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Perspective

How does Palindromic Rheumatism fit into the Rheumatoid Arthritis Continuum?

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Abstract

Palindromic rheumatism (PR) is a distinctive syndrome which has a long-recognised association with rheumatoid arthritis (RA). PR is characterised by intermittent flares of pain, erythema and swelling in and around the joints, which are typically severe and unpredictable. The observation that most PR patients have RA-related autoantibodies and that many eventually develop RA has led to PR often being viewed as a relapsing-remitting variant of RA. However, the clinical and imaging phenotypes of PR suggest important distinctions from RA and imply underlying mechanistic differences between the two conditions. Furthermore, there are interesting parallels between the pattern of inflammation seen in PR with that seen in other groups of symptomatic individuals at risk of RA development. In this article we will explore the concept of PR as part of the RA continuum and propose an updated disease paradigm for this unique syndrome.

Introduction

Palindromic rheumatism (PR) is a clinical syndrome characterised by debilitating flares of pain, swelling and erythema centred around the joints. PR is encountered by most rheumatologists in routine clinical practice, yet the diagnosis can be challenging and the pathogenesis and optimal treatments are unclear. Patients with PR often go on to develop rheumatoid arthritis (RA). The shared risk factors, including genetics and autoantibodies, and the typical distribution of affected joints, suggest PR may be a relapsing-remitting form of RA, which progresses to persistent disease. However, the flares that define PR are not typical of an autoimmune phenotype but appear to be more closely related to an autoinflammatory process (see later for explanation). In this article we will focus on the unique phenotype of PR and its relationship with RA. We will describe the similarities between PR and RA prodromes and what this tells us about RA pathogenesis. Finally we will outline an overarching hypothesis for PR and explore how this may refine the management of this curious syndrome.

Is PR simply relapsing-remitting RA?

Conventional wisdom tells us that PR is closely associated with RA. This is largely based on observations of the natural history and the clinical and serological features of this syndrome. The authors of some of the earliest clinical studies of PR reported high rates of progression to RA in their respective PR cohorts (1-4). In the first longitudinal study of PR, Ansell and Bywaters reported progression to RA in 18/28 (64%) patients within 8 years of follow up (1). Subsequently, high rates of progression were also reported in two other UK cohorts; Mattingly observed 10 of 20 PR patients developed RA over 10 years of follow up

(2), while Wajed et al reported progression to RA in 17/39 (44%) of their patients (3). Similarly, in a Finnish cohort, Hannonen et al described progression to persistent arthritis in 35/60 (58%) PR patients (4). Based on these observations, most investigators proposed that PR represents an atypical, relapsing-remitting form of RA and if patients were followed up for long enough, the development of full-blown RA would be inevitable for most. Indeed, when the Finnish PR cohort described by Hannonen et al was re-examined after over twenty years of follow up, two-thirds of all patients had developed RA, with all but two patients having progressed within the first 10 years of follow up (5).

A further argument for a close association between PR and RA is the two conditions have a similar prevalence of RA-related autoantibodies. A high prevalence of rheumatoid factor positivity was identified in early PR studies, prior to the availability of anti-citrullinated protein antibody (ACPA) testing (3, 4) . In a cross-sectional analysis of a Spanish PR cohort, the frequency of anti-CCP antibodies was similar in PR compared with early RA patients (53% vs 55% respectively) (6). Other international PR cohorts report similarly high frequencies of anti-CCP positivity (between 46% and 68%) (7-11). A notable outlier is a recently described Taiwanese PR cohort where only 11/84 (13%) of patients were anti-CCP positive and 12/84 (14%) were RF positive (12). Variable inclusion criteria, recruitment strategies, geographical differences in patient profiles and possible pathogens could all explain the apparent disparity in these data.

There is also evidence of immunogenetic similarity between PR and RA. The initial genetic studies in PR were performed in relatively small groups of patients and used serological rather than DNA typing for HLA antigens, producing mixed results (13-16). However, in a larger more recent study, an increased prevalence of HLA-DR shared epitope (SE) alleles in

PR patients compared with controls was reported (17). That study found homozygosity of SE alleles to be predictive of progression to chronic arthritis, although SE status was not found to be as predictive in a subsequent smaller study of Japanese PR patients (8).

Thus the immunogenetic and serological profile of PR, added to its propensity to become full-blown RA suggests it could be considered as a 'relapsing-remitting form of RA', which, over time, naturally progresses from an intermittent to a persistent arthritis.

For this to be true, one would expect the pattern of joint inflammation in flares of PR to be similar to that seen in RA. However, a recent imaging study of treatment-naïve PR patients observed the opposite (11). PR flares were characterised by a high frequency of extra-capsular inflammation on ultrasound (US); 61% of patients had this finding and interestingly in 63% of these cases there was no co-existent synovitis. In contrast, only 23% of patients had evidence of US synovitis during flare. Isolated extra-capsular inflammation appeared to distinguish PR from RA as this pattern was rarely seen in the RA patients. As may be expected, US inflammation was rarely seen in PR patients when they were not flaring (11). These new data suggest PR is not in fact characterised by relapsing-remitting synovitis but instead by a different pattern of inflammation, focused on peri-articular rather than intra-articular structures (figure 1).

