ACR Open Rheumatology
Vol. 7, No. 5, May 2025, e70027
DOI 10.1002/acr2.70027
© 2025 The Author(s). *ACR Open Rheumatology* published by Wiley Periodicals LLC on behalf of American College of Rheumatology.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Clinical Manifestations and Treatment in Patients With Relapsing Polychondritis: A Multicenter Observational Cohort Study

Roger Yang,[1] Rennie L. Rhee,[2] Kaitlin A. Quinn,[3] Naomi A. Amudala,[2] Carol A. McAlear,[2] Peter C. Grayson,[3] Peter A. Merkel,[2] Marcela Ferrada,[4] and Shubhasree Banerjee,[2] for the Vasculitis Clinical Research Consortium

Objective. Relapsing polychondritis (RP) is a rare, heterogeneous, multisystem disease lacking standard treatment guidelines. This study describes clinical manifestations in association with approaches to treatment.

Methods. Adults with physician-diagnosed RP were recruited into a multicenter observational cohort study. Clinical manifestations, organ damage, and medication history were recorded at the baseline study visit. Treatments received for RP at any time point before the initial visit were categorized into three groups: group 1 was treated with glucocorticoids (GCs) or no drugs, group 2 was treated with nonbiologic immunosuppressive (IS) drugs excluding JAK inhibitors (JAKis) with or without GCs, and group 3 was treated with JAKis or biologic IS drugs with or without nonbiologic IS drugs or GCs.

Results. Included in the study were 195 patients with RP who were predominantly female (167, 86%) and White (174, 89%), with a mean age of 49 ± 13years. All patients had ear, nose, or airway involvement, and 163 (83%) had musculoskeletal manifestations of RP. All patients had at least three clinical manifestations with median of 11 (range 3–19). GC treatment was given to 186 (95%) patients. Organ damage was seen in 80 (41%) patients. Treatment groups 1, 2, and 3 had 37 (19%), 55 (28%), and 103 (53%) patients, respectively. Patients in group 3 were more likely to have organ damage, arthritis, and subglottic stenosis.

Conclusion. Patients with RP have a high burden of clinical manifestations with resultant damage. Physicians typically treat RP with GCs, and the use of other immunosuppressive medications is variable. Absence of a consensus approach to treatment underscores the need for clinical trials and treatment guidelines for RP.

INTRODUCTION

Relapsing polychondritis (RP) is a rare immune-mediated systemic inflammatory disease affecting the cartilaginous structures and other tissues throughout the body, particularly the ears, nose, eyes, joints, and respiratory tract. Less commonly, it causes inflammation of the cardiovascular system, vasculitis, nervous system, and skin.[1,2]

Clinical manifestations of RP are heterogeneous.[2] Two sets of published diagnostic criteria, by McAdam et al[3] and Damiani et al,[4] rely heavily on presence of chondritis in different organ systems or histologic confirmation of chondritis. However, it is now recognized that RP exists in different clinical forms and many

Dr Yang's work was supported by the Vasculitis Clinical Research Consortium, the Vasculitis Foundation, the Penn Vasculitis Center, Association des médecins rhumatologue du Québec (Visithan-Khy Grant), and the CIUSSS de l'Est-de-l'Île-de-Montréal Specialist Fellowship Program. Dr Banerjee's work was supported in part by the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania. This work was also supported by the Relapsing Polychondritis Foundation and other generous donors to the Penn Relapsing Polychondritis Program.

[1]Roger Yang, MD: University of Pennsylvania, Philadelphia, and University of Montreal, Montreal, Canada; [2]Rennie L. Rhee, MD, MSCE, Naomi A. Amudala, CRNP, Carol A. McAlear, MA, Peter A. Merkel, MD, MPH, Shubhasree Banerjee, MD: University of Pennsylvania, Philadelphia; [3]Kaitlin A. Quinn, MD, MHS, Peter C. Grayson MD, MSc: NIAMS/NIH, Bethesda, Maryland; [4]Marcela Ferrada, MD: NIAMS/NIH and University of Maryland.

Drs Ferrada and Banerjee are senior authors.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/acr2. 70027).

Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr2.70027.

