Position Statement: Immunomodulator Therapy for Inflammatory Bowel Disease

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The term “inflammatory bowel disease” includes ulcerative colitis and Crohn’s disease, and a smaller number of cases of indeterminate colitis. We estimate that the number of patients in Israel is at least 6,000. These diseases may begin at any age, but in most cases the onset is in young adulthood. These are chronic, lifelong diseases. There is no cure except for total colectomy in ulcerative colitis. Therapy is aimed at the control of symptoms, improvement of quality of life and minimizing complications of the diseases and the treatments [1].

With the introduction of many new therapeutic agents, there is a need to establish written guidelines for their use in clinical practice, based on an extensive review of the current literature. The guidelines given herein concern pharmaceutical and biological agents, and are to be considered as flexible recommendations that should help the physician with his or her therapeutic decisions regarding the best course suitable for individual patients. These guidelines were written by the Inflammatory Bowel Diseases Section Committee of the Israel Gastroenterology Association, and were reviewed by the heads of all the gastroenterology departments in Israel.

Azathioprine and 6-mercaptopurine

Clinical pharmacology

The thioguanine derivative azathioprine (AZA) is converted non-enzymatically into 6-mercaptopurine (6-MP). 6-MP is transformed in a series of steps (by hypoxanthine phosphoribosyltransferase, inosine monophosphate dehydrogenase, guanosine monophosphate synthetase) into the active products 6-thioguanine nucleosides (6-TGN). A competing pathway (xanthine oxidase and thiopurine S-methyltransferase, TPMT) converts 6-MP into catabolites lacking pharmacologic activity [2]. How these drugs act is not entirely known. 6-TGN are purine antagonists and cause immunosuppression when incorporated into the DNA of lymphocytes. AZA/6-MP suppresses the formation of a long-lived subgroup of T lymphocytes [1].

Indications for therapy in ulcerative colitis

AZA/6-MP are indicated for the induction and maintenance of remission in steroid-dependent or steroid-refractory cases of ulcerative colitis. The drugs are given to patients on corticosteroids with the aim of weaning them off the steroids. Clinical studies have shown the efficacy of these agents when given in adequate doses in ulcerative colitis cases [2]. In ulcerative colitis AZA induced and maintained remission for at least 2 years. AZA induced remission and was steroid-sparing in 87% of ulcerative colitis patients. A factors favoring remission was a lower white blood cell or neutrophil count.

Indications for therapy in Crohn’s disease

AZA/6-MP are indicated for induction and maintenance of remission in steroid-dependent or steroid-refractory cases. The use is in steroid-treated patients as with ulcerative colitis. AZA had a significant steroid-sparing effect in adult [3] and adolescent [4] patients with Crohn’s disease, including cases with fistula. AZA induced remission and was steroid-sparing in 64% of Crohn’s disease patients; a factor favoring remission was colonic rather than ileal disease.

Mode of administration

These drugs are given by mouth. Both drugs are slow acting, which is why clinical efficacy cannot be expected until several weeks or even months of treatment have elapsed. The slow onset of action of AZA/6-MP is not improved by intravenous loading [5]. The use of intravenous AZA in ulcerative colitis requires further study.
Optimizing safety: measurements of AZA/6-MP metabolites

The clinical importance of TPMT and 6-TGN measurements is still being defined. Recent reports suggest that 6-TGN levels (>235 pmol per 8 x 10⁶ red blood cells) independently correlate with remission. 6TGN determination can confirm compliance with therapy and indicate where escalating the AZA/6-MP dose could be useful in non-responding, non-leukopenic patients [6]. Inability to achieve a therapeutic 6-TGN level characterizes a subgroup of patients resistant to AZA/6-MP. There is, however, a broad overlap in 6TGN levels as well as hematologic parameters in responders and non-responders. In patients with sub-therapeutic 6-TGN levels, dose escalation causes a significant rise in 6-TGN levels in most patients. In those who continued to fail despite dose escalation, there were only minor changes in 6-TGN, yet a significant increase in catabolic products.

