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Adéquation et efficacité de l'Adalimumab dans une cohorte suisse multicentrique de patients avec maladie de Crohn

THESE

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Adéquation et efficacité de l'Adalimumab dans une cohorte suisse multicentrique de patients avec maladie de Crohn

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Madame le Professeur Stephanie Clarke
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Adéquation et efficacité de l'adalimumab dans une cohorte suisse multicentrique de patients avec maladie de Crohn

Résumé

De nombreux essais cliniques randomisés ont démontré l'efficacité de l'adalimumab chez les patients atteints de maladie de Crohn modérée à sévère. Néanmoins, l'expérience sur le long terme est très limitée dans la pratique médicale quotidienne.

But : Vérifier l'efficacité, la sureté et l'adéquation de l'adalimumab dans une cohorte suisse multicentrique de patients atteints de maladie de Crohn.

Méthode : Nous avons étudié rétrospectivement les dossiers de patients atteints de la maladie de Crohn traités par adalimumab sur une période de 3 ans. L'activité de la maladie a été mesurée par l'Index de Harvey-Bradshaw (HBI). Une rémission correspondant à un score $\leq$4 points et une réponse clinique à une diminution du HBI de >3 points par rapport au score pré-traitement. Pour évaluer l'adéquation de l'adalimumab, nous avons utilisé les critères développés par l'European Panel on the Appropriateness of Crohn's disease Therapy (EPACT II).

Résultats : Les dossiers de 55 patients ont été analysés. Le taux de rémission et de réponse observés après 4 à 6 semaines était respectivement de 52.7% et 83.6%. La rémission a été maintenue à 12, 24 et 52 semaines chez respectivement 89.6%, 72.4% et 44.7% des patients. La rémission et la réponse clinique au traitement n'étaient pas correlés au status tabagique du patient, à la localisation ou la durée de la maladie, à la dose totale reçue le premier mois ou à un précédent traitement par infliximab. Le taux de rémission après 4 à 6 semaines de traitement était significativement plus élevé chez les patients ayant développés une intolérance à l'infliximab par rapport à ceux devenus réfractaires à ce traitement. L'adalimumab a été globalement bien toléré. 59 % des indications à l'adalimumab ont été adéquates.

Conclusion : L'adalimumab peut être considéré comme un traitement efficace et approprié à long terme chez les patients avec une maladie de Crohn modérée à sévère.

Clinical Experience and Appropriateness of Adalimumab in a Multicenter Swiss Cohort of Patients With Crohn's Disease

Running head: Adalimumab in Crohn's disease

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Abstract

Background: Controlled clinical trials have demonstrated the efficacy and safety of adalimumab in patients with moderate-to-severe Crohn's disease (CD), but there is, however, only limited long-term experience with adalimumab in daily practice.

Aim: To assess the long-term effectiveness, safety and appropriateness of adalimumab in a multicenter cohort of practice-based patients with moderate-to-severe CD.

Methods: We retrospectively reviewed the charts of CD patients who received adalimumab over a 3-year period. Disease severity was scored using the Harvey-Bradshaw Index (HBI). Remission was defined as HBI of ≤ 4 and response as a reduction in the HBI of >3 points at evaluation compared to the baseline. To assess appropriateness of adalimumab, we used the criteria developed by the European Panel on the Appropriateness of Crohn's disease Therapy(EPACT II). Univariate logistic regression analysis was used to identify the predictive variables associated with response.

Results: The charts of 55 patients were reviewed; remission and response rates observed at week 4-6 were 52.7% and 83.6% respectively. Remission was maintained at week 12, 24 and 52 in 89.6%, 72.4% and 44.7% of patients respectively. Remission and response rates were not influenced by smoking status, disease location or duration, the first-month total dose, or previous infliximab therapy. Remission rate at week 4-6 was significantly higher in patients intolerant of infliximab as compared to those who lost response to this drug. Adalimumab was well tolerated overall. 59% of adalimumab indications were rated appropriate.

Conclusion : Adalimumab can be considered a suitable and appropriate option in patients with moderate-to-severe CD, demonstrating sustained long-term effectiveness.

Introduction

Tumor necrosis factor α (TNF-α) has emerged as a central cytokine in the pathogenesis of Crohn's disease (CD), as is confirmed by the central role that TNF-α antagonists have now acquired in the treatment of patients with moderate-to-severe or refractory CD. Infliximab (IFX), the first chimaeric monoclonal TNF-α antibody, is an effective treatment for induction and maintenance of remission in patients with moderate-to-severe Crohn's disease, including those with draining fistulas [1-4]. However, a proportion of patients develop antibodies to infliximab (ATI), in particular with episodic therapy or in the absence of concomitant immunosuppressant medication. The presence of ATI leads to infusion reactions, loss of response and delayed hypersensitivity reactions [5-7].

Adalimumab is a subcutaneously-administered recombinant, fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNF. Four pivotal, randomised, double-blind trials (CLASSIC-I, CLASSIC-II, CHARM and GAIN) in >1400 patients demonstrated clinical efficacy and safety of adalimumab in patients with moderate-to-severe Crohn's disease [8-11]. Adalimumab was significantly more effective than placebo for induction of remission in patients naive to anti-TNF therapy (CLASSIC-I trial, 36% vs 12% at week 4 with 160/80 mg regimen, $p=0.004$) or in those who had either lost responsiveness or developed intolerance of infliximab (GAIN trial, 21% vs 7.2% at week 4, $p<0.001$). The CHARM trial showed that, among patients who responded to open-label adalimumab induction, maintenance therapy with adalimumab 40mg weekly or every other week for up to 1 year was associated with significantly greater remission rates than placebo at weeks 26 (47%, 40% vs 17%, $p<0.001$) and 56 (41%, 36% and 12%, $p<0.001$). In another maintenance trial (CLASSIC-II), patients who were in remission after a short course of adalimumab and who were randomised to receive up to 1 year of treatment with adalimumab 40mg weekly (ew) or every other week (eow), were significantly more likely to remain in remission than those who received placebo (83%, 79% vs 44%, $p<0.05$). Loss of efficacy can also be observed with

adalimumab and an increased dose can be used to restore clinical response or remission. The role of antibodies to adalimumab in the loss of response is to date poorly characterized.

Adalimumab is generally well tolerated. In clinical trials, the rate of serious adverse events was low in patients treated with adalimumab and was similar to those treated with placebo [8-11].

Patients with Crohn's disease seen in daily practice may differ from the selected patients included in randomized trials [12-15]. In a multicenter open-label single-arm study (CARE), adalimumab therapy showed substantial efficacy at week 4 (43% remission rate), which was sustained through week 20 (52% remission rate), including in patients who had never responded to IFX[16]. Neither concomitant steroids nor immunosuppressants notably affected the results [17]. In this study, we analyzed our experience with adalimumab in current clinical practice over the past three years.

For many of the clinical situations in Crohn's disease, there is no high-grade evidence, based on randomized controlled trials, concerning the right choice of treatment. In this context, appropriateness criteria derived from a validated and well-accepted panel method have the potential to assist the clinician in decision-making and to improve quality of care.

