Review

Treatment of relapsing polychondritis: a systematic review

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ABSTRACT

Objective. *Due to the rarity of relapsing polychondritis (RP), no randomised clinical trial has been conducted to date and treatment remains empirical. We performed a systematic literature review to assess the efficacy of the main conventional immunosuppressants and biotherapies used in RP.*

Methods. *We searched MEDLINE for original articles without language restriction. Abstracts from American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) were also considered for inclusion. Observational studies and clinical trials reporting on the efficacy of conventional immunosuppressants and biotherapies in adult patients with RP were selected and pooled response rates for each treatment were computed.*

Results. *Of 304 articles and abstracts identified, 31 underwent full-text review, and 11 were included. The studies involved a total of 177 patients, exposed to a total of 247 lines of treatments. The main treatments studied (by number of lines) were: TNF inhibitors (TNFi), n=92; methotrexate (MTX), n=38; tocilizumab (TCZ), n=26; anakinra (ANA), n=21; rituximab (RTX), n=16; abatacept (ABT), n=14; cyclophosphamide (CYC), n=14; azathioprine (AZA), n=13. The pooled response rates across studies were: 72% [95% CI: 42-95] for ABT, 66% [95% CI: 49-82] for TCZ, 64% [95% CI: 53-74] for TNFi, 56% [95% CI: 37-73] for MTX, 47% [95% CI: 26-68] for ANA, 43% [95% CI: 20-68] for RTX. Based on more limited data, response rates for AZA and CYC ranged from 38 to 100% and from 25 to 100%, respectively.*

Conclusion. *In this systematic review of available evidence regarding the treatment of relapsing polychondritis, ABT, TCZ and TNFi were the drugs associated with the best outcomes. ABT efficacy must be interpreted in light of the small number of patients treated. While MTX had slightly less efficacy, it is one of the drugs for which data are the most robust.*

Introduction

Relapsing polychondritis (RP) is a systemic inflammatory disease primarily affecting the cartilaginous structures of the ears, nose and tracheobronchial tree, but also the joints, the inner ear, the eyes and the cardiovascular system among several other systemic manifestations (1). The course of the disease is often unpredictable and varies from mild intermittent auricular and/or nose chondritis to life-threatening manifestations such as tracheobronchial and cardiovascular involvement. Furthermore, it has recently been discovered that a subset of patients with RP bears somatic mutations in the gene encoding for ubiquitin activating enzyme 1 (*UBA1*), which are causal for the Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome. Patients with VEXAS-RP are mostly middle-aged or older men and are distinguished by frequent haematologic abnormalities and increased mortality, among others specific features (2).

Since RP is a very rare disease, with a prevalence estimated to be as low as a few cases per million (3), it remains an under-researched area. Also, given the rarity of the disease and the fact that the exact cause of RP is still unknown (4), the treatment of RP is not standardised. Apart from the recent French therapeutic guidelines (5), no other recommendations have been published to date. Patients with mild inflammation are usually treated with non-steroidal anti-inflammatory drugs (NSAIDs) or low

doses of glucocorticoids. Conversely, patients with severe disease may require high doses of glucocorticoids associated with conventional immunosuppressants or biologic therapies (1). Here, we conducted a systematic literature review to synthesise the available evidence on the medical treatment of RP. The review has been carried out under the framework of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET).

Material and methods

This systematic review has been performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist 2020.

Literature search and information sources

We searched MEDLINE from database inception to September 2021 for original articles without language restriction. The search strategy combined free text search, exploded Medical Subject Headings (MeSH) terms and synonyms for identifying observational studies and clinical trials which assessed medical treatment of RP in adult patients (see Supplementary document S1 for the detailed search strategy). We also searched for additional articles from the reference list of those original articles. Finally, we also considered for inclusion abstracts from American College of Rheumatology (ACR) since 2009 and from the European Alliance of Associations for Rheumatology (EULAR) congress since 2001.

