Abstract

Graves Orbitopathy (GO) is a potentially sight-threatening and disfiguring, extrathyroidal manifestation of Graves Disease. It often impairs patients’ quality of life, causing severe social and psychological sequelae. Intravenous glucocorticosteroids is currently the mainstay of therapy but the efficacy is often underwhelming and recurrence rate is high. For many years clinicians have been searching for new methods of treatment. Rituximab (RTX), a chimeric monoclonal antibody targeted against CD20 which is a surface antigen present on B cells. It is frequently used to treat non-hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis or various types of vasculitis. Numerous clinical trials employing RTX in the treatment of GO have shown promising results. RTX is currently considered to be a valid second line treatment option in patients unresponsive to previous interventions or in disease reactivation. This
review summarizes available literature on this topic, including two largest, randomized, controlled studies. Potential benefits, as well as the limitations of RTX therapy are discussed.

**Keywords:** Graves Orbitopathy, Rituximab, Thyroid eye disease, Graves Disease

**Epidemiology, Clinical presentation and Pathophysiology**

Graves Orbitopathy (GO) otherwise referred to as Graves eye disease, or thyroid eye disease is an autoimmune, inflammatory disorder of the retroocular tissue occurring in patients with autoimmune thyroid disease (ATD). It is mainly associated with Graves Disease (GD) but may also be seen in patients with chronic lymphocytic thyroiditis. Most commonly it accompanies hyperthyroidism, but it may also occur in euthyroid patients, preceding the diagnosis of ATD by months or even years. The onset of GO may also be observed many years after the diagnosis of ATD. (1) Recent research suggests that as many as 70% of patients with GD have evidence of GO in MRI. (2) The incidence of clinically relevant cases was 16 per 100,000 in females and 2.9 per 100,000 in males. (2-4) The symptoms of GO include excessive tearing, foreign body sensation, photophobia and/or pain in the orbit, either resting or gaze-evoked. Diplopia, blurring, desaturation of colors may also be present. Patients commonly present with swelling or redness of upper or lower eyelids and conjunctivae or proptosis. It is not rare that these symptoms are asymmetrical, or even unilateral. (5) Severity
of the symptoms determines the prognosis and the preferred management. Natural course of
the disease, described by Rundle FF et al, consists of active phase when the inflammatory
process is progressing lasting usually up to 24 month, Plateau phase when the inflammation
is ongoing but not progressive and lastly inactive state.(6)
There are several known risk factors of severe course of the disease including: male sex,
smoking, thyroid dysfunction, treatment with radioiodine, high TSH-receptor antibodies
(TSH-R Ab, TRAb) levels, oxidative stress or hypercholesterolemia. Several genetic factors
were also investigated, but the results are inconclusive up to date.(7)
In GO the inflammation in the orbit is believed to occur mainly due to stimulating
influence of TRAb secreted by B-cells infiltrating the thyroid gland. In consequence the
fibroblasts of the periorbital tissue are stimulated to produce extracellular matrix components
and pro-inflammatory cytokines such as Interleukin 6 (IL-6), Interleukin 12 (IL-12) or
Interleukin 17 (IL-17).(8, 9) Specific chemokines are also related to the pathogenesis of this
disease: C-X-C motif chemokine ligand 9 (CXCL9), C-X-C motif chemokine ligand 10
(CXCL10), C-X-C motif chemokine ligand 11 (CXCL11) and their receptor - Chemokine
receptor CXCR3. Those cytokines act by combined Interferon gamma + interferon alfa (IFN-
\(\gamma\)+TNF-\(\alpha\)) stimulation of thyroid follicular cells and take part in the Th1-mediated immune
response.(10, 11) Increased serum Th-1 chemokines have been linked with the active phase
of GO, especially during early stages of the disease, as well as hyperthyroidism in GD but not
in toxic nodular goiter .(10, 12-14) It was reported that treatment with Methimazole
decreases the concentration of CXCL10 and that decrease was linked with a reduction of
TRAb titers.(13, 15)

Current management
For a very long time, the mainstay of GO treatment has been the administration of intravenous glucocorticosteroids (ivGCS), which was frequently followed by orbital decompression or squint/eyelids rehabilitative surgery. Only recently the European Group on Graves Orbitopathy (EUGOGO), in its updated guidelines proposed the Mycophenolate to be added to ivGCs as a first line treatment in active, moderate-to-severe GO, considering its beneficial effect on long-term outcome and less frequent recurrences which has been shown in two large, randomized studies. (16-18) Considering the complex pathogenesis of the disorder involving many molecular pathways, a number of agents are proposed as second line treatment in the event of poor response to ivGCs or disease relapse. Among the potential drugs are antiproliferative agents such as Azathioprine and Cyclosporine, biological molecules that target different pathogenetic pathways eg. Tocilizumab – a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R) or Rituximab, a chimeric monoclonal antibody targeted against CD20 which is a surface antigen present on B cells. (16)

Lately it has been suggested that cross-talk between TSHr activated by TRAbs and insulin-like growth factor 1 receptor (IGF-1R), which is overexpressed in the orbital connective tissue, plays a great role in the pathogenesis of this process. (19, 20) A novel therapeutic agent under investigation is Teprotumumab, which is a monoclonal, blocking antibody against IGF-1R. Recent studies suggest that this agent is an effective and safe medication in the treatment of active, moderate-to-severe GO. (21-23)

Lastly, a second course of ivGCs treatment or teleradiotherapy in combination with intravenous or oral steroids may be of benefit in selected patients as a second line of therapy. Nevertheless studies provide only limited evidence to support any of the mentioned drugs.