In 2004, the European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT) convened in Lausanne and brought together 15 experts (10 gastroenterologists, 2 internists/general practionners and 3 surgeons) from 12 European countries (Austria, Croatia, Denmark, France, Germany, Ireland, Israel, Italy, Spain, Sweden, The Netherlands, United Kingdom) to develop detailed and specific criteria for the appropriateness of care, using the RAND/UCLA appropriateness method [18]. In 2007, the second European Panel on the Appropriateness of Crohn's Disease Therapy (EPACT II) aimed to update and redefine appropriateness criteria for Crohn's disease taking into account recent advances in medicine and published literature available [19-23]. The aim of the

appropriateness criterias were to serve as the basis for guidelines concerning therapy in order to assist practitioners and patients in choosing correct treatment.

Although the criteria are designed to be used prospectively, we decided in this study to evaluate the appropriateness of adalimumab retrospectively and to see if there was a relationship between appropriateness and clinical response of treatment. This approach has been validated in a prior study by our group using the same criteria in CD patients, not restricted to anti-TNF users [24].

Patients and Methods

We performed a retrospective chart review of patients with CD who had been treated with adalimumab at the University Hospitals of Lausanne, Geneva, Zurich and Olten between April 2005 and April 2008, and fifty-five patients who had received adalimumab were identified. The diagnosis of Crohn's disease was confirmed in all cases by a review of patients' medical records including clinical notes, endoscopic, radiographic or histological documents.

The information collected included patient demographics, disease location, disease phenotype, disease duration, prior surgical procedures, smoking status, previous anti-TNF and immunosuppressant use, concomitant medication, disease activity at baseline and during treatment. Disease severity for luminal Crohn's disease was scored using the Harvey-Bradshaw index (HBI) [25]. For patients with previous surgical resections, other causes of diarrhoea, such as bile salt malabsorbtion, small bowel bacterial overgrowth, or deficient water absorption secondary to proctocolectomy, were eliminated before considering them for adalimumab therapy.

First clinical evaluation was performed at week 4-6. Subsequent assessments of efficacy of treatment were performed at week 12, 24 and 52. The clinical evolution of luminal CD was classified into three categories: remission, response and non-response. Remission was defined as an HBI of ≤ 4

and response as a reduction in the HBI of ≥3 points at the evaluation week compared to the baseline index[26]. The non-response category included all the remaining patients.

Data on clinical safety were collected at every medical visit and the patients were also instructed to contact the physician's office if any illness or adverse reaction occurred. Patients were considered intolerant to IFX if they were unable to continue the treatment due to reactions judged by the clinician to be linked to the perfusion. Loss of responsiveness to IFX was accepted if patients did not achieve remission with an increased IFX regimen after loss of efficacy at a standard dose.

To evaluate appropriateness, CD category was established for each patients using EPACT criteria available on the EPACT website (www.epact.ch). It must be emphasized that a patient could be in more than one category. For example, a patient could have an active luminal disease and extra-intestinal manifestations of his CD. EPACT criteria are based on the Crohn's Disease Activity Index (CDAI) known to correlate closely with HBI [25]. In an article published in 1980, William R. Best evaluated the two scores and found that a 1 point increase in HBI corresponds to a 27-point increase in the CDAI [27]. A remission (HBI of <4 points) corresponded to a mean CDAI from 26 ± 26 to 134 ± 39 and a clinical response (reduction in the HBI of >3 points) to a CDAI reduction of 81 points.

We used univariate logistic regression analysis to see if the predictive variables tested (table 2,3) were implicated in the response rate. The variables which had a p value <0.3 were tested, then together in a multivariate analysis in order to control for the confounding effect of each. A p value of <0.05 was considered to be statistically significant. Data are expressed according to a per-protocol analysis. All quantitative variables are expressed as the mean ± standard error.

Results

This cohort comprised 55 patients (21 men and 34 women), mean age 37.5 years (±11.4 years) treated with adalimumab between April 2005 and April 2008. The demographic data and baseline clinical characteristics are summarized in Table 1. The mean duration of Crohn's disease was 12.7 years (range 1-41 years). Description of disease location of luminal CD followed the usual distribution. One patient had ileal, colonic and oesophageal disease. The mean HBI before treatment was 10.9 points (±5 points). Twenty-nine patients were smokers. Adalimumab was administered to patients intolerant to IFX, to those who had lost response to IFX, or to those who were corticodependent. Seven patients were treated thus for other reasons, two of whom had severe spondylarthropathy. The indication for adalimumab therapy in the 4 patients who had an HBI<4 points at inclusion was intolerance to IFX (1 patient), lupus-like syndrome with IFX (1 patient) and corticodependence (2 patients). These patients were considered to be in remission if their HBI remained below 4, or were deemed non-responders if their HBI value rose during the follow-up period. Of those who had already received IFX, 25 patients had episodic infusions and 18 patients had regular treatment. All patients received subcutaneous injections of adalimumab at week 0 and 2 at a dose of 160mg/80 mg (31 patients) or 80mg/40mg (24 patients) and then 40mg every other week. The results of detailed subgroup analysis are summarized in Table 2 and Table 3.

Adalimumab induces and maintains clinical remission and response in CD patients. At week 4-6, in per protocol analysis, remission had been induced in 29 patients (52.7%) and response was noted in 46 patients (83.6%). An adalimumab-induced remission was maintained in 26 patients (89.6%) at week 12 and in 21 patients (72.4%) at week 24, respectively. The evolution over time of remission and response rates in per-protocol analysis is shown in Figure 1. However in a intention-to-treat analysis remission was noticed in 47.3% patients et week 24 and in 31% patients at week 52, respectivelly. Response rates at the same time-points were 54.5% and 34.5% respectively. Thirteen patients (23.6%) required an increase in the adalimumab dose: nine patients to 40 mg every week,

two patients to every 10 days, one patient to 80 mg every week and another to 80 mg every 2 weeks, because of incomplete response or loss of response. Of these 13 patients, 6 (46.1%) achieved remission and another 2 patients responded. In one patient, the dose was reduced to 40 mg every 4 weeks because of fatigue. The response rate was not significantly higher in the group of patients with previous abdominal surgery (Table 2).

Effect of smoking on Adalimumab efficacy at week 4-6. The remission and response rates were higher among the non-smoker, but without any statistically significant difference.

Effect of disease duration or location on adalimumab efficacy at week 4-6. Because of the long mean disease duration in our cohort, we chose to separate the patients in three almost equal groups: CD known for <7 years, for 7-15 years and for >15 years. The remission and response rates were almost similar within these 3 groups. The location of the intestinal segment(s) involved was not found to play a significant role in patients' clinical response to the adalimumab therapy.

Effect of the first-month total dose on adalimumab efficacy at week 4-6. Remission and response rates were not different between the groups who received adalimumab 240mg or 120mg during the first month of treatment. The total first-month adalimumab dose was divided by the patient's weight and patients were then grouped into 3 dose-adjusted groups according to the total dose per kg over the first month: <2.5 mg/kg, 2.5-3.5 mg/kg and >3.5 mg/kg. We did not find any statistically significant difference between these three groups with regard to the response rate.

