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Review

The Relapsing Polychondritis Disease Activity Index: Development of a disease activity score for relapsing polychondritis

Laurent Arnaud [a,b,*,1], Hervé Devilliers [a,c,1], Stanford L. Peng [d], Alexis Mathian [a,b,e], Nathalie Costedoat-Chalumeau [a,e], Jane Buckner [d], Lorenzo Dagna [f], Clement Michet [g], Aman Sharma [h], Ricard Cervera [i], Julien Haroche [a], Thomas Papo [j], David D'Cruz [k], Philippe Arlet [l], Jochen Zwerina [m], Alexandre Belot [n], Noboru Suzuki [o], Jean-Robert Harle [p], Robert Moots [q], David Jayne [r], Eric Hachulla [s], Isabelle Marie [t], Toshio Tanaka [u], Robert Lebovics [v], David Scott [w], Eugene J. Kucharz [x], Martin Birchall [y], Kok Ooi Kong [z], Guy Gorochov [b,e], Zahir Amoura [a,e]
for the RPDAI study group

[a] Department of Internal Medicine & French Reference Center for Rare Auto-immune & Systemic Diseases, AP-HP, Pitié-Salpêtrière Hospital, 47-83 bd de l'hôpital, 75013 Paris, France
[b] Institut National de la Santé et de la Recherche Médicale, INSERM UMR-S 945, Paris, France
[c] Service de médecine interne et maladies systémiques, CHU, Dijon, France
[d] Benaroya Research Institute at Virginia Mason Medical Center, 1201 9th Avenue, Seattle, WA 98101, USA
[e] Université Pierre et Marie Curie, UPMC Univ Paris 06, Paris, France
[f] Unit of Medicine and Clinical Immunology, Vita-Salute San Raffaele University School of Medicine, San Raffaele Scientific Institute, Via Olgettina, 60 I-20132 Milano, Italy
[g] Mayo Clinic, E15 200 First Street SW, Rochester, MN 55905, USA
[h] Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India
[i] Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain
[j] Internal Medicine Department, Hopital Bichat, Université Paris-Diderot, 46 rue Henri Huchard 75018 Paris, France
[k] The Louise Coote Lupus Unit, Ground Floor Gassiott House, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom
[l] Service de Médecine Interne, Pavillon Sénac, 2ème étage, Hôpital Purpan, Place du Dr Baylac, 31059 Toulouse Cedex 9, France
[m] Department of Internal Medicine 3, University of Erlangen-Nuremberg, 91054 Erlangen, Germany
[n] Service de Néphrologie et Rhumatologie Pédiatrique & UMR 5239 CNRS, Hôpital Femme Mère Enfant & Université de Lyon, 69677 Bron Cedex, France
[o] Department of Immunology and Medicine, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki City, 215-8511, Japan
[p] Service de médecine Interne, Hôpital de la Conception 13385 Marseille Cedex 05, France
[q] Department of Musculoskeletal Biology, Institute for Chronic Diseases and Ageing, University of Liverpool, Clinical Sciences Centre, University Hospital Aintree, Longmoor Lane, Liverpool, L9 7AL, United Kingdom
[r] Vasculitis Office, Box 57, Addenbrooke's Hospital, CB220Q, Cambridge, England, United Kingdom
[s] Service de Médecine Interne, Hôpital Huriez, 59037 Lille Cedex, France
[t] Department of Internal Medicine, CHU Rouen, 76031 Rouen Cedex, France
[u] Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita City, Osaka 565-0871, Japan
[v] Department of Otolaryngology Head and Neck Surgery, St Lukes-Roosevelt Hospital Center, 425 West 59 Street, 10th Floor, NY 10019, USA
[w] Department of Rheumatology, Norfolk and Norwich University Hospital, Norwich NR4 7UY, United Kingdom
[x] Department of Internal Medicine and Rheumatology, Medical University of Silesia, ul. Ziolowa 45/47 PL 40-635 Katowice, Poland
[y] University College London, The Royal National Throat Nose and Ear Hospital, Gray's Inn Road, London WC1X 8DA, United Kingdom
[z] Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore

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ABSTRACT

Objective: The rarity of relapsing polychondritis (RP) has hindered the development of standardized tools for clinical assessment. Here, we describe the development of a preliminary score for assessing disease activity in RP, the Relapsing Polychondritis Disease Activity Index (RPDAI).
Methods: Twenty-seven RP experts participated in an international collaboration. Selection and definition of items for disease activity were established by consensus during a 4-round internet-based Delphi survey. Twenty-six experts assessed the Physician's Global Assessment (PGA) of disease activity on 43 test cases on a 0–100 scale, yielding a total of 1118 PGA ratings. The weight of each item was estimated by

Abbreviations: 95%CI, 95% confidence interval; ARF, acute respiratory failure; GEE, generalized estimating equation; ICC, intraclass correlation coefficient; PGA, Physician's Global Assessment; RP, relapsing polychondritis; RPDAI, Relapsing Polychondritis Disease Activity Index.

* Corresponding author at: Service de Médecine Interne 2, Groupe Hospitalier Pitié-Salpêtrière, 47-83 bd de l'Hôpital, 75013 Paris, France. Tel.: +33 1 42 17 80 40; fax: +33 1 42 17 80 44.
E-mail address: Laurent.arnaud@psl.aphp.fr (L. Arnaud).

[1] Contributed equally to this work.

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multivariate regression models with generalized estimating equation, using PGA as the dependent variable.

Results: Experts decided in consensus that the RPDAI should consider the 28-day period before each RPDAI assessment. Inter-rater reliability assessed by the intra-class correlation coefficient for the 1118 PGA ratings was 0.51 (CI95%: 0.41–0.64). The final RPDAI score comprised 27 items with individual weights ranging from 1 to 24 and a maximum theoretical RPDAI score of 265. Correlation between the RPDAI scores calculated based on the weights derived from the final multivariate model, and the 1118 PGA ratings was good ($r = 0.56$, $p < 0.0001$).

Conclusion: We have developed the first consensus scoring system to measure disease activity in relapsing polychondritis (see www.RPDAI.org for online scoring). This tool will be valuable for improving the care of patients with this rare disease.

Contents

1. Introduction

Relapsing polychondritis (RP) is a rare multi-systemic disorder characterized by recurrent, destructive, inflammatory lesions of the auricular, nasal, and laryngo-tracheo-bronchial cartilages [1]. Additional clinical features include ocular inflammation, audio-vestibular impairment, vasculitis, skin involvement, valvular insufficiency, and non-erosive arthritis [2–10]. The rarity of the disease makes it difficult to provide a standardized approach for treatment and follow-up of RP patients, and there is no consensus agreement on any outcome measures in this disease [1]. Standardized disease activity scores would help facilitate the assessment of disease activity in RP, assess the efficacy of novel treatments, and provide prognostic stratification of patients [2]. The lack of such consensual indices has hampered clinical studies in RP and the disease remains an under-researched area. Here, we describe the development and initial validation of a score designed to assess disease activity in RP, the Relapsing Polychondritis Disease Activity Index (RPDAI). This index was developed with the help of a worldwide panel of physicians with significant experience in the care of RP patients. Our main goal was to develop the RPDAI in a manner that this score could be used to standardize disease activity evaluation in RP.

