

Management of arthropathy in inflammatory bowel diseases

Rosario Peluso, Francesco Manguso, Maria Vitiello, Salvatore Iervolino and Matteo Nicola Dario Di Minno

Ther Adv Chronic Dis

2015, Vol. 6(2) 65–77

DOI: 10.1177/
2040622314563929

© The Author(s), 2014.

Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: The most common extra-intestinal manifestation in patients with inflammatory bowel disease (IBD) is articular involvement, with a prevalence ranging between 17% and 39%. It is frequently characterized by an involvement of the axial joints but may also be associated with peripheral arthritis. The target of therapy in the management of arthritis associated with IBD is to reduce the inflammation and prevent any disability and/or deformity. This requires active cooperation between gastroenterologist and rheumatologist. The treatment of axial involvement has focused on the combination of exercise with nonsteroidal anti-inflammatory drugs. Immunomodulators have been efficacious in patients with peripheral arthritis and other extra-intestinal manifestations, but they are not effective for the treatment of axial symptoms of spondylitis. Tumor necrosis factor (TNF) α inhibitors have been proven to be highly effective in the treatment of IBD patients which are steroid-dependent or refractory to conventional therapy and in patients with associated articular manifestations. The treatment of peripheral involvement and/or enthesitis and/or dactylitis is based on local steroid injections, while sulfasalazine and/or low doses of systemic steroids may be useful in case of inadequate response to intra-articular steroids. Sulfasalazine induces only a little improvement in peripheral arthritis. Immunomodulators such as methotrexate, azathioprine, cyclosporine and leflunomide show their efficacy in some patients with peripheral arthritis and other extra-intestinal components. TNF- α inhibitors should be considered the first-line therapeutic approach when moderate-to-severe luminal Crohn's disease or ulcerative colitis is associated with polyarthritis. The aim of this review is to provide a fair summary of current treatment options for the arthritis associated with IBD.

Keywords: enteropathic arthritis, inflammatory bowel disease, TNF- α inhibitors

Introduction

Rheumatic manifestations have been described in patients with inflammatory bowel disease (IBD) for many years, but it was only in the late 1950s that the arthritis occurring in IBD patients was made distinct from classic rheumatoid arthritis (RA) [Steinberg and Storey, 1957; Bywaters and Ansell, 1958; McBride *et al.* 1963; Stewart and Ansell, 1963]. In 1964, the American Rheumatism Association classified arthritis occurring in IBD as an independent clinical form [Blumberg *et al.* 1964] and later Wright and Moll included enteropathic arthritis (EA) definitively in the spondyloarthritis (SpA) group [Wright and Moll, 1976].

The most common extra-intestinal manifestation in IBD patients is articular involvement, with a

prevalence ranging between 17 and 39%. It is frequently characterized by an involvement of the axial joints, but may also be associated with peripheral arthritis such as synovitis and/or dactylitis and/or enthesopathy [Peluso *et al.* 2013b].

The spectrum of axial involvement ranges from inflammatory lower back pain with or without radiological evidence of sacroiliitis (sometimes asymptomatic) to spondylitis characterized by the classic clinical and radiologic features of the idiopathic ankylosing spondylitis (AS). The onset of axial involvement often precedes the onset of IBD and is not influenced by bowel surgery [Baeten *et al.* 2002].

The peripheral arthritis was categorized by Orchard and colleagues at the end of 1990s as

Correspondence to:

Rosario Peluso, MD, PhD
Rheumatology Research
Unit, Department of
Clinical Medicine and
Surgery, University
Federico II, Via Sergio
Pansini 5, 80131 Naples,
Italy

rosario.peluso2@unina.it

Francesco Manguso, MD, PhD
Complex Operating Unit of
Gastroenterology, AORN
'A. Cardarelli', Naples,
Italy

Maria Vitiello, MD
Rheumatology Research
Unit and Department
of Clinical Medicine
and Surgery, University
Federico II, Naples, Italy

Salvatore Iervolino, MD
Rheumatology and
Rehabilitation Research
Unit 'Salvatore Maugeri'
Foundation, Telesse Terme
(BN), Italy

Matteo Nicola Dario Di Minno, MD
Department of Clinical
Medicine and Surgery,
University Federico II,
Naples, Italy

two subtypes: type 1, the pauci-articular form (acute and self-limited, which may precede the diagnosis of IBD, generally running parallel to the intestinal disease); and type 2, the polyarticular form (with symptoms lasting for months or years, independently from IBD [Orchard *et al.* 1998]. Moreover, Smale and colleagues have supposed another type of peripheral arthritis (type 3) that includes patients with both axial and peripheral forms [Smale *et al.* 2001]; its onset was more recently studied by our research group [Peluso *et al.* 2012] using magnetic resonance imaging (MRI), an imaging technique usually accepted to evaluate the peripheral [Soscia *et al.* 2009; Amrami, 2012] and axial involvement of SpA [Lambert *et al.* 2009]. MRI may be useful for the early diagnosis of EA, or when there are not findings with conventional X-ray examination.

Moreover, the clinical spectrum of EA is also characterized by several extra-articular (intestinal) manifestations such as skin and mucous membrane lesions, eye involvement, genitourinary inflammation and cardiac complaints [Peluso *et al.* 2014]. Erythema nodosum and pyoderma gangrenosum are described as the most common cutaneous manifestations occurring in 10–25% of IBD patients [Ampuero *et al.* 2014]. Interestingly, in association with active bowel disease, family history of IBD, appendectomy, cigarette smoking, they are potential risk factors for arthritis in IBD patients [Manguso *et al.* 2004, 2005]. Acute anterior uveitis, aortic insufficiency and cardiac conduction disturbances are described with a frequency of 25%, 4–10% and 3–9%, respectively [Peluso *et al.* 2014]. They seem to be related to disease duration, axial joint involvement and to HLA-B27 positivity [Bergfeldt, 1997]. In addition, some data clearly suggest that IBD patients, as well as those with SpA [Di Minno *et al.* 2012a; 2012b], show an increased cardiovascular and thrombotic risk [Yarur *et al.* 2011]. A frequent occurrence of metabolic syndrome is also documented in IBD, particularly in ulcerative colitis (UC) [Yorulmaz *et al.* 2011]. Finally, renal and/or urinary involvement occurs in a range between 4 and 23%, and urolithiasis is the most common urogenital manifestation (12–28%) [Oikonomou *et al.* 2011].

The target of therapy in the management of arthritis associated with IBD is to reduce the inflammation and to prevent the disability and/or deformity; this requires an active cooperation between gastroenterologist and rheumatologist.

Nevertheless, when IBD and SpA coexist, the therapeutic strategy should be modulated, taking into account the variable manifestations of IBD in terms of intestinal and extra-intestinal features, and the clinical manifestations of SpA with particular attention to peripheral enthesitis and dactylitis [Olivieri *et al.* 2014].

The aim of this review is to provide a fair summary of current treatment options for the arthritis associated with IBD.

