Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that affects at least 1.3 million adults in the United States. Symptoms include pain, stiffness, swelling, and limited motion and function of many joints, particularly the small joints in the hands and feet. A diagnosis of RA is made on the basis of symptoms, physical examination results, and blood tests that are positive for anemia, rheumatoid factor, antibodies, and elevated erythrocyte sedimentation rate. Continued inflammation of the synovium can lead to cartilage and bone damage.

Although the etiology of RA is unknown, there is an association with genetic factors and environmental exposures. Risk factors include smoking, reproductive hormone exposures, dietary factors, and microbial exposure, as well as having human leukocyte antigen class II genotypes (eg, DR4 and DRB1 molecules).

In addition to affecting the functioning and quality of life of patients, RA exacts a heavy economic toll on patients, employers, and payers. A recent study highlights the significant cost borne by American workers who live with RA and their employers. The research was conducted using a database of US employees' administrative healthcare and payroll data for individuals enrolled in an employer-sponsored insurance plan for at least 1 year. Compared with employees who do not have RA, an employee with RA incurs approximately $5200 more in annual healthcare costs. Workers with RA also pay an average of $1500 more per person for prescription medications annually, and are absent from work approximately 3.5 more days annually. On the whole, patients with RA cost their employers across the United States approximately $5.8 billion annually.

Today’s treatment of RA is symptom-based and often requires a combination of agents. Typically, therapy begins with disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine. DMARDs are administered along with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or low-dose corticosteroids to reduce swelling, pain, and fever.

The treatment course for more serious cases of RA includes biologic agents, which are also considered DMARDs, that target specific aspects of the immune system. These drugs include abatacept (Orencia), adalimumab (Humira), anakinra (Kinert), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), and tocilizumab (Actemra). The most recently approved agent for RA in adults, tofacitinib (Xeljanz), is an oral inhibitor of Janus kinase–mediated cell signaling.

As unique biomarkers, genetic defects, and drug targets are identified, the development of novel RA agents continues. A recent genome-wide association study identified 42 new genes that confer the risk for RA at a genome-wide level of significance, bringing the total of known RA risk genes to 101. Although many current RA therapies target these genes, these findings suggest that drugs that are currently approved for other indications may be repurposed for use in patients with RA. Other novel targeting agents, including inhibitors of granulocyte-macrophage colony-stimulating factor receptors, have been shown to suppress cytokine responses in patients with RA.

Otrexup: Novel Delivery of Methotrexate

In October 2013, the US Food and Drug Administration (FDA) approved the first methotrexate injection (MTXI) for subcutaneous (SC) use (Otrexup; Antares Pharma). This once-weekly self-administered injection is indicated for adults with severe active RA who have had inadequate response to or are intolerant of first-line therapy. MTXI was also approved for use in children with active polyarticular juvenile idiopathic arthritis.

The approval of MTXI was based on the demonstration of bioavailability in a 12-week, open-label, crossover study comparing the relative bioavailability of MTXI with oral methotrexate. Data from this study were presented at the 2013 annual meeting of the American College of Rheumatology.

Originally developed as an oncology drug, methotrexate has become a cornerstone in the treatment of RA. In a recent interview regarding his experience in the study of MTXI, Michael Schiff, MD, Clinical Professor
of Medicine in the Division of Rheumatology at the University of Colorado, stated, “This new delivery system for methotrexate provides a welcome option for physicians and their patients to continue effective use of methotrexate... The availability of an easy and safe way to administer subcutaneous methotrexate may... enable more patients to realize the possibility of continued disease control.”

The use of parenteral methotrexate for the treatment of RA is less popular as a result of the challenges related to self-administration. Patients with RA may have compromised manual dexterity, needle phobia, and/or a lack of confidence in safely self-injecting with a vial, a needle, or a syringe, which can be barriers to use.7 Kevin Deane, MD, of the Division of Rheumatology at the University of Colorado stated, “Injectable [methotrexate] to date has come in a large vial, and [the] patient draws up medication and injects it... Drawing up and administering this medication may be somewhat difficult for some patients to do, especially with arthritic conditions.”10

Mechanism of Action

Methotrexate, an inhibitor of dihydrofolate reductase, interferes with DNA synthesis, repair, and cellular replication.11 Cells that are actively proliferating are particularly susceptible to these effects. The mechanism of action of methotrexate in RA is unknown. It may work by altering immune function.11

Dosing and Administration

MTXI is a single-dose, easy-to-use autoinjector for once-weekly SC use.11 It is available in doses ranging from 10 mg to 25 mg in 5-mg increments and is administered in the abdomen or thigh.11 The MTXI dose can be adjusted gradually for optimal outcomes.

