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Original article

Short and long-term results of adalimumab treatment of patients with active Crohn's disease: Experience of a Greek single center for inflammatory bowel disease

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SUMMARY

The aim of this study was to analyze our initial experience on the short and long-term efficacy of adalimumab *(Humira)* - a monoclonal antibody against Tumor Necrosis Factor-alpha - in patients with active Crohn's disease. Patients-Methods: A total number of 27 patients with moderately active Crohn's disease (15 men, 12 women, and aged 44.6+/-16.6 yr) were enrolled to 4-wk trial with treatment with subcutaneous adalimumab 160mg injection at week 0, 80mg at week 2 and then 40mg every other week. Outcome measures included the ability to tolerate adalimumab and clinical remission (defined as a CDAI score < or =150 points) and clinical response (defined as a decrease in the CDAI) > or =70 points). The total period of treatment with adalimumab was 7.3+/-5.8 months and the total number of injections was 476. Results: *a) Induction period:* Remission was observed in 14(51.8%) and clinical response in 8(29.6%) patients. Five (18.5%) patients showed no response. One death –unrelated to adalimumab treatment - appeared during the induction period. *b) Maintenance period:* At the time of elaboration of the results, 20 patients continued to be on adalimumab for 9+/-5.3 months. Fourteen patients (70%) continued to be on remission, and 4(20%) in partial remission. Recurrence was noticed in 1 patient (5%). One death (5%) was noticed six months after initiation of maintenance treatment because of severe complications related to cholecystectomy. *c) Side-effects:* Respiratory infections appeared in 6 patients (2 with severe infection), incomplete bowel obstruction in 2, intraabdominal abscess in 1, and development of antinuclear antibodies in 5 patients (18.5%). None of the patients experienced acute or delayed hypersensitivity reactions during treatment with adalimumab. Conclusion: Our initial experience with adalimumab is in accordance with the published series claiming that the drug represents a beneficial option for patients with Crohn's disease, either for induction or maintenance treatment. The drug seems to be well tolerated. Deaths appearing in this cohort of patients were unrelated to the use of adalimumab.

Key Words: Inflammatory bowel disease, Crohn's disease, biologic agents, adalimumab, infliximab, monoclonal antibodies

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INTRODUCTION

Adalimumab (Humira® Abbott Laboratories) is a subcutaneously administered fully human recombinant IgG_1 anti-tumor necrosis factor (TNF-alpha) monoclonal antibody, consisting of human-derived heavy and light chain variable regions and human IgG_1 constant region. Adalimumab binds to both soluble and cell-bound TNF-alpha, thus modulating biological responses linked to this cytokine.[1,2]

Different trials have proved the efficacy of adalimumab and accumulated experience in Crohn's disease (CD), rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis shows adalimumab as a safe drug sharing a similar adverse effects profile with the other anti-TNF-alpha molecules. Adalimumab was approved for the treatment of rheumatoid arthritis in 2003, and for induction and maintenance of remission in moderate to severe CD

in 2007. It has shown efficacy in both the induction and maintenance of remission in CD for patients who are naive to or have failed prior anti-TNF therapy.[3-13]

The aim of this study was to present the short and long-term results of the administration of adalimumab in patients with moderately active CD. The results express the initial experience of a single Greek centre devoted to the diagnosis and treatment of inflammatory bowel disease.

PATIENTS AND METHODS

A total number of 27 patients with moderately active CD (15 men, 12 women, and aged 44.6+/-16.6 yr) were enrolled to a 4-week trial with treatment with subcutaneous adalimumab 160mg injection at week 0, 80mg at week 2 and then 40mg every other week. Outcome measures included clinical remission (defined as a CDAI score < or =150 points), clinical response (defined as a decrease in the CDAI) > or =70 points) as well as the ability to tolerate adalimumab.

The clinicoepidemiological characteristics of the cohort of patients enrolled in the study are shown in table 1.

