Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Tacrolimus for Crohn's Disease

Issue 88 • September 2006

Summary

- ✓ Tacrolimus (FK-506) is an immunosuppressant that is being investigated for use in patients with Crohn's disease, mainly in those with refractory illness and fistulizing patterns of the disease.
- ✓ Evidence from a small, randomized controlled trial indicates that, compared with placebo, tacrolimus is associated with higher rates of improvement and similar rates of remission in those with fistulizing patterns of disease.
- ✓ Nephrotoxicity, which has been reported with the use of tacrolimus in clinical trials, seems to improve with dose reduction, but may be associated with irreversible histologic changes.
- ✓ More studies are needed to determine the optimal dose and duration of therapy, and whether the drug is beneficial to patients with non-fistulizing patterns of Crohn's disease.

The Technology

Tacrolimus (FK-506) has an established role as an immunosuppressant in patients who have undergone solid organ transplantation.[1,2] It inhibits calcineurin, an enzyme involved in activating the immune system, thereby decreasing the risk of organ rejection.[1] Tacrolimus prevents T-cell activation, and prevents the production of lymphokines, notably interleukin-2.[2] Based on these effects, there has been increasing interest over the last decade in its use as a therapeutic alternative for patients with Crohn's disease. In Canada, tacrolimus is marketed by Astellas Pharma Canada, Inc. as Prograf® (systemic) and Protopic® (topical).[3]

Regulatory Status

In 1995, tacrolimus was approved for use as a systemic immunosuppressant in Canada.[4] Its indications include prophylaxis of organ rejection in patients with liver or kidney transplants, and rheumatoid arthritis.[3] In 2001, tacrolimus was approved for use as a topical immunomodulator for the treatment of atopic dermatitis.[5] Astellas Pharma Canada, Inc. is not developing tacrolimus for Crohn's disease, and did not disclose its development strategy for additional indications (Niten Barua, Astellas Pharma Canada Inc., Markham, ON: personal communication, 2006 Jul 20).

Patient Group

Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract.[6] It can affect the mucosa anywhere from the mouth to the anus.[6,7] The disease may be classified according to the location affected (e.g., terminal ileal, colonic, upper gastrointestinal), or the pattern (i.e., inflammatory, fistulizing, stricturing).[6,8] Exacerbations and remissions characterize the clinical course, and extra-intestinal manifestations, such as inflammation of the joints, skin, or eyes, occur in ≤30% of patients.[6,9-11] Approximately 80% of patients need surgical intervention, which underscores the limitations of current drug therapies.[9,12]

The prevalence of Crohn's disease in Canada is estimated at 198.5 cases per 100,000 population based on provincial statistics, and the annual incidence is estimated at 14.6 cases per 100,000 population.[13]

The cause of Crohn's disease is unclear, but genetic susceptibility and an abnormal immune response to environmental triggers are believed to be involved.[6,7] When these factors are present, an overproduction of pro-inflammatory cytokines at the mucosal level results.[12] Proposed environmental triggers include smoking, use of non-steroidal anti-inflammatory drugs, and infections.[7,14]

Current Practice

The choice of therapy for patients with Crohn's disease depends on the severity of illness, site of involvement, pattern of disease, and presence of complications or extra-intestinal manifestations.[8,15,16] Therapy commonly comprises treatment of acute disease, or induction of remission; and maintenance of remission.[16]

Pharmacological agents that are used in treatment include corticosteroids (budesonide, methylprednisolone, prednisone), 5-aminosalicylates (mesalamine, sulfasalazine), immunomodulators (azathioprine, 6-mercaptopurine, cyclosporine, methotrexate), biologic agents (infliximab), and antibiotics (ciprofloxacin, metronidazole).[15,16] Dietary interventions, such as elemental or polymeric diets, or total parenteral nutrition, may be used as adjunctive therapy in certain situations.[6] Surgery is generally reserved for patients with stenotic obstructions, infectious complications, pre-cancerous or cancerous lesions, or medically refractory disease.[16]

