# First report of therapeutic drug monitoring of azathioprine in long-term renal transplant survivors – what is the desirable range to treat?

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## Background and Objectives

Azathioprine (AZA) has been largely superseded by mycophenolate mofetil (MMF) as the antimetabolite immunosuppressive drug in renal transplantation (RTx). However, the data on which this strategy is based did not include dose optimisation of AZA by measurement of AZA metabolites including thioguanine nucleotides (TGN), or assessment of thiopurine-S-methyltransferase (TPMT), which are routinely used in other medical disciplines.

In 2012 we reviewed the long-term (> 10 years) RTx patients and found that the distribution of TMPT within our cohort mirrored that seen in the general population. Most patients had potentially sub-therapeutic TGN levels. Our objectives now were to:

a) review the clinical outcomes of the cohort
b) see if the biomarkers measured could help identify patients at risk of AZA under-dosing or toxicity.

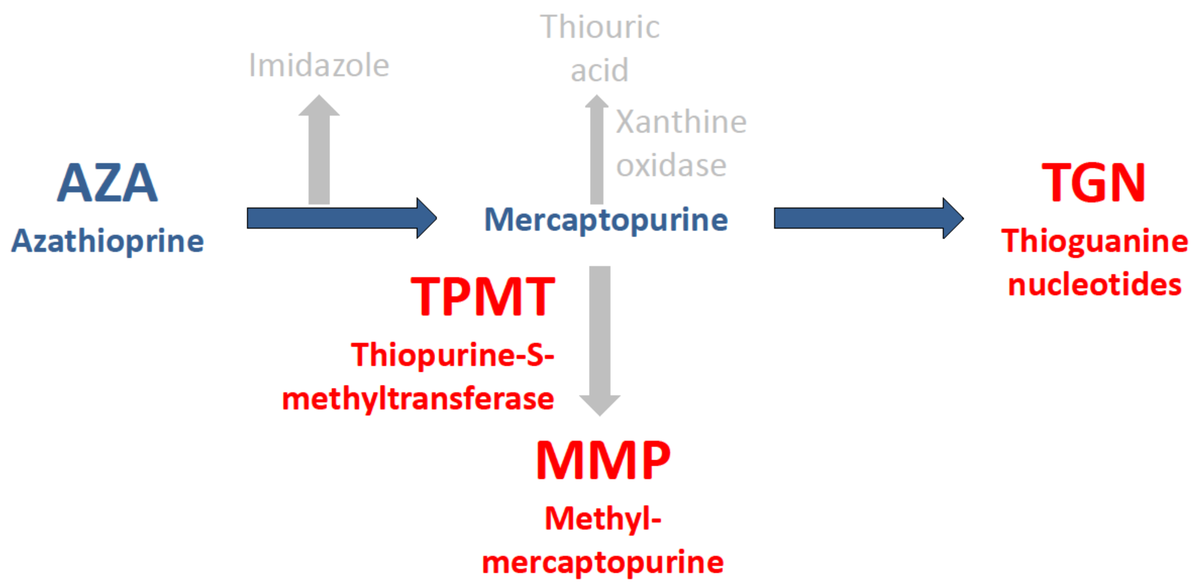


*Figure 1*: AZA is metabolised to TGN (thought to mediate main therapeutic effect) via mercaptopurine. However, there is competitive catabolism of mercaptopurine, notably to MMP via the enzyme TPMT

## Methods

Single unit observational study. 93 long-term RTx patients on AZA were initially tested in 2012 for TPMT activity and TGN profile. These results have now been correlated with current (December 2014) clinical outcomes

## Results

- Updated 2014 results and outcomes were available for 91 patients. Mean duration of RTx in 2012 was 21.7 years. Mean AZA dose was 1.08mg/kg.
- The reference range from other non-transplant cohorts is 240-400pmol/8x10$^8$RBC. In 2012 54/91 were potentially sub-therapeutic, 24/91 were within range, and 13/91 potentially over-dosed.

- TGN levels ≤240pmol/8x10$^8$RBC do not appear to have been associated with increased mortality, graft failure, or new biopsy proven rejection. (Table 1)

- TGN levels >400pmol/8x10$^8$RBC were not associated with increased anaemia, leukopenia, hepatotoxicity (Table 2) or rates of skin cancer (4/13 v 19/78, P=0.751).
- A significant correlation was seen between TGN and Red Blood Cell mean cell volume (ρ(84)= 0.3, P=0.004).

*Table 1*: Outcomes based on mean TGN levels

| | TGN (pmol/8x10$^8$RBC) | | P-value |
|---|---|---|---|
| | ≤240 n=54 | >240 n=37 | |
| Death | 1 | 4 | 0.154 |
| Graft failure | 3 | 2 | 1 |
| Biopsy proven rejection (2012-2014) | 4 | 1 | 0.406 |

*Table 2*: ANOVA of 2014 blood parameters based on mean TGN levels

| | TGN (pmol/8x10$^8$RBC) | | | P-value |
|---|---|---|---|---|
| | ≤240 n=53 | 241-400 n=22 | >400 n=11 | |
| Hb (g/L) | 128.4 | 127.3 | 124.3 | 0.698 |
| WBC (x 10$^9$) | 7.0 | 6.8 | 6.3 | 0.585 |
| ALT (U/L) | 17.0 | 20.0 | 14.8 | 0.193 |

- The effects of TGN on bone marrow suppression are thought to be dose-related. TGN concentration x years on AZA (taken to be years with graft) was used as a proxy for lifetime TGN exposure. There was no correlation seen between this product and Hb, WBC, or lymphocyte count.
- There was a non-significant difference in mean proxy lifetime TGN exposure between those who had skin cancer at any time versus those who had not (6792 v 5069 pmol/8x10$^8$RBCxyears, P=0.209). One patient in the cohort died of lymphoma, and he had a proxy lifetime TGN exposure of 12393 pmol/8x10$^8$RBCxyears, more than double the mean for the cohort (5766 pmol/8x10$^8$RBCxyears).

- Between 2012 and 2014 5/91 patients passed away. A further 5/86 grafts failed. 2 of these and 3/81 with on-going graft function had biopsies between 2012-2014 showing at least borderline antibody mediated rejection, and AZA was stopped in all. 7 further patients switched from AZA to MMF either because of gout and the need for allopurinol, or for trial purposes.

## Conclusions

- This is the first report of the potential impact of therapeutic drug monitoring of AZA in renal transplantation.
- The majority of patients in our long-term RTx surviving cohort had a TGN level less than the range considered therapeutic in other disciplines (240-400pmol/8x10$^8$RBC). We did not see evidence of worse outcomes for those 'under-treated' over a 2 year period.
- This begs the question of what the desired TGN level ranges might be in the early and later post transplantation periods.
- Increased macrocytosis was however seen in patients with higher TGN levels and this may reflect AZA marrow toxicity.

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