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Original Research

Tranexamic Acid and Supportive Measures to Treat Wasting Marmoset Syndrome

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Wasting marmoset syndrome (WMS) has high incidence and mortality rates and is one of the most important problems in captive common marmoset (*Callithrix jacchus*) colonies. Despite several reports on WMS, little information is available regarding its reliable treatment. We previously reported that marmosets with WMS had high serum levels of matrix metalloproteinase 9 (MMP9). MMP9 is thought to be a key enzyme in the pathogenesis of inflammatory bowel disease, the main disease state of WMS, and is activated by plasmin, a fibrinolytic factor. In a previous study, treating mice with an antibody to inhibit plasmin prevented the progression of inflammatory bowel disease. Here we examined the efficacy of tranexamic acid, a commonly used plasmin inhibitor, for the treatment of WMS, with supportive measures including amino acid and iron formulations. Six colony marmosets with WMS received tranexamic acid therapy with supportive measures for 8 wk. The body weight, Hct, and serum albumin levels of these 6 marmosets were increased and serum MMP9 levels decreased after this regimen. Therefore, tranexamic acid therapy may be a new and useful treatment for WMS.

Abbreviations: MMP9, matrix metalloprotein 9; WMS, wasting marmoset syndrome

The number of common marmosets (*Callithrix jacchus*) used for experimental purposes has increased due to several advantages, including their small body size, ease of handling, ease of breeding in captivity, and absence of severe zoonotic issues.[1] Wasting marmoset syndrome (WMS) is a disease unique to this species and is one of the most serious problems in the management of common marmosets. The main symptoms of WMS include weight loss, decreased muscle mass, and chronic diarrhea, and 50% to 80% of deaths of captive marmosets involve WMS.[5,8,14,17,24,25,29] Marmosets with WMS are characterized by their low body weight, anemia, hypoalbuminemia, and alopecia.[5,24,28] Few effective treatments for WMS are available.[25,29]

The main disease state in WMS is inflammatory bowel disease (IBD) anchored by chronic enteritis.[5,25,28] In humans, IBD (including Crohn disease and ulcerative colitis) is a serious disease with no curative treatment.[11,38] Although the specific cause of IBD remains poorly defined, the disease is thought to arise due to interactions between genetic and environmental factors and uncontrolled autoimmunity. Various inflammatory cytokines, including TNFα and IL6, play an important role in IBD.[30] Antibody treatments targeting these inflammatory cytokines are a mainstay of IBD management but can lead to adverse events, including infusion reactions, loss of response, and serum sickness.[33]

Matrix metalloproteinase 9 (MMP9), a member of the matrix metalloproteinase family, plays an important role in tissue remodeling, tumor growth, and inflammation by controlling inflammatory cytokine.[9,10,18,26] MMP9 is implicated in the development of inflammation by controlling various inflammatory cytokines, including TNFα. MMP9 contributes to IBD in humans and mice,[13,37,38,40] and we reported that serum MMP9 levels are elevated in marmosets with WMS.[41]

Plasmin, a key enzyme in the fibrinolytic cascade, activates MMP, including MMP9.[42] In addition, the use of antibodies to inhibit plasmin protected against colitis in a mouse model of IBD, and plasmin was a potential new treatment target for IBD in addition to other inflammatory cytokines.[27] Tranexamic acid is a plasmin inhibitor that has hemostatic and antiinflammatory effects. It is widely used in a several animal species, including humans, for various reasons, including trauma, hyperpigmentation, and surgery.[2,20,32,39] However, the efficacy of tranexamic acid for targeting MMP9 and treating IBD in humans or other animals has not yet been assessed. We therefore assessed the efficacy of tranexamic acid therapy with supportive measures, including amino acid and iron formulations, in WMS.

Materials and Methods

Animals. This study was approved and overseen by the Animal Experiments Committee of RIKEN (Saitama, Japan) and was conducted in accordance with the Institutional Guidelines for Experiments using Animals. Common marmosets (*Callithrix jacchus*) were reared at the RIKEN Brain Science Institute (Saitama, Japan) and maintained on a 12:12-h light:dark cycle at 27 °C and 50% humidity. All marmosets in this study were 2 to 6 y old. Marmosets had unrestricted access to water and food pellets (CMS-1M, Clea Japan, Tokyo, Japan) with added vitamins C and D, calcium, and acidophilus. Hot water and comb honey were added to soften the pellets and to increase the animals' preference for the food. Animals were given pieces of Calorie Mate (Otsuka Pharmaceutical,

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Tokyo, Japan), castella cake (Yamazaki Baking, Tokyo, Japan) or banana pudding (Kewpie, Tokyo, Japan) as treats.

