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TITLE

How should we treat palindromic rheumatism? A systematic literature review.

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ABSTRACT

The purpose of this systematic literature review (SLR) is to analyse all studies that reported the efficacy and safety of pharmacological treatments for palindromic rheumatism (PR). We performed a SLR using PubMed, Embase and Cochrane databases. Three main aspects of PR were considered: treating flares, preventing recurrence of flares (i.e. achieving remission), and preventing progression to RA or to other persistent arthritis. Quality assessment of the studies was performed using the Newcastle-Ottawa Scale (NOS).

Twenty-seven articles met the inclusion criteria: 6 (22.2%) retrospective studies, 8 (29.6%) longitudinal studies, and 13 (48.1%) case series/case reports. No randomized controlled trials (RCTs) were found. Most of the studies (21/27, 77.7%) had a high risk of bias according to NOS. Non-steroidal anti-inflammatory drugs were the most commonly reported treatments for flares of PR, with variable results. Anti-malarials, such as hydroxychloroquine and chloroquine phosphate, showed efficacy in reducing the frequency of the flares and, to a lesser extent, in preventing progression to RA. There was minimal evidence in support of other conventional/biological disease modifying anti-rheumatic treatments or corticosteroids.

Therefore, although a frequent clinical dilemma for rheumatologists, the pharmacological management of PR has not been thoroughly evaluated, with no RCTs reported. Of all therapies, antimalarials have been the best studied and may be capable of reducing the recurrence of flares. The optimum treatment strategy for PR remains largely undefined and should be evaluated by robust RCTs in well-defined PR cohorts.

INTRODUCTION

Palindromic rheumatism (PR) is an inflammatory condition which is characterised by recurring flares of debilitating pain and swelling in and around the joints. These flares are characteristically unpredictable and transient, with patients being asymptomatic in between[1].

The relapsing-remitting clinical presentation of PR is the key distinguishing feature from rheumatoid arthritis (RA), where the joint involvement is generally persistent and does not remit unless treated[2]. A significant link between these two conditions has been hypothesized. PR and RA have a similar prevalence of RA-related autoantibodies, as the presence of anti-citrullinated protein antibodies (ACPA)[3] or rheumatoid factor (RF) has been reported in up to 50% patients with PR[4]. Moreover, around 50% of patients with PR eventually develop persistent polyarthritis, mostly RA[5,6]. Indeed, up to 20% of RA patients may have a palindromic onset to their disease[7]. As such, PR may be considered a clinically recognisable 'pre-rheumatoid' state and a potential window of opportunity for preventative intervention[8].

However, the relationship between PR and RA is complex. Despite the shared risk factors and epidemiological association between the two diseases, PR and RA appear to have very different patterns of joint involvement on ultrasound imaging. PR flares are characterized by extra-capsular inflammation on ultrasound (US), often in absence of synovitis[9]. US synovitis is, on the other hand, the hallmark of the articular involvement of RA[10]. Not all patients with PR will develop RA; clinical remission is seen in about 15% of cases[11], and recurrent attacks without persistent joint involvement continue in 40%-50% of cases[12]. Whether PR should be considered as part of the spectrum of RA, or as an independent and distinct disease with shared risk factors, it is still a matter of debate[13,14].

The uncertainties around pathogenesis underpin the more pragmatic clinical uncertainties around the management of this disease. Since the first description of PR in 1944[1], no agreed treatment guidelines have been stipulated and, therefore, there is still no consensus on how these patients should be managed. This leaves rheumatologists in a quandary; the therapeutic approach for patients with PR is notoriously difficult and is largely decided according to the clinician's personal preferences and experience.

However, over the last 75 years, several therapeutic strategies for the treatment of PR have been described in the literature. These include non-steroidal anti-inflammatory drugs (NSDAIDs), colchicine, corticosteroids, conventional disease modifying anti-rheumatic drugs (DMARDs) and, to a lesser extent, biological DMARDs[15].

By conducting a systematic literature review, we aimed to comprehensively examine all studies that have investigated pharmacological treatments for PR. This includes studies focusing on the treatment of acute flares, the prevention of the recurrences of such flares, and prevention of progression to RA.

