Comparative effectiveness of risk mitigation strategies to prevent fetal exposure to mycophenolate

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ABSTRACT

Background In 2012, the US Food and Drug Administration approved a Risk Evaluation and Mitigation Strategy (REMS) programme including mandatory prescriber training and a patient/provider acknowledgement form to prevent fetal exposure to mycophenolate. Prior to the REMS, the teratogenic risk was solely mitigated via written information (black box warning, medication guide (MG period)). To date, there is no evidence on the effectiveness of the REMS.

Methods We used a national private health insurance claims database to identify women aged 15–44 who filled ≥1 mycophenolate prescription. To compare fetal exposure during REMS with the MG period, we estimated the prevalence of pregnancy at treatment initiation in a pre/post comparison (analysis 1) and the rate of conception during treatment in a retrospective cohort study (analysis 2). Pregnancy episodes were measured based on diagnosis and procedure codes for pregnancy outcomes or prenatal screening. We used generalised estimating equation models with inverse probability of treatment weighting to calculate risk estimates.

Results The adjusted proportion of existing pregnancy per 1000 treatment initiations was 1.7 (95% CI 1.0 to 2.9) vs 4.1 (95% CI 3.2 to 5.4) during the REMS and MG period. The adjusted prevalence ratio and prevalence difference were 0.42 (95% CI 0.24 to 0.74) and −2.4 (95% CI −3.8 to −1.0), respectively. In analysis 2, the adjusted rate of conception was 12.5 (95% CI 8.9 to 17.6) vs 12.9 (95% CI 9.9 to 16.9) per 1000 years of mycophenolate exposure time in the REMS versus MG periods. The adjusted risk ratio and risk difference were 0.97 (95% CI 0.63 to 1.49) and −0.4 (95% CI −5.9 to 5.0), respectively. Sensitivity analyses on the estimated conception date demonstrated robustness of our findings.

Conclusion While the REMS programme achieved less pregnancies at treatment initiation, it failed to prevent the onset of pregnancy during treatment. Enhanced approaches to ensure effective contraception during treatment should be considered.

INTRODUCTION

In 2007, the US Food and Drug Administration (FDA) was authorised by the US Congress to require implementation of Risk Evaluation and Mitigation Strategies (REMS) if deemed necessary.[1] REMS are safety programmes for medications with serious safety concerns that help ensure the benefits of the medication outweigh its risks. They are designed to reinforce medication use behaviours and actions that support the safe use of that medication through enhanced communication of drug risk and other 'elements to assure safe use' (ETASU), which may include a broad spectrum of requirements such as mandatory training for providers, lab test monitoring or restrictions in drug access.[2]

After more than a decade of experience with REMS policy and approval of over 200 REMS programmes, there remains a knowledge gap about the real-world effectiveness of REMS and the comparative effectiveness of different ETASUs.[3 4] In 2013, the Office of the Inspector General noted concerns about the effectiveness of REMS programmes and concluded that most of the assessments provided by manufacturers were incomplete or did not satisfy what the FDA had required on drug approval.[5] Furthermore, with predominant focus on assessment of patient and provider knowledge, evidence on REMS' effectiveness on actual drug use behaviour and reduced risk of adverse events is scarce. Indeed, a recently completed evaluation of FDA internal documents related to a REMS programme for transmucosal immediate-release fentanyl products reported substantial inappropriate prescribing despite high level of risk awareness among patients and providers.[6] Thus, research that compares the net benefit of various ETASUs in terms of patient outcomes is crucial to inform risk management policies in the USA.

In this study, taking advantage of a natural experiment, we evaluated the sequential strategies implemented to

