Impact of New Treatments on Hospitalisation, Surgery, Infection, and Mortality in IBD: a Focus Paper by the Epidemiology Committee of ECCO

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Abstract
The medical management of inflammatory bowel disease has changed considerably over time with wider use of immunosuppressant therapy and the introduction of biological therapy. To what extent this change of medical paradigms has influenced and modified the disease course is incompletely known. To address this issue, an extensive review of the literature has been carried out on time trends of hospitalization, surgery, infections, cancer, and mortality rates in inflammatory bowel disease [IBD] patients. Preference was given to population-based studies but, when data from these sources were limited, large cohort studies and randomised controlled trials were also considered. In general, data on hospitalisation rates are strikingly heterogeneous and conflicting. In contrast, the consistent drop in surgery/colectomy rates suggests that the growing use of immunosuppressants and biological agents has had a positive impact on the course of IBD. Most clinical trial data indicate that the risk of serious infections is not increased in patients treated with anti-tumour necrosis factor alpha [TNFα] agents, but a different picture emerges from cohort studies. The use of thiopurines increases the risk for non-melanoma skin cancers and to a lesser extent for lymphoma and cervical cancer [absolute risk: low], whereas no clear increase in the cancer risk has been reported for anti-TNF agents. Finally, the majority of studies reported in the literature do not reveal any increase in mortality with immunosuppressant therapy or biologicals/anti-TNF agents.

Key Words: Ulcerative colitis; Crohn’s disease; hospitalisation; surgery; infections; cancer; mortality; anti-tumour necrosis factor α; immunosuppressant therapy
therefore important to ensure reliable estimates of the burden of IBD and realistic discussions with patients on the results they can expect to achieve with these drugs.

To address this issue, members of the Epidemiological Committee [EpiCom] of the European Crohn’s and Colitis Organisation [ECCO] conducted a review of the literature published on or before June 30, 2015, dealing with hospitalisation, surgery, infection, cancer, and mortality rates in IBD patients. Preference was given to population-based studies but, when data from these sources were limited, large cohort studies and randomised controlled trials [RCTs] were also considered. Searches targeted online databases [Medline/PubMed, the Cochrane database, and other relevant sources] with the appropriate key words [outcome, hospitalisation, surgery, colectomy, surgical resection, mortality, infection, cancer, temporal trends, immunomodulators, immunosuppressants, biologicals, anti-TNFα].

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [Col]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The Col statement is not only stored at the ECCO Office and the editorial office of JCC but also is open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of all the authors.

Table 1. Changes in hospitalisation rates in population-based and hospital discharge cohorts.

<table>
<thead>
<tr>
<th>Author year</th>
<th>Population</th>
<th>Time periods</th>
<th>Method</th>
<th>Changes observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vester-Andersen 2014</td>
<td>Denmark [513 UC, 213 CD]</td>
<td>2003–2004</td>
<td>Inception registry</td>
<td>CD: from 7 days/person at Year 1 to 0.9 days/person at Year 5; UC: from 4.7 days/person at Year 1 to 0.4 days/person at Year 5</td>
</tr>
<tr>
<td>Bewtra 2007</td>
<td>United States</td>
<td>1990–2003</td>
<td>National Hospital Discharge Survey</td>
<td>CD: from 9.3 to 17.1/100 000 [p &lt; 0.002]; UC: from 8.2 to 12.4/100 000 [p = 0.83]</td>
</tr>
<tr>
<td>Pant 2013</td>
<td>United States</td>
<td>2000–2009</td>
<td>Discharges for children with IBD</td>
<td>From 43.5 to 71.5 cases / 10 000 discharges/year</td>
</tr>
<tr>
<td>Sandberg 2014</td>
<td>USA</td>
<td>1988–2011</td>
<td>Discharges for children with IBD</td>
<td>From 6.1 to 8.2/100 000/years [p &lt; 0.001]</td>
</tr>
<tr>
<td>Meregaglia 2015</td>
<td>Italy</td>
<td>2005–2011</td>
<td>National Health Service discharges</td>
<td>CD 1% reduction; UC 7% reduction</td>
</tr>
</tbody>
</table>

UC, ulcerative colitis; CD, Crohn’s disease; IBD, inflammatory bowel disease.

2. Hospitalisation

Inflammatory bowel disease in children is often diagnosed in an inpatient setting. In adults, the disease is occasionally associated with acute presentations requiring hospitalisation (eg bowel obstruction or perforation in Crohn’s disease [CD], acute severe colitis and massive bleeding in ulcerative colitis [UC]). More frequently, however, the diagnosis and initial management of adult IBD can be and is in fact managed on an outpatient basis, and most healthcare providers also attempt to avoid inpatient care whenever possible during subsequent phases of the disease. Decreases in the frequency of hospitalisation can thus be evaluated as evidence of improved medical management of IBD. In addition, reductions in the costs directly and indirectly related to hospitalisation can obviously offset to some extent the increasing expenditures related to the use of TNFα antagonists and newer biological agents.

