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Drug-Induced Rheumatic Disorders

Incidence, Prevention and Management

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Abstract

The purpose of this article is to review the causes, the clinical manifestations and the management of the more frequent drug-induced rheumatic disorders. These include: (i) articular and periarticular manifestations induced by fluoroquinolones, nonsteroidal anti-inflammatory drugs, injections of corticosteroids, and retinoids; (ii) multisystemic manifestations such as drug-induced lupus and arthritis induced by vaccination, Bacillus Calmette-Guérin therapy and cytokines; (iii) drug-induced disorders of bone metabolism (corticosteroid-induced osteoporosis, drug-induced osteomalacia and osteonecrosis); and (iv) iatrogenic complex regional pain syndromes. Disorders caused by nonpharmacological and rarely used treatments have been deliberately excluded.

Knowledge of these drug-induced clinical symptoms or syndromes allows an

earlier diagnosis and treatment, and earlier drug withdrawal if necessary. With the introduction of new medications such as the recombinant cytokines and antiretroviral treatments, the number of drug-induced rheumatic disorders is likely to increase.

Treatment with pharmacological agents may be a secondary cause of rheumatic disorders. A multiplicity of compounds are associated with these disorders, and with the introduction of new medications the number of new associations is likely to increase. Arthralgia is the only feature of drug-induced rheumatic symptoms in many cases, and it may be difficult to recognise when a patient's rheumatic complaints are attributable to drugs because of the diversity of clinical presentations and the large number of compounds that have been implicated. Recognition of a drug-induced rheumatic disorder is important because symptoms often disappear after stopping the drug. Physician awareness of these risks also highlights the need for treatment monitoring and allows for intervention with preventive actions when possible, for example prevention of corticosteroid-induced osteoporosis.

This review focuses on the common drugs or vaccines associated with rheumatological adverse effects, with particular emphasis on controversial points [the articular adverse effects of fluoroquinolones, the chondrotoxicity of nonsteroidal anti-inflammatory drugs (NSAIDS), and the arthritis after hepatitis B vaccination] and the newly implicated drugs such as cytokine and protease inhibitor therapy. The literature search was based on the MEDLINE database between 1970 and 1999.

1. Articular and Periarticular Disorders

1.1 Fluoroquinolones

The new generation fluoroquinolones are synthetic antibacterials that act by inhibiting bacterial DNA gyrase (topoisomerase II).[1] They have widespread use because of their bactericidal action with low minimal inhibitory concentration, wide spectrum, extensive gastrointestinal absorption, widespread tissue diffusion and long half-life, allowing 2 daily doses.[1-3] Adverse effects are infrequent (usually in 4 to 8% of patients) and are often minor, dose-dependent and reversible.[1-4] Rheumatological adverse effects are rare and consist of myalgia (0.8%), arthralgia, arthritis (0.4%) and tendinitis. A single study has reported a higher frequency of rheumatological events, about 7%.[5]

1.1.1 Arthropathies

In animal models, fluoroquinolones are responsible for cartilage lesions. The animal studies demonstrated the presence of superficial large vesicles with decreased proteoglycan content and chondrocyte necrosis.[6] The lesions are predominantly located on areas with high mechanical constraint. *In vitro* studies with primary cartilage culture showed that fluoroquinolones increased the oxidative metabolism of immature chondrocytes. In humans, the lesions described are nonerosive bilateral symmetric arthropathies that frequently affect the lower extremities. Analysis of synovial fluid revealed predominantly lymphocytes.

These arthropathies preferentially occurred in adolescents during long term treatment (>3 months) with fluoroquinolones. The incidence may reach 45%.[7] Accordingly, fluoroquinolones are contraindicated in children and adolescents in the growing phase as well as during pregnancy and lactation. All quinolones appear to be chondrotoxic. The risk seems to be higher with pefloxacin.[8] The incidence of arthropathies associated with these antibacterials may have been overestimated in patients with cystic fibrosis, since the disease itself is also known to induce joint disturbances.[8]

In 1991, Chysky et al.[9] reported a retrospective study of 634 children treated with ciprofloxacin. The incidence of arthralgia was 1.3%, reversible in all cases. In 1995, Pradhan et al.[10] reported 58 children treated with ciprofloxacin for 9 to 16 days.[10] No articular pain was observed and in 22 cases, magnetic resonance imaging (MRI) of the knee was performed before and after treatment and showed no

cartilage signal modification nor synovial fluid effusion.

1.1.2 Tendinitis

The frequency of fluoroquinolone-induced tendinitis is difficult to evaluate, but is estimated to be 15 to 20 per 100 000 persons treated.[11] This tendinitis is characterised by an abrupt onset and sharp pain that occurs spontaneously. Involvement is frequently bilateral.[11] There is a predilection for the Achilles tendon, but other tendons may be affected: the quadriceps, extensor pollicus longus, peroneus brevis and those of the rotator cuff.[11] Tendon rupture is possible, almost always with preceding pain. It may be partial or complete, spontaneous or after activity.[11] This adverse effect may occasionally arise only hours after the initial dose of fluoroquinolone and for up to 10 weeks after the last dose. It can occur with all the fluoroquinolones at normal dosages and durations of treatment.[12] The severity is usually proportional to treatment duration, with increased frequency of tendon rupture after the third week of treatment. Predisposing factors are age over 60 years and long term corticosteroid therapy. More rarely, and controversially, the other factors are peripheral vascular disease, kidney failure, gout, spondyloarthropathy and rheumatoid arthritis.[11]