Methods

PubMed (National Library of Medicine) was the main electronic database that was searched, using the search terms ‘arthritis’ and ‘spondyloarthritis’ in combination with ‘treatment’. Similar separate searches were made with ‘Crohn’s disease’ and ‘ulcerative colitis’ in combination with ‘treatment’ to ensure that no articles were missed. Search limits included links to full text only, humans, English language articles, males and females, and all adult ages. The ‘Related Articles’ function of PubMed was used to crosscheck for any additional relevant studies. There was no restriction set on how far back the literature was cited, but the studies that were generated were primarily from the 1980s to the present. Titles and abstracts identified in the broad search were examined, and the studies were included in the review if they were directly relevant to IBD and one of the trigger areas. Retrieved articles were also reviewed for relevant citations. Research studies published only in abstract form were excluded. Finally, each article was then reviewed for quality and clinical relevance.

Management of axial involvement

The treatment of axial involvement in SpA has focused on the combination of exercise with non-steroidal anti-inflammatory drugs (NSAIDs) (Table 1) [Dougados *et al.* 2002]. Traditional NSAIDs or selective COX-2 inhibitors (COXIBs) improve spinal pain and stiffness in the axial subset, although radiographic progression ankylosis may occur. Nevertheless, considering the activity of the intestinal disease in IBD patients, the use of traditional NSAIDs should be avoided in the treatment of axial symptoms, due to the probability of exacerbation of bowel inflammation, particularly in UC patients [Kaufman *et al.* 1996]. Likewise, therapy with COXIBs is not recommended because there are no data about their use

Table 1. Therapy of arthritis associated with inflammatory bowel disease (IBD).

Axial involvement and active IBD	Axial involvement and IBD in remission	Peripheral involvement and IBD	Peripheral involvement and IBD in remission
Physical activity	Physical activity	Local (type 1) or systemic (type 2) steroids	Local (type 1) or systemic (type 2) steroids
TNF- α inhibitors	NSAIDs/COXIBs TNF- α inhibitors	Sulfasalazine TNF- α inhibitors	NSAIDs/COXIBs Sulfasalazine TNF- α inhibitors

COXIBs, selective inhibitors of COX-2; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumour necrosis factor.

in active IBD. Theoretically, COXIBs could have deleterious effects on the bowel in patients with IBD [O'Brien, 2000], but some studies have shown that COXIBs improve the severity of experimental colitis and the endoscopic relapse compared with placebo [Smale *et al.* 2001; Sandborn *et al.* 2006]. Despite the worry of a potential worsening of bowel inflammation with NSAIDs or COXIBs, rheumatologists have used these drugs successfully in patients with IBD. However, if symptoms and/or signs of bowel inflammation develop or worsen during the use of NSAIDs or COXIBs treatment it is prudent to discontinue their use [Voulgari, 2011]. As a consequence, in order to manage joint symptoms, these drugs are recommended for patients with mild exacerbations but their use should be limited to the lowest effective dose and only for short periods of time.

Rest and physical therapy have been indicated as important additional treatments in the therapy of spondylitis in IBD patients. Physical therapy is important to improve the spinal mobility and to prevent deformities of the spine with subsequent respiratory compromise and disability. Breathing exercises, spinal exercises and swimming should be preferred. However, a recent systematic review showed that there is limited evidence to indicate that controlled physical therapy may be better than individualized home programs [Dagfinrud *et al.* 2005].

Corticosteroids are used in short-term treatment or intermittent pulsing therapy at large doses in moderate-to-severe nonresponsive cases of IBD [Dignass *et al.* 2010], but they are often ineffective in controlling axial symptoms of spondylitis [Braun *et al.* 2011].

Sulfasalazine has been shown to be useful both in the chronic management treatment of bowel

disease and in flare-ups of UC, but the effectiveness on Crohn's disease (CD) is not well proven [Nikfar *et al.* 2009]. Sulfasalazine has no effect on the evolution of joint damage to severe forms of arthritis and its usefulness in the axial subset is marginal. In fact, in a combined analysis of patients with SpA, sulfasalazine produced better treatment response rates, compared with placebo, in patients with peripheral arthritis than in those with exclusively axial disease [Clegg *et al.* 1999]. Finally, sulfasalazine does not seem to prevent the possible onset of intestinal inflammation in patients with SpA [Ferraz *et al.* 1990]. An earlier report indicated that the sulfapyridine component of sulfasalazine is responsible for the drug's toxicity such as cyanosis, transient reticulocytosis, frank hemolysis and vomiting [Das *et al.* 1973]. Regarding serious blood disorders, there has been an earlier report of neutropenia due to sulfasalazine [Hopkinson *et al.* 1989]. In addition, sulfasalazine-associated thrombocytopenia has been reported in arthritis patients [Farr *et al.* 1989; McKenna and Burrows, 1994]. Finally, Ransford and colleagues reported that interstitial nephritis and pancreatitis constituted only the 3% of reports for sulfasalazine [Ransford and Langman, 2002].

Methotrexate, the second most commonly used immunosuppressive agent for IBD, has been used as an effective treatment in CD [van Dieren *et al.* 2006], but the evidence is less robust in UC, for which results of supplementary studies are pending (METEOR in Europe and MERIT in the United States of America) [Carbonnel, 2011]. With regard to axial involvement, efficacy is not well recognized. Responses to methotrexate in spondylitis have shown a modest efficacy in peripheral subsets, with little improvement noted in axial involvement [Ostendorf *et al.* 1998]. Recently, in a study conducted on AS patients

who received oral methotrexate at a dose of 10 mg weekly or placebo for 24 weeks, methotrexate did not result in any significant improvement in the disease activity scores or spinal metrology scores compared with patients receiving placebo [Roychowdhury *et al.* 2002]. A potential new indication of methotrexate in EA could be combination therapy with tumor necrosis factor (TNF) α inhibitors, but data in the literature are lacking and further studies are needed. Interestingly, several gastroenterologists prefer subcutaneous administration for the potential erratic oral bioavailability in CD; however, there is very little on specific methotrexate bioavailability data in CD. Finally, methotrexate is thought to be safe and tolerable. Nausea can occur in 15% of patients, but can typically be prevented by co-administration of folate. Leukopenia, hepatotoxicity, hypersensitivity pneumonitis and opportunistic infections have been reported but are uncommon. Methotrexate is teratogenic and should never be used in pregnant women or those contemplating pregnancy [Regueiro, 2000; Feagan and Alfadhli, 2004]. The incidence of hepatotoxicity of methotrexate in patients with IBD is thought to be significantly lower than that in patients with other SpA. Although methotrexate-induced hepatotoxicity can occur in patients with IBD, this risk is likely low in properly selected patients (not obese, regular alcohol users, having fatty liver or other pre-existing liver disease).

