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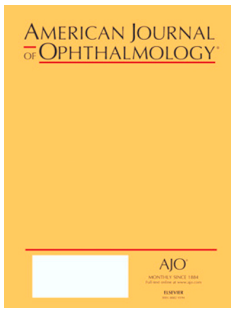

Efficacy of tocilizumab in patients with moderate to severe corticosteroid resistant Graves´ orbitopathy: A randomized clinical trial

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ABSTRACT

Objective: To demonstrate the efficacy of the anti- interleukin-6 receptor monoclonal antibody tocilizumab in patients with moderate to severe corticosteroid resistant Graves´ orbitopathy (GO).

Design: Double-masked randomized clinical trial

Setting and Participants: Thirty-two adults with moderate to severe corticosteroid-resistant GO from ten medical centers in Spain were randomized (1:1)

Intervention: Randomization to either 8 mg/kg body weight tocilizumab or placebo administered intravenously at weeks 0, 4, 8, and 12, and follow-up for an additional 28 weeks.

Main Outcomes and Measures: The primary outcome was the proportion of patients with a change from baseline to week 16 of at least 2 in the clinical activity score (CAS).

Results: The primary outcome was met by 93.3% (95% confidence interval [CI] 70.1%-98.8%) of the patients receiving tocilizumab and 58.8% (36%-78.3%) receiving placebo (P=.04; odds ratio, 9.8 [CI 1.3-73.2]). A significant difference was also observed in the proportion of patients achieving a CAS< 3 (86.7% [CI 62.1%-96.2%] vs. 35.2% [CI 17.3%-58.7%], P=.005; OR 11.9 [CI 2.1-63.1]) at week 16. Additionally, a larger proportion of patients with improvement in the European Group on GO proposed composite ophthalmic score at week 16 (73.3% [CI 48%-89.1%] vs 29.4% [CI 13.2%-53.1%]; P=.03), and exophthalmos size change from baseline to week 16 (-1.5 mm [-2.0- 0.5] vs. 0.0 mm [-1.0.5]; P=.01) were seen with tocilizumab. One patient experienced a moderate increase in transaminases at week 8; another had an acute pyelonephritis at week 32 in the tocilizumab-treated group.

Conclusion: Tocilizumab offers a meaningful improvement in activity and severity in corticosteroid-resistant GO. This trial justifies further studies to characterize the role of tocilizumab in GO

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Short title: Tocilizumab for the treatment of Graves´ Orbitopathy

Graves´ orbitopathy (GO) is an inflammatory disease of the orbital tissues with an estimated incidence of 16 women or men per 100,000 persons per year in the USA.[1] The incidence of GO is around 20% of the incidence of Graves' disease (GD). Approximately 5% of patients with GD have moderate to severe disease. In 5% of cases, GO can occur without evident GD. Eyesight can be severely threatened from corneal exposure or compressive optic neuropathy in 3% to 7% of cases.[2-4]

Corticosteroids alone or associated with orbital irradiation[5-7] are the first-line treatment for patients with moderate to severe active GO. Corticosteroids are administered orally, intravenously, or into the soft orbital tissue. GO flare-ups after corticosteroid discontinuation occurs in 12% of patients, and a small percentage of patients do not respond adequately to this treatment.[8] Corticosteroids can also produce severe adverse events or provide an incomplete response followed by relapse or progression of GO. In addition, the ability of corticosteroids to modify the final disease outcome remains unclear.

When this is the case, treatments targeting T and B cells, cytokines, and peroxisome proliferator-activated receptor-γ are recommended, but these treatments have failed to demonstrate efficacy[7,9] or achieve consistent results.[10-11] Recent European guidelines advise a second course of intravenous corticosteroids, oral corticosteroids combined with orbital radiotherapy, cyclosporine, or rituximab as a second-line treatment[12] in these patients. More recently, teprotunumab—a human monoclonal anti-body inhibitor of IGF-IR—has demonstrated efficacy in reducing exophthalmos.[13]

In GO pathogenesis, orbital fibroblasts are activated by autoantibodies against the thyrotropin receptor TSHR and the insulin-like growth factor-1 receptor. The fibroblasts then secrete IL-6, macrophage chemoattractant protein-1, and transforming growth factor-β,[14-17]. These factors recruit T-lymphocytes into the orbit, and these cells interact with fibroblasts to produce soluble factors that induce synthesis of hydrophilic glycosaminoglycans that result in swelling of the orbital tissues and differentiation of

fibroblasts into mature adipocytes. Interleukin-6 has relevant effects on cells of the immune system.[18] In orbital pre-adipocyte fibroblasts, IL-6 increases expression of the thyrotropin receptor TSHR, and the orbital volume is relative to IL-6 mRNA expression.[16-18] Therefore, IL-6 may have several roles in the pathogenesis of GO.[14,15,19] Interleukin-6-driven rheumatoid arthritis is successfully treated with the IL-6R monoclonal antibody tocilizumab (TCZ, RoACTEMRA, Roche Pharmaceuticals).[20] In this study, we report an investigator-initiated, multicenter, randomized, and double-blind study to test the efficacy and safety of TCZ to treat patients with GO who were unresponsive to glucocorticoid therapy.

PATIENTS AND METHODS

TRIAL DESIGN AND OVERSIGHT

This was an investigator-initiated, parallel, randomized, double-blind, and placebo-controlled trial performed at nine Spanish centers. The patients were randomly assigned in a 1:1 ratio to receive placebo or intravenous TCZ 8 mg/kg on weeks 0, 4, 8, and 12 (Figure 1). Patients were then monitored for 28 weeks so that the total study duration was 40 weeks. The use of methotrexate, cyclosporine, systemic steroids, or other biological therapies were not allowed during the study. At each visit, patients were blindly evaluated by an ophthalmologist, rheumatologist, and endocrinologist or internist. The protocol (Supplement 1) was approved by the review boards/ethics committees of each institution; written informed consent was obtained from each patient before study participation (ClinicalTrials.gov identifier NCT01297699). The study was conducted in full accordance with the principles of the Declaration of Helsinki and with the laws and regulations of Spain. A full description of the protocol appears in the appendix. The first patient was enrolled on March 8, 2012, and the last observation was recorded on October 27, 2015.

