Title: What is the incidence of methotrexate or leflunomide discontinuation related to cytopenia, liver enzyme elevation or kidney function decline?

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Abstract

Objectives: To examine incidence of treatment changes due to abnormal blood-test results and, to explore rates of treatment changes due to liver, kidney and haematological blood-test abnormalities in autoimmune rheumatic diseases (AIRD) treated with low-dose methotrexate or leflunomide.

Methods: Data for people with AIRDs prescribed methotrexate or leflunomide were extracted from the Clinical Practice Research Datalink. Participants were followed-up from first prescription of methotrexate or leflunomide in primary-care. Primary outcome of interest was drug discontinuation, defined as a prescription gap of ≥90 days following an abnormal (or severely abnormal) blood-test result. Dose reduction was examined between consecutive prescriptions. Incidence rates per 1,000 person-years were calculated.

Results: 15,670 and 2,689 participants contributing 46,571 and 4,558 person-years follow-up were included in methotrexate and leflunomide cohorts respectively. The incidence of methotrexate and leflunomide discontinuation with abnormal (severely abnormal) blood-test was 42.24(6.16) and 106.53(9.42)/1,000 person-years in year-1, and 22.44(2.84) and 31.69(4.40)/1,000 person-years respectively thereafter. The cumulative incidence of methotrexate and leflunomide discontinuation with abnormal (severely abnormal) blood-tests was 1 in 24(1 in 169), 1 in 9(1 in 106) at 1-year; and 1 in 45(1 in 352), 1 in 32(1 in 227) per-year respectively thereafter. Raised liver enzymes were the commonest abnormality associated with drug discontinuation. Methotrexate and leflunomide dose reduction incidence were comparable in year-1, however, thereafter methotrexate dose was reduced more often than leflunomide (16.60(95% CI; 13.05-21.13) vs. 8.10(95% CI; 4.97-13.20)/1,000 person-years).

Conclusion: Methotrexate and leflunomide were discontinued for blood-test abnormalities

after year-1 of treatment, however, discontinuations for severely abnormal results were uncommon.

Key words

Autoimmune rheumatic diseases

Methotrexate

Leflunomide

Blood-test monitoring

Key messages

- Treatment discontinuation and dose reductions were more common in the first year of treatment and occurred at a stable but lower rate thereafter.
- Severely abnormal blood-test results were uncommonly associated with methotrexate and leflunomide discontinuations.
- Elevated liver enzymes were the commonest reason for discontinuing methotrexate and leflunomide.

Introduction

Autoimmune rheumatic diseases (AIRDs) affect >1% adults and are treated with disease modifying anti-rheumatic drugs (DMARDs) (1-5). These drugs can cause cytopenia, raised liver enzymes, and acute kidney injury (AKI) and, fortnightly to monthly monitoring blood-tests are recommended when initiating treatment with less frequent testing thereafter (6). In the UK, DMARDs are initiated in a rheumatology clinic with prescriptions dispensed from the hospital and fortnightly blood monitoring overseen by the rheumatology team. Once an effective, tolerated and stable dose is reached, the responsibility for prescribing and arranging 2-3 monthly blood-tests is handed to the GP under shared-care policy supported by the British Society for Rheumatology (BSR) and Royal College of General Practitioners (6). The rheumatology team is contacted if there are side-effects, including blood-test abnormalities, and oversee treatment changes. Monitoring blood-tests are discontinued after two years for sulfasalazine whilst long-term testing is continued for low-dose methotrexate and leflunomide (6, 7). Whether such long-term testing influences the decision to discontinue treatment is not known because most clinical trials are shorter than one year, and many observational studies report cumulative toxicity including outcomes from the treatment initiation phase during which reversible drug-induced target organ injury is common (8-10). However, evidence from a large 2-year clinical trial suggests that DMARD discontinuation due to target organ damage becomes less common with increasing duration of treatment (10). With growing use of DMARDs and the corresponding increased burden and cost of testing, it is important to evaluate the benefit from regular monitoring blood-tests for long-term low-dose methotrexate or leflunomide treatment (11). Thus, the objectives of this study were to examine the incidence of drug discontinuation and dose reduction with abnormal blood-test results in AIRDs treated with long-term low-dose methotrexate or leflunomide. We also explored the data to

examine whether the incidence of methotrexate discontinuation due to any abnormal blood-test result, elevated liver enzymes, AKI or cytopenia differed in Rheumatoid Arthritis (RA) and psoriatic arthritis as there is evidence that psoriasis increases the risk of hepatotoxicity from methotrexate (12, 13).

Methods

Data source Data from Clinical Practice Research Datalink (CPRD) Gold was used. Incepted in 1987, CPRD-Gold is a longitudinal anonymized electronic database of health records from over 19 million participants in 927 GP practices across the UK and covers 4.52% of UK residents currently. CPRD participants are representative of the UK population in terms of age, sex, and ethnicity (14). CPRD includes information on demographic details, lifestyle factors (e.g. smoking, alcohol intake), diagnoses, results of investigations including blood tests and physical examination, and details of all GP prescriptions (14). Diagnostic and prescription data are recorded as Read codes, and product codes respectively. Blood-test results are stored as numeric values. Additionally, GPs may record abnormal blood-test results using Read codes.

