**Increased prevalence of anti-TNF therapy in paediatric inflammatory bowel disease is associated with a decline in surgical resections during childhood**

Short title: Anti-TNF therapy and childhood surgery

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Abstract

Background-Anti-tumour necrosis factor-α (anti-TNF) therapy use has risen in paediatric-onset inflammatory bowel disease (PIBD). Whether this has translated into preventing/delaying childhood surgery is uncertain. The Wessex PIBD cohort were analysed for trends in anti-TNF-therapy and surgery.

Design-All patients diagnosed with PIBD within Wessex from 1997-2017 were assessed. Prevalence of anti-TNF-therapy and yearly surgery rates (resection and perianal) during childhood (<18 years) were analysed (Pearson’s correlation, multivariate regression, Fisher’s exact).

Results- Eight-hundred-and-twenty-five children were included (498 Crohn’s disease, 272 ulcerative colitis, 55 IBD-unclassified), mean age at diagnosis 13.6 years (1.6-17.6), 39.6% female. Prevalence of anti-TNF-treated patients increased from 5.1% to 27.1% (2007-2017), p=0.0001. Surgical resection-rate fell (7.1% to 1.5%, p=0.001), driven by a decrease in Crohn’s disease resections (8.9% to 2.3%, p=0.001). Perianal surgery and ulcerative colitis resection-rates were unchanged. Time from diagnosis to resection increased (1.6 to 2.8 years, p=0.028) but mean age at resection was unchanged. Patients undergoing resections during childhood were diagnosed at a younger age in the most recent five years (2007-2011=13.1 years, 2013-2017=11.9 years, p=0.014).

Resection-rate in anti-TNF-therapy treated (16.1%) or untreated (12.2%) was no different (p=0.25). Patients started on anti-TNF-therapy <3 years post-diagnosis (11.6%) vs later (28.6%) had a reduction in resections, p=0.047. Anti-TNF-therapy prevalence was the only significant predictor of resection-rate using multivariate regression (p=0.011).

Conclusion-The prevalence of anti-TNF-therapy increased significantly, alongside a decrease in surgical resection-rate. Patients diagnosed at younger ages still underwent surgery during childhood. Anti-TNF-therapy may reduce the need for surgical intervention in childhood, thereby influencing the natural history of PIBD.

Keyword: Anti-TNF; Surgery, IBD; Crohn’s disease; ulcerative colitis, paediatric

Introduction

The treatment of inflammatory bowel disease (IBD) in children has been revolutionised by the use of anti-tumour necrosis factor-α (anti-TNF) monoclonal antibody therapy [1]. There has been a rapid increase in the use of anti-TNF medications over the last 15 years (since initial adult licencing in 2003), with symptomatic control, intestinal healing and a reasonable safety profile [2,3]. Deep remission (mucosal healing) is increasingly seen as the end-point of treatment [4]. However modifying the natural history of IBD in childhood should also result in reduction in surgical resections (for both stricturing and penetrating disease), a reduction in non-diagnostic perianal procedures (abscess drainage, seton placement) and preservation of normal growth [5].

The long-term impact of anti-TNF medications on the rates of surgery before transition to adult services in paediatric IBD is uncertain. Previous data appears to suggest that anti-TNF therapy delays but not avoids the need for surgery in childhood [6]. A recent review of surgery in adult disease found no reduction in surgical resections in those treated with anti-TNF agents, although it was expected that the individuals with the most severe disease are both exposed to anti-TNF therapy and are at the highest risk of requiring surgery [7]. Other studies considered surgical rates at a population level; work from Rungoe *et al* comparing two cohorts (1979-86 and 2003-11) demonstrating a significant reduction in surgical rates for both Crohn’s disease and ulcerative colitis paralleled by an increase in anti-TNF medication [8]. However Lazarev *et al* (2010) did not find a reduction in small bowel resection rates over time in adults with Crohn’s disease, despite increased anti-TNF use [9]. The recent ‘Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease’ (LIRIC) trial in adults, comparing outcomes after randomised escalation to either anti-TNF therapy or limited ileocaecal resection in Crohn’s disease, concluded that surgical resection remained a viable alternative to medical therapy [10]. There are potential drawbacks to long-term anti-TNF use in patients, including the risk of serious infections, immune reactions and malignancy, which must be considered and discussed when starting patients on therapy and reviewed during ongoing treatment in an open fashion [3,10,11].

In children, the rates of surgery vary depending on underlying diagnosis and severity of disease [12,13]. In previous data from our Southern United Kingdom (Wessex) region (1997-2014), 9% of patients with ulcerative colitis underwent colectomy prior to transition to adult service [13]. Three other studies over a 25 year time period (from 1996) reported colectomy rates varying between 6-24% [14–16]. In Crohn’s disease, 24% of Wessex patients underwent a surgical procedure during childhood (2002-2012) [12]. This number was comparable with other studies reporting around 1/3 patients undergoing a surgical procedure during childhood [17,18]. In contrast to the increasing incidence of disease the rates of paediatric surgery have not been reported to change over time [19,20].

The impact of increasing use of anti-TNF therapy on surgical procedure rates during childhood is important to guide use of these medications and understand prognoses for patients and families. In this study we looked at surgical and anti-TNF data in the context of disease incidence and prevalence, over an 11 year period. We aimed to determine the relationship between anti-TNF prevalence and surgical resection rates.

Methods

Southampton Children’s Hospital is specialist referral centre caring for a population of approximately 650,000 children. Patients diagnosed with inflammatory bowel disease aged <17 years of age from January 1st 1997 to December 31st 2017 in Southampton were considered for inclusion into the study (n=825). Patients who were >18 years of age on January 1st 2007 (transitioned to adult serviced) were excluded. All patients included were diagnosed in line with the modified Porto criteria applicable to that time period [21,22]. Patients were prospectively entered onto the Wessex paediatric IBD database at the time of diagnosis [23]. This is an established clinical database collating data on all patients diagnosed in Southampton (referral centre for 12 district hospitals). Data on surgical procedures and anti-TNF use were available from January 1st 2007 to December 31st 2017.

