Anti-TNF Therapy Reduces Ionizing Radiation Exposure in Patients with Ulcerative Colitis

Abstract
Background: Patients with ulcerative colitis (UC) may be exposed to ionizing radiation for evaluation of disease with inherent risks from protracted exposure. Meanwhile, evolving definitions of disease control with evolving treatment paradigms have led to earlier introduction of biological therapy. Our aim was to compare the effective radiation dose prior to and 1 and 3 years after initiating anti-TNF therapy or corticosteroid in patients with UC.

Methods: We performed a retrospective review of UC patients treated with Infliximab or corticosteroids at our institution from 2005-2012.

Results: We analysed 102 patients with ulcerative colitis (66 anti-TNF and 36 corticosteroid treated). Demographics and disease characteristics between the two groups were similar. The decrease in mean number of radiology studies between the year preceding and the year following initiation of therapy was significantly larger in the Infliximab group compared to the corticosteroid group (-2.5 vs. -0.6, CI=-3.3 to -0.4, p=0.009). Linear regression analysis suggested a statistically significant decrease in the number of imaging studies by 2 with the use of Infliximab compared to the corticosteroid group within a year of therapy. Differences between the two groups in the number imaging studies 3 years after therapy and in the cumulative effective radiation dose exposure 1 and 3 years after therapy did not reach statistical significance.

Conclusion: Anti-TNF therapy is associated with a significant reduction in diagnostic imaging exposure at 1 year after therapy.

Keywords: Ulcerative colitis, Infliximab, Corticosteroid, Diagnostic radiation exposure

Introduction
Ulcerative colitis (UC) is an idiopathic, chronic inflammatory disease affecting the colon characterised by a relapsing and remitting course. It mostly affects the young and middle aged generally requiring lifelong therapy [1]. The prevalence in the UK is approximately 200 per 100,000 of the population with an increasing incidence globally in ethnic and racial groups in developed and developing countries [2,3]. Chronic active disease has a significant and negative impact on patient’s lives as evidenced by reduced health related quality of life scores and adverse effect on work productivity [4-7]. Patients with UC have a higher risk of developing colorectal cancer than the general population, which in itself is a function of the duration of and inflammatory burden from the disease [8-10].

Classical therapy for UC until recently has consisted of the stepwise introduction of mesalazine, corticosteroids and immunomodulators or consideration of surgery. Significant limitations of this therapeutic armamentarium include a lack of consistent remission, side effects of corticosteroid therapy, concerns regarding increased lymphoma risk and non-melanoma skin cancer with thiopurine therapy [8,11]. Longitudinal follow-up data have shown colectomy rates for extensive colitis at 10 years to be as high as 30% with relapsing disease noted in 83% at 10-year follow-up [12,13].

A little over a decade ago, Anti-tumour necrosis factor antibodies (Anti-TNF), biologics hitherto evaluated and used in Crohn’s disease (CD), were evaluated in controlled trials for UC demonstrated efficacy in moderate to severe UC in pivotal trials [14-17].
Rapid strides in the understanding of the immuno-pathogenesis of inflammatory bowel disease (IBD) coupled with bolder definitions of disease control and emphasis on mucosal healing rather than symptom control alone have changed the therapeutic paradigm with earlier introduction of Anti-TNF therapy in well selected patients.

Meanwhile, patients with IBD are frequently exposed to diagnostic medical radiation for the diagnosis and evaluation of disease, its complications and extra-intestinal manifestations [18-22]. It is widely appreciated that protracted exposure to diagnostic imaging with its potential cumulative downstream effects may contribute to risk of malignancy [22-25]. Although radiation exposure with its inherent risks is higher in CD, several groups including ours have shown that the risk in UC is also disparate but real and of clinical concern [19-22].