Approvals Independent Scientific Advisory Committee of the MHRA (Reference: 19_275R).

Study design Cohort study. Two separate cohorts were constructed comprising of participants prescribed methotrexate and leflunomide respectively.

Study duration 1st January 2007 to 31st December 2019. The study began on 1st January 2007 as the BSR guidelines recommending aggressive treatment of RA and shared-care monitoring of DMARDs were published in 2006 (4, 15).

Inclusion criteria Participants were required to meet the following criteria:

- Diagnosed with either RA, systemic lupus erythematosus (SLE), psoriatic arthritis, reactive arthritis, ankylosing spondylitis, inflammatory bowel disease associated arthritis, giant cell arteritis, polymyalgia rheumatica, or connective tissue diseases (CTDs) at age ≥18 years, within the study period.
- ≥1 GP prescription of methotrexate (oral or subcutaneous) or leflunomide after the first record of AIRD diagnosis in CPRD.
- Continuous registration for ≥1 year before the first AIRD diagnosis date in a GP practice contributing research quality data to CPRD..

The latter two criteria prevents prevalent AIRD cases on long-term DMARDs that have recently changed GP surgeries from entering the cohort as incident cases.

Exclusion criteria: Chronic liver disease (autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B or C, cirrhosis); haematological malignancies (lymphoma, leukaemia); myelodysplasia; haemolytic anaemia, neutropenia, idiopathic thrombocytopenic purpura; or chronic kidney disease (CKD) stage >=4 prior to cohort entry.

Cohort entry: First shared-care GP prescription of methotrexate or leflunomide respectively.

Cohort exit: The earliest of date of outcome, death, transfer out of the GP practice, last data collection from the GP practice, or 31/12/2019. For the dose reduction analysis, follow-up was censored on the first prescription date at which dose data were missing.

Outcomes:

[1] Drug discontinuation with abnormal blood-test result: Prescription gap of >=90 days following an abnormal blood-test result or Read code indicating abnormal blood-test result within +/-60 days of the date of last prescription. The thresholds for abnormal blood-test results were: white blood cells (WBC) $<3.5x10^9$/L, neutrophils $<1.6x10^9$/L,

platelets <140x10^9/L, ALT/AST >100 IU/L(6); and kidney function decline defined as either CKD progression based on Read codes entered by the GP using KDIGO CKD guidelines (16), or a creatinine increase of >26 μmol/L, the threshold for consideration of AKI (17).

[2] Drug discontinuation with severe abnormal blood-test result: Prescription gap of ≥90 days, with severely abnormal monitoring blood-test result within +/-60 days of the date of last prescription. Severe blood-test abnormalities were defined as: WBCs <2.5x10^9/L, neutrophils <1.0x10^9/L, platelets <50x10^9/L, ALT or AST >200 IU/L or serum creatinine >2 times the previous value. These thresholds were selected as they reflect grade-3 cytopenia according to Common Terminology Criteria for Adverse Events, stage 2 acute kidney injury according to the KDIGO guidelines, and meet the criteria for drug induced liver injury with ALT or AST >5-times upper limit of normal (17-19).

[3] Dose reduction with abnormal, and severely abnormal blood-test result: Dose reduction between two consecutive prescriptions.

[4] Drug discontinuation (any reason): Gap of ≥90 days between the last prescription date and the earliest of date of death, transfer out of the GP practice, last data collection from GP practice, or 31/12/2019.

Data management: Read code and product code lists were developed to ascertain AIRDs, inclusion and exclusion criteria, prescriptions, and outcomes (Available on request).

Outcome validation: A random sample (40%) of methotrexate discontinuations with a blood-test abnormality was drawn. Data for all consultations within +/- 60 days of the abnormal blood-test result was extracted. AA (Consultant Rheumatologist trained in General Medicine and Rheumatology) screened all Read codes to exclude

administrative codes e.g. reminder letter sent, telephone appointment etc. All clinical experts in the study team (two rheumatologists, one nephrologist, one hepatologist, one gastroenterologist, one haematologist (CF) and one academic GP) reviewed the remaining Read codes. Each expert could vote in any condition if they felt that the condition, its treatment, or its complications could cause blood, liver, or kidney injury. The final list was reviewed by all clinicians and four Read codes were excluded as they were non-specific or could imply DMARD side effects if used alone (Table S 1).

Statistical analyses Mean (standard deviation(SD)) and n(%) were used for descriptive purposes. The proportion of methotrexate discontinuations with blood test abnormality that could potentially be explained by an underlying illness was determined. Survival analysis was undertaken to calculate the incidence of outcomes (95% confidence intervals (CI)) per 1,000 person-years for entire follow-up period, first 12-months of follow-up, and the subsequent period. Incidence of drug discontinuation or dose reduction with individual blood-test abnormalities were calculated. Missing data on doses were not imputed as they were missing not at random and imputation could create spurious outcomes. Life tables were constructed to estimate the cumulative incidence at 1-year and 5-year follow-up. Cumulative hazards were plotted using Nelson-Aalen graphs.

