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REVIEW ARTICLE

Relapsing polychondritis: a review

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Abstract Relapsing polychondritis is a rare multisystem disease involving the cartilaginous and proteoglycan rich structures. The spectrum of clinical presentations may vary from intermittent episodes of painful and often disfiguring auricular and nasal chondritis, to occasional organ or even life-threatening manifestations like airway collapse. There is lack of awareness about this disease due to its rarity. Relapsing polychondritis disease activity index has recently been validated and may help in clinical decision making and research. This article reviews the literature on this disease entity.

Keywords Auricular chondritis · Nasal chondritis · Polychondritis · Polychondropathia · Relapsing polychondritis · Relapsing polychondritis disease activity index

Key messages • Relapsing polychondritis is a rare disease affecting the cartilaginous and proteoglycan rich structures.
• It should be suspected whenever there is a multisystem presentation with cartilaginous inflammation like auricular chondritis, nasal chondritis, airway involvement, arthralgias, arthritis and involvement of proteoglycan rich structures like eye.
• Relapsing polychondritis disease activity index is a validated tool for assessment of disease activity
• Institution of therapy may retard the progression of disease manifestations like aortic root dilatation.

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Introduction

Relapsing polychondritis (RP) is a multisystem disease characterised by recurrent and progressive inflammation of the cartilaginous tissue in various sites of the body. Jaksch-Wartenhorst [1] described the first case in literature in 1923 when he used the term "polychondropathia". The term "relapsing polychondritis" was first used by Pearson et al. [2] in 1960 in their review of 12 cases. Since then, a large number of cases have been reported and the knowledge on the clinical spectrum, pathogenesis, and management has been growing considerably.

Epidemiology

The peak age of onset is the fifth decade of life, with most of the patients between 44 to 51 years at the time of diagnosis [3] though cases have been reported in both the extremes of life. A systematic review of 37 pediatric cases of RP [4] concluded that the childhood form shares the main clinical features of its adult counterpart. Though most studies [5, 6] report an equal sex distribution, Trentham et al. [3], in their study, found a female preponderance of 3:1. As most of the data available is on the Caucasian population, the racial distribution of RP is controversial. Though it appears to be equally prevalent in all racial groups, some series have noted predominance in the white population. In a case series conducted in an Oriental population [7], it was observed that the disease course was similar to that in the Caucasian population except that cutaneous, renal or nervous system involvement was not seen and the incidence of airway complications was more. Another series from North India [8] reported that the clinical features were similar, but laryngotracheal involvement was less frequent in these patients, whereas that from Southern India [9] inferred that auricular and skin involvement were less common.

Familial or geographical clustering has not been noticed in the studies on RP so far. There is one report [10], of a pregnant woman with RP giving birth to a child with saddle nose deformity and self limiting recurrent arthritis. However, a retrospective study [11] of 25 pregnancies in 11 women with RP inferred that pregnancy does not modify the course of the disease and RP was not observed in any of the neonates.

Etiopathogenesis

The etiology of RP remains unknown so far. Studies have shown the association of both cellular immunity changes and abnormal autoantibody response in RP.

Cellular immune reactivity towards cartilage extracts has been demonstrated using lymphocyte transformation or macrophage migration inhibition techniques [12]. Buckner et al. [13] described T cell clones with specificity for peptide corresponding to residues 261–273 of the type II collagen molecule in a patient with RP. Abnormal cellular response to cartilage proteoglycans and imbalance of T lymphocyte subsets has also been described with RP [14].

Both circulating antibodies and immune complex deposits in the affected tissues have been demonstrated in patients with RP. They are generated against native and denatured collagen type II and collagen types IX and XI [15], which form the major extracellular scaffold in the cartilage. Studies [16, 17] have shown that 33 % of patients with RP had circulating antibodies to type II collagen in the active phase of the disease and their titres also corresponded to disease activity. Autoimmunity to type II collagen has also been described in systemic lupus erythematosis (SLE) and rheumatoid arthritis, while the epitope specificity of the autoantibodies are different in these conditions [18, 19].

HLA class II molecules also seem to be associated with RP. A substantial increase in HLA-DR4 antigen frequency was found [20] in RP as compared to those without the disease though no subtype predominance was noted. Another study [21] of 62 patients concluded that the extent of organ involvement in patients diagnosed with RP was negatively associated with the presence of HLA-DR6. A cellular response directed towards matrillin-I was also demonstrated in these patients [22, 23].