The number of patients under the care of the paediatric gastroenterology service was estimated for each year of the study (2007-17) based on-

1. The number of years a patient was in paediatric care (calculated using age at diagnosis and transition to adult care before the 18th birthday). All patients in Southampton are transitioned by their 18th birthday based on the ‘Ready, Steady, Go’ policy defined locally [24]. Patients attend joint clinic between the age of 17 and 18 years and it is not possible to list the precise age for transition of individual patients.
2. Patients reaching the age of 18 years being removed from the analysis for the following year
3. The number of patients in paediatric care in our service in 2007 (n=198) and the number of patients diagnosed for each subsequent year (table 1) [19].

From these data the annual prevalence of anti-TNF treated patients (number of patients who have received anti-TNF therapy/number of patients under paediatric care, per year-presented as % per year))and the annual rate of surgical resection (number of resections/number of patients under paediatric care, per year-presented as % per year) were derived. Mean time to surgery or anti-TNF therapy is from date of diagnosis.

Anti-TNF medication administrations (infliximab and adalimumab) were sourced from the Wessex paediatric IBD database (2007-2012) or recorded from pharmacy or electronic patient records (2013-2017). Electronic records were reviewed for the whole cohort to ensure completeness.

All initial operative procedures (stricturoplasty, small or large bowel resections, primary stoma formation) and all perianal procedures (at any time) conducted from 2007-2017 were recorded either on the Wessex paediatric IBD database (2007-2012) or sourced automatically from the electronic patient record (2013-2017). The date of procedure was also retrieved. Second stage operations (pouch formation), re-do resections and perianal examinations under anaesthetic with no surgical operation, were excluded. Data on surgical procedures occurring between 2002 and 2012 have been previously published for both Crohn’s disease and ulcerative colitis and are included in this study [12,13].

Statistical analysis was performed using Pearson correlation (expressed as Pearson’s correlation coefficient, PCC) to analyse the trend across the 11 year study period between surgery rate (perianal and resections), prevalence of patients started on anti-TNF therapy, time to surgery, time to anti-TNF and time (year of study Data are presented as mean values, with values from first and last year of study. A backward stepwise multiple linear regression model was produced to examine the relationship between surgical resection rate per year (dependant variable) and clinically relevant independent variables i) time to surgery per year, ii) time to anti-TNF per year, iii) prevalence of anti-TNF per year, iv) age at surgery per year. Year of study was incorporated into the model by using outcomes per year (independent variables above). Additional univariate regression was performed to assess the relationship between the independent variables and surgical resection rates

Due to small patient numbers in some groups Fisher’s exact test was used to assess for differences between treated and untreated groups (surgery, anti-TNF) and disease subtypes. Comparison of mean values was with Student’s T-test. Shapiro-Wilk was used to assess the distribution of the data.

Kaplan-Meier survival curves were constructed using both surgical resection and anti-TNF therapy as outcome measures, with patients data being censored at the point of transition to adult care. Additional survival analysis was conducted for surgery (event) by grouping patients into those treated with anti-TNF and those not treated, survival was to surgery (event) or transition to adult care (censored). Statistical significance was considered p=<0.05. All analysis was with SPSS v24 (IBM).

This study was registered as a service evaluation project with University Hospital Southampton NHS foundation trust department of child health.

Results

All eligible children (n=825) were included in the analysis (498 Crohn’s disease, 272 ulcerative colitis, 55 IBDU), the mean age at diagnosis was 12.59 years (1.59-17.64 years), 327 (39.6%) patients were female. The number of patients under paediatric gastroenterology care increased from 198 in 2007 to 343 in 2017, in line with the increase in disease incidence [19]. A summary of the data can be seen in table 1.

*Anti-TNF therapy*

The number of patients newly started on anti-TNF therapy increased from 2007 to 2017 (5 in 2007 to 24 in 2017); 168 patients (26.8%) had anti-TNF therapy during the study period and were treated initially with either infliximab (n=162) or adalimumab (n=6), in line with local guidelines.

The prevalence of patients who had been treated with anti-TNF increased significantly from 2007, from 5.05% patients in 2007 to 27.11% patients in 2017 (PCC=0.968, p=1x10-6). There was significant correlation between mean time to surgical resection per year and prevalence of anti-TNF treated patients (PCC=0.917, p=7x10-5). Table 2 and figure 1.

There was a no significant correlation between time from diagnosis to starting anti-TNF therapy and year of study (PCC=-0.57, p=0.067). However there was a significant positive correlation between time to starting anti-TNF and surgical resection rate per year (PCC=0.681, p=0.021). Table 2.

*Surgical resections*

There were 91 surgical resections over the 11 year period. This included six patients who had a resection at presentation, as part of making their diagnosis (one patient in each of 2007, 2009, 2010, 2012, 2013 and 2017). The rate of surgical resections per year and the actual number of resections fell across the study period from 7.07% (14 resections/198 patients) in 2007 to 1.46% (5 resections/343 patients) in 2017 (PCC=-0.833, p=0.001). See table 1 and figure 1. There was no significant difference in the rate of surgical resection between those exposed to anti-TNF medication (16.1%) and those anti-TNF naïve patients across the entire study period (12.2%) (p=0.25). When categorising patients into those who started anti-TNF <3 years after diagnosis and >3 years after diagnosis there was a statistically significant difference between surgical resection rates. In patients treated with early anti-TNF (17/146 patient - 11.6%) there was a lower rate of resection compared to those with late anti-TNF (6/21 patients 28.6%), p=0.047.

