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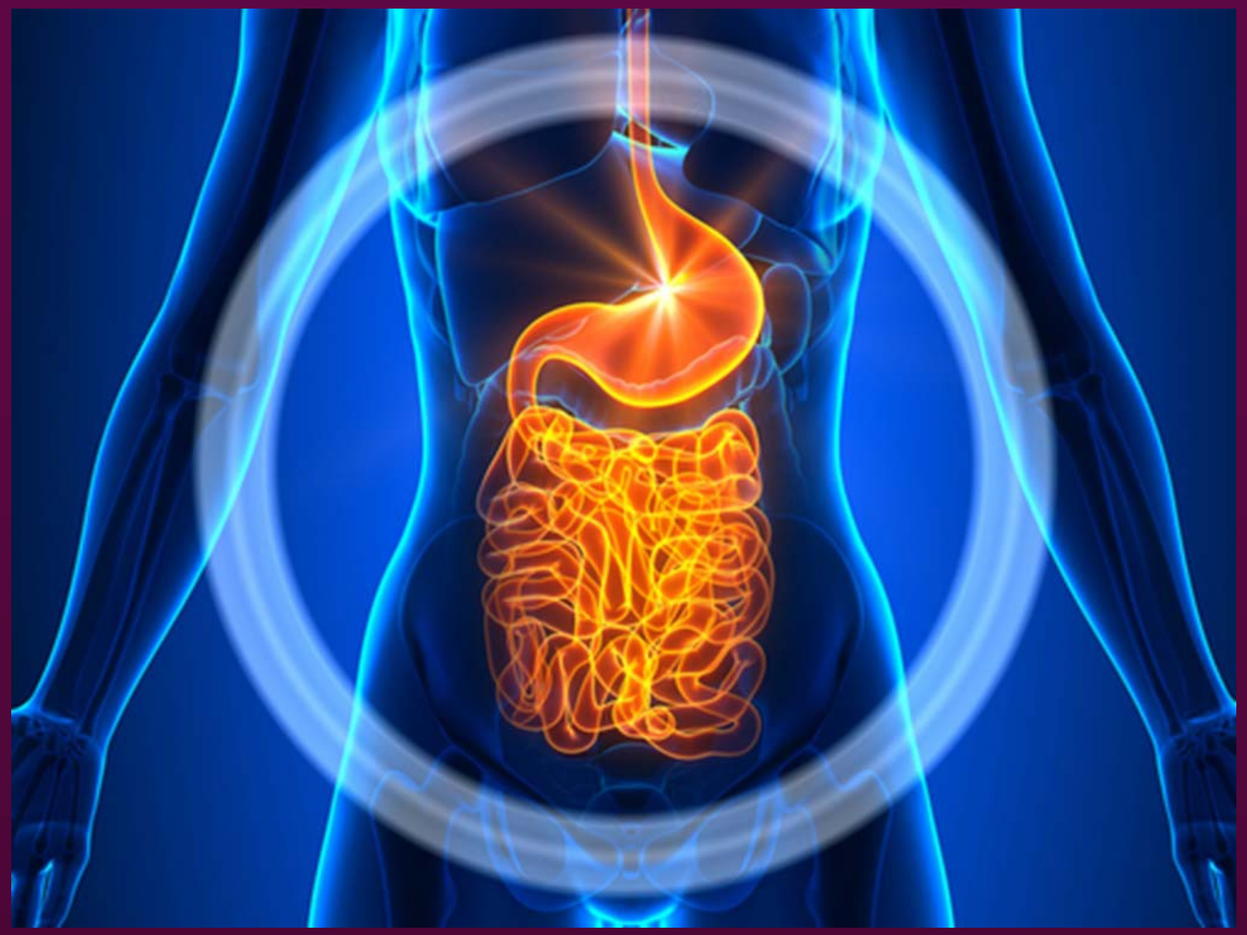
Azathioprine Compendium In Gastroenterology



