Real-life biological experience in > 500 paediatric UK IBD patients: high co-immunosuppression and response rates but difficulties in qualifying and quantifying treatment response

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Background and aims: The biological therapy audit aimed to measure the efficacy, safety and use of anti-TNFα therapy in paediatric patients with inflammatory bowel disease (IBD) in the UK.

Methods: A prospective UK audit of patient's newly starting biological therapy during 12/9/11-28/4/14. Disease severity was assessed using Physician Global Assessment (PGA) +/or the Paediatric Crohn's Disease Activity Index (PCDAI).

Results: 30 UK centres treating PIBD patients with biologics submitted data. 524 patients (with 562 initial infusions) were included; 429 Crohn's disease (CD), 76 ulcerative colitis (UC) and 19 IBD unclassified (IBDU). The commonest indication for biologic initiation was active luminal CD 77% (330/429) or chronic refractory UC/IBDU 56% (53/95). At biologic initiation 79% (445/562) had concomitant co-immunosuppression given of which 89% (398/445) were thiopurines and 11% (47/445) methotrexate. 429 CD datasets were analysed in further detail (267 male); median age at diagnosis 12.0 years (IQR 9.4-13.8). 396 had initial treatment with IFX and 63 with ADA; 30 CD patients received both IFX and ADA (not concurrently). Median time from diagnosis to treatment was 1.42 years (IQR 0.63-2.97). At initial treatment, PGA was moderate or severe in 91% (156/171) compared to 41% (88/217) when determined by PCDAI indicating only 'fair agreement' with Kappa statistic (K) of 0.28 ($p<0.001$). Where documented (94% [493/524]), pre-treatment tuberculosis (TB) screening was widely carried out with only 3% (15/493) not screened with at least 1 test.

Where post-induction response was documented, 77% (53/69) CD patients responded with 65% (46/71) who entered remission. Children with CD receive biological therapy significantly earlier in their disease course than adults; 1.42 vs. 5.23 years ($p<0.001$). Overall this data represents 2287 infusions and 301.96 years of patient follow-up (n=385); 1389/1414 IFX treatments were seen for follow up at some point. 10% (32/316) CD patients experienced ≥ 1 adverse event; no deaths or malignancies were recorded. Surgical resection rates 6 months pre/post initiation were comparable; 7% (36/524) vs. 5% (27/524). Drainage of perianal abscess was a significantly less common

procedure in CD after initiation with biologic 26% (27/102) vs. 7% (3/42) after (p=0.01); however pre and post biologic data collection was not over equal time periods.

Conclusion: The data confirm biologics are effective treatments, are normally given with thiopurine co-immunosuppression but that formal documentation of effect is not frequently recorded. Disparity between disease severity scoring tools needs to be addressed; we suggest with a weighted PCDAI. Initial adverse events are uncommon but longer term follow up data than this is required to fully answer safety questions.

Keywords: Paediatrics

INTRODUCTION

The Inflammatory Bowel Diseases (IBD), comprising Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU) are increasing in incidence and prevalence, notably in the paediatric population.[1] Paediatric care has been revolutionised in the last decade by the widespread introduction of anti-tumour necrosis factor (anti-TNF) therapy in the form of infliximab (IFX) and adalimumab (ADA). Clinical trials have shown these agents to be effective where other therapies have failed and use is proportionately greater in the paediatric population compared to adults.[2,3]

The UK IBD audit is a national gastrointestinal audit first commenced in 2006 (reporting in 2008). Reports are available online from the Royal College of Physicians at www.rcplondon.ac.uk/ibd and data has previously been published on the outcomes of paediatric and adult patients with UC.[4,5] The UK IBD audit has been collecting data on biological therapies, including in the paediatric population, since 2011 with the purpose of assessing efficacy, safety and appropriate use (according to national guidelines) in clinical practice. Unselected, large scale national data will help to quantify and categorise adverse events where real life clinical data is lacking.

MATERIALS AND METHODS

Sites (either a single hospital or a represented health board or trust) were eligible to participate in the biological therapies audit if they prescribe and administer biological therapies to their patients with IBD. There are 25 specialist paediatric IBD (PIBD) sites in the UK, of which 23 contributed data to this audit. Additionally there are another 14 paediatric sites providing biological therapy and submitting data, giving a total of 37 sites.

Children of all ages with a diagnosis of IBD who were *newly* started on biological therapy for treatment of their IBD from 12/09/11 were eligible for inclusion. Patients already on biological therapy prior to this date were not included. Data was collected prospectively and entered into a web based database with security maintained through local site codes and the lead clinician for the site authorising local access. Data capture for the results included here ended on 28/02/14.

Demographic details were pseudo-anonymised at the point of data entry and identifiable only to the participating site. IBD disease details were phenotyped according to Montreal criteria for disease location and behaviour.[6] Physician Global Assessment (PGA), Paediatric Crohn's Disease Activity Index (PCDAI) or Paediatric Ulcerative Colitis Activity Index (PUCAI) scores were also collected at initial and follow-up treatments, along with details of comorbidities and any surgery.[7,8] A full list of all data items collected is available on request.