Unfortunately, determining whether inpatient care for IBD is indeed declining is more complicated than it appears. Analyses of hospital discharge rates are subject to a number of limitations. First, data from population-based studies are scarce. Second, in most studies, the impact of introducing immunosuppressants and biologicals on hospitalisation rates has been evaluated indirectly. Rates for the past two decades [during which the use of these agents is presumed to have increased] have been compared with those from earlier periods, when other approaches were used. Moreover, there is generally no way to distinguish disease-related hospitalisations from those provoked by the adverse events of drug therapy. Third, temporal trends in hospitalisation need to be adjusted for changes in the prevalence of IBD, but data on the latter are frequently incomplete. And finally, the specific impact of biologicals and/or immunosuppressants on IBD hospitalisation rates has never been assessed prospectively. Consequently, much of the data on this question come from retrospective analyses of cohort series or post-hoc analyses of data from RCTs [usually sponsor-driven] with follow-ups of 1–3 years.

3. Population-based studies

The three population-based cohort studies that emerged from our searches are summarised in Table 1. Samuel et al.4 followed 369 UC patients [58.5% males] in Olmsted County, MN, from 1970 through 2004 [a total of 5401 person-years]. During those four decades, the incidence rate of hospitalisations decreased by approximately 35%, although the cumulative probability of a first hospitalisation increased by 21.2/100 000 population; UC: from 8.9 to 21.2/100 000 population.
cases of 3403 Canadian patients diagnosed with CD between 1988 and 2008. They compared the risks of hospitalisation and the use of immunosuppressants and specialist care in three sub-cohorts defined by era of diagnosis [before 1996, 1996–2000, 2001, and later]. They found that specialist care within 1 year of diagnosis might improve outcomes in CD, with a 3% reduction of hospitalisation rates. However, hospitalisation rates at 5 years in the three cohorts were not significantly different. Vester-Andersen et al.² followed 531 individuals in Denmark with UC [n = 300] or CD [n = 231] diagnosed in 2003–2004. During the 7 years of follow-up, over half these patients had at least one IBD-related hospitalisation. From Year 1 to Year 5, the hospitalisation rate decreased markedly: from 7.0 to 0.9 days/person-year for patients with CD and from 4.7 to 0.4 days/person-year for those with UC.

4. Cohort studies

The six studies that looked at hospital discharge cohorts yielded conflicting results.²³,²⁰,²¹,²² Using National Hospital Discharge Survey data, Bewtra et al.²³ analysed trends in hospitalisation and surgery for CD and UC in the USA from 1990 through 2003. During the 14-year study period, hospitalisation rates for patients with a primary diagnosis of IBD ranged from 9.3 to 17.1 / 100,000 for CD and 8.2 to 12.4 / 100,000 for UC. A significant trend toward increasing rates was observed for CD [p = 0.002] but not UC. Herrinton et al.²⁰ analysed data from the Kaiser Permanente Health Service of Northern California, which included 2892 adults with CD and 5895 with UC. Compared with IBD-related hospitalisation rates for the period 1998–1999, those for 2004–2005 displayed substantial reductions [-33% for CD patients, -29% for those with UC]. In contrast, discharge rates for children with IBD in the USA²¹,²² have increased by approximately one-third. Even more striking increases have been observed among adults in Poland, where hospitalisation rates for IBD rose from 12.50 per 100,000 to 30.00 during the years 1991–1996 to 2001–2002.²³ In Italy, a recent study of national hospital discharge records found that hospitalisations for CD and UC both declined slightly during the period 2005–2011 [1% and 7%, respectively].²⁴

5. Case-control studies

Given the conflicting data that emerged from studies of population-based and discharge cohorts, we also looked at data from recent observational and case-control studies with information on the use of biological therapy. Costa et al. conducted a systematic review and meta-analysis of studies that assessed the impact of infliximab on rates of hospitalisation and/or major surgery for IBD.²⁵ Of the 27 studies they evaluated, 16 were informative regarding hospitalisation rates [6 RCTs and 10 observational studies] (Tables 2 and 3).²⁶-²⁸ Infliximab reduced the risk of hospitalisation in both pooled RCTs [odds ratio [OR] = 0.51; 95% confidence intervals [CI], 0.40–0.65] and observational studies [OR = 0.29, 95% CI, 0.19–0.43], with no differences between CD and UC. Since that report, a few other RCTs and cohort studies have been published, and all confirm that hospitalisation rates are on the decline. Abraham et al.²⁹ conducted a retrospective study of a large cohort of US veterans with IBD [8042 with CD, 12,432 with UC] in the period 2001–2009. Their adjusted model revealed a 50% relative reduction of hospitalisation rates in those who received at least 8–9 months of treatment with immunosuppressants, TNF-α inhibitors, or both. Park et al.³⁰ used the Stanford Translational Research Integrated Database to evaluate anti-TNF drug utilisation trends and their correlation with hospitalisation and surgery rates among IBD patients [438 children, 2514 adults] during the period 2007–2012. Hospitalisation declined by over 20% in adult patients using anti-TNF agents compared with non-users. In children, however, hospitalisations increased among those using biological therapy [OR 2.68; 95% CI, 2.49–2.88] although the need for surgery decreased [OR 0.57; 95% CI, 0.46–0.70].

