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SPECIAL TOPIC

Invited review

Clinical and epidemiological data on inflammatory bowel disease, colorectal cancer and Helicobacter pylori infection in Israel*

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This review is concerned with inflammatory bowel disease (ulcerative colitis and Crohn's disease), colorectal cancer and Helicobacter pylori infection, which are the topics for discussion in a round table session at the 22nd Panhellenic Congress of Gastroenterology (Athens, November 2002). These are timely and pressing issues for today's gastroenterologist in all countries. Herein the published experience in Israel is presented.

INFLAMMATORY BOWEL DISEASE

Clinical Data

The inflammatory bowel diseases (IBD) are ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis (IC). In Israel UC and CD are dominant while IC is rare, as in most western countries.[1] The clinical features of UC and CD are the same in Israel as in the European countries.[2] The dominant phenotype of CD is the fibro-stenotic syndrome. This accounts for the relatively high surgical rate. In UC the Israeli approach is more conservative, with fewer operations than in many European centers.

Medical treatment of IBD in Israel follows European and USA standards. 5-Aminosalicylic acid in high dosage may be used for mild flares of UC and for maintenance of remission.[3] Corticosteroids are used extensively as the first line drug for moderate or severe exacerbation of disease in both CD and UC. Budesonide is an alternative to corticosteroids in CD. Budesonide is as effective as prednisone in the treatment of moderately active CD involving the terminal ileum and right colon.[4] Budesonide has significantly fewer steroid-related adverse reactions. Immunosuppression (6-mercaptopurine or azathioprine) may be added when patients do not respond to corticosteroids or become steroid-dependent. Of note, 6-thioguanine levels are not measured routinely in Israel as yet. Cyclosporine is used in severe UC (but not CD), where it induces long-term remission in one-third of patients, and in those who still require surgery the treatment results in an improved clinical condition before the operation.[5] Infliximab (Remicade^{R}) in Israel is approved for use in CD resistant to corticosteroids and immunosuppression; the efficacy seems to be like that reported in the literature, but the published Israeli data are preliminary[6] and further evaluation is needed. Infliximab is also very expensive. Immunosuppression and/or 5-aminosalicylic acid are used for maintenance of remission of CD.

Certain pioneering studies were performed in Israel with methotrexate. Methotrexate (12.5 mg weekly, orally) in 84 chronic steroid-dependent CD was only moderately better in controlling symptoms than 6-mercaptopurine or placebo.[7] When each patient was evaluated as his own control, however, methotrexate treated patients were all significantly better in the parameters of general well being, abdominal pain and steroid dose. The effect is apparent after one month. This is the first evidence that oral methotrexate might have a place in the man-

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**This article is a summary of current practice in Israel. All the references refer to work carried out partially or totally in Israel.*

agement of CD. In UC methotrexate (12.5 mg weekly, orally) was not at all effective; the dose however was likely too low.[8] Use of methotrexate in UC is the subject of ongoing investigation.

Hyperbaric oxygen is used occasionally in treating perianal CD since it increases tissue oxygenation. Six unresponsive CD patients were sent to the Dead Sea in eastern Israel, this being the lowest point on earth, 400 m below sea level, with an increased pO_2. In all cases the Harvey-Bradshaw index decreased, and the mean index of 9.0 ± 1.4 dropped to 3.5 ± 1.4 (SEM, $p = 0.006$). Also, three of four patients showed advanced healing of perianal fistulae.[9]

While the commonest rheumatological complication of CD and UC is peripheral arthritis, fibromyalgia appears to be equally common. In an Israeli study fibromyalgia was documented in 49% of CD patients and 19% of UC ($p = 001$ between these diseases). Subjects with CD exhibited more tenderness and reported more frequent and more severe fibromyalgia-associated symptoms than UC. Patients with CD had a higher tender point count ($p = 0.001$) than those with UC.[10] Other complications of CD and UC are less common.

The relationship of smoking with IBD has intrigued Israeli investigators. Of Israeli Jewish patients with CD, 24.5% are current smokers. Unlike other countries, in Israel a multi-hospital case-control study failed to demonstrate any epidemiological association of smoking with CD.[11] The usual association with non-smoking however is present in Israeli UC patients, the majority being nonsmokers or past-smokers, and only 12.9% current smokers.[11] Current cigarette smoking has no adverse effect on the course of CD in Israel, an astonishing observation indeed.[12] No differences were found between CD smokers and nonsmokers for hospitalizations (number and duration), operations, and requirement for corticosteroid and immunosuppressive treatment. By contrast, UC smokers had less extensive disease than nonsmokers ($P < 0.02$) and fewer hospitalizations ($P = 0.01$) and operations ($P = 0.025$). This confirms the protective effect of smoking in UC.[12] In an interesting recent multi-center study UC (but not CD) patients in Israel were significantly less exposed to passive smoking before onset of illness than their community matched controls.[13]

