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Medium to long-term efficacy and safety of oral tacrolimus in moderate to severe steroid refractory ulcerative colitis

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SUMMARY

Background: Oral tacrolimus is an effective drug that induces clinical remission in patients with moderate to severe ulcerative colitis refractory to steroids. However, there is little data with regard to its medium to long-term efficacy and safety. The aim of this study was to assess the medium to long-term efficacy and safety of oral tacrolimus in this challenging clinical situation.

Methods: This was a retrospective observational review of the clinical charts of 34 patients with moderate to severe ulcerative colitis refractory to steroids treated with oral tacrolimus at our hospital (July 2001-July 2016). Remission was defined as a Lichtiger index score < 3 and response was defined as a score < 10 with a reduction of at least three points compared to the baseline score.

Results: Seven patients (20.58%) required colectomy during the follow-up period (mean 65 months). Nine patients required rescue with infliximab (four patients during the first six months of follow-up and the other five after the first six months). The short

to medium clinical efficacy combining both remission and clinical response was 82% at six months. Kaplan-Meier analysis showed that the percentage of patients free from colectomy and additional sequential rescue therapy was 75% at 54 months (median follow-up). The early introduction of thiopurines (< 2 months from start of tacrolimus) showed no significant improvement in prognosis (p = 0.72). Fifty-three per cent of patients experienced adverse effects, none of whom required treatment withdrawal. No severe infections were noted during the follow-up.

Key words: Ulcerative colitis. Tacrolimus.

INTRODUCTION

Flares of moderate to severe ulcerative colitis (UC) still pose a clinical challenge. Although the introduction of steroids during the 1950s led to a dramatic reduction in mortality (1), 20-30% of patients treated with steroids in this context still require colectomy during the first year of the disease presentation (2).

Medical treatment options for patients with moderate to severe UC refractory to steroids are limited. The European Crohn's and Colitis Organisation (ECCO) guidelines recommend the use of calcineurin inhibitors (cyclosporine or tacrolimus) or anti-TNFα agents (infliximab, adalimumab and golimumab) (3). The latter are the only drugs approved by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for this condition. The Japanese health authorities have authorized the use of oral tacrolimus as an induction therapy for a flare-up of moderate to severe steroid refractory UC for a maximum period of three months.

A few retrospective non-controlled studies, mainly in Germany, the United Kingdom and Japan, have explored the role of tacrolimus as a rapid acting agent for moderate to severe flare-ups of UC (4,5). The overall short-term response was 70-80% (6-8). The positive open-label experience led to two randomized clinical trials in Japan, which obtained response figures similar to the open-label experience, although the sample size of steroid refractory patients was small (9,10).

Very few data are available with regard to the medium and long-term efficacy and safety of oral tacrolimus used as a bridge to thiopurines. In particular, with regard to

the rates of colectomy and the need for a rescue treatment such as infliximab to maintain a prolonged clinical response.

The choice of the type of agent to use as a rescue if steroid therapy fails needs to be clarified as there are no head to head studies comparing different drugs. A controlled trial found no differences in the rate of treatment failure at 98 days (principal outcome) nor in the immediate response or rate of colectomy at three months between infliximab and cyclosporine in steroid refractory patients (11). On the other hand, a retrospective study showed a colectomy-free survival rate at three months of 67% in the infliximab group *versus* 93% in the cyclosporine group (12). Studies comparing the efficacy and safety of tacrolimus and infliximab (all retrospective) report similar results for both agents in the short-term induction of remission, and infliximab appears to be superior to tacrolimus for bridging to thiopurines (13). Thus, although the short-term efficacy of oral tacrolimus appears similar to that reported for cyclosporine and infliximab, further data are required with regard to its short-term and medium to long-term efficacy and safety.

Over ten years ago we reported our early experience with tacrolimus in steroid-resistant moderate to severe UC and in multi-refractory severe Crohn's disease (14). Since then, another Spanish group has recently reported its experience with tacrolimus in refractory UC and Crohn's disease, and identified a reduction at one month in C-reactive protein (CRP) concentrations and the absence of prior treatment with anti-TNFα agents as factors predicting a drug response (15).

The aim of this study was to analyze the medium to long-term efficacy and safety of oral tacrolimus in the difficult setting of steroid-refractory UC flare-ups after an accumulated experience of over 15 years with this drug.