It seems plausible that Anti-TNF therapy through its ability to induce clinical remission and to its extent mucosal healing, should also reduce the exposure to ionizing radiation which itself is often a function of disease activity that drives investigations. Despite this there are very limited data on modern therapeutic paradigms influencing radiation exposure in IBD and virtually no data exist for the effect of Anti-TNF therapy on radiation exposure in UC [26]. The objective of our study was to study the effective radiation dose in the year before and 1 and 3 years after initiating Anti-TNF or corticosteroid therapy in patients with UC.

**Methods and Results**

**Study design and patient population**

We conducted a retrospective review of ulcerative colitis patients who were treated with Infliximab or corticosteroids at our institution. Our institution is a large secondary care centre serving a population of 1 million and manages a just over 2500 patients with IBD. Patients who were initiated on treatment with Infliximab or corticosteroids (Prednisolone) between October 2005 and December 2012 were identified from the electronic database system. Patients were excluded from the study if they were less than 18 years old or started on either treatment before October 2005 or after December 2012. The diagnosis of UC in these patients had been established by histology with extent determined by endoscopy. Patients with all any extent of ulcerative colitis, including proctitis, were included if they met other eligibility criteria.

Patients who were started on Infliximab received a loading regimen of 5 mg/kg IV infusion at weeks 0, 2 and 6, followed by maintenance infusions every 8 weeks. Patients in the corticosteroid group had no exposure to Infliximab in the year before or the year after initiation of steroids.

**Data Collection**

Clinical data including patient demographics (age, gender, age at diagnosis and smoking status) disease phenotype (Montreal classification), duration of disease, presence of extra-intestinal manifestations (EIM) and drug therapy were collected from the electronic database. Our Institutional Review Board approved the study.

**Radiologic studies**

All diagnostic-imaging studies performed at our institution 1 year before, and 1 and 3 years after initiation of Infliximab or corticosteroid in each patient were obtained from the electronic medical record. The effective and cumulative radiation doses were calculated from published tables from the Royal College of Radiologists, UK (Table 1) [27].

**Statistical analysis**

Statistical analysis was performed using Stats Direct Version 2.8.0 (27/10/2013, StatsDirect Ltd.), with a level of statistical significance set at 95%. Normally distributed data were summarized and analyzed using parametric methods, and data found to be skewed and not normally distributed were summarized and analyzed using non-parametric methods. Categorical data were presented and analyzed using cross tabulations, frequencies and percentages.

Demographic and disease characteristics were compared between the Infliximab and corticosteroid cohorts using the chi-square test for categorical variables and Student’s t-test for continuous variables. The total number of radiologic exams and cumulative effective dose of radiation were calculated for each patient for the year before, 1 year and 3 years after initiation of therapy. The mean cumulative effective dose of radiation and number of radiologic exams for each year were calculated for both groups and compared within the groups using the Wilcoxon signed rank test. The differences in the mean number of studies and mean annual cumulative effective dose of radiation were separately compared between the two groups using Student’s t test for 1 year before and 1 year after, and 1 year before and 3 years after therapy. Linear regression was used with change in dose or number of imaging studies as the dependent variable. The independent variables included in the model were treatment group, age, sex, disease duration, smoking, location and presence of extra-intestinal manifestations.

**Results**

**Patient characteristics**

Between October 2005 and December 2012, 66 patients were initiated on Infliximab and 36 were initiated on corticosteroids. Out of the 66 Infliximab treated patients, 22 were on Infliximab for at least 3 years. Demographic and clinical characteristics of the 102 patients are shown in Table 2.

There was no significant difference in mean age, gender, disease duration, age of diagnosis, EIM, smoking status or disease severity between the Infliximab and corticosteroid treated groups.

