Combination of Corticosteroids with 5-Aminosalicylic Acids Compared to Corticosteroids Alone for Hospitalized Patients with Active Ulcerative Colitis

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ABSTRACT: **Background:** Although 5-amino-salycilic acids (5-ASA) are often used with corticosteroid treatment in moderate-to-severe ulcerative colitis, the value of continuing/initiating 5-ASA in this clinical setting has not been explored.

Objectives: To investigate the impact of a combination 5-ASA+corticosteroid therapy on the outcome of hospitalized patients with acute moderate-severe ulcerative colitis.

Methods: We conducted a retrospective study of patients hospitalized with moderate-severe ulcerative colitis in two centers, Israel and South Korea. Patients were classified into those who received 5-ASA and corticosteroids and those who received corticosteroids alone. Analysis was performed for each hospitalization event. The primary outcome was the rate of treatment failure defined as the need for salvage therapy (cyclosporin-A/infliximab/colectomy). The secondary outcomes were 30 days re-admission rates, in-hospital mortality rates, time to improvement, and length of hospitalization.

Results: We analyzed 209 hospitalization events: 151 patients (72%) received 5-ASA+corticosteroids and 58 (28%) corticosteroids alone. On univariate analysis the combination therapy group had a lower risk for treatment failure (11% vs. 31%, odds ratio 0.28, 95% confidence interval 0.13–0.59, $P = 0.001$). However, this difference disappeared on multivariate analysis, which showed pre-admission oral corticosteroid treatment to be the most significant factor associated with the need for salvage therapy.

Conclusions: A signal for possible benefit of a combination 5-ASA and corticosteroids therapy was found, but was confounded by the impact of pre-admission corticosteroid treatment.

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KEY WORDS: ulcerative colitis (UC), corticosteroids, 5-amino-salycilic-acid (5-ASA)

The role of corticosteroids in the treatment of a moderate-to-severe ulcerative colitis (UC) exacerbation is well established and endorsed by professional societies [1]. This recommendation is based on pivotal studies carried out 50–60 years ago by Truelove and Witts [2] and on extensive clinical experience since then. As a result, there are scarce data comparing steroids to 5-aminosalycilates (5-ASA) in the treatment of severe UC exacerbation. In 1962, a clinical trial by Truelove and colleagues [3] found topical and systemic corticosteroid therapy to be superior to sulphasalazine therapy. Although 5-ASA agents are efficacious in mild-to-moderate active UC [4,5], their use in moderate-to-severe UC has seldom been investigated. In particular, there are scant data as to whether the addition/continuation of 5-ASA agents as combination therapy with systemic corticosteroids is superior to corticosteroids alone in patients with moderate-to-severe active UC. Thus, in practical terms, virtually all moderate-to-severe UC patients admitted to the hospital are treated with steroids, but the decision regarding cessation of 5-ASA medications or their continuation is made on an arbitrary basis. Presumably, 5-ASA would have little clinical efficacy in these moderate-to-severe active patients. Nonetheless, it may be still plausible to hypothesize that their addition to steroids may confer some clinical benefit secondary to two different mechanisms of action acting in concert. If so, this may justify a combination of corticosteroid and 5-ASA in all patients, particularly given the excellent safety profile and low cost of 5-ASA. Conversely, if no benefit of the combination is proven, then continuing or adding 5-ASA to steroids in this setting may expose the patient to unnecessary medications. Therefore, the aim of the present study was to investigate if the combination of steroids with 5-ASA was superior to steroids alone in the treatment of hospitalized patients with UC exacerbation.

PATIENTS AND METHODS

This was a retrospective two-center study to evaluate corticosteroids alone (monotherapy) versus corticosteroids with oral

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5-ASA (combination therapy) in UC patients hospitalized with a flare. The study population comprised all adult UC patients (> 18 years of age) who were hospitalized in two academic tertiary centers due to a UC flare: Sheba Medical Center in Israel and Yonsei University College of Medicine, Severance Hospital, in South Korea. Patients with inflammatory bowel disease (IBD)-colitis unclassified, were not included. Data were retrieved from the electronic databases of the two institutions, which included all hospitalizations in Sheba for the years 2008–2014 and Yonsei for the years 2002–2013. Patients found on admission to harbor an enteric infection and patients who were not treated with steroids (intravenous or per os) during the hospitalization were excluded. Patients discharged from the hospital after less than 72 hours from admission were also excluded in order to reduce confounding effects by possible undiagnosed infections (e.g., gastroenteritis) or other etiologies imitating a flare with a very prompt resolution, which is unlikely in a genuine moderate-to-severe UC exacerbation.

