Recent advances in inflammatory bowel disease

We have come some way in understanding the aetiology of inflammatory bowel disease, which has allowed advances in its management.

KEITH E PETTENGELL, *MD, FCP (SA), FRCP (Lond)*
Gastroenterologist, Parklands Hospital and Umhlanga Hospital, Durban

Keith Pettengell graduated at the University of Liverpool and lectured in Gastroenterology at the University of KwaZulu-Natal between 1984 and 1989. Since then he has been in private practice in Durban. He has a special interest in inflammatory bowel disease. He is also Honorary Physician to St Mary's Hospital, Mariannhill.

Pathophysiology

Genetics

In 2001 the first susceptibility gene for Crohn's disease (CD) (IBD1) was identified. This encodes for a product (NOD2 or CARD15), the CD variant of which is associated with increased intestinal permeability in both CD patients and their unaffected relatives.[1] It is also associated with ileal and fibro-stenosing diseases in Western populations.[2] The mechanism of the permeability changes is uncertain but the CD variant of NOD2 impairs the secretion of antibacterial peptides (defensins) which help contain the bacteria that penetrate the intestinal wall. Subsequently, many other possible candidate genes have been identified. TLR4, which encodes for proteins involved in bacterial recognition, has recently been associated with CD in several populations,[3] as have the IL23R gene in both CD and UC[4] and ATG16L1 and IGRM in CD.[5] The latter genes encode proteins that control autophagy, which is a major defense against intracellular pathogens such as mycobacteria and salmonella. These observations support the central hypothesis that the principal abnormality in irritable bowel disease (IBD) patients is the dysfunction of the intestinal epithelial barrier separating the lumen of the gut from the *milieu intérieur*.

The level of risk for developing IBD conferred by any one gene is small, and multiple hits on the genetic mechanism that controls intestinal permeability and host mucosal immune responses are probably required to induce and perpetuate the intestinal inflammation of IBD.

A history of an appendicectomy is rare in patients with UC.

Environmental factors

A recent meta-analysis confirms the association of CD with current cigarette smoking, former smoking with ulcerative colitis (UC) and the protective effect of current smoking in the development of UC.[6] A history of an appendicectomy is rare in patients with UC. A recent study of 212 963 patients showed a 50% decreased risk of developing UC in those who had surgery for appendicitis or lymphadenitis, but not in those with nonspecific abdominal pain. The beneficial effect was limited to those who had surgery before the age of 20.[7] Evidence implicating the contraceptive pill in IBD has not been confirmed by recent studies. The roles of measles virus, mycobacteria and paromyxoviruses remain unproved, but a recent cohort study of 93 013 patients has suggested an increased incidence of both UC and CD following an episode of gastroenteritis. The relative risk of developing CD was higher than that for UC and highest in the first year after an infective episode.[8]

A recent meta-analysis comparing capsule endoscopy with small-bowel barium radiology, colonoscopy with ileoscopy, computer tomography enterography and push enteroscopy showed that in patients with suspected or established CD capsule endoscopy was superior to all other modalities for diagnosing non-stricturing small-bowel CD.

Diagnostic imaging

Capsule endoscopy

This technique provides for the first time a non-invasive method of obtaining high-resolution images of the small bowel. It can detect villous atrophy as well as ulcerated mucosal lesions missed by other imaging techniques. Magnification is higher than with conventional endoscopes. The 11 mm by 26 mm video capsule is swallowed with water and its images are passed to a sensor array fastened to the abdomen and connected to a recorder and battery pack worn on a belt. The recorder acquires up to 55 000 images over approximately 8 hours. Reviewing the images may take an experienced operator up to 2 hours. A recent meta-analysis comparing capsule endoscopy with small-bowel barium radiology, colonoscopy with ileoscopy, computer tomography enterography and push enteroscopy[9] showed that in patients with suspected

or established CD capsule endoscopy was superior to all other modalities for diagnosing non-stricturing small-bowel CD, with the number needed to test of 3 to yield one additional diagnosis of CD over small-bowel radiology and 7 over colonoscopy and ileoscopy. The disadvantage of this technique is the current lack of therapeutic and biopsy facilities.

