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Medical Management of Children with Juvenile Rheumatoid Arthritis

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Contents

Abstract

One of the most important and changing areas of research in paediatric rheumatology is the optimum approach to the treatment of children with chronic arthritis. Until recently all medications for children with arthritis were nonspecific in terms of our understanding, albeit poor, of the pathogenesis of these diseases. Of current therapies, low dose, once-a-week methotrexate has emerged as the therapeutic agent of choice for children who fail to respond adequately to administration of a nonsteroidal anti-inflammatory drug. Thereby, it has displaced the more traditional slower acting anti-rheumatic drugs, although one or more of them are often combined with methotrexate in the polypharmaceutical approach to childhood arthritis.

Better and more specific agents are needed, especially for systemic onset disease, unremitting polyarticular involvement, and certain complications such as resistant chronic uveitis. At this time the introduction of the cyclo-oxygenase 2 inhibitors and etanercept (soluble tumour necrosis factorα.p75 fusion protein) may herald an era of more specific and effective therapy.

One of the most important, and changing, areas of clinical research in paediatric rheumatology is the optimum approach to the treatment of children with chronic arthritis. The majority of children with juvenile rheumatoid arthritis (JRA) have a good to excellent outcome, but it is not usually possible at the onset of the disease to predict which child will recover promptly, and who might go on to have unremitting disease with lingering disability or enter adulthood with serious functional impairment. Therefore, the initial therapeutic approach must be vigorous in all children. Furthermore, JRA is a heterogeneous syndrome and therapy needs to be modified in recognition of its 3 principal types of onset: polyarthritis, oligoarthritis, and systemic disease (fig. 1). Eventually, evolution of the course subtypes of the disease, and recognition of prognostic indicators, will lead to modifications of the initial program in keeping with the response of the child. Finally, although the major focus of medical therapy is on the arthritis, other extra-articular complications of the disease may require intervention, such as development of uveitis, growth retardation, osteopenia, or amyloidosis.

Medical management of children with JRA should begin with the safest and simplest therapy judged to be effective (table 1). If this approach proves to be inadequate, other therapeutic modalities are promptly selected in an orderly progression. Because remissions are often of limited duration, medical therapy should be reasonably prolonged after all manifestations of disease have abated, perhaps for a period of at least 1 and often 2 years. Summaries of approaches to selection and management of medical therapy in JRA, and the pharmacology of the agents, used have been previously published.[1,2]

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

In most children, one of the nonsteroidal anti-inflammatory drugs (NSAIDs) is the basic approach to therapy (table II).[3] All of these drugs have antipyretic, analgesic and anti-inflammatory actions, and for those that have been approved for use in children, a record of long term safety. All current drugs inhibit the activity of both cyclo-oxygenases 1 and 2.[4-6] Hopefully cyclo-oxygenase 2-specific NSAIDs will soon be available for use in children.

1.1 Aspirin (Acetylsalicylic Acid)

Aspirin (acetylsalicylic acid) was the first of these agents and in many instances is still a satisfactory approach to basic therapy in much of the world. Treatment is started at an approximate dosage of 80 mg/kg/day depending upon the age and bodyweight of the child with higher doses tolerated best in younger children.[1,7-10] Aspirin is the only NSAID for which blood concentrations are measured, and these measurements occasionally are useful as guides to correct dosage in the preverbal child. The approximate serum level 2 hours after the morning dose is 20 to 25 mg/dl.[8-10]

Like many NSAIDs, aspirin must be given 4 times a day with meals and at bedtime with milk or food in order to minimise gastrointestinal irritation and ensure therapeutic blood concentrations. Because the serum half-life of aspirin is prolonged to approximately 16 hours once therapeutic concentrations are achieved, it does not have to be given during the night time.[10] There are numerous types of salicylate available besides the preferred dosage form of aspirin, including magnesium and choline salts, buffered preparations, and enteric coated pills. Children should be discouraged from chewing aspirin because it will erode the biting surfaces of the teeth and irritate the gums.[11,12]

Some epidemiological studies have demonstrated a potential association between use of aspirin and development of Reye's Syndrome.[13-18] Warnings about this possible association by the US Food and Drug Administration have resulted in a dramatic decrease in the use of aspirin in the United States. However, salicylates, or indeed any other NSAID, should be discontinued in a sick child who may have a viral illness with fever or who is vomiting. All children with chronic arthritis should be

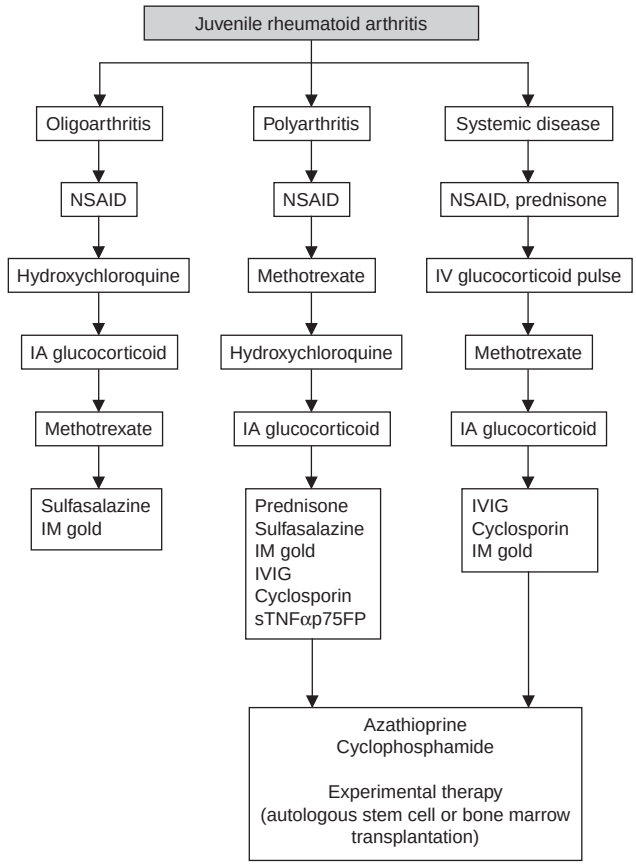

Fig. 1. Juvenile rheumatoid arthritis: 3 principal types of onset and their treatment: **IA** = intra-articular; **IM** = intramuscular; **IV** = intravenous; I**VIG** = intravenous human immunoglobulin therapy; **NSAID** = nonsteroidal anti-inflamatory drug; **sTNFαp75FP** = soluble tissue necrosis factor a receptor p75 fusion protein.

immunised each year for influenza, and initially, for varicella.

