CHAPTER 6

THIOPURINE METABOLITE MEASUREMENT
– NOT FOR EVERYONE

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SIRS, Measurement of thiopurine metabolites is currently widely available, but its clinical usefulness has been debated\(^1\). Gonzales-Lama et al. reported about the relation between thiopurine metabolite concentrations and clinical response in IBD patients\(^3\). When comparing patients in corticosteroid-free clinical remission with patients who did not respond favourably (steroid dependency, additional medical or surgical treatment), or experienced adverse events during thiopurine treatment, no difference in 6-thioguanine nucleotide (6-TGN) concentrations was observed. In addition, prediction of beneficial outcome using the previously proposed 6-TGN threshold value of 230 pmol/8x10^8 red blood cells was poor.

In our opinion, these results are difficult to interpret. IBD is characterised by a relapsing and remitting course, contributing to high placebo-response rates in clinical trials\(^4\). Distinguishing between a therapeutic beneficial response due to therapy or due to a natural course is difficult, whatever the metabolite levels may be. As pharmacodynamics and pharmacokinetics are not directly associated, it is unsurprising that the clinical assessment of outcome is not necessarily related to 6-TGN concentrations. On the other hand, accounting for the low specificity of 6-TGN metabolite measurement, patients can actually be thiopurine refractory despite having allegedly therapeutic 6-TGN concentrations (table 1). In addition to this important limitation of routine thiopurine metabolite measurement, other methodological concerns exist. First, chemical stability of 6-TGN is limited and influenced by storage temperature, hence sampling and processing conditions are of major influence on concentrations being measured\(^5\). Second, 6-TGN is measured in red blood cells, which are a surrogate for the actual target cells – the leucocytes. Nevertheless, although not prospectively confirmed, a thiopurine metabolite-directed algorithm was recently shown to be beneficial\(^2\). Moreover, patients exhibiting a skewed thiopurine metabolism (low 6-TGN and high 6-methyl mercaptopurine concentrations), which frequently coincides with adverse events or therapeutic resistance, can profit from drug modification, e.g. allopurinol co-treatment\(^6\). In conclusion, thiopurine metabolites have limited value in predicting response when determined routinely in all thiopurine-using patients, but remain valuable in case of refractory disease or to counteract adverse events.

The presence of two different subgroups of patients hampers the routine use of 6-thioguanine nucleotide (6-TGN) measurement. As a result of the relapsing course of IBD, a clinical response can be observed even if 6-TGN concentrations are below the allegedly therapeutic concentration (C). In addition, patients can actually be unresponsive despite adequate 6-TGN, suggestive of a contrast between pharmacokinetic parameters and the actual pharmacodynamic effect (B). Ideally, there would only be nonresponsive patients with sub-therapeutic 6-TGN (D) and responsive patients with therapeutic 6-TGN concentrations (A).

| Table 1. Possible outcomes with routine thiopurine metabolite measurement |
|------------------------------------------|-----------------|-----------------|
| **Response** | **Nonresponse** | **Total** |
| Therapeutic [6-TGN] | A | B | A+B |
| Sub-therapeutic [6-TGN] | C | D | C+D |
| | A+C | B+D | Total |
REFERENCES


