Anti-TNF alpha therapy in the management of extraintestinal manifestation of inflammatory bowel disease

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Abstract. – Inflammatory bowel disease, Crohn’s disease and ulcerative colitis, are immune-mediated disorders of unknown etiology that primarily affect the gastrointestinal tract. In addition, other organ systems can be involved such as joint/bones, skin, eyes, hepatobiliary tract, lungs and kidney. Overall, they represent extraintestinal manifestations of inflammatory bowel disease and may present before, in conjunction or after the onset of bowel disease. Extraintestinal manifestations are observed in 20-40% of patients and frequently have a negative impact on quality of patients’ life. Some extraintestinal manifestations such as arthritis, erythema nodosum, pyoderma gangrenosum, iritis, uveitis have a pathogenic tumor necrosis factor alpha-dependent mechanism common with Crohn’s disease and ulcerative colitis. Early recognition and treatment of extraintestinal manifestations can minimize potential severe complications. In this review we provide an overview on the prevalence and clinical aspects of the more commonly reported extraintestinal manifestations of Crohn’s disease and ulcerative colitis and the role of tumor necrosis factor alpha inhibitors in their treatment.

Key Words: Extraintestinal manifestations, Inflammatory bowel disease, Anti TNF-α agents.

Introduction

Crohn’s disease (CD) and ulcerative colitis (UC), should be considered as systemic diseases as they are associated with clinical manifestations involving the organs outside the alimentary tract. Inflammatory bowel diseases (IBD) are associated with a variety of extraintestinal manifestations (EIMs) which have observed in up to 20-40% of patients. The development of one EIM appears to increase the risk of developing a second EIM and few studies have specifically examined whether an EIM is a patient’s symptom at the time of diagnosis or it occurs later in the disease course. The resolution of most of EIMs is not always related to the parallel resolution of IBD activeness in terms of timing. EIMs frequently affect joints, skin, eyes and the biliary tract, but sometimes they can produce small bowel dysfunctions (cholelithiasis, nephrolithiasis and obstructive uropathy) or are non specific disorders (osteoporosis, hepatobiliary disease and amyloidosis). Treatment of EIMs is often empirical. The first step is to determine whether or not intestinal disease activity is responsible for the EIM, which could direct subsequent management. The acute development of EIM in CD, even if intestinal disease activity is low, is an indication for systemic corticosteroid therapy in clinical practice, but this should be limited to topical use (eyedrops, cutaneous or intra-articular injections) or short-term treatment, given their toxicity. Other immunosuppressive agents, such as thiopurines, methotrexate, cyclosporine, tacrolimus can be considered as alternative treatments. The advent of biologic therapy, such as tumor necrosis factor alpha (TNF-α) inhibitors (infliximab, adalimumab, certolizumab pegol), represents a new approach able to modify the patient’s clinical course. This review focuses on the role of anti TNF-α therapy in some of the IBD-related EIMs. We have separated the EIMs into ocular, skin and joint manifestations.

Ocular Manifestations

Ophthalmologic manifestations have been reported to occur in up to 12% of patients according to the published literature and these compli-
cations seem to occur more frequently in CD patients. Up to 68% of patients with ophthalmic complications also have at least one other extraintestinal complication, with arthritis and ankylosing spondylitis (AS) being frequently associated with the IBD-associated uveitis, particularly in IBD patients who are HLA-B27 positive. The ocular complications appear to be independent of the extent of bowel involvement and often occur in early years of IBD.

**Episcleritis and Scleritis**

Inflammation of the episclera is the most common complication of IBD and develop in up to 29% of patients. It has been reported to be closely related to intestinal IBD activity and often resolves with treatment of the underlying disease. It may be diffuse or nodular unilateral or bilateral and it is more commonly present in women. Scleritis is a less frequent, but a potentially more serious occurrence, and has been reported to occur with a prevalence of 18% in IBD patients, although IBD patients account for only 2% of cases of scleritis. Most reported cases are of diffuse or nodular anterior scleritis. It may be associated with peripheral corneal infiltrates or limbal guttering.