Is PR a distinct disease entity?

Despite the shared genetic and immunological risk factors, the distinct pattern of inflammation in PR suggests the notion of this syndrome as a relapsing-remitting prodrome of RA may be an oversimplification. Indeed, a minority of PR patients will go on to develop other chronic diseases, e.g. connective tissue disorders or vasculitis and not necessarily RA

(4, 18). Furthermore, seropositive and seronegative PR may be mechanistically and phenotypically distinct. While there is little published data that directly addresses this, the genetic and immunological risk factors that link PR and RA are clearly specific to seropositive disease. It is therefore possible that seronegative PR is more genetically and phenotypically heterogeneous. This is certainly an area which warrants further exploration. The evidence for distinct disease mechanisms in PR will now be discussed in the context of clinical features, genetics, imaging findings and response to treatment.

Clinical features

PR and RA have a predilection for the same joints. Studies of different PR cohorts have consistently reported the wrists, metacarpophalangeal joints (MCPJs) and proximal interphalangeal joints (PIPJs) as the most commonly affected sites in PR (2, 4, 8, 9, 19, 20). In contrast, the spine and sternoclavicular joints are the least frequently affected sites (mean 4% and 2% of patients respectively) (19). However, despite the distribution of affected joints being similar, the nature of the inflammation seen in these syndromes appears to be different. Painful inflammatory flares are the hallmark of PR and are frequently characterised by peri-articular soft tissue inflammation (19). Indeed, in the original description of PR, Hench and Rosenberg chose the name ‘palindromic rheumatism’ rather than ‘palindromic arthritis’ based on the striking peri-arthritis and para-arthritis observed in some of their patients (20). Subsequent clinical descriptions have confirmed peri-articular involvement and skin erythema as typical clinical signs of PR (2, 19). Whether peri-articular inflammation occurs in the presence or absence of co-existent synovitis is difficult to establish on clinical examination alone and requires high resolution imaging (see below). Peri-articular inflammation is a less frequent clinical finding in early RA, which is

characterised by small joint synovitis and tenosynovitis (i.e. inflammation centred on synovial tissues). Indeed, on clinical signs alone, PR in many respects appears closer to crystal arthritidies and other autoinflammatory diseases than RA; in common with these inflammasome driven diseases, PR is inherently periodic and characterised by intermittent self-abortive flares of acute pain, swelling and erythema.

Genetics

As noted above, the increased prevalence of HLA-DR SE alleles in PR (17) highlights immunogenetic similarities with RA that may be expected given the epidemiological relationship between these diseases. However, an inflammasome related disease mechanism in PR is also supported by genetic studies. In a Spanish PR cohort, a high frequency of mutations in the MEFV gene, mutations of which are responsible for Familial Mediterranean Fever (FMF), have been identified; in that study 8/65 (12.3%) of PR patients carried at least one mutated MEFV allele (21). Interestingly, mutations were more commonly found in ACPA-negative PR patients. MEFV mutations were also identified in a small series of intermittent hydrathrosis (IH) patients (22). This periodic syndrome is characterised by intermittent flares of joint inflammation, usually affecting the knees (often with effusions). Patients are seronegative and rarely develop a persistent arthritis, with long periods of remission often seen. The same group went on to report successful treatment of refractory IH using IL-1 inhibition with anakinra (23), further supporting a role for autoinflammation in this PR-mimic. Although there are no reports of IL-1 inhibition in PR, there are data suggesting a favourable response to colchicine (24), a treatment effective in auto-inflammatory disorders.

A distinct genetic susceptibility in PR was also identified in a Korean study where 110 PR patients were genotyped for 33 HLA-DRB1 alleles (25). Of these, only two alleles, HLA-DRB1*03 and *1302, had a significant association with PR compared with healthy controls. Importantly, no associations have been reported for these alleles in RA, suggesting distinct immunogenetic mechanisms may be relevant.

Imaging features

High resolution imaging of treatment-naïve PR patients suggests a distinct disease process compared with RA; ultrasound indicates inflammation in PR is predominantly centred on extra-capsular rather than intra-articular targets (11). Extra-capsular inflammation (including tenosynovitis and peri-articular soft tissue inflammation) in the absence of synovitis was also identified in another US study of PR patients (26). Early US studies in PR were performed on small numbers of patients, most of whom had a long disease duration and were treated with disease-modifying anti-rheumatic drugs (DMARDs) (27, 28). Although these studies reported US synovitis in flares of PR, they are difficult to interpret: it is possible that the phenotype of PR changes significantly after DMARDs are used (29). For example, in one of the studies the authors noted that none of the patients had clinical peri-articular inflammation during flares (28). This highlights how different case definitions for PR have led to heterogeneous groups of patients being studied (see 'research agenda for PR below). The discrepancy in imaging findings suggests it would be inappropriate to include treated patients alongside untreated patients in studies seeking to understand the PR phenotype and in clinical trials using imaging biomarkers.

Taken together, clinical and imaging findings in treatment-naïve *de novo* PR suggest a distinct syndrome to RA, in which the focus of inflammation appears to be extra-capsular rather than primarily centred on intra-articular structures.