Sensitivity analysis: The incidence of methotrexate discontinuation for blood-test abnormalities was examined in a sensitivity analysis after excluding cases with SLE and other CTDs as these conditions can cause cytopenia. The incidence of methotrexate discontinuation with abnormal blood-test results was calculated separately for RA and psoriatic arthritis. Data management and analysis were performed in Stata v16.

Results Data for 24,871 and 3,897 participants with AIRDs prescribed methotrexate and leflunomide were ascertained. Of these, 15,670 and 2,689 participants contributing 46,571 and 4,558 person-years follow-up were included in the methotrexate and leflunomide cohorts, respectively (Figures S1-S2). The median (IQR) methotrexate and leflunomide dose at cohort entry was 10 (7.5-15) mg/week and 10 (10-20) mg/day respectively. 2.1% participants were prescribed both drugs at cohort entry or within the first six-months. The majority of participants in the methotrexate cohort had RA (65.8%), were female (64.6%) and their mean (SD) age was 57 (15) years. In the leflunomide cohort, 63.9% had RA, 67.3% were female and the mean (SD) age was 57 (13) years (Table 1). The median (IQR) follow-up in the methotrexate and leflunomide cohorts was 2.31 (0.82-4.92) and 1.03 (0.33-2.94) years, and there were 1,262 and 259 drug discontinuations due to abnormal monitoring blood test results respectively. Of these 95.6% and 95% were ascertained using values of blood-test results while the remainder were ascertained using Read codes. The 40% random sample of methotrexate discontinuations with blood-test abnormalities consisted of 505 cases and yielded 27 (5.35%) discontinuations that could potentially be explained by another underlying illness or its treatment or complications.

The incidence of methotrexate and leflunomide discontinuation for any reason, with any blood-test abnormality, and with any severe blood-test abnormality was highest in the first 12-months of shared-care prescribing (Table 2, Figure 1). The cumulative annual incidence of discontinuing methotrexate with abnormal, and severely abnormal blood-test results was 1 in 24 and 1 in 169 at 1-year, and this reduced to 1 in 45 and 1 in 352 per-year respectively thereafter. Similarly, for leflunomide, the cumulative annual incidence of discontinuing treatment with abnormal and severely abnormal

blood-test results was 1 in 9 and 1 in 106 at 1-year, reducing to 1 in 32 and 1 in 227 per-year, respectively thereafter. The proportion discontinuing methotrexate with abnormal blood test results was lower than that of leflunomide at 1-year and 5-year follow-up, being 4.2% (95%CI: 3.7%-4.4%) for methotrexate versus 9.3% (8.1%-10.7%) for leflunomide at 1 year, and 12.2% (11.5-12.9%) for methotrexate versus 20.5% (17.8%-23.5%) for leflunomide at 5-year (Figure S3). However, the cumulative incidence of methotrexate and leflunomide discontinuation with severe blood-test abnormalities were comparable at both time points.

The incidence of methotrexate discontinuation with raised liver enzymes, and decline in kidney function was higher in the first 12-months than subsequently, whereas the incidence of methotrexate discontinuation with cytopenia remained stable throughout (Table 3, Figure 2, and Figure S4). On the contrary, the incidence of leflunomide discontinuation with cytopenia, elevated liver enzymes, and kidney function decline was higher in the first 12-months (Table 3, Figure 2). Leflunomide discontinuation with severe individual blood-test abnormalities was numerically more common in the first 12-months than subsequently (Table 3).

Sensitivity analysis: On excluding people with SLE or CTDs, the incidence (95%CI) of methotrexate discontinuation was 27.40 (25.90-28.98)/1,000 person-years for any blood-test abnormality and, 5.88 (5.21-6.63)/1,000 person-years for leucopenia, 4.40 (3.83-5.05)/1,000 person-years for neutropenia and 5.75 (5.09-6.49)/1,000 person-years for thrombocytopenia. This was comparable to that observed in the entire dataset (Table 2). There were no differences when the analyses were stratified for duration of follow-up (Data not shown).

The incidence of methotrexate discontinuation due to elevated liver enzymes was higher in psoriatic arthritis than RA. This difference was present both early and late in

the treatment course and for any or severely elevated liver enzymes. However, the incidence of methotrexate discontinuation due to cytopenia or renal function decline was comparable in the two populations (Table S2).

Dose reduction: 85.3% and 30% participants in the methotrexate and leflunomide cohorts had at least one dose data missing, and their follow-up was censored at this time point. Methotrexate dose was reduced more often with abnormal blood-test results than leflunomide after the first 12 months (Table 4). However, the cumulative incidence of dose-reduction with any blood test abnormality and with severe blood-test abnormalities were comparable for methotrexate and leflunomide at 1 and 5 years. (Figure S3). On evaluating individual blood-test abnormalities, leflunomide dose was more likely to be reduced with neutropenia than methotrexate, and less likely to be reduced with abnormal LFTs (Table 4).