Address correspondence via email to Shubhasree Banerjee, MD, at shubhasree.banerjee@pennmedicine.upenn.edu.

Submitted for publication October 28, 2024; accepted in revised form February 19, 2025.

patients with RP may not fulfill these diagnostic criteria.[2–5] Therefore, reliance on the fulfillment of these diagnostic criteria for clinical or research purposes may lead to missed diagnoses and biased study populations. Timely diagnosis in RP is critical to avoid longstanding inflammation in cartilage leading to organ damage or life-threatening complications, such as tracheomalacia, bronchomalacia, subglottic stenosis, saddle nose deformity, external ear deformity, and permanent hearing loss.[5,6]

Because of its rarity, poorly understood pathophysiology, heterogeneous clinical manifestations, and lack of diagnostic tests, no randomized clinical trials have been conducted in patients with RP, and treatment is based on case reports, case series, and expert opinion.[7–9] Many patients become dependent on moderate to high doses of glucocorticoids (GCs) leading to multiple treatment-related complications.[6,10,11] This study aimed to describe the clinical manifestations, current treatments, and potential associations between clinical manifestations and the use of immunomodulatory medications in a large multicenter prospective cohort of patients with RP.

PATIENTS AND METHODS

Study population. This study included patients at least 18 years old with physician-diagnosed RP enrolled in a multicenter prospective observational cohort, the Vasculitis Clinical Research Consortium Longitudinal Study of Relapsing Polychondritis conducted at the University of Pennsylvania and the NIH. Patients at the two centers were recruited from January 2017 to 2023. A diagnosis of RP was confirmed by at least one of the investigators through detailed clinical evaluation, including comprehensive laboratory, radiographic, and other investigations. Every patient in the study was proteinase 3 (PR3) and myeloperoxidase (MPO) negative. All patients provided written informed consent, and the study protocol was approved by the University of Pennsylvania Institutional Review Board and the NIH Office of Human Subjects Research Protections.

Data collection. All patients had an initial consultation at one of the two referred centers with a detailed standardized clinical assessment performed by the investigative study team (baseline visit). The patients' data were compiled in a secure online electronic database.

Standardized case report forms were used to record data at all study visits, including demographic information, detailed clinical aspects of RP ever experienced, and objective findings of organ involvement. Also recorded was a history of immunosuppressive (IS) treatments ever received for RP, including GCs, nonbiologic IS drugs (eg, azathioprine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil); biologic IS drugs (eg, adalimumab, etanercept, certolizumab, golimumab, infliximab, rituximab, secukinumab, tocilizumab, ustekinumab); and JAK inhibitors (JAKis, eg, tofacitinib). These medications were prescribed by the treating clinicians independent of the study investigators. All patients at the NIH location and all patients with respiratory manifestations at the University of Pennsylvania location underwent a dynamic chest computed tomography (CT) scan.

Definitions of clinical manifestations. The following are examples of clinical manifestations of RP:

- Constitutional manifestations: fever, fatigue, or weight loss.
- Musculoskeletal manifestations: arthralgias, arthritis, morning stiffness, or costochondritis.
- Ear chondritis: pain, tenderness, erythema, and/or swelling of the external ear or ear canal, confirmed by a clinician and attributed to RP.
- External ear damage: clinician-observed deformity of the external ear cartilage (Figure 1).
- Nasal chondritis: pain, tenderness, erythema, and/or swelling of the nose.
- Nasal damage: clinician-observed saddle nose deformity (Figure 1).
- Respiratory symptoms: hoarseness, cough, dyspnea, wheezing, or stridor.
- Airway chondritis: direct observation or imaging demonstrating tracheal or bronchial thickening or calcification.
- Upper airway damage: subglottic stenosis visualized using laryngoscopy.
- Lower airway damage: evidence of tracheomalacia or bronchomalacia, on dynamic chest CT or bronchoscopy (Figure 1).
- Ocular inflammation: ophthalmologist- or optometrist-documented scleritis, episcleritis, iritis, or uveitis.
- Hearing loss: documented hearing loss by audiometry.
- Skin involvement: clinician-observed skin lesions attributed to RP.

