Incidence and pattern of mycophenolate discontinuation associated with abnormal monitoring blood-test results: cohort study using data from the Clinical Practice Research Datalink Aurum

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Abstract

Objective. The aim was to examine the incidence and pattern of MMF discontinuation associated with abnormal monitoring blood-test results.

Methods. Data from people prescribed MMF for common inflammatory conditions in the Clinical Practice Research Datalink were used. Participants were followed from the first MMF prescription. The primary outcome was drug discontinuation with an associated abnormal blood-test result within 60 days. Secondary outcomes were drug discontinuation for any reason and discontinuation associated with severely abnormal blood-test results within 60 days. Multivariable Cox regression was used to examine factors associated with the primary outcome.

Results. The cohort included 992 participants (68.9% female, mean age 51.95 years, 47.1% with SLE) contributing 1885 person-years of follow-up. The incidence of MMF discontinuation associated with any (severely) abnormal blood-test results was 153.46 (21.07) per 1000 person-years in the first year of prescription and 32.39 (7.91) per 1000 person-years in later years. Of those patients prescribed MMF, 11.5% (1.7%) discontinued treatment with any (severely) abnormal blood-test results in the first year of prescription. After this period, a mean of 2.6% (0.7%) of patients discontinued treatment with any (severely) abnormal blood-test results per year. Increased serum creatinine and cytopenia were more commonly associated with MMF discontinuation than elevated liver enzymes. Chronic kidney disease stage 3 or higher was significantly associated with MMF discontinuation with any blood-test abnormalities [adjusted hazard ratio (95% CI) 2.22 (1.47, 3.37)].

Conclusion. MMF is uncommonly discontinued for blood-test abnormalities and even less often discontinued for severe blood-test abnormalities after the first year of prescription. Consideration can be given to less frequent monitoring after 1 year of treatment, especially in those without chronic kidney disease stage 3 or higher.
Key words: Mycophenolate, drug monitoring, inflammatory conditions

Key messages
- One in 40 patients on MMF discontinued treatment with abnormal monitoring blood-test results in each year, after 6-months of shared care prescription from primary care.
- Chronic kidney disease stage 3 or higher was associated with MMF discontinuation with abnormal monitoring blood-test results.
- These data can be used to risk stratify blood-test monitoring after 1 year of MMF prescription.

Introduction
MMF is used in the management of ANCA-associated vasculitis, SLE, diverse skin conditions, including atopic dermatitis, psoriasis and autoimmune blistering disorders, and to prevent transplant rejection [1–4]. Its efficacy and safety have been evaluated in several clinical trials in SLE, ANCA-associated vasculitis, RA, uveitis and vitiligo [1, 2, 5–8]. Several of these studies reported high cumulative incidence of cytopenia (5–23%) and elevated liver enzymes (7%) [2, 5, 8]. Consequently, indefinite monitoring with 1- to 3-monthly blood tests is recommended after an initial period of closer monitoring [9, 10]. However, the long-term safety of MMF regarding renal, bone marrow and liver toxicity is poorly understood.

The objectives of this study were to examine the incidence of MMF discontinuation with abnormal and severely abnormal blood-test results in inflammatory conditions, to ascertain the pattern of abnormal blood-test results leading to MMF discontinuation and to explore risk factors for stopping MMF with abnormal monitoring blood-test results. Sensitivity analyses were undertaken to explore whether rates of MMF discontinuation with abnormal blood-test results differed between SLE and other inflammatory conditions, because the former can cause cytopenia and acute kidney injury as a result of increased disease activity.

Methods
Data source
Data from the Clinical Practice Research Datalink (CPRD) Aurum was used. Launched in 2017 [11], this is a longitudinal anonymized electronic database of health records from 19 million patients from 738 general practices; the general practitioner (GP) practice records date back to 1995 [11]. It includes information on demographic details, lifestyle factors (e.g. alcohol intake), diagnoses, results of investigations, including blood tests, and details of all primary-care prescriptions. Diagnostic and prescription data are recorded using medical codes (a combination of Read 2, SNOMED and local EMIS codes) and product codes, respectively. Blood-test results are stored as numerical values. Additionally, GPs can record abnormal blood-test results using SNOMED codes.