Seven participants prescribed methotrexate had dose reduction for severely abnormal blood-test results with incidence of 1.03 (0.49-2.16) per 1,000 person-years. Fewer than five participants prescribed leflunomide had dose reduction for severely abnormal blood-test results during shared care prescribing. Due to office for national statistics and CPRD policy to avoid accidental identification, we are unable to present incidence for outcomes with <5 events.

Discussion This is the largest study to examine the incidence of treatment changes with abnormal blood-test results during long-term methotrexate or leflunomide therapy. In comparison, the largest systematic review (SR) of low-dose methotrexate included data on liver and bone-marrow toxicity from 3,806 and 3,463 participants from 29 studies, and the previous largest study of leflunomide included data for 3,325 participants (9, 20).

This study focussed on patients successfully initiated on long-term DMARDs as there is lack of data on benefit from monitoring during this period (6). It reports that treatment changes with abnormal blood-test results are common in the first 12-months after hospital-supervised treatment initiation and stabilization, and becomes less frequent thereafter. Treatment changes with severe blood-test abnormalities were uncommon and became less frequent over time .

Our observation that 3.3% participants discontinued low-dose methotrexate with elevated liver enzymes are comparable to the 3.7% incidence reported in the SR (9), and, are higher than those in the CORRONA registry (21). In our study, 2.8% participants discontinued methotrexate with cytopenia. This is lower than the 6.7% cumulative incidence of cytopenia during methotrexate therapy in the SR (9). The incidence of methotrexate discontinuation with leucopenia (0.6% vs 1.2%) and neutropenia (0.5% vs. 1.8%) at 1-year was lower than the cumulative incidence reported in a recent SR of clinical trials that included events from the treatment initiation phase (22). This may be due to the fact that our outcome definition required drug discontinuation with cytopenia, whereas the SRs reported on the incidence of any cytopenia, including those not requiring treatment discontinuation (9, 22).

Solomon *et al* reported a lower cumulative incidence of elevated liver enzymes (0.56%) and haematological abnormalities (0.95%) using data from a 3-year trial of

low-dose methotrexate for preventing cardiovascular events in a population without AIRD (23). The lower incidence may be due to non-prescription of other DMARDs and less NSAID use (23).

As reported previously, raised liver enzymes were the commonest abnormality associated with methotrexate discontinuation, and the risk reduced after 12-months (9, 10, 23-25). On the contrary, the incidence of methotrexate discontinuation with cytopenia was similar throughout the treatment period. Previous 2-year trials of methotrexate have reported cytopenia only occasionally, and unrelated to treatment duration (10, 24).

The cumulative incidence of leflunomide discontinuation with elevated liver enzymes (3.0% vs. 3.1%), and with either cytopenia or elevated liver enzymes (7.7% vs. 7.0%) were comparable to previous reports (20, 21). As reported previously, there was a higher incidence of leflunomide discontinuation with blood-test abnormalities in the first 12-months (10).

Leflunomide was more likely to be discontinued with abnormal blood-tests than methotrexate. These findings are contrary to the results of a trial in which folate supplementation was not mandatory for participants randomised to methotrexate(10). However, in another trial where folate supplementation was mandatory for participants randomised to methotrexate there were more leflunomide than methotrexate discontinuations for elevated liver enzymes (7.7% vs 4.4%) (26). Folic acid supplementation was recommended in the BSR guidelines and became common practice in the early 2000s, and our findings of greater liver toxicity with leflunomide are expected.

Methotrexate and leflunomide discontinuation with kidney function decline was uncommon, though more frequent in the first 12-months, raising the possibility that

these drugs may be nephrotoxic. However, published data suggests that nephrotoxicity is uncommon with these drugs. Only one case of reversible kidney failure due to methotrexate was reported in a clinical trial, and there is one case-report of leflunomide induced interstitial nephritis but this was associated with chronic over-dosing and with no cases of leflunomide nephrotoxicity reported in clinical trials (10, 26-29). The largest clinical trial to examine the side-effects from low-dose methotrexate albeit in a non-AIRD population reported an average 1.9 mL/min/1.73 m^2 improvement in estimated glomerular filtration rate, and 15% lower risk of renal adverse events compared to placebo (23). A previous 2-year clinical trial reported no change in creatinine with leflunomide, and only a marginal increase in creatinine with methotrexate (10). These findings suggest that there is low risk of nephrotoxicity with leflunomide and low-dose methotrexate.

Methotrexate was twice as likely to be discontinued with elevated liver enzymes in psoriatic arthritis than in RA, as reported previously (12, 13). However, the rates of methotrexate discontinuation due to cytopenia and renal function decline were comparable suggesting this risk is target-organ specific. Further research is required to understand the underlying mechanism. However, these findings suggest that psoriatic arthritis patients treated with methotrexate should be monitored carefully for hepatotoxicity and advised to minimise risk factors for the latter.

