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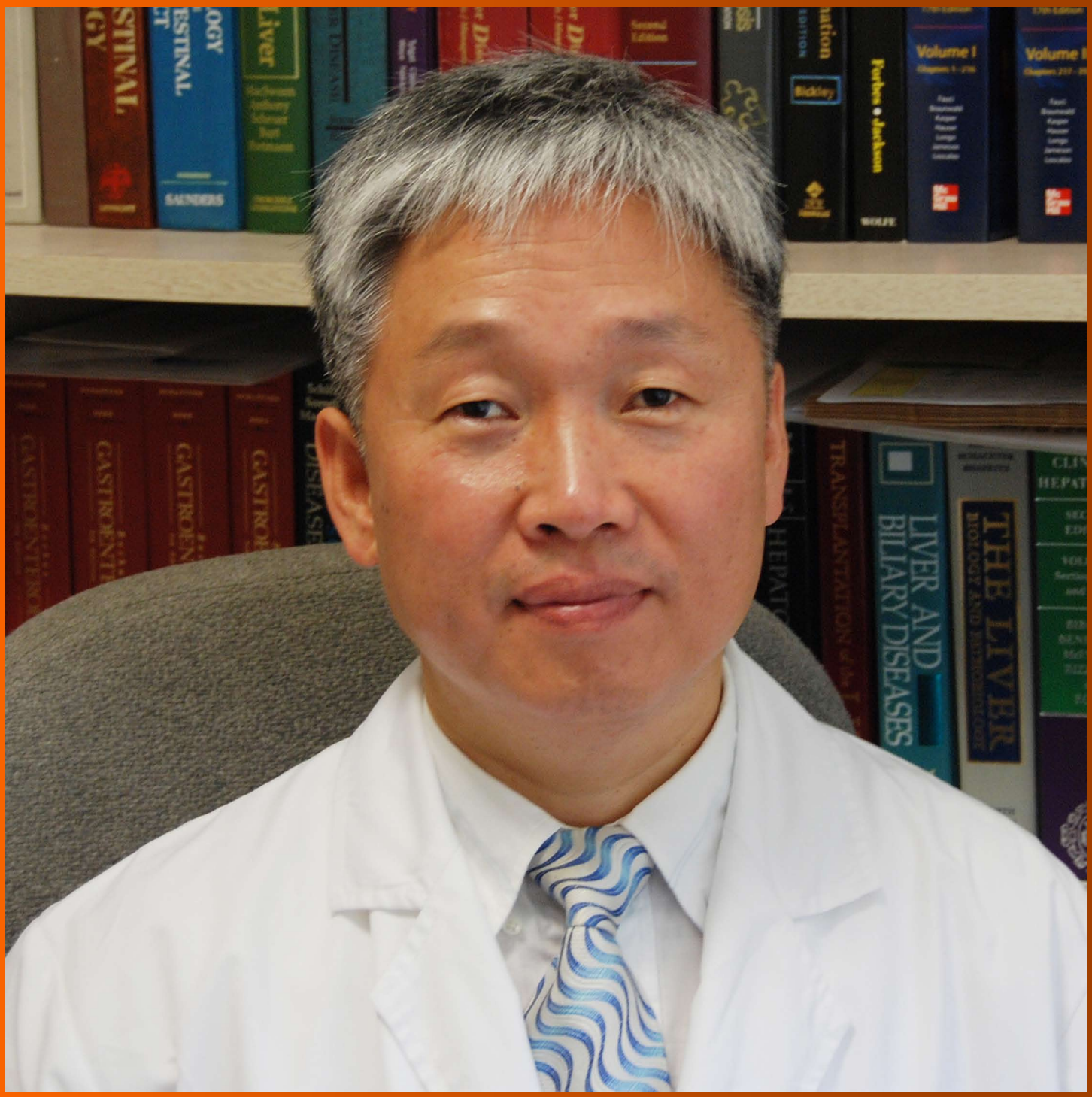

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MINIREVIEWS

Inflammatory bowel disease: Efficient remission maintenance is crucial for cost containment