This retrospective cohort study used anonymized patient health records from the CPRD and was not required to obtain participant informed consent [12]. Approvals were granted by the Independent Scientific Advisory Committee of MHRA (reference: 20_000236). The study used data originating from the period 1 January 2007 to 31 December 2019.

Inclusion criteria
Participants were included if they had been diagnosed with RA, SLE, psoriasis with or without arthritis, reactive arthritis, AS, SLE or IBD at age ≥18 years during the study period, they had at least one GP prescription of MMF (Supplementary Table S1, available at Rheumatology Advances in Practice online) after the first record of the above conditions in CPRD Aurum, and they had continuous registration for ≥1 year in a GP practice contributing data to CPRD Aurum before the first record of any of the above conditions or prescription of MMF. The last two criteria prevent prevalent patients on long-term treatment who have recently changed GP surgeries from entering the cohort as incident cases and new MMF users.

Exclusion criteria
Exclusion criteria were as follows: chronic liver disease (autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B or C, or cirrhosis); myelodysplasia; or haemolytic anaemia, neutropenia, idiopathic or thrombocytopenic purpura before the first primary-care prescription of MMF.

Cohort entry: first primary-care prescription of MMF
In the UK, immunosuppressant drugs are initiated in hospital outpatient clinics, and dose escalation with monitoring is overseen by specialists. However, once a stable, well-tolerated dose is reached with acceptable monitoring blood-test results (typically after 3 months of the first prescription) the responsibility for prescribing and monitoring, including periodic blood tests, is often handed over to the patient’s GP under shared care.
agreements. Any decisions to change the dose, interrupt or stop treatment are guided by the hospital specialists.

Cohort exit
Cohort exit was assigned as the earliest of date of the following outcomes: death, transfer out of the GP practice, last data collection from the GP practice, 5-year follow-up, or 31 December 2019.

Outcomes
The primary outcome was drug discontinuation associated with abnormal or severely abnormal blood-test results, defined as a prescription gap of ≥90 days, with an abnormal or severely abnormal blood-test result or SNOMED code indicating such a result within ≤60 days of the last prescription date [9, 13, 14]. Secondary outcomes were as follows: any abnormal blood test, defined as cytopenia (white blood cells <3.5×10⁹/l, neutrophils <1.6×10⁹/l or platelets <140×10⁹/l) or elevated liver enzymes [Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST)] >100 IU/l] or an increase in serum creatinine by ≥26 μmol/l; a severely abnormal blood test, defined as cytopenia (white blood cells <2.5×10⁹/l, neutrophils <1.0×10⁹/l or platelets <50×10⁹/l), elevated liver enzymes (ALT or AST >200 IU/l) or doubling of serum creatinine; or any drug discontinuation, defined as a prescription gap of ≥90 days between the last prescription date and the earliest of date of the following outcomes: death, transfer out of the GP practice, last data collection from the GP practice or 31 December 2019.

Covariates
Age at first prescription was defined using date of birth and date of first primary-care MMF prescription. Sex, smoking, BMI (in kilograms per square metre; classified according to World Health Organization categorization), alcohol intake status [non-user, ex-user, low (1–14 units/week), medium (15–21 units/week) or hazardous (>21 units/week) user], inflammatory condition and chronic kidney disease were defined using the latest CPRD record before cohort entry. Chronic kidney disease stage 3 or higher was defined using SNOMED codes or latest estimated glomerular filtration rate <60 ml/min before cohort entry. Concurrent immunosuppressive prescriptions were defined using GP prescriptions in the first 6 months of follow-up, provided such prescriptions were followed by a MMF prescription.

Outcome validation
All MMF discontinuations with a blood-test abnormality were selected. Data for all consultations within ≤60 days of the abnormal blood-test result were extracted. A.A. (Consultant Rheumatologist trained in General Medicine and Rheumatology) screened all codes to draw up a list of other diagnoses that could potentially cause abnormal blood-test results. All clinical experts in the study team (one rheumatologist, one nephrologist, one hepatologist, one gastroenterologist, one haematologist, one dermatologist and one academic GP) reviewed these codes. A code was removed from the list if all experts agreed that it would not cause blood, liver or kidney injury. The proportion of MMF discontinuations with abnormal blood-test results potentially explained by an alternative illness was calculated.

