Rheumatology, 2025, **64**, 895–897
https://doi.org/10.1093/rheumatology/keae448
Advance access publication 24 August 2024
Letter to the Editor

British Society for Rheumatology RHEUMATOLOGY OXFORD

Letter to the Editor (Case report)

A case of refractory IgG4-related disease successfully treated with daratumumab and lenalidomide

Denis Coulomb[1], Vanessa Szablewski[2], Nicolas Robert[3], Anne-Marie Dupuy[4], Rayane Berrahouane[1], Radjiv Goulabchand[5], Jérôme Moreaux[3,7,8], Alexandre Thibault Jacques Maria[9,10], Charles Herbaux[1,7,*]

[1]Department of Clinical Hematology, CHU de Montpellier, Montpellier, France
[2]Department of Pathology, CHU de Montpellier, Montpellier, France
[3]Department of Biological Hematology, CHU de Montpellier, Montpellier, France
[4]Department of Biochemistry, CHU de Montpellier, Montpellier, France
[5]Desbrest Institute of Epidemiology and Public Health, University of Montpellier and INSERM, Montpellier, France
[6]Department of Internal Medicine, CHU de Nîmes, Nîmes, France
[7]UMR CNRS-UM 9002, Institute of Human Genetics, Montpellier, France
[8]Institut Universitaire de France (IUF), Paris, France
[9]Department of Internal Medicine & Onco-Immunology (MedI2O), CHU de Montpellier, Montpellier, France
[10]Institute for Regenerative Medicine and Biotherapy (IRMB), University of Montpellier, Montpellier, France

*Correspondence to: Charles Herbaux, Department of Clinical Hematology—CHU de Montpellier & Institute of Human Genetics, UMR 9002—CNRS, University of Montpellier, School of Medicine, Montpellier, France. E-mail: c-herbaux@chu-montpellier.fr

Rheumatology key message

- A case of IgG4-related disease refractory to steroids and rituximab was successfully treated with daratumumab, lenalidomide and dexamethasone.

Dear Editor, IgG4-related disease (IgG4-RD) is a rare chronic systemic autoimmune disorder. This disease is characterized by severe fibro-inflammation, elevated serum IgG4 concentration, and polytypic tissue infiltrate of lymphocytes and plasma cells enriched with IgG4-positive plasma cells that can lead to organ failure. The diagnosis is based on the classification criteria determined by the ACR and the EULAR [1]. It is commonly accepted that first-line therapy is based on steroids. Although this treatment is efficient in >90% of the cases, the history of the disease is marked by relapses, corticodependence and corticoresistance [2]. Rituximab may be the best option for patients dependent on or refractory to steroids [2, 3]. Because of its recent description, the optimal therapeutic management of IgG4-RD refractory to steroids and rituximab remains unclear. Many studies suggest using immunosuppressive drugs or targeted therapies based on theoretical or retrospective data and several clinical trials are ongoing [4, 5]. Plasma cells and activated lymphocytes of IgG4-RD express CD38, which the daratumumab can target [2]. On the other hand, lenalidomide is an immunomodulatory drug that has direct anti-lymphocyte and plasma cell activity, as well as indirect effects mediated through various immune cells [6]. Moreover, the safety of combining daratumumab, lenalidomide and dexamethasone (D-RD) in MM has been well established [7]. Therefore, we hypothesized that this triplet could be efficient and well-tolerated in targeting IgG4-RD.

