



Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: The ENTRANCE study

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Abstract

Background: Vidofludimus (SC12267) is a novel oral immunomodulator inhibiting dihydroorotate dehydrogenase (DHODH) and the expression of proinflammatory cytokines including interleukin-17 (IL17A and IL17F) and interferon-gamma. The objective of the study was to explore the efficacy, safety and tolerability of vidofludimus in steroid-dependent inflammatory bowel disease (IBD).

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Methods: The open label uncontrolled ENTRANCE study (ClinicalTrials.gov NCT00820365) has been conducted at 13 study centers in Germany, Bulgaria and Romania. Thirty-four steroid-dependent patients with a confirmed diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) were treated with a once daily 35 mg oral dose of vidofludimus over 12 weeks. Steroids were tapered during the first 8 weeks followed by a steroid-free treatment period of 4 weeks. Complete response was defined as steroid-free clinical remission at week 12; partial response was defined as being in remission at steroid dose equal or lower than the individual patient's threshold dose for relapse.

Results: Of the thirty-four patients enrolled in this trial 26 were evaluable for primary efficacy assessment. After completion of the 12 weeks treatment phase 8 out of 14 (57.1%) patients with CD and 6 out of 12 (50.0%) patients with UC were in steroid-free remission (complete responders). Another 4 (28.6%) patients in CD and 5 (41.7%) patients in UC were partial responders. Vidofludimus was well tolerated, no drug-related serious adverse events were observed.

Conclusions: This trial provides first evidence of clinical efficacy of vidofludimus in IBD. Although the safety and tolerability profile seems favorable, long-term controlled studies are needed to further investigate its potential as novel IBD therapy.

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1. Introduction

Between 20% and 30% of patients with inflammatory bowel disease (IBD) develop steroid dependence upon steroid-induced remission.^{1–3} For these patients, immunosuppressive therapy is indicated in order to taper steroids and avoid toxicity of long-term corticosteroid therapy.^{4,5} The thiopurine analogues azathioprine and mercaptopurine represent the gold standard for immunosuppression in both Crohn's disease (CD) and ulcerative colitis (UC).^{6,7} Despite their proven efficacy the use of thiopurines is limited for several reasons. The onset of action is delayed for 3 to 6 months necessitating a prolonged steroid weaning period and, despite adequate treatment dosing and duration, at least one third of patients fail to respond to therapy. In addition, recent data have suggested that up to 28% of patients stop medication due to intolerable side effects.⁸ Alternatives for long-term remission maintenance are scarce. Methotrexate (MTX) is the established second-line immunosuppression in CD,⁹ but remission maintenance results are rather disappointing.¹⁰ Furthermore, MTX exhibits a clinically relevant toxicity profile.^{11–13} The anti-TNF antibody infliximab has been tested in combination with azathioprine in steroid-dependent CD.¹⁴ Although the combination of both agents was more effective than azathioprine alone results were significantly worse in those patients with a previous failure of azathioprine emphasizing the importance of concomitant thiopurine treatment. Furthermore, long term results from this study and large controlled infliximab trials¹⁵ were rather poor. In steroid-dependent UC no alternatives to thiopurine therapy have been established and the evidence of efficacy with MTX and infliximab is limited to small case series. Therefore, alternatives for standard immunosuppressive therapy in steroid-dependent IBD are urgently needed.

Vidofludimus (SC12267, 4SC-101) is a novel small molecule with a dual mode of action. Vidofludimus *in vitro* inhibits the proliferation of activated T- and B-cells via blocking the key enzyme of the *de novo* pyrimidine synthesis dihydroorotate dehydrogenase (DHODH).¹⁶ Furthermore, vidofludimus inhibits the expression of pro-inflammatory cytokines like interleukin-17 (IL-17A and IL-17F) and interferon-gamma by interference with the JAK/STAT and NFκB pathways.^{17,18}