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Abstract

The inflammatory bowel diseases (IBD) are chronic incurable inflammatory disorders of the gut. Some 10% run a downhill course, requiring emergency medical support and often surgery; another small subset are monogenic, and, threatening pediatric patients, are the challenge of these days. The majority of the IBDs, however, are polygenic low-penetrance diseases, running a lifetime waxing-and-waning course. The prevalent trend is towards a slow worsening and steady cost increase. Each and all drugs of the available arsenal exhibit strengths and weaknesses: Mesalamines are chiefly effectively for mild-moderate colitis, and do not work in Crohn's; steroids do not control some 40% of the ulcerative colitis cases, and are not indicated for Crohn's; thiopurines are effective in the maintenance of the IBDs but do not prevent relapses on withdrawal; biologics are still being used empirically (not monitored) causing further increase of their cost over that of hospitalization. Against all these caveats, two simple rules still hold true: Strict adherence maintenance and avoidance of colitogenic drugs. This matter is expanded in this minireview.

Key words: Inflammatory bowel disease; Therapy; Cost containment; Budget; Treatment adherence; Inflammatory bowel disease managed care

Core tip: Cost-effective maintenance of remission of inflammatory bowel diseases (IBD) is a traditionally unsolved challenge for care-takers and budget supervisors. The newly released (biologic) formulations, though purported to act as disease terminators, have failed to pay back their initial cost. We have faced the issue by reappraising initial simple tenets and found the following: (1) usually, uncomplicated IBD rests in remission by using cheap traditional drugs, provided the indication is correct, and, chiefly, that adherence is tightly maintained. Non compliant IBD patients cost manifold the compliant ones, and are the main cause of budget distortion; and (2) third-party drugs (nonsteroidal anti-inflammatory drugs, *e.g.*, should be avoided. A frozen steady-state is the regime to

effectively maintain IBD.

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EPIDEMIOLOGY

The Italian health service does not cover medical expenses in full, but requires patients to partially contribute to extents that vary according to income and social positions. Patients suffering from chronic incurable disease including inflammatory bowel diseases (IBD) may apply for full coverage. Hence, the number of applications may yield an estimate of the prevalence of IBD in Italy. Such estimates, dating back to 2009[1], are showing an IBD prevalence in Italy of 177-254 cases/10^5. Regional incidence data of pooled Crohn's disease (CD) and ulcerative colitis (UC) yield figures between 2.7 and 13 cases per 10^5 per year. A recently published Survey of Italian Gastroenterology Societies[2] indicates that: (1) Despite a recent increase between 1970 and 1990, the incidence of IBD in Italy is still exceeded by the Northern Europe figures; (2) Pediatric incidence figures of both IBD phenotypes has gone up from 0.89 to 1.39 between 1996 and 2003; (3) With UC being slightly more frequent in males, general data confirm the existence of two incidence peaks, at 25/35 years and around the sixth life decade; and (4) An increased family risk, various extra-intestinal manifestations, and the association with immune-mediated disease (multiple sclerosis, psoriasis, and celiac disease just as examples) all mark the clinical IBD presentations.

MORBIDITY AND MORTALITY

Large population studies demonstrate that active IBD does significantly reduce quality of life, with young fertile women being mostly affected[3,4]. In Italy, IBD-dependent disability is quantified in classes from the lowest 15% to the maximum of 70% (fourth class) if surgery has been needed. By contrast, IBD does not seem to significantly reduce life expectancy; notably, however, mortality is estimated to be increased in the first year of diagnosis as well as in patients younger than 30 years[5].

ADMISSIONS

IBD patients do need hospitalization more frequently than the general population, with most of admissions ending in surgery. About 4.6%-7.5% of UC cases and 36% of CD patients become operated at 5 years. The figure is 17% for pediatric cases[4].

THERAPEUTIC ARSENAL

There are two main challenges in the management of IBD, and these divide the list of the available drugs into two distinct chapters: induction of a response, and maintenance of the remission.

