

Review Articles

Disease Modifying Anti-rheumatic Drugs (DMARDs)

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Abstract:

Disease modifying anti-rheumatic drugs (DMARDs) is a group of drugs that slow or stop the immune system from destroying the joints. Evidence shows Methotrexate is superior to conventional treatment (NSAIDs and/or intra-articular corticosteroids). Among children who have responded to a biologic DMARD, randomized discontinuation trials suggest that continued treatment decreases the risk of having a flare. Although these studies evaluated DMARDs with different mechanisms of action (hydroxychloroquine, azathioprine, sulfasalazine, methotrexate, leflunomide, cyclosporine, etanercept, tocilizumab, infliximab, anakinra, rituximab). There are few direct comparisons of DMARDs. There are insufficient evidence to determine whether any specific drug or group of drugs has greater beneficial effects. Adverse events are found similar between DMARDs. Limited data suggest that short-term risk of cancer is low. Future trials are needed to evaluate the effectiveness of DMARDs against both conventional therapy and other DMARDs in different pediatric rheumatic diseases.

Keywords: DMARDs, Methotrexate, Rheumatology, Paediatrics

Introduction

Disease modifying anti-rheumatic drugs (DMARDs) is a group of drugs that slow or stop the immune system from destroying the joints. DMARDs are not used for immediate analgesic or anti-inflammatory effect but rather for their long term beneficial effects in controlling disease activity¹. These medications also play an important role in reducing the long term exposure to medications such as prednisolone and non-steroidal anti-inflammatory drugs (NSAIDs). The introduction of DMARDs in the treatment of rheumatic diseases over the last two decades has significantly improved clinical outcomes. First to be introduced were the non-biologic DMARDs, methotrexate being chief of them. Many years later the biologic DMARDs

were introduced; first were the tumor necrosis factor alpha (TNF) inhibitors which were followed by several other biologic therapeutic agents with different mechanisms of action including inhibition of interleukin 1 (IL-1), interleukin 6 (IL6), and T-cell co-stimulation. Pediatric Rheumatology comprises of a broad range of inflammatory disorders. Evidence suggests that these diseases may be largely genetic in origin, with variable environmental components. There is also a group of rare auto-inflammatory diseases described elsewhere, many of which result from mutations of genes that affect the innate immune response².

DMARDs represent the most important measure in the successful treatment of these diseases. These agents can retard or prevent disease progression and thus, joint destruction and subsequent loss of function. Successful DMARD therapy may eliminate the need for other anti-inflammatory or analgesic medications. Before the onset of full action of DMARDs, anti-inflammatory or analgesic medications may be required as bridging therapy to reduce pain and swelling¹.

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Classification DMARDs

There are two types of DMARDs- biologic and nonbiologic. Nonbiologic DMARDs are produced from chemicals. Biologic DMARDs are antibodies that are similar to those made in the body but these antibodies are created in laboratories.

The nonbiologic or conventional DMARDs includes hydroxychloroquine(HCQ), azathioprine (AZA), sulfasalazine(SSZ), methotrexate(MTX), leflunomide, cyclosporine, gold salts, D-penicillamine, and minocycline. In terms of frequency of remission and time to onset of action, MTX and SSZ are the most active compounds and provide the best risk benefit ratios.

Biologic DMARDs- the recognition of TNF- α and interleukin IL-1 as central proinflammatory cytokines has led to the development of biologic agents that block these cytokines or their effects. In addition to improving signs and symptoms and quality of life, all biologic agents significantly retard radiographic progression of joint erosions. These include agents such as adalimumab, etanercept, infliximab, anakinra, abatacept, rituximab, tocilizumab.

Both nonbiologic and biologic DMARDs can be added to standard treatment for children with more severe symptoms of JIA or when they are not getting enough relief from their symptoms. DMARDs may be taken with each other and with NSAIDs and corticosteroids. DMARDs work to suppress the body's overactive immune and/or inflammatory systems.

