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ABSTRACT

Introduction: Adalimumab is effective in inducing and maintaining response/remission in patients with Crohn's Disease (CD) either naive to biological therapies or following secondary failure of infliximab.

Aim: To present the first 'real-life' survey data from England and Ireland on the use of adalimumab.

Method: A retrospective audit conducted by a web-based questionnaire in England/Ireland.

Results: We analysed data on 61 patients (35 female) with a median age of 33 years (range 17-71) with average follow-up of 8 months. Maximal maintenance dose was 40mg every other week in 84% of patients, 40mg weekly in 13% and 80mg weekly in 3%. Maintenance adalimumab achieved remission in 57% of patients. The ongoing response rate was 83.6%. An additional 8% had a secondary loss of response after average of 8.4 months (range 2-17). 23% had adverse effects, of which local pain 29%, infection 36%, headaches 14%, leucopenia (on AZA) 7%, a painful rash 7%, serum-sickness type reaction 7%. Adverse events led to discontinuation in 2 patients.

Conclusion: This English/Irish audit show acceptable response/remission and safety profile of adalimumab in the treatment of CD. In contrast to previous data from Scotland, dose escalation was only seen in 16% of patients. The majority of responders were steroid-free at follow-up.

Keywords: Adalimumab, Anti-TNF, Crohn's disease, survey, response/remission

INTRODUCTION

Natural History of Crohn’s disease

Crohn’s disease is a chronic idiopathic inflammatory disease of the gastrointestinal tract characterized by the presence in the gut of extensive ulcerations. Intestinal ulceration can result in bleeding and anemia, perforation with abscess or fistula formation, or subsequent fibrosis with intestinal obstruction.

The incidence is 6.7 (range 1.6 to 14.6) cases per 100,000 annually and the prevalence is 140 (range 10-199) cases per 100,000 in UK. The incidence and prevalence in Southern Europe is somewhat lower than in Northern Europe.

The onset of Crohn's disease has a bimodal age distribution. The first and largest peak occurs between the ages of 15-30 years; the second much smaller peak is between 60-80 years.

The natural history of CD suggest that 33% of patients with chronic or intermittently active disease developed complications requiring hospitalization and surgery in the first year after diagnosis, 13% in the second year, and 3% in each subsequent year . Surgery is rarely curative and does not stop the progression of disease. In fact endoscopic recurrence occurred in 75% of patients at 1 year after ileal resection surgery, and symptomatic recurrence in 50% of patients at 5 years [1-5]

Immune Dysregulation

Optimal control of inflammation has considerable target organ as well as potential systemic benefits. From the current understanding it is likely that chronic inflammation in Crohn disease is due to aggressive cellular immune responses to a subset of luminal bacteria. Studies have provided evidence that IBD is a result of a genetic predisposition that leads to a mucosal immune regulatory cell defect, barrier defects and susceptibility to environmental triggers, including luminal bacteria and specific antigens. Tumor necrosis factor (TNF)-α has been described as one of the most relevant cytokine mediators that contributes to intestinal inflammation in CD. There have been several studies demonstrating the abundance of TNF-α in sera, stool and mucosal specimens of small and large bowel from patients with Crohn Disease (CD), derived from macrophages and T-lymphocytes.[6-8] Anti-TNF-α biological therapies are believed to work by inducing apoptosis of TNF-α-expressing inflammatory cells in addition to neutralising soluble TNF and depleting immune cells by antibody dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).[9] These biological therapies have been extensively used in the management of chronic inflammatory conditions such as rheumatoid arthritis, spondyloarthropathies and psoriasis, and such therapies are also effective in treating extra-intestinal manifestations of CD.

Mucosa healing after biological therapy era a "New Disease Course of Crohn Disease"

Many biological therapies are being evaluated for the treatment of the chronic inflammatory bowel diseases.

Infliximab and other monoclonal antibodies targeting tumor necrosis factor (TNF-α) have shown efficacy in inducing, maintaining clinical remission and achieving mucosa healing in patients with Crohn disease.

Mucosa Healing (MH) has been proposed to be an important prognostic feature of the efficacy of treatment in inflammatory bowel disease. Mucosal healing is assessed by endoscopy and is a component of intestinal healing which is comprised of endoscopic healing, histological healing, transmural healing and fistula healing. There is a growing body of evidence that suggests that mucosal healing is an appropriate parameter of treatment efficacy and secondary endpoint in clinical trials in CD patients. It is presumed that if the mucosa is healed, disease complications are unlikely to occur and demands for hospitalization and surgery should be decreased.

