

Rheumatology: 8. Advanced therapy

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The case

A 37-year-old woman with rheumatoid arthritis has recently been prescribed methotrexate (a disease-modifying antirheumatic drug) by her rheumatologist and is taking 10 mg/week orally. She visits her general practitioner complaining of nausea and asks whether she should stop taking the drug. She wonders if she really needs methotrexate because it "isn't working" and "arthritis is crippling anyway." She has read about methotrexate on the Internet and is worried about its side effects.

For most rheumatic diseases, nonsteroidal anti-inflammatory drugs (NSAIDs) relieve symptoms but do not control the disease adequately. Furthermore, they do not alter the underlying disease and, therefore, do not prevent damage to the joints or other involved organs. For this reason, disease-modifying antirheumatic drugs (DMARDs) are indicated in the treatment of deforming inflammatory arthritides, and corticosteroids or immunosuppressive agents, or both, are indicated in the treatment of vasculitides and connective tissue diseases with the involvement of internal organs. This article concerns the practical aspects involved in the administration of DMARDs, corticosteroids and immunosuppressive agents, with emphasis on the treatment of rheumatoid arthritis.

Treatment with DMARDs

Dramatic changes have occurred in the treatment of rheumatoid arthritis and other inflammatory arthritides. Early aggressive treatment, the continuous use of DMARDs and the use of combinations of DMARDs to eradicate inflammation have become the accepted standard treatment.¹ DMARDs can modify the natural course of rheumatic disease by preventing or delaying cartilage and bone destruction. The effect of these agents is 2-fold: by controlling joint inflammation, they provide symptomatic relief of pain, swelling and stiffness, and by preventing cartilage and bone destruction, they reduce joint damage and subsequent disability. The latter effect distinguishes this class of agents from other drugs such as NSAIDs.

The importance of treating rheumatoid arthritis early cannot be overemphasized. There is a window of opportunity for good control of the disease and prevention of joint damage early in the course of the illness. Irreversible erosion can be seen on x-ray films within the first 1–2 years after the onset of the disease, and even earlier using magnetic resonance imaging. Delays in treatment as short as 8–9 months have been associated with significantly greater damage and disability at 3 years² and 5 years³ of follow-up.

Current recommendations include starting DMARD therapy as soon as the diagnosis of rheumatoid arthritis has been established.^{1,4} This means after 6 weeks of inflammation despite treatment with anti-inflammatory drugs.

The aim of therapy is no longer simply to control the symptoms at a level of comfort that is satisfactory to the patient but also to eradicate inflammation and, thus, have a greater impact on the associated disability. More aggressive therapy means continuous use of DMARDs; increasing the dosage to the maximum tolerated or recommended until minimal or no inflammation is achieved; switching to a

Review

Synthèse

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The Arthritis Society salutes CMAJ for its extensive series of articles on arthritis. The Society believes that this kind of information is crucial to educating physicians about this devastating disease.

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different DMARD if no benefit is obtained after a trial at the maximum dose for an appropriate duration; and using combination therapy.

Although DMARDs are potentially toxic, their skilful use by an experienced clinician can help prevent problems. The incidence of serious side effects in long-term studies is rare.⁵ Consultation with a rheumatologist is desirable before initiating DMARD treatment. It is important to have a definite diagnosis of rheumatoid arthritis before beginning DMARD therapy to avoid exposing patients to the risk of serious side effects for a benign transient arthritis.

The trend toward earlier and more aggressive treatment is not limited to rheumatoid arthritis. It has also been shown to affect the prognosis in other rheumatic diseases,

such as lupus nephritis, polymyositis, dermatomyositis and vasculitides, especially Wegener's granulomatosis.