**Purpose of this review**
In this review we would like to focus on Rituximab (RTX), a molecule that is of particular interest among clinicians and investigators. RTX is a chimeric, monoclonal murine-human antibody targeted against CD-20 antigen expressed on the surface of B-lymphocytes in different stages of maturation. (24) RTX causes the depletion of B-lymphocytes, which happens via different mechanisms, including antibody-dependent cytotoxicity, complement cytotoxicity, regulation of intracellular calcium and apoptosis. (25) Despite its main use in CD20+ B-cell lymphomas, over the years the evolving understanding of immunology led to its usage in different autoimmune diseases eg. Lupus Erythematosus or Rheumatoid Arthritis. (26, 27)

**Rituximab in Graves Disease**

The use of RTX in Graves Disease was first proposed by El Fassi, D et al. in 2006. (28) In 2007 they published the results of a pilot study assessing the efficacy of RTX in GD. Patients were treated for GD with antithyroid drug alone (RTX-) or in combination with RTX (RTX+). Four out of ten RTX+ patients but only one patient out of ten in RTX- remained euthyroid at 12 months. The RTX+ group presented with fewer relapses compared to the RTX- group in the follow up period. (29) In another study 13 patients with recurrent GD were treated with RTX (2 doses of 1000mg each). 9 of them achieved euthyroid state and were still in remission after concluding the 27 month observation period. (30) Lately a second phase prospective study of RTX in individuals ages 12-20 with newly diagnosed GD was conducted. Twenty seven patients received a single dose of 500mg of RTX and were concurrently treated with titrated doses of antithyroid drugs for 12 months. After 24 months of observation almost 50% (13 of 27) patients
remained in remission. This suggests that RTX might affect the natural course of disease, as expected remission rate was between 20% and 30%. (31) To our knowledge, up to date there were no controlled, randomized studies investigating this subject.

The concept of rituximab in Graves Orbitopathy

In 2003, Hasselbalch H.C. in his letter proposed the possibility of utilizing this agent in the treatment of active, moderate-to-severe GO based on the rising evidence of its efficacy in different autoimmune diseases and potential role of B-cells in their pathogenesis. (32) Later in 2006 Bartalena, L and Tanda M.L. argue that among many different novel agents, rituximab might be an interesting molecule worth further investigation. (33) They quote two reported cases of successful treatment of GO with RTX (34) In 2013 Salvi M. et al. conducted a review in order to assess the potential utility of RTX for GO. (35) The authors in their analysis point to the role of B-cells in the pathogenesis of thyroid autoimmune disease, especially B-cells' ability to activate CD4+ T-cells and their regulatory function on human immune response through regulation of cytokines production (eg. Interleukin 10, Interleukin 4, Interleukin 6 lymphotoxin-α, Transforming growth factor-β, interferon-γ;)(Fig. 1). They also explain that the maintained levels of TRAb or Thyroid stimulating antibodies (TSAb) after treatment is due to the fact that CD20 antigen is not expressed on the long-lived antibody-producing plasma cells residing in the bone marrow.

Later the authors analyze all the available reported studies of patients treated for GO with RTX. Gathered data consists of 43 patients across 8 different small, uncontrolled studies between the years of 2006-2013. Nearly all the studies utilized 1g dose of RTX administered twice in 2-week interval, however few studies differed from this pattern employing smaller
doses (500 mg x 2 in 2 weeks interval or a single dose of 100mg). The results, although the authors acknowledge the limitation of the data, were very promising. Mean Clinical Activity Score (CAS) was reduced from 4.9 at baseline to 2.2 points at 16 weeks after therapy. 91% of patients achieved clinical improvement. Most studies also report improvement in Hertel exophthalmometry, visual acuity and eye muscle motility. In a few patients progression to dysthyroid optic neuropathy (DON) was observed, but it is argued that this attributes to the natural course of the disease representing rather failure to treat than the unfavorable action of the drug itself. Side effects reported affected 13% of patients treated, but most of adverse effects were minor and transient, 1 death due to cardiac incident was reported as unrelated to treatment. During the observation period GO relapsed in only 1 patient.

Effect on TRAb and the possible mechanisms of action

Research carried out in the following years provided new insight into our current understanding of GO. There are numerous evidence that TSH receptor overexpressed in the periorbital tissue of patients with GO plays an important role in the pathogenesis of the disease. (36, 37) There is evidence for correlation between TRAb titers and clinical activity, as well as severity of the disease, although not all studies confirm that. (38) Karasek D. et al observed a significant reduction in TRAb titers after treatment with RTX, but this change was not reflected in clinical activity and severity. (39) There are numerous studies showing a reduction in TRAb titers after the infusion of RTX. (39-42) However data on this subject is conflicting, as there are also studies showing no reduction in TRAb concentration after such treatment. (29, 43-45) Later, El Fassi D. and colleagues demonstrated that the stimulatory capacity of TRAbs was reduced markedly (by 66 ± 22%), upon treatment with rituximab and methimazole for 21 days, compared to an increase by 33% on average (NS) in patients.
receiving methimazole alone. The overall levels of TRAbs decreased by around 15% in both
groups. (40) This revelation was not confirmed by the study conducted by Vannucchi et al.
The authors studied the TSH receptor stimulating antibodies (TSab) subpopulation in patients
treated with RTX and reported no significant decrease in correlation to TRAb titers (45). A
recent meta-analysis of 152 patients across 12 published studies treated with RTX for GO
showed no effect on TRAb titers in 1 month observation, however there was a significant
decline after 6 and 12 months. (46) Considering inconsistent data on the fluctuation of TRAbs
and their correlation to the clinical activity and disease severity, it might be reasonable to
assume that the changes in this parameter rather reflect the natural course of the disease and
the treatment with RTX do not affect the production of those specific antibodies.

It was suggested that beneficial effects of RTX might occur due to inhibition of
certain cytokines, mainly interleukin-6 or its soluble receptor (sIL-6R), which acts as an IL-
6R agonist. Those molecules have been found to be elevated in the serum of patients with
active GO independently of the thyroid function or treatment, but after depletion of B-cells
there was no significant reduction in IL-6 or IL-6r concentrations despite clinical
improvement of the patients. (47) In patients treated with GCS there was no significant
change in those mediators as well. (45) The studies mentioned suggest that the beneficial
effect of RTX on inflammatory process in the orbits is not mediated by changes in humoral
immunity, in particular proinflammatory cytokines.

It is believed that the B-cells’ ability for antigen presentation and activation of helper
CD4+ T cells plays a crucial role in the pathogenesis of GO, but our understanding of this
pathway is still incomplete. (35)

Clinical Trials
There are several trials of RTX in the treatment of GO. Their characteristics are presented in table 1.