Double-balloon endoscopy

This technique allows not only visualisation but also endoscopic intervention throughout the small bowel. It uses an insertion technique that, with the aid of a soft over-tube and two balloons, pleats the small bowel over the endoscope. Complete visualisation of the small bowel can be achieved in around 85% of cases.[10] The technique has been evaluated in patients with CD[11] and comparison with other modalities is awaited. However, its usefulness is likely to be limited by long procedure times involved.

Anaemia

Anaemia is the most common systemic manifestation of IBD. Guidelines for its management have recently been published.[12] Iron deficiency anaemia (IDA) and the anaemia of chronic disease (ACD) are the most common causes. In patients without biochemical or clinical evidence of inflammation iron deficiency is present when the serum ferritin is below 30 µg/l. In the presence of inflammation the lower limit of serum ferritin consistent with normal iron stores is 100 µg/l.[13] In patients with active IBD there may be evidence of reduced iron absorption, the retention of iron within the reticular endothelial system and the inhibition of erythropoiesis. These mechanisms lead to ACD and this condition is likely in the presence of anaemia with a serum ferritin greater than 100 µg/l. If the serum ferritin is between 30 µg/l and 100 µg/l a combination of iron deficiency and ACD is likely. In all patients where IDA is present iron supplementation should be considered. The preferred route in IBD patients is intravenous even though many patients will respond to oral iron. Intravenous iron is more effective, better tolerated and improves the quality of life to a greater extent than oral iron supplements.[14] Moreover, animal models of IBD have demonstrated increases in oxidative stress, disease activity and intestinal inflammation in response to oral iron supplements. Where anaemia is due to ACD erythropoietic agents are indicated and should be combined with intravenous iron supplements. When used together, response rates of between 75% and 100% have been reported in clinical trials.[12]

Intravenous iron is more effective, better tolerated and improves the quality of life to a greater extent than oral iron supplements.

The relative risk of fractures is 40% greater among IBD sufferers than among the general population and increases with age.

Metabolic bone disease

Osteoporosis has been increasingly recognised in patients with IBD. Physiological factors include the frequent onset of IBD at a young age, impaired calcium and vitamin D absorption and the chronic inflammatory state of IBD. The most important factor however is the use of glucocorticoids in treatment.[15] The bone mineral density in patients with IBD is inversely correlated with a lifetime glucocorticoid dose.

Low bone mineral density has been found in approximately 30% of patients with IBD, but the effect appears to be modest, with a mean bone mineral density about 10% lower in normal subjects.[16] Whether IBD sufferers are male or female or have CD or UC, the risk of osteoporosis appears similar. The relative risk of fractures is 40% greater among IBD sufferers than among the general population and increases with age. In CD and UC patients carry comparable risks of fracture as do men and women.[17] Management in all patients involves education in the importance of lifestyle changes, i.e. undertaking regular exercise, stopping smoking and avoiding excess alcohol intake.

Dual-energy X-ray absorptiometry (DXA) is the current gold standard for the measurement of bone mass, and in the American Gastroenterological Association Medical Position Statement[18] it is recommended that such scans should be performed in IBD patients who have had prolonged corticosteroid use, a low trauma fracture and in postmenopausal women or men aged over 50. If there is evidence of osteopenia it is recommended that the scan should be repeated in 2 years and bisphosphonate therapy considered in patients on prolonged corticosteroid treatment. In patients with established osteoporosis (T score greater than –2.5) screening for other causes of low bone and mineral density should be undertaken and treated where necessary. Bisphosphonate therapy is indicated, as it is in any patient with vertebral compression fractures regardless of the DXA result.

