Thiopurines in Inflammatory Bowel Diseases : New perspectives to optimise safety and efficacy

Valorisation addendum

The inflammatory bowel diseases (IBD) Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis are chronic, relapsing inflammatory disorders primarily affecting the gastrointestinal tract, which may lead to disability and severe complications.
IBD may begin at any age, although it usually starts in young adults with a peak incidence between 20-40 years. Over the past decades, both the incidence and prevalence of IBD are gradually increasing, particularly in developed countries worldwide and the highest incidence and prevalence rates are seen in North America and Europe.[1] IBD is associated with a high economic burden to the society resulting from increased healthcare costs and decreased work productivity.[2]
There is currently no curative treatment for IBD available, therefore most patients need lifelong medicinal therapy and many will eventually need to undergo surgery, which have important consequences for their quality of life.
Health care professionals are expected to deliver optimal cure and care for their IBD patients. Society and government are reducing financial budgets so that health care providers are forced to optimise efficacy and work according to guidelines and treatment protocols. Therapy in IBD is focussed to reduce disease activity and improve quality of life, but should be cost effective.
Conventional IBD drugs, including aminosalicylates, corticosteroids, thiopurines and methotrexate, are used to achieve and maintain remission of disease in order to prevent a complicated disease course.
The immunomodulating thiopurines azathioprine (AZA) and mercaptopurine (6MP) have proven their efficacy in active disease to induce remission, but also to maintain clinical remission in both CD and UC. The alternative thiopurine drug, 6-thioguanine (6TG) is a therapeutic option in strictly defined indications as an off-label rescue drug in patients who fail due to intolerance or resistance to the conventional thiopurines AZA or 6MP.
Monoclonal antibodies directed against the pro-inflammatory cytokine TNF-α (i.e. infliximab, adalimumab) are used to treat patients with moderate-to-severe IBD and/or patients who are refractory to conventional therapy.
Combined anti-TNF and thiopurine therapy seems to have beneficial therapeutic value in the treatment of moderate-to-severe active CD and UC, and has been recommended to minimise the immunogenicity of anti-TNF monoclonal antibodies to prevent loss of response and infusion reactions.
Since the introduction of the fast acting anti-TNF-α agents IBD treatment paradigm has evolved towards a rapid escalation therapy to achieve more stringent goals, including rapid induction of clinical remission, maintenance of steroid-free clinical remission, mucosal healing, healing of fistulae, reducing rates of hospitalisation and surgery, and improvement of quality of life. These clinical outcomes have partly been driven by large clinical trials of (new) biological agents, which are notably also achievable with the

much less expensive conventional IBD drugs, such as aminosalicylates, and the immunomodulators methotrexate and thiopurines.[3-6]
Moreover, approximately one-third of the patients with IBD show primary non-response to an inductive anti-TNF regimen. After initial achievement of induction response up to 40% loses response during long-term maintenance therapy as a result of a shift in the mechanism of inflammation or increased drug clearance induced by immunogenicity or other factors, which may lead to inadequate concentrations.[7] Consequently, more than 10% of patients will eventually lose response each year and require dose intensification and/or decrease in infusion interval, which of course has important financial consequences.[8]

Thus, it is important that medical treatment of IBD is tailored to the individual patient outweighing the risks and benefits of the available drugs.

Optimising strategies of thiopurines in inflammatory bowel diseases

The thiopurine drugs are considered the mainstay of medical management of IBD, especially in steroid-dependent and steroid-refractory patients. Thiopurines are effective in approximately two-third of the patients with IBD. The onset of the immunosuppressive effect is usually slow, as it only can be expected within 8-16 weeks. Following an initial response the efficacy is well sustained with remission rates of 95%, 69% and 55% after 1, 3 and 5 years, respectively.[9]

Thiopurine metabolite testing

Azathioprine and mercaptopurine are extensively metabolised ultimately to their main pharmacologically active metabolites, 6-methylmercaptopurine ribonucleotides (6-MMPR) and 6-thioguanine nucleotides (6-TGN). The 6-TGN are responsible for the immunosuppressive effects of thiopurines causing apoptosis and thereby preventing proliferation of activated T-lymphocytes, whereas 6-MMPR metabolites are associated with hepatotoxicity and treatment failure due to intolerable adverse reactions.
6-TGN and 6-MMPR metabolite concentrations can be measured in the erythrocytes.