The time from diagnosis to initial surgical resection increased from 1.64 years in 2007 to 2.78 years in 2017 (PCC=0.811, p=0.002) although there was no significant increase in the age at initial surgery (14.93 in 2007 to 14.53 in 2017) (PCC=0.2, p=0.555). This suggests only patients who were young at diagnosis are still having surgery during childhood, due to a longer delay between diagnosis and surgery. The cohort was divided into two groups (2007-2011 and 2013-2017) which demonstrated a statistically significant reduction in the age at diagnosis of those undergoing surgery in 2013-17 (11.86 years), compared to the 2007-2011 group (13.05 years), p=0.014.

Univariate linear regression identified anti-TNF prevalence per year (R2 0.528, p=0.011) and mean time to anti-TNF per year (R2 0.464, p=0.021) as significant predictors of surgical resection rate. Mean time to surgery per year (R2 0.266, p=0.104) and mean age at surgery per year (R2 0.065, p=0.451) were not significant predictors. A stepwise backward multiple linear regression model was applied. Anti-TNF prevalence per year was the only variable to remain significantly associated with reduction in surgical resection rate and remain in the multivariate model. Table 3.

*Crohn’s disease and Ulcerative Colitis*

The overall use of anti-TNF agents in Crohn’s disease (136 patients, 27.3%) was greater than in ulcerative colitis (27 patients, 9.9%, p=0.00001) or IBDU (5 patients, 9.1%, p=0.045). Over the whole study period the average surgical resection rate was lower in ulcerative colitis compared to Crohn’s disease (1.5% vs 4.19%).

Of the 91 surgical resections occurring, 76 were in Crohn’s disease (66 right hemi-colectomy and 10 isolated small bowel resections) and 15 were in ulcerative colitis (all subtotal colectomy). Numbers of patients undergoing surgery were significantly higher in Crohn’s disease compared to ulcerative colitis (13.25%, vs 4.59% p=4x10-5). The reduction in surgical resections was more pronounced in the larger group of Crohn’s disease patients over the study period, the rate of resection falling from 8.9% (11/198) in 2007 to 2.3% (5/214) in 2017 (p=0.001). In smaller group of ulcerative colitis patients there was no observable significant reduction in resection rate observed with substantial variation in number of procedures per year, 4.6% (3/65) in 2007 to 0.0% (0/114) in 2017 p=0.290. See figure 1.

*Perianal surgery*

There were 37 perianal surgical procedures performed on 20 patients over the 11 year period. There was no significant change in the perianal procedure rate from 2007 to 2017 (1.52% to 2.33% respectively, R2=0.281, p=0.402).

*Survival analysis*

A survival analysis of the entire cohort was performed for anti-TNF therapy (figure 2) and surgical resections (figure 3), an event was classified as starting anti-TNF or surgical resection respectively. Patients were censored when reaching the age of transition to adult care (at 18 years). Surgery at diagnosis (in some cases leading to diagnosis) accounts for an early fall in surgical survival. Following 8 years in paediatric care 30% of patients (still in paediatric care) have been started on an anti-TNF agent and 20% have undergone a surgical resection.

Additional survival analyses were performed to compared surgery in those treated with anti-TNF and those not treated with anti-TNF (event was defined as surgical resection, patients censored at age of transition). See figure 4a. There was no significant difference between survival in either group p=0.412 (Log Rank). Surgical rates are very similar for patients in paediatric care up to 7 years post-diagnosis. At this point patients on anti-TNF (presumed more severe disease) have an increase in surgery, compared to anti-TNF naïve patients (presumed milder disease).

Sub analysis of Crohn’s disease (figure 4b) and ulcerative colitis (figure 4c) was conducted. Crohn’s disease patients treated with anti-TNF were less likely to undergo surgery until 5 years after diagnosis. After five years there was an increased risk of surgery in those treated with anti-TNF, presumably reflecting a high disease severity in this group. There was no overall difference in survival between the two groups (p=0.297, Log Rank). In contrast patients with ulcerative colitis treated with anti-TNF were at higher risk of surgery throughout the disease course (p=0.0001, Log Rank), reflecting more severe disease in this group of patients.

Discussion

These data show a significant increase in the use of anti-TNF agents from 2007-2017, with over 25% of paediatric IBD patients having had infliximab, adalimumab or both in 2017. Over the same time period there was a significant reduction in childhood surgical resection rates in paediatric IBD, largely accounted for by a reduction in the surgical resection rate in Crohn’s disease. This was accompanied by a significant increase in the time from diagnosis to surgery (a delay in time from diagnosis to surgery). There was no reduction in the rates of perianal surgery across the study period. Following stepwise multiple linear regression analysis the increase in anti-TNF therapy was the only significant predictor of surgical resection rate in the analysis. These data suggest a relative and absolute reduction in surgical resection in paediatric IBD over the last 11 years associated with an increase in anti-TNF therapy. This may be due to patients with severe or progressive disease previously requiring surgery now being treated with anti-TNF agents at an early stage, delaying or preventing the need for surgical resection.

Despite the decrease in overall surgical resection across the entire cohort there was no difference in surgical resection rates between patients treated with anti-TNF therapy and those not treated with anti-TNF therapy, which has been previously reported in other cohorts [7,25].

Analysis of the paediatric RISK IBD cohort from North America concluded that early intervention with anti-TNF is the best predictor of improved remission rates, with this group also having better growth outcomes, although surgical resection rates were not reported [26]. Recent adult data from Ma *et al* (2016) and Oh *et al* (2017) has also pointed towards early initiation of anti-TNF therapy being effective at reducing the need for intestinal surgery whereas starting anti-TNF later (>2 years post diagnosis) was associated with increased risk of surgery, presumably due to complications already having arisen [27,28]. Further adult data from 2014 and 2016 also points towards initiation during early inflammation, rather than when complications occur, as the key driver in the reduction of intestinal resections in Crohn’s disease [29,30]. Data from our cohort reflects a mix of early and late anti-TNF initiation. When comparing those starting early and late there is a statistical difference in surgical resection rates for our cohort, with lower rates in those treated early with anti-TNF (11.6% treated with anti-TNF vs 28.6% untreated, p=0.047), echoing previous findings [26]. Data on the indication for starting anti-TNF was not available.

