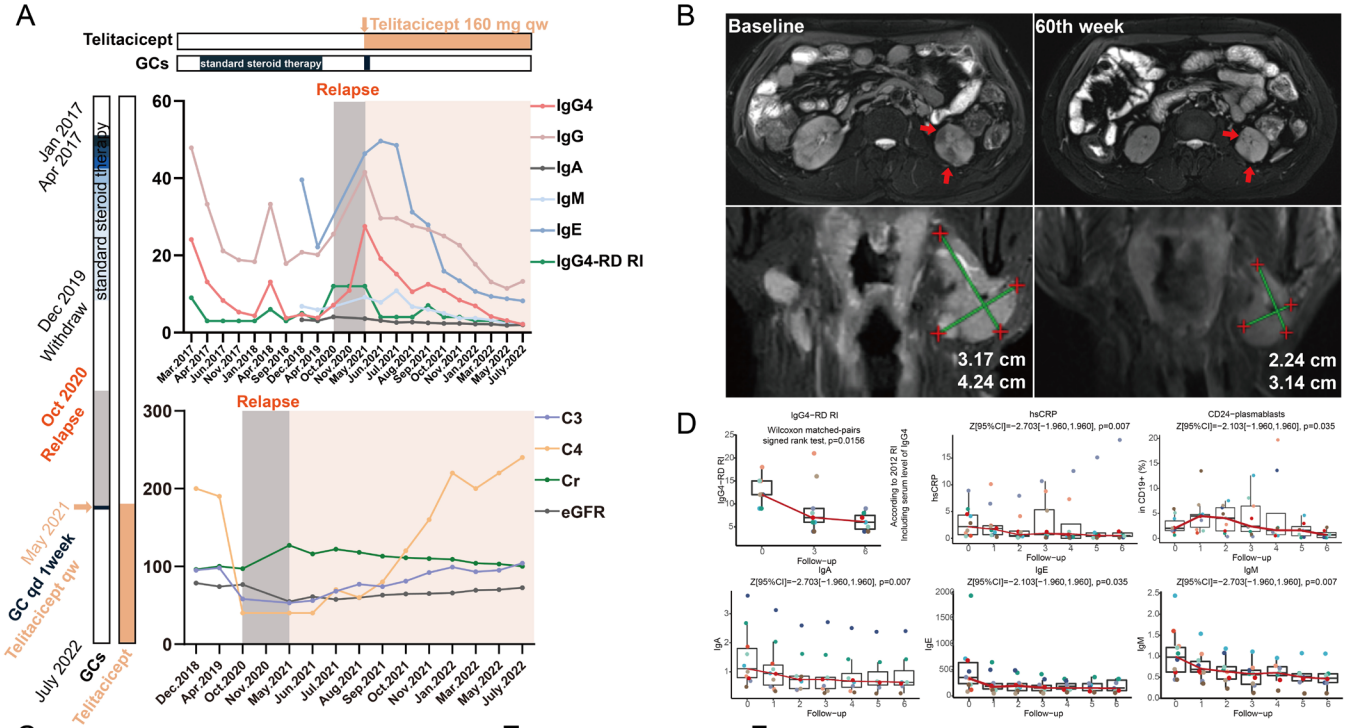
BLyS/APRIL dual inhibition for IgG4-RD: a prospective single-arm clinical trial of telitacicept

IgG4-related disease (IgG4-RD) is a newly recognised fibro-inflammatory clinical entity with multiorgan involvement. Although most patients with IgG4-RD respond well to glucocorticoids, they have limited treatment options for disease control and high relapse rates were reported during long-term treatment.[1] We report here a series of IgG4-RD cases treated with telitacicept, a novel bioagent (TACI-immunoglobin fusion protein) simultaneously targeting B cell maturation signals BLyS (BAFF) and APRIL,[2] in the absence of long-term glucocorticoids.

