European Review for Medical and Pharmacological Sciences 2013; 17: 84-87

Inflammatory bowel diseases and primary sclerosing cholangitis: hepatic and pancreatic side effects due to azathioprine

F. PALLAVICINO, R. PELLICANO, S. REGGIANI, D. SIMONDI, C. SGUAZZINI, A.G. BONAGURA, F. CISARÒ, M. RIZZETTO, M. ASTEGIANO

Department of Gastroenterology and Hepatology, Molinette Hospital, Torino, Italy

Abstract. – BACKGROUND AND OBJECTIVES: In up to 80% of cases primary sclerosing cholangitis (PSC) is associated with inflammatory bowel diseases (IBD). The efficacy of azathioprine (AZA), in the maintenance of remission of IBD has been suggested by several studies. However, AZA tends to exter varied well-known toxicity. Since the rate of hepato-pancreatic side-effects in patients with IBD and PSC is still unclear, we investigated this issue.

MATERIALS AND METHODS: Consecutive subjects who underwent Outpatient Clinic admission for both IBD and PSC were included. Both conditions were diagnosed according to International Guidelines.

RESULTS: Data of 43 patients were elaborated. Twelve of them underwent therapy with AZA. Five (41.7%) presented hepatic (n=4) or pancreatic toxicity. Eighty percent of the patients with hepato-pancreatic reactions versus 28.6% of those without ($p < 0.001$) were males, with 60% affected by ulcerative colitis and 40% by Crohn's disease versus 57% and 43%, respectively. Forty percent of patients with reactions versus 43% of those without needed an operation for IBD, and the same percentage underwent orthotopic liver transplantation, with a 100% versus 66.7% ($p < 0.001$) need of second transplantation. Colonic neoplasia (20%) was detected only in the former group while cholangiocarcinoma (28.6%) only in the latter.

CONCLUSIONS: The occurrence of hepato-pancreatic reactions from AZA in our caseload is higher (41.7%) compared to that reported in literature (4%). Therefore, the presence of PSC, in association to IBD, may strongly affect AZA tolerability compared to presence of IBD only.

Key Words:
Azathioprine, Ulcerative colitis, Crohn's disease, Side effects, Primary sclerosing cholangitis.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic syndrome affecting both extra- and intrahepatic bile ducts. It is characterized by inflammation and fibrosis with the development of bile duct stenosis. A chronic but variable course follows, with possible progression towards cirrhosis and hepatic failure[1]. Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic pathologies of still unknown origin[2]. The main hypotheses of the pathogenesis of IBD are based on an encounter of the gut immune system with an antigen relevant to microbiota species as the initiating factor. The intestinal lamina propria contains a complex population of immune cells that balance the requirement for immune tolerance of luminal microbiota with the need to defend against pathogens, the excessive entry of luminal microbiota, or both. The hallmark of active IBD is a pronounced infiltration into the lamina propria of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B and T cells). Increased numbers and activation of these cells in the intestinal mucosa elevate local levels of tumor necrosis factor α, interleukin-1β, interferon-γ, and cytokines of the interleukin-23–Th17 pathway. The initial immune response to intestinal microbiota is tightly regulated, and this regulation determines whether immune tolerance or a defensive inflammatory response ensues. Disturbance of the balance of these responses inducing the dysregulation of intestinal CD4+ T-cell subgroups can lead to IBD[3].

The diagnosis of IBD and the differentiation between CD and UC are usually made through the evaluation of clinical, laboratory, radiological, endoscopic, and pathological features[4]. In up to 80% of cases, PSC is associated with IBD[5]. Guidelines recommend total colonoscopy with biopsies in patients in whom the diagnosis of PSC has been established without known IBD[1].

Conventional glucocorticosteroids are the main treatments for active IBD of any severity,

Corresponding Author: Rinaldo Pellicano, MD; e-mail: rinaldo_pellican@hotmail.com

but are associated with problems like steroid dependence and steroid-related adverse events[6,7]. Maintenance of remission of IBD is crucial for at least two circumstances: unchecked bowel inflammation behaving as an independent factor in colon cancer development; the inflammatory pathways mutating in relapsing inflammatory bouts, thus, favoring the development of drug unresponsiveness and the activation of apoptosis-resistant so-called non professional immunocytes[8]. Two classes of drugs are traditionally employed for IBD remission maintenance: mesalamine and thiopurines. The efficacy of the thiopurine, azathioprine (AZA), in this process has been suggested by several multi- and monocentric studies[9]. Owing to the high degree of genetic polymorphism that affects a few of the key enzymes in their metabolic pathway, thiopurines tend to exert varied toxicity. The most common adverse events include: leukopenia, infections, liver damage, pancreatic damage, gastric intolerance, and idiosyncratic reactions[8]. The rate of hepatic and pancreatic side effects in the subgroups of patients with IBD and PSC is still unclear.

