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DRUG NEWS

Subcutaneous Methotrexate for Rheumatoid Arthritis

Summary

- Subcutaneous administration of methotrexate is recommended in the treatment of rheumatoid arthritis by the Canadian Rheumatology Association as either initial treatment or after failure or intolerance to oral methotrexate
- Parenteral methotrexate products indicated for parenteral use may be given subcutaneously (multi-dose vials, acquisition cost for 25 mg once weekly ~ $40/28 days)
- MetoJect® is the only Health Canada-approved product indicated to be given subcutaneously (single-use, prefilled syringes, acquisition cost for 25 mg once weekly ~ $280/28 days)
- Price, safety and convenience should be considered when choosing which product to use

Background

Rheumatoid arthritis (RA) is an autoimmune condition affecting connective tissues; it commonly presents as chronic inflammation of the synovial fluid leading to joint pain, stiffness and irreversible deformities in the later stages.[1] Methotrexate (MTX) is the disease-modifying anti-rheumatic drug (DMARD) of choice in most cases of RA[1]; the maintenance dosing regimen is commonly prescribed as 7.5-25mg once weekly[1] via the oral route.[2] Since MTX acts as a folate antimetabolite, certain toxicities may be reduced via folate supplementation.[1] However, some patients still find its adverse effect profile to be intolerable.[2] This is when rheumatologists may turn to the option of subcutaneous (SC) MTX instead; pharmacists who receive these prescriptions, however, may be unfamiliar with this route of administration in RA.

Why Subcutaneous Methotrexate?

The latest recommendations released by the Canadian Rheumatology Association support the use of SC MTX in patients with RA: "Initial therapy with sc MTX (e.g., > 15 mg) or switching to sc administration after failure of oral MTX due to intolerance or inefficacy were recognized as appropriate options. In the latter case, other alternatives such as adding or switching DMARD could also be considered."[3]

SC MTX has been shown to be potentially more efficacious than oral MTX[4-9]; this is speculated to be due to higher and more stable bioavailability when administered SC.[4,10,11,12] In regards to tolerability, SC MTX (especially in doses ≥15mg) is equally or possibly more tolerable (particularly gastrointestinal-wise) as when it is administered at the same dose orally.[4,5,7,8,11-13] A cost-minimization analysis conducted in the UK demonstrated that the use of SC MTX following oral MTX failure has the potential to have significant cost-savings as it may delay the introduction of a biologic.[14] Details of the studies can be found in Appendix I.

A pharmacokinetic study comparing intramuscular and SC administration of MTX demonstrated that IM and SC routes are interchangeable.[15] Another small pragmatic study concluded that serum MTX levels were not significantly affected by the route of administration and noted no differences in safety and efficacy.[16] IM injections tend to be more painful and require administration by a certified healthcare professional; SC injections cause very little pain and can be self-administered or administered by a family member or caregiver.[15,16]

Products Available in Canada

MTX has been administered SC by patients and/or caregivers for more than the last ten years.[17] However, no marketed product had the labeled indication for SC use until the latter half of 2016.[18] Instead, MTX vials indicated for various parenteral routes other than SC are used; the administration technique is similar to that used to self-administer insulin.[17] The newly Health Canada-approved MetoJect®, a single-use prefilled syringe, is the only parenteral product officially indicated for SC use.[18] It is available in a variety of strengths; currently only a few strengths are available but the remaining are expected in the near future.[18] (See Appendix II) Several considerations should be taken into account when choosing which product to use such as price, safety, and convenience (Table 1); this should be discussed with the patient, family, and/or caregivers.

Table 1: Comparison of MTX vial to Prefilled Syringe

MTX Vial (SC is off-label)	MetoJect®
• Acquisition cost for 28 day supply of 25 mg/week: ~$40[1] + cost of syringes and needles • Available as multi-dose vials (containing preservative), usually 25 mg/ml, 2 ml • Patient and/or family members need to be counseled on supplies needed and appropriate administration technique • Greater risk of dosing errors • Risk of spillage, which is important considering MTX is a hazardous product	• Acquisition cost for 28 day supply of 25 mg/week: ~$280[1] • Syringes are single dose • Available in multiple strengths (see Appendix I) • Patient and/or family members need to be counseled on appropriate administration techniques; fewer additional supplies needed. • More convenient to use • Risk of spillage significantly reduced.

Conclusion

SC MTX is purported to have higher efficacy and same or better tolerability compared to the oral route. Switching from oral to SC MTX may delay the need for biologics, which has substantial cost-savings. MetoJect® Subcutaneous is currently the only parenteral product officially indicated for SC use, although MTX vials indicated for IM/IV use may be used off-label. Price, convenience and safety need to be considered when choosing which product is the most appropriate for the patient.