The most important determinant of individual variations in 6-MP metabolism is the enzyme TPMT, which exhibits autosomal codominant polymorphism. It was found that 0.3% of individuals have low to absent enzyme activity, 11% intermediate activity, and 89% normal or high activity [16]. Low TPMT activity is found in patients intolerant to AZA/6-MP; these patients will have increased 6-TGN levels and a high rate of toxic effects, such as bone marrow suppression. However, since a recent study revealed that 73% of leukopenic patients on AZA/6-MP had normal TPMT levels, it appears that myelosuppression is more often caused by other factors.

Interaction with mesalazine

Many patients will be taking mesalazine with AZA. In a study of patients on a stable dose of AZA plus mesalazine, aminosalicylate withdrawal led to a modest but significant decrease in mean 6-TGN levels, from 148 to 132 pmol per 8 x 10⁶ red blood cells (without change in TPMT activity) [7]. This may imply that simultaneous use of AZA and aminosalicylate carries a higher risk of bone marrow depression.

The real need for 5-aminosalicylate treatment in conjunction with AZA for remission maintenance in inflammatory bowel disease patients has been questioned. In 104 patients with Crohn's disease and 82 with ulcerative colitis, with median follow-up 4.3 years, relapse rates per year of follow-up were little different in an AZA + 5-aminosalicylate group versus AZA alone. The time to first relapse was also not different.

Toxic effects

Dose-related bone marrow suppression with leukopenia (<3 x 10⁹ leukocytes/L) and neutropenia was found in 4% of AZA/6-MP-treated patients [4,8]. The onset is abrupt and occurs at a median time of 9 months after starting therapy [8]. Lymphopenia and thrombocytopenia occur as well. Patients with low TPMT activity produce more 6-TGN and are at increased risk to develop leukopenia. It is essential to monitor the blood count in these patients. It was suggested that patients with AZA-6-MP therapy are not being 'properly dosed' until neutropenia manifests. In a recent study, however, no difference in relapse rates was noted between neutropenic and non-neutropenic patients with Crohn's disease and ulcerative colitis [9]. Hepatotoxicity has a prevalence of less than 2% [6], and patients with high TPMT activity are at risk for this complication. The onset is variable, ranging from 2 to 16 months. Three main types of injury have been reported: hypersensitivity and cholestasis, which are usually reversible, and veno-occlusive disease, which can lead to portal hypertension and death. Pancreatitis and renal adverse effects occur in 2% of cases receiving AZA/6-MP therapy [6]. Recent data suggest that the risk of malignancy, other than colorectal cancer, is not increased with AZA/6-MP treatment in ulcerative colitis and Crohn's disease [10]. However, this may not be the end of the story, and patients need to be informed of the potential risk as reported in previous studies.

The safety of AZA/6-MP in women with inflammatory bowel disease who are pregnant has not been studied extensively [10]. The literature on non-inflammatory bowel disease elicits various concerns. All immunosuppressive drugs cross the placenta, raising questions on the long-term outcome in children exposed in utero. There is no higher risk of congenital anomalies. However, an increased incidence of prematurity, intrauterine growth retardation and low birth weight has been reported. Immunologic disturbances with AZA were reported. The long-term follow-up of infants exposed to immunomodulators in utero is still uncertain. The risk of disease to the mother must be balanced against theoretical risks to the fetus. Breast-feeding is contraindicated since these drugs are excreted substantially in breast milk.

Of note, there is now evidence showing that men receiving AZA/6-MP should not father a child until the drug has been stopped for a period of 6 months, because of the risk of congenital anomalies and spontaneous abortions.

