Therapy of spondylarthropathy in inflammatory bowel disease

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ABSTRACT

Musculoskeletal manifestations represent the most common extra-intestinal complication of inflammatory bowel diseases (IBD) and are usually included in the clinical spectrum of the spondyloarthropathies (SpA). Although control of intestinal inflammation often ameliorates articular symptoms, sometimes arthropathy is independent of the gut disease course and may require the same therapeutic options which apply to primary SpA diseases, but with caution so as not aggravate the IBD.

At the moment, salicylates (sulphasalazine and mesalazine) and selective COX-2 inhibitors (which are preferable to traditional NSAIDs although they cannot be assumed to be safe for the gastrointestinal tract) are the first choice treatment.

Several immunosuppressive and biological agents including methotrexate, thalidomide and TNFα antagonists have efficacy for both articular and intestinal inflammation and are currently in use for the induction of remission and for maintenance in more severe cases. New combination therapies and novel biologically-driven treatments, targeted to specific pathophysiological processes, might offer less toxicity and the potential for better treatment outcomes.

Introduction

The most common extra-intestinal complications of inflammatory bowel diseases (IBD) – Crohn's disease (CD) and ulcerative colitis (UC) – involve musculoskeletal manifestations, which are usually included in the clinical spectrum of spondylarthropathies (SpA). A wide range of prevalences of extra-intestinal manifestations has been reported, depending in part on the criteria used to define spondylarthropathy and on the selection of patients. Palm *et al.* reported a prevalence of SpA in IBD of 22% (2), while Salvarani *et al.* reported that at least 33.1% of the patients with IBD experience at least one musculoskeletal manifestation (3).

Although the association of CD with articular manifestations is well known, few scientific publications and clinical trials have addressed this problem. This dearth might be explained by several reasons. First of all, the presence of concomitant gut inflammation has often been considered to be an exclusion criterion for clinical trials of anti-rheumatic drugs, to avoid possible activation or worsening of the intestinal disease. Furthermore, the natural course of the disease is characterized by periods of flares and remission which complicate the interpretation of treatment efficacy. Finally, articular involvement in IBD includes a wide clinical spectrum of manifestations that may require different therapeutic approaches.

Two primary patterns of arthritis have been described in IBD: 1) peripheral, often asymmetric, arthritis, and 2) an SpA resembling idiopathic ankylosing spondylitis (AS) in 10% of patients with ulcerative colitis and less commonly in patients with CD (4). This peripheral arthritis recently has been subdivided into three types: type I, peripheral pauciarticular arthritis with < 5 joints involved; type II, peripheral non-symmetric polyarthritis with ≥5 joints involved; and type III, an SpA, sometimes with peripheral joint involvement (5). In addition to axial and peripheral articular symptoms, enthesitis,tenosynovitis, and dactylitis commonly occur, sometimes representing the only extra-intestinal manifestation of IBD (6). Type I arthritis may precede the diagnosis of IBD and, once established, often parallels the activity of the intestinal manifestation. Types II and III arthritis generally do not reflect the activity of the underlying IBD and rarely precede the diagnosis of IBD.

The general treatment

A general rule in managing arthritis complicating IBD can be formulated as

"what is good for the gut is also helpful for the joints" (7). Unfortunately this statement does not always reflect adequate therapeutic management of the joint disease, resulting in significant impairment of the quality of life. Nonetheless, there is consensus that treatment of the IBD should be the prime consideration, since control of intestinal inflammation will often reduce joint inflammation as well. When the course of arthropathy is apparently independent of the course of gut disease, the same therapeutic options which apply to primary SpA diseases may be considered, but used with caution so as not to aggravate the IBD.

No preventive measures for SpA associated with CD are available, as with AS, but most patients can be well managed. Better outcomes are associated with an early diagnosis, a compliant patient, and a competent physician. The treatment includes physical measures with an adequate balance of rest and activity, physical therapy, non-steroidal anti-inflammatory drugs, and local (intra-articular or peri-articular) steroid injections. When these treatments do not control joint inflammation adequately or patients are intolerant to such drugs, a second line treatment may be initiated.

If active inflammation is apparent in both the intestine and joints, clearly one should choose a therapy which is effective on both. However, the IBD often may be completely silent over long periods and the only clinically apparent problem and obvious therapeutic concern may be the SpA. Therefore, caution is mandatory in the management of all patients with SpA to be aware of the possibility of IBD, but especially in patients who have a history of IBD.

We present below a brief summary of the second line drugs that appear to have a beneficial effect on both SpA and IBD and thus are used in patients with both of these conditions.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay in the treatment of spondyloarthropathies, and often are the only treatment with the capacity to control articular pain and stiffness due to axial involvement and enthesitis; they are in wide clinical use also in arthropathies associated with IBD. Their use in Crohn's disease is problematic. It has been convincingly shown that NSAIDs increase gut permeability and may induce colitis in healthy subjects (8) or activate a quiescent IBD (9). The administration of indomethacin to rats induces inflammatory pathology of the small bowel which closely resembles ileal Crohn's disease and is used as an experimental animal model for IBD (10, 11). Selective cyclooxygenase-2 (COX-2) inhibitors have been developed to avoid gastrointestinal damage associated with traditional NSAIDs. In general, better gastrointestinal tolerability of these drugs is seen primarily in patients with a normal gastrointestinal tract, and possible selective sparing of an abnormal gastrointestinal tract is controversial.