Initial anti-TNFα treatment: questions were generated depending on biologic selected i.e. IFX or ADA and included data on screening and investigations up to completion/abandonment, concomitant therapies and any adverse effects. Each follow-up treatment relates to an initial submission and records outcome as intention to continue or stop; response with or without remission using reduction in PCDAI/PUCAI or Harvey Bradshaw Index (HBI), another commonly used disease activity scoring tool.[9] Unlimited numbers of follow-up treatments are permitted and any adverse events recorded.

Details of IBD related surgery can be added at any time along with any escalation of treatment at each initial or follow-up treatment. Patient Reported Outcome Measures (PROM) data was collected using the IMPACT III questionnaire (a validated tool to measure health related quality of life in paediatric IBD, where a higher score indicates a better quality of life) at initiation and subsequently.[10,11]

Some children received treatment with multiple biologics resulting in more initial treatments than patients. Since the number of submissions per patient is variable (e.g. multiple initial or follow-up treatments), the denominators vary considerably and results tables should be scrutinised carefully in conjunction with any explanatory notes for accurate data interpretation.

Guidance on the use of biological therapy in the UK comes via the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). NICE Technology Appraisals TA187 (CD) and TA329 (UC) recommend Infliximab within its licensed indication as an option for "the treatment of people aged 6-17 years with severe active disease who have not adequately responded to conventional therapy (including corticosteroids, immunomodulators and exclusive enteral nutrition [CD]), or who cannot tolerate or have contraindications to conventional therapy". Data were collected on disease type and severity as well as previous therapies to assess prescribing against these criteria.

Data were analysed using SPSS version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Data manipulation was performed using SAS software v9.4 for Windows. Copyright (c) 2002-2012 by SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. Chi-squared test and the kappa statistic were used to examine categorical data; the Mann-Whitney U test was used to examine continuous data; Kolmogorov-Smirnov (KS) test was used to analyse PROM data. Kappa statistic is expressed as per the boundaries

156 described by Landis and Koch; range is from ‘poor/slight’ agreement (K ≤0.2) through ‘fair’,
157 ‘moderate’ and ‘substantial’, to ‘almost perfect’ agreement (K 0.81-1.00).
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RESULTS

Overview

By 28/02/14, demographic submissions were entered on 817 individual paediatric patients; 156 patients with no initial treatment details entered were excluded leaving 661 patients with 746 initial treatments. Further exclusions for treatments commenced prior to 12/09/11 and repeat 'initial' treatments or insufficient disease details resulted in data analysis on 524 patients (429 CD, 76 UC and 19 IBDU) with 562 initial treatments (Figure 1).

Of these patients 61% (321/524) were male with a median age (IQR) at diagnosis of 12.0 years (9.4-13.9). Median age (IQR) at initial treatment with a biologic was 14.1 years (12.3-15.7) and median time from diagnosis to initial treatment with a biologic was 1.4 years (IQR 0.6 - 2.9), (table 1). 30 CD, 4 UC and 4 IBDU patients were treated with both anti-TNFs.

Infliximab was the commonest choice of biological therapy in all IBD sub-types; 87% (488/562) of initial treatments. Patients were co-immunosuppressed with a thiopurine or methotrexate; 79% (386/488) IFX (91% thiopurines [351/386], 9% methotrexate [35/386]) and 80% (59/74) ADA (80% thiopurines [47/59], 20% methotrexate [12/59]). Consent to start treatment was established in 99% (559/562) at treatment initiation either verbally (46% [257/559]) or as written (54% [302/559]) consent; verbal consent was significantly more common with ADA 51/74 (69%) compared with IFX 206/485 (42%), p=0.00002. 51% (223/437) of patients had failed on an immunosuppressant and/or steroids prior to treatment with a biologic. 5.2% patients (27/524) had no previous medication or concomitant therapies documented at time of biologic initiation, suggesting a 'top-down' therapy approach.

Crohn's Disease

40% (151/379) of patients starting IFX and 37% (22/60) starting ADA had extensive disease i.e. L3 (ileocolonic) at initiation and 80% (310/388) had upper GI involvement (proximal = L4). Clinical indication for starting treatment (ADA+IFX) was severe perianal CD in 17% (77/458), whilst the

commonest indication for starting therapy was active luminal CD; 78% (355/458) (supplementary table 1).

Disease severity at time of initiation of biological therapy (where documented) was moderate-severe in 91% (156/171) CD patients when scored by PGA, but only 41% (88/217) when determined by PCDAI score as shown in table 2.

Cross-tabulation of PCDAI and PGA (grouping mild and remission together for comparison) reveals a Kappa statistic (K) of 0.28 (SE=0.055, $p<0.001$) indicating only 'fair agreement'.

