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Efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF

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Abstract:

Adalimumab (ADA) and certolizumab pegol (CZP) have demonstrated efficacy in Crohn's disease (CD) patients previously treated with infliximab (IFX). **Aim:** To assess the efficacy and tolerability of a third anti-TNF in CD after failure of and/or intolerance to two different anti-TNF. **Methods**: CD patients who received ADA or CZP after loss of response and/or intolerance to two anti-TNF were included in this retrospective study. Data were collected using a standardized questionnaire. Clinical response, duration, safety and reasons for discontinuation were assessed. **Results**: Sixty-seven patients treated with CZP (n=40) or ADA (n=27) were included. A clinical response was observed in 41 (61%) at week 6 and 34 patients (51%) at week 20. The probability of remaining under treatment at 3 months, 6 months and 9 months was 68%, 60% and 45%, respectively. At the end of follow-up, the third anti-TNF had been stopped in 36 patients for intolerance (n=13), or failure (n=23). Two deaths were observed. **Conclusion**: Treatment, with a third anti-TNF (CZP or ADA) agent, of CD patients who have experienced loss of response and/or intolerance to two anti-TNF antibodies, has favorable short- and long-term efficacy and is an option to be considered in patients with no other therapeutic options.

Tumor necrosis factor (TNF) plays a key role in the pathogenesis of Crohn's disease (CD) (1). Infliximab (IFX), a chimeric monoclonal antibody to TNF, is effective in inducing and maintaining response and remission in patients with moderate to severe CD (2-8). However, some patients do not respond to IFX, while others experience a loss of efficacy over time or become intolerant to it (9-14). Two other anti-TNF agents, ADA and certolizumab pegol (CZP), are effective in treatment of CD which is refractory to standard medical therapy with corticosteroids or immunomodulatory agents (15-20). ADA is a recombinant human IgG1 human monoclonal antibody that binds with high affinity and specificity to human soluble TNF. CZP is a pegylated humanized antibody fragment [Fab'] to TNF. In clinical trials, both ADA and CZP were effective at inducing and maintaining remission in a broad population of patients with CD who were previously exposed to IFX ~~and then discontinue treatment despite a sustained response, loss of response, intolerance or both~~ (17-19).

Several open-label studies have shown that ADA is effective in inducing remission in patients with active CD who had previously responded to IFX and then lost the response or became intolerant (21-25). ADA efficacy after IFX failure has also been evaluated in a placebo-controlled study (26). At 4 weeks, ADA induced remission and response more frequently than did the placebo, respectively 21% vs. 7% and 52% vs. 34%. The efficacy of CZP after IFX failure was evaluated in an open label trial. At 6 weeks, CZP induced remission and response in, respectively, 39% and 68% of patients (27). Nevertheless, some patients who respond to a second anti-TNF may lose the response or become intolerant. As no other biologic agents are currently available in Europe, use of a third anti-TNF antagonist seems a rational option in these patients.

The aim of this retrospective study was to collect data regarding efficacy and tolerability of a third anti-TNF agent in CD following discontinuation of two other anti-TNF monoclonal antibodies for failure and/or intolerance.

Methods

Selection of patients

Eligible patients were males and females at least 18 years of age. Patients who received ADA or CZP as a third anti-TNF monoclonal antibody were eligible. Only patients who received a third anti-TNF after primary failure or loss of response and/or intolerance to two previous anti-TNF antibodies were included. Patients were recruited from GETAID centers (France, Belgium, Switzerland) and two other European centers (Leuven, Roma). A questionnaire was sent to all centers to retrospectively collect data on patients fulfilling inclusion criteria.

Primary failure of a previous anti-TNF was defined as no response to induction therapy, as judged by the clinician (28).

Loss of response to a previous anti-TNF was defined as the presence of symptoms or evidence of disease activity, as evaluated by the physician, despite optimization of dosage. Optimization for IFX was defined as increasing the dosage to 10 mg/kg and shortening the interval between infusions to less than 8 weeks. Optimization for ADA was defined as shortening the interval between 40 mg injections from two to one week. Optimization for CZP was defined as shortening the interval between 400 mg injections from 4 to 2 weeks.

