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: To examine the incidence and pattern of mycophenolate discontinuation associated with abnormal monitoring blood-tests.

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

Results: The cohort included 992 participants (68.9% female, mean age 51.95 years, 47.1% with SLE) contributing 1,885 person-years of follow-up. The incidence of mycophenolate discontinuation associated with any (severely) abnormal blood-test results was 153.46 (21.07) per 1000 person-years in the first, and 32.39 (7.91) per 1000 person-years in later years of prescription, respectively. 11.5% (1.7%) patients prescribed mycophenolate discontinued treatment with any (severely) abnormal blood-test results in the first year of prescription. After this period mean 2.6% (0.7%) patients discontinued treatment with any (severely) abnormal blood-test results per year. Increased serum creatinine and cytopenia were more commonly associated with mycophenolate discontinuation than elevated liver enzymes. CKD-stage ≥3 was significantly associated with mycophenolate discontinuation with any blood-test abnormalities (aHR (95%CI) 2.22 (1.47-3.37)).

Conclusion: Mycophenolate is uncommonly discontinued for blood-test abnormalities, and, even less often discontinued for severe blood-test abnormalities after the first year of prescription. Consideration may be given for less frequent monitoring after one-year of treatment, especially in those without CKD-stage ≥3.

Key words: Mycophenolate, drug monitoring, inflammatory conditions.

Key messages

- One in 40 patients on mycophenolate discontinued treatment with abnormal monitoring blood-tests after one year.
- CKD stage ≥3 associated with mycophenolate discontinuation with abnormal monitoring blood-test results.
- These data may be used to risk-stratify blood-test monitoring after one year of stable prescription.

INTRODUCTION

Mycophenolate is used in the management of ANCA vasculitis, systemic lupus erythematosus (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 systemic lupus erythematosus (SLE), ANCA vasculitis, rheumatoid arthritis (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 one to three-monthly blood-tests is recommended after an initial period of closer monitoring (9, 10). However, the long-term safety of mycophenolate regarding renal, bone marrow and liver toxicity is poorly understood.

Thus, the objectives of this study were to [1] examine the incidence of mycophenolate discontinuation with abnormal and severely abnormal blood-test results in inflammatory conditions, [2] ascertain the pattern of abnormal blood-test results leading to mycophenolate discontinuation, and [3] explore risk factors of stopping mycophenolate with abnormal monitoring blood-test results. Sensitivity analyses were undertaken to explore whether rates of mycophenolate discontinuation with abnormal blood-test results differed between SLE and other inflammatory conditions, as the former can cause cytopenia and acute kidney injury due to increased disease activity.

METHODS

Data source

Data from the Clinical Practice Research Datalink (CPRD) Aurum was used. Launched in the year 2017 (11), it is a longitudinal anonymized electronic database of health records from 19 million patients from 738 general practices; the GP 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 numeric values. Additionally, general practitioners (GPs) may 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 took place from 1 January 2007 to 31 December 2019.

Inclusion criteria

[1] Diagnosed with RA, SLE, Psoriasis +/- arthritis, reactive arthritis, Ankylosing Spondylitis (AS), SLE, or IBD at age ≥18 years during the study period.

[2] ≥1GP prescription of mycophenolate mofetil (Supplementary Table S1, available at *Rheumatology Advances in Practice* online) after the first record of above conditions in CPRD Aurum, and

[3] 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 mycophenolate. The above two criteria prevent prevalent cases on long-term treatment that have recently changed GP surgeries from entering the cohort as incident cases and new mycophenolate users.

Exclusion criteria

Chronic liver disease (autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B or C, cirrhosis); myelodysplasia; hemolytic anaemia, neutropenia, idiopathic or thrombocytopenic purpura prior to the first primary-care prescription of mycophenolate.

Cohort entry: First primary-care prescription of mycophenolate.

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

Cohort exit: The earliest of date of outcome, death, transfer out of the GP practice, last data collection from the GP practice, five-year follow-up, or 31st December 2019.