99% (347/349) of initial IFX was given at 5mg/kg i.e. standard dosing. 71% (45/63) ADA was given at 80mg/40mg whilst 25% (16/63) was given at 160mg/80mg induction dose. 98% (387/396) of initial IFX infusions were successfully completed at the prescribed rate. 98% of subsequent infusions were associated with clinical follow-up at a median of 167 (IQR 46, 350) days for IFX and 81 (IQR 35, 232) days for ADA (table 4). 97% (1346/1388) IFX treatments were planned to continue at follow-up and 91% (84/92) ADA treatments. Where treatment was stopped, 29% (12/42) IFX and 50% (4/8) ADA was for poor response; loss of response accounted for 17% (7/42) IFX and 38% (3/8) ADA termination. Planned discontinuation following effective treatment occurred in just 21% (9/42) of IFX cessation and no cases with ADA (table 3).

Response to induction treatment was infrequently recorded (16% [69/443]) but where documented, 77% (53/69) of patients demonstrated a response at 10-14 week follow-up (fall in PCDAI of ≥15) and 65% (46/71) achieved remission (PCDAI score ≤10).

Ulcerative Colitis

The majority of patients had extensive disease (E3) at initiation of biologic; 73% (51/70) with IFX and 86% (6/7) with ADA (table 1). Overall 59% (47/79) of biological treatments (57% [43/76] patients) were started for chronic refractory UC and 39% (31/79) for acute severe UC (supplementary table 1).

100% (66/66) of IFX infusions were prescribed at 5mg/kg and 86% (6/7) of ADA given at 80mg/40mg induction dose.

Disease severity in colitis was moderate-severe in 92% (35/38) UC at initiation by PGA, where documented, compared to 85% (45/53) by PUCAI. Median PUCAI score at initiation was 55 (IQR 40, 70), equivalent to moderate disease (see table 2 for categorical breakdown). Cross-tabulation and Kappa statistic demonstrates better correlation between PGA and PUCAI, with K 0.58 indicating 'moderate' agreement (0.41-0.60).[12]

There was 97% follow-up for ongoing IFX treatments (168/174) at a median of 94 days (IQR 21, 215) and 83% (5/6) for ongoing ADA treatments at a median of 130 days (IQR 114, 304). 12% treatments were stopped (21/173), with poor response or lack of response equally accounting for 76% (16/21). Where PGA was documented, disease severity was mild in 53%, moderate in 35% and severe in 12% treatments (N=100) at follow-up compared with 8% (3/38), 45% (17/38) and 47% (18/38), mild, moderate and severe respectively, at initiation (table 2).

IBD Unclassified

95% (20/21) of IBDU patients had extensive disease (E3) at initiation of biological therapy. Acute severe IBDU and chronic refractory IBDU accounted for an equal proportion of initial treatments with biological therapy i.e. each 48% (11/23) when IFX and ADA combined. There was 97% follow-up for ongoing biological treatments at a median of 44 days (IQR 14, 98) for IFX and 220 days (IQR 75, 364 N=2) for ADA. 16% treatments were stopped (N=5), with poor response and adverse effects each accounting for 2 cases and loss of response in the other case. Disease severity where recorded at follow-up was mild in 10%, moderate in 76% and severe in 14% (N=21), compared to 0% mild, 22% moderate and 78% severe at initiation (n=9).

Disease severity was moderate-severe in 100% (9/9) IBDU at initiation by PGA, where documented, compared with 62% (5/8) by PUCAI.

Surgery

In total 105 paediatric patients had surgery totalling 166 IBD-related surgical procedures. There was no significant difference between number of patients with surgery in the 6 months pre and post initiating biologic; 7% (36/524) pre and 5% (27/524) post (p= 0.30). 87% (144/166) were in CD patients, 8% (14/166) in UC patients and 5% (8/166) in patients with IBDU. The commonest surgical procedure in both UC and IBDU was sub-total colectomy with ileostomy formation. The commonest procedures (by disease type) are detailed in supplementary table 2. The majority of procedures were pre-biologic initiation in CD 71% (102/144), post-biologic in UC 100% (14/14) and equally split in IBDU. The commonest procedure overall was examination under anaesthetic (EUA) of fistula, 24% (40/166) of all surgical procedures; this was also the commonest procedure in CD accounting for 27% (39/144). Drainage of perianal abscess was significantly less common in CD after initiation with biological therapy than before 26% (27/102) vs. 7% (3/42) (p=0.01)*;* note however that the time period of data collection was not equal pre and post biologic and was variable from patient to patient. In total, 16% (12/74) of UC patients went on to have colectomy despite biological therapy and 3% (2/74) a partial resection; see supplementary table 2 for details.

Safety data

Overall this data represents 2287 infusions and 301.96 years of patient follow-up (n=385); median 0.65 (IQR 0.27-1.19).