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Domínguez (Hospital Clínico Universitario, Santiago, Spain). Roche, Inc. donated the TCZ and supported the pharmacovigilance and the final monitoring of the study but had no role in the design of the study, the collection or analysis of the data, the writing, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Patients

All subjects were ≥18 years of age and were enrolled regardless of current treatment. They had normal thyroid hormone levels and active GO defined by the presence of a clinical activity score (CAS) of at least 4 (10 points score) with a severity grade of moderate-to-severe or sight-threatening GO according to EUGOGO classification (Supplement, Table S1); they were incomplete responders to corticosteroid pulses. The sight-threatening criteria were limited to patients with compressive optic neuropathy resolved by medical or surgical treatment who still required further anti-inflammatory treatment.

The criterion of corticosteroid resistance refers to the following: a) incomplete response (defined as a CAS improvement <2) to at least three doses of 500 mg of intravenous methylprednisolone; or b) recurrence of GO defined as an increase in CAS ≥ 1 after treatment with corticosteroids pulses. The 10-point CAS was used in this study.[21] The exclusion criteria included the need for immediate surgery for orbital decompression, thyroidectomy or radioactive iodine treatment, active smoking, chronic or active infection, history of intestinal ulceration or diverticulitis, neutrophil count less than 0.5 x 10^9/liter, platelet count less than 50 x 10^3/liter, and aspartate transaminase (AST) or alanine transaminase (ALT) levels exceeding 1.5-fold of the upper normal limit. A full description of the inclusion and exclusion criteria is in Supplement 2. Patients were required to have a normal-appearing chest radiograph less than 3 months before randomization and were screened for latent tuberculosis (TB) using a

purified protein derivative skin test before trial treatment. Patients with latent TB were treated according to national recommendations.[22]

Randomization and masking

The randomization was performed after informed signed consent was obtained and after confirmation of compliance with the selection criteria. The treatment was started within four weeks following randomization. The process was performed centrally by the Bio-statistics Department of the Spanish Consortium to Support Network Biomedical Research with an electronic application of the case report form using SAS software version 9.2 to automatically and randomly assign the treatment groups. The treatment assignments used a pseudo-random process to ensure that both groups were similarly sized. This process allocated the patients enrolled at all centers. Pharmacists at the participant centers prepared tocilizumab in a sterile and pyrogen-free solution of 0.9% sodium chloride as well as a similar placebo solution, but the pharmacists were blinded to the participants. Participants, people giving the interventions, those assessing outcomes, and those analyzing the data were masked to group assignment. There were no cases of unmasking throughout the entire blinding process.

TRIAL OUTCOMES

The primary outcome was the proportion of patients with improvements in CAS by at least 2 at week 16. The secondary outcomes included the proportion of patients showing improvement in CAS by at least 2 at week 40, and the proportion of patients showing a CAS less than 3 at weeks 16 and 40. We also studied changes in the patient global assessment (PtGA) of pain, in the levels of thyroglobulin antibodies (anti-TG), in thyroid peroxidase antibodies (anti-TPO), TSI, and TSH; disease severity assessed by the European Group on Graves´ orbitopathy (EUGOGO)[21] and quality of life evaluated by the generic SF-36 and the disease-specific GO quality of life (GOQoL) were secondary outcomes.[23] *Post hoc* analysis studied the proportion of patients with improvements in the EUGOGO-proposed composite ophthalmic score (Supplement 2,

Table 2) and the extent of improvements in exophthalmos. Patients were monitored for adverse events (AEs), serious AEs, infections, withdrawals due to AEs, death, and clinically significant changes in vital signs and laboratory tests.

STATISTICS

A sample size of 32 patients was determined to provide at least 90% power to test the null hypothesis. The intention-to-treat population included all randomized patients who received at least one infusion of the study treatment. The Fisher test analyzed the categorical variables, and non-parametric tests were used to compare changes from baseline in levels of anti-TPO, anti-TG, TSH, TSI, SF-36, and GOQoL. The odds ratio (OR) estimation was used to measure the effect size. The last observation was carried forward when a data point was missing. Patients discontinuing the study were imputed as non-responders. A two-sided $P<.05$ was considered the limit for statistical significance. Stata version 14.0 (Stata/MC 14.0 for Windows; StataCorp LP, Texas, USA) was used for all statistical analyses. The entire statistics plan is in Supplement 1. Results are reported according to the "CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomized trials"

RESULTS

BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

Of the thirty-nine patients screened, thirty-two were randomly allocated within the study. Patient disposition and randomization are shown in Figure 1. One patient in the treatment group had prior orbital decompressive surgery. Baseline demographics and laboratory parameters of both groups were similar (Table 1, and Table S3 in Supplement 2). The mean duration of GO showed no differences between placebo and TCZ groups with a mean duration of 1 year ranging from 5 months to 5 years.

However, baseline patient GOQoL was significantly different. Higher numbers in GOQoL translate to greater perceived disability. The TCZ group did seem to be more affected by their disease than the placebo group. During the 40-week trial, four patients

withdrew from the study after week 16 for reasons other than AEs and/or possible drug-related toxicity. All thirty-two randomized patients were included in the safety population.

