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AGA CLINICAL PRACTICE UPDATE—COMMENTARY

Evolving Considerations for Thiopurine Therapy for Inflammatory Bowel Diseases—A Clinical Practice Update: Commentary

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Thiopurines (azathioprine, mercaptopurine, thioguanine) and methotrexate are widely used in a variety of clinical management scenarios for ulcerative colitis and Crohn's disease. With the introduction of biologic therapies over the last 2 decades, controversies have emerged as to how these immunomodulators should be used in clinical practice, either alone as monotherapies or in combination with biologic therapies. Here, we provide a summary of evidence and our interpretations regarding how physicians can or should incorporate these agents into clinical practice. We have organized the review into sections regarding their utility as monotherapy or as combination therapy with biologics and safety considerations. Clinical pharmacologic considerations are important regarding both efficacy and safety.

Keywords: Crohn's; Ulcerative Colitis; Immunomodulators; Inflammatory Bowel Disease.

Thiopurines (azathioprine [AZA], mercaptopurine [6MP], and thioguanine [6TG]) and methotrexate (MTX) are widely used in a variety of clinical management scenarios for ulcerative colitis and Crohn's disease. With the introduction of biologic therapies over the last 2 decades, controversies have emerged as to how these immunomodulators should be used in clinical practice, either alone as monotherapies or in combination with biologic therapies. Here, we provide a summary of evidence and our interpretations of best practices from expert opinion regarding how physicians can or should incorporate these agents into clinical practice. We have organized the review into sections regarding their utility as monotherapy or as combination therapy with biologics and safety considerations. Clinical pharmacologic considerations are important regarding both efficacy and safety.

Pharmacology

AZA and 6MP undergo both constitutive and inducible enzyme conversions to the active metabolites, 6-thioguanine nucleotides (6TGNs), and inactive catabolites, 6-methyl-mercaptopurine (6MMP) and 6-thiouracil.[1] Thiopurine methyltransferase (TPMT), the enzyme that converts 6MP to 6MMP, has genetic polymorphisms that affect enzymatic activity, affecting conversion to 6MMP, which can lead to subtherapeutic concentrations of 6TGN and excess concentrations of 6MMP (which has been associated with hepatic enzyme abnormalities and transaminitis). Most of the clinical trial literature with AZA and 6MP is based on trials that used weight-based dosing.[2] Although there is a rationale for using therapeutic drug monitoring (TDM)–based dosing, there is very limited clinical trial data to show that TDM-based dosing is safe and effective.[3] 6TG has been used in patients with allergies to AZA or 6MP but has an increased risk of veno-occlusive disease and nodular regenerative hyperplasia,[4] and allopurinol has been used to reduce shunting of 6MP to 6MMP in nonresponders to AZA/6MP who develop transaminitis.[5]

MTX is a folate antagonist targeting thymidylate biosynthesis and the enzyme thymidylate synthase. However, an exact mechanism of action in inflammatory disorders has not been elucidated. MTX has a relatively short serum half-life of 6–8 hours, and more than 80% of the drug is excreted in the urine by glomerular and tubular secretion. Different dosing regimens and routes of administration have been efficacious in active disease (parenteral, 25 mg weekly), maintenance therapy (parenteral 15 mg weekly), and in combination with biologic therapies (7.5–15 mg oral weekly).[1] The bioavailability of oral MTX is variable and averages 73% of parenteral administration. In rheumatoid arthritis, co-administration of folic acid reduces the risk of adverse effects. At present, TDM for MTX polyglutamates has not been useful in clinical practice.[6]

Thiopurine Monotherapy

Crohn's Disease Induction Therapy

Thiopurines, primarily AZA, were initially studied in patients with steroid-refractory Crohn's disease, but for the most part, they were only minimally effective. However,

Abbreviations used in this paper: **6MMP, 6-methyl-mercaptopurine; 6MP, mercaptopurine; 6TG, thioguanine; 6TGN, 6-thioguanine nucleotide; AZA, azathioprine; IBD, inflammatory bowel disease; MTX, methotrexate; NMSC, nonmelanoma skin cancer; NRH, nodular regenerative hyperplasia; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase.**