In general, data on changes in hospitalisation rates are difficult to summarise because they are strikingly heterogeneous. Aside from the confounders already mentioned, organisational differences in national healthcare services should also be taken into account. A clear example emerged in the ECCO-EpiCom 2011 inception cohort:³¹ during the first year after diagnosis, hospitalisation rates for CD patients were significantly higher in Eastern Europe than in Western Europe/Australia, and significantly more CD patients received biological therapy in the Western Europe/Australian centres.

5.1. Surgery

The primary indications for surgical interventions in patients with IBD are emergency events and failure to respond to medical therapy. Intractable or fulminant UC is treated with total colectomy. Surgical resection is the treatment of choice for localised CD of the small bowel or colon that is unresponsive to medical treatment.

Table 2. Impact of anti-TNF therapy on hospitalisation rates based on post-hoc analysis of RCT data.

<table>
<thead>
<tr>
<th>Author year</th>
<th>Trial Name</th>
<th>Follow-up</th>
<th>Drug</th>
<th>Difference vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targan 1999</td>
<td>----</td>
<td>12 wk.</td>
<td>Infliximab</td>
<td>1% vs 4%</td>
</tr>
<tr>
<td>Hanauer 2002</td>
<td>ACCENT I</td>
<td>54 wk.</td>
<td>Infliximab</td>
<td>0% vs 46% when mucosal healing achieved</td>
</tr>
<tr>
<td>Rutgeerts 2004</td>
<td>ACCENT II</td>
<td>54 wk.</td>
<td>Infliximab</td>
<td>10% vs 35%</td>
</tr>
<tr>
<td>Sands 2004</td>
<td>----</td>
<td>3 yr.</td>
<td>Infliximab</td>
<td>16% vs 28%</td>
</tr>
<tr>
<td>Lichtenstein 2004</td>
<td>ACT I – ACT II</td>
<td>54 wk.</td>
<td>Infliximab</td>
<td>20% vs 40%</td>
</tr>
<tr>
<td>Gustavsson 2010</td>
<td>CHARM</td>
<td>1 yr.</td>
<td>Adalimumab</td>
<td>57% reduction</td>
</tr>
<tr>
<td>Rutgeerts 2010</td>
<td>ADHERE</td>
<td>3 yrs.</td>
<td>Adalimumab</td>
<td>42% reduction</td>
</tr>
<tr>
<td>Sandborn 2010</td>
<td>EXTEND</td>
<td>52 wk.</td>
<td>Adalimumab</td>
<td>0% when deep remission achieved</td>
</tr>
<tr>
<td>Colombel 2007</td>
<td>ULTRA 1 &amp; 2</td>
<td>52 wk.</td>
<td>Adalimumab</td>
<td>10% reduction in UC-related [p = 0.002] and drug-related [p = 0.005] rates</td>
</tr>
</tbody>
</table>

TNF, tumour necrosis factor; RCT, randomised controlled trial; wk., weeks; UC, ulcerative colitis.

