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Personalised therapy during preconception and gestation in SLE: usefulness of 6-mercaptopurine metabolite levelswith azathioprine

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To cite: Lambert-Fliszar F, Bernatsky S, Kalache F, *et al*. Personalised therapy during preconception and gestation in SLE: usefulness of 6-mercaptopurine metabolite levelswith azathioprine. *Lupus Science & Medicine* 2021;**8**:e000519. doi:10.1136/lupus-2021-000519

Received 4 May 2021
Accepted 9 July 2021

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Although azathioprine (AZA) is the immunosuppressive of choice in SLE pregnancies, no one has evaluated 6-mercaptopurine (6-MP) metabolite levels in this population. Even outside pregnancy, the use of metabolite testing has not been widely applied in SLE.[1] AZA is a prodrug that is cleaved to 6-MP, which is converted to the active nucleotides 6-thioguanine (6-TG) and via the enzyme thiopurine methyltransferase (TPMT) to 6-methylmercaptopurine (6-MMP) (figure 1).[1] Studies in inflammatory bowel diseases (IBD) established the therapeutic range for 6-TG concentrations between 235 and 450 pmol/8×10^8 red blood cells (RBC), as higher concentrations are associated with higher risk of myelotoxicity without increased efficacy.[1] 6-MMP levels >5700 pmol/8×10^8 RBC are associated with a higher risk of hepatotoxicity.[1] Additionally, a subgroup of patients resistant to AZA shunts 6-MP towards the overproduction of 6-MMP, which is reflected in an inability to achieve therapeutic 6-TG levels despite dose escalation.[1] In one study, 31% of patients on AZA were identified as 'shunters'.[2]

Identifying patients as non-adherent, treatment-refractory or undertreated, as well as identifying drug toxicity, could improve the efficacy and safety of clinical decision-making. As pregnancy is a particularly critical period to optimise disease control and minimise drug toxicity, we evaluated 6-MP metabolite levels in women with SLE taking AZA during the preconception and/or gestational periods.

We performed a retrospective assessment of women with SLE aged 18–40 years with at least one McGill Lupus Cohort annual study visit between January 2017 and July 2019. Among all females on AZA who were pregnant or trying to conceive, we identified those with 6-MP metabolite levels during this interval. All patients in this cohort are tested for TPMT enzymatic levels and only those with normal levels are started on AZA. We characterised patients with undetectable, low or normal 6-TG levels, as well as 'shunters' (ie, 6-MMP to 6-TG ratio ≥20 with high 6-MMP) using therapeutic reference ranges for IBD, since none exist for SLE.[2] We suggested a possible metabolite interpretation as 'shunter' (ie, 6-MMP to 6-TG ratio ≥20 with high 6-MMP[2]), non-adherent (undetectable or barely detectable metabolite levels despite appropriate dosing) or subtherapeutic (low metabolite levels with AZA dose ≤2.0 mg/kg/day). We summarised key clinical characteristics (ie, prior lupus nephritis, lupus low disease activity state attainment, pregnancy outcomes) of these patients.

Among 29 women of reproductive age with SLE over the study period, eight were pregnant or trying to conceive. Of these, six had 6-MP metabolite levels performed at least once (see table 1 for patients' characteristics). All except one had prior lupus nephritis

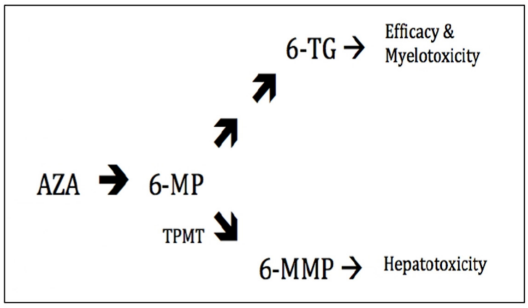

Figure 1 Azathioprine metabolism. AZA, azathioprine; 6-MP, 6-mercaptopurine; 6-TG, 6-thioguanine; 6-MMP, 6-methylmercaptopurine; TPMT, thiopurine methyltransferase.

Table 1 Characteristics of patients with SLE on AZA who were pregnant or trying to conceive at the time of 6-mercaptopurine metabolite level monitoring

