Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon affecting mainly young people, with a peak incidence between the ages of 10 and 40 years; 15% of patients are over the age of 60 at diagnosis. Its incidence is approximately 10–20 per 100 000 per year with a reported prevalence of 100–200 per 100 000 and is stable over time. The value of prevalence is less reliable, but it is probably underestimated because it implies an average disease duration of 10 years for a condition that is known to last for life [1]. A hospital serving a population of 300 000 will typically see 45–90 new cases per year and have 500 under follow-up.

Patients find symptoms of UC and CD embarrassing and humiliating. Inflammatory bowel diseases (IBD) can result in loss of education and difficulty in gaining employment or insurance [2]. It can also cause psychological problems, growth failure or a retardation in the sexual development of young people. Medical treatments with corticosteroids or immunosuppressants may cause major health problems, and surgery may result in complications such as impotence or intestinal failure. There is only a small increase in mortality for both UC (hazard ratio 1.44) and CD (hazard ratio 1.73), largely dependent on age and extension of the disease [3]. However, even if some patients have only functional symptoms (which are not in themselves an indication to potentiate the treatment and which may benefit from symptomatic drugs such anti-diarrheals, anti-spasmodics or fibres), the impact of IBD on society is disproportionately high, as presentation often occurs at a young age and has a potential to cause lifelong illness.

These considerations explain the peculiar expectations that patients with inflammatory bowel diseases have concerning both the pharmacological treatment and the overall clinical management. These considerations and their rationale have been summarised in recent clinical guidelines by the British Society of Gastroenterology, and reported in Table 1 [4].

Therapy

The peculiar expectations of patients and the need of a complex multidisciplinary approach to these patients, support the referral of patients to units with specific competence in this field. Therapy for IBD is a rapidly evolving field with many new biological agents under investigation that are likely to change therapeutic strategies radically in the next decade. We will try to summarise recent evidence concerning the effect of the drugs and some warnings recently outlined.

Aminosalicylates

Aminosalicylates act on epithelial cells via a variety of mechanisms to moderate the release of lipid mediators, cytokines and reactive oxygen species. These drugs are available as oral tablets, sachets or suspension, liquid or foam enemas, or suppositories. Different formulations deliver millimolar concentrations to the gut lumen. Oral forms include:

- pH dependent release/resin coated mesalazine;
- time controlled release mesalazine;
- Delivery by carrier molecules, releasing 5-ASA after splitting by bacterial enzymes in the large intestine (sulfasalazine, olsalazine, balsalazide).

Mesalazine has been recommended both for inducing and for maintaining remission.

Induction of Remission

Sutherland et al. [5, 6], in a meta-analysis of controlled trials, observed that 5-ASA was superior to placebo in active colitis (OR for maintaining remission 2). The same Authors, in an update of the aforementioned meta-analysis, confirmed that 5-ASA was superior to placebo for all outcome variables (global/clinical remission, global/clinical improvement, endoscopic remission or improvement).

When 5-ASA was compared to sulfasalazine, there
were no differences for all the endpoints, but there was a tendency for a greater efficacy and lower side effects of 5-ASA preparations over sulfasalazine [5]. It was concluded that for their higher cost, 5-ASA preparations should be reserved for selected groups such as sulfasalazine-intolerant patients or men concerned about infertility.

The best dosage of mesalazine for inducing remission remains open to debate. Higher doses seem to produce better results, doses below 2 g/day did not show any benefit over placebo [5]. Disease extension does not influence the response to therapy in that similar responses are found in pancolitis and distal colitis [7].

Few data are available on the different outcomes concerning the efficacy of various 5-ASA formulations. Only a single study suggested that balsalazide induces more rapid clinical remission with less adverse effects compared to a pH-dependent formulation of mesalazine [8], but this requires confirmation. On the other hand, olsalazine was not superior to an enteric-coated mesalazine in inducing endoscopic remissions [9].