One of the principal reasons why mucosal healing in the past was not considered a goal of treatment in inflammatory bowel disease was the fact that most available medications were not able to heal the bowel mucosa in a significant proportion of patients. A dilemma arises regarding management when

a patient in apparent symptomatic remission of disease shows an absence of mucosal healing, often the case with steroid therapy.

Conventional therapy as mesalamine, corticosteroids and immunosuppressive agents are not fully effective in inflammatory bowel disease and is often continued for long periods without optimum efficacy or assessment of mucosal healing. Consequently many patients are under-treated and remain clinically active without a healed mucosa, increasing the risk of hospitalization, surgery and complications. Lack of MH may represent an indication for intensified therapeutic strategies to prevent serious complications of disease. The past decade has seen an explosion of therapies aimed at altered immune response observed in patients with inflammatory bowel disease .The goal of this highly effective and targeted approach is to induce rapid remission in a steroid free environment and promote MH. This new “top –down” strategy has been associated with encouraging medium term rates of mucosal healing and could potentially modify the natural history of disease by leading to remission with fewer complications and reduced surgical intervention.

The introduction of biological therapy, and particularly the use of anti-tumor necrosis factor alpha (TNF-α) therapy, has significantly changed the treatment and management of CD. Anti-TNF therapy has been associated with steroid sparing and mucosal healing, and may contribute to fistula closure or a reduction in fistula drainage. Infliximab (Remicade®), a murine-chimeric

monoclonal antibody directed against tumour necrosis alpha (TNF-α) was approved by the Food and Drug Administration (FDA) in 1998 and has shown to have significant benefits in patients with refractory luminal and fistulizing Crohn's disease but adalimumab(Humira®), has been more recently licensed for use in CD since 2007 .

Adalimumab (ADA) is a fully humanised IgG1 monoclonal antibody to tumour necrosis factor alpha (TNF-α), a key pro-inflammatory cytokine in inflammatory bowel disease (IBD) and other chronic inflammatory conditions.

Both adalimumab and infliximab have demonstrated efficacy for induction and maintenance of remission in patients with moderate and severe CD.[12-16] Remarkable clinical remission and mucosal healing was reported with initial use of infliximab in Crohn's disease and this provided a compelling evidence for use of infliximab in clinical practice. In the pivotal ACCENT1 maintenance study, scheduled 8 weekly infusions of infliximab led to superior remission and response rates, superior mucosal healing, and decreased need for hospitalizations and surgery compared with placebo or episodic infusions of infliximab.[·] In the scheduled treatment group, 31% of patients had evidence of complete mucosal healing at 10 wk and 50% of patients had complete mucosal healing at wk 54. [·]Patients with mucosal healing had a numerically fewer hospitalizations than patients without healing (18.8% Vs 28% p= not significant), [16]and a trend towards fewer surgery.

In the recently reported SONIC study, a randomized, double-blind, controlled trial comparing infliximab plus azathioprine to infliximab alone or azathioprine alone in Crohn's disease naïve to immunomodulators and biological therapies. In this study, 508 patients naïve to immunomodulators and biologic therapies were randomized to receive azathioprine 2.5 mg/kg, azathioprine 2.5 mg/kg + infliximab 5 mg/kg infusions, or infliximab 5 mg/kg alone. The primary endpoint was the proportion of patients in steroid-free remission (CDAI < 150) at week 26. The infliximab + azathioprine group (56.8%) was superior to the infliximab monotherapy group (44.4%; *P* =0 .022), which in turn was superior to the azathioprine alone group (30.6%; *P* = .009), in achieving steroid-free remission. Mucosal healing was also statistically superior with combination therapy, with 43.9%, 30.1%, and 16.5% of patients treated with infliximab + azathioprine, infliximab alone, and azathioprine alone showing mucosal healing respectively. This may serve as a compelling argument for choosing combination therapy in immunomodulator and biological therapy naïve patients, after consideration of risk versus benefit, as combination therapy may be associated with a small increase in risk for infection and possibly lymphoma. [17]