Outcomes:

- Drug discontinuation associated with abnormal, and 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).
    - Any abnormal blood test defined as cytopenia (WBC <3.5 x 10^9/L, neutrophil <1.6 x 10^9/L or platelet <140 x 10^9/L) or elevated liver enzymes (ALT or AST >100 IU/L) or increase in serum creatinine by >26 µmol/l.
    - Severely abnormal blood test defined as cytopenia (WBC <2.5 x 10^9/L, neutrophil <1.0 x

10^9/L, or platelet <50 x 10^9/L), elevated liver enzymes (ALT or AST >200 IU/L) or doubling of serum creatinine.

- Any drug discontinuation, defined as a prescription 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 December 2019.

Covariates

Age at first prescription was defined using date of birth and date of first primary-care mycophenolate prescription. Sex, smoking, body mass index (BMI) (kg/m^2) (classified according to WHO categorization), alcohol intake status (non-user, ex-user, low (1-14 units/week), medium (15-21 units/week) and hazardous (>21units/week) user), inflammatory condition, and chronic kidney disease (CKD) were defined using the latest CPRD record prior to cohort entry. CKD stage 3 or higher was defined using Snomed codes or latest eGFR <60 mL/min before cohort entry. Concurrent immune suppressive prescriptions were defined using GP prescriptions in first six months of follow-up, provided such prescriptions were followed by a mycophenolate prescription.

Outcome validation

All mycophenolate discontinuations with a blood-test abnormality were selected. Data for all consultations within ±60 days of the abnormal blood-test result was 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 will not cause blood, liver or kidney injury. The proportion of mycophenolate discontinuations with abnormal blood-test results potentially explained by an alternate illness was calculated.

Statistical analyses

Mean (standard deviation (S.D.)) and n (%) were used for descriptive purposes. Survival analysis was undertaken to calculate the incidence [95% confidence intervals (CIs)] of outcomes per 1000 person-years for the entire follow-up period, and then separately for the first 12 months and the subsequent period. Cumulative hazards were plotted using Nelson-Aalen graphs. The incidence of mycophenolate discontinuation with abnormal blood-test results was calculated separately for SLE and other inflammatory conditions separately. Cox proportional hazard ratios (HRs) and 95% confidence interval (CI) were calculated to determine the factors associated with mycophenolate discontinuation with any blood-test result abnormality. We used fractional

polynomials to model potential non-linear relations between primary outcome and continuous covariates. Missing data for BMI and alcohol was 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 mycophenolate 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 v16.

RESULTS

Data for 1,969 participants with inflammatory conditions prescribed mycophenolate were ascertained (Supplementary Figure S1, available at *Rheumatology Advances in Practice* online). Of these, 992 participants contributing 1,885 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 mycophenolate had SLE (n= 467, 47.1%). The other conditions were RA (n=248), psoriasis (n=168), IBD (n=94), and axial-spondyloarthritis (n=15). There was no prescription of mycophenolic acid.

There were 389, 118, 20 mycophenolate discontinuations due to any reason, with any abnormal, 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 per 1,000 person-years respectively (Table 2). Among the 118 mycophenolate 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 mycophenolate 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 and Fig. 1). 11.5% (1.7%) patients prescribed mycophenolate discontinued treatment with any (severely) abnormal blood-test results in the first year of prescription. After this period mean 2.6% (0.7%) 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 were comparable in those with and without SLE (Table 2). Increased serum creatinine and cytopenia were the commonest reasons for mycophenolate discontinuation (Table 3, Figure 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, CKD ≥stage 3 significantly increased the risk of stopping mycophenolate associated with abnormal blood-test

results with aHR (95%CI) 2.22(1.47-3.37) (Table 1). Other factors did not associate with the outcome.