Inability to tolerate previous anti-TNF was defined as the occurrence of an adverse event considered to be related to treatment and which led to discontinuation of anti-TNF.

Acute hypersensitivity reactions were defined as adverse events that occurred during or within 1 h after administration of the anti-TNF agent. Reactions occurring later were considered as delayed hypersensitivity reactions. Patients were ineligible if discontinuation of the first or second anti-TNF was not due to failure or intolerance.

Data collection

The following characteristics were recorded: age, sex, disease duration, disease location and behavior (Montreal classification), surgery, use of immunosuppressants (azathioprine, 6 mercaptopurine, methotrexate) before the first anti-TNF treatment, occurrence of previous complications (fistulas, strictures) and smoking history. For the first two anti-TNF treatments, the following data were recorded: date of first administration, date of dose intensification (i.e. increasing dose or shortening interval), concomitant administration of steroids, use of concomitant immunosuppressants (azathioprine/mercaptopurine or methotrexate), adverse events, date of last administration and reasons for discontinuation.

Primary analysis

Primary analysis took into account the proportion of patients with a clinical response at weeks 6 and 20 upon the third anti-TNF. Secondary analysis concerned the probability of remaining under treatment (no discontinuation) throughout the entire follow-up so as to identify predictors of short-term and sustained clinical responses and the rate of adverse events throughout the period after initiation of treatment with the third anti-TNF.

Clinical response was assessed by clinicians at weeks 6 and 20. Due to the retrospective character of the study, an effort was made to obtain all components of the Harvey-Bradshaw index (HBI) (29). Clinical response was defined as a decrease in the HBI of more than three points. However, in a few patients, HBI could not be calculated (one patient with an ileostoma) or because items were not available. In those patients, response was

defined as improvement in symptoms of the disease, as judged by the treating physician. No response at week 6 was defined as the absence of clinical benefit after at least three injections of ADA or CZP (at week 0, 2 and 4). Remission was defined as HBI below or equal to 4 (or complete absence of symptoms), and no steroids.

When used as third line anti-TNF, induction therapy with adalimumab consisted in injections of 160mg and 80 mg or 80mg and 40 mg at week 0 and 2. Induction therapy with certolizumab pegol consisted in injections of 400 mg at week 0, 2 and 4.

All adverse events were recorded. Severe adverse events (SAE) were defined as any adverse event that resulted in hospitalization or prolongation of hospitalization, was fatal or life-threatening, or led to significant disability.

Statistical analysis

All patients were followed for at least for 20 weeks. The probability of remaining under treatment (no discontinuation) was analyzed using the Kaplan-Meier method. The predictive value of the following factors for clinical response at weeks 6 and 20 (chi-2 test), and of the probability of discontinuation (log rank test) was analyzed: age, disease duration, type of third anti-TNF, combined immunosuppressants, combined steroids, Montreal classification. Characteristics of patients who achieved a clinical response at weeks 6 and 20 were compared to those of patients who did not use the non-parametric Mann-Whitney test.

Results

Patient characteristics

Sixty-seven patients were included. All patients had active luminal disease. Characteristics of patients at the start of the third anti-TNF are given in table 1. ~~Twelve (18%) also had perianal disease and 12 (18%) had extraintestinal manifestations. Twenty-nine patients were under steroids at the start of the third anti-TNF and 26 (39%) were under immunosuppressants (azathioprine/6-mercaptopurine, n=13; methotrexate, n=13).~~

Treatment schedule of the 67 patients is given in figure 1. Forty patients received CZP as the third anti-TNF; 27 received ADA. The first anti-TNF was IFX in 63 patients, CZP in 3 patients and ADA in 1 patient. Median duration between the first and last administration of the first anti-TNF was 18 months (0.1-88). Among the 63 patients who received IFX as a first line, 38 started with on-demand treatment and 47 were under immunosuppressants (32 under azathioprine and 15 under methotrexate). Reasons for discontinuation of the first anti-TNF were: loss of response in 38 patients (57%, associated with intolerance in 6 patients), primary failure in 4 patients and intolerance in 31 patients (46%, associated with loss of response in 6 patients), including 13 immediate hypersensitivity reactions, 13 delayed hypersensitivity reactions, 4 skin inflammatory disorders and 1 lupus.