Table 1. Characteristics of the patients at admission

		Entire cohort (n=209)	Combined CS+5-ASA (n=151)	CS monotherapy (n=58)	*P* value
Females, n (%)		107 (51.2)	74 (49)	33 (56.9)	0.35
Mean age, years ± SD (median)		39.9 ± 16.3 (37.3)	40.6 ± 16.4 (38.7)	38.2 ± 16.7 (34.7)	0.36
Smokers, n (%) *3		28 (13.4)	23 (15.2)	5 (8.6)	0.26
Mean disease duration, years ± SD (median)		4.7 ± 6.1 (2)	4.4 ± 5.7 (2)	5.6 ± 7 (2)	0.26
Extent of colitis *9	Proctitis + left-sided	96	72	24	0.52
	Extensive colitis	104	73	31	0.52
Oral 5-ASA at admission, n (%) *3		141 (67.4)	121 (80.1)	20 (36.3)	‹0.001
Topical 5-ASA at admission, n (%) *6		55 (27)	51 (33.7)	4 (7.5)	0.001
Oral steroids at admission, n (%)*2		80 (38.6)	54 (35.7)	26 (46.4)	0.19
Topical steroids at admission, n, (%) *9		7 (3.5)	6 (4)	1 (1.9)	0.67
Antibiotics at admission, n, (%) *3		28 (13.3)	16 (10.6)	12 (20.7)	0.069
6 mp at admission, n (%) *1		34 (16.3)	20 (13.2)	14 (24.5)	0.059
Temperature › 37.8 in 1st 24 hours, n (%)		55 (26.3)	48 (31.8)	7 (12)	0.004
Tachycardia › 90, n (%)		81 (38.7)	62 (41)	19 (32.7)	0.34
Body mass index, average ± SD, (median) *59		22.7 ± 11.6 (21.1)	22.8 ± 12.6 (21)	22.5 ± 5.8 (21.6)	0.83
Mean bowel movements, n ± SD (median) *16		10.6 ± 5.4 (10)	10 ± 5.3 (10)	12.2 ± 5.7 (10)	0.02
Abdominal tenderness, n (%) *1		118 (56.7)	91 (60.6)	27 (46.5)	0.085
WBC, K/µl ± SD (median)		10.6 ± 4.6 (9.7)	10.7 ± 4.6 (9.6)	10.3 ± 4.4 (9.9)	0.64
Hb, g/dl ± SD (median)		11.6 ± 2.1 (11.8)	11.6 ± 2.1 (11.8)	11.2 ± 2 (11.3)	0.14
Albumin, g/dl ± SD (median) *16		3.3 ± 0.6 (3.4)	3.4 ± 0.7 (3.4)	3.2 ± 0.6 (3.1)	0.03
CRP, mg/L ± SD (median) *20		43.6 ± 58.3 (15)	42.7 ± 63.9 (11.3)	46.3 ± 41.6 (40.1)	0.65

*Denotes the number of patients with unavailable data for the designated parameter at the time point of admission

CS = corticosteroids, 5-ASA = aminosalicylates, mp = mercaptopurine, Hb = hemoglobin, WBC = white blood cells, CRP = C-reactive protein

The primary outcome of the study was the rate of treatment failure defined as the need for rescue intervention (cyclosporine-A/infliximab or urgent colectomy) in hospitalized UC patients treated with steroids alone compared to those treated with combination steroid+5-ASA medications. Secondary outcomes included the duration of hospitalization, the time to first improvement during hospitalization, and re-admission rates. The study was approved by the institutional ethics review board of each participating center.