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after the novel study of 6MP in Crohn's disease by Present and Korelitz,[7] it became apparent that the onset of action might be too slow (approximately 12 weeks) to have a demonstrable induction benefit. This was also confirmed by the National Cooperative Crohn's Disease Study, in which 2 mg/kg of AZA had no induction benefits compared with placebo over 16 weeks.[8] Numerous subsequent trials have been performed in a variety of clinical scenarios in active Crohn's disease, usually in conjunction with corticosteroids. Results from subsequent Cochrane meta-analyses[9] and a recent summary statement from the American Gastroenterological Association[10] have concluded that although there may be some short-term steroid-sparing effects, thiopurines are not effective for induction therapy. Two recent trials of early use of AZA failed to show its benefits as an inductive agent in the absence of steroid-induced remissions.[11,12]

Crohn's Disease Maintenance Therapy

In contrast to the lack of utility as induction therapy, AZA and 6MP have shown modest efficacy as steroid-sparing agents.[10,13] Association studies have suggested that the use of TDM to ensure adequate 6TGN concentrations may improve efficacy.[3,14] 6TG has been shown to have clinical benefits for patients with inflammatory bowel disease (IBD) who have a history of allergy to AZA or 6MP,[15] but because of an increased risk of veno-occlusive disease or nodular regenerative hyperplasia of the liver, it has been relegated to rescue status.[16] However, only 1 small underpowered trial used TDM prospectively.[17] Thiopurines also have the potential to reduce postoperative recurrence of Crohn's disease,[18] particularly when administered with imidazole antibiotics.[19]

Ulcerative Colitis Induction Therapy

There are scarce data regarding the role of thiopurine monotherapy as induction therapy in ulcerative colitis. One small investigator-unblinded trial comparing AZA 2 mg/kg/day with mesalamine 3.2 g/day in steroid-dependent patients showed a greater impact for AZA on clinical and endoscopic assessments after 6 months.[20]

Ulcerative Colitis Maintenance Therapy

Similar to the situation in Crohn's disease, a recent Cochrane review of 6 studies using AZA and 6MP as maintenance therapy for ulcerative colitis concluded that AZA appears to be modestly effective in patients for whom aminosalicylates have failed, who cannot tolerate aminosalicylates, or who require repeated courses of steroids.[21] The level of evidence was rated as low. Again, none of the trials used TDM.

MTX Monotherapy

Crohn's Disease Induction Therapy

A single large study of MTX 25 mg intramuscularly on a weekly basis in conjunction with corticosteroids showed induction of clinical remission and steroid-sparing benefits in Crohn's disease,[22] whereas a number of smaller trials failed to show significant benefits with oral MTX.[23]

Crohn's Disease Maintenance Therapy

Patients who responded to induction therapy with intramuscular MTX 25 mg/week who were randomly reassigned to maintenance therapy with MTX 15 mg/week had superior outcomes vs patients randomly reassigned to receive placebo.[24] No other controlled clinical trials have been reported; however, a number of clinical series have described beneficial long-term results for patients who initially responded to MTX induction therapy.[6]

Ulcerative Colitis Induction Therapy

There are even less data regarding MTX in ulcerative colitis than there are with thiopurines. Initial trial results of MTX in ulcerative colitis were negative. Recently, a large study of 25 mg parenteral MTX for steroid-dependent ulcerative colitis failed to show efficacy for clinical remission or mucosal healing over 24 weeks.[25]

Ulcerative Colitis Maintenance Therapy

There are currently no controlled data regarding the efficacy of MTX as a maintenance therapy in ulcerative colitis. A large US study recently failed to show efficacy of MTX in maintaining steroid-free remission over 54 weeks.[26] Hence, the use of MTX in ulcerative colitis is limited to a potential role in combination with biologics (see the next section).