IBD is associated with the increased local production of prostanoids derived through COX-2 (12) and the effect of selective COX-2 inhibitors on these substances at the intestinal level is not substantially different from that of traditional non-selective NSAIDs (12), although the significance and therapeutic implications of these observations are not completely defined. There is evidence that these prostaglandins may be an important component of the mucosal defense in the small intestine and colon (promoting the healing of mucosal injury, protecting against bacterial invasion, and down-regulating the mucosal immune system) (13). Suppression of COX-2 in a setting of gastrointestinal inflammation and ulceration has been shown in experimental models to impair healing and exacerbate inflammation-mediated injury (14). However, COX-2 derived prostaglandins may also contribute to bowel dysfunction during acute inflammation (sustaining inflammatory edema, hyperemia and increased permeability), and some have suggested that inhibitors of COX-2 may have a beneficial effect in gut inflammation (15).

In conclusion, although selective COX-2 inhibitors are probably preferable to traditional NSAIDs in the treatment of musculoskeletal symptoms when an underlying IBD is present, these compounds should be used carefully until they have been tested adequately in IBD. In a patient with established AS who is taking NSAIDs, it may be necessary to distinguish clinically between effects of NSAIDs on the small intestine and the ileitis of AS and CD, especially if intestinal obstruction, anemia, or hypoalbuminemia occurs (16). The distinction between NSAID enteropathy and the ileitis of AS can be important, because SSZ, metronidazole, and misoprostol reduce inflammation, bleeding, and protein loss in NSAID enteropathy (17), while only SSZ is known to benefit spondylarthropathic ileitis.

Sulphasalazine and mesalazine

Sulfsalazine (SSZ) was synthesized in the late 1930s and used for the treatment of IBD. Its efficacy in the treatment of UC has been demonstrated both in the treatment of active disease (18) and in the prevention of relapses (19). Efficacy of SSZ in active CD has been reported on the basis of some double-blind controlled trials (20,21) but not confirmed in others (22), and the efficacy of SSZ in preventing recurrences of CD is even more controversial (23).

After a long period of indifference to the possible value of SSZ as an antirheumatic drug, studies by Svartz, McConkey, Amos and others in the late 1970s rekindled interest in its effects on rheumatic symptoms. Since arthritis is a major manifestation in SpA and since the gut plays a crucial role in this disease, it seemed logical to use SSZ to treat patients with various SpA. Several reports indicate the efficacy and safety of SSZ in the short-term treatment of AS and other SpA (24). However, controlled trials on the efficacy of SSZ in IBD arthropathy do not exist. Nonetheless, SSZ has become a first choice treatment for entheropathic arthropathies on the basis of theoretical considerations and clinical experience. SSZ appears to have greater efficacy in patients with early disease. While it may be effective in patients with peripheral arthritis, it has no appreciable influence

on the persistence of axial disease and peripheral enthesopathy (25, 26).
SSZ cannot prevent the onset of an IBD in patients affected by SpA (27). 5-aminosalicylic acid (mesalazine) is more effective than SSZ for active CD and for maintenance of remission, including CD of the small intestine, with lower levels of adverse effects (27). Mesalazine has some efficacy in the treatment of SpA (28), which is however much lower than SSZ (29).

Corticosteroids
Corticosteroids should be used systemically only to control bowel disease, and appear to have no therapeutic effect in terms of retarding disease progression or improving axial involvement (30). Despite this general rule, the short-term administration of systemic corticosteroids may be of value to control peripheral arthritis. Intra-articular injections may also be useful, in particular if only a small number of joints are involved.

Methotrexate
Methotrexate (MTX) is a relatively safe, easily managed, and effective second line drug for patients with various articular and connective tissue diseases. Because of its efficacy and safety, MTX also may be used in combination with other a wide range of second line drugs (31). However, most studies of MTX used as a single agent or in combination have been performed in patients with rheumatoid arthritis. Few well-conducted studies have been performed on the efficacy of MTX in AS, and no specific studies exist concerning the possible efficacy of MTX in IBD arthropathies.
A few open prospective studies suggest that MTX (7.5 – 12.5 mg/week) has variable positive effects in the treatment of patients with SpA (32-35). The primary benefit appeared on peripheral joints, rather than on the axial skeleton and enthesis, although Biasi *et al*. (but not others) reported benefit for enthesistic and axial symptoms (34). Further long-term, placebo-controlled studies to address spinal symptom relief and the suppression of long-term ankylosis in enthesitis would be desirable.
MTX is emerging as an effective treatment for CD, although it is probably undervalued (36) and often considered a second choice drug with respect to azathioprine by gastroenterologists (37). Low-dose methotrexate has been reported to be effective in inducing remission in chronically active CD (37-39), and maintenance MTX provides long-term benefit with steroid sparing benefits and acceptable remission rates for up to 3 years (38,41-43), particularly in younger patients and when given parenterally (43).
Although MTX toxicity from long-term use (e.g. hepatotoxicity) has been a prominent concern of gastrointestinal physicians, side effects are usually only moderate and their consequences can be limited by appropriate monitoring and concomitant use of folic acid (44-46).

Azathioprine
Azathioprine (AZT) is rarely used in the treatment of SpA. An intravenous loading dose of AZT has been used in severe and refractory AS, but this regimen has limited efficacy and considerable toxicity (47). There is anecdotal evidence that AZT is helpful in intractable enthesopathy, although controlled observations are lacking.
AZT is regarded as an effective therapy for both UC and CD, and has been widely used in the treatment of IBD with (48). The efficacy of AZA is sustained over at least five years, with minimal toxicity (48).