In vivo vidofludimus has been shown to improve both TNBS- and DSS-induced colitis in mice.¹⁷ Clinical experience in humans exists from two studies in healthy volunteers and two studies with rheumatoid arthritis (RA) patients. In a randomised, double-blind, placebo-controlled trial in 121 patients with RA 35 mg of vidofludimus induced response (ACR20) in about 50% of patients and was effective especially in the subgroup of DMARD pre-treated patients.¹⁹ In a second trial with 241 RA patients on methotrexate background vidofludimus demonstrated anti-inflammatory activity and a safety profile similar to the placebo group (preliminary, unpublished data). We conducted a 3-month open-label study to evaluate the efficacy, safety and tolerability of vidofludimus in steroid-dependent IBD. The objective of the trial was to investigate if disease control in an IBD population in remission could be transferred from steroids to vidofludimus.

2. Materials and methods

2.1. Patients

Thirty-four patients (18 females; 16 males; median age 40.5 years; range 22–71 years) with steroid-dependent CD ($n=18$) and UC ($n=16$) were enrolled in this open-label, prospective study (Table 1). The median duration of disease in CD was 8.2 years (± 9.8 years) and 3.5 years (± 3.2 years) in UC. All patients were in remission at baseline while on systemic steroids (see study protocol). The median individual prednisolone threshold dose for relapse was 10 mg/day in CD (range 0–17.5 mg/day) and 15 mg/day in UC (range 10–17.5 mg/day). No concomitant medications apart from steroids were allowed. Fifteen patients had received azathioprine, mercaptopurine (1), methotrexate (2), adalimumab (3) or infliximab (2), respectively in their prior disease history.

2.2. Inclusion and exclusion criteria

All patients had a diagnosis of CD or UC confirmed by established criteria including endoscopy and histology. All

Table 1 Patient demographics and baseline characteristics.

Patients enrolled (ITT analysis set)	34
Ethnic origin	Caucasian
Median age (range)	40.5 years (22–72 years)
Ratio male:female	16:18
Mean height (SD)	1.72 m (\pm 0.12 m)
Mean weight (SD)	73.38 kg (\pm 18.32 kg)
Mean BMI (SD)	24.64 kg/m ² (\pm 4.97 kg/m ²)
Cigarette smoker (<20 cigarettes/day)	9 (CD = 8; UC = 1)
Ratio CD:UC	18:16
Ratio male CD:UC	5:11
Ratio female CD:UC	13:5
Mean duration of disease (SD)	CD 8.2 years (\pm 9.8 years) UC 3.5 years (\pm 3.2 years)
Median CDAI/CAI at baseline (range)	CDAI:70.5 (4–229) CAI:0.5 (0–3)
Median prednisolone threshold dose at baseline (range)	CD 10 mg/day (0–17.5 mg/day) UC 15 mg/day (10–17.5 mg/day)

(CDAI range from 4 to 229 due to incorrect calculation of baseline CDAI in one patient).

patients had a steroid-dependent course of disease defined as follows:

- unable to taper steroids completely within 3 months of starting steroids or
- previously relapsed within 2 months after stopping steroids.

Reasons for exclusion were short bowel syndrome, present colostomy or ileostomy, relapse during screening, history or existence of active infections including tuberculosis, HIV, hepatitis B or C, previous opportunistic infections, vaccination with life attenuated viruses within 4 weeks prior to study entry, history or existence of urolithiasis, pregnancy, serious second illness, active cancer or history of cancer, compromised hepatic or renal function and prohibited medication according to study protocol (see below).

2.3. Rationale for the study design

Because data about onset of action of vidofludimus in humans were not available and based on pre-clinical safety data for three months only we decided to include patients with steroid-dependent disease in remission in this study. Efficacy of vidofludimus should be demonstrated after tapering steroids in the proportion of patients with steroid free remission and patients reducing their individual threshold dose. Furthermore, during an observational follow-up period without vidofludimus we were able to determine the proportion of patients relapsing off vidofludimus.