Statistical analyses
The mean (s.d.) and number (percentage) were used for descriptive purposes. Survival analysis was performed to calculate the incidence (95% Confidence Interval (CI)) of outcomes per 1000 person-years for the entire follow-up period, then separately for the first 12 months and the subsequent period. Cumulative hazard estimates were plotted using Nelson–Aalen graphs. The incidence of MMF discontinuation with abnormal blood-test results was calculated separately for SLE and for other inflammatory conditions. Cox proportional regression analysis was used to determine the factors associated with MMF discontinuation with any blood-test result abnormality. We used fractional polynomials to model potential non-linear relationships between the primary outcome and continuous covariates. Missing data for BMI and alcohol were handled by multiple imputation using chained equations. Ten imputations were carried out, and the imputation model included all covariates, Nelson–Aalen cumulative hazard function and MMF discontinuation with blood-test result abnormality as the outcome variable. Results from the imputed datasets were combined using Rubin’s rule. Data management and analysis were performed in STATA v.16 (StataCorp LLC).

Results
Data for 1969 participants with inflammatory conditions prescribed MMF were ascertained (Supplementary Fig. S1, available at Rheumatology Advances in Practice online). Of these, 992 participants contributing 1885 person-years of follow-up were included. Their mean (s.d.) age was 51.95 (17.12) years, and they were predominantly female (Table 1). The majority prescribed MMF had SLE (n = 467, 47.1%). The other conditions were RA (n = 248), psoriasis (n = 168), IBD (n = 94) and axial spondylarthropathy (n = 15). There was no prescription of mycophenolic acid.

There were 389, 118 and 20 MMF discontinuations attributable to any reason, with any abnormal monitoring blood-test results and with any severely abnormal monitoring blood-test results at a rate of 244.19 (221.09–269.71), 76.20 (63.62–91.27) and 12.65 (8.16–19.61) events/1000 person-years, respectively (Table 2). Among the 118 MMF discontinuations with a blood-test abnormality, there were 13 (11.0%) discontinuations that could potentially be explained by another illness or its treatment or complications (Supplementary Table S2, available at Rheumatology Advances in Practice online).
The incidence of MMF discontinuation for any reason, with any blood-test abnormality and with any severe blood-test abnormality was higher in the first 12 months of prescriptions than in subsequent years (Table 2; Fig. 1). Of those patients who were prescribed MMF, 11.5% (1.7%) discontinued treatment with any (severely) abnormal blood-test results in the first year of prescription. After this period, a mean of 2.6% (0.7%) of patients discontinued treatment with any (severely) abnormal blood-test results per year. The incidence of drug discontinuation for any blood-test abnormality or severely abnormal blood-test results was comparable in those with and without SLE (Table 2).

On multivariate analysis, increased serum creatinine and cytopenia were the commonest reasons for MMF discontinuation (Table 3; Fig. 2).

There were no non-linear risk relationships with continuous predictors (BMI and age) and any blood-test result abnormality, hence BMI and age were not transformed. On multivariate analysis, chronic kidney disease stage 3 or higher significantly increased the risk of stopping MMF associated with abnormal blood-test results, with an adjusted hazard ratio (95% CI) of 2.22 (1.47, 3.37) (Table 1). Other factors were not associated with the outcome.

Discussion

This is the largest study to evaluate the incidence and pattern of MMF discontinuation with abnormal monitoring blood tests. It used real-world data from routine treatment and included patients successfully initiated on MMF in secondary care, for whom the prescribing and monitoring responsibilities were handed to primary care. It reports that MMF is frequently discontinued in association with abnormal blood-test results in the first 12 months of shared-care prescription. However, discontinuations associated with this reason became approximately fivefold less frequent thereafter. MMF discontinuation associated with severe blood-test abnormalities occurred uncommonly in the first 12 months and became approximately threefold less frequent after this. Similar findings were observed in SLE and other inflammatory conditions.

