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Infliximab as rescue medication for patients with severe ulcerative/indeterminate colitis refractory to tacrolimus

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SUMMARY

Background:

The calcineurin inhibitor tacrolimus and the anti-TNF-antibody infliximab are established options in steroid refractory ulcerative colitis (UC). The aim of this study was to determine the efficacy of infliximab as rescue medication in patients failing to respond to tacrolimus.

Aim:

To evaluate the efficacy of infliximab-salvage therapy in patients with refractory ulcerative colitis failing to respond to tacrolimus

Methods:

Twenty-four patients were enrolled in this evaluation. Reasons for tacrolimus therapy were steroid-refractory disease in 19 patients and steroid dependency in 5 patients. All patients receiving infliximab had tacrolimus refractory active disease (Lichtiger score >10) and were treated with 5mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter if tolerated.

Results:

Six of 24 patients (25%) achieved remission following infliximab infusion and 4/24 (17%) had an initial response only but underwent proctocolectomy later due to loss of response (3) or development of a delayed hypersensitivity reaction (1). Fourteen patients (58%) completely failed to respond with 10 undergoing colectomy. Eight patients experienced side effects under infliximab including two infectious complications (herpes zoster and herpes pneumonia).

Conclusions:

Infliximab offers a therapeutic option as rescue therapy in about a quarter of patients with active UC after failing to respond to tacrolimus. This benefit has to be weighed against the risks of infectious complications.

Key words: ulcerative colitis, tacrolimus, infliximab, steroid-resistant

INTRODUCTION

Steroids still represent the mainstay of remission induction in severe ulcerative colitis ⁽¹⁾. Nevertheless, almost 20% of patients with a severe attack of ulcerative colitis do not respond sufficiently to systemic steroids ^(2, 3). Azathioprine is the mainstay of immunosuppressive therapy in ulcerative colitis but of limited value in this situation because its delayed onset of action. The first fast-acting immunosuppressant to be successfully used in this situation was ciclosporin A ⁽⁴⁾. In a small placebo-controlled study including 20 patients with severe steroid-refractory disease ciclosporin was able to induce response (and avoid colectomy) in 80% of patients. These results were confirmed in several larger uncontrolled observations with a long-term response after ciclosporin in roughly half of steroid refractory patients ⁽⁵⁻⁷⁾. Similar results are reported for tacrolimus, another calcineurin inhibitor, from uncontrolled trials ⁽⁸⁻¹⁰⁾ and one controlled study ⁽¹¹⁾ with short-term response rates of 70-80%. In 2005 a placebo-controlled trial in patients with severe steroid-refractory ulcerative colitis showed efficacy of infliximab, a chimeric antibody against TNF- α , with 71% of patients avoiding colectomy upon a single infusion compared to only 33% in the placebo arm ⁽¹²⁾. In two large controlled long-term trials infliximab achieved sustained long-term remission in about 20-25% of moderate to severely active patients ⁽¹³⁾. According to these results all three therapeutic regimens appear to be equivalent options in severe ulcerative colitis failing to respond to steroids ⁽¹⁾ although a head-to-head comparison is still lacking.

Until now there are only limited data concerning the efficacy of one or the other substance class in case of failure to first line therapy. A small retrospective study involving 19 patients tested the efficacy of ciclosporin or infliximab in severe ulcerative colitis after failure of the other drug ⁽¹⁴⁾. Efficacy rates of infliximab after ciclosporin failure and ciclosporin after infliximab failure reached 40 and 33%, respectively.

When using potent immunosuppressive drugs in a **combined** manner the risk of cumulative toxicity is a matter of concern ⁽²⁰⁾. When given sequentially, the potential interaction also depends on the different half-lives: whereas tacrolimus is eliminated within days infliximab levels can be determined even after weeks of treatment ⁽¹⁵⁾. To avoid cumulative immunosuppressive toxicity if the first drug fails and salvage therapy with the other is needed it is our common practise to start with tacrolimus in this situation. Therefore this study reports on the efficacy of infliximab as rescue medication in patients failing to tacrolimus.

