Topical therapy is underused in patients with ulcerative colitis☆

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Abstract

The availability of new topical preparations for the treatment of left-sided ulcerative colitis offers a therapy optimization for many patients. Rectal application of steroids and 5-aminosalicylic acid (5-ASA) is associated with fewer side effects and has a higher therapeutic efficacy in left-sided colitis as compared to a systemic therapy. Therefore, we were interested in the use of topical therapy in patients with ulcerative colitis. The key question was whether topical treatment is more frequently used than oral therapy in patients with proctitis and left-sided colitis. Data of 800 patients of the Swiss IBD cohort study were analyzed.

Sixteen percent of patients of the cohort had proctitis, 21% proctosigmoiditis and 41% pancolitis. Topical therapy with 5-ASA or corticosteroids was given in 26% of patients with proctitis, a combined systemic and topical treatment was given in 13%, whereas systemic treatment with 5-ASA without topical treatment was given in 29%. Proportion of topical drug use decreased with respect to disease extension from 39% for proctitis to 13.1% for pancolitis (P = 0.001). Patients with severe colitis received a significantly higher dose of topical 5-ASA than patients in remission.
1. Introduction

Ulcerative colitis (UC) is a chronic relapsing inflammatory disorder of the colon and besides Crohn's disease (CD) one of the two major forms of inflammatory bowel disease (IBD). Its incidence in Europe is estimated to be around 5 to 25 new patients per 100,000 inhabitants per year. The etiology of UC remains unclear and subsequently medical therapies are not available that may completely cure the disease. The clinical presentation of UC is characterized by abdominal pain, diarrhea with or without hematochezia and mucosal ulcerations. UC is limited to the mucosa of the large intestine. It always involves the rectum and shows variable extension to the left side or entire colon. 70% of the UC patients in population based studies exhibit only a proctitis/procto-sigmoiditis or left sided colitis. Only 30% will have extended disease. This may be different in a cohort such as the Swiss IBD cohort study (SIBDCS, 28) which includes 2/3 of hospital treated patients having more severe of extensive disease.

In addition to the varying extent of the disease there is a wide variation in the severity of UC. Clinically mild disease is associated with less than four bowel movements per day, with or without bloody stools but without systemic manifestations. Blood tests in patients with mild disease are usually normal. Moderate disease has been defined as more than four bowel movements per day with minor systemic manifestations. Severe disease description is attributed to patients with more than six bowel movements a day, fecal loss and systemic signs of inflammation. Classifications for disease severity show minor differences, however, the criteria for the discrimination of mild, moderate and severe disease remain more or less the same.

The basic treatment in mild to moderate UC is 5-aminosalicylic acid (5-ASA; mesalazine or mesalamine) irrespective of the disease localization. However, in patients with proctitis or left sided colitis topical application of 5-ASA as suppository, enema or foam preparation is more effective as compared to systemic treatment. Topically administrated steroids are superior to placebo in this situation, however, inferior if compared to topical 5-ASA. Therefore the treatment of choice in mild to moderate left-sided colitis is 5-ASA foams or enemas. During acute flares of the disease enemas are frequently less well tolerated due to their volume of up to 100 ml than suppositories. As usually the rectum is affected by the most severe inflammation while containing the highest number of sensory nerves it is easily understandable that high volume enemas cause discomfort and urgency. Foam preparations are usually better tolerated and accepted by patients with acute flares of left sided colitis. Mesalazin suppositories seem to be well tolerated in patients with proctitis and recommended by the ECCO guidelines as first line treatment.

Compliance and patient acceptance are essential for the success of a rectal therapy. In general patients well accept to perform topical therapy if explained properly. It is not the case that a topical therapy per se is associated with lower adherence and compliance. Only in very severe disease application of topical therapy may cause pain and discomfort. Therefore, topical therapy may be paused during severe disease flares.

As mentioned foam preparations are better tolerated as compared to enemas. 5-ASA foam preparations have a similar distribution pattern as compared to enemas. 5-ASA suppositories in a dosage of 1 g/day are the preferred therapy of mild to moderate proctitis. A meta-analysis of 11 studies showed a median remission rate of 67% for rectal 5-ASA (as compared with 7 to 11% for placebo). A study by Eliakim and co-workers with a low volume rectal 5-ASA foam preparation showed remission rates of 78% in patients with mainly proctitis.

Topical steroids should be used for patients that are intolerant to 5-ASA. However, an additive therapy of topical 5-ASA and steroid may also be beneficial.