2. Methods

2.1. Expert panel selection

This study reflects a multi-center, international and interdisciplinary collaboration of experts involved in the management of RP, headed by a steering committee composed of an internist specializing in the care of RP (LA) and a fellow in clinical epidemiology (HD). Experts for participation in this study were identified using four sources: (i) PubMed, searching for lead authors of RP case series published between January 2000 and December 2010; (ii) www.clinicaltrials.gov, searching for principal investigators of current clinical trials in RP; (iii) Board members of European societies of internal medicine and rheumatology, who were contacted for professional referrals; and (iv) French, UK, and US national RP patient associations, who were contacted for personal referrals. This process yielded 37 experts; all were contacted, 29 responded and 27 agreed to participate. Among them were 19 European experts and 8 non-European, their median age was 50 (32–62) years, and the panel included 15 internists, 8 rheumatologists, 2 otolaryngologists, 1 nephrologist and 1 pediatrician. All but 3 (89%) had ≥10 years of experience in managing RP patients.

2.2. Preliminary item selection

For the selection and definition of disease activity items, the steering committee prepared a preliminary list grouped by organ system based upon clinical experience [3] and literature review. Eighty-seven items belonging to 10 different domains (constitutional, rheumatologic, chondritis, ophthalmologic, respiratory, otolaryngological, cutaneous, renal, cardiovascular and neurologic) were identified and submitted to the international panel of 27 experts for further selection.

2.3. Delphi survey for item selection

Final item selection was achieved by expert consensus during a four-round internet-based password-protected Delphi survey, a systematic process to derive expert consensus on a topic where the evidence-based data is lacking or scarce [11–13]. Here, all 27 experts rated the importance of each of the 87 preliminary items during four consecutive rounds, and were permitted to suggest new items for

disease activity assessment. We underlined that experts should only retain reversible (reflecting disease activity) but not fixed manifestations (reflecting damage) [14–16]. After each round, experts were provided with the aggregate responses of prior rounds and the process repeated until achieving a consensus (>80% agreement) for inclusion or exclusion of individual items. Item definitions were also obtained by consensus during this 4-round Delphi survey. At the end of the process, each expert was asked to confirm acceptability of the final RPDAI score as well as the RPDAI glossary (see Appendices A and B for final RPDAI scoring sheet and glossary).

2.4. Weighting of items

Twenty-six (96%) of the 27 experts involved in the Delphi survey took part in the weighting phase. During this step, each of these 26 experts rated the Physician's Global Assessment (PGA) of disease activity (the physician's evaluation of disease activity for a given test case) of 43 test cases using a dedicated password-protected website, which yielded a total of 1118 PGA ratings. PGA ratings were performed using a 0–100 drop-down list, anchored by zero being no disease activity at all and 100 being the highest imaginable disease activity. Patients described in these test cases were considered to have RP as defined by the Michet Criteria [1]. The 43 test cases included 27 test cases in which each item selected by experts during the Delphi survey (except the "increased C-reactive protein" item) was shown one by one as being the sole manifestation of the disease, and 16 test cases obtained by combining 2 to 5 of these 27 items (see Appendix C for case description). Each item was used a median of 52 (26–364) times among the 1118 PGA ratings. Because of the limited literature data and the difficulty of assessing the PGA of a laboratory result, the item "increased C-reactive protein" was not assessed in this way, but was nonetheless subjected to multivariate analysis. Weights for RPDAI items were generated using multivariate regression models with generalized estimating equation (GEE) as a way to account for the clustering of measurements by experts [17]. In these models, we used the PGA values of disease activity as the dependent variable and the individual RPDAI items as explanatory variables. Item weights were assigned based on the beta regression coefficients of the models, rescaled and rounded to the nearest integer [18]. The RPDAI score is obtained by adding the weights of all items present. To evaluate the fit of the preliminary and final models to the data, we calculated the RPDAI scores of the test cases using the weights obtained for each model, and the square of Pearson's correlation coefficient (R^2) to evaluate the model ability to explain the PGA.

2.5. Statistical analyses

Quantitative values were expressed as median (minimum–maximum) values and qualitative items as numbers and percentages. The normal range of PGA ratings was computed as the mean ± 2 standard deviations of the difference between each PGA rating for a given test case and the mean of all PGA ratings for this given test case. The inter-rater reliability was assessed using intraclass correlation coefficient (ICC) for the PGA. Correlations between the PGA and the RPDAI score were assessed using Pearson's correlation coefficient. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using the software SAS version 9.1.3 (SAS institute Inc., Cary, NC).

