Treatment of Extraintestinal Manifestations in Inflammatory Bowel Disease

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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 alarmingly 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 B_6 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.

Treatment of rheumatologic complications

Diet and lifestyle

- Regular physical exercise improves (axial) joint performance [8].

Pharmacologic treatment

- Therapy is aimed at relief of symptomatic pain and reduction of joint inflammation.
- More extensive description of agents that are rarely prescribed in IBD patients is presented in a prior issue of this journal [49].

First-line agents

Acetaminophen

Standard dosage	Doses from 500 mg to 1 g three times per day.
Contraindications	Severe hepatic or renal insufficiency.
Main drug interactions	Alcohol may increase hepatotoxicity.
Main side effects	Hepatic injury. 25 g at once is considered lethal.
Special points	Acetaminophen has limited efficacy.
Cost effectiveness	Inexpensive.

Sulfasalazine

Standard dosage	Initial dose 500 mg three times a day, to be increased to 1 g three times a day combined with folic acid 0.5 mg/d.
Contraindications	Hypersensitivity to aspirin or sulfa-derivatives. Hepatic or renal insufficiency. Glucose-6-phosphate-dehydrogenase (G6PD) deficiency.
Main drug interactions	Antibiotics may inhibit colonic release of the active moiety.
Main side effects	Nausea, vomiting, and headaches, especially in slow acetylators; exanthema and pruritus; fever; reversible oligospermia; induction of asthma attack. Cytopenias occur infrequently, but minor side effects are very common [50].
Special points	Regular control of blood cell counts and hepatic and renal function is recommended. Sulfasalazine has beneficial effects as induction and maintenance therapy for ulcerative colitis, and maybe, but to a lesser extent, of Crohn's disease.
Cost effectiveness	Inexpensive.

Mesalamine

Standard dosage	Initial dose 500 mg three times a day, to be increased to 1 g three times a day to four times a day or in a 2-g dose two times a day.
Contraindications	Hypersensitivity; renal insufficiency.
Main drug interactions	None.
Main side effects	Interstitial nephritis; pancreatitis. Major side effects are uncommon [50].
Special points	Dubiously effective. Concern about renal toxicity is a matter of debate.
Cost effectiveness	Moderately expensive.

Second-line agents

Intra-articular corticosteroids/oral corticosteroids

Standard dosage	Intra-articular corticosteroids are supplied in a dosage between 10 and 25 mg depending on the joint involved. The initial oral dosage is a 20-mg prednisolone equivalent, in a tapering schedule. Dosing at double dose at alternate days may reduce systemic side effects. Dose depends on severity and persistence of inflammation.
Contraindications	Acute bacterial infections, tuberculosis.
Main drug interactions	Phenytoin and rifampicin decrease the efficacy of corticosteroids. Combination with NSAIDs or aspirin may lead to peptic ulcers.
Main side effects	Frequently, fluid retention and electrolyte disbalances; delayed wound healing; diabetes mellitus; psychic disturbances or emotional disbalance. Regularly, myalgia or myopathy. Seldom, aseptic bone necrosis; convulsions; pancreatitis. Osteoporosis. Cushing syndrome. Cataract and glaucoma.
Special points	Treatment with intra-articular injections needs to be done by an experienced practitioner. Arthrography can be performed at same session. Maintenance treatment with corticosteroids induces many long-term side effects, and substitution with immunosuppressive drugs is preferable. Concomitant primary prevention of osteoporosis is advocated.
Cost effectiveness	Inexpensive and effective for short-term treatment.