EFFICACY ASSESSMENT

At week 16, the primary outcome of an improvement in CAS by at least 2 (Figure 2A). This was achieved by 14 of 15 patients receiving TCZ compared with 10 of 17 patients receiving placebo (93.3%, [95% confidence interval, CI 70.1%-98.8%] vs. 58.8% [CI 36%-78.3%], P=.04; OR, 9.8 [CI 1.3-73.2]; Figure 2A). A CAS < 3 was achieved by a larger proportion of patients in the TCZ group than in the placebo group (86.7% [CI 62.1%-96.2%] vs. 35.2% [CI 17.3%-58.7%], P=.005; OR 11.9 [CI 2.1-63.1]; Figure 2B). A significant improvement was observed in the disease severity assessed by EUGOGO in 10 of 15 patients in the TCZ group compared with four of 17 patients in the placebo group (66.7% [CI 41.7-84.8] vs. 23.5% [9.6-47.2], P=.03).

At week 40, a change in CAS of at least 2 was achieved by 13 of 15 patients receiving TCZ compared with 10 of 17 patients receiving placebo (86.7% [CI 62.1-96.2] vs. 58.9% [CI 36.0-78.3]; P>.05; Figure 2A). A CAS < 3 was achieved by 12 of 15 patients in the TCZ group compared with 8 of 17 in the placebo group (80.0% [CI 54.8-92.9] vs. 47.1% [CI 26.1-69.0]; P>.05; Figure 2B). The individual analysis of the CAS components shows a larger proportions of patients remaining stable or improving with tocilizumab than placebo in all components of the CAS score except for exophthalmos (Table 2). The difference was significant for the improvement in hyperemia and chemosis at 16 weeks (Table 2).

Lessened disease severity as assessed by EUGOGO were observed in nine of 15 patients in the TCZ group compared with four of 17 patients in the placebo group (60% vs. 24%; P=.03). In a *post hoc* analysis, there was a significantly larger proportion of patients with improvement in the EUGOGO-proposed composite ophthalmic score (Table 3) at week 16 (73.3% [CI 48%-89.1%] vs. 29.4% [CI 13.2%-53.1%]; P=.03) and week 40 (66.7% vs. 17.7% [CI 6.2-41.0], P=.01). The analysis of

the components in the EUGOGO composite score demonstrated a change in the score both at 16 and 40 weeks. This change pertains mainly to an improvement in signs of soft tissue involvement by at least two grades as well as improvements in CAS by at least two points (Table 3, and Supplement 2 Tables S4 and S5). Also, there was a significant median diminution in the exophthalmos from baseline to week 16 in the TCZ group (21 mm [IQR, 19.5-23]) compared with placebo group (20.5 mm [18-22]; P=.01) (Table S6 in Supplement 2). However, at week 40, the improvement was in significant (21 mm [19.5-23] vs. 20.7 mm [18.5-22]; P=.04). The median change was -1.5 mm (-2.0 to 0.5) at week 16 and at week 40.

The GOQoL and SF-36 significantly improved at week 16 in patients receiving TCZ compared with placebo. Forty-seven percent of patients in the TCZ group and 35% in the placebo group experienced an improvement of at least 8 points, which is considered clinically meaningful.[18] Non-significant numeric increments in the physical and mental domains of the SF-36 were seen at weeks 16 and 40 in TCZ-treated patients. Non-significant differences in the decrements were seen in the placebo group.

No significant changes were observed in levels of anti-TG, TSI, or TSH at weeks 16 and 40 compared with baseline in placebo and TCZ groups. A small but significant improvement was observed in the anti-TPO levels (Table 4) in the TCZ group versus placebo at week 16 (P=.003) and at week 40 (P=.04).

Three patients in the placebo group were treated with corticosteroids after week 16. One received 5 mg prednisone twice daily for four days starting at week 20 because of unrelenting active GO. Another received 60 mg methylprednisolone at week 24 to treat urticaria. The third was administered three doses of 500 mg methylprednisolone weekly for 6 weeks starting at week 28 as a result of active GO. These three patients were considered non-responders at week 40. Nevertheless, the treatment of these patients did not affect the primary outcome because CAS did not improve. Nevertheless, this could have affected the estimation of the differences in secondary outcomes. Several patients did not complete the visual analog scale for

pain. In addition, the reassessments reported by the other patients were unreliable Thus, changes in visual analog scale for pain from baseline is not reported.

SAFETY

A total of 93 AEs were reported across twenty-seven patients (Table 5); 23 patients experienced more than one AE. Before randomization, one patient withdrew from the study because of elevated transaminases possibly related to the treatment of latent TB. Another had mildly elevated levels of transaminases—the subject was diagnosed as autoimmune hepatitis and was treated with azathioprine. The patient was randomized after normalization of transaminase levels. No patient withdrew from the study because of AEs after randomization. No tumors, active TB, opportunistic infections, or serious infusion reactions were noted during the study period. Lipid levels remained stable during the trial (Supplement 2 Table S7). Serious AEs were observed in two patients in the TCZ-treated group. One had a moderate increase in transaminase levels at week 8. This patient had been diagnosed as having latent TB and was treated with hydrazides. Transaminase levels were normalized after discontinuing hydrazides. Another patient had acute pyelonephritis at week 30.

DISCUSSION

This trial studied patients with moderate to severe GO resistant to corticosteroid therapy. The primary outcome was an improvement in CAS of at least 2 at week 16. This was achieved in 14 of the 15 patients in the treatment group.