PATIENTS AND METHODS

Patients

Twenty-seven patients were enrolled consecutively between 2005 and 2009 in two centers (Stuttgart and Lübeck, Germany). Nineteen patients had ulcerative colitis and 8 had a diagnosis of indeterminate colitis. Two patients with indeterminate colitis developed perianal fistulae during follow up and were excluded from this analysis. One patient with ulcerative colitis developed high fever and bacteremia and therefore underwent colectomy directly without receiving infliximab. Patient characteristics of the remaining 24 patients are shown in table 1. Eleven patients were female; the median age was 33 years (16-67). Twelve patients had extensive colitis and 12 had left-sided colitis. Reasons for rescue medication with tacrolimus were steroid-refractory disease (prednisolone dose: 1mg/kg body weight, maximum 100mg/day) in 19 patients and steroid dependency for >6 months (and intolerance to thiopurines) in 5 patients. To avoid excessive steroid toxicity, these 5 patients were not given a steroid boost but tacrolimus instead. All patients had active disease with a Lichtiger score (modified Truelove-Witts severity index) of >10 at enrollment. All patients were offered colectomy instead of infliximab but all decided for medical treatment first. Immunohistochemistry staining for cytomegalovirus (monoclonal antibody clones CCH2 and DDG9, 1:50, Daco) was performed prior to initiation of salvage therapy to exclude infection. The single patient with positive immunohistochemistry received antiviral treatment with gancyclovir before infliximab therapy. This patient developed perianal fistulae suggesting Crohn's disease and was excluded from the analysis.

Medication

The median tacrolimus dose before switching to infliximab was 0.1mg/kg (range 0.07-0.23mg/kg). In case of insufficient response doses were adapted according to trough levels, levels of 10ng/ml were aimed for before stopping the drug unless patients developed toxicity. The median duration of tacrolimus therapy before switching to infliximab was 12 weeks (range 1-60). Nine patients completely failed to respond to tacrolimus therapy, eleven patients responded initially but experienced a loss of response and four patients had to stop therapy due to toxicity. Tacrolimus therapy was stopped at least one week before starting infliximab. For security reasons tacrolimus blood levels were determined prior to initiation of infliximab and had to be negative. All patients receiving infliximab were treated with 5mg/kg at weeks 0, 2 and 6 followed by eight-weekly infusions in case of response. Concomitant medication is shown in table 1. All patients received systemic steroids with a median daily dose of

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3 prednisolone of 50mg (20-100mg). Fourteen patients (58%) received additional
4 immunomodulator therapy (azathioprine or methotrexate); all other patients had been
5 intolerant or refractory to immunosuppressive therapy previously. One patient received
6 tacrolimus and infliximab in parallel for three months and was treated with infliximab alone
7 subsequently.
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10 11 12 *Data collection*

13 Patients were followed on a regular basis in an out patient clinic and response was assessed
14 by clinical symptoms according to the Lichtiger score (Table 2). Treatment response was
15 analysed at week six after the third infusion if tolerated and if not colectomised. Response
16 was defined as a Lichtiger index score < 10 points and remission was defined as a Lichtiger
17 index score \leq 3 points with or without the requirement of systemic steroids. Patients were
18 screened for side effects at every visit.
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RESULTS

Twenty-four patients were enrolled in this study and received infliximab after failure of tacrolimus.

Efficacy Reasons for infliximab were the following: Nine patients did not respond to tacrolimus, 11 had a loss of response after responding initially and 4 had to stop tacrolimus due to side effects. Outcome of infliximab rescue therapy is shown in table 3 and figure 1. After infliximab infusions 6 patients (25%) achieved **sustained** long-term remission (median time to follow-up 48 weeks (26-68 weeks) with 4 of them being able to taper steroids completely. Two of these patients received follow-up endoscopy and showed complete endoscopic remission. There was no difference in remission rates to infliximab between the subgroups of patients having failed tacrolimus for intolerance (1/4 - remission rate 25%) or resistance (5/20 - remission rate 25%). Four patients (17%) had an initial response (median number of infusions 5, range 4-12) but had to undergo proctocolectomy later due to loss of response (3) or development of a delayed hypersensitivity reaction (1). Fourteen patients (58%) failed to respond at all with 10 of them undergoing colectomy. Two of these patients had to stop infliximab due to side effects before efficacy could be evaluated (allergic reaction, viral pneumonia, respectively). **Median CRP levels were 4.05 mg/dl (range 0.4-14.9) before and 3.15 mg/dl (range 0.2-39.9) after initiating infliximab therapy. In patients achieving remission median CRP levels decreased from 6.2 mg/dl (0.4-14.9) to 0.9 mg/dl (0.3-4) whereas in patients not achieving remission CRP levels rose from 3.9 mg/dl (0.9-14.9) to 5.4 mg/dl (0.3-39.9).** Four patients (all in the failure group) refused colectomy and were switched to alternative treatments (1 x azathioprine, 1 x adalimumab, 1 x low-dose tacrolimus, 1 x lecithine). In summary 14/18 patients with therapeutic failure underwent colectomy (78%). A Kaplan-Meier analysis of colectomy-free survival is shown in Figure 2.

