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# Temporal Trends in Biologic Prescriptions for Patient with Inflammatory Bowel Disease: A Retrospective Cohort Study

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**Abstract: Background:** Biologic therapies, such antitumour necrosis factor-alpha agents (infliximab and adalimumab), as well as newer agents (ustekinumab and vedolizumab), all have well-demonstrated safety and efficacy profiles in the management of inflammatory bowel disease (IBD). The choice of an optimal first-line biologic remains unclear due to a lack of comparative randomised trials and real-world studies; however, certain patient and disease characteristics may influence this choice. The aims of this study were to explore temporal trends in the choice of a first-line biologic therapy and the factors that influence this choice. **Methodology:** This study is a retrospective observational cohort study of all patients with IBD who commenced induction and completed at least one maintenance dose of a biologic therapy between 1 January 2015 and 31 December 2021. Relevant patient and disease-specific factors were collected, including history of malignancy and opportunistic infections at time of diagnosis, for each eligible patient. Factors affecting the choice of biologic therapy were compared using ANOVA and chi-square tests. **Results:** 280 patients were included in the study. Ustekinumab has overtaken infliximab and adalimumab as the first-line choice for Crohn's disease since its introduction in 2018. Infliximab has remained the preferred first-line therapy for ulcerative colitis over adalimumab and vedolizumab. Ustekinumab has become he preferred biologic agent for older patients and those with a history of malignancy. **Conclusions:** Whilst an older agent such as infliximab is still preferred for the management of UC, novel agents such as ustekinumab are now more readily considered as a first-line agent for the management of CD.

**Keywords:** biologic therapies; biologic therapy sequencing; ulcerative colitis; Crohn's disease; inflammatory bowel disease



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## 1. Introduction

Inflammatory bowel disease (IBD) is a condition characterised by inflammation of the gastrointestinal system, typically manifesting in relapsing and remitting abdominal pain, weight loss, diarrhoea, and rectal bleeding [1]. The pathological and clinical features of IBD are broadly classified as either ulcerative colitis (UC) or Crohn's disease (CD). Whilst the exact etiopathogenesis of IBD remains unknown, it is understood that immune dysregulation, genetic susceptibility, environmental exposures, diet, and perturbations of the intestinal microbiome are key to disease development [2,3].

The introduction and expansion of biologic therapies over the past two decades have been crucial for early and long-term management of IBD. Our arsenal of biologic therapies has grown to comprise antitumour necrosis factor-alpha (anti-TNF-α) agents, which include infliximab, certolizumab, golimumab, and adalimumab; the anti-integrin inhibitor vedolizumab; and ustekinumab, which targets interleukin-12/23 [4,5]. Janus

kinase (JAK) inhibitors, which are orally prescribed, have also recently been demonstrated to be efficacious and approved for the management of UC [6].

Anti-TNF-α agents continue to be the most frequently commenced first-line biologic therapy for IBD, with a plethora of evidence demonstrating their efficacy for the management of both UC and CD [7]. However, there are multiple drawbacks to the use of anti-TNF-α agents, including high rates of non-response to initial treatment [8], a significant proportion of secondary non-responders over time [9], and increased risk of malignancy and infectious disease in susceptible patients [10]. There is a growing body of evidence that the newer biologic medications, including vedolizumab, ustekinumab, and the oral small molecule therapies, are as efficacious in disease suppression as anti-TNF-α agents whilst demonstrating a more favourable safety profile. Consequently, gastroenterologists are more willing to trial these medications as first-line therapies for the management of IBD [10]. The aim of our study is to establish the rates and choice of first-line biologic therapies being commenced and explore patient and disease factors that influence this choice.

## 2. Methods

This study is a retrospective observational cohort study of all patients who had a new or an established endoscopy and histopathology-proven diagnosis of CD or UC and received at least one dose of biologic therapy at Royal Perth Hospital (RPH), a tertiary hospital in Western Australia, between 2015 and 2021. All patient data were extracted from iSOFT and WEBPAS, two Department of Health Medical records applications currently in use at RPH. For each eligible patient, data were extracted regarding IBD subtype (CD or UC), age of diagnosis, year of diagnosis, sex, first-line biologic therapy, date of first-line therapy commencement, second-line biologic therapy, date of second-line therapy commencement, concomitant IBD medications, Montreal score, cigarette smoking at time of diagnosis, and comorbid diseases at time of diagnosis. Any patient who had been commenced on biologic therapy prior to 2015 or were diagnosed with unclassified IBD were excluded. The Montreal classification was primarily included to clarify the anatomical location of disease burden; therefore, it was simplified as L1–L3 +/− perianal involvement for CD and E1–E3 for UC. Patients with solely upper gastrointestinal CD ('L4') were excluded.