The potential for biologics to induce mucosal healing and potentially change the natural history of Crohn's Disease has been further confirmed by the Top Down/Step Up trial. This is an open-label, multicenter trial conducted in 26 centers in the Netherlands and Belgium. Patients with predominantly newly

diagnosed active Crohn's Disease were randomized to a top-down arm (infliximab induction 0, 2, 6 wk with azathioprine maintenance, with on-demand infliximab for flares; systemic steroids were added only if patients did not respond to infliximab and azathioprine) or a step-up arm (Prednisone 40 mg daily induction; permitted 2 steroid tapers before starting azathioprine; and then infliximab if failed treatment with immunosuppressive drugs). At 6 and 12 months, significantly more top-down patients were in steroid-free remission (75% and 77% respectively) than in the step-up group (48% and 64%,respectively) At 24 months, no statistically significant difference was found between the two groups. The most remarkable finding in this cohort was the result of the endoscopic sub-study, in which 71% (17/24) of patients in the top-down arm achieved mucosal healing versus 30% (6/20) in the step-up arm at year 2. Some of the patients in the top-down arm had only received an induction dose of infliximab.[18]The results suggest that if MH is established as a desirable outcome of therapy, steroid induction even for newly presenting patients will be found to be wanting in this reg Subcutaneous generally self-administered administration distinguishes adalimumab from the intravenous infusion of infliximab.

Episodic administration of infliximab is immunogenic, and this can cause infusion reactions, loss of efficacy, and delayed hypersensitivity reactions.[20] There is no equivalent experience with episodic administration of adalimumab.

Controlled trials have demonstrated the efficacy and safety of adalimumab in the treatment of patients with moderate and severe CD who were naïve to anti-TNF treatment or had lost response or were intolerant to infliximab . The CLASSIC I[10] and GAIN[11] trials have demonstrated the efficacy of ADA in the induction of response in patients with moderate to severe CD. For longer term therapy, CLASSIC II[7] and CHARM[8] demonstrated the superiority of adalimumab in maintaining this response over placebo.

The CLASSIC I comprised a total of 299 patients with moderate-to-severe CD naive to TNF_ inhibitor therapy who were randomized to receive adalimumab (40/20mg, 80/40mg, or 160/80 mg) or placebo at weeks 0 and 2. The primary endpoint was remission at week 4 defined by a CD activity index (CDAI) <150. The remission rates at week 4 (primary endpoint) in the adalimumab 40/20mg, 80/40mg, and 160/80mg groups were 18% (p=0.36), 24% (p=0.06), and 36% (p=0.001), respectively, and 12% in the placebo group. The authors concluded that adalimumab was superior to placebo for inducing remission in CD patients with moderate to- severe disease who were naive to TNF-α inhibitor therapy with the 160/80mg having the most robust response. Response rates were also measured in this study. In the highest dosing group (160/80 mg), 50 and 59% of patients had a response defined by a 100-point and 70-point.

There were 275 patients from CLASSIC I who were entered into the CLASSIC II trial. They received open label adalimumab 40mg at weeks 0 (week 4

CLASSIC I) and at week 2. Patients who were in remission at both week 0 (end CLASSIC I/beginning CLASSIC II) and week 4 were re-randomized to 40mg every other week (eow), weekly, or placebo through 56 weeks.

In this re-randomized cohort of 55 patients, 79% who received adalimumab 40mg eow and 83% who received 40mg weekly maintained remission through week 56 (primary endpoint) compared with 44% for placebo ($p<0.05$ for both adalimumab groups vs placebo). The patients from CLASSIC I who had not been in remission entered an open-label arm and received adalimumab 40 mg eow (dosages could be increased to 40mg weekly if there was a non response or flare).

There were 204 patients in the open-label arm and 46% were in clinical remission at week 56.

Thus, CLASSIC I and II showed that adalimumab induced and maintained clinical remission in patients with moderate-to-severe CD naive to TNF-α inhibitor treatment.

In CHARM, 854 patients with moderate to- severe CD received open-label adalimumab SC at doses of 80mg at week 0 and 40mg at week 2 (this dose was chosen before the results CLASSIC I were known).

Patients who had been exposed to infliximab in the past and either lost response or had become intolerant to infliximab were eligible for this trial. Approximately 60% of patients responded at week 4 (identified by a drop in

CDAI of 70 points) and were then randomized to one of three treatment arms: adalimumab 40mg eow, adalimumab 40mg weekly, or placebo.

The primary study endpoints were clinical remission at weeks 26 and 56 amongst responders.