Recommendations

- AZA (2.0–3.0 mg/kg/day) and 6-MP (1–1.5 mg/kg/day) are the most useful immunomodulator drugs in second-line therapy in ulcerative colitis and Crohn's disease where steroid therapy is not adequate or possible.
- These agents may have benefit in treating fistulae in Crohn's disease.
- These drugs are very effective agents in maintenance of remission in ulcerative colitis and Crohn's disease.
- AZA and 6-MP have no place as monotherapy in acute attacks of ulcerative colitis and Crohn's disease.
- Use in pregnancy requires careful judgment. Potential fathers should discontinue taking AZA and 6-MP.
- Monitoring procedures are an integral part of the follow-up.

Monitoring procedures for patients receiving AZA/6-MP

- Full blood count is measured at 0, 2, 4 and 12 weeks, then every 3 months.
- Creatinine, urea and hepatic enzymes are determined at 0 week and periodically.
- Monitoring of TPMT and 6TGN is advised in the situations given above.

Methotrexate

Clinical pharmacology

Methotrexate (MTX) is a folic acid derivative that acts as an antimetabolite that inhibits the activity of dihydrofolate reductase.
The exact therapeutic mechanism of MTX in inflammatory disorders is unknown.

**Indications for therapy in Crohn’s disease**

Data supporting the efficacy of methotrexate in the treatment of inflammatory bowel diseases are limited. Much has to be learned to define proper dosing schedules and the selection of patient populations. One randomized clinical trial demonstrated a definite statistical benefit of methotrexate for induction of remission in patients with Crohn’s disease [11]. Two further studies failed to show unmistakable efficacy, but there was a steroid-sparing effect in selected patients [12] and an arithmetic reduction in flares. The dosage and route of methotrexate administration and the patient populations varied among these studies; meta-analysis is not possible. Methotrexate is effective in the maintenance of remission in Crohn’s patients who previously responded to this drug [13]. Conflicting information exists regarding the therapeutic dose response. The period wherein methotrexate remains effective for maintenance of remission in Crohn’s disease is not yet defined, and ranged from 40 weeks in a controlled trial [13] to 48 months in a retrospective analysis.

**Indications for therapy in ulcerative colitis**

Few studies have examined the efficacy of methotrexate in the treatment of ulcerative colitis. In the largest study, no significant effect relative to placebo was seen [14]. Owing to the small number of patients and dosing schedules, further studies are needed to determine the efficacy of methotrexate for the treatment of ulcerative colitis. The use of methotrexate in ulcerative colitis should thus be in the setting of a controlled trial.

**Toxic effects**

In general, methotrexate has been shown to have an acceptable profile of side effects. Such toxic effects were reported as being mild [13]. In an open study however, 27% of these side effects were reported as significant, and in 18% of patients they led to cessation of treatment. While the hepatotoxicity of methotrexate in patients with psoriasis is well known, the incidence of hepatic side effects in rheumatoid arthritis is lower [15]. Few data are available regarding patients with inflammatory bowel disease. The most informative study included 31 patients who received more than 1,500 mg of methotrexate and where liver biopsy was performed in 18 patients [16]. Fifteen patients were classified as grade I, two were grade II and one patient had grade IIIb changes; this last patient was obese and diabetic. No correlation was found between elevation of liver enzymes and histologic changes. Unlike other maladies for which methotrexate treatment is used, the authors concluded that routine liver biopsies are not warranted in inflammatory bowel disease. This approach is supported by two other small studies. Additional potentially life-threatening side effects of methotrexate include bone marrow suppression and pneumonitis. No conclusive data are currently available regarding long-term risk for malignancy or the risk for infections. The use of methotrexate is contraindicated during pregnancy and lactation.