2.4. Study design

Patients received 35 mg of vidofludimus once daily for 12 weeks. No IBD-related co-medication was allowed. In case of prior immunosuppressive treatment, therapy with azathioprine, 6-mercaptopurine, methotrexate, calcineurin-inhibitors or anti-TNF-antibodies had to be stopped three months prior to study entry. 5-ASA compounds had to be stopped four weeks and budesonide one week prior to study entry, respectively. Patients had to be in stable remission for two weeks prior to study entry while on steroid treatment. In case of active disease and a history of steroid dependence remission was induced by steroids prior to entry into the study. Patients were stratified into three steroid arms (40 mg/day, 30 mg/day or 20 mg/day starting doses) according to their individual threshold dose for relapse in order to avoid unnecessary steroid doses. Out of 26 patients evaluable for efficacy analysis (mITT) 6 patients entered the study on 40 mg/day steroids (23%), 6 patients on 30 mg/day (23%), and 14 patients on 20 mg/day (54%). Steroids were tapered from week 1 in the group starting with 40 mg/day, from week 2 in the group starting with 30 mg/day and from week 3 in the group starting with 20 mg/day. From week 3 all patients received the same prednisolone dose tapering steroids according to Fig. 1 until week 8. During the last four weeks of the trial patients were steroid-free receiving vidofludimus only.

The study medication was provided by 4SC AG, Planegg-Martinsried, Germany. The study was approved by the local ethical committees of all centres and written informed consent was given by every patient prior to study entry. The study was conducted according to the Declaration of Helsinki and in accordance with the guidelines of Good Clinical Practice.

2.5. Study end-points

The primary endpoint of the study was the number of patients with response to vidofludimus (complete and partial response). Complete response was defined as steroid-free clinical remission at week 12, while partial response was defined as being in remission at any steroid dose equal or lower than the individual threshold dose for relapse of the individual patient. The threshold dose is defined as the individual steroid dose at which a patient experienced a relapse in medical history. Remission is defined as CDAI \leq 150 (CD) or CAI \leq 4 (UC), while a relapse is defined as CDAI $>$ 220 (CD) or CAI $>$ 6 (UC). Secondary endpoints included CDAI/CAI at each visit, CRP, ESR, calprotectin, IL-17, and change of prednisolone threshold dose at week 12 or at the time of relapse.

2.6. Safety laboratory

Laboratory controls for haematology, coagulation status, clinical chemistry including liver and kidney function, C-reactive protein, erythrocyte sedimentation rate, vidofludimus plasma levels, IL-17 serum levels, faecal calprotectin, and urine analysis were regularly performed during the 12 week treatment period.