Mesalamines and its derivatives

Pioneered by Nanna Svartz studies on salazopyrin, mesalamines and its derivatives have been a mainstay for IBD treatment for the last 60 years. The modern version of salazopyrin, 5-aminosalycilic acid (5-ASA), has been tested in a large population study employing a range of doses between 1 and 4 daily g. Such dosages were shown to induce remission in 30% of the cases (12% for placebo); the figures rose to 80% if limiting the end-point to the clinical response[6]. Looking at remission maintenance, a series of Cochrane studies have shown that each and all of the FDA-approved formulations can yield a 30% advantage over placebo[7]. Mesalamines have proven not so readily effective for the treatment of CD. Initial data suggesting that daily 4 g could strongly reduce the Crohn's Disease Activity Index (CDAI) score *vs* placebo, achieving remission in 43% of the treated patients (placebo 18%) were not duplicated[8].

Antibiotics

Some antibiotic molecules of the imidazole class have shown effectiveness in CD. A study already completed in 2005 showed that post-operative administration of ornidazole could reduce relapse rates from 37% to 7%[9]. By contrast, UC has proven unresponsive to antibiotics[10]. Ciprofloxacin and metronidazole are advantageous for CD; this issue is exhaustively illustrated in a freshly updated review[11].

Corticosteroids

Population studies have shown that 34% and 44% of UC and CD patients, respectively, need a variable number of steroid courses to achieve remission[12]; by contrast, steroids are contraindicated for remission maintenance.

Thiopurines

Experience achieved over the last 30 years has consistently indicated that thiopurines are effective in the maintenance of remission of both IBD phenotypes. A classic controlled study published in 1980, including steroid-dependent and/or fistulizing CD patients, showed that 31% experienced fistula closure, and 75% were weaned from steroids if treated with 6-mercaptopurine (6-MP); these figures were respectively 6% and 36% in the placebo-treated subgroup[13]. By contrast, evidence favoring the use of thiopurines to treat UC has lingered a little behind: A recent study from us has shown that of 127 Italian patients who had had their azathioprine withdrawn, one-third, 50%, and two-thirds did relapse

at 12 mo, at 2 years, and at 5 years respectively[14]. A significant added value of thiopurines has been documented in a recent Dutch study. This nationwide survey has shown that chronic thiopurine treatment significantly protects patients from developing colitic cancer[15]. This breakthrough finding represents an authoritative correction of previous limited work that had claimed negative results[16].

RESCUE TREATMENTS FOR REFRACTORINESS TO CONVENTIONAL DRUGS

Preliminary work published in 1990 showed that cyclosporine, a fungal derived peptide able to inhibit T-lymphocyte responses, could achieve remission in a significant proportion of patients facing colectomy for refractory acute UC[17]. Later in 1994 such initial data were then confirmed in a controlled fashion[18]. The number of refractory colitic patients that had received cyclosporine was estimated to reach the number of 700 in 2005[19]. Interestingly, an English survey showed that only 7%-8% of all hospitalized IBD patients do receive cyclosporine; however, if asked whether they would opt to be treated, their positive responses often outweigh their own doctors' intentions[20]. The literature consistently indicates that cyclosporine effectively avoids immediate colectomy in 60% to 80% of steroid refractory UC patients; subsequent ability to maintain remission may fall around 60%, and is potentiated by the concomitant administration of a thiopurine[21]. In the suggestion of a leading center[22] cyclosporine must be considered a mainstay treatment for refractory colitis. Along this line, we have recently reviewed the pharmacologic profiles of cyclosporine, mesalamine, and thiopurines on the basis of the experience of treatment of 100 consecutive patients between 1991 and 2007. We succeeded in confirming the data discussed above, and stressed the need for further efforts in the direction to improve the pharmacologic profile of these drugs[23]. As of today, official position statements[24] hold that cyclosporine is as effective as infliximab to control severe refractory colitis, whereas it is not indicated for Crohn disease.

Recent Cochrane reviews have shown that tumor necrosis factor (TNF)-inhibitors (chiefly infliximab and adalimumab) can effectively treat steroid-dependence and fistula formation in CD[25]; similar but weaker evidence (owing to patient heterogeneity) have been published for UC[26]. Such favorable evidence seems not to be reflected in real-world practice, whereby it is estimated that not more than 15% of candidate IBD patients do receive an anti-TNF molecule [27]. A recent in-depth analysis conducted in Europe[28] has found that the healthcare costs for IBD are mainly influenced by medication, chiefly anti-TNF molecules, despite the potential of these measures to restrict resort to hospitalization; notably, similar research carried out in Canada has come to the same conclusions[29]. The implications of such findings can probably be re-shaped by the evidence that in losers of response, replacement of a blind dose escalation with therapeutic drug monitoring (test-based strategy) can lead to major cost saving[30].