Impact of prior infliximab treatment on adalimumab efficacy at week 4-6.The response rate was not influenced by the absence of previous IFX treatment or by its regular as opposed to episodic use. In contrast, the remission rate at week 4-6 was significantly higher among patients intolerant to infliximab, compared to those who had lost response to this medication (78.9% vs 42.1%, p=0.02).

Safety of adalimumab treatment. Overall, subcutaneous injections of adalimumab were well tolerated (Table 4). Thirty of the 55 patients reported no adverse event. The most common side-effect was pain at the injection site (10.9%), followed by asthenia (9%) and infections (7.2%). One patient stopped the treatment because of intolerable fatigue and another because of gynaecological side-effects. One case of lupus-like syndrome was noted. In our cohort, no fatal complication, malignancy, neurologic or cardiovascular complication was noted during the whole of the observation period.

Appropriateness of Treatment. Crohn's disease EPACT II category was established for each of the 55 patients. We analysed the appropriateness of adalimumab for the different categories of CD (Table 5). It showed that adalimumab was appropriately used for 59% of clinical situations, uncertain for 34.5%, while 6.5% were inappropriate. All fistulizing cases were rated uncertain, mostly due to a lack of randomized controlled studies evaluating adalimumab in penetrating CD. Fibro-stenotic cases were all inappropriately treated.

Appropriateness and clinical response at week 4-6. The response rate was higher in cases where adalimumab was either appropriate or uncertain compared to inappropriate cases, without any statistically significant difference (Table 6).

Discussion

The purpose of our retrospective cohort study was to evaluate the effectiveness of adalimumab in daily clinical practice in our Crohn's patients over a period of 3 years. Adalimumab treatment was effective in induction and maintenance of remission in patients with moderate-to-severe Crohn's disease. The results in our cohort appear better than the remission and response rates noticed in the CLASSIC I trial (36% and 59% respectively at week 4) [8] and the GAIN trial (21% and 52% respectively at week 4) [11]. The fact that in our cohort the first evaluation occurred later than that in those trials, i.e. that our patients had a supplementary third injection, may have

contributed to the improved results. In per-protocol analysis, 44.7% patients were in remission and 50% still in response at week 52. These long term results for remission are similar to those at week 56 in the CLASSIC II trial [9]. The limited size of our cohort, the lack of placebo controls and the absence of restricted inclusion criteria may have contributed to the differences noticed in our patients. In addition, we used the HBI rather than the Crohn's Disease Activity Index to evaluate patients, which could also in part explain the difference from the randomized trial. The remission and response rates in our cohort are also comparable to those of the CARE study [16,17], although in this multicenter cohort all patients received a 160/80mg induction regimen.

The proportion of our patients who needed a dose increase, and the benefit obtained with this strategy, was similar to that reported in the CHARM trial [28]. In our cohort, the mean time to dose increase was relatively long: 7 months (range 1-24 months). Our results thus confirm that in clinical practice this strategy should be explored before considering another treatment in patients who lose response or fail to achieve complete remission with a standard adalimumab regimen. In a small study, a higher percentage of patients were previously reported to require adalimumab dose-increase (nearly 60% at 6 months), using a suboptimal induction regimen of 80mg/40mg [12]. In another two cohorts, only 13.2% and 29% of patients respectively required dose-increase [14,15].

In a per-protocol analysis, we observed that, over 52 weeks, adalimumab treatment was stopped in half of the patients. This dropout rate was progressive during the observation period. The reasons for discontinuation were either no response, loss of response despite dose-increase (14/19 patients) or adverse reaction (5/19 patients).

Smoking status had no effect either on the rate of clinical remission or on response rate in patients treated with adalimumab. This observation is consistent with the results of the sub-analysis in the CLASSIC I trial, where the efficacy of adalimumab treatment at week 4 was not affected by

smoking status [29]. Hinojosa et al also reported no difference in the 4-week response rate of active smokers with luminal CD as compared to former smokers [13].

The efficacy of adalimumab therapy in our cohort was not influenced by disease duration. In the CHARM trial, Colombel et al showed a significantly better remission rate at week 26 and 56 with adalimumab in patients with CD duration of <2 years or >5 years (10). We were unable to separate our patients into the same three groups (disease duration <2 years, 2-5 years and >5 years) because our patients had a longstanding diagnosis of Crohn's disease. Our results suggest that beyond 7 years disease duration has no greater impact on response.

We failed to show a correlation between the total first-month dose adapted to body-weight or the response or remission rate to adalimumab therapy. These results suggest that the dose during the first month as currently administered should suffice in the majority of patients. However, the small size of the cohort and the retrospective nature of the analysis do not exclude the possibility that a dose-weight relationship might exist in a larger group of patients. Indeed, as the affinities and molecular weight of IFX and adalimumab are comparable, one could have expected that such a relationship might exist. Other characteristics of adalimumab may explain this difference as compared to IFX, such as the human nature of the antibody or differences in the binding sites of the antibodies.

The majority of our patients had been treated with IFX before receiving adalimumab. The remission and response rates at week 4-6 were not statistically different in patients naive to IFX compared to those who had already been treated with IFX. Similarly, no difference was found in the response to adalimumab between patients whose previous IFX therapy was interrupted because of loss of response or because of intolerance. This last observation was also reported by Hinojosa et al [13]. In contrast, however, the remission rate at week 4-6 was significantly higher in the subgroup of patients intolerant to IFX. This suggests that patients who did not lose their response to IFX may

benefit more from another anti-TNF agent. Patients who have lost response may represent a group of patients that may better benefit from a change in the treatment target, different from TNF.

Overall, adalimumab was well tolerated in our cohort. The rate of side-effects was similar to that already reported in randomized trials, in which patients underwent more stringent selection and monitoring [8-10]. Pain at injection site, asthenia and infections were the most common adverse events. Despite these reassuring results, the safety issues surrounding anti-TNF therapies continue to be of great significance and clinicians need to remain vigilant. JF Colombel recently assessed global adalimumab safety in a collective of 2228 patients exposed to adalimumab in pivotal randomized trials, open-label extensions and phase IIIb studies, CHOICE and CARE. The rates of opportunistic infections and of malignant neoplasms were found to be <2% of patients [30]. Such rates justify careful monitoring of all patients, even when stable in remission.

Our study has several limitations. Firstly, the data presented are based on a retrospective review and not on a uniform analysis with precise time-points. Secondly, even if this is the largest cohort of open-label clinical experience in patients with Crohn's disease to date, the number of patients analyzed at 24 and 52 weeks is still low. Thirdly, our patients had a long standing Cronh's disease history prior to adalimumab therapy. It remains to be studied if adalimumab used in a top-down scheme might improve the results reported here. Although non-significant, the odds ratio values cannot be taken as proof that none of the variable mentioned in Table 2 may have an effect. The large confidence intervals indicate that the calculated odds ratio remains imprecise.