DISCUSSION

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

CKD stage ≥3 was associated with mycophenolate discontinuation associated with abnormal blood-test results. This is expected as mycophenolate is renally excreted. We found no significant association with the other potential factors we examined. Age was not associated with mycophenolate discontinuation with abnormal blood-test result, consistent with previous studies (15, 16). Elevated liver enzymes were a significantly less common cause of mycophenolate 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 mycophenolate, but at six-months follow-up (5).

Using a similar study design, we previously reported on incidence of methotrexate and leflunomide discontinuation with abnormal and severely abnormal blood-test results (18). The incidence of mycophenolate discontinuation was higher than leflunomide or methotrexate 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) /1,000 person-years for mycophenolate, leflunomide, and methotrexate respectively. These results suggest that methotrexate may be preferred over mycophenolate where there is no evidence for a superior efficacy of the latter.

Strengths of this study included inclusion of a broad range of inflammatory conditions, and the use of real-world data, thus increasing generalisability. 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 mycophenolate 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 specialised services, or those at high risk of side-effects that may be prescribed treatment from secondary care were excluded from this study. Similarly, some services where shared care prescription and monitoring does not extend to mycophenolate were excluded. The patient population in this study did not include those with small vessel vasculitis or myositis further limiting generalizability. Next, due to missing data on the dose of mycophenolate provided by CPRD, missing information on number of tablets prescribed and/or length of prescription, and large dose range (0.5 to 4.0 g/day), we were unable to calculate daily dose of mycophenolate. 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 it was difficult to establish when this occurred. Multiple imputation was used to account for missing data on alcohol intake and BMI. Additionally, increase in serum creatinine by >26 µm/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 hours. We were unable to apply this part of the definition due to monitoring blood-tests being performed 3-monthly. This may have overestimated the incidence of mycophenolate discontinuation with elevated serum creatinine. Our results therefore represent a worst-case scenario for kidney function. Some of the abnormal blood-test results could be due to concurrent prescription of other drugs. This can potentially elevate the outcome rate. However, this is unlikely to play a large part as 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. Additionally, some treatment discontinuations in SLE may be due 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 due to mycophenolate. We are unable to attribute causality with certainty to abnormal blood tests for the decisions to cease MMF. However, this in no way interferes with our conclusion that abnormal blood tests are not causing frequent cessations of MMF after one year of use in general practice. Reassuringly, in our validation exercise only 11% outcomes were potentially explained by alternate medical condition (18). Gastrointestinal intolerance, a common reason for mycophenolate discontinuation, was not an outcome in this study as the study focussed on asymptomatic target organ damage. This is another limitation to our study. 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 relatively large sample size, there were relatively few events and several 95% CI are wide raising the risk of imprecision.

In conclusion, mycophenolate appears to be commonly discontinued for abnormal blood-test results within the first year of prescription, however this becomes less frequent after the first year. Discontinuations for

severely abnormal blood-test results were even less common. These data may be used when counselling patients of their risks and benefits when considering mycophenolate. They should also be considered by guideline writing groups when recommending blood-test monitoring in people with inflammatory conditions on long-term mycophenolate, with respect to whether the frequency of blood-tests could be reduced after the first year of shared-care prescription.

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

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 PPI group and modes of dissemination of study findings were also discussed and agreed with them.

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Table 1: Baseline participant characteristics (n=992) and their association with discontinuation of mycophenolate mofetil associated with abnormal blood test results