STUDY DEFINITIONS

UC was diagnosed based on conventional clinical, endoscopic and histologic findings. Eligible hospitalization records were scrutinized with the following definitions: UC flare was defined as worsening of UC-related digestive tract symptoms which required hospitalization of the patient according to the treating physician's judgment. Drug treatment was recorded only if the drug was given for at least 72 hours during the hospitalization (if less, the drug was regarded as not given). Treatment failure (the primary outcome) was defined as the need for rescue interventions, i.e., cyclosporine-A/infliximab (CsA/IFX) or urgent colectomy. Response to treatment was defined as clinical improvement based on the treating physician's judgment noted in the medical chart coupled with discharge of the patient without in-house rescue intervention, as specified above. Re-admission was considered as a hospitalization occurring between 4 and 30 days after a previous admission, whereas re-admission within 3 days of discharge was considered an extension of the prior hospitalization, as these prompt re-admissions probably represented premature discharge. For patients who had been hospitalized more than once during the course of their disease, each hospitalization event was included separately in the analysis, provided that any such two admissions were at least one month apart (if less, this was considered a re-admission event, as specified above). 5-ASA usage was defined as any use of oral 5-ASA (mesalamine/mesalazine) at doses > 1.6 g/day for at least 3 days, regardless of the specific 5-ASA used. Steroid treatment with topical 5-ASA but without oral 5-ASA was not considered a combination therapy, and these patients were included in the steroid monotherapy arm in the main analysis. However, a sensitivity analysis was performed whereby these patients were included this time in the combination arm of the analysis. Because nine patients were receiving infliximab or cyclosporine-A on admission, a repeat analysis was performed after exclusion of these patients. Cytomegalovirus colitis diagnosis was based on tissue immunohistochemistry,

Table 2. Primary and secondary outcomes comparing combined treatment with 5-ASA and corticosteroids to corticosteroids monotherapy

		CS+5-ASA (n=151)	CS monotherapy (n=58)	OR (95%CI)	*P* value
Primary endpoint: Need for salvage therapy (CsA/IFX) or colectomy, n (%)		17 (11.2%)	18 (31.0%)	0.28	0.001
Sub-analysis of the primary endpoint	Total number of urgent colectomies after CsA/IFX failure, endpoint/total, n (%)	9/17 (52.3%)	7/18 (38.9%)	1.76	0.4
	Total number of IFX/CsA only, endpoint/total, n (%)	8/151 (5.2%)	11/58 (18.9%)	0.23	0.003
30 days re-admission, n (%)		10 (6.6%)	8 (13.8%)	0.44	0.1
In-hospital mortality, n		2	0	–	–
Time to improvement*, average days ± SD (median)		4.7 ± 3.9 (4)	4.9 ± 3.8 (4)	–	0.98
Duration of hospitalization*, average days ± SD (median)		12.7 ± 12.3 (10)	11.1 ± 8.1 (7.5)	–	0.12

*Outliers in the top 95–100% of the parameter were excluded

CS = corticosteroids, 5-ASA = aminosalicylates, CsA = cyclosporine-A, IFX- = infliximab

Table 3. Analysis of clinical and background parameters for their association with the primary outcome