Cyclosporine
Cyclosporine A (CyA) has been successfully used in the treatment of psoriatic arthritis (49,50). Intravenous high dose CyA may be used to attempt to induce remission or significant improvement in acute corticosteroid refractory IBD (51,52). However, the remission can be maintained only for a short period even with subsequent oral CyA (52, 53), which is associated with a high rate of adverse effects (53, 54). Intravenous high dose CyA is effective in inducing remission or significant improvement in steroid-refractory IBD (50,51). However, with subsequent oral CyA the remission can be maintained only for a short while (51, 52) and with an elevated incidence of adverse events (52, 53).

Cyclophosphamide
One report indicates that cyclophosphamide (Cyc) given intravenously in 200 mg doses on alternate days for 3 weeks, followed by a 100 mg oral dose weekly for 3 months, resulted in a reduction in peripheral joint synovitis and spinal pain although no improvement in spinal movement (55). This was accompanied by a significant fall in the sedimentation rate. However, no controlled studies have been yet undertaken.
Cyc has a role in the therapy of IBD only in intractable cases (56) or for the management of severe systemic complications such as vasculitis (57-59) or malingnances (60)

Thalidomide
Thalidomide, which was developed as a non-barbiturate sedative agent, was taken off the market in 1961 after it was linked to major birth defects. Gradually, thalidomide was reintroduced for the treatment of a few skin diseases including leprous erythema nodosum, severe mucosal ulcers (e.g., associated with HIV infection or Behcet's disease), lymphocytic skin infiltrations, cutaneous lupus erythematosus, and chronic graft-versus-host disease. It has now been established that its effect may linked to inhibition of the release of the cytokine tumor necrosis factor-α (TNF-α) from activated inflammatory cells (61, 62).
On the basis of this observation, thalidomide has been used in other TNF-α mediated diseases. Several open-label studies and case reports have described the short-term effectiveness of thalidomide in CD (62) and AS (63, 64). However, minor but dose-limiting side effects were common, and concern about long-term tolerability will limit the use of thalidomide in SpA. Perhaps the identification of a less toxic thalidomide molecule such as CC-3052 17 may enable the safe use of a non-neurotoxic, non-teratogenic, anti-inflammatory agent for the treatment of IBD and SpA (65, 66), as an effective oral alternative to monoclonal anti-TNF-α antibody

Biologic treatments

Recent experience with the TNF-α blocking drugs infliximab (a chimeric monoclonal anti TNF-α antibody) and etanercept (a recombinant human TNF receptor (p75):Fc fusion protein) has opened up a new approach to the management of CD patients with SpA.

Infliximab is highly effective and well tolerated for both axial and peripheral joint disease in patients with active AS (62-72) and other SpA (70, 73, 74) even at doses lower than those used to date (72). Etanercept has been successfully used in psoriatic arthritis (75,76) and there is evidence of its efficacy in AS (77, 78).

Infliximab is is an effective and well tolerated therapy for the management of acute CD (79, 80) and the drug has obtained FDA and European Medicines Evaluation Agency approval. The results of the Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen (ACCENT) I study showed that the maintenance with infliximab in moderate to severe CD prolonged the response and remission of the disease (81, 82). Higher response rates are seen with methotrexate as concomitant medication (83). Etanercept appears to have less efficacy in IBD and its use is not yet approved in CD, though an open-label trial for the treatment of CD is in progress in Belgium (84). The higher avidity of infliximab in binding the transmembrane TNF and the capacity to form stable complexes with soluble and transmembrane TNF in comparison to Etanercept may explain the different efficacy in CD of these two drugs (85).

Two open, short-term studies on SpA associated to CD (86, 87) have shown that infliximab induces rapid and substantial improvement of the articular manifestations and remission of the active intestinal disease. Personal observations suggest that infliximab is relatively safe and very effective over up to 2 years in the treatment of SpA associated with active and inactive IBD (88). Infliximab controlled peripheral arthritis, axial involvement, and enthesitis independently from the intestinal inflammatory condition and from the basal levels of acute phase reactants. The tolerability profile was excellent in quiescent IBD, with an effective prevention of intestinal inflammatory relapses. Thus, infliximab might be considered as a reliable therapeutic option also in those patients affected by an IBD without evident gastrointestinal inflammatory activity, no joint swelling and no laboratory signs of systemic inflammation, but characterized by severe axial and periarticular enthesitic pain, and severe articular stiffness.

Although there are some concerns about the immunogenicity of infliximab resulting in the formation of human antichimeric antibodies (HACA) as well as tuberculosis reactivation and lymphoproliferative disorders, the clinical benefit in the treatment of SpA associated with CD is a major therapeutic breakthrough. Further development of new anti-TNF agents with a better tolerability profile such as CDP-571 (humanized anti-TNF ab) may lead to greater tolerability with similar therapeutic advantages (89).

Associations between SpA and IBD lead to a hypothesis that interfering with gut inflammation in patients with SpA could yield a potential target for modulating the synovitis in these patients. Thus, besides TNF-alpha blockade, other strategies with potential efficacy on gut inflammation can be envisioned, such as IL-10, IL-11, IL-1 receptor antagonist, ICAM-1 antisense (ISIS 2302), anti-alpha 4 beta 7 integrin antibodies and humanized antibody to alpha4 integrin (Natalizumab) (90-94), although these exciting novel approaches remain unproven at this time. A further logical step in the biologic treatment of the inflammation will be combination therapy for SpA and IBD. Combinations of anti TNF-α agents and MTX is efficacious and safe (83, 95), while combinations of various anti-cytokine agents is encouraging in experimental animals (96), but has not been extensively studied in patients.