Choice of therapy

The treatment of early rheumatoid arthritis is now recognized as crucial to long-term outcome, and the selection of agents is a complex task owing to the rapidly increasing number of treatments available, alone or in combination. When possible, a rheumatologist should be involved in this decision-making process. There is no consensus as to the order in which DMARDs should be chosen for the treatment of rheumatoid arthritis or other inflammatory arthritides. Choice must be tailored to the patient's profile and prefer-

Table 1: Disease-modifying antirheumatic drugs (DMARDs) used in the treatment of rheumatoid arthritis

Drug	Onset of action	Adequate trial duration*	Usual dosage	Common or important toxicity	Drug interactions
Hydroxychloroquine	3–6 mo	6 mo	≤ 6.5 mg/kg of lean body weight daily	Usually well tolerated; nausea, rash, insomnia, nightmares can occur; delayed accommodation and corneal deposits† are common; retinal toxicity is rare but potentially serious; hemolytic anemia in G6PD deficiency	No important interactions
Sulfasalazine	1–2 mo	3 mo	1 g twice daily (gradual increase from 500 mg/d)‡	GI intolerance (anorexia, nausea, vomiting and skin rash [sulfa allergy]) is fairly common; myelosuppression and hepatitis are rare but potentially serious; reduced fertility in males (reversible); hemolytic anemia in G6PD deficiency	Antibiotics, cholestyramine, iron (decreased absorption), anticoagulants, anticonvulsants, oral hypoglycemics, digitalis, phenylbutazone, methenamine, probenecid, sulfapyrazone
Gold, intramuscular	2–3 mo	6 mo	25–50 mg every 1–4 wk	Stomatitis, pruritus and rash are fairly common; myelosuppression, immune thrombocytopenia and proteinuria are rare but potentially serious	None
Methotrexate	6–8 wk	4 mo	7.5–25 mg/ wk Folate: ≥ 1 mg/d	Anorexia, nausea, stomatitis, mild alopecia and increased liver enzyme activity are fairly common; myelosuppression, hepatic fibrosis and hypersensitivity pneumonitis are rare but potentially serious; increased risk of infections (especially viral); teratogenesis (high risk); increased toxicity with renal impairment; folate supplementation reduces toxicity	Sulfa drugs (especially sulfamethoxazole–trimethoprim: marrow toxicity), phenytoin, phenylbutazone, probenecid, oral antibiotics, hepatotoxic drugs; avoid ethanol
Azathioprine	2–3 mo	4 mo	1.25–2.5 mg/kg daily	GI intolerance (nausea, abd pain, diarrhea) is fairly common; hepatotoxicity (very rare) and myelosuppression are potentially serious; increased risk of infections and of lymphoma (very rare); increased toxicity with renal impairment	Allopurinol, ACE inhibitors, myelosuppressive drugs
D-Penicillamine	3–6 mo	6 mo	250–750 mg/d on empty stomach	Stomatitis, nausea, dysgeusia, pruritus and rash are common; myelosuppression, immune thrombocytopenia and proteinuria are rare but potentially serious; increased risk of autoimmune disorders	Antacids, iron (decreased absorption)

ence, disease activity and prognostic markers of disease severity. For rheumatoid arthritis, intramuscular gold, methotrexate, hydroxychloroquine and sulfasalazine are all adequate first choices. The last 2 tend to be used in patients with indicators of less severe disease. For the peripheral arthritis of psoriatic arthritis, methotrexate is the DMARD of first choice when NSAIDs fail to control symptoms. Its ability to control both the skin disease and the arthritis is a major advantage. Intramuscular gold and sulfasalazine are adequate alternatives, and hydroxychloroquine and azathioprine can also be used. Sulfasalazine has the advantage of potentially controlling both the peripheral arthritis and the spinal disease in patients with psoriatic arthritis or ankylosing spondylitis. For further discussion of the diagnosis and management of inflammatory polyarthritis, please refer to the

previously published article in this series by Alice Klinkhoff.⁶

Tables 1 and 2 list issues related to the practical management of DMARDs.

Initial period of therapy

Because a response may not be observed for up to several months after DMARD therapy is started, it is important to offer support to patients during the waiting period. One or more intra-articular corticosteroid injections may be beneficial in alleviating the symptoms of joint inflammation. Alternatively, low-dose prednisone administered orally may be prescribed as "bridging therapy" until the effect of the second-line agent is felt. Patients may be referred to physiotherapy and occupational therapy for treat-