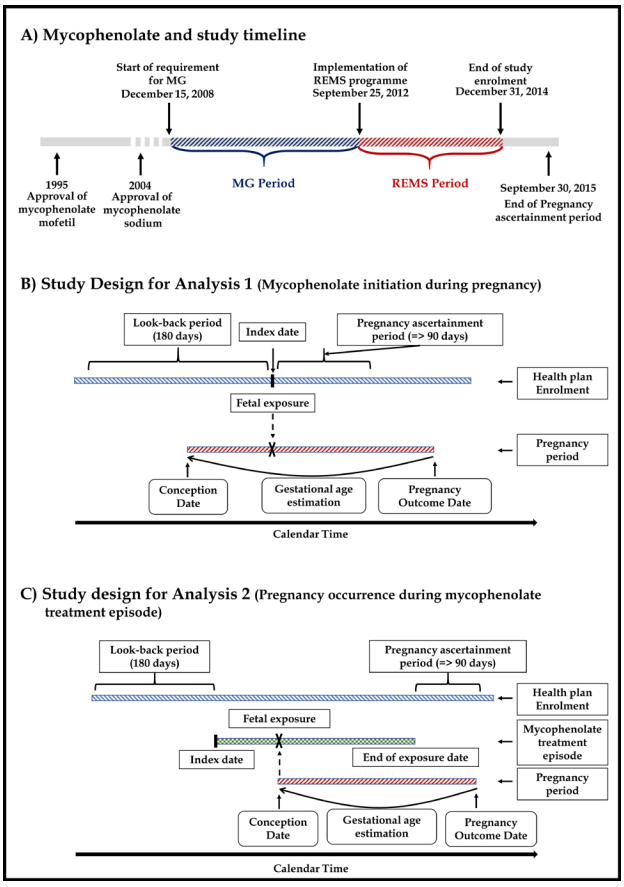

Figure 1 Mycophenolate timeline (A) and study design for analysis 1 (B) and analysis 2 (C). MG, medication guide; REMS, Risk Evaluation and Mitigation Strategy.

mitigate fetal exposure to mycophenolate (mycophenolate sodium or mycophenolate mofetil).[7] Mycophenolate, initially approved in 1995, is commonly used as immunosuppressant in solid organ transplantation,[8] and has also been recognised as an option for several autoimmune disorders.[9–11] Regarding its teratogenicity risk, drug labelling was updated in 2007 to category D with a new black box warning about fetal risk. Following label changes, a medication guide (MG) was approved in 2008, which emphasised fetal risk and use of contraception. In 2012, the FDA approved a REMS programme for all mycophenolate products with two goals: to discourage pregnant women from initiating treatment and to avoid conception during a treatment episode.[12] The REMS includes the original MG, a mandate for manufacturers to train prescribers, a prescriber-patient acknowledgment form, a website and a centralised pregnancy registry.[13] Despite the comparably broad set of REMS components, raising concerns about REMS cost-benefit, no study has quantified the incremental effectiveness of the programme in reducing fetal exposure to mycophenolate.

We used a large national private insurance claims database to evaluate the rate of fetal exposure to mycophenolate during the REMS programme period compared with the former period that relied on warnings (black box and MG) only.

STUDY DATA AND METHODS

Design

This retrospective study compared the risk for fetal mycophenolate exposure during two distinct scenarios of risk mitigation. We evaluated the effectiveness of REMS versus MG in each scenario separately. In analysis 1, we compared the proportion of mycophenolate users who were pregnant on the mycophenolate initiation day during the MG versus the REMS period using prevalence ratios in a pre/post comparison. In analysis 2, we used a cohort design with a historical control period to compare the rate of conception during mycophenolate treatment that occurred in the REMS or MG periods. The MG period extended from 15 December 2008 until the REMS approval date on 25 September 2012. The REMS period started from the latter approval date until 31 December 2014 (figure 1A). Due to intermittent treatment pattern for the broad range of non-transplant indications, we allowed multiple treatment episodes for each patient and the unit of analysis for both studies was the treatment episode.

Data source

We used the IBM MarketScan Research Databases (2008–2015) which provide billing records from a sample of private insurance plans in the USA. The data include beneficiaries' enrolment detail, diagnoses and procedures associated with medical encounters, and pharmacy claims with appropriate linkage capability to follow patients longitudinally.

Study population

We included female patients aged 15–44 (childbearing age) at index date who filled at least one prescription for oral mycophenolate during the REMS or MG periods. The index date was defined as the dispensing day of the first prescription in a given mycophenolate treatment episode (see "Mycophenolate treatment episodes" below). We required a minimum of 6 months' continuous enrolment in the health plan (<30-day gap in coverage) before the index date referred to as look-back period.

We excluded patients with infertility identified by diagnosis/procedure codes for bilateral oophorectomy, hysterectomy, total abdominal hysterectomy, sterilisation, premature menopause or natural menopause on medical encounters during the look-back period. In analysis 2, we further excluded patients who had pregnancy supervision encounters without any pregnancy outcome during the look-back period and patients who were pregnant on the mycophenolate initiation date (see "Pregnancy/conception" below). Illustrations of analyses 1 and 2 are provided in figure 1B,C.