**Corneal Involvement**

Corneal involvement is uncommon in IBD, although it may complicate episcleritis or scleritis. It is characterized by small, irregular, nodular sub-epithelial corneal infiltrates located 2-3 mm inside the limbus. The infiltrates may coalesce into peripheral opacities with corneal haze, thickening of the epithelium and associated pannus. Peripheral corneal thinning may also occur and cause visual deterioration through progressive astigmatism.

**Uveitis**

Uveitis is the most commonly diagnosed ocular manifestation of IBD, as episcleritis generally has a mild self-limiting course and patients typically do not require treatment. Uveitis has been reported in up to 17% of patients with IBD. It has been reported that 2% of uveitis patients have IBD and that IBD is responsible for 15% of cases of uveitis associated with a systemic disorder. Women with IBD are at a higher risk of developing uveitis than men, and uveitis is strongly related to sacro-iliac joint abnormalities, arthritis and HLA-B27 positivity. Posterior uveitis is a recognized complication of IBD and chorioretinitis was described in 10% of patients in one series.

**Retinal Complications**

The overall prevalence of posterior segment manifestations is low, at less than 1% in patients with IBD, but serious visual loss can result from the vitritis and retinal ischemia associated with retinal vasculitis. Central and branch retinal vein occlusions, cystoids macular oedema, multifocal central serous retinophaty, serous retinal detachments, choroidal folds and macular haemorrhages have all been reported in patients with IBD.

**Neuro-Ophthalmic Complications**

Optic neuritis is the most common type of optic neuropathy encountered in IBD and optic disk oedema has been reported as occurring in 4% of patients with ocular complications of IBD. Retrobulbar neuritis, papillitis and neuroretinitis have all been described in IBD and may be associated with iritis, vitritis, retinal vasculitis, and choroiditis.

**Anti TNF-α Therapies (Table I)**

Anti-tumor necrosis factor drugs have important effects on anergic regulatory T cells, restoring their capacity to inhibit cytokine production and convey a suppressive phenotype to effector T-cells. The three main anti-tumour necrosis factor drugs currently available are infliximab (a mouse-human chimeric anti-TNF antibody), etanercept (a recombinant human TNF receptor blocker) and adalimumab (a recombinant human anti-TNF antibody). Infliximab results to be effective for acute and chronic uveitis, in particular it appears to be helpful in patients with ocular disease refractory to other immunosuppressants. Kahn et al, in a retrospective study, observed that 17 children with refractory uveitis have a favorable response to infliximab, with 13 of the 17 patients having no ocular inflammation after only 2 infusions. Shuler et al performed a prospective trial investigating infliximab for the treatment of refractory autoimmune uveitis. They studied the effects of infliximab loading dose regimen on 23 cases of uveitis. At week 10, 18 patients had responded to treatment based on a composite clinical assessment. Moreover, 7 of 14 patients who went on receiving infliximab for 1 year continued to benefit from therapy. Adalimumab also appears to be effective for immune-mediated ocular disease based on a published retrospective study in which 16 of 18 juvenile idiopathic arthritis patients with associated eye disease had significantly fewer relapses of uveitis upon initiation of treatment.
may develop multiple dermatologic manifestations along the natural course of their IBD 23. Erythema nodosum (EN) and pyoderma gangrenosum (PG) are the most common cutaneous manifestations associated with IBD, presenting in 3%-20% and 0.5%-20% of patients, respectively 24-26.

**Erythema Nodosum**

Erythema nodosum (EN) is the most common cutaneous manifestation associated with IBD. Women are affected more commonly than men. EN is believed to be a delayed hypersensitivity reaction, identified in approximately 40% of patients. However, in most patients, the manifestation is without an apparent cause 27. Lesions deep red, tender, warm, and around nodules (1-5 cm diameter) distributed symmetrically over the anterior lower legs. Occasionally, they appear on the trunk, upper extremities, and face. EN typically is associated with exacerbation of the IBD but not with the severity or extent. The diagnosis may be secured on the characteristic clinical appearance. The differential diagnosis of EN includes other types of panniculitis, cutaneous infections, and subcutaneous lymphomas 27.

