Mechanisms underlying the anti-inflammatory actions of boswellic acid derivatives in experimental colitis

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Anthoni, C., M. G. Laukoetter, E. Rijcken, T. Vowinkel, R. Mennigen, S. Müller, N. Senninger, J. Russell, J. Jauch, J. Bergmann, D. N. Granger, and C. F. Kriegstein. Mechanisms underlying the anti-inflammatory actions of boswellic acid derivatives in experimental colitis. Am J Physiol Gastrointest Liver Physiol 290: G1131–G1137, 2006. First published January 19, 2006; doi:10.1152/ajpgi.00562.2005.—Recent clinical trials of the gum resin of Boswellia serrata have shown promising results in patients with ulcerative colitis. The objective of this study was to determine whether a semisynthetic form of acetyl-11-keto-β-boswellic acid (sAKBA), the most potent anti-inflammatory component of the resin, also confers protection in experimental murine colitis induced by dextran sodium sulfate (DSS) to compare its effects with those standard medications of ulcerative colitis like steroids and to examine whether leukocyte-endothelial cell adhesion is a major target of action of sAKBA. Clinical measurements of disease activity and histology were used to assess disease progression, and intravitral microscopy was employed to monitor the adhesion of leukocytes and platelets in postcapillary venules of the inflamed colon. sAKBA treatment significantly blunted disease activity as assessed both grossly and by histology. Similarly, the recruitment of adherent leukocytes and platelets into inflamed colonic venules was profoundly reduced in mice treated with sAKBA. Because previous studies in the DSS model have shown that P-selectin mediates these blood cell-endothelial cell interactions, the expression of P-selectin in the colonic microcirculation was monitored using the dual-radioabeled antibody technique. The treatment of established colitis with sAKBA largely prevented the P-selectin upregulation normally associated with DSS colitis. All of the protective responses observed with sAKBA were comparable to that realized in mice treated with a corticosteroid. Our findings demonstrated an anti-inflammatory effect of sAKBA and indicated that P-selectin-mediated recruitment of inflammatory cells is a major site of action for this novel anti-inflammatory agent.

inflammatory bowel disease; dextran sodium sulfate; intravitral microscopy; leukocyte-endothelial adhesion

The practice of traditional Ayurvedic medicine in India has long included boswellic acids for the treatment of inflammatory diseases (1). These acids derive from the resin of Boswellia trees known as frankincense (24). Pharmacological analyses have revealed acetyl-11-keto-β-boswellic acid (AKBA) to be the most powerful of the acids contained in ethanolic extracts of Boswellia serrata, with in vitro experiments demonstrating cytostatic and proapoptotic actions of AKBA (2, 16, 28, 33, 34). We have been able to confirm the anti-inflammatory properties of these compounds in an experimental model of colitis in rats (21). Furthermore, recent clinical trials with formulations containing boswellic acids have demonstrated some effectiveness in the treatment of asthma, osteoarthritis, and inflammatory bowel diseases (IBD) (12, 14, 15, 20). Although these clinical studies have drawn attention to boswellic acids as potentially powerful anti-inflammatory drugs, little progress has been made in defining the mechanisms that underlie the beneficial effects of these agents. This lack of progress has largely resulted from the limited availability of AKBA in a highly purified form. However, a simple and efficient strategy for the large-scale synthesis of purified AKBA and other boswellic acids has been recently developed, which yields different semisynthetic AKBA (sAKBA) that can be applied to large-scale studies of drug efficacy in experimental animals and humans (17). Furthermore, sAKBA allows, for the first time, standardized treatment conditions with which to study mechanisms underlying the anti-inflammatory effects of B. serrata.

There is growing recognition that the microvasculature plays a major role in the pathogenesis of experimental colitis and that endothelial cell activation is an early and rate-determining component of the inflammatory response (8, 23, 27). An important consequence of endothelial cell activation is an increased expression of glycoproteins that regulate the adhesion of blood cells to the endothelial cell surface and consequently regulate the recruitment of leukocytes into inflamed tissue. ICAM-1, VCAM-1, and MadCAM-1, as well as E- and P-selectin, are dramatically upregulated on endothelial cells of the colonic vasculature during experimental colitis (4, 5, 18, 22, 25, 32, 36). The importance of these endothelial CAMs in the pathogenesis of intestinal inflammation is evidenced by reports demonstrating reduced disease activity and tissue injury in mice that are genetically deficient in specific adhesion molecules and in wild-type mice treated with blocking antibodies directed against a specific adhesion molecule (25, 31, 32). For example, the greatly enhanced recruitment of adherent leukocytes and platelets normally observed in colonic venules of mice with dextran sodium sulfate (DSS)-induced colitis is largely abolished in P-selectin-deficient mice as well as in wild-type mice treated with an anti-P-selectin antibody (25). Similarly, immunoneutralization or genetic blockade of P-selectin is also known to reduce disease severity in DSS colitis.