Adverse events

Adverse reactions are listed in table 4. Of the 24 patients receiving infliximab as rescue therapy eight patients experienced at least one side effect including allergic reactions (2), flush (1), arthralgia (2), worsening of depression (1) and infectious complications (herpes zoster and herpes simplex pneumonia). Two of these adverse events were judged as severe (allergic reaction and viral pneumonia) and therapy with infliximab was stopped.

DISCUSSION

Therapeutic options in patients with severe steroid-refractory ulcerative colitis are limited. Both, the calcineurin-inhibitor tacrolimus and the anti-TNF-antibody infliximab are established therapeutic options in steroid-refractory ulcerative colitis^(8, 11, 12, 21). Short term response rates with avoidance of colectomy approach roughly 70% for both drugs but loss of response occurs frequently under infliximab and successful bridging to immunosuppression fails in a substantial proportion of patients with tacrolimus as well. Little data are available for the efficacy of either drug after failure to the other. The only small case series to date comparing ciclosporin and infliximab reports remission rates of 40% in the infliximab-salvage group compared to 33% in the ciclosporin-salvage group⁽¹⁴⁾.

Cumulative immunosuppressive effects are a major concern if potent immunosuppressive drugs are used sequentially. Infliximab levels can be detected in serum for at least 8 weeks following treatment⁽¹⁵⁾. Therefore it is our common practise to use tacrolimus as first line drug in steroid refractory ulcerative colitis due to its short half-life. We report data from 24 patients receiving infliximab-salvage therapy after failing to respond to tacrolimus. Initial success rates were remarkably high with more than 40% of patients responding, having in mind that we dealt with a very sick patient cohort refractory to systemic steroids in combination with a calcineurin inhibitor. This is reflected by the high rate of colectomy in 14/18 patients failing to respond to rescue therapy (78%). Although long-term success was achieved by a substantial proportion of patients (25%) loss of the initial response occurred quite frequently. This is in line with the large controlled maintenance trials on infliximab therapy in ulcerative colitis⁽¹³⁾ with (steroid-free) remission rates at weeks 30 and 54 between 35 and 37%. The recruitment criteria for the ACT1 and ACT2 population excluded patients with high dose steroids indicating a group of patients with less severe disease. This is reflected by the low rate of colectomy in the placebo group (17%) compared to our study population⁽¹⁶⁾. Interestingly, we could not detect a difference in response rates to infliximab between patients receiving salvage therapy due to intolerance or refractoriness to tacrolimus. Efficacy does not seem to be negatively influenced by failure to the other drug probably due to the different mechanisms of action of both therapeutic regimens^(17, 18).

We also investigated the efficacy of tacrolimus-salvage therapy in a small group of three patients failing first-line therapy with infliximab. (data not shown). Two patients achieved remission whereas one patient failed therapy and underwent colectomy. Although it is

