction of eyelid retraction and reduction of eyelid hyperemia and edema. An orbitopathy-specific quality of life (GO-QOL) questionnaire, adapted to Spanish, was completed by the included participants at baseline and after treatment, and the results were used as a secondary outcome.[15, 16] This questionnaire includes 16 questions and measures the "visual functioning" in the first 8 items, and the psychosocial effects of the altered appearance in the remaining 8 items. The visual functioning is evaluated on a three-point scale (not limited, a little limited or strongly limited) and the appearance is evaluated on another three-point scale (strongly, a little, not at all). The

scoring includes the summed points and can be transformed into a scale from 0 to 100, where 0 represents the worst Quality of Life and 100 the best. GO-QOL has been described as the best validated questionnaire for the assessment of quality of life in patients with endocrine orbitopathy. [16] Adverse events reported during the treatment period were included as a secondary outcome. Recurrence was defined as an increase of CAS of 2 points at any time from the date of disease stabilization until the end of the individual follow-up period and was used as a secondary outcome.

All the ophthalmological evaluations were performed by the same Orbital Ophthalmologist (JPM) at baseline and during each follow-up visit. Proptosis was assessed using a Hertel's exophthalmometer and the value was registered in millimeters. Eyelid retraction was measured in millimeters. For the upper eyelid the normal position was considered 1 mm bellow the superior corneal limbus and retraction was measured above this line. For the lower eyelid the normal position was considered at the level of the inferior limbus and the retraction was measure below this level. Eyelid edema was evaluated in a scale from 0 (no edema) to 3 (severe edema).

Statistical Analysis

Quantitative variables are presented as mean and standard deviation for normally distributed data or as median with range for non-normally distributed data. When the assumption of normality in the model's hypothesis failed, nonparametric tests were used. The Wilcoxon matched-pairs signed-rank test was used for within-subject comparisons (e.g., CAS, TSI, exophthalmos, eyelid retraction, and GO-QOL scores). For between-group comparisons, the Mann–Whitney U test (nonparametric) or the independent samples t-test (parametric) was used, depending on data distribution. Qualitative variables are presented as absolute frequencies and percentages, and comparisons between groups were made using the chi-squared test or Fisher's exact test, as appropriate.All statistical tests were two-sided and performed at the level of significance of $\alpha = 0.05$. The analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA).

Results

Demographics and Clinical Characterization

A total of 62 patients with GO and CAS between 1 and 3 met the inclusion criteria. Complete baseline characteristics of the study population can be found on Table 1. Mean age was 44.23 years (sd 14.12, range 12 – 73 years), from which 50 (80.6%) were woman. Fifteen (24.2%) participants reported smoking. Nine (14.5%) patients had previous treatment with iodin radioactive 9 months previous to GO clinical manifestations and 5 participants (8.2%) had a previous orbital decompression 4 months before activation of GO. Two (3.2%) participants had diabetes mellitus. The mean follow-up time (between first treatment with Sarilumab and last post treatment appointment) was 27.7 months (sd 13.9 months).

Regarding clinical manifestations of GO at baseline, 10/62 (16.1 %) patients reported vertical diplopia at primary position, and 5/62 (8.1%) reported diplopia only in the extreme positions of gaze. Considering the CAS of the included participants at baseline, as described by EUGOGO, 7 presented with CAS 1, 34 with CAS 2 and 21 with CAS 3. Considering imaging exams, both ultrasound and MRI/CT revealed enlargement of at least one extra-ocular muscle in 41 participants (66.1%). Complete characterization of the study outcomes at baseline can be found on Table 2.

The mean number of Sarilumab sessions was 3.42 (sd 1.17, range 2 – 6). Each session included 2 injections of sarilumab spaced 20 days apart.

Table 1 – Characteristics of the study population at baseline

Variable	Baseline
Age – mean (sd), yr	44.23 (14.12)
Female sex - % (No of patients)	80.6 (50)
Smoker - % (No of patients)	24.2 (15)
Diabetes - % (No of patients)	3.2 (2)
Thyroid status % (No of patients)	
Hyperthyroidism	1.6 (1)
Subclinical hyperthyroidism	30.6 (19)
Euthyroidism	59.7 (37)
Hypothyroidism	1.6 (1)
Subclinical hypothyroidism	6.5 (4)
Previous treatment - % (No of patients)	
Steroids	33.3 (29)
Radioactive iodine	14.5 (9)
Orbital decompression	8.2 (5)

Legend: SD, standard deviation; No, number; yr, years.