Appendix I. Available Strengths of Metoject[18]

* 1 mL syringe with 0.15 mL solution for injection, equivalent to 7.5 mg methotrexate
* 1 mL syringe with 0.2 mL solution for injection, equivalent to 10 mg methotrexate
* 1 mL syringe with 0.25 mL solution for injection, equivalent to 12.5 mg methotrexate
* 1 mL syringe with 0.3 mL solution for injection, equivalent to 15 mg methotrexate
* 1 mL syringe with 0.35 mL solution for injection, equivalent to 17.5 mg methotrexate
* 1 mL syringe with 0.4 mL solution for injection, equivalent to 20 mg methotrexate
* 1 mL syringe with 0.45 mL solution for injection, equivalent to 22.5 mg methotrexate
* 1 mL syringe with 0.5 mL solution for injection, equivalent to 25 mg methotrexate

Appendix II. Studies Comparing Oral vs SC MTX in Patients with RA

Study	Outcome	Result	Conclusion
Hoekstra[10] **2004 RCS**	F, AUC of oral and SC MTX (≥25mg) in the same patient with RA one week apart (n=15)	AUC (mcg.hr/L): Oral: 2466±785 SC: 3786±873 Oral F = 0.21-0.96, mean 0.64 SC F assumed to be 1	Orally administered MTX had lower serum MTX concentrations than SC MTX as well as highly variable F in doses ≥ 25mg
Braun[5] **2007 RCT**	Primary: achievement of a response (ACR20) at 24 weeks in RA patients on SC vs oral MTX (15mg)* Secondary: tolerability during treatment (n=375) *patients who did not achieve ACR20 by week 16 were switched from 15mg oral to 15mg SC and 15mg SC to 20mg SC	ACR20 response: SC - 78% Oral - 70% p>0.05 AEs reported: SC: 66% Oral: 62%	SC administration was significantly more effective than oral administration of the same MTX dosage. There was no difference in tolerability.
Rutkowska[13] **2009 RCS**	RA patients' survey responses regarding AEs on oral vs subsequent same dose of SC MTX* (7.5, 15mg) (n=70) *Max duration of treatment 24 months. Mean duration: Oral:17.8 ±7.0 months SC: 7.3 ±4.2 months	GI AEs intensity points MTX 15mg (SC vs. oral) Vomiting: 0 vs 0.9 Nausea: 1.1 vs 3.3 Abdominal pain: 0.1 vs 2.0 Diarrhea: 0 vs 0.9 Loss of appetite: 2 vs 2	Lower intensity of GI AEs following SC MTX compared with the same dose administered orally among patients with long-lasting RA.

Study	Outcome	Result	Conclusion
Bakker[6] **2010** **ROL** **Post-hoc analysis**	Response rates (DAS28) when RA patients were switched from oral to SC MTX (same dose) at one month (n=57)	DAS28 response rate: Total - 36 patients 63%, [95% CI, 50% - 70%] To SC due to AEs: 57% To SC due to insufficient effect*: 67% *previously on max oral dose of 30mg	Stepping to SC from oral MTX is a useful strategy regarding a further decrease in disease activity, specifically for those in the insufficient effect subgroup
Islam[7] **2013** **RCT**	Response rate of ACR20, ACR50, ACR70 and AEs of RA patients on oral or SC MTX (15mg) at six months (n=92)	SC vs oral: ACR 20: 93% vs. 80%, $p=0.02$ ACR 50: 89% vs. 72%, $p=0.03$ ACR 70: 11% vs. 9 %, $p=0.72$ Most common AEs: -nausea (37% vs. 63%) -vomiting (11% vs. 30%) -dyspepsia (29% vs. 48%) -dizziness (4l% vs. 52%) -alopecia (72% vs. 85%)	SC MTX was significantly more effective than oral MTX at the same dosage in active RA patients with no increase in AEs
Borman[8] **2014** **RCS**	Response rate of DAS28, ESR, CRP, RF, pain by VAS and GI AEs after RA patients were switched from oral to SC MTX (15mg) due to intolerance or inefficacy at 3 months (n=80)	Oral to SC: GI AEs: 95% to 33.8%, $p<0.05$ DAS28: 4±0.9 to 3.4±0.8, $p<0.01$ ESR: 42.5±21 to 29.7±15 $p<0.05$ CRP: 2.3±2.8 to 0.8±0.9, $p<0.05$ Pain by VAS: 66.9±18.9 to 51.6±14.4, $p<0.05$	SC MTX has better efficacy for disease activity and better tolerability than oral MTX that is ineffective or causing GI intolerance.
Pichlmeier[11] **2014** **RCS**	AUC, C_{max} and AEs of single-dose oral vs SC MTX (7.5, 14, 22.5, 30mg) in the same healthy subject at 2 different periods (n=59)	MTX SC/MTX tablet AUC, C_{max} (%): 7.5 mg: 135, 100 15 mg: 149, 129 22.5 mg: 151, 131 30 mg: 168, 128	Single-dose SC MTX pen resulted in higher relative F compared with oral. 80 AEs reported in 35/62 subjects. Fewer GI AEs with SC than oral. Single SC well- tolerated at injection site.
Schiff[12] **2014** **RCS**	Primary: F of oral and SC (abdomen and thigh) MTX (10, 15, 20, 25mg) in the same RA patient one week apart. Secondary: safety, other PK parameters (n=47)	Systemic F SC/oral (%): 10 mg: 121 15 mg: 114 20 mg: 131 25 mg: 141 No new treatment-related safety signals identified within the study.	Unlike oral MTX, F of SC MTX did not plateau over the doses studied, particularly at doses ≥15 mg/week. Higher systemic MTX exposure not associated with increases in AEs.