2% (10/488) of all initial IFX infusions reported an acute reaction. 1% of all follow-up IFX infusions (23/1587) reported an acute reaction. There were no acute reactions with any initial or follow-up ADA treatment (0/173); no significant difference from IFX, *p=0.1*. Other adverse events occurred slightly more frequently; 3% (49/1587) of IFX infusions and 2% (2/98) ADA cases reported an adverse event, most commonly infection (supplementary table 3). 10% of CD patients (32/316) experienced at least one adverse event over the course of their treatment. No malignancies or mortality were reported.

Pre-treatment Screening

Screening practice appears to vary widely. Where documented (493/524 patients with information on at least 1 test), tuberculosis (TB) screening was widely carried out: 97% (478/493) had at least 1 test for TB ; 88% (433/492) patients had a chest x-ray (CXR), 47% (224/481) a gamma interferon TB test and 3% (15/469) a Mantoux test. 71% (343/485) patients were screened for varicella immunity prior to commencing biological therapy; 46% (221/482) for Hepatitis B infection and 37% (176/480) for Hepatitis C infection whilst 12% (57/476) were screened for HIV infection.

Comparison to adult data

There was a male preponderance in the paediatric cohort with 61% (321/524) and 49% (1599/3272) in paediatric and adult cohorts respectively ($p<0.001$). Time from diagnosis to biologic (median, IQR) was shorter in the paediatric population as a whole, 1.3 years (0.61, 2.62) vs. 4.55 years (1.31, 11.03) $p<0.001$. Extensive disease (L3 or E3) was more common in the paediatric population compared to adults; CD 41% (166/410) vs. 32% (806/2553) $p<0.001$, UC 74% (54/73) vs. 47% (208/441) $p<0.001$ and IBDU 94% (16/17) vs. 52% (45/87) $p=0.001$.

Response to treatment (PCDAI fall ≥15 or HBI fall >3) was comparable between the paediatric and adult CD cohorts with 77% (53/69) and 87% (195/224) response respectively ($p=0.04$). There was also no significant difference in remission rates between paediatric and adult CD cohorts; 65% (46/71) of children and 70% (170/224) adults achieved remission at any follow-up between 10 and 14 weeks ($p=0.07$). Significantly more children with CD were co-immunosuppressed at the time of starting treatment than adults however, both for IFX 81% (320/396) vs 55% (755/1363) $p<0.001$ and ADA 76% (48/63) vs 54% (787/1450) $p<0.001$.

Patient Reported Outcome Measures (PROM)

19% (98/524) patients had IMPACT III scores recorded at baseline and of these only 33% (32/98) went on to have a repeat PROM recorded at follow-up, therefore only 6% of the whole cohort had PROM data recorded pre and post treatment. The median (IQR) score at baseline for all IBD was

297 110.5 (91.0, 129.0) and at follow-up 113.5 (82.0, 141.0); for CD (n=78) 110.5 (92.0, 130.0) and 128.5
298 (85.0, 147.5) at baseline and follow-up respectively. However, when considering only those patients
299 with both baseline and follow-up scores (CD n=25, all IBD n=32) this modest difference diminishes in
300 CD; 98.0 (87.0, 136.0) to 109.0 (72.0, 156.0), and is lost altogether as 'all IBD'; 103.5 (87.0, 131.5) to
301 101.0 (68.0, 147.5). The change is not significant in either case by KS test; p=0.63 for CD and p=0.51
302 for all IBD, however it should be noted that a change of 10.8 or more is considered a significant
303 change by the IMPACT 3 design team.

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DISCUSSION

This audit represents data from a large cohort of paediatric patients receiving biological therapy over a 2.46 year period across the United Kingdom and gives a snapshot of its use in clinical practice for PIBD. Overall response and remission rates appear to be good although formal documentation of this is infrequently done, despite patients going on to receive maintenance therapy after their induction course. We highlight here the need for post-induction assessment of response to appropriately determine on-going treatment and suggest the best method of documenting this.

The majority of biological therapy is used for CD and whilst use appears to be increasing in patients with IBDU, effectiveness appears attenuated in this group, with moderate disease severity persisting at follow-up in the majority of patients, contrasting to patients with CD. The predominant use of biological therapy for chronic refractory UC and IBDU rather than acute severe colitis is surprising.

There is a clear discrepancy between PGA score and PCDAI scores in this data. Documentation of PCDAI at follow up was low as has been noted in previous studies, thought potentially due in part to the inclusion of items that are less readily obtained such as height velocity, perianal examination and laboratory indices.[13,14] Recently, the weighted PCDAI (wPCDAI) has been proposed as an alternative measure; shown to have validity despite the exclusion of haematocrit, abdominal examination and height velocity as parameters.[15] Replacing PCDAI with wPCDAI in subsequent rounds of the audit may encourage increased completion and thereby facilitate more objective clinical assessment and aid decision making. PUCAI appeared to have better correlation with PGA than PCDAI, in keeping with other studies specifically designed to test this which show excellent agreement.[14] The major obstacle to drawing any conclusion regarding scoring from this data is the variability in reporting.