A low body weight of less than 325 g reportedly indicates WMS, with a positive predict value of 96%.[5] Furthermore, WMS-affected animals are anemic and hypoalbuminemic[5,24,41] and have increased serum MMP9 levels.[41] In the current study, we defined marmosets with WMS as adult animals presenting with body weight of 325 g or less, Hct of 32% or less, serum albumin concentration of 4.4 g/dL or less, and serum MMP9 concentration of 27.9 ng/mL or greater. The Hct and albumin threshold values were determined according to previously reported the normative parameters of marmosets,[12] and the threshold value for serum MMP9 was determined on the basis of the highest value of the control group in our previous report.[41] Prior to treatment, adult marmosets weighing less than 325 g and with alopecia received a physical exam, CBC analysis, and serum chemistry evaluation. Animals that met the described criteria were used for this study (n = 6, Table 1). All animals had diarrhea or unformed stools before therapy.

WMS treatment regimen. All marmosets received tranexamic acid therapy, amino acid and iron supplementation, and rehydration. Tranexamic acid (1%) was made by diluting 5% tranexamic acid (Vasolamin Injection, Meiji Seika Pharma, Tokyo, Japan) 5-fold with saline (Otsuka Pharma Factory, Tokyo, Japan); 0.5-mL doses was administered intraperitoneally once daily by using 26-gauge needles. Amino acid supplementation (3 mL, Aminoleban Injection, Otsuka Pharma Factory) was administered into the saphenous vein 3 times each week by using 27-gauge butterfly needles. Ringers lactate (5 mL, Lactec Injection, Otsuka Pharma Factory) was administered with 0.5 mL of a vitamin formulation (C-PARA, Takata Pharma, Saitama, Japan) subcutaneously 3 times each week by using 26-gauge needles. An iron supplement (0.1 mL, Pet-Tinic, Pfizer, New York, NY) was administered orally each day. Marmoset were retrained manually for all procedures. The treatment regimen continued for 8 wk, and animals were monitored for an additional 4 wk after the treatment period.

Body weight measurement and appearance. The body weight and appearance of all animals were monitored weekly, before any other procedures were performed.

Blood collection. Blood samples (0.5 mL) were drawn from the femoral vein of manually restrained marmosets by using 26-gauge needles. A portion of the sample was used for CBC analysis, and the rest of the blood was allowed to stand for 1 h at room temperature before being centrifuged (1800 × g, 20 min, 4 °C). The serum was stored at −80 °C until further use. Blood collection and physical exams were performed every 2 wk, before any treatment was administered.

CBC and serum chemistry testing. CBC analysis, including Hct, was performed by using an automated analyzer (Celltac Alpha, MEK-6450, Nihon Kohden, Tokyo, Japan). The serum albumin test was performed using a DryChem 4000 system (FujiFilm, Tokyo, Japan).

Serum MMP9 concentration. Serum MMP9 levels were measured by using a commercial ELISA kit (Quantikine ELISA Human MMP9, SMP900, R&D Systems, Minneapolis, MN).

Statistical analysis. The Friedman test was performed to evaluate the effect of tranexamic acid therapy with supportive measures on body weight, Hct, albumin, and serum MMP9 levels before treatment, after the 8-wk treatment phase, and after the 4-wk follow-up phase. Two comparisons (before compared with after treatment and before treatment compared with follow-up) for each value were analyzed by using the Bonferroni post hoc test. A P value of less than 0.05 was considered statistically significant (GraphPad Prism version 6 for Windows, GraphPad Software, San Diego, CA). Data are presented as the mean ± SEM.

Table 1. Pretreatment characteristics of the 6 marmosets included in the study

Marmoset	Sex	Age (y)	Weight (g)	Hct (%)	Albumin (g/dL)	MMP9 (ng/mL)
1	Female	4	278.8	21.9	3.2	40.3
2	Female	2	259.3	27.9	4.3	190.5
3	Female	2	272.1	26.4	4.0	43.8
4	Male	4	242.0	27.1	3.5	46.2
5	Male	4	264.6	26.3	4.2	142.8
6	Male	2	254.8	31.1	3.4	52.0

Results

Changes in body weight. The body weight of our 6 marmosets with WMS differed significantly ($P < 0.05$) between the pretreatment, posttreatment, and follow-up time points. Bonferroni post hoc testing revealed that body weight (mean ± SEM) was higher after treatment (342.9 ± 15.0 g) and during follow-up (344.4 ± 20.8 g) compared with before treatment (270.7 ± 5.4 g; $P < 0.05$ for both comparisons; Figure 1).

Changes in Hct value. The Hct level were higher at follow-up (42.2% ± 2.4%) than before treatment (26.8% ± 1.2%; $P < 0.05$) but did not differ significantly between the pretreatment and posttreatment (39.5% ± 2.1%) time points (Figure 2).

Changes in serum albumin level. The serum albumin concentration of our 6 marmosets with WMS was higher after treatment (5.4 ± 0.3 g/dL) and at follow-up (5.2 ± 0.4 g/dL) compared with before treatment (3.8 ± 0.2 g/dL; $P < 0.05$ for both comparisons; Figure 3).