Response to treatment

In keeping with the clinical, genetic and imaging features described above, the therapeutic response in PR is also different to RA and reveals similarities with autoinflammatory disorders. While disease-modifying anti-rheumatic drugs (DMARDs) are often used in the management of PR, there are no controlled trials to support this approach. One small study reported sulfasalazine was effective for palindromic flares (30) but there have been no studies on the efficacy of methotrexate, leflunomide or biologic therapies. Retrospective data suggest anti-malarials can reduce the frequency and severity of palindromic flares (31) and also the time to development of persistent arthritis (32). Whereas hydroxychloroquine monotherapy is not usually sufficient to treat RA, one preliminary randomised controlled trial has shown ,it to be effective for the treatment of refractory pseudogout (33), although this has yet to be replicated in a definitive study. Interestingly**,** in one small study PR appeared to respond well to colchicine (24), a drug not effective for RA, but known to be effective in autoinflammatory diseases (34, 35), autoimmune-autoinflammatory overlap cases (36) and crystal arthritidies (37). Although no definitive conclusions can be drawn from this small study, our own personal observations support these preliminary data, and use of colchicine in PR seems appropriate for further investigation. Indeed, IH, a periodic syndrome which clinically resembles PR, can be treated successfully with anakinra (23), an IL-1 inhibitor known to be effective in autoinflammatory diseases (38-41) and crystal arthritidies (42) .

The distinct phenotype, genotype and therapeutic response in PR clearly highlights important underlying differences from RA and suggests the notion of PR as a 'relapsing-remitting RA' is not accurate. . However, the immunogenetic and epidemiological relationship between PR and RA cannot be overlooked. To better understand PR, it may be more appropriate to consider it in the context of the RA continuum as a whole, rather than by comparing it only with established RA.

PR and the RA disease continuum

RA is not a fixed phenotype but should be considered as a disease continuum encompassing a series of pathogenic phases which culminate in the development of arthritis (43, 44). As such it is well recognised that musculoskeletal symptoms can develop before the emergence of clinical arthritis (45). Therefore at-risk individuals (who do not have PR) may be identified on the basis of symptoms in the presence of RA-associated autoantibodies i.e. seropositive arthralgia (46, 47), or solely by inflammatory-type symptoms which are suspicious for an evolving arthritis, called 'clinically suspect arthralgia (CSA)' (48). For the reasons described above, it would be appropriate to consider PR alongside seropositive arthralgia and CSA as an at-risk phenotype (figure 2). As described above, the clinical and imaging pattern of inflammation in PR is different to that found in established RA. However, as seen in PR, a high prevalence of extra-capsular inflammation has also been reported in CSA patients (49) and anti-CCP positive at-risk individuals (50, 51) who do not have PR. CSA patients with subclinical inflammation (synovitis, bone marrow oedema or tenosynovitis) on MRI are more likely to progress to clinical arthritis than those with normal MRI findings (hazard ratio

of 6.12) (49). Of note, the strongest association was seen for extra-capsular inflammation, i.e. tenosynovitis, and this was the only MRI variable that was independently associated with arthritis development (HR 8.39). Tenosynovitis was also the most prevalent MRI abnormality identified in two separate cohorts of anti-CCP positive at-risk individuals (50, 51) and was the most predictive of all MRI features for arthritis development in a prospective analysis (50). Furthermore, a novel site of extra-capsular inflammation has also been recently described in symptomatic anti-CCP positive at-risk individuals without PR (52). This study identified MRI inflammation of the interosseous tendons of the hands, often in the absence of a MRI synovitis at the adjacent MCP joints. The identification of extra-capsular inflammation, often in the absence of synovitis clearly parallels the clinical and imaging findings in PR.

Where the 'second hit' in RA, i.e. the tissue-specific factors that focus systemic autoimmunity to the joints, takes place is still a matter for debate (53). While the high prevalence of extra-capsular inflammation in at-risk individuals (with and without PR) supports the disease first localising outside the joints , the alternative 'inside-out' hypothesis considers arthritis to start as bone marrow infiltration of inflammatory cells which then migrate outward, through cortical channels, to the synovium (53). In favour of the latter, MRI osteitis occurs in early arthritis and is associated with disease progression (54). Also, structural bone changes have been identified on micro-CT imaging in ACPA-positive individuals without PR who have no clinical synovitis (55).

When considered together, the existing MRI data in at-risk individuals (including anti-CCP positive at-risk individuals, CSA and PR patients) suggest extra-capsular inflammation is more prevalent than intra-articular inflammation (including osteitis) before the onset of