Experimental studies in animal models have confirmed that autoimmunity towards extracellular matrix proteins especially collagen II and matrillin-I can lead to polychondritis closely resembling the clinical picture of RP seen in humans [24, 25].

Clinical features

The onset of the disease is usually abrupt and there is a characteristic clinical picture. Table 1 summarises the organ involvement in patients with RP in five case series.

Auricular and vestibular involvement

Auricular chondritis is present in most patients, with inflammation limited to the cartilaginous portion of the pinna and characteristic sparing of the lobule. Pain, discolouration or tenderness of the pinna is the initial symptom in most patients [26, 27]. The pinna assumes a nodular or verrucous appearance or loses shape and becomes soft and flabby. Auricular collapse, closure of the external auditory meatus, eustachian tube edema or obstruction with serous otitis media can lead to conductive hearing loss. A possibility of stapedial foot plate fixation is also to be considered in these patients as the abnormality is correctable surgically [28]. The hearing loss can also be sensorineural as a result of inflammation of the vestibular structures or vasculitis of the internal auditory artery [3, 5]. Vestibular dysfunction can also lead to nausea, vomiting, vertigo and ataxia.

Arthropathy

Joint pain is the second most common clinical feature in patients with RP. It is the initial presenting symptom in 33 % and ultimately is seen in 50 to 75 % [29]. Though any joint may be affected, the metacarpophalangeal, proximal minterphalangeal joints, knees and wrist are most commonly affected. Classically it is an episodic, self-remitting, asymmetric, usually migratory, non-erosive and non-deforming polyarthritis or oligoarthritis with or without synovitis lasting weeks to months.

Nasal chondritis

Nasal chondritis presents as a sudden onset of pain and tenderness, sometimes with mild epistaxis or serosanguinous exudation [30]. It is present at the time of diagnosis in 24 % and is seen at some stage of the disease in 53 % [27]. The inflammatory process might destroy the nasal cartilage leading to flattening of the nasal bridge or the tip, the former resulting in a saddle nose deformity. Such deformities are more common in patients who are less than 50 years and in females [3, 6].

Respiratory tract involvement

Laryngotracheal involvement by RP is a major cause of morbidity and mortality and is seen in about 50 % of patients. Early symptoms include pain and tenderness over the thyroid cartilage and trachea. Inflammation of cartilages in the larynx and tracheobronchial tree leads to hoarseness of voice, non-productive cough, dyspnea, stridor and wheezing [5, 31].

Table 1 Comparison of clinical features in five case series

	Mc Adam et al. [5]	Michet et al. [6]	Trentham and Le [3]	Kong et al. [7]	Sharma et al. [8]
No. of patients	159	112	66	12	10
Mean age at diagnosis	44	51	46	34	49
Female/male	76:83	55:57	49:17	3:1	3:2
Mean follow-up (months)	NR	72	96	96	36
Auricular chondritis (%)	89	85	95	83	100
Reduced hearing (%)	46	30	42	17	40
Arthritis (%)	81	52	85	75	80
Saddle nose (%)	NR	29	20	17	30
Ocular involvement (%)	65	51	57	67	50
Laryngotracheal involvement (%)	56	48	67	50	20
Cardiovascular involvement (%)	9	6	8	8	10[a]
Skin involvement (%)	17	28	38	0	30
Tracheostomy (%)	6	NR	5	42	10[a]
Death (%)	6	NR	3	0	10[a]

NR not recorded

[a] Only one patient

Complications include destruction of the thyroid cartilage, acute upper airway collapse and obstruction necessitating emergency tracheostomy. Strictures from chronic inflammation are especially common in the subglottic region. Sporadically costochondral cartilage tenderness, dislocation or flial chest can occur. Effectiveness of cough in clearing the secretions is reduced due to airway collapse and inflammation [32]. These respiratory complications, largely tracheal collapse and infections, are the leading cause of mortality in patients with RP and is reported variedly between 10 and 50 % [3, 6].