Most treatment discontinuations in this study were not due to abnormal blood-test results. The cumulative incidence of all-cause methotrexate and leflunomide discontinuation at 1-year and 5-year in this study were comparable to previous reports (30-32). Given a wide methotrexate dosing range, dose reduction was more common for methotrexate than for leflunomide.

Strengths of this study include large sample size allowing us to provide precise estimates for anticipated low event rates. Additionally, this study used real-world data, thus increasing generalisability. Outcomes were stratified according to their severity and time-course to add granularity to the results and increase clinical utility. Data from the period when methotrexate or leflunomide was commenced were excluded by design and the results are applicable to long-term maintenance treatment where the greatest burden of testing lies. Although this may be viewed as a limitation, it does not reduce the validity of our findings. Missing outcome data is a concern with studies using consultation-based databases. However, the cumulative estimates of drug discontinuation reported in this study are consistent with those from previous trials and observational studies. Additionally, our validation exercise revealed that only 5% outcomes were potentially related to another condition, its complication or its treatment. We used a parsimonious list of conditions in this exercise including those for which there was only a remote possibility of abnormal blood-test results.

However, this study has several limitations. Firstly, our findings are not applicable to patients at very high risk of drug toxicity and not transferred to shared-care prescribing e.g. CKD-4, pre-existing chronic liver disease. However, it is extremely uncommon to offer methotrexate or leflunomide to such patients, and the results of our study will therefore apply to the vast majority of AIRD patients. Secondly, dose data were missing for the majority of methotrexate and a large proportion of leflunomide prescriptions. This limits the validity of dose-reduction analysis. Thirdly, CKD progression and a serum creatinine increase of >26 μm/L, the minimum change required to consider the presence of AKI, was used to ascertain drug discontinuation with kidney function decline (17). The guideline specifies that the increase in creatinine should occur within 48 hours. We were unable to meet this part of the definition due

to inherent large gaps between blood-tests, potentially resulting in an overestimate of the incidence of AKI. Our results therefore represent a worst-case scenario with respect to impact on kidney function. Some of the abnormal blood-test results could be due to concurrent prescription of other DMARDs e.g. sulfasalazine. This can potentially elevate the outcome event rate. However, this is unlikely to play a large part as our outcome definition required a prescription gap of at-least 90 days and, it can reasonably be expected that in this period most rheumatologists will be able to ascertain the actual drug responsible for the blood-test abnormality. Moreover, some patients prescribed first-line subcutaneous methotrexate for RA from the hospital clinic, and stepping down to GP prescribed and monitored oral methotrexate may appear as incident users of methotrexate. However, this is likely to be uncommon as most patients with RA in the UK are commenced on oral methotrexate first-line and, if commenced on subcutaneous methotrexate first-line may have a contraindication to oral therapy. Research suggests that patients prescribed subcutaneous methotrexate change to the oral route in <3% instances (33). Additionally, some treatment discontinuations in people with SLE may be due to increased disease activity e.g. cytopenia resulting in treatment escalation. However, a sensitivity analysis excluding cases with SLE or CTD reported similar event rates as the main analysis. Finally, it is difficult to attribute causality for adverse events and some potential adverse events may be unrelated to the treatment.

. Methotrexate and leflunomide are uncommonly discontinued for blood-test abnormalities after the first year of shared-care prescription and discontinuations for severely abnormal blood-test results are even less frequent. These data will be useful when counselling patients in routine clinical practice. Elevated liver enzymes were the commonest blood-test abnormality to cause treatment discontinuations. This

underlines the need to advise patients treated with DMARDs to minimise other risk-factors for hepatotoxicity. Further research is required to identify risk-factors of target-organ damage, and, to develop a prognostic model for risk-stratified blood-test monitoring. This is being evaluated by our team in another ongoing study that will also assess the acceptability and cost-effectiveness of risk-based monitoring.

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Data availability statement: This study used data from the Clinical Practice Research Datalink. Due to the CPRD data sharing policy, we unable to share this study's data. However, access to CPRD data can be directly requested from the CPRD.

Table 1: Baseline characteristics of participants in the methotrexate (n= 15,670) and leflunomide (n=2,689) cohorts.