1.2 Other NSAIDs

Most of the newer NSAIDs have unfortunately not been widely tested for safety or effectiveness in JRA. In the United States and Canada, only aspirin, naproxen, ibuprofen and tolmetin have been approved for use in children. In Australia, only aspirin, naproxen and ibuprofen have been licensed for paediatric use. Among the most commonly used agents and the conservative dosages are: ibuprofen 35 mg/kg/day given as 4 divided doses;[19,20] naproxen 15 mg/kg/day given as 2 divided doses;[21-25] tolmetin 25 mg/kg/day given as 4 divided doses;[25-27] and diclofenac 2 to 3 mg/kg/day given as 2 divided doses.[25,28,29] Naproxen and ibuprofen are available in suspensions which are convenient for younger children who have difficulty swallowing tablets. The dosage of liquid ibuprofen should be 45 mg/kg/day because of differential absorption of the 2 enantiomers of the drug.[30]

Indomethacin is also an effective and potent anti-inflammatory agent with pronounced antipyretic actions for children with systemic disease.[31,32] It has been of particular value in the older child, but its overall use has perhaps been limited by occa-

sional serious adverse effects and early reports of masked infections and sudden deaths.[33]

The meticulous and numerous clinical trials of NSAIDs by the Paediatric Rheumatology Collaborative Study Group (PRCSG) led to the conclusion that approximately 65% of the children who were going to respond did so by 4 weeks of therapy. However, there were some children who were late responders; a 100% level of response was not obtained before 12 weeks in 72 (57%) of the 127 children who experienced a favourable outcome.[34] Clinical response to an NSAID is variable and relatively unpredictable. A child may fail to respond to 1 drug and yet respond to another. If a child has not responded to one NSAID, or tachyphylaxis has seemingly developed, a subsequent trial with another agent is warranted. In such situations it is logical to select an NSAID from a different chemical class than that first used (salicylic, proprionic, indoleacetic, pyrrolealkanoic, N-phenylanthranilic acids, or oxicams).

A number of specific toxicities related to NSAIDs may be observed in children with JRA. Nonsteroidal hepatitis or transaminasaemia may develop with elevations of the aspartase and alanine transaminases. The transaminase enzymes were observed to be intermittently increased in up to 45% of the children receiving therapeutic amounts of aspirin.[35] Overt manifestations of liver disease are uncommon and jaundice does not occur. Transient low grade elevation in the levels of these enzymes in a child who is otherwise showing no clinical signs of toxicity is not an indication for withdrawing the drug. It is an impression that transaminasaemia has become less frequent in children receiving the newer NSAIDs than was previously observed with aspirin.

These drugs may also rarely result in renal adverse effects in children.[36,37] They inhibit prostaglandin synthesis and modulation of the renovascular smooth muscle, which results in suppression of renal blood flow and glomerular filtration.[38] However, these observations are almost totally confined to children who already have compromised renal function, but have also been observed in the rare child with debilitating arthritis, limited mobility, and potential intermittent dehydration because of a desire not to drink adequate amounts of fluids in order to limit the frequency of urination, particularly while attending school.[36,37] In these children elevation of the blood urea nitrogen (BUN) or creatinine levels, haematuria, and hypertension may together or singly be the first indication of toxicity.

Another specific adverse effect of the NSAIDs which is observed with variable frequency is photosensitivity with the development of a pseudoporphyria reaction. In these children, small vesicles with ulceration and scar formation occur repeatedly on the exposed surfaces of the body, par-

Table I. Antirheumatic drugs: dose, indications and contraindications

Drug	Maintenance	Indications	Contraindications
NSAID	Varies	Active arthritis	Peptic ulcer disease, asthma, azotaemia, hepatitis
Methotrexate	10 mg/m^2/week	Polyarthritis unresponsive to NSAID therapy	Hepatitis, obesity, malnutrition, illicit drug or alcohol use, diabetes mellitus, malignancy, pregnancy
Hydroxychloroquine	5-7 mg/kg/day	Chronic arthritis	Inability to perform a satisfactory ophthalmological examination
Parenteral gold	0.75-1.00 mg/kg/week	Polyarthritis unresponsive to NSAID therapy	Impaired bone marrow, renal or hepatic function, prior severe adverse reaction to another gold compound
Sulfasalazine	40-60 mg/kg/day	Arthritis unresponsive to NSAID therapy	Hypersensitivity to salicylate or sulfa-containing drug; glucose-6-phosphate dehydrogenase deficiency, porphyria
Penicillamine	10 mg/kg/day	Polyarthritis unresponsive to NSAID therapy	Impaired bone marrow, renal or hepatic function; prior severe adverse reaction to gold or penicillin

NSAID = nonsteroidal anti-inflammatory drug.

Table II. Dosages of nonsteroidal anti-inflammatory drugs in children with juvenile rheumatoid arthritis

Drug	Dosage (mg/kg/day)	Maximum dosage (mg/day)
Naproxen	15	750
Ibuprofen	35	2400
Tolmetin	25	1600
Aspirin	80	4800
Diclofenac	3	150
Indomethacin	1.5	150
Sulindac	4	300

ticularly the forehead, cheeks, and back of the hands. This reaction may be somewhat more common with naproxen than the other drugs.[39-43] When it is observed, another agent should be chosen for treatment and the family cautioned again about the potential of photosensitisation and measures to avoid it.