Study selection and eligibility criteria

Observational studies and clinical trials which assessed medical treatment of RP in adult patients and which reported the number of responders to each treatment were included. Studies that exclusively assessed interventional or surgical procedures were excluded. Single case reports, case series of less than three patients, reviews, editorials and guidelines were excluded. Articles were selected for inclusion by two authors (A.P. and C.S.) independently of each other according to the predefined inclusion criteria. A first selection was performed on the basis of titles and abstracts and a second one after reading the full-text articles.

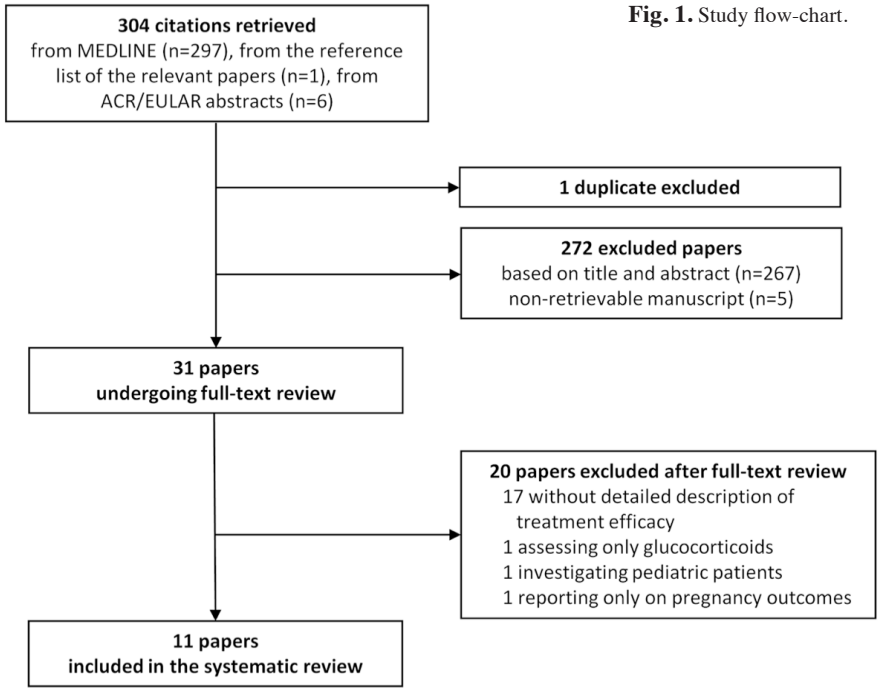

Fig. 1. Study flow-chart.

Data extraction

The following data were extracted from each selected study: study design, number of RP patients, age of patients at inclusion, gender, RP diagnostic criteria used for patient inclusion, duration of follow-up, treatments studied (excluding NSAIDs and glucocorticoids), and outcomes for drug efficacy, *i.e.* overall response rates as well as partial and complete response rates, when available.

Statistical analyses

For biologic therapies and methotrexate, the pooled response rates across studies (with their 95% confidence interval (CI)), weighted according to the number of patients in each study, were calculated using the RevMan software (version 5.3).

Levels of evidence and treatment recommendation

The strength of clinical data was graded according to the modified Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendation (6).

Results

The MEDLINE search yielded 297 citations of potential interest, from which seven studies met the inclusion criteria and were included in this systematic review. One additional article was identified from the reference list of those papers. Also, we further identified three abstracts which met the eligibility criteria. The flow chart of the study is shown in Figure 1.

The 11 selected studies consisted of eight retrospective observational studies, two case series and one open-label non-randomised clinical trial. All but two were published in the 2010s. Two studies focused on specific RP subpopulations (patients with scleritis and patients with respiratory involvement, respectively).

The studies involved a total of 177 patients, with a mean age 50.3 years and of whom 62.0% were women. These patients were exposed to a total of 247 lines of treatments. Of note, the study by Yudoh was not included in the count of the total number of patients and treatment lines because the number of patients exposed to each treatment was not reported.