At week 26, 40% of the adalimumab 40mg eow, 47% of the adalimumab 40 mg weekly and17% of the placebo groups were in remission ($p<0.001$ for both groups compared to placebo, no difference between active groups). This benefit was maintained out to week 56 with 36% adalimumab 40mg eow, 41% adalimumab 40mg weekly, and 12% placebo groups remaining in remission ($p<0.001$). There was no difference in the proportion of patients who were able to maintain remission or response according to their previous infliximab exposure. In addition, the GAIN study using 160mg/80mg induction dose showed switching to adalimumab was effective in patients intolerant of or losing response to infliximab. In GAIN, 325 patients with moderate-to-severe Crohn's disease who had previously been exposed to infliximab and lost response and/or become infliximab-intolerant were randomized to receive either adalimumab 160 mg or 80 mg subcutaneously at weeks 0 and 2, respectively, or placebo. In the group receiving adalimumab, 21% of patients entered remission (CDAI < 150), 52% had a CDAI decrease of 70 points or more, and 38% had a CDAI decrease of 100 points or more at week 4, compared with 7%, 34%, and 25% of patients in the placebo group, respectively ($P < .05$). There was no difference in overall efficacy if the patients lost response to, or were intolerant

to, infliximab upon study entry. Although the 4-week remission rates reported in GAIN may appear low at first glance, recently presented data from an open-label extension of this trial demonstrated that over time, remission and response rates increased during the maintenance phase with adalimumab therapy .At 6 and 12 months, 57% and 40%, respectively, of the week 4 responders to adalimumab were in clinical remission. Thus, 4 weeks may be too short a time point to assess induction of response in Crohn's disease patients with prior exposure to infliximab. [11]

Safety and side effects

Adalimumab was well tolerated in the efficacy based RCTs reported earlier. An analysis of an open-label extension study of over 1100 CD patients from the CHARM and GAIN studies presented at the ACG in 2007 showed the safety profile of adalimumab was similar to its safety profile in other conditions and similar to infliximab in CD. [13]

Serious adverse events were reported in 25% of patients, injection-site reactions in 20%, malignant neoplasms (1.7%), opportunistic infections (2.1%), tuberculosis (TB) (0.2%).

More extensive safety data for adalimumab in CD is relatively lacking compared to efficacy data; therefore, this section will look at safety of TNF-α inhibitors in general. The AGA stated that all TNF-α inhibitors have similar safety profiles. SC adalimumab can be associated with injection site reactions.

In the CHARM trial, injection site reactions occurred in 2% of patients during induction and in up to 4.8% of those treated with the 40mg weekly maintenance regimen. Irritation and pain at the injection site were reported by over 4% of patients during induction.

Antibody formation against biologic therapies is common. Their formation may be related to an increased risk of infusion reactions but it is not possible to predict this on an individual basis.

Also, it is possible that antibodies will attenuate the degree and duration of response. The fact that adalimumab is not comprised of non human or artificial sequences suggest it should have a low potential for immunogenicity. There were 0.7% of patients in CLASSIC I and 2.6% in CLASSIC II who developed anti-adalimumab antibodies. [21-25]

It is becoming apparent that serum trough levels relate to efficacy of biological therapies, both infliximab and adalimumab. Low or absent serum trough levels may be related to immunogenicity and loss of response.

Malignancy

However, with this more aggressive treatment strategy, safety concerns clearly arise. Recently, the description of a series of a particularly severe form of T cell lymphoma in pediatric and young adult patients with IBD under

immunomodulator and biological combination therapy raised the question of the risks of treatment-induced side effects or complications.

Recently presented results from the very large French population-based CESAME study suggest a doubling of the risk of lymphoma in patients with IBD, with the majority of cases occurring in association with immunosuppressive therapy. Similarly, a meta-analysis of previous cohort studies concluded that the risk of lymphoma is increased fourfold in patients with IBD on thiopurine treatment (azathioprine and 6-mercaptopurine) compared with those not receiving such therapy. The growing number of reports of HSTCL mandates urgent assessment of the optimal strategies for reducing combined exposure to thiopurines and anti-TNF agents in all patients, including those currently receiving such therapies and those requiring escalation of therapy. Recently, a meta-analysis involving twenty-six studies and 8905 patients was performed to determine the rate of non-Hodgkin lymphoma (NHL) in adult CD patients who have received anti-TNF therapy, and to compare this rate to that of a population based registry, and a population of CD patients treated with immunomodulators. Among anti-TNF treated subjects, 13 cases of NHL were reported (6.1 per 10,000 patient-years). The majority of these patients had previous immunomodulator exposure. Patients anti-TNF treated had a significantly elevated risk to NHL (SIR 3.23, 95% CI 1.5-6.9). When compared to the NHL rate in CD patients treated with immunomodulators alone

(4 per 10,000 patient-years) the SIR was 1.7 (95% CI 0.5-7.1). This concept need to be re-evaluated in light of the expanding reports of potential risk of lymphoma in patients with CD treated concurrently with IFX and immunosuppressant, although the absolute rate of these events remains low and should be weighed against the substantial benefits associated with treatment[27-28.]