### Maintenance

Four out of six studies demonstrated that 5-ASA is superior to placebo in remission maintenance at 6–12 months [10–15]. In a meta-analysis of randomised, double-blinded, placebo-controlled trials with a duration of at least 6 months, 5-ASA was able to halve the number of relapses compared to placebo, with a number needed to treat of 6 to prevent one relapse [6]. Sulfasalazine and 5-ASA have similar efficacy in long-term maintenance remission and the choice among the drugs should be based on factors such as cost or tolerance. For maintenance therapy, doses of 5-ASA ranged between 2 to 4.4 g/day. In the acute phase, while disease extension did not influence the efficacy in maintaining remission [16], no information exists on the different effects of various ASA formulations.

### Topical Therapy

Topical mesalazine is an effective alternative to steroids enemas during the acute phases of left-sided colitis [17–24]. In two recent meta-analyses, rectal 5-ASA was superior to rectal steroids in inducing clinical, endoscopic and histologic improvement [25, 26].

Mesalazine enemas were as effective as oral sulfasalazine but with fewer adverse effects in left-sided mild/moderate UC [27]. The drug induced remission in a duration-dependent but not in a dose-dependent way [26].

In a recent comparison of the use of these old drugs according to international guidelines in IBD patients, it was concluded that (1) 64% of patients received suboptimal dosages of oral 5-ASA, despite the evidence that their efficacy is dose-related; (2) topical aminosalicylates were not used in 75% of patients with distal colitis, despite the evidence that combined oral and topical therapy is more effective than systemic therapy alone [28, 29].

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**Table 1. Expectations expressed by members of the British National Association of Colitis and Crohn’s Disease for their medical management**

<table>
<thead>
<tr>
<th>Before diagnosis</th>
<th>At diagnosis</th>
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<tbody>
<tr>
<td>– Rapid access to hospital investigation</td>
<td>Availability of suitable written information and audio-visual material</td>
</tr>
<tr>
<td>– Referral to a hospital that has a gastroenterologist specialised in IBD</td>
<td>Information about patient support groups and sources of help</td>
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<tr>
<td>Hospital management</td>
<td>Opportunity to meet non-medical members of staff, such as a clinical nurse specialist or medical social worker familiar with IBD</td>
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<tr>
<td>– Sufficient information to make a rational personal choice about treatment options</td>
<td>Hospital management</td>
</tr>
<tr>
<td>Close integration of medical and surgical management</td>
<td>Sufficient information to make a rational personal choice about treatment options</td>
</tr>
<tr>
<td>Straightforward access to support services, including dieticians, psychological support, and social workers</td>
<td>Close integration of medical and surgical management</td>
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<tr>
<td>Clearly stated management plans on discharge with well defined roles and responsibilities</td>
<td>Straightforward access to support services, including dieticians, psychological support, and social workers</td>
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<td>Continuity of care, both in hospital and in primary care</td>
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<td>Continuity of care, both in hospital and in primary care</td>
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<td>A system that allows a choice about appropriate long term follow up</td>
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<tr>
<td>Direct telephone access</td>
<td>A system that allows a choice about appropriate long term follow up</td>
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<td>Attention to physical, emotional, and quality of life issues</td>
<td>Direct telephone access</td>
</tr>
<tr>
<td>Help with problems related to insurance, employment, or social security</td>
<td>Attention to physical, emotional, and quality of life issues</td>
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**Adverse Effects of Aminosalycilates**

Mild side effects of sulfasalazine (mainly headache, nausea, epigastric pain, and diarrhoea) occur in 10–45% of patients, whereas serious idiosyncratic reactions (including Stevens Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis) are rare. These reactions are mainly associated with the sulphonamidic part of the molecule, which explains why mesalazine or olsalazine are associated with a frequency of adverse events (diarrhoea, headache, nausea, and rash, bloody diarrhoea) similar to placebo [30, 31]. No comparison between balsalazide and placebo has been published, but adverse events are lower than with sulfasalazine [31]. A population based study found that renal derangement (interstitial nephritis and nephrotic syndrome) is associated with disease severity rather than with dosage or type of mesalazine and that, in any case, the risk is only marginally increased (OR 1.60 vs. normal) [32]. Patients with pre-existing renal impairment or using other potentially nephrotoxic drugs, should have renal function monitored during 5-ASA therapy.