The treatments studied were (by descending order of lines prescribed): TNF inhibitors (TNFi), n=92 (including adalimumab [ADA], n=32; inflixi-

Table I. Characteristics and outcomes of included studies.

Author	Year	Study type	Study population	Diagnostic criteria	Number of patients	Age at inclusion (mean ± SD)	% of women	Follow-up (median or mean), months	Treatments studied (number of treatment lines administered)*	Outcome, n (%)§	
Moulis *et al.*¶ (7)	2018	Multicentric retrospective study	RP	McAdam, Damiani & Michet	41	46.9±12.5	53.6	6	TNFi (60) *IFX (20)* *ADA (25)* *ETN (11)* *GOL (3)* *CTZ (1)* TCZ (17) ANA (15) RTX (7) ABT (6)	R=38 (63.3) R=12 (60) R=16 (64) R=8 (72.7) R=2 (66.7) R=0 R=12 (70.6) R=8 (53.3) R=5 (71.4) R=3 (50)	CR=14 (23.3) CR=7 (35.0) CR=5 (20.0) CR=0 CR=2 (66.7) CR=0 CR=2 (11.8) CR=2 (13.3) CR=1 (14.3) CR=1 (16.7)
Mathew *et al.* (8)	2012	Monocentric retrospective study	RP	McAdam	43	48.5±20.5	63.6	NA	MTX (18)†	R=8 (44.4)	
Moulis *et al.* (9)	2013	Monocentric retrospective study	RP	Damiani & McAdam	9	44.7	66.7	28	TNFi (14) *IFX (2)* *ADA (7)* *ETN (4)* *CTZ (1)* TCZ (2) ANA (2) ABT (3)	R=11 (78.6) R=1 (50) R=6 (85.7) R=4 (100) R=0 R=2 (100) R=0 R=3 (100)	CR=8 (57.1) CR=1 (50) CR=4 (57.1) CR=3 (75) CR=0 CR=2 (100) CR=0 CR=1 (33.3)
Leroux *et al.* (10)	2009	Monocentric retrospective study	RP	Michet	9	57.2±9.7	66.7	12	RTX (9)‡	*At 6 months (n = 9):* R=2 (22.2) Stable disease=4 (44.4) Worsening disease=3 (33.3)	*At 12 months (n= 6):* R=0 Stable disease=2 (33.3) Worsening disease=4 (66.7)
Pinto *et al.* (11)	2006	Case series	RP	NA	6	NA	33.3	NA	MTX (2) LEF (1)	R=1 (50) R=1 (100)	
Hoang-Xuan *et al.* (12)	1990	Case series	RP with scleritis	Damiani	11	52	81.8	36	MTX (2) CYC (5) AZA (3) DAP (8) COL (1)	R=0 R=5 (100) R=2 (66.7) R=3 (37.5) R=0	
Dubey *et al.* (13)	2020	Multicentric retrospective study	RP with respiratory involvement	Damiani	13	65	69.2	NA	MTX (6) AZA (2) MMF (2) CYC (4)** TNFi (4) ABT (1) SCK (1)§§	R=6 (100) R=2 (100) R=2 (100) R=1 (25) R=1 (25) R=1 (100) R=0 (0)	
Peng *et al.* (14)	2013	Open-label prospective study	RP	Michet	4	50.5	75	16	ABT (4)	R=3 (75)¶¶	
Nakajima *et al.* (abstract) (15)	2016	Monocentric retrospective study	RP	Damiani	33	NA	NA	NA	MTX (10) AZA (8) CYC (5) IFX (5) TCZ (4)	R=NA R=NA R=4 (80) PR=5 (100) R=1 (33.3)††	
Baldini *et al.* (abstract) (16)	2013	Monocentric retrospective study	RP	NA	8	NA	NA	NA	TNFi (9) *ETN (6)* ANA (4) TCZ (3)	*At 6 months:* R=NA (12) R=NA (40) R=NA (50) R=NA (100) ‡‡	*At 12 months:* R=NA (67) R=NA (60) R=NA (50) NA ‡‡
Yudoh *et al.* (abstract) (17)	2010	Retrospective declarative study	RP	NA	239	NA	46.9	NA	MTX (NA) CYC (NA) CSA (NA) AZA (NA) TNFi (13) *IFX (10)* *ETN (3)* TCZ (3)	R=NA (64) R=NA (66) R=NA (74) R=NA (38) R=8 (53.8) R=6 (60) R=1 (33) R=1 (33)	