A recent report Scottish 'real-life' experience in the use of adalimumab in CD, followed by an abstract in the recent annual meeting of the British Society of Gastroenterology, have provided very useful clinical experience as it is important to confirm that large clinical trial results regarding efficacy and safety can be reproduced in a local country specific clinical setting. This is especially relevant as in UK more severely affected patients generally receive biological therapies. The study from Scotland also reported a very high proportion of patients requiring dose escalation from 40mg every other week to 40 mg every week regimen in order to maintain response.[19]

We report current experience from eight hospitals in England and Ireland on the efficacy of adalimumab in maintaining remission/ response as well as its adverse effect profile. We specifically aimed to determine the frequency of dose escalation in this English CD patient cohort.

PATIENTS AND METHODS

Participants

We obtained and collated retrospective survey data from eight centres who provided data on sixty one patients with CD treated with adalimumab. These patients represented all patients with refractory CD treated with adalimumab in these centres. We specifically requested from participating physicians to report on all patients who have had exposure to adalimumab under their care, including patients who had discontinued therapy at the time of the survey. We excluded patients on adalimumab already enrolled in other multicentre clinical trials assessing its use in CD.

Methods

A secure anonymised web-based questionnaire was designed. It enquired about the demographics of the patients, and the phenotypic features of the illness (distribution of disease, rectal and/or perianal involvement, the presence and distribution of fistulae, whether perianal, visceral or both). It also enquired on the concurrent or previous use of 5-ASA compounds, corticosteroids, immunomodulators and IFX, and the duration of disease prior to the introduction of ADA.

Our questionnaire did not however enquire on the actual timing and duration of each therapy as above, the specific dosage of each drug and alterations thereof, or the circumstances of discontinuation of each therapy.

In patients who were not naive to biological therapies, the indication of switching from IFX to ADA (intolerance, loss of response or both) was recorded.

Assessment of the severity of the condition at the start of therapy, and assessment of response to induction and maintenance was assessed using the Crohn's Disease Activity Index (CDAI) or the simplified Harvey-Bradshaw Index (HBI) where available, as well as Physicians Global Assessment (PGA) of the response immediately post induction, as well as during maintenance. Where CDAI or HBI were used we defined response as a drop in CDAI by at least 70 points, or a drop in HBI by at least 3 points. Remission was defined as a CDAI $\leq$150 or HBI $\leq$4.

We did not ask for participating physicians to retrospectively score severity at the start of therapy, following induction and during maintenance if this had not already been assessed and documented in the case-notes during the patient consultations in real time. When an accurate scoring of severity was not recorded, physicians' qualitatively evaluated the severity in retrospect. We also did not seek to establish whether the patients received adalimumab in an in-patient or an out-patient setting.

Furthermore, endoscopic assessment of severity was not addressed in our analysis.

Patients who, during the follow-up period, had either entered ongoing remission, or had reduced disease activity on any of the three scales (CDAI, HBI, and PGA) as defined above, were classified as responders.

If a patient on assessment following induction, and subsequently during maintenance therapy had achieved a difference of 70 points in the CDAI score, or a difference of equal or greater than 3 points in the HBI score they were classified as a responder. If the benefit at induction and/or during maintenance satisfied the scoring criteria for remission of Crohn's Disease, the patient was classified as being in remission. If such a scoring was not available, the physician offered a subjective evaluation of activity of the disease at the time of assessment (e.g. "active disease", "response" or "remission"), as well as their PGA of the overall outcome.

Patients were classified according to their maximal response, provided it was ongoing at the time their data was submitted, and not lost prior to that time.

Patients who had no demonstrable clinical benefit following an induction regimen were classified as non-responders.

A third category of patients demonstrating an initial response which was subsequently lost were described as secondary loss of response. This group was

characterised by a surgical resection or a flare interrupting a period of response/remission on adalimumab, which was not overcome by increasing the dose, when the physician selected such strategy, and which led to discontinuation of treatment. We did not seek a specific level of deterioration in activity indices to classify patients as having a "secondary loss of response".

As investigators conducting the survey we (MI, ER, SG) had no access to the case-notes, or played any role in evaluating the response of the patients. In view of the retrospective nature of the survey, the above criteria were pragmatic rather than rigid trial criteria.