Methotrexate

Standard dosage	In Crohn's disease patients, 25 mg intramuscular weekly during gastrointestinal exacerbation and 15 mg intramuscular weekly during remission are well-documented dosages. We prefer subcutaneous administration. Rheumatologists tend to start with an oral dose of 7.5 mg once weekly, eventually to be elevated to a maximum of 25 mg. Subcutaneous or parenteral administration is started with 10 mg once weekly, and, if necessary, increased to 25 mg once weekly. Fifty percent of dosages in patients with moderate renal insufficiency (creatinine clearance 40 to 70 mL/min). Supplementation of folic acid (0.5 mg three times a day) decreases side effects.
Contraindications	Renal failure. Pneumonial interstitial fibrosis due to methotrexate use. Hepatic enzyme elevation, alcoholism. Pregnancy. Bone marrow insufficiency.
Main drug interactions	Nonbound methotrexate can be increased by salicylates, sulfonamides, phenytoin, tetracycline, and, in particular, NSAIDs and cotrimoxazole. This leads to increased toxicity. Avoid use of the latter two when methotrexate greater than 10 mg weekly is used. Avoid (other) hepatotoxic agents.
Main side effects	Bone marrow suppression. Nausea and vomiting, diarrhea, ulcerative stomatitis. Tiredness and fever. Seldom, alopecia, gastrointestinal ulcerations, nephropathy, allergic pneumonitis (1%), cirrhosis (0.1%), cytopenias.
Special points	Regular monitoring of hemogram. Respiratory, renal, and hepatic function must be assessed; liver biopsy is only necessary when indicated. Carcinogenesis has not been proven for dosages used in these patients, but is likely, though at low risk. Methotrexate is teratogenic. It may potentiate infliximab efficacy [51].
Cost effectiveness	Not expensive, but long-term rheumatologic efficacy of axial disease is not without discussion [20].

NSAIDs/COX-2–specific inhibitors

Standard dosage	Many nonsteroidal prostaglandin synthesis inhibitors with equivalent efficacy are available. Gastrointestinal side effects are partially dependent on the type of prescribed NSAID, and COX-2–specific inhibitors seem superior regarding gastrointestinal side effects [14,15]. In IBD patients, NSAIDs and COX-2–specific inhibitors are contraindicated [17,18•].
Contraindications	Gastrointestinal bleeding. Cerebrovascular bleeding. Severe hepatic failure or (imminent) renal failure.

Main drug interactions	Prolongation of prothrombin time in case of anticoagulant use. Concomitant use of corticosteroids may potentiate gastrointestinal side effects. Increased nephrotoxicity with concurrent use of cyclosporine or diuretics. Angioedema.
Main side effects	Gastrointestinal discomfort and peptic ulceration [14,15,52]. Exacerbation of IBD. Induction of renal failure. Rash. Seldom, pancreatitis and hepatitis.
Special points	Superior efficacy or safety in IBD patients of COX-2–specific inhibitors is unlikely.
Cost effectiveness	In general, COX-2–specific inhibitors are more expensive than NSAIDs.

Third-line agents

Infliximab

Standard dosage	In rheumatologic practice, infliximab therapy is started at a dose of 3 mg/kg, to be repeated after 8 weeks, in combination with immunosuppressive drugs [51]. In our opinion, in Crohn's disease patients, 5 mg/kg in combination with an immunosuppressive is more appropriate [22••].
Contraindications	Multiple sclerosis. Heart failure. Sepsis, active infection, or abscess. Tuberculosis. Pregnancy or scheduled pregnancy in the first 6 months.
Main drug interactions	(Still) unknown.
Main side effects	Allergy and anaphylactic shock. Opportunistic infection, fever, headache, flu-like symptoms, and fatigue. Reactivation of (abdominal) tuberculosis.
Special points	Long-term safety is unknown. Increased risk of hematologic malignancy is still debated. Concomitant therapy of infliximab with immunosuppressive drugs seems to protect from antibody development and allergic reactions. Etanercept is also effective in rheumatoid arthritis, but not in Crohn's disease.
Cost effectiveness	Expensive.

Mycophenolate mofetil

Standard dosage	Oral dose of 2 g/d, which is effective after about 2 months [53].
Contraindications	Infections. (Intended) pregnancy.
Main drug interactions	Antacids and resins decrease bioavailability.
Main side effects	Gastrointestinal complaints. Cytopenias. Myalgia, fever. Increased risk of lymphoma and (cutaneous) malignancies.
Special points	Experimental in rheumatologic treatment.
Cost effectiveness	Expensive.

