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Feasibility and response to budesonide as topical corticosteroid therapy for acute intestinal GVHD

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Summary:

Therapy of acute intestinal GVHD is still one of the main challenges after allogeneic transplantation. Increasing systemic immunosuppression (IS) is the first choice and includes corticosteroids and lymphocyte antibodies, often associated with severe side-effects. In inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, topical steroid therapy is used very successfully. Because of the similarity between these and acute intestinal GVHD we conducted a trial with oral budesonide (Budenofalk), a new topically active glucocorticoid, to treat patients with acute GVHD ⩾ grade II. After a diagnosis of aGVHD ⩾ grade II, 22 patients received increased IS, mainly systemic corticosteroids, and additionally budesonide 9 mg/day divided into three doses. Improvement in aGVHD, infectious side-effects, reduction of systemic IS and outcome were documented. Results were compared with the results of 19 control patients, who were treated only by increasing IS dose. In 17/22 patients (70%), treated with budesonide, the acute intestinal GVHD resolved and no relapse occurred after decreasing the systemic IS, while continuing budesonide. In only 8/19 patients in the control group did the acute intestinal GVHD resolve and 2/8 patients had a relapse of intestinal GVHD after decreasing IS, with an overall response of 33%. No severe intestinal infections occurred. We conclude that budesonide may be effective in acute intestinal GVHD as a topical corticosteroid and prospective, randomized studies should demonstrate its efficacy in allowing reduction of systemic immunosuppressive therapy, and its side-effects.

Keywords: acute intestinal GVHD; budesonide; endoscopy; topical corticoid therapy

Successful treatment of hematological malignancies by allogeneic transplantation is commonly limited by relapse of the malignancy, by infection or by GVHD. The gastrointestinal tract is one of the prominent target organs involved in acute GVHD after allogeneic transplantation and morbidity to it is an important cause of death. Therapy includes intensification of immunosuppressive therapy (eg cyclosporin A (CsA), monoclonal antibodies, increased doses of systemic glucocorticoids, ATG).[1] Systemic corticosteroid therapy may lead to severe side-effects such as myopathy, osteoporosis, cataract and increased susceptibility to infections. With beclomethasone dipropionate, a topical corticosteroid administered orally, promising results have been reported in the treatment of acute intestinal GVHD.[2,3] Budesonide (BUD) is a new topical active glucocorticoid with a high affinity for the glucocorticoid receptor[4] and high anti-inflammatory activity. Budenofalk capsules (Dr Falk Pharma GmbH, Freiburg, Germany) are a preparation releasing budesonide at pH ⩾ 6.4 which is mainly resorbed in the terminal ileum and ascending colon.[5] Half-life of this preparation is 3.0 h.[6] The systemic bioavailability of BUD is extremely low[7] due to rapid first pass metabolism in the liver.[8] Budesonide is already used very safely and successfully in bronchial asthma and allergic rhinitis[9] and in chronic inflammatory bowel diseases (ulcerative colitis[10] and Crohn's disease[4,5]). It has been shown that the side-effects in the BUD treatment group in Crohn's disease were comparable to a placebo group.[11] In patients with ulcerative colitis it was also demonstrated that treatment with BUD is safe, and as effective as treatment with prednisolone. Interestingly, the typical corticoid side-effects are dramatically diminished and the plasma corticoid level remained normal in the BUD treatment group in contrast to the systemic prednisolone treatment group.[12] Additional studies showed that treatment with a daily dose of 9 mg BUD does not disturb pituitary–adrenal function.[13–15] Because of the promising results in the treatment of inflammatory bowel disease, all patients from December 1994 to April 1997 with acute GVHD of the gastrointestinal tract ⩾ grade II were offered treatment with oral budesonide in addition to standard increases in systemic immunosuppression. Reduced treatment efficiency was unlikely as budesonide was given in addition to standard increases in systematic immunosuppression after a diagnosis of acute intestinal GVHD. The aims of this study were to avoid and/or reduce corticoid side-effects by rapid tapering of the systemic corticosteroid dose and to reach a faster resolution of aGVHD. Here, we show the feasibility of budesonide therapy and the response to this drug in 22 patients with acute intestinal GVHD. Clinical grading, macroscopic staging of endoscopically visible lesions and histological grading were used as parameters. Data of efficacy from all adult patients since 1990 until April 1997, who suffered from acute intestinal GVHD ⩾ II and did not

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receive BUD were reviewed as a control group in respect of clinical characteristics and outcome. These patients did not receive BUD because they were treated before BUD was available ($n = 13$) or because they refused to participate ($n = 6$).

