WHAT IS THE IMPACT OF AGE ON ADULT PATIENTS WITH INFLAMMATORY BOWEL DISEASE?

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Abstract

Inflammatory bowel disease (IBD) is a chronic disease that affects both young adults and also the elderly. This article emphasises the particularities related to age in the epidemiology, diagnosis, natural course of the disease, prognosis and therapy of adult patients with IBD. Even though the main characteristics in geriatric populations with IBD may not differ much from those in younger patients, distinct problems exist.

The majority of IBD studies were performed on young subjects, younger than 40 years of age. The optimal therapeutic choice in young individuals with IBD is a challenge for the physician who needs to take in account the risk of untreated or suboptimally treated chronic intestinal inflammation, long term prognosis, quality of life, the impact of side-effects of aggressive therapeutic approaches, the impact on pregnancy, as well as personal and healthcare costs.

The diagnosis in elderly patients can be challenging due to the large number of conditions that mimic IBD. The treatment options are those used in younger patients, but a series of considerations related to potential pharmacological interactions and side effects of the drugs must be taken in account. The risks associated with the use of some IBD medications may be increased in older patients, but so is the risk of under-treated IBD and surgery.

Keywords: elderly, diagnosis, inflammatory bowel disease, therapy, young adults.

Background

Inflammatory bowel disease (IBD) is a complex disease process that is highly prevalent. The condition includes ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis. IBD has a high rate of disease exacerbation and recurrence, being both difficult to diagnose and incurable, as well as having a variable therapeutic response. Furthermore, IBD sufferers may require outpatient follow-up for 10-20 years or even for their entire lives.

In Europe, the number of patients with IBD is greater than 2.1 million [1]. Its incidence is variable, being higher in the USA, UK and Scandinavian countries and lower in Central and Eastern Europe, South America and Africa. Recently, IBD has undergone an epidemiologic change marked by a rise in its incidence in Eastern Europe, with a lower rise in Western Europe and the USA [2]. In Asia there has been an exponential rise in the incidence of UC in the last 20 years, with a more gradual rise in the rate of CD, as a result of changes in genetic and environmental factors (industrialisation, change in nutrition, etc). In India a rise in the incidence of IBD was noted from 0.2/100,000 inhabitants to 1.2 per 100,000 [3].

Epidemiology

The Montreal Classification categorises patients according to age: A1 under 17 years, A2 17-40 years (category which contains many young individuals) and A3

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over 40 years. The definition of an elderly patient refers usually to individuals over the age of 65.

Whilst 7-20% of IBD sufferers are children, 60-85% are adults, most of them being under 40 years of age [4]. Classically, CD has two incidence peaks: one in the 20-30 year group and another in the 60-70 year age group. UC incidence peaks between the ages of 20 and 30 [5]. Recent studies suggest that the bimodal distribution of CD is most often seen in American cohorts, whilst large European and Canadian data suggest a peak incidence of CD in the 15-29 age group and a maximal incidence of UC in the 20-29 year age group. In smokers, the onset of UC is later compared to non-smokers [7]. These epidemiological data suggest that IBD is a disease affecting predominantly young individuals.

In contrast, the global population is aging. In Europe, 16% of the population is over the age of 65. There is little data regarding the IBD in the more elderly population due to the heterogeneity of the studied cohorts and diagnostic confounding factors (NSAID, ischaemic and infective colitis as well as diverticulitis). 8-20% (12-15% mean) of patients diagnosed with IBD are thought to be over the age of 60 and more than half of these are aged 60-69 [2].

In individuals over the age of 65 years, the incidence of UC in the USA is $8x10^5$, being twice greater in men. In CD the incidence is $4x10^5$, being equally prevalent in men and women [8]. In Europe the incidence of IBD over the age of 60 is $8\text{-}10x10^5$, being similar in UC and CD [9]. Hospital admissions in individuals over the age of 65 represent 25% of all hospital admissions for IBD [2,10].

