Biological agents in paediatric inflammatory bowel disease : a clinical observation study from Greece

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Abstract

***Objectives* : Biological agents have contributed significantly in controlling inflammatory bowel disease during the last 15 years. This study aimed at recording and evaluating paediatric data regarding the efficacy and safety of infliximab and adalimumab during the last decade.**

***Patients and methods* : A total of 31 patients (43% males) with a mean age of 13.5 ± 3.0 years were included and the majority (74%) had Crohn's disease (CD). Failure of previous treatment and steroid dependency were the main reasons for initiating anti-TNF-α therapy. Mean age at the first infusion was 11.0 ± 2.8 years, while the mean disease duration at the introduction of infliximab was 2.6 ± 2.7 years. The number of infusions per patient ranged from 1-25 (median 7, IQR : 4-13).**

***Results* : Initial response was achieved in 82.8% of patients. After one year of treatment the estimated rate of remission was 53%. The rate of surgery-free disease at 12, 36 and 60 months, after the first dose of infliximab, was 89.6%, 89.6% and 74.7% respectively. The incidence of serious anaphylaxis was 4/268 infusions (1.5%) or 4/31 patients (12.3%). At three months after the first infusion only 2 children were on steroids. Adalimumab was administered to 5 patients for a mean duration of 7.4 months, as a second option after infliximab failure or infusion reaction. Two out of five patients failed to achieve remission with adalimumab and these two patients were also infliximab failures.**

***Conclusion* : Biological agents are valuable and safe options for children with refractory IBD. The results, so far, have been satisfactory, although, long-term outcomes remain yet to be determined.** (Acta gastroenterol. belg., **2010,** 73**, 342-348**).

Key words : Anti-TNF-α**,** Infliximab, adalimumab, Crohn's disease, ulcerative colitis, IBD, biological agent.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC), often collectively referred to as inflammatory bowel disease (IBD), are chronic and not rarely progressive, inflammatory conditions of the intestine. They require frequent hospitalizations as well as long and burdensome treatments, which result in considerable physical and psychosocial consequences (1-3). Especially in children, the disease presents some unique clinical features which require special considerations (4). Reduced final height and delay of puberty, which are exclusively seen in paediatric IBD, require early and effective intervention in order to arrest and reverse the process. Furthermore the early onset of the disease increases the risk of malignancy in the absence of complete histological remission.

Steroids and immunosuppressive agents such as purine analogs (azathioprine and 6-mercaptopurine) have been, so far, the preferred options for the induction and maintenance of remission in IBD (5-7). The long term experience with the abovementioned medications has revealed several disadvantages including steroid dependency (8), failure to retain long term remission (9,10) and in some cases azathioprine- and 6-mercaptopurine-related toxicity. These observations are leading research efforts to new alternatives capable of retaining remission in patients with refractory IBD (11). During the last 20 years monoclonal antibodies have proven to be a valuable group of drugs in therapeutic research. They are being used in a constantly expanding spectrum of clinical conditions and new agents are currently under development. To date, various human and chimeric monoclonal antibodies are approved for a number of diseases including rheumatoid arthritis, psoriasis, allograft rejection and IBD. Infliximab (chimeric murine-human anti-TNF-α antibody) is the most widely used monoclonal antibody in IBD (11). In paediatric patients, infliximab was the first member of the family used (12) and since then it has contributed greatly in controlling refractory forms of the disease. With the growing number of children receiving the drug significant experience regarding its administration, safety and benefits has been gathered and reviewed in recent literature. Adalimumab, a fully human monoclonal anti-TNF-α antibody has also been used, but to a significantly less extent than infliximab in patients with IBD (13,14). It has been used mainly as treatment for patients intolerant or unresponsive to infliximab (15). In children with IBD limited experience with respect to the use of adalimumab exists. In this clinical observational study we present our experience after 10 years of infliximab and 2 years of adalimumab use in the largest population of IBD paediatric patients followed in Greece.

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Material and Methods

Patients

This study was conducted in the First Department of Paediatrics of Athens University, which is a referral centre for paediatric IBD patients in Greece. Over the last thirty years more than 450 children have been followed in our Unit. Currently, more than 150 children are followed on a regular basis as outpatients, or hospitalized in case of relapse.

