The inexorable increase of biologic exposure in paediatric inflammatory bowel disease: a Scottish, population-based, longitudinal study

Christopher J. Burgess1,2 | Rebecca Jackson3 | Iain Chalmers4 | Richard K. Russell2 | Richard Hansen5 | Gregor Scott5 | Paul Henderson1,2 | David C. Wilson1,2

1Child Life and Health, University of Edinburgh, Edinburgh, UK
2Department of Paediatric Gastroenterology and Nutrition, Royal Hospital for Children and Young People, Edinburgh, UK
3Department of Paediatric Gastroenterology and Nutrition, Royal Hospital for Children, Glasgow, UK
4Department of Paediatric Gastroenterology, Royal Aberdeen Children’s Hospital, Aberdeen, UK
5Department of Paediatric Gastroenterology, Royal Hospital for Children, Glasgow, UK

Correspondence
David C. Wilson, Child Life and Health, University of Edinburgh, 50 Little France Crescent, Edinburgh EH16 4TJ, UK.
Email: d.c.wilson@ed.ac.uk

Summary

Background: The use of biologics in paediatric-onset inflammatory bowel disease (PIBD) is rapidly changing.

Aims: To identify the incidence and prevalence of biologic use within Scottish PIBD services, and to describe patient demographics and outcomes for those patients who required escalation of therapy beyond anti-tumour necrosis factor alpha (anti-TNFα) agents.

Methods: We captured a nationwide cohort of prospectively identified patients less than 18 years of age with PIBD (A1 phenotype; diagnosed <17 years of age) within paediatric services over a 4.5-year period (1 January 2015–30 June 2019). All patients who received infliximab, adalimumab, vedolizumab or ustekinumab during the study period and/or received their first dose of these biologics were audited retrospectively.

Results: Scotland-wide PIBD-prevalence cases increased from 554 to 644 over the study period. A total of 495 incident new-start biological therapies were commenced on 403 PIBD patients: 295 infliximab (60%), 161 adalimumab (32%), 24 vedolizumab (5%) and 15 ustekinumab (3%). The proportion of new-start biologics changed with infliximab initiation rates decreasing (87%–54%) while adalimumab (13%–31%), vedolizumab (0%–9%) and ustekinumab (0%–6%) all increased. The incidence rate (first dose of new biologic not including biosimilar switch) increased from 6.9% to 8.1% over the study period and point prevalence rates (any biologic use) increased from 20.2% to 43.5% - an average annual percentage increase of 20%. Biosimilar penetration of new-start anti-TNFα agents increased from 3% to 91%. Demographics and outcomes of those patients receiving vedolizumab and ustekinumab were similar.

Conclusions: Complete accrual of Scottish nationwide biologic usage within paediatric services demonstrates a rapidly changing, inexorably increasing PIBD biologics landscape.
Inflammatory bowel disease (IBD) comprises Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBDU). Approximately 8% of all patients are diagnosed in childhood or adolescence, with paediatric-onset IBD (PIBD) known to demonstrate a more severe phenotype, characterised by extensive intestinal involvement and rapid early disease progression. The incidence of PIBD has risen rapidly over the last two decades, with Scotland demonstrating the highest incidence of PIBD in the United Kingdom and one of the highest worldwide. Robust epidemiological data on medical therapies used to treat IBD is, therefore, vital to planning current and future health care provision within both paediatric and adult IBD services.

Infliximab (IFX), an anti-tumour necrosis factor alpha (anti-TNFα) biologic, has been used off-label in PIBD since the late 1990s with official licencing delayed until 2010. It has revolutionised the clinical management of PIBD by demonstrating improved long-term disease outcomes with early intensified therapy, especially for high-risk patients. Biologic therapies beyond anti-TNFα have subsequently become available with different modes of action, improved safety profiles and more convenient home care options. Anti-TNFα biosimilars have also been developed, helping to overcome significant cost pressures. In general, PIBD treatment guidelines have become more permissive of earlier and more widespread biologic use over time.