The diagnosis is essentially clinical. Ultrasonography can occasionally confirm partial or complete tendon rupture. MRI can be helpful in establishing an early diagnosis (intermediate signal flame-shaped intratendinous foci on T1 weighted images, an increased signal surrounding the lesions on T2 weighted images).[13] Nevertheless, MRI has frequently disclosed intratendinous foci during fluoroquinolone treatment in the absence of any clinical signs. The treatment consists of immediate discontinuation of the fluoroquinolone with the placement of the tendon at rest.[11] Forearm crutches, heel pieces, splints in case of partial rupture, and even below-the-knee casts if the rupture is complete, are helpful for periods of 6 weeks to 6 months.[11] Early and prolonged physical therapy is often necessary and surgery is rarely performed.[12] Thus, prevention is crucial, requiring close surveillance of high risk patients, especially those receiving corticosteroid therapy and the elderly.

1.2 Nonsteroidal Anti-Inflammatory Drugs

The potential chondrotoxicity of NSAIDS is very difficult to appreciate because of the contradictory and unconvincing data in the literature. In 1979, Ronningen and Langeland[14] reported the deleterious effect of indomethacin on osteoarthritic hip joints in a retrospective study with 58 patients treated with indomethacin and 128 patients untreated or treated with analgesics or with other NSAIDs.[14] The course of osteoarthritis was evaluated by examining radiographs performed at 3-year intervals. In the indomethacin group, the disease progressed more frequently. However, the treated patients had, when compared with the controls, a slightly greater severity index at first examination, and reliable information about duration and dosage of indomethacin administered was not available in all cases. In 1989, Rashad et al.[15] reported that hip osteoarthritis progressed more rapidly in patients treated with indomethacin than in those who received azapropazone. Other studies, although small and uncontrolled, founded no correlation between rapidly destructive arthropathy and NSAID intake. Watson et al.,[16] in a prospective study of 89 patients with hip osteoarthritis, found no correlation between femoral head height loss and indomethacin or phenylbutazone intake, implicating instead obesity as a major determinant of destructive change. The retrospective study of Loyau et al.[17] revealed the same conclusions: among 50 patients with osteoarthritic hip observed until hip replacement, the time between the first symptoms and the surgery was the same in the group treated with NSAIDs and in the group treated with analgesics. In 1989, Lequesne et al.[18] compared 27 cases of rapidly destructive hip osteoarthritis with common hip osteoarthritis. They found no difference in NSAID use.

One of the aetiopathogenic hypotheses is based on the reduction of protective painful stimuli from osteoarthritic joints: the proved efficacy of NSAIDs in reducing pain can lead patients to increase their activities sufficiently to cause relative joint abuse

with acceleration of articular damage. *In vivo*, in some animal models, NSAIDs have been shown to accelerate spontaneous cartilage destruction, but that is not the case with all drugs or in all experimental models.[19-21] *In vitro*, NSAIDs inhibited glycosaminoglycan synthesis in human cartilage and bone remodelling in rabbit and rat models.[22] A recent study demonstrated that the interleukin-1–mediated production of pro-matrix metalloproteinase 9, which play a critical role in cartilage destruction, is increased by diclofenac and indomethacin in rabbit articular chondrocytes in primary culture.[23] Conversely, phenylbutazone did not affect proteoglycan synthesis in cultured explants of equine carpal joint articular cartilage.[24]

Thus, despite various *in vivo* (animal models and humans) and *in vitro* studies, the causal relationship between more severe joint damage and NSAID intake is by no means proven. The chondrotoxicity of NSAIDs has not been demonstrated and these questions warrant further investigations.

1.3 Injections of Corticosteroids

A standard textbook on adverse effects of drugs[25] comments that 'destruction of joints after local injections of corticosteroids is so well known that isolated reports are hardly worth mentioning', which is very surprising and not confirmed by the data in the recent literature.[25] Although a case of Charcot's arthropathy of the shoulder in a 65-year-old man who had received a total of 18 injections of triamcinolone acetonide over a period of 18 months has been reported,[26] recent studies have shown the capacity of corticosteroids to inhibit collagenases and other metalloproteases that may mediate cartilage destruction.[27] Furthermore, Roberts et al.[28] reported that corticosteroid injection does not increase the rate of total joint arthroplasty in rheumatoid arthritis; however, this was a nonrandomised observational study on only 13 patients. An experimental study in 1995 demonstrated the protective effect of triamcinolone hexacetonide injections on osteoarthritis cartilage lesions, with reductions in the expression and synthesis of a proteolytic enzyme, stromelysin, and with inhibition of interleukin-1–induced protease synthesis.[29] Careful use of intra-articular corticosteroid injections is probably well tolerated and may even have protective effects on cartilage. An acceptable rate of injection ranges from 3 to 4 injections per year and per joint.