Group treatment definitions. The history of immunosuppressive treatment was categorized as follows:

- Group 1: GC monotherapy.
- Group 2: nonbiologic IS drugs excluding JAK inhibitors (JAKi) with or without GCs.
- Group 3: JAKi or biologic drug treatment with or without nonbiologic IS drugs or GCs.

Statistical analysis. Mean values with SDs were reported. Chi-square test was used to compare organ damage in three treatment groups. Logistic regression and multivariable regression models were used to evaluate correlations between demographics, and clinical features, disease damage manifestations versus the three treatment groups. All analyses were performed using JMP (version 14). $P \leq 0.05$ defined statistical significance.

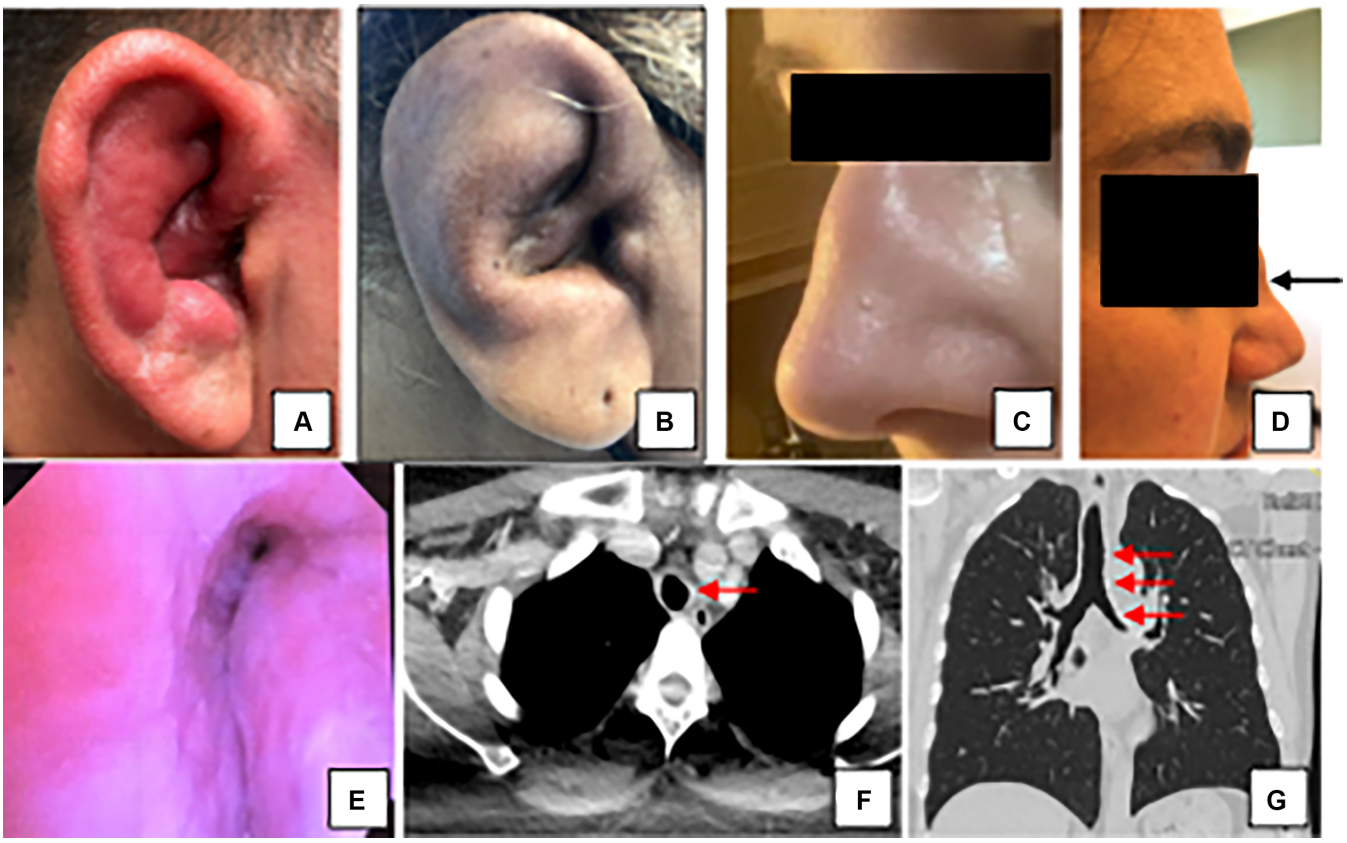

Figure 1. Clinical manifestations of relapsing polychondritis. (A) auricular chondritis, (B) auricular deformity, (C) nasal chondritis, (D) saddle nose deformity, (E) tracheal stenosis, (F) tracheal thickening; (G) tracheal and bronchial wall calcification. The red arrows show (F) areas of tracheal thickening and (G) tracheal and bronchial wall calcifications.

