The treatment of inflammatory bowel disease (IBD) has changed over the past decade to include new agents (specifically the anti-TNF class) and trends towards more aggressive therapy (e.g., combination therapy, earlier treatment with immunomodulators and top-down therapy). Early data show that these more aggressive treatment plans have the potential to alter the natural history of disease and avoid excessive corticosteroid use, but they are not without costs. Physicians and patients need to consider not only the benefits of these treatments, but also the potential adverse events. With the vast amount of data now available on the risks of IBD therapy, it is difficult to quickly and effectively communicate these data to patients in the limited time we have in the office. In addition, it is hard to know exactly what data to report. This review discusses techniques for optimizing communication with our patients and an update on safety data for immunomodulators, anti-TNF agents and natalizumab.

Communicating Risks to Patients

Effectively communicating risk is challenging. Some simple “rules” should be followed to help avoid confusion by patients and other providers. Framing is the unintentional (or perhaps intentional) presentation of data in such a way to influence a decision. Not surprisingly, patients will change their preferences when risks are framed in absolute (e.g., “a 2% risk reduction” to describe a decrease of risk from 4-2%) versus relative risk reductions (e.g., “a 50% decreased risk”). Risk data (or benefit for that matter) should never be communicated to patients as relative risk on its own; absolute risks are preferable. Small percentages are difficult to conceptualize (e.g., 0.01% is 1 per 10,000) and comparative numbers with different denominators are confusing (e.g., is 5/36 different than 11/80?). Presenting risk as an absolute number over a common denominator is probably the most effective. For example, the annual risk of NHL in the general population is about 2/10,000 persons per year, the risk of NHL while on immunomodulator monotherapy is about 4/10,000 persons per year, and the risk of NHL on combination infliximab plus immunomodulator therapy is about 6/10,000.

Risks Associated with Immunomodulators

6-mercaptopurine (6MP) and azathioprine (AZA) have been used for the treatment of inflammatory bowel disease since the 1970s and safety data were reported as early as 1979. Serious adverse events are fortunately rare, but well reported. Most side effects of 6MP/AZA fit into the categories of either direct or indirect toxicity. Direct toxicities include pancreatitis, bone marrow suppression, allergic reactions and drug-induced hepatitis. Indirect toxicity refers to processes that result as sequelae from direct toxicity, and include infections, lymphomas and other cancers (specifically skin and cervical). Many of the non-Hodgkin’s lymphomas (NHL) reported are Epstein-Barr Virus related, and a meta-analysis summarized the lymphoma risk associated with 6MP/AZA as 4-fold higher than the general population. When specifically looking at patients with Crohn’s disease and NHL from this meta-analysis (as opposed to Hodgkin’ disease which has different age distribution), the absolute rate is 4 patients per 10,000 patient-years. A large, population based study from France recently reported a similar relative risk (5.28) for patients currently taking thiopurines compared to those never exposed – with an absolute rate of lymphoma of 9 per 10,000 patient-years. A recently described, almost universally fatal sub-type of NHL is hepatosplenic T-cell lymphoma (HSTCL) and has been associated with IBD therapy. Most reported cases were with combination immunomodulator plus anti-TNF therapy, however, to date there have been at least sixteen cases in the literature in patients treated with azathioprine alone. Table 1 summarizes estimated risks of the most significant direct and indirect toxicities associated with 6MP/AZA. Based on uncertainty of the denominator (i.e., we don’t know how many have actually been exposed in the group at risk), we are unable at this time to comment on the rate of HSTCL with monotherapy or combination therapy using immunomodulators plus anti-TNF agents.

Methotrexate (MTX) is used less frequently than 6MP/AZA, in part due to its perceived toxicity. In practice, when used for

<table>
<thead>
<tr>
<th>Event</th>
<th>Frequency (annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3% (3/100)</td>
</tr>
<tr>
<td>Severe infection</td>
<td>5% (5/100)</td>
</tr>
<tr>
<td>Death (sepsis)</td>
<td>0.15% (15/10,000)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0.04% (4/10,000)</td>
</tr>
</tbody>
</table>

Corey A. Siegel, MD

In the treatment of Crohn’s disease, it is generally well tolerated. The most hesitation comes from concerns over lung disease (hypersensitivity pneumonitis) and liver toxicity. Hypersensitivity pneumonitis is reported in up to 1% of patients with rheumatoid arthritis, but only rare cases have been reported in IBD. Liver toxicity also appears to vary based on the underlying disease in which MTX is being used to treat. In patients with psoriasis, nearly a quarter of patients have evidence of liver disease, however, in IBD patients (more similar to rheumatoid arthritis patients), the majority have either normal biopsies or only mild steatosis/inflammation. Leukopenia is much less common as compared to 6MP/AZA, but has been reported and can be life-threatening. Lymphoma associated with methotrexate is well reported in the rheumatoid arthritis literature, but probably rare in IBD. There have been no cases reported of HSTCL associated with the use of MTX.

**Risks Associated with Biologics**

The currently available biologics for the treatment of Crohn’s disease include infliximab, adalimumab, certolizumab pegol and natalizumab. Infliximab is the only biologic agent approved for the treatment of ulcerative colitis. Infliximab is a chimeric monoclonal antibody against tumor necrosis factor alpha (anti-TNF), adalimumab is a human monoclonal anti-TNF agent and certolizumab pegol is a recombinant, humanized antibody Fab’ fragment, with specificity for TNF. Natalizumab is a humanized monoclonal antibody against alpha4 integrin that inhibits leukocyte adhesion and migration into inflamed tissue.