Epidemiological Data

Data are available in Israel since the 1960s. The incidence rates of UC and CD in Israeli Jews have increased with time. For 1981-1986, the mean annual incidence rates (Negev region of Israel, rates expressed per 10^5 population) were: UC 5.8 and CD 2.9. In 1987-1992 the mean annual incidence rates were: UC 8.0 and CD 4.2. Our most recent mean annual incidence rates, for 1995-2000, are: UC 7.3 and CD 10.2. These data show that the incidence of CD has increased while that of UC is static.[14] A similar change has been noted in several European countries.

CD has become more common in Israel in all three Jewish population groups (defined by place of birth in Israel or Africa-Asia or Europe-Americas). The age of presentation has declined and is now lower in Israel-born patients than immigrants, and lower in ileocolonic versus other sites of disease.[15]

In Israeli Arabs the incidence (expressed per 10^5 population) is significantly lower compared with Jews living in the same area: for Arabs in 1995-2000, UC 1.65 and CD 1.1. The age at diagnosis and the clinical features of both diseases however resembled those in Jews.[16]

There are no comprehensive genetic studies of inflammatory bowel disease in Israel. One study however showed that 6.4% of CD patients demonstrated first-degree relatives with CD or (less commonly) UC. The rate of first-degree relatives with CD was similar in Ashkenazi and non-Ashkenazi Jews.[17]

COLORECTAL CANCER

Clinical and Epidemiological Data

Colorectal cancer (CRC) is the second commonest cancer in Israeli males, after prostate cancer, and the second commonest cancer in Israeli females, after breast cancer.[18] Over 2,000 individuals are diagnosed with colorectal cancer each year, constituting about 14% of all documented cancers (Table 1). The incidence rate per 10^5 population/year varies considerably by sex and population group (Table 2). It is higher in Jews born in Europe, North America and Israel, and lower in Jews born in Africa or Asia. The incidence rate has been increasing faster in Jews than Arabs.[18]

Israeli Arabs have much less CRC than Israeli Jews. In a recent cohort of CRC 93% were Jews and 7% Arabs ($p < 0.001$). Arabs had a lower average age at disease diagnosis 62 yr versus Jews 74 yr ($p < 0.001$), with more right colonic and fewer rectal tumours than Jews.[19] The cause of this difference might be their less western lifestyle.

A recent study shows that the I1307K APC variant may represent a susceptibility gene for colorectal cancers in European-born Jews,[20] but this is not proven. In

Table 1. Occurence of colon and rectal cancer in Israel, 1995

Site	ICD-9 Codes	Males		Females	
		Cases	%of all cancers	Cases	% of all cancers
Colon	154	811	10.7	764	9.5
Rectum	154	313	4.2	300	3.4

Adapted from ref. 18

Table 2. Age-adjusted incidence rates (per 10^5 population/year) of colon and rectal cancer in Israel, 1995

Site	Jewish		Arab	
	Males	Females	Males	Females
Colon	33.5	24.4	14.1	8.1
Rectum	12.7	9.8	4.0	3.5

Adapted from ref. 18

persons at average risk for colorectal cancer, the I1307K APC gene variant occurred in 15% of European-born Israelis with familial cancer and was not detected in non-European Jews at increased cancer risk (P = 0.02). There is good evidence that the I1307K polymorphism may reflect a founder mutation.[21] Although the colon cancer frequency in the non-European Jews is lower, the genetic component may be more important than for European Jews. The non-European Jews may represent a distinct subgroup that differs with respect to either primary genetic susceptibility to colorectal cancer and/or may have been subjected to peculiar, environmental carcinogenic exposures.[22]

Cancer screening is given top priority by the Israeli Cancer Association, addressing its messages to physicians and the general public. Population screening with a sensitive fecal occult blood test is capable of detecting a high proportion of tumors at a favorable stage. Given its proven power to significantly reduce mortality, use of this test has been strongly advised to both medical organizations and the healthy population at average risk. Persons offered or requesting screening often misunderstand their relative risk of developing colorectal cancer.[23] Compliance with fecal occult blood testing is somewhat low among the Israeli population. Mailing a kit request card within the framework of a screening program was found to achieve a substantial increase (to 17.9%) in the level of compliance.[24] First-degree relatives of colorectal cancer patients are at great risk for developing this disease, but in a recent study only a minority reported having been counseled to undergo screening, although most had seen their family physician in the previous 3 years.[25]

