CHAPTER 25

METHOTREXATE

İlteriş Oğuz Topal, MD

Methotrexate (MTX) is a derivative of aminopterin, an analogue and antimetabolite of folic acid.[1] In 1951 Gubner et al. recognized aminopterin to be effective in the treatment of psoriasis.[2] This led to the development of the more stable and less toxic derivate, methotrexate.[3] MTX was licensed for treating psoriasis at the beginning of the 1970s in the United States.[4] It has been used effectively for many other diseases, including collagen vascular diseases, cutaneous T cell lymphomas, atopic dermatitis and blistering disorders.[5]

PHARMACOLOGY AND PHARMACOKINETICS

Methotrexate (4-amino-N10 -methyl pteroglyglutamic acid) is a folic acid analogue with a similar structure to folic acid.[5] It can be administered orally, subcutaneously or intramuscularly.[3,5] MTX has good oral bioavailability. It is rapidly absorbed in the gastrointestinal tract, primarily in the proximal jejunum.[5,6] Orally administered MTX is absorbed via the GI tract and passes through the portal vein to the liver. While parenterally administered MTX would also enter the liver via the hepatic artery.[7]

In the circulation, the drug and its primary active metabolite, 7-hydroxymethotrexate are approximately 35-50 % and 90-95% protein bound, respectively.[3,5] Maximum blood levels of MTX occur 1-2 h after administration. A total of 50-90 % of the drug is excreted unchanged in the urine after 24 h.[3] MTX has been reported to cause slight decreases in the clearance of creatinine in romatoid artritis patients during the first 6 months of treatment, but the precise mechanism of this effect is unclear. In patients who have received long-term MTX treatment, the effect of MTX itself on renal functions must be considered when other causes for a reduced serum creatinine level have been ruled out.[7]

Excretion of MTX is inhibited by weak organic acids such as aspirin, nonsteroidal antiinflammatory drugs, piperacillin, penicillin G, and probenecid. Cephalosporins may also inhibit renal excretion, propably by competition for tubular secretion.[7]

In adults, MTX absorption has not been found to be affected by food in most investigations.[8] However, a single report did find an unquantifiable but significant decrease in serum MTX concentrations when given with food.[9] Absorption may be reduced in a setting of intestinal pathology, such as inflammatory bowel disease, shortened bowel, or other malabsorption syndromes.[10]

Bioavailability is relatively high, but there is individual variability among patients. The absorption of MTX administered orally at 7.5 mg/week is roughly equivalent to that of parenterally administered drug, but the absorption of oral MTX drops off by as much as 30% when the weekly dose is 15 mg or greater. The bioavailability of intramuscular (im) and subcutaneous (sc) MTX is similar to that of intravenous (iv) MTX.[10]

MECHANISM OF ACTION

The drug has a role in inhibiting dihydrofolate reductase (DHFR) and, therefore, in the activation of folic acid. This leads to the inhibition of the activity of thymidylate synthase which is a necessary component for the synthesis of purines and pyrimidines, and thus for the synthesis of DNA.[1] Other immunsuppressant effects of the drug include the inhibition of T and B lymphocytes, suppression of proinflammatory cytokines, and inhibition of chemotaxis of neutrophils and monocytes.[2] MTX inhibits 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, which catalyzes one of the final stages of de novo purine synthesis. Inhibition of AICAR transformylase leads to increased levels of AICAR, which in turn results in a net increase in intra- and extracellular adenosine. Adenosine have potent anti-inflammatory effects on a number of different target cells.[5,11] It inhibits the oxidative burst in neutrophils and monocytes, and inhibits including tumor necrosis factor-alpha, interleukin (IL)-10 and IL-123.[11,12]

The other effects of MTX: The drug could induce in vitro apoptosis of mitogen activated CD4+ and CD8+ lymphocytes, but not resting T cells. It has a significant suppressive effect on neutrophil chemotaxis, It reduces the numbers of macrophages and inflammatory cells in synovial tissue, it reduces intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in synovial tissue, it decreases metalloproteinase-1 production, which is

lymphoma, and nearly 3-fold increase in lung cancer.[115]