RESULTS

Patient characteristics. The study included 195 patients with RP. The mean age at the time of evaluation was 49 ± 13 years, with 167 (86%) women and 174 (89%) of White race. The mean age at diagnosis was 43 ± 13 years, and the mean disease duration was 5 (interquartile range [IQR] 3–8) years.

Clinical manifestations of RP. All patients had at least three clinical manifestations of RP ever experienced, with a median of 11 manifestations per patient (3–19; Table 1). All patients had ear, nose, or airway involvement. External ear pain was noted in 184 (94%) patients; redness and swelling of the external ear were found in 174 (89%) and 145 (74%) patients respectively. Symptoms of nasal chondritis were reported in 148 (76%) patients. The majority of patients (n = 163, 83%) had musculoskeletal manifestations. Fatigue was the most common constitutional symptom (n = 155, 79%). Manifestations of pulmonary and airway disease were common, including hoarseness (n = 123, 63%), dyspnea (n = 120, 61%), and cough (n = 107, 55%). Sixty-six (34%) patients had ophthalmological manifestations, and 43 (22%) had cutaneous manifestations. Cardiovascular and neurologic manifestations were rare.

Organ damage from RP. Many patients had organ damage (n = 80, 41%), including sensorineural hearing loss (n = 50, 25%), auricular deformity (n = 23, 12%), saddle nose deformity (n = 23, 12%), and subglottic stenosis (n = 18, 9%). Among patients who underwent dynamic chest CT testing (n = 162), tracheomalacia and bronchomalacia were found in 50 (31%) and 32 (20%) patients, respectively.

Treatments and treatment groups. Group 1 (no treatment or treatment only with GC) included 37 (19%) patients; most patients received another treatment in addition to GCs (158, 81%). Group 2 (treatment with nonbiologic IS drugs, excluding JAKis with or without GCs) included 55 (28%) patients. Group 3 (treatment with JAKis or biologic IS drugs with or without nonbiologic IS drugs or GCs) included 103 (53%) patients. The majority of patients (n = 158, 81%) received immunomodulatory treatment other than GCs. The median number of immunomodulatory drugs used per patient was 2 (range 1–9). Most patients (n = 186, 95%) received GCs. The most common nonbiologic therapy used was methotrexate (n = 126, 65%). Tumor necrosis factor inhibitors (TNFis) were the most commonly-used biologic agents (n = 57, 29%), with adalimumab (n = 35, 18%) and infliximab (n = 28, 14%) as the most frequently used TNFi drugs.

Table 1. Demographics and clinical characteristics of patients with RP the study cohort