Current guidelines recommend intravenous administration of 500 mg methylprednisolone weekly for 6 weeks followed by 250 mg weekly for another 6 weeks[12] for moderate to severe active GO. GO flare-ups after corticosteroid discontinuation occurs in 12% of patients, and a small percentage of patients do not respond adequately to this treatment.[24] In addition, corticosteroids produce severe adverse events or provide an incomplete response followed by relapse or progression of GO. A review of intravenous methylprednisolone in 1045 patients showed morbidity

in 6.5% and mortality in 0.6% of them.[24] Also, a randomized controlled trial comparing rituximab to intravenous methylprednisolone in active moderate to severe GO reported significant effectiveness and disease-modifying effects.[9] In contrast, another randomized trial comparing rituximab to placebo showed no difference in the improvements of disease activity.[10,25] Treatment with other targeted therapies have been unsuccessful.[10]

Teprotunumab was previously studied in a multicenter, double-masked, randomized, placebo-controlled trial. There, it achieve significant improvement in CAS and proptosis in 69% of treated patients compared with 20% of placebo group.[13] The main difference with our study is that our patients were corticosteroid-resistant; therefore, the results are not comparable. Patients treated with teprotunumab showed a reduction in exophthalmos at week 40; the patients treated with tocilizumab in our study had no such reduction. The different therapeutic effects of the drugs and/or the different population of patients could explain the difference in the reduction of proptosis—teprotumumab was not tested in CS-resistant patients.

This study evaluated alternatives for treating this population of patients. The CAS is a validated scoring system to distinguish inflammatory from non-inflammatory GO. The system is widely used in clinical trials[26] because it has high predictive value for the outcome of immunosuppressive treatment. Nevertheless, there are patients with high CAS with inactive congestive disease, and this is a limitation of the CAS in clinical trials. To minimize this limitation, patients included here must have active GO and a high CAS. No single feature can distinguish activity from congestion. Nevertheless, congestive features are typically manifested by involvement of orbital muscles. In our study, the proportion of patients achieving a state of inactive disease (CAS<3) is one piece of evidence supporting the efficacy of TCZ—congestive signs usually do not abate promptly. At week 16, 86.7% of patients treated with TCZ and 35.3% treated with placebo ($p < 0.05$) have a CAS<3. This implies that the significant improvements seen were not part of the natural history of GO.[27,28]

Further support for efficacy comes from the significant number of patients in the TCZ-treated group with a large effect-size. Nevertheless, it has been suggested that the use of CAS might not be an ideal outcome for an intervention trial given the lack of significance for the patient's long-term outcome and QOL. On the contrary, a combined outcome proposed by EUGOGO might be better from a clinical perspective.[25] Thus, we *post hoc* reanalyzed the results using this outcome as recently reported in trials with various doses of IV glucocorticoids[8] and rituximab.[25] The analysis demonstrates that a significantly larger proportion of tocilizumab-treated patients achieved improvement in the clinically relevant composite ophthalmic score versus placebo at weeks 16 and 40. Although there was significant improvement in exophthalmos, the improvement was not clinically meaningful. Thus, the main effect of tocilizumab seems to be improvements in soft tissue and CAS and, to a lesser extent, the improvement in eyelid aperture. Indeed, no significant benefit was observed in exophthalmos and diplopia at 40 weeks.

The 36-Item Short Form Health Survey (SF-36) is a generic, self-reporting, and easily administered quality-of-life measure. It is widely utilized for routine monitoring and assessment of care outcomes in adult patients. The consequences of changes in visual functioning and appearance in patients with GO over time are measured using the GOQoL. The QoL questionnaire includes two subscales: one for visual function and one for appearance. It is a reliable tool in clinical studies.[23]

Several studies have shown a weak correlation between GOQoL and scores of the disease activity or severity.[23,29,30] There was significant difference in baseline GOQoL between the placebo and TCZ groups. However, GOQoL was not incorporated in the inclusion criteria. Thus, uneven distribution of GOQol after randomization was a possibility because of the low number of patients included in the trial. Moreover, objective measures of eye pathology do not correlate well with subjective symptoms.

In the TCZ-treated group, the median function score of 72.2 at baseline makes improvements (increases) more difficult than in the placebo group, which had a median

function score of 25.0. Nevertheless, 47% of patients in the TCZ group and 35% in the placebo group experienced such an improvement, i.e., a change of at least 8 points.[29] A similar trend was seen in the appearance subscale. The effect size of the significant SF-36 improvement was small. The CAS decrease of two points at 16 weeks is also clinically small and may account in part for the small improvement in QoL. Whether longer-term use of TCZ would have achieved better outcomes remains unknown.

Previously, a randomized clinical trial of rheumatoid arthritis demonstrated non-inferiority of 162 mg weekly of TCZ subcutaneous compared to 8 mg/kg every 4 weeks of intravenous TCZ.[31] We suggest that the efficacy of subcutaneous TCZ in GO is similar to intravenous TCZ.

There were 672 eye measurements performed from baseline to week 16; of these, 41 data were missing (6.8%). The effect of this small number on the precision estimates is negligible. The three patients treated with corticosteroids from week 16 to week 40 were considered treatment failures for all purposes. This could have affected the estimation of the differences in secondary outcomes. In RA patients treated with TCZ, there was a small increase in the overall rate of serious infection. A single case of serious infection as pyelonephritis in our study is not surprising.

Our study does have some limitations. The number of patients with corticosteroid-resistant GO in the population is small. This led to a long recruitment period. Although the sample size was small, it did allow us to demonstrate a significant difference in efficacy versus placebo. At baseline, the median exophthalmometry was 23 mm. It is conceivable that the population captured in our trial was not as affected as those typically associated with corticoid resistance. Also, the duration of active therapy was short and may have been insufficient. In rheumatoid arthritis treated with TCZ, significant responses are usually seen at 12 weeks; better responses are seen with sustained therapy.[20] Some patients could have entered the stable phase or could have been experiencing congestion and inflammation at trial initiation because there was no limit in disease duration in our inclusion criteria.