3. Results

3.1. Selection and definition of items

Experts decided in consensus during the Delphi survey that the RPDAI should consider the 28-day period before each RPDAI assessment. All 10 domains and 27 (31%) of the 87 items initially proposed by the steering committee were selected by experts to be included in the final RPDAI score. Experts decided to add a laboratory domain (measurement of the C-reactive protein) and to regroup laryngeal, tracheal and bronchial chondritis items within a single "respiratory chondritis" item. They also decided to consider the severity of respiratory chondritis by distinguishing between patients with or without respiratory failure, which was further defined as a dyspnea due to acute airway obstruction from glottic, laryngeal and/or subglottic inflammation requiring oxygen use or artificial ventilation. They further decided that "respiratory chondritis" should be included within the respiratory rather than chondritis domain. An RPDAI glossary was developed in consensus during the Delphi survey and all experts agreed on both the RPDAI scoring sheet and final glossary (Appendices A and B).

3.2. Weighting of items

During this phase, each of these 26 experts was asked to rate the PGA of the same 43 test cases, yielding a total of 1118 PGA ratings (Appendices C and D). Inter-rater reliability assessed by the ICC was 0.51 (CI95%: 0.41–0.64) for these 1118 PGA ratings. Only 30 (2.7%) of the 1118 PGA ratings were out of the theoretical normal range (see Statistical analyses section). The weight of each item was then determined using both multiple linear and least-median-of-squares GEE regression models, which provided similar results (data not shown). First, all RPDAI items selected by experts during the Delphi survey were entered in a preliminary multivariate model. In this preliminary model, all items but "arthralgia" ($p=0.56$) and "arthritis" ($p=0.24$) were significantly associated with the PGA (Whole-model $R^2=0.31$), and individual item weights ranged from 1 to 51, yielding a maximum theoretical RPDAI score ranging of 561. Because a score with such a wide range of item weights and high maximal theoretical score would not be easy to use in a clinical setting, we then built the final RPDAI model by removing the subjective "arthralgia" item but by keeping the more objective "arthritis" item from the model. In this final model, all RPDAI items but "arthritis" ($p=0.25$) were associated with the PGA (Whole-model $R^2=0.31$). The final RPDAI score comprised 27 items with individual weights ranging from 1 to 24 and a maximum theoretical RPDAI score of 265 (Table 2).

Correlation was good between the RPDAI scores calculated for each of the test cases based on the weights derived from the final multivariate model, and the PGA rating for these cases ($r=0.56$, $p<0.0001$) (Fig. 1).

4. Discussion

RP is a rare multi-systemic disorder characterized by recurrent, destructive, inflammatory lesions of the auricular, nasal, and laryngo-tracheo-bronchial cartilages. Because of the rarity of the disease, the therapeutic management of RP patients is not well-codified. Disease activity scores allow standardization of measurements between centers and studies. Unlike many other inflammatory diseases [18–23], no activity score for adults or children has been available for RP, limiting clinical assessments of disease activity and response to treatment. Here, we have developed the RPDAI, the first consensus index designed to measure disease activity in RP patients. This tool was developed based on an international consensus of multidisciplinary experts involved in the care of this very rare disease.

A major challenge in designing evaluation indexes in inflammatory diseases is to distinguish adequately between disease activity and damage. One approach to avoid scoring damage is to consider only reversible manifestations, by excluding long-lasting (>6 months) and stable manifestations [23]. Such distinctions were defined in the RPDAI glossary (see Appendix B).

Another critical issue when designing disease activity indexes is validity assessment, ensuring satisfactory psychometric properties of

Table 1
Median PGA values of the 27 test cases where each RPDAI item was shown as single feature.