Changes in serum MMP9 levels. MMP9 levels were lower ($P < 0.05$) at follow-up (42.2 ± 2.4 ng/mL) than before treatment (85.9 ± 26.3 ng/mL) but did not differ significantly between the pretreatment and posttreatment (41.9 ± 7.7 ng/mL) periods (Figure 4). Figure 5 shows the overall clinical course in a single marmoset (no. 4) throughout the experimental period.

Changes in appearance. All 6 marmosets had alopecia, especially at the tail base, and ulcers on the tail base before they began tranexamic acid therapy with supportive measures (Figure 6 A), and a trend for improvement in appearance was apparent after treatment. At follow-up of all animals, the alopecia had almost resolved, and the ulcers at the tail base showed signs of healing (scarring; Figure 6 B).

Discussion

The results of this study indicate that tranexamic acid therapy, combined with amino acid and iron supplementation, ameliorates alopecia; increases body weight, Hct, and serum albumin values; and decreases serum MMP9 levels in marmosets with WMS.

One of the most important marmoset diseases, WMS is a significant risk factor for wasted research resources due to its high incidence and death rate.[19] A reported 60% of captive marmosets have WMS, which contributes to 50% to 80% of deaths in these animals.[5,8,14,17,24,25,29] The main symptoms of WMS are weight loss, decreased muscle mass, chronic diarrhea, and alopecia; associated

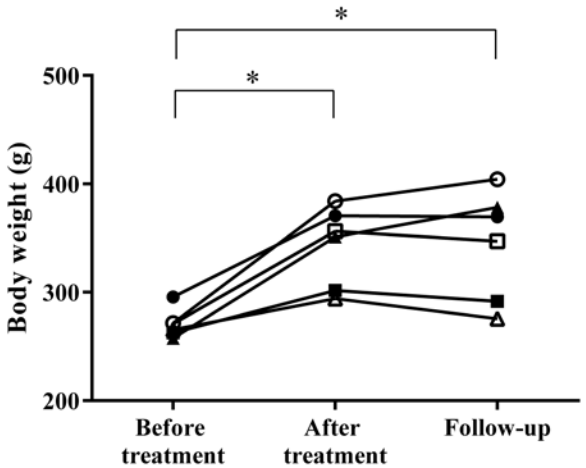

Figure 1. Body weights of all 6 marmosets before and after the 8-wk treatment and after 4 wk of follow-up. In all animals, body weight was increased after treatment and follow-up compared with before treatment. *, $P < 0.05$ compared with value before treatment.

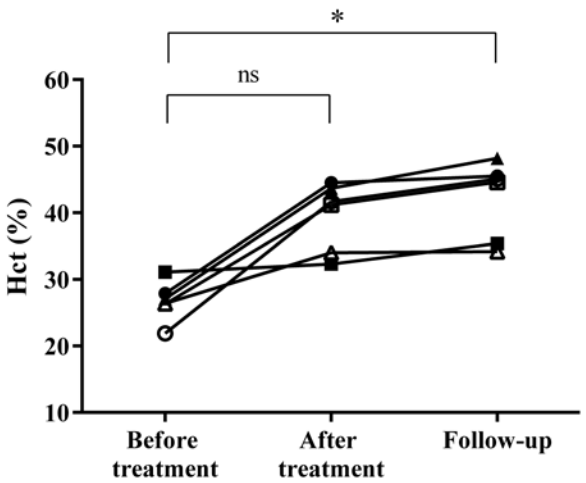

Figure 2. Hct values of all 6 marmosets before and after the 8-wk treatment and after 4 wk of follow-up. In all animals, Hct showed an increasing trend between before and after treatment and were significantly increased at follow-up compared with before treatment. *, $P < 0.05$ between values; ns, nonsignificant difference.

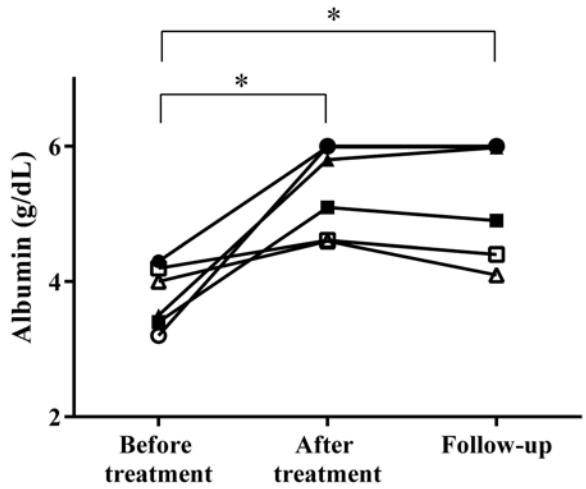

Figure 3. Serum albumin of all 6 marmosets before and after the 8-wk treatment and after 4 wk of follow-up. In all animals, serum albumin levels were increased after treatment and follow-up compared with before treatment. *, $P < 0.05$ between values.