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The objectives of this study were to determine whether AKBAs 1) are able to treat established inflammation and tissue injury associated with DSS colitis; 2) exert anti-inflammatory effects in DSS colitis that are comparable those afforded by dexamethasone, which is widely used in the treatment of human IBD; 3) alter the recruitment of leukocytes and platelets into the inflamed colonic microvasculature 4) interfere with the endothelial expression of P-selectin in DSS colitis.

Materials and Methods

Animals. All procedures using animals were reviewed and approved by the Institutional Animal Care and Use Committee of Louisiana State University Health Sciences Center and were performed according to the criteria outlined by the National Institutes of Health. Inbred female BALB/c mice (Jackson Laboratory, Bar Harbor, ME; and Charles River, Sulzfeld, Germany; ~20 g body wt) were housed in standard cages (2 mice/cage) under stable conditions (12:12-h light-dark cycle, 60 ± 10% humidity, 21 ± 1°C constant temperature). The mice had free access to standard laboratory diet and to purified water (Millipore, Bedford, MA) or DSS in purified water.

Histological colitis score. The mice had free access to standard laboratory diet and purified water (Millipore, Bedford, MA) or DSS in purified water. (13, 32). Because of the critical role of adhesion molecules in the pathogenesis of experimental colitis, previous studies have addressed whether drugs commonly used in the clinical management of IBD affect the expression of adhesion molecules in the intestinal microvasculature (26). These studies have revealed that both dexamethasone and 5-aminosalicylic acid are effective in attenuating the increased endothelial cell expression of E- and P-selectin, VCAM-1, and ICAM-1 induced by endotoxin challenge. However, it remains unclear whether these IBD drugs are similarly effective in reducing CAM expression and the consequent recruitment of inflammatory cells in animal models of experimental colitis (e.g., DSS) and whether other novel anti-inflammatory agents, such as boswellic acids, also exert their beneficial effects by targeting endothelial cell-mediated adhesion of inflammatory cells.

Table 1. DAI

<table>
<thead>
<tr>
<th>DAI Score</th>
<th>Weight Loss</th>
<th>Stool Consistency</th>
<th>Peranal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>1–5</td>
<td>Loose stools</td>
<td>Hemoccult +</td>
</tr>
<tr>
<td>2</td>
<td>5–10</td>
<td>Loose stools</td>
<td>Hemoccult +</td>
</tr>
<tr>
<td>3</td>
<td>11–20</td>
<td>Loose stools</td>
<td>Hemoccult +</td>
</tr>
<tr>
<td>4</td>
<td>&gt;20</td>
<td>Diarrhea</td>
<td>Gross bleeding</td>
</tr>
</tbody>
</table>

DAI, disease activity index.

Table 2. Histological colitis score

<table>
<thead>
<tr>
<th>Histological score</th>
<th>Inflammation</th>
<th>Extent</th>
<th>Crypt Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Slight</td>
<td>Mucosa</td>
<td>Basal 1/3 damaged</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Mucosa and submucosa</td>
<td>Basal 2/3 damaged</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Transmural</td>
<td>Only surface epithelium intact</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>Entire crypt and endothelium lost</td>
</tr>
</tbody>
</table>

Product of score and percent involvement factor (1–4)

<table>
<thead>
<tr>
<th>Percent involvement</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–25</td>
<td>×1</td>
</tr>
<tr>
<td>26–50</td>
<td>×2</td>
</tr>
<tr>
<td>51–75</td>
<td>×3</td>
</tr>
<tr>
<td>76–100</td>
<td>×4</td>
</tr>
</tbody>
</table>

Drugs. Animals were treated with sAKBA, which was synthesized in the laboratory of Prof. J. Jauch (17). The semisynthetic method of synthesis used yields a purity of acetyl-β-boswellic acids in the compound used in this study of > 98%. sAKBAs were dissolved in Sesam oleum raffinatum (S 3547; Sigma, St. Louis, MO). Dexamethasone (Decortin) was purchased from Jenapharm (Jena, Germany).