Therapeutic response to methotrexate is usually seen within 3 to 6 weeks and continues for 12 weeks or more.11 The optimal duration of MTXI therapy is unknown.11

Healthcare professionals should ensure that patients understand that MTXI is administered once weekly. The daily use of methotrexate has resulted in fatal toxicity.11

Clinical Trials

Bioavailability Study

The bioavailability of MTXI was assessed in an open-label, crossover study in which 49 adults with RA who had been receiving methotrexate for 3 months or more were given 10 mg, 15 mg, 20 mg, or 25 mg of methotrexate.8 They were randomized to receive either oral methotrexate, MTXI injected in the abdomen, or MTXI injected in the thigh.8 Blood samples were collected for analysis before the drug’s administration and at 13 time points of 15 minutes to 12 hours after drug administration.8 The average age of patients with RA who enrolled in the bioavailability study was 61 years and they had been diagnosed with RA for an average of 13 years.8 Their mean body mass index was 30.7 kg/m².8

Pharmacokinetic parameters of interest included the area under the plasma concentration time curve (AUC), the maximum drug concentration, and the time of occurrence for maximum drug concentration. Safety was determined using the incidence of treatment-emergent adverse events (AEs), including injection-site reactions, as well as by monitoring laboratory parameters and vital signs.8

The analysis of pharmacokinetic parameters demonstrated that 4 hours after administration, the bioavailability of MTXI (administered in the thigh) was consistently greater than oral methotrexate at all dose levels (10-25 mg).8 At doses of 10 mg, 15 mg, 20 mg, and 25 mg, the relative bioavailability calculations (AUC of MTXI vs oral methotrexate) were 121%, 114%, 131%, and 141%, respectively, as summarized in Table 1.8 No bioavailability plateau was seen for MTXI, whereas the bioavailability of oral methotrexate plateaued at a dose of 15 mg.8

“The availability of an easy and safe way to administer subcutaneous methotrexate may... enable more patients to realize the possibility of continued disease control.”

Phase 2 Clinical Trial

A phase 2, multicenter, open-label, single-dose, single-arm, in-clinic study enrolled 101 adults with RA to evaluate the ease of use of MTXI.12 The autoinjected product was tested with the intention of addressing the concerns of patients with RA regarding self-administering methotrexate using a conventional vial and syringe.12

The patients in the trial received MTXI at a dose of 10 mg, 15 mg, 20 mg, or 25 mg weekly.12 Dosing was
determined by investigators based on each patient’s previous methotrexate regimen and disease status (ie, controlled or uncontrolled) at the time of study enrollment.

Of the 101 patients enrolled, 99 patients were evaluable. Most patients (79%) were female, with an average age of 61 years. These patients had been diagnosed with RA for an average of 13 years. All patients had received methotrexate for at least 3 months before enrolling in the study. Overall, 20% of patients had received SC methotrexate, and their functional status ranged from mild to severe; 89% were in American College of Rheumatology Functional Class II or III.

Of the 99 evaluable patients, 94% reported VAS scores of ≤10 on day 1, and 87% had scores of ≤5 on day 1. All 99 patients handled the autoinjector successfully.

The primary outcome measure in this phase 2 trial of MTXI was pain associated with SC administration as measured using a 100-mm visual analog scale (VAS).

The administration sites were evaluated before administration and at 15 minutes, 1 hour, 6 hours, and 24 hours after self-administration. The mean administration-site pain ratings for all enrolled patients (N = 101) were 3.6 on day 1 and 1.4 on day 2 (standard deviations, ±9.1 and ±3.2, respectively).

