IS THERE A RISK FOR LYMPHOMA OR EXTRACOLONIC CANCER IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE?

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IS THERE A RISK FOR LYMPHOMA OR EXTRACOLONIC CANCER IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE? (Abstract). An important issue in the management of inflammatory bowel disease (IBD) is the risk for lymphatic or extracolonic malignancies reported in patients receiving prolonged immunosuppressive therapy and/or therapies with biological agents. Azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, and anti-TNF (infliximab, adalimumab) are reference drugs for IBD forms unresponsive to conventional therapies. The administration of these drugs is a high responsibility because IBD itself is associated with an increased risk for cancer, namely colon cancer. The possibility of a drug-induced additional risk remains controversial, the relative risk for lymphoma being estimated at 1.2%. For extracolonic malignancies, there are variations in standardized incidence per reference population in terms of location (skin, liver and biliary tract, uterine cervix, prostate, etc.), and also IBD phenotype (ulcerative colitis or Crohn's disease). The uncertainty regarding the occurrence of neoplasia in IBD patients for many years on immunosuppressive therapy and/or biological agents is a strong argument both for treatment discontinuation and it’s monitoring by inclusion in screening programs. In this paper we aimed to approach the conceptual model risk-benefit in the therapy with immunosuppressive and biological agents given the controversies in the literature generated by the drug-induced risk for malignant lymphatic and extracolonic tumor in patients with IBD. Key-words: INFLAMMATORY BOWEL DISEASE, EXTRACOLONIC CANCER, LYMPHOMA.

Inflammatory bowel disease (IBD) is a condition of chronic intestinal inflammation of unknown cause that includes two entities with distinct clinical and morphological features: ulcerative colitis (UC) and Crohn's disease (CD). In UC inflammation is limited to mucosa and is present only in the rectum and colon, and in CD the inflammatory process is transparietal and may affect any segment of the digestive tract, from mouth to near the anus (perianal disease). Descriptive epidemiology data show that IBD is a common disease worldwide, with large region-to-region variations in incidence. In the United States about 2 million people are affected and the worldwide incidence of UC is 0.5 to 24.5/10^5 inhabitants (1). Europe is characterized by an uneven distribution of the disease, while South-Eastern Europe is less exposed to the risk of disease occurrence, fact supported by the low incidence in this area. In Romania the incidence of IBD is low, with an epidemiological profile dominated by the frequency UC, the incidence of which is approximated to 1/10^5 inhabit-
ants. Regional data from a 2006 study in North-Eastern Romania show an IBD incidence of $1.75 \times 10^5$ inhabitants, with an upward trend for CD and severe forms, mainly of UC (2).

**IBD AND COLORECTAL CANCER**

An IBD feature is the occurrence during disease progression of colorectal cancer (CRC), first recognized as a complication of UC in 1925 by Crohn and Rosenberg (3). Since then, several epidemiological studies have confirmed this increased risk, but its magnitude remains controversial due to variations in diagnostic methods. CRC occurs in 2-4% of patients with UC and accounts for 1% of all colorectal cancers in the general population (4). A number of factors that define the clinical features and progression of this disease, alone or in combination, may increase or decrease the risk for CRC. Factors associated with this increased risk are: disease duration, extension of colitis, sclerosing cholangitis (SC), family history of CRC, early onset of disease, and severity of inflammation (5). Main factors correlated with the risk for CRC are disease duration and extension. Early and prolonged exposure of intestinal mucosa to chronic inflammation is responsible for the occurrence of metaplasia - dysplasia - neoplasia sequence (6).

This context requires the use in this population group of endoscopic surveillance methods (colonoscopy) for cancer detection. A prerequisite in lowering this risk is mucosal healing with restoration of normal structure and function. This goal requires the administration of drug groups with immune mediation actions which are responsible for inducing long-term immunosuppression, thus increasing the risk for the occurrence of lymphoma and extracolonic cancer. The risk of extracolonic cancer in IBD patients is increased both by chronic intestinal inflammation and immunosuppressive treatment. This is a concern both for doctors and patients when treatment with purines and/or anti-TNF agents is considered.

One example is azathioprine (AZA), which by being incriminated in the increased risk for malignancy in patients with rheumatoid arthritis or kidney transplant, drew attention to the likelihood of increased risk in IBD patients on long-term immunomodulatory therapy. However, the risk of long-term immunomodulatory therapy-induced cancer remains controversial in both theory and practice, because IBD itself is associated with an increased risk for cancer, and most published studies found no risk for lymphoma or cancer with 5-year treatment; this needs to be also demonstrated for much longer treatments (7). It clearly comes out that the responsibility of gastroenterologists who use these drugs is high, and that he has to be aware of both its benefits and risks in order to provide optimal care to IBD patients.

We now present the drug classes used in IBD and the results of studies on the risk of extracolonic cancer and lymphoma.