Thiopurine Combination Therapy

Crohn's Disease Induction and Maintenance Therapy

There is only a single prospective trial of combination therapy with AZA and biologic therapy with infliximab in Crohn's disease.[27] This study showed that combination therapy was more effective than either AZA or infliximab monotherapy for induction and maintenance of steroid-free clinical remission at weeks 26 and 52 and for induction of mucosal healing at week 26. Combination therapy with AZA resulted in low rates of antibodies to infliximab and higher infliximab concentrations, factors that were associated with greater efficacy. There were no increased safety concerns in the 52 weeks with combination therapy. A meta-analysis of subgroup analyses from clinical trials of infliximab, adalimumab, and certolizumab pegol reported that combination therapy with AZA or 6MP and biologic therapy was more effective for infliximab but not adalimumab or certolizumab.[28] However, these studies were not designed to answer this question, and so the validity of the meta-analysis results is unclear. How long combination therapy should be continued is also unclear. One small underpowered study suggested that it may be possible to discontinue AZA after 6 months if the patient is in clinical and endoscopic remission while receiving combination therapy.[29]

Ulcerative Colitis Induction and Maintenance Therapy

There is only a single prospective trial of combination therapy with AZA and biologic therapy with infliximab in

ulcerative colitis.[30] This study showed that combination therapy was more effective than either AZA or infliximab monotherapy for induction of steroid-free clinical remission and clinical response. Combination therapy was numerically and statistically superior for mucosal healing compared with AZA but not statistically different than infliximab monotherapy at week 16. Combination therapy with AZA did result in low rates of antibodies to infliximab and higher infliximab concentrations, factors that were associated with greater efficacy.

MTX Combination Therapy

Crohn's Disease Induction and Maintenance Therapy

There is only a single prospective trial of combination therapy with MTX and biologic therapy with infliximab in Crohn's disease.[31] This study showed that combination therapy with MTX, infliximab, and corticosteroids was not more effective than infliximab and corticosteroids for induction and maintenance of steroid-free clinical remission at week 52. It was unclear whether MTX was truly ineffective or whether the study was confounded by the enrollment of patients with low disease activity and/or the concomitant use of corticosteroids in both treatment groups. Combination therapy with MTX resulted in low rates of antibodies to infliximab and higher infliximab concentrations, factors that in other studies have led to greater efficacy.

Ulcerative Colitis Induction and Maintenance Therapy

There are currently no controlled data regarding the efficacy of combination therapy with MTX and infliximab or other biologics as induction or maintenance therapy in ulcerative colitis.

Safety

Thiopurines

Both dose-independent events and pharmacologically explainable dose-dependent events have been documented with thiopurines. Among dose-independent events, potential idiosyncratic or allergic reactions include rash, fever, arthralgias, pancreatitis, and hepatitis. The dose-dependent toxicities of thiopurines are mainly explained by the complex metabolism of thiopurines, resulting in a number of potentially effective (6TGN) or toxic metabolites (high concentrations of 6TGN or 6MMP). Hepatotoxicity (associated with high 6MMP) and myelotoxicity (associated with high 6TGN and possibly 6MMP) are usually considered to be dose-dependent reactions.[32]

Idiosyncratic adverse events that occur in patients with the use of AZA or 6MP include nausea, malaise, drug fever, arthralgia, and acute pancreatitis. These occur commonly and require discontinuation of AZA. Discontinuation followed by re-exposure can lead to a septic shock–like syndrome.

Nausea occurs in approximately 12% of patients exposed to thiopurines and is one of the most common reasons that individuals may not tolerate therapy with AZA or 6MP. This adverse event has been reported to occur in 12% of patients in prospective trials. Of patients who did not tolerate AZA, some tolerated 6MP, and vice versa.[33] The frequency of 6MP tolerability in patients with AZA intolerance ranges from 48% to 77%, particularly for those with nausea and vomiting as the limiting adverse event.