Table 1. characteristics of recent studies involving RTX in the treatment of GO. RTX – Rituximab, ivGCs – intravenous glucocorticosteroids, GO – Graves Orbitopathy, GCs – Glucocorticosteroids, TRAb – thyroid receptor antibodies, CAS – Clinical Activity Score, DON – Dysthyroid Optic Neuropathy, SAE – Serious Adverse Events,

A study by Salvi M. et al, (which will be referred to as Italian study) compared RTX to i.v. pulses of methylprednisolone in the treatment of patients with active, moderate-to-severe GO.(41) Simultaneously a study by Stan M.N. and colleagues compared RTX to placebo in the treatment of patients with active and moderate to severe GO, and will be referred to as US trial.(48)

In the US trial, out of 25 enrolled patients (12 in the placebo arm and 13 in the RTX arm) 21 completed the primary endpoint of 24 weeks and 19/21 completed the 52 week observation. Both groups were similar at baseline in regards to age, sex, smoking status, prior corticosteroid treatment, current thyroid status, TRAb level, CAS scores, as well as the quantitative ocular parameters or the disease duration. After 24 weeks the primary endpoint, which was reduction in CAS, was similar in both groups. No significant difference in proptosis or composite clinical index was noted. Two patients developed DON. Both were treated with RTX, but no change in proptosis was observed in those patients. In the Italian trial 15 patients were treated with two infusions of 1g RTX 2 weeks apart and 16 patients were treated with ivGCs in standard EUGOGO regimen. After 24 weeks of observation more patients treated with RTX improved in comparison to the ivGCs group. The recurrence rate
after 52 and 76 weeks was lower as well. There was also an increase in proptosis (>2mm) in
3 patients treated with RTX and 2 treated with ivGCs. In this study patients were initially
given two 1000mg doses of RTX, but the protocol was amended to a single 500mg dose, after
the observation that even dose as low as 100 mg causes complete peripheral B-cell
depletion.(49) The characteristics of both groups in the Italian study were similar as well.

In the Italian study a significant reduction of CAS was noted in both groups but was greater
in the RTX arm. After 24 weeks 100% of patients improved compared to 69% in the ivGCs
group. Reactivation of the disease was noted in 5 patients treated with ivGCs and in none
treated with RTX. After 76 weeks of follow up, rehabilitative surgery was performed in 12/16
patients in the ivGCs group and in 5/15 of the RTX group. The US authors found that there
was no benefit of RTX when compared to placebo in the reduction of CAS at 24 or 52 weeks,
Similarly there was no significant difference in the improvement of ophthalmic parameters.
During follow up, of the 11 patients treated with RTX that returned the survey 5 needed
additional surgical treatment. In the placebo group 5 out of 9 patients not lost to follow up
required such procedures, thus showing no additional benefit of RTX. There was a transient
increase in proptosis in 3 RTX-treated patients from the US study and 1 in the Italian Study,
all of which returned to baseline after 24 of 52 weeks. No such change was noted in the
placebo group. This raises concerns about the development of DON during treatment, which
might occur or worsen due to increased intraorbital volume, most likely caused by post-
infusion oedema of the orbital tissues.

In order to better assess the results of those two studies a very thorough analysis was
carried out by the authors of both RCT’s a few years later.(50) The authors point out a few
differences between both studies. Key discrepancy was the characteristics of the participants
treated with RTX. In the Italian study most patients were females, while in the US study the percentage of men was higher. The participants’ mean age was also markedly lower in the Italian study (51.9 vs 57.6) which might predispose to a favorable clinical outcome. Another factor which might contribute to a better response to treatment is a shorter disease duration. Again, the population treated with RTX in the US study had nearly three times longer disease duration than the Italian study. Last factor that might indicate a better response in the Italian study was the lower mean TRAb in the RTX group in comparison to the parallel group in the US trial (Mean 10.7 ± 9.1 Italian vs Mean: 28.1 ± 23.4Median: 20 (9–60) US).

It’s worth noting that the percentage of smokers was higher in the study by Salvi. Smoking is a known factor which predisposes to poor effect of ivGCs therapy, however it is not known if this translates to worse response in GO patients treated with RTX.

When comparing the protocol of both studies, main difference of the Italian study were partial unblinding of the endocrinologists (but not ophthalmologist conducting the examination), explained by pursuing maximum safety for the patients (investigators believe that this did not cause any bias), as well as adjustment of dosage in the Italian study from 2x1g initially used in both trial to a single 500mg dose (the response to the high dose (2x1g of RTX) and the low dose (1x500mg of RTX) was not significantly different, when analyzed statistically (ANOVA)). The authors of the review point out that the self-limiting course of the disease might influence the outcome when using the CAS as primary endpoint. It also does not take into account additional benefits that therapeutic interventions might bring. In their comparison authors used a comprehensive score of disease improvement proposed by EUGOGO to analyze the data from those trials. Interestingly, the results were similar in their significance but different in magnitude to when CAS was used as outcome measurement.

Both RTX-treated groups remained different on the EUGOGO response, but the comparison
to their respective control groups did not change.

In the years following the two RCT’s, a number of clinical studies investigating RTX in active GO were published up to date. Unfortunately, these are mostly small, single-centered, uncontrolled studies without a control group. This obvious limitation requires caution when interpreting the results of said studies, nevertheless the results of most of these studies are consistent and might serve as grounds for further research.

In 2017 a study was conducted by Karasek et al. (39) Ten euthyroid patients, (6 of the patients were after total thyroidectomy and 3 after radioiodine treatment.), 8 women and 2 men, three smokers and seven nonsmokers; age range 27–74 years, average age 49.3 ± 13.4 years, with active, severe-to-moderate GO (mean disease duration 8.9 ± 5.7 months) were treated with a single 100mg dose of RTX. Four of the patients were corticoid-resistant (persistent GO activity despite ivGCs), 3 patients had GO relapse after previous steroid treatment and 3 patients had contraindications to ivGCs. Disease activity was measured with CAS and was reduced significantly from 3.6 ± 0.9 at baseline to 2.0 ± 0.8 at 1 month, 0.8 ± 0.4 at 6 months and to 0.4 ± 0.9 (p < 0.01). All patients had disease deactivation at 6 months, however one patient experienced disease reactivation which might have been related to resumption of smoking. Proptosis was reduced from 22.3 ± 1.6 at baseline to 21.1 ± 1.8 at 12 months (p < 0.05). Furthermore, depletion of CD19+ and CD20+ B-cells positively correlated with the reduction of CAS at 6 and 12 months. The severity of the disease, except for minor decrease of proptosis, did not change significantly in the studied population. Two patients (GCs resistant) developed DON requiring orbital decompression, and were
subsequently excluded from statistical analysis. In the observation period one patient
underwent elective decompression for exophthalmos with intermittent, spontaneous eyeball
subluxation. No other side effects were noted by the authors of the study. Similarly to other
reports, a reduction of TRAbs was also noted.