Previous studies have reported a delay in time to surgery with anti-TNF therapy in adults, which is also evident in this paediatric cohort [28]. However multivariate linear regression analysis did not result in the increase in time to surgical resection being a significant predictor of reduction in surgical resection rate during childhood. Univariate analysis significantly associated the reduction in time to starting anti-TNF with surgical resection rate, but this did not survive multivariate analysis. This does potentially support starting anti-TNF earlier to reduce surgical resection rates.

Whether the delay results in reduced surgery in the long term (beyond childhood) is uncertain, however the benefits of remaining well throughout this growth and secondary education period is likely to have positive impacts in later life even if surgery is still required.

A potential confounding variable, accounting for an increase in time from diagnosis to surgery is improved, earlier diagnosis. However within this cohort referral patterns to the Southampton paediatric IBD referral centre have not changed over the study period, routine use of faecal calprotectin in children was not introduced to the region until 2016-17 and we have not observed a reduction in the disease severity at diagnosis [31]. Additionally, data recently published does not indicate a general shift to earlier diagnosis or improved diagnostics in children with IBD, with significant diagnostic delay remaining common in recent years [32,33]. These data suggest that the increased time from diagnosis to surgery is not accounted for by improved diagnosis. Moreover data from Coughlan *et al* described patients diagnosed at an earlier age to have higher relapse rates than older patients, suggesting a more severe phenotype [34]. This high relapse rate was unchanged from 2000-2014.

A recent study from Nordenvall *et al* did not show an overall decrease in abdominal surgery in children with IBD over a 13 year period (2002-2014), although these did show a significant difference between patients diagnosed 2002-04 and 2010-14 [35]. This study was unable to comment on the prevalence of anti-TNF medication over time due to incomplete data. Data from 1998-2013 from Larsen *et al* concluded that there was decreased surgery in children with UC and a trend towards decreased surgery in CD patients over time, with a parallel increase in anti-TNF use in both groups [36]. Both studies include data predating routine use of early anti-TNF therapy, and the authors conclude that analysis of more recent data may reveal a true decrease/delay in surgery during childhood alongside an increase in early anti-TNF use, as seen in our work.

Assessment of growth outcomes in Crohn’s disease can be used as a proxy measure of effective treatment, with improved growth reflecting adequately treated patients. Previously published 3 year outcome data from 2013-16 were available for this cohort, including patients undergoing surgery, and reported a height standard deviation score (SDS) for this group as -0.25 [37]. Patients undergoing surgery from 2002-12 had a height SDS at 1.8 years of -0.4 [12]. These data suggest comparable growth outcome over the study period, with no worsening of growth despite decreased use of surgery [12,37]. Previously surgery has been used as a treatment to promote growth in children with severe deficits [38]. These previously published data indicate there is no worsening of growth in more recent years despite lower surgery rates, something that may be related to disease control with anti-TNF therapy. Previous reports from Assa *et al* (2013) and Bamberger *et al* (2016) both report anti-TNF agents preventing height SDS falls but not restoring full growth potential [39,40]. Older data from Vasseur *et al* (2010) and Pfefferkorn *et al* (2009) both describe persistent poor growth in Crohn’s disease despite immunomodulation or biological therapy, specifically anti-TNF agents did not appear to improve height velocity [41,42].

There is a trend towards top-down medicine when treating IBD in adult populations, with early initiation of anti-TNF therapy aiming to modify disease course [43]. Whilst this is not yet recommended in paediatric practice the promise of reducing surgical resection rates with prompt initiation of anti-TNF therapy is one of the reasons leading to increased use. However it is important to remember not all patients will be at risk of requiring surgery, or of disease progression, and therefore not all require anti-TNF therapy. This is part of a complex risk-benefit strategy and discussion. There is the potential to both over-treat and for significant side-effects. Nevertheless some will progress rapidly and early intervention appears to modify risk in at least a subset patients [29,44]. Additional factors such as dose optimisation, concurrent immunosuppression and nutritional strategies are likely provide additional benefits [45,46].

Our survival analysis shows that the risk of surgery increases over time and is around 20% at 8 years. Similarly, those children remaining in paediatric care have a 30% chance of being prescribed an anti-TNF agent after 8 years. After 5 years in paediatric care around 25% of children will have been started on an anti-TNF agent, similar to previously reported data showing at 3 years a third of patients treated in North America were on an anti-TNF agent [47].

The promise of personalising therapy at diagnosis to start anti-TNF agents earlier where required and prevent high resection rates may become a reality in the next 5-10 years through application of clinical and multi-omic data [48,49]. Tools to predict and identify patients most likely to benefit from early anti-TNF therapy are now emerging, potentially providing the ability for the clinician to predict severe patients at risk of requiring surgery and modifying their risk at an early stage [50].

This study benefits from a complete and prospectively entered Wessex paediatric IBD database, although some data (surgical and anti-TNF) were added through automated integration of the electronic patient record at the time of analysis. Additional data on other medications (thiopurines, 5-aminosalicylates, methotrexate etc.) was not available throughout the entire study period, preventing comparison or correction (as potential confounders) over time. However prescribing practices of thiopurines based on local, national and international guidance has not changed significantly over this time [38,51–53]. Other potential confounders include improved imaging, improved staff training and improved supportive therapy which we were unable to account for. Surgical decision making was made by a team of four paediatric gastroenterologists, eight paediatric surgeons and two adult surgeons over the study period, reflecting shared decision making over the 11 years. Additionally there is no well established longitudinal disease severity score, describing disease severity over several years, preventing normalisation of data by disease severity.