Table 1 continued

Drug	Onset of action	Adequate trial duration*	Usual dosage	Common or important toxicity	Drug interactions
Cyclosporine	2–3 mo	4 mo	3–5 mg/kg daily	Hirsutism and gingival hyperplasia are fairly common; hypertension and renal insufficiency are relatively common, but usually reversible; hepatotoxicity, myelosuppression and hyperkalemia are rare; increased risk of infections (especially viral) and of lymphoma (very rare)	Diuretics (especially K sparing), ACE inhibitors, antifungals (especially ketoconazole), lipid-lowering agents, acyclovir, erythromycin, doxycycline, imipemen, rifampin, verapamil, diltiazem, anticonvulsants, colchicine
Leflunomide	1–2 mo	3 mo	100 mg/d for 3 d (loading), then 20 mg/d. Use 10 mg/d if toxicity or in comb mtx	Diarrhea is common; rash, mild alopecia, increased liver enzyme activity and nausea are fairly common; increased risk of infections (especially viral and URTI); teratogen, drug may persist up to 2 yr after d/c; increased toxicity with renal or hepatic impairment	Cholestyramine or charcoal: use for drug elimination; hepatotoxic drugs, rifampin, tolbutamide
Etanercept	2 wk	3 mo	25 mg subcut twice weekly; rotate injection sites	Injection-site reactions are common; increased formation of autoimmune Ab (ANA, anti-DNA); long-term effect on development of autoimmune diseases unknown; increased URTI; increased risk of serious infections and malignancies are potential concerns; no reported increased risk, but long-term data are lacking	None known
Infliximab	2 wk	3 mo	3 mg/kg (2-hr intravenous infusion) @ 0, 2 and 6 wk (induction), then q 8 wk	Hypersensitivity reactions (< 2 hr post infusion) are rare but potentially serious and are an indication for d/c; increased formation of autoimmune Ab (ANA, anti-DNA); long-term effect on development of autoimmune diseases unknown; increased URTI; increased risk of serious infections and malignancies are potential concerns; no reported increased risk, but long-term data are lacking	None known

Note: comb mtx = combination with methotrexate, subcut = subcutaneously, G6PD = glucose-6-phosphate dehydrogenase, GI = gastrointestinal, abd = abdominal, URTI = upper respiratory tract infections, d/c = discontinuation of drug, Ab = antibodies, ANA = antinuclear antibodies, ACE = angiotensin-converting-enzyme, K = potassium, q = every.

*Adequate trial duration = duration of therapy required to assess efficacy of drug.

†Accommodation refers to the length of time the pupil takes to readjust focus when one looks from a distant object to a closer one, or vice versa, (i.e., the duration of blurred vision when changing focus). Corneal deposits cause halos around lights, especially at night.

‡The following regime of gradually increasing dosages improves GI tolerance: 500 mg/day for 1 week, then 500 mg twice a day for 1 week, then 500 mg in the morning and 1 g in the afternoon, then 1 g twice a day thereafter. The dose can be increased to a maximum of 3 g/day if necessary.

Source: Adapted from American College of Rheumatology, p. 717.¹ The order in which the drugs are presented does not represent any particular treatment algorithm.

ments such as icing, the applying of wax and ultrasonography to reduce the symptoms of inflammation. They may also be referred to the Arthritis Self-Management Program, or other educational programs offered by the Arthritis Society of Canada (www.arthritis.ca) and others, to help them understand their disease and, thus, improve their ability to cope with symptoms. (In Canada, information on these services can be obtained by calling 800 321-1433.)

Side effects

Patients must be made aware of the need for monitoring. The incidence of serious side effects is markedly re-

duced with regular monitoring, because adverse effects are more likely to be discovered before serious or irreversible consequences arise. Despite the long list of side effects, which often intimidates patients, long-term series of rheumatoid arthritis patients treated with DMARDs have found that serious side effects are rare.⁵

When counselling a patient who expresses concern about potential side effects, it is also important to remind him or her of the consequences of the alternative; doing nothing will result in irreversible disability, progressive joint damage and premature death. It is also important to recognize that information on the use of antirheumatic drugs in other fields of medicine may not be applicable to patients with rheumatic diseases. Drugs such as methotrex-

Table 2: Recommended monitoring strategies for patients with rheumatoid arthritis treated with DMARDs