Study	Outcome	Result	Conclusion
Hazlewood[9] **2016** **CS**	Rate of treatment changes of RA patients on oral vs those on SC MTX* after one year (n=666) *patients prescribed SC MTX were prescribed a higher dose of MTX (mean dose over first three months 22.3 mg vs 17.2 mg/week)	Rate of treatment changes: SC - 49% Oral - 77% (HR 0.55 95% CI 0.39 to 0.79)	Initial treatment with SC MTX was associated with lower rates of treatment changes. Most treatment failures were due to inefficacy with no difference in failure due to toxicity.

ACR20, 50, 70 = American College of Rheumatology response criteria, improvement of ≥20%, ≥50%, ≥70%; AE = adverse effect; AUC = area under the curve; CI = confidence interval; C_{max} = peak serum concentration; ; CRP = C-reactive protein; CS = cohort study; DAS28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate; F = bioavailability; GI = gastrointestinal; HR = hazard ratio; MTX = methotrexate; PK = pharmacokinetic(s); RCS = randomized cross-over study; RCT = randomized controlled trial; RF = rheumatoid factor; ROA = route of administration; ROL = randomized open-label study; SC = subcutaneous; VAS = visual analogue scale

References

1. RxTx [Internet]. Ottawa (ON): Canadian Pharmacists Association; 2017. Rheumatoid Arthritis; [updated 01 Apr 2015; cited 9 Jan 2017]. Available from: https://www.e-therapeutics.ca/
2. Lexi-Comp Online, Bethesda, MD: American Society of Health-System Pharmacists; 2017; accessed 13 Jan 2017.
3. Bykerk V, Akhavan P, Hazlewood G et al. Canadian Rheumatology Association Recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012 Aug;39(8):1559-1582.
4. Li D, Yang Z, Kang P et al. Subcutaneous administration of methotrexate at high doses makes a better performance in the treatment of rheumatoid arthritis compared with oral administration of methotrexate: A systematic review and meta-analysis. Semin Arthritis Rheum. 2016 Jun;45(6):656-62.
5. Braun J, Kästner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008; 58(1):73-81.
6. Bakker MF, Jacobs JWG, Welsing PMJ et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Ann Rheumatic Dis. 2010 Oct;69(10):1849–52.
7. Islam M, Haq S, Islam M et al. Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis. Mymensingh Med J. 2013 Jul;22(3):483-8.

8. Borman P, Demir G, Okumus M. AB0473 Is subcutaneous methotrexate is better than oral methotrexate in the treatment of rheumatoid arthritis? Ann Rheum Dis 2014;73:964.
9. Hazlewood GS, Thorne JC, Pope JE, et al. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis. Ann Rheumatic Dis. 2016;75(6):1003–8.
10. Hoekstra M, Haagsma C, Proost J et al. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol. 2004 Apr;31(4):645–8.
11. Pichlmeier U, Heuer K. Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. Clin Exp Rheumatol. 2014 Jul-Aug;32(4):563-71.
12. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheu Dis. 2014 Aug;73(8):1549–51.
13. Rutkowska L, Rell-Bakalarska M, Lisowska B. Oral vs. subcutaneous low-dose methotrexate treatment in reducing gastrointestinal side effects. Reumatologia. 2009;47(4):207–11.
14. Fitzpatrick R, Scott DG, Keary I. Cost-minimisation analysis of subcutaneous methotrexate versus biologic therapy for the treatment of patients with rheumatoid arthritis who have had an insufficient response or intolerance to oral methotrexate. Clin Rheumatol. 2013 Nov;32(11):1605–12.
15. Brooks P, Spruill W, Parish R et al. Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis. Arthritis Rheum. 1990 Jan;33(1):91-4.
16. Arthur V, Jubb R, Homer D. A study of parenteral use of methotrexate in rheumatic conditions. J Clin Nurs. 2002 Mar;11(2):256-63.
17. Thompson A, Craig-Chambers M. Learning to self inject methotrexate at home [Internet]. Canadian Rheumatology Association. [cited 13 Jan 2017] Available from: http://rheuminfo.com/wp-content/uploads/2011/04/METHOTREXATE_INJECTION_SHEET.pdf
18. Health Canada. Drug Product Database Online Query. Ottawa, ON: Health Canada; [updated 30 Sep 2016; cited 10 Jan 2017]. Available from: http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
19. McKesson Canada; c2017 [cited 23 Jan 2017] PharmaClik; Available from http://clients.mckesson.ca. Account required.

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