Induction of chronic colitis. Colonic inflammation was induced by cyclic administration of a 3% (wt/vol) solution of DSS (40 kDa; ICN Biochemicals, Aurora, OH) in water that was filter purified or in purified water alone for a period of 30 days. Each cycle consisted of 5 days of DSS in purified water, followed by 5 days of purified water alone. Three cycles were completed (30 days). This strategy leads to a reliable and reproducible chronic colitis (3, 9).

Disease activity index. All animals treated with DSS were examined once a day, and the disease activity index (DAI) was assessed as previously described (7). The score consists of three parameters: weight loss, stool consistency, and the presence of blood in the stools determined by a guaiac paper test (ColoScreen; Helena Laboratories, Beaumont, TX). The scoring system is shown in Table 1.

Histological colitis score. The animals were killed by an overdose of anesthesia. The whole colon was removed, opened longitudinally, and divided into four segments (cecum and appendix, proximal third, middle third, and distal third). For each segment, 4 different sections were stained with hematoxylin and eosin, producing 16 different sections per animal. The sections were scored using a histological colitis score, as previously described (9). In brief, for each category of the score (inflammation, extent, and crypt damage), points were multiplied by a factor of involvement of the visible epithelium. The sum of the three categories makes up the total score of a section (0–40 points; Table 2). The average of four sections was representative for the colon segment, and the average of the four colon segments was representative for the whole colon.

Blood sampling and platelet preparation. Platelets were derived from untreated BALB/c mice for all intravital experiments. Donor mice were anesthetized using ketamine hydrochloride (150 mg/kg ip) and xylazine (7.5 mg/kg ip). As described previously, ~0.9 ml of blood were harvested via a catheter placed in the carotid artery (6). The blood was collected in polypropylene tubes containing 0.1 ml acid-citrate-dextrose buffer (Sigma). Platelet-rich plasma was obtained by two sequential centrifugations (120 g for 8 min and 120 g for 3 min). The platelet-rich plasma was removed and centrifuged again at 550 g for 10 min, and the pellet was resuspended in PBS (pH 7.4). Platelets were then incubated for 10 min at room temperature with the fluorochrome carboxyfluorescein diacetate succinimidyl ester (CFSE) (90 μM final concentration; Molecular Probes, Eugene, OR). The fluorescently labeled platelet solution was then centrifuged, and the pellet was resuspended in 500 μl PBS and protected from light until infused into a recipient animal. Leukocytes accounted for <0.01% of the cells in the platelet suspension. The number of fluores-
cently labeled platelets obtained from one donor mouse was sufficient for two recipient mice.

Surgical preparation for intravital microscopy. Animals were anesthetized as described above. The right carotid artery was cannulated for blood pressure measurements using a disposable pressure transducer (Cobe Laboratories, Lakewood, CO) attached to a pressure monitor (BP-1; World Precision Instruments, Sarasota, FL). The right jugular vein was cannulated for the infusion of rhodamine 6G (Sigma) for leukocyte labeling and the subsequent infusion of CFSE-labeled platelets. On an adjustable acrylic microscope stage, a laparotomy was performed, and the animal was placed on its right side. The proximal large bowel (initial 2–3 cm adjacent to the cecum) was exteriorized with moist cotton swabs, covered with a nonwoven sponge, and superfused at 37°C with bicarbonate-buffered saline solution (pH 7.4).

Intravital fluorescence microscopy. Platelets and leukocytes were visualized with an inverted microscope (Nikon, Tokyo, Japan) equipped with a 75-W XBO xenon lamp. Visualization of CFSE (excitation, 490 nm; emission, 518 nm) and rhodamine 6G (excitation, 525 nm; emission, 550 nm) required a Nikon filter block with an excitation filter (470–490 nm), a dichroic mirror (510 nm), and a barrier filter (520 nm). With a ×40 objective (0.85 numerical aperture; Nikon), the magnification on the television screen (Trinitron PVM-2030, 50.6 cm diagonal; Sony, Tokyo, Japan) was ×1,280. The microscopic images were received by a charge-coupled device (CCD) video camera (model C2400; Hamamatsu Photonics, Hamamatsu, Japan) and optimized by a CCD camera controller (model C2400; Hamamatsu Photonics). The images were recorded on a videocassette recorder (model VWM 900; Sanyo Electric, Osaka, Japan). A video time-date generator (Panaasonic WJ810; Matsushita Electric Industrial, Osaka, Japan) projected the time, date, and stopwatch function onto the monitor. Five randomly chosen postcapillary venules of the proximal large bowel were each recorded for 1 min.