*Not included in the meta-analysis of Costa J et al. 2013.*³²
**Table 3.** Hospitalisation rates in large cohort studies of patient using anti-TNF therapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>Jurisdiction</th>
<th>Era / Follow-up</th>
<th>Study characteristics</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnitzler 2009</td>
<td>Belgium</td>
<td>4.6 years</td>
<td>Single-centre, 619 CD pts.</td>
<td>Scheduled vs episodic treatment: 25.7% vs 46.7%</td>
</tr>
<tr>
<td>Kane 2009</td>
<td>USA</td>
<td>1</td>
<td>Review of health-care insurance claims, 571 CD pts.</td>
<td>Noncompliance vs compliance; OR 2.5 for hospitalisation + 115% cost increase 29/100 patient-years</td>
</tr>
<tr>
<td>Oussalah 2010</td>
<td>France</td>
<td>2000–2009</td>
<td>Multicentre, 191 UC pts.</td>
<td>70% reduction in acute admissions [vs nonusers of anti-TNF drugs]</td>
</tr>
<tr>
<td>Sprakes 2010</td>
<td>UK</td>
<td>2</td>
<td>Single-centre, 100 CD pts.</td>
<td>Hazard ratio [HR] for hospitalisation = 0.73; 95% CI, 0.63–0.85 [vs nonusers of anti-TNF drugs]</td>
</tr>
<tr>
<td>Carter 2011</td>
<td>USA</td>
<td>2005–2008</td>
<td>420 UC</td>
<td>Reduction hospital days 155 vs 495 [p &lt; 0.05]</td>
</tr>
<tr>
<td>Loomes 2011</td>
<td>Canada</td>
<td>2</td>
<td>105 CD pts.</td>
<td>Hospitalisation for UC reduced from 15.1% to 3.5%</td>
</tr>
<tr>
<td>Waters 2012</td>
<td>USA</td>
<td>2</td>
<td>268 IBD pts.</td>
<td>73% reduction after 9 months of IM or infliximab or both</td>
</tr>
<tr>
<td>Abraham 2013</td>
<td>USA</td>
<td>2001–2009</td>
<td>20,474 US veterans with IBD [8042 with CD]</td>
<td>24% reduction with infliximab; 21% reduction with adalimumab, OR = 2.7 kids [CI, 2.5–2.9]</td>
</tr>
<tr>
<td>Mandel 2014</td>
<td>Hungary</td>
<td>From 2008</td>
<td>194 pts. on anti-TNF therapy</td>
<td></td>
</tr>
</tbody>
</table>

UC, ulcerative colitis; CD, Crohn’s disease; IBD, inflammatory bowel disease; TNF, tumour necrosis factor; pts., patients; OR, odds ratio; IM, immunomodulators.

*Not included in the meta-analysis of Costa J et al. 2013.*

We know from population-based studies that in the pre-biologicals era [ie before 1998], approximately 40–50% of patients with IBD underwent intestinal surgery within 10 years of diagnosis, and the risk of postoperative recurrence was about 50% by 10 years.50,51 Declines in surgery rates were already evident in the final years of the pre-biologicals era [1998–2003].51,52 The most recent reports indicate that surgery rates at 1 and 5 years in the post-biologicals era [2001–2008] are lower than those recorded for 1988.51,52,53 However, confounding factors make it impossible to reliably attribute this decline to the increased use of immunosuppressants and/or anti-TNF biologicals.

We therefore decided to see whether specific therapies have influenced colectomy rates over time. In patients with extensive UC, cyclosporine and infliximab are both known to reduce the short-term risk of urgent colectomy.54 In a randomised placebo-controlled trial, the colectomy rate at 1 year was significantly lower in patients randomised to treatment with infliximab.55 Because colectomy rates are strongly related to the extent of the disease, it is important to determine whether declining rates are actually due to changes in medical treatment or whether they reflect trends toward generally milder disease or diagnosis of UC at earlier stages of disease. A long-term population-based study of all patients within a defined region is the most effective way to answer this question.

In three Danish population-based studies, surgery rates during the first year after IBD diagnosis were lower in patients diagnosed after immunosuppressant therapy had been developed [as compared with cohorts diagnosed before these drugs were used].41,42,43 However, the follow-up periods in these studies were all fairly short [ie 1–7 years], so it is impossible to say how long-lasting the surgery-reducing effects of immunosuppressant therapy are.

A Swiss cross-sectional registry study found that administration of immunomodulator therapy within 12 months after the first ileocolic resection for CD reduced the need for subsequent resections.57

The same picture emerged from a recent Australian referral-based study, in which the use of immunomodulators early in the course of CD was significantly associated with a reduced long-term need for CD-related abdominal and perianal surgery.58 Similarly, treatment with infliximab and an immunomodulator was associated with protective effects in patients with CD or UC in a large registry-based study from the U.S. Veteran Affairs Hospitals, which included 9 years of follow-up.59

Sjøberg et al. found that the diagnosis of UC in Sweden increased markedly after 2005 [compared with historical data], but colectomy rates and the proportion of patients with severe disease were unchanged, suggesting that the nature of UC has not changed over time.60 A Canadian group analysed data for over 3000 UC patients with up to 25 years of post-diagnosis follow-up.61 They found a cumulative incidence of UC-related colectomy that was lower than that previously reported, and additional decreases were noted in the more recently diagnosed patient cohorts.