Other therapeutic options

Some other specific problems which are shared by IBD and SpA worth to be mentioned: Osteoporosis is a common complication of IBD (97, 98) and in SpA also it is frequently observed, even in the early stages and in mild patterns of disese (99-101). In both diseases,the incidence of fractures is remarkably higher than in general population (101, 102).

The pathogenetic mechanism seems to be multifactorial and is not completely understood yet. Corticosteroid therapy, disease activity, systemic inflammation, hormonal and genetic factors, malabsorption and mechanical factors such as decreased mobility and the support provided by extraspinal bone may all be important determinants of bone loss in these conditions (101, 103, 104).

Bisphosphonates are effective in the prevention and treatment of corticosteroid-induced osteoporosis and are widely used in SpA, but a study of the relative efficacy of different bisphosphonate agents in patients with AS is required (101). Patients with inflammatory bowel disease have been usually excluded from the largest studies on bisphosphonates because of the uncertainty of the potential relationship between the gastrointestinal adverse events of the treatment and the symptoms of the disease. Recently, alendronate has been shown to increase spine bone mineral density in a small group of patients with Crohn's disease in remission (105).

Intravenous formulations are now available for some bisphosphonates, and may be of interest in patients with inflammatory bowel disease and SpA. Recent studies suggest that cyclical and prolonged intravenous administration of pamidronate, may possess a dose dipendent antiinflammatory activity in patients with AS (106-108).

Studies of the rheumatological complications of IBD have focused on peripheral arthritis and spondylitis, and less is known about soft tissue rheumatism, specifically the fibromyalgia syndrome. Fibromyalgia is common in IBD, particularly CD. The lower pain threshold in Crohn's disease may suggest a disease-specific effect.(109). Fibromyalgia does not appear to be a major problem in SpA (110) but the possible coexistence of this problem has to be considered, especially in patients with CD, in order to prevent misdiagnosis and ensure correct treatment.

Aortitis, an uncommonon complication of both IBD and SpA, has been successfully treated with leukopheresis (111).

Discussion

The choice of appropriate medical treatment for SpA in IBD requires consideration of many variables: the type, activity and disease duration of SpA; the status of intestinal disease; the influence that the IBD may have directly or indirectly on the articular disease; and the risk of exacerbation of gut inflammation. The therapeutic strategy must carefully balance efficacy and potential toxicity in both diseases at that time. Several immunosuppressive and biological agents including MTX, thalidomide and TNF antagonists have efficacy for both articular and intestinal inflammation, including induction of remission and for maintenance. A key question is when to start and how long to maintain these aggressive treatments. Up to now immunosuppressive and biological therapies have been reserved for patients with severe and active disease when the antinflammatory drugs (NSAIDs or salicyycilates in SpA and IBD, respectively) had failed.

We believe that current therapies for both IBD and SpA, especially those with axial involvement, are often neither sufficient nor disease-modifying. The current therapeutic end-point in the treatment of CD is the remission of symptoms, but recent data suggest that mucosal inflammation may continue in the absence of symptoms (112), and that such subtle, sub-clinical mucosal inflammation may lead to clinical relapse. Current anti-inflammatory therapy often leaves low-grade mucosal inflammation untreated, allowing for recurrent relapses (112).

In SpA recent histological and magnetic resonance imaging studies indicate the presence of synovitis and subchondral bone marrow changes, which may explain the widespread joint destruction more than does enthesitis alone (35). Furthermore, enthesis lesions adjacent to synovial joints occur frequently and may be intimately linked to peripheral joint synovitis. Although there is no firm evidence at this time that second line agents have efficacy in axial disease, these observations raise the possibility that the early and prolonged suppression of synovitis through more aggressive immunosuppressive treatment might be of value in the spine (113). At the same time, this therapy could offer mucosal healing and reduction of IBD relapses. Moreover, the consequent normalisation of intestinal permeability might contribute to maintain SpA quiescence. However, safety is a key issue if the aggressive and prolonged use of immunosupressants/ immunomodulatory agents is to become more widespread. Novel biologically-driven therapies targeted to specific pathophysiological processes might offer lower toxicity and the potential for better treatment outcomes.