A 54-year-old man, who was diagnosed with IgG4-RD in 2017, presented in our department with re-enlarged bilateral submandibular glands, parotid glands and 12 lymph nodes after withdrawal of glucocorticoids (with a new onset of renal involvement). His 2019 American College of Rheumatology/European League Against Rheumatism classification criteria (ACR/EULAR)[3] classification criteria score was 41 and IgG4-RD Responder Index (RI)[4] was 12



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Adverse Effects (AE)#, possibly associated with the Telitacicept usage	Cases (%) (N=10)
Injection site reaction*	8 (80%)
Elevated total triglycerides	1 (10%)
Elevated low density lipoprotein	4 (40%)
Decreased neutrophil count	1 (10%)
Decreased lymphocyte count	2 (20%)
Leucopenia	1 (10%)
Upper respiratory infection	1 (10%)
Lung infection	1 (10%)
Rash	1 (10%)

* Redness or mass formation at the injection site
\# All the AE recorded were grade 1.

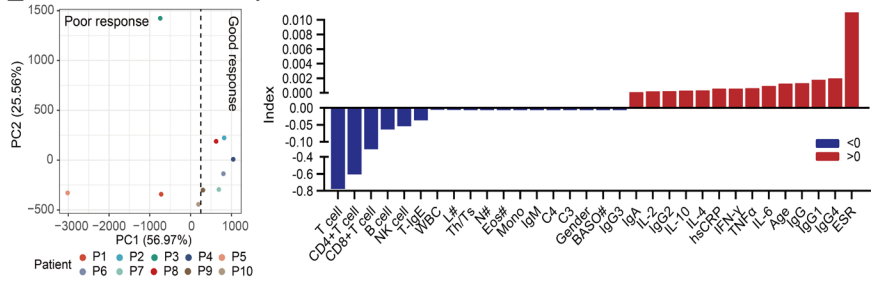

Figure 1 Clinical and laboratory parameters in IgG4-related disease (IgG4-RD) treated with telitacicept. (A) Left part shows previous IgG4-RD treatment strategy. The patient was diagnosed with IgG4-RD in Tongji Hospital in April 2017. At this point, the patient was treated with oral prednisone (30 mg orally) for 2 months. Prednisone dosage decreased regularly by 5 mg every 2 or 3 months to 5 mg in April 2018, which was maintained for 20 months until December 2019. And then withdrawal of prednisone sustained for 17 months until May 2021. (A) Right part shows serum levels of IgG (g/L), IgM (*10 g/L), IgE (*0.1 IU/L), IgA (g/L), IgG1-4 (g/L), C3 (g/L), C4 (g/L), Cr (μmol/L), eGFR (ml/min/1.73m^2) and IgG4-RD RI before and after treatment with telitacicept. Pink areas indicate the period of telitacicept treatment. Bar plot on the left and upper area shows the timeline of treatment from the first onset of IgG4-RD. (B) The maximum lesion area of left submandibular gland and lymph node in coronal plane, and the largest maximum lesion area of kidneys (red arrows) in transverse plane before and after 60 weeks of telitacicept treatment. (C) The safety data recorded during the telitacicept treatment. (D) Mann-Kendall trend analyses of the IgG4-RD RI, CD24-plasmablasts, IgE and IgM during the follow-up. (E) Principal component analysis of the baseline immune laboratory data of the enrolled cases. (F) Analysis of the coefficients of x-variables of the PC1's linear combination with the following baseline indices: gender, age, WBC, N#, L#, Mono#, Eos#, Baso#, ESR, hsCRP, IgG, IgA, IgM, C3, C4, IgG1, IgG2, IgG3, IgG4, IgE, IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, T cell, CD8+T cell, CD4+T cell, NK cell, B cell, Th/Ts. Data were analysed and plotted with Prism software (V.8.0.2) or R software (V.4.1.1). Baso#, absolute basophil count; Eos#, absolute eosinophil count; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitive C-reactive protein; L#, absolute lymphocyte count; N#, absolute neutrophil count; Mono#, absolute monocyte count; RI, Responder index Index; WBC, white blood cell.

at admission. After the discontinuation of glucocorticoids within 1 week, we initiated the treatment of telitacicept (160 mg every week hypodermic injection) for 60 weeks due to his unwillingness to use long-term systemic glucocorticoid therapy. His symptoms were gradually relieved after the initiation of treatments. IgG4-RD RI decreased from 12 to 1 at week 60 (figure 1A). The levels of IgG4, IgE, IgG and IgM decreased and serum complement C3, C4, creatinine and eGFR returned to normal during the treatment of telitacicept (figure 1A). MRI detections showed a gradual and persistent reduction in the sizes of the involved salivary glands (returned to normal size at week 60) and the renal cortex lesions (almost diminished) during the 60 weeks' treatment with telitacicept (figure 1B and online supplemental figure S1).