Emerging therapies

- Analogues of thalidomide, presumed to interfere with tumor necrosis factor α (TNF-α) production and with a more acceptable adverse events profile, are currently in development.
- Leflunomide, an inhibitor of pyrimidine synthesis, has potential as a disease-modifying drug in rheumatoid arthritis, but side effects are insufficiently examined, particularly in IBD patients [20,54].
- Pamidronate (and other bisphosphonates?) may be beneficial in treatment of rheumatologic EIM, but mechanism of action is obscure [23,24••].

Treatment of osteoporosis

Diet and lifestyle

- The diet should include sufficient vitamin D and calcium [55]. Western diet should contain 2.5 to 5 μg of vitamin D (150 to 200 IU) and 1 to 1.5 g of calcium (adults). Intake of these amounts can be impaired in patients with IBD due to lack of appetite, abdominal discomfort, and reduced intestinal function, particularly in Crohn's disease.
- In the absence of sunshine exposure, oral vitamin D requirement is 10 μg/d (400 IU/d), or tanning beds may be used [31]. High intake of vitamin A should be avoided [29].
- Regular physical exercise is able to maintain bone mineral density (BMD), or reduce the age-dependent decrease of BMD [30].
- Smoking and excessive alcohol intake (more than 4 units daily) increase the risk of bone fractures.

Pharmacologic treatment

- The aim of therapy in osteoporosis is prevention of bone fractures.
- When using corticosteroids in a dosage of at least 7.5 mg/d of a prednisolone equivalent, prophylaxis of bone loss is the treatment goal.
- More extensive description of agents that are rarely prescribed in IBD patients is presented in a prior issue of this journal [49].

First-line agents

Calcium

Standard dosage	Calcium is given orally as carbonate, citrate, phosphate, glubionate, gluconate, or lactate salt in a dose equivalent of 1 to 1.5 g before night, which is the equivalent of 4 to 5 daily dairy consumptions.
Contraindications	Hypercalcemia, hypercalciuria, renal failure.
Main drug interactions	Calcium interferes with the absorption of tetracycline and bisphosphonates; it forms insoluble calciumfluoride in combination with fluoride. An interval of at least 3 hours is recommended. Coadministration of vitamin D improves the intestinal absorption of calcium. Corticosteroids interfere with calcium absorption. High-dose calcium and vitamin D may interfere with the efficacy of calcium-channel blockers. Thiazide diuretics decrease the renal clearance of calcium.
Main side effects	Abdominal discomfort. Constipation. Flatulence. Hypercalcemia.
Special points	Calcium is prescribed to prevent further bone loss, in practice nearly always concomitantly with vitamin D. Combined use of calcium and vitamin D is effective to prevent bone loss in steroid-using patients [33]. In case of nephrolithiasis or hypercalciuria, dosage should be adapted and oral fluid intake must increase. In Crohn's disease patients, calcium may help to minimize hyperoxaluria.
Cost effectiveness	Calcium is moderately expensive.

Vitamin D

Standard dosage	The most commonly used vitamin D derivative is cholecalciferol 400 IU/d. The active vitamin D metabolites α-calcidol 0.25 μg/d or calcitriol 0.25 μg/d are other options, but need careful monitoring of blood calcium level. Parenteral use of vitamin D for the prevention of bone loss is seldom indicated.
Contraindications	Hypercalcemia. Hypermagnesemia. Hyperparathyroidism. Sarcoidosis.