Measurement of study variables

Mycophenolate treatment episodes

We used the 'days of supply' variable in pharmacy claims to construct mycophenolate treatment episodes. The end date of a prescription was defined as dispensing date plus days of supply. If the interval between the end date of a prescription and the start date of a subsequent prescription was ≤42 days, the mycophenolate treatment episode was considered as continuous. The 42 days' gap was chosen based on the labelling information that recommends avoiding pregnancy for 6 weeks after treatment discontinuation.[13] To account for possible medication stockpiling (ie, overlapping days of supply for two consecutive prescriptions), we extended the end date of the second prescription by the number of overlapping days, capped at 10% of the first prescription's days of supply. If we observed a gap >42 days between prescriptions, we created a new treatment episode for the patient. Finally, applying the same rationale, we added 42 days to the end of each treatment episode to have an accurate measure of exposure to the REMS provisions.

Mycophenolate treatment episodes were assigned to MG or REMS based on their index date. For episodes that started during the MG period and continued into the REMS period, we used the REMS approval date as the end of the treatment episode. If the same patient had a new pharmacy claim for mycophenolate in the REMS period, a new treatment episode was assigned to the REMS period given that the patient was then newly exposed to the REMS.

Pregnancy/conception

We identified pregnancy episodes based on pregnancy-related claims for the following pregnancy outcomes: live births (preterm, post-term or full term), stillbirth, abortion (spontaneous or induced), ectopic pregnancy, delivery procedures with unknown vital status and pregnancy supervision visits/prenatal screening procedures with unknown pregnancy outcome. A list of diagnosis and procedure codes for pregnancy determination as well as all covariates is provided in the online supplementary appendix 2. In brief, based on previously published and validated approaches, we established pregnancy episodes within each pregnancy outcome category using a clinical washout time between pregnancies (eg, live births must occur at least 182 days apart from each other for the same patient).[14] Subsequently, the gestational age for each pregnancy episode was estimated using an algorithm for live births that was previously validated in our research group[15] and fixed gestational age estimates for other pregnancy outcomes used in previous studies.[14 16 17] We used the gestational age estimates to assign a conception date to each pregnancy episode. Finally, we used a hierarchical approach to prioritise pregnancy episodes with different outcomes using a clinical washout period (eg, stillbirths must occur at least 168 days after a live birth). In the hierarchy, live births were considered the most reliable birth outcome for estimation of gestational age followed by ectopic pregnancy, stillbirth, abortions, unclassified delivery with unknown vital status and pregnancy supervision visits/prenatal screening categories.

We required patients to have a minimum continuous enrolment of 90 days in a health plan after the index date in analysis 1 and 90 days after the end of treatment episode in analysis 2 to allow for adequate lag time to detect new pregnancies and for retrospective assignment of conception date (ie, pregnancy ascertainment period, figure 1 B,C). Based on previous analyses in our database, >90% of pregnancies have medical encounters for pregnancy supervision or early screening procedures within 90 days after conception.

Follow-up time

In analysis 1, pregnancy status was determined at the beginning of each new mycophenolate treatment episode; therefore, no follow-up time was assessed. In analysis 2, patients were followed from the index date of each treatment episode until: (1) conception, (2) end of exposure (ie, mycophenolate treatment episode plus 42 days), (3) initiation of other teratogenic medications defined as moderate or high-risk teratogenic drugs based on the Teratology Information System database,[18] (4) new infertility status, and (5) end of MG or REMS periods. We restricted follow-up to a maximum of 827 days, which was equal to the time between REMS approval and 31 December 2014 and thus balanced for potentially longer follow-up during the MG period.

Covariates

Indications for mycophenolate use were ascertained from medical encounters during the look-back (ie, baseline) period. Labelled indications were kidney, liver, heart or lung transplant status. Off-label indications included autoimmune hepatitis (non-viral chronic hepatitis), systemic sclerosis, psoriasis, myasthenia gravis and lupus nephritis (systemic lupus erythematosus). We identified other possible off-label indications for mycophenolate based on a literature review and a pilot assessment of mycophenolate users' medical encounter claims within 30 days before the first prescription, which revealed: other tissue disorders, other skin disorders, rheumatoid arthritis, multiple sclerosis, arteritis (vasculitis), inflammatory neuritis, iridocyclitis and bone marrow transplantation.