Adverse reactions to corticosteroid injections include septic arthritis, crystal-induced synovitis and soft tissue calcifications. The symptoms of septic arthritis appear 24 to 48 hours after the injection, frequently with fever, inflammatory local signs and leucocytosis. The frequency is difficult to establish, but is estimated to be about 1 infection per 14 000 to 50 000 injections. Iatrogenic infections are generally caused by nonadherence to aseptic procedures, and staphylococci are the predominant infecting organism.[30] The intra-articular injection of corticosteroid occasionally produces crystal-induced synovitis which may develop a few hours after injection and last up to 48 hours. The difficulty of distinguishing this reaction from an infection may be worrisome. The symptoms relieve spontaneously in 24 to 72 hours. This adverse effect is noted more frequently with needle-shaped corticosteroid crystals, such as triamcinolone hexacetonide. Analysis of synovial fluid shows the presence of leucocytes phagocytosing the crystals of corticosteroid. The frequency is about 1 to 4%.[30] The treatment is based on application of ice and oral NSAIDs. Other complications of corticosteroid injections include soft tissue atrophy and calcifications, especially noted in periarticular injections and in intra-articular injections of small joints such as finger proximal interphalangeal joints. This is more common with the longest acting corticosteroids such as triamcinolone hexacetonide.[30,31]

Systemic absorption of intra-articular corticosteroids occurs in almost all patients. Suppression of the hypothalamic-pituitary-adrenal axis occurs for 1 to 7 days after injection. Generally, there is no evidence of clinically significant adrenal insufficiency. There may be other effects, such as eosinopenia, lymphopenia and changes in serum and urine cortisol levels. Patients with diabetes mellitus may

note a short-lived several-fold rise in their blood glucose levels.[31]

1.4 Retinoids

Retinoids, used in dermatology, can cause bone tenderness and joint pain. Possible complications include periosteal new bone formation, hyperostosis and, in children, premature closure of the epiphysis of the long bones causing growth arrest.[32] Isotretinoin is responsible for ankylosing hyperostosis of the spine (mainly lower cervical and midthoracic spine) associated with ossifications of the anterior and posterior longitudinal vertebral ligaments. The hyperostosis involves costovertebral articulations and sacroiliac ligaments. In the appendicular bone, the ossifications appear later and are usually asymmetric (olecranon process of the elbow, acromion process of the shoulder, around the hip, the feet). These adverse effects of isotretinoin are dose- and time-related.[32]

As with isotretinoin, spinal hyperostosis has been reported with etretinate. The most frequent lesions associated with long term etretinate administration is usually bilateral extraspinal calcifications of tendons and ligaments (ankle, pelvis, knee, shoulder and elbow).[32] Other skeletal adverse effects have been reported: periosteal thickening of the ulna and fibula, disc degeneration and osteoporosis (without densitometry). Hypercalcaemia has been described in only few cases, and retinol (vitamin A) is considered to have no adverse effect on calcium metabolism.[33]

In fetal bovine chondrocyte culture, addition of tretinoin (all-*trans*-retinoic acid) is followed by a decreased synthesis of total protein and of type II collagen.[34] However, there is no evidence for tretinoin–induced osteoarthritis in humans.

1.5 Drug-Induced Hyperuricaemia and Gout

The underlying mechanism of drug-induced hyperuricaemia and gout is decreased uric acid excretion. At low dosages, salicylate intake is accompanied by accumulation of organic acids (β-hydroxybutyrate, acetoacetate, lactate) that compete with urate for tubular secretion.[35] Diuretics (furosemide, thiazides) are the main causes of hyperuricaemia associated with enhanced reabsorption of uric acid distal to the site of secretion.[36] Interestingly, tophi and urate deposits may develop in the absence of acute attacks of gout. Urate concentrations greater than 100 mg/L requires initiation of antihyperuricaemic therapy if withdrawal of the diuretic is not possible. Ethambutol and pyrazinamide can induce hyperuricaemia and require regular serum urate level determinations.[37] Cyclosporin is responsible for increased uricaemia in about 50% of cases. Patients who have had renal and heart transplants and are receiving cyclosporin develop acute gouty arthritis in 5 to 30% of cases. The clinical course of gout in these patients is often accelerated, with management complicated by the patient's renal insufficiency and interaction with transplant-related medications.[38]

Uricosuric agents are generally ineffective when the glomerular filtration rate is less than 50 ml/min. Renal insufficiency may increase the risk of marrow and neuromuscular toxicity from colchicine, as well as the risk of hypersensitivity reactions to allopurinol. Allopurinol is quite effective in lowering serum uric acid levels by inhibition of xanthine oxidase, but because azathioprine is also metabolised by this pathway, combining these 2 agents may result in life-threatening leucopenia.[38] Colchicine may be prescribed with lower and fractioned doses and haematological monitoring. Intravenous urate oxidase should only be used in hospital settings because of the risks of allergic reactions.[36]

Other drugs can induce hyperuricaemia: levodopa, thiamine (vitamin B_1), cyanocobalamin (vitamin B_{12}), retinoids, fibrates, cimetidine and ranitidine, nicotinic acid and fructose (intravenously).[36,37]

2. Multisystemic Manifestations

2.1 Drug-Induced Systemic Lupus Erythematosus

Several drugs are able to induce systemic lupus erythematosus (SLE) or SLE-like disorders. Drug-induced SLE is characterised by at least 2 criteria:

Table I. Drug-induced lupus: the most frequent offenders

Acebutolol
Carbamazepine
Chlorpromazine
Hydralazine
Isoniazid
Methyldopa
Minocycline
Penicillamine
Practolol
Procainamide
Quinidine
Sulfasalazine

recovery within 1 year when the drug is withdrawn, and the absence of features suggestive of idiopathic lupus or antibodies before taking the drug.[39] It is sometimes difficult to distinguish drug-induced systemic lupus erythematosus and idiopathic SLE revealed by the drug. In the latter case, clinical symptoms persist 1 year after drug withdrawal, as described with hydralazine and carbamazepine. Agents causing drug-induced SLE are classified into 2 groups: (i) those with definite proof of association (table I), and (ii) those with unproven association and isolated cases (table II).