Drug	Baseline evaluation	Monitoring	
		Physical examination	Laboratory tests
Hydroxychloroquine	None unless patient has had an eye disease	Visual changes, fundoscopic and visual fields every 12–18 mo	None
Sulfasalazine	CBC and AST or ALT level; check G6PD in patients at risk	Myelosuppression,* photosensitivity, rash, GI intolerance	CBC, LFTs every 2–4 wk for first 3 mo, then every 3 mo
Gold, intramuscular	CBC, platelet count, creatinine level, urine dipstick for protein	Myelosuppression,* edema, pruritus, rash, oral ulcers, diarrhea	CBC, platelet count, urine dipstick every 1–2 wk for first 20 wk, then every 3rd to 4th injection
Methotrexate	CBC, chest radiography within past year, hepatitis B and C serology in high-risk patients, AST or ALT level, albumin, alkaline phosphatase, BUN and creatinine levels, pregnancy test if appropriate	Myelosuppression,* shortness of breath, nausea/vomiting, lymph node swelling, mouth sores, alopecia	CBC, platelet count, AST, ALT, albumin, creatinine levels every 4–8 wk
Azathioprine	CBC, platelet count, creatinine, AST or ALT levels	Myelosuppression,* lymph node enlargement	CBC and platelet count every 1–2 wk with changes in dosage, and every 1–3 mo thereafter; LFTs every 1–3 mo
D-Penicillamine	CBC, platelet count, creatinine level, urine dipstick for protein	Myelosuppression,* edema, rash	CBC, urine dipstick for protein every 2 wk until dosage stable, then every 1–3 mo
Cyclosporine	CBC, creatinine level, LFTs, BP, hepatitis B and C serology (optional)	BP every 1–2 wk until dosage stable, then monthly; review of symptoms and exam every 6 mo for evidence of lymphoma	Creatinine level every 2 wk until dose is stable, then monthly; periodic CBC, potassium and LFTs
Leflunomide	CBC, hepatitis B and C serology in high-risk patients, AST or ALT level, albumin, alkaline phosphatase, BUN and creatinine levels; pregnancy test if appropriate; exclude active infection or malignancy	Infection, diarrhea, nausea, hair loss, rash	AST, albumin, CBC, creatinine levels monthly
Etanercept	Exclude active infection or malignancy	Infection, malignancy, autoimmune diseases	None
Infliximab	Exclude active infection or malignancy	Infection, malignancy, autoimmune diseases	None

Note: CBC = complete blood cell count (hematocrit, hemoglobin, white blood cell count) including differential cell and platelet counts, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, LFTs = liver function tests, BP = blood pressure.

*Signs of myelosuppression include fever, infection, bruising easily and bleeding.

Source: Adapted from American College of Rheumatology.⁷

ate and cyclosporine, which are used in cancer therapy and transplant programs respectively, are used in lower doses for rheumatoid arthritis, and the incidence of adverse events is lower.

Long-term use of DMARDs

Persistence in the use of DMARDs is of great importance. DMARDs are used to treat incurable, chronic diseases where treatment will be lifelong and the number of available options is limited.

Typically a patient with rheumatoid arthritis will use a succession of DMARDs over the years. After an initial response, a drug is often eventually discontinued, either because of adverse side effects or loss of effect. To ensure the best result, it is important to give each drug a full trial, namely, the maximum dose for sufficient time, before declaring it not efficacious. In addition, there are a number of strategies for dealing with common side effects. Rather than stopping treatment, the patient may be referred to a rheumatologist, or one can be consulted by the physician, regarding the management of persistent side effects.

Combining DMARDs

The use of a combination of DMARDs is now widely practised. Some rheumatologists advocate the use of combination therapy from the onset of disease for early control, with a subsequent gradual withdrawal of therapy, as necessary to maintain control. Others prefer the opposite strategy: successively adding DMARDs to agents to which the patient has shown a partial response. Proponents of the latter view believe it prevents unnecessary exposure to potentially toxic drugs of patients who may respond to single therapy. This approach may also be more acceptable to patients. Commonly used combinations include hydroxychloroquine with most DMARDs, especially methotrexate or intramuscular gold; sulfasalazine and methotrexate with or without hydroxychloroquine; and cyclosporine and methotrexate.