Concerning appropriateness of adalimumab, we failed to demonstrate a link between appropriateness and response to treatment at week 4-6. If we consider uncertain treatment as appropriate, we observe that 94.5% of adalimumab indications were appropriate in our cohort. This high appropriateness index can be explained by several factors. Firstly, the use of adalimumab at this early stage after introduction was mostly restricted to tertiary centers with extensive experience of

Crohn's therapy. Secondly, the patients were all at the end of the therapeutic possibilities, which made the choice of adalimumab appropriate in this setting in most cases. Thirdly, the number of inappropriate cases limited the value of the statistical analysis. More cases would be required to detect a difference if there would be one. In any case, this high appropriateness index is reinsuring regarding a proper resource consumption of this costly therapy in our country.

In conclusion, our data suggest that adalimumab is as effective in inducing and maintaining remission in patients with moderate-to-severe or refractory Crohn's disease seen in daily practice as reported during randomized trials. Our results further suggest that patients with intolerance to IFX represent a group particularly well-suited to further adalimumab therapy. Adalimumab was appropriate for a high majority of our patients. The safety of adalimumab is also confirmed in daily practice. However, results from larger cohorts should be awaited before reaching firm conclusions.

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Table 1: Demographic and Baseline Clinical Characteristics

Patient characteristics	N=55 (%)
Gender	
Male	21 (38.2)
Female	34 (61.8)
Mean age (years) ± SD	37.5
Disease duration (years)	
Mean ± SD	12.67±11.4
Range	1-41
Smokers	
Yes	29 (52.7)
No	26 (47.3)
Disease location (Vienna Classification)	
L1: Ileal	9 (16.3)
L2: Colonic	11 (20)
L3: Ileocolonic	35 (63.6)
L4-: Upper (esophageal)	1 (1.8)
Disease behavior (Vienna Classification) - patients may appear more than once	
B1: non-stricturing non-penetrating	35 (63.6)
B2: stricturing	7(12.7)
B3: penetrating	23 (41.8)
Surgery for Crohn's disease	
Ileal resection	5 (9)
Ileocolonic resection	12 (21.8)

Colonic resection	7 (12.7)
Proctocolectomy	4 (7.3)
None	23 (41.8)
Previous Infliximab (IFX) therapy	n=43
Side-effects	23 /43 (53.4)
Loss of response	19 /43 (41.1)
No/insufficient response	1/43 (2.3)
Never given	12/55 (21.9)
Type of infliximab therapy	
Regular	18/43 (41.9)
Episodic	25/43 (51.8)
Concomitant treatment	
Budesonide	4 (7.3)
Prednisone	25 (45.4)
Azathioprine	5 (9)
Methotrexate	3 (5.4)
Indication of Adalimumab	
Intolerance to IFX	19 (34.5)
Loss of response to IFX	19 (34.5)
Corticodependance	10 (18.1)
Other reason [a]	7 (12.7)
Adalimumab induction regimen	
160mg/80mg	31 (56.4)
80mg/40mg	24 (43.6)

[a] refractory to Certolizumab (3), to Azathioprine(1),extra-intestinal manifestations (2), no response to IFX (1)

Table 2: Response by subgroups at 4-6 weeks

Variable	Category	Response W4-6, n (%)	Non-response W4-6, n (%)	Univariate regression		Multivariate regression	
				OR (95%CI)	p	OR (95%CI)	p
Age (years)		38.3	33.4	1.04 (0.97-1.12)	0.249	1.04 (0.97-1.12)	0.268
Gender	Female	29 (85.3)	5 (14.7)	1			
	Male	17 (80.9)	4 (20.1)	0.73 (0.17-3.10)	0.673		
Smoking status	Non-smoker	23 (88.5)	3 (11.4)	1			
	Smoker	23 (79.3)	6 (20.7)	0.50 (0.11-2.24)	0.366		
Disease duration (years)	< 7	15 (83)	3 (17)	1			
	7 – 15	16 (84)	3 (17)	1.00 (0.17-5.72)	1		
	> 15	15 (83)	3 (17)	0.94 (0.16-5.39)	0.942		
Disease	Ileitis (L1)	8 (80)	2 (20)	1			

location	Colitis (L2)	10 (91)	1 (9)	2.22 (0.17-8.86)	0.542		
	Ileocolitis (L3)	28 (82.3)	6 (17.3)	1.04 (0.19-6.07)	0.968		
Previous resection (any segment)	No	18 (78.3)	5 (21.7)	1			
	Yes	28 (87.5)	4 (12.5)	1.94 (0.46-8.22)	0.366		
Previous IFX therapy	Never	9 (75)	3 (25)	1			
	Episodic	21 (84)	4 (16)	1.57 (0.29-8.41)	0.595		
	Regular	16 (88.9)	2 (10.1)	2.40 (0.34-6.97)	0.380		
Indication for adalimumab	Loss of response to IFX	17 (89.4)	2 (10.6)	1		1	
	Intolerance to IFX	17 (89.4)	2 (10.6)	0.94 (0.12-7.48)	0.957	1	
	Other*	12 (70.5)	5 (20.5)	0.27 (0.04-1.61)	0.149	0.33 (0.07-1.68)	0.182

First-month total dose (mg)	120 (80+40)	19 (79.2)	5 (21)	1			
	240 (160+80)	27 (87.1)	4 (13)	1.00 (0.99-1.02)	0.434		
First-month total dose/weight (mg/kg)	< 2.5	17 (80.9)	4 (19.1)	1		1	
	2.5 – 3.5	13 (76.4)	4 (23.6)	0.72 (0.15-3.43)	0.682	1	
	> 3.5	16 (94.1)	1 (5.9)	3.56 (0.36-5.20)	0.278	3.87 (0.38-39.03)	0.251

* Corticodependence (n=10) and other (n = 7) merged because of small numbers.

Table 3: Remission by subgroups at 4-6 weeks

Variable	Category	Remission W4-6, n(%)	Non-remission W4-6, n(%)	p-value
Smoker status	Smoker	12 (41.4)	17 (58.6)	0.075
	Non-smoker	17 (65.4)	9 (34.6)	
Previous IFX therapy	Regular	10 (55.5)	8 (44.5)	0.719
	Episodic	12 (48)	13 (52)	
	Never	7 (58.3)	5 (41.7)	
Indication for adalimumab	Loss of response to IFX	8 (42.1)	11 (57.9)	0.012
	Intolerance to IFX	15 (78.9)	4 (21.1)	

Table 4: Adverse events observed over the 3-year period

Type of adverse event	N
None	35
Perianal abscesses	2
Asthenia	5
Pain at injection site	6
Pruritis at injection site	2
Rash	1
Headache	3
Nausea	2
Diarrhoea	1
Dizziness	2
Phlebitis	1
Gynecological side-effect	1
Labial herpes	1
Lupus-like syndrome	1