**Recommendations**

- Methotrexate is an acceptable drug for the induction and maintenance of remission in Crohn’s disease patients.
- Doses of 25 mg/week intramuscularly are to be used. No reliable data are available regarding effective oral administration of methotrexate.
- Following induction of remission, an attempt should be made to lower the dose to 15 mg intramuscularly per week.
- No definitive guideline for the time of stopping treatment can be recommended.
- Methotrexate should be administered after an attempt to treat with AZA or 6-MP, unless specific reasons to avoid such treatment are present, or if the patient is included in a clinical trial.
- Treatment should be carefully thought out in patients with the following conditions: hepatic disease, consumption of more than seven alcoholic drinks per week, obesity (body weight = 40% above normal), diabetes mellitus, renal dysfunction (serum creatinine >1.7 mg/dL), clinically significant lung disease, systemic infections, a history of cancer or hypersensitivity to methotrexate, and women who wish to become pregnant or to breast-feed.
- Routine liver biopsy during treatment is usually not indicated.
- Methotrexate use in ulcerative colitis requires further study.

**Anti-tumor necrosis factor-alpha in Crohn’s disease**

Increasing knowledge regarding the immune system and the role of cytokines in promoting chronic inflammation has led to many attempts at intervention at specific points by biological therapy [17]. A variety of therapeutic approaches are used to achieve TNF inhibition. Present anti-TNF agents are shown in Table 1. Most experience to date has been accumulated using the monoclonal antibody Infliximab, with fewer clinical studies of CDP571, thalidomide and the other agents listed [18,19]. This consensus statement relates to infliximab.

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**TNF = tumor necrosis factor**

**Table 1. Classification of anti-TNF agents**

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<th>TNF-binding biological antibodies</th>
<th>Infliximab: murine monoclonal antibodies against human TNF-α replaced in 75% by human IgG1 molecule</th>
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<td></td>
<td>CDP571: murine monoclonal antibodies against human TNF-α replaced in 95% by human IgG4 molecule</td>
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<td>CDP870: human PEGylated Fab fragment against TNF-α</td>
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<td></td>
<td>Etanercept: human TNF-RII (p75) constructed with human IgG1Fc fragment, binding TNF-α and lymphotoxin-A</td>
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<td>D2E7: completely human monoclonal antibodies against human TNF-α</td>
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<th>TNF natural binding proteins</th>
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<th>Inhibitors of TNF de novo synthesis</th>
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A single infusion of infliximab (5 mg/kg) induced remission in 33% of severe Crohn's disease patients and improvement in 81% compared to 4% and 17% respectively in placebo-treated patients; one-third of patients were able to discontinue corticosteroids [18]. Placebo-controlled trials in refractory Crohn's disease showed clinical response in up to 54% of patients following single infusion of 10 mg/kg body weight of CDP571 [19]. A small number of patients who did not respond to the first infliximab infusion may benefit from a second one. There is no apparent benefit from a third infusion if the first two were ineffective. Infliximab is effective both in severe active Crohn's disease and in fistulating disease [20].

**Indications in Crohn's disease**

- The use of infliximab (5 mg/kg) is warranted in an active Crohn's disease patient who relapsed while under adequate immunosuppressive therapy. Infusions are given every 8 weeks or as indicated. Information regarding use for more than one year is not available, therefore infliximab therapy should be part of a long-term treatment strategy. Data concerning the higher dose of 10 mg/kg are presently being collected.
- A small number of patients not responding to the first infusion of infliximab may benefit from a repeat infusion within 1 month [21]. There is no benefit from a third infusion if the first two were ineffective.
- Infliximab (5 mg/kg) is indicated in a patient with a fistula who did not respond to other conservative options. In this case, infusions should be given at 0, 2 and 6 weeks, and thereafter every 8 weeks as needed. The recommended dosage is 5 mg/kg. There are as yet insufficient data regarding higher doses [22].
- Additional indications may include extraintestinal manifestations of Crohn's disease, such as arthropathy, pyoderma gangrenosum, erythema nodosum, ocular and oral manifestations. Data regarding these issues are limited, uncontrolled, and based on case reports.

**Anti-TNFα treatment in ulcerative colitis**

Present knowledge is based on case reports. Therefore such use must be restricted to clinical trials at present.