In 2020 Eid, L. published the results of a retrospective study of 14 patients (11 of
whom were refractory to ivGCs), treated with RTX for active, moderate-to-severe GO.(54)
Rituximab was administered intravenously, 1000 mg twice at a 2-week interval. Nearly all
the patients received ivGCs prior to the study. Majority of them also underwent other
concomitant treatments such as radiotherapy, thyroidectomy, Radio-iodine treatment, orbital
decompression or eyelid surgery. Median age was 60 years (range 55-69) with a mean
baseline CAS of 4/10 (range 3-4.5). Mean duration of GO was 26 months (range: 14–48), 1
patient was an active smoker , 9 were ex-smokers and 5 never smoked. 5 patients received
antithyroid drug (AT) combined with levothyroxine (LT), 1 patient received AT alone and 9
received LT alone. CAS had improved by ≥ 2 points in 2/14 patients at week 12 and in 5/14
patients at week 24. Disease inactivation (CAS < 3) occurred in 4/14 patients at week 12 and
in 50% of patients (7/14) at week 24. Overall, the CAS improved significantly with a median
improvement at 24 weeks of 1 point. Improvement in proptosis was observed in 3/9 patients
at week 24 and improvement in diplopia was noted in only 1/10 patients. No effect on TRAb
levels was observed. 60% of patients experienced adverse events during treatment. Majority
of them occurred during the first infusion and were mild and transient. One patient
experienced exacerbation of arthritis and headaches that required discontinuation of RTX
(225mg/m2 was administered). None of the patients developed DON. In a longer observation
relapse occurred in 5/12 patients between 6 and 12 months after RTX therapy. This study,
while still providing benefit for patients, shows a lesser efficacy of RTX when compared to
other available studies. Patients in this study had significantly longer disease duration, lower
mean CAS, higher mean age and the group consisted of a significant portion of men.

In 2020 results of a French retrospective study were published.(55) 40 patients either not
responding to ivGCs or with relapse after administration of ivGCs were treated for GO with
two doses 1g each, 2-week apart infusions of RTX. 32 patients received RTX in
monotherapy, 1 was excluded due to a severe adverse event (cytokine release syndrome). 8
patients needed concomitant optic decompression ⅝ before RTX administration and ⅜ after.
Patient was considered to have a good response if either CAS, oculomotor or visual function
improved without deterioration in any of the functions. Authors emphasized that their cohort
had a significant portion of patients (26%) with CAS between 1 and 3 points but with recent
onset of GO (confirmed by imaging techniques), which was responsible for visual or
oculomotor deterioration. Mean age of patients included in the analysis was 51.2 ± 10.7 years
with a majority of women (67%), 63% were smokers. Average duration of orbitopathy before
administration of RTX was 19.1 ± 27 months. What is important is that only 32% of patients
were euthyroid at the time of treatment with RTX. Proportion of patients with
hypothyroidism was significantly higher in the group of patients who qualified for orbital
decompression (4/7 versus 2/26, p = 0.04). At week 24, 20 out of 31 patients treated with
RTX alone met the primary endpoint of improvement in either parameter without
deterioration in the other. Favorable and significant effect on both inflammatory activity and
visual function was noted, but only 1 patient improved in regards to oculomotor function.
Patients treated with RTX and orbital decompression presented a more severe disease course.
100% had visual dysfunction and mean CAS was higher. The results in these group were
similar, as ⅝ patients improved in CAS and ⅜ improved in visual function but no significant
effect on oculomotor function was observed. Of note, the authors also reported a 63%
reduction of TRAb at week 24. Tolerance of the treatment was good, with only 1 serious adverse event in the aforementioned patient. This study is also limited by its nature - being retrospective, without a control group. Nevertheless, a few conclusions can be drawn. RTX was used as a second line agent after unsuccessful ivGCs treatment. In this setting improvement in 64.5% of patients may be seen as clinically significant. Response was significantly better in patients with higher TRAb levels. Moreover, the negative correlation between smoking and clinical outcome of the treated patients was confirmed. The authors also suggest that the improvement in the oculomotor function was underestimated. They were only able to detect complete strabismus resolution due to oculomotor functions being assessed in multiple ways, preventing a reliable comparison of the outcomes.

The authors also point out that duration of the disease is highly influential on the outcome of therapy. They refer to the two randomized studies by Stan N.M. and Salvi M., which were reviewed here earlier in detail. Patients in the Italian study had significantly shorter disease duration, thus oculomotor changes were less frequent and responded well to treatment, whereas in the study by Stan N.M. et al. as well as this study, disease duration was significantly longer, opthalmic changes more advanced and more resistant to treatment.(41, 48)

Rituximab was compared to Tocilizumab in the treatment of GO in a study by French authors.(56) They retrospectively analyzed patients treated in their hospital for GO with either drug. Doses used were 8 mg/kg of tocilizumab on weeks 0, 4, 8, 12, and rituximab at 100 mg at days 1 and 15. All patients were refractory to ivGCs or were relapsing after previous disease inactivation. 7 patients on Tocilizumab and 14 patients on RTX were included in this study. Primary endpoint of this review was reduction in CAS of at least 2 and this was achieved in all the patients treated with Tocilizumab and 9/14 (64%) patients on...
RTX. Secondary outcomes (visual acuity, presence of diplopia, chemosis, eye aperture, and relapse rates) were not statistically different between those two groups. TRAb levels and proptosis decreased significantly in both groups with mean values slightly favoring the Tocilizumab group. The number of relapses was not significantly different as well.

In their work, the authors suggest that the efficacy of both agents might be similar. The difference in response in favor of Tocilizumab might be due to discrepancies in the treated groups, in particular higher number of male patients, higher mean age and TRAb levels in the RTX group. Both drugs however did not show a satisfactory effect on proptosis or diplopia.