With regard to other immunomodulators, azathioprine, 6-mercaptopurine, cyclosporine and leflunomide have been efficacious in patients with peripheral arthritis and other extra-intestinal manifestations [De Keyser *et al.* 2000; Haibel *et al.* 2005], but they are not effective for the treatment of axial symptoms of spondylitis. However, these results should be interpreted with caution because there are not controlled studies that have confirmed their efficacy; these data belong to uncontrolled studies or case reports. Moreover, dose-independent or hypersensitivity reactions have been described with use of these drugs. In particular, hepatitis, pneumonitis, arthritis and fever have been reported in IBD patients treated with azathioprine and 6-mercaptopurine. Perhaps the most serious dose-independent reaction is pancreatitis, occurring in 4% of patients [Chaparro *et al.* 2013]. This side effect generally occurs early in the course of therapy and typically resolves with discontinuation of the drug. Minor side effects such as nausea, vomiting and flu-like illness are

possible and typically well tolerated in most IBD patients [Cummings *et al.* 2008]. Serious opportunistic infections are possible, as with any immunosuppressant agents, but are uncommon [Katz, 2005; Khan *et al.* 2011]. With regard to the development of cancer, and in particular of lymphoma, following the use of these therapies, a recent meta-analysis [Kandiel *et al.* 2005] concluded that IBD-patients have a four-fold increased risk of lymphoma, but whether this increase was due to the medication or to the underlying disease could not be established.

Cyclosporine is generally considered to be less safe than other IBD therapies because of the risk of serious side effects such as anaphylaxis, seizure, pneumocystis carinii pneumonia and permanent nephrotoxicity [Katz, 2005]. Moreover, potential easy use is limited by the need for close monitoring of drug serum levels because there is a narrow gap between the therapeutic and the toxic ranges [Cohen *et al.* 1999]. Therefore, cyclosporine is typically reserved as a rescue agent for severe, refractory disease.

TNF- α inhibitors have been proven to be highly effective in the treatment of IBD patients who are steroid-dependent or refractory to conventional therapy, and in patients with associated articular manifestations. Therefore, in active but not complicated CD associated with axial involvement, therapy with TNF- α inhibitors is recommended, excluding etanercept, which has been reported to be ineffective in CD [Sandborn *et al.* 2001]. Moreover, etanercept is a possible triggering factor for new onset of CD [Haraoui and Krelenbaum, 2009]. Indeed, a recent meta-analysis showed that, compared with infliximab, etanercept is rarely, although more frequently, associated with IBD activity in patients affected by AS [Braun *et al.* 2007]. However, etanercept has been demonstrated to be effective in the treatment of joint symptoms in IBD patients [Marzo-Ortega *et al.* 2003].

Infliximab is the best studied among TNF- α inhibitors in IBD; it is strongly effective in moderate-to-severe CD and UC, promoting fistula closure, mucosal healing and sparing use of steroids [Present *et al.* 1999; Hanauer *et al.* 2002; Sandborn *et al.* 2009]. There is also evidence that infliximab is effective for axial involvement in EA [van den Bosch *et al.* 2000; Herfarth *et al.* 2002; Generini *et al.* 2004]. Induction and maintenance doses for infliximab should be those that are effective for both diseases: 5 mg/kg at weeks 0, 2 and 6,

and then every 8 weeks [Dignass *et al.* 2010; Orlando *et al.* 2011].

Adalimumab is also efficacious in inducing and maintaining remission in moderate-to-severe CD [Devlin and Panaccione, 2008] and in treatment of spondylitis [van der Heijde *et al.* 2006; Lichtiger *et al.* 2010]. Adalimumab was described to be useful against the short- and long-term effects on disease signs and symptoms in AS. Moreover, in patients with axial involvement, a reduction of signs and symptoms of sacroiliitis is also described with its use. The efficacy of adalimumab in AS is mainly sustained by the results of a recent multicenter study that showed that the response for most patients treated with adalimumab was better than that observed in patients treated with placebo [Lichtiger *et al.* 2010]. No published studies have addressed yet the effect of switching from infliximab to adalimumab in EA [Atzeni *et al.* 2009]. Induction and maintenance doses should be effective for both diseases: 160 mg at week 0, 80 mg at week 2 and then 40 mg every 2 weeks [Dignass *et al.* 2010; Orlando *et al.* 2011].

Golimumab has been demonstrated to be effective in the improvement of sign and symptoms in patients with AS [Inman *et al.* 2008] and in maintaining clinical response in patients with moderate-to-severe active UC [Sandborn *et al.* 2014]. Its safety profile was consistent with that reported for other TNF- α inhibitors. Moreover, AS patients treated with golimumab, with no syndesmophytes and less systemic inflammation at baseline, had considerably less radiographic progression [Braun *et al.* 2014].

Patients with axial involvement, in a persistent and stable remission, have a high probability of relapse of articular disease; in these patients TNF- α inhibitors should be continued [Braun *et al.* 2011; van der Heijde *et al.* 2011]. The possibility of reducing TNF- α inhibitors doses according to SpA treatment recommendations [Braun *et al.* 2011; van der Heijde *et al.* 2011] may be considered in CD patients with prolonged and stable clinical, radiological, endoscopic and biochemical remission [Olivieri *et al.* 2014]. Moreover, TNF- α inhibitors should be started when NSAIDs are insufficient to control axial symptoms. The choice of a specific TNF- α inhibitor should be influenced by the possible effect on underlying IBD [Olivieri *et al.* 2014].

While there are several studies on novel biologics in the treatment of other SpA, data for the use of

these agents in EA are lacking. Although certolizumab is approved for the treatment and the maintenance of response in moderate-to-severe CD with an inadequate response to conventional therapy in the US, there are no data on its utility in the therapy of EA. The recommended dosing for induction is 400 mg subcutaneously at weeks 0, 2 and 4, and then every 4 weeks for maintenance of response. Studies evaluating the efficacy of infliximab, adalimumab and certolizumab have usually shown similar results but no studies have directly compared these agents. Preliminary data suggest that certolizumab can be effective in patients who respond to infliximab and then become nonresponders or intolerant to it [Hanauer *et al.* 2010; Sandborn *et al.* 2010].

Ustekinumab has been demonstrated to have clinical efficacy in CD and may be useful in patients refractory to infliximab [Sandborn *et al.* 2008]. Abatacept was in theory useful in IBD, but a preliminary study evaluating this drug in CD patients was stopped because of a lack of efficacy [Mozaffari *et al.* 2014]. Rituximab has demonstrated to be useful in the treatment of RA patients and it is theorized to be effective in IBD. Nevertheless, there are some case reports where worsening or development of IBD during rituximab treatment has been reported [Goetz *et al.* 2007; Ardelean *et al.* 2010]. Tocilizumab has been demonstrated to have clinical efficacy in RA patients who do not respond to TNF- α inhibitors [Genovese *et al.* 2008]. Although interleukin-6 (IL-6) may be important for healing mucosal lesions in the gut [Tebbutt *et al.* 2002], tocilizumab is associated with intestinal ulcers and perforation [Nishimoto *et al.* 2010] and therefore cannot be recommended as an ideal choice for treatment of EA. Natalizumab and vedolizumab were effective in the treatment of moderate-to-severe active CD and UC [McLean *et al.* 2012; Sakuraba *et al.* 2013], but have not been studied in SpA.