THE IBDS: NATURAL HISTORY

Before the release of drugs such as mesalamines and steroids, and the availability of adequate resuscitation and surgical techniques, UC turned out to be a rather ominous disease: 33% risk of death in the first year; 12% mortality rate at relapse; the cumulative death risk 20 years following diagnosis was 40%; 40 years after diagnosis the colon carcinoma risk was 40%[31]. The scenario of 1983[32], namely 30 years after Truelove and Witts demonstration of the effectiveness of steroids had begun to change, contradictory areas persisted. The survival rate of those diagnosed with mild/moderate disease matched that of controls; yet, severe disease presentation still entailed mortality rates of 31% as distributed in the first 4 years. Nowadays, severe UC is expected to present with a frequency of 10-15% at any time of disease course: According to updated evidence the expected mortality is null, but sporadic fatal cases cannot be excluded[33].

Some 50% to 80% of the patients run a waxing-and-waning course, whereas a chronic active course may be observed in 15%-30%[34]. According to a reference publication: Young age, previous relapses, and presence of residual histologic disease (plasmacytosis) are all predictors of relapse[35]. The frequencies of resort to surgery are reported to range between 9.6% after 5 years and 31% after 18 years[36].

The natural history of CD is driven by disease localization and its strength to evolve. In population studies, a non-stenosing pattern, a stenosing pattern, and a penetrating course may be described with frequencies of 70%, 17%, and 13% respectively. In the follow-up, a switch to a stenosing pattern and to a penetrating one was recorded in 27% and 28% respectively. Some 50% of the patients did exhibit an ileal localization, an ileo-colic one by contrast affected the other half[37].

The data of two population studies including some 600 patients were rewarding: 10%-30% of the cases may expect a relapse in the first year of diagnosis; 15%-25% linger in a condition of low disease activity, whereas remission might remain the outcome in 50%-65%. Resort to surgery is a likely outcome in CD: 30% probability in the first year; the patient majority undergoes an operation after 20 years of disease. Those with ileo-cecal disease are the most likely to undergo operation: Specifically, the risk of an emicolectomy is 35% after 10 years[38,39].

THE BUDGET OF UC

According to a study of 1992, the annual cost per

patient was dollars 1488[40]. The 24% of this sum included three items of 8% each: The diagnostic algorithm, the out-patient services, the drug cost; direct and indirect costs of hospitalization made the remaining 47%. Two further data are to be emphasized: In a sample observation year, 39% of the bills charged to providers had been meant to cover the needs of only 2% of the insured clients (the subset with the worst disease forms), whereas from another point of evaluation, the majority of the insured subjects were responsible for less than 7% of the costs.

This data are a spy of the heterogeneity of the sources of expense in an IBD population: As a general rule, firmly controlled disease costs dramatically less than the chronically uncontrolled presentations that often face surgery.

This trend of surgery to make the most part of the budget is further strengthened by several factors. The three-steps reconstructive proctocolectomy with pouch anal anastomosis has significantly benefited patients by ensuring digestive tract continuity, but, making the patient hospital-dependent for 6 mo, have raised the costs sky-high. One other factor is the natural tendency of the disease to worsen, to increase the need for drugs and care, and to become laden with complications, including neoplasia.

The need to aggressively maintain the disease in remission to minimize costs stems clear from the above discussion[41]. To achieve this goal one may need a costly drug armamentarium (including biologic drugs in the last years) but most American providers do retain that this cost can be paid back by the advantages of managing a disease in remission. Direct costs (hospitalization) and indirect costs (drugs, sick leaves, family disruption) are to be chiefly accounted for in an unstable disease, and can be abolished by its stabilization[42].

TWO MAIN FACTORS THREATENING REMISSION MAINTENANCE IN IBD

Lack of adherence

Among the main missions of private care systems relies the identification and control of conditions of major cost. The American health care system has long pursued this goal, eventually collecting a large wealth of data. The essential message is that disease management is mostly expensive in unstable phases[43]. Lack of compliance has been identified as one of the capital factors in the loss of IBD remission. This matter may be discussed by differentiating four main topics: (1) The facts; (2) The causes and modalities of non-compliance; (3) The costs; and (4) Possible counter measures.