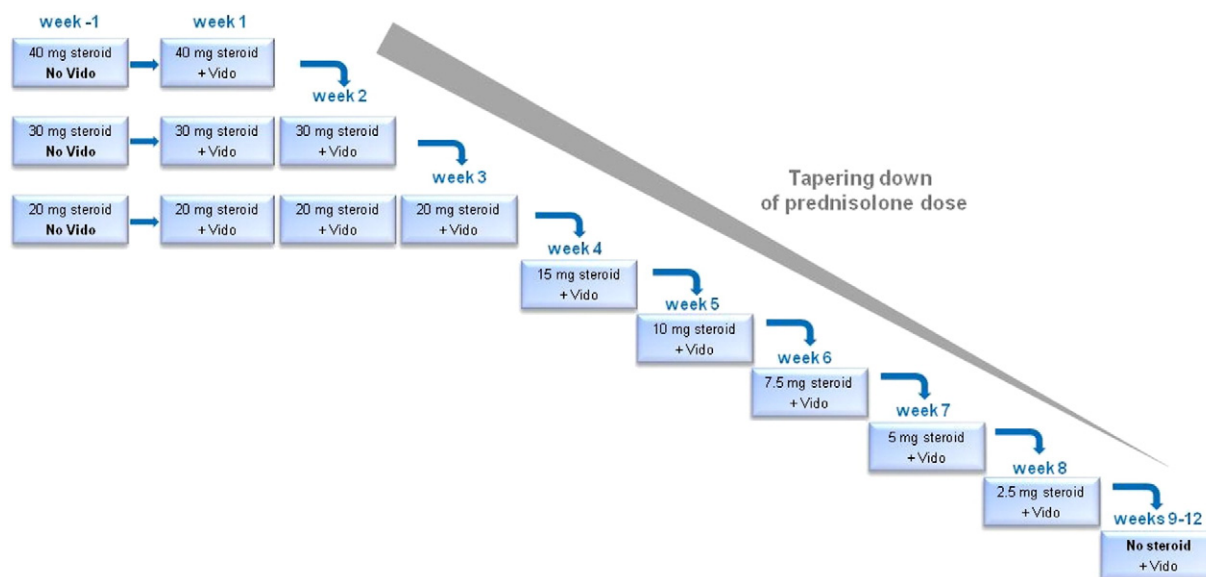


Figure 1 Study design and steroid tapering scheme.

2.7. Statistical analysis

All patients who fulfilled the inclusion criteria and received at least one single dose of study medication were included in the intention-to-treat analysis (ITT, $n=34$). All patients with a minimum of efficacy variables were included in the modified ITT analysis set (mITT). After exclusion of eight patients due to various reasons (see below) the mITT population comprised 26 patients eligible for the assessment of the primary efficacy endpoint. If not indicated specifically, variables are described as medians with ranges throughout the text. The Wilcoxon–Mann–Whitney test was used for the analysis of steroid reduction. A p value of <0.05 was considered to be statistically significant.

3. Results

Thirty-four patients received treatment and were included in the intention-to-treat (ITT) analysis. Eight patients had to be prematurely withdrawn and excluded from the assessment of the primary efficacy endpoint due to non-compliance (2), wrong inclusion (3), major protocol violation (1), adverse event (1) or withdrawal of informed consent (1). Therefore, the modified intention-to-treat (mITT) analysis comprised 26 patients.

3.1. Clinical remission and response in Crohn's disease and ulcerative colitis

Response rates of vidofludimus as the primary efficacy endpoint of the trial in Crohn's disease patients are shown in Fig. 2. After completion of the 12 weeks treatment phase 8 out of 14 patients (57.1%) were in remission off corticosteroids (complete responders). Another four patients (28.6%) were in remission at a corticosteroid dose equal or lower than their individual threshold dose for relapse (partial responders). Two patients (14.3%) were non-responders.

Response rates of vidofludimus as the primary efficacy endpoint of the trial in ulcerative colitis patients are also shown in Fig. 2. After completion of the 12 weeks treatment phase 6 out of 12 patients (50%) were in remission off corticosteroids (complete responders). Another five patients (41.7%) were in remission at a corticosteroid dose equal or lower than their individual threshold dose for relapse (partial responders). One patient (8.3%) failed to respond.

In summary, a total response rate of 88.5% (23 of 26 patients) was observed in the mITT population (complete and partial responders). Evaluating the 8 patients excluded from the mITT analysis set as non-responders, total response rate in the ITT population ($n=34$) was 67.6% (23 out of 34 patients). Also in the ITT analysis set total response rates for Crohn's disease and ulcerative disease patients were comparable (66.7% and 68.8%, respectively). Forty-four percent (8 out of 18 patients) of patients with Crohn's disease and 37.5% (6 out of 16 patients) of patients with ulcerative colitis were complete responders in the ITT population.

3.2. Subgroup analyses

Twelve patients of the mITT population had received azathioprine or methotrexate in their prior history. Medication had been stopped in six patients due to intolerance and in four due to lack of efficacy, three patients only reported good efficacy. Complete response (total of 14 patients) to vidofludimus was slightly higher in AZA/MTX-naïve patients (9/14=64%) compared to complete responders with AZA/MTX pre-treatment (5/14=36%), while partial response (total of 9 patients) to vidofludimus was reported in 4 of 9 (44%) AZA/MTX-naïve patients compared to 5 of 9 (56%) AZA/MTX-pretreated patients. 1 out of 3 (33%) non-responders was AZA/MTX-naïve, while 2 of 3 (67%) non-responders were pretreated with immunosuppressants. Within the AZA/MTX pretreated sub-population ($n=12$) of the mITT analysis set no correlation between efficacy of prior immunosuppressive treatment and response to vidofludimus could be observed.