There was a significant reduction in the need for drainage of perianal abscess after initiation with biologics, however we note that time periods pre and post initiation were not equal or defined, limiting any conclusions to be drawn. Despite this, we know that perianal disease is recognised as a

342 debilitating CD phenotype and biologics have been shown to be an effective treatment in large
343 studies.[16] The rate of colectomy in UC patients at 16% is in keeping with adult studies[17,18], rate of
344 colectomy post biologic in IBDU patients is notable at 21% but numbers are small (4/19).

345 Although the follow-up period in this audit is relatively short (max 2.46 years), the large number of
346 patients allows us some confidence in the short term safety profile of the biological therapies, as
347 2287 infusions and 302 years of patient follow-up are represented. Infection was the commonest
348 adverse event, in keeping with other published studies[19] and whilst risks are minimised where
349 possible, total prevention will never be possible. The absence of malignancy and mortality, whilst
350 encouraging, could be argued carries less weight given the population age and short length of time
351 on treatment.

352 Screening practice appears to be variable; exclusion of TB infection is an obligatory part of national
353 and international guidelines and this was widely performed, although there remains room for
354 improvement in the final 3%.[20,21] VZV screening is recommended in adult guidelines if history of
355 previous infection is unknown and this was performed in almost three quarters of cases. HIV
356 screening was not widely performed, presumably due to the low-risk nature of the cohort; adult
357 guidelines recommend screening is considered prior to immunomodulation.[22]

358 The male predominance and extensive disease compared with data from the adult audit is expected
359 in keeping with previously published data[23] but the shortened time from diagnosis to starting
360 biologics in the paediatric population compared to adults is striking; it suggests aggressive
361 progression of disease and rapid cycling though medical therapeutic options, although potentially
362 could also reflect poorer tolerance of standard treatments.

363 It is difficult to draw any meaningful conclusion regarding impact on quality of life due to the small
364 numbers of documented patient reported outcome measures. A higher score indicates a better
365 quality of life[10] so an increase in score would be expected; the small upward trend here perhaps

suggests this but is not significant. The data is novel however and completion in subsequent audit rounds should be promoted; improvement in quality of life is an important outcome and cannot necessarily be assumed from other markers of response.

A limitation of this study is the variability in completeness of data capture which is reflected in the changing denominator for different categories of data. This audit relies on clinical centres finding time to enter patient data and it is often only possible for them to supply the minimum data set. Its strength however lies in the nationwide collaborative nature of the project and relatively large numbers represented, with over 90% of specialist sites participating and the 'real-world' clinical data which should mean conclusions that can be drawn are broadly generalizable to the PIBD population. The large number of treatments represented here in routine clinical use support biological therapy as safe and effective in paediatric IBD with the majority of patients achieving response or remission and just 2% of initial infusions and 1% of follow-up infusions associated with acute adverse reactions.

Future rounds of the audit should focus on encouraging and facilitating more complete data collection, in particular response and remission rates both after induction and longer term follow up, as well as documenting the outcome on patient reported quality of life as measured through the IMPACT III questionnaire. If the results are a true reflection of screening practice then efforts should be made to improve this and ensure TB is always excluded when initiating treatment. Future audit is increasingly important in the advent of bio-similars which are now licensed for use in PIBD in the UK; large scale clinical data on their efficacy and safety profile is essential to evaluate their use given the current lack of any published evidence in IBD and national collaboration is the best way to achieve this.

CONCLUSIONS

This UK wide real-life data supports biological therapy as a safe and effective treatment for PIBD and shows it is commonly used with co-immunosuppression in the paediatric population. Screening guidelines are largely adhered to but there is still room for improvement and discrepancy between PGA and PCDAI for scoring disease severity lends support to the case for a modified tool such as the weighted PCDAI. Comprehensive recording of response and remission is essential, particularly in the era of biosimilars, for ongoing evaluation of PIBD therapy and outcome.

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VMM and KM drafted the manuscript and analysed the data, HE and LJW analysed data and revised the manuscript, RM, MA, ME, JMEF, RMB, SL, FT, MM, CC, NMC, AR, MF, BV, HJ, JP, SM, SC, MC, AA and DCW collected data and appraised the manuscript, RKR oversaw project design, data collection and analysis and manuscript revision.