clinical arthritis (table 1). On this basis it is tempting to speculate the following: First, that extra-capsular rather than intra-articular inflammation may be responsible for pain and stiffness often reported by at-risk individuals before the onset of arthritis (45). Second, at least in a subset of patients, the tendons and extra-capsular structures may be the primary site of disease in RA, and third BME may determine clinical presentation as RA. Longitudinal imaging studies with serial assessments in prospective at-risk cohorts will be critical to test these hypotheses. If indeed a primary phase of extra-capsular inflammation heralds the onset of symptoms, and this progresses to intra-synovial disease when arthritis becomes more imminent, it is possible that the extra-capsular phase may be an opportunity for intervention to prevent arthritis development (figure 3). Once intra-articular inflammation (including BME) develops in at-risk individuals, particularly in those with autoantibodies, persistent arthritis may be inevitable for most; power Doppler (PD) synovitis (score ≥2) on ultrasound is strongly predictive of imminent clinical arthritis, both at patient (HR 3.7) and joint level (HR 31.3) in anti-CCP positive at-risk individuals without PR (56). Similarly, intra-articular PD is strongly predictive of persistent arthritis in seronegative patients with very early disease (57). Thus, as demonstrated by the characteristic ability of PR to relapse and remit while leaving no residual damage, extra-capsular inflammation may be a clinically useful marker for potential reversibility in at risk individuals. This clearly has implications for preventative strategies and it may be that targeting symptomatic at-risk individuals with isolated extra-capsular disease requires less intensive (and perhaps different) immunomodulation to prevent progression to intra-articular disease, at which point persistence is likely to occur. Indeed retrospective studies suggest hydroxychloroquine is effective in ameliorating PR flares and preventing RA development, although robust trials to assess this have never been performed (32). It is certainly encouraging that emerging

qualitative work suggests symptomatic at-risk individuals are much more likely to accept potential preventative interventions than those without any clinical symptoms (58). Future clinical trials could potentially test this hypothesis, stratifying at-risk individuals (including PR patients) for therapeutic strategies tailored to the anatomical pattern of inflammation.

An overarching hypothesis for PR

While flares of PR do not look like RA (especially on imaging), they appear to have similarities (in anatomical targets) to the inflammation seen in other groups of at-risk individuals. Like these other at-risk subgroups, PR may be considered as a manifestation of the prodromal phase of RA rather than simply being a relapsing-remitting form of the final disease. However, PR is made unique by the *type* of inflammation that occurs in this prodromal phase and it is here that differences from the other at-risk phenotypes are readily apparent. The acute yet transient flares of pain, swelling and erythema that characterise PR are suggestive of an innate immune response rather than a typical autoimmune phenotype. It is possible that PR is an overlap syndrome, with two mechanistic axes; autoimmunity driving the development of RA but also discrete attacks that have an autoinflammatory component (figure 4). This component is generally localised and more akin to crystal arthritis rather than systemic autoinflammatory diseases (SAIDs) but may be more marked in certain cases, where attacks of fever, high C-reactive protein levels and serositis have been reported in anti-CCP positive patients with arthritis (36). In these more extreme cases typical SAID mutations are often found. It is therefore possible that in classical PR, a milder localised phenotype occurs due to a related genetic predisposition which causes an individual to develop autoinflammatory flares in the prodromal phase of RA

rather than a more typical autoimmune phenotype (e.g. arthralgia and stiffness). This supposition is supported by the favourable response to colchicine, which alleviated PR flares in a small preliminary study (24) but is not effective for autoimmune synovitis. This hypothesis could be further tested by investigating gene expression signatures in PR compared with other at-risk phenotypes, RA patients and SAID patients. Furthermore, given the favourable response of autoinflammatory diseases (34-36, 38-41), autoimmune-autoinflammatory overlap cases (36) and crystal arthritidies (42, 59-62) to colchicine and IL-1 blockade, it is possible that true PR patients may respond better to these types of therapies than to other conventional DMARDs. Indeed even though IL-1 blockade does not appear to be as effective in RA compared with other biologic therapies (63, 64), it is plausible that it may be particularly effective in treating subgroups of RA patients with clinically evident autoinflammatory characteristics (e.g. patients with palindromic-onset RA who continue to have typical flares). Proof-of-concept clinical trials of IL-1 blockade in PR would be important future work as developing a targeted treatment approach for PR remains a major unmet clinical need.

Research agenda for PR

A major difficulty in interpreting PR research is the lack of an accepted case definition for this disease. Variable inclusion criteria in small patient cohorts make clinical, imaging and therapeutic studies difficult to compare and consequently there is a paucity of robust evidence upon which to base clinical decisions (table 2). Many of the older studies did not explicitly specify diagnostic criteria and several different criteria have been used in the more recent ones. There is therefore a pressing need for consensus diagnostic or classification

criteria for PR so that future research can be better aligned and more clinically meaningful. This is especially important given PR is uncommon and untreated patients are notoriously difficult to recruit. Multi-centre clinical studies including untreated patients who fulfil accepted diagnostic criteria will be critical to adequately address key research questions (Box 1).

Conclusions

PR is a unique and intriguing syndrome that is routinely seen by rheumatologists but remains poorly understood. Its close relationship with RA as well as clear differences from that syndrome have been recognised since its first description over seventy years ago (20). Disease mechanisms and targeted treatments remain elusive and most patients are treated with DMARDs despite limited evidence and no controlled trials. A distinct clinical and imaging phenotype means PR cannot be considered simply as relapsing-remitting RA. Instead, shared disease targets with other groups of at-risk individuals and phenotypic similarities with autoinflammatory disorders suggest PR may be considered as a prodrome of RA with a mixture of autoimmune and autoinflammatory characteristics. Affected individuals may have a genetic predisposition to develop autoinflammatory type flares rather than the arthralgia and stiffness more commonly associated with RA. Importantly, unravelling disease mechanisms in PR will provide important insights into the pathogenesis of RA and may inform future preventative approaches. It will also refine the treatment of this interesting and elusive disease.