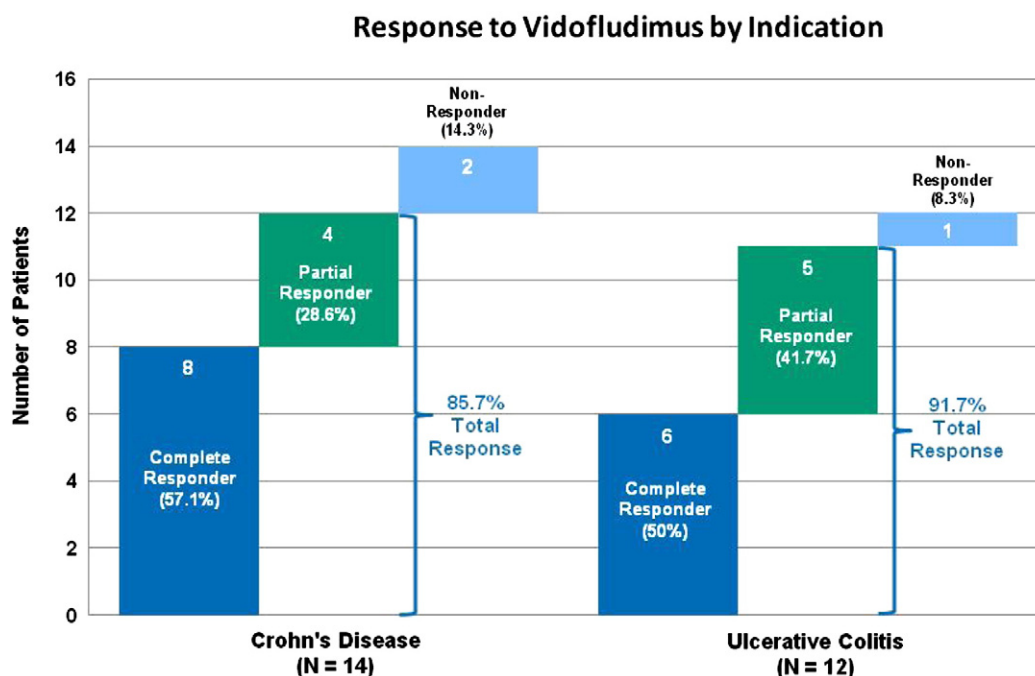


Figure 2 Response rates in Crohn's disease and ulcerative colitis (mITT).

3.3. Steroid reduction according to the individual threshold dose

Overall, median prednisolone dose decreased from 20 mg/day (range 20–40 mg/day) at baseline to 0 mg/day (range 0–10 mg) at week 12 (data not shown). As stated above 14 patients were completely weaned from corticosteroids. Change of prednisolone threshold dose between baseline and end of the study is illustrated in Fig. 3. All complete responders ($n=14$) were in steroid-free remission at the end of the study. In addition, median prednisolone threshold dose of partial responders ($n=9$) decreased significantly ($p<0.001$) from 10 mg/day (range 10–17.5 mg/day) to 0 mg/day (range 0–7.5 mg/day). All m-ITT patients except the three non-responders achieved a relapse-free prednisolone dose significantly lower ($p<0.001$) compared to their individual threshold dose (data not shown).

3.4. Follow-up data

Complete responders ($n=14$) had follow-up visits at weeks 20 and 36 to inquire the occurrence of relapses since the end of study treatment at week 12. Only 5 out of 14 (36%) complete responders were relapse-free until week 36, while 9 out of 14 (64%) complete responders experienced relapses either before week 20 (4) or week 36 (5).