Diagnosis

IBD is a diagnostic challenge. In young individuals the average duration of diagnosis from the onset of symptoms is 2 years, whilst in the elderly this process may last up to 6 years. The frequency of a wrong initial diagnosis is 15% in young individuals and up to 60% in the elderly [11]. We highlight the fact that the method of establishing the diagnosis is similar irrespective of age.

In CD there no specific symptoms related to old age. Elderly patients are often admitted to hospital with hypovolaemia, anaemia, malnutrition or rectal bleeding, as opposed to younger individuals who are admitted with complications of CD (fistulas or stenosis). There are however correlations between age and disease location: colonic involvement occurs between the ages of 20-40 is 20%, increasing to 48% in those diagnosed after the age of 40 and in 60% of those diagnosed after the age of 65. Similarly, there is a correlation between age and disease manifestation, where elderly patients have predominantly lumen-limited disease with few fistulas, stenoses or fissures due to the reduced immune response seen in this patient group [12,13,14].

In UC, irrespective of age, the same symptoms are seen: rectal bleeding and diarrhoea. Nevertheless, patients over the age of 65 with UC may have more atypical manifestations, such as constipation [15,16,17]. In young patients pancolitis is more often seen, whilst after the age of 55 proctitis and left-sided colitis is seen [18,19]. UC exacerbations/recurrences after the age of 55 are more severe, longer in durations and the need for steroid use is higher [20]. Considering the age-related clinical variations in UC, a similar "Montreal classification" should be considered.

Extraintestinal manifestations of IBD are similar in all groups, with the exception of a higher risk of osteoporosis in the geriatric population. In order of frequency, elderly patients may present with peripheral arthritis, uveitis, spondylitis and erythema nodosum [16,21].

In the differential diagnosis of IBD in young patients it is important to consider infective colitis, acute appendicitis, tuberculosis and intestinal lymphoma.

Due to the complex nature of IBD and the comorbidities associated with old age, its differential diagnosis in the elderly is wide. This includes:

- NSAID induced colitis - associated with ulceration, strictures or even perforation which can mimic IBD or complicate its management. Elderly patients with IBD being treated with NSAIDs have a higher risk of disease exacerbation compared to those not taking NSAIDs (2.5 x greater in UC and 1.3 x greater in CD). In these circumstances, the use of COX1 and COX2 inhibitors is recommended as they have a reduced negative impact on IBD [9].

- Ischaemic colitis is frequent over the age of 65, especially in patients with organ failure, thromboembolism, etc. It is characterised by severe abdominal pain, rectal bleeding, diarrhoea and segmental colonic involvement with a rectal sparing. This always requires endoscopic exploration and/or CT scanning to exclude colon cancer which is also common in this age group [22].

- Segmental colitis associated with diverticulosis (SCAD) syndrome represents inflammation around diverticuli and is a different entity from diverticulitis. Half of the population after the age of 60 has diverticuli, but SCAD syndrome is seen in only 3-8% of cases. Clinically it manifests as abdominal pain, changes in bowel habit and rectal bleeding [23].

- **Infectious colitis:** the elderly population is at a higher risk of developing infections compared to younger individuals. Population based studies explain this through changes in the concentration of 'probiotic bacteria' (bifidobacteria and lactobacilus) which raise the risk of enteral infections [24]. Practically, in any case of diarrhoea in the elderly (with or without known IBD) infections with Salmonella, Shigella, Campylobacter, E.Coli and Clostridium difficile (fulminant, watery diarrhoea) must be excluded and ultimately investigated. IBD is known to increase the risk of infections, in particular those with Clostridium difficile. Infections are twice more common

if they complicate CD and three times more frequent if they occur on a background of UC. Recently it has been demonstrated that the use of corticosteroids increases the risk of infection with Clostridium difficile compared to other immunosuppressants [25]. Superinfections complicate the evolution of IBD, increase the frequency of complications, lead to longer duration of hospital stay and a mortality that four times greater compared to IBD without infections [25,26].