The Evidence

In one high-quality, randomized, double-blind, placebo-controlled trial that evaluated the use of tacrolimus in patients with Crohn's disease,[17] 48 participants with antibiotic-resistant draining enterocutaneous fistulas were randomized to receive oral tacrolimus (0.2 mg/kg/day, adjusted to whole blood concentrations of 10 ng/mL to 20 ng/mL) or placebo for 10 weeks. Stable doses of corticosteroids, immunosuppressants (other than cyclosporine), 5-aminosalicylates, and oral antibiotics were permitted. The primary outcome measure was fistula improvement, defined as closure of ≥50% of draining fistulas, with maintenance of closure for ≥4 weeks. Fistula remission (defined as complete closure of all fistulas, with maintenance of closure for ≥4 weeks) was a secondary outcome.

Results based on the intention-to-treat population (n=46) showed significantly better fistula improvement with tacrolimus than with placebo [nine of 21 (43%) versus two of 25 (8%); p=0.01]. The rates of fistula remission were not significantly different between the groups [two of 21 (10%) for tacrolimus versus two of 25 (8%) for placebo; p=1.0]. Concomitant therapy with azathioprine or 6-mercaptopurine, or previous therapy with infliximab, did not seem to influence the response to tacrolimus. Most patients had peri-anal fistulas, so the results may not apply to those with abdominal fistulas.

Data from small, prospective, open-label studies; retrospective, observational studies; and case reports or case series suggest that the use of tacrolimus leads to beneficial effects in patients with disease that is refractory to steroids[18-20] or other conventional therapies,[21-25] and in those with fistulizing[26,27] or peri-anal disease,[28,29] extra-intestinal manifestations,[30,31] or toxic megacolon.[32]

Adverse Effects

The most serious adverse event reported in clinical trials was nephrotoxicity.[17,20,22,23,28] In the randomized controlled trial, nephrotoxicity (defined as an increase in serum creatinine from baseline to >132 µmol/L) occurred with a significantly higher frequency in patients treated with tacrolimus than in those treated with placebo [eight of 21 (38%) versus zero of 25 (0%); p=0.008].[17]

Other common adverse events that were reported more often with tacrolimus than with placebo included headache (p=0.01), insomnia (p=0.006), leg cramps (p=0.01), paresthesias (p<0.001), and tremor (p=0.006).[17] The authors reported that adverse events were successfully managed with dose reduction.

A Health Canada advisory has been issued regarding the use of topical tacrolimus for eczema and potential cancer risk, based on a US advisory that cited information from animal studies, case reports, and pharmacological activity.[33,34]

Administration and Cost

The optimal dosage of tacrolimus for the treatment of Crohn's disease remains to be determined. It is usually administered at 0.1 mg/kg/day to 0.2 mg/kg/day when given orally, or 0.01 mg/kg/day to 0.02 mg/kg/day when given intravenously.[35] Dosages are adjusted based on blood levels and toxicity, with a common target range of 10 ng/mL to 20 ng/mL.[35] As many adverse effects of tacrolimus seem to be dose-related, it has been suggested that the efficacy of lower doses (e.g., 0.05 mg/kg/day to 0.15 mg/kg/day orally, adjusted to target levels of 3 ng/mL to 10 ng/mL) be determined.[17]

Regimens ranging from 0.05% applied twice daily[29] to 0.3% applied daily[36] have been used topically for peri-anal disease or pyoderma gangrenosum related to Crohn's disease. The daily use of tacrolimus enemas (containing 2 mg or 4 mg per 150 mL) for left-sided colitis has been reported.[37]

Monitoring of whole blood tacrolimus concentrations, and levels of electrolytes and serum creatinine, is recommended during systemic therapy. These parameters are generally measured weekly for the first month, biweekly during the second month, and monthly thereafter.[35,38]