EXECUTIVE SUMMARY

AZATHIOPRINE IN GASTROENEROLOGY

- In-silico simulation identifies microbial butyrate synthesis predictive of therapeutic efficacy in IBD.
- Patients treated with MP were relatively higher dosed, which resulted in more dose-dependent side effects and a higher rate of dose reductions.
- Maintaining therapeutic levels of antiTNFa drugs without antibodies formation is feasible with lower doses of azathioprine, minimizing its side effects.
- Under combination therapy, AZA dose reduction, but not withdrawal, appears to be as effective as continuation of AZA at full dose.
- By changing the treatment strategy from standard weight-based dosing of azathioprine to weight-based low-dose azathioprine in combination with allopurinol, we can increase remission rates in patients with IBD.
- The clinical efficacy of a combination of adalimumab and azathioprine at Week 26 did not differ from that of adalimumab monotherapy in patients with Crohn's disease naïve to both medications.
- Azathioprine and 6-mercaptopurine are effective therapy for inducing remission in active Crohn's disease. The OR of response increases after > 17 weeks of therapy, suggesting that there is a minimum length of time for a trial of azathioprine or 6-mercaptopurine therapy.

AZA: Azathioprine,
IBD: Inflammatory Bowel diseases,
MP: Mercaptopurine,
OR: Overall Response,
MTX: Methotrexate,
AD: Atopic Dermatitis,
ANCA: Antineutrophil cytoplasmic antibodies,
TPMT: Thiopurine methyltransferase,
MMF: Mycophenolate Mofetil,
ASyS: antisynthetase syndrome,
SNVs: Systemic necrotizing vasculitides,
EGPA: Eosinophilic Granulomatosis with Polyangiitis,
LN: Lupus Nephritis,
CsA: cyclosporine
CRR: Complete Renal Remission, prednisone (PRED)

AZATHIOPRINE IN GASTROENTEROLOGY

ORIGNAL ARTICLES

CLINICAL TRIALS

RANDOMIZED CONTROLLED TRIALS

SYSTEMATIC REVIEWS

Original Articles

Microbial Butyrate Synthesis Indicates Therapeutic Efficacy of Azathioprine in IBD Patients

M Effenberger, S Reider, S Waschina, C Bronowski, B Enrich, T E Adolph, R Koch, A R Moschen, P Rosenstiel, K Aden, H Tilg

Journal of Crohn's and Colitis, jjaa152, published: 28 December 2020

Background and Aims

The microbial ecosystem seems to be an important player for therapeutic intervention in inflammatory bowel disease [IBD]. We assessed longitudinal microbiome changes in IBD patients undergoing therapy with either azathioprine [AZA] or anti-tumour necrosis factor [anti-TNF] antibodies. We predicted the metabolic microbial community exchange and linked it to clinical outcome.

Methods

Faecal and blood samples were collected from 65 IBD patients at baseline and after 12 and 30 weeks on therapy. Clinical remission was defined as Crohn's Disease Activity Index [CDAI]<150 in Crohn´s disease [CD], partial Mayo score <2 in ulcerative colitis [UC], and faecal calprotectin values <150 µg/g and C-reactive protein <5 mg/dl. 16S rRNA amplicon sequencing was performed. To predict microbial community metabolic processes, we constructed multispecies genome-scale metabolic network models.

Results

Paired Bray-Curtis distance between baseline and follow-up time points was significantly different for UC patients treated with anti-TNF antibodies. Longitudinal changes in taxa composition at phylum level showed a significant decrease of Proteobacteria and an increase of Bacteroidetes in CD patients responding to both therapies. At family level, Lactobacilli were associated with persistent disease and Bacteroides abundance with remission in CD. In-silico simulations of microbial metabolite exchange predicted a 1.7-fold higher butyrate production capacity of patients in remission compared with patients without remission [p=0.041]. In this model, the difference in butyrate production between patients in remission and patients without remission was most pronounced in the CD group treated with AZA [p=0.008].

Conclusions

In-silico simulation identifies microbial butyrate synthesis predictive of therapeutic efficacy in IBD.

https://pubmed.ncbi.nlm.nih.gov/32687146/

Clinical Trials

More Dose-dependent Side Effects with Mercaptopurine over Azathioprine in IBD Treatment Due to Relatively Higher Dosing

Mark M. T. J. Broekman, MD, Marieke J. H. et.al.