Characteristics	Number of patients, n (%)
Demographics	
Total number of patients	195
Age, median (IQR), y	48 (41–58)
Female sex	167 (85.6)
Race[a]	
White	174 (89.2)
Asian	9 (4.6)
African American	10 (5.2)
Age at diagnosis, median (IQR), y	43 (34–52)
Disease duration, median (IQR), y	5 (3–8)
Clinical characteristics	
Constitutional manifestations	
Fatigue	155 (79.5)
Weight loss	33 (16.9)
Fever	34 (17.4)
Musculoskeletal	163 (83.5)
Arthralgia	131 (67.2)
Costochondritis	142 (72.8)
Morning stiffness	94 (48.2)
Arthritis	115 (58.9)
Skin involvement	43 (22.1)
Mucosal disease	
Oral ulcer	49 (25.1)
Genital ulcer	23 (11.8)
Ear, throat, nose	
External ear pain	184 (94.4)
External ear redness	174 (89.2)
External ear swelling	145 (74.4)
Nose pain or nasal chondritis	148 (75.9)
Anterior neck tenderness	92 (47.2)
Tinnitus	103 (52.8)
Vertigo	88 (45.1)
Ophthalmological	66 (33.8)
Episcleritis	34 (17.4)
Uveitis	18 (9.2)
Scleritis	29 (14.9)
Pulmonary	
Cough	107 (54.9)
Hoarseness	123 (63.1)
Dyspnea	120 (61.5)
Wheezing	52 (26.7)
Stridor	28 (14.4)
Tracheal thickening[b]	25 (15.4)
Cardiovascular manifestations	
Valvulopathy	7 (3.6)
Pericarditis	8 (4.1)
Aortitis or thoracic aortic aneurysm	6 (3.1)
Raynaud phenomenon	43 (22.1)
Neurologic manifestations	3 (1.5)
Damage	
Tracheomalacia[b]	50 (30.9)
Bronchomalacia[b]	32 (19.8)
Subglottic stenosis	18 (9.2)
Hearing loss	50 (25.6)
Permanent auricular deformity	23 (11.8)
Nasal bridge collapse or septal perforation	23 (11.8)

Abbreviations: CT, computed tomography; IQR, interquartile range.
[a]Race was unknown or not reported in two patients.
[b]Reported in patients who underwent dynamic CT chest scan.

Fifteen (7%) patients received treatment with IL-6 inhibitor. Other biologics used in this cohort were rituximab (n = 7), ustekinumab (n = 3), and secukinumab (n = 2). Tofacitinib treatment was used by eight (4%) patients. The frequency of use of individual IS agents is shown in Figure 2.

Association between treatment groups and clinical manifestations. Organ damage was more likely associated with treatment group 3 (62%) compared with 22% in group 2 and 15% in group 1 (P = 0.02). Patients in treatment group 3 were more likely to have arthritis (odds ratio [OR] 2.4; 95% confidence interval [CI] 1.2–4.6, $P < 0.01$) and subglottic stenosis (OR 6.4, 95% CI 1.3–30, $P = 0.01$). Patients in Group 1 were less likely to have nose pain (OR 0.36, 95% CI 0.16–0.79, $P < 0.01$).

DISCUSSION

This study in a large cohort with RP revealed that patients have heterogeneous clinical manifestations, with ear, nose, and throat and musculoskeletal manifestations representing the most common clinical features. Most patients also exhibited other aspects of this multiorgan system disease, and many patients had organ damage. GCs were almost universally used, and most patients were treated with additional nonbiologic and/or biologic immunomodulatory treatments. Clinical manifestations such as inflammatory arthritis, subglottic stenosis, and nose pain were associated with the use of immunomodulatory medications other than GCs. Overall, use of biologics was more likely among patients with organ damage.

This study expands the understanding of the range of manifestations of disease in patients with RP. In Supplementary Table 1, the current data are compared with previous cohorts of RP.[2,3,6,12–16] The prevalence of many manifestations was variable among the different studies. Several clinical symptoms such as tinnitus, fatigue, unintentional weight loss, arthralgia, morning stiffness, cough, hoarseness, wheezing, stridor, and Raynaud phenomenon described in the present study were not reported in the majority of prior publications. Organ damage was quite prevalent in the current cohort, consistent with other studies. Some differences in clinical data among the various studies may be related to differences in study designs and methods of evaluation. The current study's use of prospective design using standardized data collection forms likely partly explains why a wider range of clinical manifestations was observed compared with prior studies.

Most patients (95%) in the current study were prescribed GCs, similar to other studies.[2,6,12] The majority of patients in the present study were on immunomodulatory medications besides GCs, and more than half were treated with biologic drugs or JAKis. TNFis and tocilizumab were the most commonly-used bio-