**Pyoderma Gangrenosum**

Pyoderma gangrenosum (PG) is an immune-mediated inflammatory condition that is characterized by the unpredictable development of chronic ulcerative skin lesions, commonly on the lower extremities 28. It occurs in approximately 1-5% of patients with IBD and may bear no rela-
TNF-α inhibitors for IBD-related EIMs

tion to the clinical activity of the intestinal disease\textsuperscript{29,30}. Conversely, up to 36-50% of patients with PG have IBD. The pathogenesis of PG is unknown. Reports of cell-mediated, humoral, and complement abnormalities as well as immune complex deposition in patients with PG and association of PG with other immunological disorders, suggest than an aberrant immune system is central to disease pathogenesis\textsuperscript{29}.

Antithrombin therapy (Table II)

Table II. Studies on anti-TNF alpha therapy in IBD-related skin manifestations.

<table>
<thead>
<tr>
<th>Autor</th>
<th>RCT/open label/case report</th>
<th>N° Patients</th>
<th>Anti-TNFα</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan MH, et al.\textsuperscript{32}</td>
<td>Case report</td>
<td>2 patients with CD and pyoderma gangrenosum and 1 patient with CD and psoriasis</td>
<td>Infliximab</td>
<td>Effective in the treatment of pyoderma gangrenosum and psoriasis associated with CD</td>
</tr>
<tr>
<td>Regueiro M, et al.\textsuperscript{29}</td>
<td>Multicenter retrospective study</td>
<td>13 patients with moderate to severe pyoderma gangrenosum and IBD</td>
<td>Infliximab</td>
<td>Effective for IBD-associated pyoderma gangrenosum</td>
</tr>
<tr>
<td>Sapienza MS, et al.\textsuperscript{33}</td>
<td>Case report</td>
<td>4 patients with active fistulizing CD and pyoderma gangrenosum</td>
<td>Infliximab</td>
<td>Rapid healing of pyoderma gangrenosum within 4 weeks of the first infusion in all patients</td>
</tr>
<tr>
<td>Hubbard VG, et al.\textsuperscript{36}</td>
<td>Case report</td>
<td>A young man with 3 years history of pyoderma gangrenosum</td>
<td>Infliximab and Adalimumab</td>
<td>Cutaneous and extracutaneous pyoderma gangrenosum cleared with infliximab and adalimumab</td>
</tr>
<tr>
<td>Brooklyn TN, et al.\textsuperscript{34}</td>
<td>RCT</td>
<td>30 patients with pyoderma gangrenosum, 19 of them with associated-IBD</td>
<td>Infliximab</td>
<td>After randomisation, 13 patients received infliximab and 17 patients received placebo. At week 2, significantly more patients in the infliximab group had improved (46% (6/13)) compared with the placebo group (6% (1/17); ( p = 0.025 )). Overall, 29 patients received infliximab with 69% (20/29) demonstrating a beneficial clinical response. Remission rate at week 6 was 21% (6/29). There was no response in 31% (9/29) of patients. Adalimumab as an alternative for use in severe PG that failed conventional therapy or in patients with adverse reactions or lack of response to infliximab.</td>
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<tr>
<td>Pomerantz R, et al.\textsuperscript{37}</td>
<td>Case report</td>
<td>A 61 years old woman with IBD, inflammatory arthritis and pyoderma gangrenosum</td>
<td>Infliximab and Adalimumab</td>
<td>Rapid improvement of the PG lesions in all patients 19/23 patients with erythema nodosum at baseline healed at week 20 (( p &lt; 0.001 )). 2/4 patients at baseline with pyoderma gangrenosum healed at week 20</td>
</tr>
<tr>
<td>Carinanos I, et al.\textsuperscript{38}</td>
<td>Case report</td>
<td>4 patients with IBD and pyoderma gangrenosum</td>
<td>Adalimumab</td>
<td>Rapid improvement of the PG lesions in all patients 19/23 patients with erythema nodosum at baseline healed at week 20 (( p &lt; 0.001 )). 2/4 patients at baseline with pyoderma gangrenosum healed at week 20</td>
</tr>
<tr>
<td>Lofberg R, et al.\textsuperscript{22}</td>
<td>Open label trial</td>
<td>23 patients with CD and erythema nodosum and 4 patients with CD and pyoderma gangrenosum</td>
<td>Adalimumab</td>
<td>Rapid improvement of the PG lesions in all patients 19/23 patients with erythema nodosum at baseline healed at week 20 (( p &lt; 0.001 )). 2/4 patients at baseline with pyoderma gangrenosum healed at week 20</td>
</tr>
</tbody>
</table>