In a retrospective study conducted at the Gastroenterology Outpatient Clinic of the Molinette Hospital (Turin, Italy)[9], that represents the main facility of Regione Piemonte (Northwest of Italy, with a population of 4.5 million people) dedicated to the management of IBD, we reviewed the rate of hepatic and pancreatic side effects due to AZA in a group of patients suffering from both IBD and PSC.

Materials and Methods

Among a cohort of 2206 patients followed-up for IBD, the charts of consecutive subjects who underwent Outpatient Clinic admission from 1990 to 2009 for both IBD and PSC were reviewed.

According to International Guidelines, clinical, biochemical, endoscopic, histologic and radiographic criteria were used to diagnose both IBD and PSC[1,4]. Mean disease duration in CD and UC patients was 11.7 and 11.5 years, respectively. Disease localization was established on the basis of previously performed endoscopic, histological and radiological investigations. Disease activity was defined according to recent pathological history, physical examination and laboratory results, mainly considering inflammatory markers[4]. All consultations were recorded in both a paper archive and a computerised data bank.

Classical causal agents of liver disease[10] as well as of pancreatic disease (cholelithiasis) were excluded.

Statistical Analysis

Statistical analyses and data processing were performed using the software Instat Plus version 4.36. Chi-square test (χ^2) and, for small sample size, Fisher exact test, were used. A p value < 0.05 was considered statistically significant.

Results

Forty-three outpatients with both IBD and PSC followed-up between 1990 and 2009 (average: 16.2 ±6.9 years) were included. Twelve (6 males; mean age: 24.8±16 years at the diagnosis of IBD and 27.7±17.5 years at the diagnosis of PSC) of these subjects underwent therapy with AZA as well as ursodeoxycholic acid (UDCA) (15 mg/kg/die) for PSC. Seven (58.3%) had UC and 5 (42.7%) CD. Among patients with UC, two had serum anti-neutrophil cytoplasmic antibodies, one had both antinuclear and anti-smooth muscle antibodies. Among patients with CD, none had autoantibodies. Considering associated manifestations, in the UC group two patients had arthralgias and in CD group one patient had nephrolitiasis. All CD patients had a Crohn's Disease Activity Index < 150 (80-150).

According to World Health Organization (WHO) criteria, 5 (41.7%) of the 12 patients treated with AZA presented hepatic (n=4) or pancreatic (n=1) toxic reactions, within 2 months since the beginning of the therapy. In Table I the detailed features of both the subgroups are reported: subjects with (Group A) and those without hepatic or pancreatic reactions to AZA (Group B). In particular, 80% of the patients in Group A *versus* 28.6% in Group B ($p < 0.001$) were males, with a mean age at diagnosis of IBD of 27.2±8.1 and 23±20.4, respectively, and at diagnosis of PSC of 30.5±11.8 and 25.6±21.4, respectively. Among patients of Group A, 60% was affected by UC and 40% by CD; in Group B, 57.1% was affected by UC and 42.9% by CD. Regarding IBD localization, a pancolic involvement occurred in 60% of cases in Group A *versus* 71.5% of cases in Group B. Concerning the behaviour of IBD, in Group A there was chronic activity in 20% and intermittent course in 80% of cases while in Group B, there was chronic activi-

Table I. Characteristics of the study population.

	Group A (%)	Group B (%)
Total	5 (41.7)	7 (58.3)
Male	4 (80)	2 (28.6)*
Mean age at IBD diagnosis (SD), years	27.2 ± 8.1	23 ± 20.4
Mean age at PSC diagnosis (SD), years	30.5 ± 11.8	25.6 ± 21.4
IBD type		
Crohn's disease (CD)	2 (40)	3 (42.9)
Ulcerative colitis (UC)	3 (60)	4 (57.1)
IBD behaviour		
Chronic	1 (20)	4 (57.1)
Intermittent	4 (80)	1 (14,3)*
Remittent		2 (28.6)
Surgical operation for IBD	2 (40)	3 (42.9)
OLT for PSC	2 (40)	3 (42.9)
Re-OLT	2/2 (100)	2/3 (66.7)*
Colonic neoplasia	1 (20)	0
Cholangiocarcinoma	0	2 (28.6)
Other neoplasia	2 (40)	1 (14.3)

Group A: subjects who presented hepatic or pancreatic toxic reactions; Group B: subjects who had no problems with the intake of AZA. *$p < 0.001$; PSC: Primary sclerosing cholangitis; OLT: Orthotopic liver transplantation.

ty in 57.1%, intermittent course in 14.3% ($p < 0.001$ *versus* A) and remittent course in 28.6% of cases. As far as surgery is concerned, 40% of Group A *versus* 42.9% of Group B needed an operation for IBD, and the same percentage (40% and 42.9%) underwent orthotopic liver transplantation (OLT). Regarding the latter cohort, all Group A patients successively received a second transplantation, while in Group B, 66.7% of the transplanted subjects needed a re-OLT ($p < 0.001$). Colonic neoplasia was detected only in Group A in 20% of cases while cholangiocarcinoma affected 28.6% of patients only in Group B; other types of neoplasia were developed by 40% and 14.3% of patients in Groups A and B, respectively.