The most common DMARD given to children with JIA is a nonbiologic called "methotrexate" and it has become the first-choice in childhood arthritis.

Difference between nonbiologic and biologic DMARDs

Nonbiologic DMARDs can be given as pills or as shots and can be given at home and hospital. Biologic DMARDs must be given through an IV (intravenous) route or as a shot. The IV treatment must be given in a hospital.

Because nonbiologic and biologic DMARDs work in different ways, they have different safety concerns. There is not enough research yet to know what all of the differences may be or how important they are.

Benefits of DMARDs

Researchers know much more about using DMARDs in adults than they know about using them in children.

For this reason, researchers cannot say with much certainty how well these drugs work for children.

Researchers found that:

- Adding the nonbiologic DMARD methotrexate to treatment works well than NSAIDs and corticosteroids alone to improve the symptoms of JIA.
- Biologic DMARDs can improve the health of children with JIA.

Side effects of DMARDs

- The FDA warns that certain biologic DMARDs may rarely lead to the development of unusual infections like tuberculosis (called "TB") and fungal infections like yeast. Children are usually tested for these infections before starting biologic DMARDs.
- Serious infections were seen most often in children taking methotrexate and the biologic DMARD infliximab at the same time.
- The FDA warns that certain biologic DMARDs called "TNF-alpha blockers"-adalimumab, etanercept, and infliximab have been associated with cancer in children, but this is rare. The cancer that usually occurs is lymphoma.

Nonbiologic or conventional DMARDs

Methotrexate³⁻⁸

Methotrexate is now considered the DMARD of first choice to treat childhood arthritis. It is active in this condition at much lower doses.

Mechanism of action

Methotrexate's principal mechanism of action is to inhibition of aminoimidazole carboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase, with secondary effects on polymorphonuclear chemotaxis. There is some effect on dihydrofolate reductase and this affects lymphocyte and macrophage function. Methotrexate has direct inhibitory effects on proliferation and stimulates apoptosis in immune-inflammatory cells and inhibition of pro-inflammatory cytokines linked to rheumatoid synovitis.

Pharmacokinetics

The drug is approximately 70% absorbed after oral administration. It is metabolized to a less active hydroxylated metabolite, and both the parent

compound and the metabolite are polyglutamated within cells, where they stay for prolonged periods. Methotrexate's serum half-life is usually only 6–9 hours with normal renal function, although it may be as long as 24 hours in some individuals. Methotrexate's concentration is increased in the presence of hydroxychloroquine, which can reduce the clearance or increase the tubular reabsorption of methotrexate. This drug is excreted principally in the urine (more than 80%), but up to 30% may be excreted in bile.

Indications:

Rheumatic diseases other than juvenile idiopathic arthritis include SLE, some vasculitides, juvenile dermatomyositis (JDM), systemic sclerosis, localized scleroderma, uveitis.

Dosage:

Although the most common methotrexate dosing regimen for the treatment of juvenile arthritis is 10–15 mg/m²/ week or 0.3 to 0.6 mg/kg/wk, dosage can be an increased upto 20–25 mg/m²/ week or 1.1mg/kg/wk in resistant cases. Oral bioavailability is 15% less than intramuscular and subcutaneous administration. Improvement seen in 6-12 weeks of administration.

Adverse effects

Nausea, mucosal ulcers, abdominal discomfort, stomatitis are the common toxicities. Progressive dose-related hepatotoxicity in the form of enzyme elevation occurs frequently. These elevations are usually transient and resolve without intervention, with lowered dose or after brief interval off treatment. The incidence of gastrointestinal and liver function test abnormalities can be reduced by the use of daily folic acid.

Hydroxychloroquine

Mechanism of action

The mechanism of the anti-inflammatory action of these drugs in rheumatic diseases is unclear. The proposed mechanism is suppression of T-lymphocyte responses to mitogens, decreased leukocyte chemotaxis, stabilization of lysosomal enzymes, inhibition of DNA and RNA synthesis, and the trapping of free radicals.