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Summary table	CD N=429	UC N=76	IBDU N=19	All IBD N=524
General patient characteristics				
Gender: Male	62% (267/429)	58% (44/76)	53% (10/19)	61% (321/524)
Age at diagnosis, years, median (IQR)	N=411 12.0 (9.4, 13.8)	N=74 12.3 (9.5, 14.2)	N=17 11.7 (8.9, 12.8)	N=502 12.0 (9.4, 13.9)
Age at initial treatment, years, median (IQR)	N=427 14.2 (13.5, 15.7)	N=76 13.1 (11.7, 15.4)	N=19 13.5 (11.0, 14.8)	N=522 14.1 (12.3, 15.7)
Time from diagnosis to biologic, years, median (IQR)	N=411 1.43 (0.65, 3)	N=74 1.08 (0.3, 2.23)	N=17 0.82 (0.06, 3.5)	N=502 1.36 (0.61, 2.92)
Commonest disease distribution at decision to initiate treatment (by Montreal classification)				
Colonic (L2)	40% (164/410)	-	-	40% (164/410)
Ileocolonic (L3)	41% (166/410)	-	-	41% (166/410)
Any gut proximal to TI (L4)	79% (288/364)	-	-	79% (288/364)
Perianal involvement = Yes	54% (146/270)	-	-	54% (146/270)
Extensive colitis (E3)	-	74% (54/73)	94% (16/17)	78% (70/90)

Table 1: Overview of demographics and disease details by IBD type. IQR, Inter Quartile Range; PCDAI, Paediatric Crohn's Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index

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Disease severity at initial treatment (per patient)	CD N=429	UC N=76	IBDU N=19	All IBD N=524
PGA	N=171	N=38	N=9	N=218
Mild	9% (15/171)	8% (3/38)	0% (0/9)	8% (18/218)
Moderate	55% (94/171)	45% (17/38)	22% (2/9)	52% (113/218)
Severe	36% (62/171)	47% (18/38)	78% (7/9)	40% (87/218)
PCDAI	N=217	-	-	N=217
median (IQR)	29 (20, 38)	-	-	29 (20, 38)
≤10 (Remission)	12% (26/217)	-	-	
11-30 (Mild)	47% (103/217)	-	-	59% (129/217)
31-37.5(Moderate)	17% (36/217)			
≥40 (Severe)	24% (52/217)			
PUCAI	-	N=53	N=8	N=61
median (IQR)	-	55 (40, 70)	43 (15, 58)	55 (39, 66)
0-9 (Remission)	-	4% (2/53)	25% (2/8)	7% (4/61)
10-34 (Mild)	-	11% (6/53)	13% (1/8)	11% (7/61)
35-64 (Moderate)	-	42% (22/53)	38% (3/8)	41% (25/61)
65-85 (Severe)		43% (23/53)	25% (2/8)	41% (25/61)

Table 2: Disease severity at initial treatment. PGA, Physician Global Assessment; IQR, Inter Quartile Range; PCDAI, Paediatric Crohn's Disease Activity Index; PUCAI, Paediatric Ulcerative Colitis Activity Index.

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Crohn's Disease Follow-up anti-TNFα treatment	Infliximab (Frequency%) N=1414	Adalimumab (Frequency %) N=97
Follow-up outcome		
Seen for follow-up	98% (1389/1414)	91% (88/97)
Transitioned to adult care	2% (23/1414)	8% (8/97)
Transferred to another service	0.1% (2/1414)	1% (1/97)
Median days from initial dose to follow-up (IQR)	167 (46, 350)	81 (35, 232)
Current plan		
Continue treatment	97% (1346/1388)	91% (84/92)
Stop treatment	3% (42/1388)	9% (8/92)
Reason for stopping (if treatment stopped)		
Treatment effective and discontinued	21% (9/42)	0% (0/8)
Loss of response	17% (7/42)	38% (3/8)
Poor response	29% (12/42)	50% (4/8)
Side effects / adverse events	14% (6/42)	0% (0/8)
Other	19% (8/42)	13% (1/8)
Disease severity (PGA)		
Mild	69% (500/726)	26% (17/65)
Moderate	26% (186/726)	51% (33/65)
Severe	6% (40/726)	23% (15/65)

Table 3: Outcome at follow-up in Crohn's Disease; IQR, Inter Quartile Range; PGA, Physician Global Assessment

PROM (IMPACT III)	CD	UC	IBDU	All IBD
At initial treatment				
Number of patients	429	76	19	524
Completed IMPACT III	18% (78/429)	24% (18/76)	11% (2/19)	19% (98/524)
IMPACT Score, median (IQR)	111 (92, 130)	115 (86, 127)	-	111 (91, 129)
Patients with no follow-up PROM	68% (53/78)	72% (13/18)		67% (66/98)
At follow up				
Number of treatments	1511	180	34	1725
Completed IMPACT III	4% (65/1511)	4% (7/180)	12% (4/34)	4% (76/1725)
IMPACT III score, median (IQR)	130 (96, 153)	110 (79, 114)	59 (56, 64)	123 (85, 147)

Table 4: Patient reported outcome measures; IMPACT III is a validated paediatric IBD health-related quality of life assessment tool; IQR, inter quartile range.