Patients and methods

Between July 1990 and April 1997, 274 patients underwent allogenic bone marrow or peripheral stem cell transplantation at the University Medical Center and Children's Hospital of the Albert Ludwig University Freiburg. During this period 41 patients were diagnosed with acute intestinal GVHD > grade I (15%) (Table 1). Since December 1994 BUD has been available and all of these patients were asked to participate in a trial with addition of BUD. Nineteen adults and three children (nine females/13 males) agreed and received budesonide for intestinal GVHD. The median age was 31 years (range 6–53). Underlying diseases were CML $n = 4$, AML $n = 6$, ALL $n = 6$, multiple myeloma (MM) $n = 2$, JMML $n = 1$ and MDS $n = 3$. In 10 patients a sibling, in 11 patients a MUD and in one patient a haploidentical relative served as the donor. Conditioning therapy consisted of BU/CY/MEL ($n = 1$), BU/CY ($n = 15$), TBI/CY ($n = 3$), TBI/VP16/CY ($n = 3$). Nine patients received CsA/MP/MTX, $n = 6$ CsA/MP, $n = 1$ CsA/MTX, $n = 3$ CsA/MP/ATG and $n = 2$ only CsA for GVHD prophylaxis (Table 1).

Table 1 Patients' characteristics

	Study group n = 22	*Control group n = 19*
Study period	1994–1997	1990–1997
		1990 $n = 1$
		1991 $n = 3$
		1992 $n = 2$
		1993 $n = 3$
	1994 $n = 4$	1994 $n = 4$
	1995 $n = 12$	
	1996 $n = 4$	1996 $n = 4$
	1997 $n = 2$	1997 $n = 2$
F/M	9/13	7/12
Age (years) Median range	31 (6–53)	38 (21–54)
Donor		
MUD	11	11
Sib	10	8
MmSib	1	
Diagnosis		
CML	4	6
AML	6	4
ALL	6	2
MM	2	1
JMML	1	
MDS	3	3
SAA		3
Onset of aGVHD		
Day + (range)	30.5 (10–310)	38 (15–73)
Other sites involved	11 (50%)	13 (70%) NS

NS = not significant.

Nineteen adult patients (seven female; 12 male) with a median age of 40 years (range 21–54) who were treated for acute intestinal GVHD ≥grade II without budesonide because they denied participation ($n = 6$) or were treated before December 1994 ($n = 13$), served as a control group. In 11 patients a MUD and in eight patients a sibling served as graft donor (CML $n = 6$, AML $n = 4$, SAA $n = 3$, ALL $n = 2$, MM $n = 1$, MDS $n = 3$).

All transplants were performed as standard procedures as published before.[16] Routinely on day +30 and +100, or in the case of diarrhea, a sigmoidoscopy was performed for macroscopic and histologic evaluation of the colon. In cases of vomiting, nausea and stomach pain a gastroscopy was performed. Clinical grading of GVHD was defined according to Glucksberg.[17] Histological classification of the biopsies for aGVHD was done according to Snover[18] and Lerner *et al*[19] and macroscopic grading was done according to Kreisel.[20] None of the patients had culture or histologically proven intestinal bacterial, fungal or viral infections. After diagnosis of acute GVHD ⩾ II in one of the above mentioned gradings immunosuppressive therapy was intensified mainly by increasing the systemic corticosteroid dose to a total dose of 2×1 mg/kg bw, and by increasing CsA to reach an estimated blood level of 250 ng/ml whole blood. For prophylaxis of infectious complications patients received metronidazole 800 mg/day, ciprofloxacin 500 mg/day and amphothericin B 0.5 mg/kg bw/day. Since 1994 pre-emptive CMV therapy has been initiated in the event of two positive PCR samples on two occasions, but even before 1994 no patient suffered from CMV colitis. Additionally, patients in the study group received budesonide (Budenofalk) after informed consent, at a daily dose of 9 mg divided into three doses in order to obtain constant corticoid levels in the gut. Diarrhea volume and frequency as well as abdominal pain were registered. Stool analysis was performed regularly for micro-biological pathogens. A control endoscopy was done, if clinical symptoms did not resolve. If the symptoms improved the systemic corticoid dose was rapidly tapered, but the dosage of budesonide was still maintained. Resolution of GVHD was documented. Decrease of stool volume and frequency of bowel movements were taken as markers for the resolution of intestinal GVHD. Potential side-effects of budesonide such as vomiting, nausea were documented. Special attention was paid to possible occurrence of a new intestinal infection by weekly, regularly stool surveillance cultures.