In 2021 the results of an open-label, prospective study of RTX in GO was published.(57) 17 patients (14 with GD and 3 with Hashimoto thyroiditis) were treated with a single 100mg dose of RTX. This group consisted of 14 women and 3 men with mean age of 51.5 ± 11.6 (range 28 to 72). Duration of the disease ranged between 0.8 and 10.4 months (mean ± SD, 4.2 ± 3.3). Twelve patients were previously treated with steroids while 5 received RTX as 1st line treatment. Results of this study are very promising. CAS was reduced from 4.56 ± 0.96 at baseline to 1.25 ± 1.14 at 24 weeks (p = 0.001). Disease inactivation occurred within 24 weeks in >90% of patients and was unrelated to disease duration. Severity of the disease (assessed as Composite Ophthalmic) improved in 58.3% of patients (7/12), remained stable in 3/12 and deteriorated in 2 patients. No relapses were noted in the 72 week observation period. Two patients required surgical decompression due to development of DON between 12 and 24 weeks of observation. One patient experienced a serious adverse event, which was cytokine release syndrome, and required cessation of RTX infusion. Otherwise treatment was well tolerated. One woman reported mild urticaria, which resolved with low-dose steroids. After concluding the 72 week observation period, 6 patients did not require any additional treatment, 5 patients underwent elective surgical
decompression, 7 patients had squint surgery and 2 eyelid surgery. TRAb concentrations were studied and a significant reduction was noted after 24 weeks. The efficacy of RTX, contrary to other studies, was slightly better in patients with longer disease duration, however all participants of this study had relatively short disease duration. Data regarding safety profile was similar to other studies. Moreover, no data on smoking status is available.

Discussion

RTX as a treatment of GO has been in the spotlight for many years now and several studies, both well-designed, randomized, prospective trials and small, limited, retrospective analyses have been published up to this date. In this review we focused especially on efficacy and safety profile. We looked closely at the characteristics of studied populations, including risk factors, disease duration and initial activity and severity of GO. However, it must be taken into account that results of those studies are often difficult to compare, as different primary or secondary endpoints were employed or different parameters of disease severity were measured and reported.

Safety Profile

Probably the most important aspect when considering new treatments is the safety profile. According to the review by van Vollenhoven R,F, et. al., in the population of patients with rheumatoid arthritis the incidence of serious infections was no greater in patients treated with RTX in comparison to patients treated with placebo+methotrexate.(58) Neither increased risk of malignancy was observed, nor a higher risk of myocardial infarction or stroke than in the general rheumatoid arthritis population. Most common side effects are
infusion-related symptoms caused by release of proinflammatory cytokines. The most
concerning side effect reported was Progressive multifocal leukoencephalopathy (PML), it
was mainly observed in patients with systemic lupus erythematosus (SLE), treated previously
with other immunosuppressive agents.

In the reviewed papers, the majority of reported side effects were mild, transient and
self limiting. These were easily preventable with premedication or managed by additional
doses of paracetamol or hydrocortisone. Adverse events considered as serious were far less
common. A total of 6 cases of DON after treatment with RTX were reported across all the
above studies. (39, 48, 57) Salvi M. et al. reported two cases of cytokine release symptom
with transient edema of periorbital tissue, requiring drug cessation and additional treatment
with hydrocortisone. (49) Also Vannucchi G. and Deltour J.B. each reported one case of
cytokine release syndrome. (55, 57) Stan M. in the US randomized trial, reported 5 AE’s
classified as moderate/severe in the group treated with RTX (while only 1 in the placebo
group). Risk of DON after administration of RTX is the main safety concern in patients with
GO. It is suggested that sudden release of cytokines from destroyed B-cells infiltrating the
ocular tissue might contribute to sudden swelling of tissues, in result causing DON. (50)
Some authors believe that this happens only when there is already a subclinical form of DON
present. It is also postulated that progression to DON represents failure to treat, rather than
adverse event of RTX, as in some patients it’s the natural course of the disease. This
hypothesis is supported by RCT by Salvi, where 1 case of DON was reported in a patient
treated with ivGCs and none in the RTX group. According to Blandford A.D. RTX might
even be of benefit in patients with DON, but the author emphasizes that more studies of this
agent are necessary. (59)

Efficacy
Lack of unification in reporting results of trials in GO is a major concern. The most commonly used scale for assessing disease activity is CAS. Unfortunately it has its obvious limitations, being highly subjective and binary (yes/no) in nature. In almost all the trials a significant reduction in CAS was observed. Results vary from $4.4 \pm 0.7$ points at baseline reduced to $0.6 \pm 3$ at week 24 in the Italian randomized trial, to reduction as minor as 4 points at baseline to 3 points at week 24 in the study by Eid et al. Also disease inactivation (CAS $<3$) was assessed. Here also results are different. In the studies by Salvi M. or Karasek D. 100% of patients treated with RTX were found to be inactive at week 24. Over 90% of patients achieved remission in the prospective study published by Vannucchi G. On the other hand Stan M. et al shows that less than 50% of patients had inactive GO after observation period with the rest of the studies in between. A reduction in disease severity is the other desired outcome when treating patients with GO. To evaluate the severity of GO proptosis, lid aperture, eye mobility, diplopia and few other parameters should be measured. The results of above studies are difficult to compare because of different methods of reporting this data. Nevertheless, based on the provided data RTX does not seem to significantly impact the disease severity. Nearly all the studies report no significant improvement in the evaluated ophthalmic parameters. Only recently a unification in reporting the outcomes of ophthalmic parameters in clinical trials of GO was proposed in the form of Composite ophthalmic Index, which consists of following items: $\geq 2$-mm reduction of lid aperture, $\geq 1$ point reduction in five-item CAS (excluding subjective, patient-reported spontaneous or gaze-evoked pain), $\geq 2$ mm reduction in exophthalmos, $\geq 8^\circ$ increase of eye muscle duction.(60) Utilizing this tool might be of great use in future trials.