Cardiovascular disease

Cardiovascular involvement is seen in 24 to 52 % [33] and is the second most frequent cause of death [5, 6] in patients with RP. Vasculitis of any vessel may be seen and the clinical spectrum ranges from cutaneous leukocytoclastic vasculitis to large vessel vasculitis and aneurysmal involvement is most common in the thoracic and abdominal aorta [34]. Kobak et al. [35] described a case of RP with auricular chondritis who had concomitant Takayasu arteritis. Arterial and venous thrombosis in RP may be due to vasculitis or associated antiphospholipid syndrome [36]. Vasculitis in RP may be local or systemic, indolent or fulminant. Valvular heart disease is present in 5 to 10 % of all patients with RP. Aortic regurgitation is seen in 4 to 6 % and mitral regurgitation or mitral valve prolapse in 2 to 4 % [5, 6]. Rhythm disturbances include incidentally discovered electrocardiographic abnormality, paroxysmal atrial tachycardia, first-degree heart block and complete heart block [6, 27, 37]. Coronary artery involvement by vasculitis can cause ischemic heart disease. Less commonly reported are myocarditis, pericarditis and silent myocardial infarction [38].

Ocular involvement

Common manifestations are scleritis, episcleritis and conjunctivitis [5, 39–43]. Ocular adnexal involvement in the form of periorbital edema causing proptosis or extraocular muscle palsy from vasculitis affecting the muscle or its nerve supply may be seen [5, 40, 43]. Diffuse anterior scleritis is most common, though other types of scleritis including the necrotising variant have also been reported. Uveitis is seen in up to 25 % and is generally in the form of sclerouveitis or iridocyclitis [44]. Corneal involvement ranges from ulceration and thinning in 10 % of patients which rarely causes perforation to severe inflammation resulting in macropannus formation or corneal melting [41, 42]. Retinopathy has been reported in 10 % of patients in the series by Isaak et al. [27]. Others rarely seen are ischemic optic neuropathy [30], probably related to vasculitis, cystoids macular edema and cataract [27] which may be a result of disease activity or a complication of steroid therapy.

Neurologic involvement

Neurological manifestations from RP are related to vasculitis of the central or peripheral nervous system. These include headache, cranial neuropathies, seizures, hemiplegia, organic

brain syndrome, aseptic meningitis, meningoencephalitis and cerebral aneurysms [45, 46]. Optic neuropathy is the most common type of cranial nerve involvement in RP. Autopsy study in a patient with nervous system involvement by RP revealed perivascular lymphocytic infiltrate of the pia and cerebral white matter and inflammatory destruction of the myelin sheath [47].

Renal involvement

Renal involvement in RP may be a part of an associated disorder like SLE or systemic vasculitis or may be primarily due to the disease itself [48–50]. Although rare, its presence predicts a grave prognosis in RP; a 10-year survival rate of 10 % has been reported [49]. Deranged creatinine levels are seen in 10 % whereas an abnormal urinalysis is reported in 26 % of patients with RP [49]. Renal biopsy most frequently shows a mild mesangial expansion and cellular proliferation [3]. Other findings include crescentic glomerulonephritis, glomerulosclerosis, tubular loss, IgA nephropathy and tubulointerstitial nephritis [51]. Mesangial deposits of C3, IgG or IgM are seen on immunofluorescence studies. If coexistant lupus is present, any type of lupus nephritis may be seen.

Dermatological involvement

About 35 % of patients with RP alone have non-specific skin manifestations which may precede the onset of chondritis by a variable period [52]. These include purpura, papules, macules, vesicles, bullae, aphthosis, nodules over the extremities, livedo reticularis and superficial thrombophlebitis [27]. MAGIC syndrome represents a subset of patients with RP who also have features of Behcet's disease [53, 54]. Sweet syndrome has been reported as a presenting feature in a patient with RP [55]. Skin involvement is very common in patients with underlying myelodysplastic syndromes and is more frequent in males, and progresses independently of the treatment of RP [3].

Systemic features

Constitutional symptoms like fever, fatigue, weight loss and lethargy may be seen during the initial presentation and they also commonly accompany disease flares.

Prognosis

The majority of patients with RP manifest a fluctuant course with intermittent inflammatory episodes. In a given patient, the sites and severity of involvement rarely remain constant in each disease flare. Most patients experience persistent symptoms between the acute episodes. With the better management of the complications of RP, the survival has improved from 55%at 10 years in 1986 to 94 % at the end of 8 years in 1998 [3, 5]. The leading causes of mortality in these patients are lower respiratory tract infections, airway collapse, cardiac complications including valvular disease and advanced systemic vasculitis [6].

