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The pharmacokinetic effect of adalimumab on thiopurine metabolism in Crohn's disease patients

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Abstract

Background and aims: A drug interaction between infliximab and azathioprine has previously been reported in Crohn's disease patients: the concentration of the main active thiopurine metabolites, the 6-thioguanine nucleotides (6-TGN), increased 1–3 weeks after the first infliximab infusion by 50% compared to baseline.
The aim of this prospective study was to determine the effect of adalimumab on thiopurine metabolism in Crohn's disease patients, evaluated by 6-TGN and 6-methylmercaptopurine ribonucleotides (6-MMPR) concentration measurement.

Abbreviations: AZA, azathioprine; CDAI, Crohn's disease activity index; 95% CI, 95% confidence interval; CRP, C-reactive protein; CD, Crohn's disease; HGPRT, hypoxanthine-guanine phosphoribosyl transferase; HPLC, high performance liquid chromatography; IBD, inflammatory bowel disease; IMP, inosine monophosphate; ITPase, inosine triphosphate pyrophosphatase; 6-MMPR, 6-methylmercaptopurine ribonucleotides; 6-MP, mercaptopurine; MCV, mean corpuscular volume; RBC, red blood cells; TDM, therapeutic drug monitoring; 6-TGN, 6-thioguanine nucleotides; 6-TGTP, 6-thioguanine triphosphate; TPMT, thiopurine S-methyltransferase; UC, ulcerative colitis.

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Methods: Crohn's disease patients on azathioprine or mercaptopurine maintenance therapy starting with concomitant adalimumab treatment were included. 6-TGN and 6-MMPR concentrations were determined before initiation of adalimumab and after 2, 4, 6 and 12 weeks of combination therapy. The activity of three essential enzymes involving thiopurine metabolism, thiopurine S-methyltransferase (TPMT), hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and inosine-triphosphate pyrophosphatase (ITPase), was evaluated at baseline and week 4. Clinical outcome was evaluated by the Crohn's disease activity index and C-reactive protein concentrations at baseline, week 4 and week 12.
Results: Twelve Crohn's disease patients were analyzed. During the follow-up period of 12 weeks the median 6-TGN and 6-MMPR concentrations did not significantly change compared to baseline. TPMT, ITPase and HGPRT enzyme activity did not change either after 4 weeks. In two patients (17%) myelotoxicity was observed within 2–4 weeks, in whom both low therapeutic 6-TGN and 6-MMPR concentrations were found.
Conclusions: In this study in Crohn's disease patients no pharmacokinetic interaction was shown between adalimumab and the conventional thiopurines, azathioprine and mercaptopurine.

1. Introduction

The immunomodulating thiopurines, azathioprine (AZA) and mercaptopurine (6-MP), are effective for induction and particularly maintaining remission in the treatment of moderate to severe inflammatory bowel disease (IBD). Additionally, these drugs act as steroid-sparing agents.[1–3]

Neither AZA nor 6-MP has intrinsic pharmacological activity. AZA is a pro-drug that is converted to 6-MP by glutathione-S-transferase in the liver. 6-MP needs to undergo extensive metabolic transformations, involving pivotal enzymes like thiopurine S-methyltransferase (TPMT), xanthine oxidase (XO), hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and inosine triphosphate pyrophosphatase (ITPase), yielding to a variety of pharmacologically active metabolites. The thiopurine metabolites 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMPR) are considered to be clinically the most important. The proposed thiopurine metabolism in humans is given in Fig. 1.[4]

Patients with 6-TGN concentrations above the proposed therapeutic threshold of 235 pmol/8 × 10^8 red blood cells (RBCs) are more likely to be in clinical remission than patients with a 6-TGN concentration below this threshold.[5,6] Further, the risk for myelotoxicity increases with 6-TGN above 490 pmol/8 × 10^8 RBC.[7,8] High concentrations of 6-MMPR (above 5700 pmol/8 × 10^8 RBC) are associated with an increased risk of hepatotoxicity and treatment failure.[8]

In clinical practice therapeutic drug monitoring (TDM) of the thiopurine metabolites 6-TGN and 6-MMPR is a practical tool to optimise drug therapy in order to improve efficacy or avoid thiopurine toxicity.[9,10]

The biological drugs infliximab and adalimumab are monoclonal antibodies directed against tumour necrosis factor-α (TNF-α), a pro-inflammatory cytokine produced by macrophages and activated T-cells, which plays a key role in the pathophysiology of inflammatory bowel diseases. Infliximab and adalimumab are effective for induction and maintenance of remission of Crohn's disease (CD) and ulcerative colitis (UC).[11]

According to national and international guidelines, anti-TNF-α treatment is indicated for steroid-refractory, steroid-dependent, or complex fistulizing CD.[11–13]

In the SONIC-trial it was shown that patients with moderate-to-severe CD, who were treated with infliximab in combination with AZA, were more likely to have a corticosteroid-free clinical remission than those receiving AZA or infliximab monotherapy.[14]

In 2003, Roblin et al. described a pharmacokinetic interaction between infliximab and AZA in CD patients: 1–3 weeks after the first infliximab infusion the mean 6-TGN concentration increased in infliximab responders with 1.5 times the baseline level. Interestingly, the increase of 6-TGN concentration correlated with the clinical response to infliximab and AZA combination therapy. Three months after the first infliximab infusion, 6-TGN concentrations were comparable with the baseline levels, which suggests a reversible effect of infliximab on AZA metabolism.[15] Elevation of the active 6-TGN may result to an increased clinical efficacy, but may also increase the risk of severe myelotoxic side effects.[8,16] Stringent safety monitoring is thus warranted.

The aim of this prospective study was to evaluate the effect of adalimumab on thiopurine pharmacokinetics in CD patients being treated with stable thiopurine maintenance therapy.

2. Materials and methods

2.1. Patient selection

A prospective study was performed in a group of CD patients under surveillance between July 2009 and December 2011 in five hospitals in the Netherlands (two university hospitals (Maastricht University Medical Centre and the VU University Medical Centre) and three general district hospitals (Orbis Medical Centre Sittard, Laurentius Hospital Roermond and Catharina Hospital Eindhoven)).

Steroid-dependent or steroid-refractory patients with ileocolonic, colonic or peri-anal (fistulizing) CD during maintenance AZA/6-MP therapy, who were scheduled for concomitant treatment with adalimumab, were prospectively included when meeting the following inclusion criteria: age between 18 and 70 years old, diagnosis of CD for at least 6 months