**Incidence and mortality of relapsing polychondritis in the United Kingdom: a population-based cohort study**

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**Disclosures:** There are no relevant disclosures to be declared.

**External Funding:** None

**Abstract**

**Purpose:**  Relapsing Polychondritis (RP) is a rare disease characterised by cartilage inflammation. We estimate the incidence, prevalence and mortality of RP and describe the clinical features of RP in a large population.

**Methods:** All participants diagnosed with RP were sampled from the Clinical Practice Research Datalink (CPRD). Prevalence and incidence rates for 1990-2012 were estimated. Relative mortality rates were estimated in a time-to-event framework using reference UK life tables. A questionnaire validation study assessed diagnostic accuracy.

**Results:** There were 117 participants with RP ever recorded. 50/61 (82%) of cases were validated by a physician and unconfirmed cases were excluded. The analysis included 106 participants (42 men, 64 women) diagnosed with RP. The mean age (range) at diagnosis in men was 55 (17 to 81) years and in women 51 (11 to 79) years. The median interval from first symptom to diagnosis was 1.9 years. The incidence of RP between 1990 and 2012 was 0.71 (0.55 to 0.91) per million population per year. There were 19 deaths from any cause. There were 16 observed deaths eligible for survival analysis and 7.4 deaths expected for the UK population of the same age, sex and period. The standardised mortality ratio was 2.16 (1.24 to 3.51), p<0.01. Respiratory disease, cardiac conditions and cancer were the most frequent causes of death.

**Conclusion:** The incidence of RP may be lower than previously estimated and diagnostic misclassification and delay are common. Mortality in RP is more than twice that of the general population.

**Key words:** Relapsing polychondritis, incidence, prevalence, therapy, mortality, Clinical Practice Research Database.

**Key messages:**

- Relapsing Polychondritis is a rare disease and its incidence may be lower than previously estimated.

- Diagnostic delay and misclassification are common.

- Mortality is more than twice that of the general population.

**Introduction**

Relapsing polychondritis (RP) is a rare autoimmune rheumatic disorder characterized by episodic inflammation of cartilaginous tissue throughout the body [1,2]. Typical presenting features include chondritis of the nasal bridge, auricular cartilage, ocular inflammation and involvement of the tracheobronchial tree [3,4]. Destruction of the laryngeal and tracheal cartilage rings may lead to collapse of the airways and is associated with a high risk of morbidity and mortality [2-4]. Its rarity often leads to considerable delay in establishing a diagnosis [4].

RP is part of the spectrum of systemic autoimmune disorders and may present with similar clinical features to other autoimmune rheumatic diseases such as Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) (GPA), eosinophilic Granulomatosis with Polyangiitis (Churg Strauss syndrome) (eGPA) or rheumatoid arthritis [5-7]. Treatment for RP is usually with steroids and immunosuppressive drugs but there are no randomised trials and treatment remains empirical and based on expert opinion [7].

The rarity of relapsing polychondritis makes it difficult to obtain accurate epidemiological data. Most reports are of small case series from specialist centers. These generally describe a female preponderance and one of the largest studies in the literature consisting of 200 patients had a female to male ratio of 1.8:1 [8]. The peak age of onset is between the fourth and fifth decade but the disease has been described in young children and the very elderly. All ethnic groups may be affected but the majority of reported cases in the literature are of white Caucasian descent. Only about 800 cases have been reported in the literature worldwide and this almost certainly underestimates the frequency of the condition. Given the rarity of RP and the non-specific clinical manifestations, patients often experience significant delay in diagnosis after the onset of symptoms [1]. There is no standard medical therapy for RP. Treatment is based on controlling symptoms and an individual approach is necessary [6]. For patients with mild auricular or nasal symptoms, short term use of non-steroidal anti-inflammatory drugs (NSAIDs) are generally adequate [6]. Corticosteroids may be required for more serious manifestations, however steroid therapy is usually tapered off after acute attacks.

The aim of this study was to investigate the epidemiology of RP, including the incidence, prevalence, and mortality, in a population-based epidemiological study. We also aimed to examine the clinical features of RP, as well as age at diagnosis, duration and type of symptoms, patterns of treatment, prognosis, survival and causes of death.