Main drug interactions	Phenytoin and barbiturates are able to decrease vitamin D levels. Coadministration of magnesium (antacids, laxatives) may lead to hypermagnesemia, especially when kidney function is reduced. High-dose calcium and vitamin D may interfere with the effectiveness of calcium-channel blockers. Thiazide diuretics and vitamin D decrease the renal clearance of calcium.
Main side effects	Hypercalcemia.
Special points	Monotherapy with vitamin D appears insufficient to treat osteoporosis, notwithstanding one favorable study. Concomitant use of calcium is advisable. Vitamin D and calcium in steroid-using patients prevent to some extent bone loss. Vitamin D deficiency or osteomalacia occurs regularly in IBD and should be treated with calcitriol.
Cost effectiveness	Inexpensive.

Second-line agents

Bisphosphonates

Standard dosage	Oral, cyclic use of etidronate and continuous or weekly use of several other bisphosphonates prevents osteoporotic fractures. Comparative trials are sparsely available. Etidronate is prescribed for 14 days of 400 mg/d, followed by a 2.5-month period of calcium use at 500 mg/d. This 3-month cycle can be repeated. Alendronate and risedronate can be used in daily or weekly dosages. Pamidronate is also available for intravenous use (90 mg every 2 months) [35].
Contraindications	Hypocalcemia. Esophageal strictures or esophageal motility disturbances (achalasia).
Main drug interactions	Calcium-containing agents decrease the uptake of bisphosphonates. An interval of at least 3 hours is recommended.
Main side effects	Abdominal pain, dyspepsia, nausea, and flatulence. Esophagitis or esophageal ulcer. Psychic disturbances.
Special points	Pamidronate, etidronate, and alendronate have proven efficacy in steroid-induced osteoporosis. Alendronate has also proven efficacy in Crohn's disease-associated osteoporosis [56]. Intravenously administered pamidronate is an alternative, but zoledronic acid and clodronate can also be given intravenously.
Cost effectiveness	Moderately expensive, but cost effective.

Third-line agents

Hydrochlorthiazide

Standard dosage	Hydrochlorthiazide inhibits renal calcium excretion, and may thus improve calcium homeostasis. Its use should be restricted to patients with a high calcium excretion (>300 mg/24 h). The usual dosage varies from 25 to 50 mg/d.
Contraindications	Renal insufficiency. Liver cirrhosis with ascites. Hypersensitivity to sulphonamide derivatives.
Main drug interactions	Lithium clearance decreases. Sensitivity to insulin and oral antidiabetics may decrease. Concomitant use of corticosteroids increases renal potassium loss. It potentiates antihypertensives.
Main side effects	Hypopotassemia and other electrolyte disturbances. Increase of lipid concentration.
Special points	Use of thiazide diuretics in the treatment of osteoporosis is only indicated in case of hypercalciuria [57].
Cost effectiveness	Inexpensive.

Emerging therapies

- Hormonal regulation of bone metabolism is a productive field of research, and in addition to well-known modulation of bone metabolism by sex hormones (estrogens and androgens), bone-modifying properties of partial calcitonin agonists, growth hormone, and parathyroid hormone have been studied [58,59•,60]. Teriparatide (recombinant human parathyroid hormone) shows good promise [60].

- In addition, statins [58], and especially leptin, appear to be major players in regulation of bone metabolism [61]. This knowledge is expected to lead to new drug strategies.

Treatment of cutaneous manifestations

Diet and lifestyle

- There are no specific diet recommendations to prevent or improve cutaneous manifestations of IBD.

Pharmacologic treatment

- The aim of therapy is to relieve pain of cutaneous eruptions and to restore cutaneous integrity.

First-line agents: Erythema nodosum

Acetaminophen

Standard dosage As in rheumatologic complications (see previous).
Special points Rest and elevation of the affected limbs with compression therapy with short stretch bandages may be helpful (especially for pain relief).

NSAIDs/COX-2 inhibitors

Standard dosage As in rheumatologic complications (see previous).

Second-line agents

Oral corticosteroids

Standard dosage Initially high-dose prednisolone (1 mg/kg of body weight) in a tapering schedule.
Contraindications As in rheumatologic complications (see previous).
Main drug interactions As in rheumatologic complications (see previous).
Main side effects As in rheumatologic complications (see previous).
Special points Topical corticosteroids tend to fail, because erythema nodosum is an inflammatory response of the deep skin layers.
Cost effectiveness Inexpensive and often effective.