Facts: One hundred UC patients had mesalamine prescribed and were then followed prospectively for two years, with checkups at 6, 12, and 24 mo; the reappearance of at least 4 bloody urgent stools a day was defined as relapse. Non-adherent patients showed a 5-fold higher relapse rate; at 24 mo, 39% of non-adherent subjects were in remission, as opposed to 89% of adherent ones[44]. IBD patients seem to be maximally keen at non-compliance, as suggested by the following data. The adherence percentages during clinical trials may attain 80%; this contrasts with data in population studies, whereby the majority of subjects in remission opt for taking the risk of relapse for non-compliance than to accept the burden of a daily drug administration[45].

Causes and modalities: Pooled results from different studies indicated that favoring factors for non-adherence were a condition of male-single, and a left-sided colitis; a colonoscopy in the preceding 2 years and being married were opposing factors, instead[46]. When requested to declare their reasons for non-adherence, the answers were: Forgetfulness (50%); two many daily administrations (30%); doubts on the indication (20%).

Costs: Non-adherence entails extra-costs: increased morbidity; rescue drugs are more expensive; risk for complications including cancer; sick leaves; stress and family disruption. In pure terms of numbers, one should bear in mind that any single failure of a mesalamine prescription costs dollars 11500 per person[41].

Countermeasures: According to the experience of American health providers, patient counseling and release of single-dose drugs are the only worthy measures to reduce non-adherence.

Improper use of third-party drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics have long been suspected as factors of IBD reactivation or *de-novo* IBD causation. Recently, our attention got specifically concentrated on the role of macrolide antibiotics. Capable to favor gut colonization by Candida, these antibiotics might increase intestinal permeability, a favorable ground for IBD triggering[47]. In our out-patient clinic, it has become routine to warn referring doctors and patients against the unjustified use of macrolide molecules or NSAIDs. Dental surgery and orthopedic traumatology remain the main indication source for these drugs, and merit careful surveillance by academic gastroenterology centers.

CONCLUSION

While the prevalence of IBD is roughly stable in the Western World, the figures are on the rise of its incidence in two other contexts: Pediatric IBD and migrants.

As an incurable chronic disorder capable to disable the GI tract, IBD can easily impact a country's budget. In moments of financial restriction, care providers may duly concentrate their attention on the list of "traditional therapies", seeking optimization (increasing therapeutic

effects while diminishing costs). Current evidence recommends now that this optimization path be based on the evidence that the easiest at maintenance and less costly are the quiescent phases of IBD. Thus, such phases are to be vigorously achieved and tenaciously maintained, adhering to the following rules: (1) Pursue remission by early giving steroids and/or mesalamines at full doses. Proceed to a prompt and rapid steroid tapering once clinical remission is achieved. Continue mesalamines in most of the cases; (2) Respecting safety rules, use thiopurines as the best option in maintaining remission, smartly minding the strong synergism that might develop with mesalamines, both in terms of therapeutic or toxic effects[48]; (3) As said above, patients' compliance must strictly be monitored and corrected, as faulty compliance has been shown to be a strongly negative factor in remission maintenance and cost control; (4) Instruct family physicians and patients to carefully consider prescriptions of antibiotics and NSAIDs: Though some antibiotics may be therapeutic for IBD's, some other commonly prescribed formulations (macrolides) may activate or generate de-novo IBD, as NSAIDs can do[49]; and (5) Bear in mind that average IBD can be controlled by the timely use of correctly dosed traditional molecules: Sometime the need for costly therapies is provoked by the late or inadequate use of common treatments[50].

To give the reader an idea of how important it might be to fully exploit conventional therapies before resorting to biologic strategies, we like to implement the end of this paragraph by showing the cost for one day of treatment with the molecules mentioned in this text (expressed in euro) as reported by us in 2010[51]: Mesalamine: 3.06; first-generation steroids: 1.02; thiopurines 0.87; infliximab/adalimumab: 894/1675.

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