Table 2 – Outcomes at baseline and after treatment

	Baseline	Post treatment	P value[3]
Hormones, mean (SD)			
FT4 - ng/dL	2.12 (3.07)	2.37 (3.93)	0.99
TSH - ng/dL	2.88 (3.29)	2.46 (2.21)	0.63
Antithyroid antibodies			
Thyroid stimulating immunoglobulin (TSI) – mean (SD) U/L	38.70 (36.84)	10.53 (7.49)	<0.001
Normal TSI[1] - % (No of patients)	17.7 (11)	62.9 (39)	
Clinical Activity Score[2]			
Mean points (SD)	2.23 (0.64)	0.05 (0.22)	<0.001
0 - % (No of patients)	-	95.2 (59)	
1- % (No of patients)	11.3 (7)	4.8 (3)	
2- % (No of patients)	54.8 (34)	-	
3- % (No of patients)	33.9 (21)	-	
GO Clinical signs			
Exophthalmos - mean (SD) mm			

OD	19.02 (1.73)	18.10 (1.39)	<0.001
OS	19.56 (2.22)	18.35 (1.69)	<0.001
Eyelid edema score, % (No of patients)			
0 1 2	20.6 (13) 66.7 (42) 11.1 (7)	96.8 (61) 1.6 (1)	
Eyelid retraction - mean (SD) mm			
Upper OD	-0.49 (1.62)	1.17 (0.86)	<0.001
Upper OS	-0.93 (1.68)	1.08 (1.00)	<0.001
Lower OD	-0.27 (0.77)	-0.11 (0.52)	0.018
Lower OS	-0.29 (0.84)	-0.15 (0.65)	0.021
Diplopia % (No of patients)			
Primary gaze (Gorman grade 3, constant diplopia)	16.1 (10)	9.7 (6)	
Extreme gaze (Gorman grade 1 and 2, intermittent and inconstant diplopia)	27.4 (17)	9.7 (6)	

Legend: FT4, thyroxine (normal range: 0.8–1.8 ng/dL); SD, standard deviation; TSH, Thyrotropin (normal range: 0.55–4.78 mU/L); yr, years. [1] Normal TSI value considered bellow 10; [2]The Clinical Activity Score is based on a scale of 10 items, each of which is scored as present or absent (1 or 0, respectively): spontaneous orbital pain, pain with extraocular movement, eyelid edema, eyelid erythema, conjunctival hyperemia, chemosis, inflammation of caruncle or plica; and an increase of ≥2 mm in proptosis, decrease in visual acuity of ≥1 Snellen lines, or a decrease in ocular motility in any direction during a period of 1–3 months. [3]Mean values are shown to facilitate interpretation, while p-values were calculated with the Wilcoxon test (which compares sample medians from both groups)

Reported quality of life evaluated with GO-QOL

The responses to the orbitopathy-specific quality of life (GO-QOL) questionnaire can be found in Table 3. The baseline mean total score was 64.72% (sd 14.44). The reported scores were lower in the topics related to appearance (lower scores reflect a higher impact in the quality of life). After treatment with sarilumab the mean total score was 96.38%. The difference before and after treatment was statistically significant (p value < 0.001 for both Visual Function Scores and Appearance Scores).

Table 3 – GO - QOL

	Baseline mean score (SD)	Post-treatment mean score (SD)	P Value[1]

Visual Function scores	88.59 (21.12)	96.74 (12.13)	<0.001
Appearance scores	40.85 (14.61)	96.31 (12.43)	<0.001
Conversion to a total out of 100	64.72 (14.44)	96.52 (12.25)	<0.001

Legend: SD standard deviation, [1] Wilcoxon non-parametric test for correlated variables

Primary outcomes

Comparing CAS at baseline and after treatment with Sarilumab, we observed a statistically significant reduction (p-value <0.001) from an initial mean CAS of 2.22 (sd 0.65) to a final mean CAS of 0.05 (sd 0.22). After treatment, 95.2% of the included participants achieved a CAS of 0, and the remaining participants achieved a CAS of 1. (Figure 2)