Indications for adalimumab administration were no response or appearance of side-effects during infliximab treatment and no response to conservative treatment [11 patients (39%) and 16 patients (59%) respectively].

The total period of adalimumab administration (induction of remission and maintenance treatment) was 7.3+/-5.8 months (mean+/-1SD) and the total number of injections was 476.

Concerning statistical analysis, differences in proportions were tested using the Pearson chi-square test or Fisher's exact test as appropriate. A P value <0.05 was considered as statistically significant.

Table 1. Clinicoepidemiological characteristics of the patients studied.

Parameter	Number of patients
Total number of patients	27
Men	15
Women	12
Age *(years)*	44.4+/-16.6 (range 22-75)
Age at diagnosis *(years)*	33+/-17
Smoking habits	
Smokers	9(33.3%)
ex-smokers	6(22.2%)
Non-smokers	12(44.5%)
Positive family history for IBD	5/27(18.5%)
Duration of disease (years)	11.4+/-8.2
Extraintestinal manifestations	16(59.3%)
Joints	12(44.4%)
Skin	2(7.4%)
Eyes	2(7.4%)
Surgical treatment in the past	12(44.5%)
Type of disease	
Inflammatory	15(55.5%)
Fistulizing	5(18.5%)
Stenotic	7(26%)
Location of disease	
Small bowel	6(22.2%)
Colon	4(14.8%)
Small bowel & colon	17(63.0%)

RESULTS

A) Induction phase:

The results showed that adalimumab administration achieved remission in 14 (51.8%) and clinical response in 8 (29.6%) patients. Five patients (18.5%) showed no response (Figure 1). One patient with no response to adalimumab treatment died after completion of the induction period due to extremely severe condition (short bowel syndrome accompanied by many biochemical and nutritional disturbances).

Response to treatment according to age, sex, smoking habits, duration, location, and type (inflammatory, fistulizing and stenotic) of disease as well as the presence or not of extraintestinal manifestations showed no statistically significant differences (Table 2).

B) Maintenance phase

Twenty out of the 27 patients initially included in the study, continued to be on adalimumab at a dose of 40mg every other week, for a mean period of 6.3+/-4.9 months. At the end of the follow-up period, 14 patients (70%)

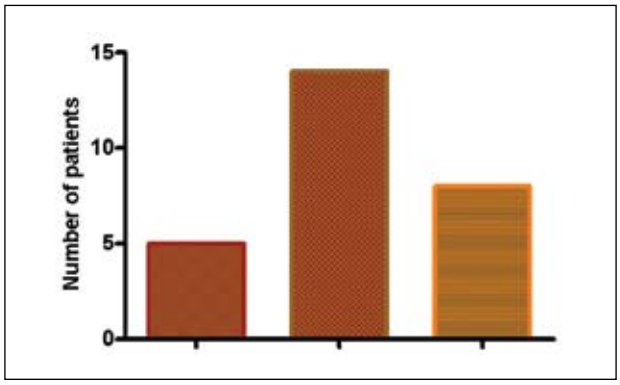

Figure 1. Results of induction treatment with adalimumab

Table 2. Response to treatment according to age, sex, smoking habits, duration, location, and type of Crohn's disease and the presence or not of extra-intestinal manifestations