Cigarette smoking was defined as active smoking at time of first biologic therapy dose. Information regarding extent of cigarette smoking (i.e., number of cigarettes smoked per day), history of smoking (i.e., pack years smoked), and incidence of cessation during the period of biologic therapy administration or at the time of 2nd-line biologic therapy commencement was not taken into consideration. In confirming medical comorbidities, we included a lifetime look-back period if relevant (e.g., a lifetime incidence of cancers). Information regarding a history of ischaemic heart disease (IHD), malignancy, and opportunistic infection risk at time of first biologic therapy dose was extracted for each eligible patient. The comorbidity of IHD was defined as at least one episode of acute coronary syndrome or evidence of coronary artery disease. A history of malignancy included both haematological malignancy and solid tumour cancers (including skin cancers). Opportunistic infection risk accounted for any previous infection of varicella zoster virus, hepatitis B virus, hepatitis C virus, Epstein–Barr virus, human immunodeficiency virus, herpes simplex virus, and tuberculosis (mycobacterium tuberculosis complex) prior to commencement of biologic therapy. Five different biologic therapies were included for the study: infliximab/Remicade®, adalimumab/Humira®, vedolizumab/Entyvio™, and ustekinumab/Stelara®. Intravenous biologic therapies were either administered in an inpatient ward setting or IBD infusion clinic.

Adalimumab, infliximab, ustekinumab, and vedolizumab are Australian government Pharmaceutical Benefits Scheme (PBS)-subsidised treatments under the National Health Act 1953, section 85 and section 100, for adult patients with CD. Adalimumab, infliximab, tofacitinib, and vedolizumab are Australian government Pharmaceutical Benefits Scheme-subsidised treatments under the National Health Act 1953, section 85 and section 100, for adult patients with UC. Ustekinumab had not been approved for UC at time of study.

### 2.1. Statistical Analysis

All temporal data (e.g., date of IBD diagnosis and date of 1st-line biologic commencement) were expressed per year. Active cigarette smoking and the presence of a comorbidity (i.e., history of IHD, malignancy, and opportunistic disease infection) at time of 1st-line biologic therapy commencement was expressed as either 'Yes' or 'No'. As noted earlier, location of disease was denotated as a simplified version of the Montreal score. Univariate analysis using $\chi 2$ for categorical variables and the independent *t*-test for continuous variables was conducted using Stata (StataCorp Stata Statistical Software: Release 15) with $p$-value $< 0.05$ considered significant.

### 2.2. Ethical Approval

Approval was obtained via a Governance, Evidence, Knowledge, Outcomes (GEKO) ethics quality improvement initiative as per Department of Health (DOH), Government of Western Australia.

## 3. Results

A total of 280 patients met the study inclusion criteria for primary analysis; their background characteristics are summarised in Table 1. The mean age of (IBD) diagnosis was 29 years (interquartile range, 21–41), with the mean age of first-line biologic therapy commencement being 36 years. Smoking was noted in 10.36% of the patient population at the time of the first biologic commencement. However, there were incomplete data regarding ongoing smoking habits; thus, this parameter was excluded from data analysis. The percentage of patients with a prior medical history of malignancy, opportunistic infection, or ischaemic heart disease was 5.0%, 7.86%, and 3.93%, respectively.

There was a general increase in the number of patients commencing first-line biologic therapies between 2015 and 2021 (Figure 1), with an average annual increase of 23.27%.

The disease- and patient-related factors that may affect first-line biologic choice are summarised in Table 2. There was a significant difference in first-line agent used based on age. Patients commenced on ustekinumab had a higher median age (53 years) as compared with those commenced on vedolizumab, adalimumab, or infliximab (39, 35, and 34 years, respectively). Likewise, ustekinumab was more likely to be commenced for patients with a history of malignancy.

With regards to IBD subtype, adalimumab was used significantly more for CD over UC (90.54% vs. 9.46%, respectively). A larger, albeit statistically non-significant, proportion of patients with CD who were commenced on first-line adalimumab therapy had perianal disease (17.57%) compared to patients commenced on infliximab (12.77%), vedolizumab (7.14%), and ustekinumab (8.7%).