We identified comorbidities to calculate the Charlson Comorbidity Index.[19] We also extracted diagnoses for depression as a possible confounder not included in the comorbidity score. Use of moderate or high-risk teratogenic drugs during the look-back period was measured to adjust for patients' higher awareness about teratogenicity risks. We created a

variable to identify treatment episodes with prior mycophenolate treatment during the look-back period to adjust for prior awareness of the teratogenicity risk. Other possible confounders were age (transformed into a categorical variable), insurance holder status (employee, spouse, other dependents) and geographic location (four regions in the USA). For analysis 2, we further measured history of recent pregnancy during the look-back period. We also identified contraception use (hormonal contraception medications and intrauterine devices) between −180 and −60 days from the index date. Use of contraception immediately preceding mycophenolate initiation was ignored because it might reflect differential effects of the MG and REMS, which both emphasise initiation of contraception before treatment.

Statistical methods

We used absolute standardised differences to examine the balance of covariates between REMS and MG periods and a difference >0.1 was considered as significant imbalance. For each analysis, a propensity score for exposure groups (REMS vs MG) was calculated using a logistic regression model including all measured confounders. We then used stabilised inverse probability of treatment weights (S-IPTW) to adjust for confounding.[20 21]

In analysis 1, we used a generalised estimating equation model with Poisson distribution to consider an independent correlation structure for multiple observations per patient. We estimated the proportion of patients who were pregnant on the mycophenolate initiation day in each study period and calculated the prevalence ratio. Adjusted differences in proportions were also calculated using the *NLEstimate* macro provided by SAS (http://support.sas.com/kb/37/344.html). Likewise, in analysis 2, we used a generalised estimating equation model with Poisson distribution to estimate incidence rates of conception during mycophenolate treatment episode and the risk ratio by adding an offset of follow-up time to the model. The *NLEstimate* macro was used to calculate the risk difference. All data management procedures and analyses were conducted using SAS/STAT V.15.1 (Cary, NC).

RESULTS

We identified 36 499 mycophenolate treatment episodes among females of childbearing age. In analysis 1, the final cohort included 24 277 treatment initiations from 12 680 unique patients (15 017 in the MG period and 9260 in the REMS period). Approximately 65% of patients were 30–44 years old at the beginning of a treatment episode in both study groups. Among all treatment episodes, 34.7% of episodes in the MG cohort and 44.0% in the REMS cohort had recent treatment with mycophenolate. Tissue disorders were the most common indication (~45%) followed by kidney transplant (~22%). In analysis 2, a total of 20 937 treatment episodes from 11 431 patients were included in the final cohort (12 868 in the MG period and 8069 in the REMS period). Distributions of age, treatment history and mycophenolate indications between REMS and MG were similar to analysis 1. Overall, baseline characteristics were well balanced in both studies except for the insurance holder status and recent mycophenolate treatment. The S-IPTW method was successful in balancing all baseline variables and the resulting absolute standardised differences were close to zero (tables 1 and 2). (See propensity score and IPTW distributions in the online supplementary figures 1–4 in appendix 1.)

In analysis 1, we identified a total of 80 new treatment episodes with pregnancy on the initiation day (17 in the REMS period and 63 in the MG period). Most pregnancies had live birth or abortive outcomes (online supplementary figure 5 in appendix 1). In the MG period, 4.2 per 1000 treatment initiations resulted in fetal exposure compared with 1.9 per 1000 treatment episodes in the REMS period. The adjusted prevalence ratio was 0.42 (95% CI 0.24 to 0.74) and the adjusted prevalence difference was −2.4 (95% CI −3.8 to −1.0) per 1000 treatment initiations (table 3).

In analysis 2, the mean follow-up time for patients in the MG and REMS periods was comparable (121 days vs 127 days). We identified 90 pregnancies during mycophenolate treatment episodes (34 in the REMS period and 56 in the MG period), with a slightly higher proportion of pregnancy episodes with abortion outcomes in the MG period compared with the REMS period (41.0% vs 29.0%, see the online supplementary figure 5 in appendix 1). The crude incidence rate was 12.1 (95% CI 8.6 to 16.9) new pregnancies per 1000 years of treatment in the REMS period compared with 13.1 (95% CI 10.0 to 17.1) in the MG period (table 3). The adjusted risk ratio was 0.97 (95% CI 0.63 to 1.49) and the adjusted risk difference was −0.4 (95% CI −5.9 to 5.0).

