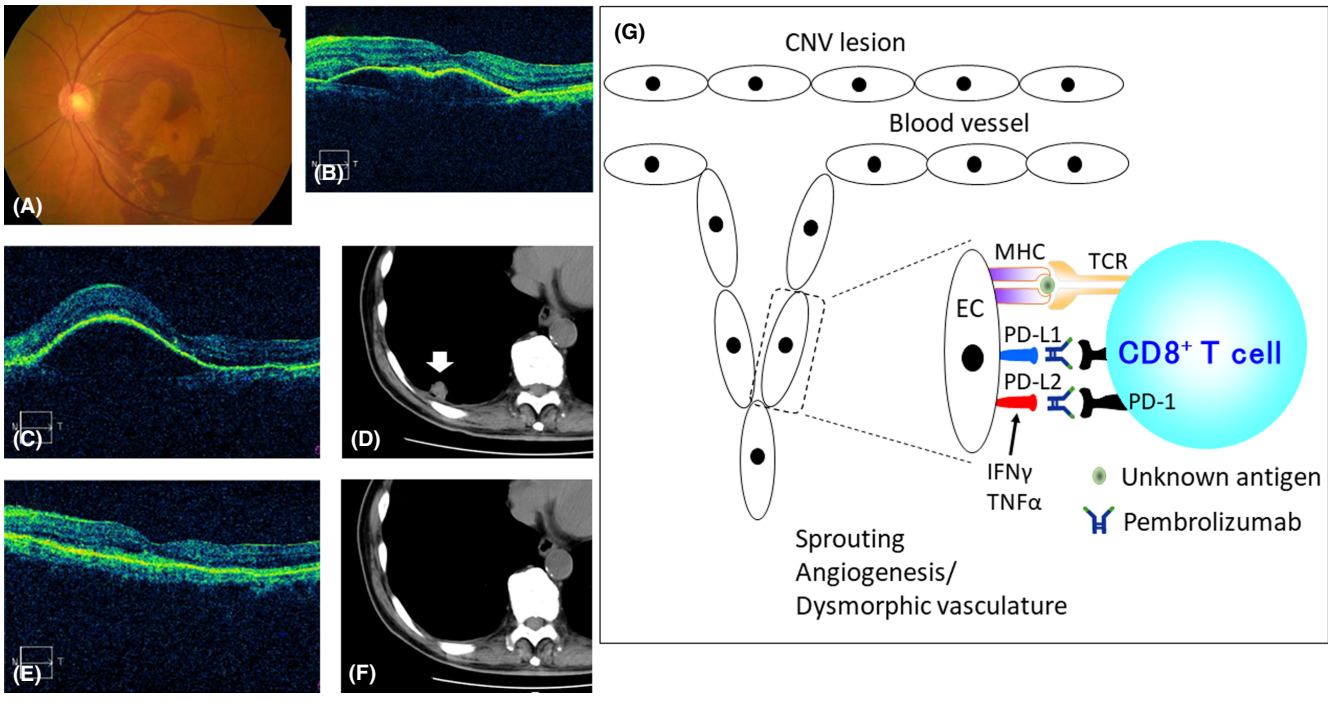

Fig. 1. At presentation, fundus photography of the left eye shows submacular haemorrhage (A) and OCT of the left eye shows haemorrhagic retinal pigment epithelium detachment (PED) involving the fovea (B). After 15 doses of intravitreal VEGF inhibitor administered regularly for a period of 24 months, OCT of the left eye shows no obvious reduction of serous PED (C) and CT shows squamous cell carcinoma in the lung (white arrow) (D). At week 6 after starting systemic therapy with the immune checkpoint inhibitor pembrolizumab for lung cancer, OCT of the left eye shows obvious reduction of serous PED (E) and CT shows marked reduction in size of lung cancer (F). (G) Schematic diagram showing hypothetical molecular mechanisms underlying regression of choroidal neovascularization (CNV) lesion by pembrolizumab. The most important cell type activated during angiogenesis is the endothelial cell (EC). ECs may express MHC, and co-stimulatory and co-inhibitory molecules including PD-L1 and PD-L2. The latter can be upregulated by cytokines such as IFNγ and TNF-α, and act as ligands for PD-1 expressed on $CD8^+$ T cells. By blocking PD-1/PD ligands interaction, pembrolizumab may allow more activated T cells to engage in EC killing in sprouting angiogenesis or dysmorphic vasculature, and ultimately destruction of CNV lesion.