Recombinant protein molecules, such as interferons and interleukin-2, have recently been implicated in a syndrome that resembles SLE.[40] In 1 study, symptoms of autoimmune disease were observed in 20% of patients with chronic myelogenous leukaemia or essential thrombocytopenia receiving interferon-α. In 18 of 25 (72%) patients tested, antinuclear antibody titres were elevated and 3 patients fulfilled criteria for the diagnosis of SLE.[40] The administration of interleukin-2, in melanoma and renal cell carcinoma, has been reported to be associated with clinical and serological features which overlap with drug-induced SLE.

Clinical manifestations of drug-induced SLE are similar to those of idiopathic SLE, but often less severe. Arthralgias/arthritis and myalgias are usually prominent, associated with pericarditis, pleurisy, fatigue, anorexia, fever and bodyweight loss.[39] The classic malar rash is rare, but skin rash is seen in up to one-quarter of patients with drug-induced SLE. Renal involvement or neurological disorders are rare.[39] Anaemia, leucopenia, thrombocytopenia, cryoglobulins, rheumatoid factors and positive direct Coomb's test can occur. The majority of patients have antinuclear antibodies.

Antihistone antibodies are commonly associated with drug-induced SLE (in up to 80% of patients with symptomatic drug-induced SLE), in the absence of antibodies to double-stranded DNA (which occur in <1% of patients with drug-induced SLE) and hypocomplementaemia.[41] However, antihistone antibodies are detected in 20 to 30% of cases of idiopathic SLE. There is varying antihistone antibody specificity, with antibodies reactive with chromatin, with (H2A-H2B) histone complexes or with (H2A-H2B)-DNA complexes, depending on the technique used [immunofluorescence, western blot, enzyme-linked immunoassay (ELISA)]. With the use of individual denatured histones as antigen by the ELISA technique, antihistone antibodies have been found in a wide range of diseases besides SLE and drug-induced SLE (juvenile rheumatoid arthritis, primary biliary cirrhosis, autoimmune hepatitis, various cancers, undifferentiated rheumatic diseases, scleroderma).[42] Conversely, antibodies directed against native chromatin or (H2A-H2B)-DNA complexes detected by ELISA have been frequently described in drug-induced SLE, especially with procainamide, hydralazine, isoniazid, penicillamine, acebutolol and sulfasalazine.[42,43] The anti-Sm antibodies are rarer, but were observed in penicillamine-, hydralazine- and acebutolol-induced lupus.[41] The anti-Ro (SS-A) and anti-La (SS-B) antibodies are rare. Antiphospholipid antibodies were reported in chlorpromazine-induced lupus.[44] Antimyeloperoxidase antibodies can be positive, especially in minocycline-related lupus.[45]

The underlying mechanisms by which drugs induce SLE are unclear. Recent investigations have yielded new information regarding how procainamide and hydralazine may affect the immune system to produce drug-induced SLE.[46] These findings could have important implications for mechanisms causing lupus-like diseases or other forms of

autoimmunity. Both procainamide and hydralazine can bind to polynucleotides *in vitro*, raising the possibility that DNA may be modified by these agents in a fashion analogous to haptens, making the DNA antigenic. The drugs could have various effects on cellular immune responses with decreased T cell proliferative response, T cell activation defect, decreased T suppressor cell activity, abnormal B cell activation with antibody production.[46] However, other studies have failed to confirm this, leaving the issue unresolved. The modification of T cell DNA methylation by various agents may play an important role in the pathogenesis of drug-induced SLE. For certain genes, hypomethylation of the regulatory sequences correlates with gene expression, and methylation of the same sequences results in transcriptional suppression. Thus, drugs could alter T cell gene expression and induce autoreactivity. DNA methylation inhibitors modify gene expression and induce autoreactivity in cloned antigen-specific CD4+ cells *in vitro* in DBA/2 mice.[46] Similar changes of T cell DNA methylation are found in patients with active SLE.

On the other hand, there is a genetic predisposition determined by drug acetylation rates. Individuals with a mutation of the *N*-acetyltransferase 2 gene have an impaired enzyme function and are thus slow acetylators, and have been reported to have a higher incidence of drug-induced SLE.[39]

The initial therapeutic approach to drug-induced SLE is withdrawal of the offending drug. Most patients improve in a few weeks. Symptoms rarely persist more than 6 months. Antinuclear antibodies may persist for years. Arthralgias and arthritis can be treated with NSAIDs. If symptoms are severe (pleuropericarditis, severe arthritis), corticosteroids are indicated for a short period (2 to 10 weeks). In the case of nephritis, the treatment is the same as for idiopathic SLE.