MATERIAL AND METHODS

This is a retrospective analysis of the efficacy and safety of oral tacrolimus in refractory moderate to severe UC and was undertaken in the Digestive Disease Clinical Management Unit of the Hospital Regional Universitario de Málaga (july 2001-july 2016).

Patients

The study comprised 34 patients with moderate to severe UC refractory to steroids. All the patients signed the informed consent for the use of a medicine for a condition not included in the product label after being thoroughly informed about the characteristics of the treatment and the other medical and surgical options available. The clinical records were retrospectively reviewed from the start of the treatment up to the study date, colectomy, use of additional rescue therapy or loss to follow-up. All the data were gathered anonymously and coded in a computerized database. The hospital Ethics Committee approved the study.

Diagnosis of UC was made according to standardized clinical, endoscopic, radiological and histological criteria. An infectious etiology was discarded by serial coprocultures, serology, immunohistochemistry and/or blood analysis of cytomegalovirus DNA. All the patients had moderate to severe steroid-refractory UC (1 mg/kg intravenous 6-methylprednisolone for one week). Systemic steroids were progressively reduced in an individualized manner. Patients who had previously received treatment with azathioprine or 6-mercaptopurin continued to receive the treatment at the previous doses. For patients who were naïve to azathioprine or 6-mercaptopurin (the majority), the immunosuppressive treatment was started within three months of beginning tacrolimus treatment in accordance with the criteria of the responsible physician after dose determination of thiopurine-methyltransferase at 2-2.5 mg/kg/day and 1-1.5 mg/kg respectively. One patient with intolerance to azathioprine received subcutaneous methotrexate at 25 mg per week.

Treatment administration and dose adjustment

All the patients were hospitalized at the start of treatment. Oral tacrolimus was given to all the patients at 0.15-0.3 mg/kg/day and divided into two doses two hours before meals. In accordance with the unit protocol, the levels were monitored daily for the first two weeks, adjusting the dose daily in order to achieve concentrations of 5-10 ng/ml. Later, tacrolimus levels were measured every two weeks for the first three months of treatment and then monthly until the end of treatment.

Evaluation of short, medium and long-term efficacy

Short-term efficacy, assessed at 12 weeks after starting the treatment, was performed with the Lichtiger activity index (16). Clinical remission was considered as a score < 3 and response was considered as a reduction in the score to below 10 (with a decrease of at least three points from the baseline score). We evaluated the proportion of patients who achieved remission and clinical response at 12 weeks as well as the proportion of patients free from colectomy with no need for a second rescue therapy during these first 12 weeks. Medium to long-term efficacy was assessed by colectomy-free survival with no need for a second rescue therapy.

Safety study

Adverse events were also assessed. Renal dysfunction was defined as an increase of 30% or more above the baseline in serum creatinine concentrations. An adverse event was classified as severe if it required treatment withdrawal.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges and qualitative variables, as absolute frequencies and percentages. The analysis of factors predicting a short-term response and remission (six months from start of treatment) was performed by comparing independent samples using the Mann Whitney U-Wilcoxon test. The rate of event-free survival in the overall population (colectomy and/or use of sequential rescue therapy with infliximab) was evaluated using Kaplan-Meier analysis. Additionally, patients were stratified into two groups (early *versus* late immunosuppression with thiopurines) to assess the prognostic differences using a log-rank test. The analysis was performed with the R Project version 3.2.2. Statistical significance was set at $p < 0.05$.

RESULTS

Patients and treatment characteristics

The baseline clinical, demographic and pathological characteristics of the 24 men (72.7%) and ten women included in the study are summarized in table 1. The median

age at diagnosis was 31.5 years (23.25-39.75) and the median age at start of treatment with tacrolimus was 37.5 months (23.5-44.75). The median duration of the disease prior to starting treatment was four months (0-37.5). For 13 patients (38.23%), it was their first flare-up of the disease. The median baseline Lichtiger index was 14 (13-15) and 94% of the patients had extensive involvement (E3).