The risk of development of squamous cell carcinoma may increase in patients treated with psoralen puls ultraviolet A therapy.[3]

Infections

Reactivation of tuberculosis and hepatitis are reported in patients on low-dose MTX. MTX is considered to be safe in the setting of HIV, given there is close monitoring of patients for signs of infections, although its use in this group of patients remains controversial.[3]

Osteoarticular complications

Long-term high doses of MTX may reduce bone density. Osteopathy induced by MTX is characterized by bone pain, osteoporosis, and fractures (particularly of the distal tibia and vertebral region).[12]

Drug interactions

Numerous medications may interact with MTX by a variety of mechanisms that can result in elevated drug levels, thereby increasing the risk of toxicity as summarised in table 2.[2]

Table 2.

Reduced renal elimination of MTX
Ciclosporin
Salicylates
Sulphonamides
Probenecid
Penicillin
Colchicine
Cyclooxygenase inhibitors
Increased myelosuppression and digestive disorders
Ethanol
Cotrimoxazole
Pyrimethamine
Chloramphenicol
Sulphonamides
Cyclooxygenase inhibitors
Cytostatics
Cytostatics Separation of the MTX molecule from the plasma complex of the drug-binding protein
Cyclooxygenase inhibitors
Probenecid
Barbiturates
Phenytoin
Retinoids
Sulphonamides
Tetracyclines
Cotrimoxazole
Chloramphenicol
Sulphonylurea derivatives
Intracellular accumulation of MTX
Dipyridamole
Increased hepatotoxicity
Retinoids
Ethanol
Leflunomide

Methotrexate intoxication

When MTX intoxication is suspected, calcium folinate/folinic acid/citrovorum factor (leucovorin) 20 mg (10 mg/m2) must be administered as rapidly as possible parenterally (im,iv). Inpatient monitoring of renal and bone marrow function is required. Folinic acid administered every six hours in the same dosage until the MTX serum level has dropped below 10-8 M.[4]

Discontinuation of therapy

Therapy must be discontinued when severe unwanted side effects, pregnancy or severe infections occur.[4]

REFERENCES

1. Czarnecka-Operacz M, Sadowska-Przytocka A. The possibilities and principles of methotrexate treatment of psoriasis - the updated knowledge. Postepy Dermatol Alergol. 2014;31(6):392-400.
2. Dogra S, Mahajan R. Systemic methotrexate therapy for psoriasis: past, present and future. Clin Exp Dermatol. 2013;38(6):573-88.
3. Shen S, O'Brien T, Yap LM, Prince HM, McCormack CJ. The use of methotrexate in dermatology: a review. Australas J Dermatol. 2012;53(1):1-18.
4. Reich K, Domm S, Mrowietz U. Methotrexate therapy in dermatology. J Dtsch Dermatol Ges. 2012;10(5):363-70.
5. Bangert CA, Costner MI. Methotrexate in dermatology. Dermatol Ther. 2007;20(4):216-28.
6. Braun J. Optimal administration and dosage of methotrexate. Clin Exp Rheumatol. 2010;28(5 Suppl 61):S46-51.
7. Kremer JM. Toward a better understanding of methotrexate. Arthritis Rheum. 2004;50(5):1370-82.
8. Hamilton RA, Kremer JM. Why intramuscular methotrexate may be more efficacious than oral dosing in patients with rheumatoid arthritis. Br J Rheumatol. 1997;36(1):86-90.
9. Godfrey C, Sweeney K, Miller K, Hamilton R, Kremer J. The population pharmacokinetics of long-term methotrexate in rheumatoid arthritis. Br J Clin Pharmacol. 1998;46(4):369-76.
10. Swierkot J, Szechiński J. Methotrexate in rheumatoid arthritis. Pharmacol Rep. 2006;58(4):473-92.
11. S. L. Hider, I. N. Bruce and W. Thomson The pharmacogenetics of methotrexate. Rheumatology. 2007;46:1520–4.
12. Bressan AL, Silva RS, Fontenelle E, Gripp AC. [Immunosuppressive agents in Dermatology]. An Bras Dermatol. 2010;85(1):9-22.
13. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60(5):824-37.
14. Chiaravalloti AJ, Strober BE. The use of self-administered subcutaneous methotrexate for the treatment of psoriasis. J Drugs Dermatol. 2014;13(8):929-31.
15. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology (Oxford). 2004;43(3):267-71.