**Table 1** Standardized radiation dose for common GI-related diagnostic imaging procedures.

<table>
<thead>
<tr>
<th>Diagnostic procedure</th>
<th>Effective dose of radiation (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXR</td>
<td>0.7</td>
</tr>
<tr>
<td>Barium enema</td>
<td>7.2</td>
</tr>
<tr>
<td>CT abdomen/pelvis</td>
<td>10.0</td>
</tr>
<tr>
<td>CT enteroclysis/Enterography</td>
<td>10.0</td>
</tr>
<tr>
<td>CT colonography</td>
<td>10.2</td>
</tr>
</tbody>
</table>
location between the two groups. Sixty percent of patients in the corticosteroid group were treated with immunosuppressant’s such as thiopurines (6-mercaptopurine or azathioprine), methotrexate or cyclosporine during the study period vs. 52% in the Infliximab cohort (p=0.06).

Table 3 shows the various sources of radiation exposure in both groups in the year before and 1 year after therapy.

### Demographic Parameters

<table>
<thead>
<tr>
<th>Demographic Parameters</th>
<th>Anti-TNF group, n=66</th>
<th>Corticosteroid group, n=36</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Mean +/- SD</td>
<td>Mean +/- SD</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>49.9 (+/-14.5)</td>
<td>51.0 (+/-17.4)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>25 -76</td>
<td>18 -90</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Males</td>
<td>Female</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>43 (65%)</td>
<td>22 (61%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>23 (35%)</td>
<td></td>
</tr>
<tr>
<td>Disease duration (yrs)</td>
<td>Mean +/- SD</td>
<td>Mean +/- SD</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>9.1 (+/-7.9)</td>
<td>7.7 (+/-7.6)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>Mean +/- SD</td>
<td>Mean +/- SD</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>40.8 (+/-15.5)</td>
<td>43.9 (+/-16.2)</td>
<td></td>
</tr>
<tr>
<td>Smokers (current/ex)</td>
<td>Mean +/- SD</td>
<td>Mean +/- SD</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>20 (30%)</td>
<td>10 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

### Extent

<table>
<thead>
<tr>
<th>Extent</th>
<th>Anti-TNF group, n=66</th>
<th>Corticosteroid group, n=36</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1 (Proctitis)</td>
<td>0%</td>
<td>5 (14%)</td>
<td></td>
</tr>
<tr>
<td>E2 (Left sided)</td>
<td>32 (48%)</td>
<td>16 (44%)</td>
<td>0.95</td>
</tr>
<tr>
<td>E3 (Extensive)</td>
<td>34 (52%)</td>
<td>15 (42%)</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>38 (+/-2)</td>
<td>30 (+/-4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hb</td>
<td>9.8 (+/- 0.5)</td>
<td>10.2 (+/-0.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>EIM</td>
<td>11 (17%)</td>
<td>5 (14%)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Number of radiologic studies

**One year after therapy:** The mean numbers of radiologic studies in the year before and 1 year after initiation of Infliximab (n=66) or corticosteroid therapy (n=36) are shown in Figure 1. In the year preceding initiation of therapy, patients in the Infliximab group underwent a mean of 4.0 ± 3.9 studies. In the year following initiation of Infliximab, the mean number of studies per patient dropped significantly to a mean of 1.5 ± 2.9 (p=0.02). In the year before initiation of corticosteroids, a mean of 1.9 ± 2.0 radiological studies were performed. In the year after treatment with steroids, there was no significant change in the mean number of studies (1.3 ± 2.4, p=0.1). The decrease in mean number of radiology studies between the year preceding and the year following initiation of therapy was significantly larger in the Infliximab group compared to the corticosteroid group (-2.5 vs. -0.6, CI= -3.3 to -0.4, p=0.009).

**Three years after therapy:** The mean numbers of radiologic studies in the year before and 3 years after initiation of Infliximab (n=22) or corticosteroid therapy (n=24) are shown in Figure 2. The mean baseline number of radiological studies, that is, the number of radiological studies a year before therapy, was different in the 3 year after therapy subgroup compared to the 1 year after therapy subgroup as there were less number of patients (n=22) on Infliximab for 3 years. In the year preceding initiation of therapy, patients in the Infliximab group underwent a mean of 2.7 ± 2.7 studies. In 3 years following initiation of Infliximab, the mean number of studies per patient dropped to a mean of 1.9 ± 2.9 (p=0.3). In the year before initiation of corticosteroids (n=24), a mean of 1.6 ±2.0 radiological studies were performed. Three years following treatment with steroids, there was no significant change in the mean number of studies (1.7 ± 1.44, p=0.8). The difference in mean number of radiology studies between the year