In moderate active distal colitis topical 5-ASA therapy in combination with oral 5-ASA therapy has proven to be highly effective (88% response after 6 weeks). A meta-analysis of 33 studies showed that topical 5-ASA is more effective as compared to topical conventional steroids or budesonide. Remission also can be maintained by topical treatment of at least two years duration. For maintenance 3 g of 5-ASA total per week is recommended. A topical therapy in distal UC has several advantages. The majority of patients have a distal disease type. Thus a topical therapy should be applied in the majority of patients with UC as the success rate is higher as compared to oral therapy and side effects are fewer. However, there are reports of an underuse of topical therapies despite guideline recommendations.

Given the above mentioned facts we expected a more frequent use of topical 5-ASA use compared to systemic treatment in patients with proctitis.

The aim of this study was to investigate the use of topical and systemic therapies in patients with ulcerative colitis of the SIBDCS.

2. Methods

Data of the Swiss Inflammatory Bowel Disease Cohort study (SIBDCS) were used to perform this study. The cohort goals and methodology are described elsewhere. The aim of the present study was the characterization of the use of topical versus oral therapies in UC patients within IBD patients included in the SIBDCS. We first performed a descriptive
analysis to assess the use of therapies, based on data collected when patients were included in the cohort. Then a longitudinal data analysis was done in a subgroup of patients where the data is available.

Treatments of interest were classified as follows: systemic (oral 5-ASA, budesonide), topical (topical 5-ASA, topical steroids), combination of both systemic and topical, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), anti-TNF alpha antibodies (infliximab, adalimumab, certolizumab-pegol), other therapies (e.g. antibiotics, steroids), and no therapy at all.

Self-completed SF36 quality of life questionnaires were used to assess life conditions of patients at the different stages of follow-up.

2.1. Statistics

We used QQ-plots to assess the normality of continuous variables. Gaussian variables are presented as mean ± SD and range, while non-Gaussian variables are presented as median, interquartile range (IQR) and range. Categorical data are presented as count and as percentage of the group total. We used chi-squared test to estimate differences between independent groups for categorical variables, and Kruskall–Wallis one way analysis of variance to compare medians of non-Gaussian continuous variables among independent groups. A level of 5% was considered to be statistically significant. Bonferroni’s correction was applied in case of multiple testing.

3. Results

3.1. General description of the study population

Among 1961 patients with IBD enrolled in the Swiss IBD Cohort between 2006 and 2011, 800 (40.8%) were originally diagnosed with UC. During follow-up, 10 patients experienced a change of diagnosis, either to CD or to indeterminate colitis. Therefore, a total of 790 patients were included in this study. 538 of those patients (68.1%) completed a 1st-year follow-up, 381 (48.2%) completed a 2nd-year follow-up, and 263 (33.3%) completed a 3rd-year follow-up.

The baseline clinical characteristics of the study population are presented in Table 1. Pancolitis was found in 40.5% of the patients, whereas proctitis in 16% (Table 1). Males more often had an extensive colitis (44.3% vs 36%) and women a proctosigmoiditis or proctitis (23.3% vs 18.0%, respectively 18.8% vs 14.2%, P = 0.025).

Among the 526 patients that were followed for at least one year and for which disease location was documented, 74 (14.1%) experienced a regression of the disease extension, 40 (7.6%) an expansion of the disease extension.

3.2. Medication

We analyzed the use of medication for all 773 patients with known disease location according to the subgroups of patients with different intestinal involvement. Topical treatment was mainly used in patients with proctitis and proctosigmoiditis. Twenty-nine percent of the patients with proctitis were exclusively orally treated with 5-ASA, whereas topical therapy was given in 25.6% of these patients. A fraction of patients (13%) received oral treatment and topical treatment simultaneously. A total of 50.5% of proctitis patients were treated exclusively with oral or IV medication. The use of systemic drugs was less frequent for proctitis (29.5%) than for the other disease locations (P = 0.009) (Table 2).

In patients with proctosigmoiditis a total 17% of patients were treated topically. Proportion of topical drug use decreased with respect to disease extension from 24% for proctosigmoiditis to 13.1% for pancolitis (P = 0.001) (Fig. 1).

Interestingly the use of immunomodulators differed significantly between the groups. They were most frequently used in patients with left sided colitis, followed by patients with a pancolitis (P = 0.001). However, 4.7% of patients with proctitis and 12.4% of patients with proctosigmoiditis were treated with immunomodulators (P = 0.021) (Table 2).