Inflammatory Bowel Diseases, Volume 23, Issue 10, 1 October 2017.

Background and Aims

There are substantial global differences in the preference for mercaptopurine (MP) or its Prodrug azathioprine (AZA) as first-choice thiopurine to treat inflammatory bowel diseases. Studies comparing both agents are scarce. Our aim was to compare AZA and MP in thiopurine-naive patients with inflammatory bowel disease for the frequency of side effects and efficacy.

Methods

Post hoc analysis of the “Thiopurine response Optimization by Pharmacogenetic testing in Inflammatory bowel disease Clinics” (TOPIC) trial, in which thiopurine-naive patients with inflammatory bowel disease with an indication for a thiopurine were randomized for a genotype-based dose versus standard of care. For this study, Cox proportional hazard ratios (HRs) were calculated to compare AZA and MP for discontinuation rates within 5 months, incidence of hepatotoxicity, leukopenia, and gastrointestinal side effects. Treatment efficacy was compared by logistic regression.

Result

Patient characteristics were similar for patients treated with AZA (n = 494, 64.4%) and MP (n = 273, 35.6%), yet patients with MP were relatively higher dosed compared with those on AZA. Discontinuation rates within 5 months were not different, 39.3% (AZA) and 38.1% (MP), HR 0.92 (95% confidence interval, 0.72–1.17; P = 0.50); however, patients on MP were more often subjected to dose reductions (30% versus 14%, P < 0.01). Higher rates of hepatotoxicity, HR 1.93 (95% confidence interval, 1.35–2.76; P < 0.01) and leukopenia, HR 2.55 (95% confidence interval, 1.51–4.30; P < 0.01) were observed with MP, which annulled in a secondary analysis with adjustment for the higher dose and metabolite levels.

Conclusion

Patients treated with MP were relatively higher dosed, which resulted in more dose-dependent side effects and a higher rate of dose reductions.

https://pubmed.ncbi.nlm.nih.gov/28644183/

AZATHIOPRINE IN GASTROENEREOLOGY

Clinical Trials

Combination therapy in inflammatory bowel disease patients: do we need to maximize the dose of Azathioprine?

Catia Arieiraa, et.al.

Scandinavian Journal of Gastroenterology, Volume 55, Issue 8, 20 Jul 2020.

Background and Aims

The use of combination therapy of anti-TNFa and thiopurines in inflammatory bowel disease (IBD) is associated with greater efficacy and lower immunogenicity. However, the dose of thiopurine in this setting remains to be elucidated. To Aim is to compare the trough levels, anti-TNFa antibodies and the inflammatory biomarkers between three groups in combotherapy: group 1 (dose of azathioprine <1 mg/kg); group 2 (dose of azathioprine >/1 and <2 mg/kg), and group 3 (dose of azathioprine >/2 mg/

Method

A retrospective study was performed, selecting all patients with established diagnosis of IBD who were on combined maintenance treatment.

Result

We included 99 patients, 52.5% female with median age 33 (17–61) years. Eighty patients (80.8%) were diagnosed with Crohn's disease and 19 (19.2%) with ulcerative colitis. Seventy-one (71.8%) patients were on infliximab (IFX) and 28 (28.3%) were on adalimumab (ADA). In patients treated with IFX, there were no differences in trough levels (p¼.976) or formation of antibodies antiIFX (p¼.478) between groups. Moreover, there were no differences in inflammatory biomarkers: CRP (p¼.385) and fecal calprotectin (p¼.576) among the three groups. Regarding patients treated with ADA, there were no differences in trough levels of ADA (p¼.249), formation of antibodies anti-ADA (p¼.706) or in inflammatory biomarkers: CRP (p¼.738) and fecal calprotectin (p¼.269) among the three groups.