**Methods**

*Data Source*

We conducted a population-based cohort study of patients diagnosed with relapsing polychondritis in the Clinical Practice Research Datalink (CPRD). The CPRD comprises the electronic health records of more than 5 million active patients from over 660 family practices in the UK. The CPRD is designed to capitalize on the registration of more than 98% of the UK population with National Health Service (NHS) family practices [9]. The CPRD population is representative of the UK general population (7% of the total UK population) [9,10]. Data elements include demographics, prescriptions, clinical events and diagnoses, referrals to hospitals and additional patient information such as height, weight, age, smoking status, alcohol use, immunizations and deaths. Diagnoses recorded into the CPRD have been shown to have high predictive value in validation studies [10]. For entry into the CPRD, practice data must be up to standard for research as set out by the CPRD group. Fully anonymised data are available for analysis. This study received scientific and ethical approval from the CPRD Independent Scientific Advisory Committee for CPRD studies (Ref 13-005).

*Study Population*

A cohort of participants with Relapsing Polychondritis was identified from CPRD clinical and referral records based on the single Read code for RP, N33z500. The index date, or diagnosis date, was defined as the date of the first recorded RP event. In view of the rarity of RP, all diagnoses ever recorded were included. The start of record for each case was defined as the later of the patient’s registration date at a CPRD practice, or the date the practice joined CPRD and provided up-to-standard data. The end of record for each case was defined as the earliest of the death date, the end of registration date, the last data collection date or 31st January 2012. Cases were classified as incident if they were diagnosed more than one year after the start of the CPRD record, and as prevalent if they were diagnosed before the start of the record or up to one year after the start of the record.

*Validation study*

In order to confirm that RP diagnoses were accurately coded into electronic health records, a validation study was performed. A questionnaire was sent to the family practice associated with each of 117 cases of suspected RP. The questionnaire was self-completed by a general practitioner at the practice using electronic health records for the individual patient with RP. The questionnaire included five items: whether the patient had a confirmed diagnosis of RP; whether a specialist confirmed the diagnosis and specialty involved; whether the patient had a biopsy; the main clinical features; and whether any related autoimmune diseases were present. In order to achieve a high response rate, three mailings of the questionnaire were used.

*Statistical Analysis*

Prevalence rates were estimated using mid-year counts for RP cases and the CPRD denominator population. These were aggregated by five year periods. Incidence rates were estimated using incident RP cases as the numerator and person years from the CPRD population as the denominator. Confidence intervals were estimated from the Poisson distribution. Age-standardisation was not performed because the data were sparsely distributed. However, the age distribution of the CPRD population is very similar to that of the UK general population.

The relative mortality of RP cases was estimated in a time to event framework [11]. The start date was the later of the RP diagnosis date, the start of the CPRD record, or the date the practice joined CPRD and provided up-to-standard data. The end date was the earliest of the death date, the last collection date, or the end of the CPRD record. Relative survival was estimated using UK life tables, which provided estimates of the probability of death by sex, single year of age and period [12]. Expected deaths by year following RP diagnosis were estimated using the ‘strs’ command in Stata version 12.0 [13]. A standardised mortality ratio was estimated as the ratio of observed to expected deaths, with a 95% confidence interval estimated from the Poisson distribution.

Clinical features of the cohort were then determined by evaluating the frequency distribution of ‘Read codes’, ‘Read terms’, and type of symptom in the clinical records of study patients. The NHS Browser and CPRD Medical Dictionary were used to develop a list of Read codes for RP related clinical manifestations. These included symptoms and conditions affecting the ear, eye, joints, nose, skin and throat. Details of the codes used are available from the authors. These codes were used to understand and describe the symptoms presented by RP patients before and after diagnosis, as well as the time from the first reported symptom to diagnosis. New onsets of coronary heart disease, stroke or diabetes, as common comorbidities, were additionally evaluated before and after the diagnosis of RP. The British National Formulary [14] and the CPRD Product Dictionary were used to develop a list of codes for different drug therapies, and to subsequently determine any therapeutic trends in treatment course and treatment type. For these analyses, only clinical and therapy events in patients’ up-to research standard records were included.

**Results**

A cohort of 117 patients was initially identified as being registered in CPRD with one or more medical (Read) codes for RP ever recorded in CPRD up to 31st December 2012. There were nine cases with index dates before 1990 and 37 in total with index dates before 2000. There were 61 completed questionnaires received from the validation study. The overall response rate was 52% and the diagnosis was confirmed for 50/61 (82%) of cases. The most frequent reported clinical features were external ear inflammation (70%), arthritis (36%) and nasal inflammation (26%) (Table 1). The diagnosis was supported by specialist opinion including rheumatology (60%) dermatology (32%) and ENT (28%).