Items	PGA values Median (range)
Arthralgia	20.0 (5.0–50.0)
Fever	22.5 (10.0–90.0)
Purpura	22.5 (10.0–95.0)
Episcleritis	30.0 (10.0–90.0)
Arthritis	30.0 (10.0–95.0)
Manubriosternal chondritis	35.0 (10.0–80.0)
Sternoclavicular chondritis	37.5 (10.0–80.0)
Costochondritis	37.5 (10.0–83.0)
Hematuria	40.0 (10.0–90.0)
Proteinuria	40.0 (10.0–90.0)
Nasal chondritis	42.5 (20.0–100.0)
Auricular chondritis	45.0 (20.0–100.0)
Scleritis	47.5 (15.0–100.0)
Uveitis	47.5 (15.0–95.0)
Vestibular dysfunction	47.5 (20.0–90.0)
Pericarditis	50.0 (10.0–85.0)
Corneal ulcer	50.0 (10.0–95.0)
Sensorineural deafness	50.0 (15.0–100.0)
Motor or sensorimotor neuropathy	55.0 (10.0–100.0)
Retinal vasculitis	55.5 (20.0–100.0)
Myocarditis	65.0 (10.0–100.0)
Renal failure	65.0 (20.0–100.0)
Large and/or medium sized vessel involvement	70.0 (10.0–100.0)
Respiratory chondritis without acute respiratory failure	70.0 (25.0–100.0)
Acute aortic or mitral insufficiency	75.0 (10.0–100.0)
Encephalitis	80.0 (10.0–100.0)
Respiratory chondritis with acute respiratory failure	85.0 (40.0–100.0)
Raised C-reactive protein	NA[a]

[a] The PGA associated with this item was not directly assessed by experts, but indirectly through the multivariate analysis of test cases including this item.

the new scale. In the absence of a "gold standard", the most recognized method to model disease activity is based on the physician's global judgment, i.e. the PGA, as done in this study.

The content validity of the RPDAI, –i.e. the extent to which it represents all aspects of disease activity in RP–, was ensured by the broad range of clinical symptoms included in the RPDAI, as well as by the addition of a laboratory domain, as agreed upon by experts [24]. Moreover, these experts were recruited through four different sources and represented various medical fields. We also used the systematic, anonymous and iterative Delphi process, which facilitates the identification of relevant disease activity items in a more representative manner than open discussions, where a small number of individuals can dominate discussions and influence the global opinion [12,13]. This process ensured that most relevant descriptors of disease activity were included in the RPDAI. The face validity of the RPDAI, i.e. its believed ability to evaluate disease activity in RP, was considered satisfactory by the panel of experts. Importantly, all items included in the RPDAI may reasonably be assessed during a routine patient evaluation, in only a few minutes using the standard scoring sheet (see Appendix A), as individual items have been aggregated into a summary score using simplified weights.

Finally, the construct validity of the RPDAI, i.e. whether it correlates well with the PGA, was confirmed by the significant association of all its items but one with disease activity in the final multivariate model (Table 2) as well as by the good correlation between the RPDAI scores calculated for each of the test cases and the PGA rating of these cases.

Although we were able to build a score with satisfactory psychometric properties, this study has a few limitations. First, the panel of experts participating to the Delphi survey was limited, which may be explained by the rarity of the disease and the lack of an identified network of care. However, as stated above, these experts were representative of various medical specialties and originated from different countries. Second, the test cases used for the weighting exercise were fictitious but based on typical clinical features of RP, as identified during both the literature review as well as during a previous cohort study by our group [2]. By using test cases including both single and multiple RPDAI items we were able to be representative of different disease patterns such as localized and disseminated disease as well as to reflect different disease

Table 2
Final regression model with generalized estimating equation (Whole model $R^2 = 0.31$).