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3 difficult to draw any conclusions from these three patients the response rate of 2/3
4 corresponds well with efficacy data from the uncontrolled trials ^(8, 9, 19). Further studies are
5 needed to evaluate the effect of tacrolimus in patients with refractory ulcerative colitis failing
6 to respond to infliximab but caution in the use of this combined medication is advisable due
7 to the long half life of infliximab.
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14 Special attention has to be drawn to infectious complications in this situation. Maser and
15 colleagues report on frequency of severe adverse events of 16% in their patient cohort
16 including one death due to gramnegative sepsis. Two other patients developed infectious
17 complications including herpes esophagitis and *Klebsiella* and *Enterococcus* septicemia. In
18 our patient population 2/24 patients developed severe adverse reactions necessitating a
19 withdrawl of the drug resulting in a frequency of 8%. Two patients developed infectious
20 complications; one patient developed shingles under combination therapy with steroids and
21 infliximab and the other patient experienced a herpes pneumonia under combination
22 immunosuppression with infliximab and mercaptopurine. These results are in line with a
23 recent study from the Mayo-Clinic ⁽²⁰⁾ reporting on the increasing risk of opportunistic
24 infection under combined immunosuppression.
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35 In conclusion the presented data show a substantial short-term efficacy of salvage therapy
36 with infliximab after failure to tacrolimus in steroid refractory ulcerative colitis. The short-
37 term efficacy is comparable to results reported from first line therapy and therefore might be
38 worth considering in the individual patient. Nevertheless, long-term outcome is rather poor.
39 Additionally, consecutive and combined immunosuppression is associated with a substantial
40 risk of developing (infectious) complications. These risks and benefits have to be weighted
41 carefully against the risks and benefits of proctocolectomy.
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Table 1: Clinical characteristics of patients

Total number	24
Sex (f/m)	11/13
Age at diagnosis (yr)	
• median (range)	22 (8-56)
Age at salvage therapy	
• median (range)	33 (16-67)
Disease	
• ulcerative colitis	18
• indeterminate colitis	6
Extend of disease	
• left-sided	12
• extensive	12
Course of disease	
• steroid refractory	19
• steroid dependent	5
Reasons for infliximab salvage therapy	
• tacrolimus failure	9
• loss of response	11
• tacrolimus intolerance	4
Concomitant immunosuppressive treatment	
• thiopurine	10
• methotrexate	4
• none (prior intolerance)	10

For Peer Review

Table 2: Lichtiger Index (Modified Truelove and Witts severity index)

Variable	Scores					
	0	1	2	3	4	5
Number of daily stools	0-2	3-4	5-6	7-9	≥10	
Nocturnal diarrhea	No	Yes				
Visible blood in stool (% of movements)	0	<50	≥50	100		
Fecal incontinence	No	Yes				
Abdominal pain or cramps	None	Mild	Moderate	Severe		
General well-being	Perfect	Very good	Good	Average	Poor	Terrible
Abdominal tenderness	No	Mild and localized	Mild to moderate and diffuse	Severe or rebound		
Need for antidiarrheal drugs	No	Yes				

Table 3: Efficacy analysis

	Patients (n)	infliximab infusions (n)	steroids initial dose (mg)	steroids end dose (mg)	colectomy rate (%)	follow up or time to colectomy (weeks)
Total	24	3 (1-12)	50 (20-100)	15 (0-100)	58	48 (4-112)
Remission (steroid-free)	4	6 (54-10)	60 (50-100)	0	0	48 (26-64)
Remission with steroids	2	12 (10-12)	30 (20-30)	10	0	68 (48-68)

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Response only	4	5 (4-12)	50 (20-60)	40 (5-40)	100	96 (64-112)
Failure	14	3 (1-6)	50 (20-80)	20 (4-100)	72	26 (4-104)

For Peer Review

Table 4: Adverse events during salvage therapy

Adverse reaction	N	SAE
Infliximab (total)	8	2
allergic reaction	2	1
arthralgia	2	-
flush	1	-
shingles	1	-
pneumonia (herpes simplex)	1	1
worsening of depression	1	-