- Microscopic colitis (lymphocytic and collagenous) is an exclusive histopathological diagnosis in the presence of a normal macroscopic colonoscopic examination. It is characterised by watery diarrhoea without rectal bleeding or fever and is more common in women over the age of 50, being twice as common after the age of 65. It is exacerbated by the use of NSAIDs.

- Radiation colitis can mimic IBD or complicate its natural history. It occurs after radiotherapy for genital, rectal or prostatic cancers.

- Neoplasms are commonly found in the elderly. Diagnostic challenges are particularly found in lymphomas which can present with a variety of symptoms, being more common in the elderly population irrespective of IBD status [20,27]. Colonoscopic surveillance targets the elderly population with a good quality of life who may benefit from a colectomy should severe dysplasia or adenocarcinoma be identified. Elderly patients with ileo-anal pouches require careful surveillance as the risk of neoplasia is 5.1% at 25 years from surgery [9].

Disease evolution and prognosis

Young age of onset is considered to be an unfavourable prognostic factor in CD. Many studies suggest a correlation between age under 40 at the time of diagnosis and the severity of IBD [28]. Beaugerie et al identified disabling CD in a cohort of 1188 patients, who required more than 2 courses of steroid therapy, the use of immunotherapy, the need for hospital admission and surgery within the first years from diagnosis. They identified the following risk factors: age under 40, need for initial corticosteroid therapy and perianal involvement [29]. The IBSEN cohort in a prospective study over 10 years identified the following risk factors for surgical intervention in CD: ileal involvement, symptoms and signs of stenosis or bowel penetration and age under 40 [30]. Together with localisation (ano-perineal or rectal), the formation of fistulas or stenoses, the need for steroid therapy and age under 40 represent poor prognostic factors in CD. In UC predicative risk factors are less well documented, but young age and degree of bowel involvement can be linked to more aggressive forms of the disease and need for colectomy [28].

Negative prognostic factors in the elderly are associated comorbidities, delayed diagnosis, poor mobility and associated bowel cancer [9,31]. Published data are homogenous regarding IBD mortality in the elderly. In UC, mortality is similar to that of the general population irrespective of age [15,16]. In CD mortality is slightly higher in those over the age of 55 compared to the general population, being proportional to increased duration of disease [31]. Age is an independent risk factor for inpatient mortality in those with IBD, together with the development complications and the need for surgery. Post-operative complications are similar irrespective of age, with a slightly higher incidence of cardiovascular and pulmonary morbidity in those over the age of 65. Infections, especially Clostridium Difficile, represent another risk factor for mortality in elderly inpatients [32,33].

Therapeutic features

Therapeutic strategies in the management of IBD are implemented according to current guidelines irrespective of patient age, taking in account the intestinal localisation of the disease, its extent, severity and natural evolution, both for CD and UC.

Treatment of young patients

The classical therapeutic pyramid of IBD starts with the use of 5-aminosalicylic acid derivatives (in UC) or budesonide and antibiotics (CD) in mild to moderate forms of the disease. The next step involves the use of parenteral corticosteroids and immunomodulator therapy (azathioprine and methotrexate). The peak of the therapeutic pyramid involves biological agents and surgical therapy.

Biological agents have revolutionised therapeutic approaches to the management of IBD. Until recently therapeutic goals in CD or UC was to induce and maintain disease remission. Current clinical practice however aims at ‘deep remission’ which targets not only the clinical and biological outcomes, but also ‘mucosal healing’ [34]. This last outcome can be achieved using biological agents which can change the evolution and natural history of IBD.

Anti-TNF agents (infliximab, adalimumab, certolizumab) target intestinal inflammatory mediators and have a proven efficiency in inducing and maintaining remission, the healing of fistulas, improvement in extraintestinal manifestations of IBD (arthritis, pyoderma gangrenosum, erythema nodosum), reduction in the need for corticosteroid therapy, need for surgical intervention and hospital admission [35]. Furthermore, they can facilitate mucosal healing and can modify disease evolution in the long term. On the other hand, biological therapies can lead to significant healthcare costs, as well as side effects. These include severe infections and T-cell hepato-splenic lymphoma, which poses a significant risk to patients [36].