	Methotrexate	**Leflunomide**
Age at cohort entry; mean (SD)	57.2 (14.8)	57 (13.4)
Female, n (%)	10,115 (64.6)	1,807 (67.3)
Smoking status		
Non-smoker, n (%)	7,339 (46.8)	1,221 (45.5)
Current smoker, n (%)	3,300 (21.1)	555 (20.7)

Ex-smoker, n (%)	4,972 (31.7)	902 (33.6)
Missing, n (%)	59 (0.4)	8 (0.3)
Alcohol use		
Non-user, n (%)	3,132 (20)	606 (22.6)
Low, n (%)	8,714 (55.6)	1,452 (54.1)
Medium, n (%)	573 (3.7)	80 (3.0)
Hazardous, n (%)	875 (5.6)	140 (5.2)
EX-user, n (%)	563 (3.6)	149 (5.6)
Missing, n (%)	1,813 (11.6)	259 (9.6)
AIRD type		
RA, n (%)	10,306 (65.8)	1,715 (63.9)
Lupus/other CTD, n (%)	468 (3.0)	26 (1.0)
PMR/GCA, n (%)	1,597 (10.2)	203 (7.6)
Spondyloarthropathy, n (%)	3,299 (21.1)	742 (27.6)
Other DMARDs		
Leflunomide, n (%)	331 (2.1)	-/-
Methotrexate, n (%)	-/-	57 (2.1)
Sulfasalazine, n (%)	2,660 (17.0)	395 (14.7)

RA=Rheumatoid arthritis; CTD=Connective tissue disease; PMR=polymyalgia rheumatic; GCA=Giant cell arteritis; MTX=Methotrexate; LEF=Leflunomide; -/-= value <5

Table 2: The incidence of methotrexate and leflunomide discontinuation

Outcome		Methotrexate			Leflunomide		
		Events (n)	Person-time (years)	Event rate (95% CI) /1000 person-years	Events (n)	Person-time (years)	Event rate (95%CI)/ 1000 person-time
Any reason							
	Ever	3,584	46,571	76.96 (74.48-79.52)	946	4,558	207.54 (194.73-221.20)
	First 12 months	2,185	12,327	177.25 (169.97-184.84)	765	1,593	480.10 (447.26-515.36)
	After12 months	1,399	34,244	40.85 (38.81-43.00)	181	2,965	61.05 (53.01-70.30)
With any blood-test abnormality							
	Ever	1,262	45,435	27.78 (26.29-29.35)	259	4,449	58.22 (51.55-65.76)
	First 12 months	517	12,239	42.24 (38.75-46.05)	168	1,577	106.53 (91.58-123.92)
	After 12 months	745	33,196	22.44 (20.90-24.09)	91	2,872	31.69 (25.89-38.79)
With severe blood-test abnormality							
	Ever	170	46,466	3.66 (3.15-4.25)	28	4,548	6.16 (4.25-8.92)
	First 12 months	73	12,317	5.93 (4.71-7.45)	15	1,592	9.42 (5.68-15.63)
	After 12 months	97	34,149	2.84 (2.32-3.47)	13	2,956	4.40 (2.56-7.56)

Table 3: The incidence of methotrexate and leflunomide discontinuation due to individual blood-test abnormalities

Outcome	Methotrexate			Leflunomide		
	Events (n)	Person-time (years)	Event rate (95% CI) /1000 person-years	Events (n)	Person-time (years)	Event rate (95%CI)/ 1000 person-time
Leucopenia (WBC <3.5x10^9/L)						
Ever	286	46,425	6.16 (5.49-6.92)	76	4,535	16.76 (13.39-20.98)
First 12 months	97	12,322	7.87 (6.45-9.61)	55	1,590	34.58 (26.55-45.04)
After 12 months	189	34,103	5.54 (4.81-6.39)	21	2,945	7.13 (4.66-10.91)
Severe leucopenia (WBC <2.5x10^9/L)						
Ever	28	46,555	0.60 (0.42-0.87)	5	4,558	1.10 (0.45-2.64)
First 12 months	11	12,327	0.89 (0.49-1.61)	-/-	-/-	1.88 (0.61-5.84)
After 12 months	17	34,228	0.50 (0.31-0.80)	-/-	-/-	0.68 (0.17-2.70)
Neutropenia (Neutrophil <1.6x10^9/L)						
Ever	216	46,476	4.65 (4.07-5.31)	77	4,528	17.01 (13.60-21.26))
First 12 months	70	12,324	5.68 (4.49-7.18)	45	1,589	28.31 (21.14-37.92)
After 12 months	146	34,152	4.28 (3.63-5.03)	32	2,939	10.89 (7.71-15.37)
Severe neutropenia (Neutrophil <1.0x10^9/L)						
Ever	31	46,552	0.67 (0.47-0.95)	5	4,557	1.10 (0.46-2.64)
First 12 months	8	12,326	0.65 (0.32-1.30)	-/-	-/-	1.88 (0.61-5.84)
After 12 months	23	34,226	0.67 (0.45-1.01)	-/-	-/-	0.67 (0.17-2.70)
Thrombocytopenia (Platelet <140x10^9/L)						
Ever	264	46,428	5.69 (5.04-6.42)	59	4,537	13.00 (10.08-16.78)
First 12 months	66	12,323	5.36 (4.21-6.82)	32	1,591	20.11 (14.22-28.44)
After 12 months	198	34,105	5.81 (5.05-6.67)	27	2.946	9.17 (6.30-13.34)
Severe thrombocytopenia (Platelet <100x10^9/L)						
Ever	14	46,571	0.30 (0.18 -0.51)	-/-	-/-	0.44 (0.11-1.75)
First 12 months	6	12,327	0.49 (0.22-1.08)	-/-	-/-	1.26 (0.31-5.02)
After 12 months	8	34,244	0.23 (0.12-0.47)	0	2,965	0
ALT or AST >100 IU/L						
Ever	517	46,209	11.19 (10.26-12.20)	80	4,524	17.68 (14.20-22.02)
First 12 months	272	12,292	22.13 (19.65-24.92)	60	1,586	37.84 (29.38-48.73)
After 12 months	245	33,917	7.22 (6.38-8.18)	20	2,938	6.81 (4.40-10.54)
ALT or AST >200 IU/L						
Ever	83	46,526	1.78 (1.44-2.21)	13	4,549	2.86 (1.66 -4.92)
First 12 months	48	12,321	3.90 (2.94-5.17)	8	1,592	5.03 (2.51-10.05)
After 12 months	35	34,205	1.02 (0.73-1.42)	5	2,957	1.69 (0.70-4.06)
CKD progression/creatinine + >26 μmol/L						
Ever	312	46,081	6.77 (6.06-7.57)	51	4,532	11.25 (8.55-14.81)
First 12 months	118	12,284	9.61 (8.02-11.51)	30	1,590	18.87 (13.19-26.98)
After 12 months	194	33,797	5.74 (4.99-6.60)	21	2,942	7.14 (4.66-10.93)
Creatinine >2 times previous value						
Ever	32	46,534	0.69 (0.49-0.97)	5	4,558	1.10 (0.46-2.64)
First 12 months	6	12,325	0.49 (0.22-1.08)	0	0	0
After 12 months	26	34,209	0.76 (0.52-1.12)	5	4,558	1.10 (0.46-2.64)