**Corticosteroids**

Corticosteroids are potent anti-inflammatory agents for moderate to severe relapses of both UC and CD. They have no role in maintenance therapy for either disease. They act through inhibition of several inflammatory pathways via the suppression of interleukin transcription, induction of IκB (an inhibitor of the NFκB complex), suppression of the arachidonic acid metabolism and stimulation of apoptosis of lymphocytes within the lamina propria of the gut. Many strategies attempt to maximise their topical effects, while limiting systemic side effects. As for example, budesonide is a poorly absorbed corticosteroid with limited bioavailability and extensive first-pass metabolism which reduces its systemic toxicity in ileocecal CD or UC.

**Efficacy for Active CD**

Trials are all over 30 years old, but results are consistent: oral prednisolone (starting at 40 mg daily) induced remission in 77% of 118 patients with mild to moderate disease within 2 weeks, compared with 48% treated with 8 g/day sulfasalazine. A combination of oral and rectal steroids is better than either alone. Adverse events are more frequent with a dose of 60 mg/day compared with 40 mg/day, without added benefit; doses of prednisolone of 15 mg/day are ineffective for active disease. The optimal dose for “outpatient” management of acute UC appears to be 40 mg.

Efficacy should be balanced against side effects, but decisive treatment of active disease in conjunction with a strategy for complete withdrawal of steroids is often appreciated by patients suffering miserable symptoms. Regimens of steroid therapy vary among centres. A standard weaning strategy helps to identify patients who relapse rapidly or do not respond and need adjunctive therapy with thiopurines or hospital admission [4].

**Adverse Effects of Steroids**

Three broad groups can be identified, although 50% of patients report no adverse event. Early effects are mainly due to high doses and include cosmetic effects (acne, moon face, oedema), sleep and mood disturbance, dyspepsia, or glucose intolerance. Effects associated with prolonged use (usually 12 weeks) include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy, and susceptibility to infections. Effects during withdrawal include acute adrenal insufficiency (from sudden cessation), a syndrome of myalgia, malaise, and arthralgia (similar to recrudescence of UC), or raised intracranial pressure. Complete steroid withdrawal is facilitated by early introduction of azathioprine, adjuvant nutritional therapy, or timely surgery.

One of the most frequent mistakes in the therapy of UC is the prolonged use of steroids (effective only in inducing clinical remission but not in maintenance). There is no excuse either for using them repeatedly for either frequent relapses, either for fruitless attempts at tapering them or for continuing them at homeopathic doses to maintain remission. Steroids are neither safe nor effective in any of these situations. Corticosteroids are often used for an excessive duration even in patients with mild disease without a clear “exit” strategy, utilising alternative drugs to maintain remission. The standard of practice worldwide is currently to maintain long-term remissions with either a high-dose of 5-ASAs, antimetabolites, anti-TNF drugs, or even surgery, rather than with long-term or frequently repeated steroids [29].

**Immunomodulators**

Purine anti-metabolites inhibit ribonucleotide synthesis, but the mechanism of immunomodulation is carried out by inducing T-cell apoptosis. Azathio-
prine (AZA) is metabolised to 6-mercaptopurine (6-MP) and subsequently to 6-thioguanine nucleotides. Thioguanine has been used for treatment of IBD, but caution is appropriate because of potential hepatotoxicity.

**Maintenance of Remission**

Despite the general acceptance of these drugs in UC, there are few randomised controlled trials (RCT) evaluating the efficacy of AZA and 6-MP. This is mainly due to the fact that researchers must adjust the dosage of the drugs to their haematological effects, which makes the maintenance of blindness difficult. The first trials in the seventies showed a steroid-sparing effect, but not an improvement in disease activity [33–34].