3.5. Biomarker

Compared to baseline (median CRP 2.2 mg/l in the mITT population), CRP values remained unchanged or relatively stable over time, except at Visits 6 and 8, where CRP values had increased (data not shown). Subgroup analyses showed a similar time course of CRP changes in both, complete

and partial responders as in the overall population. Increases in CRP values were more pronounced in the partial responder subgroup. Similar results were obtained with ESR and calprotectin (data not shown). IL-17 serum concentrations were below the limit of quantification for all tested patients except two patients, therefore, IL-17 data were not evaluated.

3.6. Safety

Vidofludimus was safe and well tolerated by the majority of patients. No clinically relevant changes for pulse rate, blood pressure, ECG, body temperature, hematology and biochemistry were recorded. A total of 75 adverse events (AEs) were reported in the ITT analysis set (53 mild, 18 moderate, 4 severe). Nineteen AEs were judged by the investigators as “possibly” or “probably” drug-related including nasopharyngitis, abdominal pain, fatigue, insomnia, glucosuria, leucocyturia, microhematuria, musculoskeletal pain, myalgia, tachycardia, and dyspepsia (Fig. 4). Four out of 6 reported cases of microhematuria based on home-based dipstick test results were not confirmed by laboratory analysis. Three patients stopped therapy due to adverse events, all patients had hematuria. In one patient pyelonephritis and microhematuria were diagnosed and treated and the patient recovered. This AE was judged by the investigator as unlikely related to vidofludimus. In the second patient several positive dip-stick results could not be confirmed by urine sediment analysis. In the follow-up no positive dipstick results were reported. The third patient had hematuria after intake of amoxicillin for sinusitis. In parallel the patient developed a flare of disease. The patient was withdrawn from the study and hematuria was judged as possibly related to the study drug. Only after the end of the study, it was

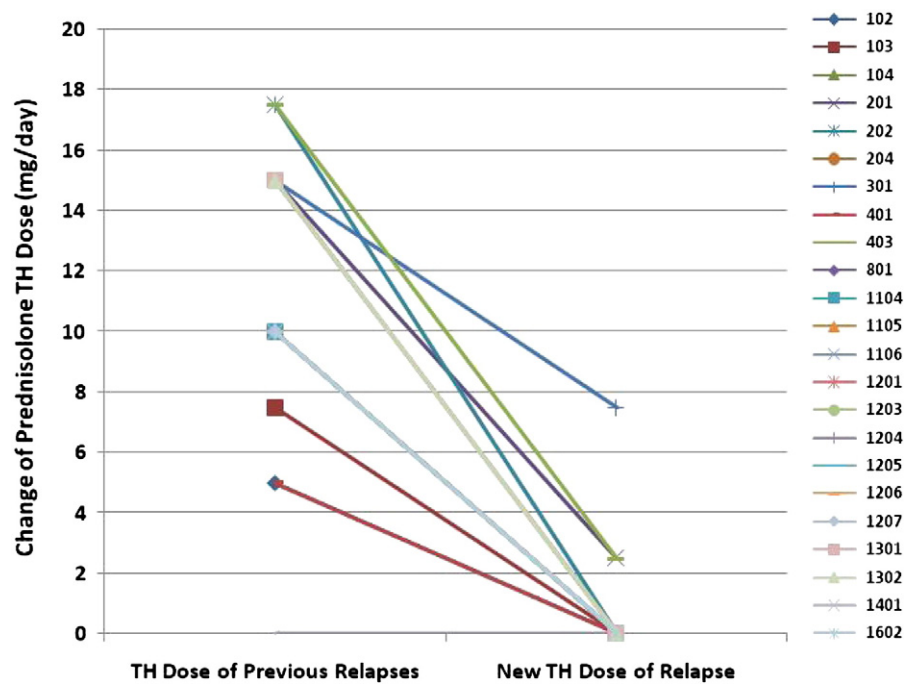


Figure 3 Change of the individual prednisolone threshold dose (TH) of partial and complete responders ($n=23$). The new threshold dose of relapse is set to 0 for complete responders. Curves of several patients graphically overlap.

noted that the patient had been enrolled despite the history of urolithiasis.