The use of biologics is generally considered to be safe and tolerable. However, a risk-benefit analysis should be undertaken when considering their potential for serious complications [Peluso *et al.* 2013a]. The immunosuppressive effect of currently used biologic agents leads to an increased risk of specific infections during therapy. Most commonly, these infections arise from the upper respiratory tract and the urinary tract. In a recent study on CD patients treated with biologics, an infectious adverse event occurred in about 40% of

patients. Less than 3% of patients showed a serious infectious adverse event [Colombel *et al.* 2007]; severe infections during TNF- α inhibitor therapy include the reactivation of latent tuberculosis [Sanduzzi *et al.* 2012]. These patients should be treated with chemoprophylaxis (e.g. isoniazid for 6 months, during which TNF- α inhibitors can be introduced). Moreover, the development of antibodies to infliximab or to adalimumab is frequently observed in patients treated with biologics. It was associated with a shorter duration of response to therapy and a higher rate of infusion reactions [Baert *et al.* 2003]. The overall percentage of infusion reactions with TNF- α inhibitors was 6.1% and included a burning sensation, itching, erythema and pain, while injection site reactions, attributed to local irritation, were observed in about 4% [Colombel *et al.* 2007; Sandborn *et al.* 2007].

TNF- α plays a role in apoptosis and tumor suppression; it is believed that interference with these pathways can potentially lead to an increased risk of malignancies. The odds ratio for all types of cancer was 3.3 in a pooled analysis of both CD and RA patients receiving TNF- α inhibitors [Bongartz *et al.* 2006]. Neurological disorders following treatment with TNF- α inhibitors have been described. In a review of the Adverse Events Reporting System of the United States of America Food and Drug Administration (FDA), 90 cases of demyelinating events were reported following administration of TNF- α inhibitors [Mohan *et al.* 2001]. Abnormal liver function, such as cholestatic disease and hepatitis-like syndromes, are associated with TNF- α inhibitor treatment [Menghini and Arora, 2001; Moum *et al.* 2007]. Mildly elevated liver enzymes do occur and stopping TNF- α inhibitor treatment is recommended when these increases exceed three times the upper limit of normal in the case of alanine aminotransferase. Abnormal liver function tests generally return to normal after discontinuation of TNF- α inhibitor therapy. Moreover, this therapy can lead to an increase in the rate of heart failure with an increased risk of death. Therefore, its use is contraindicated in patients with class III–IV New York Heart Association congestive heart failure.

Management of peripheral involvement

The treatment of peripheral oligo-articular involvement (type 1) and/or enthesitis and/or dactylitis is based on local steroid injections, while sulfasalazine and/or low doses of systemic steroids

may be useful in cases of inadequate response to intra-articular steroids (Table 1) [Ritchlin *et al.* 2009; Gossec *et al.* 2012]. Moreover, as oligo-articular involvement can parallel the course of bowel disease, treatment of IBD may resolve the arthritis. In fact, in UC patients, colectomy may be an effective treatment for IBD and may be efficacious also for articular involvement, in particular for type 1 peripheral arthritis. Nevertheless, there are case reports of arthritis developing *de novo* after proctocolectomy for UC, particularly with ileo-pouch anal anastomosis, in the setting of pouchitis [Balbir-Gurman *et al.* 2001; Abi Karam *et al.* 2003].

NSAIDs and COXIBs, with a short-term course (no more than 2 weeks), are usually prescribed to control peripheral arthritis (type 1 and 2) in quiescent IBD, but their use should be avoided in case of active bowel disease. Moreover, low doses of both systemic steroids and COXIBs may be considered as a ‘bridge therapy’ to oral sulfasalazine [Olivieri *et al.* 2014]. It is important to remember that steroids are not indicated to maintain remission from IBD. Additionally, intra-articular steroid injection into the affected joints provides rapid but only temporary relief.

The choice of disease-modifying antirheumatic drugs (DMARDs) depends on the activity of IBD and their efficacy in the management of articular manifestations should be considered.

Sulfasalazine induces only a little improvement in peripheral arthritis (type 1 and 2). It is better when used in patients with active bowel disease and if they are employed in UC rather than CD. Consequently, sulfasalazine (2–3 g/day) is indicated in the case of mild-to-moderate IBD with peripheral articular involvement and early disease (<5 years) in cases of failure of local injections of steroids [Olivieri *et al.* 2014]. Aminosalicylates were found to be of little benefit for peripheral arthritis and enthesitis [Thomson *et al.* 1994]. Moreover, sulfasalazine or mesalazine should be continued regardless of other systemic treatments used, considering their efficacy in maintaining clinical remission [Sutherland and Macdonald, 2006] and their possible chemopreventive effect on colorectal cancer [Velayos *et al.* 2006].

Immunomodulators such as methotrexate, azathioprine, cyclosporine and leflunomide show their efficacy in some patients with peripheral arthritis (type 1 and 2) and other extra-intestinal

components [De Keyser *et al.* 2000; Padovan *et al.* 2006; Peluso *et al.* 2013b]. Methotrexate has greater utility in CD than in UC for gut inflammation; further evaluation is ongoing in two randomized multicenter trials (METEOR in Europe and MERIT in the United States of America) [Carbonnel, 2011]. Methotrexate, which has long-standing use in RA, may be beneficial for arthropathy in IBD as well as for IBD itself. Recently, our research group has been studying the efficacy and the tolerability of methotrexate at a dose of 20 mg/week in patients with peripheral arthritis under UC. We have shown a rapid and effective reduction of joint symptoms with significant improvement in laboratory parameters and in rates of disease activity [Peluso *et al.* 2009].

Many rheumatologists use methotrexate in patients with IBD and peripheral arthritis. Moreover, methotrexate can be preferred to azathioprine, but this is an empirical approach not based on trial evidence [Williams *et al.* 2008]. Orally administered methotrexate is adequately absorbed, even in patients with active IBD. Subcutaneous injection of the drug can reduce gastrointestinal side effects.

TNF- α inhibitors have been found to be highly effective for IBD patients who are steroid dependent or refractory to conventional treatments, particularly for CD, and they are useful in patients with associated articular involvement [van den Bosch *et al.* 2000; Generini *et al.* 2004; Rispo *et al.* 2005].

Infliximab, an important progress in the treatment of IBD with or without concomitant arthropathy [Barrie and Regueiro, 2007], rapidly improves peripheral arthritis in IBD patients. At the beginning of the 2000s some authors reported, in open-label studies, an improvement in peripheral arthritis in IBD patients treated with infliximab at 5 mg/kg; these patients had previously been refractory to steroids, 6-mercaptopurine, azathioprine or methotrexate [Ellman *et al.* 2001; Herfarth *et al.* 2002; Kaufman *et al.* 2005].

In the following years, Generini and colleagues confirmed that infliximab has been proven to be highly effective on the inflammation of the entheses and of periarticular structures in patients with CD, temporarily inducing and maintaining the remission of bowel disease. Consequently, infliximab has a good efficacy on all the articular manifestations of the disease, in addition to the well-known positive

effect on IBD [Generini *et al.* 2004]. Recently, a randomized controlled study confirmed infliximab as an effective therapy for bowel manifestations in UC patients with moderate–severe intestinal disease. There are no data about its efficacy on articular manifestations in course of UC [Järnerot *et al.* 2005]. Therefore, on the basis of available data, it seems that most IBD patients with active intestinal inflammation and concurrent peripheral arthritis are likely to experience an improvement in their joint symptoms after receiving infliximab.