Video analysis. Venular diameter (between 20 and 40 μm) was measured with a video caliper (Micrcirculation Research Institute, Texas A&M University, College Station, TX), and venular length was set at 100 μm. Platelets and leukocytes were classified according to their interaction with the venular wall as either free flowing or adherent (when cells remained stationary for 30 s or more). We determined whether a platelet or leukocyte was adherent directly to the endothelium itself or indirectly by attachment to another blood cell, suggesting binding of blood cells to other blood cells and to endothelium. Platelet and leukocyte adherence were expressed as numbers of cells per square millimeter of venular surface, calculated from diameter and length, assuming cylindrical vessel shape.

Measurement of colonic P-selectin expression. Measurements of endothelial P-selectin expression were performed on day 30, similar to the intravital microscopy experiments. The binding MAbs used for the in vivo characterization of P-selectin expression were RB40.34, a rat immunoglobulin (IgG1) that is specific for mouse CD62P (P-selectin) (BD Biosciences-Pharmingen, San Diego, CA), and P23, a nonbinding murine IgG1 directed against human P-selectin (Pharmacia-Upjohn, Kalamazoo, MI). The binding (RB40.34) and nonbinding (P23) MAbs were labeled with 125I and 131I (DuPont NEN Research Products, Boston, MA), respectively, using the iodogen method as described previously and stored at 4°C (11). Mice were anesthetized as described above and then equipped with right jugular and carotid catheters. A mixture (200 μl) of 125I-labeled binding MAb and 131I-labeled nonbinding MAb was administered through the jugular vein catheter. Five minutes after the injection of the MAb mixture, a blood sample was obtained from the carotid artery. Immediately thereafter, the animal was rapidly exsanguinated by jugular perfusion with bicarbonate-buffered saline. This was immediately followed by carotid perfusion with bicarbonate-buffered saline after the inferior vena cava was severed at the thoracic level. The large bowel was harvested and divided into proximal and distal portions. The method for calculating P-selectin expression has been described previously (11). Briefly, activity of 125I and 131I (marking the binding MAb and the nonbinding MAb, respectively) in the tissue and in 50-μl samples of cell-free plasma was counted in a gamma counter (14800 Wizard 3; Wallac, Turku, Finland). The accumulated activity of the labeled MAb in the colon was expressed as the percentage of the injected activity per gram tissue. P-selectin expression was calculated by subtracting the accumulated activity per gram tissue of the nonbinding MAb from the activity of the binding P-selectin-binding MAb. This value, expressed as the percent injected dose per gram tissue, was converted to nanograms of MAb per gram tissue by multiplying the above value by the total injected binding MAb.

Experimental protocols. In the first series of experiments (n = 9), we focused on the macroscopic and histological responses of the colon to DSS in mice treated with either sAKBA or dexamethasone (Jenapharm). For 25 days, BALB/c mice received either water or water alternating with DSS following the regimen described above. From days 26 to 30, animals in the treated groups received either sAKBA (5 mg/kg body wt · day−1 · ip) or dexamethasone (1 mg/kg body wt · day−1 · ip) during the last cycle of purified water. In a second series of experiments (n = 6), we examined the effects of sAKBA and dexamethasone treatment on leukocyte and platelet adhesion in the colonic microvasculature using intravital fluorescence microscopy. Following the identical regimen of treatment as in the first series, microscopy was performed on the afternoon of day 30. Rhodamine 6G (0.02%, 100 μl) was infused via the jugular vein over 5 min and allowed to circulate for an additional 5 min. Immediately thereafter, fluorescently labeled platelets (100 × 106) were infused over a period of 5 min and then allowed to circulate for an additional 5 min before image recording. In the third series of experiments (n = 8), we quantified the expression of P-selectin in the colonic microvasculature using the dual-radiolabeling technique. The same treatment protocols for sAKBA and dexamethasone were applied as described above.

Data analysis. Statistical analyses were performed with StatView 4.5 software (Abacus Concepts, Berkeley, CA) using one-way ANOVA followed by the Scheffé or Fisher exact test where appropriate. All values are reported as means ± SE. Statistical significance was set at P < 0.05.