**THERAPEUTIC PRINCIPLES IN IBD**

IBD is a group of chronic diseases, continuous or recurring in flares interrupted by remission, which requires long term, sometimes lifetime, treatment. The therapeutic goals are focused on inducing remission and maintaining it, with the ultimate goal of mucosal healing, which decreases the risk of cancer. Induction treatment aims at controlling clinical signs, reducing acute complications rate, and improving the qual-
Remission induction therapy uses the following drugs classes over a limited period of time:

- 5-aminosalicylate acid derivatives (5-ASA, mesalazine), used only in mild and moderate UC; historically, sulfasalazine and mesalazine, were used for remission induction in mild and moderate forms of CD, but cumulative evidence from different studies indicate that these drugs are less or even ineffective in treating patients with CD (8);

- corticosteroids, represent the most effective therapeutic group in inducing clinical remission used in the treatment of flares in the moderate and severe forms of IBD, or in cases with insufficient response to aminosalicylate treatment; corticosteroids include agents with oral, parenteral and topical administration. The use of corticosteroids in the treatment of IBD is based on its multiple immunosuppressive and anti-inflammatory actions intervening as a modulator or suppressor (high dose) in the production of inflammatory and immune response mediators; their effectiveness is proven if used properly, but no more than three months to avoid corticodependence (inflammatory recurrence when drug discontinuation or dose reduction are attempted) or corticoresistance (persistence of clinical manifestations on treatment) reported in approximately 50% of patients who required hormone treatment (9);

- biological therapy, represented by anti TNF alpha antibodies, is useful both in moderate-severe UC and CD (10);

- cyclosporine, is the drug of choice in toxic megacolon from UC; side effects limit its long term use and dosage (11).

Long-term maintenance of remission is sometimes a life time treatment. If some therapeutic classes, such as 5-ASA derivatives, prevent the risk for CRC, other drug groups (immunomodulators and biological agents) are incriminated in the increased risk for lymphoma and extracolonic cancer.

The drug classes used for maintenance of remission are (12):

- 5-ASA (mesalazine), used only in UC;
- purines, represented by azathioprine, 6-mercaptopurine, and methotrexate, used in CD and in patients with UC who developed corticodependence;
- anti TNF alpha antibodies.

The groups of drugs with risk of extracolonic cancer are purines and biological agents. If data on long term purine therapy are numerous, for biological agents data are available since 1998, when Infliximab was approved for the treatment of moderate and severe CD. In 2007, Adalimumab (humanized monoclonal antibody) and in 2008 Certolizumab (Fab fragment of humanized anti-TNF) (13) were introduced in the treatment of these diseases. The latest class of biological agents is represented by Natalizumab, an anti-integrin α monoclonal antibody.

**IBD AND HEMATOLOGIC CANCERS**

Studies on large series of patients with IBD demonstrate an association between CD and non Hodgkin's lymphoma (NHL) and between UC and leukemia. CD-myelodisplasic syndrome relationship has not been proven, and in terms of increased risk of lymphoma in patients exposed to purines the available results are controversial. In IBD patients followed up for long periods of time (18 years, between 1983 and 2001) 9 cases of lymphoma were found, with the mention that no patient had received purines prior to the diagnosis (14).
Is there a risk for lymphoma or extracolonic cancer in patients with inflammatory Bowel disease?

Conversely, other studies show an increased risk of lymphoma in patients exposed to purines. AZA and 6-MP are involved in lymphoma occurrence in patients treated for rheumatoid arthritis and prevention of graft rejection. A therapeutically-induced additional risk remains controversial, the relative risk for lymphoma being estimated at 1.2% with an estimated incidence in the multiple IBD patient series of 0.2-0.4%.

In terms of quality of life, the benefits of a 4-year immunosuppressive therapy outweigh the risk of developing cancer, and with a 5-year treatment no risk of lymphoma or cancer was found. The uncertainty regarding the occurrence of neoplasia in UC patients for many years on immunosuppressive therapy is strong reason for treatment discontinuation (15).

With biological therapy, IBD patients undergo prolonged immunosuppression with increased risk for hematological cancer in cases previously treated with purines. But given that most patients treated with biological agents have a positive therapeutic history for purines (corticodependent and corticorezistant severe illness), it is not clear whether the event is specific to this class of drugs or may be considered as a side effect of purine treatment. Conclusions on the adverse effects of biological therapy are still a subject for debate. Experts have tried to answer these questions by multicenter, randomized, case control, case studies (ex. reference studies for the validation of biologic therapy in IBD - ACCENT I and ACCENT II). In a series of 1107 patients with CD who received infliximab, 9 cases of lymphoma (0.81%) were found, percentage similar to that in the control group (CD patients not receiving infliximab) (16).

In the Mayo Clinic study conducted on 500 patients with IBD treated with infliximab, of 7 detected cancers (non-lymphomas) two were lung cancers, possibly due to infliximab treatment (17). In a Danish series of 561 patients with CD treated with infliximab for the 4 cancers reported no such association was found, the conclusion being that the treatment with infliximab is cancer-risk free (18). Similar conclusions come from a series of 2319 CD patients treated with infliximab: 30 patients (1.29%) developed cancer, percentage comparable with the general population and placebo group (19). A meta-analysis of 21 placebo-controlled trials including 5356 patients treated with biological agents concluded that cancer risk is not increased by biological therapy (20). An Italian study on 404 patients with CD treated with infliximab vs. 404 CD patients without infliximab demonstrated the similar malignancy rate in the both groups (9 vs. 7). The conclusion is that anti-TNF alpha agents seem not to increase cancer risk.