ings, leg elevation, and rest may be sufficient. For severe cases, glucocorticoids may be applied. Infliximab has been reported to be successful in treating severe or refractory lesions. A multicenter retrospective study of medically refractory PG patients reports a positive response to infliximab. The mechanism of action is in line with the putative involvement of immune-mediated mechanisms in the pathogenesis of PG and with the premise that long-term management of PG involves suppression of inflammatory processes. In the study by Tan et al, two patients with refractory Crohn’s fistula and PG had a dramatic improvement shortly after the first infusion with infliximab. In the study by Sapienza et al, it has been reported a dramatic response of PG lesions of four patients with Crohn’s disease when treated with infliximab. It has been supposed that the rapid response to infliximab in these patients is the result of blunted T cell activation early in the inflammatory cascade. This may lead to a decrease in neutrophil infiltration and tissue destruction. In a multicenter, randomized, placebo-controlled trial by Brooklyn et al, 30 patients with PG were enrolled, 19 of whom also had IBD. Patients received infliximab (5 mg/kg of body weight) or placebo infusions at week 0 and were evaluated for response, defined as physician and patients assessment of the appearance of the lesion based upon reduction in size, depth, and degree of undermining at 2, 4, and 6 weeks. At week 2, subjects in both arms were offered open-label infliximab (5 mg/kg). Two week after the initial infusion, 6 of 13 (46%) patients, treated with infliximab had a response, compared with one of 17 (6%) who received placebo ($p = 0.025$). The majority of patients (20 of 29, 69%) who then received open-label infusions of infliximab had a positive response by week 6. There was no difference in response between PG patients who had underlying IBD and those who did not. Additional evidence in favor of infliximab and adalimumab for IBD-associated mucocutaneous disease has been derived from clinical study of psoriasis. Etanercept has also been successfully used in same cases of PG without underlying IBD. However, the value of a molecule that has less effect on digestive disease in CD-associated PG is still controversial. A case report described a first patient with idiopathic PG who responded to adalimumab after prior failure of etanercept and had an anaphylactic reaction to infliximab. Pomerantz et al reported a case of a 61-year-old woman with an history of IBD, inflammatory arthritis, and pyoderma gangrenosum treated initially with etanercept, with response only of bowel disease and related-arthritis. Because of the progression of pyoderma gangrenosum, she had been treated with infliximab with rapid improvement of cutaneous lesions, but infliximab treatment was discontinued when the patient developed a systemic reaction. She was then initiated on adalimumab with further improvement of cutaneous lesions. Cariñanos et al observed good clinical response to adalimumab in four patients affected by IBD (3 CD and 1 UC) and pyoderma gangrenosum. All patients were refractory to conventional therapy (steroids and/or cyclosporine) and infliximab was previously attempted in two of them but had to be discontinued because of loss of response and acute infusion reaction, respectively. The results of CARE study (Crohn’s Treatment with Adalimumab: Patients Response to a Safety and Efficacy Study) showed that 19 of 23 patients with erythema nodosum at baseline healed at week 20 ($p < 0.001$) and that 2 of 4 patients at baseline with pyoderma gangrenosum healed at week 20.

**Joint Manifestations**

Joint complaints are the most common EIMs in IBD patients, as they are prone to develop both peripheral and axial arthropathy. Classically, inflammatory arthritis is defined by pain, an increase in local temperature, and joint swelling with or without effusion, leading to decrease joint mobility. IBD-related arthropathy is part of a subset of diseases broadly termed “seronegative spondyloarthropathies”. In addition to IBD-related arthritis, this category includes psoriatic arthritis, reactive arthritis, and idiopathic ankylosing spondylitis (AS). IBD-related arthritis occurs equally in males and females and is generally more common in patients with colonic disease than those with small-bowel disease. In addition, arthritis is more common in CD with colonic involvement than UC and is more common in UC with pancolitis than isolated left-sided disease. Peripheral arthropathy occurs in 10-20% of IBD patients, typically presents in large joint, and is often further characterized as pauciarticular, asymmetrical, and migratory. IBD-related peripheral arthropathy has a recurring nature, often flaring with bowel disease relapse. Therefore, medical or surgical treatment of colitis is usually associated with improvement in peripheral arthri-
Anti TNF-α Therapies (Table III)

