Cost benefit of longterm follow-up of uncomplicated Crohn's disease

Martine De Vos

University Hospital Ghent, Department of Gastroenterology, De Pintelaan 185, B-9000 Gent, Belgium.

Crohn's disease is a chronic disease with onset early in life and an unpredictable course with ups and downs during many years and perhaps lifelong. To my knowledge, only one study has been published about the medical cost for CD (1). This study used a literature-based medical decision algorithm to estimate the expected costs of the illness per patient. From this study, it appears that surgery and hospitalization make up 70% of the total costs, medication 11% and outpatient medical care only 3%.

Outpatient medical care cost is principally determined by 4 factors :

1. *Frequency of visits*

Many clinical as well as endoscopical and biological indices has been developed to estimate the activity of disease and to help to predict relapses. Correlation between these indices is low, predictive value variable and information rather complementary. Therefore no index has gained universal acceptance. Physicians prefer patient self evaluation and their clinical evaluation to determine outpatient strategy. Need for extensive biological and morphological investigations is therefore very low.

Very few data are available about the ideal type and timing of follow-up visits. Because the length of previous remission has very strong prognostic value, it can be used as guideline for the timing. Patients with a long remission ($>$ 24 months) can be checked yearly because the estimated relapse risk is only 17%. In contrast, patients with shorter remission will be followed more regularly. If laboratory tests are normal, estimated risk of relapse is 41% and 6-monthly visit recommended. If laboratory tests are abnormal, risk for relapse is high (87%) and 3-monthly visits recommended (2).

2. *Laboratory tests*

Laboratory tests can be separated in 3 categories :

1. Markers of inflammation including :
   — Routine markers like sedimentation rate, acute phase protein CRP, RBC, WBC and albumin. From these markers, CRP seems most suitable because of its fast synthesis by hepatocytes secondary to stimulatory cytokines IL1-IL6-IL11-TNFα.
   — Less acceptable for the patients are determinations of CrEDTA gut permeability, faecal loss of α1-antitrypsin and faecal excretion of 111-Indium labelled granulocytes.
   — Non routine biochemical tests include cytokines IL6-IL2 receptors and TNFα. Correlation has been found between these cytokines and disease activity. Serum concentrations of coagulation factor XIIIA, intestinal enzyme cholinesterase and phospholipase A2 should also correlate with disease activity.
2. Control of peripheral blood cell count, kidney, liver and pancreatic function in patients under medication.
3. Determinations of concentrations of fat soluble vitamins, Vit B12 and folic acid in patients with extensive ileal disease.

3. *Endoscopy and radiology*

Whereas endoscopy and radiology have a predominant role in diagnosis, their role in follow-up of patients in remission is very low. Moreover, no benefit of endoscopic monitoring in the weaning of corticosteroids could be demonstrated (3).

4. *Medication*

Although the contribution of medication in the total cost of IBD patients is limited, it is much more important in the cost of follow-up of the patient in remission. In the absence of an ideal maintenance treatment, many interest has been given to aminosalicylates. The meta-analysis of Messori (4) included 8 trials (4 as full length articles and 4 as abstracts). Doses of 5-ASA ranged from 1.0 tot 2.4 g per day. The pooled results demonstrated a reduction of relapses at 1 year from 40% to 16% ($p < 0.001$). During last year, 7 additional studies were published with higher doses (3 g per day) and variable results (5-11). In 5 of these 7 studies a trend to efficacy could be demonstrated although differences were not statistically significant.

Using the results of its meta-analysis, Missori made a cost-effectiveness balance of the treatment with 5-ASA. Considering a hypothetical group of 100 patients treated with 5-ASA, drug cost at 2 g per day during 1 year is actually 1,898,000 BF. According to the most optimistic results of the meta-analysis, this treatment can prevent 24 relapses. Therefore, the cost

Correspondence to : Martine De Vos, University Hospital Ghent, Department of Gastroenterology, 1K12-E, De Pintelaan 185, B-9000 Gent, Belgium.

for preventing each relapse is *79,000 BF.* These costs are calculated based on Belgian price of 5-ASA preparation and are about 40% lower than reported costs in USA.

Based on the study of Hay and Hay (1), Missori calculated the cost of managing one relapse of CD. This cost can be as low as 700 US dollar for outpatient management of an uncomplicated case, but can rise to 17,000 US dollar for inpatient management. If we made a similar conversion to Belgian norms, mean cost of a relapse can be estimated as *172,800 BF.* Although these data seem to favor continuous treatment, several remarks should be made :

— these data are based on 2 g 5-ASA per day. Actually higher doses are recommended. At 4 g 5-ASA no more economic advantage can be seen ;

— few data are available about longer maintenance treatment but a tendency to decreased efficacy is noted.

Therefore it seems unreasonable to treat every patient with Crohn's disease in remission indefinitively with high doses of 5-ASA. Definition of subgroups at risk are necessary (ex. ileal localisation, short duration of remission ...) to select patients who will benefit from this long term treatment.

