Crohn's disease is an inflammatory disease that affects the gastrointestinal tract. It commonly involves the small bowel, though it may involve other areas. Crohn's disease along with ulcerative colitis is collectively termed inflammatory bowel disease, which is estimated to affect 1.4 million Americans, with approximately 30,000 new cases per year. Patients with Crohn's disease typically experience exacerbations and periods of remission; symptoms such as abdominal pain, diarrhea, weight loss, malaise, and fever can be debilitating for patients. Pharmacologic treatment options for maintenance or remission of Crohn's disease include corticosteroids, aminosalicylates, antimicrobials, purine analogues, and tumor necrosis factor modifiers. Once the purine analogues (e.g., azathioprine and mercaptopurine) have failed or are not tolerated, patients with Crohn's disease may be prescribed subcutaneous injection of methotrexate. Typically, patients have to make weekly visits to a physician's office or hospital in order for a nurse to administer the medication; however, recent literature has shown that methotrexate can be safely administered subcutaneously at home with the appropriate education and training. To ensure optimal therapeutic outcomes, improve patient adherence, and minimize potential adverse effects, a pharmacy-based methotrexate self-injection training program was developed for patients with Crohn's disease.

Pharmacists at The Ohio State University (OSU) College of Pharmacy Clinical Partners Program (Clinical Partners), an ambulatory care clinic located within the OSU Medical Center outpatient building, provide a variety of clinical services focusing on the areas of medication management, wellness and prevention, patient self-management of chronic diseases, and training in the use of specialty medications. In addition to a long-standing hepatitis C education program, Clinical Partners has recently expanded its specialty medication services to include education on a variety of injectable medications including those for anemia, rheumatoid arthritis, multiple sclerosis, and now Crohn's disease.

The methotrexate injection program began when Clinical Partners was approached by physicians at The OSU Gastroenterology Practice to provide an educational service for its patients with Crohn's disease. The program was headed by one of the Clinical Partners pharmacists whose responsibilities included developing the education program and training each pharmacist on the disease state, drug treatment, and injection technique. Patients are seen on a case-by-case basis during the regular clinic hours, 8:30 a.m. to 5:00 p.m. Monday–Friday, at a mutually convenient time for both the patient and pharmacist.

Methotrexate is currently used in the treatment of refractory Crohn's disease. Once weekly subcutaneous administrations of methotrexate are found to be effective for inducing and maintaining remission of Crohn's disease and for reducing the requirements for
corticosteroids, which are often poorly tolerated when used long-term.\textsuperscript{3,4} Low-dose methotrexate for the treatment of inflammatory conditions is most conveniently administered orally, although intramuscular or subcutaneous administration may reduce the incidence of intolerable gastrointestinal adverse effects often seen with oral dosage forms.\textsuperscript{5,6} The bioavailability of oral methotrexate is highly variable in patients with Crohn’s disease; therefore, subcutaneous administration may be most appropriate.\textsuperscript{8} Treatment dosages are typically 25 mg injected subcutaneously once weekly, while the dosage of 15 mg once weekly appears to be effective for maintenance therapy. A specific guideline on the duration of therapy has not been established, though some literature indicates that 16 weeks at treatment dosages induce remission; maintenance dosages have been studied for up to 40 weeks.\textsuperscript{2-4}

Methotrexate is different from most self-administered injectable medications because it is considered a cytotoxic agent. Thus, special attention must be given to safety precautions when handling and disposing of methotrexate. Goals of the patient education session should include a proper demonstration of injection technique, a thorough understanding of important safety precautions and the adverse effects of therapy, and a strict compliance with follow-up appointments.

At Clinical Partners, candidates for methotrexate instruction are identified through a physician referral; once referred, patients are contacted to schedule an appointment and discuss the items they should bring with them to the visit. Regardless of the practice setting (e.g., community pharmacy or clinic), it is important that both the pharmacist and patient are prepared for the visit. The pharmacist should gather educational materials on the drug and disease state and make sure the patient has the correct medication and supplies. The physician can indicate on the referral form if he or she would like the pharmacist to provide 0.9% sodium chloride for injection training purposes. Patients should be instructed on the supplies they need before the visit and where they can purchase these items: methotrexate 25 mg/mL solution (single-dose vials), insulin syringes with needles (1/2 in 29–30 gauge), alcohol swabs, gloves, and a sharps container. Alternatively, these items could be provided by the clinic or pharmacy if desired. Patients should be asked to bring a complete list of all their current medications, including nonprescription and herbal medicines. Pharmacists at Clinical Partners often encourage patients to invite a family member or friend along to the appointment for support.

To reinforce why the patient needs the medication, the appointment should begin with a brief discussion of Crohn’s disease and the role methotrexate plays in its treatment. Patients should be given written education materials and receive counseling that includes additional information on the disease state, injection technique, adverse effects of therapy, safety precautions, and storage and disposal of medication vials and used syringes.