---

**Table 2** Demographics and disease characteristics of patients with Ulcerative Colitis treated with anti-TNF or corticosteroid therapy from 10/2005 till 12/2012.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Infliximab group</th>
<th>Steroid group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXR</td>
<td>121</td>
<td>21</td>
<td>0.001</td>
</tr>
<tr>
<td>CT-A/P or CT-E</td>
<td>12</td>
<td>7</td>
<td>0.21</td>
</tr>
<tr>
<td>MR-E</td>
<td>2</td>
<td>5</td>
<td>0.16</td>
</tr>
<tr>
<td>Barium-FT</td>
<td>4</td>
<td>1</td>
<td>0.53</td>
</tr>
</tbody>
</table>

**Table 3** Various sources of radiation exposure in both groups in the year before and 1 year after therapy.
preceding and three years following initiation of therapy was not statistically significant (-0.8 in the Infliximab group vs. +0.1 in the steroid group, CI=-3.1 to +1.2, p=0.3).

**Cumulative Radiation Dose**

**One year after therapy:** The cumulative effective dose of diagnostic medical radiation in the year before and 1 year after initiation of Infliximab or corticosteroid therapy are shown in Figure 3. Compared to the year preceding initiation of therapy, patients in the Infliximab group had a significant reduction in cumulative radiation dose exposure in the year following therapy (reduction from 4.1 ± 7.0 mSv to 1.2 ± 3.9 mSv, p=0.002). The corticosteroid group showed a decrease in cumulative radiation dose exposure 1-year post therapy (3.2 ± 5.2 mSv 1 year prior vs. 1.0 ± 3.1 mSv 1 year after, p=0.6). The difference in radiation doses between the two groups in the year preceding and the year following initiation of therapy was not significant (-2.2 mSv in the Infliximab group vs. -1.4 in the steroid group, CI=-2.3 to +3.7, p=0.6).

**Three years after therapy:** The cumulative effective dose of diagnostic medical radiation in the year before and 3 years after initiation of Infliximab (n=22) or corticosteroid therapy (n=24) are shown in Figure 4. Compared to the year preceding initiation of therapy, patients in the Infliximab group had a reduction in cumulative radiation dose exposure three years following therapy (reduction from 1.8 ± 3.2 mSv to 1.0 ± 3.1 mSv, p=0.4). The corticosteroid group showed a decrease in cumulative radiation dose exposure 3 years post therapy (2.5 ± 4.4 mSv 1 year prior vs. 1.1 ± 2.5 mSv 3 years after, p=0.2). The difference in radiation doses between the two groups in the year preceding and 3 years following initiation of therapy was not significant (-0.8 in the Infliximab group vs. -1.4 in the steroid group, CI=-2.3 to +3.7, p=0.6).

**Multiple linear regression analysis**

A multiple linear regression model was used to determine predictors for high diagnostic radiation exposure. Exposure variables in the model included gender, disease duration, age of diagnosis, smoking, disease location and presence of EIM. The analysis suggested a statistically significant decrease in the number of imaging studies by 2 with the use of Infliximab after 1 year (r=0.2, p =0.03). The regression analysis for change in number imaging studies 3 years after therapy and change in cumulative effective radiation dose 1 and 3 years after therapy did not reach statistical significance. None of the other predictor variables (gender, disease duration, age of diagnosis, smoking, disease location and presence of EIM) showed statistically significant associations with high radiation dose.