	Number (%)†	Crude HR (95% CI)	Adjusted HR (95% CI)‡
Age (years) at first prescription; mean (SD)	51.95 (17.12)	1.01 (1.00-1.02)	1.01 (0.99-1.02)[1]
Sex			
Male	309 (31.2)	1.00	1.00
Female	683 (68.9)	0.83 (0.57-1.22)	0.75 (0.50-1.12)
Body mass index (kg/m²)			
18.5 – 24.9	302 (30.4)	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 (30.1)	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	862 (86.9)	1.00	1.00
Yes	130 (13.1)	0.74 (0.41-1.35)	0.71 (0.39-1.30)
Alcohol use			
None	240 (24.2)	1.00	1.00
Low (1-14 units/week)	344 (34.7)	0.86 (0.56-1.30)	0.86 (0.54-1.37)
Medium (15-21units/week)	50 (5.0)	0.52 (0.19-1.42)	0.57 (0.20-1.64)
Hazardous (>21 units/week)	107 (10.8)	0.81 (0.43-1.52)	0.85 (0.43-1.68)
Ex-use	91 (9.2)	0.65 (0.30-1.43)	0.53 (0.24-1.14)
Missing data	160 (16.1)	-	-
SLE			
No[2]	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)
CKD >=stage 3			
No	772 (77.8)	1.00	1.00
Yes	220 (22.9	2.46 (1.70-3.56)	2.22 (1.47-3.37)

†Percentage unless otherwise stated, ‡ Adjusted for other variables in the Table. MTX-methotrexate, LEF-leflunomide, AZA-azathioprine, 6-MP-mercaptopurine.[1]Per 1-year increase. [2]Includes cases with RA, Psoriasis, IBD, Axial spondyloarthritis. Missing data was imputed.

Table 2: Incidence of mycophenolate discontinuation associated with abnormal blood test results

	Entire cohort			SLE			Other conditions		
Outcome	**n**	**p-yr[1]**	**Incidence (/1,000 p-yr.)**	**n**	**p-yr**	**Incidence (/1,000 p-yr.)**	**n**	**p-yr**	**Incidence (/ 1,000 p-yr.)**
Any reason									
Ever	389	1593	244.19 (221.09-269.71)	152	912	166.64 (142.14-195.35)	237	681	348.11 (306.49-395.37)
First 12 months	356	571	623.08 (561.61-691.29)	140	299	468.93 (397.34-553.41)	216	273	791.80 (692.95-904.76)
After12 months	33	1022	32.30 (22.96-45.44)	12	614	19.56 (11.11-34.44)	21	408	51.47 (33.56-78.94)
Any blood-test abnormality									
Ever	118	1549	76.20 (63.62-91.27)	65	877	74.15 (58.15-94.55)	53	673	78.88 (60.26-103.25)
First 12 months	86	560	153.46 (124.22-189.58)	46	290	158.55 (118.75-211.67)	40	270	148.00 (108.56-201.77)
After 12 months	32	988	32.39 (22.90-45.80)	19	587	32.40 (20.66-50.79)	13	402	32.37 (18.80-55.75)
Severe blood-test abnormality									
Ever	20	1581	12.65 (8.16-19.61)	12	902	13.30 (7.55-23.42)	8	679	11.79 (5.89-23.57)
First 12 months	12	570	21.07 (11.96-37.09)	7	297	23.56 (11.24-49.46)	5	273	18.33 (7.63-44.04)
After 12 months	8	1011	7.91 (3.96-15.82)	5	605	8.26 (3.44-19.85)	-/-	406	7.39 (2.38-22.92)

[1]p-yr: person years. -/-: data suppressed as <5 events. Numbers in parentheses represent 95% confidence intervals

Table 3: Incidence of mycophenolate discontinuation associated with abnormal blood test results

Outcome	n	p-yr[1]	Incidence (/1,000 person-years)		
	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					
Ever	6	1590	3.77 (1.70-8.40)	4.39 (1.65-11.71)	2.94 (0.74-11.76)
First 12 months	-/-	571	5.26 (1.70-16.30)	6.72 (1.68-26.85)	3.67 (0.52-26.02)
After 12 months	-/-	1020	2.94 (0.95-9.12)	3.27 (0.82-13.06)	2.45 (0.35-17.43)
ALT or AST >100 IU/L					
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	-/-	1020	3.92 (1.47-10.45)	1.63 (0.23-11.58)	7.38 (2.38-22.88)
ALT or AST >200 IU/L					
Ever	-/-	1591	2.51 (0.94-6.70)	1.10 (0.15-7.79)	4.42 (1.42-13.69)
First 12 months	-/-	571	1.75 (0.25-12.43)	0	3.67 (0.52-26.02)
After 12 months	-/-	1020	2.94 (0.95-9.12)	1.63 (0.23-11.58)	4.92 (1.23-19.67)
CKD 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	8	570	14.02 (7.01-28.04)	16.80 (6.99-40.36)	11.00 (3.55-34.10)
After 12 months	-/-	1015	1.97 (0.49-7.88)	3.29 (0.82-13.17)	0