Of the 99 evaluable patients, 94% reported VAS scores of ≤10 on day 1, and 87% had scores of ≤5 on day 1. All 99 patients handled the autoinjector successfully.

Of 404 skin sites that were evaluated after MTXI administration, 92% reported no erythema, with the balance showing “very slight, barely perceptible” erythema. Three patients experienced AEs while taking MTXI, including sick sinus syndrome, exostosis, and headache. None of these was considered to be related to the study drug.

Safety

Methotrexate and MTXI were safe and well tolerated in the bioavailability study. The few AEs that were observed with MTXI were deemed transient and manageable. None required medical treatment. Two serious AEs were deemed unrelated to treatment, including 1 death from myocardial infarction in a 79-year-old man with a history of heart disease.

Contraindications

MTXI is contraindicated in pregnant women, nursing mothers, patients with alcoholism or liver disease, patients with immunodeficiency syndromes, patients with preexisting blood dyscrasias, and patients with hypersensitivity to methotrexate.

Warnings and Precautions

Boxed warning. Like the oral formulation of methotrexate, MTXI labeling includes a boxed warning for multiple safety risks, including embryo-fetal toxicity and death. These warnings include:

- Serious toxic reactions and death; patients taking methotrexate should be closely monitored for bone marrow depression, liver, lung, skin, and kidney toxicities
- Fetal death and congenital anomalies; methotrexate is contraindicated in pregnancy
- Unexpectedly severe and sometimes fatal bone marrow suppression, aplastic anemia, and gastrointestinal toxicity; these events were reported when methotrexate and some NSAIDs were administered concurrently
- Hepatotoxicity, fibrosis, and cirrhosis after prolonged use
- Interstitial pneumonitis
- Diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and death from intestinal perforation
- Severe and occasionally fatal skin reactions
- Potentially fatal opportunistic infections.

Laboratory tests needed. Patients who are candidates for MTXI should undergo a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest x-ray before initiating therapy.

During MTXI therapy, clinicians should monitor hematologic parameters at least monthly, and monitor renal and liver function parameters every 1 to 2 months.

Embryo-fetal toxicity. Fetal death and congenital anomalies have been reported with methotrexate use. MTXI is not recommended for women of childbearing age unless its benefits outweigh risks. Steps to avoid conception should be taken if either partner is receiving MTXI therapy.

Malignant lymphomas. Non-Hodgkin lymphoma and other tumors have been observed in patients taking low-dose oral methotrexate. In some cases, however, malignancies that arose during treatment regressed completely after methotrexate withdrawal. Before initiating antilymphoma treatment, MTXI should be discontinued.

Additional warnings. Additional warnings and precautions related to MTXI include organ-system toxicity, infection, skin reactions, dizziness and fatigue, malignant lymphomas, as well as gastrointestinal, hematologic, hepatic, neurologic, pulmonary, and renal complications. Additional information regarding these warnings and precautions is listed in Table 2.

Conclusion

The FDA approval of a new delivery system for the administration of methotrexate adds a new and conve-
### Table 2  System-Specific Warnings and Precautions for Subcutaneous Methotrexate