The efficacy of adalimumab in the treatment of inflammatory rheumatic disease such as RA, SpA and AS is well known, but no published studies have yet addressed the effect of switching from infliximab to adalimumab in patients with CD and associated arthritis. Recently, in a study on CD patients having associated arthritis who discontinued infliximab (because of intolerance or loss of efficacy) the clinical response to adalimumab was evaluated: it successfully controlled both articular and intestinal disease activity [Järnerot *et al.* 2005].

Etanercept can control the arthritis associated with CD, but it has no effect on bowel disease itself [Marzo-Ortega *et al.* 2003]. There are no data on the efficacy of golimumab and other novel biologic agents in the treatment of peripheral arthropathy associated to IBD.

In conclusion, TNF- α inhibitors should be considered the first-line therapeutic approach when moderate-to-severe luminal CD or UC are associated with polyarthritis (Table 2). The choice of a specific TNF- α inhibitor should be influenced by the possible effect on underlying bowel disease. In cases of severe activity of UC, the patients should be hospitalized and treated with systemic intravenous steroids and infliximab as rescue therapy [Monterubbiansi *et al.* 2014] in association with a daily consultation with a surgeon [Olivieri *et al.* 2014]. Moreover, in cases of prolonged and stable remission for patients with both peripheral and intestinal manifestations, given the high probability of articular involvement relapse, TNF- α inhibitors should be continued [Olivieri *et al.* 2014]. The possibility of reducing TNF- α inhibitor doses according to SpA treatment recommendations [Braun *et al.* 2011; van der Heijde *et al.* 2011] may be taken into account in CD or UC patients with prolonged and stable clinical, radiological, endoscopic and biochemical remissions [Olivieri *et al.* 2014].

Table 2. When to start treatment with TNF- α inhibitors.

Axial involvement	Persistently high disease activity (BASDAI >4) Failure at least two NSAIDs
Peripheral involvement	Failure of local or systemic steroids Failure of DMARDs
Enthesitis/dactylitis	In severe case or after failure of traditional therapy.
Poor prognostic factor risk	High CRP/ESR bone edema at MRI
Active inflammatory bowel disease	Moderate or severe form in case of fail to respond at least one DMARDs
Inflammatory bowel disease complicated by abdominal abscess or stricture	Abdominal surgery before starting TNF- α inhibitors

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drug; TNF, tumour necrosis factor.

Conclusion

Although arthropathy is a common feature in patients with IBD, there are few studies specifically examining the treatment of arthritis in IBD. Therefore, the management of patients with SpA requires active cooperation between gastroenterologist and rheumatologist. The use of corticosteroids and/or DMARDs and/or of TNF- α inhibitors, helpful to contain intestinal inflammation, usually also leads to the reduction of peripheral type 1 arthritis symptoms, which also respond well to rest, to physical therapy and to local steroid injections. On the contrary, the management of types 2 and 3 is more complex and they may persist despite the reduction of IBD. Our experience suggests that the majority of patients respond promptly to anti-inflammatory drugs, useful to control joint and entheses inflammation [Peluso *et al.* 2013b]. However, they do not stop the development of joint damage and, at the same time, they may also be responsible for important side effects on the bowel, such as the exacerbation of IBD. As a consequence, in order to manage joint symptoms, these drugs are recommended for patients with mild exacerbations but their use should be limited to the lowest effective dose and only for short periods of time. Sulfasalazine is often used for the treatment of IBD and its effectiveness is also confirmed for the management of mild peripheral arthritis, particularly in patients with UC [Dissanayake and Truelove, 1973]. Its effectiveness in CD has not yet been well proven. These drugs have no effect on the evolution of joint damage to severe forms of arthritis and their usefulness in the axial subset is marginal; they do not seem to prevent the possible onset of bowel inflammation in patients with SpA [Ferraz

et al. 1990]. Immunomodulators such as methotrexate, azathioprine, cyclosporine and leflunomide show their efficacy in some patients with peripheral arthritis and other extra-intestinal components [De Keyser *et al.* 2000; Padovan *et al.* 2006; Peluso *et al.* 2013b]. TNF- α inhibitors are highly effective in the treatment of SpA [Atteno *et al.* 2010; Baraliakos and Braun, 2012; Bruner *et al.* 2014]. In IBD patients, they have been shown to be successful in moderate-active disease, not only against IBD but also for the SpA component (axial and peripheral), and particularly in patients with CD, although these drugs show several side effects [Peluso *et al.* 2013a]. Finally, advances in the understanding of the molecular basis of CD and UC have led to the development of promising new biologic therapies, which will likely be studied further both as monotherapeutic agents, and for use in combination with immunomodulators.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Abi Karam, G., Awada, H., Nasr, F. and Uthman, I. (2003) Ileal pouchitis and arthritis. *Semin Arthritis Rheum* 33: 215.
- Ampuero, J., Rojas-Feria, M., Castro-Fernández, M., Cano, C. and Romero-Gómez, M. (2014). Predictive