RESULTS

Disease activity index. All animals survived the DSS protocol and were killed on day 30. Mice fed with DSS had Fig. 1. Changes in disease activity index (DAI) over 30-day period of alternating dextran sodium sulfate (DSS) treatment. Drug therapy (arrow) started on day 26 and ended on day 30. *P < 0.05 vs. water treatment. #P < 0.05 vs. DSS treatment. sAKBA, semisynthetic form of acetyl-11-keto-β-boswellic acid.
symptoms of colitis 3–4 days after the start of the first cycle (diarrhea, weight loss, and perianal bleeding). The time course of change in DAI over the 30-day period is shown in Fig. 1. All groups exhibited a similar DAI up to day 26, when treatment with sAKBA or dexamethasone was initiated. On day 30, the DAI of mice in the treatment groups was significantly lower than in untreated controls (DSS 2.62 ± 0.2 vs. sAKBA 0.49 ± 0.12 and dexamethasone 0.48 ± 0.1; Fig. 1). The cyclic feeding of DSS produced an inflammatory state that was also manifested by a shortened and heavier large bowel and a significant increase in the weight-to-length ratio (Fig. 2). Treatment with either sAKBA or dexamethasone significantly reduced DSS-induced bowel shortening and the weight-to-length ratio.

**Histology.** Colonic tissue in healthy control mice exhibited normal microscopic anatomy, with infrequent areas of mild inflammatory infiltrate that resulted in a histological colitis score of >0 (Fig. 3A). After three cycles of DSS, colonic tissue showed signs of inflammation, including a dense infiltrate of leukocytes and loss of epithelium and crypt shortening, as previously described (Fig. 3B) (7). Treatment with either sAKBA or dexamethasone significantly blunted the histological alterations (Fig. 3, C and D), i.e., the histological score was reduced from 16.13 ± 0.46 in the DSS (untreated) group to
Intravital measurements of microcirculation. Compared with healthy mice, feeding of DSS to mice resulted in a significant increase in numbers of adherent leukocytes and platelets in colonic venules (Fig. 5). The total number of adherent leukocytes increased 16-fold, with a comparable contribution of platelet-bearing (48.3%) and platelet-free leukocytes (51.7%). The total number of adherent platelets increased from 26.2 ± 16.8 platelets mm² in venules of control mice to 537.78 ± 93.7 mm² in venules of DSS-treated mice, where 21.0% of the platelets adhered directly to colonic endothelium while the remaining platelets were bound to adherent leukocytes (79.0%). Treatment with sAKBA significantly reduced leukocyte adherence by 90.0% and the adherence of platelets by 92.2%. The ratio of platelet-bearing and platelet-free leukocytes remained unchanged after AKBA treatment, as did the ratio of platelets directly adherent to colonic endothelium and platelets adherent to leukocytes. Dexamethasone treatment exerted similar effects on the inflamed colonic microcirculation, decreasing the number of adherent leukocytes by 94.7% and the number of adherent platelets by 94.6%. Similarly, the ratio of platelet-bearing and platelet-free leukocytes remained unchanged, as did the ratio of platelets adherent to the endothelium and platelets adherent to leukocytes (Fig. 5, A and B).

P-selectin expression. All measurements of endothelial P-selectin expression were performed on day 30, following the same regimen as described above. Long-term feeding of DSS in mice led to significant activation of the endothelium in the entire colon, as reflected by an intense upregulation of P-selectin detected with the dual-radiolabeled MAb technique. Treatment with either sAKBA or dexamethasone dramatically attenuated the upregulation of P-selectin induced by DSS. These attenuating effects of the drugs were evident in both the proximal and distal regions of the colon (Fig. 6).

Fig. 4. Blinded histological score of colonic mucosa in DSS colitis of untreated, sAKBA-treated, and Dex-treated mice. *P < 0.05 vs. water treatment. #P < 0.05 vs. DSS treatment.

Fig. 5. Effects of treatment with sAKBA or Dex on the numbers of adherent platelets (A) and leukocytes (B) in the colonic microcirculation during DSS colitis. *P < 0.05 vs. water treatment. #P < 0.05 vs. DSS treatment.
inflammation. The intensity of the suppression of inflammation and reduction in disease activity exhibited in mice receiving sAKBA were comparable with those afforded by dexamethasone, an agent that is widely used for the treatment of IBD. Furthermore, our findings indicate that interference with leukocyte-endothelial cell adhesion may represent a major target of action of sAKBAs in colonic inflammation.