In type I peripheral arthritis treatment should concentrate on the active disease and include steroids, immunomodulators and anti-tumor necrosis factors-α (TNF-α)48. However, several forms of IBD-related arthritis are initially treated with sulfasalazine despite the lack of supportive evidence49. Symptoms can be relieved using simple analgesics, rest and physiotherapy. Non-steroidal anti-inflammatory drugs (NSAIDs) may aggravate the underlying colitis50, but the findings of a randomized study on the safety of celecoxib51 indicate that its short-term use (< 2 week) does not exacerbate colitis. Local steroid injection into the affected joints provides rapid, but only temporary relief. The treatment of AS should include intensive physiotherapy, together with the administration of disease-modifying drugs such as sulfasalazine and methotrexate. However, since TNF-α has been shown to play a key role in the pathogenesis of IBD-associated AS, the treatment of this articular manifestation has changed. The advent of biological response modifiers such as TNF-α blockers has improved the treatment of IBD and its associated peripheral and axial arthritis, and their safety and efficacy have been clearly established in the case of IBD-associated spondyloarthritis. Infliximab represents a significant advance in the treatment of IBD with or without associated arthropathies52.

Herfarth et al53 conducted a prospective, open-label, multicenter trial on the use of infliximab in patients with active CD and arthritis or arthralgia. The study showed a significant therapeutic effect of infliximab on arthritis and arthralgia in patients with refractory Crohn’s disease: 61% of patients showed improvement in arthritis or arthralgia, and 46% were free of symptoms. Ellman et al54, in an open label study, reported that four patients with refractory peripheral arthritis responded to treatment with infliximab. A large-scale prospective, open label trial demonstrated an improvement in peripheral arthritis of IBD patients who had previously been refractory to corticosteroids, thiopurines or methotrexate55. An open pilot study documented an improvement in the arthralgia of seven out of 11 IBD patients after a single infusion of infliximab55. On the basis of the available data, it seems that most of IBD patients with active intestinal inflammation and concurrent peripheral arthritis are likely to experience an improvement in their joint symptoms upon receiving infliximab55. In a multicenter, randomized, placebo-controlled trial by Braun et al56 18 of 34 (53%) AS patients treated with infliximab, 5 mg/kg at 0, 2 and 6 weeks showed symptomatic improvement at 12 weeks compared with only three of 25 (9%) placebo-treated patients (p < 0.05). In addition to induction of remission in patients with AS, infliximab has shown to be effective for maintenance of remission. Open label follow-up of the initial study by Braun et al56 at 1, 2 and 3 years demonstrated...
Table III. Studies on anti-TNF alpha therapy in IBD-related joint manifestations.