| Characteristic | Number (%) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---------------|------------|-------------------|---------------------|
| Age at first prescription, mean (s.d.), years | 68.9 (17.12) | 1.01 (1.00, 1.02) | 1.01 (0.99, 1.02) |
| Sex | | | |
| Male | 862 (31.2) | 1.00 | 1.00 |
| Female | 663 (31.2) | 0.83 (0.57, 1.22) | 0.75 (0.50, 1.12) |
| BMI, kg/m² | | | |
| 18.5–24.9 | 302 (31.2) | 1.00 | 1.00 |
| <18.5 | 40 (4.0) | 0.74 (0.26, 2.06) | 0.89 (0.33, 2.43) |
| 25–29.9 | 299 (31.2) | 0.95 (0.59, 1.54) | 0.90 (0.55, 1.49) |
| ≥30 | 257 (25.9) | 1.29 (0.80, 2.06) | 1.18 (0.73, 1.92) |
| Missing | 94 (9.5) | – | – |
| Current smoking status | | | |
| No | 682 (68.9) | 1.00 | 1.00 |
| Yes | 130 (13.1) | 0.74 (0.41, 1.35) | 0.71 (0.39, 1.30) |
| Alcohol use | | | |
| None | 240 (24.1) | 1.00 | 1.00 |
| Low (1–14 units/week) | 344 (34.1) | 0.86 (0.56, 1.30) | 0.86 (0.54, 1.37) |
| Medium (15–21 units/week) | 50 (5.0) | 0.52 (0.19, 1.42) | 0.57 (0.20, 1.64) |
| Hazardous (>21 units/week) | 107 (10.8) | 0.45 (0.34, 1.25) | 0.35 (0.24, 1.14) |
| Ex-use | 91 (9.2) | 0.65 (0.30, 1.43) | 0.53 (0.24, 1.14) |
| Missing data | 160 (16.1) | – | – |
| SLE | | | |
| No | 525 (52.9) | 1.00 | 1.00 |
| Yes | 467 (47.1) | 1.14 (0.79, 1.64) | 1.28 (0.85, 1.93) |
| Other drugs | | | |
| None | 934 (94.2) | 1.00 | 1.00 |
| Amino-salicylates | 44 (4.4) | 0.14 (0.02, 0.99) | 0.17 (0.02, 1.27) |
| MTX, LEF, AZA or 6-MP | 14 (1.4) | 0.84 (0.21, 3.42) | 1.06 (0.26, 4.42) |
| Chronic kidney disease stage 3 or higher | | | |
| No | 772 (77.8) | 1.00 | 1.00 |
| Yes | 220 (22.2) | 2.46 (1.70, 3.56) | 2.22 (1.47, 3.37) |

aPercentage unless otherwise stated. bAdjusted for other variables in the table. cPer 1-year increase. dIncludes cases with RA, psoriasis, IBD or axial spondyloarthritis. Missing data were imputed. Abbreviations: HR, hazard ratio; 6-MP, 6-mercaptopurine.
Chronic kidney stage 3 or higher was associated with MMF discontinuation associated with abnormal blood-test results. This is expected because MMF is excreted renally. We found no significant association with the other potential factors that we examined. Age was not associated with MMF discontinuation with abnormal blood-test results, consistent with previous studies [15, 16]. Elevated liver enzymes were a significantly less common cause of MMF discontinuation than cytopenia in our study, as reported in most previous trials [1, 2, 8, 17]. However, a single previous trial reported a higher incidence of elevated liver enzymes than of cytopenia with MMF, but at 6 months of follow-up [5].

Using a similar study design, we previously reported on incidence of MTX and LEF discontinuation with abnormal and severely abnormal blood-test results [18]. The incidence of MMF discontinuation was higher than that of LEF or MTX for abnormal (and severely abnormal) blood-test results across the entire study period, with crude incidence rates of 76.20 (12.65), 58.22 (6.16) and 27.78 (3.66)/1000 person-years for MMF, LEF and MTX, respectively. These results suggest that MTX might be preferred over MMF where there is no evidence for a superior efficacy of the latter.

Strengths of this study included the inclusion of a broad range of inflammatory conditions and the use of real-world data, thus increasing generalizability. Outcomes were stratified according to their severity and time course, adding detail to the results. However, this study has several limitations. First, patients included in this study had been commenced on MMF in secondary care, were stabilized on treatment, and prescribing responsibilities had been handed to primary care. Consequently, patients with severe, unstable or uncommon diseases that are managed in specialized services or those at high risk of side-effects that might be prescribed treatment from secondary care were excluded from this study. Second, some services where shared care prescription and monitoring does not extend to MMF were excluded. Third, the patient population in this study did not include those with small vessel vasculitis or myositis, further limiting generalizability. Fourth, owing to missing data on the dose of MMF provided by CPRD, missing information on the number of tablets prescribed and/or the length of prescription, and the large dose range (0.5–4.0 g/day), we were unable to calculate the daily dose of MMF. Therefore, we did not evaluate the incidence of dose reduction with abnormal monitoring blood-test results as an outcome because incomplete information on dosing meant that it was difficult to establish when this occurred. Multiple imputation was used to account for missing data on alcohol intake and BMI. Fifth, an increase in serum creatinine by >26 μmol/l is the minimum change required to consider presence of acute kidney injury according to guidelines and was used to ascertain drug discontinuation with renal function decline [13]. However, the guidelines require that this increase occurs within 48 h. We were unable to apply this part of the definition owing to