[1]p-yr: person years. -/-: data suppressed as <5 events. Numbers in parentheses represent 95% confidence intervals.

Figure legends

Figure 1: Nelson-Aalen cumulative hazard estimates for mycophenolate discontinuation associated with any reason, any abnormal and severely abnormal blood-test results.

Figure 2: Nelson-Aalen cumulative hazard estimates for mycophenolate discontinuation associated with any cytopenia, liver enzyme elevation and kidney function decline.

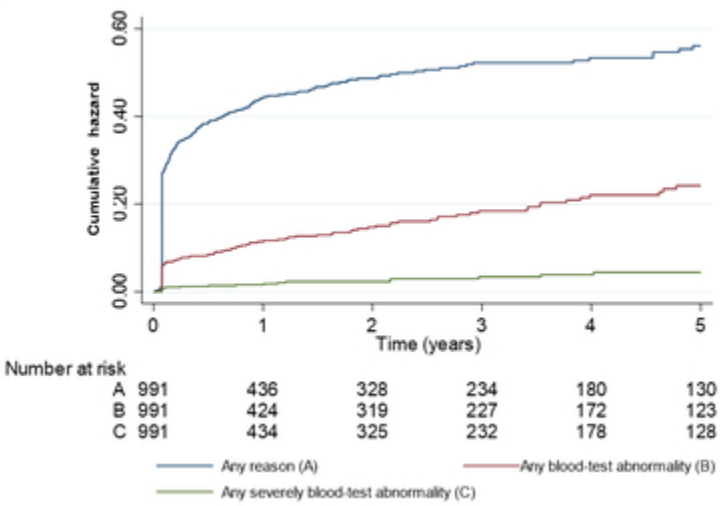

Figure 1: Nelson-Aalen cumulative hazard estimates for mycophenolate discontinuation associated with any reason, any abnormal and severely abnormal blood-test results.

33x23mm (300 x 300 DPI)

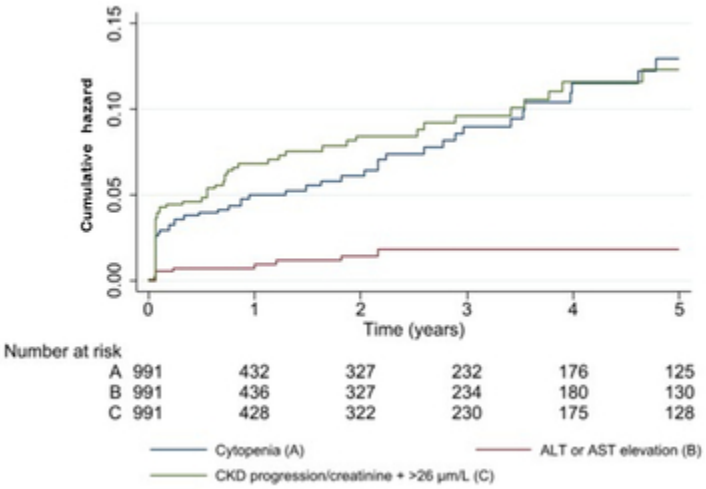

Figure 2: Nelson-Aalen cumulative hazard estimates for mycophenolate discontinuation associated with any cytopenia, liver enzyme elevation and kidney function decline

32x23mm (300 x 300 DPI)