In a large and long-term retrospective clinical survey, AZA was significantly more effective in inducing remissions in patients with UC compared with CD (87% vs. 64%) [35]. This was also true in a recent prospective, randomised, controlled study on the efficacy and safety of AZA and 5-ASA in inducing remission in steroid dependent UC [36]. Seventy-two patients were randomised to receive AZA 2 mg/kg/day or oral 5-ASA 3.2 g/day, for a 6-month period. At the beginning, all patients were taking 40 mg of prednisolone, which was gradually tapered according to the clinical improvement. Endoscopic and clinical remission was achieved in 19 of 36 AZA patients compared to 7 of 36 in the 5-ASA group. Four AZA and 3 5-ASA patients underwent colectomy. Significantly more AZA than 5-ASA patients complained of mild to moderate adverse events.

Patients with UC in whom remission was induced by AZA benefited from maintenance treatment, since withdrawal of therapy doubled the relapse rate [37]; moreover, AZA is effective in avoiding colectomy in steroid-dependent or steroid-resistant UC [38].

**Pharmacodynamics**

AZA is a prodrug that is rapidly cleaved in the liver by glutathione-S-transferase to 6-MP. This active component is metabolised in the liver and in the gut by one of three enzymes: (1) thiopurin-S-methyltransferase (TPMT), (2) xanthine-oxidase, (3) hypoxanthine-guanine-phosphoryl transferase.

**Side Effects of Immunosuppressants**

AZA and 6-MP inhibits the proliferation of T and B lymphocytes, thereby reducing cytotoxic T cells and plasma cells. During AZA or 6MP, 6-thioguanine nucleotides accumulate slowly in tissues, probably accounting for the protracted action of these drugs upon their suspension. This intracellular accumulation of 6-thioguanine nucleotides is responsible for the cytotoxic effects of these drugs by the inhibition of purine synthesis, nucleotide interconversions, DNA and RNA synthesis and chromosomal replication. Measurements of erythrocyte 6-thioguanine may be helpful in optimising the dose of AZA/6-MP for a clinical response without myelosuppressive effects.

In has been suggested that leukaemic patients deficient in TPMT are at increased risk of myelotoxicity [39], but this does not necessarily apply to IBD. In one study, 31 of 41 IBD patients with AZA-induced myelosuppression did not carry a TPMT mutation. Evidence that TPMT activity predicts other side effects or outcome is limited, and so far, it cannot be recommended as a prerequisite to therapy [40].

AZA should be introduced at a low dose, 0.5–1.5 mg/kg daily, and increased gradually within 2 weeks to 2.5 mg/kg daily. Blood monitoring (haematology and liver function tests) should be performed weekly until the maintenance dose is reached, and monthly thereafter. The equivalent dose of 6-MP is initially 0.25–0.5 mg/kg daily, increasing to 1.0–1.5 mg/kg daily. If white blood cells decrease below 3000/mm³ or platelets below 120 000/mm³, the drug should be discontinued or the dose reduced until these parameters normalise. Furthermore, if liver biochemistry (and/or serum amylase) exceeds more than 50% of the upper normal limit, AZA/6MP should be discontinued, and then cautiously reintroduced.

Both AZA and 6-MP are considered slow-acting drugs, with an effect expected after 12–17 weeks. A recent study suggests that AZA works faster than previously believed, showing effects after 4 weeks [41]. In any case, for their slow onset of action, these drugs have no place as a monotherapy in acute relapses of UC. Allopurinol blocks the metabolism of 6-MP by the inhibition of xanthine-oxidase, so that patients on allopurinol should receive half doses of AZA/6-MP.

Side-effects of immunosuppressants can be categorised as (1) bone-marrow suppression, 2) short-term effects and 3) long-term effects. The side-effects occur in about 10–15% of patients with IBD and are either dose-dependent (bone marrow suppression) or idiosyncratic (pancreatitis, allergic reactions or hepatitis).