The use of biologics in PIBD is therefore rapidly changing, with both clinical and resource implications for paediatric services and follow-on effects when these patients transition to adult care. At present, no nationwide paediatric data is available to objectively capture this shifting landscape and its potential effect on healthcare resources. Using our ongoing Scottish PIBD biologicals registry, we aimed to identify the incidence and prevalence of biologic use within Scottish PIBD services, as well as describe patient demographics and outcomes in more detail for those patients who commenced vedolizumab (VDZ) or ustekinumab (UST).

### RESULTS

#### 3.1 Incident (new-start) biologic treatments

In total, 495 incident biological therapies were commenced on 403 PIBD patients over the study period. The number of patients commenced on a new biologic therapy increased overall from 38 to 52 between the first and last 6-month epochs, with a maximum number of 74 new-start patients. When increasing numbers of prevalent patients are considered, the overall incidence rate increased only moderately from 6.9% to 8.1% (Table 1). Biologic naive patients were commenced on anti-TNFα therapies only, with VDZ and UST reserved as second- or third-line biologics. Patient demographics were comparable for biologic naive patients commenced on IFX or ADA (Table 2). An increasing proportion of biologic naive patients commenced on ADA, from 0% to 21% over the study period (Table 3).
3.2 | Biologic type and biosimilar use

Anti-TNFα medications constituted the majority of new-start therapies; 295 IFX (60%), 161 ADA (32%). In total, 24 patients were commenced on VDZ (5%), and 15 patients on UST (3%). The proportion of patients commenced on each biologic type changed over time with IFX initiation rates decreasing (87%–54%) while ADA (13%–31%), VDZ (0%–9%) and UST (0%–6%) all increased (Figure 1). Biosimilar penetration of anti-TNFα biologics increased from 3% to 91% between the first and last 6-month epochs (Figure 2).

3.3 | Prevalent biologic treatments

The overall number of point prevalent PIBD patients increased from 525 to 586 during the study period. Point prevalent rates of current

---

Table 1: New-start biologic treatments (incident cases)

| 6-month epochs | IFX  | ADA  | VDZ  | UST  | New starts | Prevalent PIBD cases | Incidence rate (%) |
|----------------|------|------|------|------|------------|----------------------|-------------------|
| Epoch 1 (1 January 2015–30 June 2015) | 33   | 5    | 0    | 0    | 38         | 554                  | 6.9               |
| Epoch 2 (1 July 2015–31 December 2015) | 21   | 13   | 1    | 0    | 35         | 585                  | 6.0               |
| Epoch 3 (1 January 2016–30 June 2016) | 42   | 11   | 2    | 0    | 55         | 591                  | 9.3               |
| Epoch 4 (1 July 2016–31 December 2016) | 37   | 25   | 1    | 0    | 63         | 622                  | 10.1              |
| Epoch 5 (1 January 2017–30 June 2017) | 51   | 18   | 4    | 1    | 74         | 629                  | 11.8              |
| Epoch 6 (1 July 2017–31 December 2017) | 27   | 19   | 2    | 1    | 49         | 633                  | 7.7               |
| Epoch 7 (1 January 2018–30 June 2018) | 31   | 27   | 5    | 2    | 65         | 626                  | 10.4              |
| Epoch 8 (1 July 2018–31 December 2018) | 25   | 27   | 4    | 8    | 64         | 620                  | 10.3              |
| Epoch 9 (1 January 2019–30 June 2019) | 28   | 16   | 5    | 3    | 52         | 644                  | 8.1               |
| Total          | 295 (60%) | 161 (32%) | 24 (5%) | 15 (3%) | 495        | —                    | —                 |

Abbreviations: ADA, adalimumab; IFX, infliximab; PIBD, paediatric-onset inflammatory bowel disease <17 years of age; UST, ustekinumab; VDZ, vedolizumab.

