# Thiopurines

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| 1971 | AZA-CD | RCT/ AZA vs placebo/ CD/Induction<br>Conclusion:<br>**Azathioprine was not better than placebo to induce improvement in active CD.** |
| 1971 | AZA-CD II | RCT/ AZA vs placebo/ CD/ Maintenance<br>Conclusion:<br>**Azathioprine was more effective than placebo in maintaining remission induced by prednisolone.** |
| 1974 | AZA-UC | Randomized blind crossover trial/ AZA vs placebo /UC/ Induction<br>Conclusion:<br>**In the treatment of an actual attack of UC the addition of azathioprine showed no benefit to a standard course of corticosteroid therapy.** |
| 1974 | AZA-CD | Randomized blind crossover trial/AZA vs placebo / CD/ Induction<br>Conclusion:<br>**This study does not provide evidence to support the effectiveness of AZA in the treatment of CD.** |
| 1979 | Prednisone sulfasalazine AZA | RT/ AZA vs sulfasalazine vs prednisone vs placebo /CD/ Induction<br>Conclusion:<br>**Prednisone & sulfasalazine are better than placebo inducing remission in CD but not azathioprine. Colonic CD was especially responsive to sulfasalazine & small bowel CD to prednisone.** |

# Thiopurines II

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| 1980 | MCP | Randomized double blind crossover/ MCP vs placebo/ CD/Induction<br>Conclusion:<br>**Mercaptopurine was better than placebo inducing clinical remission, reduction of steroids dosage and fistula healing.** |
| 2000 | MCP kids | RCT/ MCP vs placebo/ pediatric CD/ Induction & Maintenance<br>ceboConclusion:<br>**Addition of 6-MP to corticosteroids significantly lessens the need for prednisone and improves maintenance of remission.** |
| 2000 | MCP-MTX 5ASA | RCT/ MCP vs MTX vs 5ASA / IBD / Induction<br>Conclusion:<br>**These results suggest that 6-MP or MTX added to prednisone could be effective in steroid sparing, as well as in achieving and maintaining remission in steroid-dependent IBD patients.** |
| 2004 | MCP/5ASA postop | RCT /MCP vs 5ASA vs placebo / post surgery CD/Disease recurrence<br>Conclusion:<br>**MCP was more effective than placebo at preventing postoperative recurrence but not 5ASA. MCP should be considered as a maintenance therapy after ileocolic resection.** |
| 2004 | 5ASA/ AZA postop | Open label, RCT/ AZA vs 5ASA /post surgery CD/ Disease recurrence<br>Conclusion:<br>**While no difference was observed in the efficacy of AZA and 5ASA in preventing recurrence after surgery, AZA is more effective in patients who have undergone previous intestinal resection** |

# Thiopurines III

**2006 — AZA vs 5ASA**

RCT/ AZA vs 5ASA/ steroid dependent UC / Induction & Maintenance
Conclusion:
**Azathioprine is significantly more effective than 5-aminosalicylic acid in inducing clinical and endoscopic remission and avoiding steroid requirement in the treatment of steroid dependent ulcerative colitis.**

**2008 — SUTD**

Open randomized trial/ IFX+AZA vs conventional (steroids)/ New CD/ Induction remission
Conclusion:
**Combined therapy more effective than conventional for induction and reduction of steroid use in recently diagnosed CD.**

**2008 — METRO +/- AZA**

RCT/Metronidazol 3 months +/- AZA for 12 months / post surgery CD/ Disease recurrence
Conclusion:
**Concomitant AZA resulted in lower endoscopic recurrence rates and less severe recurrences 12 months post-surgery.**

**2010 — 5ASA/AZA**

RCT/ AZA vs 5ASA/ post surgery CD/ Disease recurrence
Conclusion:
**In this population of patients with postoperative CD at high risk of clinical recurrence, superiority for azathioprine versus mesalazine could not be demonstrated for therapeutic failure.**

**2012 — STORI**

Prospective cohort/ stop IFX in CD in remission & maintenance on AZA/ Relapse
Conclusion:
**Aprox 50% of patients with CD treated for a year with IFX+AZA relapsed within 1 year after discontinuation.**