MATERIAL AND METHODS

Study protocol

A literature search was carried out by one of the authors of the study (DC) and an experienced librarian at "Leeds Teaching Hospitals NHS Trust", following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16]. The literature search was conducted using Medline/Pubmed (from 1944 to August 2019), OVID Embase (from 1944 to August 2019) and Cochrane Central Register databases (from 1944 to August 2019). References of the identified articles were taken into consideration for the identification of further relevant data (hand searched). Any disagreement in the selection process was resolved by consensus between two of the study authors (DC and ADM).

The following key terms were used: "palindromic rheumatism", "palindromic rheumatism and therapy", "palindromic rheumatism and management", "palindromic rheumatism and treatment", "palindromic rheumatism and NSAIDs", "palindromic rheumatism and analgesics", "palindromic rheumatism and hydroxychloroquine", "palindromic rheumatism and gold", "palindromic rheumatism and corticosteroids",

"palindromic rheumatism and colchicine", "palindromic rheumatism and sulphasalazine", "palindromic rheumatism and methotrexate", and "palindromic rheumatism and disease modifying", "palindromic rheumatism and biologic".

Eligibility criteria and study selection

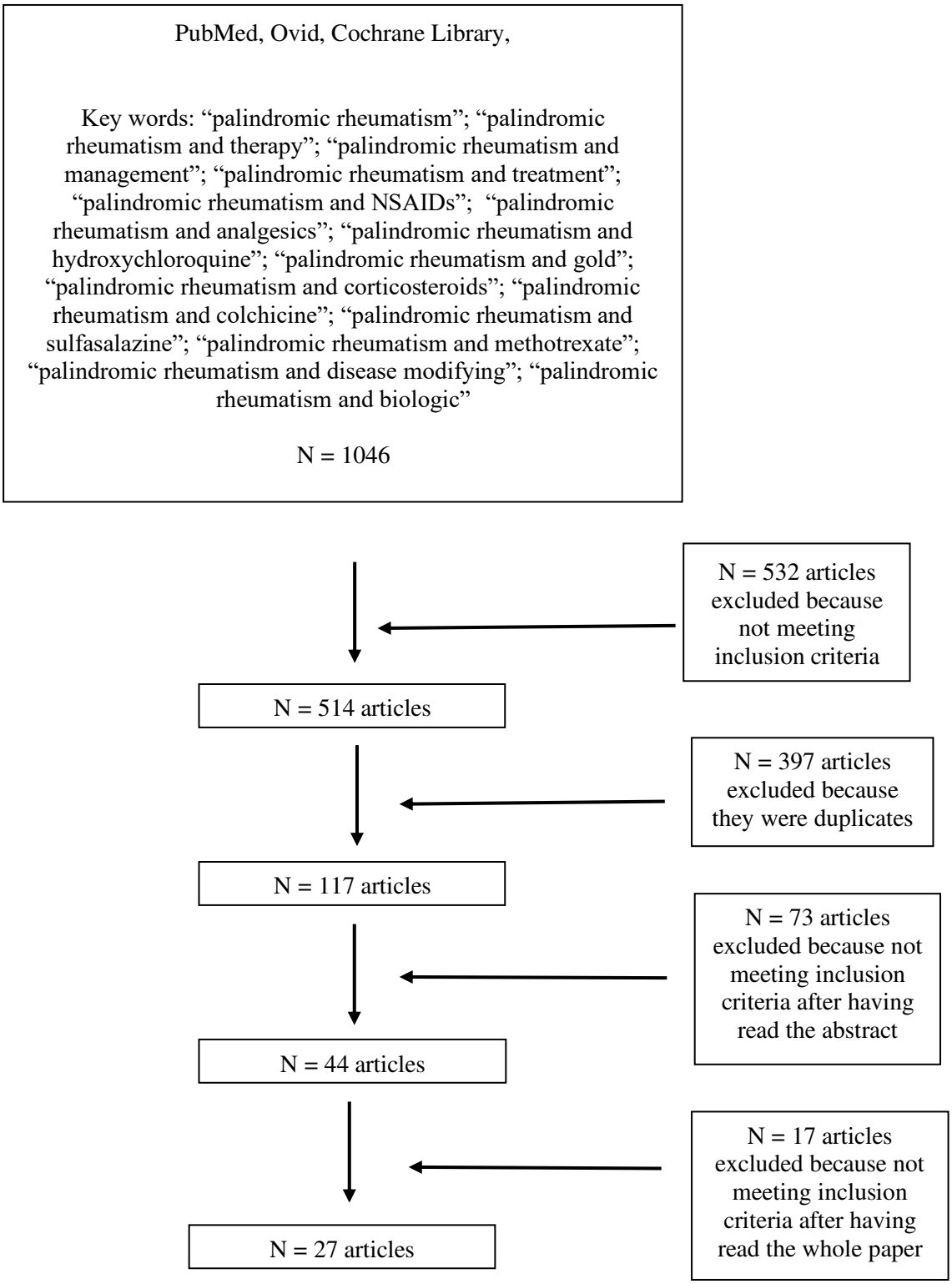
The initial search included all original articles, reviews, case reports and case series, including 'letters to the editor', that reported pharmacological treatments of PR in adults. Abstracts, reviews (excluding meta-analyses), articles that included paediatric patients, and articles which were not written in English were excluded.