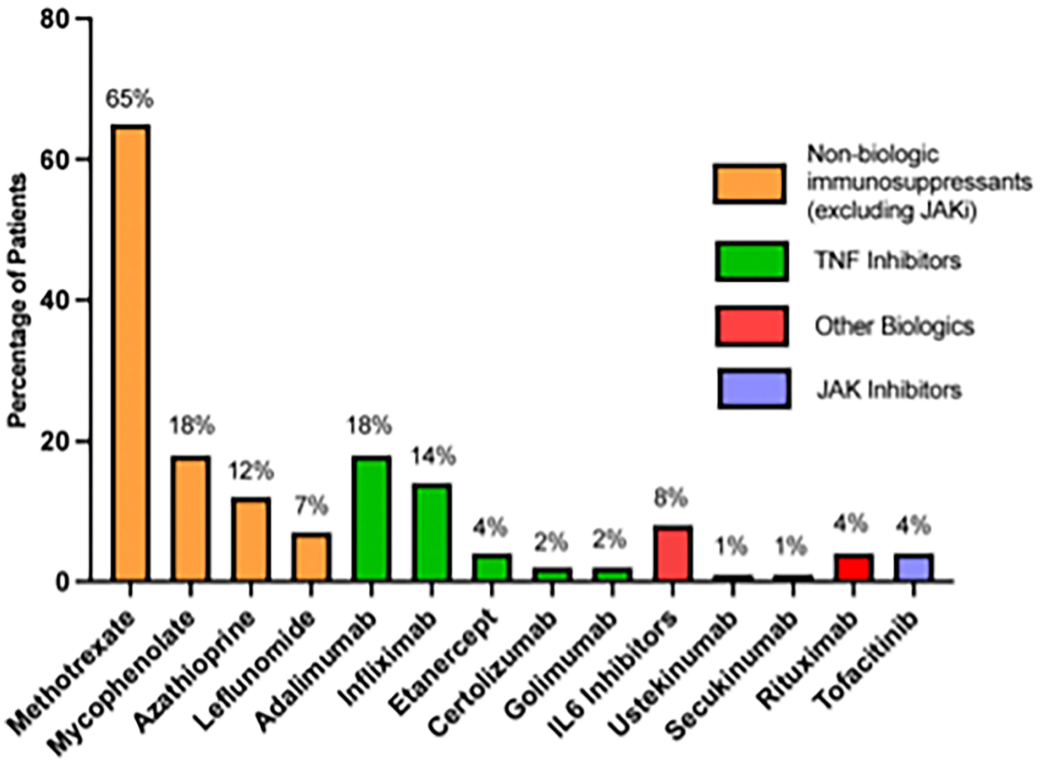

Figure 2. Different immunomodulatory medications used in patients with relapsing polychondritis in the study cohort. JAKi, JAK inhibitor; TNF, tumor necrosis factor.

logic drugs in this study, whereas use of other biologics was rare.[2,7–9,16] Few patients in this cohort were treated with tofacitinib.[17,18] Similar to the current findings, previous studies demonstrated use of numerous biologic agents with variable outcomes.[8,9] These case reports and case series reinforce the lack of knowledge regarding the indications, efficacy, and safety of specific therapies for RP. The present cohort demonstrated use of biologics and/or JAKis was more frequent in patients with organ damage in general, particularly among patients with arthritis and subglottic stenosis. This finding is similar to prior reports in which use of biologics or JAKis was more common in patients with severe or refractory disease and airway manifestations.[16–18]

This study has several strengths, including the large size of the cohort and prospective, standardized data collection. Most patients underwent advanced testing for evaluation of airway disease. Systematic prospective data collection enabled extraction of comprehensive clinical manifestations which may be useful to understand the varied presentations of each organ system involvement in RP and eventually help develop organ-specific disease definitions.

Limitations of this study to consider include a lack of data on the dose and duration of different immunomodulatory medications used in this cohort and the clinical manifestations present at the time of specific treatment decisions. Because the treatment decision was made by the clinicians independent of the study investigators, the rationale for selecting specific immunosuppressive medications was not available. The choice of therapy could have been influenced by drug availability and other factors, such as insurance approval. Since both centers were academic referral institutes, there could be a selection bias and some of the findings may not be generalizable. For example, the current cohort has a high predominance of women, which is atypical in this disease. Women are more likely to participate in support groups and foundations that were the referral sources for many patients, and women also have a higher likelihood of seeking advanced medical care.[19] This is a cross-sectional study and does not report follow-up or outcome data. There are plans to analyze the clinical data and outcomes when a longer follow-up of the cohort occurs.