**Discussion**

Results from landmark clinical trials ACT 1 and ACT 2 and by long term real-life cohort studies have shown that Infliximab is superior to placebo in achieving clinical response, remission, mucosal healing and corticosteroid sparing effects with some evidence from extension studies demonstrating maintenance of benefit and health related QoL up to 3 years with Infliximab therapy [15-17, 22-26,28-30]. Similarly, recent trial data has confirmed these findings in patients treated with Adalimumab [31-34] although a recent network meta-analysis showed no clinical superiority of either Anti-TNF agent [35]. Bolder definitions of disease control fuelled by optimism from effective Anti-TNF therapy have changed clinician perception of what can be achieved for our patients with recognition of the impact on disability for which little or no data exist [36]. To the best of our knowledge however our study is the first to evaluate the impact of anti-TNF therapy on imaging and effective radiation doses from diagnostic imaging in patients with UC.

We observed that UC patients treated with Anti-TNF therapy underwent fewer diagnostic-imaging investigations in the year following initiation of therapy when compared to the preceding year. Linear regression analysis suggested a statistically significant decrease in the number of imaging studies by 2 with the use of Infliximab within a year of therapy, after adjusting for age, gender, disease duration, disease location and disease behavior. This reduction was mainly attributable to the reduction in the
number of plain abdominal radiographs performed the year after Anti-TNF therapy.

Although there has been an increasing trend in our institution towards magnetic resonance enterography or enterolysis (MR-E) in IBD patients the changes in the number of MR-E scans both our cohorts was not statistically significant and would not account for the reduction in imaging studies in as seen in the Anti-TNF group. Furthermore, small bowel imaging in UC should be reserved for the well-selected patient and driven by the clinical question or diagnostic uncertainty and is not routinely performed unless there is clinical suspicion of Crohn’s disease [37].

Disease extent was comparable in both groups with 48% and 44% having Montreal E2 disease, and 52% and 42% having E3 disease in the Anti-TNF and corticosteroid treated groups respectively. We were unable to ascertain the exact smoking status as ex-smokers or current amongst those patients who had a smoking history through the study period and although it is plausible that “current” smoking may have had a protective effect on UC the percentages in both groups were similar (30% in Anti-TNF and 28% in corticosteroid group) and it is unlikely in our opinion that this would have influenced our observations significantly.

Our study is probably the first to report the effect of Anti-TNF therapy on the number of radiological imaging investigations and cumulative effective dose in UC patients. The retrospective design is however, subject to inherent flaws. Our sample size was relatively small. A larger sample size may have permitted us to perform sub-group analyses on cohorts with different disease extents. Despite this we were able to detect significant and clinically detectable differences in diagnostic imaging between the Anti-TNF and corticosteroid groups. It is likely that radiation exposure was underestimated as we could only include procedures that were completed at our center. Furthermore we used standardized tables to record typical radiation received from various procedures although variability in technique used within procedures, patient size, equipment and adequacy of views obtained could result in individual variations in doses received. That said, our cohort was followed at our center for the entire period of observation and as the sole provider for this patient population through the British National Health Service, it is extremely unlikely that significant investigation would have been performed outside our institution.

Our data from a cohort from a large secondary care center, is likely to be reflective of “real-life” experience with Anti-TNF therapy in UC and thus more generalizable than controlled trial evidence. As Anti-TNF therapies are used for the induction and then maintenance of remission in UC it seemed logical to assess their effect on diagnostic radiation exposure with long-term therapy, which could address the possibility of regression to the mean. We extended our observations to 3 years after Anti-TNF therapy and noted that in the Anti-TNF group (n=22), there was a reduction in the cumulative radiation dose (1.8 vs 1.0 mSv, p=0.4) and number of imaging studies (2.7 vs 1.9, p=0.3). In the corticosteroid group, although there was a reduction noted in the cumulative radiation dose (2.5 vs. 1.1 mSv, p=0.2), there was nearly no change in the number of imaging studies (1.6 vs. 1.7, p=0.8).