Maintenance treatment with azathioprine (Imuran®) 100-200 mg per day seems less expensive (yearly cost for treatment of 100 patients : 1,423,500-2,135,200 BF) and more effective (relapses rate of 11% at 1 year-32% at 60 months). However these data are based on retrospective results (12). Actually no data are available about the effect of the drug in the prevention of postoperative recurrence although a multicentric controlled trial with 5-ASA, 6-mercaptopurine and placebo is going on.

In conclusion, cost benefit balance of CD patients in remission can be improved in several ways :

— development of medication more effective in prevention of hospitalisation and surgery ;

— reduction of follow-up visits according to the length of remission ;

— selection of patients for long term efficacious maintenance therapy.

References

1. HAY A.R., HAY J.W. Inflammatory bowel disease : medical cost algorithms. *J. Clin. Gastroenterol.*, 1992, **14** : 318-27.
2. BRIGNOLA C., BELLOLI C., DE SIMONE G., CAMPIERI M., BARBARA L. Assessment and monitoring in known Crohn's disease. *Eur. J. Gastroenterol. Hepatol.*, 1994, **6** : 78-84.
3. LANDI B., ANH T.N., CORTOT A., SOULE J.C., RENE E., GENDRE J.P. *et al.* Endoscopic monitoring of Crohn's disease treatment : a prospective, randomized clinical trial. *Gastroenterology*, 1992, **102** : 1647-53.
4. MESSORI A., BRIGNOLA C., TRALLORI G., RAMPAZZO R., BARDAZZI G., BELLOLI C., D'ALBASIO G., DE SIMONE G., MARTINI N. Effectiveness of 5-aminosalicylic acid for maintaining remission in patients with Crohn's disease : a meta-analysis. *Am. J. Gastroenterol.*, 1994, **89** : 692-8.
5. ARBER N., ODES S.H., FIREMAN Z., LAVIE A., BROIDE E., BUJANOVER Y., BECKER S., POMERANTZ E., MOSHKOWITZ M., PATZ G., GILAT T. A controlled double blind multicentre study of the effectiveness of 5-aminosalicylic acid in patients with Crohn's disease in remission (abstr). *Gastroenterology*, 1994, **106** : A646.
6. BRIGNOLA C., IANNONE P., PASQUALI S., CAMPIERI M., GIONCHETTI P., BELLUZZI A., BASSO O., MIGLIOLI M., BARBARA L. Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. *Dig. Dis. Sci.*, 1992, **37** : 29-32.
7. DE FRANCHIS R., BRIGNOLA C., DEL PIANO M., OMODEI P., PERA A., RANZI T., ROCCA R., VECCHI M. Oral 5-aminosalicylic acid (5-ASA) in the prevention of early relapse of Crohn's disease. Interim analysis of a multicenter double blind randomized placebo controlled trial (abstr) ; *Gastroenterology*, 1994, **106** : A670.
8. BRIGNOLA C., COTTONE M., PERA A., ARDIZZONE S., SCRIBANO M.L., DE FRANCHIS R., D'ARIENZO A., D'ALBASIO G., PENNESKI D., Italian Cooperative Group. Mesalazine in the prevention of endoscopic recurrence after intestinal resection in Crohn's disease. *Gastroenterology*, 1995, **108** : 345-9.
9. THOMSON A.B.R., WRIGHT J.P., VATN M., BAILEY R.J., RACHMILEWITZ D., ADLER M., WILSON-LYNCH K.A. Mesalazine (Mesasal/Claversal) 1.5 g bid daily versus placebo in the maintenance of remission of patients with Crohn's disease. *Aliment. Pharmacol. Ther.*, 1995, **9** : 673-84.
10. MCLEOD R.S., WOLFF B.G., STEINHART A.H., CARRYER P.W., O'ROURKE K., ANDREWS D.F., BLAIR J.E., CANGEMI J.R., COHEN Z., CULLEN J.B., CHAYTOR R.G., GREENBERG G.R., JAFFER N.M., JEEJEEBHOY K.N., MACCARTY R.L., READY R.L., WEILAND L.D. Prophylactic mesalazine treatment decreases postoperative recurrence of Crohn's disease. *Gastroenterology*, 1995, **109** : 404-13.
11. SUTHERLAND L.R., MARTIN F., BAILEY R.J., FEDORAK R.N., POLESKI M., DALLAIRE C., ROSSMAN R., SAIBIL F., LARIVIERE L. and the Canadian Mesalazine for Remission of Crohn's Disease Study Group. A randomized, placebo-controlled, double-blind trial of mesalazine in the maintenance of remission of Crohn's disease. *Gastroenterology*, 1997, **112** : 1069-77.
12. BOUHNIK Y., LÉMANN M., MARY J.Y., SCEMANA G., TAÏ R., MATUCHANSKY C., MODIGLIANI R., RAMBAUD J.C. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *The Lancet*, 1996, **347** : 215-9.