After excluding 11 unconfirmed cases, there were 106 cases of RP for further analysis (Table 2). There were slightly more female patients (60%) in the cohort than males (40%) with males being slightly older than females at diagnosis (Table 2). The mean age (range) at diagnosis for males and females was 55 (17 - 81) and 51 (11 - 79), respectively. There were 44 prevalent cases diagnosed within one year after the start of the CPRD record, and 62 incident cases diagnosed later than one year after the start of the CPRD record.

The number of patients with RP during each 5 year period increased over time; however this increase was accompanied by a concurrent increase in patients registered in the CPRD (Table 3). The prevalence of RP for the 3 year period from 2010 to 2012 was 9.0 per million (95% CI: 7.6 – 10.5), and the overall incidence rate between 1990 and 2012 was 0.71 per million person years (95% CI: 0.55 – 0.91), being slightly higher in women than men (Table 3).

*Relative mortality*

A total of 19 patients died in the cohort, and the median survival was 3.5 years for male and 3.7 years for female patients who died. The most frequent conditions coded before death were respiratory and cardiac complications, old age, and cancer. Eight of the 19 patients who died suffered from depression. One of the patients who died was also diagnosed with Wegener’s granulomatosis, suggesting that polychondritis may have been the initial presenting diagnosis.

Table 4 shows observed numbers of deaths by two year periods following diagnosis. There were 6, 4 and 3 deaths observed in the first three periods of two years, while the number of deaths expected based on UK mortality rates were 1.7, 1.4 and 1.2. These data suggest that the relative mortality in RP may be 2-3 times higher than in the general population, particularly in the earlier years following diagnosis. After allowing for age, sex, and period, the standardised mortality ratio (SMR) for the entire period of follow-up was 2.16 (1.24 to 3.51, P<0.01).

*Clinical Manifestations/Symptoms*

The symptoms that patients reported before and after RP diagnosis are described in Table 5. The most commonly reported symptoms were of the skin, throat, joints, eye, and ear. Such symptoms were frequently recorded more than two years before the diagnosis of RP and were also commonly recorded after RP diagnosis, with the exception of ear symptoms, which were most frequently recorded in the year before diagnosis. In this study cohort, the median time from first reported symptom to diagnosis was 1.9 years. Four (4%) patients were diagnosed with myelodysplasia.

New diagnoses of comorbidity were observed before diagnosis including coronary heart disease (two cases), stroke (two cases) and diabetes (seven cases). During the period after the diagnosis of RP, there were seven new diagnoses of coronary heart disease, one of stroke and eleven of diabetes mellitus.

*Treatment*

Overall, the most frequently used drugs among this RP cohort after diagnosis were glucocorticoids (64%) and NSAIDs (45%) (Table 6). The number of patients using these drugs increased steadily from 2 years before diagnosis to after diagnosis. Methotrexate (24%) and azathioprine (13%) were also prescribed to significantly more patients after diagnosis compared to before. Biological therapeutic agents such as infliximab and etanercept have been introduced into routine clinical practice for the treatment of autoimmune rheumatic diseases. However, in this cohort, there were no reports of biological agents being used. The total number of prescriptions in the cohort was 6,448 or 5.8 prescriptions per person year. Specific drugs prescribed before and after diagnosis are outlined in Table 6. Diabetes mellitus was numerically more prevalent after the diagnosis of RP and may have been related to the high usage of glucocorticoids (Table 5 and 6).

**Discussion**

RP is a rare disease and our data has confirmed this with the identification of 106 cases recorded during 87 million person years in a primary care database. The prevalence and annual incidence rates of RP between 2010 and 2012 were very low. Our data suggests that the mean age at diagnosis is older than previously suggested, with an average age at disease onset between the fourth and fifth decade [8]. The study confirms that both young children and the very elderly may be at risk of developing RP. There were 19 deaths and we estimated that the relative mortality in RP may be 2-3 times higher than in the general population, particularly in the early years following the diagnosis.