Paracetamol (acetaminophen) 2 to 3 times a day made be useful for control of pain or fever in the systemically ill child, although it is not an anti-inflammatory agent. This drug should not be used regularly for a long period of time because its renal safety in children with JRA has been questioned because it is an active metabolic product of phenacetin.

2. Methotrexate

It is somewhat difficult to be sure whether to categorise methotrexate as an anti-inflammatory drug, or perhaps a remittent drug, but it is often the next drug chosen for use in JRA if basic treatment with an NSAID has not achieved the goals of therapy.[44-51] Methotrexate in many ways is an ideal medication for use in paediatric practice because it is efficacious at dosage levels below those expected to produce adverse effects, and because of its lack of apparent oncogenicity or the production of sterility.[48,50,52,53]

Methotrexate is administered once a week orally with clear liquids 60 minutes before breakfast on an empty stomach.[54] The slower absorption of methotrexate that results when it is combined with food produces a lower level of efficacy and probably does little to avoid gastrointestinal upset in children. In children predisposed to gastrointestinal upset, liquid methotrexate may be given in the morning, often preferred in order to achieve the correct dose in children in any case, or subcutaneous injection may be substituted for the oral route. In a few children, giving the oral medication late at night before bedtime and certainly 3 hours after the evening meal may also suffice.

Methotrexate inhibits dihydrofolate reductase and blocks the transfer of single carbon units in the methylation of deoxynucleotides. The efficacy of the drug is generally evident after 2 months treatment, or 3 months at a maximum, and 9 months should be considered an adequate trial of the drug. Methotrexate is almost always at least partially efficacious, but if not, treatment should be stopped at that time. It should also be stopped if serious toxicity develops. Reports by Wallace[55] and Giannini and Cassidy[56] have suggested that virtually all children respond to methotrexate, at least in part, and 5 to 45% achieve a remission.

The dosage of methotrexate that was determined to be effective was 10 mg/m^2/week or approximately 0.3 mg/kg/week.[47] This dosage may be gradually increased to the range of 1 mg/kg/week depending upon the response of the child.[57-59] In some children at low dosages, and in most children at dosages greater than 0.5 to 0.6 mg/kg/week, absorption of methotrexate may be inadequate from the gastrointestinal tract and subcutaneous administration should be substituted. Adequate absorption can be verified by performing a 1-hour methotrexate blood concentration, which should be in the range of 6 to 12 x 10^{-7} mol/L.[60-62] The effective dose of methotrexate may not be constant over time and may require readjustment if the level of initial improvement appears to regress. Folic acid 1 mg/day is generally administered along with methotrexate.[63]

Systemic toxicities include bone marrow suppression, acute pulmonary insufficiency and interstitial pneumonitis, gastrointestinal irritation with potential ulceration and diarrhoea (a complication that seems to be less frequent in children than in adults), and alopecia. Cirrhosis of the liver is not

an expected toxicity in children on weekly therapy[64-66] as long as appropriate monitoring for toxicity is meticulously followed and known risks that have been primarily identified in adults are avoided, such as malnutrition, previous viral hepatitis (HIV should also be considered), diabetes mellitus, obesity, and, less likely except in the teenager, smoking or alcoholism. The recommendations of the Subcommittee on Hepatic Toxicity and Methotrexate of the American College of Rheumatology are used as guidelines in this regard.[67]

The protocol developed for monitoring toxicity by the PRCSG recommends that the following be undertaken at baseline: a complete blood count (CBC) with differential and platelet counts; BUN; urinalysis; tests for previous hepatitis including A, B, and C; and an assessment of liver function (measurement of AST, ALT, serum albumin and serum bilirubin levels).[47] Chest radiographs and, if indicated, pulmonary function studies should also be performed. If there is any history of renal disease, a creatinine clearance should be done as methotrexate is excreted through the kidneys although it *per se* does not cause renal disease. Monitoring during the course of treatment should include a repeat CBC and liver function tests every 4 weeks initially, and then eventually every 8 weeks during therapy.

The bioavailability of methotrexate after absorption is to a large extent dependent upon the serum albumin level. It was formerly considered that serum albumin levels below 28 mg/L were a major risk factor for toxicity. However, more experience has indicated that this is not necessarily the case.[47,48] Nevertheless, potential drug interactions with albumin binding, particularly those involved with the NSAIDs, are important.[68] Therefore, the dose of the NSAID should remain constant during therapy. These interactions are probably less pronounced with the newer NSAIDs than with aspirin. In a study by Wallace et al.,[68] a variety of NSAIDs including aspirin, tolmetin, and ibuprofen did not produce significant changes in the 1-hour or 24-hour methotrexate blood concentrations. In addition, prednisone, hydroxychloroquine, and sulfasalazine had no effect. However, methotrexate may prolong, the half-life of an NSAID by up to 24% by delaying the renal clearance of that drug.

The initial double-blind controlled trial of methotrexate in children with JRA conducted by the PRCSG included the study of 2 dosages of 5 mg/m^2/week and 10 mg/m^2/week along with a placebo control group.[47] Statistical improvement in articular severity scores were observed with a mean of 36% for the placebo group, a mean of 32% for the 5mg group, and a mean of 63% for the 10mg group. Recalculating these data by the newer Pavia criteria for response in JRA[69-71] (≥3 of any 6 core variables improved by ≥30% with up to 1 variable worse) indicated that 72% of children improved with methotrexate versus 44% of the placebo group,[51,72] a highly significant difference. There was no difference between the placebo and the 5 mg/m^2/week dosage. Adverse effects developed in 2 of 45 patients: 1 child developed haematuria and the other developed persistent transaminacaemia. One of the placebo patients developed gastrointestinal irritation severe enough to be removed from the study. The results of these observations established methotrexate as the most effective anti-inflammatory agent that had been tested for the amelioration of chronic arthritis in children.[48,49,55,56,73,74] Clinical improvement of arthritis and a relatively low level of adverse effects have also been reported in a number of other studies.[44,45] Objective assessment has included the number of swollen joints, morning stiffness, systemic features of the disease, the mean daily dose of glucocorticoid required, and erythrocyte sedimentation rate (ESR) and C-reactive protein level.