New DMARDs

The immunomodulatory agent leflunomide is now available in Canada; leflunomide is superior in efficacy to placebo and equivalent to sulfasalazine or methotrexate. Two biologic agents that block the tumour necrosis factor cytokine, etanercept and infliximab, will soon be available in Canada. They are available in the United States and can be obtained under special circumstances in Canada. Etanercept is superior to

placebo, when used alone in moderate to severe rheumatoid arthritis refractory to previous DMARDs, or when used in combination with methotrexate in partial responders to that drug. Infliximab is superior to placebo when used in combination with methotrexate again in partial responders to that drug. Long-term data on the safety of these new DMARDs are still lacking, but they have been well tolerated in short-term studies. No consensus has, as yet, been reached as to when they should be used, but Canadian guidelines are currently being developed. Their prohibitive cost will probably limit their use to patients whose condition is refractory to standard DMARD therapy.

Antibiotics

The use of antibiotics, particularly minocycline, in the treatment of rheumatoid arthritis has recently

received widespread media attention. The treatment of rheumatoid arthritis with anti-infectious agents is not a new concept. Gold was first introduced because of its presumed effect against tuberculosis. Sulfasalazine and hydroxychloroquine are used widely for mild to moderate rheumatoid arthritis and are undoubtedly effective.

Minocycline, and perhaps doxycycline, also appear to be effective clinically in early disease;⁸ however, as yet, studies have shown no improvement visible on x-ray films.⁹ Minocycline does not appear effective in later rheumatoid arthritis,¹⁰ and it may cause autoimmune disease as a side effect. Its exact role is still not clearly established, and its effectiveness is not thought to be because of its antibiotic properties. Other immunologic or cartilage-protective ef-

Key points

- Disease-modifying antirheumatic drugs (DMARDs) not only control symptoms of inflammation but also modify the natural course of rheumatic disease by preventing joint damage and disability.
- New trends in the treatment of rheumatoid arthritis include early, aggressive and continuous treatment with DMARDs and the use of a combination of DMARDs. The goal of therapy is the absence of inflammation.
- With close supervision and regular monitoring, serious side effects in patients taking DMARDs are rare.
- The choice of DMARD must be tailored to the individual. Because onset of action is delayed, support must be provided in the meantime.
- A full trial is necessary before a DMARD is declared ineffective; rather than discontinuing a drug, strategies should be used to control side effects.
- Anti-infectious agents, such as sulfasalazine and hydroxychloroquine, are effective in the treatment of early or mild to moderately severe rheumatoid arthritis; minocycline may be effective in early disease. Their effectiveness is not because of their antibiotic properties.
- Although corticosteroids result in rapid, potent and reliable suppression of inflammation, their precise role in treating rheumatoid arthritis remains controversial.
- In rheumatoid arthritis, oral or intra-articular steroids may be used for bridging therapy while waiting for DMARDs to take effect or to control a flare-up.

fects seem more likely. Minocycline is prescribed at a dose of 100 mg, taken orally twice a day, and requires monitoring by complete blood counts and liver function tests every 4–12 weeks.

Immunosuppressive agents

Immunosuppressive agents are used in the management of systemic manifestations of autoimmune diseases and vasculitis. These agents include azathioprine, cyclophosphamide, chlorambucil, cyclosporine and methotrexate. Cyclophosphamide can be administered orally in daily doses or in intravenous monthly pulses; the latter method has been best studied in the treatment of lupus nephritis¹¹ but is now used more widely. Its main advantage over oral administration is the reduction in risk of some of the side effects (Table 3). Contraception is essential for men and women in view of the high risk of teratogenesis. Strategies are available to reduce the risk of sterility.

Corticosteroids

Use in treating rheumatic diseases

The use of corticosteroids results in rapid, potent and reliable suppression of inflammation. This explains their wide use for the inflammatory manifestations of rheumatic diseases and for systemic vasculitis. However, their effect in suppressing the synovitis in rheumatoid arthritis is not sustained and requires a progressive increase in dosage to maintain the benefit. The precise role of orally administered corticosteroids in rheumatoid arthritis remains controversial. Despite recent evidence suggesting that corticosteroids may reduce the rate of radiologic progression,^{12–14} most clinicians prefer to limit their use to the short term because of the substantial side effects associated with long-term use (e.g., osteoporosis,

osteonecrosis, hyperglycemia, hypercholesterolemia) and the difficulty in tapering off the dose.