- factors for erythema nodosum and pyoderma gangrenosum in inflammatory bowel disease. *J Gastroenterol Hepatol* 29(2): 291–295.
- Amrami, K. (2012). Imaging of the seronegative spondyloarthropathies. *Radiol Clin North Am* 50: 841–854.
- Ardelean, D., Gonska, T., Wires, S., Cutz, E., Griffiths, A., Harvey, E. *et al.* (2010) Severe ulcerative colitis after rituximab therapy. *Pediatrics* 126: 243–246.
- Atteno, M., Peluso, R., Costa, L., Padula, S., Iervolino, S., Caso, F. *et al.* (2010) Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol* 29: 399–403.
- Atzeni, F., Ardizzone, S., Bertani, L., Antivalle, M., Batticciotto, A. and Sarzi-Puttini, P. (2009) Combined therapeutic approach: inflammatory bowel diseases and peripheral or axial arthritis. *World J Gastroenterol* 15: 2469–2471.
- Baert, F., Noman, M., Vermeire, S., van Assche, G., D’Haens, G., Carbonez, A. *et al.* (2003) Influence of immunogenicity on the long-term efficacy of infliximab in Crohn’s disease. *N Engl J Med* 348: 601–608.
- Baeten, D., De Keyser, K., Mielants, H. and Veys, E. (2002) Ankylosing spondylitis and bowel disease. *Best Pract Res Clin Rheumatol* 16: 537–549.
- Balbir-Gurman, A., Schapira, D. and Nahir, M. (2001) Arthritis related to ileal pouchitis following total proctocolectomy for ulcerative colitis. *Semin Arthritis Rheum* 30: 242–248.
- Baraliakos, X. and Braun, J. (2012) Biologic therapies for spondyloarthritis: what is new? *Curr Rheumatol Rep* 14: 422–427.
- Barrie, A. and Regueiro, M. (2007) Biologic therapy in the management of extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 13: 1424–1429.
- Bergfeldt, L. (1997) HLA-B27-associated cardiac disease. *Ann Intern Med* 127: 621–629.
- Blumberg, B., Bunim, J., Calkins, E., Pirani, C. and Zvaifler, N. (1964) Aranomenclature and classification of arthritis and rheumatism (tentative). *Arthritis Rheum* 7: 93–97.
- Bongartz, T., Sutton, A., Sweeting, M., Buchan, I., Matteson, E. and Montori, V. (2006) Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 295: 2275–2285.
- Braun, J., Baraliakos, X., Hermann, K., Deodhar, A., van der Heijde, D., Inman, R. *et al.* (2014) The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. *Ann Rheum Dis* 73: 1107–1113.
- Braun, J., Baraliakos, X., Listing, J., Davis, J., van der Heijde, D., Haibel, H. *et al.* (2007) Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. *Arthritis Rheum* 57: 639–647.
- Braun, J., van den Berg, R., Baraliakos, X., Boehm, H., Burgos-Vargas, R., Collantes-Estevez, E. *et al.* (2011) 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 70: 896–904.
- Bruner, V., Atteno, M., Spanò, A., Scarpa, R. and Peluso, R. (2014) Biological therapies for spondyloarthritis. *Ther Adv Musculoskelet Dis* 6: 92–101.
- Bywaters, E. and Ansell, B. (1958) Arthritis associated with ulcerative colitis; a clinical and pathological study. *Ann Rheum Dis* 2: 169–183.
- Carbonnel, F. (2011) Methotrexate: a drug of the future in ulcerative colitis? *Curr Drug Targets* 12: 1413–1416.
- Chaparro, M., Ordás, I., Cabré, E., Garcia-Sanchez, V., Bastida, G., Peñalva, M. *et al.* (2013) Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. *Inflamm Bowel Dis* 19: 1404–1410.
- Clegg, D., Reda, D. and Abdellatif, M. (1999) Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the seronegative spondylarthropathies: a Department of Veterans Affairs cooperative study. *Arthritis Rheum* 42: 2325–2329.
- Cohen, R., Stein, R. and Hanauer, S. (1999) Intravenous cyclosporine in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 94: 1587–1592.
- Colombel, J., Sandborn, W., Rutgeerts, P., Enns, R., Hanauer, S., Panaccione, R. *et al.* (2007) Adalimumab for maintenance of clinical response and remission in patients with Crohn’s disease: the CHARM trial. *Gastroenterology* 132: 52–65.
- Cummings, J., Keshav, S. and Travis, S. (2008) Medical management of Crohn’s disease. *BMJ* 336: 1062–1066.
- Dagfinrud, H., Kvien, T. and Hagen, K. (2005) The Cochrane review of physiotherapy interventions for ankylosing spondylitis. *J Rheumatol* 32: 1899–1906.
- Das, K., Eastwood, M., McManus, J. and Sircus, W. (1973) Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 289: 491–495.

- De Keyser, F., Van Damme, N., De Vos, M., Mielants, H. and Veys, E. (2000) Opportunities for immune modulation in the spondyloarthropathies with special reference to gut inflammation. *Inflamm Res* 49: 47–54.
- Devlin, S. and Panaccione, R. (2008) Adalimumab for the treatment of Crohn's disease. *Expert Opin Biol Ther* 8: 1011–1019.
- Dignass, A., Van Assche, G., Lindsay, J., Lemann, M., Soderholm, J., Colombel, J. *et al.* (2010) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 4: 28–62.
- Di Minno, M., Iervolino, S., Lupoli, R., Russolillo, A., Coppola, A., Peluso, R. *et al.* (2012a) Cardiovascular risk in rheumatic patients: the link between inflammation and atherothrombosis. *Semin Thromb Hemost* 38: 497–505.
- Di Minno, M., Iervolino, S., Peluso, R., Scarpa, R. and Di Minno, G. (2012b) Platelet reactivity and disease activity in subjects with psoriatic arthritis. *J Rheumatol* 39: 334–336.
- Dissanayake, A. and Truelove, S. (1973) A controlled therapeutic trial of long term maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin). *Gut* 12: 923–926.
- Dougados, M., Dijkmans, B., Khan, M., Maksymowych, W., van der Linden, S. and Brandt, J. (2002) Conventional treatments for ankylosing spondylitis. *Ann Rheum Dis* 61(Suppl 3): iii40–iii50.
- Ellman, M., Hanauer, S., Sitrin, M. and Cohen, R. (2001) Crohn's disease arthritis treated with infliximab: an open trial in four patients. *J Clin Rheumatol* 7: 67–71.
- Farr, M., Tunn, E., Symmons, D., Scott, D. and Bacon, P. (1989) Sulphasalazine in rheumatoid arthritis: haematological problems and changes in haematological indices associated with therapy. *Br J Rheumatol* 28: 134–138.
- Feagan, B. and Alfadhli, A. (2004) Methotrexate in inflammatory bowel disease. *Gastroenterol Clin North Am* 33: 407–420.
- Ferraz, M., Tugwell, P., Goldsmith, C. and Atra, E. (1990) Meta-analysis of sulfasalazine in ankylosing spondylitis. *J Rheumatol* 17: 1482–1486.
- Generini, S., Giacomelli, R., Fedi, R., Fulminis, A., Pignone, A., Frieri, G. *et al.* (2004) Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. *Ann Rheum Dis* 63: 1664–1669.
- Genovese, M., McKay, J., Nasonov, E., Mysler, E., Da Silva, N., Alecock, E. *et al.* (2008) Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* 58: 2968–2980.
- Goetz, M., Atreya, R., Ghalibafian, M., Galle, P. and Neurath, M. (2007) Exacerbation of ulcerative colitis after rituximab salvage therapy. *Inflamm Bowel Dis* 13: 1365–1368.
- Gossec, L., Smolen, J., Gaujoux-Viala, C., Ash, Z., Marzo-Ortega, H., van der Heijde, D., FitzGerald, O. *et al.* (2012) European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 71: 4–12.
- Haibel, H., Rudwaleit, M., Braun, J. and Sieper, J. (2005) Six months open label trial of leflunomide in active ankylosing spondylitis. *Ann Rheum Dis* 64: 124–126.
- Hanauer, S., Feagan, B., Lichtenstein, G., Mayer, L., Schreiber, S., Colombel, J. *et al.* (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 359: 1541–1549.
- Hanauer, S., Panes, J., Colombel, J., Bloomfield, R., Schreiber, S. and Sandborn, W. (2010) Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. *Aliment Pharmacol Ther* 32: 384–393.
- Haraoui, B. and Krelbaum, M. (2009) Emergence of Crohn's disease during treatment with the anti-tumor necrosis factor agent etanercept for ankylosing spondylitis: possible mechanisms of action. *Semin Arthritis Rheum* 39: 176–181.
- Herfarth, H., Obermeier, F., Andus, T., Rogler, G., Nikolaus, S., Kuehbacher, T. *et al.* (2002) Improvement of arthritis and arthralgia after treatment with infliximab (Remicade) in a German prospective, open-label, multicenter trial in refractory Crohn's disease. *Am J Gastroenterol* 97: 2688–2690.
- Hopkinson, N., Saiz Garcia, F. and Gumpel, J. (1989) Haematological side-effects of sulphasalazine in inflammatory arthritis. *Br J Rheumatol* 28: 414–417.
- Inman, R., Davis, J., Jr, Heijde, D., Diekmann, L., Sieper, J., Kim, S. *et al.* (2008) Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis Rheum* 58: 3402–3412.
- Jarnerot, G., Hertvig, E., Friis-Liby, I., Blomquist, L., Karlen, P., Granno, C. *et al.* (2005) Infliximab as rescue therapy in severe to moderately ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 128: 1805–1811.
- Kandiel, A., Fraser, A., Korelitz, B., Brensinger, C. and Lewis, J. (2005) Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 54: 1121–1125.