Pancreatitis has been reported in approximately 5% of IBD patients treated with thiopurines, typically with an onset within the first month of therapy.[34,35] Asymptomatic increases in serum amylase or lipase after AZA induction are not predictive for AZA-induced acute pancreatitis.[36] Recently, preliminary data suggest a strong association of AZA-induced acute pancreatitis with HLA-DQA1*02:01-HLA-DRB1*07:01. Patients with heterozygous mutation at rs2647087 had a 9% risk of developing thiopurine-induced pancreatitis, whereas patients with homozygous mutations had a 17% risk of acute pancreatitis.[37]

Dose-Dependent Reactions

Dose-dependent adverse effects are also related to genetically determined enzymatic activity of TPMT that directs 6MP metabolism to either 6MMP (high TPMT activity) or 6TGN (low TPMT activity). Hence, the same dose may or may not be tolerated, or be efficacious, because of TPMT enzyme activity. Based on the risk of bone marrow suppression in hematologic indications, measurement of TPMT activity has been recommended before weight-based thiopurine therapy is initiated.[38]

Myelosuppression and severe pancytopenia have been reported in patients with low or intermediate TPMT activity.[38] However, TPMT levels do not predict most myelotoxicity cases, and ongoing hematological monitoring is crucial,[39] because reports indicate that between 50% and 75% of thiopurine-related leukopenia occurs in patients with normal TPMT enzyme activity.[40,41] Measurement of complete blood count at every 1–2 weeks initially and then subsequently at 3-month intervals is suggested to monitor for myelotoxicity.

Hepatotoxicity related to thiopurine antimetabolite use is classically associated with minor, usually transient and asymptomatic, elevations in serum aminotransferase levels during therapy, and in rare situations is associated with acute cholestatic liver injury.[42] Asymptomatic mild dose-related serum aminotransferase elevations can occur during AZA/6MP therapy associated with high functional TPMT activity (increased conversion of 6MP to 6MMP) and often are associated with inadequate concentrations of 6TGN to induce clinical responses. Because thiopurine doses are increased, there is a disproportionate production of 6MMP to 6TGN, typically when high doses are used, especially during the first 12 weeks of therapy.[43] These elevations are generally asymptomatic, resolving rapidly either with cessation of medical therapy or with continuation of medication at a lower dose. ALT elevations during AZA/6MP therapy may be due to a direct toxic effect of the drug; ALT elevations and myelotoxicity have been linked to higher levels of 6MMP.[43]

With long-term use, noncirrhotic portal hypertension as a result of nodular regenerative hyperplasia (NRH) or sinusoidal obstruction syndrome may ensue. The risk of developing NRH is estimated to be approximately 1% at 10 years. The presence of chronic hepatic injury marked by peliosis hepatis, veno-occlusive disease, or nodular regenerative hyperplasia that typically arises is present 0.5 years or longer after starting AZA/6MP. Screening evaluating for thrombocytopenia is suggested and if present screening with ultrasonography or magnetic resonance imaging scanning is appropriate. High 6TGN concentrations have been associated with NRH in up to 62% of cases.[44]

Infection

Thiopurines are considered immunosuppressive, particularly, when associated with myelosuppression. Even in the presence of normal leukocyte counts, there is an increased risk of viral infections, and in the presence of myelosuppression, opportunistic bacterial and fungal infections can occur, particularly in the setting of multiple immune-suppressing therapies (ie, corticosteroids, anti-tumor necrosis factor [TNF] agents, or calcineurin inhibitors).[45] Young women should be encouraged to have cervical cancer screening. Patients should be vaccinated before thiopurine initiation for varicella zoster virus, human papillomavirus, influenza, pneumococcus, and hepatitis B.[46] Live vaccines are contraindicated once immunomodulator therapy has begun; however, zoster vaccination can be given while patients are receiving AZA at less than 2 mg/kg.[47] When AZA and 6MP are used in combination with corticosteroids and biologic therapy, there is a significantly higher infectious complication risk, apparently driven primarily by the corticosteroid use.[45]

Lymphoma is probably the most significant neoplastic concern for thiopurine therapy for IBD. A recent meta-analysis showed that the risk becomes significant after 1 year of exposure.[48] Men have a greater risk than women (standardized incidence ratio, 1.98). Patients younger than 30 years had the highest relative risk (standardized incidence ratio, 7), with younger men having the highest risk (standardized incidence ratio, 9). The absolute risk to any patient younger than 50 years (with the exception of men younger than 30 years) is less than 1 in 2000 per year.