Clinical Indication for starting anti-TNFα therapy	Infliximab Frequency %	Adalimumab Frequency %
Crohn's Disease		
Severe perianal Crohn's disease	19% (74/395)	5% (3/63)
Active luminal Crohn's disease	77% (304/395)	81% (51/63)
Fistulating Crohn's disease	1% (4/395)	0% (0/63)
Other clinical indication	2% (6/395)	2% (1/63)
Unknown	2% (7/395)	13% (6/63)
Ulcerative Colitis		
Acute severe ulcerative colitis	43% (31/72)	0% (0/7)
Chronic refractory ulcerative colitis	56% (40/72)	100% (7/7)
Not known	1% (1/72)	0% (0/7)
Inflammatory Bowel Disease Unclassified		
Acute severe IBDU	47% (9/19)	50% (2/4)
Chronic refractory IBDU	53% (10/19)	25% (1/4)
Not known	-	25% (1/4)

Supplementary table 1: Indication for starting biological therapy IBDU, Inflammatory Bowel Disease

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Crohn's Disease IBD related surgery 87% (144/166)	Pre-biologic starting 71% (102/144)	Post-biologic starting 29% (42/144)
Right hemi-colectomy	6% (6/102)	17% (7/42)
Ileo-caecal resection	4% (4/102)	2% (1/42)
Small bowel resection	7% (7/102)	7% (3/42)
Colectomy + ileostomy (retained rectal stump)	6% (6/102)	7% (3/42)
Partial colectomy	4% (4/102)	2% (1/42)
Drainage of perianal sepsis	26% (27/102)	7% (3/42)
Insertion of Seton	9% (9/102)	5% (2/42)
EUA fistula procedure	26% (27/102)	29% (12/42)
Radiological drainage of abscess	2% (2/102)	10% (4/42)

UC 8% (14/166) IBDU (5% (8/166) IBD related surgery	Pre-biologic starting		Post-biologic starting	
	UC 0% (0/14)	IBDU 50% (4/8)	UC 100% (14/14)	IBDU 50% (4/8)
Colectomy + ileostomy (retained rectal stump)	-	0% (0/4)	79% (11/14)	100% (4/4)
Colectomy + colostomy (retained rectal stump)	-	25% (1/4)	7% (1/14)	-
Partial colectomy	-	25% (1/4)	7% (1/14)	-
Ileo-caecal resection	-	25% (1/4)	7% (1/14)	-
EUA fistula procedure	-	25% (1/4)	-	-

Supplementary Table 2. IBD related surgery EUA, examination under anaesthetic; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified

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Safety data Frequency (%)	CD		UC		IBDU		All IBD	
	IFX N=396	ADA N=63	IFX N=73	ADA N=7	IFX N=19	ADA N=4	IFX N=488	ADA N=74
Initial treatment (more than one type of reaction may have been recorded)								
Any acute reaction recorded = yes	**1% (5/396)**	**0% (0/63)**	**4% (3/73)**	**0% (0/7)**	**11% (2/19)**	**0% (0/4)**	**2% (10/488)**	**0% (0/74)**
Angioedema of upper airway	0.5% (2/396)	0% (0/63)	-	-	-	-	-	-
Bronchospasm (cough/wheeze/SOB)	0.3% (1/396)	0% (0/63)	-	-	-	-	-	-
Flushing	0.5% (2/396)	0% (0/63)	1% (1/73)	0% (0/7)	-	-	-	-
Hypotension	0.3% (1/396)	0% (0/63)	1% (1/73)	0% (0/7)	-	-	-	-
Nausea	0.3% (1/396)	0% (0/63)	1% (1/73)	0% (0/7)	-	-	-	-
Rash	0.3% (1/396)	0% (0/63)	1% (1/73)	0% (0/7)	-	-	-	-
Dizziness	-	-	1% (1/73)	0% (0/7)	-	-	-	-
Panic attacks	-	-	1% (1/73)	0% (0/7)	-	-	-	-
Itching	-	-	-	-	5% (1/19)	0% (0/19)	-	-
Other	0.3% (1/396)	0% (0/63)	-	-	5% (1/19)	0% (0/19)	-	-
Follow-up treatment	IFX N=1414	ADA N=97	IFX N=174	ADA N=6	IFX N=32	ADA N=2	IFX N=1620	ADA N=105
Acute reactions								
Any acute reaction = yes	**1%(16/1389)**	**0% (0/92)**	**2% (4/168)**	**0% (0/5)**	**10% (3/30)**	**0% (0/2)**	**1% (23/1587)**	**0% (0/99)**
Adverse events								
Any adverse event = yes	**3%(41/1389)**	**2% (2/91)**	**4% (7/168)**	**0% (0/5)**	**3% (1/30)**	**0% (0/2)**	**3%(49/1587)**	**2% (2/98)**
Alopecia	-	-	0.6% (1/168)	0% (0/5)	-	-	-	-
Blood abnormality	0.1%(2/1389)	0% (0/91)	0.6% (1/168)	0% (0/5)	-	-	-	-