However, approximately 45% of the children in these studies, which employed a relatively low dose of methotrexate by current recommendations, did not respond or had an inadequate response.[46,48] A report of Wallace et al.[55] included 23 children with seropositive polyarthritis that were treated with dosages of methotrexate that ranged from 0.1 to 0.6 mg/kg/week. 21 improved significantly and a remission was noted in 2 chil-

dren. Glucocorticoid dosage was reduced successfully in 6 of 9 children, and no serious toxicity was encountered. An important observation was that the average time to clinical response was approximately 3.3 months with a range of 1 to 8 months, which at that time was interpreted as suggesting that children might take longer to respond to methotrexate than adults with rheumatoid arthritis. It was not possible in this study to identify clinical features that would predict improvement such as the type of onset, duration of disease, presence of erosions, early versus late response to methotrexate, initial versus maximum dosage of the drug, or being seropositive for antinuclear antibody (ANA) or rheumatoid factor.

The work of Ravelli et al.[75] provides further evidence of the effectiveness of methotrexate in that they showed radiological improvement or a slowing of deterioration of carpal length in children who had responded to methotrexate during a 2-year period of observation. Conversely, carpal length was significantly worse in the nonresponders. A young age at onset of disease and being a male correlated with a risk for poor radiological outcome. Therefore, the authors concluded that methotrexate might be considered a disease-modifying antirheumatoid drug (DMARD) in the therapy of JRA. A study by Harel et al.[76] also found that carpal length was significantly improved in 11 of the 17 children who responded to 2.5 years of methotrexate therapy, whereas all of the nonresponders had a deterioration of carpal length.

In children who are seemingly in a remission from chronic arthritis, however, it is necessary to discontinue antirheumatic therapy at some time.[51] The question is when. Answering this query has been an exercise in experience and judgment by the responsible rheumatologist. A study by Ravelli et al.[75] indicated that one-third of children relapsed after discontinuation of methotrexate. They concluded that the child most at risk was the one who had an oligoarticular onset with a subsequent polyarticular course.

Recent studies by Gottlieb et al.[77] have also strengthened the conclusion that long term methotrexate is a DMARD or remittive agent. In their study, approximately 50% of children in all onset groups who achieved a remission during methotrexate therapy relapsed approximately 11 months after withdrawal of the drug. Approximately 50% of the children regained control of their disease an average of 15 months after reinstitution of the drug. Perhaps the most convincing evidence of the remittive or disease-modifying nature of methotrexate in this investigation was the relatively long period of time after withdrawal before relapse occurred (range 1.5 to 36 months). A younger age of onset was identified by the authors as indicating a more likely chance of relapse. Perhaps this study indicates that therapy with methotrexate should be reasonably prolonged (for 1 or 2 years) after a remission has been achieved. It might also be appropriate to institute a different mode of withdrawal such as decreasing methotrexate administration to every 2 weeks for a defined period of time before eventual discontinuation.

A number of studies indicate that methotrexate may be more effective than other modes of therapy in special situations accompanying chronic arthritis in children. Among the most important of these in terms of severity of outcome is the study by Weiss et al.[78] indicating that methotrexate was an effective mode of therapy in children with severe chronic uveitis and approaching blindness whose condition had failed to respond to all other forms of therapy.

3. Slow Acting Antirheumatic Drugs

Up to approximately 10 years ago, the slow acting rheumatic drugs (SAARDs) were used as the next line of therapy after NSAIDs and before methotrexate, but this is no longer the case.[53,74,79] SAARDs can be added to the medical program for children who have not responded adequately during an initial trial period to therapy with a combination of an NSAID and methotrexate.[50,80,81] There is certainly no uniform agreement on which drug would be preferred in this group: perhaps hydroxychloroquine, intramuscular gold, sulfa-

salazine, and penicillamine should be considered in that order.

The reason for naming these drugs SAARDs is that they do not produce an immediate anti-inflammatory effect and often they produce an effect which is difficult to assess except over a long period of time, or sometimes, regrettably, after discontinuation of the drug and the observation of a flare of the disease. SAARDs are thought to slow the development of severe joint disease, and to delay or abort destructive synovitis and erosions. However, few control studies in children have been published. As some of these drugs can cause serious toxicity and sometimes death, they should be reserved for the child who has progressive articular disease.

It should be emphasised that children with systemic onset JRA may be at much greater risk of toxic reactions from any of the SAARDs, and sometimes even NSAIDs, than children with other types of onset.[82-87] The most serious of these is the so-called macrophage activation syndrome characterised by the acute onset of neutropenia and disseminated intravascular coagulation.[86]

3.1 Hydroxychloroquine

Hydroxychloroquine is the least toxic of the 4-aminoquinoline antimalarial drugs and has generally replaced chloroquine in paediatric practice in the US.[88-90] The initial starting dosage for JRA is approximately 5 mg/kg/day.[91,92] In children, it is often not possible to achieve this dose each day because of the tablet size of 200mg. An alternative schedule involves calculating the weekly dose and then distributing the correct number of tablets over a week. The drug should be taken with food as it can be an irritant to the gastrointestinal tract. Bone marrow suppression, dermatitis, and gastrointestinal disorders are occasional adverse effects.[93] The drug has no antidote and use in small children must be carefully considered as acute respiratory suppression which may occur after the ingestion of large doses can be fatal.[94]

When hydroxychloroquine is administered in large doses it may be deposited in the cornea, a complication which is asymptomatic and usually without long term sequelae. However, the principal ocular adverse effect is a progressive retinopathy involving colour vision initially but which may progress to blindness, although this is rare at the dosages currently recommended.[95-98] This retinopathy has been noted to occur without early warning signs and therefore ophthalmological examinations are mandatory before therapy is started and every 4 to 6 months thereafter. Stillman investigated the use of hydroxychloroquine and chloroquine in 125 children who were treated with antimalarial drugs.[99] Three of the children developed a nonprogressive macular pigmentation. Corneal deposition was observed in a few children and was deemed an indication for lowering the dose of the drug.