Tacrolimus was given orally in all 34 patients. The median oral dose was 7.70 mg/d (6.07-9.92). The median whole blood level of tacrolimus during the first four weeks was 8.35 (5.97-11.25), and at week 12 it was 9.05 (7-9.6) ng/ml. All the patients received intravenous steroids at a mean dose of 50 mg methylprednisolone. Tacrolimus was used as a bridge to slow-onset immunosuppressants to maintain remission, mostly azathioprine (82%; median dose 100-137.5) in 29 (85%) patients. The mean latency period from starting tacrolimus to the introduction of immunosuppressants was 120 days (0-1,560), and this was decided using the criteria of the physician responsible for the follow-up of the patients whilst bearing in mind the conditions of each particular case. The median baseline concentration of CRP obtained from all the patients was 72.15 mg/l (21.5-144.65).

Efficacy of tacrolimus

Colectomy in the short and long term

A total of seven patients (20.58%) underwent colectomy during the follow-up period, after a median of 54 months. Only one patient (2.94%) required colectomy during the first six months. However, four patients required sequential rescue therapy with infliximab to avoid colectomy during the first six months. The median time for patients who underwent colectomy after the first six months (18.18%) was 18.5 months (9.75-39.75) after starting tacrolimus. Another five patients required rescue with infliximab after the first six months due to reactivation of the disease and all were able to avoid late colectomy. Survival free of colectomy and sequential rescue therapy was 75% after a median follow-up of 54 months figure 1. Survival analysis with no events (colectomy or rescue therapy) and differentiating the early (< 60 days) and late immunosuppression groups showed no significant differences (p = 0.72) (Fig. 2).

Remission and clinical response

The median Lichtiger index score at 12 and 24 weeks fell to 3 (3-3.5) and 3 (3-3.25) respectively. The median levels of CRP fell to 3 (2.45-8.8) and 2.9 (2-4.8) at 12 and 24 weeks, respectively. Clinical remission was achieved by 21 (61%) and 20 (58%) of the patients at weeks 12 and 24. Another seven (20%) and eight (23.52%) patients had a clinical response at these weeks (Table 2).

Steroid withdrawal

Total withdrawal of steroids was achieved in 25 patients (73.5%) and the median time to withdrawal was 63.5 days (42.25-86). Two of the four patients in whom steroid withdrawal was not achieved underwent colectomy at 11 and 57 months of follow-up, while the other two were rescued with infliximab beyond six months after starting tacrolimus.

Factors predicting short and medium term clinical response

Significant differences were found in the median Lichtiger scores at three months depending on remission at six months. These were 6 (4-7.5) in those who had no remission *versus* 3 (3-3) in those with remission ($p < 0.001$). Significant differences were also found in the scores depending on clinical response at six months, these were 3 (3-3) in responders *versus* 6 (4-6.5) in non-responders ($p < 0.001$). Analysis of the disease time showed no significant differences in CRP or tacrolimus levels in relation to remission or short-term response.

Monitoring tacrolimus levels

Therapeutic levels of tacrolimus (5-10 ng/ml) during the first week of treatment were achieved in 26 patients (76.5%). The median tacrolimus levels at weeks 2, 4 and 12 were 7.50 (6-10.1), 8.35 (5.97-11.25) and 9.05 (7-9.6) ng/mL, respectively.

Adverse effects

No patient experienced a severe adverse reaction requiring treatment suspension. Over half the patients (53%) experienced some sort of mild and temporary adverse

effect. There were two episodes of infectious non-enteroinvasive gastroenteritis. No opportune infections were noted. All the patients received prophylaxis with cotrimoxazole if they were on triple immunosuppression (decreasing dose of steroids, azathioprine and tacrolimus) (Table 3).

DISCUSSION

Almost 20 years have now passed since the first case series was reported of the use of tacrolimus in patients with inflammatory bowel disease (17). The first randomized, controlled clinical trial of the use of oral tacrolimus in UC was reported in 2006 (9). In this study, 60 patients with moderate to severe steroid-refractory UC were randomized to receive tacrolimus with target plasma levels of 10-15 ng/ml (19 patients), tacrolimus with target plasma levels of 5-10 ng/ml (21 patients), or placebo (20 patients). The percentages of response at two weeks were 68.4% and 38.1% in the high and low target groups, respectively, and 10% in the placebo group. The same authors undertook a second placebo-controlled clinical trial with 62 patients with moderate to severe UC, although the target plasma level in the treatment arm was 10-15 ng/ml (10). The results were similar, with a 50% response rate in the oral tacrolimus group *versus* 13.3% in the placebo group. These are the only placebo-controlled clinical trials with regard to the efficacy of tacrolimus in inducing remission of moderate to severe steroid-refractory UC to date.

