Opinion statement

Extraintestinal manifestations (EIM) of inflammatory bowel disease (IBD) occur rather frequently and may be found in up to 30% of patients. However, surprisingly few randomized, controlled studies have been conducted that were specifically aimed at the treatment of EIM of IBD patients. Therefore, most therapies of EIM are empiric or deduced from studies in populations with other type of patients. EIM may be associated with active IBD. Treatment of active IBD is, therefore, the mainstay of treatment of EIM. Lifestyle modification as a means of therapy is a recent subject of study in chronic conditions, such as IBD. Based on epidemiologic and experimental findings, EIM of various tracts can be modified by optimizing alimentary intake, refraining from sedentary lifestyle, and adapting smoking habits. Not many new drugs for treatment of EIM have been developed during the past few years; the role of infliximab has been extended in particular in Crohn's disease-related EIM. Careful consideration of prescribed drugs remains necessary due to potential interaction with the course of IBD.

Introduction

A wide variety of extraintestinal manifestations (EIM) is recognized in inflammatory bowel disease (IBD). Symptoms of extraintestinal involvement, distinct or in combination, may be established in every organ system. EIMs are most commonly found in active IBD, but may occur in quiescent IBD or even precede its diagnosis. Several manifestations are generally observed in patients with ulcerative colitis or Crohn's disease, whereas other manifestations are more commonly associated with colonic instead of ileal disease. Nevertheless, these subdivisions do not change therapy strategies. Overall, pathogenesis of EIM remains to be elucidated.

Prevalence and incidence of EIM are difficult to estimate, because population-based studies have been sparsely conducted. Most EIMs occur infrequently, but rheumatologic complications, osteoporosis, ocular, cutaneous, and vascular symptoms can be observed regularly (ie, in percentages varying from 2.5% to 25%) [1–4,5–6].

TREATMENT APPROACHES

Treatment of uncommon EIM is based on empiric approaches, but disappointingly, treatment of frequently observed extraintestinal disease has almost never been studied in well-designed, randomized, controlled trials. In general, active IBD should be treated to induce remission, which may positively influence the course of any concomitant EIM.

In rheumatologic complications, including peripheral arthritis, tendonitis or painful tendon insertions, and axial arthritis [7], therapy is directed toward reducing joint inflammation and preventing disability and deformity, particularly axial symptoms. An active approach is recommended with initiation of guided physical therapy, and, if necessary, simple pain-reducing medication such as acetaminophen [7–9]. In addition, sulfasalazine may be considered, particularly in axial involvement or, though less evaluated, mesalamine [7,10–12].
Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) selective inhibitors, are effective in arthralgia, enthesiopathy, or central and peripheral arthritis [13–16], but NSAIDs (including COX-2 selective inhibitors) may activate IBD, and remain, therefore, contraindicated [17,18•].

Many patients with chronic symptomatic arthritis or ankylosing spondylitis need additional therapy during the course of disease. A second-line option is corticosteroid use, preferably intra-articular [12,19]. Oral corticosteroids are usually very effective, but have burdensome side effects. Methotrexate is a third-line option. Disappointingly, immunosuppressive drugs showed limited potential [12,20]. Recently, anti–tumor necrosis factor therapy has been highlighted. In combination with Crohn’s disease, infliximab has proven efficacy against both rheumatologic and gastrointestinal disease, as well as against IBD-related arthritis [21,22••]. Interestingly, pamidronate, a bisphosphonate, has recently been shown to modify the course of spondyloarthropathies [23,24••].

The reported prevalence of osteoporosis in IBD patients varies considerably, but next to studies concerning decreased bone mass density, several studies reported high numbers of (clinically nonapparent) bone fractures [1,6•,25,26••]. Elevated vitamin A levels, as a result of overconsumption of vitamin supplements, are associated with bone fractures and thus should be avoided [27–29]. Although not completely unexpected due to the many risk factors for osteoporosis that occur in IBD patients (chronic disease, corticosteroid use, hypogonadism, calcium and vitamin D deficiency, low body mass index, insufficient physical exercise, genetic makeup, and smoking), treatment strategies are mainly deduced from other settings. Insufficient data determine what may be necessary. The alarming high bone fracture prevalence indicates the necessity of well-designed studies. A calcium-rich diet and an active lifestyle are important; vitamin D deficiency must be corrected, eventually by using tanning bed ultraviolet radiation [30,31]. It is advocated that osteoporosis should be treated more aggressively according to standard osteoporosis guidelines, including prophylactic use of bisphosphonates [32]. However, many questions need to be resolved: 1) at what T score and age may bisphosphonates be beneficial (to avoid bone fractures); 2) is (oral) bisphosphonate therapy tolerable during active disease or even beneficial in concomitant spondylarthropathy [24••]; 3) is pretreatment with calcium and vitamin D necessary or may such a supplementary diet therapy suffice? These and many other questions remain to be resolved before firm recommendations can be supplied. Clearly, risk factors for osteoporosis should be avoided or minimized when possible. Corticosteroids to treat IBD should only be prescribed when unambiguously indicated. Corticosteroid-induced bone loss should be counteracted by calcium and vitamin D supplementation, and, according to a number of experts, in combination with a bisphosphonate [32,33]. Bisphosphonates have proven efficacy, but oral intake in patients with exacerbated IBD is often associated with extensive gastrointestinal discomfort. In others and our experience, intravenously administered pamidronate is an alternative [34,35], and newer bisphosphonates show even more promise [36]. Overall, a more active medical approach—diagnostic, therapeutic, and investigational—is warranted to avoid late-onset problems associated with osteoporosis [32].

Commonly established cutaneous manifestations of IBD are erythema nodosum and pyoderma gangrenosum. Rare cutaneous manifestations include Sweet’s syndrome and aphthous or granulomatous stomatitis, of which the prevalence seems to increase [37]. Standard therapy of erythema nodosum still consists of pain relief, bandage, and elevation of affected limbs, and typically responds to treatment of active IBD. Pyoderma gangrenosum is usually more refractory to therapy. Topical management is aimed at prevention of secondary contamination. Biopsy, which can lead to persistent lesions, should be avoided [38•]. High-dose corticosteroids (eventually topically) may be effective, but cyclosporine, tacrolimus [39–41], colchicine [42] and, more anecdotal, mycophenolate mofetil and thalidomide, are additional options for difficult lesions. Topical tacrolimus 0.5% shows promise in the management of childhood perineal and oral Crohn’s disease, with no evidence of significant systemic absorption. However, rapid weaning or abrupt cessation of therapy may cause rebound worsening of disease [39]. Recently, encouraging data concerning the efficacy of infliximab, concurrent with immunosuppressive drugs in the treatment of several refractory cutaneous lesions, have been presented [43,44].

Thromboembolism is now firmly established to be an EIM of IBD [3], partly ascribed to a hypercoagulable state, usually, but not necessary, in the setting of active disease [45]. Prophylactic anticoagulant therapy, however, has not yet been investigated. Hyperhomocysteinemia may be another risk factor, as is vitamin B₆ deficiency, but in an independent way [46–48]. Therefore, dietary advice may be beneficial. Treatment of thromboembolism as EIM of IBD is similar to patients with noninflamed bowel, but trials are not available. Questions of duration of therapy, risk of gastrointestinal bleeding, and potential effects of comedication for IBD remain unresolved.