Conclusion

In our cohort, there were no differences between anti-TNFa trough levels, formation of anti-TNFa antibodies or inflammatory biomarkers among patients in combotherapy with azathioprine, irrespective of its dosage. In conclusion, our study suggests that maintaining therapeutic levels of antiTNFa drugs without antibodies formation is feasible with lower doses of azathioprine, minimizing its side effects.

https://pubmed.ncbi.nlm.nih.gov/32689833/

RCT'S

Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial

X Roblin, G Boschetti, N Williet, et.al.

Aliment Pharmacol Ther. 2017 Jul; 46(2):142-149.

Background and Aims
Infliximab (IFX) combined with azathioprine (AZA) is more effective than IFX monotherapy in inflammatory bowel disease (IBD). The Aim is to identify the AZA optimal dose that is required for efficacy when receiving combination therapy.

Method
Patients with IBD in durable remission on combination therapy were enrolled in a 1-year, open-label, prospective trial after randomisation into three groups: AZA steady (2-2.5 mg/kg/day, n=28) vs AZA down (dose was halved 1-1.25 mg/kg/day, n=27) vs AZA stopped (n=26). Primary endpoint was failure defined as occurrence of a clinical relapse and/or any change in IBD therapy.

Result
Eighty-one patients were included. Five (17.9%), 3 (11.1%), and 8 (30.8%) patients experienced failure at 1 year in groups AZA steady, AZA down and AZA stopped, respectively (P=.1 across the groups). The median trough levels of IFX at inclusion were close to those measured at the end of follow-up in group AZA steady (3.65 vs 3.45 µg/mL, P=.9) and in group AZA down (3.95 vs 3.60 µg/mL, P=.5), whereas these levels dropped from 4.25 to 2.15 µg/mL (P=.02) in group AZA stopped. Four (14.3%), four (14.8%) and 11 (42.3%) patients experienced an unfavourable evolution of IFX pharmacokinetics in groups AZA steady, AZA down and AZA stopped, respectively. A threshold of 6-TGN <105 pmoles/8.108 RBC was associated with an unfavourable evolution of IFX pharmacokinetics.

Conclusion
Under combination therapy, AZA dose reduction, but not withdrawal, appears to be as effective as continuation of AZA at full dose.

https://pubmed.ncbi.nlm.nih.gov/28449228/

AZATHIOPRINE IN GASTROENEREOLOGY

RCT'S

Randomized clinical trial: a pilot study comparing efficacy of low-dose azathioprine and allopurinol to azathioprine on clinical outcomes in inflammatory bowel disease.

Marianne Kiszka-Kanowitz, et.al.

Scand J Gastroenterol. 2016 Dec; 51(12):1470-1475.

Background and Aims
Treating inflammatory bowel diseases (IBD) using thiopurines is effective; however, a high rate of adverse effects and lack of efficacy limit its use. Retrospective studies have suggested that treatment with low-dose thiopurines in combination with allopurinol is associated with higher remission rates and lower incidence of adverse events. The Aim is to compare the rates of clinical remission and the rates of adverse events in IBD patients treated with either standard treatment with azathioprine or low-dose azathioprine in combination with allopurinol.

Method
A prospective, open-label study, randomizing thiopurine-naïve IBD patients with normal thiopurine methyltransferase to 24 weeks of treatment with either standard azathioprine dose or low-dose azathioprine and allopurinol.

Result
A total of 46 patients with ulcerative colitis or Crohn's disease were randomized. We conducted an intention to treat analysis and found a significant (69.6%) proportion of the patients treated with low-dose azathioprine in combination with allopurinol was in clinical remission without the need for steroid or biologic treatment at week 24 compared to 34.7% of the patients treated with azathioprine monotherapy (RR, 2.10 [95% CI: 1.07-4.11]). In the azathioprine group, 47.8% of the patients compared to 30.4% of the patients in the azathioprine-allopurinol group had to withdraw from the study due to adverse events (RR, 1.47 [95% CI: 0.76-2.85])

Conclusion
This study indicated that by changing the treatment strategy from standard weight-based dosing of azathioprine to weight-based low-dose azathioprine in combination with allopurinol, we can increase remission rates in patients with IBD.

https://pubmed.ncbi.nlm.nih.gov/27686002/

RCT'S

Adalimumab Monotherapy and a Combination with Azathioprine for Crohn's Disease: A Prospective, Randomized Trial

Takayuki Matsumoto, et.al.