Box 1

Research Agenda

- Can consensus diagnostic or classification criteria for PR be developed
- How prevalent are SAID-associated genes in PR?
- Is the genotype and phenotype of anti-CCP positive PR different from anti-CCP negative PR?
- What is the role of the HLA-SE in determining anti-CCP positivity and disease progression in PR?
- Do those PR patients who progress to RA have a distinct phenotype of RA, with autoinflammatory manifestations? Does this relate to underlying genetic differences?
- Can flares of PR be ameliorated by autoinflammatory therapies (e.g. colchicine, anti-IL-1 therapy) and can these treatments prevent progression of PR to RA?

Box 2

Key Points

- PR has a distinct clinical and imaging phenotype and cannot simply be considered as 'relapsing-remitting RA'.
- PR has an immunogenetic link with RA, but shares clinical features, genetic associations and therapeutic responses with SAIDs and crystal arthritidies.
- PR may be considered as an overlap syndrome, with both autoimmune and autoinflammatory characteristics.
- PR shares disease targets with other groups of at-risk individuals and may be a genetically-determined manifestation of the prodromal phase of RA.

Reference	*At-risk cohort*	*Patients included*	*Number (n)*	*Key findings*
Van Steenbergen et al(49)	Clinically suspect arthralgia. Leiden, NDL	Arthralgia without synovitis No PR	144	Subclinical MRI inflammation (tenosynovitis, BME, synovitis) was identified in CSA patients and predicted arthritis development. MRI TSV was the most prevalent abnormality (29% of patients) and the only to independently predict arthritis development.
Kleyer et al(51)	Anti-CCP positive with arthralgia. Erlangen, DEU	Arthralgia without synovitis No PR	20	MRI TSV was the most prevalent MRI abnormality, affecting 80% of anti-CCP positive patients and no controls. TSV at ≥2 sites was predictive of arthritis development.
Hunt et al(50)	Anti-CCP positive with MSK symptoms. Leeds, UK	MSK symptoms without synovitis No PR	98	MRI TSV was the most prevalent MRI abnormality affecting 40% of anti-CCP positive at-risk individuals (score adjusted for controls). At patient level, MRI TSV predicted arthritis development. At joint level, MRI TSV and BME were predictive of arthritis development.
Mankia et al(52)	Anti-CCP positive with MSK symptoms. Leeds, UK	MSK symptoms without synovitis No PR	93	MRI interosseous tendon inflammation (ITI) was detected in 19% of anti-CCP positive at-risk individuals but no healthy controls. MRI ITI was more prevalent at tender MCP joints compared with non-tender MCP joints.
Mankia et al(11)	DMARD-naïve PR. Leeds, UK	PR	11	MRI synovitis was identified in 7/11 (64%) PR flares, MRI TSV in 5/11 (45%) flares and peri-tendinous oedema in 6/11 (55%) flares. Peri-articular inflammation was identified in 6/11 (55%) flares. BME identified in only 1/11 (9%) flares. No erosions were seen.
Bugatti et al(27)	Established, treated PR. Pavia, Italy	PR	4	4 patients underwent MRI during PR flares: 'mild' synovitis was identified in 3, and BME in 4. Extra-capsular inflammation was not reported.

Table 1: MRI studies in individuals at-risk of RA reveal a high frequency of extracapsular inflammation.

Reference/year	*Case definition*	*Study size*	*Study type*	*Key findings*
Ansell & Bywaters 1959	Physician clinical diagnosis	28	Clinical cohort	64% developed RA at 8 years
Mattingly, 1966	Physician clinical diagnosis	20	Clinical cohort	50% developed RA at 10 years
Wajed et al, 1977	Physician clinical diagnosis	39	Clinical cohort	44% developed RA
Koskinen et al, 2009	Authors own proposed case definition	60	Clinical cohort	67% developed RA at 20 years
Tamai et al, 2010	Gonzalez-Lopez criteria	28	Clinical cohort; RA-related autoantibodies	Anti-CCP, PIP joint involvement and HLA-SE predicted RA development
Emad et al, 2014	Authors own proposed case definition	90	Clinical cohort; RA-related autoantibodies	Anti-CCP and hand joint involvement predicted RA development at 1 year
Salvador et al, 2003	Guerne criteria	63	RA-related autoantibodies	56% of PR patients were anti-CCP positive and 36% were anti-keratin antibody positive
Gonzalez-Lopez et al, 1999	Authors own proposed case definition	127	Clinical cohort	34% developed RA or CTD
Sanmarti et al, 2012	Guerne criteria	71	Clinical cohort; RA-related autoantibodies	34% progressed to persistent disease. Positive likelihood ratio of ACPA status for RA was 1.45
Khabbazi et al, 2012	Authors own proposed case definition (incorporating Pasero and Barbieri's criteria)	69	Clinical features and RA-related autoantibodies	Anti-CCP positive PR associated with more frequent attacks of shorter duration associated with MCPJ involvement
Russell et al, 2006	Authors own proposed case definition	61	Clinical cohort; RA-related autoantibodies	48% developed RA after mean 5 years
Maksymowych et al, 2002	Gonzalez-Lopez criteria (same cohort)	147	Genetic	31% of patients developed RA or CTD. Increased prevalence of HLA-DRB1 SE in PR compared with controls
Kim et al, 2006	Authors own proposed case definition (not specified)	110	Genetic	HLADRB1*0803 identified in 59% of PR patients compared with 12% of controls
Bugatti et al, 2012	Guerne criteria	15	Imaging	US synovitis identified in 9/15 patients during flare. 4 patients underwent MRI: 'mild' synovitis was identified in 3, and BME in 4
Chen et al, 2009	Guerne criteria	84	Imaging	Increased prevalence of US synovitis during flare in anti-CCP positive PR
Cabrera-Villalba et al, 2014	Guerne criteria	54	Imaging	Absence of US synovitis in the intercritical period of PR