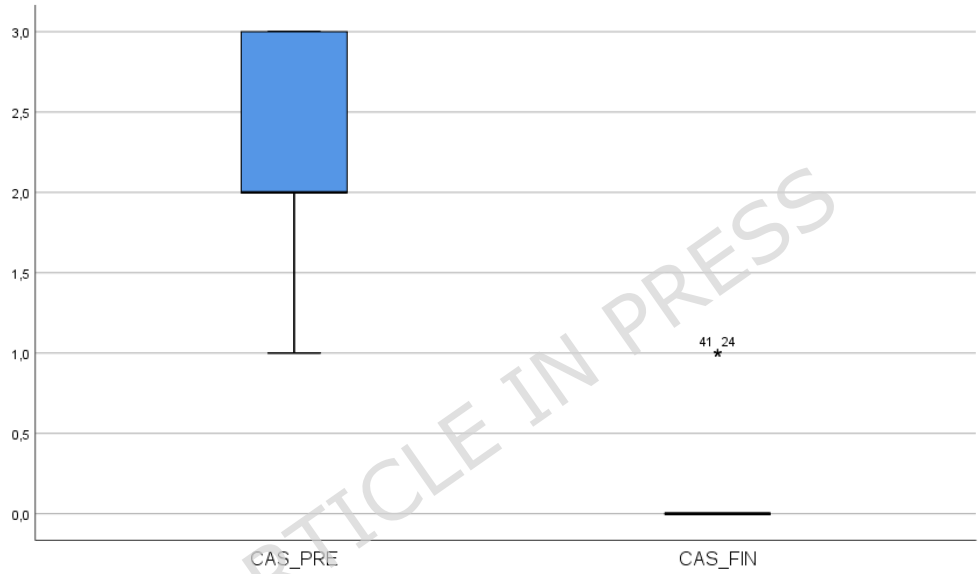

Figure 2 – Clinical Activity Score Pre- and post-treatment with Sarilumab

Thyroid stimulating immunoglobulin (TSI) levels (Figure 3) were also reduced after treatment, from an initial mean TSI of 38.70 (sd 36.84) U/L to a final mean TSI of 10.53 (7.49) U/L, which also achieved statistical significance (p-value<0.001). We observed a significant improvement in TSI levels, with the proportion of participants showing normal TSI values (<10 U/L) increasing from 17.7% at baseline to 62.9% after treatment.

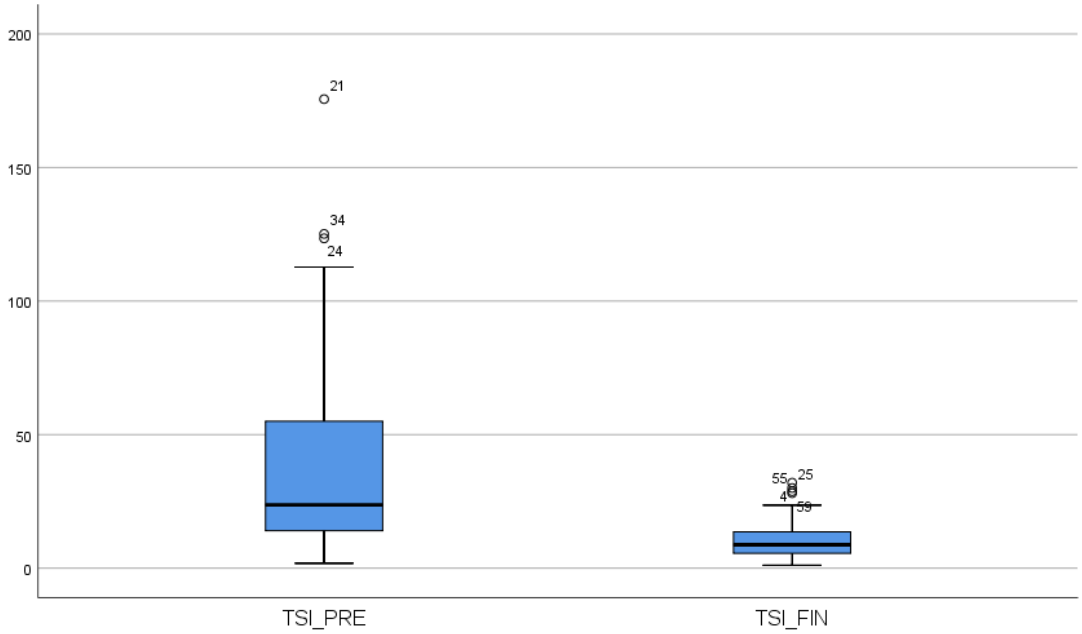

Figure 3 - Thyroid stimulating immunoglobulin levels pre- and post-treatment with Sarilumab

Considering the subgroup of patients with baseline CAS of 1, TSI was raised at baseline in 5 of the 10 participants, and after treatment remained elevated in only two cases. In the subgroup of patients with a baseline CAS of 2, TSI was raised in 16 out of 32 patients before treatment and in 6 out of 32 after treatment. In the subgroup with baseline CAS of 3, TSI was elevated in 17 out of 20 before treatment and 6 out of 20 after treatment.