*Conclusions*

There is a statistically significant increase in the prevalence of anti-TNF therapy over the 11 year study period. Over the same time, there was a significant decrease in the surgical resection rate in paediatric IBD. These data suggest that anti-TNF therapy may be modifying the natural history of IBD in childhood. Progression to personalising therapy within paediatric IBD now appears to be the next major challenge, balancing which patients would benefit from early introduction of anti-TNF therapy and those where an expectant approach can be adopted.

References

1 Oliveira SB, Monteiro IM. Diagnosis and management of inflammatory bowel disease in children. *BMJ* 2017;**357**:j2083. doi:10.1136/BMJ.J2083

2 Adler J, Sandberg KC, Shpeen BH, *et al.* Variation in Infliximab Administration Practices in the Treatment of Pediatric Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr* 2013;**57**:35–8. doi:10.1097/MPG.0b013e31828f1ea2

3 Hyams JS, Dubinsky MC, Baldassano RN, *et al.* Infliximab not Associated With Increased Risk of Malignancy or Hemophagocytic Lymphohistiocytosis in Pediatric Patients With Inflammatory Bowel Disease. *Gastroenterology* Published Online First: 2017. doi:10.1053/j.gastro.2017.02.004

4 Dave M, Loftus E V. Mucosal healing in inflammatory bowel disease-a true paradigm of success? *Gastroenterol Hepatol (N Y)* 2012;**8**:29–38.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3277196/pdf/GH-08-29.pdf

5 de Buck van Overstraeten A, Wolthuis A, D’Hoore A. Surgery for Crohn’s disease in the era of biologicals: a reduced need or delayed verdict? *World J Gastroenterol* 2012;**18**:3828–32. doi:10.3748/wjg.v18.i29.3828

6 Afzal NA, Ozzard A, Keady S, *et al.* Infliximab Delays but Does Not Avoid the Need for Surgery in Treatment-Resistant Pediatric Crohn’ Disease. *Dig Dis Sci* 2007;**52**:3329–33. doi:10.1007/s10620-007-8102-1

7 Kotze PG, Magro DO, Saab B, *et al.* Comparison of time until elective intestinal resection regarding previous anti-tumor necrosis factor exposure: a Brazilian study on patients with Crohn’s disease. *Intest Res* 2018;**16**:62–8. doi:10.5217/ir.2018.16.1.62

8 Rungoe C, Langholz E, Andersson M, *et al.* Changes in medical treatment and surgery rates in inflammatory bowel disease: a nationwide cohort study 1979–2011. *Gut* 2014;**63**:1607–16. doi:10.1136/gutjnl-2013-305607

9 Lazarev M, Ullman T, Schraut WH, *et al.* Small bowel resection rates in Crohnʼs disease and the indication for surgery over time: Experience from a large tertiary care center. *Inflamm Bowel Dis* 2010;**16**:830–5. doi:10.1002/ibd.21118

10 Ponsioen CY, de Groof EJ, Eshuis EJ, *et al.* Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn’s disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol* 2017;**2**:785–92. doi:10.1016/S2468-1253(17)30248-0

11 Joosse ME, Aardoom MA, Kemos P, *et al.* Malignancy and mortality in paediatric-onset inflammatory bowel disease: a 3-year prospective, multinational study from the paediatric IBD Porto group of ESPGHAN. *Aliment Pharmacol Ther* 2018;**48**:523–37. doi:10.1111/apt.14893

12 Blackburn SC, Wiskin AE, Barnes C, *et al.* Surgery for children with Crohn’s disease: indications, complications and outcome. *Arch Dis Child* 2014;**99**:420–6. doi:10.1136/archdischild-2013-305214

13 Ashton JJ, Versteegh HP, Batra A, *et al.* Colectomy in pediatric ulcerative colitis: A single center experience of indications, outcomes, and complications. *J Pediatr Surg* 2016;**51**. doi:10.1016/j.jpedsurg.2015.10.077

14 Hyams JS, Davis P, Grancher K, *et al.* Clinical outcome of ulcerative colitis in children. *J Pediatr* 1996;**129**:81–8.http://www.ncbi.nlm.nih.gov/pubmed/8757566

15 Gower-Rousseau C, Dauchet L, Vernier-Massouille G, *et al.* The natural history of pediatric ulcerative colitis: a population-based cohort study. *Am J Gastroenterol* 2009;**104**:2080–8. doi:10.1038/ajg.2009.177

16 Soon IS, Wrobel I, deBruyn JC, *et al.* Postoperative complications following colectomy for ulcerative colitis in children. *J Pediatr Gastroenterol Nutr* 2012;**54**:763–8. doi:10.1097/MPG.0b013e318245265c

17 Vernier-Massouille G, Balde M, Salleron J, *et al.* Natural history of pediatric Crohn’s disease: a population-based cohort study. *Gastroenterology* 2008;**135**:1106–13. doi:10.1053/j.gastro.2008.06.079

18 Gupta N, Cohen SA, Bostrom AG, *et al.* Risk Factors for Initial Surgery in Pediatric Patients With Crohn’s Disease. *Gastroenterology* 2006;**130**:1069–77. doi:10.1053/j.gastro.2006.02.003

19 Ashton JJ, Cullen M, Afzal NA, *et al.* Is the incidence of paediatric inflammatory bowel disease still increasing? *Arch Dis Child* 2018;:archdischild-2018-315038. doi:10.1136/archdischild-2018-315038

20 Su HY, Gupta V, Day AS, *et al.* Rising Incidence of Inflammatory Bowel Disease in Canterbury, New Zealand. *Inflamm Bowel Dis* 2016;**22**:2238–44. doi:10.1097/MIB.0000000000000829

21 Levine A, Koletzko S, Turner D, *et al.* The ESPGHAN Revised Porto Criteria for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents. *J Pediatr Gastroenterol Nutr* 2013;**58**:795–806. doi:10.1097/MPG.0000000000000239

22 IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis--the Porto criteria. *J Pediatr Gastroenterol Nutr* 2005;**41**:1–7.http://www.ncbi.nlm.nih.gov/pubmed/15990620 (accessed 19 Feb 2018).