The powerful protection against colonic inflammation that we observed with sAKBA in DSS-induced colitis is comparable to the blunt inflammatory responses previously reported for the natural boswellic acid compound (H15) and a highly purified AKBA in an indomethacin model of rat intestinal inflammation (21). Others, however, have been unable to demonstrate any benefit to disease activity in both the dextran sulfate- or trinitrobenzene sulfonic acid-induced models of colitis where mice received dietary supplements with either hexane or methanolic boswellia extracts (19). These reports also described hepatotoxic effects of boswellia with pronounced hepatomegaly and steatosis when high doses of the compounds were delivered as dietary supplements. However, a number of differences distinguish our model and experimental design from the abovementioned report. In our study, parenteral (vs. oral) administration was used as well as a highly purified compound of a single well-defined boswellic acid, a more chronic model of colitis, and a shorter treatment period compared with the study by Kiela et al. (19). Whether these differences in the route of administration, purity, bioavailability, and/or dose of AKBA account for the discrepant anti-inflammatory responses to these agents remains unclear and underscores the need for a systematic evaluation of the influence of these factors on therapeutic efficacy of AKBA in different models of experimental colitis.

An increased expression of CAM and enhanced leukocyte recruitment are critical steps in the pathogenesis of experimental and human IBD (35). In DSS-induced colonic inflammation, P-selectin expression is significantly increased in the colonic microvasculature, and it has been demonstrated that immunological or genetic ablation of P-selectin largely prevents the recruitment of both leukocytes and platelets and protects both the mucosa and microvasculature in this model of colitis (25, 32). The findings of the present study demonstrate that the DSS-induced adhesion of leukocytes and platelets is profoundly attenuated in mice treated with sAKBA. Since the semisynthetic boswellic acids were highly effective in blunting the DSS-induced upregulation of P-selectin, it appears likely that sAKBA exerts its inhibitory influence on blood cell recruitment by inhibiting the upregulation of P-selectin on endothelial cells in the inflamed colonic microvasculature. Because a large proportion of the platelets that accumulate in inflamed colonic venules are bound to adherent leukocytes, which has been previously shown to be mediated by an interaction between platelet P-selectin and leukocyte-associated P-selectin glycoprotein ligand-1, we cannot exclude the possibility that sAKBA also interferes with the expression of P-selectin on activated platelets (25).

Previous efforts to interfere with leukocyte-endothelial adhesion in other models of intestinal inflammation have also shown beneficial effects. Pretreatment with a blocking MAb against MadCAM-1 significantly and profoundly reduced leukocyte-endothelial adhesion in colitic mice in the CD45RBhigh, transfer model of colitis and significantly reduces tissue injury (36). Similar prior protection has been shown using an anti-E-selectin antibody in the cotton-top tamarin model of spontaneous colitis (29). These studies demonstrate that while the contribution of specific adhesion molecules differ between experimental models of colitis, interference with leukocytes/endothelial cells remains an important target for therapeutic intervention in IBD.

Our study indicates that sAKBA and dexamethasone are equally effective therapeutic agents in DSS colitis at their respective doses. Both agents significantly attenuated the recruitment of both leukocytes and platelets, blunted P-selectin expression, protected the colonic mucosa against tissue injury, and reduced disease activity. Although the two agents appear equally effective in this model, it is not clear to what extent they share similar modes of action at the cellular and/or molecular level. Cortisol is known to exert immunomodulatory effects that have not yet been attributed to AKBA, including effects on lymphocyte differentiation, cytokine synthesis, and chemokine release from mast cells (30, 37). However, dexamethasone and AKBA do appear to share some common targets, including downregulation of 5-lipoxygenase (5-LO) and inhibition of endothelial CAM expression (26, 33, 37). Since it has been shown that 5-LO inhibition abrogates the P-selectin upregulation elicited by intestinal ischemia-reperfusion, it is possible that either or both agents down-regulate the expression of this adhesion molecule, at least in part, via 5-LO (10).

Although cortisol is widely used in the treatment of IBD, it has major side effects that limit its chronic use in these patients. The boswellic acids have not shown such deleterious side effects in any of the clinical studies published to date. It appears likely that purified AKBAs will manifest even fewer adverse effects than the heterogeneous natural compound used in most clinical trials (1). Consequently, AKBAs may warrant further attention as a potential alternative to existing medications (such as dexamethasone) that are used to treat patients with IBD.
GRANTS
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REFERENCES