Data on the issue of disease recurrence does not seem to be consistent across the available studies. While some (eg. Salvi M. et al, Karasek D. et al. Vannucchi G. et al.) report
no disease recurrence after 52 or 72 week observation period, other studies either do not provide such long follow up, or report a significantly higher percentage. Eid L. et al. for example reports relapse of the disease in as much as 41.7% of patients with a median time of 8 months from the initial treatment with GO. Bennedjai A. et al. reports that 4 of 14 patients on RTX experienced disease recurrence with median of relapse free survival of 18 ± 3.5 months. It’s difficult to judge what might have influenced this outcome. In the study by Eid L. et al. high median age of patients was significantly higher than in other studies. Furthermore, in both aforementioned trials disease duration at baseline was very long with 26 and 27 months median respectively. This might have contributed to poor response to treatment. Patients in the study by Deltour J.B. et al. also had long disease duration with a median of 19 months, but the rate of disease free survival was not reported.

The patient's perception of the disease and the outcome of treatment is equally important when evaluating its efficacy, as GO might be highly disfiguring and limiting disease, affecting physical appearance as well as visual functions. That can further lead to work absence, limitations in other activities and withdrawal from social life. Even disease classified as mild according to ophthalmic criteria may impair the patient’s quality of life (QoL) drastically. It is recommended to questionnaire patients with standardized forms to assess their QoL, which might help to monitor the subjective treatment results, as well as help make better therapeutic decisions.(16) Unfortunately evaluation of QoL was often not included in the reported data. Stan M.N. et al. reports a similar improvement in QoL in both placebo and RTX groups. Salvi M. et al, in his RCT reports a significant improvement in QoL both in the appearance and visual function parts of the survey in the RTX-treated group, while ivGCs providing little to no benefit on QoL. Also Vannucchi G. in the prospective study of small-dose RTX provides results of QoL surveys. More than 50% of patients improved in the appearance part of the questionnaire and 50% improved in the visual
function part. Hopefully, future studies will be more focused around the problem of QoL in an effort to provide personalized care for patients with GO.

There are a few factors that need to be taken into consideration when analyzing the efficacy of RTX in the context of available studies. Most important aspect is the characteristics of studied populations. Age of patients seems to be a very important prognostic factor, as in the studies showing worse results, a higher median age of patients was noted. Also higher percentage of women treated, commonly yielded better response to treatment. The other important and known risk factor for a more severe course of GO is smoking. This however was not reflected in the analyzed studies. Interestingly, the opposite trend seems to be observed, as eg. in the retrospective study by Eid L. et al. only 1 of 15 patients was a smoker at the time of the treatment, however the reduction of CAS and percentage of disease inactivation was among the lowest of analyzed studies. When looking at the studied populations, there are of course other factors in play. In the majority of studies, all, or almost all the patients received previous steroid treatment. This represents a group of already increased risk of severe disease course, as RTX was used as a second line treatment in the event of disease being resistant to steroids or recurrence after initial positive therapeutic outcome. Only two RCTs included a majority of patients naive to ivGCs.

**Dose of medication**

Initially patients were treated with doses of RTX used in rheumatology or hematology - most commonly 2 doses of 1000mg in two week intervals, but later Salvi M. et al. demonstrated that even a dose as low as single 100mg of RTX causes full peripheral b-cell depletion. (49) Most investigators, in an effort to minimize the risk of adverse events while
not giving up on efficacy, started employing lower doses of this agent, mostly single doses of 100mg or 500mg. This approach is also more cost-effective, which might sometimes be a very important factor in the decision-making process. Smaller dose of RTX did not seem to affect the outcome of the treatment. The authors of most recent studies also decided to use smaller doses. Recently Campi I. et al compared post-hoc different doses of RTX used in patients with GO across three different trials.(61) A total of 40 patients across two open label prospective studies and one randomized study were treated with 100mg, 500mg and 2x1000mg of RTX respectively. The authors investigated the efficacy of the treatment as well as safety profile or economic aspect of therapy. They conclude that any of the employed treatment regimens is equally effective in inactivating the disease, with no significant difference in regards to it’s duration. There were, however, differences in disease severity.

Higher doses provided more benefit on diplopia than the dose of 100mg. The authors suggest that greater doses can be more effective in preventing fibrosis in the ocular tissues, thus reducing the severity of diplopia and potential need for surgery.

**Position of RTX among other therapeutic options**

We believe there are a few reasons why, in certain patients, RTX might be favorable to other second-line treatments proposed by EUGOGO. The main advantage of this agent seems to be it’s potential ability to modify the natural course of GD (Greater percentage of patients achieving stable remission), which was suggested in the phase II trial by Cheetham el. Al.(31) It seems likely that similar effect could be observed in the course of GO.

The other factor to consider is the relative simplicity of the therapy regimen. A single dose of RTX (compared to e.g. 12 consecutive, weekly doses of ivGCs) might be more easily accepted by the patients, thus ensuring compliance.
Conclusion

In our opinion, RTX is a relatively safe alternative in the treatment of GO, especially in the population of patients who could not be treated successfully with ivGCs, either due to lack of satisfying response, disease recurrence or contraindications. Current data suggest that if administered early, it can modify the natural course of GO, shortening the active phase, thus contributing to limiting the damaging influence of inflammatory processes in the orbit. While it provides limited benefit in reducing the disease severity, its beneficial influence on quality of life cannot be overlooked. Furthermore it’s possible effect on the course of GD is an interesting aspect, which might affect the choice of second line therapy in some cases. However in the light of possibly high amount of adverse events reported in the trial, a number of them being severe, careful selection of candidates for treatment is necessary. We believe that current data warrants particular caution when DON is suspected. It must be emphasized that this treatment must be carried out in multidisciplinary centers with access to emergency surgery when needed. Patients at risk of optic neuropathy should be carefully monitored throughout the treatment.

We also believe, as most authors, that there is a need for further studies of Rituximab in the treatment of Graves Orbitopathy before considering it a treatment of choice either in the first, or the second line. It’s potential benefits when administered early in the course of disease should be the focus of investigation in the future studies.

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.


25
unresponsive to steroid immunosuppression. European journal of endocrinology. 2006;154
4:511-7.