23 Ashton JJ, Wiskin AE, Ennis S, *et al.* Rising incidence of paediatric inflammatory bowel disease (PIBD) in Wessex, Southern England. *Arch Dis Child* 2014;**99**:659–64. doi:10.1136/archdischild-2013-305419

24 Nagra A, McGinnity PM, Davis N, *et al.* Implementing transition: Ready Steady Go. *Arch Dis Child Educ Pract Ed* 2015;**100**:313–20. doi:10.1136/archdischild-2014-307423

25 Eberhardson M, Söderling JK, Neovius M, *et al.* Anti-TNF treatment in Crohn’s disease and risk of bowel resection-a population based cohort study. *Aliment Pharmacol Ther* 2017;**46**:589–98. doi:10.1111/apt.14224

26 Walters TD, Kim M-O, Denson LA, *et al.* Increased Effectiveness of Early Therapy With Anti-Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn’s Disease. *Gastroenterology* 2014;**146**:383–91. doi:10.1053/j.gastro.2013.10.027

27 Oh EH, Oh K, Han M, *et al.* Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn’s disease with poor prognostic factors. *PLoS One* 2017;**12**:e0177479. doi:10.1371/journal.pone.0177479

28 Ma C, Beilman CL, Huang VW, *et al.* Anti-TNF Therapy Within 2 Years of Crohnʼs Disease Diagnosis Improves Patient Outcomes. *Inflamm Bowel Dis* 2016;**22**:870–9. doi:10.1097/MIB.0000000000000679

29 González-Lama Y, Suárez C, González-Partida I, *et al.* Timing of Thiopurine or Anti-TNF Initiation Is Associated with the Risk of Major Abdominal Surgery in Crohn’s Disease: A Retrospective Cohort Study. *J Crohn’s Colitis* 2016;**10**:55–60. doi:10.1093/ecco-jcc/jjv187

30 Moran GW, Dubeau M, Kaplan GG, *et al.* Phenotypic Features of Crohn’s Disease Associated With Failure of Medical Treatment. *Clin Gastroenterol Hepatol* 2014;**12**:434–442.e1. doi:10.1016/j.cgh.2013.08.026

31 Ashton JJ, Coelho T, Ennis S, *et al.* Presenting Phenotype of Paediatric Inflammatory Bowel Disease (PIBD) in Wessex, Southern England 2010-13. *Acta Paediatr* Published Online First: 2015. doi:10.1111/apa.13017

32 Ricciuto A, Fish JR, Tomalty DE, *et al.* Diagnostic delay in Canadian children with inflammatory bowel disease is more common in Crohn’s disease and associated with decreased height. *Arch Dis Child* 2017;:archdischild-2017-313060. doi:10.1136/archdischild-2017-313060

33 Ashton JJ, Harden A, Beattie RM. Paediatric inflammatory bowel disease: improving early diagnosis. *Arch Dis Child* 2017;:archdischild-2017-313955. doi:10.1136/archdischild-2017-313955

34 Coughlan A, Wylde R, Lafferty L, *et al.* A rising incidence and poorer male outcomes characterise early onset paediatric inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;**45**:1534–41. doi:10.1111/apt.14070

35 Nordenvall C, Rosvall O, Bottai M, *et al.* Surgical Treatment in Childhood-onset Inflammatory Bowel Disease–A Nationwide Register-based Study of 4695 Incident Patients in Sweden 2002-2014. *J Crohn’s Colitis* 2018;**12**:157–66. doi:10.1093/ecco-jcc/jjx132

36 Larsen MD, Qvist N, Nielsen J, *et al.* Use of Anti-TNFα Agents and Time to First-time Surgery in Paediatric Patients with Ulcerative Colitis and Crohn’s Disease Anti-TNF α Agents and Surgery in Paediatric IBD Patients. Published Online First: 2016. doi:10.1093/ecco-jcc/jjw017

37 Ashton JJ, Bonduelle Q, Mossotto E, *et al.* Endoscopic and Histological Assessment of Paediatric Inflammatory Bowel Disease over a 3-Year Follow-up Period. *J Pediatr Gastroenterol Nutr* 2018;**66**. doi:10.1097/MPG.0000000000001729

38 Sandhu BK, Fell JM, Beattie RM, *et al.* Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. *J Pediatr Gastroenterol Nutr* 2010;**50 Suppl 1**:S1-13. doi:10.1097/MPG.0b013e3181c92c53

39 Assa A, Hartman C, Weiss B, *et al.* Long-term outcome of tumor necrosis factor alpha antagonist’s treatment in pediatric Crohn’s disease. *J Crohn’s Colitis* 2013;**7**:369–76. doi:10.1016/j.crohns.2012.03.006

40 Bamberger S, Martinez Vinson C, Mohamed D, *et al.* Growth and Adult Height in Patients with Crohn’s Disease Treated with Anti-Tumor Necrosis Factor α Antibodies. *PLoS One* 2016;**11**:e0163126. doi:10.1371/journal.pone.0163126

41 Vasseur F, Gower-Rousseau C, Vernier-Massouille G, *et al.* Nutritional Status and Growth in Pediatric Crohn’s Disease: A Population-Based Study. *Am J Gastroenterol* 2010;**105**:1893–900. doi:10.1038/ajg.2010.20