ABT: abatacept; ADA: adalimumab; ANA: anakinra; AZA: azathioprine; CNS: central nervous system; COL: colchicine; CSA: cyclosporine A; CTZ: certolizumab; CYC: cyclophosphamide; DAP: dapsone; ETN: etanercept; GOL: golimumab; IFX: infliximab; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; NA: not available; RP: relapsing polychondritis; RTX: rituximab; SCK: secukinumab; SD: standard deviation; TB: tracheobronchial; TCZ: tocilizumab; TNFi: tumour necrosis factor inhibitors.

* A given patient may have received more than one treatment during the study period.

§CR: complete response; PR: partial response; R: response (without further detail).

¶Three patients in this cohort had also been included in Leroux's analysis.

†The number of patients treated and the outcomes for treatments other than MTX were not precisely described.

‡RTX was given in combination with glucocorticoids (n = 9), MTX (n = 4), MMF (n = 1), AZA (n = 3), and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (n = 1) (for an associated lymphoma).

** CYC was only used after failure of conventional DMARDs and was used primarily for tracheobronchomalacia.

§§Secukinumab was started for concomitant ankylosing spondylitis.

¶¶ABT was effective on chondritis and articular involvement, but two patients presented worsening pulmonary and/or neurological disease leading to treatment discontinuation.

††Outcome was described in only 3 out of 4 patients treated with TCZ.

‡‡As reported in the abstract.

mab [IFX], n=27; etanercept [ETN], n=21; golimumab [GOL], n=3; certolizumab [CTZ], n=2; and TNFi without precision, n=7); methotrexate (MTX), n=38; tocilizumab (TCZ), n=26; anakinra (ANA), n=21; rituximab (RTX), n=16; abatacept (ABT), n=14; cyclophosphamide (CYC), n=14; azathioprine (AZA), n=13; dapsone (DAP), n=8; mycophenolate mofetil (MMF), n=2; and colchicine (COL), leflunomide (LEF) and secukinumab (SCK) (initiated for concomitant ankylosing spondylitis), with one each.

The pooled response rates across studies were: 72% [95% CI: 42–95] for ABT, 66% [95% CI: 49–82] for TCZ, 64% [95% CI: 53–74] for TNFi (IFX, 59% [95% CI: 42–75]), 56% [95% CI: 37–73] for MTX, 47% [95% CI: 26–68] for ANA, 43% [95% CI: 20–68] for RTX.

The detailed characteristics and outcomes of the included studies are reported in Table I.

Discussion

In this systematic review of 11 studies, we assessed the efficacy of the main conventional immunosuppressants and biologic therapies used in RP, based on available evidence to date.