Short courses of low-dose steroids can be useful as “bridging therapy” to control symptoms while waiting for DMARDs to take effect or to control severe flare-ups. Patients can decrease the dose as soon as symptoms are under control. The injection of steroids into the most affected joints can often alleviate the need for oral steroids (at the rate of 1–2 large joints every 2–6 weeks). Intramuscular injections of corticosteroids are advocated by some to prevent difficulties in tapering off the dose of oral corticosteroids.

Practical management

It is useful to think of corticosteroid administration in 3 broad ranges: low dose (i.e., the equivalent of orally administered prednisone, 15 mg daily or less), as used in the treatment of polymyalgia rheumatica, active arthritis and mildly active systemic lupus erythematosus; moderate dose (i.e., 15–25 mg daily); and high dose (i.e., 25–60 mg daily), as used in the treatment of acute manifestations of systemic vasculitis and the more severe manifestations of systemic lupus erythematosus. Side effects associated with systemic steroids are listed in Table 4. Prophylaxis for osteoporosis should be addressed as soon as steroids are instituted (see the upcoming article in this series on osteoporosis by John P. Wade).

Methylprednisolone can also be administered by intravenous pulse for the treatment of severe or potentially life-threatening manifestations of systemic vasculitis or systemic lupus erythematosus when rapid and maximum efficacy is desired (Table 5).

Reducing the dose is a challenge faced by any clinician prescribing corticosteroids. Problems encountered with tapering off include adrenal insufficiency with abrupt reductions or discontinuations, exacerbation of the underlying disease (the most common problem with vasculitides and connective tissue diseases) and corticosteroid withdrawal

Table 3: Immunosuppressive agents used in the treatment of rheumatic diseases

Drug	Usual dosage	Toxicity	Monitoring
Cyclophosphamide	Oral:* 2 mg/kg daily IV pulse:*† 0.75–1 g/m ² of body surface monthly for 6 mo, then every 3 mo for a total of 10 doses	Myelosuppression; infections; hypogammaglobulinemia; malignancies (especially hematopoietic‡); hemorrhagic cystitis, bladder fibrosis and carcinoma;‡ nausea, vomiting; alopecia; gonadal failure;‡ pulmonary fibrosis;‡ risk of teratogenesis	CBC for oral dose: every 1–2 wk for first 2 mo and after dose changes, then every 1–2 mo; for IV pulse: 7–14 d after pulse and before next pulse; urine analysis monthly; urine cytology yearly, even after drug cessation
Chlorambucil	0.1–0.2 mg/kg orally per day	Myelosuppression; infections; malignancies (especially hematopoietic); nausea, vomiting; gonadal failure; dermatitis; risk of teratogenesis	CBC every 1–2 wk for first 2 mo, every 1–3 mo after dose changes

Note: IV = intravenous.

*Adjust dose according to white blood cell (WBC) count: for oral dose, keep WBCs > 3 × 10⁹/L; for IV pulse, keep lowest WBC count > 3 × 10⁹/L and WBC count > 4 × 10⁹/L before dose.

†IV pulse must be preceded by IV hydration, with or without use of mesna, to reduce bladder toxicity.

‡Lower risk of these side effects with IV pulse than with daily oral dose.

syndrome. The latter consists of fatigue, malaise, nausea, anorexia, weight loss, myalgias and arthralgias and must be differentiated from an exacerbation of the underlying disease. It occurs fairly frequently in patients treated with moderate- or high-dose prednisone for long periods and requires very gradual reduction of the dosage.¹⁸

No specific guidelines for tapering off corticosteroids can be provided, as the pattern depends on the particular clinical situation. Generally, however, one can use high doses for short periods (until severe exacerbations have been controlled), such as 1–2 weeks, followed by rapid reduction to the moderate range and slower reduction thereafter (e.g., reducing every week by 10 mg from 60 mg/day

to 40 mg/day; by 5 mg every week to 25 mg/day; by 2.5 mg every week to 15 mg/day; followed by 2.5-mg or even 1-mg reductions at longer intervals such as every 2–4 weeks depending on the situation, until discontinuation).¹⁷ Patients with exacerbation of the underlying disease or withdrawal syndrome may require even more gradual tapering off, especially in the low-dose range. The addition of corticosteroid-sparing agents can be useful when disease exacerbations prevent tapering off. Depending on the clinical situation, azathioprine, methotrexate, cyclophosphamide or chlorambucil can be used for this purpose.