Hydroxychloroquine is generally considered in adult studies as the safest and least costly of all advanced therapies (methotrexate, SAARDs, and the newer entities) as laboratory evaluation for adverse effects is not necessary except for ophthalmological assessment of vision and colour recognition. Even the necessity of this assessment has now been called into question.[98] Generally, the drug cannot be used in children younger than 4 years of age, and occasionally in children younger than 7 years of age, because of their inability to discern colour vision adequately for testing on grids or visual fields.

The therapeutic effect of hydroxychloroquine is often subtle, delayed by up to 3 months, and has not been conclusively proven in randomised double-blind studies.[80] If after an observation period of approximately 6 months no objective articular improvement can be demonstrated, the drug should be discontinued, and treatment with another SAARD should be discussed with the child's family. In a number of therapeutic trials of the antimalarials involving approximately 240 children,[80] clinical improvement occurred in approximately 15 to 75% of children and remission was noted in 45%. Toxicity was relatively high in some studies, frequently involving up to 60% of the children with discontinuation of the medication because of ad-

verse effects being required in 10%. This level of toxicity does not reflect my current experience in the long term treatment of children with JRA.

An extensive double-blind trial of hydroxychloroquine was performed by the PRCSG in the United States and the former Soviet Union, and compared this drug to penicillamine and a placebo which was an NSAID.[92] In this study, 162 children with severe, poorly controlled arthritis were observed over a 12-month clinical trial. 88% of the children completed 6 months of the trial and 76% completed 12 months: at that time the 3 evaluation groups included 43, 46 and 34 children, respectively. Although no statistically significant differences could be shown between the children treated with hydroxychloroquine or penicillamine compared with placebo, it has been always difficult to explain why children on placebo in many of these studies did so well, since failure of a therapeutic trial with an NSAID had always been an entry criterion. The authors noted that 60% of the hydroxychloroquine group, 46% of the penicillamine group, and 39% of the children on placebo showed clinical benefit at 12 months of therapy.[100] Benefit later during the trial was unlikely to be documented if a favourable response had not occurred by 6 months. Improvement of pain on motion was noted, however, in the hydroxychloroquine group more often than in children treated only with the placebo.

3.2 Intramuscular Gold

A number of organic gold compounds (aurothioglucose and sodium aurothiomalate) have been used in the treatment of children with JRA.[101-110] Gold therapy is indicated in polyarticular disease which has not been responsive to the basic program, or when there has been rapid progression of the arthritis. It is used in addition to an NSAID and potentially methotrexate, and is often added to hydroxychloroquine. Before the start of therapy, the paediatric rheumatologist needs to document that haematological, renal, and hepatic functions are normal. An initial test dose for hypersensitivity of 5mg is given intramuscularly in an extremity. Depending on the age and bodyweight of the child, weekly dosages of gold are then gradually increased to 0.75 to 1.0 mg/kg/week, or a maximum of 50mg.[101,107,109,111,112] This maintenance dosage is given for 20 to 24 weeks (or 6 months) and the child evaluated for improvement. If objective articular improvement can be documented, the physician may consider decreasing the dose to every 2 weeks for approximately 3 months, and then every 3 weeks for approximately an additional 3 months. If improvement has continued the child is then placed on a program of intramuscular gold every 4 weeks thereafter with the dose adjusted periodically for increases in bodyweight with growth. After many years of clinical improvement, discontinuation of gold should be cautiously considered. Relapses, if they occur, are generally delayed by at least 3 months after cessation of treatment with the gold compound.

The principal adverse effects of intramuscular gold involve the bone marrow, kidneys, skin, and gastrointestinal tract.[101] Before each administration a CBC and urinalysis should be performed, and the child assessed clinically for any obvious adverse effects such as development of mucosal ulcerations or dermatitis. A decrease in the white blood cell count below 4500/mm^3, a decrease in the neutrophil count by 50%, or the development of thrombocytopenia or eosinophilia, haematuria, or clinical signs of gold toxicity are indications for immediate discontinuation of the drug.[113,114] In current experience, the most common toxicities are microscopic haematuria or dermatitis. In carefully selected children, gold therapy may be cautiously resumed at a lower dose after the adverse effect has resolved; however, it is sometimes preferable at that juncture to consider switching therapy to an alternative agent. Absolute contraindications to restarting gold therapy are severe leucopenia or neutropenia, proteinuria, or exfoliative dermatitis.

Approximately 25% of children on gold therapy experience adverse events and will be unable to continue treatment, 25% will not improve objectively, and the remaining 50% will experience objective improvement in their articular dis-

ease.[80,84,102-105,107,110] In a number of studies evaluating gold therapy in children, improvement was noted in 20 to 80% and remission in up to 60%; however, adverse effects developed in 20 to 50% and were severe enough to lead to discontinuation of the drug in 10 to 60% of the children.[80]

Levinson et al.[105] summarised the results of early studies of gold therapy in 44 children. There was improvement in the arthritis and the systemic manifestations of the disease in approximately 75% of the children. Brewer et al.[107] reported on a 6-month trial of gold therapy in 51 children. The dosage was 1 mg/kg/week for 20 weeks which was then reduced gradually to once every 2 to 4 weeks. Arthritis improved in approximately 65% of children, especially in those who had more severe joint disease. The type of onset of the disease and its duration did not predict a favourable response. During treatment, only 1 child developed radiological evidence of disease progression (an observation that has been well documented in adult studies of rheumatoid arthritis). However, 5 children experienced adverse effects including fever, nephrotic syndrome, haematuria, anaemia, or psychological disturbances (there was no placebo group in this study). Eight children continued on gold therapy had mild adverse effects which did not require discontinuation of the medication (dermatitis, nausea, headache, mild anaemia, swelling at the injection site, or occult blood in the stool).

In children with active systemic disease, a gold compound should be used with great caution because of the possibility of precipitating the macrophage activation syndrome.[87] In a study by Manners and Ansell,[84] 48 children with systemic onset disease were studied with no improvement of the systemic features of the disease noted and only 10 of the 24 children with unremitting polyarthritis experienced objective benefit. However, 14 children developed potentially life threatening toxicities that included disseminated intravascular coagulation and cholestatic jaundice.