Our therapeutic strategy is a "step up" approach, including infliximab as the ultimate measure of controlling the disease, prior to surgical interventions, after failure of conventional treatment with steroids and immunomodulators. After 01/01/2003 the applied regimen includes infusions of 5 mg/kg infliximab at 0, 2 and 6 weeks and every 8 weeks after the third infusion. Prior to 2003 only 3 doses were being administered. In those patients who were receiving steroids at the time of the first infusion the objective was to achieve remission while gradually discontinuing oral steroids within 3-5 months. The rate of reduction depended on previous dose and the extent of time the patients were receiving steroid therapy. Until recently, an immunomodulator was being used concurrently to infliximab. From the beginning of 2009 any adjacent to infliximab immunosuppressive medication is being discontinued after six months of concurrent use. Infliximab has been used in cases unresponsive to other immunomodulators as well as in cases with high index of steroid dependency. Some children, depending on the severity of the disease, may have received more than one immunomodulator before the institution of infliximab, while in selected patients with extremely severe disease infliximab may have been used as the first line of treatment**.** A detailed laboratory evaluation including tuberculin skin testing, chest X-ray and interferon based testing as well as a complete history for suspect contacts is undertaken in all candidates for infliximab treatment prior to the first infusion. Vaccinations are also updated whenever required. Furthermore parents are advised about the risks of infections as with any immunosuppressed child.

After reviewing our registry we retrospectively included all IBD children, with a confirmed diagnosis according to the ESPGHAN Porto-criteria(16,17), who had received infliximab between 2000, when the drug was first administered in our Department and 31/12/2008. Hospital records for each one of these patients were available, following approval by the local ethical committee, for a comprehensive review. Every history was divided in two periods : Firstly data were collected regarding the pre-infliximab era : disease characteristics and previous medications. Patients with CD were characterized, according to the disease duration at the first infusion, as early-CD (< 2 years) and late CD (> 2 years). The second period was the subsequent clinical course after the introduction of infliximab. The activity of the disease was assessed, in every occasion, by the paediatric Crohn's disease activity index (PCDAI) (18,19) and the ulcerative colitis activity index (PUCAI) (20,21). For several patients with UC the indices were retrospectively calculated using data from the hospital records.

The major criterion for the initiation of infliximab was unresponsiveness to standard immunosuppressive agents including steroids, azathioprine or 6-mercaptopurine, methotrexate and cyclosporine, allowing for a time frame of response of three months after the introduction of each treatment ; however in cases with extremely severe disease this interval was significantly shorter. In particular, for CD, unresponsiveness was defined as PCDAI > 10, while for UC and IBD unclassified (IBDU) it was suggested by the presence of at least one of the following : more than 5 bowel movements per day, significant amount of blood in stools, completely unformed stools or significant abdominal pain. A second criterion was steroid depended disease defined as relapse within 30 days of cessation of steroids or when a dose reduction was attempted and in cases of more than 16 cumulative weeks of steroids per year. Finally, infliximab was chosen for patients intolerant to previous immunosuppressive treatments.

We evaluated two aspects of response to infliximab. The initial response component was assessed at the 10^{th} week of treatment (4 weeks after the third infusion). For patients with CD a positive initial response was defined as PCDAI $\leq$10 for those with baseline score between 10 and 30 or drop of at least 15 points for those with initial score > 30. For UC and IC the initial response was defined as absence of bloody stools, absence of abdominal pain and less than 5 bowel movements per day. Subsequently, remission was evaluated for those who achieved initial response. A patient was considered to be in remission if the PCDAI was equal to or less than 10 for CD, or when his/her bowel movements and laboratory tests (hemoglobin, albumin, ESR and CRP) had normalized for UC and IBDU. For CD, relapse was defined as PCDAI > 10 for those who had achieved remission or PCDAI > 30 for those who were initial responders but did not reach remission. For UC and IBDU relapse was identified by the re-occurrence of at least one of the above mentioned criteria. Finally for all IBD patients the need for re-administrating steroids was considered a relapse of the disease, irrespective of whether they fulfilled the abovementioned criteria.

Initial response, attainment of remission, occurrence of relapse and the necessity for surgery were evaluated through a time to event approach. Starting point was the date of the first infusion. The study end point was the 31/12/2008. All patients who had received infliximab prior to 01/01/2003, when the three-dose regime was replaced by the continuing course of therapy, were evaluated only in the initial response component. Subsequently, they were excluded from the analysis even if infliximab was reinstituted at a later point.

All infusion-related side effects were available and reviewed through the hospital records in our department. Adalimumab was used only as an alternative treatment in cases of infliximab failure or side-effects. The drug was administered subcutaneously with a loading dose of 80 mg followed by 40 mg every other week.