The second anti-TNF was IFX in 4 patients, CZP in 24 patients and ADA in 39 patients. Median duration of the second anti-TNF was 4.2 months (0.1-58). Thirty-four patients were under immunosuppressants at the start of the second anti-TNF treatment (17 under azathioprine and 17 under methotrexate). Reasons for discontinuation of the second anti-TNF were: loss of response in 35 patients, primary failure in 16 patients and intolerance in 16 patients (5 immediate hypersensitivity reactions, 6 delayed hypersensitivity reactions, 5 inflammatory skin disorders).

Efficacy

Clinical response at week 6

Clinical response was observed in 41 patients (61%) at week 6 ~~(figure 2)~~; it was defined as a decrease in the HBI of more than three points in 34 patients, and as judged by the clinician in 7 patients. No predictive factors of clinical response at week 6 were identified (Table 2). Interestingly, several patients who experienced primary failure with the first and/or second anti-TNF responded to the third anti-TNF (figure 2).

Clinical response at week 20

Clinical response was observed in 34 patients (51%) at week 20, including 30 patients who responded at week 6, and 4 who did not; it was defined as a decrease in the HBI of more than three points in 29 of these 34 patients, and as judged by the clinician in 5 patients. Fifteen patients (22%) were in remission and off steroids. Clinical benefit at week 6 was the only clinical predictive factor of clinical benefit at week 20 ($p<0.001$) (Table 2).

Discontinuation of the third anti-TNF

Median follow-up until discontinuation of the third anti-TNF was 26 weeks (0-159). At the end of follow-up, the third anti-TNF was stopped in 36 patients. Mean duration of treatment for the 31 patients remaining on treatment was 44 weeks (20-159). The probability of remaining under treatment with the third anti-TNF is shown in Figure 3. Probabilities at 3, 6 and 9 months were 68%, 58% and 45%, respectively. Reasons for discontinuation were intolerance and/or side effects (n=13) (table 3), primary failure (n=8) and loss of efficacy (n=15) ~~(figure 5)~~. There was no difference in probability of remaining under treatment according to age, disease duration, type of third anti-TNF (i.e. CZP vs. ADA) (figure 4), combined immunosuppressant and/or steroids, or Montreal classification. In patients who presented a clinical benefit at week 6, the probability of remaining under treatment at 3 months, 6 months and 9 months was 87%, 80% and 64%, respectively (Figure 5).

Safety

A total of 16 (24%) adverse events were observed (Table 3). SAE occurred in 5 patients (7%), and included two deaths. Sudden death occurred in a 37-year-old male patient with no previous history of cardiac disease and no risk factors for coronary heart disease. Death occurred several days after the third injection of ADA (week 4), although an excellent response had been reported. The interval between the second (CZP) and third anti-TNF (ADA) was 3 days. The other patient died while being treated with the third anti-TNF agent (CZP) for 7 months. This 45-year-old female patient was hospitalized for acute obstruction. Endoscopic dilatation of an ileal stricture was performed. Two days later, she developed fatal septic shock (cultures positive for *Escherichia Coli* and *Enterococcus faecalis*) related to central venous line infection.

Severe pulmonary infection also occurred in a patient who received one injection of CZP (as the third anti-TNF) one week after the final injection of ADA.

Heart failure developed in a 37-year-old patient after two injections of CZP used as the third anti-TNF, with a favorable outcome after discontinuation of treatment. This patient had been previously treated with IFX, episodically and then regularly, for more than one year, with no signs of intolerance. ADA had been started after an immediate hypersensitivity reaction to IFX, but was stopped 3 months later due to loss of response.

Five patients had inflammatory skin disorders under the third anti-TNF (ADA, n=3, CZP, n=2). In three patients, psoriasis-like lesions had occurred under the first anti-TNF treatment, relapsing with the second and third anti-TNF. One patient developed de novo psoriasis with the third anti-TNF (CZP). Another had worsening of psoriasis with the third anti-TNF (CZP), while it was quiescent with the first two anti-TNFs. These inflammatory skin disorders led to discontinuation of the third anti-TNF in 4 cases.