Therapeutic guidelines in IBD clearly recommend biological therapy in patients with CD which do not respond to or are dependent on corticosteroid therapy, those with recurrences, failed immunotherapy, patients

with complex fistulas and moderate to severe forms of recurrent UC. Biological agents are contraindicated in infections (acute infections, abscesses or untreated chronic infectious diseases such as tuberculosis or viral hepatitis B), fibrous stenoses, lymphoproliferative diseases, severe heart failure, demyelinating diseases and those with a past history of cancer [37,38,39]. There is a separate category of patients which international guidelines identify as having an unfavourable prognosis in which early introduction of biological therapy could positively impact on disease evolution and prognosis. As previously mentioned, early onset of disease is considered to be a negative prognostic indicator. Young patients may therefore be ideal candidates for a reversed therapeutic approach, where biological agents may be introduced earlier than usual. In fact, the majority of IBD studies were performed on young subjects younger than 40 years of age (classical studies such as ACCENT I and ACCENT II demonstrated the therapeutic efficiency of biological therapy in CD in individuals with a mean age of 35 and 37, respectively) [40,41]. Furthermore a number of cohort studies (Vermeire 2002, Laharie 2005, DETAID 2006, EXTEND 2010) have identified young age as a favourable prognostic factor in biological therapy [39].

It is however important to remember that the use of biological agents in young patients with IBD has associated side-effects, in particular a higher risk of infections and neoplasia. In 2006 the FDA warned against the risk of hepato-splenic T-cell lymphoma, especially in young male patients treated with anti-TNF agents in association with azathioprine or 6-mercaptopurine. There have been over 20 reports of IBD patients treated with biological agents that have had sinister outcomes. As a result the Austrian Consensus regarding Infliximab therapy in IBD recommends the avoidance of the use of anti-TNF agents in association with thiopurines in young male patients [42].

Another aspect of IBD therapy in young patients involves the so called "transition period" from childhood to adulthood as a teenager. The challenges involved with this period are related to the childhood-specific aspects of IBD, such as radiation exposure, compliance with therapy and psycho-social support. This transition process requires a good collaboration between paediatricians and gastroenterologists. Although formal guidelines do not currently exist, the ECCO consensus recommends the establishment of special units where teenagers with IBD can receive support in undergoing the transition to adulthood [43].

In conclusion, the optimal therapeutic choice in young individuals with IBD is a challenge for the physician who needs to take in account a number of patient-specific parameters: the risk of untreated or suboptimally treated chronic intestinal inflammation, long term prognosis, quality of life, the impact of side-effects of aggressive therapeutic approaches, the impact on pregnancy, as well as personal and healthcare costs.

Treatment of elderly patients

In the choice of clinical goals and optimal therapy it is important to distinguish between the fit and health elderly patient and the frail individual who presents with multiple comorbidities. Furthermore, it is also important to distinguish between the "young elderly" (65-75 years), the "middle aged elderly" (75-85 years) and the "truly elderly" patient (over 85 years) [44].

In elderly patients IBD therapy aims to control symptoms, avoid complications and maintain a quality of life similar to that preceding disease onset. Mucosal healing is a desirable outcome in the elderly and there is no evidence to suggest an age limit in achieving this end-point. The aging process does however involve certain changes which can impact on IBD management: the aging process of the immune system with an associated increased vulnerability to infections and reduced efficiency of vaccines, reduced pain thresholds, reduced liver volume and perfusion, changes in anorectal physiology and reduced anal incontinence [44]. Individuals over the age of 65 often have three, four or even five comorbidities which require the use of polypharmaceutical therapies with the associated risks of drug interactions (both enhancement and diminution of drug effect on introducing a new agent). The risk of drug interaction rises from 13% when taking two drugs to 38% for 4 drugs and 82% for 7 drugs [45]. Therefore, apart from mucosal healing, the main therapeutic goal in the elderly population suffering from IBD is to avoid disability through an overly-aggressive therapeutic approach.