In a recently published population-based study from Denmark [with over 30 years of data on 49,000 patients with IBD], the 5-year cumulative probability of first major surgery for CD or UC declined significantly between 1979–1986 and 2003–2011. A significant increase over time in the use of thiopurines and TNF-α blockers to treat IBD was accompanied by a persistent and significant decrease in surgery rates.62

In conclusion, decreasing surgery/colectomy rates suggest that the growing use of immunosuppressants and biological agents has had a positive impact on the course of IBD. Colectomy rates have clearly decreased since the introduction of these drugs, and a review of the epidemiological data tends to exclude the possibility that this change reflects changes in the nature or severity of UC or its increasingly early diagnosis. When analysing rates of surgery in general, it is important to consider that preventing intestinal resection may not be the ultimate goal of IBD treatment. Surgery can undoubtedly be
a good solution in certain cases characterised by obstructive symptoms. The need for surgery will not disappear with an earlier use of biologicals, as surgery remains an appropriate therapeutic choice for CD and UC in some patients.

5.2. Infections
The majority of preparations used to treat IBD have immunomodulating properties, which are the basis of their anti-inflammatory effects, but they can also increase the risk of infectious complications. Several studies have been conducted to assess this risk. Most were undertaken after the introduction in clinical practice of anti-TNFα agents. The results vary widely, depending in part on the type of study conducted and the definition of infectious complication used.

6. Cohort-controlled studies
In a nationwide study of propensity score-matched cohorts in Denmark, the risk of serious infection within 90 days of the initiation of treatment was 63% higher in anti-TNFα users than in non-users (hazard ratio [HR] = 1.63; 95% CI, 1.01–2.63). Interestingly, the risk declined when the follow-up was extended to the first 365 days of treatment [HR = 1.27; 95% CI, 0.92–1.75]. The most substantial increase in risk involved skin and soft tissue infections [HR = 2.51; 95% CI, 1.23–5.12], urological or gynaecological infections [HR = 2.31; 95% CI, 0.64–8.29], and sepsis [HR = 2.45; 95% CI, 0.65–9.19].

Prospective assessment of registry data on North American CD patients [the TREAT trial] with over 5 years of follow-up revealed increases in the risk of serious infection amounting to 43% and 57% for patients treated with infliximab and prednisone, respectively. No significant increase was associated with immunosuppressant use. It is important to note, however, that the strongest independent predictor of serious infection was disease activity [HR = 2.24; 95% CI, 1.57–3.19], which was significantly greater in patients receiving infliximab than in those receiving other drugs. Furthermore, no attempt was made to evaluate the potential impact of concomitant immunosuppressant therapy. Similar findings emerged from a case-control study conducted at the Mayo Clinic: use of immunomodulating drugs [systemic steroids, thiopurines, or infliximab] was associated with an elevated risk of opportunistic infections, which was even higher when combinations of these drugs were used.

A case-control study of IBD patients in Japan also flagged systemic steroids and thiopurines as major risk factors for opportunistic infection, but no increased risk was associated with infliximab. The latter finding is consistent with the results of three studies of patients with autoimmune disease retrieved from four large databases in the USA: patients with IBD placed on anti-TNFα therapy appeared no more prone to contract serious infections, non-viral opportunistic infections, or herpes zoster than those started on thiopurines [OR = 0.88; 95% CI, 0.69–1.11] which was significantly greater in patients receiving infliximab than in those receiving other drugs.

7. Meta-analyses
Results have been published for five pooled analyses of RCTs assessing the risk of infections in IBD patients treated with biological agents [11% vs 36.3% in the placebo group, p < 0.001]. This difference was not observed in patients with CD. As for adalimumab, it did not appear to increase the risk of infection or serious infection over that associated with placebo in six clinical trials conducted in CD patients.

Another meta-analysis looked at 22 RCTs on anti-TNFα therapy for IBD [follow-up range: 2–56 weeks] and found a higher frequency of opportunistic infections in anti-TNFα-treated patients than in those allocated to placebo (0.9% vs 0.3%; relative risk [RR] = 2.05; 95% CI, 1.10–3.85). Wang et al. analysed RCTs on biological agents that also included natalizumab and ustekinumab. The risk of herpes zoster and/or herpes simplex infection was increased 3-fold in CD patients treated with biologicals [RR = 2.99; 95% CI, 1.03–8.68] but there was no excess risk for serious infections.

8. Combination therapy
The safety of combined anti-TNFα–immunosuppressant therapy for CD was investigated in a meta-analysis that included five RCTs. During a median follow-up of 51.6 weeks [range: 48–54 weeks], the risk of infections or serious infections in patients on combination therapy [OR = 0.88; 95% CI, 0.69–1.11] was not significantly different from that associated with TNF-inhibition or immunosuppressant therapy alone [OR = 0.68; 95% CI, 0.37–1.24]. Similar results emerged from a combined analysis of data from four RCTs of infliximab in patients with IBD: concomitant therapy with immunomodulators had no impact on the risk of infections or serious infections. A retrospective study of a cohort of new TNFα inhibitors users also found similar rates of serious infection in combination and anti-TNFα monotherapy groups [HR = 0.93; 95% CI, 0.88–1.34]. However, combination therapy was associated with an almost 3-fold increase in the rates of non-<i>Candida</i> opportunistic infections and herpes zoster [HR = 2.65; 95% CI, 1.05–6.66 and HR = 3.38; 95% CI, 1.15–9.94, respectively].