Besides the aforementioned case, based on the criteria listed in online supplemental table S1, we recruited additional nine IgG4-RD cases (eight belonged to the 'Mikulicz and Systemic' group and one belonged to the 'Head and Neck-Limited' group,[5] online supplemental table S2) and treated with the same therapeutic strategy to examine the remission rate after telitacicept treatment. No severe adverse event was observed, however, injection site reactions (redness or mass formation), which were mild and controllable, were observed in 80% of the patients (figure 1C). Similar high ratio of injection site reactions of telitacicept administration could also be observed in clinical trials for other diseases.[6] Trend analyses showed significant decreases in IgG4-RD RI, serum IgM, IgE and $CD19^{+}CD24^{-}CD38^{hi}$ plasmablast levels during the 24 weeks of follow-up (figure 1D, online supplemental figure S2), while no statistical significances were observed in ESR, complement C3 and C4, total IgG and its subclasses (online supplemental figure S3). However, there were four patients without response to telitacicept (improvement of IgG4-RI less than 2) during the 24 weeks of follow-up, resulting in a partial remission rate of 60% to telitacicept. Principal component analysis based on the baseline laboratory data distinguished the responsive and nonresponsive patients well on the first principal component (contributing rate: 56.97 %) (figure 1E). Analyses to the baseline data indicated that ESR, serum IgG4, IgG and plasmablast ratio contributed substantially to the status of 'remission', while total T, $CD4^{+}$ T, $CD8^{+}$ T and B cell counts contributed to the status of 'non-remission' (figure 1F and online supplemental table S3). This result suggested that patients with therapeutic response to telitacicept had relatively higher levels of serum immunoglobulin and plasmablast at baseline, while non-remission patients had relatively higher counts of lymphocytes.

To the best of our knowledge, this is the first study reporting the therapeutic potential of BLyS/APRIL-targeting biologics in IgG4-RD. Patients with IgG4-RD patients have limited treatment options, especially for those who were unable or unwilling to use long-term glucocorticoid therapy due to various conditions. Here, we reported a 60% partial remission rate at week 24, a duration widely adopted for the observation of IgG4-RD remission[7] under the treatment of telitacicept, which showed potential effects on reducing lesion size, relieving symptoms and improving laboratory parameters in patients with IgG4-RD, especially in those who had high levels of ESR, IgG4, IgG and plasmablasts. Although future larger sample size studies are required to optimise the dosage and duration, this study may provide an important basis for developing a treatment strategy for IgG4-RD patients who are not suitable for glucocorticoid therapy.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study was approved by the Institutional Review Board and Medical Ethics Committee of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, and written informed consents were acquired before medication administration, sample/data collection, and subsequent analyses. Participants gave informed consent to participate in the study before taking part.

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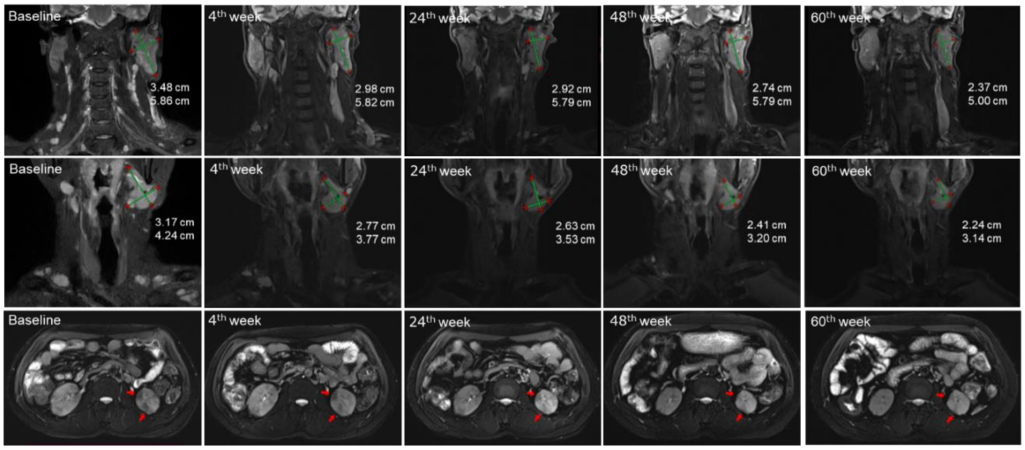