In addition we enquired on adverse effects of adalimumab therapy, and whether these resulted in discontinuation of treatment with adalimumab.

Proportions between groups were compared by Fisher's Exact test and continuous variables compared by Mann-Whitney U test.

RESULTS

Demographic details

We obtained and analysed data on 61 patients (35 female; 26 male) with a median age of 33 years (range 17-71 years). These were submitted by 8 centres in England and Ireland (7 teaching hospitals, 1 district general hospital). The median time between establishing the diagnosis of CD and commencing adalimumab was 11 years (range 0-34 years). In terms of anatomic disease

pattern, 21% had ileal, 46% ileo-colonic and 25% had colonic disease. Rectal involvement was observed in 54%, perianal disease in 46% and fistulising disease in 41% of the cohort. The fistulae were only perianal in 72%, only visceral in 4%; 16% of patients with fistulising CD had both perianal and visceral fistulae. The type of fistulae was not reported in 8%.

In terms of previous management, 100% of patients had received steroids and 96.7% 5-ASA compounds. 96.7% have been on immunomodulators prior to adalimumab and finally 93.4% had been on infliximab. Patients who were previously exposed to IFX were switched to ADA due to IFX intolerance (43.9%), no response to IFX (5.3%), secondary loss of response to IFX (47.4%) and due to both intolerance and loss of response to IFX (3.5%). The average follow-up period was 8 months.

Adalimumab dosing and Response Rates

Induction dosing was 160-80mg at weeks 0 and 2 in 46% of patients and 80-40mg at weeks 0 and 2 in 54% of patients. All patients received maintenance dose of 40mg EOW initially. At 8 months, 13% of patients had been escalated to 40mg weekly and 3% of patients to 80mg weekly.

57% of patients were in remission as per CDAI, HBI or PGA for an average of 7.9 (range 1-35) months. Of these patients only 6% were on concurrent corticosteroid (i.e 54% of the entire cohort had maintained steroid-free

remission) and 43% were on an immunomodulator. In addition, 30% of the entire cohort was in remission at 8 months, whilst on no other therapy for CD (i.e. no steroids, no immunomodulators).

84% of patients had an on-going response to adalimumab for an average of 8.6 (range 1-35) months. Of these patients only 4% were on concurrent corticosteroid (i.e 80% of the entire cohort had maintained steroid-free response) and 33% were on an immunomodulator. In addition, 49% of the entire cohort had an ongoing response at 8 months, whilst on no other therapy for CD (i.e. no steroids, no immunomodulators)

An additional 8% percent of the cohort demonstrated an initial response to adalimumab, which was subsequently lost, an average of 9 (range 2-17) months following start of therapy.

Eight percent (8%) of the cohort showed no response to induction with adalimumab and therapy was discontinued.

We analysed the data to document possible predictors to response such as age, gender, duration of disease prior to commencement of therapy, and disease pattern and distribution (table 2). However the number of non-responders was small and we did not perform formal statistics – no pattern was evident.

Adverse effects

Adverse effects were observed in 14 of 61 patients (23%). When analysed, 29% of the adverse effects were localised pain at the injection site, 36% were infection related (chest infection, urinary tract infection, development of rectal abscess, and a persistent upper respiratory tract infection) none of which were fatal. 18% of adverse effects were complaints of headache. One patient (representing 7% of events) developed leucopenia, whilst on concurrent azathioprine. One patient developed a painful rash, which appeared drug-related on histology. Finally, one patient developed a delayed-type hypersensitivity reaction, with generalised joint aches a few days following each dose. Therapy was discontinued in the latter two patients, which represent a drop-out rate due to adverse effects of 3.3% in the entire cohort.

DISCUSSION

This UK audit survey reports on our experience regarding the efficacy and safety of adalimumab therapy across 8 centres in England and Ireland and confirms the value of adalimumab in maintaining response in CD as demonstrated in the pivotal CHARM and the earlier and smaller CLASSIC II trials.

The clinicians in UK used the two widely accepted induction regimens of 160mg-80mg and 80mg-40mg in weeks 0 and 2 in roughly equal proportions. Physician preference rather than patient characteristics generally dictated the dosage choice. Our results show the efficacy of adalimumab therapy in maintaining response or remission in the majority of patients (84%) with moderate to severe CD. In addition, the overwhelming majority of these patients (96%) had achieved corticosteroid-free response/remission and a good proportion of them (67%) were not on immunomodulators. Importantly, half of the patients in the ongoing response /remission group were enjoying the outcome on adalimumab monotherapy; examining the subgroup of patients in clinical remission, one third were enjoying the outcome on adalimumab monotherapy, being free of corticosteroids, immunomodulators and 5-ASA compounds.