16. Morgan SI, Baggot JE, Vaughn WH, Austin JS, Veitch TA, Lee JY, Koopman WJ et al. Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis: a double-blind, placebo-controlled trial. Ann Intern Med. 1994,121(11): 833–41.

17. Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, Laan RF. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis. 2003;62 (5):423–6.

18. Holliday AC, Moody MN, Berlingeri-Ramos A. Methotrexate: role of treatment in skin disease. Skin Therapy Lett. 2013;18(3):4-9.

19. Akhyani M, Chams-Davatchi C, Hemami MR, Fateh S. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. J Eur Acad Dermatol Venereol. 2010;24(12):1447–51.

20. Flytström I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. Br J Dermatol. 2008;158 (1): 116– 21.

21. Heydendael VM, Spuls PI, Opmeer BC, de Borgie CA, Reitsma JB, Goldschmidt WF, Bossuyt PM, Bos JD, de Rie MA. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. N Engl J Med. 2003; 349(7): 658–65.

22. Sandhu K, Kaur I, Kumar B, Saraswat A. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. J Dermatol. 2003;30(6): 458–63.

23. Ranjan N, Sharma NL, Shanker V, Mahajan VK, Tegta GR. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study. J Dermatolog Treat. 2007;18(5):295–300.

24. Fallah Arani S, Neumann H, Hop WC, Thio HB. Fumarates vs. methotrexate in moderate to severe chronic plaque psoriasis: a multicentre prospective randomized controlled clinical trial. Br J Dermatol. 2011;164(4):855–61.

25. Gupta R, Gupta S. Methotrexate-betamethasone weekly oral pulse in psoriasis. J Dermatolog Treat. 2007;18(5):291–4.

26. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB photo therapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. J Am Acad Dermatol. 2006; 54(6):1013–18.

27. Shehzad T, Dar NR, Zakria M. Efficacy of concomitant use of PUVA and methotrexate in disease clearance time in plaque type psoriasis. J Pak Med Assoc. 2004;54 (9):453–5.

28. Zachariae C, Mørk NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, Johannesson A, Claréus B, Skov L, Mørk G, Walker S, Qvitzau S. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol. 2008;88(5):495-501.

29. Griffiths WAD. Pityriasis rubra pilaris. Clin Exp Dermatol. 1980;5(1):105-12.

30. Clayton BD, Jorizzo JL, Hichcock MG, Fleischer AB Jr, Williford PM, Feldman SR, White WL. Adult pityriasis rubra piiaris: a 10-year case series. J Am Acad Dermatol. 1997;36(6 Pt 1):959-64.

31. Dicken CH. Treatment of classic pityriasis rubra pilaris. J Am Acad Dermatol. 1994;31(6):997-9.

32. Weiner MJ. Methotrexate in corticosteroid-resistant urticaria. Ann Intern Med 1989; 110(10): 848.

33. Gach JE, Sabroe RA, Greaves MW, Black AK. Methotrexate- responsive chronic idiopathic urticaria: a report of two cases. Br J Dermatol 2001; 145(2): 340–3.

34. Perez A, Woods A, Grattan CE. Methotrexate: a useful steroid-sparing agent in recalcitrant chronic urticaria. Br J Dermatol 2010; 162(1): 191–4.

35. Ellis C, Luger T, Abeck D, Allen R, Graham-Brown RA, De Prost Y, et al; ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. Br J Dermatol 2003;148: 3-10.

36. Lyakhovitsky A, Barzilai A, Heyman R, Baum S, Amichai B, Solomon M, Shpiro D, Trau H. Low-dose methotrexate treatment for moderate-to-severe atopic dermatitis in adults. J Eur Acad Dermatol Venereol. 2010; 24(1): 43–9.

