Effect of anti-rheumatic drugs on diabetic foot problem among patients with type 2 diabetes and rheumatoid arthritis

EPH-289

Abstract 143790

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INTRODUCTION

Given the strong comorbidity of rheumatoid arthritis (RA) and T2DM, and the potential impact of RA on the development of diabetic foot problems, there is a need to understand how pharmaceutical treatment of RA can be conducted in a manner that reduces the risk of T2DM complications, in order to improve overall quality of life, and reduce economic impact on patients, health systems and societies.

The potential effects of conventional disease-modifying anti-rheumatic drugs (cDMARDs) on T2DM and its complications have been demonstrated in various studies.(1-5) Previous studies have mainly evaluated the effect of anti-rheumatic drugs on T2DM, diabetic retinopathy, or kidney disease. The cDMARDs may also reduce the risk of diabetic foot problems; however, these need to be weighed up against the potential deleterious effect of cDMARDs, which may lead to an increased risk.(6)

OBJECTIVE

By evaluate the effect of anti-rheumatic drugs on diabetic foot problems among patients diagnosed with T2DM and RA, this study may help clinicians to better support patients with T2DM and RA.

METHOD

- **Study design:** a population-based retrospective cohort study, using a time-dependent exposure design.
- **Population:**individuals diagnosed with both T2DM and RA.
- **Data source:** Clinical Practice Research Datalink (CPRD) database; data extracted using Data extraction for epidemiological research (DExtER) platform
- **Intervention:** 1) methotrexate (MTX) with or without any other anti-rheumatic drugs other than hydroxychloroquine (HCQ); 2) HCQ with or without any other anti-rheumatic drugs other than MTX; 3) MTX and HCQ with or without other anti-rheumatic drugs; 4) other anti-rheumatic cDMARD drugs (sulfasalazine, leflunomide, glucocorticoids) without a prescription for MTX and/or HCQ; 5) no drug use (periods of no cDMARD prescription after previous initiation of cDMARDs when considering as a time-dependent exposure).
- **Outcome:** incident composite diabetic foot problems (peripheral neuropathy, foot ulcer, amputation, gangrene and Charcot foot), peripheral neuropathy and foot ulcer.
- **Statistical analysis:** time-dependent Cox proportional hazards regression model .