Group	Remission	Partial response	No response	P-value *(Pearson Chi-square)*
Age 22-45 (n=15)	7(46.7%)	5(33.3%)	3(20.0%)	0.636 (NS)
Age 46-75 (n=12)	7(58.3%)	3(25.0%)	2(16.7%)	
Men (n=15)	7(46.7%)	6(40.0%)	2(13.3%)	0.239 (NS)
Women (n=12)	7(58.3%)	2(16.7%)	3(25.0%)	
Non-smokers (n=13)	9(69.2%)	1(7.7%)	3(23.1%)	0.078 (NS)
Smokers (n=10)	5(50.0%)	4(40.0%)	1(10.0%)	
ex-smokers (n=4)	0(0%)	3(75.0%)	1(25.0%)	
1-9 years duration (n=15)	9(60.0%)	5(33.3%)	1(6.7%)	0.354 (NS)
>9 years duration (n=12)	5(41.7%)	3(25.0%)	4(33.3%)	
Small bowel (n=6)	5(83.3%)	0(0%)	1(16.7%)	0.307 (NS)
Colon (n=4)	2(50.0%)	1(25.0%)	1(25.0%)	
Small bowel & colon (n=17)	7(41.2%)	7(41.2%)	3(17.6%)	
Inflammatory type (n=15)	9(60.0%)	4(26.7%)	2(13.3%)	0.687 (NS)
Fistulizing disease (n=5)	2(40.0%)	2(40.0%)	1(20.0%)	
Stricturing disease (n=7)	3(42.8%)	2(28.6%)	2(28.6%)	
Presence of EM (n=13)	8(61.5%)	3(23.1%)	2(15.4%)	0.675 (NS)
Absence of EM (n=14)	6(42.9%)	5(35.7%)	3(21.4%)	

NS= no significant

continued to be on remission, 4(20%) showed partial response, 1(5%) presented with recurrence, and 1(5%) died after cholecystectomy (performed because of cholelithiasis clinically presented with acute pancreatitis six months ago) accompanied by severe complications and abdominal sepsis (Figure 2).

It is of interest that patients who developed antinuclear antibodies during the induction or maintenance phase showed significantly poorer results compared to the group of patients who did not (P=0.028, Table 3).

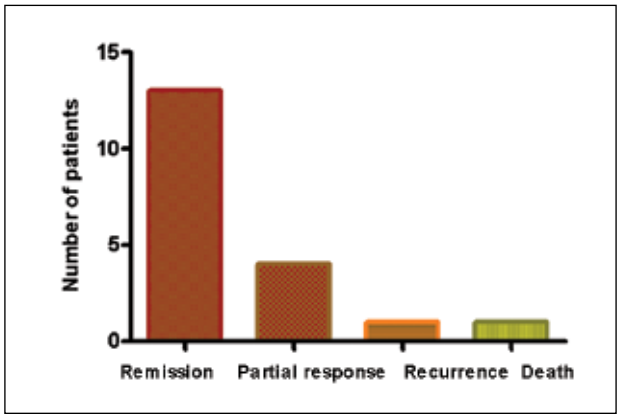

Figure 2. Results of maintenance treatment with adalimumab

C) Side-effects

Side effects of adalimumab administration, including those appearing during the follow-up period, developed in 9 patients (33.3%). Some of the patients developed more than one side-effect. They included infections (6 patients 22%), abscess formation (1 patient 3.7%), incomplete bowel obstruction (2 patients 7.4%) and development of antinuclear antibodies (5 patients 18.5%). Mild pain and erythema at the injection site were noticed in 3 patients (11.1%). None of the patients experienced any kind of acute or delayed hypersensitivity reaction during treatment with adalimumab. There was no difference in the side-effect rate between patients who previously received infliximab or not.

Patients with longer duration of treatment with adalimumab (7-15 months) developed side-effects in a statistically significantly higher proportion compared to the group of patients with smaller (1-6 months) duration of treatment (53.8% *vs* 14.3%, P=0.046) (Table 4).

DISCUSSION

The results of the present study showed that treatment of moderately severe CD with adalimumab can achieve remission or clinical improvement in the majority of patients who had either received biologic agents or not in the

Table 3. Outcome according to the development of antinuclear antibodies (ANA)

ANA	Remission	Partial response	No response	P-value (Pearson Chi-square)
Negative (n=21)	13(61.9%)	4(19.0%)	4(19.0%)	0.028
Positive (n=5)	1(20.0%)	4(80.0%)	0(0%)	

(*) (One missing value)

past. The results also showed that the majority of patients who went into remission with adalimumab continued to be on remission using adalimumab as maintenance treatment. Other interesting results of this study were related to the development of antinuclear antibodies. Patients who developed ANA Abs showed statistically less favourable response rates compared to patients who did not develop these antibodies.