Notwithstanding the above, almost 20 retrospective cohort studies have been published in real practice settings. The largest study evaluated the induction of remission in 130 patients from three centers in Germany and found a percentage of clinical remission at 12 weeks of 72% with 13.8% of patients requiring colectomy (8). High efficacy rates have been reported in children, with rates of around 90% that avoid the need for colectomy in the short-term (18). Considering these data, tacrolimus seems to be an effective treatment in the induction of remission of steroid-refractory or dependent moderate to severe UC. The ECCO and GETECCU *(Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa)* guidelines consider oral tacrolimus to be a rescue option for severe flare-ups of steroid-refractory UC and for outpatients with moderate steroid refractory flare-ups (19).

In this study, the percentages of short-term success of the treatment (remission and response) are similar to those of most of the previously reported clinical practice studies. The low colectomy rate found in this study in the first six months is clearly conditioned by the use of a second rescue therapy (infliximab) in four of the patients, who avoided the need for colectomy in the short term. The only factor significantly predicting response and remission at six months was the median Lichtiger score at three months of treatment. This is in accordance with other studies, such as that of Miyoshi, which had a similar design to this study, 11/13 patients (84.6%) who switched to infliximab after failure of tacrolimus were rescued (20).

Another two studies have examined the efficacy of infliximab as a rescue therapy in patients refractory to tacrolimus, with short-term response rates of 46.2% (6/13) and 50% (6/12) (21,22). Yamamoto reported colectomy-free rates of 53.8% at 41.4 months after the use of infliximab in this situation (23). The opposite approach, i.e. using tacrolimus as a rescue after failure of infliximab, was evaluated in 30 patients. This study achieved response rates of 70% at four weeks of treatment and almost 30% of patients remained in remission after one year (24). These data seem to show that switching from one drug to another may be an effective option in selected patients, although long term data with regard to maintenance of the response are limited. The safety of this strategy is another concern, particularly relating to the development of opportunistic infections and perioperative complications in the case of colectomy.

Information about the direct comparison of anti-TNFα drugs and tacrolimus in this situation is also limited and of a retrospective nature. A recent Japanese study examined the short-term prognosis (12 weeks) in 100 patients with moderate to severe UC treated with tacrolimus or anti-TNF agents (50 patients in each group) and found no significant differences in the outcome variables (remission, response and colectomy rate) (25). However, other researchers questioned the ideal patient profile for which oral tacrolimus would have the best results. The consensus was that in the case of the moderately severe patient, it should not be used in severe flare-ups of fulminating colitis where perhaps cyclosporine or infliximab would have a greater efficacy to avoid later colectomy (26).

Data concerning the long-term efficacy of tacrolimus after its use are equally scarce. Yamamoto et al. reported a colectomy-free survival of almost 65% at 65 months, although they made no reference to the sequential use of biological treatment at some time during the course of the disease (27). Other retrospective cohorts have found colectomy-free survival rates of 56.5% at 43.8 months (28), 59.3% at two years (29) and 62.3% at 65 months after treatment (30). Miyoshi et al. reported a rate of event-free patients (colectomy or rescue with other therapies) of 50% at one year and almost 40% at two years, attributing the lower percentages of recurrence as compared to other series to the inclusion of more severe patients in their study. However, stratifying according to the presence of endoscopic improvement (Mayo 0 and 1) showed a marked increase in event-free survival (survival of 69% at one year and 61.3% at two years) (21). Notably, in the latter study about half the patients were already receiving thiopurines, which could hamper the maintenance of tacrolimus-induced remission without competition from other agents as the failure was prior to receiving immunosuppressive therapy. This is in contrast with this series where most patients were naïve to immunosuppressors. This may explain the difference in the long-term event free efficacy of tacrolimus in our series (75% with a median follow-up). Indeed, the concomitant introduction of thiopurine immunosuppressors was the only predictive factor of short-term success in most observational retrospective series of tacrolimus (8). An interesting aspect that we attempt to clarify in our study is whether the time of introduction of thiopurine immunosuppressors with respect to the start of tacrolimus as a maintenance therapy of remission influenced the greater colectomy-free survival or rescue with infliximab in the medium to long term. In our case, event-free survival stratified according to early (before reaching two months of tacrolimus treatment) or late introduction (after two months) showed no significant differences.