Discussion

Out of every 90 IBD patients followed in the out-patient setting, 10 CD and 4 UC may present with extra-intestinal manifestations[11]. Hence, a multidisciplinary approach and a cautious follow-up becomes important, especially regarding pharmacological treatment.

The incidence of drug induced liver injury is as high as 10 to 15 cases per 100,000 patients year[12]. In a recent study, in patients with IBD but without PSC, azathioprine has been reported to cause hepatotoxicity in 2.4% of cases and acute pancreatitis in 2.7%[13]. Similar data have been reported in literature (4%)[14] while higher percentages (19%) were found in our day hospital in patients with IBD only[15]. Recently, a group has reported similar rates in patients with only IBD but the hepatic background of patients was not clear[16].

The retrospective design of the study represents a limitation[17]. However, the potential heterogeneity arising from this is dampened by the fact that in our Outpatient Clinic[9], all participants follow International Guidelines. Furthermore, during the last 20 years, all consultations have been recorded in both a paper archive and a computerised data bank.

Conclusions

The occurrence of hepato-pancreatic toxic reactions from AZA detected within our study (41.7%) is higher compared to that hitherto reported in literature (4%). Thus, the presence of PSC in association to IBD may strongly affect AZA tolerability compared to the presence of IBD only. The risk seems to be particularly high in male patients and the toxicity seems to be re-

lated to a major occurrence of unsuccessful transplants, with consequent necessity of re-OLT.

Prospective studies designed to provide a direct estimate of the risk of hepato-pancreatic side effects in patients with both PSC and IBD will be of great importance in this field.

Acknowledgements

We are indebted to Sharmila Fagoonee for her help in English revision.

References

1) EASL Clinical practice guidelines: management of cholestatic liver diseases. J Hepatol 2009; 51: 237-267.
2) Sartini A, Castellani L, Buonfiglioli F, Roda G, Belluzzi A, Roda E. Update on Crohn's disease: a polymorphic entity. Minerva Gastroenterol. Dietol 2011; 57: 89-96.
3) Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361: 2066-2078.
4) Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho G, Satsangi J, Bloom S, on behalf of the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60: 571-607.
5) Torres J, Pineton de Chambrun G, Itzkowitz S, Sachar DB, Colombel J-F. Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. Aliment Pharmacol Ther 2011; 34: 497-508.
6) Guidi L, Marzo M, Felice C, Mocci G, Sparano L, Pugliese D, De Vitis I, Papa A, Armuzzi A. New biological agents for the treatment of the "high risk" IBD patients. Eur Rev Med Pharmacol Sci 2010; 14: 342-346.
7) Maruotti N, Corrado A, Cantatore FP. Glucocorticoid induced risk of fractures. Panminerva Med 2010; 52: 339-343.
8) Actis GC, Pellicano R, Rizzetto M, Ayoubi M, Leone N, Tappero G, Pazienza P, Rosina F. Individually administered or co-prescribed thiopurines and mesalamines for inflammatory bowel disease. World J Gastroenterol 2009; 15: 1420-1426.
9) Pellicano R, Bonardi R, Smedile A, Saracco G, Ponzetto A, Lagget M, Morgando A, Balzola F, Bruno M, Marzano A, Ponti V, Debernardi Venon W, Ciancio A, Rizzetto M, Astegiano M. Gastroenterology outpatient clinic of the Molinette Hospital (Turin, Italy): the 2003-2006 report. Minerva Med 2007; 98: 19-23.
10) American Gastroenterological Association Medical position Statement: evaluation of liver chemistry tests. Gastroenterology 2002; 123: 1367-1384.
11) Actis GC, Rosina F. Out-patient care for inflammatory bowel disease at a primary referral hospital in Turin. Minerva Gastroenterol Dietol 2010; 56: 27-34.
12) Rangnekar AS, Fontana RJ. An update on drug induced liver injury. Minerva Gastroenterol Dietol 2011; 57: 213-229.
13) Lòpez-Martin C, Chaparro M, Espinosa L, Bejerano A, Maté J, Gisbert JP. Adverse events of thiopurine immunomodulators in patients with inflammatory bowel disease. Gastroenterol Hepatol 2011; 34: 385-392.
14) Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. Aliment Pharmacol Ther 2005; 22: 1-16.
15) Actis GC, Fadda M, Pellicano R, David E, Rizzetto M, Sapino A. The 17-year single-center experience with the use of azathioprine to maintain remission in ulcerative colitis. Biomed Pharmacother 2009; 63: 362-365.
16) Ansari AR, Patel N, Sanderson J, O'Donouhe J, Duley JA, Florin THJ. Low dose azathioprine or 6-mercaptopurine in combination with allopurinol can bypass many adverse drug reactions in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2010; 31: 640-647.
17) Lilinfield AM, Lilinfield DE. Foudations of Epidemiology. New York: Oxford University Press, 1980.