Sensitivity analyses where we varied the estimated conception date by ±14 days showed consistent results (online supplementary table 1 in appendix 1). Sensitivity analysis restricted to the first treatment episode per patient in each of the study periods also showed consistent results (online supplementary table 2 in appendix 1). The overall fetal exposure rates either via treatment initiation during pregnancy or conception during mycophenolate treatment were similar in the MG and REMS periods (6.7 per 100 000 pregnancies). Note that fetal exposure rate estimation using overall pregnancies as denominator can reflect both changes in the effect of risk mitigation as well as changes in mycophenolate utilisation.

DISCUSSION

In this large national sample of privately insured women, we found that the REMS implementation

Table 1 Baseline characteristics of mycophenolate treatment episodes in analysis 1 (proportion of treatment initiations that coincide with pregnancy)

	Before propensity score weighting			After propensity score weighting		
Covariates	**MG period (n=15 017)**	**REMS period (n=9260)**	**ASD**	**MG period (n=15 018)**	**REMS period (n=9259)**	**ASD**
Age at index date (%)						
15–19	1541 (10.3)	887 (9.6)	0.02	1504 (10.0)	925 (10.0)	0.00
20–29	3350 (22.3)	2196 (23.7)	0.03	3430 (22.8)	2119 (22.9)	0.00
30–39	5921 (39.4)	3404 (36.8)	0.05	5778 (38.5)	3567 (38.5)	0.00
40–44	4205 (28.0)	2773 (29.9)	0.04	4306 (28.7)	2647 (28.6)	0.00
Indications* (%)						
Tissue disorders†	6762 (45.0)	4468 (48.2)	0.06	6944 (46.2)	4279 (46.2)	0.00
Kidney transplant	3263 (21.7)	1961 (21.2)	0.01	3233 (21.5)	1993 (21.5)	0.00
Other solid organ transplants	1024 (6.8)	623 (6.7)	0.00	1019 (6.8)	630 (6.8)	0.00
Skin disorders‡	1040 (6.9)	723 (7.8)	0.03	1090 (7.3)	674 (7.3)	0.00
Nephrology disorders	1145 (7.6)	627 (6.8)	0.03	1097 (7.3)	677 (7.3)	0.00
Myasthenia gravis	380 (2.5)	221 (2.4)	0.01	372 (2.5)	232 (2.5)	0.00
Autoimmune hepatitis	332 (2.2)	210 (2.3)	0.00	335 (2.2)	207 (2.2)	0.00
Multiple sclerosis	290 (1.9)	122 (1.3)	0.05	256 (1.7)	159 (1.7)	0.00
Rheumatoid arthritis	989 (6.6)	587 (6.3)	0.01	972 (6.5)	594 (6.4)	0.00
Arteritis	552 (3.7)	261 (2.8)	0.05	505 (3.4)	315 (3.4)	0.00
Iridocyclitis	276 (1.8)	177 (1.9)	0.01	282 (1.9)	175 (1.9)	0.00
Blood disorder/bone marrow transplant	223 (1.5)	107 (1.2)	0.03	214 (1.4)	116 (1.2)	0.00
Neuroinflammatory disorder	186 (1.2)	95 (1.0)	0.02	183 (1.2)	99 (1.1)	0.02
Unknown	1474 (9.8)	804 (8.7)	0.04	1408 (9.4)	868 (9.4)	0.01
Recent mycophenolate treatment episode	5218 (34.7)	4077 (44.0)	0.19	5751 (38.3)	3546 (38.3)	0.00
Charlson Comorbidity Index (%)						
0–1	7629 (50.8)	4830 (52.2)	0.03	7313 (48.7)	4509 (48.7)	0.00
>1	7388 (49.2)	4430 (47.8)	0.03	7705 (51.3)	4750 (51.3)	0.00
Depression	1470 (9.8)	1013 (10.9)	0.04	1542 (10.3)	951 (10.3)	0.00
Use of teratogenic drugs (%)	7846 (52.2)	4596 (49.6)	0.05	7700 (51.3)	4751 (51.3)	0.00
Insurance holder status (%)						
Employee	7751 (51.6)	4492 (48.5)	0.06	7571 (50.4)	4664 (50.4)	0.00
Spouse	4280 (28.5)	2568 (27.7)	0.02	4230 (28.2)	2609 (28.2)	0.00
Other dependent	2986 (19.9)	2200 (23.8)	0.09	3216 (21.4)	1986 (21.4)	0.00
Region of residence						
Northeast	2218 (14.8)	1492 (16.1)	0.04	2290 (15.2)	1411 (15.2)	0.00
North central	3255 (21.7)	1822 (19.7)	0.05	3139 (20.9)	1932 (20.9)	0.00
South	6170 (41.1)	3757 (40.6)	0.01	6146 (40.9)	3792 (40.9)	0.00
West	3144 (20.9)	1967 (21.2)	0.01	3162 (21.1)	1950 (21.1)	0.00
Unknown	230 (1.5)	222 (2.4)	0.06	281 (1.9)	173 (1.9)	0.00