Discussion

Loss of efficacy or the occurrence of intolerance is a significant problem in CD patients treated with anti-TNF antibodies. There is now solid evidence that, after loss of response or intolerance to an initial anti-TNF, a second anti-TNF can be effective, at least over the short term (26, 27). In this retrospective study, we analyzed, for the first time, switching of three TNF antagonists in treatment of CD. Overall, our results show that this strategy may be useful: 61% responded at 6 weeks, while the probability of retaining the third anti-TNF was 45% at 9 months.

These results are comparable to those observed in open series and clinical trials assessing the efficacy of ADA and CZP after IFX failure as a second line (26, 27). Information on switching from a second to a third anti-TNF in CD has not been previously available. In rheumatoid arthritis, preliminary experience suggested that sequential use of three TNF antagonists was successful, but that the probability of retaining the third anti-TNF was lower than that of retaining the second or first such drug (29-33).

We failed to identify a predictor of clinical benefit at week 6. Interestingly, several patients from our series who experienced primary failure with a second anti-TNF (ADA or CZP) responded to a third anti-TNF (ADA or CZP). This suggests that these antibodies, which have different structural, pharmacokinetic and pharmacological properties, may also differ in their modes of action (34). Of note, the only patient who discontinued IFX as a first line for primary failure also experienced primary failures with the second and third anti-TNF agents. Subgroup analyses demonstrated similar benefits with CZP and ADA used as a third-line anti-TNF, suggesting that the order of administration of the latter two drugs does not impact upon the efficacy of the third agent. IFX was used as the first anti-TNF in most patients. Information regarding switching from ADA or CZP used as the first drug is not yet

available. The benefit of combining immunosuppressants (azathioprine/6-mercaptopurine, methotrexate) with TNF antagonists remains subject to debate. In our series, there was no benefit of combination therapy over the short or long term. The probability of retaining the drug at week 20 was influenced by the initial response: when a clinical benefit was obtained at week 6, the probability of retaining the drug was over 60% at 9 months. In contrast, in the absence of a response at 6 weeks, this probability fell below 20%. This suggests that assessment of clinical response at week 6 may permit distinguishing patients who will best benefit from the drug as maintenance therapy, and those for whom unnecessary exposure should be avoided.

Our series raises some safety concerns. We observed serious adverse events, including two deaths. Adverse events enforced discontinuation of the third anti-TNF in 14 patients. Infection represents the most frequent adverse event associated with use of anti-TNF agents in CD (35-37). In our series, two cases of severe infection were observed: one severe pulmonary infection with favorable outcome, and one central line infection with fatal septicemia. Sudden death occurred in a 37-year-old patient successively treated with CZP and ADA at an interval of less than one week. This suggests that a “wash-out” period between administrations of two different anti-TNF monoclonal antibodies may be desirable. IFX, ADA and CZP, although given via different routes, have a similar life span in sera of patients; indeed, their presence can be detected in sera of patients up to three months after the final injection. Overlapping of different biotherapies may increase the risk of adverse events through an increase in immunosuppression, or possibly by inducing rare adverse events such as heart failure.

Inflammatory skin disorders occurring under anti-TNF therapy are an emerging problem. Their mechanisms are unclear, although TNF is clearly pro-inflammatory in human skin. A recent study showed that the incidence rate of new-onset psoriasis was high in rheumatoid arthritis patients treated with anti-TNF therapy, while no cases of new-onset

psoriasis were seen in a large cohort of patients treated with traditional therapy (38). Interestingly, the risk of developing psoriasis varied with the anti-TNF agent. In our series, psoriasis-like lesions occurred under the first anti-TNF treatment in 3 patients, relapsing with the second and third lines. One patient developed de novo psoriasis with the third anti-TNF. In all cases, improvement was observed when anti-TNF was stopped. However, psoriasis relapsed in all cases with the next anti-TNF. In most cases, anti-TNF had to be stopped, but one patient used topical treatment and continued anti-TNF. Finally, in 4 cases in our series, anti-TNF could no longer be used due to psoriasis-related adverse events.