IBD therapy in the elderly has a number of specific characteristics:

Corticosteroid therapy is used to induce disease remission (1-1.5 mg/Kg/day) with a gradual dose reduction by 5 mg per week. The prevalence of steroid resistance or steroid dependence is estimated to occur in 30% of the elderly [46]. There are many secondary effects, ranging from the purely cosmetic to more severe ones, such as arterial hypertension, diabetes mellitus, increased risk of osteoporosis, fractures and gastrointestinal haemorrhage, especially in association with NSAID use. The risk of fractures is high in the elderly especially if it is associated with malabsorption, malnutrition and concomitant cyclosporin or methotrexate therapy. It is necessary to measure bone density (initially at 6 and 18 months, followed by regular surveillance based on initial results) [47]. Prolonged steroid therapy increases the risk of infections (especially fungal infections), the need for hospital admission or surgery. It is estimated that the risk of death in these patients doubles [48]. In addition, steroid therapy interferes with anticoagulants requiring intense monitoring.

Budesonide is as effective as prednisolone irrespective of age. It is used in CD affecting the ileum and ascending colon. It has fewer side effects compared to

prednisolone [48].

5-aminoslicylic acid derivatives are not effective in CD. In mild to moderate forms of UC these may maintain a state of remission. In the elderly, who have a high incidence of proctitis and left-sided colitis, these can be used topically as suppositories or micro-enemas. Their volume needs to be adjusted due to the presence of faecal incontinence (present in 4% of individuals treated as outpatients and 10-25% of inpatients) [37].

Mesalazine interacts with different classes of drugs used in the elderly population. It reduces the serum concentration of digoxin, reducing its efficiency, increasing the concentration of hydralazine and second generation of anti-tuberculosis drugs (in which case hepatotoxicity is often found and must be carefully monitored) [49]. Normally the half-life of 5-ASA derivatives is 0.5-2 hours with a clearance of 300-600 ml/min. In the elderly, sulphasalazine has a half-life of 13.7 hours due to the reduction in glomerular filtration and renal clearance; this process is aggravated by the presence of renal lithiasis. Consequently 5-ASA derivatives should not be administered to elderly patients with poor renal function or renal lithiasis [44].

Antibiotics are indicated in CD which evolves to develop fistulas and abscesses. Metronidazole (side effect: peripheral neuropathy) and ciprofloxacin (side effect: Achilles' tendon pain/rupture, especially if there is concomitant steroid use) can be used in these circumstances [50].

Thiopurines and methotrexate. Conventional immunomodulators (azathioprine – AZA, 6-mercaptopurine – 6MP, methotrexate) have no significant difference in terms of efficiency, metabolism and toxicity in the elderly as compared to those under the age of 60 [36,51]. Immunomodulators maintain remission and are used in conjunction with steroid therapy (especially in the elderly) in order to reduce the dose of prednisolone in inducing remission. The maximal clinical effect is achieved on average after three months. They can interact with allopurinol, often used in the elderly patients, by raising the bone marrow toxicity due to the inhibition of xanthine oxidase by allopurinol. When given in conjunction with allopurinol the dose must be reduced to a third or quarter for AZA and 6-MP, together with assessment of 5-methyltransferase activity and monitoring of liver function [45,49]. Hepatotoxicity in the elderly is greater if there is prior liver impairment [48,52]. Old age and IBD are risk factors for thromboembolism. AZA increases the effect of coumarin derivatives, requiring close monitoring of the prothrombin time [45,49].

Methotrexate has the same safety profile irrespective of patient age. Its use together with 5-ASA derivatives may impact on liver function, especially in those with impaired renal function. Consequently, close monitoring of renal function is needed (serum creatinine, creatinine clearance, glomerular filtration etc.) [53].

Treatment with biological agents. Currently there are no studies looking at the effects of biological therapy in the elderly [54]. Data on the safety of biological agents in individuals over the age of 65 is derived from their use in rheumatology and are often inconclusive. Biological therapy should therefore be carried out cautiously. Active and chronic infections, in particular tuberculosis in countries with a raised prevalence, hepatitis B and HIV, should be identified and treated before starting biological therapy. Those who have been recently vaccinated should wait 3 months before commencing therapy, remembering that the immune response in the elderly is delayed [39].