The initial search identified 1046 articles, 532 of which were eliminated after title screening for meeting the exclusion criteria. Subsequently, 397 articles were excluded because they were duplicates. After reviewing the 117 remaining manuscripts, 73 were excluded because, in the abstract, no referring about pharmacological strategies evaluation were found. The 54 articles remaining were deeply examined and 17 of them were excluded or because the study design did not consider evaluation of pharmacological strategies or because the therapeutic strategy were mentioned but no further information concerning the outcome of it was added.

A total of 27 articles were included and further analysed. For each article, the following data were recorded: authors and year of publication, study design (i.e., case report, case series, retrospective study, longitudinal study and cross-sectional study), criteria used for the diagnosis/classification of PR, total number of patients included in the study, number of treated patients with a specific therapy, presence/absence of a control group, efficacy and safety of the therapy. For information on efficacy, each article was investigated for thematic content in the following areas: outcome of the therapy on management of PR flares, prevention and/or reduction of the frequency of further PR flares, prevention of progression to RA (or other persistent arthritis).

Results are reported as absolute frequency and/or corresponding percentage for the qualitative variables. Figure 1 shows the PRISMA flowchart of the systematic review process.

Figure 1 PRISMA diagram for systematic literature review and Meta-Analysis.



Quality assessment

The quality assessment of the studies was performed using the "Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-randomized Studies in Meta-Analysis"[17]. This was carried out by two independent investigators (DC and ADM). Any disagreement between the two investigators was resolved by consensus. The NOS consists of a scoring system based on three items: selection, comparability and outcome. The final score is based on the sum of the item scoring, which ranges from 0 to 9. The higher the score, the better the methodological quality of the study; studies with ≥ 6 stars were considered at low risk of bias, those with 4 or 5 stars at intermediate risk of bias, and those with < 4 stars at high risk of bias.

RESULTS

Of the 27 articles included, 6 (22.2%) were retrospective studies, 8 (29.6%) were prospective studies, and 13 (48.1%) case series/case reports. These articles had been published over a period of more than 70 years, from 1944, when PR was also described for the first time[1], to 2019. Seventeen (63%) articles were published before 2000. No randomised controlled trials (RCTs) were found. Only 2 (7.4%) studies included a control group[6,18] and 14 (53.8%) reported on side effects of the treatments.

Table 4 shows the results of the quality assessment. The majority of the articles (21/27, 77.7%) were considered high risk of bias according to the NOS score. The remaining 6 (22.3%) were considered intermediate (4/27, 14.8%) or low risk of bias (2/27, 7.4%).

Treatment of PR flares

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics

As illustrated in Table 1, NSAIDs and analgesics are the most commonly reported treatments for flares of PR.

In the first description of PR in 1944, Hench and Rosemberg[1] reported that some attacks were relieved by the use of acetylsalicylic acid (ASA) in some of the 34 patients with PR included in the study. However, neither the number of patients who received ASA, nor the extent of the benefit from the treatment, was specified by the authors. Since then, several other studies have investigated the efficacy of NSAIDs and analgesics in the control of symptoms during the flares. In a longitudinal study carried out by Eliakim et al. in 1989, 30 patients with PR were treated with a NSAID (drug not specified). Flares remitted completely in 5 (16.6%) patients and duration of symptoms was reduced in 15 (50.0%). The remaining 10 (33.3%) patients did not show any clinical improvement. In this study, paracetamol was administered to 7 (23.3%) patients, with no benefit.