Table II. Drug-induced lupus: drugs with unproven association and isolated cases

Aminoglutethimide	Leuprorelin	Pindolol
Anthiomaline	Levomeprazine	Practolol
Atenolol	Lithium	Prazosin
Betaxolol	Lovastatin	Primidone
Captopril	Mephenytoin	Prinolol
Chlorprothixene	Mesalazine	Promethazine
Cinnarazine	Methylthiouracil	Propanolol
Clobazam	Methysergide	Propylthiouracil
Clonidine	Metoprolol	Psoralens
Danazol	Metrizamide	Pyrithioxine
Deferiprone (L1)	Minoxidil	Simvastatin
Diclofenac	Nalidixic acid	Sotalol
Diltiazem	Nitrofurantoin	Spironolactone
Disopyramide	Nomifensine	Streptomycin
Enalapril	Olsalazine	Sulfonamide
Ethosuximide	Oral contraceptives	Sulindac
Gold salts	Oxprenolol	Tetracycline
Griseofulvin	Oxyphenisatine	Thiamazole (methimazole)
Guanoxan	*p*-Aminosalicylate	Thionamide
Hydrochlorothiazide	Penicillin	Timolol eye drops
Ibuprofen	Perphenazine	Tolazamide
Interferon-α and -γ	Phenelzine	Trimethadione
Interleukin-2	Phenylbutazone	Valproic acid (sodium valproate)
Labetolol	Phenytoin	Verapamil

2.2 Vaccinations and Arthritis

2.2.1 Rubella Vaccine

Arthropathy has been associated with rubella vaccine, rarely in children and more frequently in adult women, since 1974. In a large cohort at a single institution in Vancouver, Canada, evidence of viral persistence in peripheral blood mononuclear cells and synovial fluid mononuclear cells was demonstrated in a few individuals with chronic arthropathy following administration of the vaccine RA 27/3.[47] In 1996, Weibel et al.[48] reported the outcome of 124 claims of chronic arthropathy associated with rubella vaccine submitted to the National Vaccine Injury Compensation Program. Among the 124 vaccine recipients, the onset occurred between 1 week and 6 weeks after the vaccination in 58% of cases. Various conditions developed, including unspecified arthritis in 30 cases, specified arthritis in 30 cases (e.g. rheumatoid arthritis, Sjögren's syndrome), arthralgia in 31 cases, fibromyalgia in 15 cases and multiple symptoms with arthralgia or myalgia in 18 cases. In 112 of the 124 patients, rubella vaccine was the RA 27/3 strain.

Ray et al.[49] reported a retrospective cohort study based on computerised laboratory data and medical record review, concerning the symptoms occurring within 2 years before and after the date of serological testing. Seronegative women immunised within 1 year of serotesting (n = 971) were defined as exposed. Primary comparison groups included all unvaccinated seronegative women (n = 924) and randomly selected seropositive unvaccinated women (n = 2421). The prevalence and incidence of chronic joint symptoms were evaluated during 1-year follow-up period after RA 27/3 rubella vaccination. There was no evidence of any increased risk of new onset chronic arthropathies in women receiving the rubella vaccine.

Tingle et al.[50] conducted a randomised double-blind placebo-controlled study on adverse effects of rubella immunisation (RA 27/3 strain) in 546 seronegative women followed during 1 year. Results indicated a significantly higher incidence of acute joint manifestations in rubella vaccine recipients (30%) than in placebo recipients (20%). Concerning chronic arthralgia or arthritis, differences between the groups were only marginally significant. Therefore, the lack of significant difference does not negate the possibility that true chronic arthropathies can occur. Larger numbers of participants or longer follow-up may be needed.

2.2.2 Hepatitis B Vaccination

There have been sporadic reports of inflammatory polyarthritis after vaccination of adult healthcare workers and other at-risk adults with recombinant hepatitis vaccine.[51,52] Many of these individuals have been rheumatoid factor positive and developed transient or persistent arthritis shortly after the second or third vaccination. Since 1994, several cases of post vaccine arthritis have been published.[53,54] Maillefert et al.[54] retrospectively reported 19 cases with rheumatoid-like arthritis in 5 cases, lupus in 2 cases, spondyloarthropathy with positive human leucocyte antigen (HLA) B27 in 2 cases, vasculitis with arthritis in 4 cases, arthralgias in 5 cases and monoarthritis in 1 case.

Recently, Pope et al.[55] described the clinical and serological characteristics and HLA antigens of 11 patients who developed arthritis after recombinant hepatitis B vaccination. 10 of 11 patients fulfilled the revised American College of Rheumatology (ACR) criteria for rheumatoid arthritis. At 48 months follow-up, only 2 cases no longer had inflammatory arthritis. Five patients were HLA DR4 positive, and HLA class II genes expressing the rheumatoid arthritis shared motif were identified in 9 of 11 patients. The authors expressed the hypothesis that recombinant hepatitis vaccine may trigger the development of rheumatoid arthritis in major histocompatibility complex (MHC) class II genetically susceptible individuals, but there are undoubtedly other determining factors, given the frequency of these HLA class II molecules in the general population.

Further studies are required to confirm whether this association is a causal relationship or whether it is coincidental. In the meantime, hepatitis B vaccination should be reserved for at-risk adults.