Figure S1 The maximum lesion area changes of multiple organs by MRI. The figure shows the maximum lesion area of left submandibular gland, bilateral parotid gland and lymph node in coronal plane, and the largest maximum lesion area of kidneys (red arrows) in transverse plane before (baseline) and after treatment with Telitacicept (at 4th, 24th, 48th and 60th week).

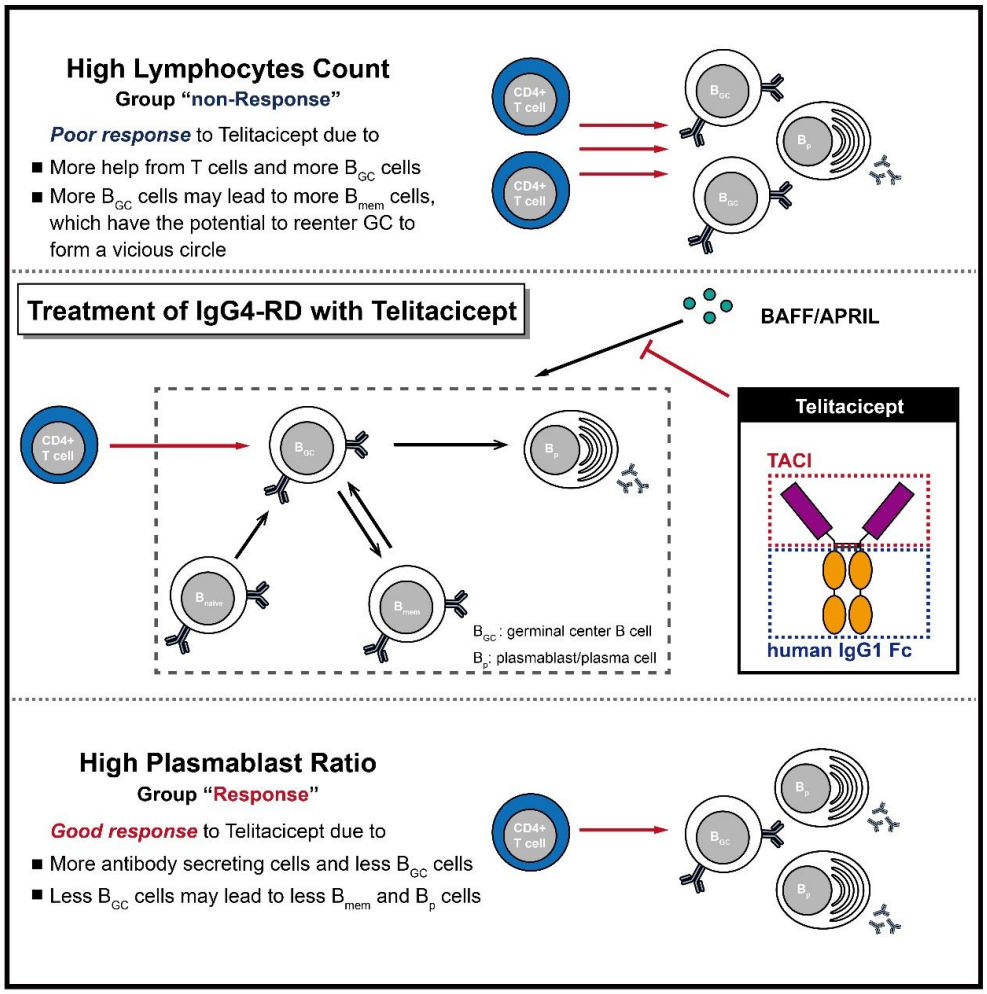

Figure S2 Treatment of IgG4-RD with Telitacicept, and an assumption of the dynamic of plasmablasts ratio observed in this clinical trial. For the plasmablasts' dynamic of IgG4-RD patients observed in Telitacicept treatment, although we didn't further investigate the detailed mechanism, some previous mechanistic studies related to BAFFR signaling may provide some clues: Zarnegar et al's study reveals that both canonical and non-canonical NF-κB signaling pathway can be activated by CD40L, while only non-canonical NF-κB signaling pathway can be stimulated by BAFF1; Lau et al's study shows that although BAFF/BAFFR signaling is important for the generation of germinal center independent, unmutated memory B cells, BAFFR is not essential for the survival and function of germinal center B cell and memory B cells that have undergone somatic hypermutations2; Guo, R. et al have also found that simultaneous activation of both BCR and CD40 was more potent in promoting B cell proliferation, when compared with the simultaneous activation with BCR and BAFFR3. Our recently published data also indicated a significant enrichment of germinal center reaction (GC reaction) related signatures in IgG4-RD involved tissues, and a large part of the B cells infiltrated into the involved tissue were germinal center B cell-like (revealed by single cell RNA-sequencing). GC reaction can promote the development