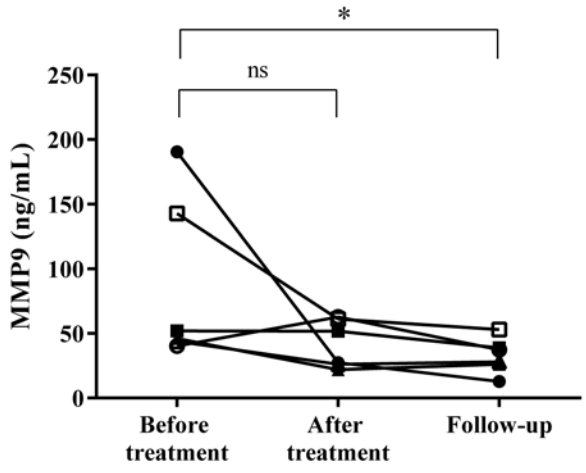

Figure 4. Serum MMP9 levels of all 6 marmosets before and after the 8-wk treatment and after 4 wk of follow-up. In all animals, the serum MMP9 levels showed a decreasing trend between before and after treatment and were significantly decreased at follow-up compared with before treatment. *, $P < 0.05$ between values; ns, nonsignificant difference.

clinical pathology findings include decreased Hct and serum albumin levels.[5,8,14,17,19,24,25,28,29] Several reports have implicated IBD as a key component of WMS.[5,25,28]

Without treatment, WMS is a deadly progressive disease.[5,29] Although several studies have reported nutritional therapeutic interventions for WMS,[4,14,36] including a gluten-free diet,[22] the results are inconsistent, and the diets do not achieve remission during the terminal stages of WMS.[5] In humans, glucocorticoids are considered the most effective treatment of IBD and are commonly used for the induction of its remission.[23,35] Prednisolone, one of the most commonly used glucocorticoids, induced remission in 77% of IBD patients within 2 wk.[6] However, the use of prednisolone as therapy for WMS has not been reported and, in our experience, does not consistently lead to remission of WMS. This inconsistency could be due to prednisolone's severe adverse effects, which may prompt treatment cessation before remission occurs. Similarly, adverse effects are the most significant problems associated with glucocorticoid therapy in humans with IBD.[16] In comparison, budesonide, a relatively new glucocorticoid, increased body weight and serum albumin levels in marmosets with WMS.[29] Because budesonide is considered to have fewer side effects than do other glucocorticoids,[19] it may be a potential option for WMS treatment. However, budesonide treatment reportedly is relatively ineffective in animals with acute forms of WMS,[29] and several human patients with IBD have developed budesonide-related adrenal insufficiency.[3] Therefore, WMS treatment options other than glucocorticoids are desirable.

Tranexamic acid combined with supportive care measures did not cause any noteworthy adverse effects in any of our animals during the course of the current study. In addition, all 6 marmosets continued to thrive for at least 3 mo after the experiment, during which they maintained or continued to gain body weight. To our knowledge, our study is the first to demonstrate effective treatment of WMS without the use of glucocorticoids.