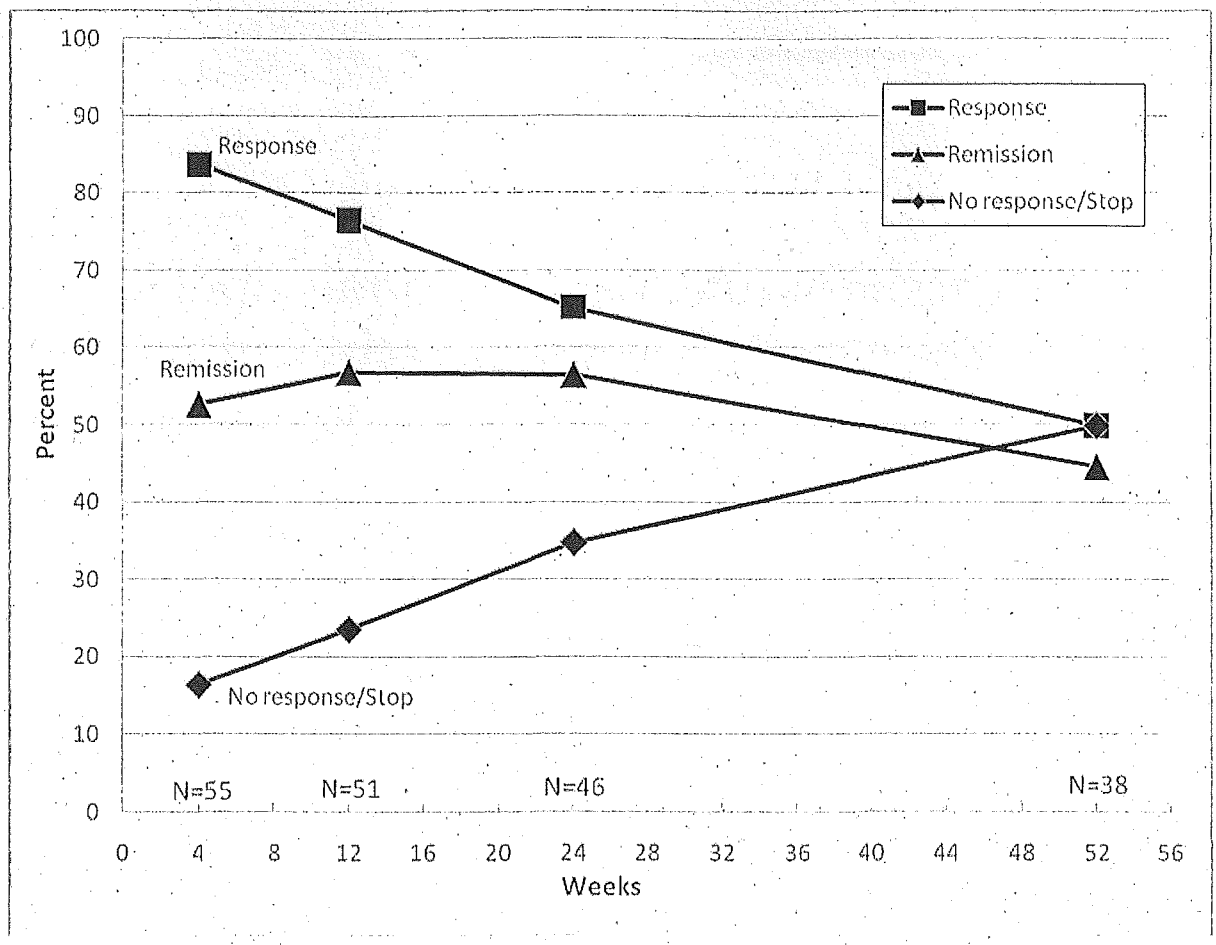
Table 5: Appropriateness of adalimumab by EPACT II criteria

EPACT II category	Number	Appropriate	Uncertain	Inappropriate
Mild to Low Moderate Active Luminal	21	16	2	3
High Moderate to Severe Active Luminal	21	17	4	-
Steroid-Dependent	24	16	8	-
Steroid-Refractory	20	20	-	-
Fistulizing	25	-	25	-
Fibro-stenotic	4	-	-	4
Maintenance of Medically-induced Remission	4	1	2	1
Upper Gastroduodenal	1	-	1	-
Extraintestinal Manifestations	5	4	1	-
Total	125 (100%)	74 (59%)	43 (34.5%)	8 (6.5%)

Table 6: Appropriateness and clinical response

n=125	Response n (%)	No response n (%)	Total	P value
Appropriate and Uncertain	103 (88)	14 (12)	117	0.21
Inappropriate	6 (75)	2 (25)	8	

Figure 1 : Response and remission rate over time in per-protocol analysis.



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Clinical Experience with Adalimumab in a Multicenter Swiss Cohort of Patients with Crohn's Disease

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Key Words
Crohn's disease · Adalimumab · Response, adalimumab · Remission, Crohn's disease

Abstract
Background: Controlled clinical trials have demonstrated the efficacy and safety of adalimumab in patients with moderate-to-severe Crohn's disease (CD), but there is, however, only limited long-term experience with adalimumab in daily practice. ***Aim:*** To assess the long-term effectiveness and safety of adalimumab in a multicenter cohort of practice-based patients with moderate-to-severe CD. ***Methods:*** We retrospectively reviewed the charts of CD patients who received adalimumab over a 3-year period. Disease severity was scored using the Harvey-Bradshaw index (HBI). Remission was defined as an HBI of ≤4 and response as a reduction in the HBI of >3 points at evaluation compared to the baseline. Univariate logistic regression analysis was used to identify the predictive variables associated with response. ***Results:*** The charts of 55 patients were reviewed; remission and response rates observed at weeks 4–6 were 52.7 and 83.6%, respectively. Remission was maintained at weeks 12, 24 and 52 in 89.6, 72.4 and 44.7% of patients, respectively. Remission and response rates were not influenced by smoking status, disease location or duration, the first month total dose, or previous infliximab therapy. The remission rate at weeks 4–6 was significantly higher in patients intolerant of infliximab as compared to those who lost response to this drug. Adalimumab was well tolerated overall. ***Conclusion:*** Adalimumab can be considered a suitable option in patients with moderate-to-severe CD, demonstrating sustained long-term effectiveness.

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C.N. and M.S. contributed equally to this work.

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Introduction

Tumor necrosis factor α (TNF-α) has emerged as a central cytokine in the pathogenesis of Crohn's disease (CD), as is confirmed by the central role that TNF-α antagonists now play in the treatment of patients with moderate-to-severe or refractory CD. Infliximab (IFX), the first chimeric monoclonal TNF-α antibody, is an effective treatment for induction and maintenance of remission in patients with moderate-to-severe CD, including those with draining fistulas [1–4]. However, a proportion of patients develop antibodies to IFX, in particular with episodic therapy or in the absence of concomitant immunosuppressant medication. The presence of antibodies to IFX leads to infusion reactions, loss of response and delayed hypersensitivity reactions [5–7].

Adalimumab is a subcutaneously administered recombinant, fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNF. Four pivotal, randomized, double-blind trials (CLASSIC-I, CLASSIC-II, CHARM and GAIN) in >1,400 patients demonstrated the clinical efficacy and safety of adalimumab in patients with moderate-to-severe CD [8–11]. Adalimumab was significantly more effective than placebo for induction of remission in patients naive to anti-TNF therapy (CLASSIC-I trial, 36 vs. 12% at week 4 with 160/80 mg regimen, $p = 0.004$) or in those who had either lost responsiveness or developed intolerance to IFX (GAIN trial, 21 vs. 7.2% at week 4, $p < 0.001$). The CHARM trial showed that, among patients who responded to open-label adalimumab induction, maintenance therapy with adalimumab 40 mg weekly or every other week for up to 1 year was associated with significantly greater remission rates than placebo at weeks 26 (47, 40 vs. 17%, $p < 0.001$) and 56 (41, 36 and 12%, $p < 0.001$). In another maintenance trial (CLASSIC-II), patients who were in remission after a short course of adalimumab and who were randomized to receive up to 1 year of treatment with adalimumab 40 mg weekly or every other week, were significantly more likely to remain in remission than those who received placebo (83, 79 vs. 44%, $p < 0.05$). Loss of efficacy can also be observed with adalimumab and an increased dose can be used to restore clinical response or remission. The role of antibodies to adalimumab in the loss of response is poorly characterized to date.