In conclusion, most clinical trial data indicate that the risk of serious infections is not increased in patients treated with anti-TNFα agents, but a different picture emerges from cohort studies. This discrepancy may reflect the selective nature of the populations studied in RCTs, where the proportion of ‘low-risk’ patients is likely to be higher than that encountered in actual clinical practice. Additional research is needed to determine whether the risk of infection is additionally increased when anti-TNFα therapy is given with immunosuppressants. Of note, the risk of infectious complications seems to be higher in older patients treated with combination therapy.
8.1. Cancer

Nearly a century has passed since Burrill B. Crohn and Herman Rosenberg first suggested that UC might be associated with colorectal cancer. Since then, a substantial amount of work has been done to elucidate the links between IBD and cancer. The relevance of this issue has increased markedly with the growing use of biological and non-biological immunosuppressant therapies, owing to the major role in cancer prevention played by the immune system. Immunosuppressants are also being used earlier in the course of IBD, which means that a growing number of patients are being exposed over longer periods. Verifying the safety of these drugs, in particular their potential impact on the risk of cancer, is thus a high priority.

On the basis of data on thiouanine use in kidney transplant recipients, the International Agency for Research on Cancer classified azathioprine as a human carcinogen in 1981. Studies conducted since then in patients with IBD have found an excess risk of cancer in those exposed to thiopurines. Plausible mechanisms for the carcinogenic effects of these drugs include direct damage to cellular DNA, impaired immune control of chronic infection by mutagenic viruses, and reduced immunosurveillance of tumour cells. Population-based studies of IBD patients have revealed thiopurine-related increases in the overall risk of cancer ranging from 48% to 68% [after adjustment for potential confounders]. The excess risk seems to be driven mainly by increases in non-melanoma skin cancers and those involving the lymphoproliferative system. Population-based study data suggest that thiouiran therapy for IBD is associated with an approximately 3-fold increase in the risk of lymphomas. The probability of skin cancer is less well defined: some studies have found no excess risk at all, whereas others have demonstrated multiple-fold increases in risk. Findings from a recent meta-analysis suggest that the risk of non-melanoma skin cancer in IBD patients treated with thioupurines may be increased more than 2-fold.

In a recent meta-analysis of data from eight studies, the risk of high-grade cervical dysplasia and cervical cancer in patients with IBD on immunosuppressants was increased 34% compared with healthy controls. The clinical relevance of these findings is limited, however, since the small number of studies and substantial variation in data reporting diminished the meta-analysis analytical capacity [eg to assess the impact of treatment duration, or to differentiate between the effects of different drugs or drug combinations]. Nonetheless, female patients with IBD should be encouraged to undergo regular screening for cervical neoplasia and also vaccination against human papillomavirus [HPV], according to current guidelines. If possible, both should be done before any immunosuppressant therapy is started. An excess risk of kidney and bladder cancer has been found in thiouarine-treated transplant recipients, and one study suggests that urinary tract cancers may also be increased in thiouanine-exposed patients with IBD.

In discussions with patients on the association between thiopurines and cancer, it is important to emphasize that the absolute risk is still quite low, particularly for lymphoma and cervical cancer. In addition, past thiopurine exposure is not significantly associated with cancer, so withdrawal of the drug may eliminate whatever excess cancer risk there is. Indeed, some studies have failed to demonstrate any association between thiouarine therapy and cancer, and the roles played by other drugs that are often administered with thiopurines are poorly defined. IBD patients who are receiving thiopurines are at increased risk for non-melanoma skin cancers, but it is not clear whether the excess risk persists after thiopurine withdrawal. In short, the full picture of thiopurine-related cancers is far from complete.

Treatment with TNF-α inhibitors was approved in the late 1990s. It has revolutionised the medical management of IBD, and its use continues to increase. A few years after the introduction of anti-TNF therapy, concern over its potential cancer-facilitating effects began to grow in light of the results of a meta-analysis of data from nine randomised clinical trials. The possibility that TNF-α inhibition might be associated with cancer is by no means implausible: the immune system plays an important role in the prevention of tumours, and its suppression with TNF-α antagonists may lead to cancer. However, later meta-analyses and larger population-based studies published in recent years have not revealed any increase in the cancer rate among patients exposed to these drugs. Since the progression of cancer is often protracted, ongoing assessment of the long-term cancer risk posed by anti-TNF-α biologicals is nonetheless warranted.