Statistical analysis

Continuous variables are presented by mean values ± standard deviation while discrete variables are described using absolute and relative frequencies. Means were compared by t-test or the Mann-Whitney test in cases of small samples (≤ 30). Categorical variables were compared by Fisher's exact test.

In order to evaluate the efficacy of infliximab in children with IBD a Kaplan-Meier time to event analysis was applied. In the beginning, all patients were included and the rate of initial response at 10 weeks of treatment (4 weeks after the third infusion) was assessed. In this analysis starting point was the time of first infusion while end point was the end of 4th week after the third infusion when the standard clinical assessment was performed. Patients who discontinued infliximab prior to receiving 3 doses were not included.

Subsequently, four different outcomes were evaluated using the Kaplan-Meier method : likelihood of achieving remission, rate of relapse, rate of discontinuation due to severe adverse events and the rate of surgery. These outcomes were assessed both in the population of initial responders, as well as in the entire population of patients who received even one infusion. The rates of initial response and remission were assessed overall as well as according to the disease duration at the first infusion. Survival functions were compared by the long-rank test. Patients who were lost to follow up or discontinued infliximab after the third infusion were considered censored observations. Data analysis was performed using Stata 10.0 statistical analysis software (Stata Corporation, College Station, Texas, USA

Results

Thirty one patients (57% females) have received a total of 268 infusions of infliximab since 2000 when the drug was introduced in our Department. Twenty three patients had CD (60% females) five patients had UC (60% females) while 3 patients were classified as indeterminate colitis (33% females). Table I presents disease characteristics and data of the administration of infliximab in the study population.

In 22 of the 31 patients (71%) infliximab was administered due to the unresponsiveness to previous treatment and 4/31 (13%) were steroid depended. Five patients (16%) presented with severe symptoms which did not allow the 3-month period for the assessment of response to conventional treatment. Therefore infliximab was started earlier. Intolerance to preceding medications was not recorded as an indication for administering infliximab in our population. Immunosuppressive medications prior to the initiation of infliximab are presented in Table II.

Table I. — **Characteristics of patients included in the study**

	Mean ± SD	Median	Range
Age (yrs, at 31/12/2008)	13.5 ± 3.0	13.7	5.2-21.3
Disease duration (yrs, at 31/12/2008)	5.1 ± 3.5	5.1	0.2-12.4
Age of diagnosis (yrs)	8.7 ± 4.1	8.8	1.6-14.1
Age at 1st infusion (yrs)	11.0 ± 2.8	10.8	3.9-14.9
Disease duration at 1st infusion (yrs)	2.6 ± 2.7	1.2	0.1-8.8
Infusion duration (yrs)	1.3 ± 1.4	0.8	0.1-3.5
Infusion (per patient)	8.8 ± 6.4	7	1-25

Table II. — **Immunomodulators in the study population before the administration of infliximab**

Medication	CD (N = 23)		UC (N = 5)		IBDU (N = 3)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Steroids	23	(100)	5	(100)	3	(100)	31	(100)
Azathioprine or 6-MP	23	(100)	5	(100)	3	(100)	31	(100)
Methotrexate	3	(13)	1	(20)	0	(0)	4	(13)
Cyclosporine	6	(26)	2	(40)	1	(33)	9	(29)

Initial response was recorded in 24 of 29 (82.8%, 95% CI : 64%-94%) patients who received at least 3 infusions prior to the end-point of the study. Of the two excluded patients, one had received less than 3 doses until the end of the study while in a second patient infliximab was discontinued due to a severe anaphylactic reaction during the second infusion. Fisher's exact test (p = 0.6) did not detect significantly different rates of initial response between CD (18/21, 85.7%), UC (4/5, 80.0%) and IBDU (2/3, 66.7%).

All patients who achieved initial response simultaneously fulfilled the criteria of remission. Thus, the analysis of the rate of achieving remission, among the initial responders who did not achieve remission by the third infusion, was not feasible.

Figure 1 demonstrates the estimated Kaplan-Meier function of remission for the 24 patients who attained initial response. At the 52th week of treatment the estimated percentage of patients in remission was 53% (95% CI : 27.6-73.0). When only patients with CD were included, the corresponding rate at the 52th week was 50% (95% CI : 21.8-72.0). After repeating the analysis on the entire population starting at the first infusion the estimated rate of remission at the 52th week was 43.8 % (95% CI : 22.9-63.0). For CD patients the overall rate of remission at the 52th week was 42.9% (95% CI : 19.7-64.3).

When a stratified analysis, according to the disease duration before the first infusion, was undertaken, no differences with respect to initial response and achievement of remission were found between early-CD and late CD (Fisher's exact test, p = 0.7 and long-rank test p = 0.7 respectively).