Whilst only representing 15% of the initial biologic therapy choices, vedolizumab was particularly selected for the management of UC (i.e., 73.81% of patients). Additionally, vedolizumab was disproportionately used for colonic (Montreal L2) and ileocolonic (Montreal L3) CD (40% and 50% of patients, respectively).

**Table 1.** Total eligible patient population demographics and characteristics (n = 280).

| | |
|---|---|
| Age of IBD diagnosis, in years (interquartile range [IQR]) | 29 (21–41) |
| Age of 1st-line biologic therapy commencement, in years (IQR) | 36 (26–50) |
| Sex, male (% of total population) | 142 (50.71%) |
| Total number of patients with Crohn's disease (% of total population) | 168 (60%) |
| Crohn's disease subtypes (% of patients with Crohn's disease) | |
| Montreal L1 | 68 (40.48%) |
| Montreal L2 | 33 (19.64%) |
| Montreal L3 | 63 (37.5%) |
| Montreal L4 | 4 (5.88%) |
| Perianal disease (B1-3p) | 36 (21.43%) |
| Total number of patients with ulcerative colitis (% of total population) | 112 (40%) |
| Ulcerative colitis subtypes (% of patients with ulcerative colitis) | |
| Montreal E1 | 3 (2.68%) |
| Montreal E2 | 42 (37.5%) |
| Montreal E3 | 67 (59.82%) |
| Comorbidities (% percentage of total population) | |
| IHD | 11 (3.93%) |
| Malignancy | 14 (5.0%) |
| Opportunistic infections (including latent TB) | 22 (7.86%) |
| Smoking (active) | 29 (10.36%) *1 |

*1 Based on incomplete data.

**Table 2.** Factors affecting individual choice in biologic therapy.

| | **Infliximab N = 141 (50.36%)** | **Adalimumab N = 74 (26.43%)** | **Vedolizumab N = 42 (15.0%)** | **Ustekinumab N = 23 (8.21%)** | ***p*-Value** |
|---|---|---|---|---|---|
| Age (years, IQR) | 34 (24–47) | 35 (26–49) | 39 (30–50) | 53 (38–67) | <0.01 |
| Sex (male, %) | 64 (45.39%) | 42 (56.76%) | 23 (54.76%) | 13 (56.52%) | 0.35 |
| IBD subtype | | | | | |
| Crohn's | 67 (47.12%) | 67 (90.54%) | 10 (23.81%) | 23 (100%) | <0.01 |
| UC | 74 (52.48%) | 7 (9.46%) | 31 (73.81%) | 0 * | <0.01 |
| Crohn's | | | | | |
| L1 | 21/67 (31.34%) | 35/67 (52.24%) | 1/10 (10%) | 11/23 (47.82%) | 0.01 |
| L2 | 19/67 (28.36%) | 7/67 (10.45%) | 4/10 (40%) | 3/23 (13.04%) | 0.02 |
| L3 | 26/67 (38.81%) | 23/67 (34.33%) | 5/10 (50%) | 8/23 (34.78%) | 0.78 |
| L4 | 1/67 (1.49%) | 2/67 (2.99%) | 0/10 (0%) | 1/23 (4.35%) | 0.81 |
| Ulcerative colitis | | | | | |
| E1 | 1/74 (5.88%) | 1/7 (14.39%) | 1/32 (3.13%) | 0 * | 0.12 |
| E2 | 29/74 (39.19%) | 3/7 (42.86%) | 10/32 (31.25%) | 0 * | 0.70 |
| E3 | 44/74 (59.45%) | 3/7 (42.86%) | 21/32 (66.63%) | 0 * | 0.53 |
| Perianal | 18 (12.77%) | 13 (17.57%) | 3 (7.14%) | 2 (8.70%) | 0.39 |
| Comorbidities | | | | | |
| IHD | 3 (2.13%) | 5 (6.76%) | 1 (2.38%) | 2 (8.70%) | 0.64 |
| Malignancy | 5 (3.55%) | 3 (4.05%) | 1 (2.38%) | 5 (21.74%) | <0.01 |
| Opportunistic infections | 10 (7.09%) | 8 (10.81%) | 2 (4.76%) | 2 (8.70%) | 0.66 |
| Smoking | 10 (7.09%) | 10 (13.51%) | 2 (4.76%) | 7 (31.43%) | <0.01 ** |

* Ustekinumab was approved for use in UC at time of study. ** Based on statistical analysis of incomplete data.