J Crohns Colitis. 2016 Nov; 10(11):1259-1266.

Background and Aims

The efficacy of azathioprine for Crohn's disease under adalimumab treatment remains obscure.

Method

In an open-labelled prospective study, we evaluated the efficacy of adalimumab with and without azathioprine in patients with active Crohn's disease, who were naïve to biologics and thiopurines. The patients were randomly assigned to subcutaneous administration of adalimumab [monotherapy group] or to exactly the same schedule of adalimumab with azathioprine [25-100mg daily] [combination group] for 52 Weeks. The primary endpoint was clinical remission at Week 26. We also evaluated the score for simple endoscopic severity of Crohn's disease before the therapy and at Weeks 26 and 52.

Result

A total of 176 patients were randomized to either the monotherapy group [n = 85] or to the combination group [n = 91]. Eighteen patients [21.2%] from the monotherapy group and 7 patients [7.7%] from the combination group withdrew owing to active disease, and 15 patients [16.5%] from the combination group and 1 patient [1.2%] from the monotherapy group withdrew due to side effects of the medications. Non-responder imputation analysis revealed that the remission rate at Week 26 did not differ between the monotherapy group and the combination group [71.8% vs 68.1%; OR 0.84, p = 0.63]. The rate of endoscopic improvement at Week 26 was significantly higher in the combination group [84.2%, n = 57] than in the monotherapy group [63.8%, n = 58] [p = 0.019].

Conclusion

The clinical efficacy of a combination of adalimumab and azathioprine at Week 26 did not differ from that of adalimumab monotherapy in patients with Crohn's disease naïve to both medications.

https://pubmed.ncbi.nlm.nih.gov/27566367/

AZATHIOPRINE IN GASTROENEREOLOGY

Systematic Review

Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease.

Eliza Prefontain, et.al.

Cochrane Database Syst Rev. 2009 Oct 7 ;(4):CD000545.

Background and Aims

The results from controlled clinical trials investigating the efficacy of azathioprine and 6-mercaptopurine for the treatment of active Crohn's disease were conflicting and controversial. A meta-analysis was performed to assess the effectiveness of these drugs for the induction of remission in active Crohn's disease. The objective is to determine the effectiveness of azathioprine and 6-mercaptopurine in inducing remission of active Crohn's disease.

Method

Randomized, double-blind, placebo-controlled trials of oral azathioprine or 6-mercaptopurine involving adult patients (> 18 years) with active Crohn's disease were selected for inclusion.

Result

Eight randomized placebo controlled trials of azathioprine and 6-mercaptopurine therapy in adult patients were identified: five dealt with active disease and three had multiple therapeutic arms. The odds ratio (OR) of a response to azathioprine or 6-mercaptopurine therapy compared with placebo in active Crohn's disease was 2.43 (95% CI 1.62 to 3.64). This corresponded to a number needed to treat (NNT) of about 5 to observe an effect of therapy in one patient. When the two trials using 6-mercaptopurine in active disease were excluded from the analysis, the OR was 2.06 (95% CI 1.25 to 3.39). Treatment > 17 weeks increased the OR to 2.61 (95% CI 1.69 to 4.03). A steroid sparing effect was seen with an OR of 3.69 (95% CI 2.12 - 6.42), corresponding to a NNT of about 3 to observe steroid sparing in one patient. Adverse events requiring withdrawal from a trial, principally allergy, leukopenia, pancreatitis, and nausea were increased with active therapy with an odds ratio of 3.44 (95% CI 1.52 to 7.77). The NNT to observe one adverse event in one patient treated with azathioprine or 6-mercaptopurine was 14.

Conclusion

Azathioprine and 6-mercaptopurine are effective therapy for inducing remission in active Crohn's disease. The OR of response increases after > 17 weeks of therapy, suggesting that there is a minimum length of time for a trial of azathioprine or 6-mercaptopurine therapy.

https://pubmed.ncbi.nlm.nih.gov/31425621/