Nevertheless, we believe that the orbitopathy was in an active phase because the placebo group showed a high rate of improvement, and congestive signs usually do not improve without orbital decompression. The ophthalmopathy could also have resolved because some GO had more that one year of evolution. This might account for the otherwise unexpectedly high rate of improvement in CAS in the placebo group. In this study, the primary outcome was evaluated at week 16 when significant efficacy was seen in other chronic inflammatory conditions. The long-term impact on the need for decompressive surgery remains unknown. Active smokers were excluded from the study, and this selection bias might limit the study's external validity. However, the impact of smoking on the efficacy of tocilizumab in rheumatoid arthritis is disputed.[32] Patients treated with RAI or thyroidectomy were also excluded to avoid the possible impact of these interventions on the outcome. Patients with active compressive optic neuropathy were excluded because randomization to placebo was not considered appropriate. Thus, some of the most active patients who might benefit from anti-IL-6 therapy were excluded from consideration. Therefore, external applicability of the results is limited. Further studies including specific groups of patients are still needed. Strengths of our RCT include the use of objective response measures, patient reported outcomes (GOQOL and SF-36), and safety evaluation by expert ophthalmologists, endocrinologists, internists, and rheumatologists. Overall, given the biphasic nature of GO, TCZ is an attractive candidate for induction of remission early in this eye disease.

In conclusion, while our study has limitations, there was a significant difference between the placebo and the TCZ-treated group in the primary outcome. Furthermore, all secondary outcomes did numerically or statistically better with TCZ than placebo. This consistency suggests a true effect that requires further study.

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Conflict of interests: J Gomez-Reino reports fees from Roche Spain, during the conduct of the study; all the other authors have nothing to disclose.

REFERENCES

1. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Trans Am Ophthalmol Soc.* 1994;92:477-588.

2. Laurberg P, Berman DC, Bulow Pedersen I, Andersen S, Carle A. Incidence and clinical presentation of moderate to severe graves' orbitopathy in a Danish population before and after iodine fortification of salt. *J Clin Endocrinol Metab.* 2012;97(7):2325-32.

3. Tanda ML, Piantanida E, Liparulo L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab.* 2013; 98(4):1443-9.

4. Bahn RS. Graves' orbitopathy. *N Eng J Med. 2010;362(4):726-38.*

5. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for Graves' orbitopathy:systematic review and metaanalysis. *J Clin Endocrinol Metab.* 2009;94(8):2708-16.

6. Gao G, Dai J, Qian Y, Ma F. Meta-analysis of methylprednisolone pulse therapy for Graves' orbitopathy. *Clin Exp Ophthalmol.* 2014;42(8):769-77.

7. Rao R, MacIntosh PW, Yoon MK, Lefebvre DR. Current trends in the management of thyroid eye disease. *Curr Opin Ophthalmol.* 2015;26(6):484-90.

8. Bartalena L, Krassas GE, Wiersinga W, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab.* 2012;97(12):4454-63.

9. Salvi M. Immunotherapy for Graves' orbitopathy. *Curr Opin Endocrinol Diabetes Obes.* 2014;21(5):409-14.

10. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. *J Clin Endocrinol Metab.* 2015;100(2):432-41.

11. Salvi M, Vannucchi G, Curro N, et al. Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy:a randomized controlled study. *J Clin Endocrinol Metab.* 2015;100(2):422-31.

12. Bartalena L, Baldeschi L, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016;5(1):9-26.

13. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med.* 2017;376(18):1748-1761.

14. Mesquida M, Leszczynska A, Llorenc V, Adan A. Interleukin-6 blockade in ocular inflammatory diseases. *Clin Exp Immunol.* 2014;176(3):301-9.

15. Chen B, Tsui S, Smith TJ. IL-1 beta induces IL-6 expression in human orbital fibroblasts:identification of an anatomic-site specific phenotypic attribute relevant to thyroid-associated orbitopathy. *J Immunol.* 2005;175(2):1310-9.

16. Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: implications for immunotherapy. *Curr Opin Ophthalmol.* 2011;22(5):385-90.

17. Khong JJ, McNab AA, Ebeling PR, Craig JE, Selva D. Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. *Br J Ophthalmol.* 2016;100(1):142-50.

18. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol.* 2015;16(5):448-57

19. Perez-Moreiras JV, Alvarez-Lopez A, Gomez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. *Ophthal Plast Reconstr Surg.* 2014;30(2):162-7.

20. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs:the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum.* 2008;58(10):2968-80.

21. Bartalena L, Baldeschi L, Dickinson AJ , et al. 2008 Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid* 2008;18(3):333–346.

22. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005;52(6):1766-72.

23. Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with Graves' orbitopathy:the GO-QOL. *Br J Ophthalmol.* 1998;82(7):773-9.

24. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab.* 2011;96(2):320-32.

25. Stan MN, Salvi M. Rituximab therapy for Graves' orbitopathy - lessons from randomized control trials. *Eur J Endocrinol.* 2017;176(2):R101-R109

26. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' orbitopathy. *Clin Endocrinol (Oxf). 1997;47(1):9-14.*

27. Menconi F, Profilo MA, Leo M, et al. Spontaneous improvement of untreated mild Graves' orbitopathy: Rundle's curve revisited. *Thyroid.* 2014;24(1):60-6.

28. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated orbitopathy. *Clin Endocrinol (Oxf).* 1995;42(1):45-50.

29. Terwee CB, Dekker FW, Mourits MP, et al. Interpretation and validity of changes in scores on the Graves' orbitopathy quality of life questionnaire (GO-QOL) after different treatments. *Clin Endocrinol (Oxf).* 2001;54(3):391-8.

30. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with Graves' orbitopathy is markedly decreased: measurement by the medical outcomes study instrument. *Thyroid.* 1997;7(6):885-9.

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Legend for Figure 1. Disposition of patients showing randomization, number of patients completing or withdrawing from the trial, and reason for withdrawal in seventeen patients with Graves orbitopathy treated with placebo (PBO) and fifteen patients treated with tocilizumab (TCZ).

Legend for Figure 2. Percentage of patients with CAS improvement of at least 2 in seventeen patients with Graves orbitopathy treated with placebo and fifteen patients treated with tocilizumab at weeks 16 and 40 (A). Percentage of patients with CAS < 3 at weeks 16 and 40 (B).