There existed several limitations to our study, mainly linked to its retrospective nature. First, the definition of failure of the first and second anti-TNF was not standardized. Since it was a real-life study, the decision to withdraw one anti-TNF and to switch to another depended only on the treating physician's decision. Second, duration of therapy with a third anti-TNF was used as a surrogate marker of drug efficacy. Even if continuation of therapy suggests a response to the treatment, discontinuation depended again on the treating physician's decision. Third, we did not analyze an entire cohort of IBD patients treated with anti-TNF, so we were unable to compare results of the three lines of anti-TNF. Thus, we could not make comparisons between the different lines, since patients were selected for intolerance to or failure of the first two antibodies. Relevant comparison could only be performed in a randomized control trial. Finally, median follow-up was only 26 weeks; thus, the long-term benefit of this strategy is unknown.

We conclude that treatment of CD patients, who had earlier experienced loss of response and/or intolerance to two monoclonal anti-TNF antibodies, with a third anti-TNF (CZP or ADA in this series) may be an effective therapeutic option. However, since two deaths were reported in our series, this strategy for patients with no other therapeutic options should only be considered after careful case-by-case discussion.

Legend to figures

Figure 1: Treatment schedule, with reasons for discontinuation of first and second anti-TNF.

~~Figure 2: Rate of clinical response and remission at weeks 6 and 20. Clinical response was defined as a decrease in the HBI of more than three points (or improvement of symptoms of disease, as evaluated by the attending physician when HBI was not available). Remission was defined by HBI below or equal to 4 (or complete absence of symptoms) and no steroids.~~

Figure 2: Response at week 6 to a third anti-TNF in patients who had experienced primary failure with the first and/or second anti-TNF (n=18). Each row represents one patient. Only patients who had primary failure with the first and/or second anti-TNF are shown. The first two first columns indicate reasons for discontinuation of the first and second anti-TNF: primary failures are indicated by a dark bar and loss of response/intolerance by a white bar. The third column indicates clinical response (white bar) or no response (dark bar) at week 6.

Figure 3: Probability of discontinuation of the third anti-TNF in all patients.

~~Figure 5: Probability of discontinuation due to intolerance and/or side effects (– – –) compared to discontinuation due to failure (….).~~

Figure 4: Probability of discontinuation of CZP or ADA.

Figure 5: Probability of discontinuation of a third anti-TNF in patients who presented a clinical benefit at week 6.

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Table 1: Characteristics of the 67 patients at the start of the third anti-TNF

All patients – n	67
Sex (M/F) – n (%)	15 (22%) / 52 (78%)
Median age (years)*	36 (16-81)
Median disease duration (years)*	10 (1-36)
Location – n (%)	
Ileum only	7 (10%)
Colon only	10 (15%)
Both	50 (75%)
Perianal disease	34 (50%)
Behavior – n (%)	
Non-stricturing, non-penetrating	39 (58%)
Stricturing	18 (27%)
Penetrating	10 (15%)
Tobacco – n (%) previous/at start of the third anti-TNF	20 (30%) / 28 (42%)
Previous surgical resection – n (%)	31 (46%)
Immunosuppressive agents – n (%) previous/at start of the third anti-TNF	
Azathioprine/6-MP	54 (81%) / 13 (19%)
Methotrexate	38 (57%) / 13 (19%)
Anti-TNF therapy	
First anti-TNF	
Type of anti-TNF – n (%)	
IFX	63 (94%)
CZP	3 (4.5%)
ADA	1 (1.5%)
Median duration of anti-TNF therapy (months)*	18 (1- 88)
Reasons for discontinuation – n (%)	
Primary failure	4 (6%)
Intolerance	25 (37%)
Loss of response	32 (48%)
Intolerance and loss of response	6 (9%)
Second anti-TNF	
Type of anti-TNF – n (%)	
IFX	4 (6%)
CZP	24 (36%)
ADA	39 (58%)
Median duration of anti-TNF therapy (months)*	4 (1-58)
Reasons for discontinuation – n (%)	
Primary failure	16 (24%)
Intolerance	35 (52%)
Loss of response	16 (24%)

*Median (range)

Table 2: Factors associated with clinical response at weeks 6 and 20 (univariate analysis)