of memory B cells and plasma cells, and just like naïve B cells, memory B cells can reenter the germinal center and undergo further GC reactions4-6.

These clues indicated that BAFF may not be essential for the B cells in activated status, which relies more on the CD40-signaling. B cells in relatively "silent/steady" status have larger requirements for BAFF signaling. For the IgG4-RD patients, we assume: after receiving the treatment of Telitacicept, some activated B cells expanded and obtained (transformed to) the memory phenotype (influenced little by the BAFF/APRIL blockage, and therefore elevated in the early time after treatment), while the cells in relatively silent status (for the second/third/… wave attack) were "blocked" by Telitacicept, and thus cannot elicit a further autoimmune reaction, which leads to the disease remission and decrease of the corresponding cell subsets. Therefore, based on the aforementioned assumption, the ratio of plasmablasts elevated first, due to the potential unresponsiveness/poor responsiveness of already activated B cells to Telitacicept treatment, which further transformed/developed into plasmablasts, and decreased, due to the blockade of B cells that were not fully activated at the time of Telitacicept usage (if not intervened by Telitacicept, these not fully activated B cells could be further activated by pathogenic T cells).

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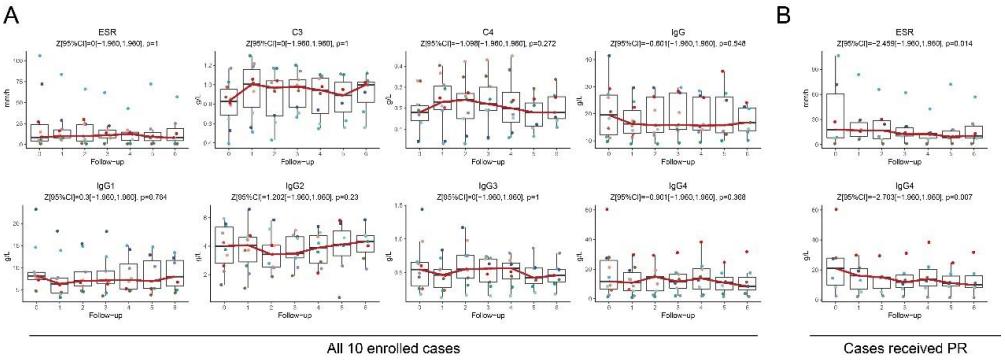

Figure S3 Trend analyses of other laboratory indices potentially reflecting the immune responses. A, Indices including ESR, C3, C4, IgG, and its subtypes (IgG1, IgG2, IgG3, and IgG4) were analyzed during the follow up period. **B**, Significant decreasing trends of ESR and serum IgG4 levels were observed in patients who received partial remission (PR) treated with Telitacicept.