- Katz, S. (2005) Update in medical therapy of ulcerative colitis: newer concepts and therapies. *J Clin Gastroenterol* 39: 557–569.
- Kaufman, H., Fischer, A., Carroll, M. and Becker, J. (1996) Colonic ulceration associated with nonsteroidal anti-inflammatory drugs. Report of three cases. *Dis Colon Rectum* 39: 705–710.
- Kaufman, I., Caspi, D., Yeshurun, D., Dotan, I., Yaron, M. and Elkayam, O. (2005) The effect of infliximab on extraintestinal manifestations of Crohn's disease. *Rheumatol Int* 25: 406–410.
- Khan, K., Dubinsky, M., Ford, A., Ullman, T., Talley, N. and Moayyedi, P. (2011) Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Am J Gastroenterol* 106: 630–642.
- Lambert, R., Pedersen, S., Maksymowych, W., Chiowchanwisawakit, P. and Østergaard, M. (2009) Active inflammatory lesions detected by magnetic resonance imaging in the spine of patients with spondyloarthritis – definitions, assessment system and reference image set. *J Rheumatol* 36(Suppl. 84): 3–17.
- Lichtiger, S., Binion, D., Wolf, D., Present, D., Bensimon, A., Wu, E. *et al.* (2010) The CHOICE trial: adalimumab demonstrates safety, fistula healing, improved quality of life and increased work productivity in patients with Crohn's disease who failed prior infliximab therapy. *Aliment Pharmacol Ther* 32: 1228–1239.
- Manguso, F., Sanges, M., Staiano, T., Gargiulo, S., Nastro, P., Gargano, D. *et al.* (2004) Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis. *Am J Gastroenterol* 99: 327–334.
- Manguso, F., Staiano, T., Astarita, C., Scarpa, R., Peluso, R., Gargano, D. *et al.* (2005) Consecutive occurrence of rhinoconjunctivitis, seronegative spondyloarthritis and pyoderma gangrenosum in a patient with ulcerative colitis. *Int J Colorectal Dis* 20: 79–80.
- Marzo-Ortega, H., McGonagle, D., O'Connor, P. and Emery, P. (2003) Efficacy of etanercept for treatment of Crohn's related spondyloarthritis but not colitis. *Ann Rheum Dis* 62: 74–76.
- McBride, J., King, M., Baikie, A., Crean, G. and Sircus, W. (1963) Ankylosing spondylitis and chronic inflammatory diseases of the intestines. *Br Med J* 2: 483–486.
- McKenna, K. and Burrows, D. (1994) Leucopenia, thrombocytopenia and lymphadenopathy associated with sulphasalazine. *Clin Exp Dermatol* 19: 419–420.
- McLean, L., Shea-Donohue, T. and Cross, R. (2012) Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. *Immunotherapy* 4: 883–898.
- Menghini, V. and Arora, A. (2001) Infliximab-associated reversible cholestatic liver disease. *Mayo Clin Proc* 76: 84–86.
- Mohan, N., Edwards, E., Cupps, T., Oliverio, P., Sandberg, G., Crayton, H. *et al.* (2001) Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 44: 2862–2869.
- Monterubbiansi, R., Aratari, A., Armuzzi, A., Daperno, M., Biancone, L., Cappello, M. *et al.* (2014) Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: early and late outcome and predictors of colectomy. *J Crohns Colitis* 8: 852–858.
- Moum, B., Konopski, Z., Tufteland, K. and Jahnsen, J. (2007) Occurrence of hepatotoxicity and elevated liver enzymes in a Crohn's disease patient treated with infliximab. *Inflamm Bowel Dis* 13: 1584–1586.
- Mozaffari, S., Nikfar, S., Abdolghaffari, A. and Abdollahi, M. (2014) New biologic therapeutics for ulcerative colitis and Crohn's disease. *Expert Opin Biol Ther* 14: 583–600.
- Nikfar, S., Rahimi, R., Rezaie, A. and Abdollahi, M. (2009) A meta-analysis of the efficacy of sulfasalazine in comparison with 5-aminosalicylates in the induction of improvement and maintenance of remission in patients with ulcerative colitis. *Dig Dis Sci* 54: 1157–1170.
- Nishimoto, N., Ito, K. and Takagi, N. (2010) Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions. *Mod Rheumatol* 20: 222–232.
- O'Brien, J. (2000) Nonsteroidal anti-inflammatory drugs in patients with inflammatory bowel disease. *Am J Gastroenterol* 95: 1859–1861.
- Oikonomou, K., Kapsoritakis, A., Eleftheriadis, T., Stefanidis, I. and Potamianos, S. (2011) Renal manifestations and complications of inflammatory bowel disease. *Inflamm Bowel Dis* 17: 1034–1045.
- Olivieri, I., Cantini, F., Castiglione, F., Felice, C., Gionchetti, P., Orlando, A. *et al.* (2014) Italian Expert Panel on the management of patients with coexisting spondyloarthritis and inflammatory bowel disease. *Autoimmun Rev* 13: 822–830.
- Orchard, T., Wordsworth, B. and Jewell, D. (1998) Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 42: 387–391.
- Orlando, A., Armuzzi, A., Papi, C., Annese, V., Ardizzone, S., Biancone, L. *et al.* (2011) The Italian Society of Gastroenterology (SIGE) and the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: the use of