There is only one previous community-based epidemiological study of RP [15]. This was a retrospective electronic medical record review of patients in the United States Department of Defense beneficiary population. The study included 50 patients identified using the ICD-9 code for RP of whom 43 (86%) met the inclusion criteria, which is similar to our validation data. Their calculated prevalence of RP was lower compared to our data (4.5 vs 9 per million), while the average disease duration was greater (7.1 years versus 3.6 years in the present data). However the mean time to diagnosis was longer in the previous study compared to the present study data (3.2 years versus 1.9 years). The smaller number of patients included in the previous study may have led to less accurate estimates which may partially explain some of the differences between the two studies. Also, the diagnosis of RP in the present study was validated by the physicians, increasing our confidence in the accuracy of study estimates.

Our data underscores the often significant delay between the onset of the first symptom and diagnosis of RP. Respiratory symptoms were associated with the longest delay to diagnosis with a median time of 10.4 years. This is perhaps not surprising given that respiratory symptoms are among the most common reasons for physician consultations in the UK and RP is an extremely rare disease. Patients with initial symptoms related to the ear and nose were associated with a shorter delay. One possible reason for this variation might be that nasal bridge chondritis and auricular inflammation, especially if recurrent, are sufficiently unusual to trigger a specialist referral.

Our data on mortality are the first to demonstrate that RP patients are at increased risk of premature mortality with an SMR of 2.16 compared to the general population. Most previous studies describe the commonest cause of death as being associated with major airways disease and recurrent respiratory infections. Predictors of a poor prognosis in patients younger than 51 years of age include saddle nose deformity, arthritis, laryngotracheal involvement, systemic vasculitis, and haematuria [16]. In older patients only anemia predicts a worse outcome [16]. As with many other systemic autoimmune diseases, a greater number of organs involved are predictive of a poorer prognosis. Our data raise a question concerning whether a delay in diagnosis might be associated with mortality but the small number of deaths gave little power to investigate this question. Problems of lead time bias (with earlier diagnosed patients appearing to survive longer) and length bias (with more severe cases being diagnosed more rapidly) may complicated interpretation of any possible association.

Our data also confirms the association of RP with myelodysplasia [8]. Most large case series in the literature collect data on clinical features retrospectively, making it difficult to interpret the prognostic impact of individual symptoms. There is now a disease activity index which is a standardized tool for clinical assessment of patients with RP [17], and should improve data collection.

One of the strengths of the CPRD is that data on prescriptions is carefully recorded. In the UK, about 98% of individuals are registered with a family practice, ensuring that these results are population-based. This also provided longitudinal information on therapies used in RP patients both before and after diagnosis. As seen in Table 6, small numbers of patients were already prescribed therapies such as methotrexate, azathioprine, dapsone, colchicine, hydroxychloroquine, gold and penicillamine prior to being diagnosed with RP. Approximately one third of patients were prescribed corticosteroids and just over half were on NSAIDs more than 2 years prior to diagnosis. These data suggest that many of these patients presented with clinical features compatible with other autoimmune rheumatic disorders before a diagnosis of RP was established. This may also have contributed to the delay in the diagnosis we observed. There was no evidence for a change in the type of drug therapy post-diagnosis, with the four most commonly prescribed drugs being corticosteroids, NSAIDs, methotrexate and azathioprine. There were no records of biological agents (i.e. infliximab, etanercept) being prescribed as these are only used in specialist hospital practices in the UK.

The limitations of this study are similar to those of other CPRD studies of rare diseases [18]. A validation study confirmed over 80% of the RP cases in the CPRD which was considered acceptable. The RP diagnoses recorded in the CPRD were confirmed by rheumatology, dermatology or ENT specialists, according to the practice records. The predictive value of an RP diagnosis in the CPRD of just over 80% is in the lower part of the range of previous validation studies in CPRD. In their systematic review, Herrett et al. and Jick et al. found that the median proportion of cases confirmed was 89% across all conditions [10, 19, 20]. We acknowledge that we excluded 11 suspected cases based on additional data obtained through the validation study but lack of equivalent data for participants with no response to the validation study could have led to over-estimation of the incidence and prevalence of Relapsing Polychondritis. However, incidence and prevalence might be under-estimated if severe cases are treated exclusively at specialist units, with no diagnosis recorded in primary care records.There was a long interval since diagnosis for many cases and clinical records may not have been retained at the practice for patients who had died or changed practice in the distant past. However, since RP is an extremely rare condition with non-specific symptoms, the 80% predictive value is acceptable. Misclassification of RP diagnoses appeared to be clinically important. Our data revealed that patients were more likely to be misdiagnosed and treated for other rheumatic diseases before being diagnosed with RP. Another limitation is that data on therapy dosage and duration with individual drugs such as corticosteroids or immunosuppressive agents is difficult to ascertain.