Optimisation of thiopurine safety and tolerability

Myelosuppression is a potential lethal adverse reaction of thiopurines, of which leukopenia is the most common presentation, resulting in a potentially increased risk of infections. Leukopenia occurs mostly within the first months of thiopurine therapy, and has been mainly attributed to high toxic 6-TGN concentrations resulting from a diminished TPMT enzyme activity in patients carrying a genetic variant in the TPMT gene.
Pre-treatment TPMT genotype-guided thiopurine dosing significantly reduces the occurrence of leukopenia in patients carrying a genetic *TPMT* variant *(Chapter 3)*.

However, the TPMT genotype cannot explain all cases of leukopenia (only in up to ~25%). Therefore, thiopurine-induced leukopenia must also be attributed to other factors, such as concomitant medication and/or viral infections. Since thiopurine-induced myelosuppression can occur at any time, and TPMT genotype or phenotype testing alone does not identify all patients at risk developing leukopenia, means that monitoring of full blood counts at week 1, 2, 4 and 8, and subsequently throughout the course of thiopurine treatment remains mandatory.
We showed that both 6-TGN and 6-MMPR assessed at week 1 are independently correlated with the development of leukopenia during week 1-8. The cytotoxic effect of these metabolites is presumably enhanced by one another. Furthermore, patients who developed leukopenia were more often treated with mercaptopurine than azathioprine. In addition, treatment with concurrent anti-TNF antagonists (i.e. infliximab or adalimumab) was demonstrated to be an independent risk factor for the development of leukopenia in patients starting thiopurine therapy.
These findings may explain, at least for a part, the fact that thiopurine-induced leukopenia is not always related to low TPMT enzyme activity (*Chapter 6*).

Early identification of patients at increased risk of leukopenia is important as it will ultimately reduce morbidity and outpatient monitoring, and to a (much) lesser extent hospitalisation or mortality. Therefore, we advise that in addition to pre-treatment TPMT genotyping, early assessment of 6-TGN and 6-MMPR metabolites at week 1 should be performed to identify patients at increased risk of thiopurine-induced leukopenia. The proposed accurate predictive algorithm may be a helpful tool for clinicians to use in daily practice (*Chapter 6*).

Unfortunately, up to 25% of the IBD patients discontinue therapy already during the first months of treatment mostly due to intolerable adverse reactions. Common adverse drug reactions prompting to discontinuation are gastrointestinal intolerance (i.e. nausea and vomiting) and hepatotoxicity.[10]

Assessment of the 6-MMPR concentration one week after thiopurine initiation identifies patients at risk of hepatotoxicity, gastrointestinal complaints and general malaise as a result from elevated 6-MMPR metabolite formation (*Chapter 7*). *The proposed algorithm can be helpful to optimise thiopurine therapy in an early stage of treatment to prevent unnecessary thiopurine withdrawal due to the occurrence of these potentially intolerable adverse events. Switching between the thiopurines azathioprine, mercaptopurine and 6-tioguanine, as well as the addition of low-dose allopurinol in combination with a thiopurine dose reduction (25-33% of standard) can prevent these adverse reactions and elevate 6TGN levels into the therapeutic range and lower the cytotoxic 6-MMPR* (*Chapter 13*).

The proposed predictive algorithms for leukopenia and thiopurine-induced hepatotoxicity, and the proposed optimisation strategies should be validated in future

prospective randomised-controlled trials to evaluate whether the proposed strategies actually result in an improved efficacy and safety profile (*Chapter 12 & 13*).