References

1. BYWATERS EGL: Historical aspects of the etiology of rheumatoid arthritis. *Br J Rheum atol* 1988; 27: (Suppl. 2): 110-5.
2. PALM O, MOUM B, ONGRE A, GRAN JT: Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: A population study (the IBSEN study). *J Rheumatol* 2002; 29: 511-5.
3. SALVARANI C, VLACHONIKOLIS IG, VAN DER HEIJDEDM, *et al.* (European Collaborative IBD Study Group): Muskuloskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol* 2001; 36: 1307-13.
4. KOUTROUBAKIS I, PENA AS: Genetics of inflammatory bowel disease. *In* ALLAN RN, RHODES JM, HANAUER SB, KEIGHLEY MRB, ALEXANDER-WILLIAMS J, FAZIO VW (Eds.): *Inflammatory Bowel Diseases*, New York, Churchill Livingstone 1997; 13-26.
5. ORCHARD TR, WORDWORTH BP, JEWELL DP: Peripheral arthropathies in inflammatory bowel disease: Their articular distribution and natural history. *Gut* 1998; 42: 387-91.
6. SALVARANI C, FORNACIARI G, BELTRAMI M, MACCHIONI PL: Musculoskeletal manifestations in inflammatory bowel disease. *Eur J Intern Med* 2000; 11: 210-4.
7. WOLLHEIM FA: Enteropathic arthritis. *In* RUDDY S, HARRIS ED JR, CLEMENT BS (Eds.): *Kelley's Textbook of Rheumatology*, 6th ed., Philadelphia, Saunders Co. 2001: 1081-8.
8. SIGTHORSSON G, TIBBLE J, HAYLLAR J, *et al*.: Intestinal permeability and inflammation in patients on NSAIDs. *Gut* 1998, 43: 506-11.
9. KAUFMANN HJ, TAUBIN HL: NSAID activate quiescent inflammatory bowel disease. *Ann Intern Med* 1987; 107: 513-6.
10. ANTHONY A, POUNDER RE, DHILLON AP, WAKEFIELD AJ: Similarities between ileal Crohn's disease and indomethacin experimental jejunal ulcers in the rat. *Aliment Phar macol Ther* 2000; 14: 241-5.
11. COLPAERT S, LIU Z, DE GREEF B, RUTGEERTS P, CEUPPENS JL,GEBOES K: Effects of anti-tumor necrosis factor, interleukin-10 and antibiotic therapy in the indometacin-induced bowel inflammation rat model. *Ali ment Pharmacol Ther* 2001; 15: 1827-36.
12. MCCARTNEY SA, MITCHELL JA, FAIRCLOUGH PD, FARTHING MJ, WARNER TD: Selective COX-2 inhibitors and human inflammatory bowel disease. *Aliment Phar macol Ther* 1999; 13: 1115-7.
13. WALLACE JL: Prostaglandin biology in inflammatory bowel disease. *Gastroenterol Clin North Am* 2001; 30: 971-80.
14. REUTER BK, ASFAHA S, BURET T, SHARKEY KA, WALLACE JL: Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. *J Clin Invest* 1996; 98: 2076-85.
15. KANKURI E, VAALI K, KORPELA R, PAAKKARI I, VAPAATALO H,MOILANEN E: Effects of a COX-2 preferential agent nimesulide on TNBS-induced acute inflammation in the gut. *Inflammation* 2001; 25: 301-10.
16. SMALE S, NATT RS, ORCHARD TR, RUSSEL AS, BJARNASON I: Inflammatory bowel disease and spondylarthropathy. *Arthritis Rheum* 2001; 12: 2728-36.
17. BJARNASON I, HAYLLAR J, SOMASUNDARAM S, et al.:Misoprostol in the treatment of NSAID-induced enteropathy: A double blind, placebo-controlled, parallel group study [Abstract]. *Gastroenterology* 1993; 104: A669.
18. DICK AP, GRAYSON MJ, CARPENTER RC, PETRIE A: Controlled trial of Sulphasalazine in the treatment of ulcerative colitis. *Gut* 1964; 5: 437-42.
19. DISSANAYAKE AS, TRUELOVE SC: A controlled trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine. *Gut* 1973; 14: 923-6.
20. SUMMERS RW, SWITZ DM, SESSION JT, *et al*.: National cooperative Crohn's disease study: Results of drug treatment. *Gastroen terology* 1979; 77: 847-69.
21. VAN HEES PA, VAN LIER HJJ, VAN ELTEREN P *et al*.: Effect of sulphasalazine in patients with active Crohn's disease: A controlled double-blind study. *Gut* 1981; 22: 404-9.
22. MALCHOW H, EWE K, BRANDS J *et al*.: European Cooperative Disease Study (ECDS): Results of drug treatment. *Gas troenterology* 1984; 86: 3328-32.
23. WENCKERT A, KRISTENSEN M, EKLUNE AE *et al*.: The long-term prophylatic effect of salicylazo-sulphapyridine (salazopyrin) in primary resected patients with Crohn's disease. *Scand J Rheumatol* 1978; 13: 161-7.
24. FERRAZ MG, TUGWELL P, GOLDSMITH CH, ATRA E: Meta-analysis of sulphasalazine in ankylsoing spondylitis. *J Rheumatol* 1990; 17: 1482-6.
25. LEHTINEN A, LEIRISALO-REPO M, TAAVITSAINEN M: Persistence of enthesopathic changes in patients with spondyloarthropathy during a 6-month follow-up. *Clin Exp Rheu matol* 1995; 13: 733-6.
26. CLEGG DO, REDA DJ, ABDELLATIF M: Comparison of sulfasalazine and placebo for the treatment of axial and peripheral articular manifestations of the spondylarthrpathies.