In conclusion, to our knowledge, this is the first study to provide population based data to estimate the incidence, prevalence, therapy and mortality of patients with RP in the United Kingdom. These data are important for improving clinical recognition of this uncommon but potentially serious condition.

**Author contributions**

All authors were involved in drafting the article and revising it critically for intellectual content, and all authors approved the final version to be published. Professors D’Cruz and Gulliford had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors have no relevant disclosures.

Study conception and design. D’Cruz, Gulliford.

Acquisition of data. Hazra, Dregan, D’Cruz, Gulliford.

Analysis and interpretation of data. Hazra, Dregan, Charlton, Gulliford, D’Cruz.

**Funding statement:**

Alex Dregan and Martin Gulliford are supported by the NIHR Biomedical Research Centre at Guy's and St Thomas' National Health Service Foundation Trust and King's College London. The authors are also grateful to the Relapsing Polychondritis Research Fund at Guys and St Thomas Charity. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute of Health Research or the Department of Health. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

**Disclosure statement**

MG, JC, AD, NH no interests to declare.

DC,

**Datasets**

CPRD is accessible for research.

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**Table 1: Results of validation study. Figures are frequencies (%) of confirmed cases.**

|  |  |
| --- | --- |
| **Total responses received** | **61 (100)** |
| Confirmed cases | 50 (82) |
| Unconfirmed cases | 11 (19) |
| Clinical features External ear inflammation Arthritis Nasal inflammation Eye inflammation Skin (vasculitis) Major airway disease | 35 (70)18 (36)13 (26)10 (20)6 (12)6 (12) |
| Specialist confirmation By rheumatologist By dermatologist By ENT | 30 (60)16 (32)14 (28) |

**Table 2: Characteristics of 106 participants with Relapsing Polychondritis from CPRD. Figures are frequencies (%) except where stated.**

|  |  |  |
| --- | --- | --- |
|  | **Male** | **Female** |
|  |  |  |
| Number  | 42(40) | 64(60) |
| Age at diagnosis (Years, mean, range) | 55 (17, 81) | 51 (11, 79) |
| Period of diagnosis  |  |  |
|  <1990 | 4 (10) | 5 (8) |
|  1990-1994 | 3 (7) | 5 (8) |
|  1995-1999 | 9 (21) | 8 (12) |
|  2000-2004 | 6 (14) | 20 (31) |
|  2005-2009 | 13 (31) | 15 (23) |
|  2010-2012  | 7 (17) | 11 (17) |
| Prevalent casesa | 14(33) | 30(47) |
|  Years from registration start to diagnosis (mean, range) | -7.5 (-23.1, 0) | -8.1 (-23.4, 1.0) |
| Incident casesb | 28(67) | 34(53) |
|  Years from registration start to diagnosis (mean, range) | 8.1 (1.1 to 19.4) | 10.1 (1.3 to 20.2) |
| Deaths | 10 (24) | 9 (14) |

 aprevalent cases were diagnosed within one year of start of patient registration

 bincident cases were diagnosed more than one year after start of patient registration

**Table 3: Incidence and prevalence of Relapsing Polychondritis in CPRD.**

|  |  |  |
| --- | --- | --- |
| **Period** | **Mean of mid-year counts in period** |  |
|  | **Relapsing Polychondritis (cases)** | **CPRD Population (millions)** | **Prevalence per million population****(95% confidence interval)** |
|  |  |  |  |
| **Prevalence** |  |  |  |
|  |  |  |  |
| 1990-1994 | 2.0 | 1.26 | 1.6 (0.8 to 2.9) |
| 1995-1999 | 5.8 | 2.39 | 2.4 (1.6 to 3.5) |
| 2000-2004 | 26.4 | 4.63 | 5.7 (4.8 to 6.8) |
| 2005-2009 | 41.0 | 5.66 | 7.3 (6.3 to 8.3) |
| 2010-2012 | 52.3 | 5.83 | 9.0 (7.6 to 10.5) |
|  |  |  |  |
| **Incidence 1990-2012** | **Incident cases** | **Person Years****(millions)** | **Incidence rate** **(per million person years)** |
| All | 62 | 87.0 | 0.71 (0.55 to 0.91) |
| Men | 28 | 42.4 | 0.66 (0.44 to 0.96) |
| Women | 34 | 44.6 | 0.76 (0.53 to 1.07) |
|  |  |  |  |