Adalimumab is generally well tolerated. In clinical trials, the rate of serious adverse events was low in patients treated with adalimumab and was similar to those treated with placebo [8–11].

Patients with CD seen in daily practice may differ from the selected patients included in randomized trials [12–15]. In a multicenter open-label single-arm study (CARE), adalimumab therapy showed substantial efficacy at week 4 (43% remission rate), which was sustained through week 20 (52% remission rate), including patients who had never responded to IFX [16]. Neither concomitant steroids nor immunosuppressants notably affected the results [17]. In this study, we analyzed our experience with adalimumab in current clinical practice over the past 3 years.

Patients and Methods

We performed a retrospective chart review of patients with CD who had been treated with adalimumab at the University Hospitals of Lausanne, Geneva, Zurich and Olten between April 2005 and April 2008, and 55 patients who had received adalimumab were identified. The diagnosis of CD was confirmed in all cases by a review of patients' medical records including clinical notes, endoscopic, radiographic or histological documents.

The information collected included patient demographics, disease location, disease phenotype, disease duration, prior surgical procedures, smoking status, previous anti-TNF and immunosuppressant use, concomitant medication, disease activity at baseline and during treatment (table 1). Disease severity for luminal CD was scored using the Harvey-Bradshaw index (HBI) [18]. For patients with previous surgical resections, other causes of diarrhea, such as bile salt malabsorption, small bowel bacterial overgrowth, or deficient water absorption secondary to proctocolectomy, were eliminated before considering them for adalimumab therapy.

The first clinical evaluation was performed at weeks 4–6. Subsequent assessments of the efficacy of treatment were performed at weeks 12, 24 and 52. The clinical evolution of luminal CD was classified into 3 categories: remission, response, and non-response. Remission was defined as an HBI of ≤4 and response as a reduction in the HBI of ≥3 points at the evaluation week compared to the baseline index [19]. The non-response category included all the remaining patients.

Data on clinical safety were collected at every medical visit and the patients were also instructed to contact the physician's office if any illness or adverse reaction occurred. Patients were considered intolerant to IFX if they were unable to continue the treatment due to reactions judged by the clinician to be linked to the perfusion. Loss of responsiveness to IFX was accepted if patients did not achieve remission with an increased IFX regimen after loss of efficacy at a standard dose.

We used univariate logistic regression analysis to see if the predictive variables tested (table 2, 3) were implicated in the response rate. The variables which had a p value of <0.3 were tested, then together in a multivariate analysis in order to control for the confounding effect of each. A p value of <0.05 was considered to be statistically significant. Data are expressed according to a per-protocol analysis. All quantitative variables are expressed as the mean ± standard error.

Table 1. Demographic and baseline clinical characteristics (55 patients)

Patient characteristics	n
Gender	
Male	21 (38.2%)
Female	34 (61.8%)
Mean age, years	37.5
Disease duration, years	
Mean ± SD	12.67 ± 11.4
Range	1–41
Smokers	
Yes	29 (52.7%)
No	26 (47.3%)
Disease location (Vienna classification)	
L1: Ileal	9 (16.3%)
L2: Colonic	11 (20%)
L3: Ileocolonic	35 (63.6%)
L4: Upper (esophageal)	1 (1.8%)
Disease behavior	
(Vienna classification; patients may appear more than once)	
B1: non-stricturing non-penetrating	35 (63.6%)
B2: stricturing	7 (12.7%)
B3: penetrating	23 (41.8%)
Surgery for Crohn's disease	
Ileal resection	5 (9%)
Ileocolonic resection	12 (21.8%)
Colonic resection	7 (12.7%)
Proctocolectomy	4 (7.3%)
None	23 (41.8%)
Previous IFX therapy (n = 43)	
Side effects	23/43 (53.4%)
Loss of response	19/43 (44.2%)
No/insufficient response	1/43 (2.3%)
Never given	12/55 (21.9%)
Type of IFX therapy	
Regular	18/43 (41.9%)
Episodic	25/43 (58.1%)
Concomitant treatment	
Budesonide	4 (7.3%)
Prednisone	25 (45.4%)
Azathioprine	5 (9%)
Methotrexate	3 (5.4%)
Indication of adalimumab	
Intolerance to IFX	19 (34.5%)
Loss of response to IFX	19 (34.5%)
Corticodependence	10 (18.1%)
Other reason[a]	7 (12.7%)
Adalimumab induction regimen	
160/80 mg	31 (56.4%)
80/40 mg	24 (43.6%)

The values are the number of patients with percentages in parentheses. IFX = Infliximab.

[a] Refractory to certolizumab (n = 3), to azathioprine (n = 1), extraintestinal manifestations (n = 2), no response to IFX (n = 1).

Results

This cohort comprised 55 patients (21 men and 34 women, mean age 37.5 ± 11.4 years) treated with adalimumab between April 2005 and April 2008. The demographic data and baseline clinical characteristics are summarized in table 1. The mean duration of CD was 12.7 (range 1–41) years. Description of disease location of luminal CD followed the usual distribution. One patient had ileal, colonic and esophageal disease. The mean HBI before treatment was 10.9 ± 5 points. Twenty-nine patients were smokers. Adalimumab was administered to patients intolerant to IFX, to those who had lost response to IFX, or to those who were corticodependent. Seven patients were treated thus for other reasons, 2 of whom had severe spondylarthropathy. The indication for adalimumab therapy in the 4 patients who had an HBI of <4 points at inclusion was intolerance to IFX (1 patient), lupus-like syndrome with IFX (1 patient) and corticodependence (2 patients). These patients were considered to be in remission if their HBI remained <4, or were deemed non-responders if their HBI value rose during the follow-up period. Of those who had already received IFX, 25 patients had episodic infusions and 18 patients had regular treatment. All patients received subcutaneous injections of adalimumab at weeks 0 and 2 at a dose of 160/80 mg (31 patients) or 80/40 mg (24 patients) and then 40 mg every other week. The results of detailed subgroup analysis are summarized in tables 2 and 3.