The use of an alternate-day regimen is associated with a lower incidence of some of the side effects (Table 4).¹⁷ Maintenance of control of the disease can be a problem. Switching from daily to an alternate-day regimen must be done gradually (by tapering off the dose on alternate days down to zero) to prevent both adrenal insufficiency and exacerbation of the disease. Administration of the dose in the evening, a divided dose and the use of longer acting forms are associated with greater adrenal suppression.

The case revisited

In our case study the physician should explain the purpose and importance of DMARD therapy to the patient. Emphasizing that such treatment *does* affect outcome is essential for the patient to accept the therapy and its potential side effects. She can be reassured that with careful monitoring, the incidence of serious side effects is rare. She should be provided with appropriate sources of patient information, such as that provided by the Arthritis Society of Canada or its provincial divisions, and cautioned about “generic” sources of information. Information about the use of methotrexate in cancer therapy is not applicable in the context of rheumatoid arthritis, where it is used in lower doses.

Strategies to manage this patient’s nausea should be tried before advising her to discontinue the drug. For example, she may add folate (1 mg/day) or folic acid (a 5–10-mg dose 10 hours after methotrexate); take the methotrexate at bedtime if the nausea occurs only after the dose; split the dose in 2 (to be taken 12 hours apart); or change from an oral to an intramuscular route of administration. Dose reduction would be another alternative in a different context.

Table 4: Adverse effects of systemic corticosteroid therapy

Metabolic*	Fatty acids (obesity, cushingoid features, localized fat deposits), glucose (hyperglycemia and insulin resistance), protein catabolism, electrolyte imbalances (Na retention and K loss), hepatic enzyme induction
Infections*	Predisposition to bacterial (especially staphylococcal, gram-negative bacteria, tuberculosis, <i>Listeria</i>), viral and fungal infections
Musculoskeletal	Proximal myopathy, osteoporosis, avascular necrosis, tendon rupture, steroid withdrawal syndrome
Gastrointestinal	Peptic ulcer disease, † pancreatitis
Ophthalmic	Cataract, glaucoma
CNS	Psychosis, insomnia, depression, benign cranial hypertension
Dermatologic	Acne, striae, alopecia, bruising, skin atrophy, decreased wound healing, sweating
Endocrine*	Growth retardation in children, ‡ hypothalamic–pituitary–adrenal axis suppression
Cardiovascular	Spectre of premature coronary and cerebral arteriosclerosis§

Note: Na = sodium, CNS = central nervous system.

*Side effects reduced with alternate-day therapy.

†Increased risk is controversial: support from anecdotal report and uncontrolled series has not been confirmed by controlled trials.¹⁵ This therapy exacerbates the ulcerogenic properties of nonsteroidal anti-inflammatory drugs.¹⁶

‡Occurs with prednisone at dosage > 7.5 mg/day.

§ Increased risk with prolonged therapy is strongly suggested by recent evidence.¹⁵

Source: Adapted from Kirwan.¹⁷

Table 5: Methylprednisolone administered by intravenous pulse in the treatment of rheumatic diseases

Dosage	Administration	Monitoring	Side effects
1 g IV daily for 1–3 doses	In 50 mL D ₅ W (or 2/3 glucose : 1/3 saline) for 30–40 min, under nursing supervision	Rule out symptoms of infection; check BP, volume status, glucose and electrolytes (K ⁺) before and after each pulse	Volume overload (CHF, acute HBP), hyperglycemia, electrolyte imbalance (especially hypokalemia),* infections, acute psychosis,* sleep disturbance, pancreatitis, GI bleeding, transient arthralgia (synovitis), sudden death from ventricular dysrhythmia,* seizures*

Note: D₅W = 5% dextrose (in water) injection, CHF = congestive heart failure, HBP = hypertension.

*Very rare events.

Regarding efficacy, the physician should ask when the last change to the dose occurred, because improvement usually takes 6 weeks. Methotrexate should not be considered ineffective until a dose of at least 15–25 mg/week has been tried.

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