checkpoint inhibitor that activates $CD8^+$ T cells may be one of the important factors that inactivated choroidal neovascularization in the present case of nAMD (Fig. 1G). Since this study was a retrospective observation of one case, a prospective study of more cases would be needed to examine the hypothesis.

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Efficacy and maintenance of rituximab treatment in non-infectious scleritis

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Editor,

Scleritis is characterized by intense pain, redness, potentially destructive complications, and frequently insufficient response to local and systemic treatments (Sainz de la Maza et al. 2012; Wieringa et al. 2013). Rituximab (RTX) was introduced as treatment for scleritis after its successful use for systemic autoimmune diseases associated with scleritis.

RTX is a monoclonal antibody that targets CD20 antigen on the surface of B-lymphocytes, resulting in their depletion. Beneficial effects of RTX were noted in non-infectious scleritis (Suhler et al. 2014; Cao et al. 2016). However, a lack of consensus in the management of RTX treatment after the phase of induction remains. We performed a retrospective study of 18 patients with non-infectious scleritis, who were treated with RTX (ocular indication), and were followed for at least 2 years after the start of RTX treatment. This study was reviewed by the local Medical Ethics Committee, and followed the Tenets of the Declaration of Helsinki.

Full ophthalmic evaluation and work-up examinations according to national uveitis and scleritis guidelines were performed. The main outcomes were the accomplishment of remission, the average time in remission, recurrences as well as adverse events. Remission was defined as an inactive disease, with or without other immunosuppressive treatment, during at least three months. Mann–Whitney–*U* test, Chi-square, or Fischer's exact test were performed to analyse results (SPSS version 25.0).

Baseline characteristics and the efficacy of RTX treatment are given in the Table 1. Remission within three months after first RTX infusion was reached in 15/18 (83%), with an average duration of 32 months. Treatment failure (no remission of scleritis) was noticed in 3/18 (17%) patients. Recurrence of scleritis within two years after RTX treatment occurred in 7/15 (47%). In addition to scheduled reinfusion, five additional patients received reinfusion of RTX due to reactivation of their scleritis. All five patients reached remission shortly after reinfusion of RTX.

No differences in recurrence rates were found when patients with

Table 1. Baseline characteristics and rituximab efficacy according to time-interval between the onset of scleritis and initiation of rituximab therapy

Section A. Characteristics and efficacy of rituximab treatment in 18 patients with non-infectious scleritis

Age at onset in years, mean ± SD (range)	54.3 ± 14.1 (22-83)
Male, No (%)	7/18 (39%)
Bilateral scleritis, No (%)	15/18 (83%)
Location, No (%)	
Anterior scleritis*	9/18 (50%)
Posterior scleritis	1/18 (6%)
Panscleritis	4/18 (22%)
Sclerouveitis	4/18 (22%)
Systemic disease, total[†], No (%)	14/18 (78%)
Previous treatment with CS, No (%)	18/18 (100%)
Previous treatment with DMARDS, No (%)	14/18 (78%)
Previous treatment with CYC, No (%)	4/18 (22%)
Interval onset scleritis – start RTX[‡] in months, mean ± SD (range)	24.6 ± 32.8 (1–131)
Remission, No (%)	15/18 (83%)
Recurrence[§], No (%)	7/15 (47%)
Time to recurrence in months[§], mean ± SD (range)	8.1 ± 3.9 (5–16)
CS dosage tapered to <10 mg/day[¶], No (%)	5/14 (36%)
DMARD stopped[¶], No (%)	4/9 (44%)
Reinfusion of rituximab, No (%)	13/18 (72%)
Scheduled from start/non-ocular indication	8/13 (62%)
Reactivation scleritis	5/13 (38%)
Adverse events**, No (%)	6/18 (33%)