Mankia et al, 2019	Authors own proposed case definition	31	Imaging	Increased prevalence of non-synovial extracapsular inflammation in PR compared with RA
Gonzalez-Lopez et al, 2000	Authors own proposed case definition	113	Treatment: anti-malarials	Reduced progression to RA in PR patients treated with antimalarials
Yousef et al, 1991	Authors own proposed case definition	71	Treatment: chloroquine	Improvement in frequency and severity of PR attacks in patients treated with chloroquine
Schwartzberg et al, 1982	Physician clinical diagnosis	5	Treatment: colchicine	Colchicine appears effective for treatment of PR flares in this small study

Table 2: A summary of PR studies highlighting the variable case definitions used and small cohort sizes.

References

1. Ansell BM, Bywaters EG. Palindromic rheumatism. Annals of the rheumatic diseases. 1959;18:330.

2. Mattingly S. Palindromic rheumatism. Annals of the rheumatic diseases. 1966;25(4):307-17.

3. Wajed MA, Brown DL, Currey HL. Palindromic rheumatism. Clinical and serum complement study. Annals of the rheumatic diseases. 1977;36(1):56-61.

4. Hannonen P, Mottonen T, Oka M. Palindromic rheumatism. A clinical survey of sixty patients. Scand J Rheumatol. 1987;16(6):413-20.

5. Koskinen E, Hannonen P, Sokka T. Palindromic rheumatism: longterm outcomes of 60 patients diagnosed in 1967-84. The Journal of rheumatology. 2009;36(9):1873-5.

6. Salvador G, Gomez A, Vinas O, Ercilla G, Canete JD, Munoz-Gomez J, et al. Prevalence and clinical significance of anti-cyclic citrullinated peptide and antikeratin antibodies in palindromic rheumatism. An abortive form of rheumatoid arthritis? Rheumatology (Oxford, England). 2003;42(8):972-5.

7. Russell AS, Devani A, Maksymowych WP. The role of anti-cyclic citrullinated peptide antibodies in predicting progression of palindromic rheumatism to rheumatoid arthritis. The Journal of rheumatology. 2006;33(7):1240-2.

8. Tamai M, Kawakami A, Iwamoto N, Arima K, Aoyagi K, Eguchi K. Contribution of anti-CCP antibodies, proximal interphalangeal joint involvement, HLA-DRB1 shared epitope, and PADI4 as risk factors for the development of rheumatoid arthritis in palindromic rheumatism. Scand J Rheumatol. 2010;39(4):287-91.

9. Emad Y, Anbar A, Abo-Elyoun I, El-Shaarawy N, Al-Hanafi H, Darwish H, et al. In palindromic rheumatism, hand joint involvement and positive anti-CCP antibodies predict RA development after 1 year of follow-up. Clinical rheumatology. 2014;33(6):791-7.

10. Khabbazi A, Hajialiloo M, Kolahi S, Soroosh M, Esalatmanesh K, Sharif S. A multicenter study of clinical and laboratory findings of palindromic rheumatism in Iran. International journal of rheumatic diseases. 2012;15(4):427-30.

11. Mankia K, D'Agostino MA, Wakefield RJ, Nam JL, Mahmood W, Grainger AJ, et al. Identification of a distinct imaging phenotype may improve the management of palindromic rheumatism. Annals of the rheumatic diseases. 2018.

12. Chen HH, Lan JL, Hung GD, Chen YM, Lan HH, Chen DY. Association of ultrasonographic findings of synovitis with anti-cyclic citrullinated Peptide antibodies and rheumatoid factor in patients with palindromic rheumatism during active episodes. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2009;28(9):1193-9.

13. Fisher LR, Kirk A, Awad J, Festenstein H, Alonso A, Perry JD, et al. HLA antigens in palindromic rheumatism and palindromic onset rheumatoid arthritis. Br J Rheumatol. 1986;25(4):345-8.

14. Gran JT, Husby G, Thorsby E. HLA antigens in palindromic rheumatism, nonerosive rheumatoid arthritis and classical rheumatoid arthritis. The Journal of rheumatology. 1984;11(2):136-40.