<table>
<thead>
<tr>
<th>Autor</th>
<th>RCT/open label/case report</th>
<th>N° Patients</th>
<th>Anti-TNFα</th>
<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Ellman MH, et al. 54</td>
<td>Open label trial</td>
<td>4 with IBD-related arthritis</td>
<td>Infliximab</td>
<td>Ability to stop or significantly decrease other antirheumatic medications after infliximab infusions</td>
</tr>
<tr>
<td>Herfart H, et al. 53</td>
<td>Open label, multicenter trial</td>
<td>153 CD, 71 of them with related arthritis or arthralgia</td>
<td>Infliximab</td>
<td>In 36 patients (61%) arthritis or arthralgia improved by at least one point in the symptom score (p &lt; 0.001). Twenty-seven of the 59 patients (46%) had no symptoms of arthritis or arthralgia, 13 (22%) had mild, 15 (25%) had moderate, and two (3%) had severe</td>
</tr>
<tr>
<td>Generini S, et al. 57</td>
<td>Open label trial</td>
<td>24 patients with spondyloarthritis and CD</td>
<td>Infliximab</td>
<td>Improvement of both gastrointestinal (p &lt; 0.01) and overall articular symptoms (BASDAI, p &lt; 0.01; general musculoskeletal and spinal pain, p &lt; 0.01; peripheral arthritis, p &lt; 0.01) in patients with active CD. Effective on axial arthritis, peripheral arthritis and enthesitis (p &lt; 0.01)</td>
</tr>
<tr>
<td>Kaufman I, et al. 55</td>
<td>Open label trial</td>
<td>23 IBD-related arthralgia</td>
<td>Infliximab</td>
<td>Seven out of 11 patients (64%) with arthralgia experienced benefit after treatment</td>
</tr>
<tr>
<td>Van der Heijde D, et al. 58</td>
<td>RCT</td>
<td>315 patients with AS</td>
<td>Adalimumab</td>
<td>At week 12, 58.2% of adalimumab-treated patients achieved an ASAS20 response, compared with 20.6% of placebo-treated patients (p &lt; 0.001). More patients in the adalimumab group (45.2%) than in the placebo group (15.9%) had at least a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index at week 12 (p &lt; 0.001). Significant improvements in the ASAS40 response and the response according to the ASAS5/6 criteria at weeks 12 and 24 were also demonstrated (p &lt; 0.001). Partial remission was achieved by more adalimumab-treated patients than placebo-treated patients (22.1% vs 5.6%; p &lt; 0.001).</td>
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Table continued
that 43 of 69 (62%) patients treated with 5 mg/kg every 6 weeks were still receiving infliximab infusions. Infliximab, etanercept and adalimumab have been found to have positive short and long-term effects on disease signs and symptoms in AS patients\textsuperscript{57-58}. In a controlled study evaluating IBD patients with spondyloarthropathy, 24 subjects (16 with active CD, 8 with inactive CD) received infliximab, 5 mg/kg at week 0, 2 and 6 followed by 3 mg/kg every 5 to 8 weeks, if CD was in remission, or 5 mg/kg every 5 to 8 week, if CD activity persisted. The infliximab treatment group was compared with 12 control subjects with active CD who were treated with a variety of medications, including corticosteroids, azathioprine, salicylates, and antibiotics\textsuperscript{57}. Patients treated with maintenance infliximab showed a rapid and continued decrease in BASDAI score at 12 months compared with noted in Crohn disease activity index (CDAI) between the two groups (18.1 vs 40.05; \( p < 0.05 \)); however, no difference was noted in CDAI between the two groups (137 vs 125)\textsuperscript{59}. Infliximab (but not etanercept) largely prevents both IBD and AS activity, but more dates are required in the case of adalimumab. The efficacy of adalimumab in the treatment of AS is mainly supported by the findings of the multicentre, randomized, double-blind and placebo-controlled trial conducted by van der Heijde et al\textsuperscript{60} who observed that the response of most of the patients treated with adalimumab was better than that observed in patients treated with

### Table III (Continued). Studies on anti-TNF alpha therapy in IBD-related joint manifestations.

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<tr>
<th>Autor</th>
<th>RCT/open label/case report</th>
<th>( N^\circ ) Patients</th>
<th>Anti-TNF( \alpha )</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Braun J, et al.\textsuperscript{56}</td>
<td>RCT</td>
<td>34</td>
<td>Infliximab</td>
<td>Data were available on 419 ankylosing spondylitis patients exposed to etanercept (625 patient-years), 366 exposed to infliximab (618 patient-years), 295 exposed to adalimumab (132 patient-years), and 434 placebo patients (150 patient-years). Among the 14 IBD cases receiving etanercept (2.2 per 100 patient-years) there were 8 CD and 6 UC cases, significantly different from infliximab (( p = 0.01 )) but not from placebo. Patients with a history of IBD had an IBD flare odds ratio of 18.0 (95% confidence interval [95% CI] 2-154) while taking etanercept and 4.2 (95% CI 0.4-44) while taking adalimumab, in comparison with infliximab. The incidence rates of new onset of IBD showed no significant difference between etanercept (0.8 per 100 patient-years) and placebo (0.5 per 100 patient-years).</td>
</tr>
<tr>
<td>Lofberg R, et al.\textsuperscript{55}</td>
<td>Open label trial</td>
<td>445 patients with arthralgia, 82 patients with arthritis and 34 with sacroiliitis</td>
<td>Adalimumab</td>
<td>252/445 patients with arthralgia at baseline showed no EIM at week 20; 18/34 with sacral ileitis at baseline had no EIM at week 20; 20/82 patients with arthritis at baseline had no EIM at week 20</td>
</tr>
</tbody>
</table>