Our results are in accordance with previous studies concerning response rate in patients who were either intolerant to or had lost the efficacy for infliximab. In an open trial, 24 patients who had lost responsiveness or developed intolerance to infliximab were treated with an initial dose of adalimumab 80 mg and then 40 mg every other week for 12 wk. Although 79% required dose escalation to 40 mg weekly, clinical remission and response at wk 12 was seen in 29% and 59% respectively.[4]

In a study of 50 patients receiving an induction dose of adalimumab, 83% of 36 patients with luminal CD achieved clinical response, and 42% achieved clinical remission at week four.[7] In 10 of 16 patients (63%) treated with adalimumab, remission was induced for at least 8 weeks independent of CARD15 or +1059G/C CRP status. Adalimumab significantly decreased CRP levels and CDAI3. In an open study 71% of patients demonstrated clinical response[6]. It must be stressed however; that in everyday clinical practice it is a common phenomenon to escalate the dose in a significant proportion of patients.[9]

The CLASSIC I trial randomized 299 moderate to severe CD patients naive to anti-TNF therapy to one of three dose combinations administered at wk 0 and 2 (160/80 mg, 80/40 mg, or 40/20 mg) or placebo. At week 4, 36% (P = 0.001), 24% (P = 0.06), and 18% (P = 0.36) in the adalimumab groups, respectively, were in clinical remission compared to 12% in the placebo group.[10]

In the CLASSIC II trial,[11] it was found that 79% of patients who received adalimumab 40 mg every other week and 83% who received 40 mg weekly were in remission at week 56, vs 44% for placebo ($p<0.05$). Our results fit well with those described in the above mentioned clinical trials, thus underlining the fact that similar large randomized trials could be reproduced in everyday clinical practice.

Concerning maintenance treatment, Colombel et al[12] found that among patients who responded to adalimumab, both adalimumab eow and weekly were significantly more effective than placebo in maintaining remission in moderate to severe CD through 56 weeks.

Finally, in the study of Palacios et al[13] aiming to describe the experience of a single centre it was found that after induction, 25% of patients with luminal disease had complete remission, and 56.3% had a partial response. Clinical response was maintained in 71.6% of patients at 1 year, in 53.7% at 18 months, and in 35.8% at 48 months.

Adalimumab also offers significant benefit to patients with active fistulas.[6] In the study of Hinojosa et al,[7] of the 22 patients with fistulizing disease, five (23%) experienced fistula remission, and nine (41%) experienced fistula improvement at week 4. Although we also observed satisfactory clinical results in patients with active fistulas, we can not draw firm conclusion due to the small number of patients treated.

Concerning side-effects, except for the appearance of an abdominal abscess, and two cases with severe respiratory infections no other serious adverse events were observed. Injection-site reactions were generally mild and occurred in a small proportion of patients, a finding similar to other studies.[3,6] Other side-effects appeared in the

Table 4. Development of any side-effect according to the duration of disease

Duration	No side-effect development	Development of side-effect	P-value (Pearson Chi-square)
1-6 months (n=14)	12(85.7%)	2(14.3%)	0.046
7-15 months (n=13)	6(46.2%)	7(53.8%)	

same proportion.[5-8] In the study of Seiderer et al[3] there was only one serious complication (fungal pneumonia), although other serious adverse events during maintenance treatment have been described ranging from 10.8% and 11% of patients respectively.[6,2]

In conclusion, our initial experience with adalimumab is in accordance with the published series claiming that the drug represents a beneficial option for patients with CD, either for induction or maintenance treatment. The drug also seems to be well tolerated. Deaths appearing in our cohort of patients were unrelated to the use of adalimumab. These results confirm that the findings obtained in controlled clinical trials are reproducible in clinical practice.

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