Two serious adverse events (SAEs) with hospital admission due to pre-existing urolithiasis were reported in one patient after the end of treatment: hydronephrosis and lithotripsy in a later hospital stay. Investigators judged these SAEs as not related to vidofludimus. Therefore, no drug-related SAEs were reported.

4. Discussion

The thiopurines azathioprine and mercaptopurine are effective in the treatment of steroid-dependent IBD, but share the disadvantage of a delayed onset of action and several side effects. Results for alternative immunosuppressive long-term options including methotrexate and anti-TNF antibodies have not been convincing. Vidofludimus, a novel oral

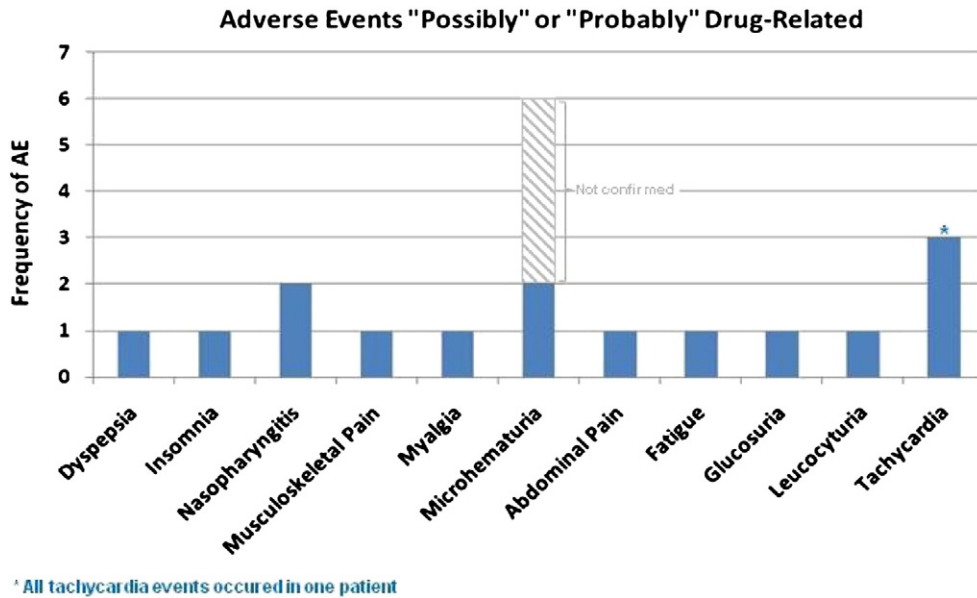


Figure 4 Adverse events profile.

immunomodulator inhibiting DHODH and pro-inflammatory cytokine release, has shown both *in vitro* and *in vivo* immunosuppressive capacity.^{16,17} Furthermore, first clinical results from patients with rheumatoid arthritis are promising.¹⁹ The aim of this study was to investigate the efficacy and tolerability of vidofludimus in steroid-dependent IBD.

Overall, 88.5% of patients responded to treatment with vidofludimus. 54% achieved complete response (complete weaning from systemic steroids) and a further 35% were able to reduce steroids below their individual threshold dose for relapse. There was no difference in response rates between patients with CD and UC. Steroid doses could be significantly reduced compared to individual threshold doses prior to study entry. Thus, besides the complete responders also the partial responders experienced a significant clinical benefit. These results are very promising and are at least comparable to results reported for the established immunosuppressants in IBD. Azathioprine enables steroid withdrawal in roughly half of patients in controlled clinical trials.⁷ Methotrexate has been used in steroid-dependent CD resulting in steroid-free remission in 39% of patients.²⁰ In a controlled trial infliximab has been tested in steroid-dependent CD randomized to receive azathioprine and infliximab or azathioprine and placebo.¹⁴ Patients in the infliximab group had significant higher remission rates throughout the trial with a loss of response from 57% at week 12 to 40% at week 52. Interestingly, this effect seems to rely substantially on concomitant azathioprine therapy. Remission rates were significantly higher in the subgroup of patients naive to azathioprine when compared to patients with previous failure to azathioprine (52% vs. 27%, the latter not being superior to placebo).