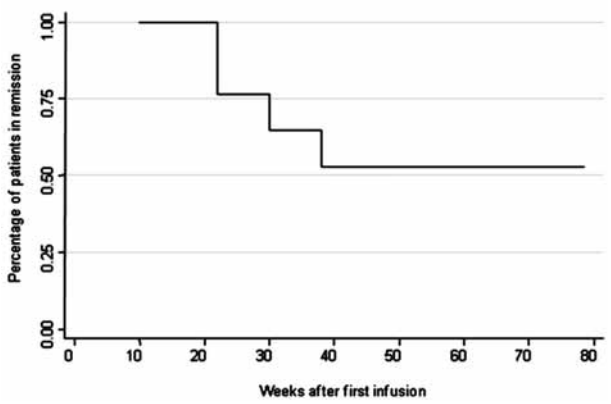

Fig. 1. — Kaplan-Meier estimation of the rate of remission for patients who attained initial response at the 10th week of treatment

Six patients had fistulizing CD and in 4 of them (66.6%) complete closure of the fistula was observed after the administration of infliximab.

At the time of initiation of infliximab 25 out of 30 patients were on steroids. Three months later only 2 children (8%) were on steroids. Twenty of these 25 patients had at least one year of follow until the 31/12/2008. In 8/20 (40%) steroids were discontinued without re-administration within the next 12 months, while in 12 (60%) steroids were required at some point during that interval.

A surgical intervention (intestinal resection) was required in 5 patients at some point after the initiation of infliximab. Of them two had CD (one total colectomy due to uncontrollable disease and one small bowel resection due to stenosis) and 3 had UC (all total colectomy due to unresponsive disease). Furthermore, a seton was placed in two patients. The estimated rate of surgery-free disease (including only intestinal resections and not setons) at both 12 and 36 months after the first dose of infliximab, irrespectively of whether the medication had been discontinued or not, was 89.6% (95% CI : 72.0-96.0). At 60 months the percentage was 74.7% (95% CI : 34.3-92.3). When only initial responders where included the corresponding rate was 95% (95% CI : 69.5-99.3) at both 12 and 36 months after the first infusion and 76.0% (95% CI : 24.4-94.8) at 60 months. Similarly to the above analysis the latter percentages of surgery-free disease were assessed independently to ongoing or not infliximab therapy.

In 4 (12.3%) patients (4/268 infusions, 1.5%) infliximab was discontinued due to a severe, infusion related, anaphylactic reaction. The estimated rate of discontinuation according to the Kaplan-Meier method was 22% at the 12th infusion, but thereafter no severe anaphylactic reactions occurred. No other severe adverse effects were recorded.

One patient who had received 3 doses of infliximab in combination with azathioprine developed B-cell lymphoma three years after the third dose of infliximab. In the mean time she had received also tacrolimus due to the unresponsive nature of the disease. Two years after the lymphoma was diagnosed, she underwent bone marrow transplantation and died one year after due to sepsis.

Adalimumab was administered to 5 patients after the discontinuation of infliximab (3 non-responders, 2 anaphylactic reactions). Two out five patients (40%) failed to achieve remission while no severe adverse reactions were recorded. These two patients were also infliximab failures.

Discussion

During the last decade, an intensive research effort to evaluate the true benefits and disadvantages of infliximab in children with IBD is being undertaken. As with any novel therapeutic agent, the increasing experience, accumulated over long periods of clinical use, provides additional evidence to conclusions extracted by clinical trials, which are usually conducted in a limited time frame. In this context, our study assessed the efficacy and safety of infliximab in the everyday clinical setting rather than in a stringent clinical trial. The results on the initial response component are similar to published observations (22-24) ; however significantly higher rates have been reported(25,26). The 1 year rate of remission is also analogous to findings in clinical trials(23) and observational studies (25,27). Surprisingly, those patients who initially responded in our study also achieved simultaneous remission (at week 10 of treatment). This observation could be partially explained by the characteristics of the patients started on infliximab. The majority of children with CD (14/23) had PCDAI between 10-30, while 5 had PCDAI > 30. Four children, who had PCDAI below or equal to 10, which was the cut-off of remission, were included due to steroid depended disease. It is clear that the activity level of the disease at the baseline was milder in our study compared to the inclusion criteria in clinical trials (23). This discrepancy could account for the observed universal remission, among the initial responders, at the 10th week of therapy in our population. For the same reason, analysis of remission in initial responders who had not reached remission by the 10th week was not feasible.