Disease associations

Concurrent autoimmune disease or less commonly, other systemic disorders are present in 25 to 35 % [5] of patients with RP. The most frequent is vasculitis, seen in 12 to 18 % of patients [3, 5] ranges from cutaneous leukocytoclastic vasculitis to systemic vasculitis with life-threatening organ involvement. They may occur in the context of RP itself, or may be associated with primary vasculitides like polyarteritis nodosa, Wegener's granulomatosis (WG), Churg Strauss syndrome or Behcet's disease. It can affect vessels of all sizes and large vessel vasculitis is a well known complication. The latter most frequently involves the aortic ring and the ascending aorta, though the thoracic and abdominal aorta may be affected by aneurysms or rupture [56]. The various conditions that may be associated with RP besides vasculitic disorders are other autoimmune rheumatic diseases.

Differential diagnosis

Auricular chondritis can occur with trauma and infection, but sparing of the ear lobule, bilateral involvement and spontaneous remission tilt the balance in favour of RP especially in the presence of other associated features. Nasal chondritis and saddle nose needs to be differentiated from various infections, congenital syphilis, Hansen's disease and WG. When another condition is associated, the clinical picture of RP generally follows the onset of the other disease.

Diagnostic criteria

Empirical diagnostic criteria to aid the clinical diagnosis of RP were first given by McAdam et al. [5] in 1976. Damiani et al. [57] suggested an expansion of the criteria in their case series of ten patients with RP. Michet et al. [6] used a modification of this for inclusion of patients for their case series. These criteria are shown in the Table 2.

As the initial symptoms are often non-specific, the diagnosis is often missed in these stages. The mean delay from the first presentation to the time of diagnosis was estimated as 2.9 years in the series by Trentham et al. [3].

Table 2 Diagnostic criteria for RP

Author	Criteria	Requirement
Mc Adam et al. [5].	Recurrent chondritis of both auricles Non-erosive inflammatory polyarthritis. Chondritis of nasal cartilages Inflammation of auricular structures (conjunctivitis/keratitis/scleritis/uveitis) Chondritis of respiratory tract (laryngeal/tracheal cartilages) Cochlear and/or vestibular damage (neurosensory hearing loss/tinnitus/vertigo)	3 of 6
Damiani et al. [57].	3 of 6 McAdam et al. criteria 1 of 6 McAdam et al. criteria and a positive histologic confirmation 2 of 6 McAdam et al. criteria and a response to corticosteroid or dapsone	Any of these
Michet et al. [6].	Proven inflammation in 2 of 3 auricular, nasal or laryngotracheal cartilages Proven inflammation in 1 of the above and two other signs among ocular inflammation, hearing loss, vestibular dysfunction or seronegative inflammatory arthritis	Any of these

Investigations

The diagnosis of RP is largely based on the clinical features and the role of laboratory investigations is purely supportive and to rule out other related or associated systemic diseases.

Blood investigations reveal elevated erythrocyte sedimentation rate and C reactive protein levels, normocytic normochromic anemia, leukocytosis, thrombocytosis and polyclonal hypergammaglobulinemia consistent with an inflammatory state. Urinalysis is usually normal, but patients with renal involvement manifest proteinuria or active sediments which may be accompanied by raised serum creatinine. Cerebrospinal fluid (CSF) analysis may show abnormalities in patients with CNS involvement, especially those with aseptic meningitis in whom neutrophilic pleocytosis and reduced glucose levels mimic the picture of pyogenic meningitis [58]. Anti-glutamate receptor (GluR) epsilon2 (NR2B) autoantibodies have been reported in the CSF and serum of a patient with RP and limbic encephalitis [59].