62. Fig. 1 Actions of B-cells - IFN-γ – interferon gamma, IL-4 – interleukin 4, IL-6 interleukin 6, IL-10 – interleukin 10, TGF-β – transforming growth factor Beta.
<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Design</th>
<th>Drug</th>
<th>Dose</th>
<th>n. Patients</th>
<th>TRAb</th>
<th>CAS</th>
<th>CAS at 24 Weeks</th>
<th>DON</th>
<th>Disease Inactivation (at Week 24)</th>
<th>Improvement in Composite Ophthalmic Index (at Week 24)</th>
<th>Recurrence</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>randomized, prospective</td>
<td>RTX</td>
<td>2x1000mg</td>
<td>15</td>
<td>10.7 ± 9.1</td>
<td>4.4 ± 0.7</td>
<td>0.6 ± 3</td>
<td>0</td>
<td>100%</td>
<td>9/15(60%) improved</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2015</td>
<td>randomized, prospective, double blinded</td>
<td>placebo</td>
<td>n.a.</td>
<td>16</td>
<td>18.2 ± 21.7</td>
<td>4.7 ± 0.7</td>
<td>2.3 ± 0.5</td>
<td>1</td>
<td>68.7%</td>
<td>6/16 (37.5%) improved</td>
<td>6/16</td>
<td>3</td>
</tr>
<tr>
<td>2017</td>
<td>prospective</td>
<td>RTX</td>
<td>2x1000mg</td>
<td>13</td>
<td>19.5 (2.2–28.8)</td>
<td>4.9 (1.0)</td>
<td>3.7 (1.9)</td>
<td>2</td>
<td>4/13 at week 24</td>
<td>no significant difference between groups in disease severity</td>
<td>0/16</td>
<td>5</td>
</tr>
<tr>
<td>2019</td>
<td>retrospective</td>
<td>RTX</td>
<td>1x100mg</td>
<td>12</td>
<td>5.7 (1.1–41.0) to 1.6 (1.0–6.9)</td>
<td>5.3 (1.0)</td>
<td>3.8 (1.4)</td>
<td>0</td>
<td>100%</td>
<td>not reported</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>retrospective</td>
<td>RTX</td>
<td>2x1000mg</td>
<td>10</td>
<td>63% reduction</td>
<td>3.6 ± 0.9</td>
<td>0.8 ± 0.4 at month 6</td>
<td>2</td>
<td>50%</td>
<td>not reported</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>retrospective</td>
<td>RTX</td>
<td>2x1000mg</td>
<td>15</td>
<td>11 ± 4</td>
<td>4</td>
<td>3.0 (2.0–3.0)</td>
<td>0</td>
<td>20/31</td>
<td>not reported</td>
<td>1/10</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>retrospective</td>
<td>RTX</td>
<td>8 mg/kg on weeks 0, 4, 8, 12</td>
<td>32</td>
<td>10 ± 7</td>
<td>3.29 ± 1.16</td>
<td>1.59 ± 1.12 at week 24</td>
<td>1</td>
<td>50%</td>
<td>not reported</td>
<td>1/7</td>
<td>3</td>
</tr>
<tr>
<td>2020</td>
<td>prospective open label no control group</td>
<td>RTX</td>
<td>2x1000mg</td>
<td>14</td>
<td>1.2 ± 0.9 at week 24</td>
<td>5 ± 0.5</td>
<td>1.2 ± 0.9 at week 24</td>
<td>1</td>
<td>50%</td>
<td>not reported</td>
<td>4/14</td>
<td>0</td>
</tr>
<tr>
<td>2021</td>
<td>open label</td>
<td>RTX</td>
<td>1x100mg</td>
<td>17</td>
<td>1.9 ± 1.7 at week 24</td>
<td>4 ± 1.2</td>
<td>1.9 ± 1.7 at 24 weeks</td>
<td>1</td>
<td>&gt;90% at 24 weeks</td>
<td>not reported</td>
<td>0 at 72 weeks</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of recent studies involving RTX in the treatment of GO.

RTX – Rituximab, ivGCs – intravenous glucocorticosteroids, GO – Graves Orbitopathy, GCs – Glucocorticosteroids, TRAb – thyroid receptor antibodies, OD – Oculus Dexter, OS – Oculus Sinister, CAS – Clinical Activity Score, DON – Dysthyroid Optic Neuropathy, SAE – Serious Adverse Events,
Fig. 1 Actions of B-cells - IFN-γ - interferon gamma, IL-4 - interleukin 4, IL-6 - interleukin 6, IL-10 - interleukin 10, TGF-β - transforming growth factor β

Fig. 1 Actions of B-cells - IFN-γ - interferon gamma, IL-4 - interleukin 4, IL-6 interleukin 6, IL-10 - interleukin 10, TGF-β - transforming growth factor Beta