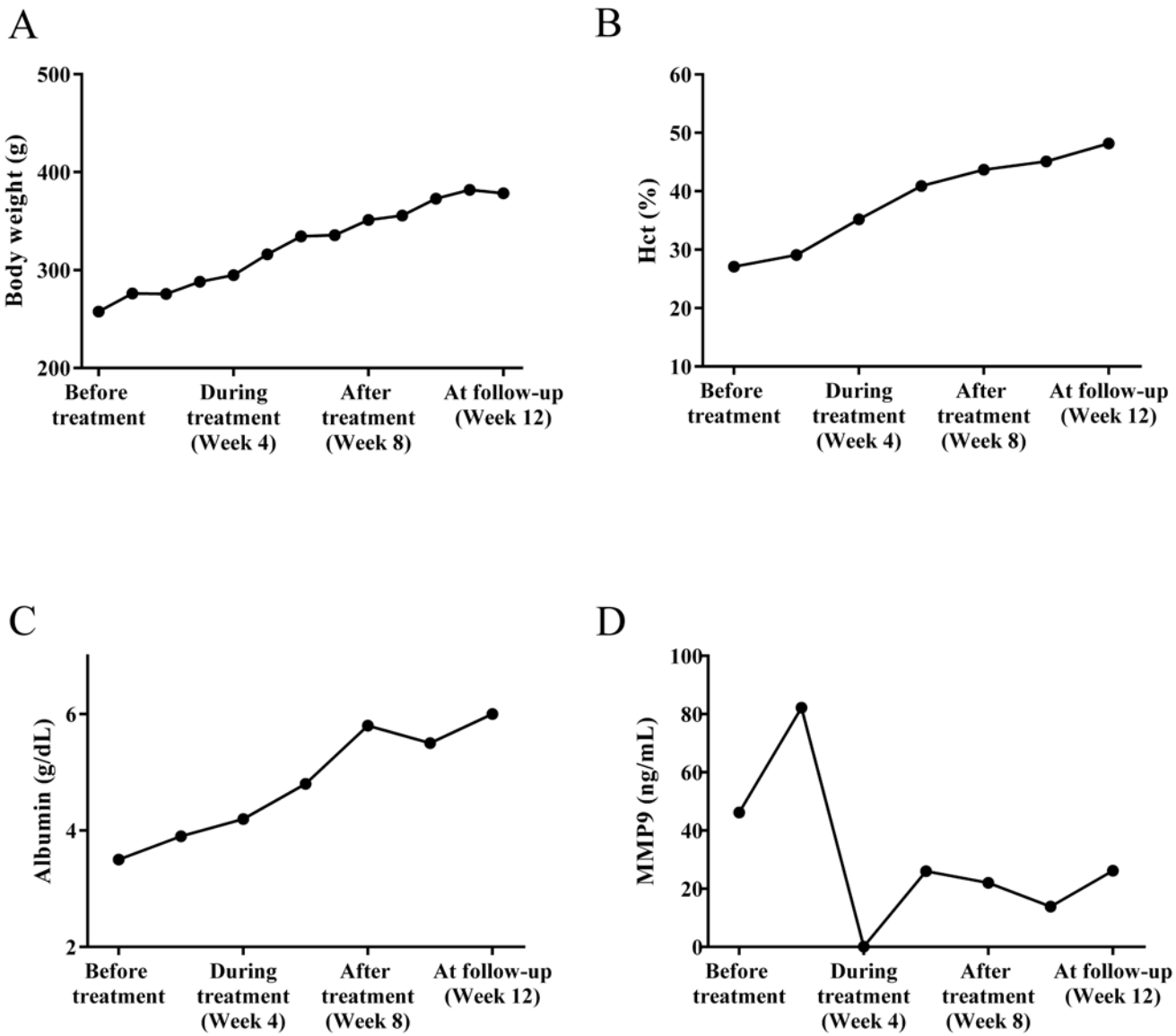

Figure 5. Changes in (A) body weight, (B) Hct, (C) serum albumin level, and (D) serum MMP9 concentration throughout the experimental period in a marmoset (no. 4) receiving tranexamic acid with supportive measures. Body weight was measured weekly, and Hct, serum albumin, and serum MMP9 levels were measured every 2 wk. Body weight, Hct, and serum albumin levels show an increasing trend, whereas serum MMP9 levels show a decreasing trend throughout the experimental period.

According to fecal occult blood tests, treatment with tranexamic acid, which has a hemostatic effect,[31] reduced the amount of blood in the stools of marmosets with chronic diarrhea.[27] Although we did not perform fecal occult blood testing in the current study, the hemostatic effect of tranexamic acid might have increased the Hct of the marmosets. In addition, our findings imply that tranexamic acid exerts a suppressive effect on MMP9, which contributes to IBD in mice and humans,[13,37,38,40] in WMS. MMP9 levels were upregulated in the colonic mucosa of mice with dextran sodium sulfate-induced colitis,[34] and fecal MMP9 levels were increased in human patients with active IBD.[21] We previously reported that WMS-affected animals had elevated serum MMP9 levels and proposed that MMP9 as a target for WMS treatment.[41]

MMP9-treated mouse intestinal epithelial cells recovered more slowly after treatment than did control cells, suggesting that MMP9 impairs wound healing and cell attachment during intestinal inflammation.[7] In our previous study, we noted epithelial damage and disruption of crypt architecture in the intestines of WMS-affected animals, which also were anemic and hypoalbuminemic, likely due to an absorption defect.[41] Other colleagues have reported various abnormalities in WMS-affected animals, such as bloody feces and poor nutritional conditions, including anemia and hypoalbuminemia.[28] These abnormalities might reflect MMP9-induced impairment of intestinal wound healing, including that of the absorptive epithelium.

In human cells, plasmin converts the precursor form of MMP3 to its active form, which in turn activates MMP9.[15] The antibody-associated inhibition of plasmin suppressed MMP9 activation and improved the survival rate in mice with induced enteritis.[27] In the current study, we used tranexamic acid, which is a less expensive and more readily available plasmin inhibitor than are antiplasmin antibodies. Tranexamic acid has high-affinity binding