Considering the variable “complete response”, defined as a CAS of 0 and normal TSI, 38 (60.3%) participants achieved a complete response after treatment with Sarilumab.

Recurrences

Three patients (4.84%) presented disease recurrence during the follow-up time, specifically at 9, 12 and 14 months after the last Sarilumab treatment. These patients required 3, 4 and 3 additional doses (2 subcutaneous injections each) of Sarilumab respectively, after which a final CAS of 0 was achieved in 2 participants and 1 participant maintained a CAS of 1/10. Considering the subgroup of patients that registered recurrence of orbital inflammation during the follow-up period, all presented an elevated TSI at the time of the final sarilumab administration before the onset of recurrence.

Secondary outcomes

The initial mean **proptosis** (Figure 4) was 19.02 (sd 1.73) mm for the right eye and 19.56 (sd 2.22) mm for the left eye, which was reduced statistically significantly (p-value < 0.001) to 18.10 (sd 1.39) and 18.35 (sd 1.69), respectively.

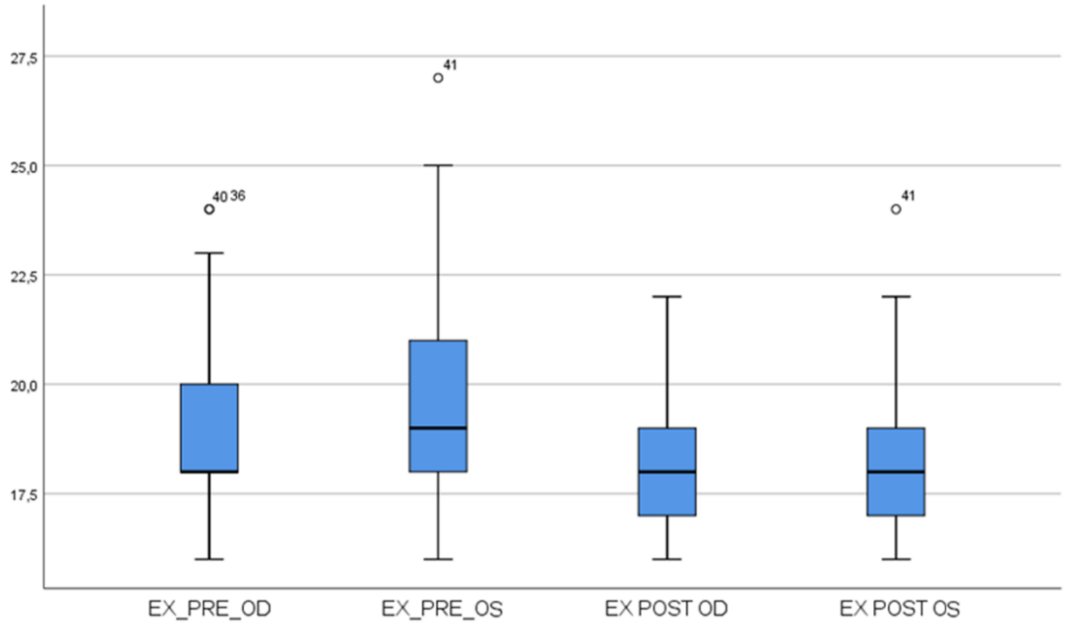

Figure 4 - Exophthalmometry evaluated with and Hertel exophthalmometer. Legend: EX_PRE_OD exophthalmometry of the right eye pre treatment, EX_PRE_OI exophthalmomnetry of the left eye pre treatment, EX_POST_OD exophthalmometry of the right eye pos Sarilumab, EX_POST_OI exophthalmometry of the left eye pos Sarilumab

Statistically significant reductions in both upper and lower **eyelid retraction** were found after treatment with sarilumab (p value <0.021). At baseline, 40 and 43 patients presented superior eyelid retraction of the right and left eye, respectively, which decreased to 12 and 8 patients after treatment with Sarilumab. The participants that maintained any degree of retraction pos treatment with Sarilumab were posteriorly treated with Muller muscle's resection, via a conjunctival microsurgery approach to reduce the remaining eyelid retraction. Considering **upper and lower eyelid edema,** present in 74.2% of participants at baseline, was only observed in 1.6% of participants after treatment with Sarilumab. An example of improvement of clinical signs can be found in Figure 5.