Management

Oral preparations of mesalazine (Asacol, Pentasa, Dipentum) appear to be as effective as sulphasalazine in both the induction, remission and prevention of relapse in UC.[19] Topical mesalazine in the form of enemas and suppositories are effective in patients with left-sided disease.[20] Moreover, in mild to moderate left-sided UC topical mesalazine has been shown to have superior efficacy to topical corticosteroids and oral mesalazine.[20] In addition, the combination or oral and rectal mesalazine produces an added benefit both in left-sided and more extensive UC.[21] This combination also reduces the time required to stop rectal bleeding. Evidence from a case-controlled study has supported the view that mesalazine may reduce the risk of patients developing colorectal cancer, which rises to 18% after 30 years of disease.[22] While sulphasalazine has been found to have a benefit over placebo in patients with CD the effect is small and largely confined to patients with colonic disease.[23] The data from clinical trials with mesalazine, however, both in the treatment of active disease and in the maintenance of a medically induced remission, have shown no benefit and the use of such compounds in this setting should be abandoned.[24]

Biological agents

Two biological agents, infliximab (Revellex; Schering Plough) and adalimumab (Humira; Abbotts), are licensed for the treatment of IBD in South Africa. Both are monoclonal IgG1 antibodies to tumour necrosis factor-α (TNF-α) and are indicated for moderate to severe UC and luminal and fistulising CD, usually in patients who have failed to respond to other medication. Long-term maintenance treatment is the rule rather than the exception. Infliximab contains both human and murine protein

Anaemia is the most common systemic manifestation of IBD.

and is hence immunogenic. Intermittent administration, in particular, leads to the development of antibodies to infliximab. Such antibodies are associated with the occurrence of infusion reactions, delayed hypersensitivity and a shortened duration of response.[25] Adalimumab is a fully humanised IgG1 monoclonal antibody and is significantly less immunogenic.[26]

The pivotal trial of infliximab in active CD showed 65% of patients responded at 4 weeks and 33% of patients achieved remission compared with 17% and 4% respectively receiving placebo.[27] These results have been confirmed in later trials. Subsequent maintenance studies confirmed the ability of 8 weekly infusions of the drug to maintain either response or remission in the majority of those responding initially. Subgroup analysis and later studies showed significantly reduced health care utilisation and surgery in those receiving maintenance therapy. Importantly, the remission rates off steroids at 54 weeks was 29% with infliximab-treated patients and 9% for the placebo group. In addition, maintenance therapy resulted in complete mucosal healing in 50% of patients (compared with 7% in an intermittently treated group).[28] This holds out the prospect of long-term modification of the natural history of CD. Infliximab is similarly efficacious in paediatric CD, and maintenance therapy results in weight gain and reverses growth failure.[29] Infliximab has also been shown to result in response or complete closure of Crohn's fistulae which can be maintained in some patients for at least a year.[30] Good results have also been achieved with infliximab in UC. In two large placebo-controlled trials the proportion of subjects responding to infliximab or who were in clinical remission was 7 times higher among the infliximab-treated group of patients than in the placebo groups.[31] Infliximab has also been shown to be effective as rescue therapy for severe to moderately severe UC. In 45 patients 71% receiving infliximab avoided surgery compared with only 33% in the placebo-treated group.[32]

Similar favourable results have been achieved with adalimumab with both induction and maintenance of remission in luminal and fistulating CD.[33,34] Adalimumab has also been shown to be an effective therapy for patients with CD who have experienced a loss of efficacy over time or become intolerant of infliximab.[35] However, direct comparative trials of the two drugs are not available.

Concerns have been raised regarding the risk of serious infections associated with these drugs. However, in placebo-controlled trials the risk of serious infection was no higher than in the actively treated groups compared with the placebo groups. Where serious infections and deaths have occurred in relation to infliximab, evidence suggests that such events are more related to the concurrent use of corticosteroids and conventional immunosuppressants than to infliximab.[36] There is, however, in the usual clinical setting, an increased risk of reactivation of latent tuberculosis and hence all patients receiving these agents should be screened for latent tuberculosis with an appropriate detailed clinical history, a chest X-ray and skin testing and receive prophylaxis where appropriate.[37].