Triethylphosphine gold, auranofin, initially appeared to be better tolerated than intramuscular gold, but a careful study of the PRCSG showed no objective improvement in arthritis compared with placebo.[115] This study and additional ones involving long term follow-up indicated that, although adverse events were infrequent, auranofin potentially provided long term benefit in only a small number of children with arthritis.

3.3 Sulfasalazine

Sulfasalazine, an analogue of 5-aminosalicylic acid and sulfapyridine, was initially synthesised based upon the hypothesis that rheumatoid arthritis was an infectious disease and would respond to a combination of an anti-inflammatory agent and a sulfonamide. This drug has a relative advantage over other SAARDs of rapid onset of benefit, i.e. usually within 6 to 8 weeks. It is indicated for children with chronic arthritis who have not responded to more conventional therapy.[116-118] The maintenance dosage of approximately 40 to 60 mg/kg/day in 3 to 4 divided doses with meals is reached by gradually increasing the frequency of administration to 3 to 4 times daily over the initial 4 to 6 weeks of therapy.[117] The maximum dosage should not exceed 2000 mg/day. Baseline studies are the same as those for gold therapy and should be performed every month.

The principle toxicities of sulfasalazine include dermatitis, mucosal ulcerations, Stevens-Johnson syndrome, gastrointestinal irritation, and bone marrow suppression. Enteric coated sulfasalazine may therefore be preferable in order to reduce dyspepsia. The drug is contraindicated in children with a history of sensitivity to sulfa drugs or salicylate, kidney or liver disease, or who have specific contraindications such as glucose-6-phosphate dehydrogenase deficiency or porphyria.

There are only a few published studies on the effectiveness and tolerability of this drug in children. In the study by Grondin et al.,[80] 4 of 12 children had significant improvement in their disease, 1 entered remission, but 2 experienced adverse effects. In a Dutch study of 24 weeks duration, 35 children with JRA (polyarticular or oligoarticular) received sulfasalazine and 34 were on placebo.[118] Those who received sulfasalazine ex-

perienced significant improvement in both joint count and laboratory indices. Ten children (almost 1 out of 3) who were receiving sulfasalazine developed serious toxicities and were removed from the study. However, these adverse reactions tended to occur early in treatment and resolved with withdrawal of the medication.

3.4 Penicillamine

Penicillamine is infrequently used in the treatment of children with JRA since the recognition of the superior effectiveness of methotrexate and publication of the PRCSG studies. The maximum dosage of penicillamine is approximately 10 mg/kg/day (≤750 mg/day).[92] This dosage is reached in approximately 3 equal steps, each of 6 to 8 weeks' duration. Penicillamine must be taken on an empty stomach early in the morning to avoid chelation by dietary metals. A CBC and urinalysis need to be preformed weekly during the initial period of therapy. Perhaps more so than with gold penicillamine acts slowly, taking 9 months to 3 years for maximum effectiveness to occur.

Previously, penicillamine was regarded as an appropriate second-line agent for children who had failed to respond to intramuscular gold as studies suggested that it might be as effective as gold therapy in inducing clinical improvement or a remission and, in general, was perhaps no more toxic.[84,92,108-110,119] Improvement was documented in 10 to 75% of patients and remission in 20%.[80] Toxicity was noted in 10 to 55% of children with discontinuation of the drug deemed mandatory in at least 65%. However, in a double-blind study conducted by Prieur et al.,[120] there was no observed difference in the rate of remission for children treated with penicillamine and those who had received placebo. The most significant adverse effects reported were renal, cutaneous or gastrointestinal, or bone marrow suppression. Other adverse effects from the literature have included a drug-induced lupus syndrome, a distinctive dermatitis resembling pemphigus, polymyositis, Goodpasture's syndrome, and myasthenia gravis.[109,119,121]

It should be noted that toxicity to penicillamine is not necessarily dose-related, and that children who have developed adverse effects while receiving intramuscular gold therapy are more likely to experience them with penicillamine, often similar in type and related to the presence of certain HLA genes such as those at the HLA-B8 and DR3 loci.[122]

4. Additional Second-Line Agents

4.1 Intravenous Human Immunoglobulin Therapy

Intravenous human immunoglobulin therapy (IVIG) has been employed in the treatment of a number of diseases of autoimmune aetiology and pathogenesis, notably immune thrombocytopenic purpura and Kawasaki's disease. There are a number of studies on the use of this agent in children with JRA.[123-126] Silverman et al.[127] treated 8 children with IVIG 2g every month for 1 year. The authors noted a decrease in systemic features of the disease in 7 children along with a reduction in the number of swollen joints, daily dose of glucocorticoid required, and ESR. Five children experienced an exacerbation of their articular disease when therapy was stopped at 1 year.

An additional study of 25 children with systemic onset JRA involved treatment with monthly IVIG for 4 to 54 months.[128] Evaluation at 6 months revealed that 18 of the 25 of the children had a significant decrease in number of days with fever or a marked decrease in number of actively inflamed joints. At approximately 4 years 10 patients were in remission and no longer receiving the medication, 8 were well but still required IVIG therapy, and 5 had active articular disease in which the IVIG therapy was deemed only to have decreased their requirement for glucocorticoids. One patient each developed systemic lupus erythematosus, membranous nephropathy, and systemic vasculitis.

Prieur and colleagues[129] used IVIG therapy in 13 children with systemic onset disease and 3 with polyarticular disease. Improvement was noted in

10 patients: the rash improved in 4, fever in 6, and lymphadenopathy and splenomegaly in 3. However, articular disease was not consistently improved and progression of systemic features such as pericarditis, or the development of adverse effects related to the IVIG, required further treatment with glucocorticoids. Eleven of the patients in this study received at least 17 months of therapy and in some the duration of therapy was as long as 52 months.