Table 1 Baseline characteristics of study population.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>429 (54.3)</td>
</tr>
<tr>
<td>Age, y</td>
<td>43 (33–53, 16–85)</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>30 (22–39, 3–78)</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
</tr>
<tr>
<td>Remission: MTWAI 0–3</td>
<td>488 (66%)</td>
</tr>
<tr>
<td>Low/moderate: MTWAI 4–10</td>
<td>215 (29.1%)</td>
</tr>
<tr>
<td>High: MTWAI &gt; 11</td>
<td>36 (4.9%)</td>
</tr>
</tbody>
</table>

The highest dose of topical 5-ASA products was given in patients with proctosigmoiditis. In patients with proctitis the dosage for topical 5-ASA was generally lower (Table 3). The dosage of topical steroids and budesonide did not differ in

3.2.1. Dosage of Topical Treatment

The highest dose of topical 5-ASA products was given in patients with proctosigmoiditis. In patients with proctitis the dosage for topical 5-ASA was generally lower (Table 3). The dosage of topical steroids and budesonide did not differ in
In patients with active disease significantly higher dosages of 5-ASA were prescribed compared to patients in remission (Table 4).

### 3.3. Side Effects of Medical Treatment

Treatment with 5-ASA and budesonide (orally or topically) was significantly less frequently associated with side effects compared to immunomodulator or anti-TNF-alpha antibody treatment ($P < 0.001$) (Table 5). Oral 5-ASA was the most common therapy (336/790, 42.5%), and patients experienced side effects in 13.1% of the cases. The treatment with immunomodulators was frequently associated with side effects (48.5%). Side effects for anti-TNF alpha antibody treatment were described in 24% of the cases (Table 5).
3.4. Change of Treatment

We were interested on how long patients will remain on a topical treatment in contrast to a systemic treatment. For patients under a topical therapy, change of medication occurs more frequently than in those under a systemic therapy (up to more than 50% of the cases). Change is made generally either to a fully systemic treatment (19 cases out of 58, 32.7%), or to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic–topical combined treatment, change of drug is mainly an interruption of the topical treatment (42 cases out of 69, 60.9%). For patients under systemic drugs only, at least 70% does not have to change their therapy at any stage of the follow-up. When they have to, in more than 30% of the cases more than 50% of the cases). Change is made generally either to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic therapy (up to more than 50% of the cases). Change is made generally either to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic–topical combined treatment, change of drug is mainly an interruption of the topical treatment (42 cases out of 69, 60.9%). For patients under systemic drugs only, at least 70% does not have to change their therapy at any stage of the follow-up. When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 over the follow-up). When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 over the follow-up). When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 over the follow-up).

3.5. Quality of Life

We were interested whether the quality of life was different in patients with limited disease in contrast to patients with pancolitis. The physical and mental components were measured by the SF36 questionnaire. Patients with limited disease had similar scores compared to patients with pancolitis. Mental score seemed to be lower in proctosigmoiditis patients than in others, at follow-up 2 (P = 0.036) (Table 7).

4. Discussion

In this study we investigated the use of rectal therapies with 5-ASA and steroids in the Swiss national IBD cohort. Topical treatment was most frequently used in patients with proctitis. The proportion of topical drug use decreased significantly with respect to an increase of intestinal involvement. The data of the SIBDCS show that 57% of the patients had a colitis limited to the rectum or to the left colon. Unexpectedly our study revealed that oral 5-ASA was more frequently given in patients with proctitis than rectal formulations. Several studies showed the efficacy of rectal treatment with suppositories at a dosage of 1 g/day. Rectal foams can be alternatively used. Rectal 5-ASA applications achieve remission rates in the literature around 67%. In another study 78% of patients came into remission using a 5-ASA foam. Topical steroids should be used in patients intolerant or refractory to 5-ASA products. They can be added to a 5-ASA treatment.

In patients with proctosigmoiditis 5-ASA therapy has also been shown to be effective at a dosage of 2 g/day. Interestingly it was demonstrated that the combination of rectal and oral 5-ASA increased the efficiency of treatment. After a treatment period of 6 weeks with 2.4 g of oral 5-ASA 33% had no fecal blood whereas 54% of rectally treated patients and 88% of patients treated with an oral rectal combination treatment did respond to the therapy.