In 1981, Mattingly[19] retrospectively analysed the medical records of 90 patients with PR. In this study analgesics were ineffective during flares. However, the types of analgesic and numbers of patients receiving the therapy were not specified. On the other hand, NSAIDs (indomethacin 75-125 mg/die or naproxen 500-1000 mg/die) were used in 23 (25.5%) patients, with clinical improvement in 7 (30.4%).

In another retrospective study[20] of 60 patients with PR, NSAID monotherapy was administered to only 2 (3.3%) patients, with good benefit. In this study, several other treatments were evaluated, including DMARDs and glucocorticoids, and it is not clear whether NSAIDs were co-prescribed, thus potentially contributing in those who showed a clinical improvement.

Several other case reports and case series[21–26] described the role of NSAIDs for controlling the symptoms during flares, with variable results. Only one of these studies, including 7 patients with PR, addressed the potential side effects of NSAIDs[26]; worsening of pre-existing hypertension (1/7, 14.2%), peri-malleolar oedema (1/7, 14.2%) and gastritis (2/7 patients, 28.5%) were reported.

Systemic corticosteroids

Given their rapid and potent anti-inflammatory properties, corticosteroids are often used in clinical practice as a short-term treatment for flares of PR. Surprisingly, the literature supporting the efficacy of such treatment for this clinical indication is very limited. Corticosteroids have been described in a case series[26], in which prednisone 10 mg/die was effective for improving symptoms in 1 patient with PR who had not previously responded to NSAIDs. Another case report described the benefits of a tapering regimen of oral prednisolone in 1 patient affected by PR presenting with a long-history (16 years) of poly-articular episodes of pain and swelling[27].

Preventing or reducing flares (i.e., disease remission)

Conventional DMARDs

- *Anti-malarial medications*

Anti-malarials, such as hydroxychloroquine (HCQ) and chloroquine phosphate (CQP), are the most frequently described therapies for the prevention of flares in PR (Table 2).

The efficacy of HCQ was reported in a large study including 90 patients with PR[3]. However, the evaluation of the efficacy of HCQ was not the primary objective of the study, which was instead focused on defining the clinical and serological characteristics of PR, and their predictive value for the development of RA. Therefore, the assessment of the benefit of HCQ is limited by the absence of relevant clinical information, such as clinical characteristics of patients receiving HCQ, and the dose and duration of HCQ therapy. However, it can be extrapolated that disease remission (defined as no further PR attacks at 1-year follow-up) was obtained in 43/90 (47.8%) patients receiving HCQ at 12 months follow-up.

In a recent study carried out by Khabbazi et al[28], the medical records of 92 PR patients were retrospectively evaluated. Eighty-six (93.5%) patients received HCQ (5 mg/kg/die) and oral prednisolone (5-10 mg/die). Complete remission was defined as absence of recurrent acute attacks for 12 weeks, while partial remission as a reduction of frequency of acute attacks >50% at the same time-point. In 38/86 (44.2%) patients, the disease

remained active despite this treatment. In these patients, methotrexate (MTX) (maximum dose 25 mg/week) was introduced (with or without HCQ) and, in resistant cases, other DMARDs were added: sulphasalazine (SSZ) 1500-2000 mg/die in 8 patients (21%), azathioprine (AZA) 2-2.5 mg/kg/die in 2 patients (5.2%) and leflunomide 20 mg/die in 1 patient (2.6%). Overall, 76/86 (82.6%) patients achieved complete or partial disease remission. Medication free remission was registered in 15/92 (16.3%) patients.

Another study on a large PR cohort was carried out by Youssef et al. in 1991[18]. In this study, the authors retrospectively evaluated the clinical history of 71 patients. Fifty-one (71.8%) patients were treated with antimalarial medications (47 with CQP 250 mg/die, 4 with HCQ 200mg/die, mean duration of therapy 1.5 years) and followed-up for an average of 3.6 years. The response to treatment was considered "very good" if patients were asymptomatic at 6 months and "good" if the attacks reduced their frequency or intensity by 50% at the same time-point; nearly 80% of the patients had a "good" or a "very good" response at follow-up. The disease relapsed in 9/51 patients (17.6%) after treatment discontinuation. Ophthalmic side effects (e.g. corneal deposits) were reported in 5/51 patients (9.8%). These disappeared rapidly when the dose of antimalarial was reduced.