Results

Clinical, endoscopic and histological results (Table 2)

Intestinal GVHD was observed at a median of 30.5 days (range 10–310) after transplantation in the study group and at a median of 35 days (range 15–75) in the control group. In 21/22 patients in the BUD group a sigmoidoscopy was performed and GVHD grade I/II was diagnosed in $n = 9$ (39%), grade III in $n = 8$ (34%) grade IV in $n = 2$ (9%) cases. In 1/21 patients macroscopic appearances were

Table 2 GVHD grading

	Study group	*Control group*
Endoscopic findings (UGI and LGI)	*n = 20*[a] *(%)*	*n = 19 (%)*
Grade		
I/II	10 (50)	9 (48)
III	8 (40)	6 (31)
IV	2 (10)	4 (21)
Histology grading (UGI and LGI)	*n = 14*[b] *(%)*	*n = 19 (%)*
same as endoscopic	8 (57)	17 (89)
1 grade difference	4 (29)	2 (11)
2 grade difference	2 (14)	
Clinical grading (LGI)	*n = 21 (%)*	*n = 17*[b] *(%)*
same as endoscopic	11 (55)	11 (65)
1 grade difference	10 (45)	5 (29)
2 grade difference		1 (6)

UGI = upper gastrointestinal tract; LGI = lower gastrointestinal tract.
[a]Not all children received endoscopy.
[b]Complete data could not be obtained in all patients.

defined as normal and in one patient as colitis. In four patients an additional gastroscopy was performed revealing grade I and II in three cases, and grade IV in one case. In UPN 960243 gastroscopy only was carried out which was macroscopically grade II. Macroscopic and histological grading of intestinal GVHD were reviewable in 14 cases. In 8/14 (57%) the same grade was seen, in 4/14 (29%) it differed by one, and in 2/14 (14%) by two grades. The clinical course of the GVHD was graded by experienced practitioners. For the lower GI tract, grade I/II was diagnosed in 10/21 (47%), grade III in 5/21 (24%) and grade IV in 6 /21 (29%) cases. Corresponding macroscopic results were identical in 11/21 cases (55%) and differed only by one grade in all other cases (45%), mainly in patients with grade III or IV.

For patients in the control group, endoscopic examination of the gut showed aGVHD grade II in nine cases (47%), grade III in six patients (32%) and grade IV in four patients (21%). In 17/19 patients (89%) endoscopic grading was identical with the histological examination, in 13/19 endoscopy showed the same result as the clinical grading and in 11/19 clinical and histological situations were identical.

Apart from the GVHD of the GI tract, 11/22 patients (50%) in the study and 13/19 patients (70%) in the control group had additional manifestations of GVHD at other sites, mainly liver and skin.

Immunosuppression at start of BUD therapy

At the start of BUD therapy 19/22 patients were still receiving systemic MP and CsA and the MP dose was increased mostly by doubling the dose. UPN 960215 was off MP, which was reintroduced with 1 mg/kg bw. UPN 950180, who received only CsA for GVHD prophylaxis, was treated only with BUD without MP, having clinical and histologically proven aGVHD grade III.

Duration of BUD therapy and side-effects

Twenty patients received BUD for a median period of 24 days (range 6–70). Two patients (10%) were enrolled in the study but no final results could be obtained, because on day 7 or 8 respectively, they could no longer swallow the capsules and received only i.v. immunosuppression (MP and CsA). Side-effects were not observed in any patient, in particular, no severe infections of the bowel. After initiating oral BUD, *Torulopsis glabrata* was found in the stool of only one patient (UPN 950159) as a new intestinal pathogen.

Resolution of GVHD in the study group (Table 3)

Clinical improvement of the intestinal GVHD was defined as decrease of stool frequency and volume. In five cases it was verified by macroscopic re-evaluation of the colon. As soon as improvement in intestinal GVHD was documented, the dose of MP was reduced to 50% of the maximum dose. In 17/22 patients (77%) (nine patients with grade II, five patients with grade III and three patients with grade IV) intestinal GVHD resolved and no relapse occurred. Both patients who could not continue the budesonide, because of deterioration in performance status, and three patients, who did not improve during BUD therapy, died due to acute GVHD with multi-organ failure. All five had grade III (two patients) or grade IV (three patients) intestinal GVHD and involvement of other organs. Four had a MUD/mismatched related and one had a matched related donor. Improvement was seen at a median of 12 days (range 3–28) after increasing the MP dose and starting the BUD therapy. The median systemic methylprednisolone dose until improvement or death was 3.8 g (range 1–12 g) and the median budesonide dose was 193 mg (54–725 mg).