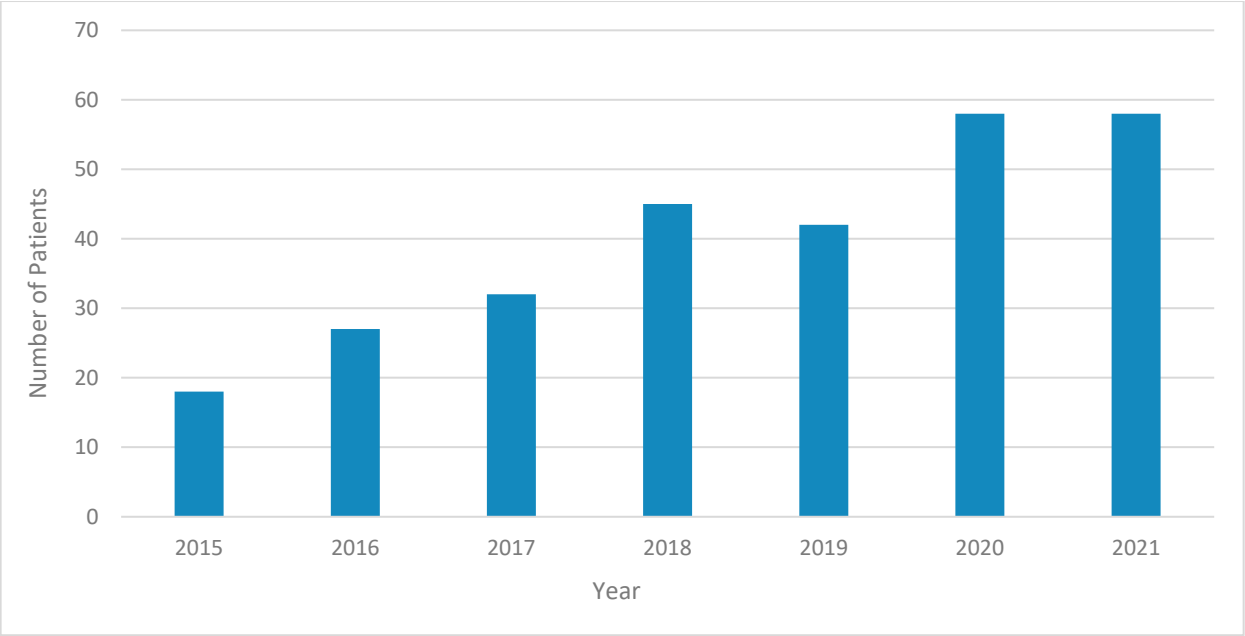


**Figure 1.** Number of patients commencing 1st-line biologic therapy from 2015 to 2021.

Figure 2 demonstrates the temporal trends in the choice of first-line biologic therapy for CD between 2015 and 2021. In 2015, infliximab represented over half (56%) of all biologic therapies chosen, followed by adalimumab (33%) and vedolizumab (11%). Ustekinumab overtook both infliximab and adalimumab as the preferred first-line therapy in 2015.