37. Zoller L, Ramon M, Bergman R. Low dose methotrexate therapy is effective in late-onset atopic dermatitis and idiopathic eczema. Isr Med Assoc J. 2008;10(6): 413–4.

38. Goujon C, Bérard F, Dahel K, Guillot I, Hennino A, Nosbaum A, Saad N, Nicolas JF.Methotrexate for the treatment of adult atopic dermatitis. Eur J Dermatol. 2006; 16(2):155–8.

39. Lazaridou E, Fotiadou C, Tsorova C, Trachana M, Trigoni A, Patsatsi A, Ioannides D. Resistant pityriasis lichenoides et varioliformis acuta in a 3-year-old boy: successful treatment with methotrexate. Int J Dermatol. 2010;49(2):215-7.

40. Cornelison RL, Knox JM, Everett MA. Methotrexate for the treatment of Mucha-Habermann disease. Arch Dermatol. 1972;106(4):507-8.

41. Lynch PJ, Saied NK. Methotrexate treatment of pityriasis lichenoides and lymphomatoid papulosis. Cutis. 1979;23(5):634-6.

42. Paul MA, Jorizzo JL, Fleischer AB Jr, White WL. Low-dose methotrexate treatment in elderly patients with bullous pemphigoid. J Am Acad Dermatol. 1994;31(4):620-5.

43. Heilborn JD, Ståhle-Bäckdahl M, Albertioni F, Vassilaki I, Peterson C, Stephansson E. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. J Am Acad Dermatol. 1999;40(5 Pt 1):741-9.

44. Tran KD, Wolverton JE, Soter NA. Methotrexate in the treatment of pemphigus vulgaris: experience in 23 patients. Br J Dermatol. 2013;169(4):916-21.

45. Smith TJ, Bystryn JC. Methotrexate as an adjuvant treatment for pemphigus vulgaris. Arch Dermatol. 1999;135(10):1275-6.

46. McCluskey P, Chang JH, Singh R, Wakefield D. Methotrexate therapy for ocular cicatricial pemphigoid. Opthalmology. 2004;111(4):796-801.

47. Hurd DS, Johnston C, Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). Br J Dermatol. 2008;158(2):399-401.

48. Tchernev G, Cardoso JC. Familial benign chronic pemphigus (Hailey-Hailey Disease): use of topical immunomodulators as a modern treatment option. Rev Med Chil. 2011;139(5): 633-7.

49. D'Errico A, Bonciani D, Bonciolini V, Verdelli A, Antiga E, Fabbri P, Caproni M. Hailey-Hailey disease treated with methotrexate. J Dermatol Case Rep. 2012;30;6(2):49-51.

50. Veien NK, Brodthagen H. Cutaneous sarcoidosis treated with methotrexate. Br J Dermatol 1977;97 (2):213–6.

51. Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med 1995; 155(8): 846–51.

52. Kasteler JS, Callen JP. Low-dose methotrexate administered weekly is an effective corticosteroid-sparing agent for the treatment of the cutaneous manifestations of dermatomyositis. J Am Acad Dermatol. 1997;36(1): 67-71.

53. Schiopu E, Phillips K, MacDonald PM, Crofford LJ, Somers EC. Predictors of survival in a cohort of patients with polymyositis and dermatomyositis: effect of corticosteroids, methotrexate and azathioprine. Arthritis Res Ther. 2012;27;14(1):R22.

54. Wenzel J, Brähler S, Bauer R, Bieber T, Tüting T. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Br J Dermatol. 2005;153(1):157-62.

55. Carneiro J, Sato E. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol 1999;26(6):1275–9.

56. Jorizzo JL, White WL, Wise CM, Zanolli MD, Sherertz EF. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behçet's disease. J Am Acad Dermatol. 1991;24(6 Pt 1):973-8.

57. Kikuchi H, Aramaki K, Hirohata S. Low dose MTX for progressive neuro-Behçet's disease. A follow-up study for 4 years. Adv Exp Med Biol. 2003;528:575-8.