Immunosuppression during and at the end of BUD

In 17 patients with improvement of GVHD it was possible to decrease the MP dose at a median of 12 days (6–25). Therapy with BUD was continued in all cases until the dose of MP was reached, which was given to patients before the

Table 3 Therapy and outcome

	Study group n = 22	*Control group n = 19*	
Methylprednisolone increased	20 (90%)	19 (100%)	
Budesonide therapy	22 (100%)	—	
Resolution of aGVHD	17 (77%)	8 (42%)	
Relapse	0	2 (10%)	
Overall response	17 (77%)	6 (32%)	$P < 0.01$ (significant)
Median day until improvement	12 (3–28)	13 (7–18)	NS

NS = not significant.

onset of GVHD. Thereafter, BUD was discontinued in 8/17 (47%) cases and tapered in 9/17. No relapse of intestinal GVHD occurred after decreasing the MP dose while patients were still on BUD and after cessation of BUD.

Resolution of GVHD in the control group (Table 3)

After intensification of systemic immunosuppressive therapy, intestinal GVHD resolved in 8/19 patients (42%) but showed no improvement in 11/19 patients (58%). In 2/8 the acute intestinal GVHD relapsed after tapering the corticosteroid dose. Overall, 13/19 patients (68%) died due to aGVHD. The median dose of systemic methylprednisolone until improvement in intestinal GVHD or death in this group of patients was 4.5 g (1–15 g) and the time prior to improvement in the six patients (32%), who survived, was 13 days median (range 7–18).

Discussion

Systemic corticosteroids are the most effective immunosuppressive agents for treatment of aGVHD. The disadvantages are the many side-effects. Through the therapy of Crohn's disease and ulcerative colitis we have learned that inflammatory reactions of the gastrointestinal endothelium induced by immunological processes respond well to topical glucocorticoids (beclomethasone, budesonide, fluticasone).[4,5,21] Both acute intestinal GVHD and Crohn's disease seem to have a similar pathogenic background, in that reactions against intestinal epithelial cells occur. Both diseases present with comparable macroscopic appearances and localization in the gastrointestinal tract. We therefore decided to treat our patients with BUD in addition to standard systemic CsA/MP therapy. The daily dose of 9 mg/day was divided into three doses to keep a constant local corticoid level.[22] In our retrospective survey BUD therapy was feasible and very well tolerated without any enteric infections or local complications, except for one new fungal infection in the stool without clinical significance. In 17/22 patients (77%) receiving BUD the acute intestinal GVHD resolved compared to 42% in the patients without additional BUD (Table 3). These data are similar to the recently published results showing a 71% response to beclomethasone treatment compared to 55% in the control group.[3] In our survey, despite the fast reduction of MP, no relapse occurred while BUD was continued. This was also observed for Crohn's disease in placebo controlled studies, showing that low-dose BUD prolongs time to relapse.[23,24] In our control group, two patients relapsed after decreasing the systemic corticosteroid dose. Overall, in this group only 32% reached a long-term resolution of acute intestinal GVHD without BUD. Although it is a nonrandomized trial these results show a significant difference ($P > 0.01$) in the unpaired *t*-test. Furthermore, our data confirm the importance of endoscopic grading for diagnosis and grading of acute intestinal GVHD, because of the good correlation of endoscopic, histological and clinical classifications of aGVHD (Table 2).[20]

We conclude that the pH-modified budesonide preparation was very well tolerated in patients with acute intestinal GVHD. Early initiation of the budesonide therapy should be performed to stop destruction of the intestinal mucosa or to allow recovery of the endothelium, thereby avoiding bacteremia or fungemia. Our retrospective analysis may form the basis for a randomized study necessary to prove our results and show whether early extensive reduction of systemic immunosuppression is possible to avoid severe corticoid side-effects. In cases of local GVHD of the recto/sigmoid the application of a budesonide foam should be considered, especially in patients who are unable to swallow.

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