		Treatment failure (n=35)	No treatment failure (n=174)	*P* value
Females, n (%)		21 (60)	86 (49.4)	0.27
Mean age, years ± SD (median)		40.8 ± 15.2 (41)	39.7 ± 16.7 (35.4)	0.7
Smokers, n (%) *3		5 (14.2)	23 (13.2)	1
Mean disease duration ± SD (median)		5.5 6 (4)	4.6 6.1 (2)	0.39
Extent of colitis *10	Proctitis & left-sided colitis	18	78	0.57
	Extensive colitis	16	88	0.57
Oral 5-ASA at admission, n (%) *3		21 (60)	120 (68.9)	0.32
Topical 5-ASA at admission, n (%) *6		8 (24.2)	47 (27.6)	0.83
Oral steroids at admission, n (%) *2		25 (73.5)	55 (31.8)	0.0001
Topical steroids at admission, n (%) *9		1 (3)	6 (3.6)	1
Antibiotics at admission, n (%) *3		4 (11.7)	24 (13.9)	1
Antibiotics during the hospitalization, n (%)		22 (62.8)	123 (70.6)	0.42
6 mp at admission, n (%) *1		6 (17.1)	28 (16.1)	1
6 mp during the hospitalization, n (%) *6		5 (14.2)	38 (22.4)	0.36
Temperature › 37.8°C in 1st 24 hours, n (%)			50 (28.7)	0.09
Tachycardia › 90, n (%)		12 (34.2)	69 (39.6)	0.7
Body mass index, average ± SD (median) *59		21.3 ± 7.4 (19.9)	22.8 ± 12.3 (21.2)	46
Mean bowel movements, n ± SD (median) *16		12.6 ± 5.4 (10)	10.1 ± 5.3 (10)	0.02
Abdominal tenderness, n (%) *1		20 (57.1)	98 (56.6)	1
WBC, K/µl ± SD (median)		10.7 ± 4.2 (9.3)	10.5 ± 4.6 (9.7)	0.82
HB, g/dl ± SD (median)		10.8 ± 1.7 (11.2)	11.6 ± 2.1 (11.8)	0.02
Albumin, g/dl ± SD (median) *16		3.1 ± 0.6 (3)	3.4 ± 0.6 (3.4)	0.01
CRP, mg/L ± SD (median) *20		64.6 ± 75.3 (48)	39.5 ± 54.3 (13.1)	0.08

Treatment failure, defined as the need for salvage cyclosporine/infliximab or urgent direct colectomy

*Denotes the number of patients with unavailable data for the designated parameter at the time point of admission

CS = corticosteroids, 5-ASA = aminosalicylates, mp = mercaptopurine, Hb = hemoglobin, WBC = white blood cells, CRP = C-reactive protein

and was ruled out by negative tissue polymerase chain reaction (PCR) or negative immunohistochemistry.

STATISTICAL ANALYSIS

Continuous variables were compared by Student's *t*-test or the Mann-Whitney U test as appropriate. Categorical parameters were compared by Fisher's exact test, and odds ratios and 95% confidence interval (CI) were computed. Because no data pertaining to the added benefit imparted by combination steroid+5-ASA were available, power analysis was based on perceived clinically meaningful benefit for effect size derivation. Thus, based on a 70% response rate with steroids alone [6,7], 72 patients in each arm were computed to be needed to detect a 20% difference in response rate with a beta error of 20% and alpha error of 5%. All statistics were carried out using MedCalc software (Mariakerke, Belgium). A two-tailed $P < 0.05$ was considered significant.

RESULTS

A total of 283 patients hospitalized 342 times with acute UC were identified at the two centers during the study period. After exclusion of ineligible patients, 209 hospitalization events (in 180 patients) remained in the main analysis. The patients' background disposition and clinical parameters at admission are shown in Table 1, along with the breakdown for the comparison between the steroid monotherapy group compared to the steroid+5-ASA group. As shown, patients in the combination steroid+5-ASA group were significantly more likely to be admitted while already receiving 5-ASA, included slightly but statistically significant more febrile patients at admission, with fewer bowel movements and higher albumin level compared to the steroid monotherapy group. The treatment outcomes are shown in Table 2. As shown, the rate of treatment failure (the primary outcome), manifested as the need for rescue intervention either by cyclosporine-A/infliximab or by urgent colectomy, was 31% in the steroid monotherapy group compared to 11.2% in the steroid+5-ASA group (OR 0.28, 95%CI 0.13–0.59, $P = 0.001$). In addition, the combination steroid+5-ASA group tended to have a lower

Table 4. Univariate and multivariate analysis

Parameter	Univariate analysis OR (95%CI)	*P* value	Multivariate analysis OR (95%CI)	*P* value
Oral steroids at admission, n *2	5.6 (2.6–12.4)	‹ 0.001	10.08 (3.11–32.67)	‹ 0.0001
Temperature › 37.8ºC in 1st 24 hours	0.43 (0.16–1.18)	0.1	0.47 (0.12–1.86)	0.28
Mean bowel movements, n *16	–	–	1.08 (0.98–1.2)	0.09
HB, g/dl	–	–	0.88 (0.66–1.17)	0.39
Albumin, g/dl *16	–	–	0.25 (0.09–0.73)	0.01
CRP, mg/L *20	–	–	1 (0.99–1.01)	0.09
CS monotherapy	0.28 (0.13–0.59)	0.001	0.61 (0.2–1.83)	0.38

*Denotes the number of patients with unavailable data for the designated parameter at the time point of admission

rate for salvage therapy with CsA/IFX without the need for colectomy ($P = 0.003$), but other secondary outcomes were not different between the two groups [Table 2].