### Table 2

Incidence of MMF discontinuation associated with abnormal blood-test results

| Outcome                          | Entire cohort | Other conditions |
|----------------------------------|---------------|------------------|
|                                  | n             | p-yr             | Incidence (1000 p-yr) |
| Any reason                       | 887           | 1583             | 24.19 (21.08–26.99) |
| First 12 months                  | 727           | 122              | 62.30 (56.11–69.42) |
| After 12 months                  | 156           | 201              | 95.92 (82.24–111.66) |
| Any blood-test abnormality       | 122           | 125              | 26.30 (22.94–30.64) |
| First 12 months                  | 88            | 57               | 102.20 (88.92–117.48) |
| After 12 months                  | 34            | 63               | 31.56 (27.59–35.81) |
| Severe blood-test abnormality    | 12            | 125              | 19.63 (16.07–23.66) |
| First 12 months                  | 7             | 57               | 17.83 (14.07–22.18) |
| After 12 months                  | 5             | 63               | 21.28 (17.12–26.76) |

Numbers in parentheses represent 95% CIs. Abbreviations: p-yr, person years. —/–, data suppressed because fewer than five events.

https://academic.oup.com/rheumap
FIG. 1 Nelson–Aalen cumulative hazard estimates for MMF discontinuation associated with any reason, any abnormal blood-test results and severely abnormal blood-test results

![Graph showing cumulative hazard estimates](image)

**Table 3** Incidence of MMF discontinuation associated with abnormal blood-test results

| Outcome                                      | n  | p-yr | Incidence (/1000 p-yr) |
|----------------------------------------------|----|------|------------------------|
|                                              |    |      | Entire cohort          | Entire cohort | SLE           | Other conditions |
| Cytopenia                                     |    |      |                        |               |               |                |
| Ever                                         | 57 | 1578 | 36.12 (27.86–46.83)    | 37.81 (27.02–52.92) | 33.89 (22.52–51.00) |
| First 12 months                              | 38 | 566  | 67.09 (48.82–92.20)    | 74.56 (49.10–113.24) | 58.97 (36.12–96.25) |
| After 12 months                              | 19 | 1012 | 18.78 (11.98–29.45)    | 19.86 (11.28–34.98) | 17.18 (8.19–36.04) |
| Severe cytopenia                             | 6  | 1590 | 3.77 (1.70–8.40)       | 4.39 (1.65–11.71)  | 2.94 (0.74–11.76) |
| Ever                                         | 10 | 1591 | 6.29 (3.38–11.68)      | 1.10 (0.15–7.79)   | 13.25 (6.89–25.46) |
| First 12 months                              | 6  | 571  | 10.50 (4.72–23.37)     | 0                 | 21.99 (9.88–48.96) |
| After 12 months                              | 10 | 1020 | 3.92 (1.47–10.45)      | 1.63 (0.23–11.58)  | 7.38 (2.38–22.88) |
| ALT or AST >100 IU/l                         |    |      |                        |               |               |                |
| Ever                                         | 6  | 1590 | 3.77 (1.70–8.40)       | 4.39 (1.65–11.71)  | 2.94 (0.74–11.76) |
| First 12 months                              | 10 | 1591 | 6.29 (3.38–11.68)      | 1.10 (0.15–7.79)   | 13.25 (6.89–25.46) |
| After 12 months                              | 10 | 1020 | 2.94 (0.95–9.12)       | 1.63 (0.23–11.58)  | 4.92 (1.23–19.67) |
| ALT or AST >200 IU/l                         |    |      |                        |               |               |                |
| Ever                                         | 6  | 1590 | 3.77 (1.70–8.40)       | 4.39 (1.65–11.71)  | 2.94 (0.74–11.76) |
| First 12 months                              | 10 | 1591 | 6.29 (3.38–11.68)      | 1.10 (0.15–7.79)   | 13.25 (6.89–25.46) |
| After 12 months                              | 10 | 1020 | 2.94 (0.95–9.12)       | 1.63 (0.23–11.58)  | 4.92 (1.23–19.67) |
| Chronic kidney disease progression/          |    |      |                        |               |               |                |
| creatinine increase by >26 μmol/l            |    |      |                        |               |               |                |
| Ever                                         | 66 | 1567 | 42.11 (33.09–53.60)    | 39.22 (28.16–54.63) | 45.94 (32.31–65.32) |
| First 12 months                              | 52 | 565  | 91.98 (70.09–120.71)   | 95.36 (65.84–138.11)| 88.33 (59.20–131.78) |
| After 12 months                              | 14 | 1002 | 13.97 (8.28–23.60)     | 11.69 (5.57–24.52) | 17.37 (8.28–36.43) |
| Creatinine >2 times previous value           |    |      |                        |               |               |                |
| Ever                                         | 10 | 1586 | 6.71 (3.40–11.72)      | 7.74 (3.69–16.23)  | 4.41 (1.42–13.66) |
| First 12 months                              | 6  | 570  | 14.02 (7.01–28.04)     | 16.80 (6.99–40.36) | 11.00 (3.55–34.10) |
| After 12 months                              | 10 | 1015 | 1.97 (0.49–7.86)       | 3.29 (0.82–13.17)  | 0 |