Arthritis Rheum 1999; 11: 2325-9.
27. MIELANTS H, VEYS EM, CUVELIER C, DE VOS M: Course of gut inflammation in spondylarthropathies and therapeutic consequences. *Baillière Clin Rheumatol* 1996; 10: 147-64.
28. THOMSON GT, THOMSON BR, THOMSON KS, DUCHARME JS: Clinical efficacy of mesalamine in the treatment of the spondylarthropathies. *J Rheumatol* 2000; 27: 714-8.
29. DEKKER-SAEYS BJ, DIJKMANS BA, TYTGAT GN: Treatment of spondyloarthropathy with 5-aminosalycilic acid (mesalazine): An open trial. *J Rheumatol* 2000; 27: 723-6.
30. KHAN MA: Ankylosing spondylitis: Clinical aspects. *In* CALIN A and TAUROG JD (Eds.): *The Spondylarthritides*, Oxford University Press, Oxford 1998, 27-40.
31. PINCUS T, O'DELL JR, KREMER JM: Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: A preventive strategy. *Ann Intern Med* 1999; 16: 768-74.
32. CREEMERS MCW, FRANSSEN MJ, VAN DE PUTTE LB, GRIBNAU FW, VAN RIEL PL: Methotrexate in severe ankylosing spondylitis: An open study. *J Rheumatol* 1995; 22: 1104-7.
33. SAMPAIO-BARROS PD, COSTALLAT LT, BERTOLO MB, NETO JF, SAMARA AM: Methotrexate in the treatment of ankylosing spondylitis. *Scand J Rheumatol* 2000; 29: 160-2.
34. BIASI D, CARLETTO A, CARAMASCHI P, PACOR ML, MALEKNIA T, BAMBARA LM: Efficacy of methotrexate in the treatment of ankylosing spondylitis: A three-year open study. *Clin Rheumatol* 2000; 19: 114-7.
35. MARSHALL RW, KIRWAN JR: Methotrexate in the treatment of ankylosing spondylitis. *Scand J Rheumatol* 2001; 30: 313-4.
36. KOZAREK RA: Long-term treatment of Crohn's disease with methotrexate, or, why's a nice drug like you still a wannabe in the treatment of inflammatory bowel disease ? *Am J Gastroenterol* 2000; 95: 1619-20
37. RUTGEERTS P: Medical therapy of inflammatory bowel disease. *Digestion* 1998; 59: 453-69.
38. FRASER AG, MORTON D, MCGOVERN D, TRAVIS S, JEWELL DP: The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002; 16: 693-7.
39. VAN DE PUTTE L, D'HAENS G, BAERT F, RUTGEERTS P: Methotrexate in refractory Crohn's disease. *Inflamm Bowel Dis* 1999; 5: 11-5.
40. EGAN LJ, SANDBORN WJ, TREMAINE WJ *et al.*: A randomized dose-response and pharmacokinetic study of methotrexate for refractory inflammatory Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 1999; 13: 1597-604.
41. YANG YX, LICHTENSTEIN GR: Methotrexate for the maintenance of remission in Crohn's disease. *Gastroenterology* 2001; 120:1553-5.
42. LEMANN M, ZENJARI T, BOUHNIK Y *et al.*: Methotrexate in Crohn's disease: Long-term efficacy and toxicity. *Am J Gastroenterol* 2000; 95: 1730-4.
43. FEAGAN BG, FEDORAK RN, IRVINE EJ: A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000; 342:1627-32.
44. CHONG RY, HANAUER SB, COHEN RD: Efficacy of parenteral methotrexate in refractory Crohn's disease. *Aliment Pharmacol Ther* 2001; 15: 35-44.
45. STEIN RB, HANAUER SB: Comparative tolerability of treatments for inflammatory bowel disease. *Drug Saf* 2000; 23: 429-48.
46. TE HS, SCHIANO TD, KUAN SF, HANAUER SB, CONJEEVARAM HS, BAKER AL: Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2000; 95: 3150-6.
47. DUREZ P, HORSMANS Y: Dramatic response after an intravenous loading dose of azathioprine in one case of severe and refractory ankylosing spondylitis. *Rheumatology (Oxford)* 2000; 39: 182-4.
48. FRASER AG, ORCHARD TR, JEWELL DP: The efficacy of azathioprine for the treatment of inflammatory bowel disease:A 30-year review. *Gut* 2002; 50: 485-9.
49. SALVARANI C, MACCHIONI P, OLIVIERI I *et al.*:A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; 28: 2274-82.
50. GEHER P, GOMOR B: Repeated cyclosporine therapy of peripheral arthritis associated with ankylosing spondylitis. *Med Sci Monit* 2001; 7:105-7.
51. HERMIDA-RODRIGUEZ C, CANTERO PERONA J, GARCIA-VALRIBERAS R, PAJARES GARCIA JM, MATE-JIMENEZ J: High dose intravenous cyclosporine in steroid refractory attacks of inflammatory bowel disease. *Hepatogastroenterology* 1999; 46: 2265-8.