Pharmacokinetics

Hydroxychloroquine is rapidly absorbed and 50% protein bound in the plasma. They are very extensively tissue-bound, particularly in melanin-

containing tissues such as the eyes. The drugs are deaminated in the liver and have blood elimination half-lives of upto 45 days.

Indications:

Paediatric SLE, JDM, Antiphospholipid Antibody syndrome and JIA

Dosage:

The recommended dosage for Hydroxychloroquine 4-6mg/kg/day. Oral administration is recommended. Although antimalarials improve symptoms, there is no evidence that these compounds alter bony damage in juvenile arthritis at their usual dosages. It usually takes 3–6 months to obtain a response.

Adverse effects

Although ocular toxicity (retinopathy) may occur at dosages greater than 6.5 mg/kg/d for hydroxychloroquine, it rarely occurs at lower doses. Nevertheless, ophthalmologic monitoring every 6–12 months is advised. Other toxicities include dyspepsia, nausea, vomiting, abdominal pain, rashes, and nightmares.

Sulfasalazine⁹⁻¹¹

It is an analogue of 5-aminosalicylic acid linked by an azo bond to sulfapyridine, a sulfonamide.

Mechanism of action

Sulfasalazine is metabolized to sulfapyridine and 5-aminosalicylic acid, and it is thought that the sulfapyridine is probably the active moiety when treating arthritis. Some authorities believe that the parent compound, sulfasalazine, also has an effect. In treated arthritis patients, IgA and IgM rheumatoid factor production are decreased. Suppression of T-cell response and inhibition of in vitro B-cell proliferation have also been documented. In vitro studies have shown that sulfasalazine or its metabolites inhibit the release of inflammatory cytokines, including those produced by monocytes or macrophages, e.g. interleukins-1, 6, 12 and TNF- α . These findings suggest a possible mechanism for the clinical efficacy of sulfasalazine in chronic arthritis.

Pharmacokinetics

Only 10–20% of orally administered sulfasalazine is absorbed, although a fraction undergoes enterohepatic recirculation into the bowel where it is reduced by intestinal bacteria to liberate sulfapyridine and 5-aminosalicylic acid. Sulfapyridine is well

absorbed while 5-aminosalicylic acid remains unabsorbed. Some sulfasalazine is excreted unchanged in the urine whereas sulfapyridine is excreted after hepatic acetylation and hydroxylation. Sulfasalazine's half-life is 6–17 hours.

Indications

Sulfasalazine is effective in childhood arthritis particularly in enthesitis related arthritis, oligoarthritis, psoriatic arthritis and reactive arthritis. It reduces radiologic disease progression.

Dosage:

The usual regimen is 30–50 mg/kg/d. Treatment is initiated at lower dosage (10-15 mg/kg/d) and increased weekly over 4 weeks to achieve maintenance levels. Satisfactory clinical response usually occurs within 4-8 weeks.

Adverse effects

Approximately 30% of patients using sulfasalazine discontinue the drug because of toxicity. Common adverse effects include nausea, vomiting, headache, rash, oral ulcer, Steven-Johnson syndrome. Hemolytic anemia and methemoglobinemia also occur, but rarely. Neutropenia occurs in 1–5% of patients, while thrombocytopenia is very rare. Pulmonary toxicity (Interstitial pneumonitis, fibrosis, alveolitis) and positive double-stranded DNA are occasionally seen, but drug-induced lupus is rare. Reversible infertility occurs in men, but sulfasalazine does not affect fertility in women.

Leflunomide¹²⁻¹⁵

It is an immunomodulatory agent.