**Table 4: Observed and expected deaths by year since diagnosis of Relapsing Polychondritis.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Years from** **RP diagnosis** | **Number at risk** **at start of perioda** | **Deaths observed** **in RP casesa** | **Deaths expectedb** |
|  |  |  |  |
|  |  |  |  |
| 0-1 | 97 | 6 | 1.7 |
| 2-3 | 66 | 4 | 1.4 |
| 4-5 | 48 | 3 | 1.2 |
| 6-7 | 32 | 0 | 1.0 |
| 8-9 | 24 | 1 | 0.8 |
| 10-11 | 18 | 1 | 0.7 |
| ≥12 | 13 | 1 | 0.6 |
|  |  |  |  |
| Total deaths |  | 16 | 7.4 |
|  |  |  |  |
| Standardised Mortality Ratio(95% confidence interval) |  | 2.16 (1.24 to 3.51), P<0.01 |
|  |  |  |  |

a two deaths in cases diagnosed before 1980, and seven cases (one death) with records ending before practice joined CPRD, were excluded

b deaths expected for persons of the same age and sex in the general population in the same time period from UK life tables

**Table 5: Symptoms recorded, and new onset of comorbidity, before and after diagnosis of RP. Figures are frequencies (%).**

**Column totals indicate number of cases with up to standard record eligible for analysis.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Symptom group | >2 yrs before diagnosis(55) | 1-2 yrs before diagnosis (58)  | 1 year before diagnosis (64) | After diagnosis(99)a |
|  |  |  |  |  |
| Ear | 15 (27) | 7 (12) | 26 (41) | 29 (29) |
| Eye | 30 (55) | 10 (17) | 16 (25) | 39 (39) |
| Joints | 21 (38) | 10 (17) | 7 (11) | 32 (32) |
| Nose | 6 (11) | 2 (3) | 2 (3) | 10 (10) |
| Skin | 22 (40) | 7 (12) | 17 (27) | 29 (29) |
| Throat / Respiratory | 35 (64) | 19 (33) | 27 (42) | 63 (64) |
| Related diagnoses | 3 (5) | 3 (5) | 4 (6) | 9 (9) |
| Myelodysplasia | 0 (0) | 0 (0) | 1 (2) | 4 (4) |
|  |  |  |  |  |
| **New onset of comorbidity** |  |  |
| Coronary Heart Disease | 2 (4) | 0 (0) | 0 (0) | 7 (7) |
| Stroke | 2 (4) | 0 (0) | 0 (0) | 1 (1) |
| Diabetes mellitusb | 3 (5) | 1 (2) | 3 (5) | 11 (11) |
|  |  |  |  |  |

a seven patient records ended before practice joined CPRD

b includes Diabetes Mellitus medical codes and drug codes

**Table 6: Therapy prescribed before and after RP diagnosis. Figures are frequencies (%).**

**Column totals indicate number of cases with up to standard record eligible for analysis.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Drug class | >2 yrs before diagnosis(55) | 1-2 yrs before diagnosis (58) | 1 year before diagnosis (64) | After + including diagnosis (99)a |
|  |  |  |  |  |
| NSAID | 33 (60) | 19 (33) | 22 (34) | 45 (45) |
| Glucocorticoids | 19 (35) | 10 (17) | 25 (39) | 63 (64) |
| Methotrexate | 2 (4) | 2 (3) | 6 (9) | 24 (24) |
| Azathioprine | 3 (5) | 2 (3) | 1 (2) | 13 (13) |
| Hydroxychloroquine | 5 (9) | 3 (5) | 5 (8) | 8 (8) |
| Dapsone | 1 (2) | 1 (2) | 1 (2) | 6 (6) |
| Colchicine | 2 (4) | 0 (0) | 1 (2) | 4 (4) |
| Sulfasalazine | 3 (5) | 2 (3) | 1 (2) | 0 (0) |
| Any of the above | 43 (78) | 30 (52) | 46 (72) | 83 (84) |
|  |  |  |  |  |

a seven patient records ended before practice joined CPRD;

cyclophosphamide, mycophenolate, penicillamine, gold and leflunomide were prescribed to one patient each