52. GURUDU SR, GRIFFEL LH, GIALANELLA RJ, DAS KM: Cyclosporine therapy in inflammatory bowel disease:Short-term and long-term results. *J Clin Gastroenterol* 1999; 29:151-4.
53. SANDBORN WJ: Cyclosporine in ulcerative colitis: State of the art. *Acta Gastroenterol Belg* 2001; 64: 201-4.
54. HASLAM N, HEARING SD, PROBERT CS: Audit of cyclosporin use in inflammatory bowel disease:Limited benefits, numerous side-effects. *Eur J Gastroenterol Hepatol* 2000; 12: 657-60.
55. SADOWSKA-WROBLEWSKA M, GARWOLINSKA H,MACZYNSKA-RUSINIAK B: A trial of cyclophosphamide in ankylosing spondylitis with involvement of peripheral joints and high disease activity. *Scand J Rheumatol* 1986; 15: 259-64.
56. RIEGER N, STAHL J, WATTCHOW D: Intractable Crohn's colitis and perianal disease responding to cyclophosphamide and epirubicin. *Dig Dis Sci* 1997; 42: 2367-9.
57. GUDBJORNSSON B, HALLGREN R: Cutaneous polyarteritis nodosa associated with Crohn's disease. Report and review of the literature. *J Rheumatol* 1990; 17: 386-90.
58. CARMONA MA, JAUME ANSELMI F, RAMIREZ RIVERA J: Cerebral thrombosis and vasculitis:An uncommon complication of ulcerative colitis. *Bol Asoc Med PR* 2000; 92: 9-11.
59. PREKATES AA, ORFANOS SE, ROUTSI CJ, PANTELIDAKI A, ROUSSOS CS: Churg-Strauss syndrome occurring 30 years after the onset of ulcerative colitis. Respir Care 2002; 47: 167-70.
60. LENZEN R,BORCHARD F, LUBKE H,STROHMEYER G: Colitis ulcerosa complicated by malignant lymphoma:Case report and analysis of published works. *Gut* 1995; 36: 306-310.
61. SAMPAIO EP, SARNO EN, GALILLY R, COHN ZA *et al.*: Thalidomide selectively inhibits tumour necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991; 173: 699-703.
62. BARIOL C, MEAGHER AP, VICKERS CR *et al.*:Early studies on the safety and efficacy of thalidomide for symptomatic inflammatory bowel disease. J Gastroenterol Hepatol 2002; 17: 135-9.
63. BREBAN M, GOMBERT B, AMOR B, DOUGADOS M: Efficacy of thalidomide in the treatment of refractory ankylosing spondylitis. *Arthritis Rheum* 1999; 42: 580-1.
64. HUANG F, GU J, ZHAO W, ZHU J, ZHANG J, YU DT: One-year open label trial of thalidomide in ankylosing spondylitis. *Arthritis Rheum* 2002; 3: 249-54.
65. MARRIOT JB, WESTBY M, COOKSON S *et al.*: CC-3052: A water-soluble analog of thalidomide and potent inhibitor of activation-induced TNF-alpha production. *J Immunol* 1998; 161: 4236-43.
66. COMBE B: Thalidomide: New indications ? *Joint Bone Spine* 2001; 68: 582-7.
67. BRAUN J, BRANDT J, LISTING J *et al.*: Treatment of active ankylosing spondylitis with infliximab: A randomised controlled multicentre trial. *Lancet* 2002; 359: 1187-93.
68. BRANDT J, HAIBEL H, CORNELY D *et al.*: Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000; 43: 1346–52.
69. BRANDT J, HAIBEL H, REDDIG J, SIEPER J, BRAUN J: Treatment of patients with severe ankylosing spondylitis with infliximab – A one-year follow up. *Arthritis Rheum* 2002; 44: 2936-37.
70. VAN DEN BOSCH F, KRUITHOF E, BAETEN D *et al.*: Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondylarthropathy. *Arthritis Rheum* 2002; 46: 755-65.
71. GORMAN JD, SACK KE, DAVIS JC JR: Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002; 346: 1349-56.
72. MAKSYMOWYCH WP, JHANGRI GS, LAMBERT RG *et al.*: Infliximab in ankylosing spondylitis: A prospective observational inception cohort analysis of efficacy and safety. *J Rheumatol* 2002; 29: 959-65.
73. BRANDT J, HAIBEL H, REDDIG J, SIEPER J, BRAUN J: Successful treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor α monoclonal antibody infliximab. *J Rheumatol* 2002; 44: 2936–37.
74. KRUITHOF E, VAN DEN BOSCH F, BAETEN D, *et al.*: Repeated infusions of infliximab, a chimeric anti-TNFalpha monoclonal antibody, in patients with active spondyloarth-