Colchicine

Standard dosage Usual dosage of 0.5 to 1 mg/d, to be decreased in case of renal or hepatic insufficiency due to the small therapeutic window.
Contraindications Moderate to severe renal or hepatic insufficiency.
Main drug interactions Cimetidine, erythromycin, and tolbutamide may increase plasma concentration of colchicine.
Main side effects Frequently, gastrointestinal complaints such as nausea, cramps, and diarrhea. During long-term use (and overdosage) alopecia, neuropathy, myopathy, agranulocytosis and aplastic anemia, and renal and hepatic toxicity have been described.
Special points Small therapeutic window. Colchicine may induce (reversible) malabsorption of vitamin B_{12}. The use of colchicine is mainly documented in Sweet's syndrome [42].
Cost effectiveness Inexpensive.

First-line agents: Pyoderma gangrenosum

Topical corticosteroids

Standard dosage	Topical corticosteroids rarely are sufficient, but when used, we prefer betamethason or betamethasondiproprionate 0.05%. We do not advocate intralesional injections, due to their potential to generate new lesions.
Contraindications	Infectious dermatitis. Ulcerative dermatitis.
Main drug interactions	None, unless systemic availability of corticosteroids increases.
Main side effects	Local cutaneous atrophy, teleangiectasia, striae, peristomal or periorbital dermatitis. At high dose, systemic side effects due to absorption may also occur.
Special points	Chronic use leads to dermal atrophy, especially of face, genitals, skin folds, and inner side of upper legs. Secondary infectious contamination of the wound needs supplementary antibiotic treatment.
Cost effectiveness	Inexpensive.

Oral corticosteroids

Standard dosage	As in erythema nodosum (see previous).
Contraindications	As in erythema nodosum (see previous).
Main drug interactions	As in erythema nodosum (see previous).
Main side effects	As in erythema nodosum (see previous).
Special points	Usually, pyoderma gangrenosum is a feature of patients with active ulcerative colitis. Secondary bacterial infection of the wound may need antibiotic treatment.
Cost effectiveness	Oral steroids are inexpensive.

Cyclosporine and tacrolimus

Standard dosage	Cyclosporine 5 mg/kg orally, divided in two doses daily, has been shown to be beneficial. Intravenously, cyclosporine is prescribed in a dose of 4 mg/kg, the equivalent of 12.5 mg/kg orally. Tacrolimus should be started at 0.1 mg/kg, also divided in two doses. Intravenously, initial dosage is 10% to 20% of the oral dose. Dosage should be adapted to blood trough levels: for cyclosporine 100 to 250 ng/mL, and for tacrolimus 10 to 20 ng/mL. Topical tacrolimus may also be considered at a concentration of 0.5% [39–41].
Contraindications	Renal insufficiency, hypertension, malignancies, and infections. Pregnancy.
Main drug interactions	Similar as in rheumatologic complications (see previous).
Main side effects	Similar as in rheumatologic complications. Tacrolimus may induce cardiomyopathy and glucose intolerance.
Special points	Cyclosporine is very effective in the treatment of pyoderma gangrenosum and induces remission in severe ulcerative colitis. Tacrolimus can be used topically, but cyclosporine cannot.
Cost effectiveness	Cyclosporine and tacrolimus are expensive drugs.

Infliximab

Standard dosage	Infliximab 5 mg/kg, to be repeated after 8 weeks in combination with immunosuppressive drugs.
Contraindications	As in IBD-associated spondyloarthropathy (see previous).
Main drug interactions	As in IBD-associated spondyloarthropathy (see previous).
Main side effects	As in IBD-associated spondyloarthropathy (see previous).
Special points	As in IBD-associated spondyloarthropathy (see previous).
Cost effectiveness	As in IBD-associated spondyloarthropathy (see previous).

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