Lofberg R, Open label trial 445 patients with Adalimumab 252/445 patients with etanercept 82 patients arthralgia at baseline showed 18/34 with sacroiliitis at baseline had no EIM at week 20; 20/82 patients with arthritis at baseline had no EIM at week 20
placebo. Finally, the CARE study (Crohn’s Treatment with Adalimumab: Patients Response to a Safety and Efficacy Study) showed that 252 of 445 patients with CD-related arthralgia at baseline showed no EIM at week 20 ($p < 0.001$); 18 of 34 with CD-related sacroiliitis at baseline had no EIM at week 20 ($p < 0.016$) and 20 of 82 patients with CD-related arthritis at baseline had no EIM at week 20 ($p < 0.001$).

**Psoriatic Arthritis**

Psoriatic arthritis (PsA) is an inflammatory arthritis found in up to approximately 30% of patients with psoriasis and in 0.3 to 1% of general population. Disease onset typically occurs between the ages of 30 and 55 years, and men and women are affected at similar frequencies. In the majority of patients, psoriasis is present for several years before the arthritis component is manifest. The number of joints affected by PsA and the severity of joint damage tend to increase progressively over time. Both the skin and joint components of the disease have a negative impact on quality of life in patients with PsA; psoriasis causes physical discomfort and disfigurement, and arthritis causes pain, stiffness, and reduced mobility and function. Progression of clinical and radiographic damage in PsA has been related to disease activity and severity, both at presentation and at follow-up. Progressive erosive disease has been reported in more than one-half of patients with PsA and is often associated with functional impairment. Patients with PsA are at increased risk of death compared with the general population, and severity of PsA at presentation is a predictor of mortality.

**Anti TNF-α Therapies**

Treatment of moderate to severe PsA has traditionally included the same disease-modifying anti rheumatic drugs (DMARDs) used for rheumatoid arthritis (RA) (e.g. methotrexate, leflunomide, sulfasalazine, azathioprine), despite the relatively little evidence for the efficacy of these drugs in PsA and very low evidence that they reduce joint destruction in PsA. The number of joints affected and the extent of joint damage frequently increase in patients with PsA, despite treatment with salicylates, DMARDs or glucocorticoids. The Psoriatic Arthritis Trial (ADEPT) demonstrated that, in patients with PsA, adalimumab significantly improved skin and joint manifestations, lessened disability caused by joint damage, inhibited structural change on radiographs and improved health-related quality of life (HRQOL), while being generally well tolerated during 24 weeks of therapy. According to the National Health Service (NHS) guidelines, patients with psoriatic arthritis are eligible for treatment with infliximab in case of peripheral arthritis with three or more tender joints and three or more swollen joints, or psoriatic arthritis that not responded to adequate trials of at least two standard DMARDs administered either individually or in combination and that patients have been shown to be intolerant to, or have contraindications to treatment with etanercept or have major difficulties with self administered injections.

**Conclusion**

Several IBD-related EIMs are reactive manifestations often associated with inflammatory bowel activity and, therefore, reflecting a pathogenic TNF-α dependent mechanism common with intestinal disease (e.g. arthritis, erytema nodosum, pyoderma gangrenosum, iritis, uveitis). The use of tumor necrosis factor-α inhibitors in the treatment of both the inflammatory conditions has shown the potential to change the history of IBD and EIMs. The early diagnosis of EIMs and related IBD is extremely important in order to establish the following treatment that, with the introduction of biologic therapy, would avoid a clinical worsening and the side effects of traditional therapy. However, further studies on when to start and for how long to maintain biological therapy are needed.

**Acknowledgements**

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