Radiographs may reveal calcification of the pinna, a non-specific finding which may be seen with frost bite, Addison's disease, acromegaly or ochronosis. In chronic RP, the nasal and tracheal cartilage might also show calcification. Joint radiographs may reveal narrowing of the joint space due involvement of the articular cartilage, but the cysts and erosions are seen rarely [52]. Computed tomography (CT) can identify early laryngotracheal disease or bronchial cartilage involvement. In a recent series of 21 patients [60], major abnormal CT findings noted were airway wall thickening (n=7), airway stenosis (n=6), airway malacia (n=6), airway wall calcification (n=8), and air trapping (n=3). Mediastinal lymph nodes were found in 12 patients. Magnetic resonance imaging or spiral CT provides better resolution and also helps to differentiate upper airway disease from vascular involvement. Virtual bronchoscopy can help in the assessment of airway lesions in patients with lung involvement [61]. Pulmonary function testing is abnormal in advanced lower respiratory tract disease. Laryngoscopy and bronchoscopy may be useful but are associated with risk of exacerbation of inflammation. Endobronchial ultrasonography can reveal soft tissue changes in the tracheobronchial cartilage in the initial stages of the disease [62]. Echocardiography is used to assess the valves and aortic root in patients with suspected cardiovascular involvement.

Histopathological examination of involved cartilage may be useful in occasional patients with diagnostic dilemma. However, no biopsy finding is pathognomonic of RP and may rather contribute to further cartilage damage. Bone scintigraphy usually reveals increased uptake of 99m technetium–methylene diphosphonate in the inflamed cartilages [63] and can help locate the site of biopsy. Meticulous sampling of the inflamed perichondral tissue is required for demonstration of characteristic histologic picture, failing which only non-specific granulation tissue will be visualised [3]. The initial change is the loss of basophilia in the cartilage matrix, corresponding to loss of matrix proteoglycans. Cellular infiltrates by lymphocytes, neutrophils and plasma cells, most evident in the cartilage-soft tissue interface and reduced number of chondrocytes are seen in areas of cartilage destruction [3].

Disease activity

Anti collagen type II antibodies are generally present in the acute phase of the disease and the titres are found to correlate with disease activity [23, 64]. The level of urinary glycosaminoglycans may also be elevated [65]. The levels of urinary collagen type II neoepitope, a specific marker of catabolism of hyaline cartilage rich in type II collagen has been found to be elevated in active inflammation and can also be used to assess response to treatment [66]. Serum levels of cartilage oligomeric matrix protein was found to be elevated during disease flares in a retrospective study and may be used as a marker of disease activity [67].

The Relapsing Polychondritis Disease Activity Index (RPDAI) [68] has been developed recently by a worldwide panel of RP experts. The experts rated the Physician's Global Assessment of disease activity (the physician's evaluation of disease activity for a given test case) of the test cases involved in the study who were diagnosed with RP based on Michet's criteria. The first scoring system for disease activity

in RP, the RPDAI will facilitate standardization of the disease activity measurement between physicians and institutions. This index, which comprises of 27 variables, is a promising step in objective clinical assessment of activity and response to treatment and is yet to be used widely in clinical trials and routine clinical practice. The online scoring is available at www.rpdai.org.

Management

Treatment in RP is largely symptomatic and a standard management protocol is yet to be established due to its rarity.

Less severe symptoms like mild auricular or nasal chondritis and arthralgia are generally treated with nonsteroid anti-inflammatory drugs. Dapsone and colchicine may also be used in these patients. Dapsone in doses of 50 to 200 mg/day has been advocated as an effective initial therapy in patients without cardiorespiratory involvement [69–71] but Trentham et al. [3] observed that it was not effective in most patients and resulted in a number of adverse reactions. Organ-threatening disease, including severe polychondritis, ocular or laryngotracheal involvement and systemic vasculitis require systemic corticosteroids. Oral prednisolone or its equivalent is generally employed in doses of 0.5 to 1 mg/kg of body weight per day. High-dose steroid therapy or intravenous pulse therapy may be required in severe cases. Doses may be tapered off after the acute flare, but most patients require low-dose steroids in between the attacks for control of symptoms though data on this is lacking. Long-term steroid therapy may reduce the frequency and severity of the acute episodes but is not known to affect disease progression or prevent vital organ involvement [72]. Inhalational corticosteroids produce marked symptomatic relief and reduce the amount of systemic steroid requirement in patients with obstructive airway disease due to RP [73]. Oral colchicine and indomethacin have also been proved useful in the remission phase in a few reports [74].