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Description of potential risk</th>
<th>Guidance</th>
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<tbody>
<tr>
<td><strong>Organ-system toxicity</strong></td>
<td>• MTXI has the potential for serious toxicity; patients using MTXI should be closely monitored for bone marrow, liver, lung, and kidney toxicities. Toxic effects may be related to dose or frequency at any dose</td>
<td>• If adverse reactions occur, MTXI should be discontinued or the dose reduced; correction with leucovorin calcium and/or acute intermittent hemodialysis with a high-flux dialyzer may be warranted. If MTXI therapy is re instituted, it should be done cautiously • Because methotrexate has not been well studied in older individuals, relatively low doses should be considered in elderly patients and they should be closely monitored</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>• MTXI should be used with extreme caution in patients with peptic ulcer disease or ulcerative colitis • Unexpectedly severe and at times fatal gastrointestinal toxicity have been documented in patients taking methotrexate (usually high dose) in combination with some NSAIDs</td>
<td>• Interruption of MTXI therapy is necessary if diarrhea and ulcerative stomatitis occur • Dehydration resulting from vomiting, diarrhea, or stomatitis warrants discontinuation of MTXI until recovery</td>
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<tr>
<td><strong>Hematologic</strong></td>
<td>• Because MTXI can suppress hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia can occur. In controlled clinical trials conducted with a different formulation of methotrexate in 128 patients with RA, 2 patients had leukopenia, 6 had thrombocytopenia, and 2 had pancytopenia • When administered with some NSAIDs, high doses of MTXI may cause severe and sometimes fatal bone marrow suppression and aplastic anemia • Patients with severe granulocytopenia and fever should be evaluated as soon as possible. Such patients usually require parenteral broad-spectrum antibiotic therapy</td>
<td>• MTXI should be used with extreme caution in patients with preexisting hematopoietic impairment. The drug should be stopped immediately if a significant drop in blood counts is observed</td>
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<tr>
<td><strong>Hepatic</strong></td>
<td>• MTXI can cause hepatotoxicity in patients with RA, ranging from elevated transaminases to fibrosis and cirrhosis • In RA, methotrexate hepatotoxicity may be associated with age at first use and duration of therapy. Other risk factors, such as total cumulative dose, diabetes, and advanced age, as well as lifestyle factors including alcoholism and obesity may be associated, but have not been confirmed • Liver function tests should be performed at baseline and at 4- to 8-week intervals in patients receiving MTXI for RA • Patients with a history of excessive alcohol use, abnormal baseline liver function test values, or chronic hepatitis B or C infection should undergo liver biopsy before MTXI treatment • During treatment, liver biopsy should be performed if liver function test abnormalities are persistent or if serum albumin levels fall below the normal range • MTXI should be discontinued in patients who show persistent abnormal liver function tests, those who do not consent to liver biopsy, and in any patient whose liver biopsy exhibits moderate-to-severe changes</td>
<td>• Special caution should be taken in patients with preexisting liver damage and impaired hepatic function</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>• Patients with an active infection should use MTXI with extreme caution • Opportunistic infections, especially Pneumocystis pneumonia, may occur with MTXI</td>
<td>• Live virus vaccines are not recommended and may be ineffective when given during MTXI therapy</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td>• Leukoencephalopathy after intravenous methotrexate administration has been reported in patients who have had craniospinal irradiation. Discontinuation of methotrexate does not always resolve neurotoxicity</td>
<td></td>
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</table>

(Continued)
Table 2  System-Specific Warnings and Precautions for Subcutaneous Methotrexate  
(Continued)

<table>
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<td>Neurologic (Continued)</td>
<td>• Transient acute neurologic syndrome has been reported in patients treated with high-dose methotrexate. This stroke-like encephalopathy can manifest as confusion, hemiparesis, transient blindness, seizures, and coma. Its exact cause is unknown</td>
<td>If pulmonary symptoms are observed, MTXI treatment should be interrupted and the patient should be closely monitored</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>• Use of methotrexate may result in lung disease, including acute or chronic interstitial pneumonitis. This may occur at any time during therapy and has occurred at low doses of methotrexate. Lung disease may not be fully reversible and can be fatal. • Symptoms of pulmonary distress, especially a dry nonproductive cough, and nonspecific pneumonitis occurring during MTXI therapy may indicate a dangerous lesion • Other symptoms can include fever, cough, dyspnea, hypoxemia, and an infiltrate on chest x-ray. Infection (pneumonia) must be excluded</td>
<td>• If pulmonary symptoms are observed, MTXI treatment should be interrupted and the patient should be closely monitored</td>
</tr>
<tr>
<td>Renal</td>
<td>• High doses of methotrexate used in the treatment of osteosarcoma can cause renal damage that may lead to acute renal failure</td>
<td>• Renal function, adequate hydration, urine alkalinization, and levels of serum methotrexate and creatinine should be monitored</td>
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<tr>
<td>Skin</td>
<td>• Dermatologic reactions, including severe reactions and fatalities, have been reported in children and adults within days of taking oral, intramuscular, intravenous, or intrathecal methotrexate administration at any dose</td>
<td>• Patients should be cautious when driving or using machinery</td>
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</table>

MTXI indicates methotrexate injection; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis.
Source: Otrexup (methotrexate) injection prescribing information; 2013.

References