- tumor necrosis factor- α antagonist therapy in inflammatory bowel disease. *Dig Liver Dis* 43: 1–20.
- Ostendorf, B., Specker, C. and Schneider, M. (1998) Methotrexate lacks efficacy in the treatment of severe ankylosing spondylitis compared with rheumatoid and psoriatic arthritis. *J Clin Rheumatol* 4: 129–136.
- Padovan, M., Castellino, G., Govoni, M. and Trotta, F. (2006) The treatment of the rheumatological manifestations of the inflammatory bowel diseases. *Rheumatol Int* 26: 953–958.
- Peluso, R., Atteno, M., Iervolino, S., Bruner, V., Caso, F., Costa, L. *et al.* (2009) Methotrexate in the treatment of peripheral arthritis in ulcerative colitis. *Reumatismo* 61: 15–20.
- Peluso, R., Cafaro, G., Di Minno, A., Iervolino, S., Ambrosino, P., Lupoli, G. *et al.* (2013a). Side effects of TNF- α blockers in patients with psoriatic arthritis: evidences from literature studies. *Clin Rheumatol* 32: 743–753.
- Peluso, R., Di Minno, M., Bruner, V., Soscia, E., Castiglione, F., Manguso, F. *et al.* (2012) Discovertebral erosions in patients with enteropathic spondyloarthritis. *J Rheumatol* 39: 2332–2340.
- Peluso, R., Di Minno, M., Iervolino, S., Manguso, F., Tramontano, G., Ambrosino, P. *et al.* (2013b). Enteropathic spondyloarthritis: from diagnosis to treatment. *Clin Dev Immunol* 2013: 631408.
- Peluso, R., Iervolino, S., Vitiello, M., Bruner, V., Ambrosino, P., Manguso, F. *et al.* (2014) Articular and other immune-mediated extra-intestinal manifestations in inflammatory bowel diseases. *Eur J Inflamm* 12: 251–259.
- Present, D., Rutgeerts, P., Targan, S., Hanauer, S., Mayer, L., van Hogezaand, R. *et al.* (1999) Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 340: 1398–1405.
- Ransford, R. and Langman, M. (2002) Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the committee on safety of medicines. *Gut* 51: 536–553.
- Regueiro, M. (2000) Update in medical treatment of Crohn's disease. *J Clin Gastroenterol* 31: 282–291.
- Rispo, A., Scarpa, R., Di Girolamo, E., Cozzolino, A., Lembo, G., Atteno, M. *et al.* (2005) Infliximab in the treatment of extra-intestinal manifestations of Crohn's disease. *Scand J Rheumatol* 34: 387–391.
- Ritchlin, C., Kavanaugh, A., Gladman, D., Mease, P., Helliwell, P., Boehncke, W. *et al.* (2009) Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis* 68: 1387–1394.
- Roychowdhury, B., Bintley-Bagot, S., Bulgen, D., Thompson, R., Tunn, E. and Moots, R. (2002) Is methotrexate effective in ankylosing spondylitis? *Rheumatology* 41: 1330–1332.
- Sakuraba, A., Keyashian, K., Correia, C., Melek, J., Cohen, R., Hanauer, S. and Rubin, D. (2013) Natalizumab in Crohn's disease: results from a US tertiary inflammatory bowel disease center. *Inflamm Bowel Dis* 19: 621–626.
- Sandborn, W., Abreu, M., D'Haens, G., Colombel, J., Vermeire, S., Mitchev, K. *et al.* (2010) Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. *Clin Gastroenterol Hepatol* 8: 688–695.
- Sandborn, W., Feagan, B., Fedorak, R., Scherl, E., Fleisher, M., Katz, S. *et al.* (2008) A randomized trial of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 135: 1130–1141.
- Sandborn, W., Feagan, B., Marano, C., Zhang, H., Strauss, R., Johanns, J. *et al.* (2014) Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 146: 96–109.
- Sandborn, W., Feagan, B., Stoinov, S., Honiball, P., Rutgeerts, P., Mason, D. *et al.* (2007) Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 357: 228–238.
- Sandborn, W., Hanauer, S., Katz, S., Safdi, M., Wolf, D., Baerg, R. *et al.* (2001) Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 121: 1088–1094.
- Sandborn, W., Rutgeerts, P., Feagan, B., Reinisch, W., Olson, A., Johanns, J. *et al.* (2009) Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 137: 1250–1260.
- Sandborn, W., Stenson, W., Brynskov, J., Lorenz, R., Steidle, G., Robbins, J. *et al.* (2006) Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. *Clin Gastroenterol Hepatol* 4: 203–211.
- Sanduzzi, A., Bocchino, M., Atteno, M., Costa, L., Ponticiello, A., Matarese, A. *et al.* (2012) Screening and monitoring of latent tubercular infection in patients taking tumor necrosis factor- α blockers for psoriatic arthritis. *J Rheumatol* 89: 82–85.
- Smale, S., Natt, R., Orchard, T., Russell, A. and Bjarnason, I. (2001) Inflammatory bowel disease and spondylarthropathy. *Arthritis Rheum* 44: 2728–2736.
- Soscia, E., Scarpa, R., Cimmino, M., Atteno, M., Peluso, R., Sirignano, C. *et al.* (2009) Magnetic resonance imaging of nail unit in psoriatic arthritis. *J Rheumatol* 83: 42–45.

- Steinberg, V. and Storey, G. (1957) Ankylosing spondylitis and chronic inflammatory lesions of the intestines. *Br Med J* 2: 1157–1159.
- Stewart, J. and Ansell, B. (1963) Ankylosing spondylitis associated with regional enteritis. *Gastroenterology* 45: 265–268.
- Sutherland, L. and Macdonald, J. (2006) Oral 5-aminosalicylic acid formaintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2: CD000544.
- Tebbutt, N., Giraud, A., Inglese, M., Jenkins, B., Waring, P., Clay, F. *et al.* (2002) Reciprocal regulation of gastrointestinal homeostasis by SHP2 and STAT-mediated trefoil gene activation in gp130 mutant mice. *Nat Med* 8: 1089–1097.
- Thomson, G., McKibbin, C. and Inman, R. (1994) Mesalamine therapy in Reiter's syndrome. *J Rheumatol* 21: 570–572.
- Van den Bosch, F., Kruithof, E., Vos, M., Keyser, F. and Mielants, H. (2000) Crohn's disease associated with spondyloarthropathy: effect of TNF- α blockade with infliximab on articular symptoms. *Lancet* 356: 1821–1822.
- Van der Heijde, D., Kivitz, A., Schiff, M., Sieper, J., Dijkmans, B., Braun, J. *et al.* (2006) Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 54: 2136–2146.
- Van der Heijde, D., Sieper, J., Maksymowych, W., Dougados, M., Burgos-Vargas, R., Landewe, R. *et al.* (2011) 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 70: 905–908.
- Van Dieren, J., Kuipers, E., Samsom, J., Nieuwenhuis, E. and van der Woude, C. (2006) Revisiting the immunomodulators tacrolimus, methotrexate, and mycophenolate mofetil: their mechanisms of action and role in the treatment of IBD. *Inflamm Bowel Dis* 12: 311–327.
- Velayos, F., Loftus, E., Jr, Jess, T., Harmsen, W., Bida, J., Zinsmeister, A. *et al.* (2006) Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology* 130: 1941–1949.
- Voulgari, P. (2011) Rheumatological manifestations in inflammatory bowel disease. *Ann Gastroenterol* 24: 173–180.
- Williams, H., Walker, D. and Orchard, T. (2008) Extraintestinal manifestations of inflammatory bowel disease. *Curr Gastroenterol Rep* 10: 597–605.
- Wright, V. and Moll, J. (1976) *Seronegative Polyarthritits*. Amsterdam: North Holland Publishing Company.
- Yarur, A., Deshpande, A., Pechman, D., Tamariz, L., Abreu, M. and Sussman, D. (2011) Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. *Am J Gastroenterol* 106: 741–747.
- Yorulmaz, E., Adali, G., Yorulmaz, H., Ulasoglu, C., Tasan, G. and Tuncer, I. (2011) Metabolic syndrome frequency in inflammatory bowel diseases. *Saudi J Gastroenterol* 17: 376–382.