Parameters for the final model	Multivariate GEE analysis					RPDAI
	β regression coefficient	Standard Error	Lower 95%CI	Upper 95%CI	p-value	Item weights
Arthritis	1.6258	1.4019	−1.1219	4.3735	0.25	1
Fever	3.9455	1.6543	0.7033	7.1878	0.02	2
Purpura	4.4554	1.4550	1.6037	7.3071	0.002	3
Raised C-reactive protein level	4.6328	1.3270	2.0320	7.2337	0.0005	3
Manubriosternal chondritis	5.1894	1.5449	2.1615	8.2173	0.0008	3
Sternoclavicular chondritis	5.9038	1.5447	2.8762	8.9314	0.0001	4
Hematuria	6.0606	1.7218	2.6859	9.4352	0.0004	4
Costochondritis	7.1781	1.5885	4.0647	10.2915	<.0001	4
Episcleritis	8.8702	2.1021	4.7501	12.9903	<.0001	5
Proteinuria	9.1793	1.9253	5.4058	12.9529	<.0001	6
Vestibular dysfunction	13.1956	1.4165	10.4192	15.9720	<.0001	8
Nasal chondritis	14.9074	1.5432	11.8828	17.9320	<.0001	9
Pericarditis	14.9858	2.3534	10.3732	19.5983	<.0001	9
Uveitis	15.0087	2.4689	10.1697	19.8477	<.0001	9
Auricular chondritis	15.0289	2.0641	10.9835	19.0744	<.0001	9
Scleritis	15.0439	2.2545	10.6251	19.4626	<.0001	9
Corneal ulcer	18.4644	2.5593	13.4481	23.4806	<.0001	11
Motor or sensorimotor neuropathy	19.2858	2.2890	14.7994	23.7722	<.0001	12
Sensorineural deafness	19.2922	1.9556	15.4592	23.1251	<.0001	12
Retinal vasculitis	22.8920	2.0898	18.7961	26.9879	<.0001	14
Respiratory chondritis without ARF	22.9948	2.1619	18.7576	27.2320	<.0001	14
Large and/or medium sized vessel involvement	26.3450	2.4795	21.4853	31.2047	<.0001	16
Myocarditis	26.8814	2.5502	21.8832	31.8796	<.0001	17
Renal failure	26.9344	1.9976	23.0191	30.8496	<.0001	17
Acute aortic or mitral insufficiency	29.5099	3.2388	23.1620	35.8578	<.0001	18
Encephalitis	35.3219	3.3427	28.7702	41.8735	<.0001	22
Respiratory chondritis with ARF	38.9336	1.8192	35.3680	42.4991	<.0001	24

95%CI: 95% confidence interval; ARF: acute respiratory failure.