As to the relationship NHL-anti-TNF therapy the results are controversial. Also controversial is the response to the question whether the association of biological agents with purines increases the risk of lymphoma. In reference studies on this topic there are both pro and con opinions. In Britain, in a series of 6,000 patients with CD and 10,000 with UC treated with biological agents the risk of lymphoma was 1.2, comparable to that of general population (21). In Sweden, the study of 47,000 patients with IBD treated with biological agents showed a slight increased risk for NHL in those within the first 5 years of CD (22).

A Canadian study on 21,000 patients with CD showed a significantly increased
risk of NHL in men, independent of the use of purine immunomodulators (23). In the Mayo Clinic study the two NHL cases of the 500 patients treated with biologic therapy also received AZA (8). The study of 3,493 patients with rheumatoid arthritis treated with biological agents without AZA identified 10 cases of NHL and no case in the control group (24). In the study on 8,905 patients with IBD treated with biological therapy, 11/13 patients with NHL were exposed to purines (25). Hepatosplenic T-cell lymphoma is a rare type of peripheral NHL, 200 cases being described in the literature most in patients on immunosuppressive therapy (post-transplant, HIV). For IBD, 8 cases of hepatosplenic T-cell lymphoma in young men (12-31 years) with CD, treated with infliximab and purines, have been reported. And with adalimumab treatment 9 NHL cases were reported in patients with CD treated with purines (26). Experts concluded that there is risk for NHL in young men (20-54 years) on biologic therapy and prior exposure to purines.

**IBD AND EXTRACOLONIC CANCERS**

Patients with IBD are at high risk for extracolonic cancer, especially those with CD. In a series of 6027 patients with IBD (2857 CD and 2672 UC) extracolonic cancer rate was 690/100,000, higher than in general population. In CD cancer rate is significantly higher than in general population, compared with UC where the risk is similar to that in general population (27). Extraintestinal cancers are localized in the liver and bile ducts, with the same risk from CD and UC, in case of associated of primary sclerosing cholangitis (28). Breast, prostate, and lung cancers in patients with IBD have the same risk as in the general population (29).

In recent years, an increased risk for cervical dysplasia associated with IBD was noticed, but it has been suggested that this risk is high in patients receiving immunomodulation therapy. However, there are few studies reporting data on the risk of cervical abnormalities in patients treated with immunosuppressants. Presumptions of therapeutic risk for cervical dysplasia in IBD are based on theories related to inadequate surveillance of human papillomavirus (HPV) infection in patients treated with immunomodulators and reactivation of latent virus in patients treated with anti-TNF. IBD patients treated with immunomodulators (AZA, MP, MTX) have an increased risk for abnormal Pap smears compared with healthy people. Regarding therapies with biological agents (anti-TNF), a recent study showed that infliximab does not increase the risk for abnormal Pap smears. Also, combination regimens of medicines prescribed for patients with IBD (oral or intravenous steroids, 5ASA and various combinations of infliximab, AZA and 6-MP) have no significant contribution to cervical abnormalities. Certain conditions, such as multiparity, prolonged use of oral contraceptives, number of sexual partners, smoking, and Chlamydia infection are considered additional risks associated with developing cervical cancer. The recommendation is that tests for Papilloma virus to be run before starting immunomodulatory and biological therapy, which, by way of action, can activate HPV (30).

**CONCLUSIONS**

Data in the literature on the theoretical potential for malignant extracolonic and lymphoma developments, practically con-
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...firmed in small number of IBD patients on treatment with immunomodulators and biological agents, are considered sufficient to promote strategies for selecting and monitoring these patients at risk for malignant complications with various locations.

REFERENCES


**NEWS**

**FIBROUS DYSPLASIA - A BENIGN BONE DISEASE WITH RARE POTENTIAL FOR MALIGNANT TRANSFORMATION**

Fibrous dysplasia (FD) is an uncommon bone disease that has a rare but clear potential for malignant transformation. The diagnosis is usually not difficult given the symptoms, radiology, and histology. The histologic picture is classically of low to moderately cellular fibrous stroma surrounding irregularly shaped bone trabeculae without osteoblastic rimming, which matches the benign appearance on radiology. The gene involved in pathogenesis is a subunit of G-protein receptors, found on chromosome 20. Recent innovation in molecular pathology has helped us understand the mechanism of the disease, pertaining to cAMP and WNT/b-catenin. The treatment of FD is limited to maintenance of maximum bone density via diet, exercise, and therapeutic medications, with many patients also choosing to avoid substances that lower bone density, such as caffeine and nicotine. Oftentimes, surgical reinforcement is needed for bowing deformities and fractures when they occur. Currently, there is no therapy for preventing disease advancement or for malignant transformation. (Riddle ND, Bui MM. Fibrous dysplasia. *Arch Pathol Lab Med.* 2013;137:134–138).

_Doina Butcovan_