Table 2: Demographics for new-start biologics in biologic naïve patients

| Patient demographics | IFX | ADA |
|----------------------|-----|-----|
| Number (incident cases) | 285 | 78  |
| Age in years (median, IQR) | 12.1 (9.7–14.1) years | 12.7 (10.5–14.3) years |
| Disease duration prior to the first dose in years (median, IQR) | 1.1 (0.3–2.6) years | 0.9 (0.2–1.9) years |
| PIBD subtype | 213 CD: 47 UC: 25 IBDU | 65 CD: 7 UC: 6 IBDU |
| Extensive disease (L3 or E4 Paris classification) | 171 (60%) | 52 (67%) |

Abbreviations: ADA, adalimumab; IFX, infliximab; IQR, interquartile range; PIBD, paediatric-onset inflammatory bowel disease <17 years of age; anti-TNFα – anti-tumour necrosis factor alpha.

Table 3: New-start biologics in biologic naïve patients

| 6-month epochs | IFX  | ADA  | VDZ  | UST  | New starts |
|----------------|------|------|------|------|------------|
| Epoch 1 (1 January 2015–30 June 2015) | 30   | 0    | 0    | 0    | 30         |
| Epoch 2 (1 July 2015–31.12.2015) | 20   | 3    | 1    | 0    | 23         |
| Epoch 3 (1 January 2016–30 June 2016) | 41   | 5    | 0    | 0    | 46         |
| Epoch 4 (1 July 2016–31 December 2016) | 35   | 11   | 0    | 0    | 46         |
| Epoch 5 (1 January 2017–30 June 2017) | 48   | 8    | 0    | 0    | 56         |
| Epoch 6 (1 July 2017–31 December 2017) | 27   | 8    | 0    | 0    | 35         |
| Epoch 7 (1 January 2018–30 June 2018) | 32   | 15   | 0    | 0    | 47         |
| Epoch 8 (1 July 2018–31 December 2018) | 25   | 21   | 0    | 0    | 46         |
| Epoch 9 (1 January 2019–30 June 2019) | 27   | 7    | 0    | 0    | 34         |
| Total          | 285 (79%) | 78 (21%) | 0    | 0    | 363        |

Abbreviations: ADA, Adalimumab; IFX, Infliximab; UST, Ustekinumab; VDZ, Vedolizumab.
biologic therapy usage increased from 20% on 30 June 2015 to 44% on 30 June 2019 ($p = 0.008$); an average annual percentage increase of 20% (Figure 3).

### 3.4 | Vedolizumab use

Patients commenced on VDZ ($n = 24$) had a median age 14.5 years (IQR 12.4–15.8) and median disease duration of 3.1 years (IQR 1.9–4.6) prior to the first dose. Breakdown of PIBD subtypes was 10 CD; 10 UC; 4 IBDU. Bridging therapy was used for all VDZ induction regimens: 16 tacrolimus; 5 prednisolone, 2 adalimumab; 1 exclusive enteral nutrition. 18 (75%) patients commenced on VDZ had extensive disease (L3 or E4 Paris classification), all 24 patients had previously failed one anti-TNFα biologic including 8 (33%) that had failed both anti-TNFα therapies. Following commencement of VDZ therapy; 14 (58%) required dose escalation with shortened dosing interval, 7 (29%) patients stopped therapy for primary non-response or adverse reaction at median 3.7 months (IQR 1.6–10.7) and 6 (25%) patients required surgery after commencing VDZ (Table 4). Adverse reactions were recorded for three patients including lower limb bruising, hallucinations, and severe itch. VDZ was stopped in all cases with resolution of symptoms.

### 3.5 | Ustekinumab use

Patients commenced on UST ($n = 15$) had a median age of 15.6 years (IQR 13.7–16.1) and median disease duration of 4.3 years (IQR 2.5–6.1). A total of 14 patients had CD and one patient IBDU favouring CD. 12 (80%) of patients had extensive disease (L3 or E4 Paris classification), all 15 patients had previously failed one anti-TNFα biologic including 10 (67%) who had failed both anti-TNFα therapies. Following commencement of UST therapy; 8 (53%) required dose escalation with shortened dosing interval, 7 (47%) patients stopped therapy for primary non-response at median 6.5 months (IQR 4.8–7.3) and 5 (33%) patients required surgery after commencing UST (Table 4). An adverse reaction was recorded for one patient only as a severe itch, which did not require cessation of UST.
3.6 | Safety

No serious adverse outcomes associated with biologic use in PIBD patients within Scotland were reported during the study period.