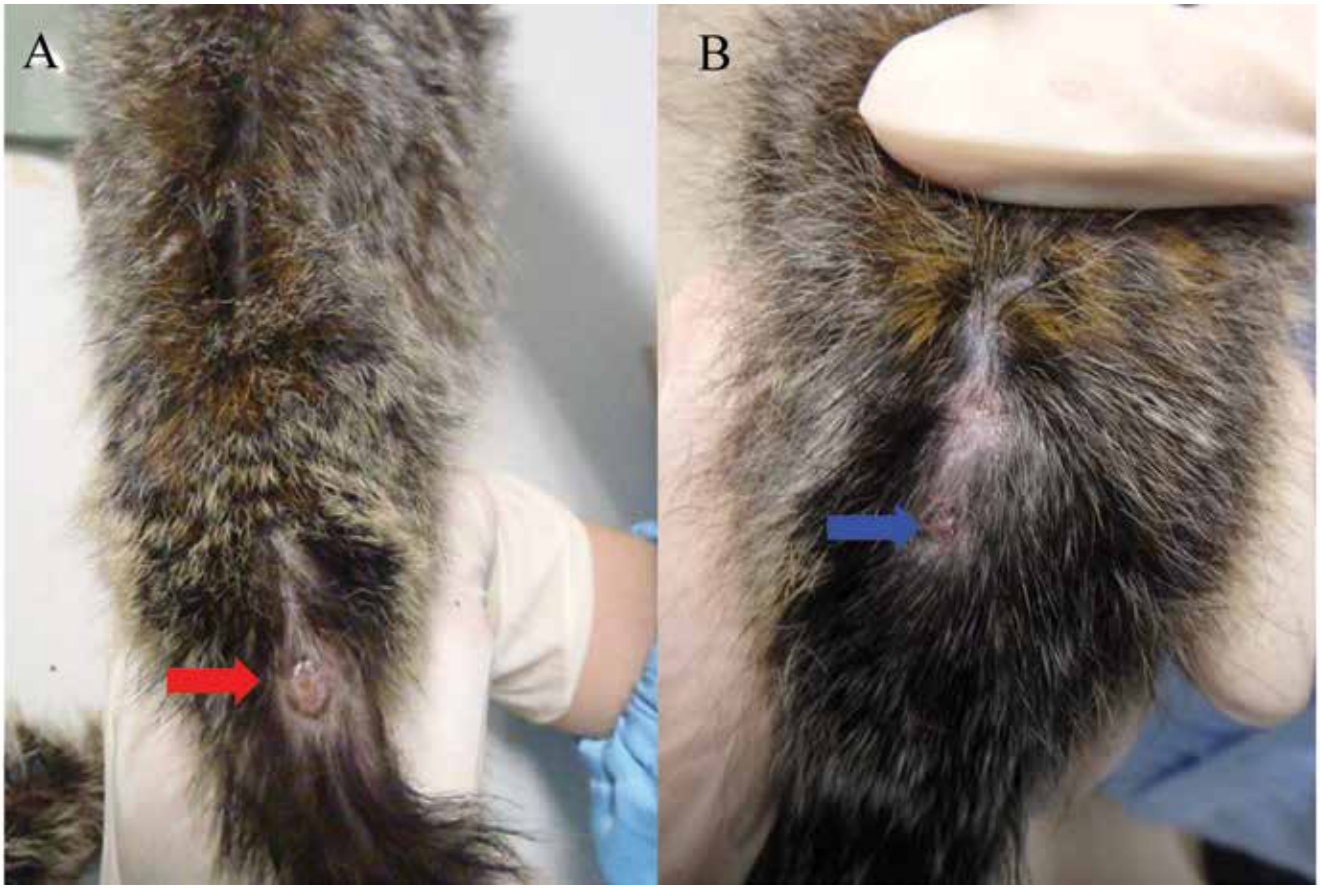

Figure 6. Appearance of a marmoset (A) before treatment and (B) at follow-up. Before treatment, all 6 marmosets showed alopecia and ulcers at the tail base. Trends of improved hair coats and decreased ulcer scarring were observed in all 6 animals after treatment and at follow-up. (A) The red arrow indicates an ulcer in an area of alopecia before treatment. (B) The blue arrow indicates a healed ulcer (scar) after tranexamic acid therapy with supportive measures.

sites on plasmin and inhibits the action of plasmin on fibrin and cells.[31] In the current study, tranexamic acid therapy decreased serum MMP9 levels, which are presumed to be associated with enteritis, in marmosets with WMS and improved their overall health status. Thus, tranexamic acid may effectively treat enteritis by suppressing MMP9.

The magnitude of improvement differed among our 6 marmosets, suggesting that the appropriate dose and duration of tranexamic acid may depend on the extent of intestinal inflammation in the individual subject. Although further studies are needed to investigate the appropriate dose and duration of tranexamic acid for WMS treatment, all 6 animals in the current study demonstrated improvement in multiple health parameters, showing that tranexamic acid has great potential as a WMS treatment. Tranexamic acid can be administered orally; advantages of oral administration include decreased restraint-induced stress and reduced costs. Future experiments aimed at evaluating the efficacy of oral administration of tranexamic acid for the treatment of WMS are warranted.