The average daily wholesale price for oral therapy at a dosage of 0.1 mg/kg/day to 0.2 mg/kg/day for a 70 kg individual is C$17.66 to C$35.32. This corresponds to an annual cost of C$6,446 to C$12,892.[39] The daily price for intravenous therapy, which is only available in hospital, is C$17.95 to C$35.90 for a 70 kg individual.[39] As the most likely role for tacrolimus seems to be in the treatment of refractory or fistulizing disease,[7,38] these costs would be in addition to those of standard therapies. Costs that are associated with the blood tests needed for monitoring of dosing and toxicity would also be incurred. If the need for hospitalization or surgery (which account for most of the costs in treating Crohn's disease) were reduced as a result of using tacrolimus, therapy would likely be cost-effective.[40]

Concurrent Development

New compounds and marketed agents are being investigated for the treatment of Crohn's disease. Phase III trials with the marketed tumour necrosis factor inhibitor, adalimumab (Humira®), are ongoing.[41] Other biologics at the same stage of development include certolizumab pegol (CDP-870) and fontolizumab (Huzaf®).[15,41] Promising results from randomized controlled trials have been demonstrated with anti-inflammatory cytokines (interleukin-10 and interleukin-11), thalidomide analogues (CC-1088), and colony-stimulating factors (sargramostim).[42] Astellas Pharma Canada, Inc. is conducting phase III studies for tacrolimus in the treatment of ulcerative colitis in Japan (Niten Barua: personal communication, 2006 Jul 20).

Rate of Technology Diffusion

Evidence is lacking to support the routine use of tacrolimus for patients with Crohn's disease. The drug's main role seems to be the treatment of patients with peri-anal fistulas that are resistant to other recommended therapies, including antibiotics, azathioprine or 6-mercaptopurine, and infliximab.[6,7,17] Such fistulas occur in approximately 2.5% to 4.5% of patients.[38]

Concerns about nephrotoxicity, which may be associated with irreversible histologic changes, will likely limit the use of tacrolimus.[17] The need for routine laboratory monitoring may also discourage use, although similar monitoring is necessary with other immunosuppressants.

Reduced toxicity would be more likely with the use of tacrolimus as topical therapy for limited cutaneous disease, compared with systemic therapy, but more study is needed before its use can be widely recommended.

Implementation Issues

Additional data from controlled clinical trials are required to assess the optimal dosage and duration of tacrolimus therapy, and whether it is beneficial in patients with non-fistulizing patterns of disease. Tacrolimus will unlikely become a viable alternative for patients with non-fistulizing disease, however, given its similar mechanism of action to that of cyclosporine,[2] the documented lack of efficacy of low-dose cyclosporine for luminal Crohn's disease,[16] and the potential for nephrotoxicity.

Until more studies are available, the use of tacrolimus will probably be limited to the small group of patients with refractory peri-anal fistulas. In these patients, the drug results in fistula improvement, but does not increase the rate of complete fistula closure, which may be a more relevant clinical outcome.[17]

The duration of treatment and follow-up in one randomized controlled trial was 10 weeks.[17] Evidence from open-label studies suggests that a longer duration of therapy (i.e., up to eight months), with possible continued preventive therapy, may be needed for optimal benefit.[19,26,28]

References

1. Kaminska B. *Biochimica et Biophysica Acta-Proteins & Proteomics* 2005;1754(1-2):253-62.
2. Letko E, et al. *Ann Allergy Asthma Immunol* 1999;83(3):179-90.
3. e-CPS. [database online]. Ottawa: Canadian Pharmacists Association; 2006.
4. Prograf. In: *Notices of compliance* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 1995. Available: http://www.nocdatabase.ca.
5. Prograf. In: *Notices of compliance* [database online]. Ottawa: Therapeutic Products Directorate, Health Canada; 2001. Available: http://www.nocdatabase.ca.
6. Carter MJ, et al. *Gut* 2004;53 Suppl 5:V1-16.
7. Isaacs KL, et al. *Inflamm Bowel Dis* 2005;11 Suppl 1:S3-S12.
8. Domènech E. *Digestion* 2006;73 Suppl 1:67-76.
9. Caprilli R, et al. *Gut* 2006;55 Suppl 1:i36-i58.
10. Juillerat P, et al. *Digestion* 2005;71(1):31-6.
11. Hanauer SB, et al. *Am J Gastroenterol* 2001;96(3):635-43.
12. Brookes MJ, et al. *Drugs* 2004;64(10):1069-89.
13. Researchers measure rate of Crohn's and colitis in Manitoba. *CCFC Journal* 2000.
14. Podolsky DK. *N Engl J Med* 2002;347(6):417-29.
15. Travis SPL, et al. *Gut* 2006;55 Suppl 1:i16-i35.

