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COVID-19 and implications for thiopurine use

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Thiopurines are used in oncology, immunology and inflammatory bowel disease (IBD). In the COVID-19 pandemic, patients taking thiopurines face uncertainty as to the risk of serious complications or death if infected.

Traditionally, thiopurine use has been associated with an increased risk of opportunistic viral infections.[1,2,3] A large IBD registry study found that thiopurines and active disease were associated risk of serious viral infection.[3] However, all identified causative agents were species of the *Herpesviridae* genus.[12,3] The risk associated with thiopurine use can therefore not yet be generalised to other virus genera and indeed only corticosteroid use is associated with risk of contracting influenza in IBD.[4]

COVID-19 is a novel coronavirus and there are no available data from previous coronavirus strains such as SARS-CoV or MERS-CoV to allow for estimation of risk in patients on thiopurines.[3, 5] Although intuitively immunosuppression with thiopurines may increase the risk from COVID-19, there are in vitro and in silico data to suggest that thiopurines constrain maturation of MERS-CoV via inhibition of a viral protease.[5] Although this study has not been replicated for COVID-19 or progressed into animal models, it does raise the possibility that thiopurines use may not necessarily increase COVID-19 risk.

Thiopurine withdrawal is associated with a 12 month relapse rate of 17-53% in Crohn's disease and 11-77% in ulcerative colitis.[6] This is an important consideration during COVID-19 as disease relapse requiring steroid use has previously been associated with increased risk of viral complications.[3, 4] The consequences of thiopurine withdrawal due to COVID-19 are not yet clear and this information is eagerly awaited as many centres collect prospective data.

Preliminary data from SECURE-IBD, a COVID-19 database for IBD, report 67 cases to date in patients on thiopurines, 39 of whom were managed as outpatients and 28 of whom were hospitalised, with one reported death.[7] These evolving data provide cautious support for the relative safety of thiopurines but cannot be interpreted conclusively in the setting of the rapidly evolving situation.

Perhaps the best advice we can currently offer patients is that effective control of disease may carry less risk than poorly considered withdrawal of therapy. The Gastroenterological Society of Australia has issued recommendations that the minimum level of immunosuppression should be continued to control disease although a drug holiday may be considered in some patients with long term stable disease.[8] This dilemma highlights the importance of online registries to gather vital data as we work together as a profession to provide evidence based advice for our patients during this pandemic.

References

1. Kirchgesner J, Lemaitre M, Carrat F et al. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018;155:337-346.
2. Toruner M, Loftus EV, Jr., Harmsen WS, et al. Risk Factors for Opportunistic Infections in Patients With Inflammatory Bowel Disease. *Gastroenterology* 2008;134:929-936.
3. Wisniewski A, Kirchgesner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterol. J* 2019; 8 :303-313.
4. Tinsley A, Navabi S, Williams ED, et al. Increased Risk of Influenza and Influenza-Related Complications Among 140,480 Patients With Inflammatory Bowel Disease. *Inflamm. Bowel Dis* 2018;25:369-376.
5. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res* 2015;115:9-16.
6. Torres J, Boyapati RK, Kennedy NA, et al. Systematic Review of Effects of Withdrawal of Immunomodulators or Biologic Agents From Patients With Inflammatory Bowel Disease. *Gastroenterology* 2015;149:1716-1730.
7. Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion [Internet]. 2020 https://covidibd.org/. (accessed April 2020)
8. Principles for Clinicians caring for Patients with IBD during the COVID-19 pandemic 2020. https://www.gesa.org.au/public/13/files/COVID-19/GESA_IBD_Clinician_Recommendations_ COVID19_26032020_FINAL.pdf.(accessed April 2020)