A blinded, controlled trial of IVIG in 31 children with systemic onset JRA by the PRCSG indicated that the drug had little significant benefit compared with placebo.[126] The authors considered the results inconclusive primarily because of the small sample size. In an additional trial of IVIG in 25 children with polyarticular disease by the same group,[130] a protocol was chosen of 1.5 to 2.0 g/kg twice a month for the first 2 months, and then monthly for up to 6 months thereafter with a maximum dose of 100g. Responders at 4 months were randomised to continuation of IVIG or placebo. Nineteen of the 25 children responded during the open phase of the study. The 10 children who were continued on IVIG (blinded to the observers) were able to complete that phase of the study; however, only 4 of those who had been randomised to placebo maintained their previous level of response. No child developed serious adverse effects. The authors therefore concluded that approximately 75% of the children with polyarticular JRA responded beneficially to the IVIG protocol.

4.2 Cyclosporin

Cyclosporin, a fungal peptide, was introduced into medical therapy for the treatment of allograft rejection. It had also been studied in the treatment of other autoimmune diseases with encouraging results. Toxicities are considerable including hypertension, progressive nephropathy, hepatotoxicity, hypertrichosis, and gingival hyperplasia.[131,132] There may also be a small but significant long term risk of lymphoma, but this has recently been disputed.[133] Few studies have been reported of the use of this agent in the treatment of children with chronic arthritis.[134-136] Ostensen et al.[135] administered cyclosporin for 6 to 20 months in 14 children in a dosage range of 4-15 mg/kg/day. Three of 11 children were able to have their glucocorticoid dose reduced; however, 4 had acute exacerbations of their disease while maintained on cyclosporin. Serum creatinine levels increased in 11 children, hypertrichosis was noted in 14, and hypertension developed in 1 child. Nine children became increasingly anaemic and in 3 the drug was discontinued because of a significant fall in haemoglobin concentration.

Cyclosporin is started at an oral dosage of 3 to 5 mg/kg/day given as 2 divided doses 12 hours apart. Blood pressure determinations should be performed at home twice a day during the initial 2 weeks of therapy and then evaluated periodically thereafter along with urinalysis and other estimates of renal function. For unexplained reasons, blood concentrations of cyclosporin which have been useful in children with kidney transplants in guiding therapy have not been helpful in those with arthritis. The status of this drug in the treatment of chronic arthritis in children is still uncertain. It likely has an important role in treating the macrophage activation syndrome.[87,137]

5. Glucocorticoids

Glucocorticoids are the most potent anti-inflammatory agents routinely employed in the treatment of children who are severely ill with chronic arthritis or its complications; however, their numerous toxicities and the development of Cushing's syndrome, growth retardation, and osteoporosis severely limit their use. Another long term adverse effect of chronic glucocorticoid administration is accelerated atherosclerosis and the early onset of myocardial dysfunction and infarction. Therefore, systemic administration is indicated only for the treatment of children with chronic arthritis who have failed to respond to other modalities of therapy or who have life threatening complications of their disease.[138-142]

Therefore, in treating a child with glucocorticoids, the family must understand that it is often

necessary to accept some moderate activity of the disease in exchange for a lower dose of the drug and fewer anticipated adverse effects. A well balanced diet restricting calories to those necessary for normal growth, moderation of sodium intake, and an emphasis on the daily ingestion of foods high in potassium is prescribed.[143] Usually a snack before bedtime to avoid dyspepsia and, occasionally, the use of medications to decrease gastric acidity are indicated.

Prednisone, the delta 1 analogue of cortisone, is usually the preferred medication for oral use. The initial dosage for systemic disease must often be in the range of 0.5 to 1.0 mg/kg/day, as a single morning dose, or in divided doses for more severe manifestations such as pericardial effusion.[141,142] It is seldom necessary to treat with more than 40 mg/day orally. Alternate-day, lower-dose prednisone may be of some benefit in selected children with severe polyarthritis who have been unresponsive to previous therapy, or initially as 'bridge therapy' to maintain ambulation and an immediate clinical response; however, the prednisone should be gradually discontinued once acceptable control of the disease with other agents is achieved.

It often becomes difficult to reduce glucocorticoid dosage in JRA because of a child's adaptation to chronic steroid excess. Steroid pseudorheumatism may complicate even the very slow withdrawal of the drug in children, particularly at the lower doses.[138,144] This syndrome, described early in the use of glucocorticoids in the treatment of adults with rheumatoid arthritis, is characterised by intermittent increased stiffness, joint pain, fever, irritability, and malaise with each reduction of dose. It can be minimised if reductions are ≤1mg in the lower dosage ranges and not more frequent than every 1 to 2 weeks.[138] It is unfortunately true that some children treated with glucocorticoids for systemic onset JRA can only be withdrawn from the drug with extreme difficulty.

Therefore, intravenous glucocorticoid pulse therapy has been recommended for the treatment of more severe manifestations of arthritis in order to minimise or abrogate daily glucocorticoid requirement.[145-147] With this approach, an immediate effect of the drug is achieved and hopefully less long term toxicity. Methylprednisolone is the drug of choice for intravenous use in a dose of 10 to 30 mg/kg per pulse given by a number of different protocols. These have consisted of single pulses spaced a month part, 3 pulses given each of 3 days a month, or 3 pulses administered on alternate days each month. Intravenous steroid pulse therapy is not without potentially alarming and serious toxicities, and therefore should be administered in a clinical setting where there can be constant cardiovascular monitoring during the infusion and for a few hours thereafter with careful attention to electrolyte and fluid balance, and observations for cardiac arrhythmias or hypertension.[148]

Specific local uses of glucocorticoids should be noted. Ophthalmic drops or injections can be used for the treatment of chronic uveitis.[149] Surveillance for the development of subtle chronic uveitis is mandatory in all children with JRA initially and periodically thereafter based on risk factors for this complication. If detected by slit-lamp examination, treatment of uveitis should be undertaken by an experienced ophthalmologist. Initial therapy often consists of glucocorticoid eye drops and the use of a mydriatic before bed. Occasionally supplemental oral prednisone at a low dose is used in addition to the ophthalmic drops.