In Japan, most studies published since the above-mentioned clinical trials of Ogata aimed to achieve plasma levels of tacrolimus of 10-15 ng/ml during the first two weeks and maintenance with 5-10 ng/ml. In Europe, as well as in this series, the aim was to achieve levels of 5-10 ng/ml, which seems to have no repercussion on the rates of initial response.

With regard to safety, just over half the patients experienced adverse events related to the treatment, but there were no cases of severe events that required drug withdrawal. The profile of secondary effects was similar to that of other series with a similar follow-up period, most notably were neurotoxicity in the form of tremors and nephrotoxicity which were the most common events (31). No severe opportune infections were seen.

Our study has certain limitations: the retrospective nature of the study and data collection, the reduced number of patients, the absence of endoscopic data in the evaluation of efficacy (it has been shown to be a predictive factor for maintenance of the response after induction) and its single-center nature.

On the other hand, the study has certain strengths such as the fact that it is a real practice setting with a long average follow-up, the homogeneity of the patients included, the uniform practice of concomitant immunosuppression and an accumulated experience of 15 years with the use of oral tacrolimus in this context.

In conclusion, we present our experience of over ten years using oral tacrolimus in a Spanish cohort of patients with moderate to severe steroid-refractory UC. Its efficacy in the induction of remission seems acceptable and comparable to that of other agents used in this context. In the long term, after using this drug as a bridge to thiopurine immunosuppressors, survival free of colectomy or rescue therapy was also acceptable. There was no apparently important influence of the precocity of the introduction of immunosuppression on long-term efficacy. In general, the safety profile was favorable, even in the group in which infliximab was used sequentially, where no severe opportune infections were noted.

Further controlled prospective studies are needed to clarify many of the unknowns that remain with regard to the use of tacrolimus in the context of steroid-refractory moderate to severe flare ups of UC (target therapeutic drug concentrations, its possible use as maintenance therapy and identification of factors predicting a response).

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Table I. Baseline demographic and clinical characteristics plus tacrolimus treatment data

n (%)	*Total patients* *34 (100%)*
Age at start of tacrolimus (median [range])	37.5 (23.5-44.75)
Prior disease duration months (median [range])	4 (0-37.5)
First disease flare	13 (38.23%)
Sex	
Male	24 (70.6%)
Female	10 (29.4%)
Weight (kg) (median [range])	63.15 (91-43) 60.5 (52-71.875)
Smoking	
Non smokers	28 (82.4%)
Ex-smokers	6 (17.6%)
Extra-intestinal manifestations	7 (20.6%)
Disease distribution (n/%)	
Pancolitis E3	32 (94%)
Left colitis E2	2 (6%)
Baseline Lichtiger (median [range])	14 (13-15)
Endoscopic activity	
Mayo 3	29 (85%)
Mayo 2	5 (15%)
Baseline C-reactive protein levels (mg/dl)	72.15 (21.5-144.65)

(median [range])	
Baseline methylprednisolone in mg/d (median [range])	56.47 (50-60)
Tacrolimus dose mg/d (median [range])	7.5 (6-10.1)
Duration of tacrolimus treatment days (median [range])	210 (6-1560)
Tacrolimus dose in mg/kg body weight (median [range])	0.22 (0.15-0.3)
Concomitant immunosuppression	29 (85.3)
Azathioprine mg/d (median [range]) n (%)	100 (100-137.5) 81%
Methotrexate mg/d (median [range]) n (%)	13.75 (13.12-14.38) (6%)
Naive to azathioprine (%)	26 (76.47%)
Months of follow-up (median [range])	54 (22.5-101)

Table II. Efficacy of tacrolimus (percentage remission and response at weeks 4, 12 and 24)

Short-term efficacy	*Week 4*	*Week 12*	*Week 24*
Remission n (%)	17 (50%)	21 (61.76%)	20 (58.82%)
Response (%)	12 (35.29%)	7 (20.58%)	8 (23.52%)
Tacrolimus levels (median [range])	8.35 (5.97-11.25)	9.05 (7-9.60)	nd
Lichtiger (median [range])	3 (3-5)	3 (3-3.25)	3 (3-3.5)
C-reactive protein levels (median [range])	4.3 (2.92-21.67)	3 (2.45-8.80)	2.9 (2-4.8)