# Thiopurines IV

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| 2013 | AZTEC | Prospective cohort/ stop IFX in CD in remission & maintenance on AZA/ Relapse<br>Conclusion:<br>**Early AZ was no more effective than placebo to achieve sustained corticosteroid free remission but was more effective in preventing moderate to severe relapse in a post hoc analysis.** |
| 2013 | AZA/METRO | RCT/ AZA vs AZA+Metronidazol/ post surgery CD/ Disease recurrence<br>Conclusion:<br>**The addition of metronidazole to azathioprine did not significantly reduce the risk of endoscopic recurrence beyond azathioprine alone in this study but does not worsen its safety profile** |
| 2013 | AZA vs IFX | Open label RT/ IFX vs AZA / post surgery CD/ Disease recurrence<br>Conclusion:<br>**Infliximab was more effective than azathioprine in reducing histological, but not endoscopic and clinical recurrence after curative ileocolonic resection in “high risk” CD patients.** |
| 2013 | ADA/AZA/ 5ASA | RCT/AZA vs ADA vs 5ASA / post surgery CD/ Disease recurrence<br>Conclusion:<br>**The administration of ADA after intestinal resective surgery was greatly effective in preventing endoscopic and clinical recurrence of CD.** |
| 2014 | UC-SUCCESS | RCT/AZA vs IFX vs AZA+IFX / UC/ Induction<br>Conclusion:<br>**IFX+AZA combotherapy superior to IFX or AZA alone achieving steroid free remission w16.** |

# Thiopurines V

**2015 — REACT**

RCT/ Early ADA+AZA vs conventional (steroids+/- thiopurine or ADA if no remission w12)CD/ Maintenance
Conclusion:
**Lower risk of major adverse outcomes in early combined immunosuppresion in CD vs conventional treatment. However, no differences in remission rates at 12 months.**

**2016 — TOPPIC**

RCT/MCP vs placebo / post surgery CD/ Disease recurrence
Conclusion:
**MCP is effective in preventing postoperative clinical recurrence of CD, but only in patients who are smokers.**

**2016 — DIAMOND**

Open Label RCT/ ADA vs ADA+AZA / CD / Efficacy & safety
Conclusion:
**Clinical efficacy of ADA+AZA did not differ from ADA monotherapy in CD naïve to both medications.**

**2017 — APPRECIA**

RCT/ AZA vs ADA/ post surgery CD/ Disease recurrence
Conclusion:
**ADA has not demonstrated a better efficacy than AZA [both associated with metronidazole] for prophylaxis of POR-CD in an unselected population.**

**2019 — DIAMOND 2**

Open label RCT/ ADA vs ADA+AZA / CD/ Maintenance
Conclusion:
**Continuation of thiopurines > 6 months offers no clear benefit over scheduled ADA monotherapy.**

# Thiopurines VI

**2020 — AZA to ADAb**

OL RCT/ Previous antiTNF immunogenicity randomized: AZA+antiTNF vs antiTNF / IBD / Maintenance
Conclusion:
**In case of immune-mediated LOR to a first anti-TNF, AZA should be associated with the second anti-TNF.**

**2020 — PIANO**

Observational/Biologics and thiopurine/ pregnant IBD/ Safety
Conclusion:
**Biologic, thiopurine, or combination therapy exposure during pregnancy was not associated with increased adverse maternal or fetal outcomes at birth or within the first year of life.**

**2021 — STRIDENT**

Open-label RCT/ADA high dose+AZA vs ADA standard / Stricturing CD/ Induction
Conclusion:
**Treat to target intensification resulted in less treatment failure, reduction in stricture-inflammation, and improvement in stricture morphology, but these differences were not different from standard therapy.**

**2022 — AAUC**

Open label RCT/ Low dose AZA+allopurinol (ALLO)vs AZA standard / UC / Maintenance
Conclusion:
**L-AZA/ALLO therapy was associated with a beneficial effect on steroid and infliximab-free clinical remission in patients with moderate-to-severe UC.**

**2023 — SPARE**

OL RCT/antiTNF or AZA withdrawal/ CD
Conclusion:
**IFX withdrawal should only be considered after careful assessment of risks/benefits, whereas withdrawal of immunosuppressant therapy could generally be preferable when considering de-escalation.**

# Thiopurines VII

2023

MCP-UC

RCT/MCP vs placebo/ UC /Maintenance

Conclusion:

**Mercaptopurine was superior to placebo in achieving clinical, endoscopic and histological outcomes at 1 year in UC patients.**