To investigate the possible impact of other factors on the outcome of patients, a further analysis was performed whereby clinical and laboratory variables were analyzed with respect to their association with the primary outcome [Table 3]. As shown, preadmission outpatient treatment with steroids was significantly associated with the risk of in-hospital treatment failure ($P < 0.001$). In a multivariate analysis incorporating all parameters found to be associated with the primary outcome in the univariate analysis, treatment by steroid monotherapy or combined steroid+5-ASA did not retain its independent effect on treatment outcome [Table 4]. In contrast, pre-admission steroid treatment remained a significant factor influencing patients' outcome. Interestingly, concomitant treatment with thiopurines (azathioprine/6-mercaptopurine) or antibiotics had no effect on patients' hospitalization course.

Because patients receiving topical 5-ASA (but not oral 5-ASA) were included in the monotherapy group in the primary analysis, we performed a sensitivity analysis, this time including these patients who received topical 5-ASA treatment with steroids in the combination treatment group (n=6). Similar to the main univariate analysis, the results of this second analysis still showed a higher risk of treatment failure in the steroid monotherapy arm compared to the combination group (OR 3.75, 95%CI 1.75–8.01, $P = 0.0006$). Furthermore, when the salvage therapy or colectomy rates were separately analyzed after this regrouping of the topical 5-ASA patients with the combination arm, the monotherapy group did not have a statistically significant higher rate of colectomy (OR 1.43, 95%CI 0.58–3.53, $P = 0.43$) but had a statistically significant greater need for infliximab/cyclosporine-A (OR 6.63 95%CI 2.84–15.45, $P < 0.0001$), as well as higher re-admission rate (OR 2.73, 95%CI 1.01–7.35, $P = 0.04$). Since nine patients were hospitalized while receiving infliximab/cyclosporine-A (and their primary outcome analyzed as need for in-hospital colectomy), we performed a repeat outcome analysis after excluding these patients. The results of this analysis were not different from those of the main analysis (results not shown). Subgrouping according to pre-admission treatment with 5-ASA showed a trend favoring the combined treatment, with OR of 2.82 (95%CI 0.95–8.4, $P = 0.06$). When analyzing only the subgroup of patients not treated with 5-ASA prior to the admission (n=65), the OR was 5.6 (95%CI 1.11–28.04, $P = 0.03$) favoring the combined treatment group. Further multivariate analysis this time incorporating only patients who had not received 5-ASA prior to hospitalization (n=65) showed similar results (data not shown). Two patients died during hospitalization (0.9%). One was a 92 year old moribund female who succumbed to hospital-acquired pneumonia, urinary tract infection and atrial fibrillation after prolonged hospitalization. The other was an 88 year old male who experienced hemodynamic compromise and shock with bilateral deep vein thrombosis. One of the patients (0.4%) had an adverse event probably related to 5-ASA in the form of acute pancreatitis which resolved with conservative treatment.

DISCUSSION

Ulcerative colitis exacerbations requiring hospitalization impose a major burden on the patient's life and on the health care system and may lead to grave consequences including colectomy and even mortality [8]. Controlling UC exacerbation rapidly is therefore of paramount importance. Corticosteroids are very effective in the treatment of hospitalized patients with moderate-to-severe UC exacerbations [1,2]. Nevertheless, 30–40% patients will prove resistant to initial intravenous steroid treatment and will require salvage therapies with cyclosporine or infliximab and/or urgent colectomy [9]. To the best of our knowledge, no data have to date addressed the addition of 5-ASA to steroids in this clinical scenario. In particular, it is presently unknown if such a combination of steroid+5-ASA is beneficial, even marginally, in reducing the need for salvage therapy or colectomy.