Infliximab v. azathioprine

A recent trial reported in an abstract[38] compares infliximab alone with azathioprine alone and azathioprine in combination with infliximab in moderate to severe CD. Infliximab alone and in combination was more likely to achieve a steroid-free remission and complete mucosal healing than the use of azathioprine alone.

Conclusion

Recent advances in the understanding of the pathophysiology of IBD have lead to the development of novel biological therapies that hold out the promise of influencing the natural history of IBD. In addition, more detailed clinical trials and meta-analyses regarding existing medication enable clinicians to make more informed choices from the range of current therapies. The prospects for patients with IBD have never been brighter.

References

1. Buhner S, Buning C, Genschel J, *et al.* Genetic basis for increased intestinal permeability in families with Crohn's disease: role of CARD 15 3020insC mutation? *Gut* 2006: 55: 342-347.
2. Economou M, Trikalinos TA, Loizou KT, *et al.* Differential effects of NOD2 variants on Crohn's disease risk and phenotype in diverse populations: a metaanalysis. *Am J Gastroenterol* 2004; 99(12): 2393-2404.
3. Franchimont D, Vemiere S, El Housni H, *et al.* Deficient host-bacteria interactions in inflammatory bowel disease? The toll-like receopto (TLR)-4-Asa299gly polymorphism is associated with Crohn's disease and ulcerative colitis. *Gut* 2004; 53: 987-992.
4. Kistner EO, Schumm LP, Lee AT, *et al.* A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; 314(58004): 1461-1463.
5. Rioux JD, Xavier RJ, Taylor KD, *et al.* Genome-wide association study identifies new susceptibility loci for Crohn's disease and implicates autophagy in disease pathogenesis. *Nat Genet* 2007; 39: 596-604.
6. Mahid SS, Minor KS, Soto RE, *et al.* Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006; 81(11): 1462-1471.
7. Andersen RE, Olaison G, Tysk C, *et al.* Appendectomy and protection against ulcerative colitis. *N Engl J Med* 2001; 344(11): 808-814.
8. Rodriguez LA, Ruigomez A, Panes J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* 2006; 130(6): 1588-1594.
9. Treister SL, Leighton JA, Leontiadis GI, *et al.* A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with non-stricturing small bowel Crohn's disease. *Am J Gastroenterol* 2006; 101(5): 954-964.
10. Yamamoto H, Kita H, Sunada K, *et al.* Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. *Clin Gastroenterol Hepatol* 2004; 2: 1010.
11. Oshitani N, Yukawa T, Yamagami H, *et al.* Evaluation of deep small bowel involvement by double-balloon enteroscopy in Crohn's disease. *Am J Gastroenterol* 2006; 101(7): 1484-1489.
12. Gasche C, Berstad A, Befrits R, *et al.* Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13(12): 1545-1553.
13. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011-1023.
14. Schroder O, Mickisch O, Seidler U, *et al.* Intravenous iron sucrose versus oral iron supplementation with inflammatory bowel disease – a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol* 2005; 100: 2503-2509.
15. Abitbol V, Roux C, Chaussade S, *et al.* Metabolic bone assessment in patients with inflammatory bowel disease. *Gastroenterology* 1995; 108: 417.
16. Pigot F, Roux C, Chaussade S, *et al.* Low bone mineral density in patients with inflammatory bowel disease. *Dig Dis Sci* 1992; 37: 1396.
17. AGA Technical Review on Osteoporosis in Gastrointestinal Diseases. *Gastroenterology* 2003; 124: 795-841.
18. American Gastroenterological Association Medical Position Statement: Guidelines on Osteoporosis in Gastrointestinal Diseases. *Gastroenterology* 2003; 124: 791-794.
19. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; 23: 841-855.
20. Cohen RD, Woseth DM, Thisted RA, *et al.* A meta-analysis and over-view of the literature on treatment options for left sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000; 95: 1263-1276.