Adalimumab Induces and Maintains Clinical Remission and Response in CD Patients

At weeks 4–6, in per-protocol analysis, remission had been induced in 29 patients (52.7%) and response was noted in 46 patients (83.6%). An adalimumab-induced remission was maintained in 26 patients (89.6%) at week 12, and in 21 patients (72.4%) at week 24. The evolution over time of remission and response rates in per-protocol analysis is shown in figure 1. However in a intention-to-treat analysis remission was noticed in 47.3% patients at week 24 and in 31% patients at week 52. Response rates at the same time points were 54.5 and 34.5%, respectively. Thirteen patients (23.6%) required an increase in the adalimumab dose: 9 patients to 40 mg every week, 2 patients to every 10 days, 1 patient to 80 mg every week, and another to 80 mg every 2 weeks, because of incomplete response or loss of response. Of these 13 patients, 6 (46.1%) achieved remission and another 2 patients responded. In 1 patient, the dose was reduced to 40 mg ev-

Table 2. Response by subgroups at 4–6 weeks

Variable	Category	Response n (%)	Nonresponse n (%)	Univariate regression		Multivariate regression	
				OR (95% CI)	p	OR (95% CI)	p
Age, years		38.3	33.4	1.04 (0.97–1.12)	0.249	1.04 (0.97–1.12)	0.268
Gender	Female	29 (85.3%)	5 (14.7%)	1			
	Male	17 (80.9%)	4 (20.1%)	0.73 (0.17–3.10)	0.673		
Smoking status	Non-smoker	23 (88.5%)	3 (11.4%)	1			
	Smoker	23 (79.3%)	6 (20.7%)	0.50 (0.11–2.24)	0.366		
Disease duration, years	<7	15 (83%)	3 (17%)	1			
	<7–15	16 (84%)	3 (17%)	1.00 (0.17–5.72)	1		
	>15	15 (83%)	3 (17%)	0.94 (0.16–5.39)	0.942		
Disease location	Ileitis (L1)	8 (80%)	2 (20%)	1			
	Colitis (L2)	10 (91%)	1 (9%)	2.22 (0.17–8.86)	0.542		
	Ileocolitis (L3)	28 (82.3%)	6 (17.3%)	1.04 (0.19–6.07)	0.968		
Previous resection (any segment)	No	18 (78.3%)	5 (21.7%)	1			
	Yes	28 (87.5%)	4 (12.5%)	1.94 (0.46–8.22)	0.366		
Previous IFX therapy	Never	9 (75%)	3 (25%)	1			
	Episodic	21 (84%)	4 (16%)	1.57 (0.29–8.41)	0.595		
	Regular	16 (88.9%)	2 (10.1%)	2.40 (0.34–6.97)	0.380		
Indication for adalimumab	Loss of response to IFX	17 (89.4%)	2 (10.6%)	1		1	
	Intolerance to IFX	17 (89.4%)	2 (10.6%)	0.94 (0.12–7.48)	0.957	1	
	Other[a]	12 (70.5%)	5 (20.5%)	0.27 (0.04–1.61)	0.149	0.33 (0.07–1.68)	0.182
First-month total dose, mg	120 (80+40)	19 (79.2%)	5 (21%)	1			
	240 (160+80)	27 (87.1%)	4 (13%)	1.00 (0.99–1.02)	0.434		
First-month total dose/weight, mg/kg	<2.5	17 (80.9%)	4 (19.1%)	1		1	
	2.5–3.5	13 (76.4%)	4 (23.6%)	0.72 (0.15–3.43)	0.682	1	
	>3.5	16 (94.1%)	1 (5.9%)	3.56 (0.36–5.20)	0.278	3.87 (0.38–39.03)	0.251

IFX = Infliximab. [a] Corticodependence (n = 10) and other (n = 7) merged because of small numbers.

Table 3. Remission by subgroups at 4–6 weeks

Variable	Category	Remission n	Non-remission n	p value
Smoker status	Smoker	12 (41.4%)	17 (58.6%)	0.075
	Non-smoker	17 (65.4%)	9 (34.6%)	
Previous IFX therapy	Regular	10 (55.5%)	8 (44.5%)	0.719
	Episodic	12 (48%)	13 (52%)	
	Never	7 (58.3%)	5 (41.7%)	
Indication for adalimumab	Loss of response to IFX	8 (42.1%)	11 (57.9%)	0.012
	Intolerance to IFX	15 (78.9%)	4 (21.1%)	

IFX = Infliximab.

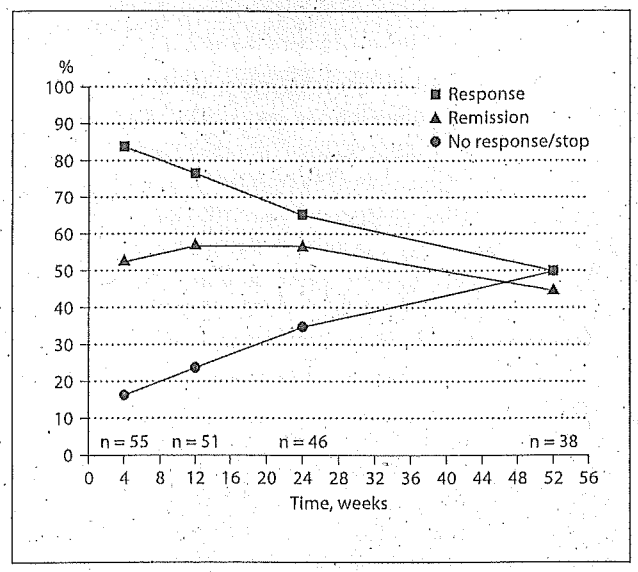

Fig. 1. Response and remission rate over time in per-protocol analysis.

ery 4 weeks because of fatigue. The response rate was not significantly higher in the group of patients with previous abdominal surgery (table 2).

Effect of Smoking on Adalimumab Efficacy at Weeks 4–6

The remission and response rates were higher among the non-smokers, but without any statistically significant difference.

Effect of Disease Duration or Location on Adalimumab Efficacy at Weeks 4–6

Because of the long mean disease duration of our cohort, we chose to separate the patients into 3 almost equal groups: CD known for <7 years, for 7–15 years and for >15 years. The remission and response rates were almost similar within these 3 groups. The location of the intestinal segment(s) involved was not found to play a significant role in patients' clinical response to the adalimumab therapy.

Effect of the First-Month Total Dose on Adalimumab Efficacy at Weeks 4–6

Remission and response rates were not different between the groups who received adalimumab 240 or 120 mg during the first month of treatment. The total first-month adalimumab dose was divided by the patient's weight and patients were then grouped into 3 dose-adjusted groups according to the total dose per kilogram over the first month: <2.5, 2.5–3.5 and >3.5 mg/kg. We did not find any statistically significant difference between these 3 groups with regard to the response rate.

Table 4. Adverse events observed over the 3-year period

Type of adverse event	n
None	30
Perianal abscesses	2
Asthenia	5
Pain at injection site	6
Pruritis at injection site	2
Rash	1
Headache	3
Nausea	2
Diarrhea	1
Dizziness	2
Phlebitis	1
Gynecological side effect	1
Labial herpes	1
Lupus-like syndrome	1

Impact of Prior IFX Treatment on Adalimumab Efficacy at Weeks 4–6

The response rate was not influenced by the absence of previous IFX treatment or by its regular as opposed to episodic use. In contrast, the remission rate at weeks 4–6 was significantly higher among patients intolerant to IFX, compared to those who had lost response to this medication (78.9 vs. 42.1%, $p = 0.02$).