Table S1 Inclusion and exclusion criteria

Inclusion Criteria
1. Patients to be included in the study must meet the classification criteria for IgG4-associated disease (2019ACR/EULAR); 2. Within half a year before enrollment, the patients did not use the following drugs: A) Telitacicept or other biological agents with the same or similar targets; B) Tumor necrosis factor inhibitor (TNFi) or tumor necrosis factor receptor antibody fusion protein; C) Rituximab (or other B cell depleting agents); 3. Patients should be at least 18 years old at the time of enrollment; 4. Patients must agree to take a reliable contraceptive measure before enrolling; 5. The subject or his/her guardian agrees to participate in the study and signs the informed consent.
Exclusion Criteria
1. Currently pregnant or breastfeeding, or planning to become pregnant within half a year; 2. Significant health problems or diseases, including (but not limited to) the following: poorly controlled hypertension (>=160/95 mmHg), congestive heart failure (New York Heart Association Level III or IV), poorly controlled diabetes or functioning so poorly that they are unable to take care of themselves, other autoimmune diseases; 3. The total number of white blood cells <3,000/ μL, or platelets < 100,000/ μL, neutrophils < 1,500/ μL, or hemoglobin <8.5 g/ dL (85 g/L) during screening; 4. Active systemic infection (except common upper respiratory tract infection) occurred within 2 weeks before screening; 5. Current infection, chronic or recurrent infectious disease, or evidence of latent tuberculosis infection (as determined by PPD or T-SPOT); 6. Known to be infected with HIV, hepatitis B, or hepatitis C at screening time; 7. A history of lymphoproliferative disease or any known malignancy or a history of malignancy in any organ system within the last 5 years; 8. Allergic to Telitacicept; 9. Participating in other clinical trials; 10. Any medical or psychiatric condition that the Investigator considers will prevent participants from following the protocol or completing the study according to the protocol; 11. Patients refuse to comply with the requirements of this study to complete the study; 12. Any other circumstances considered by the Investigator to be inappropriate for participation in this study.

Table S2 Characteristics of enrolled cases

ID	Gender	Involved Organ	Baseline IgG4-RD RI (2012)	Endpoint IgG4-RD RI (2012)	Response to Telitacicept	History	Discontinuation of the glucocorticoids in the 1st week of treatment
1	Female	Lacrimal glands,submandibular glands,kidneys,lymph nodes	15	14[#]	No	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days
2	Male	Submandibular glands,lymph nodes	9	6	Yes	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days
3	Male	Submandibular glands,parotid glands,lymph nodes	9	8	No	Relapse, no medication usage for 6 months	0.6 mg/kg methylprednisolone for 7 days
4	Male	Submandibular glands,parotid glands,kidneys,lymph nodes	12	4	Yes	Relapse, no medication usage for 18 months	0.6 mg/kg methylprednisolone for 7 days
5	Male	Lacrimal glands,musculus ocularis,submandibular glands,lung, retroperitoneum,lymph nodes	18	24	No	Relapse, no medication usage for 3 months	0.6 mg/kg methylprednisolone for 7 days
6	Male	Lacrimal glands,submandibular glands, retroperitoneum,lymph nodes	15	9	Yes	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days
7	Male	Pancreas,lacrimal glands,submandibular glands,musculus ocularis,lymph nodes	15	5	Yes	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days
8	Male	Lacrimal glands,submandibular glands,parotid glands,lymph nodes	12	7	Yes	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days
9	Male	Lacrimal glands,submandibular glands,parotid glands,lymph nodes	12	4	Yes	Relapse, no medication usage for 18 months	0.6 mg/kg methylprednisolone for 7 days
10	Female	Lacrimal glands,submandibular glands,parotid glands,lymph nodes	12	16	No	Treatment naïve	0.6 mg/kg methylprednisolone for 7 days

Note: there is no statistical difference between group "non-Response" and "Response" in index "**Number of involved organ**" ("non-Response" vs. "Response", 4.00[3.25,5.50] vs 4.00[3.50,4.25], p=0.904) and "**Baseline IgG4-RD RI (2012)**" ("non-Response" vs. "Response", 13.50[9.75,17.25] vs 12.00[11.25,15.00], p=0.737). All the aforementioned data are presented as median[IQR], and analyzed with Mann-Whitney U test. The "**Baseline IgG4-RD RI (2012)**" evaluations were based on reference [Carruthers MN, Stone JH, Deshpande V, Khosroshahi A. Development of an IgG4-RD Responder Index. International journal of rheumatology 2012;2012:259408.]. # addition of glucocorticoids in the 5[th] week without authorization based on the progressive lacrimal gland enlargement and elevated serum IgG4 level (disease relapse). Therefore, this patient discontinue the trial, and the IgG4-RD RI recorded her status at that time-point. The median age of patients at the time of screen was 51.5 years old, ranged from 25 to 71.