Factors	Clinical response at week 6	Clinical response at week 20
Age		
<36 years	22/34 (65%)	17/34 (50%)
≥36 years	19/33 (58%)	17/33 (51%)
Sex		
Male	10/15 (67%)	8/15 (43%)
Female	31/52 (60%)	26/52 (50%)
Disease duration		
<10 years	18/34 (53%)	15/34 (44%)
≥10 years	23/33 (70%)	19/33 (57%)
Disease location		
Ileum only	3/7 (43%)	2/7 (29%)
Colon only	4/10 (40%)	5/10 (50%)
Both	34/50 (68%)	27/50 (54%)
Perianal disease	19/34 (56%)	18/34 (53%)
Disease behavior		
Non-stricturing, non-penetrating	24/39 (62%)	19/39 (49%)
Stricturing	11/18 (61%)	8/18 (44%)
Penetrating	6/10 (60%)	7/10 (70%)
Tobacco		
Yes	12/18 (66%)	9/18 (50%)
No	29/49 (59%)	25/49 (51%)
Reason for discontinuation of the 1st anti-TNF		
Failure (primary failure and loss of response)	28/42 (66%)	22/42 (52%)
Intolerance	13/25 (52%)	12/25 (48%)
Reason for discontinuation of the 2nd anti-TNF		
Primary failure	11/16 (69%)	9/16 (58%)
Loss of response	20/35 (57%)	19/35 (54%)
Intolerance	10/16 (63%)	6/16 (38%)
Combination with immunosuppressants at start of the 3rd anti-TNF		
Azathioprine/6-MP	6/13 (46%)	6/13 (46%)
Methotrexate	8/13 (62%)	7/13 (54%)
No	27/41 (66%)	21/41 (51%)

Combination with corticosteroids at start of the third anti-TNF		
Yes	17/29 (59%)	12/29 (41%)
No	24/38 (63%)	22/38 (58%)
Third anti-TNF		
CZP	24/40 (60%)	19/40 (47%)
ADA	17/27 (63%)	15/27 (55%)
Clinical response at week 6		
Yes	-	22/33 (67%)
No		4/34 (12%)[£]

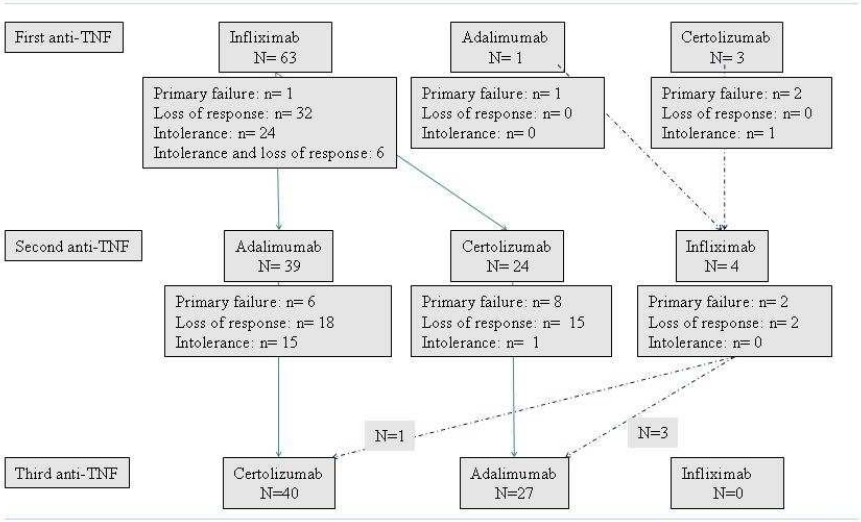
[£] Chi-2 test; p<0.001

Table 3: Adverse events occurring under the third anti-TNF

	No. of patients	SAE*	Discontinuation of the third anti-TNF
Death	2		
Sudden death		1	-
Septic shock		1	-
Cardiac failure	1	1	1
Severe pulmonary infection	1	1	1
Perianal abscess	1	1	1 (for failure)
Inflammatory skin disorder	5	0	4
Transient decreased vision	1	0	0
Immediate hypersensitivity	1	0	1
Delayed hypersensitivity	1	0	1
Herpes zoster	1	0	0
Cough	1	0	1
Diarrhea, nausea	1	0	1
Total	16	5	10