*Indications are not mutually exclusive.
†Tissue disorders include systemic lupus erythematosus, sclerosis and other tissue conditions.
‡Skin disorders include psoriasis, lupus and other skin conditions.
ASD, absolute standardised difference; MG, medication guide; REMS, Risk Evaluation and Mitigation Strategy.

resulted in overall lower fetal exposure to mycophenolate. Compared with treatment episodes in the MG period, women with new treatment episodes during the REMS period were 58% less likely to be pregnant on the initiation day when compared with the period when risk was only mitigated via an MG and black box warning. In contrast, we found no significant effect of REMS on the onset of pregnancy during a treatment episode, though CIs of the estimated risk ratio were wide.

To the best of our knowledge, this is the first study to assess the real-world effectiveness of the mycophenolate REMS programme. As such it provides valuable information about the current success of risk mitigation and insight into the comparative effectiveness of two different risk management strategies: MG and black box warning versus addition of provider training, a patient-provider acknowledgement form and a website. Based on our findings on relative and absolute risk measures, the REMS was superior to the

Table 2 Baseline characteristics of mycophenolate treatment episodes in analysis 2 (risk of pregnancy onset during treatment)

	Before propensity score weighting			After propensity score weighting		
Covariates	MG period (n=12 868)	REMS period (n=8069)	ASD	MG period (n=12 870)	REMS period (n=8067)	ASD
Age at index date (%)						
15–19	1299 (10.1)	754 (9.4)	0.03	1263 (9.7)	790 (9.8)	0.00
20–29	2866 (22.3)	1883 (23.3)	0.03	2921 (22.7)	1835 (22.7)	0.00
30–39	5036 (39.1)	2962 (36.7)	0.05	4923 (38.3)	3088 (38.3)	0.00
40–44	3667 (28.5)	2470 (30.6)	0.05	3762 (29.3)	2353 (29.2)	0.00
Indications* (%)						
Tissue disorders†	5904 (45.9)	3959 (49.1)	0.06	6062 (47.1)	3799 (47.1)	0.00
Kidney transplant	2612 (20.3)	1615 (20.0)	0.01	2600 (20.2)	1631 (20.2)	0.00
Other solid organ transplants	811 (6.3)	488 (6.0)	0.01	798 (6.2)	502 (6.2)	0.00
Skin disorders‡	938 (7.3)	660 (8.2)	0.03	979 (7.6)	615 (7.6)	0.00
Nephrology disorders	868 (6.7)	504 (6.2)	0.02	843 (6.5)	527 (6.5)	0.00
Myasthenia gravis	359 (2.8)	207 (2.6)	0.01	349 (2.7)	220 (2.7)	0.00
Autoimmune hepatitis	299 (2.3)	183 (2.3)	0.00	295 (2.3)	184 (2.3)	0.00
Multiple sclerosis	275 (2.1)	117 (1.5)	0.05	242 (1.9)	153 (1.9)	0.00
Rheumatoid arthritis	878 (6.8)	531 (6.6)	0.01	862 (6.7)	536 (6.6)	0.00
Arteritis	469 (3.6)	227 (2.8)	0.05	429 (3.3)	270 (3.3)	0.00
Iridocyclitis	263 (2.0)	166 (2.0)	0.00	265 (2.1)	168 (2.1)	0.00
Blood disorder/bone marrow transplant	174 (1.3)	82 (1.0)	0.03	168 (1.3)	8 (1.1)	0.02
Neuroinflammatory disorder	157 (1.2)	78 (1.0)	0.02	155 (1.2)	81 (1.0)	0.02
Unknown	1314 (10.2)	721 (8.9)	0.04	1250 (9.7)	784 (9.7)	0.00
Recent mycophenolate treatment episode	4153 (32.3)	3334 (41.3)	0.19	4604 (35.8)	2886 (35.8)	0.00
Charlson Comorbidity Index (%)						
0–1	6881 (53.5)	4397 (54.5)	0.02	6931 (53.8)	4347 (53.9)	0.00
>1	5987 (46.5)	3672 (45.5)	0.02	5938 (46.2)	3720 (46.1)	0.00
Depression (%)	1249 (9.7)	886 (10.1)	0.04	1317 (10.2)	826 (10.2)	0.00
Baseline contraceptive use§ (%)	1685 (13.1)	1088 (13.5)	0.01	1709 (13.3)	1075 (13.3)	0.00
Recent pregnancy (%)	113 (0.9)	60 (0.7)	0.02	106 (0.8)	67 (0.8)	0.00
Use of teratogenic drugs (%)	5784 (44.9)	3463 (42.9)	0.04	5691 (44.2)	3571 (44.2)	0.00
Insurance holder status (%)						
Employee	6649 (51.7)	3942 (48.8)	0.06	6506 (50.5)	4074 (50.5)	0.00
Spouse	3673 (28.5)	2258 (28.0)	0.01	3640 (28.3)	2282 (28.3)	0.00
Other dependent	2546 (19.8)	1869 (23.2)	0.08	2723 (21.2)	1710 (21.2)	0.00
Region of residence						
Northeast	1879 (14.6)	1303 (16.1)	0.04	1952 (12.2)	1225 (15.2)	0.00
North central	2785 (21.6)	1578 (19.6)	0.05	2680 (20.8)	1677 (20.8)	0.00
South	5292 (41.2)	3230 (40.0)	0.02	5241 (40.7)	3286 (40.7)	0.00
West	2706 (21.0)	1756 (21.8)	0.02	2744 (21.3)	1721 (21.3)	0.00
Unknown	206 (1.6)	202 (2.5)	0.06	252 (2.0)	158 (2.0)	0.00