We report the case of a 72-year-old man with systemic relapse of IgG4-RD manifested by pleural effusion, hemolytic anaemia and polyclonal hypergammaglobulinemia, refractory to steroids and rituximab, who was successfully treated with a combination therapy including daratumumab, lenalidomide and dexamethasone. This patient had been followed since 2015 for an IgG4-RD diagnosed with histological evidence of chronic sclerosing sialadenitis and a maxillary and renal IgG4-positive plasma cells infiltrate concordant with a PET scan showing renal, pulmonary and maxillary fixation. This was associated with increased serum IgG4 level (12.0 g/l), inflammatory syndrome and polyclonal hypergammaglobulinemia. Until 2019, the patient received repeated courses of steroids (Supplementary Fig. S1, available at *Rheumatology* online) with favorable responses: normalization of serum protein electrophoresis and amelioration of pulmonary function. In 2019, we chose to start another course of steroids because of symptomatic parenchymal lung involvement responsible for mixed ventilatory defect and dyspnea. Unfortunately, we observed a progression despite continued steroid use. We therefore decided to initiate rituximab followed by maintenance infusions, which led to normalization of lung function and complete regression of dyspnea with good tolerance until 2022. At that time, tomodensitometry showed us an increase in pulmonary involvement associated with increased serum IgG4. Despite the absence of clinical symptoms, we decided to intensify the treatment with increased corticotherapy and two infusions of rituximab. In February 2023, we

Accepted: 8 August 2024

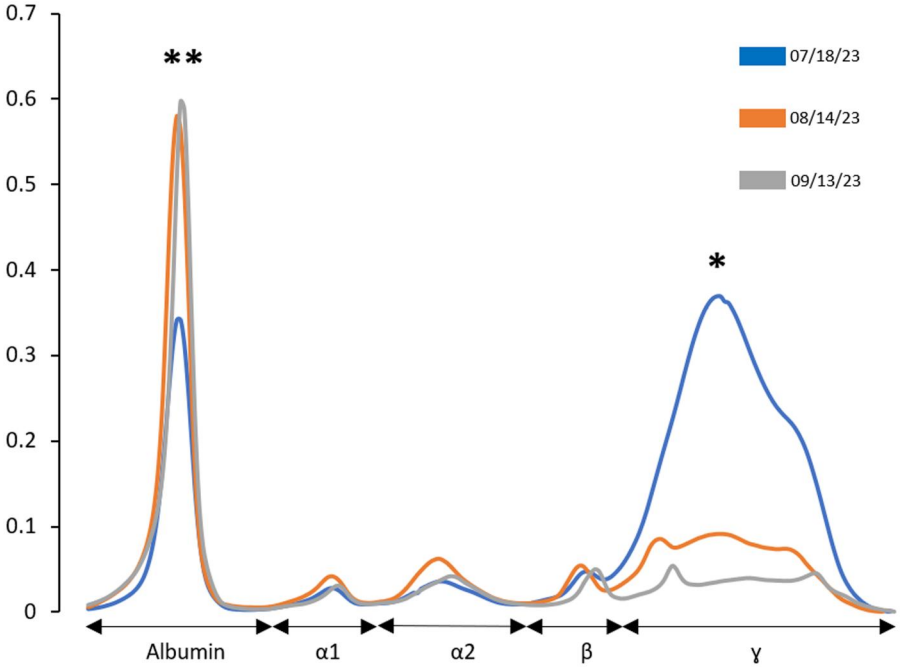

Figure 1. Serum protein electrophoresis before initiation of D-RD (July 2023) and following one and two cycles of treatment. This figure shows the patient's protein electrophoresis plot at three different times. To ensure comparability between the time points, the y-axis shows optical density normalized to the total protein level. The blue curve shows the electrophoresis plot before the initiation of the first cycle of D-RD (18 July 2023). At this time, we can observe the importance of the polyclonal hypergammaglobulinemia (72.3 g/L) (*). The orange curve shows the electrophoresis plot after the first cycle of D-RD (14 August 2023). The grey curve shows the electrophoresis plot after the second cycle of D-RD (13 September 2023) reflecting a normalization of the gammaglobulins level (9.8 g/L). A strong improvement in albumin level is also observed after one and two cycles of treatment (from 22.6 to 27.6 and 34.1 g/L, respectively) (**). α1: α1-globulin fraction; α2: α2-globulin fraction; β: β-globulin fraction; γ: γ-globulin fraction