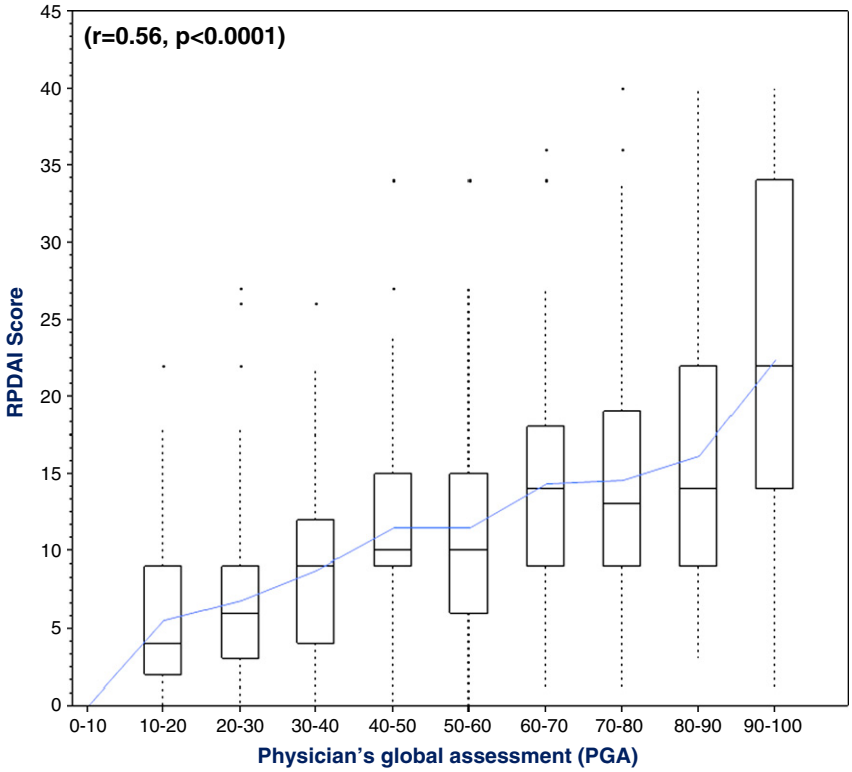

Fig. 1. Distribution of RPDAI scores in the 1118 cases for each level of disease activity as defined by the Physician's Global Assessment (PGA) on a 0–100 scale. The boxes represent the 25th and 75th percentiles; the lines within the box represent the median; the tendency line links the means; the whiskers extend to the most extreme data point, which is no more than 1.5 times the interquartile range (difference between the 75th and 25th percentiles) from the box. Values that are more extreme were considered outliers and are plotted individually (dots). The correlation between the RPDAI scores and the PGA is satisfactory ($r = 0.56$, $p < 0.0001$).

stages such as early or more evolved disease. Importantly, the face validity of the RPDAI was considered satisfactory by the panel of experts. This underlines that the test cases used for deriving the weights of RPDAI items were judged realistic enough by the broad panel of international experts involved in the RPDAI study. Third, there were some differences in ratings across experts (Table 1). While not totally unexpected, this strongly emphasizes the importance of building a standardized tool for assessing disease activity in RP. Importantly, our index was developed after adjusting for these differences as we used the GEE for data modeling [17]. Therefore, the RPDAI represents the average opinion common to a diverse panel of experts. Fourth, we were unsatisfied with the preliminary model because both the "arthralgia" and "arthritis" items were not associated with the PGA, and the broad range of item weights in this model limited its use in clinical practice. We thus decided to refine the preliminary model by removing the subjective "arthralgia" item while keeping "arthritis", as we felt the latter was a crucial dimension of disease activity assessment in RP. Importantly, this did not impair the overall significance of the model (Whole-model $R^2 \approx 0.31$ in both preliminary and final models), which is similar to what is observed in other studies for deriving activity indexes. Finally, this study represents only the first stages of the development of this tool. The next steps will include demonstrating its reliability and studying its sensitivity to change in a prospective cohort of adult and pediatric patients.

We have here developed a consensus scoring system to measure disease activity in RP, the RPDAI (see the website http://www.rpdai.org for the online scoring sheet). We have derived a simple score which may be used in clinical trials as well as in routine clinical practice. We believe this tool will improve the care of patients with this rare disease. Additionally, measures of disease damage, the main other aspect of disease evaluation scores, are currently being developed for RP by our group.

Take-home messages

- Relapsing polychondritis (RP) is a rare multi-systemic disorder.
- There is no standardized approach for treatment and follow-up of RP patients.
- There is no consensus agreement on any outcome measures in this disease.
- The RPDAI is the first score designed to assess RP disease activity in a standardized manner.

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Collaborators of the RPDAI study group

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.autrev.2012.06.005.