*Indications are not mutually exclusive.
†Tissue disorders include systemic lupus erythematosus, sclerosis and other tissue conditions.
‡Skin disorders include psoriasis, lupus and other skin conditions.
§Contraceptive use was ascertained between 180 and 60 days before index date.
ASD, absolute standardised difference; MG, medication guide; REMS, Risk Evaluation and Mitigation Strategy.

original risk mitigation approach in preventing mycophenolate initiation during pregnancy but might lack additional incremental effectiveness for preventing pregnancy during ongoing treatment.

The pregnancy rate among females at childbearing age (15–44) has been reported as 102.1 per 1000 US women in 2010,[22] which is about 10-fold the observed incidence rate during mycophenolate treatment (either during MG or REMS periods). These lower rates may be related to successful risk mitigation, and the underlying medical conditions, the age distribution of study patients and over-representation of patients with private insurance. For instance, analyses of kidney transplant patients in the US Renal Data System (1990–2000) find a pregnancy rate of ~20 per 1000 women, which is closer to the observed pregnancy

Table 3 Risk of fetal exposure on the initiation day and during the mycophenolate treatment episode

Study period	Pregnant/new pregnancy*	Prevalence/ incidence* (per 1000)	Prevalence/ rate* difference	Prevalence/rate* ratio	Follow-up time (person-years)
(A) Pregnancy prevalence on the initiation day of mycophenolate (analysis 1)					
Unadjusted analysis					
REMS period	17	1.8 (1.1, 3.0)	−2.4 (−3.8, −0.9)	0.43 (0.25, 0.77)	NA
MG period	63	4.2 (3.2, 5.4)	Reference		NA
Adjusted analysis					
REMS period	17	1.7 (1.0, 2.9)	−2.4 (−3.8, −1.0)	0.42 (0.24, 0.74)	NA
MG period	63	4.1 (3.2, 5.4)	Reference		NA
(B) Pregnancy-onset incidence rates during mycophenolate treatment (analysis 2)					
Unadjusted analysis					
REMS period	34	12.1 (8.6, 16.9)	−1.0 (−6.3, 4.3)	0.92 (0.6, 1.41)	2812.6
MG period	56	13.1 (10.0, 17.1)	Reference		4274.6
Adjusted analysis					
REMS period	34	12.5 (8.9, 17.6)	−0.4 (−5.9, 5.0)	0.97 (0.63, 1.49)	2812.6
MG period	56	12.9 (9.9, 16.9)	Reference		4274.6

*New pregnancy, incidence and rate column titles are related to analysis 2 only.
MG, medication guide; NA, not applicable; REMS, Risk Evaluation and Mitigation Strategy.

rates in our study.[23] Finally, publicity of pregnancy loss and malformations independent of FDA's actions might have influenced patient and provider behaviour, and thus the true effect size of both the MG and REMS programmes could be smaller.[24 25]

The mycophenolate REMS programme includes an ETASU to provide training for clinicians about teratogenicity risk. The training module emphasises the label recommendations and provides explicit steps that should be taken to rule out pregnancy before treatment initiation (eg, two subsequent negative pregnancy tests) and recommend contraception during treatment. Based on our findings in analysis 1, provider training may have been effective in ensuring assessment of pregnancy status prior to mycophenolate initiation. Although the teratogenic risk and the recommendation for a pregnancy test are included in both the label and the MG, our study suggests that the REMS provisions have reinforced this message.