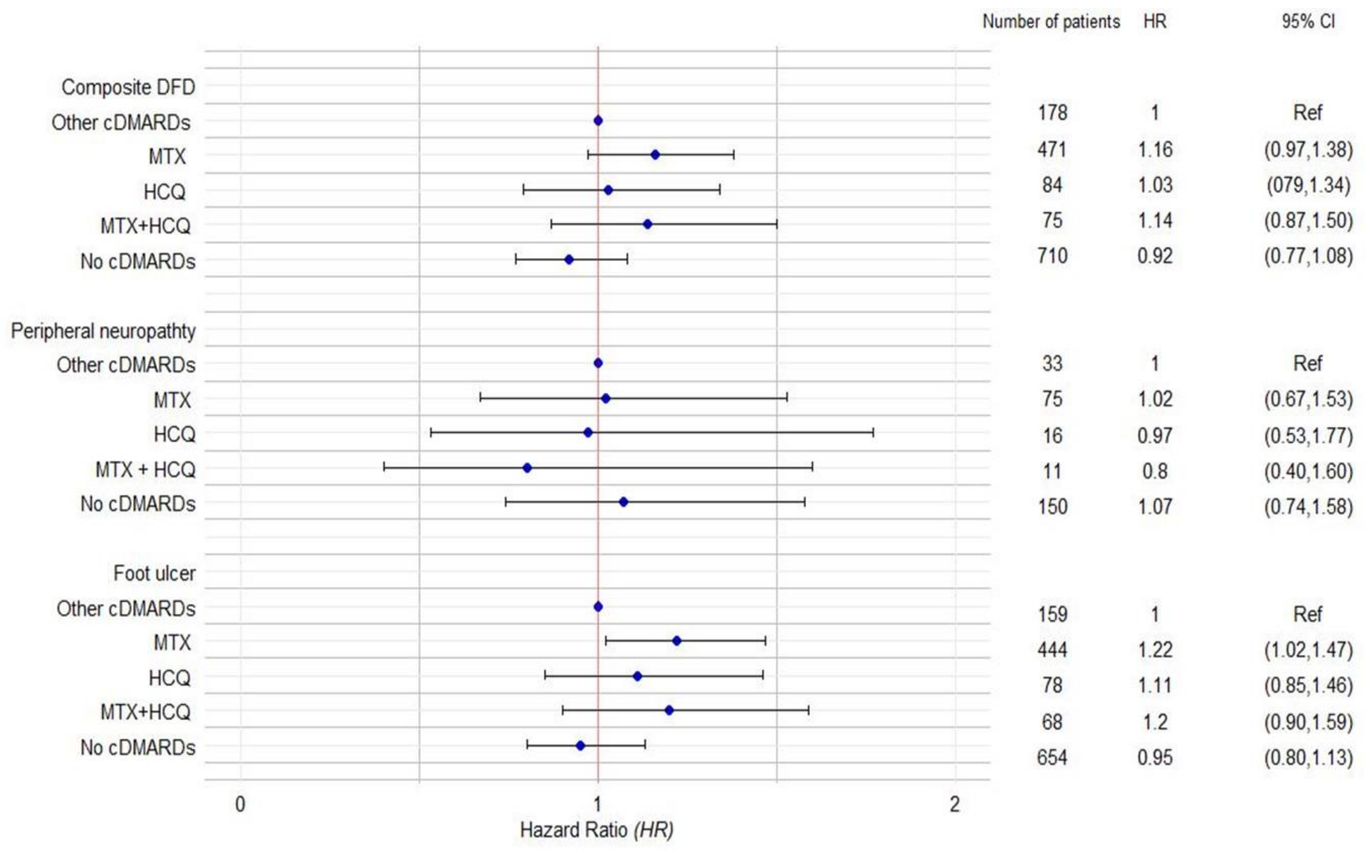
RESULTS

Composite diabetic foot problems

During the study period, 1518 out of 4694 patients were newly dianosed with composite diabetic foot problems, with 471 (31.0%), 84 (5.6%), 75 (4.9%), 178 (11.7%), 710 (46.8%) patients in the MTX, HQC, MTX + HQC, other cDMARDs and non-use groups, respectively. After the adjustment for potential confounders, the use of MTX, HQC, MTX +HQC or non-use of cDMARDs (after previous initiation of drugs) were not significantly associated with the a reduced risk of composite diabetic foot problems compared to other cDMARDs (MTX: aHR 1.16, 95% CI, 0.97-1.38; HCQ: aHR 1.03, 95% CI 0.79, 1.34; MTX +HCQ: aHR 1.14, 95% CI 0.87, 1.50; non-user: aHR 0.92, 95% CI 0.77, 1.08).

Peripheral neuropathy and foot ulcer

There were 285 and 1403 patients diagnosed with peripheral neuropathy and foot ulcer, during the study period. Similar to composite diabetic foot problems, there was no evidence of significant association between the use of HQC, or MTX + HQC and peripheral neuropathy or foot ulcer. However, while MTX was not significantly associated with peripheral neuropathy, it was associated with a significantly higher risk of foot ulcer compared to other cDMARDs (aHR 1.22, 95% CI 1.02, 1.47).



Adjusted for age, sex, ethnicity, body mass index (BMI, kg/m2), smoking status, social deprivation status, HbA1c level (mmol/mol), anti-diabetic drug use, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and chronic liver disease

The analyses were not conducted for amputation, gangrene and Charcot foot due to very small sample size.

CONCLUSIONS

We found no evidence of a reduced risk of composite diabetic foot problems among individuals prescribed MTX, HCQ or a combination of the two compared to individuals prescribed other anti-rheumatic drugs (sulfasalazine, leflunomide and/or glucocorticoids). It is notable that MTX may have a hazardous effect on foot ulcer, indicating the importance of foot screening in patients with T2DM and RA when MTX is used as a treatment. Given the potential causal links between RA treatment with cDMARDs, which reduce inflammation, and the role of microvascular and neurological inflammation, it remains plausible that cDMARDs may reduce diabetic foot problems prevalence. Targeted research, both in large cohorts such as CPRD and clinical research, is warranted to further investigate the potential links between cDMARDs in RA and diabetic foot problems.

REFERENCES

1. Baghdadi LR. Effect of methotrexate use on the development of type 2 diabetes in rheumatoid arthritis patients: A systematic review and meta-analysis. PloS one. 2020 Jul 6;15(7):e0235637.
2. Sparks JA, Vanni KM, Sparks MA, Xu C, Santacroce LM, Glynn RJ, Ridker PM, Solomon DH. Effect of Low-Dose Methotrexate on eGFR and Kidney Adverse Events: A Randomized Clinical Trial. Journal of the American Society of Nephrology. 2021 Dec 1;32(12):3197-207.
3. Quatraro A, Consoli G, Magno M, Caretta F, Nardozza A, Ceriello A, Giugliano D. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus: a new job for an old drug?. Annals of internal medicine. 1990 May 1;112(9):678-81.
4. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, Ward MM. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama. 2007 Jul 11;298(2):187-93.
5. Chakravarti HN, Nag A. Efficacy and safety of hydroxychloroquine as add-on therapy in uncontrolled type 2 diabetes patients who were using two oral antidiabetic drugs. Journal of Endocrinological Investigation. 2021 Mar;44(3):481-92.
6. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, Dixon WG. Risk of incident diabetes mellitus associated with the dosage and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. Arthritis & rheumatology. 2016 May;68(5):1089-98.

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