One significant difference between our results and the recent results of an equivalent study in Scotland was the dose escalation rate from an initial

maintenance dose of 40mg every other week to 40mg weekly or higher in 16% of our cohort versus 59% in the Scottish cohort of patients, though the follow-up period of the Scottish group was longer. In the Scottish cohort the induction dose was 80 mg followed by 40mg after 2 weeks.[19] It is possible that using 80mg/40mg induction dose may require future dose escalation more often. Dose escalation also depends on allowing sufficient time, at least 12 weeks, and prior to considering increase in ADA dose.

Non-responders to induction therapy formed 8.2% of our cohort. The GAIN trial demonstrated a lack of clinical response in 48% at week 4 in a similar cohort of patients who had previously become intolerant or lost response to infliximab. There are no strong predictors of clinical response, or lack of it at present, and we could not determine a clinically meaningful predictive factor.

In terms of adverse effects, 3.3% of our cohort had their therapy discontinued an average of six weeks into therapy . This is comparable to the drop-out rate of approximately 1% of the GAIN trial at 4 weeks. Local pain at the injection site as well as infections were observed in 29% and 36% respectively in our cohort is well described adverse effects of adalimumab. However most patients remained on adalimumab without discontinuation.

A retrospective audit such as this has significant drawbacks. The endpoints are not as rigidly defined as in trials, definitions are more prone to bias, and other endpoints such as endoscopic healing were not available. However, we did not

observe the same level of requirement of maintenance dose escalation as observed in the Scottish trial. We present in table 3 all the open label cohorts reported in the literature on efficacy and safety of adalimumab in CD, including the Scottish study. It would appear that an induction dose of 80mg-40mg has a trend towards later dose escalation in the maintenance phase to 40mg weekly.

In a systematic review which included 16 studies with 8510 rheumatoid arthritis patients reported that of the infliximab patients ,53.7% needed dose escalation.[25] Dose escalation with etanercept was less and this systematic review did not report any data on dose escalation with adalimumab. It is especially important to have more data from Europe about dose escalation with 80mg-40mg induction and with 160mg-80mg induction dosages. In North America 160mg-80mg is the licensed induction dosage.

The collective real life experience from these eight centres in England and Ireland confirms the efficacy of adalimumab in inducing and maintaining remission in patients with moderate or severe Crohn's disease, refractory to corticosteroids and immunomodulators. The majority had previously failed infliximab therapy. The conversion rate to higher maintenance doses was significantly lower in our cohort compared with previous published data. We also demonstrate an acceptable adverse effect profile.

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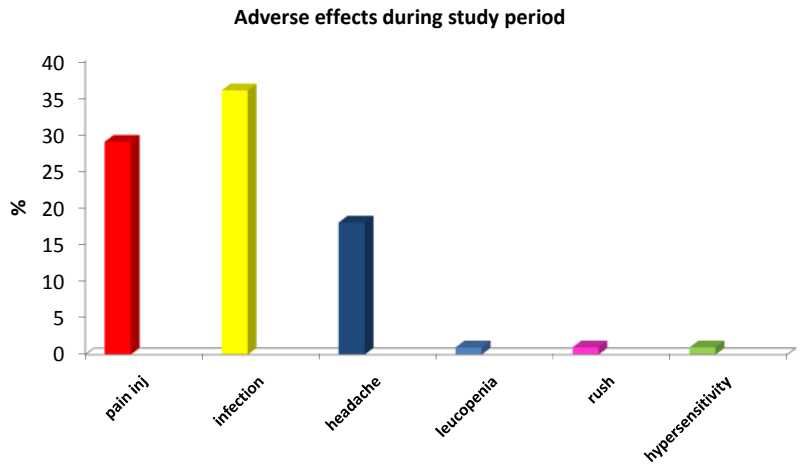
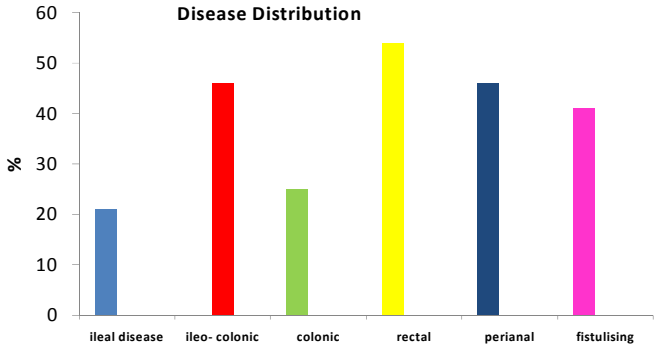
Table 1: Demographic and phenotypic details of CD patients treated with Adalimumab