Table 1. Baseline characteristics of the seventeen patients with Graves orbitopathy treated with placebo and fifteen patients treated with tocilizumab

	Placebo (n=17)	Tocilizumab (n=15)
Age (years), median (IQR)	47.5 (41.1-57.4)	45.07 (38.9-50.5)
Women, n (%)	13 (76.5)	11 (73.3)
Duration of GD in years, median (IQR)	1.45 (0.35-3.9)	2.24 (0.69-10.3)
Duration of GO in years, median (IQR)	1.07 (0.49-2.9)	1.09 (0.69-4.0)
CAS, median (IQR)	5.00 (4.0-6.0)	5.00 (5.0-7.0)
GOQoL, median (IQR)		
Function	25.0 (16.7-44.0)	72.2 (38.9-83.3)*
Appearance	45.0 (30.0-65.0)	50.0 (45.0-55.0)
SF-36, median (IQR)	59.8 (35.94-77.1)	63.9 (49.4-76.1)
Mental function	62.4 (33.1-80.5)	69.1 (44.6-82.5)
Physical function	50.0 (34.0-72.0)	71.0 (50.0-78.0)
ESR (mm/h), median (IQR)	16.0 (10.0-24.0)	12.0 (7.0-21.0)
CRP (mg/dL), median (IQR)	0.70 (0.26-1.6)	0.42 (0.10-1.0)
TSH (mIU/L), median (IQR),	0.80 (0.50-2.8)	0.15 (0.02-2.8)
TSI (IU/L), median (IQR)	7.5 (1.1-31.3)	24.4 (8.2-35.5)
Anti-TPO (IU/mL), median (IQR)	36.5 (18.41-183)	41.2 (28.0-200.0)
Anti-TG (IU/mL), median (IQR)	20.0 (8.3-100)	21.5 (15.0-456.8)
Replacement therapy, n (%)	8 (47)	11 (73)
Anti-thyroid treatment, n (%)	5 (29)	4 (27)
Prior thyroidectomy, n (%)	3 (18)	2 (13)

IQR: interquartile range, GD:

Grave's disease, GO: Graves´ ophthalmopaty; CAS: Clinical activity score; GOQoL: Graves´ orbitopathy quality of life; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; TSH: thyroid-stimulating hormone; TSI: thyroid stimulating immunoglobulins Anti-TPO: anti-thyroid peroxidase antibodies; Anti-TG: anti-thyroglobulin antibodies; IQR: interquartile range; *P=0.003

Table 2. Secondary outcomes at week 16 and week 40 in seventeen patients with Graves orbitopathy treated with placebo and fifteen patients treated with tocilizumab.

	Week 16		Week 40	
Outcome,	Placebo	Tocilizumab	Placebo	Tocilizumab
Anti-TG levels, median improvement (IQR), IU/mL	0.0 (-3.2, 0.0)	-5.1 (-29.8, 0.0)	0.0 (-14.2,0.0)	-2.5 (-4.7, 0.0)
PtGA, median improvement (IQR)	-0.0 (-1.9, 0.2)	-1.2 (-2.5, 0.0)	-0.0 (-2.2, 0.0)	-1.2 (-2.6, 0.0)
SF-36, median improvement (IQR)	0.0 (-8.0, 2.2)	2.3 (-4.7, 16.2)*	0.0 (-6.7, 1.0)	0.1(0.0, 15.3)
Mental function	-2.0 (-29.2, 8.7)	7.5 (-9.3, 21.6)	-9.3 (-27.3, 3.6)	9.6 (-8.1, 32.9)
Physical function	-3.0 (-23.5, 4.0)	2.0 (-2.5, 16.5)	-10.5 (-34.0, 12.5)	3.0 (-19.0, 19.5)
GOQol, % patients(CI) with ≥ 8 improvement				
Functioning	35.2 (17.3-58.7)	46.7 (24.8-69.9)	35 (17.3-58.7)	46.7 (24.8-69.9)
Appearance	17.6 (6.1-41.0)	40.0 (19.9-64.2)	29.4 (13.2-53.1)	33.3 (15.1-58.2)
EUGOGO composite score improvement, % of patients (CI)	29.4 (13.3-53.1)	73.3(48.0-89.1)*	17.6 (6.2-41.0)	66.7(41.7-84.8)†
Exophthalmos -Hertel-, median mm (IQR)	23.0 (19.5-24)	20.5 (18-22)	23.2 (19, 24)	20.7 (18.5, 22)
Δ Exophthalmos from week 0, median mm (IQR)	0.0 (-1.0-0.5)	-1.5 (-2.0-0.5)‡	0.0 (-0.5, 1.0)	-1.5 (-2.0-0.5)

Anti-TPO: anti-thyroid peroxidase antibodies; Anti-TG: anti-thyroglobulin antibodies; PtGA: patient global assessment of pain. IQR: interquartile range; CI: 95% confidence interval. *P=0.03; †P=0.01; ‡P=0.003

Table 3. Percentage (confidence interval, CI) of patients with no worsening in the components of the clinical activity score (CAS) at week 16 and week 40 in seventeen patients with Graves orbitopathy treated with placebo and fifteen patients treated with tocilizumab