Severe leukopenia, although rare (around 3%), may develop suddenly and unpredictably in between blood tests, even during long-term treatment. Side effects detected with short-term use often occur with-
in the first week of treatment and include pancreatitis (3.3% of patients), allergic reactions including rash, idiopathic hepatitis with cytonecrosis, cholestasis or insidious onset of liver dysfunction (3.3%) and infections (7.4%). Pancreatitis resolves upon drug withdrawal but recurs on retreatment, which precludes the use of either AZA or 6MP.

Some 5–10% of patients stop treatment on their own mainly during the first month. Nausea, vomiting and malaise are the most common problems especially if the dose is increased too fast. Infections are the theoretical risk of the long-term use of these agents, but their incidence is not higher than with high-dose prednisolone.

In patients on long-term immunosuppressants one may expect an increase incidence of neoplastic diseases. Actually, a prospective study of 1 349 non-transplant patients receiving AZA, including 280 patients with IBD, showed a significant increase in non-Hodgkin’s lymphoma, squamous cell carcinoma and other tumours (overall risk increased by a factor of 1.6) [42]. In contrast, reports from St Mark’s Hospital (755 patients) and Oxford (2 205 patients) showed a risk of neoplasia comparable with the general population, but after a treatment of only 1 year [43, 44].

A recent meta-analysis found a fourfold increase risk of lymphoma in IBD patients on azathioprine/6-MP possibly as a result of the drugs, the severity of the disease, or a combination of the two [45]. In any case, decision analysis suggests that in IBD, the benefits of AZA outweigh the risk of lymphoma [46, 47].

The main mistake in the use of anti-metabolites is probably undertreatment [29]. Three forms of undertreatment are still rampant. The first is waiting too long to introduce these agents. One relapse noted during or soon after an attempted steroid withdrawal is an indication for the introduction of anti-metabolites. Likewise, neither cyclosporine nor infliximab should be used without a previous introduction of anti-metabolites in the expectation that they will be needed over the long-term.

The second mistake is underdosing. The habit of administering 6-MP or azathioprine at a fixed dosage of 50 mg/day should have long been abandoned. A reasonable starting dose of 6-MP is 1.5 mg/kg/day and of azathioprine 2.5–3 mg/kg/day. Even more important, is not giving up with these drugs until being sure that they have been administered at the maximal doses. By definition, the dose has been pushed up enough either when success is achieved or when mild leukopenia has occurred (WBC in the 3 000–4 000/mm³ range). If there is uncertainty about efficacy, adsorption, or adherence, additional information can be gained by looking for a substantial increase in MCV or by measuring drug metabolites.

The last mistake is an early suspension of the drug. No “safe” number of years has been established after which these medications can be withdrawn without the risk of relapse. Moreover, it is of critical importance not to suspend 6-MP or azathioprine during pregnancy. Safety in pregnancy has been unequivocally established via published experience [48]. Indeed, the risk to pregnancy is infinitely greater from relapse of disease than from adverse effect of treatment.

**Methotrexate (MTX)**

Conflicting results are available on the efficacy of MTX in UC. In an early RCT, no significant differences were found between oral MTX (12.5 mg/week) and placebo at 9 months in 67 UC patients [49]. In another RCT, MTX (15 mg/week) was as effective as 6-MP (1.5 mg/kg/day) and 5-ASA (3 g/day), but less effective in maintaining remission in steroid-dependent UC patients. A dose of subcutaneous MTX at 15 and 25 mg/week showed a similar efficacy in inducing remission [50].

It is often accepted that MTX is more effective in Crohn’s disease than in UC. However, in a recent retrospective study on 22 UC and 48 CD patients treated with MTX (orally or i.m.) with a mean maintenance dose of 20 mg/week, remission was achieved in 34 of 55 patients who completed more than 3 months of treatment. Treatment was equally effective for Crohn’s disease and UC. Life-table analysis showed that the chances of remaining in remission at 12, 24 and 36 months of treatment were 90, 73 and 51%, respectively [51].