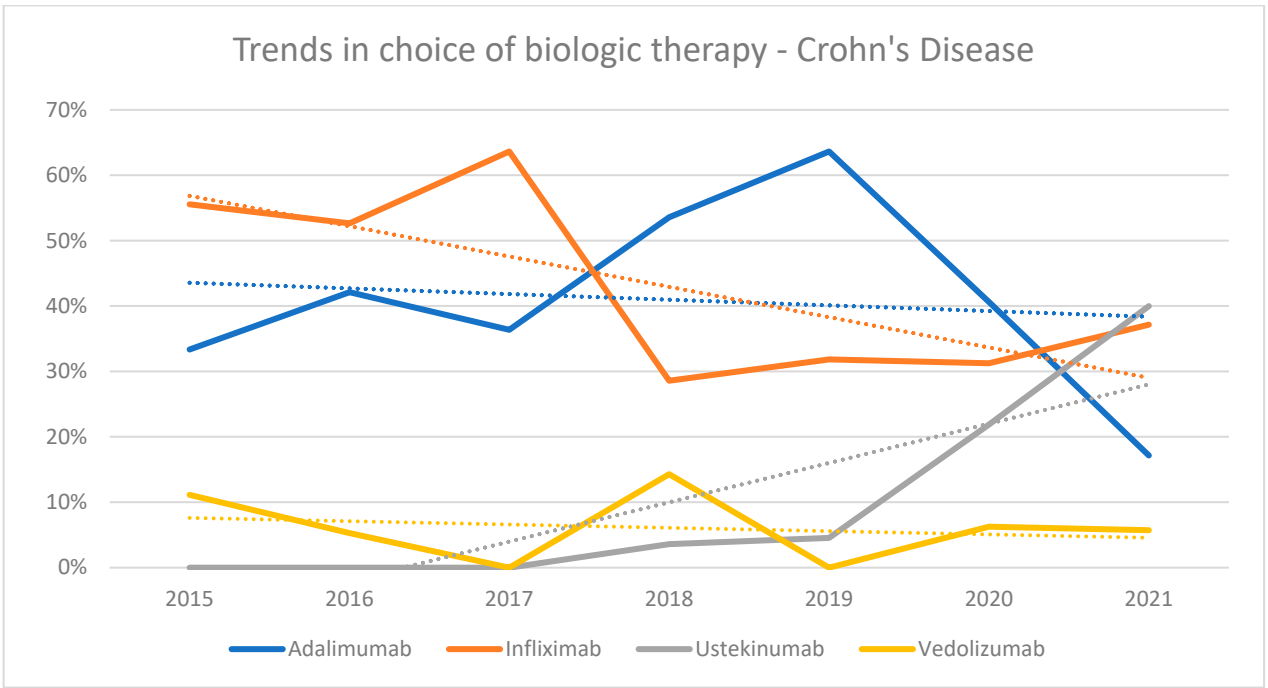


**Figure 2.** Change in choice of 1st-line biologic therapy for CD between 2015 and 2021. The dotted lines represent the trend line in use of each biologic therapy.

Figure 3 demonstrates that there has been minimal change in the trends of first-line biologic therapies used for UC between 2015 and 2021. Infliximab continues to be the most popular choice for first-line biologic therapy for UC.

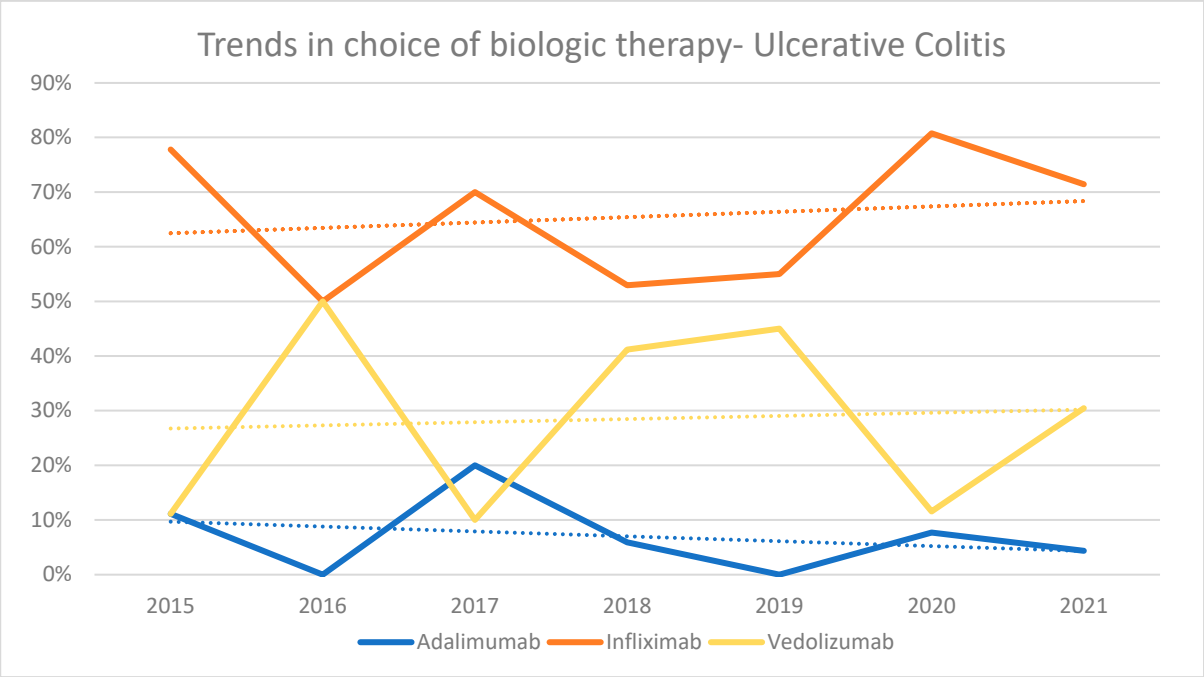


**Figure 3.** Change in choice of 1st-line biologic therapy for UC between 2015 and 2021. The dotted lines represent the trend line in use of each biologic therapy.