References

[1] Lahmer T, Treiber M, von Werder A, Foerger F, Knopf A, Heemann U, et al. Relapsing polychondritis: an autoimmune disease with many faces. Autoimmun Rev 2010;9(8):540–6.
[2] Michet Jr CJ, McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis. Survival and predictive role of early disease manifestations. Ann Intern Med 1986;104(1):74–8.
[3] Frances C, el Rassi R, Laporte JL, Rybojad M, Papo T, Piette JC. Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. Medicine (Baltimore) 2001;80(3):173–9.
[4] Belot A, Duquesne A, Job-Deslandre C, Costedoat-Chalumeau N, Boudjemaa S, Wechsler B, et al. Pediatric-onset relapsing polychondritis: case series and systematic review. J Pediatr 2009;156(3):484–9.
[5] Ananthakrishna R, Goel R, Padhan P, Mathew J, Danda D. Relapsing polychondritis—case series from South India. Clin Rheumatol 2009;28(Suppl. 1):S7–10.
[6] Sharma A, Bambery P, Wanchu A, Sharma YP, Panda NK, Gupta A, et al. Relapsing polychondritis in North India: a report of 10 patients. Scand J Rheumatol 2007;36(6):462–5.
[7] Kong KO, Vasoo S, Tay NS, Chng HH. Relapsing polychondritis—an Oriental case series. Singapore Med J 2003;44(4):197–200.
[8] McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 1976;55(3):193–215.
[9] Damiani JM, Levine HL. Relapsing polychondritis—report of ten cases. Laryngoscope 1979;89(6 Pt 1):929–46.
[10] Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B. Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. J Rheumatol 1997;24(1):96–101.
[11] Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32(4):1008–15.
[12] Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. Am J Public Health 1984;74(9):979–83.
[13] Powell C. The Delphi technique: myths and realities. J Adv Nurs 2003;41(4):376–82.
[14] Symmons DP. Rheumatoid arthritis: assessing disease activity and outcome. Clin Med 2010;10(3):248–51.
[15] Luqmani RA. Assessing disease activity in the systemic vasculitides. Curr Opin Rheumatol 2002;14(1):23–8.
[16] Carruthers D, Bacon P. Activity, damage and outcome in systemic vasculitis. Best Pract Res Clin Rheumatol 2001;15(2):225–38.
[17] Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol 2003;157(4):364–75.
[18] Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35(6):630–40.
[19] Valentini G, Della Rossa A, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, et al. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity ndexes. Ann Rheum Dis 2001;60(6):592–8.
[20] Della Rossa A, Valentini G, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, et al. European multicentre study to define disease activity criteria for systemic sclerosis. I. Clinical and epidemiological features of 290 patients from 19 centres. Ann Rheum Dis 2001;60(6):585–91.
[21] Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford) 2005;44(7):902–6.
[22] Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcon GS, Aranow C, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis 2010;70(1):54–9.
[23] Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Ann Rheum Dis 2009;69(6):1103–9.
[24] Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol 2010;63(7):737–45.

Intravenous immunoglobulin are able to prevent thrombosis relapse in patients with antiphospholipid syndrome refractory to conventional therapy

It is widely accepted that the treatment of choice for antiphospholipid syndrome (APS) is anticoagulation. Appropriate anticoagulation regimen ensure a low risk of thrombosis recurrence, but when thrombosis relapses despite adequate therapy the prognosis becomes poor and patient management very challenging. Prednisone, hydroxychloroquine, immunosuppressant (i.e. cyclophosphamide), intravenous immunoglobulin (IVIG), and plasmapheresis have been suggested in these cases.

Sciascia et al. (**Clin Exp Rheumatol 2012;30:409-13**) treated five high risk APS patients with IVIG 0.4g/Kg/day for three days/month for 3 months followed by a single day monthly infusion of 0.4 g/Kg for 9 more months. All patients had refractory disease (third thrombotic event) or severe difficulties in maintaining adequate anticoagulation, no obstetric APS was reported. After a mean follow-up of 89.2 month no new thrombotic events occurred and no adverse event were reported by the Authors.

In this small series of high risk APS patients IVIG showed efficacy in preventing recurrence of thrombosis even in a long term follow-up.

Luca Iaccarino