4 | DISCUSSION

Scottish nationwide biologic usage within paediatric services demonstrates a rapidly changing PIBD treatment landscape. We have demonstrated a significant increase in the number of prevalent patients on biologic therapy (from 20% to 43%) in just 4 years, a near-complete shift to biosimilar anti-TNFα therapy (from 3% to 91%) and increasing use of VDZ and UST, both of which remain unlicensed for PIBD. This dramatic shift is unlikely to reflect a significant change in disease severity given the short 4-year timeframe of this study, or a major change in practice of any single practitioner or centre given the use of nationwide data covering three tertiary hospitals. To our knowledge this is the first study to capture nationwide, population-based data of biologic use in paediatric IBD in the era of anti-TNFα biosimilars and biologic therapies with different modes of action beyond anti-TNFα.

Since their initial introduction, biologics have revolutionised the clinical management of IBD, encouraging a focused move towards a treat-to-target approach with early intensified therapy to improve disease outcomes. IFX and ADA have been licensed for use in PIBD in the United Kingdom since 2010 and 2013, respectively. Increasing utilisation of anti-TNFα therapy has been captured in a Canadian population-based study demonstrating 13% CD and 4.9% UC patients prescribed anti-TNFα therapy in 2010, increasing to...
60% CD and 25.5% UC by 2016.\textsuperscript{14} Within Scotland almost half of all PIBD patients were on biologics by the completion of our study, equating to an average annual increase of 20%. This rapid increase pre-dates the most recent joint ECCO-ESPGHAN guidelines for CD and UC which are more permissive in supporting earlier and more widespread biologic use.\textsuperscript{9,10}

Anti-TNFα medications constituted the majority of all new-start biologics with 60% of patients commencing IFX and 32% ADA. Over the study period the proportion of patients commencing IFX was noted to decrease (87% to 54%), whereas the proportion of patients commencing ADA increased (13%–31%). Although this result may be partly driven by patients switching from IFX within class secondary to antibody formation, our treatment naive data demonstrates that some clinicians within Scotland are increasingly using ADA as first line biologic therapy. This likely relates to multiple factors including increasing clinician familiarity, subcutaneous mode of delivery (allowing at home care options) and difference in immunogenicity.\textsuperscript{15}

Significant cost pressures related to anti-TNFα prescription were highlighted in a 2015 review of anti-TNF therapy for PIBD in Scotland, related to both drug cost and the need for dose escalation in 32% and 66% of patients on maintenance IFX and ADA.\textsuperscript{16} Quantified real-world data from the USA has demonstrated the average paediatric biologic-taking patient cost at $41,109 per year in 2015, increased from $23,616 in 2007 and outpacing the increasing cost of biologics in adult patients.\textsuperscript{17} Biosimilar IFX was approved for use in PIBD by the European Medicine Agency in 2015; however, guidelines advised caution due to concerns over efficacy and the potential for increased immunogenicity.\textsuperscript{18} Early Scottish data published in 2018 demonstrated equivalent effectiveness, no significant safety issues and a 38% cost reduction through use of biosimilar IFX.\textsuperscript{19,20} Switching patients to biosimilar anti-TNFα therapy has therefore continued, primarily as a cost-saving measure, with current data demonstrating that over a 4-year period a near-complete shift to biosimilar anti-TNFα has now occurred within Scotland (including new starts plus switching from bio-originator to biosimilar) with biosimilar penetration of anti-TNFα biologics increasing from 3% to 91%. Although not formally quantified, this may have contributed to cost savings nationally.

The increased availability and proactive use of therapeutic drug monitoring, much of which occurred over the study period, is likely to have influenced biologic prescribing. Therapeutic drug monitoring is increasingly used to optimise drug dosing and can provide an objective measure supporting loss of response. This has improved clinical decision-making around the need to modify therapy for those patients on anti-TNFα biologics not responding to dose optimised treatment.\textsuperscript{9,10} VDZ and UST are biologic therapies with different modes of action, currently used off-licence in paediatrics and therefore reserved for those children with primary non-response or secondary loss of response to anti-TNFα. These additional biologics offer an important opportunity to escalate as well as individualise therapy to include consideration of factors such as patient tolerance, patient, and family preference, altered bioavailability and dosing regimens, monotherapy options and consideration of long-term safety. Subcutaneous formulations of IFX and VDZ were not available within this study timeframe; however, these preparations will likely continue to shift the biologic landscape within PIBD in the next decade.