These medications are effective for the treatment of Crohn’s disease, however, all of them have potential serious adverse effects that require careful consideration and discussion with patients. Some of the adverse events are fairly common, but fortunately are mild and quickly reversible. Others are very rare and unfortunately life-threatening. The common events include infusion (or injection site) reactions, treatable infections and simple intolerance and these are approximately equal across the four biologic agents (Table 2). The serious adverse events that cause concern to both patients and physicians for the anti-TNF agents include serious infections (possibly leading to sepsis and death) and malignancy (specifically non-Hodgkin lymphoma). Serious infections occurred at a rate of approximately 2-4% in the landmark randomized controlled trials of these agents. In a systematic review, the rate of death related to sepsis was 0.4% (4 per 1000) but importantly, the patients who died were predominantly older patients with multiple comorbidities and typically concomitantly taking corticosteroids. Progressive multifocal leukoencephalopathy (PML) is a degenerative brain disease related to JC virus infection associated with treated with natalizumab. All cases to date of PML associated with the use of natalizumab have occurred after at least one year of therapy. PML has been described in patients with both multiple sclerosis and Crohn’s disease who have received natalizumab. Although there has only been 1 patient with Crohn’s disease reported, far fewer Crohn’s patients have been treated with natalizumab compared to the multiple sclerosis population. Other immune suppressant medications have also been associated with PML, but not in patients with inflammatory bowel disease. Serum/urine testing is being developed to help determine who is at most risk for PML and the rate of occurrence has remained stable at about 1 per 1,000 exposed patients. As of May 2011, there were 124 cases of PML reported in patients exposed to natalizumab and there were nearly 35,000 patients treated worldwide for at least 2 years.

**Table 2: Common adverse events seen in large clinical trials of ≥ 12 weeks**

<table>
<thead>
<tr>
<th>Agent</th>
<th>ACCENT 1 20</th>
<th>CHARM 19</th>
<th>PRECISE 1 22</th>
<th>ENACT 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects^</td>
<td>385</td>
<td>517</td>
<td>331</td>
<td>214</td>
</tr>
<tr>
<td>Follow-up (weeks)</td>
<td>54</td>
<td>56</td>
<td>26</td>
<td>60</td>
</tr>
<tr>
<td>Discontinued due to adverse event (%)</td>
<td>12</td>
<td>6</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Infusion/injection site reaction (%)</td>
<td>21</td>
<td>5</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Infections* (%)</td>
<td>30</td>
<td>45</td>
<td>21</td>
<td>62</td>
</tr>
<tr>
<td>Serious infections (%)</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

^ included only patients who received active treatment for the entire follow-up period

*not serious, but may have required antibiotics

IFX=infliximab; ADA=adalimumab; CTZ=certolizumab pegol; NAT=natalizumab

The association of the anti-TNF agents with non-Hodgkin lymphoma (NHL) has been a controversial topic. The difficulty on making conclusions relates to the uncertainty of the rate of NHL in Crohn’s disease without treatment and the contribution of immunomodulator therapy. Two large studies evaluating the baseline risk of NHL in Crohn’s disease have discrepant results, one showing no increased risk compared to the general population,25 and another showing a relative risk of 3.6 (but only in males)26. As noted above, there are data concluding that immunomodulator therapy (azathioprine and 6-mercaptopurine) increase the risk of NHL as well in this patient population4. A recent meta-analysis evaluated 26 trials to determine the rate of NHL in patients with Crohn’s disease who were treated with anti-TNF agents in combination with immunomodulators.27 The rate was calculated to be 6.1 per 10,000 patient-years which is a statistically significant increase over the general population (SIR 3.23, 95% CI 1.5-6.9) and a non-significant increase over those treated with immunomodulators alone (SIR 1.7, 95% CI 0.5-7.1) (Table 3). It is currently not possible to determine the rate of NHL on anti-TNF monotherapy as there are simply not enough patients treated with anti-TNFs who have never been exposed to immunomodulators. As noted above, HSTCL, a sub-type of NHL, has been described in patients with IBD treated with immunomodulators alone and approximately 30 patients who had taken infliximab in combination with an immunomodulator.28,29 The average age of these patients at the time of HSTCL diagnosis was in the mid 20’s, almost all were male and unfortunately, this type of lymphoma appears to be universally fatal.

It is becoming clear that there are risk factors for both serious infections and NHL that should play a role in decision making.
It is important for patients to understand the risks of their disease so that they can appreciate that suboptimal treatment may be their riskiest choice. Approximately 18% of patients with Crohn’s disease require surgery within the first year of their diagnosis and up to 80% have surgery by 20 years. Operative mortality is low but measurable (approximately 8/10,000), and although it is very uncommon to die from a complication of Crohn’s disease, it has been estimated to occur about 15/10,000.

Conclusion

As new biologic agents are approved for the treatment of IBD and as more potent medications are used earlier in the disease course, understanding the risks becomes even more important. Involving our patients in choosing appropriate therapies and ensuring that the risks are communicated clearly will continue to be critical as treatment algorithms evolve. To best deliver this information to our patients, we need to carefully review the available evidence, endeavor to put it into perspective for our patients, focus on the most serious risks of biologics, avoid framing, and invite patients to be involved in these preference based decisions.

REFERENCES

11. Farrell RJ, Ang Y, Kileen P, et al. Increased incidence of non-