Section B. Comparison of rituximab efficacy according to time-interval between the onset of scleritis and initiation of rituximab therapy

	RTX within 1 year after the onset of scleritis (N = 11)	RTX after one year after the onset of scleritis (N = 7)	p-value
Age at onset in years, mean ± SD (range)	58.5 (± 15.2)	47.7 (± 9.7)	0.04
Systemic disease, No (%)	9 (82%)	5 (71%)	1.00
Follow-up duration in months, mean ± SD (range)	59.0 (± 24.7)	54.7 (±37.7)	0.48
Remission, No (%)	11 (100%)	4 (57%)	0.04
Time in remission[††] in months, mean ± SD (range)	19.2 (± 17.6)	8.5 (± 5.2)	0.03
Failure / recurrence[‡‡], No (%)	4/11 (36%)	7/7 (100)	0.03

DMARDs = Disease-modifying anti-rheumatic drugs, RTX = rituximab, CS = corticosteroids, CYC = cyclophosphamide.

*Subtype of anterior scleritis was diffuse in four patients and necrotizing in five patients.

[†]Of the systemic diseases, 7/14 (50%) had granulomatosis with polyangiitis, 2/14 (14%) had rheumatoid arthritis, 2/14 (14%) had relapsing polychondritis and 3/14 (21%) had other systemic diseases.

[‡]First rituximab administration was given intravenously in a dosage of 1000mg, which was repeated after an interval of two weeks. Regular 6-month reinfusions were arbitrarily planned from the onset of RTX therapy for 7 patients; in the remainder, a "wait-and-see" strategy was followed.

[§]Within 2 years after first RTX.

Within six months after first RTX infusion. The five remaining patients were still on treatment with DMARDs at two years after start of RTX.

**All recurrent infections except one case of reaction at infection site. Two patients required additional intravenous immunoglobulin therapy due induced hypogammaglobulinemia with recurrent infections. One patient had to stop RTX treatment because chemotherapy for a lung carcinoma was required.

[††]Time in remission after first RTX, includes the first month, needed to adhere to the definition of remission, has a cut-off value of 24 months.

[‡‡]Included were recurrences occurring within 24 months after the start of rituximab treatment.

scheduled reinfusions were compared with patients on a 'wait-and-see' policy ($p = 0.61$). Remissions were more common in patients who received RTX treatment within one year after the onset of scleritis compared to longer intervals between the onset of scleritis and RTX treatment ($p = 0.04$; Table 1). The patients who received RTX later than one year after the onset of scleritis exhibited recurrences and/or failure of RTX treatment more often ($p = 0.03$). No differences were found in age at onset, laterality, gender, systemic disease, or follow-up duration between these patient groups. Previous treatment did not affect the outcomes described.

Our results are consistent with previously reported data on induction of remissions (Suhler et al. 2014; Cao et al. 2016). Thereby, our results confirm a limited number of sustained responses after the first RTX infusion (Suhler et al. 2014; Cao et al. 2016).

In our series, treatment with scheduled infusions was not superior to a 'wait-and-see' policy. In systemic diseases, beneficial results were found with scheduled reinfusion (Alba & Flores-Suarez 2016). In scleritis, one report described a slight benefit for treatment with scheduled reinfusion (nine versus five patients) (Cao et al. 2016). In our cohort, no differences in recurrence rates were found when patients with scheduled reinfusion were compared with patients on a 'wait-and-see' policy.

Despite the small number of patients in our study, we show that RTX treatment for non-infectious scleritis is effective. However, repeated infusions are commonly required to maintain quiescence of the disease. We point out that early treatment with RTX may be associated with better efficacy. Further research on the pathogenesis of scleritis, and larger treatment studies are essential for an optimal treatment approach and achievement of sustainable remission of this potentially blinding disorder.

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