Numbers in parentheses represent 95% CIs. p-yr: person years; –/–: data suppressed as fewer than five events; ALT: Alanine aminotransaminase; AST: Aspartate aminotransaminase.
the monitoring blood tests being performed every 3 months. This might have overestimated the incidence of MMF discontinuation with elevated serum creatinine. Our results therefore represent a worst-case scenario for kidney function. Sixth, some of the abnormal blood-test results could be attributable to concurrent prescription of other drugs. This can potentially elevate the outcome rate. However, this is unlikely to play a large part because our outcome definition required a prescription gap of ≥90 days, and it can reasonably be expected that in this period the drug responsible for the blood-test abnormality will easily be ascertained. Seventh, some treatment discontinuations in SLE might be attributable to treatment escalation to address increased disease activity (e.g. cytopenia). However, a stratified analysis of cases with and without SLE reported similar event rates, implying that the event rates reported in this study are a reasonably accurate reflection of target organ toxicity attributable to MMF. Eighth, we are unable to attribute causality with certainty to abnormal blood tests for the decisions to cease MMF. Reassuringly, in our validation exercise only 11% of outcomes were potentially explained by an alternative medical condition. Ninth, gastrointestinal intolerance, a common reason for MMF discontinuation, was not an outcome in this study, because the study focused on asymptomatic target organ damage. This is another limitation to our study. Tenth, information on disease severity and disease activity are not included in the CPRD and could not be evaluated as potential risk factors in this study. Finally, despite the relatively large sample size, there were relatively few events and several 95% CI are wide, raising the risk of imprecision.

In conclusion, MMF appears commonly to be discontinued for abnormal blood-test results within the first year of prescription, but this becomes less frequent after the first year. Discontinuations for severely abnormal blood-test results were less common. These data might be used when counselling patients of the risks and benefits when considering MMF. They should also be considered by guideline-writing groups when recommending blood-test monitoring in people with inflammatory conditions on long-term MMF, with respect to whether the frequency of blood tests could be reduced after the first year of shared-care prescription.

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![Fig. 2 Nelson–Aalen cumulative hazard estimates for MMF discontinuation associated with any cytopenia, liver enzyme elevation and kidney function decline](https://academic.oup.com/rheumap/)
and Pfizer Inc.; and meeting support from Roche Diagnostics. The other authors have no conflict of interest to declare.

**Patient and public involvement:** The study question was discussed at a PPI meeting in Nottingham and received support from all present. Study results were reported to the PPI group, and modes of dissemination of study findings were also discussed and agreed with them.

**Data availability statement**

This study used data from the Clinical Practice Research Datalink (CPRD) Aurum. Owing to the CPRD data-sharing policy, we are unable to share the data for this study. However, access to CPRD data can be requested directly from the CPRD.

**Supplementary data**

Supplementary data are available at *Rheumatology Advances in Practice* online.

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