ropathy: One year follow up. *Ann Rheum Dis* 2002; 61: 207-12.
75. KURSCHAT P, RUBBERT A, POSWIG A, SCHARFFETTER-KOCHANEK K, KRIEG T, HUNZELMANN N: Treatment of psoriatic arthritis with etanercept. *J Am Acad Derma - tol* 2001; 44: 1052.
76. YAZICI Y, ERKAN D, LOCKSHIN MD: Etanercept in the treatment of severe, resistant psoriatic arthritis: Continued efficacy and changing patterns of use after two years. *Clin Exp Rheumatol* 2002; 20: 115.
77. BARTHEL HR: Rapid remission of treatment-resistant ankylosing spondylitis with etanercept – A drug for refractory ankylosing spondylitis? *Arthritis Rheum* 2001; 45: 404.
78. MARZO-ORTEGA H, MCGONAGLE D, O'CONNOR P, EMERY P: Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: A clinical and magnetic resonance imaging study. *Arthritis Rheum* 2001; 44: 2112-7.
79. TARGAN SR, HANAUER SB, VAN DEVENTER SJH et al.: A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's Disease. Crohn's Disease cA2 Study Group. *N Engl L Med* 1997; 337: 1029-35.
80. PRESENT DH: Review article: The efficacy of infliximab in Crohn's disease – Healing of fistulae. *Aliment Pharmacol Ther* 1999; 13 (Suppl. 4): 23-8.
81. RUTGEERTS P, D'HAENS G, TARGAN S *et al*.: Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; 117: 761-9.
82. KEATING GM, PERRY CM: Infliximab: An updated review of its use in Crohn's disease and rheumatoid arthritis. *BioDrugs* 2002; 16: 111-48.
83. HOMMES DW, VAN DE HEISTEEG BH, VAN DER SPEK M, BARTELSMAN JF, VAN DEVENTER SJ: Infliximab treatment for Crohn's disease: One-year experience in a Dutch academic hospital. *Inflamm Bowel Dis* 2002; 8: 81-6.
84. YUNG RL: Etanercept Immunex. *Curr Opin Investig Drugs* 2001; 2: 216-21.
85. SCALLON B, CAI A, SOLOWSKI N *et al*.: Binding and functional comparisons of two types of tumor necrosis factor antagonists. *J Pharmacol Exp Ther* 2002; 301: 418-26.
86. VAN DEN BOSCH F, KRUITHOF E, BAETEN D, DE KEYSER F, MIELANTS H, VEYS EM: Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: An open pilot study. *Ann Rheum Dis* 2000; 59: 428-33.
87. VAN DEN BOSCH F, KRUITHOF E, DE VOS M, DE KEYSER F, MIELANTS H: Crohn's disease associated with spondyloarthropathy: Effect of TNF-alpha blockade with infliximab on articular symptoms. *Lancet* 2000; 25; 356: 1821-2.
88. GENERINI S, GIACOMELLI R, PIGNONE A *et al*.:Infliximab in spondylarthropaties with inactive and inactive inflammatory bowel disease:Short and long term treatment. Submitted.
89. SANDBORN WJ, FEAGAN BG, HANAUER SB *et al*.:An engineered human antibody to TNF (CDP571) for active Crohn's disease: A randomized double-blind placebo-controlled trial. *Gastroenterology* 2001; 120: 1330-8.
90. ASAKURA H: Treatment of ulcerative colitis and Crohn's disease with monoclonal antibody. *Nippon Rinsho* 2002; 60: 531-8.
91. SANDS BE, WINSTON BD, SALZBERG B *et al*. (RHIL-11 Crohn's Study group): Randomized, controlled trial of recombinant human interleukin-11 in patients with active Crohn's disease. *Aliment Pharmacol Ther* 2002; 16: 399-406.
92. VELJACA M: Anti-inflammatory peptides and proteins in inflammatory bowel disease. *Curr Opin Investig Drugs* 2001; 2: 1387-94.
93. SANDBORN WJ, TARGAN SR: Biologic therapy of inflammatory bowel disease. *Gastroenterology* 2002; 122: 1592-608.
94. GORDON FH,HAMILTON MI,DONOUGHUE S *et al*.:A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. *Aliment Pharmacol Ther* 2002; 16: 699–705.
95. IYER S, YAMAUCHI P, LOWE NJ: Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. *Br J Dermatol* 2002; 146: 118-21.
96. BENDELE AM, CHLIPALA ES, SCHERRER J *et al*.:Combination benefit of treatment with the cytokine inhibitors interleukin-1 receptor antagonist and PEGylated soluble tumor necrosis factor receptor type I in animal models of rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 2648-59.
97. COMPSTON JE, JUDD D, CRAWLEY EO *et al*.: Osteoporosis in patients with inflammatory bowel disease. *Gut* 1987; 28: 410–5.
98. PIGOT F, ROUX C, CHAUSSADE S *et al*.: Low bone mineral density in patients with inflammatory bowel disease. *Dig Dis Sci* 1992; 37: 1396–403.
99. EL MAGHRAOUI A,BORDERIE D, CHERRUAU B, EDOUARD R, DOUGADOS M, ROUX C: Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. *J Rheumatol* 1999; 26: 2205-9.
100. TOUSSIROT E, MICHEL F, WENDLING D: Bone density, ultrasound measurements and body composition in early ankylosing spondylitis. *Rheumatology (Oxford)* 2001; 40: 882-8.
101. BESSANT R, KEAT A: How should clinicians manage osteoporosis in ankylosing spondylitis? *J Rheumatol* 2002; 29: 1511-19.
102. BERNSTEIN CN, BLANCHARD JF, LESLIE W, WAJDA A, YU BN: The incidence of fracture among patients with inflammatory bowel disease:A population-based cohort study. *Ann Intern Med* 2000; 133: 795–9.
103. HABTEZION A, SILVERBERG MS, PARKES R, MIKOLAINIS S, STEINHART AH: Risk factors for low bone density in Crohn's disease. *Inflamm Bowel Dis* 2002; 8: 87-92.
104. SCHOON EJ, MULLER MC, VERMEER C, SCHURGERS LJ, BRUMMER RJ, STOCKBRUGGER RW: Low serum and bone vitamin K status in patients with longstanding Crohn's disease: Another pathogenetic factor of osteoporosis in Crohn's disease? *Gut* 2001; 48: 473-7.
105. HADERSLEV KV, TJELLESEN L, SORENSEN HA, STAUN M: Alendronate increases lumbar spine bone mineral density in patients with Crohn's disease. *Gastroenterology* 2000; 119: 639–46.
106. MAKSYMOWYCH WP, JHANGRI GS, LECLERCQ S, SKEITH K, YAN A, RUSSELL AS: An open study of pamidronate in the treatment of refractory ankylosing spondylitis. *J Rheumatol* 1998; 25: 714-7.
107. MAKSYMOWYCH WP, LAMBERT R, JHANGRI GS *et al*.:Clinical and radiological amelioration of refractory peripheral spondyloarthritis by pulse intravenous pamidronate therapy. *J Rheumatol* 2001; 28: 144-55.
108. MAKSYMOWYCH WP, JHANGRI GS, FITZGERALD AA *et al*.: A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal antiinflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum* 2002; 46: 766-73.
109. BUSKILA D, ODES LR, NEUMANN L, ODES HS: Fibromyalgia in inflammatory bowel disease. *J Rheumatol* 1999; 26: 1167-71.
110. INCEL A, ERDEM HR, OZGOCMEN S, CATAL A, YORGANCIOGLU ZR: Pain pressure threshold values in ankylosing spondylitis. *Rheumatol Int* 2002; 22: 148-50.
111. FUKUNAGA K, SAWADA K, FUKUDA Y *et al*.:A case report: First case of filtration leukocytapheresis for a patient of aortitis syndrome associated with ulcerative colitis. *Ther Apher* 2002; 6: 93-8.
112. ARNOTT ID, WATTS D, GHOSH S: Is clinical remission the optimum therapeutic goal in the treatment of Crohn's disease? *Aliment Pharmacol Ther* 2002; 16: 857-67.
113. DOUGADOS M: Treatment of spondyloarthropathies. Recent advances and prospects in 2001. *Joint Bone Spine* 2001; 68: 557-63.