Table 4: Incidence of Methotrexate and Leflunomide dose reduction

Outcome	Methotrexate			Leflunomide		
	Events (n)	Person-time (years)	Event rate (95% CI) /1000 person-years	Events (n)	Person-time (years)	Event rate (95%CI)/ 1000 person-time
Any abnormal blood-test result						
Ever	142	6,679	21.26 (18.04-25.06)	47	3,151	14.92 (11.21-19.85)
First 12 months	77	2,764	27.86 (22.29-34.84)	31	1,176	26.36 (18.54-37.48)
After first 12 months	65	3,915	16.60 (13.05-21.13)	16	1975	8.10 (4.97-13.20)
Leucopenia (WBC <3.5x10^9/L)						
Ever	36	6,785	5.31 (3.83-7.36)	19	3,185	5.97 (3.80-9.35)
First 12 months	19	2,779	6.84 (4.36-10.72)	14	1,181	11.85 (7.02-20.02)
After first 12 months	17	4,006	4.24 (2.64-6.82)	5	2004	2.50 (1.04-5.99)
Neutropenia (Neutrophil <1.6x10^9/L)						
Ever	21	6,798	3.09 (2.01-4.74)	23	3,177	7.24 (4.81-10.89)
First 12 months	14	2,779	5.04 (2.98-8.51)	13	1,182	11.00 (6.39-18.94)
After first 12 months	7	4,019	4.24 (2.64-6.82)	10	1995	5.04 (2.71-9.35)
Thrombocytopenia (Platelet <140x10^9/L)						
Ever	26	6,784	3.83 (2.61-5.63)	9	3,200	2.81 (1.46-5.41)
First 12 months	11	2,782	3.95 (2.19-7.14)	8	1,183	6.77 (3.38-13.53)
After first 12 months	15	4,002	3.75 (2.26-6.21)	-/-	-/-	0.50 (0.07-3.52)
ALT or AST >100 IU/L						
Ever	56	6,758	8.29 (6.38-10.77)	9	3,197	2.82 (1.46-5.41)
First 12 months	31	2,776	11.17 (7.85-15.88)	7	1,184	5.91 (2.82-12.40)
After first 12 months	25	3982	6.28 (4.25-9.28)	-/-	2013	1.00 (0.25-3.97)
CKD progression/creatinine + >26 μmol/L						
Ever	33	6,787	4.86 (3.46-6.84)	6	3,199	1.88 (0.84-4.17)
First 12 months	19	2,777	6.84 (4.36-10.73)	-/-	-/-	1.69 (0.42-6.76)
After first 12 months	14	4010	3.49 (2.07-5.89)	-/-	-/-	1.99 (0.75-5.28)

Figure legends

Figure 1: Nelson-Aalen cumulative hazard estimates for methotrexate and leflunomide discontinuation due to: any reason [A], any abnormal blood-test results [b], any severely abnormal blood-test results [c].