observed a worsening of the disease with the persistence of parenchymal involvement and the onset of pleural effusion responsible for dyspnea and restrictive syndrome. Moreover, one month after rituximab infusions, circulating anti-rituximab antibodies were detected along with the persistence of a substantial B-cell population. At this time, the patient had pleural effusion, cold agglutinin disease, increased rate of polyclonal gammaglobulins (72.3 g/l), free light chains (kappa 608 mg/l and lambda 238 mg/l) and serum IgG4 (21.2 g/l). Other potential diagnoses were excluded with a series of tests. These assays showed the absence of tumoral cells and confirmed the presence of a polytypic plasma cell population expressing CD38, CD45 and CD138. This plasma cell population represented 17.8% of the bone marrow cells. Regarding pleural effusion, we observed 900 cells/mm^3 with 42% being polytypic plasma cells, of which 72% exhibited a kappa phenotype. All these outcomes were consistent with the diagnosis of an IgG4-RD relapse, refractory to steroids and rituximab.

In this context of therapeutic impasse, and because of the rationale explained above, we initiated a new therapeutic approach employing a combination of D-RD, with a regimen classically used in multiple myeloma [7]. After one cycle of D-RD, we observed a decrease in serum gamma-globulins levels (to 16.3 g/l) (Fig. 1), and a weight regain (from 64 to 69 kg). The only adverse event was a grade 4 neutropenia, with no fever or infectious event. Therefore, we adjusted the lenalidomide dosage to 10 mg per day for subsequent cycles. After three cycles, we observed an important reduction of the pulmonary involvement, a normalization of gammaglobulins levels (11.3 g/l), as well as a reduction of free light chains levels (46 mg/l), and an improvement of haemoglobin levels (125 g/l *vs* 89 g/l). We also noticed an improvement in performance status from 2 to 0 and, after eight cycles, a normalization of IgG4 level (0.7 g/l). At the time of this report, after nine cycles, no new adverse events have been observed.

Overall, we are reporting here the case of IgG4-RD refractory to steroids and rituximab successfully treated with D-RD. Although the follow-up duration is still limited, our patient obtained complete remission after three cycles, the only toxicity observed was neutropenia (reversible after lenalidomide dose adjustment). These findings highlight the potential efficacy of this combination in refractory IgG4-RD and warrant further investigation.

The authors certify that they have obtained the patient's consent.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data supporting the findings of this study are available from the corresponding author on request by email.

Funding

This work did not receive any funding.

Disclosure statement: The authors have declared no conflicts of interest.

Acknowledgements

The authors thank the patient and his family whose data are presented here.

References

1. Wallace ZS, Naden RP, Chari S *et al.*; for the American College of Rheumatology/European League Against Rheumatism IgG4-Related Disease Classification Criteria Working Group. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. Arthritis Rheumatol 2020;72:7–19.
2. Lanzillotta M, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ 2020;369:m1067.
3. Patel U, Saxena A, Patel D *et al.* Therapeutic uses of rituximab and clinical features in immunoglobulin G4-related disease: a systematic review. Cureus 2023;15:e45044.
4. Katz G, Stone JH. Clinical perspectives on IgG4-related disease and its classification. Annu Rev Med 2022;73:545–62.
5. Omar D, Chen Y, Cong Y, Dong L. Glucocorticoids and steroid sparing medications monotherapies or in combination for IgG4-RD: a systematic review and network meta-analysis. Rheumatology 2020;59:718–26.
6. Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-hodgkin lymphoma. J Clin Oncol Off J Am Soc Clin Oncol 2015;33:2803–11.
7. Dimopoulos MA, Oriol A, Nahi H *et al.*; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:1319–31.

Rheumatology, 2025, 64, 895–897
https://doi.org/10.1093/rheumatology/keae448
Letter to the Editor