184x149mm (96 x 96 DPI)
<table>
<thead>
<tr>
<th>Author</th>
<th>M. Salvi</th>
<th>M.N. Stan</th>
<th>D. Karasek</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>year</strong></td>
<td>2015</td>
<td>2015</td>
<td>2017</td>
</tr>
<tr>
<td><strong>trial design</strong></td>
<td>randomized, prospective</td>
<td>randomized, prospective, double blinded</td>
<td>prospective</td>
</tr>
<tr>
<td><strong>drug</strong></td>
<td>RTX</td>
<td>ivgcs</td>
<td>RTX</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>2x1000mg</td>
<td>7.5g cumulative</td>
<td>2x1000mg</td>
</tr>
<tr>
<td><strong>n. patients</strong></td>
<td>15</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td><strong>n. women</strong></td>
<td>14</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td><strong>age (years)</strong></td>
<td>51.9 ± 13.1</td>
<td>50.4 ± 11.4</td>
<td>57.6 ± 12.7</td>
</tr>
<tr>
<td><strong>GO duration</strong></td>
<td>4.5 ± 2.9 months</td>
<td>4.6 ± 2.6 months</td>
<td>373 (240–1080) days</td>
</tr>
<tr>
<td><strong>Smokers</strong></td>
<td>10</td>
<td>9</td>
<td>(15.4)</td>
</tr>
<tr>
<td><strong>hypothyroid (at the time of treatment)</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>previous GCs</strong></td>
<td>6</td>
<td>6</td>
<td>4 (31)</td>
</tr>
<tr>
<td>time from GCs</td>
<td>at least 3 months</td>
<td>at least 3 months</td>
<td>at least 1.5 month prior</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>TRAb</td>
<td>10.7 ± 9.1</td>
<td>18.2 ± 21.7</td>
<td>20 (9–60)</td>
</tr>
<tr>
<td>eyelid aperture</td>
<td>11.4 ± 2.4 - R 11.9 ± 2.3 - L</td>
<td>11.6 ± 2.2 - R 11.5 ± 1.8 - L</td>
<td>11.1 (2.8) - L 10.9 (1.5) - R</td>
</tr>
<tr>
<td>improvement in proptosis</td>
<td>11.4 ± 2.4 - R 11.9 ± 2.3 - L</td>
<td>11.6 ± 2.2 - R 11.5 ± 1.8 - L</td>
<td>0.82 (1.4) R 0.1 (1.2) - L</td>
</tr>
<tr>
<td>CAS</td>
<td>4.4 ± 0.7</td>
<td>4.7 ± 0.7</td>
<td>4.9 (1.0)</td>
</tr>
<tr>
<td>CAS at 24 weeks</td>
<td>0.6 ± 3</td>
<td>2.3 ± 0.5</td>
<td>3.7 (1.9)</td>
</tr>
<tr>
<td>DON</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Disease Inactivation (at week 24)</td>
<td>100%</td>
<td>68.7%</td>
<td>4/13 at week 24</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------</td>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>Improvement in composite ophthalmic index (at week 24)</td>
<td>no significant difference between groups in disease severity</td>
<td>no significant difference between groups in disease severity</td>
<td>no significant difference between groups in disease severity</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0</td>
<td>Jun-16</td>
<td>no data</td>
</tr>
<tr>
<td>SAE</td>
<td>2</td>
<td>3</td>
<td>moderate/severe</td>
</tr>
<tr>
<td>No follow up treatment</td>
<td>10</td>
<td>4</td>
<td>no data</td>
</tr>
<tr>
<td>Go-QoL visual</td>
<td>significant improvement at weeks 52 and 74</td>
<td>improvement only at week 12</td>
<td>improved</td>
</tr>
<tr>
<td>GO-QoL function</td>
<td>significant improvement at weeks 12, 52 and 74</td>
<td>no significant improvement</td>
<td>improved</td>
</tr>
</tbody>
</table>

Table 1. characteristics of recent studies involving RTX in the treatment of GO. RTX – Rituximab, ivGCs – intravenous glucocorticosteroids, GO – Graves Orbitopathy, GCs – Glucocorticosteroids, TRAb – thyroid receptor antibodies, OD – Oculus Dexter, OS – Oculus Sinister, CAS – Clinical Activity Score, DON – Dysthyroid Optic Neuropathy, SAE – Serious Adverse Events, GO-QoL – Graves Orbitopathy Quality of Life scale
<table>
<thead>
<tr>
<th>L. Eid</th>
<th>J.B. Deltour</th>
<th>A. Bennedjai</th>
<th>G. Vannucchi</th>
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</thead>
<tbody>
<tr>
<td>2019</td>
<td>2020</td>
<td>2020</td>
<td>2021</td>
</tr>
<tr>
<td>retrospective</td>
<td>retrospective</td>
<td>retrospective</td>
<td>prospective open label no control group</td>
</tr>
<tr>
<td>RTX</td>
<td>RTX</td>
<td>tocilizumab</td>
<td>RTX</td>
</tr>
<tr>
<td>2x1000mg</td>
<td>2x1000mg</td>
<td>8 mg/kg on weeks 0, 4, 8, 12</td>
<td>2x1000mg 1x100mg</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>60 (range: 55–69)</td>
<td>51.2 ± 10.7</td>
<td>50 ± 12</td>
<td>50 ± 11</td>
</tr>
<tr>
<td>26 (14–48) months</td>
<td>19.1 ± 27 months</td>
<td>7.97 (8.6) months</td>
<td>27 (1.9) months</td>
</tr>
<tr>
<td>Jan-15</td>
<td>63%</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>no information</td>
<td>32% were euthyroid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>93.30%</td>
<td>all patients</td>
<td>all patients</td>
<td>all patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Duration</td>
<td>Lid Fissure OD (mm)</td>
<td>Lid Fissure OS (mm)</td>
<td>Hertel OD (mm)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>at least 3 months but 2 patients were under long-term oral GCs treatment</td>
<td>12.2±2.6</td>
<td>13±3</td>
<td>23.9±2.3</td>
</tr>
<tr>
<td>8.1 ± 26 months</td>
<td>63% reduction</td>
<td>11 ± 4</td>
<td>decreased (27.6±42.8 (n.v. &lt;1.5))</td>
</tr>
<tr>
<td>3 months</td>
<td>no significant change</td>
<td>no significant change</td>
<td>no significant change</td>
</tr>
<tr>
<td>3-4 months</td>
<td></td>
<td></td>
<td>no significant change</td>
</tr>
<tr>
<td>no information</td>
<td></td>
<td></td>
<td>no significant change</td>
</tr>
<tr>
<td>33% of patients</td>
<td>significant reduction in left eye</td>
<td>not significant</td>
<td>Hertel OD (mm) 23.9±2.3</td>
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<tr>
<td>4.56 ± 0.96</td>
<td></td>
<td></td>
<td>no significant change</td>
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<tr>
<td>3.0 (2.0–3.0)</td>
<td>1.59 ± 1.12 at week 24</td>
<td>1.2 ± 0.9 at week 24</td>
<td>1.9 ± 1.7 at week 24</td>
</tr>
<tr>
<td>3.29 ± 1.16</td>
<td>5 ± 0.5</td>
<td>4 ± 1.2</td>
<td>4.56 ± 0.96</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50%</td>
<td>not reported</td>
<td>not reported</td>
<td>7-Jul</td>
</tr>
<tr>
<td>------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------</td>
</tr>
<tr>
<td>20/31</td>
<td>not reported</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>5/12 (41.7%)</td>
<td>no data</td>
<td>1-Jul</td>
<td>Apr-14</td>
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<tr>
<td>0</td>
<td>1 (cytokine release syndrome)</td>
<td>0</td>
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<tr>
<td>not reported</td>
<td>not reported</td>
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<tr>
<td>not reported</td>
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- intravenous glucocorticosteroids, GO – Graves Orbitopathy, GCs – Glucocorticosteroids, re, DON – Dysthyroid Optic Neuropathy, SAE – Serious Adverse Events, GO-QoL – Graves
Fig. 2 B-cell development cycle

184x149mm (96 x 96 DPI)