The present study investigated the clinical impact of combination steroid+5-ASA versus steroids alone in patients hospitalized with an acute UC flare. The first important finding of the study was documenting the prevalent use of adjunct 5-ASA with steroid in hospitalized patients with moderate-to-severe UC in two academic centers in two countries, despite the absence of data supporting this practice. Indeed, physicians opted to add or continue 5-ASA with steroid in 151 of 209 hospitalizations (72.2%). This number illustrates the importance of examining the actual role of 5-ASA as adjunct to steroids in this setting.

The univariate analysis results showed that patients who received combination therapy were in less need of salvage medical therapy or urgent colectomy and reduced rate for salvage therapy with infliximab/cyclosporine-A without the

need for colectomy. As for secondary outcomes, duration of hospitalization, the time until first improvement and the rate of re-admission were similar between the groups. Nonetheless, this difference in rescue medication/colectomy rate was not retained on multivariate analysis, in which pre-admission treatment with steroids had the most robust independent effect on treatment failure during hospitalization.

5-ASA medications are known to be effective in mild-to-moderate UC but their role in moderate to severe UC has not been well studied. It is generally presumed that their lack of an immune suppressive effect may render them useless in these more severe patients who are usually treated with steroids, immune modulators or biologics [10]. However, from a mechanistic point of view, it is possible to hypothesize that the 5-ASA local mucosal anti-inflammatory effect may act in concert with the more profound immune down-regulation pathways mediating the therapeutic effects of steroids, and if so, then even in the face of prior failure of 5-ASA as a single agent it may still confer an additive therapeutic effect when administered in combination with steroids.

While the findings of the present study may provide a preliminary signal for a possible benefit of combination 5-ASA and steroids in hospitalized patients with moderate-to-severe UC flare, the results of the multivariate analysis indicate that most of the effects are mediated by confounders, thereby limiting the ability to definitively deduce the superiority of adjunct 5-ASA treatment. Until direct data derived from controlled trials are available, the decision to add or intensify 5-ASA during steroid treatment of moderate-to-severe UC remains unsupported. Although the cost of 5-ASA is low and its risk profile excellent, one of our patients experienced 5-ASA-induced pancreatitis, illustrating the need to rigorously investigate the role of 5-ASA agents for this indication.

Interestingly, and contrary to a recent study from Spain [11], we found that pre-admission outpatient treatment with steroids was the strongest predictor of subsequent failure of in-hospital intravenous treatment with steroids and need for salvage therapy or colectomy. The reason for the difference between our observation and the previous study are unclear, but may be related to different patient characteristics with more severe patients in our cohort as manifested by a higher colectomy rate. Another possible explanation may be the larger size of our study which would enable detection of this adverse association. In an era when other treatment modalities are increasingly available in the form of biologics, early stratification and identification of patients at risk of steroid treatment failure is pertinent. If corroborated by other studies, failure of outpatient treatment with steroids before admission may be one such factor for identifying patients who may benefit from expedited second-line therapy early on during hospitalization [12].

The advantages of our study are its relatively large sample size and its "real-life" nature, reflecting everyday medical practice. In addition, the heterogeneity of the patient population with different genetic and environmental backgrounds contributes to the generalizability of the study results. Nevertheless, the diversity of the study population is also a limitation, since the study results might not be applicable for specific populations. Unfortunately, data on exact dosing were not uniformly available, and when they were, the doses sometimes changed during hospitalization making a robust analysis of dosing impact to be of questionable validity. Finally, the retrospective nature of the study makes it impossible to exclude additional confounders affecting the observed results.

CONCLUSIONS

We found that combination 5-ASA with corticosteroids is often administered to hospitalized patients with moderate-to-severe UC. There seems to be a signal for reduced need for salvage therapy with this combination therapy compared to steroid monotherapy. However, this signal was not retained after confounders were accounted for. A prospective blinded controlled trial has been launched to directly evaluate the benefit of adjunct 5-ASA with steroids in this setting.

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