Table S3 Baseline parameters in remission and non-remission patients after Telitacicept treatment.

	Group		Estimated differences, Non-remission vs Remission [95% CI]	*p* value
	Non-remission (n=4)	Remission (n=6)		
T cell (/μL)	2023[1748,2471]	733[682,800]	1279[357,2912]	0.0095
CD4+T cell (/μL)	1121[1011,1623]	528[424,574]	634[338,2411]	0.0095
B cell (/μL)	268[236,300]	114[76,125]	152[75,230]	0.0095
L# ($\times10^9$/L)	2.93[1.882,4.358]	1.32[1.158,1.46]	1.645[0.19,4.55]	0.019
CD45RA-CCR7- ($\times10^4$/mL)	74.945[64.49,113.401]	24.577[14.064,29.396]	50.408[16.309,194.433]	0.019
CD27+IgD- ($\times10^4$/mL)	3.797[2.352,5.355]	1.097[0.836,1.511]	2.583[0.005,5.847]	0.0381
CD27+IgD+ ($\times10^4$/mL)	3.496[2.596,4.105]	0.605[0.379,0.796]	2.905[0.14,4.478]	0.0381
CD45RA+CCR7- ($\times10^4$/mL)	8.916[7.595,10.312]	4.878[3.745,6.239]	4.038[0.57,7.504]	0.0381
CD27+ plasmablasts (%)	0.49[0.292,0.76]	1.21[0.868,1.605]	-0.68[-2.88,0.05]	0.0667
CD27-IgD+ ($\times10^4$/mL)	17.625[15.285,18.482]	7.419[4.408,8.808]	9.668[-0.263,14.341]	0.0667
C4 (g/L)	0.205[0.188,0.248]	0.15[0.062,0.178]	0.066[-0.11,0.2]	0.1066
IgG (g/L)	12.8[10.707,17.407]	23.97[18.882,28.727]	-9.13[-26.89,5.2]	0.1143
IFN-γ (pg/mL)	0.93[0.7,1.37]	2.07[1.517,2.825]	-1.32[-5.68,0.97]	0.1143
CD8+T cell (/μL)	609[486,697]	254[192,298]	355[-69,636]	0.1143
CD20+BCMA+TACI+ (%)	3.23[2.91,3.517]	1.435[1.322,2.53]	1.51[-0.15,2.78]	0.1143
CD20+BCMA+TACI- (%)	3.005[2.713,3.84]	2.43[2.365,2.638]	0.57[-1.23,3.26]	0.1143
CD24-plasmablasts (%)	1.63[1.138,1.985]	3.035[1.8,4.818]	-1.68[-4.46,0.37]	0.1143
CD45RA-CD25+ ($\times10^4$/mL)	19.504[13.508,49.198]	10.56[4.87,16.031]	10.18[-6.158,111.978]	0.1143
Baso# ($\times10^9$/L)	0.06[0.043,0.073]	0.025[0.013,0.038]	0.03[-0.01,0.06]	0.1332
Mono# ($\times10^9$/L)	0.59[0.495,0.742]	0.375[0.363,0.418]	0.204[-0.02,0.68]	0.1344
IL-4 (pg/mL)	1.515[1.402,1.888]	2.545[1.83,3.035]	-0.586[-1.74,0.35]	0.1344
CD27-IgD- ($\times10^4$/mL)	3.872[1.977,5.539]	1.071[0.701,1.198]	2.096[-0.455,5.134]	0.1714
ESR (mm/h)	4.5[3.25,7.5]	18[8.25,60.75]	-8.09[-101,6]	0.1995