In UC azathioprine has been shown to induce steroid-free remission in steroid-dependent patients in small trials.^{21,22} The best evidence comes from a recent controlled trial by Ardizzone achieving steroid-free remission in 58% of patients compared to only 21% in the 5-ASA control group.²³ Results for other immunosuppressive therapies in UC are scarce. In a small case series methotrexate enabled steroid weaning in only 14.3% of patients.²⁴ It has to be stated that in this study the methotrexate dose was lower (15 mg/week) than the effective dose in CD (25 mg/week) similar to the only controlled (and negative) trial on methotrexate in UC so far.²⁵ Small retrospective case series with higher doses of methotrexate have shown moderate efficacy.^{26–28} Results for infliximab in steroid-dependent UC are limited to small uncontrolled case series only and suggest some clinical benefit.^{29–31} It is important to note that 42% (5/12) of our mITT patient population with azathioprine or methotrexate pre-treatment had failed prior immunosuppressive treatment with these agents before study entry. Even in this subgroup response to vidofludimus was achieved in all five patients (3 complete responders and 2 partial responders).

Although thiopurines are generally well tolerated, toxicity may be a major problem. According to recent data, up to 28% of patients with IBD stop azathioprine treatment due to intolerable side effects⁸ and at least 19% do so with methotrexate.¹¹ In the present and the previous two rheumatology trials, vidofludimus was well tolerated by the majority of patients. Most of the observed AEs were mild and unspecific. The most common AE under both, thiopurine and methotrexate therapy, is nausea and vomiting. Remarkably,

none of the patients experienced nausea or vomiting under vidofludimus treatment. Major problems in both, thiopurine and methotrexate treatment, may occur regarding bone marrow and liver toxicity. Bone marrow toxicity is observed in about 2–5% of patients treated with azathioprine or mercaptopurine^{8,32,33} and in about 4% of patients under methotrexate.¹¹ Elevated liver function tests are frequently observed under thiopurine therapy and represent about 10% of AEs that lead to treatment discontinuation. Both, bone marrow and hepatotoxicity, did not occur in our vidofludimus treated patients. Withdrawal from this study due to adverse events to vidofludimus occurred in only three patients. All these patients experienced microhematuria and this was judged as at least possibly related to vidofludimus in two patients. Overall microhematuria in dipstick analysis occurred in six patients but was not confirmed by sedimentation microscopy in four. The reason for microhematuria remains speculative but may be caused by intermittent cystitis in single patients. Nevertheless, there seems to be a signal that has to be followed up in future long-term trials. However, only two single microhematuria cases (one in the vidofludimus and one in the placebo group) were reported in the recently completed RA trial with 241 patients.

Our study has several limitations. First of all this study was small and had an uncontrolled design. When planning the study, safety data from pre-clinical studies were available for three months only. Therefore, the study design with this very selective group of steroid-dependent patients was chosen to investigate the effect of vidofludimus after 12 weeks of treatment. Long-term efficacy and safety results are urgently needed. Information regarding individual steroid threshold doses in steroid dependent disease from patient history is prone to failure and the threshold dose may not always be stable over time. Therefore, we cannot exclude that some patients with frequent relapsing disease might have been able to reduce steroids without vidofludimus. Nevertheless, our long-term observational data over 20 and 36 weeks show a high relapse rate in complete responders (64%) after stopping vidofludimus giving strong indirect evidence for its efficacy.

In conclusion, vidofludimus was well tolerated and induced response in steroid-dependent IBD. Now larger controlled clinical trials are needed to confirm these promising results and to elucidate the potential of vidofludimus in remission induction and/or maintenance in IBD.

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