The absolute risk is highest in patients older than 50 years (1:354 cases per patient years; relative risk, 4.78).

Recently, a subtype of lymphoma, hepatosplenic T-cell lymphoma, was described, typically in males under the age of 35 years, which is nearly universally fatal. This disorder has been linked to AZA/6MP monotherapy or in combination with anti-TNF therapy use for a minimum of 2 years, predominantly in young males.[49]

Nonmelanoma skin cancer (NMSC) with thiopurine use, whether current or prior use, in patients with IBD has been associated with a higher risk of nonmelanoma skin cancer, specifically squamous cell and basal cell carcinoma. A recent meta-analysis showed that the risk of developing NMSCs with thiopurine use in IBD patients is nearly 2-fold when only population-based studies were analyzed.[50] Thus, patients using thiopurines for the treatment of IBD, particularly white patients, should avoid excessive sun exposure and use high-strength sun block. Health care deliverers should ensure that patients undergo appropriate dermatologic evaluations and investigate suspicious skin lesions in these patients

Recently, an association between both myelodysplastic syndrome and acute myelogenous leukemia and past exposure to AZA/6MP in patients with IBD has been reported.[51]

Regarding patients with previously diagnosed neoplasia, a recent meta-analysis of 16 studies observed similar rates of cancer recurrence among individuals who received no immunosuppression or subsequent immune-modulator therapy.[42]

Methotrexate

There is far less published experience regarding the safety of MTX used within the standard dose range (subcutaneous or intramuscular, 15–25 mg weekly) for patients with IBD. Up to one third of patients discontinue MTX because of intolerance. Nausea and flu-like symptoms after parenteral administration are common and often can be treated with prophylactic acetaminophen and/or ondansetron.[6] At higher doses, myelotoxicity is possible, and long-term use has been associated with hepatic fibrosis that is more common in obese patients or with alcohol use.[52] Allergic pneumonitis is rare, but cough or shortness of breath should initiate an immediate pulmonary evaluation. MTX is also immunosuppressive and has been associated with viral infections, including herpes zoster.[6] With the use of MTX, it has been shown that there is an elevated risk of NMSC, specifically squamous cell and basal cell carcinoma, especially in those patients with a prior history of NMSC.[53]

Low-dose MTX used in combination with biologic therapies at oral doses of 5–15 mg/week is better tolerated, although patients should still be monitored for complete blood counts and liver enzyme levels at least every 3–6 months.[1]

Risks vs Benefits

It is important to assess risks vs benefits when using thiopurines or MTX. Although the incidence of specific malignancies (lymphoma, skin cancers, and hematologic malignancies) is increased by thiopurines, their absolute number is low. It is important to consider the risk of inadequately treated disease vs the risk of medication use. In addition, immunization for common infections with nonlive vaccines (influenza, pneumococcus, human papillomavirus) is recommended before immunosuppression is initiated. Currently, the Infectious Disease Society of America considers doses the of thiopurines and MTX that are used to treat IBD to be at low levels, which do not preclude inactivated or live vaccines if patients are receiving less than 20 mg of prednisone.[54]

Best Practices

- Thiopurines are modestly efficacious as steroid-sparing maintenance agents for both Crohn's disease and ulcerative colitis. Although weight-based dosing has been used in most clinical trials, clinical responses have been correlated best with 6TG levels. Reduced dosing in combination with allopurinol can improve clinical outcomes for patients who shunt metabolites to 6MMP, and 6TG has been used as a rescue therapy for patients allergic to AZA or 6MP but poses a risk of veno-occlusive disease or nodular regenerative hyperplasia of the liver.
- MTX is modestly efficacious as a steroid-sparing maintenance agent for Crohn's disease; 2 trials have failed to support its use in ulcerative colitis.
- Thiopurines and MTX can be used in combination with anti-TNF biologics, particularly infliximab, to reduce immunogenicity and increase blood levels.
- Combination therapy with thiopurines and anti-TNF biologics is more effective than either thiopurine monotherapy or biologic monotherapy.
- Withdrawal of thiopurines from combination therapy has led to decreased blood levels of infliximab and increased anti-drug antibodies.
- Laboratory monitoring for hematologic and hepatic toxicities are advised for both classes.
- There are increased, but uncommon, risks for lymphomas with thiopurine therapy.
- There are increased risks for NMSCs with thiopurines that require ongoing dermatologic examinations.
- Thiopurines and MTX are associated with an increased risk of viral infections and opportunistic infections.
- Appropriate vaccinations are warranted before initiating and during maintenance with immune-suppressive therapy.