A third large, retrospective study was carried out by Hannonen et al[20]. The authors evaluated the efficacy of various DMARDs in a cohort of 60 patients with PR. Of these, 15 (25%) received HCQ (200-300 mg/die) which was effective in decreasing the intensity and frequency of flares in 46.7% of cases. Mild gastrointestinal side effects were reported in 4/15 (26.6%) patients.

Two other small studies[19,29] (10 and 18 patients, respectively), reported both HCQ and CQP were efficacious in preventing the recurrence of flares. Similar positive results were also observed in a small case series[30] and in one case report[31]. Conversely, CQP was reported as ineffective in two case reports, both included only 1 patient[11,32].

- *Methotrexate*

MTX remains the anchor drug for RA. However, the number of studies evaluating its role in patients with PR is very limited. We found one case report[27] in which one patient with PR (negative anti-CCP antibodies and RF) achieved sustained remission after the administration of oral MTX (dose not reported). In another case report[11], MTX (dose not reported) was not effective in reducing the intensity or frequency of flares in one patient with PR. In the retrospective study by Khabbazi et al[28], MTX 10 mg/week was added to HCQ therapy (or replaced it) in 38/86 (44.1%) patients who did not obtain remission with HCQ monotherapy. The number of patients who benefited from this specific combination therapy has not been reported by the authors.

- *Sulphasalazine*

Like MTX, very few studies have evaluated the efficacy of SSZ for the prevention or reduction of flares in patients with PR. In a longitudinal study by Golding[32] more than 30 years ago, a good clinical response, characterized by the reduction of both the frequency and severity of the flares, was obtained in 8/14 (57.1%)

patients receiving SSZ. However, gastrointestinal side effects led to treatment discontinuation in 2 (14.2%) patients. The efficacy of DMARDs including SSZ was also evaluated by Hannonen et al[20] but neither the number of patients specifically treated with SSZ, nor the outcome of treatment, was reported by the authors. Conversely, the following side effects were described: cutaneous rash (1 patient), thrombocytopenia (1 patient), nausea (1 patient), and raised serum alkaline phosphatase (1 patient). In the retrospective study by Khabbazi et al[28], 8/38 (21%) patients who did not respond to HCQ and/or MTX were started on SSZ (1500-200 mg/die). However, the outcome of this treatment was not specifically reported by the authors.

- *Biological DMARDs*

Only one study has described biologic DMARDs in the treatment of PR. In 2019, Raghavan et al.[33], retrospectively evaluated the efficacy of rituximab (RTX) in 33 seropositive patients (RF ± ACPA) with PR, who had previously failed 3-months treatment with a combination of conventional synthetic DMARDs, mostly MTX and HCQ. Two weeks after the first infusion of RTX (500 mg), flow cytometry was performed to assess peripheral B-cell depletion. If B-cells were not depleted, or patients did not achieve complete control of disease (defined as no attacks) within 4 weeks, another infusion of RTX was given. Remission was obtained in 18 (54.5%) patients after the first cycle of RTX. Fifteen (45.5%) patients relapsed and needed a second infusion of RTX, which lead to remission in 6 (18.1%). As per protocol, RTX was administered together with intra-venous corticosteroids (dose not specified). Seven (21.2%) patients required a third cycle of RTX, and 2 (6%) patients underwent four cycles. All the patients included in this study eventually obtained clinical remission (defined as absence of attacks for at least 1 month), and no serious adverse effects were recorded.

- *Other DMARDs: D-penicillamine, Gold and Azathioprine*

Other studies have reported on DMARDs which are no longer in routine use for inflammatory arthritis. In the 1950s, D-penicillamine was part of the pharmacological armamentarium for the treatment of RA. With the advent of safer and more effective DMARDs, it has virtually disappeared from clinical practice. Two studies[19,34], in 1976 and in 1981, documented its efficacy in controlling the frequency and intensity of flares in a small number of patients with PR (5 and 2 patients, respectively). Cutaneous side effects (i.e., skin rash) were reported in one patient[34]. In the other case report, D-penicillamine was not effective[32].