Demographic characteristics of those commenced on VDZ and UST within our Scottish cohort were similar, with median age approximately 15 years, extensive disease phenotype in at least three quarters of patients and all having failed at least one anti-TNFα therapy. Adult studies have repeatedly demonstrated that there is a stepwise reduced response rate with second- and third-line biologics.\textsuperscript{21,22} It is, therefore, not surprising that the measured outcomes within this treatment-resistant paediatric population with extensive disease were generally low. We have demonstrated that 58% of PIBD patients on VDZ versus 53% on UST required dose escalation, 29% versus 47% ceased therapy for primary non-response and 25% versus 33% required surgery. All treatment decisions were at the discretion of the treating team and outcomes based on steroid and exclusive enteral nutrition free remission were unable to be determined within this retrospective descriptive study.

Our complete accrual of Scottish nationwide biologic usage within paediatric services demonstrates a rapidly changing PIBD biologics treatment landscape, with inexorably increasing PIBD biologics exposure. For children’s health services, the increasing biologic exposure of PIBD patients raises issues of medication costs, access to medications often used off licence, and increased specialist nursing and infusion centre requirements. The increased complexity and close follow-up required for PIBD patients exposed to multiple biologics will impact senior clinician workloads and must also be addressed within training programs. Importantly, all impacts will also extend beyond paediatric services, with patients now being transitioned to adult centres having potentially trialled all available PIBD biologic therapies. This new biological landscape will therefore increase the importance of formal transition, ideally with a period of joint paediatric and adult care, to ensure optimised use of appropriate biologic therapies prior to any escalation that may affect future decision-making.

AUTHOR CONTRIBUTIONS
Christopher Burgess: Conceptualization (equal); data curation (lead); writing - review and editing (lead). Rebecca Jackson: Data curation (supporting); writing – review and editing (supporting). Iain Chalmers: Data curation (supporting); writing – review and editing (supporting). Richard Russell: Conceptualization (supporting); writing – review and editing (supporting). Richard Hansen: Conceptualization (supporting); writing – review and editing (supporting). Gregor Scott: Data curation (supporting); writing – review and editing (supporting). Paul Henderson: Conceptualization (equal); writing – review and editing (supporting). David Wilson: Conceptualization (lead), data curation (supporting), writing - review and editing (supporting). All authors approved the final version of the manuscript.

ACKNOWLEDGEMENT
Declaration of personal interests: DCW has received consultancy fees, speaker fees and/or travel support from Celltrion, Abbvie.
and Nestle Health Sciences. RKR has received speaker’s fees and/or travel support from Nestle, Abbvie, Celltrion, Janssen and Tillots. RH has received speaker’s fees and/or travel support from 4D Pharma.

FUNDING INFORMATION
This work was supported by an Edinburgh Children’s Hospital Charity Research Fellowship award (to C.J.B) and by funding from Crohn’s and Colitis UK (Edinburgh network) and a joint CORE (Guts UK) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) Development Grant. RJ was supported by a Catherine McEwan Foundation IBD Clinical Research Fellowship. RH, PH & RKR are supported by NHS Research Scotland Career Researcher Fellowships.

AUTHORSHIP
Guarantor of the article: Professor David Wilson.