**Side Effects**

Measurement of full blood count and liver function tests are advisable before and within 4 weeks of starting therapy, then monthly thereafter. Early toxicity from methotrexate is primarily gastrointestinal (nausea, vomiting, diarrhoea, and stomatitis) and may be limited by 5 mg of folic acid the day following MTX injection. Treatment is discontinued in 10–18% of patients because of side effects. The principal concerns are hepatoxicity and pneumonitis. A study of liver biopsies in IBD patients taking MTX showed mild histological abnormalities despite cumulative doses of up to 5.4 grams. Surveillance liver biopsy is not warranted, but if the transaminases increase to more than twice the upper normal limit, it is sensible to withhold MTX until it returns to normal before a retrial of the drug [52]. The prevalence of pneumonitis has been estimated at 2–3 cases per 100 patient
years of exposure, but even large series have not reported any case. The main concern with this drug is its teratogenicity, which limits its use in fertile patients.

**Cyclosporin**

Cyclosporin (CyA) is an inhibitor of calcineurin, preventing clonal expansion of T-cell subsets. It has a rapid onset of action and is effective in the management of severe UC which failed to improve from the intensive steroidal therapy. Several uncontrolled studies and a few controlled studies of intravenous cyclosporine in patients with severe UC are available. Lichtiger et al. reported on 20 patients, 9 randomized to placebo and 11 to CyA, in continuous infusion, in addition to steroids for up to 14 days. Nine out of 11 patients on CyA responded after a mean period of 7 days compared with none on placebo. Responders continued on oral CyA 8 mg/kg/day and, at 6 months, 5 out of 11 maintained remission [53].

When used as a monotherapy (continuous infusion of either CyA 4 mg/kg/day or methylprednisolone 40 mg/day), a response at 8 days was obtained in 9 out of 14 of CyA vs. 8 out of 15 of methylprednisolone. Responders were slowly switched to AZA maintenance. At 12 months, 7 out of 9 patients initially treated with CyA maintained remission compared with 3 out of 8 with steroids. [54].

In a further study, 30 patients were randomised to monotherapy with CyA 4 mg/kg/day i.v. or CyA i.v in combination with methylprednisolone 1 mg/kg/day. At 7 days, a complete remission was obtained in 10 out of 15 on CyA vs. 14 out of 15 on the combination therapy [55]. While 2 and 4 mg of the drug show the same efficacy, topical treatment is not effective [56, 57].

Intravenous CyA is rapidly effective as a salvage therapy for patients with refractory colitis, who would otherwise face colectomy, but its use is controversial because of toxicity and its high long-term failure rate. There is now a trend to use CyA earlier to improve outcome. To do so, early predictors of steroid failure are needed [58–59]. For its rapid onset of action, CyA can be considered as a “bridge” to maintenance therapy with immunomodulators and only rarely should be continued for more than 3–6 months.

In a recent Cochrane Review, it was concluded that there is limited evidence that CyA is more effective than standard treatment alone in preventing colectomy in severe UC, even if its beneficial effect cannot be excluded due to the small sample size [60].

The possible efficacy of CyA in these severe cases has to be weighed against possible side effects. Minor side effects occur in 31–51%, including tremor, paresthesias, malaise, headache, abnormal liver function, gingival hyperplasia, and hirsutism. Major complications are renal insufficiency (23%), infections (20%), seizures (3%), death (2%) and anaphylaxis (1%) [61].

The risk of seizures is increased in patients on intravenous CyA with serum cholesterol less than 120 mg/dl and serum magnesium less than 1.5 mg/dl. Oral therapy is an alternative in these circumstances [62]. Using prophylaxis against *Pneumocystis carinii* pneumonia is an individual decision dependent on nutritional state, concomitant immunomodulator therapy, and duration of therapy, but other opportunistic infections (for example, *Aspergillus* sp.) may be as common.

**Tacrolimus**

Tacrolimus (FK 506) a macrolide immunosuppressant, acts by blocking the enzyme calcineurin which interrupts the signal transduction pathway in the T-cell. It is 10 to 100-fold more potent in inhibiting lymphocyte activation in vitro than CyA, and its intestinal absorption is more reliable even in the presence of gastrointestinal disease. This drug, which is expensive and rather toxic, may be effective in a subset of patients with severe disease, steroid resistant or intolerant [63–65].