Considering **extraocular muscles motility**, at baseline 16.1% of patients reported diplopia in primary gaze (Gorman diplopia score 3 – constant diplopia) and 27.4% extreme gaze (Gorman diplopia score 1, intermittent diplopia and Gorman diplopia score 2, inconstant diplopia), compared to 9.7% of patients reporting diplopia, either in primary or extreme gaze, after treatment.

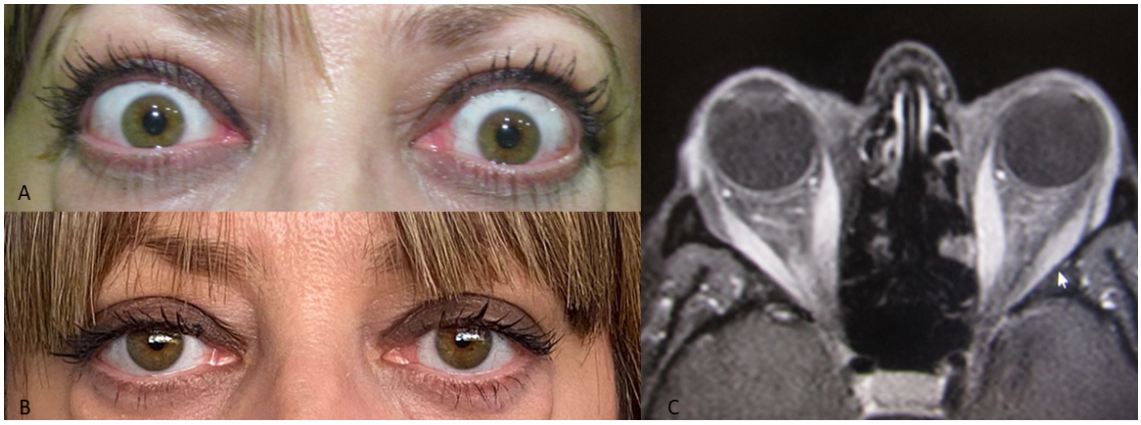

Figure 5 – A, Baseline characteristics of a patient diagnosed with Graves Orbitopathy, with exophthalmia, eyelid eadema and eyelid retraction, corresponding to a Clinical Activity Score of 3; B, the same patient after 4 sessions of sarilumab, with improved exophthalmia, eyelid eadema and retraction; C, Baseline Magnetic Resonance Imaging of the same patient showing extra-ocular muscles enlargement.

Safety

Adverse drug reactions were observed in 67.7% (42) patients (Table 4), most of all mild and spontaneously reversible. The development of neutropenia was the most frequent adverse effect and was reported in 45.2% (28) of the participants. We have classified any neutrophil value below the normal range as neutropenia, even when it was not necessary dose spacing or treatment suspension. Other reported adverse events included hypercholesterolemia that was observed in 25.8% (16) patients, thrombocytopenia 6.5% (4) patients, hypertransaminasemia in 9.7% (6) patients, asthenia in 12.9% (8) patients. Considering all the sessions of sarilumab, most adverse drug reactions were mild or moderate in severity and transient in time.

Most adverse reactions were transient but in the following it was necessary to delay the sarilumab treatment for 2 to 3 weeks, after normalization of blood analysis in: 16 cases of neutropenia, 3 cases of thrombocytopenia, 4 cases of elevation of transaminases and 2 cases of anemia. Other small adverse reactions that did not imply suspension of treatment included: gastrointestinal symptoms (4), anemia (3), articular pain (5), hair loss (2), bruises (1), cutaneous reactions (1), dysuria (1) and migraine (1).

Table 4. Adverse events during the treatment and follow-up periods

	Participants n (%)
Any adverse events	42 (67.7)
Adverse events leading to drug discontinuation	0
Neutropenia Leading to treatment delay	28 (45.2) 16 (25.8)

Thrombocytopenia Leading to treatment delay	4 (6.5) 3 (4.8)
Anemia Leading to treatment delay	5 (8.1) 2 (3.2)
Gastrointestinal symptoms	4 (6.5)
Articular pain	5 (8.1)
Asthenia	8 (12.9)
Hair loss	2 (3.2)
Bruises	1 (1.6)
Cutaneous reactions	1 (1.6)
Dysuria	1 (1.6)
Migraine	1 (1.6)
Hypercholesterolemia	16 (25.8)
Hypertransaminasemia Leading to treatment delay	6 (9.7) 4 (6.5)