58. Davatchi F, Shahram F, Chams H, Jamshidi AR, Nadji A, Chams C, Akbarian M, Gharibdoost F. Hish dose methotrexate for ocular lesions of Behçet's disease. Preliminary short-term results. Adv Exp Med Biol. 2003;528:579-84.

59. Brody M, Bohm I, Biwer E, Bauer R. Erfolgreiche Behandlung einer Panerteritis nodosa mit Methotrexat Low-dose-therapie. Hautarzt 1994;45(7): 476–9.

60. Schartz NE, Alaoui S, Vignon-Pennamen MD, Cordoliani F, Fermand JP, Morel P, Rybojad M. Successful treatment in two cases of steroid-dependent cutaneous polyarteritis nodosa with low-dose methotrexate. Dermatology. 2001;203(4):336-8.

61. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. J Am Acad Dermatol 1998; 39 (5 Pt 1):667–87.

62. Bauer R, Brody M, Boehm I. Methotrexat-low-dose-Therapie zur Behandlung infl ammatorischer and autoaggressiver Dermatosen. In: Tebbe B, Goerdt S, Orfanos CE, eds. Dermatologie—Heutiger Stand: Ergebnisse und Berichte der 38. Tagung der Deutschen Dermatologischen Gesellschaft in Berlin vol 29, April bis 3, Mai 1995. Stuttgart: Thieme, 1995: 318–20.

63. Wilson K, Abeles M. A 2 year, open ended trial of methotrexate in sytemic lupus erythematosus. J Rheumatol. 1994;21(9):1674-7.

64. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M. Methotrexate in patients with moderate systemic lupus erythematosus. Ann Rheum Dis. 1997;56(6):382-5

65. Upchurch KS, Heller K, Bress NM. Low-dose methotrexate therapy for cutaneous vasculitis of rheumatoid arthritis. J Am Acad. Dermatol 1987;17 (2 Pt 2):355-9.

66. Turan H, Baskan EB, Tunali S, Yazici S, Saricaoglu H. Methotrexate for the treatment of generalized lichen planus. J Am Acad Dermatol 2009;60(1): 164–6.

67. Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus- a case series with emphasis on therapy. Arch Dermatol 2007;143(4):511–5.

68. Nylander Lundqvist E, Wahlin YB, Hofer PA. Methotrexate supplemented with steroid ointments for the treatment of severe erosive lichen ruber. Acta Derma Venereol 2002; 82(1):63–4.

69. Jang N, Fischer G. Treatment of erosive vulvovaginal lichen planus with methotrexate. Australas J Dermatol 2008; 49(4): 216–9.

70. Duong B, Marks S, Sami N, Theos A. Lichen planus pemphigoides in a 2-year-old girl: response to treatment with methotrexate. J Am Acad Dermatol. 2012;67(4):e154-6

71. Fitch PG, Rettig P, Burnham JM, Finkel TH, Yan AC, Akin E, Cron RQ. Treatment of pediatric localized scleroderma with methotrexate. J Rheumatol. 2006;33(3):609–614.

72. Kreuter A, Gambichler T, Breuckmann F, Rotterdam S, Freitag M, Stuecker M, Hoffman K, Altmeyer P. Pulsed highdose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. Arch Dermatol. 2005;141(7):847–52.

73. Li SC, Feldman BM, Higgins GC, Haines KA, Punaro MG, O'Neil KM. Treatment of pediatric localized scleroderma: Results of a survey of North American pediatric rheumatologists. J Rheumatol. 2010; 37(1):175–181.

74. Uziel Y, Feldman BM, Krafchik BR, Yeung RS, Laxer RM. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. J Pediatr. 2000;136(1):91–9.

75. Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Low-dose methotrexate in the treatment of widespread morphea. J Am Acad Dermatol. 1998; 39(2 Pt 1):220–5.

76. van den Hoogen FH, Boerbooms AM, Swaak AJ, Rasker JJ, van Lier HJ, van de Putte LB. Comparison of methotrexate with placebo in the treatment of systemic sclerosis: A 24 week randomized double-blind trial, followed by a 24 week observational trial. Br J Rheumatol. 1996; 35(4):364–72.