In conclusion, there is a very strong body of evidence supporting the carcinogenic effects of thiopurines, particularly with regard to the risk of non-melanoma skin cancers and cancers of the lymphoproliferative system. The risk of cervical cancer may also be increased, although existing studies are difficult to compare. Nonetheless, the absolute risk of cancer in patients treated with thiopurines is still low, and it has to be weighed against the therapeutic benefits of these drugs. As for biological agents, on the basis of available evidence, they do not appear to increase the risk of cancer in patients with IBD. However, the study with the longest follow-up published thus far covers a median of 3 years after the first infusion. Therefore, close monitoring for signs of possible drug-related cancer is advisable during biological therapy.

8.2. Mortality

Anti-TNF biologicals and immunosuppressants are potent anti-inflammatory agents with the potential for improving disease control. However, there is some evidence that these drugs are associated with a higher risk of infectious complications and certain malignancies, which may translate into an increased risk of mortality. Few studies have investigated the impact of immunosuppressant or biological treatment on mortality in patients with IBD, and ever fewer are population-based.

In an unselected cohort of IBD patients diagnosed in Olmsted County, MN, [1940–2004], the risk of dying among those exposed to immunomodulators [thiopurines, methotrexate, biologicals] was similar to that of unexposed patients [for CD: standardised mortality ratio [SMR] = 0.9; 95% CI, 0.3–2.4; for UC: SMR = 1.3; 95% CI, 0.3–3.8]. Likewise, a collaborative European population-based study of UC patients found that thiopurine therapy had no negative influence on mortality rates 10 years after diagnosis. A study of American patients enrolled in the Kaiser Permanente Medical Care Programme during the period 1996–2003, found that immunomodulators produced a mild, non-significant increase in mortality among CD patients [OR = 1.3; 95% CI, 0.9–1.9], whereas their use was protective in those with UC [OR = 0.5; 95% CI, 0.3–0.9]. When cause-specific mortality was analysed, CD patients on immunomodulators seemed to have an increased risk of death from gastrointestinal diseases [OR = 2.2; 95% CI, 1.0–4.9], although the analyses were not adjusted for other IBD medications or for disease severity. Finally, when the safety profile of infliximab was assessed in a national cohort of Danish IBD patients [1999–2005], CD patients treated with the drug were found to have an about 2-fold increase in mortality [SMR = 1.9; 95% CI, 1.0–3.2] compared with the general background population. The impact of other drugs on survival was not tested.
The impact of azathioprine exposure on mortality rates in CD was studied in a retrospective-prospective study conducted in a tertiary centre in France. Patients who responded to azathioprine were matched [1:2] by age, disease duration, and gender with CD patients who had not been exposed to immunosuppressants [controls]. At the end of follow-up, 5% of the azathioprine-exposed patients had died as compared with only 1.6% of controls $[p = 0.01]$, with survival rates of 92.8% ± 2.3% and 97.9% ± 0.8%, respectively, 20 years after study entry. Death among the azathioprine-treated patients also occurred earlier in life [median age: 48 vs 56 years, $p = 0.01$] and was more frequently due to cancer [3.6% vs 1.1%, $p = 0.3$]. However, whether these differences were attributable to azathioprine exposure is unclear, since the baseline disease and demographic characteristics of the two groups were different.

A retrospective British database study evaluated the impact of corticosteroids and immunosuppressants on mortality in IBD patients treated before the era of biological therapy. Current use of steroids was associated with higher mortality than was no steroid use in both CD [HR = 2.48; 95% CI, 1.35–3.31] and UC patients [HR = 2.81; 95% CI, 2.26–3.50]. Mortality was not increased by current therapy with thiopurines. The results of this study are consistent with those of a prospective multicentre analysis of the Crohn’s Therapy, Resource, Evaluation and Assessment Tool [TREAT] registry, which assessed the safety of medical therapy in patients with CD over a median follow-up of 1.77 years. In the adjusted model, older age and steroid treatment were the only factors associated with a higher risk of dying [OR = 1.072; 95% CI, 1.050–1.094 and OR = 2.096; 95% CI, 1.147–3.832, respectively]. Neither infliximab nor immunomodulator therapy had any effect on mortality. When the follow-up was extended to 5 years, the same results emerged [ie an approximately 2-fold increase in the risk of death for corticosteroid use and no effects of immunomodulators or infliximab].

A meta-analysis of placebo-controlled trials of anti-TNFα therapy revealed no difference in mortality rates, and a safety analysis of infliximab trials in CD and UC found no excess mortality [including deaths related to infection] in treated patients. Mortality was also unaffected by use of immunomodulators. An analysis of clinical trials with adalimumab in CD and other autoimmune disorders found death rates in treated patients that were similar to or lower than those of the reference population. Similar results have emerged from a large cohort study of patients with autoimmune diseases who were treated with infliximab, adalimumab, or etanercept. However, the duration of the studies included in the papers and of patients’ exposures to anti-TNFs was relatively short [in most cases less than 2 years].