**Safety precautions**

Infliximab is given intravenously by slow infusion, with regular monitoring of vital signs. Infusion reactions are common and occur in up to 15% of patients (fever, headache, rigors); therefore adequate medical equipment and drugs (antihistaminic and adrennergic drugs, glucocorticoids) should be available in the infusion facility. Patients should be observed for at least 2 hours post-infusion. Re-treatment with infliximab following a drug-free interval of 2–4 years was associated with a high risk for delayed hypersensitivity reactions in up to 25% of patients.

The use of infliximab has led to bronchopulmonary infections, some of which are severe and life-threatening, therefore existing infections must be excluded prior to beginning therapy. Treatment with infliximab has been followed by exacerbation of preexisting, unrecognized tuberculosis [23]. A chest X-ray is mandatory prior to administering infliximab.

The long-term safety of infliximab is unknown. Patients may develop anti-DNA antibodies and, rarely, a lupus-like syndrome. Delayed hypersensitivity reactions may occur in 25% of patients (arthralgia, headache and rash). Formation of anti-infliximab antibodies may lead to loss of efficacy. Rapid healing of mucosal inflammation on a preexisting stricture may lead to fibrosis with intestinal obstruction necessitating surgery. There is some concern about the later development of lymphoma [24,25]. Care must be exercised in re-treating with infliximab after an interval of more than 1 year [26,27]. Smoking is a strong negative predictor of response to infliximab [28]; smoking should be strongly discouraged in all Crohn's patients, and especially when infliximab is indicated.

**Contraindications**

Contraindications to treatment with infliximab include active infections in the previous 3 months, especially tuberculosis, herpes zoster, cytomegalovirus, *Pneumocystis carinii* infection, and other opportunistic infections. Pregnancy, breast-feeding, previous malignant disease, prior severe allergic reactions, and known intestinal strictures preclude the use of this agent. No live attenuated vaccine may be administered within 3 months of infliximab therapy.

**Cyclosporine A**

Cyclosporine A is a metabolite of the fungi *C. lucidum* and *T. inflatum* gums. Cyclosporine, available for oral or intravenous use, is mainly absorbed in the small intestine [29]. The intravenous route is preferred when the gastrointestinal tract does not function or when therapeutic levels need to be achieved quickly and reliably. Cyclosporine has been shown to interfere in T cells with the production of interleukin-2 and other cytokines [30]. Cyclosporine is the mainstay of immunosuppressive therapy in transplantation medicine and is also used in the treatment of inflammatory bowel disease.

**Cyclosporine treatment in ulcerative colitis**

This drug is indicated as follows [31,32]:

- Inpatients with severe disease who are unresponsive to or unable to receive intravenous steroids
- Outpatients with steroid-refractory disease, or patients unable to receive steroids, as a bridge until the onset of action of azathioprine or 6-mercaptopurine given concomitantly.

**Cyclosporine treatment in Crohn's disease**

This drug is indicated in severe inflammatory or fistulating disease unresponsive to conventional therapy including infliximab [33–37].

**Efficacy**

While the indications for the use of intravenous cyclosporine (4 mg/kg/day) in severe refractory ulcerative colitis are well accepted, its use in active Crohn's disease is somewhat controversial. In the three large randomized controlled studies of cyclosporine in Crohn's disease, the drug was given orally. Cyclosporine was ineffective in the low oral dose of 5 mg/kg/day for both active disease or maintenance of remission [34,35]. However, the high cyclosporine
dose of 7.6 mg/kg/day is effective, with most patients benefiting within 2 weeks from onset of therapy [33]. A few small, uncontrolled series have reported benefit in perianal or fistulizing disease, using cyclosporine at a dose of 4 mg/kg/day intravenously [36–38]. Unless 6-MP is added to the regimen in these patients, there is a high relapse rate after discontinuation of cyclosporine.