It is unclear why the frequency of rectal therapy is relatively low in Switzerland. The data in the literature clearly show a superiority of rectal treatment compared to oral treatment in patients with proctitis and proctosigmoiditis. We assume that most Swiss gastroenterologists know of these details, therefore other factors seem to influence the treatment decisions. In the follow-up studies in this paper we realized that topical treatment was frequently stopped and not used as a

Table 3 Daily dose given in patients with proctitis, proctosigmoiditis, left sided colitis and pancolitis: The highest dose was given in patients with proctosigmoiditis.

<table>
<thead>
<tr>
<th>Dosage of topical 5-ASA related to the intestinal involvement.</th>
<th>Proctitis</th>
<th>Proctosigmoiditis</th>
<th>Left sided colitis</th>
<th>Pancolitis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>500</td>
<td>2000</td>
<td>1250</td>
<td>1500</td>
<td>1000</td>
</tr>
</tbody>
</table>

Table 4 Topical 5-ASA dosage given in patients in remission, low/moderate activity and high disease activity.

<table>
<thead>
<tr>
<th>Topical 5-ASA dosage and disease activity index (MTWAI)</th>
<th>Remission (0–3) [N = 78]</th>
<th>Low activity (4–10) [N = 51]</th>
<th>High activity (11+) [N = 10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>500</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>IQR</td>
<td>500–2000</td>
<td>500–2000</td>
<td>1000–4000</td>
</tr>
<tr>
<td>Range</td>
<td>125–4500</td>
<td>500–8000</td>
<td>500–8000</td>
</tr>
</tbody>
</table>

Table 5 Past therapies and side effects for stopped therapies.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Past therapy %</th>
<th>Side effect %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral 5-ASA</td>
<td>336</td>
<td>42.5</td>
</tr>
<tr>
<td>Budesonide</td>
<td>74</td>
<td>9.4</td>
</tr>
<tr>
<td>Topical 5-ASA</td>
<td>250</td>
<td>31.6</td>
</tr>
<tr>
<td>Topical steroids</td>
<td>149</td>
<td>18.9</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>239</td>
<td>30.3</td>
</tr>
<tr>
<td>Anti-TNF alphas</td>
<td>96</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Table 6 shows past treatment, used by UC patients, as well as reported side effects that led to therapy cessation. Oral 5-ASA was the most common past therapy (336/790, 42.5%), and patients experienced side effects in 13.1% of the cases. Topical 5-ASA or topical steroids were given in a total 334 cases (42.3%), while 65 patients (8.2%) were treated by both. Combined side effects occurrence for topical therapy is 25 cases out of 334 (7.5%). Immunomodulator drugs were given in 239 out of 790 cases (30.3%), leading to 116 occurrences of side effects (48.5%).
maintenance treatment. We speculate that patients prefer to take capsules instead of suppositories, enemas or rectal foams. To overcome this fact, better information and teaching of our patients may be helpful. Even in the maintenance of remission rectal 5-ASA formulations are helpful in patients with proctitis or proctosigmoiditis. The patients should be encouraged to maintain the treatment with a minimal weekly dose of 3 g of 5-ASA.31,32

<table>
<thead>
<tr>
<th>Change of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>From enrollment to follow-up 1:</td>
</tr>
<tr>
<td>Enroll/FUp1</td>
</tr>
<tr>
<td>Systemic</td>
</tr>
<tr>
<td>Topical</td>
</tr>
<tr>
<td>Syst &amp; topic</td>
</tr>
<tr>
<td>From follow-up 1 to follow-up 2:</td>
</tr>
<tr>
<td>FUp1/FUp2</td>
</tr>
<tr>
<td>Systemic</td>
</tr>
<tr>
<td>Topical</td>
</tr>
<tr>
<td>Syst &amp; topic</td>
</tr>
<tr>
<td>From follow-up 2 to follow-up 3:</td>
</tr>
<tr>
<td>FUp2/FUp3</td>
</tr>
<tr>
<td>Systemic</td>
</tr>
<tr>
<td>Topical</td>
</tr>
<tr>
<td>Syst &amp; topic</td>
</tr>
</tbody>
</table>

Table 6 shows the change of medication between different stages of follow-up. Overall number of patients is decreasing since not every patient has filled all yearly follow-ups. For patients under systemic drugs only, we observed a total of 118 treatment switches over the whole period, which means that at least 70% do not have to change their therapy at any stage of the follow-up. When they have to, in more than 30% of the cases an additional topical drug is given (36 cases out of 118 for over all period), while only 14% change to a fully topical treatment (16 out of 118). For patients under a topical therapy, change of medication occurs in 58 total cases over the whole period (more than 50% of the cases), which is more often than the systemic drugs' group. Change is made generally either to a fully systemic treatment (19 cases out of 58, 32.7%), or either to an additional systemic drug (13 out of 58, 22.4%). For patients under a systemic–topical combined treatment, change of drug is mainly an interruption of the topical treatment (42 cases out of 69 total switches were made towards a systemic drug only, which represents more than 60% of the cases).