2.3 Arthritis and Bacillus Calmette-Guérin Therapy

Bacillus Calmette-Guérin (BCG) is given as intravesical instillations in superficial bladder carcinoma. Arthralgias have been described in 0.5 to 5% of patients receiving this therapy, and aseptic arthritis in 0.4 to 0.8% of cases.[56] Clinically, oligoarthritis involving the lower limb joints was frequently observed. Symptoms such as dysuria, haematuria, conjunctivitis, uveitis and back pain have been also described.[57] The symptoms usually occurred 4 to 8 weeks after the BCG therapy. Patients were HLA-B27 positive in about 60% of cases. In only 7% of patients could the symptoms be attributed to worsening of pre-existent ankylosing spondylitis. Radiological sacroiliitis was observed in 18% of cases. These manifestations are suggestive of a reactive arthritis.[56] 90% of patients responded to NSAIDs with a total recovery after 6 months. The major aetiopathogenic hypothesis is cross reactivity between HLA-B27 epitopes and *Mycobacterium bovis* epitopes.

Interestingly, after intradermal BCG injections used to enhance antitumour immune response, the

clinical presentation of the induced arthritis is different with a symmetrical polyarthritis of the hands. This polyarthritis, resembling rheumatoid arthritis, has been described in 10 patients out of 159.[58] Recovery usually occurred within 1 to 3 months.

2.4 Cytokine-Induced Arthritis

Interferons have antitumoural properties and can block viral replication. Recombinant interferon-α is prescribed in chronic active hepatitis B and C. This treatment is associated with autoantibody production and can trigger autoimmune diseases such as thyroiditis and, more rarely, lupus and polyarthritis.[59] The clinical presentation is a symmetrical polyarthritis occurring 1 to 11 months after starting interferon-α. Frequently, the presence of autoantibodies is noted before the start of the treatment (rheumatoid factors, antinuclear antibodies). The prognosis is generally good after stopping interferon-α and treatment with NSAIDs or corticosteroids, but the arthritis can persist and have a chronic course.[60-62] Interferon-γ has been also implicated in the occurrence of polyarthritis or spondyloarthropathy in patients treated for psoriasis.[63]

Interleukin-2 (IL-2), a lymphokine produced by activated helper T cells, has been shown to enhance natural killer cell and antigen-specific cytotoxic T cell activity. The administration of recombinant IL-2 has resulted in both partial and complete responses in patients with malignancy refractory to traditional treatments, such as melanoma and renal cell carcinoma. Among several adverse effects, IL-2 has resulted in the induction of autoimmune diseases: autoimmune thyroiditis, anti-insulin antibodies, vasculitis, pemphigus and vitiligo. A few cases of chronic inflammatory arthropathy have been described in the literature after IL-2 therapy.[64] In each case, the patients met the ACR criteria for rheumatoid arthritis.

Granulocyte and granulocyte-macrophage colony-stimulating factors, used to correct neutropenia, have been reported to cause flare-up of arthritis in patients with Felty's syndrome.[65,66]

3. Drug-Induced Bone Diseases

3.1 Corticosteroid-Induced Osteoporosis

3.1.1 Mechanisms of Bone Loss

Effects on Calcium Homeostasis

Calcium absorption is significantly reduced in patients treated with corticosteroids compared with healthy individuals; this can be reversed by the coadministration of calcitriol (1,25-dihydroxyvitamin D3).[67] Corticosteroids also increase urinary calcium loss. Several studies have observed elevated serum parathyroid hormone concentrations, reflecting a probable secondary hyperparathyroidism.[67]

Inhibition of Bone Formation

Corticosteroids directly affect osteoblast precursors, osteoblast proliferation, attachment of osteoblasts to matrix and synthesis of both type I collagen and noncollagenous proteins, resulting in a decrease in bone formation.[68]

Effects on Sex Hormones

Corticosteroids cause a reduction in sex hormone production. Secretion of luteinising hormone from the pituitary is decreased, with a resultant decrease in estrogen and testosterone production. Circulating levels of oestradiol, estrone, dehydroepiandrosterone sulfate, androstenedione and progesterone are lowered.[69]

3.1.2 Clinical Manifestations

Corticosteroid-induced bone loss varies according to both skeletal site and duration of therapy. The major clinical manifestation, in terms of fracture, is at the spine, and to a lesser extent the ribs.[70] The most rapid bone loss occurs in the first 6 to 12 months after initiation of therapy. This loss appears to diminish with time, approaches a plateau depending upon dose, and seems to be partly reversible on the withdrawal of therapy.[67] Baseline concentrations of biochemical markers (serum osteocalcin, tartrate resistant acid phosphatase and later parathyroid hormone), or changes in markers, have not been found to predict bone loss after corticosteroid initiation.[71] Studies on bone density suggest that corticosteroid bone loss is dose-dependent, which

raises the question of whether low doses cause bone loss. Some studies in rheumatoid arthritis found no significant difference in bone density between patients who receive corticosteroids and those who do not. Others report significant effects of even low doses.[67] However, the interpretation of 'low' varies in the literature, and disease activity in rheumatoid arthritis is associated with bone loss independent of corticosteroid therapy.