	Week 16		Week 40	
	Placebo % (CI)	Tocilizumab % (CI)	Placebo % (CI)	Tocilizumab % (CI)
Retro-ocular pain	64.7 (41.3-82.7)	86.7 (62.1-96.2)	64.7 (41.3-82.7)	80.0 (54.8-92.9)
Pain extreme positions	52.9 (30.9-73.8)	60.0 (35.7-80.1)	52.9 (30.9-73.8)	80.0 (54.8-92.9)
Eyelid erythema	70.5 (46.9-86.7)	93.3 (70.1-98.8)	64.7 (41.3-82.7)	86.6 (62.1-96.2)
Hyperemia	41.1 (21.6-64.0)	80 (54.8-92.9)*	64.7 (41.3-82.7)	80.0 (54.8-92.9)
Edema	29.4 (13.2-53.1)	53.3 (30.1-75.1)	41.1 (21.6-64.0)	60.0 (35.7-80.1)
Chemosis	35.3 (17.3-58.7)	80 (54.8-92.9)†	47.0 (26.1-69.0)	60.0 (35.7-80.1)
Caruncular swelling	64.7 (41.3-82.7)	86.6 (62.1-96.2)	53.3 (30.1-75.1)	80.0 (54.8-92.9)
Exophthalmos	82.3 (60.0-94.0)	93.3 (70.1-98.8)	82.3 (60.0-94.0)	86.6 (62.1-96.2)
Motility	64.7 (41.3-82.7)	93.3 (70.1-98.8)	76.4 (52-7-90.4)	86.6 (62.1-96.2)
Visual Acuity	76.4 (52.7-90.4)	93.3 (70.1-98.8)	70.6 (46.9-86.7)	93.3 (70.1-98.8)

CI: confidence interval; *p=0.03; †p=0.01

Table 4. Improvement in relevant components of the EUGOGO composite score at week 16 and week 40 in seventeen patients with Graves orbitopathy treated with placebo and fifteen patients treated with tocilizumab.

	Placebo		Tocilizumab	
Number of patients	week 16	week 40	week 16	week 40
Improvement in eyelid aperture by at least 3 mm, n	2	2	7	5
improvement in signs of soft tissue involvement by at least 2 grades, n	10	12	14	13
Improvement in Bahn/Gorman diplopia score or at least 8 grades, n	0	0	1	1
Improvement in proptosis by at least 2 mm, n	8	4	14	6
Improvement in CAS by at least 2 points, n	10	10	14	13

Table 5. Adverse events (AE) and serious adverse events at week 16 and week 40 in seventeen patients with Graves orbitopathy treated with placebo (n=17) and fifteen patients treated with tocilizumab (n=15).

	Week 16		Week 40	
	Placebo	Tocilizumab	Placebo	Tocilizumab
Total AEs, n	19	43	33	58
Infections	5	12	7	17
Respiratory tract	2	6	1	3
Gastroenteritis	1	2	1	3
Urinary tract infections	0	2	0	2
Headache	2	9	4	11
Anemia	3	0	3	0
Ocular symptoms (pain)	0	0	3	2
Hypercholesterolemia	0	2	1	3
Neutropenia (Grade I)	0	1	0	1
Thrombocytopenia (Grade I)	0	1	0	1
Patients with >1 AEs, n	4	9*	7	12*
Total SAEs, n	0	2	0	2