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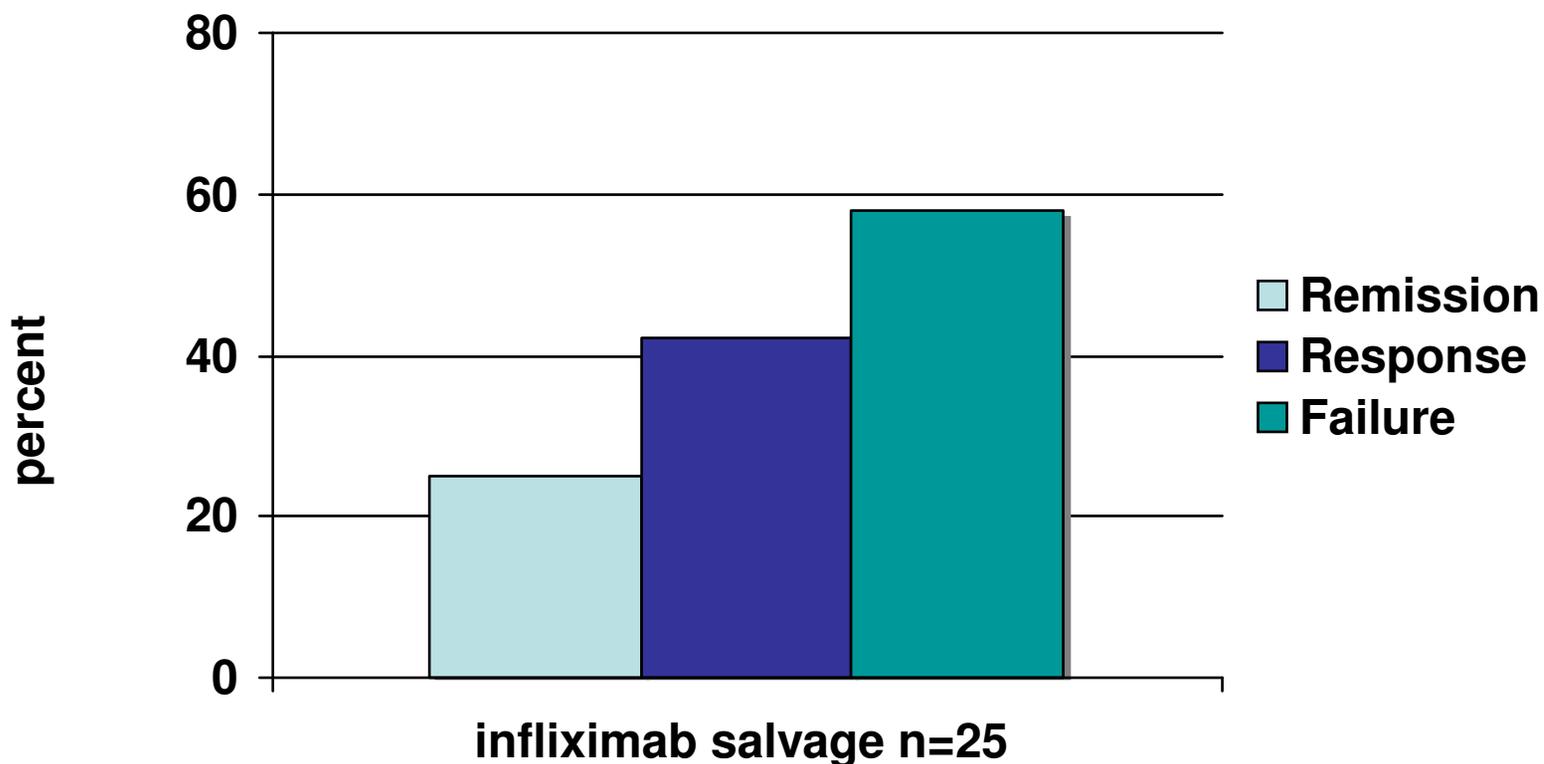
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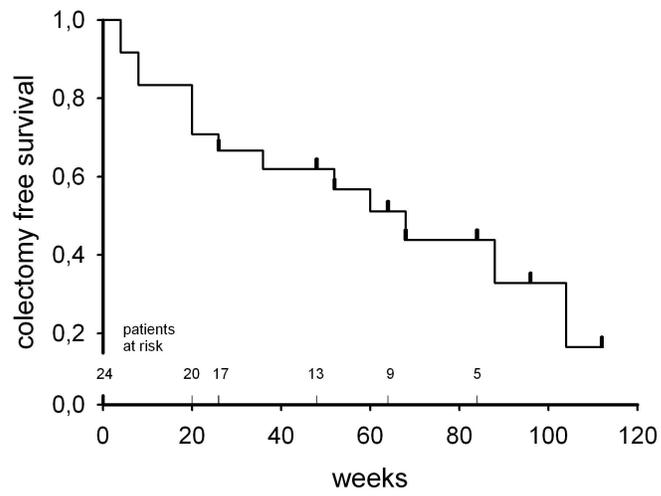
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