References

1. Coskun M, Steenholdt C, de Boer NK, et al. Pharmacology and optimization of thiopurines and methotrexate in inflammatory bowel disease. Clin Pharmacokinet 2016; 55:257–274.
2. Estevinho MM, Afonso J, Rosa I, et al. A systematic review and meta-analysis of 6-thioguanine nucleotide levels and clinical remission in inflammatory bowel disease. J Crohns Colitis 2017;11:1381–1392.
3. Moreau AC, Paul S, Del Tedesco E, et al. Association between 6-thioguanine nucleotides levels and clinical remission in inflammatory disease: a meta-analysis. Inflamm Bowel Dis 2014;20:464–471.
4. Gilissen LP, Derijks LJ, Driessen A, et al. Toxicity of 6-thioguanine: no hepatotoxicity in a series of IBD patients treated with long-term, low dose 6-thioguanine. Some evidence for dose or metabolite level dependent effects? Dig Liver Dis 2007;39: 156–159.
5. Wall GC, Muktar H, Effken C, et al. Addition of allopurinol for altering thiopurine metabolism to optimize therapy in patients with inflammatory bowel disease. Pharmacotherapy 2018;38:259–270.
6. Herfarth HH, Kappelman MD, Long MD, et al. Use of methotrexate in the treatment of inflammatory bowel diseases. Inflamm Bowel Dis 2016;22:224–233.
7. Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980; 302:981–987.
8. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. Gastroenterology 1979;77:847–869.
9. Chande N, Townsend CM, Parker CE, et al. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2016;10: CD000545.
10. Dassopoulos T, Sultan S, Falck-Ytter YT, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013;145:1464–1478.
11. Panes J, Lopez-Sanroman A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. Gastroenterology 2013;145:766–774.
12. Cosnes J, Bourrier A, Laharie D, et al. Early administration of azathioprine vs conventional management of Crohn's disease: a randomized controlled trial. Gastroenterology 2013;145:758–765.
13. Chande N, Patton PH, Tsoulis DJ, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2015;10: CD000067.
14. Nielsen OH, Coskun M, Steenholdt C, et al. The role and advances of immunomodulator therapy for inflammatory bowel disease. Expert Rev Gastroenterol Hepatol 2015; 9:177–189.
15. Dubinsky MC, Feldman EJ, Abreu MT, et al. Thioguanine: a potential alternate thiopurine for IBD patients allergic to 6-mercaptopurine or azathioprine. Am J Gastroenterol 2003;98:1058–1063.
16. de Boer NK, Reinisch W, Teml A, et al. 6-Thioguanine treatment in inflammatory bowel disease: a critical appraisal by a European 6-TG working party. Digestion 2006;73:25–31.
17. Dassopoulos T, Dubinsky MC, Bentsen JL, et al. Randomised clinical trial: individualised vs. weight-based dosing of azathioprine in Crohn's disease. Aliment Pharmacol Ther 2014;39:163–175.
18. Gordon M, Taylor K, Akobeng AK, et al. Azathioprine and 6-mercaptopurine for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev 2014:CD010233.
19. D'Haens GR, Vermeire S, Van Assche G, et al. Therapy of metronidazole with azathioprine to prevent postoperative