The FDA has implemented ETASUs that reinforce use of a pregnancy test prior to teratogenic medication initiation (or prescription refills). The REMS programme for isotretinoin products (iPLEDGE) restricts dispensing to only those patients with a confirmed negative pregnancy test. Certified clinicians can prescribe the medication and are required to schedule pregnancy tests and contraception counselling. The pregnancy test is required for each monthly prescription fill and is tracked in a web-based system.[26] A retrospective study using the Kaiser Permanente database (2004–2008) estimated the proportion of fetal exposure as 2.6 per 1000 treatment courses.[27] Using the reported average treatment duration, sample size and number of events, we estimated the pregnancy incidence during isotretinoin exposure to be 7.2 per 1000 exposure years, which is less than the observed rates in the REMS period (12.6 per 1000 years of follow-up). However, differences could be inherent in the study populations defined by indications (acne vs transplant or autoimmune conditions), age (younger in the isotretinoin study) and residential region (California vs all US regions).

While complete avoidance of fetal exposure may be infeasible, several shortcomings of the current REMS suggest opportunities for improvement. In the most recent update of the REMS programme (November 2015), FDA required sponsors to reinforce the training initiatives for clinicians because the REMS assessments conducted by the sponsors had shown deficiencies in knowledge and behaviour.[13] In addition to suboptimal training, comprehensive capture of prescribers may be further complicated given our finding of several off-label indications resulting in involvement of a broad range of provider specialties and even primary care practitioners.

Shifting the focus from prescribers to patients, our findings in analysis 2 showed that prevention of pregnancy *during* mycophenolate treatment, that is, appropriate use of contraception, was not improved through the REMS. While providers play a role in enhancing both awareness and adequate access to contraception, women's decision to use effective contraception is the ultimate determinant of this outcome metric. Thus, considering the unchanged conception rates during treatment, the current REMS approach to reinforce the requirement to use two contraceptive methods requires attention.

This study used a large insurance claims database considered representative of the privately insured population in the USA. We included patients with various mycophenolate indications treated by a variety of medical specialties, providing a generalisable

assessment of the current REMS. To ensure internal validity, we used propensity score weighting to adjust for possible confounders in both analyses. Although patients' characteristics were well balanced at baseline, this adjustment method further mitigated confounding effects. Finally, we used patients treated with mycophenolate as denominator for both analyses, which helped account for overall increases in utilisation rates over time.

We used a historical control group design in our analyses which is prone to bias by secular changes in other factors that may affect fetal exposure rates, such as the growing publicity of mycophenolate teratogenicity. More advanced approaches such as interrupted time series designs may have mitigated such concerns but lacked adequate power due to the small number of events. If publicity of teratogenicity grew independently of the REMS programme, our reports of REMS effectiveness may be overestimated in analysis 1, while our null finding on prevention of pregnancy during treatment (analysis 2) would be even more important. Alternatively, the REMS programme may have directly influenced publicity, which would yield our findings an accurate account of the aggregate REMS effectiveness (or lack thereof).

We relied on previously validated algorithms to identify pregnancies and estimate conception, yet residual error in the accuracy of both exists. In addition, some pregnancies may have gone undetected if they did not result in any reimbursed medical encounter. Thus, reported pregnancy rates may be underestimated, while exact conception dates may be misclassified in either direction. Although this should have affected the two comparison periods to a similar extent, we also conducted a sensitivity analysis to confirm limited effects of measurement bias. Finally, we observed wide CIs, especially for the risk estimate in analysis 2, owing to low incidence rates and a small number of pregnancies. Future studies should be conducted to provide further insight into the incremental effectiveness of various REMS components.

CONCLUSION

This study found that FDA's REMS programme for mycophenolate has been successful in preventing treatment initiation among pregnant women. However, the REMS effect appears minimal regarding prevention of conception during a treatment course. Further work is needed to understand the incremental effectiveness of various REMS components particularly in ensuring use of appropriate contraception during treatment with teratogens.

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