In conclusion, this large multicenter prospective cohort of patients with RP describes the diverse clinical manifestations, high prevalence of organ damage, near universal use of GCs, and varied use of immunosuppressant drugs in this complex disease. Patients with advanced airway disease, such as subglottic stenosis, other organ damage, and arthritis were more likely to be treated with biologics and/or JAKis, suggesting deficiency in the understanding and management of early disease, potentially increasing the risk of disease progression and organ damage. Standardized assessment of disease activity is warranted for patients with RP for early detection and timely initiation of treatment. These findings also highlight the absence of a consensus approach to treatment for patients with RP and underscore the

need for clinical trials and treatment guidelines in this disease to help reduce the enormous burden of disease for patients.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Banerjee confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Kingdon J, Roscamp J, Sangle S, et al. Relapsing polychondritis: a clinical review for rheumatologists. Rheumatology (Oxford) 2018; 57(9):1525–1532.
2. Dion J, Costedoat-Chalumeau N, Sène D, et al. relapsing polychondritis can be characterized by three different clinical phenotypes: analysis of a recent series of 142 patients. Arthritis Rheumatol 2016; 68(12):2992–3001.
3. McAdam LP, O'Hanlan MA, Bluestone R, et al. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 1976;55(3):193–215.
4. Damiani JM, Levine HL. Relapsing polychondritis--report of ten cases. Laryngoscope 1979;89(6 Pt 1):929–946.
5. Ferrada M, Rimland CA, Quinn K, et al. Defining clinical subgroups in relapsing polychondritis: a prospective observational cohort study. Arthritis Rheumatol 2020;72(8):1396–1402.
6. Ferrada MA, Grayson PC, Banerjee S, et al. Patient perception of disease-related symptoms and complications in relapsing polychondritis. Arthritis Care Res (Hoboken) 2018;70(8):1124–1131.
7. Kemta Lekpa F, Kraus VB, Chevalier X. Biologics in relapsing polychondritis: a literature review. Semin Arthritis Rheum 2012;41(5): 712–719.
8. Petitdemange A, Sztejkowski C, Damian L, et al. Treatment of relapsing polychondritis: a systematic review. Clin Exp Rheumatol 2022; 40(5 Suppl 134):81–85.
9. Moulis G, Pugnet G, Costedoat-Chalumeau N, et al. Efficacy and safety of biologics in relapsing polychondritis: a French national multicentre study. Ann Rheum Dis 2018;77(8):1172–1178.
10. Mertz P, Sparks J, Kobrin D, et al. Relapsing polychondritis: best practice & clinical rheumatology. Best Pract Res Clin Rheumatol 2023;37(1):101867.
11. Borgia F, Giuffrida R, Guarneri F, et al. Relapsing polychondritis: an updated review. Biomedicines 2018;6(3):84.
12. Sharma A, Law AD, Bambery P, et al. Relapsing polychondritis: clinical presentations, disease activity and outcomes. Orphanet J Rare Dis 2014;9(1):198.
13. Zhang L, Yun S, Wu T, et al. Clinical patterns and the evolution of relapsing polychondritis based on organ involvement: a Chinese retrospective cohort study. Orphanet J Rare Dis 2021;16(1):225.
14. Lin DF, Yang WQ, Zhang PP, et al. Clinical and prognostic characteristics of 158 cases of relapsing polychondritis in China and review of the literature. Rheumatol Int 2016;36(7):1003–1009.
15. Hazra N, Dregan A, Charlton J, et al. Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. Rheumatology (Oxford) 2015;54(12):2181–2187.
16. Oka H, Yamano Y, Shimizu J, et al. A large-scale survey of patients with relapsing polychondritis in Japan. Inflamm Regen 2014;34(3): 149–156.
17. Meshkov AD, Novikov PI, Zhilyaev EV, et al. Tofacitinib in steroid-dependent relapsing polychondritis. Ann Rheum Dis 2019;78(7): e72–e73.
18. Handa H, Ooka S, Shimizu J, et al. Evaluation of airway involvement and treatment in patients with relapsing polychondritis. Sci Rep 2023;13(1):8307.
19. Thompson AE, Anisimowicz Y, Miedema B, et al. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract 2016;17(1):38.