Discussion

To our knowledge we report the first study on the treatment of low CAS GO, including patients with CAS' EUGOGO score between 1 and 3, using Sarilumab, a human monoclonal antibody with a selective action against IL-6 receptors. Our study results report the efficacy of Sarilumab in a cohort of patients with low CAS GO both clinically (considering CAS) and analytically (considering TSI levels). After treatment with Sarilumab, we found a reduction in CAS to 0 in 95.2% of the included participants, and to 1 in the remaining participants. TSI levels achieved normal values in 62.9% of participants after treatment. Our group defends that achieving lower CAS in low CAS GO patients improves disease control from a global perspective and that, in the future, will reduce the proportion of patients achieving moderate to severe forms of the disease. In our perspective CAS system is not accurate to evaluate patients that present with lower inflammation signs but with important activity-related symptoms as diplopia.

Current EUGOGO guidelines do not always recommend the treatment of patients with low CAS GO. However, some of these patients report an important impact in the quality of life, both in the visual functioning and self-reported appearance, as evaluated in our population using the GO-QOL. A strong correlation between disease severity and clinical activity has been shown using the GO-QOL questionnaires suggested by the EUGOGO.[17] The GO-QOL questionnaire is a simple tool to evaluate the patients' perspective regarding the activity of GO. Despite the low CAS in the population of our analysis, the patients reported an important impact in the quality of life, evaluated in this study using GO-QOL. We acknowledge that our sample likely comprises highly demanding patients from a high socio-economic background, who may be more attuned to symptoms that might be underappreciated in other populations. This particular characteristic of our cohort is further highlighted by the fact that, despite exhibiting low CAS scores, these patients reported a significantly impaired quality of life related to GO. After treatment with Sarilumab, we found a statistically significant improvement in the self-reported quality of life, reinforcing the importance

of treatment patients with low CAS. Furthermore, a part of the participants included in this analysis could not maintain their normal daily life, including work, and after treatment with Sarilumab, they could return to daily life activities, without the burden of invasive surgery and treatments. Few publications have supported the treatment of patients with Graves orbitopathy and low CAS and, to our knowledge, only treatment with glucocorticoids is reported.[18] A recently published review regarding novel treatments on GO reinforces the importance of immunosuppressants and concludes that early intervention can significantly improve the disease course, with an important impact in the long-term prognosis and reduce the incidence of severe complications. [19]

Our study has some limitations. The immunomodulatory treatment of low CAS GO is not an established first line therapy. We reinforce the particularities of our highly demanding population, that despite a low CAS presented an highly impacted self-reported quality of life related to GO. Our patients sought treatment for their symptoms that would minimize the impact on their daily functioning. Our sample is relatively small as patients with low CAS GO are not always aware of their disease and of the possibility of treatment of their symptoms, and frequently are not referred to observation by Orbital Ophthalmologists. Despite the sample being small, we could achieve statistical significance in most of the study variables. Further studies, including multi-center, randomized controlled trials are still needed to reinforce our results and compare different immunomodulatory options. Considering the inclusion criteria, we believe that relying solely on a CAS-focused design may limit the interpretation of a complex disease such as GO. Recently, a cohort of 1439 patients with GO reported that despite low CAS, 38% of patients presented moderate-to-severe GO and 10% vision-threatening GO. The study authors reinforced the limitations and unmet need of the existing 'high-CAS only' approach, especially in managing 'non-inflammatory' GO, prevalent in non-Caucasian populations.[20] We propose that multimodal diagnostic criteria should be developed in the future to better capture GO clinical heterogeneity.[14] Finally, the absence of a control group is another limitation of the study, as we attribute the observed improvement to the treatment without including a control group with similar characteristics left to evolve naturally. There is limited published data on the natural course of GO, specifically milder presentations, without intervention. Our main argument favoring the effect of sarilumab is the rapid improvement observed.

In conclusion, there was a significant improvement in the CAS and TSI levels of patients with low CAS GO treated with Sarilumab. Furthermore, we found a statistical improvement in the quality of life of the included participants, using a GO-QOL questionnaire. This suggests that Sarilumab is an effective and safe option for the treatment of low CAS GO.

Author contribution

All authors contributed to the study conception and design. Material preparation and data collection were performed by José Perez Moreira and Dolores Abelenda. Data analysis was performed by Joana Providência, Guilherme Castela and José Perez Moreira. The first draft of the manuscript was written by Joana Providência and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Competing Interests Statement

The authors have no competing interests to declare.

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