1.COHORT	
Total cohort size	61
Male: Female	26:35
Median age (range)	33 (17-71) years
Median disease duration prior to ADA (range)	11 (0-34) years
2.DISEASE DISTRIBUTION	
Ileal disease	21%
Ileo-colonic disease	46%
Colonic disease	25%
3.RECTAL INVOLVEMENT	54%
4.PERIANAL INVOLVEMENT	46%
5.FISTULISING DISEASE	41%
Perianal fistulae only	72%
Visceral fistulae only	4%
Perianal and visceral fistulae	16%
Unknown pattern of fistulae	8%

Table 2. Characteristics of adalimumab responders and non-responders

Variable	Responders n=57 includes patients with 2° loss of response	Non-responders n=5
Age at diagnosis	26.0 yrs	19.6 yrs
Gender	50% Male	60% Male
Interval between diagnosis and start of ADA	13.2 yrs	10.6 yrs
Distribution of disease	21% ileal 45% ileo-colonic 25% colonic only	20% ileal 60% ileo-colonic 20% colonic only
Rectal involvement	55%	40%
Perianal involvement	48%	20%
Fistulising disease	47%	0%
Previous response to IFX	7% naive to biologicals 5% primary IFX failure 43% 2° loss of response 41% intolerance to IFX 4% both intolerance and loss of response	0% naive to biologicals 0% primary IFX failure 60% 2° loss of response 40% intolerance to IFX 0% both intolerance and loss of response


Adverse effects during study period
%
40
35
30
25
20
15
10
5
0
pain inj
infection
headache
leucopenia
rush
hypersensitivity


Disease Distribution
%
60
50
40
30
20
10
0
ileal disease
ileo- colonic
colonic
rectal
perianal
fistulising

Study	n=	Endpoint	Dose	Dose Escalation	Remission	Response	Side effects
Sandborn WJ et al Am J Gastroenterol. 2004 Oct;99(10):1984-9[13]	24	Tolerability, response, remission at 12/52	80-40 induction 40 EOW	79%	29% at 12/52	Additional 59% at 12/52	??
Papadakis KA et al Am J Gastroenterol. 2005 Jan;100(1):75-9.[14]	15	Response at 6/12	80-40 induction 40 EOW	46%	54% at 6/12	Additional 31% at 6/12	13% overall 0% withdrawal due to SEs
J Hinojosa et al Aliment Pharmacol Ther. 2007 Feb 15;25(4):409-18.[15]	50	Remission and Response at 4/52. Maintenance data pending	160-80 induction 40 EOW	N/A	42% of luminal CD, 23% of fistulising CD at 4/52	Total of 83% of luminal CD, 41% of fisulising CD at 4/52	38% overall 4% withdrawal due to SEs
Seiderer J et al Aliment Pharmacol Ther. 2007 Apr 1;25(7):787-96.[16]	16	Response rates at 8-weekly intervals	160-80 induction 80 EOW	N/A	63% at 8/52 37.5% at >24/52	N/A	44% overall 6% withdrawal due to SEs
L Peyrin-Biroulet et al Aliment Pharmacol Ther. 2007 Mar 15;25(6):675-80.[17]	24	Remission (CDAI<150) at 52 weeks	80-40 induction, 40 EOW	25%	58% at 52 weeks 75% steroid- free	N/A	54.2% overall 0% withdrawal du to SEs
G.-T Ho et al Aliment Pharmacol Ther. 2008 Feb 15;27(4):308-15.[12]	22	Remission at median 1 year	80-40 induction 40 EOW	59%	68% at years (censored)	N/A	14% serious
RL West et al Aliment Pharmacol Ther. 2008 Aug 8.[18]	30	Response, mean 318 days	160-80 induction, 40 EOW	27%	N/A	77% at 318 days	47% overall 20% withdrawal due to SEs

Paediatric data

Study	n=	Endpoint	Dose	Dose Escalation	Remission	Response	Side effects
Wyneski MJ et al J Pediatr Gastroenterol Nutr. 2008 Jul;47(1):19-25.[19]	15	Response at 33/52	80-40 induction 40 EOW	N/A	50%	Additional 14%	57% overall 0% withdrawal due to side-effects