42 Pfefferkorn M, Burke G, Griffiths A, *et al.* Growth Abnormalities Persist in Newly Diagnosed Children With Crohn Disease Despite Current Treatment Paradigms. *J Pediatr Gastroenterol Nutr* 2009;**48**:168–74. doi:10.1097/MPG.0b013e318175ca7f

43 D’Haens GR. Top-down therapy for IBD: rationale and requisite evidence. *Nat Rev Gastroenterol Hepatol* 2010;**7**:86–92. doi:10.1038/nrgastro.2009.222

44 Ashton JJ, Beattie RM. Improving remission rates in newly diagnosed paediatric ulcerative colitis. *lancet Gastroenterol Hepatol* 2017;**2**:838–9. doi:10.1016/S2468-1253(17)30289-3

45 Hendy P, Hart A, Irving P. Anti-TNF drug and antidrug antibody level monitoring in IBD: a practical guide. doi:10.1136/flgastro-2014-100527

46 Forbes A, Escher J, Hébuterne X, *et al.* ESPEN guideline: Clinical nutrition in inflammatory bowel disease. *Clin Nutr* 2017;**36**:321–47. doi:10.1016/j.clnu.2016.12.027

47 Hyams JS, Lerer T, Griffiths A, *et al.* Long-term outcome of maintenance infliximab therapy in children with Crohn’s disease. *Inflamm Bowel Dis* 2009;**15**:816–22. doi:10.1002/ibd.20845

48 Waljee AK, Lipson R, Wiitala WL, *et al.* Predicting Hospitalization and Outpatient Corticosteroid Use in Inflammatory Bowel Disease Patients Using Machine Learning. *Inflamm Bowel Dis* 2018;**24**:45–53. doi:10.1093/ibd/izx007

49 Mossotto E, Ashton JJ, Coelho T, *et al.* Classification of Paediatric Inflammatory Bowel Disease using Machine Learning. *Sci Rep* 2017;**7**. doi:10.1038/s41598-017-02606-2

50 Siegel CA, Horton H, Siegel LS, *et al.* A validated web-based tool to display individualised Crohn’s disease predicted outcomes based on clinical, serologic and genetic variables. *Aliment Pharmacol Ther* 2016;**43**:262–71. doi:10.1111/apt.13460

51 Ruemmele FM, Veres G, Kolho KL, *et al.* Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn’s disease. *J Crohns Colitis* 2014;**8**:1179–207. doi:10.1016/j.crohns.2014.04.005

52 Turner D, Levine A, Escher JC, *et al.* Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;**55**:340–61. doi:10.1097/MPG.0b013e3182662233

53 Kammermeier J, Morris MA, Garrick V, *et al.* Management of Crohn’s disease. *Arch Dis Child* 2016;**101**:475–80. doi:10.1136/archdischild-2014-307217

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year** | **Patients under paediatric care** | **New diagnoses per year** | **Mean age at diagnosis per year** | **Number of abdominal resections\***  | **Rate of abdominal resection per year** | **Average time to abdominal resection (years)** | **Average age at resection (years)** | **Number of perianal surgeries** | **Rate of perianal surgery per year** | **Patients treated with anti-TNF**  | **Prevalence of anti-TNF treated patients**  | **Number of patients newly starting anti-TNF**  | **Median time to starting anti-TNF (years)** |
| **2007** | 198 | 52 | 12.46 | 14 | 7.07% | 1.64 | 14.93 | 3 | 1.52% | 10 | 5.05% | 5 | 3.25 |
| **2008** | 217 | 47 | 12.00 | 11 | 5.07% | 1.59 | 14.87 | 3 | 1.38% | 13 | 5.99% | 3 | 1.55 |
| **2009** | 257 | 67 | 12.23 | 8 | 3.11% | 0.74 | 14.12 | 1 | 0.39% | 12 | 4.67% | 4 | 1.22 |
| **2010** | 269 | 47 | 13.20 | 11 | 4.09% | 1.40 | 14.23 | 0 | 0.00% | 17 | 6.32% | 7 | 3.18 |
| **2011** | 285 | 58 | 12.91 | 5 | 1.75% | 1.42 | 15.20 | 0 | 0.00% | 29 | 10.18% | 14 | 1.52 |
| **2012** | 309 | 64 | 13.05 | 12 | 3.88% | 1.79 | 15.64 | 3 | 0.97% | 48 | 15.53% | 22 | 1.52 |
| **2013** | 316 | 51 | 12.90 | 12 | 3.80% | 2.53 | 13.71 | 4 | 1.27% | 62 | 19.62% | 24 | 1.61 |
| **2014** | 327 | 58 | 12.53 | 6 | 1.83% | 3.03 | 15.88 | 10 | 3.06% | 75 | 22.94% | 24 | 1.80 |
| **2015** | 329 | 56 | 13.20 | 3 | 0.91% | 2.91 | 15.28 | 5 | 1.52% | 77 | 23.40% | 15 | 1.30 |
| **2016** | 327 | 56 | 12.54 | 4 | 1.22% | 2.50 | 15.15 | 0 | 0.00% | 79 | 24.16% | 21 | 1.48 |
| **2017** | 343 | 71 | 13.31 | 5 | 1.46% | 2.78 | 14.53 | 8 | 2.33% | 93 | 27.11% | 29 | 0.95 |
| **Total over 11 years** | **N/A** | **627** |  | **91** |  |  |  | **37** |  | **N/A** |  | **168** |  |
| **Mean over 11 years** |  |  | **12.59** |  | **3.11%** | **2.03** | **14.87** |  | **1.13%** |  | **15.00%** |  | **1.23** |

Tables and Figures

Table 1- Surgical, anti-TNF and patient data from 2007-2017. Data are expressed as absolute numbers, rates or overall prevalence per year of study. Overall absolute numbers and rates are calculated for the entire cohort.