In patients unresponsive to or more commonly intolerant to steroid therapy, or in whom a steroid sparing therapy is required due to the chronic nature of the disease, immunosuppressants play a role. Methotrexate, azathioprine, cyclosporine and chlorambucil may be used in these patients. Trentham et al. [3] observed that methotrexate was the most effective nonsteroid drug in causing symptomatic benefit and reducing the steroid requirement at an average dose of 17.5 mg/week. Minocycline, an antibiotic with immunomodulatory actions has been used effectively in a patient who was intolerant to methotrexate [75]. Intravenous cyclophosphamide and plasmapheresis are used in patients with life-threatening or organ-threatening disease including acute airway obstruction or glomerulonephritis [48]. Letko et al. [72] report that scleritis is a marker of disease activity and advocate cyclophosphamide as the initial therapy of choice in patients with RP and necrotising scleritis. However, they observed that in patients with diffuse scleritis, methotrexate alone or in combination with steroids was sufficient. Leflunomide has been tried in some patients [7], but data regarding its safety and efficacy in RP is inadequate.

Given the autoimmune theory of etiopathogenesis of RP, a number of biologics targeting the B cells and the pathways of cell-mediated immunity are being used increasingly in these patients not responding to other medical therapy. Anti-CD4 monoclonal antibody was the first biological agent tried with some efficacy in RP [76, 77]. There are isolated case reports of favourable response to rituximab in patients not responding to immunosuppressive therapy [78, 79]. However, a retrospective study [80] of 9 patients treated with rituximab showed that at the end of 12 months of therapy, no patient was in partial or complete remission though depletion of B cells was demonstrated. Anti-TNF agents have been used successfully in patients with refractory RP. Anti-TNF alpha agents infliximab, adalimumab and etanercept have been used in patients not responding to conventional immunosuppression. There are several reports of infliximab (3–10 mg/kg every 4–8 weeks) being used with good or partial response in improvement of chondritis and respiratory complications [79, 81–85]. Etanercept [86–88] and Adalimumab [89, 90] have been tried in a few occasions with response in some of the patients. Anakinra, the IL-1 receptor antagonist [91, 92] and Abatacept, the CTLA4-IgG1 fusion protein [93] are the other agents that have been tried. Kawai et al. [94] have reported satisfactory response to anti-interleukin-6 receptor antibody, Tocilizumab in two patients with refractory relapsing polychondritis. Most evidence on the use of biologics is drawn from individual experiences and data from clinical trials is lacking. Hence, more data is required to assess the efficacy and adverse reactions of these agents and their indication is currently restricted to patients not responding to conventional medical therapy.

Patients with tracheal stricture or collapse may require stenting [95] or tracheal dilatation by interventional bronchoscopy [96]. Silicon T-tubes are an effective treatment measure for preserving airway patency in patients with tracheal stenosis due to the disease [97]. Karamen et al. [98] described surgical reconstruction of the laryngotracheal region in three patients with extensive respiratory involvement. A case of life-threatening bilateral tension pneumothorax and tension pneumoperitoneum that developed after a tracheal tear during Montgomery T-tube insertion in a patient with tracheal stenosis due to RP has been described [99]. Childs et al. [100] reported the use of pulsed-potassium-titanyl-phosphate laser for the management of bilateral bamboo nodules of the vocal folds associated with RP. Cochlear implant surgeries can restore hearing in patients with sensorineural hearing loss [101]. Reconstructive surgeries with

grafting are a potential option for saddle nose deformity. Haug et al. [102] reported the use of a bone graft from the iliac crest, because the autoimmune polychondritis precludes cartilage grafting due to expected cartilage destruction. In patients with regurgitant lesions requiring valve replacement, recurrent perivalvular regurgitation and valve dehiscence are common due to the dilated aortic root and adjacent inflamed tissue. Sharma et al. [103] reported a case of RP in which aggressive early therapy prevented the progression of aortic regurgitation. In vivo immunoablation in combination with autologous stem cell transplant has shown to cause complete remission in a patient with refractory RP [104]. In RP associated with myelodysplastic syndrome, there are isolated case reports of both autologous and allogenic bone marrow transplant resulting in improvement of symptoms [105]. In a case report of RP associated with hepatitis C virus (HCV) infection, treatment with pegylated interferon and ribavirin resulted in suppression of HCV and remission of difficult to treat RP with azathioprine [106].

The emergence of the RPDAI consensus scoring system and the increasingly successful use of biologics are likely to have a considerable impact on the course of this relatively rare multisystem connective tissue disease.

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