Age over 65, comorbidities and immunosenescence are risk factors for infections in IBD. Immunosuppressant agents used in IBD (steroids, AZA, methotrexate and anti-TNF biological agents) act via different mechanisms but have a common outcome of reducing patients ability to mount an immune response to infections. Each immunosuppressor agent, according to each individual mechanism of action can predispose to a certain type of infection. Steroids lead to infections of mucosal surfaces (fungal); thiopurines lead to viral infections (cytomegalovirus, herpes simplex, varicella zoster, Epstein Barr virus); anti-TNF α increase the risk of granulomatous infections such as tuberculosis, especially in the elder patient, from 5 to 30 times [55]. The risk of opportunistic infections rises three-fold if an immunosuppressor is used and rises again with addition of further immunosuppressant agent, as demonstrated by the TREAT registry data [56]. In the case of biological agent therapy in IBD the risk of infection is controversial. Some studies suggest only a small rise in the number of infections, whilst an Italian data set indicates that there is a significant rise in infections over the age of 65 [57,58]. The TREAT Registry shows that a large number of infections in those treated with biological agents is due to the prior use of steroids and the greater severity of the disease [56].

The risk of cancer is higher in IBD patients compared to the general population. The increased incidence of colorectal cancer in IBD has been well documented, but other sites may also be affected. In CD treated with thiopurines and biological agents the most common sites for developing cancer are the small bowel, the pancreas, the endocrine glands, the kidneys, the lungs and stomach [54]. The ECCO consensus recommends that patients over the age of 65 should be investigated for neoplastic lesions prior to starting immunosuppressant therapy. This is achieved according the following algorithm: history, family history of cancer, careful physical examination of the skin (+/- dermatological examination), examination of the main lymphatic glands, chest X-ray to exclude pulmonary and mediastinal lesions, abdominal ultrasound, colonoscopy to look for dysplastic or malignant lesions, genital and urological examination [5]. The risk

of developing non-Hodgkin lymphoma (NHL) is 0.02% in the general population; this increases to 0.06% if thiopurines are prescribed together with anti-TNF agents. It is important to highlight the data looking at the risk of developing lymphoproliferative disease in IBD therapy are not conclusive, however [5].

Surgical treatment. Indications for surgery follow standard protocols with certain aspects being age-specific.

In CD after the age of 65 there is a reduced need for surgical intervention [59]. Following surgery increasing age has been identified an independent risk factor for complications requiring prolonged hospitalisation, extensive operative procedures in particular in those treated with steroids, immunomodulators and biological agents. Consequently, early surgical intervention is needed in the elderly IBD sufferers prior to escalation of medical therapy [60].

Surgical management of UC in the elderly has the same indications as in younger individuals. Coloproctectomy is recommended with ileo-anal pouch formation or even ileo-rectal anastomosis. The preservation of the anal sphincter function is more important in the elderly compared to the risk of developing rectal mucosal neoplasia in the residual mucosa or in the rectal pouch (estimated to be 1% at 10 years). In cases where patients have significant comorbidities and a high risk of complications a life-long ileostomy may be used. Postoperative infective complications are similar in both young and old [60].

The management of IBD in the elderly is difficult in terms of diagnosis, surveillance (number of colonoscopies) and therapy (choice of medication, each with their clinical benefits as well as side-effects profile). Aggressive therapeutic approaches, such as biological agents or surgery, must not be discouraged only by age criteria. It is important to differentiate between the healthy elderly patient and the clinically fragile individual, as well as to assess and monitor comorbidities, drug side-effects, drug metabolism, liver, renal and cardiac functions.

In conclusion, IBD is not a "one size fits all" diagnosis [34]. Irrespective of age, the key to optimal outcomes and patients' safety in IBD are associated with observing current guidelines and protocols, practicing patient-tailored treatment, as well as having experienced clinicians.

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