As well as D-penicillamine, gold used to be a widely used pharmacological therapy for the treatment of RA in the pre-biological era, but it is no longer used in routine clinical practice. Several studies[19,20,23,35,36] reported benefit from intramuscular injections of gold. In a retrospective study evaluating 62 patients with PR[19], the use of gold prevented the recurrence of flares in 53 (85.4%) patients, and many of these patients relapsed after therapy discontinuation. However, the incidence of side effects was high and often severe enough to require treatment discontinuation (e.g. stomatitis, dermatitis, proteinuria, fever, pneumoniae)[19,20,23,35].

In the above mentioned study by Hannonen[20], some of the PR patients were treated with AZA. However, the number of patients receiving AZA, as well as the outcome of the therapy, was not specified by the author.

Similarly in the recent study by Khabbazi et al[28], AZA (2-2,5 mg/kg/die) and leflunomide were administered to 2 and 1 patients, respectively, who did not respond to HCQ and/or MTX (number not specified). The outcome of these treatment was not reported by authors.

Colchicine

Data regarding the efficacy of colchicine in the prevention of flares in patients with PR are available from 5 studies[11,23,24,36,37]. These were all published before 2000 and included small numbers of patients. In the largest study[36], only 1/8 (12.5%) patients experienced a decrease in the frequency and intensity of flares. In one case series[23] and in two case reports[11,24] colchicine did not provide any clinical improvement.

In a small longitudinal study by Schwartzberg[37], 5 patients with PR were treated with colchicine (1-2 mg/die) for 12 months. In this study, colchicine was effective in aborting flares in 2 (40%) patients, and in reducing intensity and frequency of flares in the other 3 (60%). Interestingly, in this study, the efficacy of colchicine was noticed only after 1 or 2 months of treatment. Gastrointestinal side effects (i.e., diarrhoea) were reported in 2 patients of this study and in one patients of the above mentioned case report[24].

Systemic corticosteroids

Corticosteroids were reported for the prevention of recurrence of flares in only one study[19]. In this study, oral prednisolone (at the dose of 10 to 15 mg/die) reduced or completely suppressed the recurrence of the attacks in 9/17 (52.9%) patients with PR.

Other pharmacological therapies

In their first description of PR, Hench and Rosenberg[1] described several other treatments, such as epinephrine hydrochloride, ephedrine, amphetamine and histaminase. None of these were beneficial in terms of reducing the frequency or the duration of the attacks. Other treatments, such as contramine, sulphatyazole and pyribenzamine were also reported in other papers, with no benefit [21,38]. Dapsone was ineffective in one case report[11]. All these studies are illustrated in Table 2.

Preventing progression to rheumatoid arthritis

Conventional DMARDs

- *Hydroxychloroquine and other antimalarial medications*

Few studies have evaluated the efficacy of pharmacological therapies for the prevention of RA in patients with PR (Table 3). In particular, only in 2 studies was this the primary objective of the study. In a retrospective study carried out by Gonzalez-Lopez et al.[6], the efficacy of anti-malarial treatment (i.e., either HCQ or CQP for at least one month prior to the development of RA) in preventing progression to RA or to connective tissue diseases (CTD) was evaluated in a cohort of 113 patients with PR. Patients with PR were divided into two groups; 62 patients receiving anti-malarials (59 CPQ, 5 HCQ and 2 both medications but at different times), in monotherapy or associated with other DMARDs (e.g. gold, SSZ), and a control group made of 51 patients, not receiving anti-malarials, and all but one receiving no DMARDs. During the follow-up, 11/113 (10%) patients achieved complete disease remission, 40/113 (35%) developed a secondary CTD, including RA, and 62/113 (55%) remained as PR. Twenty out of 62 (32%) patients who received anti-malarials, and 20/51 (39%) patients who did not, progressed to RA (or to another CTD). While no significant difference between the two groups was observed regarding the rate of progression to RA or CTD, the patients with PR who did not receive anti-malarial therapy developed RA or CTD significantly earlier than patients who received it (56 months versus 162 months in the treated group, p=0.03). The results of this study suggest that use of antimalarial therapy in patients with PR might delay the development of RA, or other CTD, but not prevent it. However, there is the possibility of selection bias as this was a non-randomised study. Importantly, CPQ and HCQ were used in combination with other DMARDs in some patients and the influence of the individual drugs could not be properly evaluated. Antimalarial therapy was discontinued in 16/62 (25.8%) patients due to lack of efficacy. Moreover, 12 (19.3%) patients reported the following side effects: gastrointestinal (10 patients), ocular (6 patients), cutaneous (2 patients) and neurological system related (3 patients).