Table 7 summarizes the median and the interquartile range of both physical and mental component scores of the SF36 questionnaire at different times of follow-up and according to disease location. Mental score seems to be lower in proctosigmoiditis patients than in others, at follow-up 2 (P = 0.036). No statistical difference was found, except for mental score at follow-up 2. Applying Bonferroni’s correction for multiple testing, we found that SF36 mental score at follow-up 2 was statistically significantly different in pancolitis and proctosigmoiditis only (P = 0.004).
In our study rectal 5-ASA products were significantly more frequently given than steroids. In one study the efficacy of budesonide versus mesalazine enemas has been compared in patients with left-sided ulcerative colitis. Clinical remission at week 4 was achieved in 63.5% of budesonide and 77.2% of mesalazine treated patients (P < 0.05). Furthermore, a meta-analysis showed a higher efficiency of rectal 5-ASA treatments compared to topical steroids. However, the combination of rectal steroids and 5-ASAs seems to be beneficial.

Unexpectedly, in our cohort only a minority of patients with pancolitis received rectal therapy. Since urgency and high stool frequency are related to a rectal involvement a proportion of these patients may profit of an additional rectal therapy. A study proved the efficacy of rectal therapy in patients with mild to moderate pancolitis in the combination with oral 5-ASA. Interestingly, our data show that the prescribed dosage of topical therapy in patients with pancolitis was relatively high in contrast to patients with proctitis. This is due to the fact that patients with proctitis received mainly 5-ASA suppositories. We found a clear relationship between disease activity and dosage of 5-ASA which fits into the recommended treatment strategy of the ECCO guidelines.

No difference of quality of life was found in patients regarding to their intestinal involvement. This indicates that patients with only limited disease may suffer as much as patients with pancolitis. Therefore, patients with only a limited intestinal involvement will possibly profit of an optimization of their treatment regarding their quality of life.

Rectal treatment, however, has its limitations. A subgroup of patients is unable to retain the enema. Therefore, rectal foams have been developed. The comparison between mesalamine foams and mesalamine liquid enema in patients with active left-sided ulcerative colitis showed a not significant lower remission rate induced by the foam formulations. Despite of the fact that topical treatment may be more efficient than oral treatment a subgroup of patients does not feel comfortable to do the therapy on a daily basis. Therefore, there have been attempts for other galenic formulations to avoid the rectal administration. A new budesonide MMX extended-release tablet has been investigated in a trial that showed that 47% of patients reached a CAI reduction by 50% in contrast to placebo (33%).

In this study, the frequency of side effects in patients treated with topically or orally given 5-ASA products was low compared to those treated with immunomodulators or anti-TNF-antibodies. This is in accordance to other papers.

Due to the fact that university hospitals included the majority of the patients in this cohort, there may be a bias leading to an elevated frequency of pancolitis patients (40.5%). In another cohort only 22% of patients with ulcerative colitis suffered from pancolitis. Furthermore, the disease activity of our patients might be higher than in a population based cohort. In summary, there are several advantages of rectal treatment with 5-ASA or topical steroids in patients with ulcerative colitis. This includes a high therapeutic efficacy and low side effects. Due to these advantages physicians should encourage their patients to use rectal therapies. With the increasing number of rectal formulations on the market (suppositories, enema, low volume foam) most patients with ulcerative colitis will find an agreeable product.

5. Study Highlights

5.1. What is the Current Knowledge

- Topical treatment with 5-ASA is an effective treatment in distal ulcerative colitis.
- The combination of topical and oral 5-ASA leads to an additional benefit.

5.2. What is New Here

- Oral treatment is more frequently used in patients with proctitis compared to topical treatment. Therefore topical treatment is underused in the Swiss IBD cohort.
- Topical treatment is frequently stopped over the time.
- The quality of life of patients with limited rectal disease is the same compared to patients with extensive disease.

Conflict of interest

No conflict of interest.

References

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