## 4. Discussion

In the present study, we report a general rise in the number of patients commencing biologic therapy for IBD, with an average increase 23.27% per year, analogous to increases seen across the developed world over the last two decades [11–13]. Given the increasing number of biologic therapies available, the choice of first-line biologic and sequencing of medications has become an important consideration in the management of IBD. We demonstrated that ustekinumab has overtaken other biologic therapies as the preferred first-line treatment for Crohn's disease (CD). Ustekinumab, a human monoclonal antibody which inhibits the p40 subunit of interleukins (IL)-12 and IL-23 [14], has demonstrated clinical efficacy in the treatment of CD, with no significant safety signals regarding serious adverse effects, malignancy, or serious infections [15–22]. With regard to clinical efficacy, direct head-to-head randomised controlled trials remain limited. One recently published multicentre, randomised, controlled trial (SEAVUE) compared the efficacy of adalimumab and ustekinumab in CD [23]. There was no difference in the primary endpoint of clinical remission. Ustekinumab, however, was noted to have a more favourable safety profile and higher rates of persistence. Moreover, a network meta-analysis by Singh et al. (2021) [24] of biologic therapies in moderate-to-severe CD demonstrated that infliximab, adalimumab, and ustekinumab were equally effective at inducing remission as a first-line biologic agent, while adalimumab (after the loss of response to infliximab) and risankizumab, an IL-23a modulator, can reliably induce clinical remission as second-line agents. No difference in efficacy between biologic agents was demonstrated for maintenance trials. Ko et al. [25] demonstrated that ustekinumab had the greatest medication persistence rate at 12 months (80%) compared to adalimumab (64.2%), infliximab (68.1%), and vedolizumab (73.5%) in their retrospective analysis based on 2499 Australian patients. A favourable safety profile, expedited mechanism of action, low immunogenicity, and medication persistence is why ustekinumab is increasingly being chosen as a first-line agent for CD.

In our cohort, infliximab remained the most utilised first-line biologic therapy for treatment of ulcerative colitis (UC) over the course of the study's duration. Infliximab was the first approved biologic therapy with a fast onset of action and demonstrated efficacy

for UC [26]. It is also the only approved biologic therapy for acute severe UC [27]. A network meta-analysis by Singh et al. (2020) [28] demonstrated infliximab to be the highest-ranked biologic therapy in regard to induction of remission and endoscopic improvement in patients with moderate-to-severe UC. Further, the VARSITY trial (2019) [29], the only head-to-head randomised controlled trial comparing vedolizumab and adalimumab for UC, showed that vedolizumab was superior to adalimumab for achievement of clinical remission and endoscopic improvement. This corresponds to our data demonstrating higher use of vedolizumab as compared with adalimumab. Finally, novel small-molecule therapies such as tofacitinib and upadacitinab have established fast onset of action and clinical efficacy; thus, they may play a role as alternate first-line therapies for UC [30].

The choice of first-line therapy is not only dependant on efficacy. We explored patient- and disease-related factors that may impact choice. We found that a higher proportion of patients commenced on ustekinumab had a history of malignancy as compared to those commenced on other agents. There is a putative risk that the biologic therapy-mediated suppression of immunoregulatory cytokines may allow for de novo or recurrence of carcinogenesis and tumour spread [31]. There is inconclusive evidence whether anti-TNF-α agents increase cancer risk and recurrence [32]; whilst a handful of studies have demonstrated an increase in the incidence of melanoma and lymphoma in patients on anti-TNF-α therapy (adalimumab or Infliximab) [33,34], larger registry studies, including the TREAT [35], PYRAMID [36], and Danish national registry analysis [37], have failed to identify an increase in the incidence of malignancy, including lymphoma and melanoma, after 5 years of follow-up. Pooled analysis from registry clinical trials demonstrated no difference in the incidence of de novo malignancy in patients on ustekinumab compared to those in a placebo/control group after 1-year follow-up [38], whereas more recent retrospective real-world analyses by Hong et al. (2022) [39] and Hasan et al. (2022) [40] have noted an increased risk of malignancy with ustekinumab. Moreover, Vedamurthy et al. (2022) [41] elucidated that vedolizumab, an α4β7 integrin modulator which supresses lymphocyte trafficking and T-cell migration, does not augment the risk of new or recurrent cancer in patients with a prior history of malignancy, thus paving its way as an alternative agent for this unique population group.