Some patients may be reluctant to give themselves injections, so it is important to first discuss any apprehensions they may have to self-administration of methotrexate. If the patient is unable or unwilling to administer the injections, a caregiver, close relative, or friend may be instructed to do so. It is helpful to provide patients or caregivers with a written step-by-step guide on preparing and injecting the medication so that they can follow along as the pharmacist reviews the instructions. They can also use this guide to help recall the steps when it is time to give the next injection outside of the pharmacy. Patients or caregivers can practice drawing up the medication using 0.9% sodium chloride until they feel comfortable with the process. Then the patients or caregivers can give the first injection of methotrexate or 0.9% sodium chloride at the appointment, with the pharmacist talking them through each step.

Patients should be advised of the common adverse effects of methotrexate therapy, which include nausea, vomiting, loss of appetite, diarrhea, mouth sores, sensitivity to sunlight, and hair loss.\textsuperscript{2,9} Gastrointestinal symptoms tend to be the most common adverse effects experienced by patients. Approximately 10–18% of patients require discontinuation of treatment due to adverse effects.

Supplementation with folic acid, as either 1 mg daily or 5 mg once weekly within 24–72 hours after the methotrexate injection, may decrease the incidence of minor adverse effects including nausea, vomiting, diarrhea, and mouth sores.\textsuperscript{2,9,10} At Clinical Partners, physicians indicate on the referral form if they have prescribed folic acid for the patient. Some of the less common but more serious adverse effects that have been reported with methotrexate use include bone marrow depression; allergic reactions; and hepatic, pulmonary, and renal toxicities.\textsuperscript{29} Patients should be informed of signs and symptoms that may indicate a serious adverse effect, including fever, persistent diarrhea, nagging cough, shortness of breath, stomatitis, rash or hives, unusual bruising or bleeding, and yellowing of the skin or eyes. It is necessary that patients understand the importance of contacting their physician or pharmacist immediately to report these adverse effects. Patients should have baseline laboratory testing before beginning treatment, including a complete blood count, liver function tests, serum creatinine, and chest x-ray.\textsuperscript{7} The pharmacist can play a critical role by confirming with the patient and physician that baseline studies have been performed before methotrexate therapy has been initiated and that folic acid has been prescribed to reduce the incidence of adverse effects. Lastly, patients must be educated on the importance of keeping their follow-up appointments and scheduled laboratory tests as directed by their physician.

Methotrexate is teratogenic (pregnancy category X); thus, it is important to discuss the avoidance of pregnancy while using this medication. Pregnancy should be avoided if either partner, male or female, is using methotrexate.\textsuperscript{7} Avoidance of pregnancy through appropriate contraceptive measures should continue for three months following therapy for men.
and for at least one ovulatory cycle following therapy for women. Methotrexate is also contraindicated in breastfeeding mothers because of the potential adverse effects to the infant. Patients should be informed of potential drug interactions with nonsteroidal antiinflammatory drugs and salicylates as they may increase risk for adverse effects by decreasing tubular secretion of methotrexate. 

Trimethoprim–sulfamethoxazole may also increase risk for bone marrow suppression; therefore, it should be avoided in patients receiving methotrexate.

In order to protect the patient or caregiver preparing and administering the drug, gloves and protective eyewear are suggested to prevent accidental exposure to the skin or eyes. Syringes and vials should be disposed of in a sharps container labeled “cytotoxic.” Patients can be instructed to return the sharps container to their physician’s office, pharmacy, or hospital when it is two-thirds to three-quarters full for proper disposal. Guidelines for the self-administration of methotrexate for inflammatory conditions do not require patients to have spill kits in case of small volume spillage (<1mL). However, patients should be provided with a spill kit with which small spills can be cleaned up with water-absorbent materials such as cotton swabs and gauze pads and then washed thoroughly with soap and water by a person wearing protective apparel. All materials should be disposed of in the sharps container so that they can be discarded according to local, state, and federal guidelines.

At Clinical Partners, a follow-up phone call to the patient is conducted approximately one to two weeks after the training appointment. Referral and follow-up with the patient’s physician can then be made as necessary. Referrals would be warranted if the patient shows any signs or symptoms of toxicity or experiences intolerable adverse effects. Some clinics or pharmacies may prefer to have the patient come in for a second appointment in order to assess injection technique, adverse effects, and adherence to physician and laboratory visits. It is important to schedule a follow-up appointment with the patient whether it is by telephone or face to face.

To date, Clinical Partners has seen only a limited number of patients based on the number of referrals received from the gastroenterology practice. Currently, this education program (although Clinical Partners is actively exploring reimbursement opportunities from third-party insurers for the near future).

Whether provided in a community pharmacy or clinic setting, this approach can be used to ensure appropriate and safe use of methotrexate for patients with Crohn’s disease. These same principles can also be applied to educate patients about the use of methotrexate in other inflammatory conditions including rheumatoid arthritis and psoriasis. Self-administration of methotrexate can be a safe and convenient option for some patients, and pharmacists can play an important role in education and support.


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