3.1.3 Preventive Treatment

Several treatments are of benefit in prevention of corticosteroid-induced bone loss: calcium, vitamin D, hormone replacement therapy (HRT), fluoride and bisphosphonates.[69,72] As corticosteroids create a negative calcium balance, it is important to maintain an adequate calcium intake (at least 1500mg of elemental calcium daily) associated with 800 IU/day of vitamin D.[72] Alendronate (10 mg/day) has also shown beneficial effects on bone turnover and bone mineral density (BMD) in patients receiving corticosteroid therapy.[73]

Menopause accelerates corticosteroid-induced osteoporosis. Estrogen replacement therapy may increase BMD slightly in the lumbar spine, but may not prevent bone loss in the femoral neck.[74] The usual dosage of estrogen is 0.625 mg/day of conjugated equine estrogens or 1 mg/day of estradiol. Progesterone should be added if the uterus is still intact to prevent endometrial hyperplasia or cancer.[74]

Testosterone replacement should be offered to men with hypogonadism. This hormonal treatment may produce small increases in BMD in the lumbar spine but not in the femoral neck.[75] Depot testosterone (200mg intramuscularly every 2 weeks) or one of the transdermal testosterone preparations can be used.

Fluoride directly stimulates trabecular bone formation by enhancing the recruitment and differentiation of osteoblasts. In corticosteroid-induced osteoporosis, when sodium fluoride is given in combination with etidronate, there is an apparent additional increase in BMD.[76] A new form of fluoride, sodium monofluorophosphate, combined with calcium increased lumbar spine BMD in patients on corticosteroids (7.8 ± 2.2% with monofluorophosphate versus 3.6 ± 1.3% with calcium alone) after 18 months of treatment. Neither femoral neck nor femoral shaft mineral density was affected.[77]

In 1997, Adachi et al.[78] showed the efficacy of cyclical etidronate in the prevention of corticosteroid-induced bone loss.[78] They studied 141 patients who were beginning corticosteroid therapy and who received cyclical etidronate or placebo followed by calcium 500 mg/day to both groups for 12 months. The results showed that the BMD of spine and hip increased by 0.61% and 1.46% respectively in the etidronate group, and decreased by 3.23% and 2.74% respectively in the placebo group. There was an 85% reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group as compared with the placebo group (1 of 31 women receiving etidronate *vs* 7 of 32 women receiving placebo). The women treated with etidronate also had fewer vertebral fractures per patient. Urinary *N*-telopeptide excretion, a marker of bone loss, had decreased 44.8% by week 26 and 52.5% by week 52 in the etidronate group (the difference between etidronate and placebo was significant).

More recently, a randomised, placebo-controlled study evaluated the efficacy of 1-year cyclical etidronate therapy in preventing bone loss in 83 patients with rheumatoid arthritis, polymyalgia rheumatica or giant cell arteritis who were being treated with corticosteroids.[79] BMD decreased by 1.94 ± 0.61% in the placebo group and increased by 0.86 ± 0.6% in the etidronate group (difference 2.8 ± 0.86%). The difference was largest in postmenopausal women (3.38 ± 1.11%). At the femoral neck, the difference was not statistically significant. Four fractures occurred in the placebo group and 2 in the etidronate group.

The recommendations of the ACR task force on osteoporosis are as follows.[69] Given that bone is lost most rapidly during the first 6 months of corticosteroid use, primary prevention measures should begin as soon as corticosteroids are prescribed. The history of risk factors for osteoporosis

should be obtained, including a review of medications that increase this risk (thyroid hormone replacement, phenytoin, long term coumadin or heparin, cyclosporin or antigonadotropins). A BMD measurement of the spine and hip should be obtained. It provides a baseline measurement for monitoring changes in bone mass. For all patients starting corticosteroids, calcium and vitamin supplementation should be initiated. Women who are postmenomausal and who have an abnormal BMD value should initiate HRT. If there are contraindications to HRT, a bisphosphonate or calcitonin should be started. If the BMD is normal, postmenopausal women should be encouraged to initiate HRT. A repeat BMD measurement should be done 6 or 12 months after the initiation of corticosteroids. If the BMD has decreased more than 5% from baseline, the medication can be changed or another one added.

3.2 Drug-Induced Osteomalacia

Osteomalacia is characterised by the accumulation of increased amounts of unmineralised bone matrix (osteoid) and a decrease in the rate of bone formation. Drugs can be responsible for this bone disorder. Long term treatment with drugs that induce the hepatic mixed-function oxidase enzyme system produces an increased incidence of rickets and osteomalacia. This is particularly true for agents such as phenobarbital (phenobarbitone), phenytoin and rifampicin (rifampin).[80-82] The basis of the disorder appears to be an accelerated rate of hepatic microsomal degradation of colecalciferol and calcifediol (25-hydroxy-vitamin D) by cytochrome P450. Hypocalcaemia, hypophosphataemia, increased serum parathyroid hormone, elevated serum bone alkaline phosphatase and reduced serum calcifediol levels occur in 4 to 60% of such individuals, with the incidence and severity of the disorder determined by the patient's level of vitamin D intake, degree of sunlight exposure and total drug dose. Severe cases may require 4000 to 20 000 units of vitamin D per day for 1 year or longer to correct all abnormalities. Routine prophylaxis consists of maintaining a vitamin D intake of 800 to 1000 units per day.

Corticosteroids decrease intestinal absorption of calcium but do not induce osteomalacia. Conversely, antacid abuse can induce chronic hypophosphataemia, osteomalacia and toxic aluminium and magnesium bone deposition. Magnesium or aluminium hydroxide antacids interfere with intestinal phosphate absorption.[83] The treatment consists of discontinuing the antacid and calcium and phosphate supplementation.