Mode of administration

In the only prospective controlled study available that shows an 80% efficacy of cyclosporine in ulcerative colitis, it was used intravenously at a dose of 4 mg/kg/day in a continuous drip, achieving blood levels of 430 by monoclonal radioimmunoassay. The mean response occurred after 7 days. Uncontrolled retrospective data suggest that a lower intravenous dose of 2 mg/kg/day might also be effective in ulcerative colitis [39]. The maintenance oral dose after achieving remission with intravenous cyclosporine is 5 mg/kg/day of Neoral (Promedico, Israel) [31,40]. The oral dose is given for about 6 months, allowing azathioprine or 6-mercaptopurine to kick in. When this is done, the long-term success rate (noncolectomy survival rate) approaches 70%.

The prospective controlled studies of cyclosporine in Crohn’s disease used the drug orally. The one study that showed efficacy in Crohn’s disease used a dose of >7 mg/kg/day [33].

Optimizing safety

In order to optimize safety and reduce the risk of seizures, it is suggested that cholesterol level be above 120 mg/dl and serum magnesium at normal blood levels [39]. Renal function must be monitored routinely and the cyclosporine dose adjusted accordingly. One must also be aware of drug interactions, as calcium channel blockers, antifungal drugs, erythromycin and steroids might increase cyclosporine blood levels, while anti-epileptic drugs may decrease cyclosporine blood levels.

Recommendations

- Cyclosporine A is effective within 7 days when given intravenously (dose of 4 mg/kg/day) in 60–80% of patients with severe or refractory ulcerative colitis.
- Cyclosporine A is effective in severe Crohn’s disease at the high oral dose of 7.6 mg/kg/day. Cyclosporine given intravenously (4 mg/kg/day) may be useful in fistulizing disease, and should be followed by either 6-mercaptopurine or azathioprine.

References

Capsule

CRP screening

Only some individuals who develop coronary artery disease have high cholesterol levels, and there has been considerable interest in markers that would identify high risk individuals who might be missed in cholesterol screens. Over the past decade, C-reactive protein (CRP), a liver-derived inflammatory protein, has emerged as a strong and independent predictive marker of future cardiovascular disease. Importantly, CRP levels can be measured in a simple and relatively inexpensive blood test. Whether and how CRP tests should be incorporated into clinical practice are questions being discussed in the cardiovascular research community, as described in several articles which include the official set of recommendations from an expert panel assembled by the American Heart Association and the U.S. Centers for Disease Control and Prevention. Although Pearson et al. acknowledge that the CRP test may provide helpful data in cases where other risk factors are present (e.g., for individuals who have high blood pressure and/or moderately high levels of cholesterol), they did not endorse widespread use of the test and stressed the need for studies to determine whether interventions that lower CRP levels will, in fact, lower the rate of heart disease.

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Capsule

A full SET of apoptosis

Lymphocytes with cytotoxic activity induce cell death by delivering pro-apoptotic granzymes to the cytosol of target cells. One of the two principle granzymes, granzyme A, operates independently of caspase activation and appears to disrupt nuclear integrity and damage single-stranded DNA. Having already identified an endoplasmic reticulum-associated protein complex, called SET, as a target of granzyme A, Fan et al. provide further insight into how interference with this complex promotes apoptosis. Apurinic endonuclease-1 (Ape-1), a DNA binding protein possessing endonuclease and redox activities, was isolated from the SET complex and shown to be cleaved upon exposure to granzyme A. As a result, two putative anti-apoptotic processes of Ape-1 were disrupted: the repair of abasic sites in DNA and the ability to mediate oxidative repair of transcription factors. Disruption of Ape-1 expression in cell lines by RNA interference enhanced apoptosis, whereas transfection with a non-cleavable form of Ape-1 protected cells from granzyme A-induced cell death. Granzyme A may thus operate through the combined effects of disrupting the cellular repair activities of Ape-1 and of other members of the SET complex.

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