\*Abdominal resection refers to colectomy (total, subtotal, right hemi) and small bowel resections.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Surgical Resection rate per year** | **Mean time to resection per year** | **Perianal surgery rate per year** | **Anti-TNF prevalence per year** | **Mean time to anti-TNF per year** | **Year of study** | **Mean age at resection per year** |
| **Surgical Resection rate per year** | Pearson Correlation (p value) | 1 | -0.516 (0.104) | -0.039 (0.910) | -0.727\* (**0.011**) | 0.681\* (**0.021)** | -0.833\* (**0.001)** | -0.254 (0.451) |
| **Mean time to resection per year** | Pearson Correlation (p value) |  | 1 | 0.646\* (**0.032)** | 0.917\* (**7x10-5)** | -0.294 (0.380) | 0.811\* (**0.002)** | 0.327 (0.327) |
| **Perianal surgery rate per year** | Pearson Correlation (p value) |  |  | 1 | 0.458 (0.157) | -0.153 (0.654) | 0.281 (0.402) | 0.306 (0.360) |
| **Anti-TNF prevalence per year** | Pearson Correlation (p value) |  |  |  | 1 | -0.534 (0.091) | 0.968\* (**1x10-6)** | 0.276 (0.412) |
| **Mean time to anti-TNF per year** | Pearson Correlation (p value) |  |  |  |  | 1 | -0.570 (0.067) | -0.091 (0.790) |
| **Year of study** | Pearson Correlation (p value) |  |  |  |  |  | 1 | 0.200 (0.555) |
| **Mean age at resection per year** | Pearson Correlation (p value) |  |  |  |  |  |  | 1 |

Table 2- Pearson correlation analysis for all variables for 2007-2017. Correlation ranges from -1 (perfect negative correlation) to 0 (no correlation) to 1 (perfect positive correlation. Year of study was entered as 1 (2007) to 11 (2017).

Table 3- Stepwise backward multiple regression model. Dependant variable- surgical resection rate per year. Following application of all 4 models only anti-TNF prevalence was a significant predictor of surgical resection rate over the study period.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** |  | **Unstandardized Coefficients** |  | **Standardized Coefficients** | **t** | **P value =** | **95.0% Confidence Interval for B** |
|  |  | **B** | **Std. Error** | **Beta** |  |  | **Lower Bound** | **Upper Bound** |
|  |  |  |  |  |  |  |  |  |
| **1** | Mean age at surgery per year | -.372 | .670 | -.130 | -.555 | .599 | -2.012 | 1.268 |
|  | Anti-TNF prevalence per year | -.268 | .166 | -1.238 | -1.616 | .157 | -.674 | .138 |
|  | Mean time to anti-TNF per year | .561 | .809 | .222 | .694 | .514 | -1.418 | 2.540 |
|  | Mean time to surgical resection per year | 1.840 | 1.742 | .727 | 1.056 | .331 | -2.422 | 6.101 |
|  |  |  |  |  |  |  |  |  |
| **2** | Anti-TNF prevalence per year | -.261 | .157 | -1.204 | -1.660 | .141 | -.632 | .111 |
|  | Mean time to anti-TNF per year | .585 | .767 | .231 | .763 | .470 | -1.228 | 2.397 |
|  | Mean time to surgical resection per year | 1.659 | 1.624 | .655 | 1.021 | .341 | -2.181 | 5.499 |
|  |  |  |  |  |  |  |  |  |
| **3** | Anti-TNF prevalence per year | -.344 | .110 | -1.586 | -3.114 | .014 | -.598 | -.089 |
|  | Mean time to surgical resection per year | 2.375 | 1.290 | .938 | 1.841 | .103 | -.600 | 5.350 |
|  |  |  |  |  |  |  |  |  |
| **4** | **Anti-TNF prevalence per year** | **-.157**  | **.050** | **-.727** | **-3.172**  | **.011** | **-.270** | **-.045** |

Figure 1- Surgical resection rate per year (Red) and anti-TNF prevalence per year (Blue) from 2007 to 2017 for all paediatric inflammatory bowel disease patients. Surgical resection rates per year for Crohn’s disease (Green) and ulcerative colitis (Orange) are included as a percentage of patients with Crohn’s disease and ulcerative colitis respectively. There is a significant reduction in overall surgical resection rates (0.001), driven by a significant reduction in resection rates in Crohn’s disease (0.001) over the 11 year period. There was a significant increase in anti-TNF prevalence (p=0.000001). Data are expressed as a percentage of patients during that year.

Figure 2- Kaplan-Meier plot for anti-TNF therapy (green). Patients were included until an event (anti-TNF initiation) or until transition to adult services. No patients in paediatric care were started on anti-TNF therapy after 8 years in care.

Figure 3- Kaplan-Meier plot for surgical resection (orange). Patients were included until an event (surgery) or until transition to adult services. Overall rates of surgery are lower that anti-TNF therapy throughout childhood.

Figure 4a- Kaplan-Meier plot for surgical resection in anti-TNF treated (blue) and untreated (red) patients. Patients were included until an event (surgical resection) or until transition to adult services (censored). There was no significant difference between groups, p=0.412 (Log Rank)

Figure 4b- Kaplan-Meier plot for surgical resection, for Crohn’s disease, in anti-TNF treated (blue) and untreated (red) patients. Patients were included until an event (surgical resection) or until transition to adult services (censored). There was no significant difference between groups, p=0.297 (Log Rank)

Figure 4c- Kaplan-Meier plot for surgical resection, for ulcerative colitis, in anti-TNF treated (blue) and untreated (red) patients. Patients were included until an event (surgical resection) or until transition to adult services (censored). There was a significant difference between groups, with those treated with anti-TNF at higher risk of surgery, p=0.00001 (Log Rank)