Safety of Adalimumab Treatment

Overall, subcutaneous injections of adalimumab were well tolerated (table 4). Thirty of the 55 patients reported no adverse event. The most common side effect was pain at the injection site (10.9%), followed by asthenia (9%) and infections (7.2%). One patient stopped the treatment because of intolerable fatigue and another because of gynecological side effects. One case of lupus-like syndrome was noted. In our cohort, no fatal complication, malignancy, neurologic or cardiovascular complication was noted during the whole observation period.

Discussion

The purpose of our retrospective cohort study was to evaluate the effectiveness of adalimumab in our Crohn's patients over a period of 3 years in daily clinical practice. Adalimumab treatment was effective in the induction and maintenance of remission in patients with moderate-to-severe CD. The results in our cohort appear better than the remission and response rates noticed in the CLASSIC I trial (36 and 59%, respectively, at week 4) [8] and the GAIN trial (21 and 52%, respectively, at week 4) [11]. The fact that in our cohort the first evaluation occurred later than in those trials, i.e. that our patients had a supplementary third injection, may have contributed to the improved results. In the per-protocol analysis, 44.7% patients were in remission and 50% still in response at week 52. These long-term results for remission are similar to those at week 56 in the CLASSIC II trial [9]. The limited size of our cohort, the lack of placebo controls and the absence of restricted inclusion criteria may have contributed to the differences noticed in our patients. In addition, we used the HBI rather than the Crohn's Disease Activity Index to evaluate patients, which could also in part explain the difference from the randomized trial. The remission and response rates in our cohort are also comparable to those of the CARE study [16, 17], although in this multicenter cohort all patients received a 160/80-mg induction regimen.

The proportion of our patients who needed a dose increase and the benefit obtained from this strategy were similar to those reported in the CHARM trial [20]. In our cohort, the mean time to dose increase was relatively long: 7 (range 1–24) months. Our results thus confirm that in clinical practice this strategy should be explored before considering another treatment in patients who lose response or fail to achieve complete remission with a standard adalimumab regimen. In a small study, a higher percentage of patients were previously reported to require an adalimumab dose increase (nearly 60% at 6 months) after using a suboptimal induction regimen of 80/40 mg [12]. In another 2 cohorts, only 13.2 and 29% of patients required a dose increase [14, 15].

In a per-protocol analysis, we observed that over 52 weeks adalimumab treatment was stopped in half of the patients. This dropout rate was progressive during the observation period. The reasons for discontinuation were either no response, loss of response despite dose increase (14/19 patients) or adverse reaction (5/19 patients).

Smoking status had no effect on either the rate of clinical remission or the response rate in patients treated with adalimumab. This observation is consistent with the results of the sub-analysis in the CLASSIC I trial, where the efficacy of adalimumab treatment at week 4 was not affected by smoking status [21]. Hinojosa et al. [13] also reported no difference in the 4-week response rate of active smokers with luminal CD as compared to former smokers.

The efficacy of adalimumab therapy in our cohort was not influenced by disease duration. In the CHARM trial, Colombel et al. [10] showed a significantly better remission rate at weeks 26 and 56 with adalimumab in patients with a CD duration of <2 or >5 years. We were unable to separate our patients into the same 3 groups (disease duration <2, 2–5 and >5 years) because our patients had a longstanding diagnosis of CD. Our results suggest that a disease duration of >7 years has no greater impact on response.

We failed to show a correlation between the total first month dose adapted to body weight or the response or remission rate to adalimumab therapy. These results suggest that the dose during the first month as currently administered should suffice in the majority of patients. However, the small size of the cohort and the retrospective nature of the analysis do not exclude the possibility that a dose-weight relationship might exist in a larger group of patients. Indeed, as the affinities and molecular weight of IFX and adalimumab are comparable, one could have expected that such a relationship might exist. Other characteristics of adalimumab may explain this difference as compared to IFX, such as the human nature of the antibody or differences in the binding sites of the antibodies.

The majority of our patients had been treated with IFX before receiving adalimumab. The remission and response rates at weeks 4–6 were not statistically different in patients naive to IFX compared to those who had already been treated with IFX. Similarly, no difference was found in the response to adalimumab between patients whose previous IFX therapy was interrupted because of loss of response or because of intolerance. This last observation was also reported by Hinojosa et al. [13]. In contrast, however, the remission rate at weeks 4–6 was significantly higher in the subgroup of patients intolerant to IFX. This suggests that patients who did not lose their response to IFX may benefit more from another anti-TNF agent. Patients who have lost response may represent a group of patients who may better benefit from a change in the treatment target, different from TNF.

Overall, adalimumab was well tolerated in our cohort. The rate of side effects was similar to that already reported in randomized trials, in which patients underwent

more stringent selection and monitoring [8–10]. Pain at the injection site, asthenia and infections were the most common adverse events. Despite these reassuring results, the safety issues surrounding anti-TNF therapies continue to be of great significance and clinicians need to remain vigilant. Colombel et al. [22] recently assessed global adalimumab safety in a collective of 2,228 patients exposed to adalimumab in pivotal randomized trials, open-label extensions and phase IIIb studies, CHOICE and CARE. The rates of opportunistic infections and malignant neoplasms were found to be <2% of patients. Such rates justify careful monitoring of all patients, even when stable in remission.

Our study has several limitations. Firstly, the data presented are based on a retrospective review and not on a uniform analysis with precise time points. Secondly, even if this is the largest cohort of open-label clinical experience in patients with CD to date, the number of patients analyzed at 24 and 52 weeks is still low. Thirdly, our patients had a long-standing CD history prior to adalimumab therapy. It remains to be studied if adalimumab used in a top-down scheme might improve the results reported here. Although nonsignificant, the odds ratio values cannot be taken as proof that none of the variables mentioned in table 2 may have an effect. The large confidence intervals indicate that the calculated odds ratio remains imprecise.

In conclusion, our data suggest that adalimumab is as effective in inducing and maintaining remission in patients with moderate-to-severe or refractory CD seen in daily practice as reported during randomized trials. Our results further suggest that patients with intolerance to IFX represent a group particularly well suited to further adalimumab therapy. The safety of adalimumab is also confirmed in daily practice. However, results from larger cohorts should be awaited before reaching firm conclusions.

Disclosures

C. Nichita, A. El-Wafa Ali, A. Straumann and P. Ballabeni have no conflict of interest. S. Vavricka has received a research grant from Abbott and has served as invited speaker for Abbott. P. de Saussure has received fees as an Abbott scientific advisory board member. G. Rogler is a member of scientific advisory boards for Abbott, Essex, FALK, Neovacs, Novartis, UCB and has received sponsoring of scientific projects from Abbott, Ardeypharm, Essex Chemie, UCB, Novartis. He has also served as a paid speaker for Abbott, Essex, FALK, UCB, Vifor. P. Michetti has received fees as a consultant for Abbott and Essex Chemie in Switzerland and is a member of the international scientific advisory boards of Abbott, Ferring, Neovacs, Novartis, Schering Plough, and UCB. He also received unrestricted and research grants from Abbott, Berlex, Essex Chemie, UCB, and Novartis. He has also served as a paid speaker for Abbott, Essex Chemie, Falk, Ferring, UCB, and Vifor Chemie.

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