* SAE: severe adverse event

Figure 1



254x190mm (96 x 96 DPI)

Figure 2

First anti-TNF	Second anti-TNF	Third anti-TNF Response at W6
IFX	ADA	CZP
IFX	ADA	CZP
IFX	ADA	CZP
IFX	CZP	ADA
IFX	ADA	CZP
CZP	IFX	ADA
CZP	IFX	ADA
IFX	CZP	ADA
IFX	CZP	ADA
IFX	CZP	ADA
IFX	ADA	CZP
IFX	CZP	ADA
IFX	CZP	ADA
CZP	IFX	ADA
IFX	CZP	ADA
IFX	ADA	CZP
IFX	CZP	ADA
ADA	IFX	CZP

254x190mm (96 x 96 DPI)

Figure 3

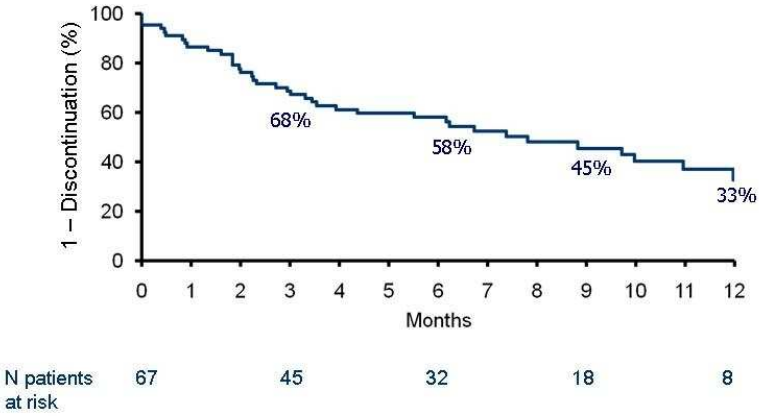


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Figure 4

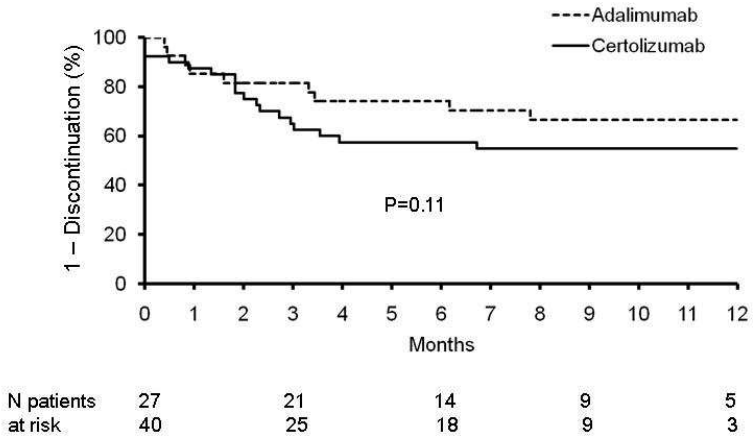

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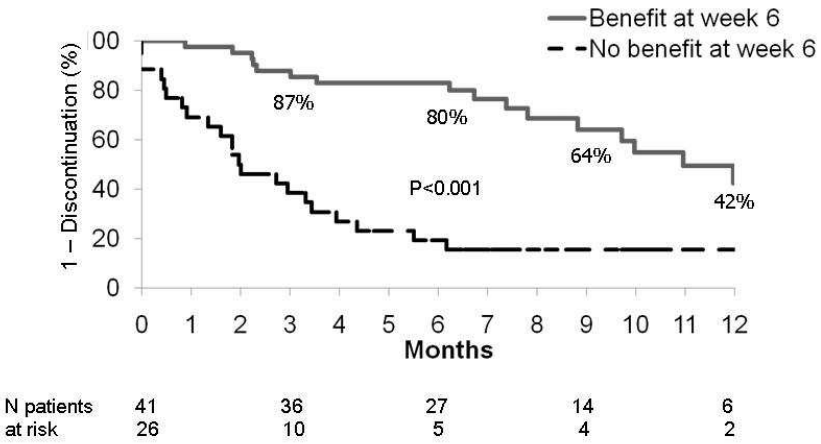
Figure 5



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