recurrence of Crohn's disease: a controlled randomized trial. Gastroenterology 2008;135:1123–1129.
20. Ardizzone S, Maconi G, Russo A, et al. Randomised, controlled trial, of azathioprine and 5- aminosalicylic acid for treatment of steroid-dependent ulcerative colitis. Gut 2006;55:47–53.
21. Timmer A, Patton PH, Chande N, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2016: CD000478.
22. Feagan BG, Rochon J, Fedorak RN, et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. N Engl J Med 1995; 332:292–297.
23. McDonald JW, Tsoulis DJ, Macdonald JK, et al. Methotrexate for induction of remission in refractory Crohn's disease. Cochrane Database Syst Rev 2012;12: CD003459.
24. Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. N Engl J Med 2000; 342:1627–1632.
25. Carbonnel F, Colombel JF, Filippi J, et al. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. Gastroenterology 2016;150:380–388.
26. Herfarth H, Barnes EL, Valentine JF, et al. Methotrexate is not superior to placebo in maintaining steroid-free response or remission in ulcerative colitis. Gastroenterology 2018;155:1098–1108.
27. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
28. Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2015; 13:2233–2240.
29. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. Gastroenterology 2008;134:1861–1868.
30. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392–400.
31. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology 2014;146:681–688.
32. de Jong DJ, Goullet M, Naber TH. Side effects of azathioprine in patients with Crohn's disease. Eur J Gastroenterol Hepatol 2004;16:207–212.
33. Lees CW, Maan AK, Hansoti B, et al. Tolerability and safety of mercaptopurine in azathioprine-intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther 2008;27:220–227.
34. Candy S, Wright J, Gerber M, et al. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995;37:674–678.
35. Ardizzone S, Maconi G, Sampietro GM, et al. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. Gastroenterology 2004;127:730–740.
36. Teich N, Mohl W, Bokemeyer B, et al. Azathioprine-induced acute pancreatitis in patients with inflammatory bowel diseases—a prospective study on incidence and severity. J Crohns Colitis 2016;10:61–68.
37. Heap GA, Weedon MN, Bewshea CM, et al. HLA-DQA1-HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurine immunosuppressants. Nat Genet 2014;46:1131–1134.
38. Higgs JE, Payne K, Roberts C, et al. Are patients with intermediate TPMT activity at increased risk of myelosuppression when taking thiopurine medications? Pharmacogenomics 2010;11:177–188.
39. Gearry RB, Barclay ML, Burt MJ, et al. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2003;18:395–400.
40. Colombel JF, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000; 118:1025–1030.
41. Ansari A, Patel N, Sanderson J, et al. Low-dose azathioprine or mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2010;31:640–647.
42. Siramolpiwat S, Sakonlaya D. Clinical and histologic features of azathioprine-induced hepatotoxicity. Scand J Gastroenterol 2017;52:876–880.
43. Sparrow MP, Hande SA, Friedman S, et al. Effect of allopurinol on clinical outcomes in inflammatory bowel disease nonresponders to azathioprine or 6-mercaptopurine. Clin Gastroenterol Hepatol 2007; 5:209–214.
44. Musumba CO. Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. Aliment Pharmacol Ther 2013;38:1025–1037.
45. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. Am J Gastroenterol 2012;107:1409–1422.
46. Rahier JF, Ben-Horin S, Chowers Y, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2009;3:47–91.
47. Centers for Disease Control and Prevention. Comprehensive recommendations and guidelines. Updated April 20, 2017, http://www.cdc.gov/vaccines/hcp/acip-recs/recs-comprehensive.html.
48. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel

disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol 2015; 13:847–858.
49. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2011; 9:36–41.
50. Ariyaratnam J, Subramanian V. Association between thiopurine use and nonmelanoma skin cancers in patients with inflammatory bowel disease: a meta-analysis. Am J Gastroenterol 2014;109:163–169.
51. Lopez A, Mounier M, Bouvier AM, et al. Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease. Clin Gastroenterol Hepatol 2014;12:1324–1329.
52. Te HS, Schiano TD, Kuan SF, et al. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol 2000; 95:3150–3156.
53. Scott FI, Mamtani R, Brensinger CM, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol 2016;152:164–172.
54. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014; 58:309–318.

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