Case	Conception status	Prior lupus nephritis	AZA dose (mg/kg/day)	Metabolite levels (pmol/8×10^8 RBC)		Disease activity at time of metabolite measurement	Pregnancy outcome	Metabolite levels interpretation	Action based on therapeutic drug monitoring
				6-TG	6-MMP				
1	Preconception	Yes	2.6	141 (low)	5899 (elevated)	LLDAS	Not applicable	'Shunter'*	Switched to tacrolimus
			2.6	129 (low)	5888 (elevated)	LLDAS			
2	Preconception	Yes	1.9	Not detectable	Not detectable	LLDAS	Not applicable	Non-adherence†	Adherence discussion
3	Pregnant	No	1.2	109 (low)	384	No LLDAS	Pre-eclampsia and preterm birth	Subtherapeutic dosing‡	Dose increased
			1.8	207 (low)	3361	LLDAS			
			2.1	Not detectable	Not detectable	LLDAS		Non-adherence	Adherence discussion
4	Preconception	Yes	2.3	330 (normal)	3019	LLDAS	Not applicable	Therapeutic dosing	Continued same dose
5	Pregnant	Yes	2.5	44 (low)	269	LLDAS	Uncomplicated term pregnancy	Non-adherence versus subtherapeutic dosing	Adherence discussion
6	Pregnant	Yes	1.5	155 (low)	3392	LLDAS	Uncomplicated term pregnancy	Subtherapeutic dosing	Discussion about dose increase (patient refused)

*Shunter: 6-MMP to 6-TG ratio ≥20 with high 6-MMP.
†Non-adherence: not detectable or barely detectable metabolite levels (ie, up to twice the minimal detectable 6-TG levels which is 30 pmol/8×10^8 RBC) despite adequate AZA dosing.
‡Subtherapeutic dosing: 6-TG levels <235 pmol/8×10^8 RBC while receiving a dose of AZA <2.0 mg/kg.
§Reference range for metabolites levels: 6-TG concentrations between 235 and 450 pmol/8×10^8 RBCs and 6-MMP levels <5700 pmol/8×10^8 RBC; LLDAS: as per previously validated definition: (1) SLEDAI-2K ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; (2) no new lupus disease activity compared with the previous assessment; (3) a Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI physician global assessment (scale 0–3) ≤1; (4) a current prednisolone (or equivalent) dose ≤7.5 mg/day and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents.
AZA, azathioprine; LLDAS, lupus low disease activity state; 6-MMP, 6-methylmercaptopurine; RBC, red blood cells; SLEDAI, SLE Disease Activity Index; 6-TG, 6-thioguanine.

and all except one had quiescent disease over the study interval. Half (3/6) of the women were planning to conceive, while the other half (3/6) became pregnant. In most (5/6), 6-TG levels were below the normal range. Among these, three patients had non-detectable or barely detectable levels, despite appropriate drug dosing, suggesting non-adherence; two of these were pregnant at the time of measurement. One patient was determined a 'shunter' (ie, case #1 in table 1) and was thus switched to tacrolimus. Of the three pregnancies, two had no adverse outcome (despite low maternal 6-TG) and one was complicated by pre-eclampsia and preterm birth (with non-detectable maternal 6-TG). Given that approximately 20% of SLE pregnancies experience placenta-mediated complications, it is unclear if the non-detectable 6-TG levels contributed to pre-eclampsia in this patient.

Our study is the first to assess 6-MP monitoring in women with SLE prior to conception and during pregnancy. Despite small numbers, our findings highlight key opportunities to personalise therapy during this critical period. In particular, identification of 'shunting' helps avoid unnecessary and potentially harmful dose escalation, with the option to switch patients to an alternative pregnancy-compatible drug, such as tacrolimus. We also demonstrate how dose escalation can be done safely, as we can avoid 6-TG and 6-MMP levels that are known to be toxic in the IBD population. Lastly, we observed a substantial number of non-adherent patients, which allows focus to be placed on discussing adherence during clinic visits and may guide future treatment approaches. The importance of appropriate control of disease is of heightened importance during pregnancy, a vulnerable time for both mother and baby.

We need to acknowledge potential limitations. We used therapeutic reference ranges for IBD, as none exist for SLE. It has been suggested that target ranges in SLE may be lower than in IBD.[1] Furthermore, in a small study (n=30), pregnancy was found to potentially affect AZA metabolism resulting in a mild decrease in 6-TG levels during gestation with a return to preconception baseline levels after delivery.[3] However, adherence to AZA was not assessed in this study and might have contributed at least in part to the findings.

In conclusion, the use of personalised metabolite monitoring is a promising strategy as it might improve efficacy and safety in our vulnerable patient population prior to or during pregnancy. A metabolite-guided approach could likely be applied to a broader SLE population. In patients with active SLE despite AZA, it may allow identification of the cause of treatment failure as non-adherence, undertreatment or treatment-refractoriness. There is a great need for larger prospective studies to establish target 6-MP levels in pregnant and non-pregnant patients with SLE.

Contributors FL-F, SB, FK, L-PG, CAP and EV interpreted the data and drafted this letter and table.

Funding This work was funded by a Canadian Institutes of Health Research (CIHR) catalyst grant number CMA-151713, project title The Lupus Pregnancy (LEGACY) Cohort. EV receives salary support from the Arthritis Society New/Mid Investigator: Stars Career Development Award number STAR-19–0597 and the Fonds de recherché en santé Québec (FRSQ) Junior 2 Award number 282 178.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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