In a large retrospective study[18], Youssef et al. reported the outcome of 71 patients with PR, 51 (71.8%) of whom were treated with anti-malarials (47 CPQ 250 mg/die and 4 HCQ 200 mg/die). After an average follow-up of 3.6 years (from 6 months to 15 years), only 16 (31%) of the patients developed persistent arthritis, specifically 12 (75%) RA, 2 (16.6%) systemic lupus erythematosus (SLE), 1 (16.6%) Crohn's disease and 1 (16.6%) asymmetric seronegative arthropathy, thus suggesting a positive role of anti-malarials, in particular CPQ, in relieving PR. Of these patients progressing to persistent arthritis, only 4 were not treated with anti-malarials.

Emad et al.[3] evaluated the efficacy of HCQ in 90 patients with PR. At 1-year follow-up, around 50% (number not reported) of patients developed persistent arthritis; of these 25 developed RA, 14 "undifferentiated" arthritis and 8 another rheumatic disease (e.g. SLE). The aim of this study was to evaluate the prevalence of ACPA and RF in a cohort of patients with PR and to find determinants for progression to RA. Consequently, detailed data concerning pharmacological therapy were not illustrated.

In the above-mentioned study by Khabbazi et al[28], only 8/86 (9.3%) PR patients receiving DMARDs progressed to persistent arthritis. These data suggest a potential role of HCQ in the prevention of RA in PR patients, as this was the most frequently used medication in the study. However, the specific details of the medications taken by the patients who developed persistent arthritis have not been reported by the authors.

Negative results come from a longitudinal study carried out by Sanmartì et al.[39] in 2012, who assessed the prevalence of progression to RA in a cohort of 71 patients with PR of whom 52 (73.2%) were treated with HCQ. Patients were divided in two groups: the first made up by patients with PR who later developed RA, or other rheumatic diseases, and the second a group of patients with PR with did not progress to persistent arthritis. The percentage of patients treated with HCQ was similar in the two groups (70% vs 78.5%, respectively) with no statistical difference observed. However, it is not possible to exclude that these results are subject to channelling bias as the decision to treat or not treat patients was made by the clinician in a non-randomised fashion.

- *Biological DMARDs*

In the above mentioned paper by Raghavan et al.[33], none of the 33 patients treated with RTX developed RA at the end of the 3-years-follow-up. However, there was no control group in this study.

- *Other DMARDs: D-penicillamine, Gold and Azathioprine*

Koskinen et al.[5] in 2009 carried out a retrospective study evaluating the long-term outcome of a cohort of 60 PR patients. The cohort evaluated was the same as that analysed 20 years earlier by Hannonen et al.[20]. All but two PR patients were treated with one or more DMARDs (namely gold, HCQ, SSZ, D-penicillamine and azathioprine). Unfortunately, from the data available it is not possible to extrapolate the number of patients treated which each DMARD. Forty out of 60 (66.6%) patients developed RA, 38 (63.3%) within the first 10 years, and 2 (3.3%) after 10 years of follow-up. In the study by Mattingly[35], almost half of the 15 PR patients treated with gold progressed to chronic arthritis during follow-up.

DISCUSSION

To the best of our knowledge, this is the first systematic literature review of studies reporting pharmacological treatments for PR. Three main aspects of the management of the disease were taken into account: the treatment of acute flares, the prevention of their recurrence, and the prevention of the development of RA, or other persistent arthritis.

We found a lack of evidence supporting the efficacy of the therapies which are used in daily clinical practice for the management of patients with PR. Most of the studies addressing the efficacy and safety of pharmacological treatment for PR were case reports, case series, or relatively small single-centre retrospective studies. Interestingly, the majority of the papers were published more than 20 years ago and many of the treatments reported, such as gold or D-penicillamine, are not part of current treatment strategies in rheumatology. Moreover, only 2 studies included a control group[6,18], many omitted relevant clinical information, or details about the efficacy or safety of the drug. Indeed, the great majority (77.7%) of the studies were at high risk of bias according to the NOS, due to methodological limitations in the selection, comparability and in reporting outcomes.