Consistent with previous results, a large retrospective cohort study conducted in Leuven found no difference in mortality between infliximab-treated IBD patients and controls who had not received the drug [OR = 1.33; 95% CI, 0.56–3.0]. However, the patients in the infliximab group were significantly younger and the duration of their follow-up was only half that in control group [median 5 and 10 years, respectively]. When the safety of infliximab and adalimumab were assessed in an older population [> 65 years] in Italy [2000–2009], the risks of infections and mortality in treated patients were found to be increased compared with those of younger adults treated with anti-TNFα agents and those of other elderly patients who had not received TNF-inhibitors.

The Porto Paediatric IBD Group conducted an international retrospective investigation of causes of death in IBD patients under 19 years of age and their association with disease- or treatment-related factors. During the period 2006–2011, 31 deaths were recorded in the 15 countries that participated in the study; 14 were due to fatal infections, and 12 [86%] of those occurred in patients treated with at least two immunomodulators, including immunosuppressants, corticosteroids, and biologicals. Whether the risk of dying in the full cohort of paediatric IBD patients was higher than expected was not analysed.

In conclusion, the majority of studies reported in the literature did not reveal any increase in mortality with immunosuppressant therapy or biologicals/anti-TNF agents. However, the studies themselves have a number of limitations, including short follow-ups, lack of adjustment for disease activity, and other confounders with potential impact on outcome. For this reason, it is still too early to draw any definite conclusions regarding this risk.

### 8.3. Conclusion

Biological and non-biological immunosuppressant therapies both offer indisputable benefits for patients with IBD, and both have

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type</th>
<th>Diagnosis</th>
<th>Drugs examined</th>
<th>Mortality risk</th>
</tr>
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<tr>
<td>Jess et al., 2006</td>
<td>PBS</td>
<td>CD; UC</td>
<td>Thiopurines + MTX + anti-TNF</td>
<td>Not increased</td>
</tr>
<tr>
<td>Huftless et al., 2007</td>
<td>Health-care programme database</td>
<td>CD; UC</td>
<td>Thiopurines + MTX</td>
<td>CD-Increased</td>
</tr>
<tr>
<td>Leyte et al., 2014</td>
<td>Registry</td>
<td>CD</td>
<td>Anti-TNF</td>
<td>Increased</td>
</tr>
<tr>
<td>Peyrin-Biroulet et al., 2008</td>
<td>Meta-analysis</td>
<td>CD</td>
<td>Anti-TNF</td>
<td>Not increased</td>
</tr>
<tr>
<td>Lichtenstein et al., 2012</td>
<td>Pooled analysis of CT data</td>
<td>CD; UC</td>
<td>Thiopurines; anti-TNF</td>
<td>Not increased</td>
</tr>
<tr>
<td>Lichtenstein et al., 2012</td>
<td>Pooled analysis of CT data</td>
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<td>Anti-TNF</td>
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<tr>
<td>Herrion et al., 2012</td>
<td>Health-care programme database</td>
<td>CD; UC</td>
<td>Anti-TNF</td>
<td>Not increased</td>
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<tr>
<td>Cottone et al., 2011</td>
<td>Multicentre</td>
<td>CD; UC</td>
<td>Anti-TNF</td>
<td>Increased</td>
</tr>
</tbody>
</table>

PBS, population-based study; CD, Crohn’s disease; UC, ulcerative colitis; MTX, methotrexate; anti-TNF, anti-tumour necrosis factor α; CT, clinical trial.

1 Not statistically significant.
2 Patients > 65 years of age.
the potential for altering the prognosis. The positive and negative effects of these drugs on disease outcomes should be reflected by changing rates of mortality, hospitalisation, surgery, infections, and cancer occurrence. However, data on these aspects are remarkably heterogeneous and difficult to summarise owing to the effects of confounding factors and organisational differences between the healthcare systems of different countries. The majority of studies published thus far have not revealed any increase in mortality or cancer onset in patients treated with immunosuppressant therapy or biologicals/anti-TNF agents. Neither have they found any excess risk of serious infections in individuals treated with anti-TNF agents [although infections in general seem to be more likely in older patients receiving combination therapy]. Colectomy rates in UC patients have clearly decreased since the introduction of these drugs, and our review of the literature tends to exclude the possibility that this change reflects changes in the nature or severity of the disease. Additional research, preferably in the form of the epidemiological ‘gold-standard’ population-based studies, is warranted to shed further light on all these important issues.

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Conflict of Interest
None.

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Impact of New Treatments in IBD