21. Marteau P, Probert CS, Lindgren S, *et al.* Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomized, double blind, placebo controlled study. *Gut* 2005; 54: 960-965.
22. van Staa TP, Card T, Logan RF, *et al.* 5-Aminosaliclate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut* 2005; 54: 1573-1578.
23. Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study [ECCDS] results of drug treatment. *Gastroenterology* 1984; 86: 249-266.
24. Sandborn WJ, Feagan BG. Review article: Mild to moderate Crohn's disease – defining the basis for a new treatment algorithm. *Aliment Pharmacol Ther* 2003; 18: 263-277.
25. Hanauer SB, Wagner CL, Bala M, *et al.* Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004; 2: 542-553.
26. Sandborn WJ, Hanaver SB, Rutgeerts R, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CALSSIC II trial. *Gut* 2007; 56: 1232-1239.
27. Targan SR, Hanauer SB, Katz S, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; 337: 1029-1035.
28. Hanauer SB, Fegan BG, Lichtensein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002; 359: 1541-1549.
29. Borelli O, Bascietto C, Viola F, *et al.* Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig Liver Dis* 2004; 36: 342-347.
30. Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab maintenance therapy for fistulizinf Crohn's disease. *N Engl J Med* 2004; 350: 934-936.
31. Rutgeerts P, Sandborn WJ, Fegan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; 353: 2462-2476.
32. Jarnerot G, Hertervig E, Ftiis-Liby I, *et al.* Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: A randomized, placebo-controlled study. *Gastroenterology* 2005; 128: 1805-1811.
33. Hanauer SB, Sandborn WJ, Rutgeerts P, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC I trail. *Gastroenterology* 2006; 130: 323-333.
34. Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. *Gastroenterology* 2007; 132: 52-65.
35. Sandborn WJ, Rutgeerts P, Enns R, *et al.* Adalimumab induction therapy for Crohn's disease previously treated with Infliximab. *Ann Intern Med* 2007; 146: 829-838.
36. Lichtenstein GR, Fegan BG, Cohen RD, *et al.* Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; 4: 621-630.
37. Keane J, Gershon S, Wise RP, *et al.* Tuberculosis associated with infliximab a tumor necrosis factor alpha-neutralising agent. *N Engl J Med* 2001; 345: 1098-1104.
38. Colombel JF, Rutgeerts P, Reinisch W, *et al.* Sonic: A randomized double blind trial, controlled trial comparing infliximab and infliximab plus azathioprine to azathioprine in patients with Crohn's disease naïve to immunomodulators and biologic therapy. UEGW 2008; OP001.

In a nutshell

- Dysfunction of the intestinal epithelial barrier is a principal abnormality in the development of IBD.
- Smoking habits, previous appendicectomy and a history of gastroenteritis may also influence the development of IBD while the role of the contraceptive pill, measles virus and micobacteria remain unproven.
- Capsule endoscopy and double-balloon endoscopy have provided major advances in the diagnosis of small-bowel CD.
- Intravenous iron is the mainstay of the treatment of iron deficiency anaemia in IBD patients.
- Erythropoietic agents should be used together with intravenous iron in IBD patients with the anaemia of chronic disease.
- Osteoporosis should be searched for and treated in susceptible IBD patients and particularly those receiving long-term corticosteroids.
- Sulphasalazine is of little use and mesalazine probably of no use in the induction of a remission and in the maintenance of a medically induced remission in CD.
- Topical mesalazine can be added to oral treatment with advantage in UC patients with both left-sided and more extensive disease.
- Biological agents can induce and maintain remission in IBD patients where no other medication has been effective.
- Biological agents, by inducing mucosal healing, offer the hope of improving the natural history of IBD and reducing the need for surgery.