It must be noticed that when we performed a stratified analysis, according to the duration of CD before the first infusion of infliximab, the rates of initial response and remission at the 52th week for late CD were comparable to those estimated for patients with early CD. Although this finding is in accordance with a recent observational study (28), two other independent reports showed that initiation of infliximab after a longer duration of CD is related to lower probability of improvement (29,30). These differences must be evaluated carefully, since all four studies share the disadvantages of the small sample sizes and different designs.

The estimated rate of surgery in our population appears lower compared to reports (31) published prior to the introduction of infliximab as a therapeutic alternative. In that previous study 28.8 % of patients with Crohn's disease had undergone some surgical intervention at three years after the diagnosis, compared to 0% at three years and approximately 16.3 % at 4 years after the initiation of infliximab in the present study. The numbers should not be directly compared since in the majority of our patients, infliximab was not administered from the date of diagnosis but at a later point. In addition, the abovementioned study (31) included patients between 1968 and 1994. The observed decrease in the risk of surgery could be attributed not only to the effect of infliximab but also to the undoubtedly improved monitoring and management in CD patients during the last 30 years. The probable beneficial effect of infliximab on preventing surgery has also been shown in two other studies which demonstrated reduction of the risk of surgery (32) and a delay in the need for such an intervention (33). In contrast, De Ridder *et al.* (28) have found a high rate of bowel resection (34.8%) in patients having received infliximab. These differences indicate that the nature of the intervention, clinician's personal perspective and parental preferences greatly influence the timing of surgery and therefore could significantly confound the results of any comparison.

In general, severe adverse events related to the use of infliximab were limited only to anaphylactic reactions. The rate of serious anaphylaxis is comparable to published data (28,34,35). No opportunistic or severe infections were recorded including tuberculosis. As we thoroughly evaluate all anti-TNF-α therapy candidate children for underlying tuberculosis and the parents are guided to provide an environment of minimal risk for infection, it is likely that this policy has prevented serious infections to occur.

The issue of increased risk for malignancies in patients receiving infliximab, especially in combination with purine analogs, has not yet been fully clarified. In our registry, one patient developed B-cell lymphoma, three years after having received three doses of infliximab. Although a large multicenter matched pair study showed no statistically significant difference of malignancy between adults CD patients treated with and without infliximab (36), it cannot be determined if the cotreatment of infliximab with azathioprine, the nature of the disease or the administration of tacrolimus contributed to the development of lymphoma in our patient. A different type of lymphoma (hepatosplenic T-cell) has been recently related to concomitant administration of infliximab and azathioprine/6-mercaptopurine in adolescents and young adults with CD (37). At this point, a consensus strategy on whether infliximab should or not be administered in conjunction with a second immunomodulator, does not exist, and clinicians often adopt different, individualized approaches. The problem of the production of neutralizing antibodies in patients who are on monotherapy with infliximab, which may reduce its efficacy, makes the decision of discontinuing any concurrent immunosupression even more complex. In our unit our current policy includes discontinuation of purine analogs after 6 months of co-administration with infliximab.

Adalimumab was administered to only five patients making, therefore, any inference inappropriate. A small number of studies have reported satisfactory results (38-41). Increasing data on adalimumab use to children will allow robust conclusions with respect to its safety and efficacy in inflammatory bowel disease.

The major drawbacks of our study are the retrospective nature of the analysis and the relatively small number of patients. For this reason large confidence intervals have been produced in several cases. Furthermore, the included group is heterogeneous in terms of the baseline status and the indication for administering infliximab. Therefore the observed outcomes might have been different if the number of patients in subgroups allowed a stratified analysis. The criteria for the evaluation of the response in the ulcerative colitis group were not based on an objective validated scale, such as the PCDAI used for CD, but on selected features of the clinical status of the patients. However, after retrospectively calculating the values of PUCAI at the time of initiation of infliximab in UC patients, the results indicate that all had active disease (PUCAI > 10) and that the criteria used for the definition of remission corresponded to PUCAI $\leq$ 10.

In conclusion, infliximab was the ultimate therapeutic choice for children with IBD unresponsive to standard treatment in our Department. Initial response and attainment of remission are satisfactory, adding a valuable option in the management of such cases. However, discontinuation due to severe allergic reactions and loss of response reduce the efficacy of infliximab. Adalimumab is a safe alternative in cases of failure or anaphylaxis with infliximab. The increasing availability of adalimumab in paediatric IBD patients will allow a valid assessment of its value in inducing remission in these patients.

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