CRC as a complication of UC and CD has been investigated in Israel. The incidence of CRC was studied in an unselected group of 1035 patients with UC residing in central Israel.[26] The cumulative incidence of colorectal cancer in ulcerative colitis was much lower than reported from abroad. The cumulative incidence of colorectal cancer was 0.2% at 10 yr, 2.8% at 15 yr, 5.5% at 20 yr, and 13.5% at 30 yr. The ratio of observed to expected cancer was 0.9 at 10 yr, 5.0 at 20 yr, and 6.4 at 30 yr. The cancer incidence was 1 case per 3895 patient-years in the first decade of disease, 1 case per 198 patient-years in the second decade, and 1 case per 100 patient-years in the third decade. All these rates were higher in patients with total colonic UC.[26] In a further study, a low incidence of significant dysplasia in a successful endoscopic surveillance program of patients with UC was reported.[27] In a cohort of 365 CD patients followed for a mean period of 9.95 years (range, 1-49 years), only one patient developed CRC.[28] The incidence of CRC was not significantly different from the expected in the population. None of the CD patients developed small-bowel cancer. Interestingly, 5 patients had extraintestinal malignancies.

HELICOBACTER PYLORI (HP) INFECTION

Epidemiological Data

Rates of HP infection in study populations are usually determined by serology. The prevalence of HP infection in Israel is higher than that in industrialized countries, but lower than in developing countries.[29] Time trends have not been studied.

Serological screening studies in the general population of Israel show that HP has a prevalence of about 50%. There is a low prevalence in children of 10%, a rapid rise in the second decade of life to 39%, and a rate of 79% in persons over 60 years old.[29] The prevalence rates of HP infection are somewhat higher in those living in communal settlements with 72% than in urban dwellers with 65%.[30] Regarding ethnic Jewish groups, the HP infection rates were much higher in persons of Mediterranean and Asian origin with 89%, compared to those

of Western European/North American origin at 57%.

In chronic care facilities the seroprevalence rates for HP were 75%[31] to 84%[32]; the seroprevalence rate was significantly associated with duration of stay, but not age. In a multivariate discriminant analysis, age, country of origin and ethnic group were found to be the most closely associated variables for HP infection. There was no significant difference with gender, occupation, educational level, blood group, smoking, gastrointestinal symptoms and use of medication.[32]

The prevalence rate of H. pylori infection in patients undergoing endoscopy for upper gastrointestinal symptoms is 71% to 92%.[29] However, patients with non-ulcer dyspepsia also had high rates of seroprevalence of 61% to 89%.[29] The frequency of H. pylori infection in dyspeptic patients in Israel is significantly increased during the winter months and decreased in the summer. This seasonal variation is identical to that found in duodenal ulcer disease. Therefore, it is tempting to speculate that seasonal variation of peptic ulcer disease could be explained by H. pylori infection.[33]

In a recent study H. pylori IgG antibodies were found in the serum of 41 (80.4%) of CRC patients compared to 32 (62.7%) of the control subjects (P = 0.05). The meaning of this association is obscure.[34]

Treatment of HP infection

In Israel seven-day triple treatment for HP is prescribed by over 80% of board-certified gastroenterologists. The standard first-line drugs are a PPI + amoxycillin + clarithromycin (or occasionally metronidazole), with a success rate estimated at 72% to 88% in various studies.[35,36] Among Israeli gastroenterologists, 95% will treat duodenal and gastric ulcer in the first presentation with anti-HP medication (even is HP was not tested for by the urease or other tests).[36] About 45% of Israeli gastroenterologists will treat non-ulcer dyspepsia with anti-HP medication, 53% treat for HP before PPI is given to patients with gastroesophageal reflux, and 60% treat HP when non-steroidal anti-inflammatory drugs are to be administered.[36]

Most Israeli gastroenterologists do check for eradication after completion of treatment, usually with the urea breath test. Second line treatment, when required, is based usually on a PPI + bismuth + tetracycline + metronidazole.[35] HP sensitivity to antibiotics is rarely tested. Antibiotic resistance is a problem as in other countries. In Israel there is no resistance to tetracycline, and resistance to amoxycillin is quite rare. Resistance to metronidazole occurs in 38% of "never treated" and 61% of "previously treated" patients; for clarithromycin the rates are much lower at 8% and 46% respectively. Resistance to cefixime is low, likely because it is seldom used for HP.[37] Of note, few Israeli gastroenterologists will use an H2-receptor antagonist in place of a PPI, and few will accept an X-ray diagnosis of duodenal ulcer without endoscopy confirmation.[36]

There is no difference in the HP eradication rate in relation to gender, endoscopic diagnosis, more advanced age, place of birth, or smoking habits.[38] The HP serostatus in Israeli backpackers following travel to tropical countries (mainly India and the Far East) does not change usually.[39] HP infection is not correlated with the O blood group.[40]

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