Glucocorticoids are also used for intra-articular therapy.[150-155] Triamcinolone hexacetonide at a dose of 5 to 40mg per injection, depending on the size of the joint, is the intra-articular preparation of choice. This approach to therapy can be very effective, particularly if 1 or 2 joints are inflamed, or when used as an aid to physical therapy.[155] Although repeated use in a child is sometimes regarded as controversial, it is perhaps prudent to limit intra-articular injection to no more than 3 times in the same joint during a 3-month period.

All children on systemic glucocorticoids should wear a bracelet or necklace indicating their name, diagnosis, and the fact that they are taking a glucocorticosteriod. This will facilitate emergency use of intravenous glucocorticoid administration which

is mandatory in any child who has undergone serious trauma or stress. Supplemental glucocorticoid is also necessary before and during surgical anaesthesia. Although a number of choices exist for the specific drug to be used in these circumstances, one preference is dexamethasone by intramuscular administration before the operation and hydrocortisone intravenously during the procedure.

6. Immunosuppressive Agents

The use of the more toxic immunosuppressive and cytotoxic drugs should be reserved for children with life-threatening complications or severe progressive erosive arthritis. A number of agents have been studied for this purpose including the purine analogues mercaptopurine and azathioprine,[156,157] and the alkylating agents cyclophosphamide and chlorambucil.[158-162] These are drugs that are difficult to use in children.[163] Bone marrow suppression may develop during therapy and there are important considerations of longer term oncogenic and mutagenic effects.[164,165] Sterility and amenorrhoea have been associated with the alkylating agents. The concomitant use of a gonadotropin releasing hormone agonist may help to preserve ovarian function. One specific indication for the use of an alkylating agent would be for treatment of secondary amyloidosis.[161,166-169] A short term use of one of these drugs as adjunctive therapy in a child with glucocorticoid toxicity might be considered in order to succeed in lowering the dose of glucocorticoid.[157] Trials of leflunomide, an inhibitor of pyrimidine synthesis, have not been published for children, but have been encouraging in adults with rheumatoid arthritis.[170-172]

7. Experimental Therapy

Although a number of experimental approaches to severe adult rheumatoid arthritis have been considered in therapeutic trials during the past 20 years, few have been entertained in children without further demonstration of efficacy and safety. Some of these experimental therapies in adults have included total lymphoid irradiation, lymphapheresis and plasmapheresis, thoracic duct drainage, and the use of monoclonal antibodies directed at T cells. None of these therapies has entered the realm of accepted use. However, more recent approaches might be considered for use in children such as the proposed vaccination against specific peptides of the T cell receptor, or the recent introduction of etanercept [soluble tissue necrosis factor (TNF)α receptor.p75 fusion protein][173-178] or monoclonal antibody to TNFα.[179-185] Autologous stem cell transplantation is being currently evaluated in a small number of children with systemic onset and polyarticular arthritis.[186-190]

8. Nutrition

An adequate protein, calorie and calcium intake, along with attention to supplemental vitamin administration [colecalciferol (vitamin D) and folic acid], if indicated, are important components of the long term management of a child with arthritis.[191-194] Growth retardation and malnutrition related to the increased catabolism that accompanies active arthritis occur during periods of uncontrolled disease and are exacerbated by glucocorticoid administration, anorexia, or relative immobilisation.[195] A formal dietetic review with particular attention to the prevention or amelioration of a decreased bone mass for age, osteopenia, is almost always indicated.

9. Psychosocial Development

Compliance with medical therapy to ensure its success can be severely compromised if the child or family do not accept the goals of the management programme, or regard the paediatric rheumatologist and the multidisciplinary team as allies in their struggle with a disease of no known cause, no known cure, and unpredictable course.[196] The child should participate in peer group activities and attendance at a regular school is mandatory. The child should also remain in the physical education program at school, if at all possible, if not as a participant then as an involved member of the class assigned to other activities, or alternatively in adaptive physical education.

Appropriate physical and occupational therapy can also aid in easing disability and pain if present, and help to prevent longer term functional disability.[197-201] Success in these endeavours will encourage the child and family to be attentive to the many aspects of the disease which must be considered if the therapeutic program is going to be a success. Children should determine to a large extent their own level of activity. Inappropriate restriction of recess time or peer group association can be harmful both physically and psychologically. It is important, however, to help the child avoid activities that are overtiring, or cause increased joint pain, and substitute low impact exercise instead such as tricycle riding and swimming.

10. Conclusions

It is almost impossible to be confident of the therapeutic benefit : risk ratio for many of the therapeutic regimens used in treating a child with chronic arthritis. Certainly, experimental data and clinical observation confirm the efficacy of appropriately administered NSAIDs, methotrexate, or glucocorticoids. It is not so certain that other medications such as hydroxychloroquine, sulfasalazine, penicillamine, IVIG, or cyclosporin have a statistically certain beneficial effect. Toxicity is often a foremost concern in the long term use of steroids or immunosuppressive agents such as azathioprine or cyclophosphamide. Better and more specific agents are needed, especially for systemic onset disease, unremitting polyarticular involvement, and certain complications such as resistant chronic uveitis.[202]

Because of the relative lack of scientific guidance by appropriately designed studies, undertaken in sufficiently large numbers of children with appropriate attention to confounding factors such as type of onset and course of the disease, it is often the experience and judgment of the paediatric rheumatologist which become the most important principles of guidance for the therapy of a child, and coordination of that care with the family. It must always be stressed, because of the overwhelming number of therapeutic studies that have been performed in rheumatoid arthritis, that adult disease may be quite different in aetiology and pathogenesis, and furthermore children may respond differently in both occurrence of toxicity and development of complications of disease. It is also important to note that JRA is often self-limited even after years of activity and is seldom fatal. The latter is an important consideration when considering the use of heroic pharmacological intervention. On the other hand, undue delay in instituting potentially effective treatment is to be assiduously avoided. However, an important factor working in favour of the therapeutic program is the unceasing potential for growth that is characteristic of children.

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