Mechanism of action

Leflunomide undergoes rapid conversion, both in the intestine and in the plasma, to its active metabolite, A77-1726. This metabolite inhibits dihydroorotatedehydrogenase, leading to a decrease in ribonucleotide synthesis and the arrest of stimulated cells in the G1 phase of cell growth. Consequently, leflunomide inhibits T-cell proliferation and production of autoantibodies by B cells. Secondary effects include increases of interleukin-10 receptor mRNA, decreased interleukin-8 receptor type A mRNA, and decreased TNF-dependent nuclear factor kappa B (NF- κ B) activation.

Pharmacokinetics

Leflunomide is completely absorbed and has a mean plasma half-life of 19 days. A77-1726, the active

metabolite of leflunomide, is thought to have approximately the same half-life and is subject to enterohepatic recirculation. Cholestyramine can enhance leflunomide excretion and increases total clearance by approximately 50%.

Indications

Leflunomide is as effective as methotrexate in polyarticular JIA, including inhibition of bony damage.

Dosage:

Less than 20kg : 10mg daily

20-30kg: 15 mg daily

More than 30 kg: 20 mg daily

Improvement seen in 6-12 weeks

Adverse effects

Diarrhea occurs in approximately 25% of patients given leflunomide to adults. Elevation in liver enzymes also occurs. Both effects can be reduced by decreasing the dose of leflunomide. Other adverse effects associated with leflunomide are mild alopecia, weight gain, and increased blood pressure. Leukopenia and thrombocytopenia occur rarely. Children usually suffers from transient rise of hepatic transaminase, abdominal pain, nausea, mouth ulcer, alopecia. These symptoms tend to be dose related.

Azathioprine¹⁶⁻¹⁸

Mechanism of action

Azathioprine acts through its major metabolite, 6-thioguanine. 6-Thioguanine suppresses inosinic acid synthesis, B-cell and T-cell function, immunoglobulin production, and interleukin-2 secretion.

Pharmacokinetics

The metabolism of azathioprine is bimodal in humans, with rapid metabolizers clearing the drug four times faster than slow metabolizers. Production of 6-thioguanine is dependent on thiopurine methyltransferase (TPMT), and patients with low or absent TPMT activity (0.3% of the population) are at particularly high risk of myelosuppression by excess concentrations of the parent drug if dosage is not adjusted.

Indications

Lupus nephritis, JDM, Behcet's disease, Psoriatic arthritis, ANCA associated vasculitis

Dosage:

Azathioprine is approved for use at a initial dose of 1-1.5 mg/kg/d and increase the dose to 2-2.5 mg/kg/d over 2-4 weeks.

Adverse effects

Azathioprine's toxicity includes bone marrow suppression, gastrointestinal disturbances, and some increase in infection risk. Lymphomas may be increased with azathioprine use. Rarely, fever, rash, and hepatotoxicity signal acute allergic reactions.

Cyclosporine^{19, 20}**Mechanism of action**

Through regulation of gene transcription, cyclosporine inhibits interleukin-1 and interleukin-2 receptor production and secondarily inhibits macrophage-T-cell interaction and T-cell responsiveness. T-cell-dependent B-cell function is also affected.

Pharmacokinetics

Cyclosporine absorption is incomplete and somewhat erratic, although a micro emulsion formulation improves its consistency and provides 20–30% bioavailability. Grapefruit juice increases cyclosporine bioavailability by as much as 62%. Cyclosporine is metabolized by CYP3A and consequently is subject to a large number of drug interactions (including many antimicrobials and non-antimicrobials).

Indications

Cyclosporine is approved for use in juvenile arthritis and retards the appearance of new bony erosions. Its usual dosage is 3–5 mg/kg/dose. Anecdotal reports suggest that it may be useful in systemic lupus erythematosus, polymyositis and dermatomyositis, Wegener's granulomatosis.

Adverse effects

Cyclosporine has significant nephrotoxicity, and its toxicity can be increased by drug interactions with diltiazem, potassium-sparing diuretics, and other drugs inhibiting CYP3A. Serum creatinine should be closely monitored. Other toxicities include hypertension, hyperkalemia, hepatotoxicity, gingival hyperplasia, and hirsutism.