Whether long-term follow-up of such cohorts continue to show clinically significant reductions in number and cumulative effective doses from radiographic procedures remains to be seen. Indeed it is plausible that concerns regarding opportunistic infection or indeed risk of malignancy over longer periods of immunosuppressant therapy might instigate further investigation and thus increase exposure to ionizing radiation or arguably mitigate any radiation sparing effect of Anti-TNF therapy. Such risk notwithstanding, the near futility of prolonged corticosteroid exposure with inherent risks underpins the need for timely escalation and treatment optimization and Immunosuppressants are likely to remain the optimal therapy in the well-selected patient despite not being necessarily risk-neutral.

It seems imperative to suggest that the radiation sparing effect of Anti-TNF therapy hinges on its ability to achieve mucosal healing thus translating into “effective” disease control. We addressed this possibility by comparing our Anti-TNF group with a corticosteroid treated cohort as both Anti-TNF and corticosteroids (as opposed to thiopurines and methotrexate) are used for induction of remission in UC. The significant differences in reduction of diagnostic radiation between the two cohorts would suggest that the radiation-sparing effect is unlikely to be solely a function of disease control. Long-term data showing the relationship between Anti-TNF therapy, disease control and effect on radiation exposure should be conducted to address this possibility.

We limited our observations to the effect of Infliximab and not Adalimumab as evidence for the efficacy of Adalimumab in UC through controlled studies has only been published relatively recently [31-33] and Anti-TNF therapy in UC has been limited to Infliximab at our centre during the period studied. It is plausible that if this is a “class-effect” it should be borne out through data from future studies.

Whether Anti-TNF Therapy could decrease the risk of cancer attributable to radiation from medical exposure is at best purely speculative at present. That protracted exposure to ionizing radiation even at levels used for diagnostic imaging with its potential cumulative downstream effects could contribute to risk of malignancy is now acknowledged beyond reasonable doubt [22-25]. This assumes greater importance when one considers inherent risk of colorectal and small intestinal cancer from longstanding disease and the association of immunosuppressive therapy with the increased risk of lymphoma and other malignancies [38-42].

Despite areas of uncertainty with regard to the actual risk of effective radiation doses below 100 mSv the literature would suggest that acute doses exceeding 50 mSv are associated with the risk of malignancy and that an increased risk might apply even at lower doses [43]. For example a 10 mSv dose may correlate with an attributable lifetime risk of solid organ cancer or leukemia of 1:1000 (Biological Effects of Ionizing Radiation Committee, National Research Council; BEIR) [44]. While we acknowledge that although radiation exposure with its inherent risks is higher in CD, the risk in UC is also real and of clinical concern [19-22].
As “radiation free” imaging with rapid advances in contrast enhanced intestinal ultrasound and MR enterography hold promise, whether they can or indeed should completely replace CT scanning is a contentious issue. The choice of investigation is likely to be driven by the clinical question, available expertise and economic factors. CT remains a valuable modality with a high sensitivity and specificity for the detection of luminal and extra-luminal disease and its complications yielding images with high temporal and spatial resolution with a relatively shorter acquisition time than MR. The real risk of cumulative radiation might be reduced by use of low-dose CT technology, non ionizing radiation whenever possible and perhaps most importantly limiting the use of radiation to those clinical situations where it is unequivocally indicated. This can only be achieved through the collaborative efforts of a multidisciplinary approach between clinicians and radiologists in planning investigation to get the best possible information and do the least possible harm.

**Conclusion**

We found that initiation of Anti-TNF therapy is associated with a significant reduction in diagnostic imaging. Further studies evaluating larger cohorts with longer follow-up with more scrupulously gathered data around confounders such as disease severity, duration and longevity of Anti-TNF response with corroborative evidence from mucosal healing are now much needed to study a possible parallelism between Anti-TNF therapy and radiation-sparing

**Acknowledgement**

This work has been supported by NHS, National Health Services; NHS grant no 13 RECNA08.
References


44 Committee to Assess the health Risks from Exposure to Low Levels of Ionizing Radiation. Available at http://nap.edu/reportbrief/11340/11340rb.pdf.