Importantly, no RCTs have been carried out in patients with PR; this could be explained by the challenges in the recruitment of patients, due to the transient and intermittent manifestations of PR, as well as its clinical course which makes the diagnosis difficult during the "inter-critical" phase between flares, when clinical assessment and investigations are normal. Another potential impediment to the recruitment of a homogenous group of PR patients, which could be suitable for clinical trials, is the lack of universally accepted and validated classification criteria for PR[1,11,20,40,41]. In the current review, we found that 4 different classification criteria (Hench and Rosenberg[1] criteria, Hannonen criteria[20], Guerne and Weissman criteria[11], and Gonzalez-Lopez criteria[40]) were used in the 27 articles evaluated. Moreover, in a few studies[3,31,38], the diagnosis of PR was made on clinical grounds according to the physicians' evaluation.

Very few data are available regarding the serological status of patients among studies, especially ACPA status[28]. Indeed, just one study[28], reported no difference in treatment efficacy between ACPA and non-ACPA group. In all the other studies where ACPA are mentioned[3,26,33,39], no further information concerning association between ACPA status and response to pharmacological therapy have been given.

To date, no agreed guideline for the management of PR has been established and the treatment approach remains empirical. As regards the management of the flares of PR, several studies have described the use of NSAIDs, with variable results. The majority of these studies lacked key information, such as the specific drug and dose used[20,23,25,26,36], and none adopted objective measures to evaluate the efficacy of the treatment (i.e. Visual Analogic Scale). Of note, only two of these papers were published after 2000[25,26]. Therefore, despite the widespread use of NSAIDs in daily clinical practice, the evidence supporting their efficacy for the treatment of the PR flares is weak. For this clinical indication, corticosteroids also seem to have potential value. However, the efficacy of medium-dose oral corticosteroids was reported in only one case series [26] and one case report[27]. Analgesics, such as paracetamol, were frequently ineffective in the few studies analysing the outcome of such therapies. No studies have evaluated the efficacy of colchicine in controlling symptoms during acute attacks.

Perhaps the best available evidence is for the prevention of recurrent flares (i.e. disease remission), where antimalarials, namely HCQ and CPQ have been shown to be efficacious. However, the studies evaluating this aspect of PR are subject to the lack of an agreed definition for disease remission (i.e., partial or complete, and at different time points) or not defined at all. The strongest evidence comes from two studies[19,20], both including a consistent number of patients, which demonstrated the potential efficacy of both HCQ and CPQ in achieving disease remission in patients with PR.A few studies[36,23,24] have evaluated the role of colchicine, showing overall negative results. There was minimal evidence in support of the role of MTX and SSZ. Several studies evaluated the efficacy of gold[19,20,23,35,36] and D-penicillamine[19,34]. This might be explained by the fact that most of the studies were carried out in a period in which these treatments were still part of the clinical practice in rheumatology. Not surprisingly, despite some efficacy, such therapies, especially gold, were stopped in several cases due to the high incidence of side effects.

Only one study[33] has evaluated the role of biological-DMARDs, with RTX apparently effective in preventing flares in a cohort of 33 patients with refractory PR. In this study, none of the 33 PR patients treated with RTX developed to RA, suggesting a potential role of such treatment also in the prevention of RA. This latter aspect (i.e., preventing progression to RA) has been evaluated in very few studies. In particular, only 2 were carried out having the evaluation of this aspect as main objective of their research. Anti-malarials, such as HCQ and CPQ, seem to have a promising role in preventing, or at least delaying, the onset of RA in patients with PR, as demonstrated by two well conducted studies including relatively large cohorts of patients with PR.

CONCLUSION

The management of patients with PR remains a frequently encountered clinical challenge. Although the evidence for therapy in treating acute flares is poor, there is evidence that antimalarials, such as HCQ, can reduce the recurrence of PR flares and help achieve disease remission. Whether progression to RA can be prevented remains unclear but will be important to investigate in future studies. On balance, the use of HCQ in PR would seem reasonable, particularly with the aim of reducing flare frequency in those with frequent flares. However, the optimum treatment strategy for PR remains largely undefined and, therefore, needs to be evaluated by robust clinical trials in well-defined PR cohorts.

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