16. Lichtenstein GR, et al. *Gastroenterology* 2006;130(3):940-87.
17. Sandborn WJ, et al. *Gastroenterology* 2003;125(2):380-8.
18. Fellermann K, et al. *Transplant Proc* 2001;33(3):2247-8.
19. Ierardi E, et al. *Aliment Pharmacol Ther* 2001;15(3):371-7.
20. Baumgart DC, et al. *Am J Gastroenterol* 2006;101(5):1048-56.
21. Bousvaros A, et al. *J Pediatr* 2000;137(6):794-9.
22. De Oca J, et al. *Rev Esp Enferm Dig* 2003;95(7):459-70.
23. Nakase H, et al. *Gastroenterology* 2005;128(4 Suppl 2):A583.
24. Foster EN, et al. *Am J Gastroenterol* 2005;100(9 Suppl S):S311.
25. Nakase H, et al. Presentation at Digestive Diseases Week 2006; 2006 May 20; Los Angeles. ID T1143.
26. Gonzalez-Lama Y, et al. *Inflamm Bowel Dis* 2005;11(1):8-15.
27. Sandborn WJ. *Am J Gastroenterol* 1997;92(5):876-9.
28. Lowry PW, et al. *Gastroenterology* 1999;116(4 Pt 2):A810.
29. Serrano MS, et al. *J Pediatr Gastroenterol Nutr* 2000;31 Suppl 2:S226.
30. Baumgart DC, et al. Presentation at Digestive Diseases Week 2006; 2006 May 20; Los Angeles. ID W1216.
31. Khurrum BM, et al. *Colorectal Dis* 2004;6(4):250-3.
32. Rahim N, et al. *Gastroenterology* 2005;128(4 Suppl 2):A585.
33. *Safety information about Elidel® cream and Protopic® ointment* [news release]. Ottawa: Canadian Adverse Drug Reaction Monitoring Program; 2005 Apr 27. Available: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2005/2005_31_e.html.
34. *Tacrolimus (marketed as Protopic)*. [Information for healthcare professionals]. Rockville (MD): U.S. Food and Drug Administration; 2005 Mar. Available: http://www.fda.gov/cder/drug/InfoSheets/HCP/ProtopicHCP.pdf.
35. Loftus CG, et al. *Gastroenterol Clin North Am* 2004;33(2):141-69.
36. Lyon CC, et al. *J Am Acad Dermatol* 2000;42(6):992-1002.
37. Van Dieren JM, et al. Presentation at Digestive Diseases Week 2006; 2006 May 20; Los Angeles. S1349.
38. Wise PE, et al. *Clin Gastroenterol Hepatol* 2006;4(4):426-30.
39. *PPS pharma publication: buyers guide.* Ontario ed. Moncton (NB): Total Pricing System; 2006 Jul.
40. Ghosh S. *Expert Rev Pharmacoecon Outcomes Res* 2003;3(5):587-98.
41. Van Assche G, et al. *Digestive Diseases* 2006;24(1-2):131-6.
42. Srinivasan R, et al. *Expert Opin Invest Drugs* 2004;13(4):373-91.

Cite as: Ruddock B. *Tacrolimus for Crohn's disease* [Issues in emerging health technologies issue 88]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006.

****

CADTH appreciates comments from its reviewers.

Reviewers: W. Remo Panaccione, MD, FRCPC, University of Calgary, **James Gregor, MD, FRCPC, University of Western Ontario**

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

ISSN 1488-6324 (online)
ISSN 1488-6316 (print)
PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8