Other DMARDs:

Colchicine, Thalidomide and Lenalidomide

Biologic DMARDs¹**Etanercept****Mechanism of action**

Etanercept is a recombinant fusion protein consisting of two soluble TNF p75 receptor moieties linked to

the Fc portion of human IgG1; it binds TNF- α molecules and also inhibits lymphotoxin- α .

Pharmacokinetics

Etanercept is given subcutaneously in a dosage of 0.8mg/kg, maximum 50 mg weekly. The drug is slowly absorbed, with peak concentration 72 hours after drug administration. Etanercept has a mean serum elimination half-life of 4.5 days.

Indications

It can be used as monotherapy although over 70% of patients taking etanercept are also using methotrexate. Etanercept decreases the rate of formation of new erosions relative to methotrexate alone.

Rituximab^{- 22,23,24}**Mechanism of action**

Rituximab is a chimeric monoclonal antibody that targets CD20 B lymphocytes. This depletion takes place through cell-mediated and complement dependent cytotoxicity and stimulation of cell apoptosis. Depletion of B lymphocytes reduces inflammation by decreasing the presentation of antigens to T lymphocytes and inhibiting the secretion of proinflammatory cytokines. Rituximab rapidly depletes peripheral B cells although this depletion neither correlates with efficacy nor with toxicity. Rituximab has shown benefit in the treatment of rheumatoid arthritis refractory to anti-TNF agents. It has been approved for the treatment of active rheumatoid arthritis when combined with methotrexate.

Pharmacokinetics

Rituximab is given as two intravenous infusions, separated by 2 weeks. It may be repeated every 6–9 months, as needed. Repeated courses remain effective. Pretreatment with glucocorticoids given intravenously 30 minutes prior to infusion decreases the incidence and severity of infusion reactions.

Indications

Rituximab is indicated for the treatment of moderately to severely active juvenile arthritis in combination with methotrexate in patients with an inadequate response to one or more TNF antagonists. Rituximab is most often used in combination with MTX.

Adverse effects

About 30% of patients develop rashes with the first inferior 1000 mg treatment; this incidence decreases

to about 10% with the second infusion and progressively decreases with each course of therapy thereafter. These rashes do not usually require discontinuation of therapy although urticarial or anaphylactoid reactions, of course, preclude further therapy. Immunoglobulins (particularly IgG and IgM) may decrease with repeated courses of therapy and infections can occur. Rituximab has not been associated with activation of tuberculosis, nor with the occurrence of lymphomas or other tumors.

Tocilizumab:

Tocilizumab, an IL-6 receptor inhibitor, is available as either an IV infusion or SC injection. It is indicated for moderate-to-severe active JIA who have had an inadequate response to 1 or more TNF-antagonist therapies. It may be used either alone or in combination with MTX or other DMARDs.

In patients with inadequate response to TNF inhibitors, tocilizumab treatment results in

significant, clinically meaningful, rapid, and sustained improvements in a number of patient reported outcomes.^{25,26} In October 2013, the FDA approved a SC injection of tocilizumab that can be self-administered after proper training. The SC formulation has been shown to be equally efficacious compared to the IV infusion and has the same safety profile except for increased injection site reactions with SC administration.²⁶

Adverse effects

Serious infections, elevated liver enzymes neutropenia, decreased platelet counts, lipids should be monitored. GI perforation has been reported when using tocilizumab in patients with diverticulitis or who are using corticosteroids.

Conclusion:

DMARDs were used late in the course of disease progression as there were initial questions regarding toxicity and safety. Moreover, the illnesses treated were not often considered life threatening and therefore DMARD therapy was considered. However, it is now recognized, that not only of these medications safe and effective for use in children but also that its use early in the course of the disease may prevent irreversible damage and decrease the burden of disease.

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