Older patients present a unique challenge in the management of IBD. Advanced age is associated with a greater number of cardiovascular comorbidities, age-related impairments in metabolic and immune function, frailty, and a higher risk of malignancy. Furthermore, advanced age may influence the pharmacokinetic and pharmacodynamic properties of a therapy in terms of absorption, distribution, and excretion in comparison to the typical young adult population [42]. Our data demonstrated that, on average, patients on ustekinumab were significantly older than patients on infliximab, adalimumab, and vedolizumab (see Table 2), with an average age of 53 years old (IQR, 38–67 years old). It is likely that the choice of ustekinumab over its primary competitor, the anti-TNF-α agents, as the first-line therapy for CD is owing to the accumulation of data demonstrating a less-favourable safety and efficacy profile of anti-TNF-α agents in older patients. This includes an increased risk of severe infections [43]; reduced clinical response [44]; lower steroid-free, clinical disease remission rate [45]; and greater likelihood of biologic therapy discontinuation at 12 months [46] compared to their younger counterparts. Indeed, a meta-analysis of six sizeable retrospective studies investigating the safety of anti-TNF-α agents calculated that older patients experienced a 3.48-fold higher risk of infection than their younger counterparts and were 11.22-fold more likely to develop an infection than their equivalent-aged patients not on biologic therapy [42]. Consequently, ustekinumab is the preferred biologic therapy for older patients given that the current data, although limited in quantity, elucidate a favourable safety and efficacy profile in this particular

patient population [47–49]. For instance, the ENEIDA Registry trial [48] observed that elderly patients had a similar steroid-free remission rate with ustekinumab compared to their younger counterparts at 1-year follow-up, with no difference in adverse effects or severe infections. Likewise, Garg et al. (2021) [49] demonstrated that elderly patients on ustekinumab had equivalent clinical outcomes, mucosal healing, adverse effects, and infusion reactions compared to their younger counterparts.

This was a large retrospective observational cohort study and one the first studies in Australia to plot the changes in the choice of biologic therapy at a large IBD speciality centre. There is some general consensus between the gastroenterology specialists at our institution regarding their choice in first-line therapy, guided by evidence-based recommendations by organisations such as the Gastroenterological Society of Australia (GESA), as well as by clinical gestalt. A major limitation of our study is its failure to elucidate the rationale behind the choice in biologic therapy by the gastroenterologists for each specific patient, whether it be related to the location or extent of their disease or relevant medical history/risk factors. Thus, we can only infer and extrapolate, based on available research, the rationale for a specific choice in biologic therapies by the gastroenterologist; ultimately, we cannot clearly determine their true reasoning.

## 5. Conclusions

The surge in the prevalence of IBD in the developed world over the recent decades, hand in hand with the rise in the number of biologic agents available, has emphasised the salience of medication sequencing in disease management. With IBD observed in such a heterogenous patient population with a myriad of comorbidities, further research is required to illuminate which biologic agents are favourable for each unique and niche patient population group. Our study illuminates the temporal trends in biologic therapies of a large, diverse patient population, providing some insight into the changing tides in choice and preference of biologic agents in the real world.

**Author Contributions:** S.F.: data collection, data analysis, and planning and writing manuscript. R.A.-R.: drafting/revision of the manuscript for content. S.M.: drafting/revision of the manuscript for content. K.S.: drafting/revision of the manuscript for content. K.V.: drafting/revision of the manuscript for content. S.P.: data analysis, co-ordinating, planning and writing manuscript, and drafting/revision of the manuscript for content. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding authors: Sunimal Fernando, Reeham Abu-Rgeef, Shankar Menon, Kenji So, Kannan Venugopal, and Sherman Picardo. The data are not publicly available due to restrictions surrounding the privacy of research participants.

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