Thiopurine metabolite testing during maintenance therapy

As a result of the large interindividual variation of active thiopurine metabolite formation due to the complex metabolism and genetic polymorphisms in the metabolising enzymes, conventional bodyweight-based thiopurine dosing frequently leads to an inadequate response or adverse events in many IBD patients.
Steady-state thiopurine metabolite concentrations are generally reached after approximately 4-8 weeks after treatment initiation. The therapeutic range of steady-state 6-TGN concentrations has been defined between 235 and 490 pmol/8x10^8 red blood cells (RBC) and 6-MMPR <5,700 pmol/8x10^8 RBC.
Until now, thiopurine metabolite assessment is the only way to reveal insight into the ultimate phenotype of an individual's thiopurine metabolism and should be used to personalise a patient's thiopurine dose regimen.

In the study in adult IBD patients on thiopurine maintenance therapy, presented in *Chapter 5*, the previous reported therapeutic 6-TGN cut-off level of 235 pmol/8x10^8 RBC in steady-state was confirmed, but showed rather poor sensitivity, specificity and positive predictive value. This is in line with the results of previous reports and may be explained by several confounding factors as described in *Chapter 12*. Nevertheless, higher 6-TGN levels were found to be significantly associated with clinical remission.

Therapeutic drug monitoring (TDM) is therefore a useful tool in thiopurine maintenance therapy in IBD to reveal underdosing and can be used to tailor thiopurine dose based on the active thiopurine metabolite levels.

Thiopurines and nonadherence

Since medication nonadherence is associated with an increased rate of relapse, clinicians should be well aware that nonadherence of aminosalicylates and thiopurines is underestimated as it occurs in up to 50% of the IBD patients.

In the study presented in Chapter 5 was demonstrated that approximately one in six patients was not adherent to thiopurine therapy, which was observed in patients with both active and quiescent disease.

Adherence behaviour of thiopurine therapy is hard to predict in clinical practice. Therefore, it is a challenging task for health care providers to promote adherence of pharmacotherapy among their patients. Thiopurine metabolite testing is the only useful tool to reveal nonadherence, especially when it is suspected, but denied by the patient. Once it is proven, patients should be supported and educated about the possible unfavourable consequences for their clinical course. Patient-related factors, such as acceptance of their chronic disease accompanied with the lifelong medicinal treatment,

should be taken into consideration. Frequently performed TDM may reveal insight whether the incentive approach works and frequent education may even help to prevent an exacerbation of disease.

Therapeutic failure of thiopurine maintenance therapy

In daily practice, when patients on thiopurine maintenance therapy present with a flare of disease, an unnecessary switch is easily made to expensive anti-TNF therapy (*Chapter 11)*.
Clinical data show that well optimised thiopurines will maintain long-term remission in the majority of IBD patients.

In order to improve the efficacy of thiopurine therapy, thiopurine metabolite testing should be undertaken. First, thiopurine nonadherence should be excluded in these patients. Second, in poorly responding patients with low 6-TGN and low 6-MMPR concentrations due to underdosing, thiopurine dose should be optimised before considering a change to methotrexate or expensive anti-TNF therapy.

Economic burden of IBD medication to society

The increasing knowledge of the pathophysiology of IBD will certainly lead to new immunological targets and consequently new expensive biological drugs against these targets in the future.
Recently it has been demonstrated that the traditional cost profile of IBD on the Dutch society has shifted over the past decades from surgical and medical hospitalisation related costs to health care costs mainly driven by medication use, in particular anti-TNF therapy.[2]
Although these (new) biologicals are a great advance in the treatment of IBD, their costs are high compared to the conventional IBD therapies and contribute to the high economic burden of IBD to the society.[2] For comparison, the average annual costs of anti-TNF antibodies infliximab and adalimumab are 15,000-19,000 euro per patient versus approximately 200-1000 euro per patient for thiopurine therapy.[11]

Considering the limited primary response rates and the loss of response of long-term anti-TNF therapy, the restricted number of alternative therapeutic options in IBD and the high costs of the novel immunosuppressive biological drugs, it is important that clinicians do not disregard conventional IBD therapy and dismiss it as having failed without a proper attempt of optimisation.

In this respect patients should be encouraged to participate actively in therapeutic decision making, which should be tailored to the individual.[12]

Finally, optimisation of safety and efficacy of first-line medical therapy with thiopurines as proposed in this thesis may contribute to efficient and cost-effective health care in IBD.

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