15. Barbieri P, Ciompi ML, Menicucci A, Pasero G. HLA antigens in palindromic rheumatism. An Italian study. Clinical rheumatology. 1988;7(4):470-3.

16. Bregeon C, Dajon JL, Renier G, Jegoude-Mauco F, Galland F, Fallah N, et al. [Palindromic rheumatism. Immunologic survey and study of development in 43 cases]. Rev Rhum Mal Osteoartic. 1986;53(7-9):441-9.

17. Maksymowych WP, Suarez-Almazor ME, Buenviaje H, Cooper BL, Degeus C, Thompson M, et al. HLA and cytokine gene polymorphisms in relation to occurrence of palindromic rheumatism and its progression to rheumatoid arthritis. The Journal of rheumatology. 2002;29(11):2319-26.

18. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri GS, Ramos-Remus C, Russell AS, Suarez-Almazor ME. Prognostic factors for the development of rheumatoid arthritis and other connective tissue diseases in patients with palindromic rheumatism. The Journal of rheumatology. 1999;26(3):540-5.

19. Guerne PA, Weisman MH. Palindromic rheumatism: part of or apart from the spectrum of rheumatoid arthritis. The American journal of medicine. 1992;93(4):451-60.

20. Hench P, Rosenberg EF. Palindromic rheumatism. A 'new' oft recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues. Report of thirty-four cases; its relation to angio-neural arthrosis', 'allergic rheumatism' and rheumatoid arthritis. Arch Int Med. 1944;73:293-321.

21. Canete JD, Arostegui JI, Queiro R, Gratacos J, Hernandez MV, Larrosa M, et al. An unexpectedly high frequency of MEFV mutations in patients with anti-citrullinated protein antibody-negative palindromic rheumatism. Arthritis and rheumatism. 2007;56(8):2784-8.

22. Canete JD, Arostegui JI, Queiro R, Sanmarti R, Ballina J, Bosch X, et al. Association of intermittent hydrarthrosis with MEFV gene mutations. Arthritis and rheumatism. 2006;54(7):2334-5.

23. Andres M, Pascual E. Anakinra for a refractory case of intermittent hydrarthrosis with a TRAPS-related gene mutation. Annals of the rheumatic diseases. 2013;72(1):155.

24. Schwartzberg M. Prophylactic colchicine therapy in palindromic rheumatism. The Journal of rheumatology. 1982;9(2):341-3.

25. Kim SK, Lee HS, Lee KW, Bae SC, Jun JB. Palindromic rheumatism: different genetic background implies a distinct disease entity. Annals of the rheumatic diseases. 2006;65(11):1539-40.

26. Chen H CD, Hsieh T, Hung G, Lan H, Hsieh C, Lan J. Predicting the progression of palindromic rheumatism to rheumatoid arthritis: the role of ultrasonography and anti-cyclic citrullinated peptide antibodies J Med Ultrasound. 2010;18(1):17-26.

27. Bugatti S, Caporali R, Manzo A, Sakellariou G, Rossi S, Montecucco C. Ultrasonographic and MRI characterisation of the palindromic phase of rheumatoid arthritis. Annals of the rheumatic diseases. 2012;71(4):625-6.

28. Cabrera-Villalba S, Ramirez J, Salvador G, Ruiz-Esquide V, Hernandez MV, Inciarte-Mundo J, et al. Is there subclinical synovitis in patients with palindromic rheumatism in the intercritical period? a clinical and ultrasonographic study according to anticitrullinated protein antibody status. The Journal of rheumatology. 2014;41(8):1650-5.

29. Mankia K, D'Agostino MA, Emery P. Response to: 'Ultrasound findings in palindromic rheumatism' by Sanmarti et al. Annals of the rheumatic diseases. 2018.

30. Golding DN. Sulphasalazine for palindromic rheumatism. Br J Rheumatol. 1988;27(1):79.

31. Youssef W, Yan A, Russell AS. Palindromic rheumatism: a response to chloroquine. The Journal of rheumatology. 1991;18(1):35-7.

32. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri G, Russell AS, Suarez-Almazor ME. Decreased progression to rheumatoid arthritis or other connective tissue diseases in patients with palindromic rheumatism treated with antimalarials. The Journal of rheumatology. 2000;27(1):41-6.

33. Rothschild B, Yakubov LE. Evidence for an effect of hydroxychloroquine in chronic pyrophosphate deposition disease. J Clin Rheumatol. 1996;2(3):170.

34. Zemer D, Livneh A, Danon YL, Pras M, Sohar E. Long-term colchicine treatment in children with familial Mediterranean fever. Arthritis and rheumatism. 1991;34(8):973-7.

35. Ozen S, Demirkaya E, Erer B, Livneh A, Ben-Chetrit E, Giancane G, et al. EULAR recommendations for the management of familial Mediterranean fever. Annals of the rheumatic diseases. 2016;75(4):644-51.

36. Savic S, Mistry A, Wilson AG, Barcenas-Morales G, Doffinger R, Emery P, et al. Autoimmune-autoinflammatory rheumatoid arthritis overlaps: a rare but potentially important subgroup of diseases. RMD Open. 2017;3(2):e000550.

37. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. Cochrane Database Syst Rev. 2014(8):CD006190.