77. Lange Wantzin G, Thomsen K. Methotrexate in lymphomatoid papulosis. Br J Dermatol. 1984;111(1):93-5.

78. Nijsten T, Curiel-Lewandrowski C, Kadin ME. Lymphomatoid papulosis in children: a retrospective cohort study of 35 cases. Arch. Dermatol. 2004;140(3):306–12.

79. Vonderheid EC, Sajjadian A, Kadin ME. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. J Am Acad Dermatol. 1996;34(3):470-81.

80. Yazawa N, Kondo S, Kagaya M, Yazawa H, Minamitsuji Y, Jimbow K. Successful treatment of a patient with lymphomatoid papulosis by methotrexate. J Dermatol. 2001;28(7):373-8.

81. Zackheim HS, Kashani-Sabet M, Hwang ST. Low dose methotrexate to treat erythrodermic cutaneous T cell lymphoma: Results in twenty-nine patients. J Am Acad Dermatol. 1996;34(4):626-31.

82. Zackheim HS, Kashani-Sabet M, McMillan A Low-dose methotrexate to treat mycosis fungoides: a retro-

spective study in 69 patients. J Am Acad Dermatol. 2003;49(5):873-8.

83. Plotner AN, Mutasim DF. Successful treatment of disseminated granuloma annulare with methotrexate. Br J Dermatol. 2010;163(5):1123-4.
84. Breuckmann F, Appelhans C, Harati A, Rotterdam S, Altmeyer P, Kreuter A. Failure of low-dose methotrexate in the treatment of scleredema diabeticorum in seven cases. Dermatology 2005;211(3):299-301.
85. Seyger MM, van den Hoogen FH, de Mare S, van Haelst U, de Jong EM. A patient with a severe scleredema diabeticorum, partially responding to low-dose methotrexate. Dermatology 1999;198(2):177-9.
86. Mehta V, Balachandran C, Rao R. Arndt gottron scleromyxedema: successful response to treatment with steroid minipulse and methotrexate. Indian J Dermatol. 2009; 54(2):193–5.
87. Helfrich DJ, Walker ER, Martinez AJ, Medsger TA Jr. Scleromyxedema myopathy: case report and review of the literature. Arthritis Rheum. 1988;31(11):1437-41.
88. Melton JL, Nelson BR, Stough DB, Brown MD, Swanson NA, Johnson TM. Treatment of keratoacanthomas with intralesional methotrexate. J Am Acad Dermatol 1991;25(6 Pt 1):1017–23.
89. Aubut N, Alain J, Claveau J. Intralesional Methotrexate Treatment for Keratoacanthoma Tumors: A Retrospective Case Series. J Cutan Med Surg. 2012;16(3):212-7.
90. Annest NM, VanBeek MJ, Arpey CJ, Whitaker DC. Intralesional methotrexate treatment for keratoacanthoma tumors: a retrospective study and review of the literature. J Am Acad Dermatol 2007;56(6):989-93.
91. Womer RB, Anunciato KR, Chehrenama M. Oral methotrexate and alternate-day prednisone for low-risk Langerhans cell histiocytosis. Med Pediatr Oncol. 1995; 25(2):70–3.
92. Fournier J, Ingraffea A, Pedvis-leftick AP. Successful treatment of indeterminate cell histiocytosis with low-dose methotrexate. J Dermatol. 2011 Sep;38(9):937-9.
93. Sun NZ, Galvin J, Cooper KD. Cutaneous Rosai-Dorfman Disease Successfully Treated With Low-Dose Methotrexate. JAMA Dermatol. 2014;150(7):787-8.
94. Trentham DE, Le CH. Relapsing polychondritis.Ann Intern Med. 1998 ; 129(2):114-22
95. Sosada B, Loza K, Bialo-Wojcicka. Relapsing Polychondritis. Case Rep Dermatol Med. 2014;2014:791951
96. Hammerschmidt M. Efficacy and safety of methotrexate in alopecia areata. An Bras Dermatol. 2014;89(5):729-34