The first generation bisphosphonates can block mineralisation and induce osteomalacia. However, this risk depends on the ratio of antiresorptive activity to formation activity of the drug. Etidronate-induced osteomalacia was described *in vivo* after preliminary trials in osteoporosis using high dosages (20 mg/kg/day) or in Paget's disease (10 to 20 mg/kg/day).[84] A lower dosage (5 mg/kg/day) was considered to be better tolerated. Nevertheless, Boyce et al.[85] showed that prolonged continuous treatment at 5 mg/kg/day in Paget's disease could affect mineralisation. In osteoporosis, several studies have shown that cyclical intermittent administration at low dosages did not reduce the mineralisation rate after several years of treatment.[86] The newly marketed aminobisphosphonates (pamidronate, alendronate, tiludronate) or under evaluation (risedronate, ibandronate) have no effect on the mineralisation rate.[87]

Fluoride therapy induces mineralisation abnormalities that are not strictly osteomalacia. Calcium and vitamin D supplementation did not completely prevent this bone disorder. Sodium fluoride is responsible for pains of the lower extremities which could be related to multiple stress fractures.[88]

3.3 Drug-Induced Osteonecrosis

A common cause of osteonecrosis is corticosteroid therapy. The mechanism by which corticosteroids are associated with osteonecrosis is unknown. There appears to be a host susceptibility, which may be genetically predetermined. Patients will generally develop osteonecrosis shortly after corticosteroid use, although symptoms may be not

present for a considerable period.[89] The proposed pathogenesis includes increased free fatty acids with obliteration of intramedullary blood supply and corticosteroid-induced vasculitis.[90] Corticosteroids are most frequently administered to chronically ill patients with disease processes that may affect blood vessels, marrow and bone. Thus, in the patients with lupus, there is often a concomitant vasculitis. In the patients with chronic renal disease, metabolic factors including renal osteodystrophy also affect the bone. In such circumstances, it has been proposed that the aetiology of osteonecrosis is multifactorial.[91,92] There also seems to be a relationship between the development of osteonecrosis and the corticosteroid dose. In the patients with rheumatoid arthritis who have been on low doses of corticosteroid, the incidence of osteonecrosis is low, whereas in patients with lupus who have been treated with high doses for a much shorter period, the incidence is considerably higher. On the other hand, in renal transplant recipients no direct correlation has been found between the dose of corticosteroid and osteonecrosis.[89] During long term high dose corticosteroid administration, the steroid itself seems to be the most important, but perhaps not the only, aetiological factor in the development of osteonecrosis.

4. Complex Regional Pain Syndromes

In 1993, the American Pain Society recognised 2 types of complex regional pain syndrome (CRPS): type I corresponding to reflex sympathetic dystrophy and type II corresponding to causalgia. Drug-induced CRPS preferentially involves the upper extremities. The contralateral side can be affected and bony demineralisation is usually moderate. Adhesive capsulitis of the shoulder is frequent. The offending drugs are barbiturates, isoniazid, ethionamide, iodine-131 and, more recently, cyclosporin at high dosages.[93,94] It seems that CRPS occurs at high dosages of the associated drug and if a classic risk factor (initiating noxious event or nerve injury) coexists.

Treatment is based on withdrawal of the drug and the usual treatments for CRPS: adrenergic blockers, NSAIDs, calcium antagonists, calcitonin, intravenous regional blockade with guanethidine or buflomedil, intra-articular injection of corticosteroids, physical therapy, forceful injection of contrast material in adhesive capsulitis.

Recently, adhesive capsulitis of the shoulder has been described with protease inhibitor therapy in HIV-positive patients. Zabraniecki et al.[95] reported the first 3 cases. The diagnosis was confirmed by arthrography and the classic causes were ruled out. This complication appeared with a mean delay of 12 months. The offending drug was indinavir in the 3 cases. Later, Léone et al.[96] described 3 other cases, preceded by polyarthralgia in 2 cases. The delay between initiation of the treatment and onset of capsulitis was shorter (2 to 6 months). Of the 3 protease inhibitors used, indinavir was the most likely culprit. Protease inhibitors, and perhaps indinavir specifically, may cause adhesive capsulitis. Interestingly, protease inhibitors are competitive inhibitors of cytochrome P450, as are barbiturates and isoniazid.

5. Conclusion

Drugs should be considered as the potential cause when patients receiving treatment present with articular or periarticular disorders, multisystemic manifestations, bone metabolism abnormalities or complex regional pain syndromes. Failure to recognise drug-induced disorders will lead to delay in diagnosis and prolonged morbidity, whereas symptoms will frequently disappear when the offending drug is stopped. Since withdrawal of the implicated drug is not always possible, the development of preventive therapy, for example bisphosphonates in corticosteroid-induced osteoporosis, remains important.

A number of drugs have recently been implicated in causing rheumatic disorders. Among them, immunological response modifiers such as cytokines may cause rheumatic and multisystemic manifestations by interfering with the natural cytokine network or with the physiological activities of immunoregulatory cells. Understanding how drugs induce these disorders could provide

important insights into aetiopathogenic mechanisms and more effective treatments for patients with the idiopathic form of these diseases.

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