

## COVID-19 and implications for thiopurine use

TO THE EDITOR: Thiopurines are used in oncology, immunology and inflammatory bowel disease (IBD). In the coronavirus disease 2019 (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.<sup>1-3</sup> A large IBD registry study found that using thiopurines and having active disease were associated with a higher risk of serious viral infection.<sup>3</sup> However, all identified causative agents were species of the *Herpesviridae* genus.<sup>1-3</sup> 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 patients with IBD.<sup>4</sup>

COVID-19 is caused by a novel coronavirus — the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — and there are no available data from previous coronavirus strains such as SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) to allow for

estimation of risk in patients taking thiopurines.<sup>3,5</sup> 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.<sup>5</sup> 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 the risk of contracting COVID-19.

Thiopurine withdrawal is associated with a 12-month relapse rate of 17–53% in patients with Crohn's disease and 11–77% in patients with ulcerative colitis.<sup>6</sup> This is an important consideration in COVID-19, as disease relapse requiring steroid use has previously been associated with increased risk of viral complications.<sup>3,4</sup> 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 87 COVID-19 cases to date in patients taking thiopurines, of whom 52 were managed as outpatients and 35 were admitted to hospital, with two reported deaths.<sup>7</sup> 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.<sup>8</sup> 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.

Thomas M Goodsall<sup>1,2</sup>  
Samuel P Costello<sup>1,2</sup>  
Robert V Bryant<sup>1,2</sup>

<sup>1</sup> Queen Elizabeth Hospital, Adelaide, SA.

<sup>2</sup> University of Adelaide, Adelaide, SA.

thomas.goodsall@sa.gov.au

**Competing interests:** No relevant disclosures. ■

The unedited version of this article was published as a preprint on [mja.com.au](https://mja.com.au) on 30 April 2020.

doi: [10.5694/mja2.50613](https://doi.org/10.5694/mja2.50613)

© 2020 AMPCo Pty Ltd

References are available online.

- 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, 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 Eur 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 Brenner EJ, Ungaro RC, Colombel JF, Kappelman MD. SECURE-IBD Database public data update (5 May 2020) [website]. SECURE-IBD, 2020. <https://covidibd.org/current-data/> (viewed May 2020).
- 8 Gastroenterological Society of Australia. Principles for clinicians caring for patients with IBD during the COVID-19 pandemic. Melbourne: GESA, 2020. [https://www.gesa.org.au/public/13/files/COVID-19/GESA\\_IBD\\_Clinician\\_Recommendations\\_%20COVID19\\_26032020\\_FINAL.pdf](https://www.gesa.org.au/public/13/files/COVID-19/GESA_IBD_Clinician_Recommendations_%20COVID19_26032020_FINAL.pdf) (viewed Apr 2020). ■