**Infliximab**

Infliximab (IFX) (Remicade) is a chimeric anti-TNF monoclonal antibody with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells, which has become the best choice in both active and fistulising CD unresponsive to standard therapy.

Additionally, TNA-α plays a crucial role in the inflammatory process in UC. In this disease, high levels of TNF-α are mainly found in the superficial colonic layers, as opposed to CD, where it is found deeper in the mucosa or submucosa. Normally the inflammatory response to TNF-α is counterbalanced by inhibitors, and there is evidence that the production of TNF-α inhibitors is down-regulated in IBD.

It has been shown that TNF-α blocking agents probably do not act by binding and inactivating TNF-α, but rather by inducing the apoptosis of TNF-expressing inflammatory cells, as proven by the inefficacy of etanercept. Resistance to apoptosis has been shown in both CD and UC, but with different mechanisms. The defect in CD occurs in the mitochondrial
pathway of apoptosis (imbalance of mitochondrial bcl-2 bax), whereas in UC it derives from the overexpression of FLICE-inhibitory protein (FLIP) and impairment of the caspase mediated apoptosis.

These data support the use of IFX in UC, mainly in steroid-refractory or severely ill patients. Open trials on such patients suggested an effect in 50–75% of cases, which was maintained long-term in 25% of cases [66–68]. Concomitant use of anti-metabolites was associated with a lower rate of relapse.

Recently, two large multicentre placebo-controlled studies—Active Ulcerative Colitis 1 and 2 (ACT 1 and 2)—evaluated the efficacy of IFX for induction and maintenance of remission in UC patients [69]. Three hundred and sixty-four patients with moderate to severe active UC according to the Mayo Index despite concurrent medications (corticosteroids alone or in combination with AZA/6-MP, in ACT 1, or with AZA/6-MP and 5-ASA in ACT 2), were randomised to receive placebo or IFX 5 mg/kg or 10 mg/kg intravenously at weeks 0, 2 and then every 8 weeks through week 46 (in ACT 1) or week 22 (in ACT 2). In both studies, a clinical response was obtained in 69% of IFX 5 mg and 61–69% IFX 10 mg, compared to 29–37% in the placebo group, with no difference between patients who are or are not steroid-refractory. At week 30 in both studies, IFX patients were more likely to have a clinical response than controls, and showed a clear steroid-sparing effect. In fact, while at baseline, 56% of patients were on steroids, by week 30, 22% of them discontinued steroids while maintaining remission. Long-term studies will clarify whether these promising results and the cost-effectiveness of this medical approach in avoiding colectomy will be maintained over the years.

Other Approaches

Interferon-β

Immunomodulatory therapy with interferon-beta (IFN-β) might represent a new strategy in UC due to the divergent effects of this cytokine on the immunological and inflammatory process. IFN-β produces an anti-inflammatory effect by inhibiting the production of IFN-γ and TNF-α and by antagonising early events in the IFN-γ signalling pathway. In addition, IFN-β increases the expression of anti-inflammatory cytokine IL-10 and enhances T suppressor and NK cell activity.

A pilot-study investigated whether IFN-β could induce clinical remission in 25 patients with steroid-refractory UC. Patients were treated with 0.5 MIU human IFN-β i.v. (n=18) or 1MIU recombinant IFN-β s.c. (n=7). Maintenance treatment was carried out for 52±78.8 weeks, 3 times a week. Twenty-two patients entered remission with a mean time to response of 3 weeks and a mean duration of remission of 13 weeks [70]. However, in two subsequent larger trials, no differences were observed between IFN-β and placebo [71–72].

Antibodies Anti-Integrin

A therapeutic approach in UC could be the inhibition of migration of leukocytes into the inflamed intestine by blocking cellular adhesion molecules. The α4β7 integrin is primarily involved in the recruitment of leukocytes in the gut; it is present on the cell surface of a small population of circulating T lymphocytes. Its major ligand is mucosal-addressin-cell adhesion molecule 1, selectively expressed on the endothelium of the intestinal vasculature especially in the inflamed bowel. MLN02 is a monoclonal antibody that specifically recognises the α4β7 heterodimer.