97. Droitcourt C, Milpied B, Ezzedine K, Hubiche T, Belin E, Akpadjan F, Taïeb A, Seneschal J. Interest of High-Dose Pulse Corticosteroid Therapy Combined with Methotrexate for Severe Alopecia Areata: A Retrospective Case Series. Dermatology. 2012;224(4):369-73.
98. Royer M, Bodemer C, Vabres P, Pajot C, Barbarot S, Paul C, Mazereeuw J. Efficacy and tolerability of methotrexate in severe childhood AA. Br J Dermatol. 2011;165(2):407-10.
99. Spring P, Gschwind I, Gilliet M. Prurigo nodularis: retrospective study of 13 cases managed with methotrexate. Clin Exp Dermatol. 2014;39(4):468-73.
100. Zaouak A, Ghorbel HH, Benmously-Mlika R, Koubaa W, Badri T, Fenniche S, Mokhtar I. A case of linear atrophoderma of Moulin successfully treated with methotrexate. Dermatol Ther. 2014;27(3):153-5
101. Sandra A, Pai S, Shenoi S D. Unstable vitiligo responding to methotrexate. Indian J Dermatol Venereol Leprol. 1998;64(6):309.
102. Egan CA, Rallis TM, Meadows KP, Krueger GG. Low-dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. J Am Acad Dermatol. 1999;40(4):612-4.
103. Teitel AD. Treatment of pyoderma gangrenosum with methotrexate. Cutis. 1996;57(5):326-8.
104. Zachariae H. Methotrexate side-effects. British J Dermatol. 1990;122 (supp 36): 127-33.
105. Lewiss JH, Schiff E.Methotrexate-Induced Chronic Liver Injury: Guidelines for Detection and Prevention. The ACG Committee on FDA-related matters. American College of Gastroenterology. Am J Gastroenterol. 1988;83(12):1337-45.
106. Kozup P, Simaljokava M. Sytemic Therapy of psoriasis: Methotrexate. Bratisl Lek Listy 2011; 112(7):390-4.
107. Chládek J, Simková M, Vanecková J, Hroch M, Vávrová J, Hůlek P. Assessment of methotrexate hepatotoxicity in psoriasis patients: a prospective evaluation of four serum fibrosismarkers. J Eur Acad Dermatol Venereol. 2013;27(8):1007-14.
108. Ramamoorthy SK, Hephziba R. Acute Renal Failure Post High Dose Methotrexate Infusion Successfully Managed with High Dose Folinic Acidand High Flux Dialysis. Indian J Hematol Blood Transfus. 2013;29(2):90-2.
109. Balbir-Gurman A, Guralnik L, Best LA, Vlodavsky E, Yigla M, Menahem Nahir A, Braun-Moscovici Y. Accelerated pulmonary nodulosis and sterile pleural effusion in a patient with psoriatic arthropathy during methotrexate therapy: a case report. J Clin Rheumatol. 2009 Feb;15(1):29-30.
110. Hyoun SC, Običan SG, Scialli AR. Teratogen update: methotrexate. Birth Defects Res A Clin Mol Teratol. 2012;94(4):187-207.
111. Fridlington JL, Tripple JW, Reichenberg JS, Hall CS, Diven DG. Acute methotrexate toxicity seen as plaque psoriasis ulceration and necrosis: A diagnostic clue. Dermatology Online Journal 2011;17 (11): 2.
112. Attar SM. Adverse effects of low dose methotrexate in rheumatoid arthritis patients. A hospital-based study. Saudi Med J. 2010;31(8):909-15.
113. Kocatürk E, Köklü N, Güngör S, Ulkümen PK, Bahçetepe N, Erhan SŞ.Solar burn reactivation reaction: an unusual side effect of methotrexate. Photodermatol Photoimmunol Photomed. 2014;30(6):338-9.
114. Primka EJ 3rd1, Camisa C.Methotrexate-induced toxic epidermal necrolysis in a patient with psoriasis. J Am Acad Dermatol 1997:36(5 Pt 2):815–8.
115. Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, Harkness A, Lewis D, Littlejohn G, Miller MH, Ryan PF, Jolley D. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 2008;59(6):794-9.