Infection	2%(30/1389)	2% (2/91)	2% (3/168)	0% (0/5)	-	-	-	-
Chest pain	0.1%(2/1389)	0% (0/91)	-	-	-	-	-	-
Headache	0.1%(1/1389)	0% (0/91)	-	-	-	-	-	-
Rash	0.1%(2/1389)	0% (0/91)	-	-	3% (1/30)	0% (0/2)	-	-
Other	0.3%(4/1389)	0% (0/91)	1% (2/168)	0% (0/5)	-	-	-	-

Supplementary Table 3: Safety data by disease subtype. SOB, Shortness of Breath; IFX, infliximab; ADA, adalimumab

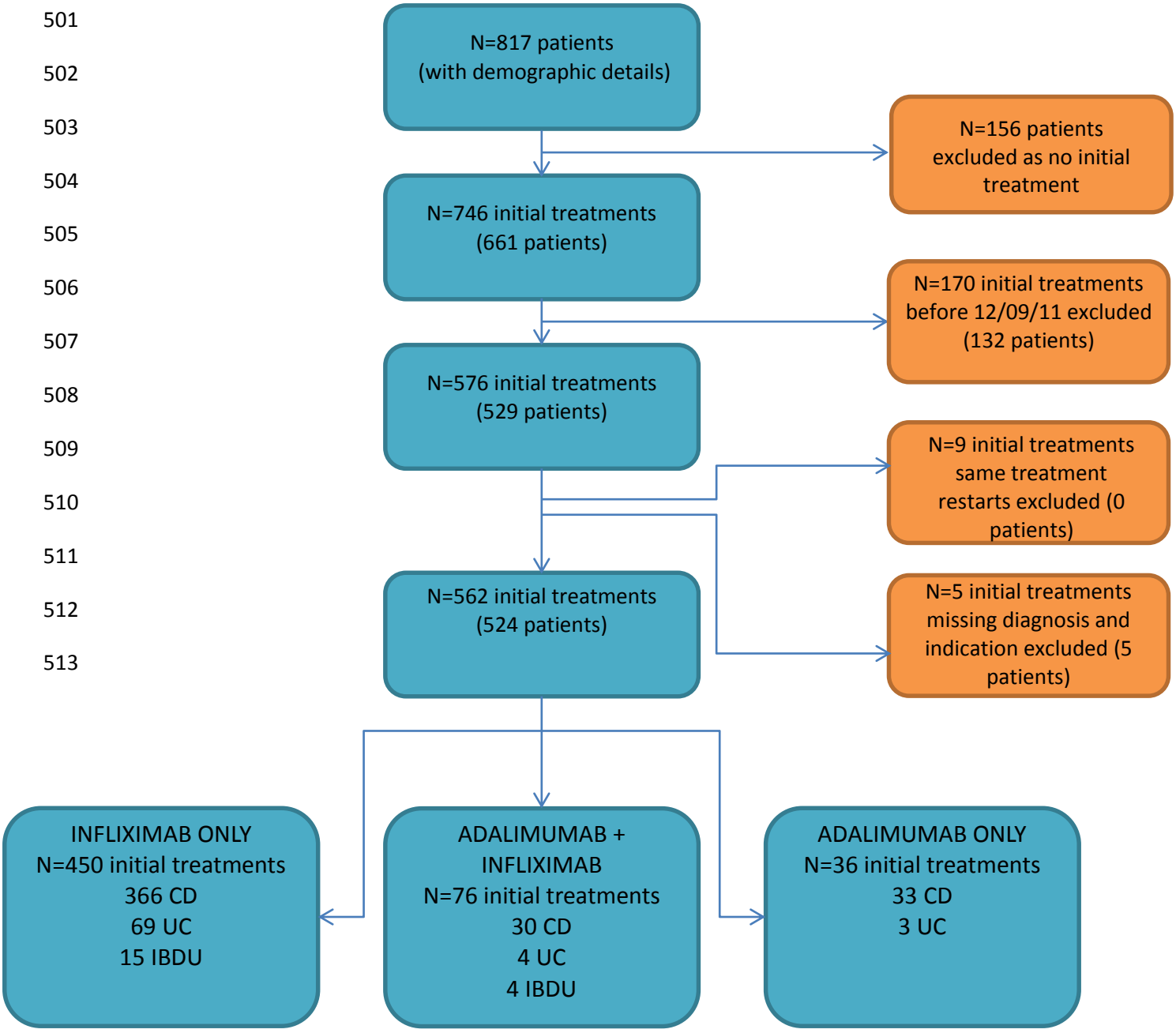

Fig 1. Patient flow chart. CD, Crohn's Disease; UC, Ulcerative Colitis; IBDU Inflammatory Bowel Disease Unclassified.