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References

1. **Abbott DH, Barnett DK, Colman RJ, Yamamoto ME, Schultz-Darken NJ.** 2003. Aspects of common marmoset basic biology and life history important for biomedical research. Comp Med **53:**339–350.
2. **Atikah N, Singh G, Maulahela H, Cahyanur R.** 2015. Tranexamic acid in the management of upper gastrointestinal bleeding: an evidence-based case report. Acta Med Indones **47:**172–175.
3. **Arntzenius A, van Galen L.** 2015. Budesonide-related adrenal insufficiency. BMJ Case Rep
4. **Barnard D, Knapka J, Renquist D.** 1988. The apparent reversal of a wasting syndrome by nutritional intervension in *Saguinus mystax*. Lab Anim Sci **38:**282–288.
5. **Baxter VK, Shaw GC, Sotuyo NP, Carlson CS, Olson EJ, Zink MC, Mankowski JL, Adams RJ, Hutchinson EK, Metcalf Pate KA.** 2013. Serum albumin and body weight as biomarkers for the antemortem identification of bone and gastrointestinal disease in the common marmoset. PLoS One **8:**e82747.
6. **Carter MJ, Lobo AJ, Travis SP, IBD Section, British Society of Gastroenterology.** 2004. Guidelines for the management of inflammatory bowel disease in adults. Gut **53:**v1–v16.
7. **Castaneda FE, Walia B, Vijay-Kumar M, Patel NR, Roser S, Kolachala VL, Rojas M, Wang L, Oprea G, Garg P, Gewirtz AT, Roman J, Merlin D, Sitaraman SV.** 2005. Targeted deletion of metalloproteinase 9 attenuates experimental colitis in mice: central role of epithelial-derived MMP. Gastroenterology **129:**1991–2008.
8. **Chalifoux LV, Bronson RT, Escajadillo A, McKenna S.** 1982. An analysis of the association of gastroenteric lesions with chronic wasting syndrome of marmosets. Vet Pathol Suppl **19 Suppl 7:**141–162.

