Development of Antibodies Against Humanized Antitumor Necrosis Factor and Loss of Efficacy in a Black Spider Monkey With Inflammatory Bowel Disease

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In July 2005, a 10-year-old red-faced black spider monkey (Ateles paniscus) (Figure 1) at the Artis Zoo in Amsterdam developed a disease comparable to ulcerative colitis in humans. The classical signs included severe diarrhea, weight loss (her weight decreased from 13–8 kg in 7 months), and rectal bleeding.

Blood tests showed typical signs of acute and chronic inflammation. In fecal cultures, neither bacterial pathogens nor parasites were detected. Ultrasound assessment of the abdomen revealed thickening of the descending colon.

Based upon these results and the results obtained through endoscopic visualization and histology performed on biopsies, the diagnosis inflammatory bowel disease was made.

The monkey was treated with sulfasalazine, prednisolone, mesalazine, probiotics, and dietary alterations subsequently. Because there was no improvement in clinical condition, treatment with adalimumab, a human monoclonal antibody to tumor necrosis factor, 20 mg (resembling a dose of approximately 2.5 mg per kg bodyweight) once every 2 weeks was initiated.

Therapy with adalimumab initially ameliorated inflammatory activity, improved stool consistency, and the animal’s weight increased from 8.55 kg to 9.80 kg.

However, after 5 weeks and 3 injections with adalimumab, the disease activity increased. Serum antibodies to the anti-TNF α medication (190 AE/mL) had developed with undetectable serum levels of adalimumab (<0.4 μg/mL); raising the dosage to 40mg every 2 weeks did not improve the clinical situation, therefore adalimumab was discontinued. A few weeks after cessation of treatment, the monkey died with wasting syndrome characterized by chronic bloody diarrhea.

At necropsy, there was mesenteric lymphadenopathy and the entire colon was found to be markedly thickened with an hemorrhagic and hyperaemic mucosa alternated by grayish lesions. The lesions were similar to those described previously for Crohn’s disease.

Terminal ileitis resembling inflammatory bowel disease in nonhuman primates has been reported before. Treatment, however, remains difficult.1

The medical therapy for inflammatory bowel disease in humans can be difficult but has improved considerably since the introduction of new agents such as “biologics.”2,3 Antitumor necrosis factor agents such as infliximab have shown to be effective in the management of active disease and as maintenance therapy in patients who have entered symptomatic remission.4,5 Some patients, however, have persistent active disease or show loss of efficacy after prolonged treatment. This may be due to the formation of antibodies against infliximab, which is associated with an accelerated clearance of the antibody. In some cases, continuation of treatment with higher dosages results in decreased levels of anti infliximab antibodies.6,7

It has been reported that in up to 40% of human patients treated with infliximab, anti-infliximab antibodies are detectable.7 Adalimumab seems to be less immunogenic; antibodies were detectable in about 10% of patients with RA.8

Humans and apes share about 99% of their genes; the genetic resemblance between this kind of monkey and humans is not known. With this case report, we have illustrated the influence of immunogenicity in the formation of antibodies against humanized antitumor necrosis factor, leading to inefficacy of the therapy.

REFERENCES