38. van der Hilst J, Moutschen M, Messiaen PE, Lauwerys BR, Vanderschueren S. Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature. Biologics. 2016;10:75-80.

39. Ben-Zvi I, Kukuy O, Giat E, Pras E, Feld O, Kivity S, et al. Anakinra for Colchicine-Resistant Familial Mediterranean Fever: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis & rheumatology (Hoboken, NJ). 2017;69(4):854-62.

40. Harrison SR, McGonagle D, Nizam S, Jarrett S, van der Hilst J, McDermott MF, et al. Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology. JCI Insight. 2016;1(6):e86336.

41. Naumann L, Feist E, Natusch A, Langen S, Krause A, Buttgereit F, et al. IL1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of

refractory adult-onset Still's disease. Annals of the rheumatic diseases. 2010;69(2):466-7.

42. Tran AP, Edelman J. Interleukin-1 inhibition by anakinra in refractory chronic tophaceous gout. International journal of rheumatic diseases. 2011;14(3):e33-7.

43. Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Annals of the rheumatic diseases. 2012;71(5):638-41.

44. Mankia K, Emery P. Preclinical Rheumatoid Arthritis: Progress Toward Prevention. Arthritis & rheumatology (Hoboken, NJ). 2016;68(4):779-88.

45. Stack RJ, van Tuyl LH, Sloots M, van de Stadt LA, Hoogland W, Maat B, et al. Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: a qualitative exploration of symptom development. Rheumatology (Oxford, England). 2014;53(9):1646-53.

46. Nam JL, Hunt L, Hensor EM, Emery P. Enriching case selection for imminent RA: the use of anti-CCP antibodies in individuals with new non-specific musculoskeletal symptoms - a cohort study. Annals of the rheumatic diseases. 2016;75(8):1452-6.

47. Bos WH, Wolbink GJ, Boers M, Tijhuis GJ, de Vries N, van der Horst-Bruinsma IE, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Annals of the rheumatic diseases. 2010;69(3):490-4.

48. van Steenbergen HW, van der Helm-van Mil AH. Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms. Rheumatology (Oxford, England). 2016;55(6):1140-1.

49. van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Annals of the rheumatic diseases. 2016;75(10):1824-30.

50. Hunt L, Nam J, Hensor EM, Mankia K, Rowbotham E, Grainger AJ, et al. OP0042 In acpa positive at-risk individuals, which mri and us findings best predict development of clinical synovitis? Annals of the rheumatic diseases. 2018;77(Suppl 2):72-3.

51. Kleyer A, Krieter M, Oliveira I, Faustini F, Simon D, Kaemmerer N, et al. High prevalence of tenosynovial inflammation before onset of rheumatoid arthritis and its link to progression to RA-A combined MRI/CT study. Semin Arthritis Rheum. 2016;46(2):143-50.

52. Mankia K, D'Agostino MA, Rowbotham E, Hensor EM, Hunt L, Moller I, et al. MRI inflammation of the hand interosseous tendons occurs in anti-CCP-positive at-risk individuals and may precede the development of clinical synovitis. Annals of the rheumatic diseases. 2019.

53. Schett G, Firestein GS. Mr Outside and Mr Inside: classic and alternative views on the pathogenesis of rheumatoid arthritis. Annals of the rheumatic diseases. 2010;69(5):787-9.

54. Duer A, Ostergaard M, Horslev-Petersen K, Vallo J. Magnetic resonance imaging and bone scintigraphy in the differential diagnosis of unclassified arthritis. Annals of the rheumatic diseases. 2008;67(1):48-51.

55. Kleyer A, Finzel S, Rech J, Manger B, Krieter M, Faustini F, et al. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. Annals of the rheumatic diseases. 2014;73(5):854-60.

56. Nam JL, Hensor EM, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. Annals of the rheumatic diseases. 2016;75(12):2060-7.

57. Freeston JE, Wakefield RJ, Conaghan PG, Hensor EM, Stewart SP, Emery P. A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. Annals of the rheumatic diseases. 2010;69(2):417-9.

58. Mosor E, Stoffer-Marx M, Steiner G, Raza K, Stack RJ, Simons G, et al. I would never take preventive medication! Perspectives and information needs of people who underwent predictive tests for rheumatoid arthritis. Arthritis care & research. 2019.

59. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis research & therapy. 2007;9(2):R28.

60. Zufferey P, Valcov R, Thomas M, Dumusc A, Forien M, So A, et al. Efficacy of anakinra in acute hydroxyapatite calcification-induced joint pain: A retrospective study of 23 cases. Joint Bone Spine. 2019;86(1):83-8.

61. Schlesinger N, Mysler E, Lin HY, De Meulemeester M, Rovensky J, Arulmani U, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Annals of the rheumatic diseases. 2011;70(7):1264-71.

62. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Annals of the rheumatic diseases. 2012;71(11):1839-48.

63. Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004;8(18):iii-iv, ix-x, 1-105.

64. Scott IC, Ibrahim F, Simpson G, Kowalczyk A, White-Alao B, Hassell A, et al. A randomised trial evaluating anakinra in early active rheumatoid arthritis. Clinical and experimental rheumatology. 2016;34(1):88-93.