ORCID
Christopher J. Burgess https://orcid.org/0000-0002-6056-2684
Paul Henderson https://orcid.org/0000-0003-3634-6428

REFERENCES
1. Ghione S, Sarter H, Fumery M, Armengol-Debeir L, Savoye G, Ley D, et al. Dramatic increase in incidence of ulcerative colitis and Crohn’s disease (1988-2011): a population-based study of French adolescents. Am J Gastroenterol. 2018;113:265–72.
2. Burgess C. Paediatric patients (less than age of 17 years) account for less than 1.5% of all prevalent inflammatory bowel disease cases. J Pediatr Gastroenterol Nutr. 2020; 71(4):521–23.
3. van Limbergen J., Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135:1114–22.
4. Kuenzig ME, Fung SG, Marderfeld L, Mak JWY, Kaplan GG, Ng SC, et al. Twenty-first century trends in the global epidemiology of pediatric-onset inflammatory bowel disease: systematic review. Gastroenterology 2022;162:1147–1159.
5. Henderson P, Hansen R, Cameron FL, Gerasimidis K, Rogers P, Bisset MW, et al. Rising incidence of pediatric inflammatory bowel disease in Scotland. Inflamm Bowel Dis. 2012;18:999–1005.
6. National Institute for Health and Care Excellence (2010). Infliximab and adalimumab for the treatment of Crohn’s disease. [NICE technology appraisal guidance TA187]. https://www.nice.org.uk/guidance/ta187.
7. Wilson DC, Thomas AG, Croft NM, Newby E, Akobeng AK, Sawczenko A, et al. Systematic review of the evidence base for the medical treatment of paediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2010;50(Suppl 1):S14–34.
8. Kang B, Choie YH. Early biologic treatment in pediatric Crohn’s disease: catching the therapeutic window of opportunity in early disease by treat-to-target. Pediatr Gastroenterol Hepatol Nutr. 2018;2:1:1–11.
9. van Rheenen PF, Aloï M, Assa A, Bronsky J, Escher JC, Fagerberg UL, et al. The medical Management of Paediatric Crohn’s disease: an ECCO-ESPGHAN guideline update. J Crohns Colitis. 2021;15:171–94.
10. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of Paediatric Ulcerative Colitis, part 1: ambulatory care-an evidence-based guideline from European Crohn’s and colitis organization and European Society of Paediatric Gastroenterology, hepatology and nutrition. J Pediatr Gastroenterol Nutr. 2018;67:257–91.
11. National Records of Scotland. Mid-year population estimates. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population/population-estimates. Accessed 11/03/2019.
12. Information Services Division Scotland. CHI number. https://www.isdscotland.org. Accessed 11/03/2019.
13. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr. 2014;58:795–806.
14. El-Matary W, Leung S, Tennakoon A, Benchimol EI, Bernstein CN, Targownik LE. Trends of utilization of tumor necrosis factor antagonists in children with inflammatory bowel disease: a Canadian population-based study. Inflamm Bowel Dis. 2020;26:134–8.
15. Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn’s disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019;4:341–53.
16. Cameron F, Wilson M, Basheer N, Jamison A, McGrogan P, Bisset WM, et al. Anti-TNF therapy for paediatric IBD: the Scottish national experience. Arch Dis Child. 2015;100:399–405.
17. Yu H, Maclsaac D, Wong JJ, Sellers ZM, Wren AA, Bensen R, et al. Market share and costs of biologic therapies for inflammatory bowel disease in the USA. Aliment Pharmacol Ther. 2018;47:364–70.
18. Danese S, Fiorino G, Raine T, Ferrante M, Kemp K, Kierkus J, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease-an update. J Crohns Colitis. 2017:11:26–34.
19. Richmond L, Curtis L, Garrick V, Rogers P, Wilson M, Tayler R, et al. Biosimilar infliximab use in paediatric IBD. Arch Dis Child. 2018:103:89–91.
20. Gervais L, McLean LL, Wilson ML, Cameron C, Curtis L, Garrick V, et al. Switching from originator to biosimilar infliximab in paediatric inflammatory bowel disease is feasible and uneventful. J Pediatr Gastroenterol Nutr. 2018:67:745–8.
21. Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary non-response to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: a systematic review and meta-analysis. J Crohns Colitis. 2018;12:635–43.
22. Casanova MJ, Chaparro M, Mínguez M, Ricart E, Taxonera C, García-López S, Guardiola J, et al. Effectiveness and safety of the sequential use of a second and third anti-TNF agent in patients with inflammatory bowel disease: Results from the Eneida registry. Inflamm Bowel Dis 2020;26:606–616.