9. **Chen LC, Noelken ME, Nagase H.** 1993. Disruption of the cysteine-75 and zinc ion coordination is not sufficient to activate the precursor of human matrix metalloproteinase 3 (stromelysin 1). Biochemistry **32:**10289–10295.
10. **Elkington PT, Friedland JS.** 2006. Matrix metalloproteinases in destructive pulmonary pathology. Thorax **61:**259–266.
11. **Flores AI, Gómez-Gómez GJ, Masedo-González Á, Martínez-Montiel MP.** 2015. Stem cell therapy in inflammatory bowel disease: a promising therapeutic strategy? World J Stem Cells **7:**343–351.
12. **Fortman JD, Hewett TA, Bennett BT.** 2001. The laboratory nonhuman primate. Boca Raton (FL): CRC Press.
13. **Gerlach K, Hwang Y, Nikolaev A, Atreya R, Dornhoff H, Steiner S, Lehr HA, Wirtz S, Vieth M, Waisman A, Rosenbauer F, McKenzie AN, Weigmann B, Neurath MF.** 2014. TH9 cells that express the transcription factor PU.1 drive T-cell-mediated colitis via IL9 receptor signaling in intestinal epithelial cells. Nat Immunol **15:**676–686.
14. **Gore MA, Brandes F, Kaup FJ, Lenzner R, Mothes T, Osman AA.** 2001. Callitrichid nutrition and food sensitivity. J Med Primatol **30:**179–184.
15. **Hahn-Dantona E, Ramos-DeSimone N, Sipley J, Nagase H, French DL, Quigley JP.** 1999. Activation of proMMP9 by a plasmin–MMP3 cascade in a tumor cell model. Regulation by tissue inhibitors of metalloproteinases. Ann N Y Acad Sci **878:**372–387.
16. **Hanauer SB.** 2002. New steroids for IBD: progress report. Gut **51:**182–183.
17. **Ialeggio DM**, **Baker AJ.** 1995. Results of a preliminary survey into wasting marmoset syndrome in Callitrichid collections. p 148–158. In: Proceedings of the first annual conference of the National Advisory Group of the American Zoo and Aquarium Association, New York. Silver Spring (MD): American Zoo and Aquarium Association.
18. **Imai K, Yokohama Y, Nakanishi I, Ohuchi E, Fujii Y, Nakai N, Okada Y.** 1995. Matrix metalloproteinase 7 (matrilysin) from human rectal carcinoma cells. Activation of the precursor, interaction with other matrix metalloproteinases and enzymic properties. J Biol Chem **270:**6691–6697.
19. **Keller R, Stoll R, Foerster EC, Gutsche N, Domschke W.** 1997. Oral budesonide therapy for steroid-dependent ulcerative colitis: a pilot trial. Aliment Pharmacol Ther **11:**1047–1052.
20. **Kim MS, Bang SH, Kim JH, Shin HJ, Choi JH, Chang SE.** 2015. Tranexamic acid diminishes laser-induced melanogenesis. Ann Dermatol **27:**250–256.
21. **Kolho KL, Sipponen T, Valtone E, Savilahti E.** 2013. Fecal calprotectin, MMP9, and human β-defensin 2 levels in pediatric inflammatory bowel disease. Int J Colorectal Dis **29:**43–50.
22. **Kuehnel F, Mietsch M, Buettner T, Vervuert I, Ababneh R, Einspanier A.** 2013. The influence of gluten on clinical and immunologic status of common marmosets (*Callithrix jacchus*). J Med Primatol **42:**300–309.
23. **Lichtenstein GR, Hanauer SB, Sandborn WJ.** 2015. Emerging treatment options in mild to moderate ulcerative colitis. Gastroenterol Hepatol (N Y) **11:**1–16.
24. **Logan AC, Khan KN.** 1996. Clinical pathologic changes in 2 marmosets with wasting syndrome. Toxicol Pathol **24:**707–709.
25. **Ludlage E, Mansfield K.** 2003. Clinical care and diseases of the common marmoset (*Callithrix jacchus*). Comp Med **53:**369–382.
26. **Lyons JG, Birkedal-Hansen B, Pierson MC, Whitelock JM, Birkedal-Hansen H.** 1993. Interleukin 1β and transforming growth factor α or epidermal growth factor induce expression of M_r 95,000 type IV collagenase or gelatinase and interstitial fibroblast-type collagenase by rat mucosal keratinocytes. J Biol Chem **268:**19143–19151.
27. **Munakata S, Tashiro Y, Nishida C, Sato A, Komiyama H, Shimazu H, Dhahri D, Salama Y, Eiamboonsert S, Takeda K, Yagita H, Tsuda Y, Okada Y, Nakauchi H, Sakamoto K, Heissig B, Hattori K.** 2015. Inhibition of plasmin protects against colitis in mice by suppressing matrix metalloproteinase 9-mediated cytokine release from myeloid cells. Gastroenterology **148:**565–578.e4.
28. **Nakashima E, Okano Y, Niimi K, Takahashi E.** 2013. Detection of calprotectin and apoptotic activity in the colon of marmosets with chronic diarrhea. J Vet Med Sci **75:**1633–1636.
29. **Otovic P, Smith S, Hutchinson E.** 2015. The use of glucocorticoids in marmoset wasting syndrome. J Med Primatol **44:**53–59.
30. **Reimund JM, Wittersheim C, Dumont S, Muller CD, Kenney JS, Baumann R, Poindron P, Duclos B.** 1996. Increased production of tumour necrosis factor α, interleukin 1 β, and interleukin 6 by morphologically normal intestinal biopsies from patients with Crohn's disease. Gut **39:**684–689.
31. **Renckens R, Weijer S, de Vos AF, Pater JM, Meijers JC, Hack CE, Levi M, van der Poll T.** 2004. Inhibition of plasmin activity by tranexamic acid does not influence inflammatory pathways during human endotoxemia. Arterioscler Thromb Vasc Biol **24:**483–488.
32. **Roberts I.** 2015. Tranexamic acid in trauma: how should we use it? J Thromb Haemost **13:**S195–S199.
33. **Rutgeerts P, Van Assche G, Vermeire S.** 2004. Optimizing antiTNF treatment in inflammatory bowel disease. Gastroenterology **126:**1593–1610.
34. **Santana A, Medina C, Paz-Cabrera MC, Díaz-Gonzalez F, Farré E, Salas A, Radomski MW, Quintero E.** 2006. Attenuation of dextran sodium sulphate-induced colitis in matrix metalloproteinase-9 deficient mice. World J Gastroenterol **12:**6464–6472.
35. **Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH.** 2008. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev **16:**CD000296.
36. **Shimwell M, Warrington BF, Fowler JS.** 1979. Dietary habits relating to 'wasting marmoset syndrome' (WMS). Lab Anim **13:**139–142.
37. **Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV Jr, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF.** 2005. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol **19 Suppl A:** 5A–36A.
38. **van der Marel S, Majowicz A, van Deventer S, Petry H, Hommes DW, Ferreira V.** 2011. Gene and cell therapy based treatment strategies for inflammatory bowel diseases. World J Gastrointest Pathophysiol **2:**114–122.
39. **Vanek T, Straka Z.** 2013. Topical use of tranexamic acid in cardiac surgery—a review and meta-analysis of 4 randomized controlled trials. Cor Vasa **55:**e184–e189.
40. **Williams IR.** 2004. Chemokine receptors and leukocyte trafficking in the mucosal immune system. Immunol Res **29:**283–292.
41. **Yoshimoto T, Niimi K, Takahashi E.** 2016. Serum matrix metalloproteinase 9 (MMP9) as a biochemical marker for wasting marmoset syndrome. J Vet Med Sci **78:**837–843.
42. **Zou T, Ling C, Xiao Y, Tao X, Ma D, Chen ZL, Strickland S, Song H.** 2006. Exogenous tissue plasminogen activator enhances peripheral nerve regeneration and functional recovery after injury in mice. J Neuropathol Exp Neurol **65:**78–86.