Its efficacy in UC was recently assessed in a multicentre double-blind placebo-controlled trial [73]. A clinical improvement was observed in 66% of patients on 0.5 mg/kg/day of MLN02, in 53% on 2 mg/kg/day of MLN02 and in 33% on placebo. The role of MLN02 in clinical practice needs to be carefully evaluated to define its safety profile. In fact, natalizumab, a similar drug that interrupts leukocyte homing through the blockade of the α4β1 integrin, reduced immune surveillance in the brain with subsequent reactivation of the JC virus. This led to progressive multifocal leuko-encephalopathy, invariably fatal, in three patients and the drug was withdrawn from the market [74].

Leukocytapheresis

Accumulating evidence suggests that an abnormal T-cell-specific immune response to host flora may be a driving force in abnormal inflammation in UC. There is also reasonable consensus that the intestinal epithelium in patients with UC is dominated by leukocytes, macrophages and CD4+ lymphocytes with a T-helper 2 phenotype. Recruitment of these inflammatory cells from the systemic circulation into the intestinal epithelium may be a critical step in the amplification of the inflammatory response. Each cell can generate pro-inflammatory mediators such as cytokines, chemokines, growth factors and nitric oxide radicals which will deteriorate inflamed epithelium. Leukocytapheresis (LCAP) is a therapy based on a selective removal of leukocytes from systemic circulation, obtained by the passage of blood either
through a column or through a filter. So far, this form of therapy has mainly been studied in Japan. Recent studies demonstrated that LCAP might be useful for active Crohn’s disease and UC after failure of conventional drug treatments.

In an early study, the effect of LCAP on maintaining remission was evaluated in steroid-refractory UC after induction of remission with the same therapeutic procedure. Via induction-LCAP, six patients reached complete remission and one reached partial remission and was then treated with maintenance-LCAP. Four of them were maintained in remission without steroid treatment over 12 months. Recurrence was observed in three patients 3–6 months after the beginning of maintenance, and two of them re-entered remission by re-induction. One patient then presented a second recurrence and underwent a total colectomy [75].

Sakata et al. evaluated 51 UC patients with severe or moderate disease, who failed to respond to conventional therapy. Thirty-three patients went into complete remission after the first induction therapy with significant improvement of the activity score. Ten of them relapsed, but 21 maintained remission with LCAP maintenance [76].

In another study [77], 60 UC patients on sulfasalazine for at least 8 weeks prior to the treatment received a total of 10 sessions of LCAP therapy (once or twice a week). Most patients were also on prednisolone at entry, and had steroids tapered or discontinued during the study depending on the level of improvement. Fifty patients responded to therapy, 14 by achieving a complete remission, with no serious adverse effects.

The endoscopic severity scores were markedly improved in 22 of 46 patients and 68% of steroid-dependent cases could stop steroids. The average dose of steroid after 10 sessions decreased from 15.3 to 3.6 mg/day. In terms of symptom activity, LCAP is more effective in patients who during the course of their disease had received a low cumulative dosage of steroids. There was a highly significant association between symptomatic improvement of diarrhoea, abdominal pain and rectal bleeding and duration of apheresis or number of sessions per week. Five of the non-responders to LCAP improved with conventional therapy, the other five underwent elective colectomy. No additional maintenance therapy was provided. The improvement continued for a mean duration of 199 days (range: 21–614). The time to relapse was negatively correlated with endoscopic and histologic findings and the cumulative dosage of steroids. Further studies will clarify whether this approach will also prove cost-effective in Western populations.

Conclusions
Many different and evolving approaches are available for the treatment of ulcerative colitis. A comprehensive treatment that includes not just the disease but also the patient (often severely debilitated by a lifelong disease, in a proportion of cases refractory to standard treatments) and an effective patient-doctor alliance may improve the overall results.

References
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