Table III. Adverse effects seen during the follow-up

Total adverse events	n = 20
Neurotoxicity (tremor/paresthesia)	11 (32%)
Increased creatinine concentrations	4 (12%)
Infections	2 (6%)
Hyperglycemia	1 (3%)
Alopecia	1 (3%)
Hypertension	1 (3%)

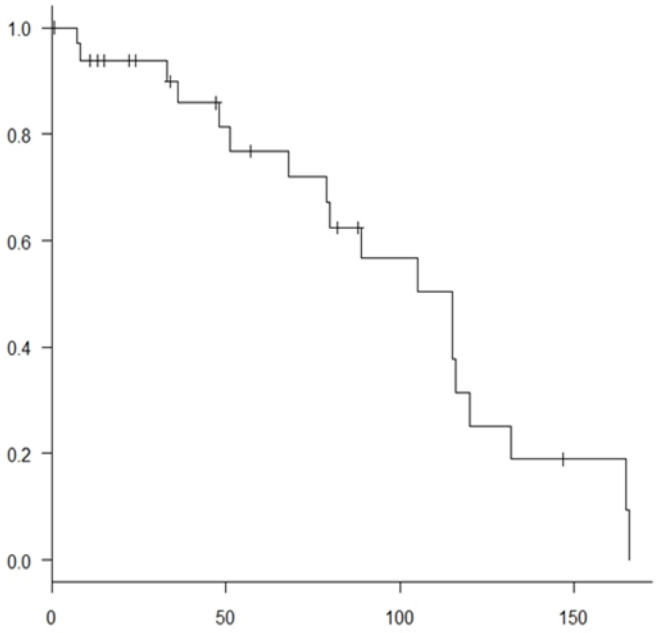

Fig. 1. Event-free (colectomy and rescue therapy in the total population) survival analysis (Kaplan-Meier). Follow-up in months.

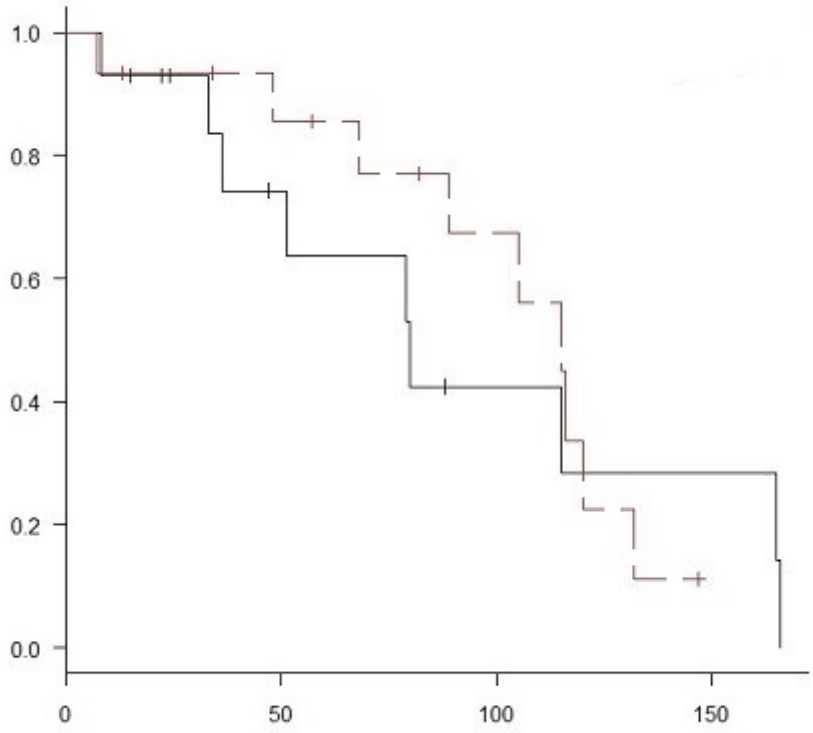

Fig. 2. Event-free (colectomy and rescue therapy) survival analysis (Kaplan-Meier) stratified by start of early (dashed line) and late (continuous line) immunosuppression (follow-up in months).