According to the summary response rates across studies, ABT, TCZ and TNFi were the drugs associated with the best outcomes, with mean response rates of 72%, 66% and 64%, respectively. However, caution is particularly needed regarding ABT given the small number of patients treated. Furthermore, in the study by Peng *et al*. (14) while abatacept was effective on chondritis and joint involvement, worsening of respiratory and neurological disease was observed in two out of four patients. MTX had a pooled response rate of 56% while ANA and RTX showed lower efficacy, with mean response rates of 47% and 43%, respectively. Of note, in the study by Leroux (10), no complete remission was observed with RTX and seven out of nine patients experienced worsening disease whereas good outcomes were reported in the study by Moulis *et al*. (7). Such a difference could be attributed to the recruitment of patients with more severe disease in the study by Leroux *et al*. (10). Among TNFi, IFX and ADA are both those for which we have the most data and those that appear to be the most effective. In the study by Moulis *et al*. (7), the high overall response rate of ETN must be balanced by a high discontinuation rate for lack of efficacy. AZA showed overall response rates ranging from 38 to 100% and CYC from 25 to 100%. In the study by Dubey *et al*. (13), the poor outcome observed with CYC may be explained by its use in refractory disease. Too few patients were exposed to other molecules to draw any conclusions.

It should be noted that, for a given drug, response rates were highly variable between the different studies. This may be due to differences in response definition, in the timing of response evaluation as well as in disease severity.

This review highlights the paucity of available evidence on the treatment of RP. Indeed, our literature search identified only 11 studies, of which all but one were retrospective studies with low levels of evidence, not exceeding 2b. To date, no randomised clinical trial has been conducted in RP. This has hampered the development of evidence-based recommendations to guide treatment, which is therefore essentially based on data provided by case reports and small case series. Minor nasal or auricular chondritis or joint involvement may respond to NSAIDs, glucocorticoids, colchicine or dapsone. Conventional and biological disease-modifying anti-rheumatic drugs (DMARDs) are used as glucorticoid-sparing agents or in cases of more severe disease. However, due to the aforementioned issues, the choice of the DMARD to use remains largely empirical. The strength of our study is to synthesise data from about 250 treatment lines, thereby providing a level of evidence that has never been achieved before and addressing one of the major unmet needs in the field of RP (1). It suggests that IFX, ADA, TCZ and MTX are the most effective DMARDs to treat RP as well as those for which the data are the most robust. Thus, when the severity of the disease or corticodependency warrants the initiation of a DMARD, we would suggest the use of one of the four abovementioned drugs. As their efficacy appears to be roughly similar, the choice of one over another should take into account the disease phenotype (*e.g*. MTX may be preferred in case of joint involvement), the patient's comorbidities and preferences, the tolerance profile of each molecule, as well as cost-effectiveness considerations. The combination of MTX with one of these biotherapies may also be considered in order to improve treatment efficacy and/or to avoid the development of antidrug antibodies. It should be noted that the use of CYC may be preferable in rapidly life-threatening forms to achieve a prompt therapeutic response. ABT, on the other hand, appears to be a good option in case of nasal or auricular chondritis or articular involvement but should be used with caution in case of respiratory or neurological disease given the results from Peng *et al*. (14). Of note, the management of VEXAS-RP patients should be considered separately, as these patients often present refractory disease with corticodependency (18). However, there is currently no published data regarding the optimal treatment of this particular population and studies investigating this issue are particularly needed.

This study has some limitations. The definition of the terms 'response', 'partial response' and 'complete response' was not systematically provided and may have varied between studies. Likewise, the characteristics of the different study populations differed. This heterogeneity limits the relevance of pooled analyses and of comparisons between studies. Moreover, the assessment of drug efficacy could have been refined by analysing information such as glucocorticoid-sparing effect or persistence of treatment. However, these data were too inconsistently reported to be relevant for inclusion in our review. The same was true for safety data, which were only rarely reported. Finally, as most studies include indistinctly different phenotypes of the disease, whether in terms of severity or organ involvement, and as response was most often not specified by organ involve-

ment, it was not possible to stratify the response rates on disease phenotype.
In conclusion, our systematic review adds substantial data to the existing body of evidence on the treatment of RP and may help clinicians choose the best therapy for their patients according to current knowledge. However, only high-quality randomised clinical trials will allow us to determine the optimal treatment of RP. Given the rarity of the disease, such a challenge will require the support of international networks for the care of rare diseases such as ERN ReCONNET.

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