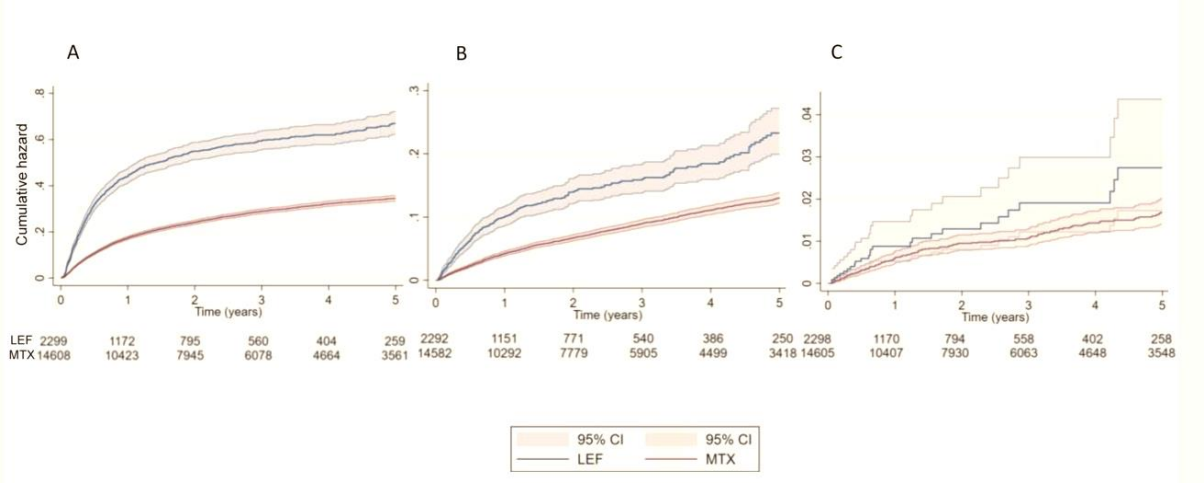

Figure 2: Nelson-Aalen cumulative hazard estimates for drug discontinuation due to the individual abnormal blood-test results: methotrexate discontinuation due to mild abnormal blood-test results [A], severely abnormal blood-test results [C]; leflunomide discontinuation due to mild abnormal blood-test results [B], severely abnormal blood-test results [D].

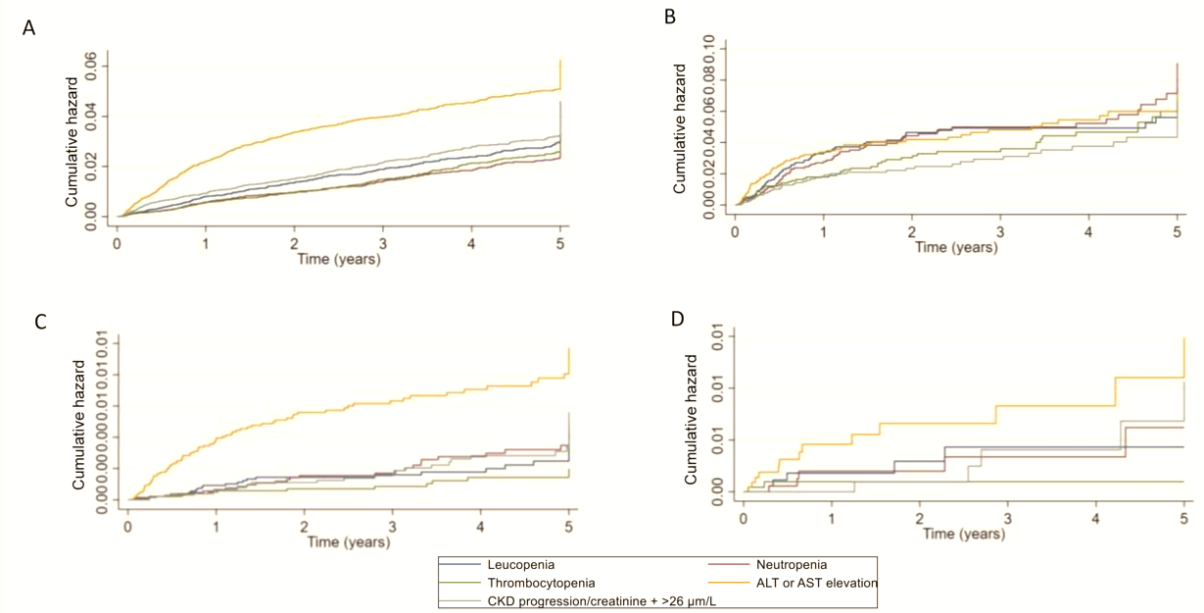

Figure S1: Study population selection criteria for inclusion in the methotrexate cohort.

Figure S2: Study population selection criteria for inclusion in the leflunomide cohort.

Figure S3: Cumulative incidence of methotrexate and leflunomide discontinuation and dose reduction at 1-year and 5-years.

Figure S4: Nelson-Aalen cumulative hazard estimates for drug discontinuation due to the individual abnormal blood-test results showing number at-risk at each follow-up year: methotrexate discontinuation due to mild abnormal blood-test results [A], severely abnormal blood-test results [C]; leflunomide discontinuation due to mild abnormal blood-test results [B], severely abnormal blood-test results [D].

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