AE: Adverse event; SAE: Serious adverse event, *p=0.05

Figure 1

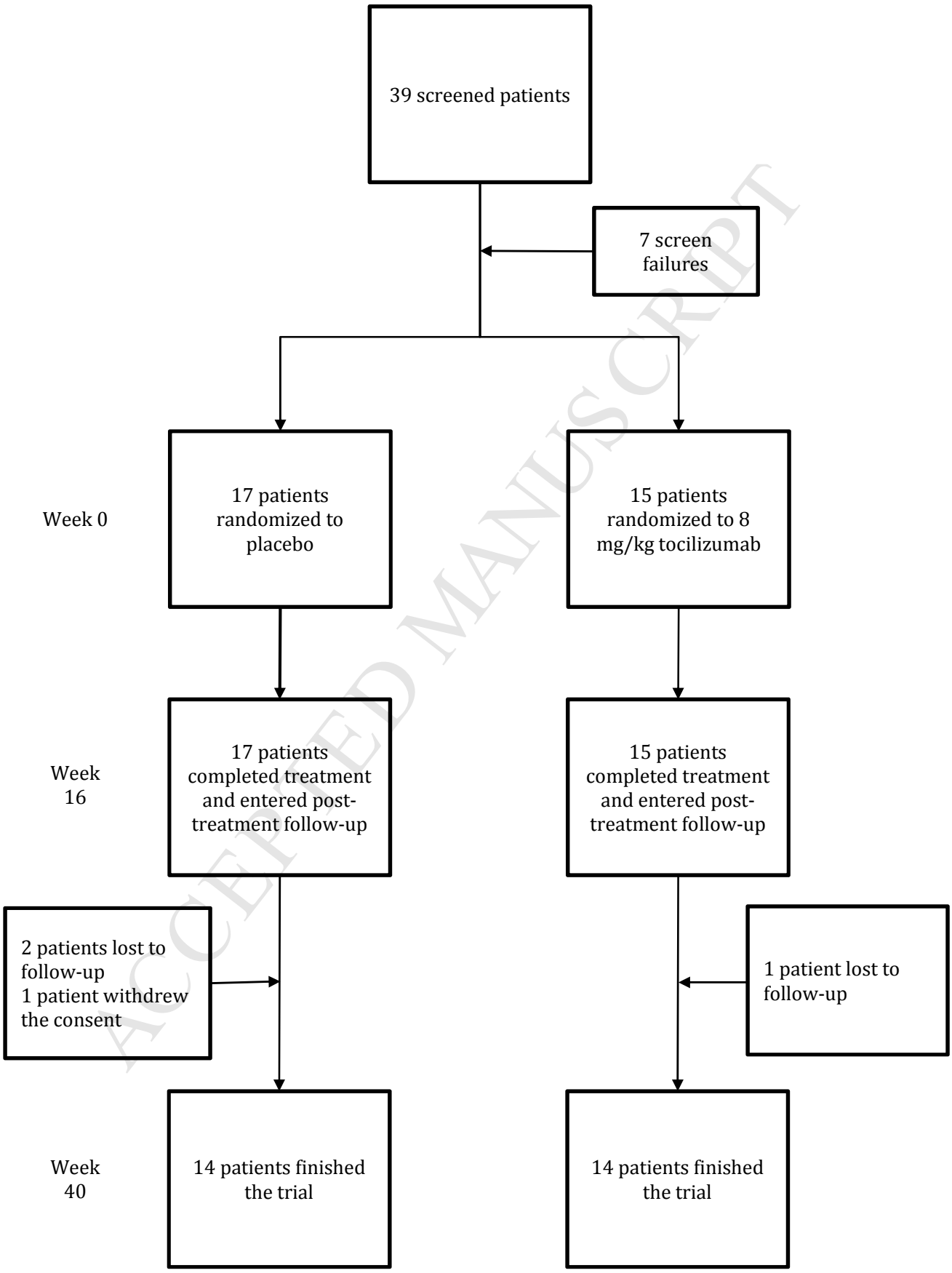
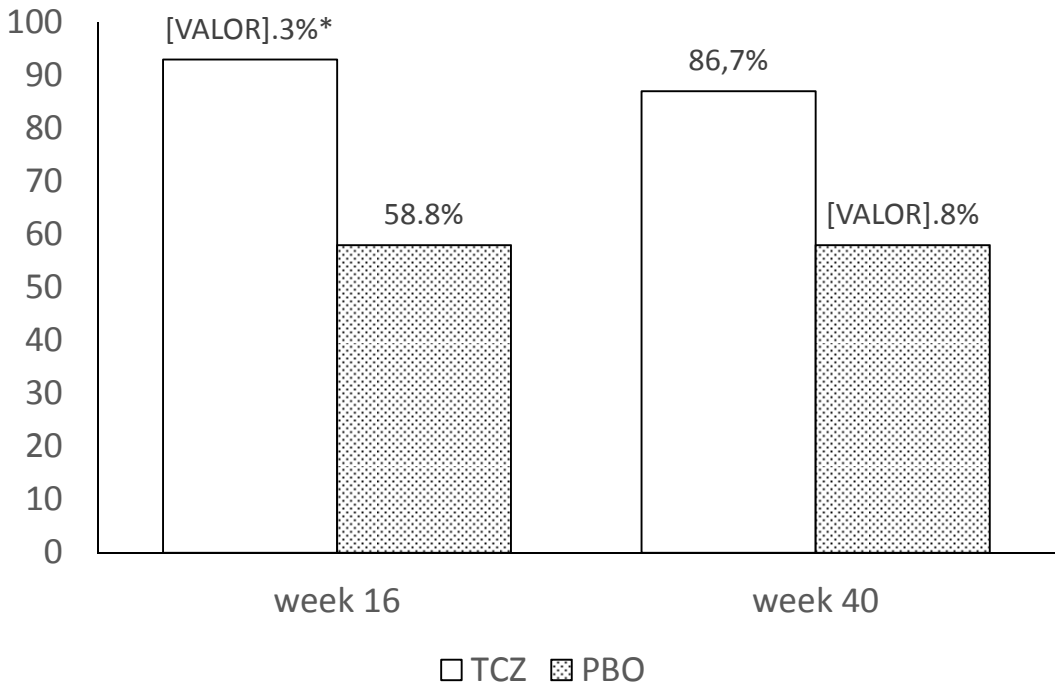


Figure 2

A



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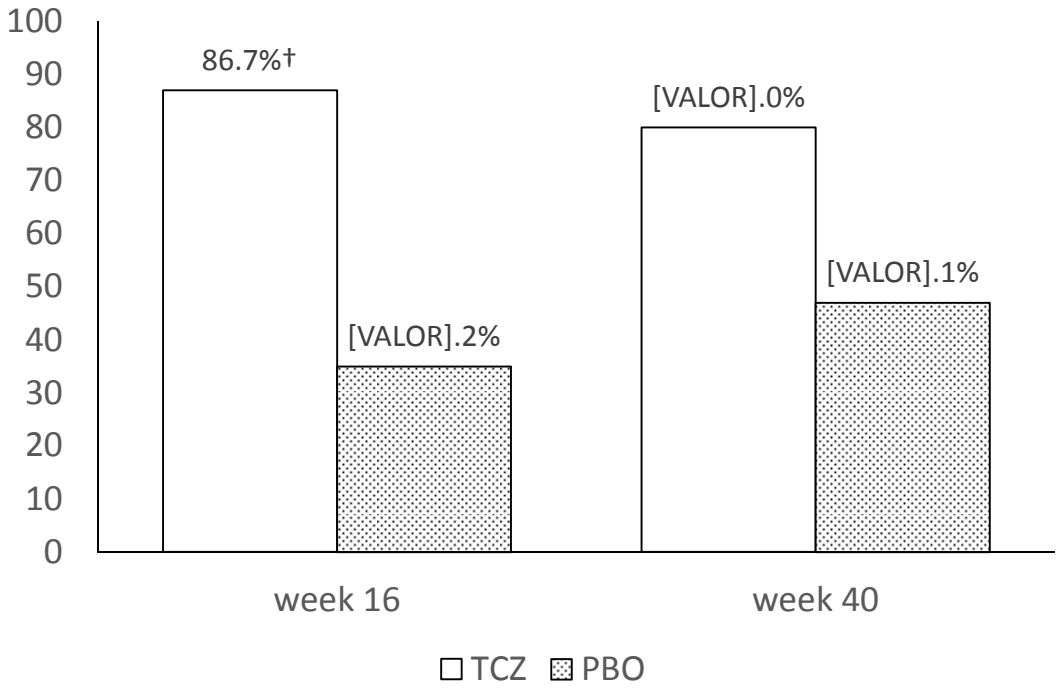

PBO: placebo; TCZ: tocilizumab; *P=.04; †P=.005