Survival analysis of time to first adverse drug reaction and drug survival in rheumatoid arthritis patients treated with methotrexate and hydroxychloroquine monotherapies or combination therapy

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Background

Methotrexate (MTX) and hydroxychloroquine (HCQ) are first line treatments of rheumatoid arthritis (RA). Adverse drug reactions (ADRs) during treatment with these drugs are common. Survival analysis on time to first ADR and on first time drug use duration have not yet been performed for these drugs in real-world settings.

Objective

To compare proportions of patients with ADRs during first time use of either MTX monotherapy, HCQ monotherapy or MTX+HCQ combination therapy and to compare surival to first ADR and drug survival between these drugs.

Method

Retrospective single centre cohort study including adult RA patients treated with either MTX monotherapy, HCQ monotherapy or MTX+HCQ combination therapy. First time users between 1 January 2003 and 30 April 2020 were followed until discontinuation of their first time drug use. The proportion of patients was defined as the percentage of patients experiencing an ADR during their first time drug use. Survival to first ADR and drug survival of first time drug use were also assessed. MTX+HCQ use was considered combination therapy when the start dates of these drugs differed less than 14 days. For both monotherapies, end of first time drug use was defined as drug discontinuation for more than 90 days.

Differences in the proportion of patients experiencing an ADR during first time drug use of MTX, HCQ or a combination of both was statistically tested using Fisher's Exact Test. Survival to first ADR and drug survival were studies by Kaplan-Meier analysis and statistically tested by performing Log Rank tests.

Results

In total, 794 patients were included (MTX 363, HCQ 77, MTX+HCQ 354). For 156 patients (19.6%) at least one ADR was registered during first time drug use (MTX 59 [16.3%], HCQ 9 [11.7%], MTX+HCQ 88 [24.9%]). Proportions of ADRs differed significantly between MTX monotherapy and MTX+HCQ combination therapy (p p=0.011).

Survival to first ADR also differed significantly for both monotherapies compared to MTX+HCQ combination therapy (medians not reached, p<0.001 and p<0.008, respectively (figure 1A)). Drug survival differed significantly between MTX and HCQ monotherapy and between MTX monotherapy and MTX+HCQ combination therapy (median survival 3.32 years (95% CI [2.81-3.83]; HCQ 1.39 years (95% CI [1.03-1.75]); MTX+HCQ 1.23 years (95% CI [1.11-1.43]), both p<0.001 (figure 1B)).

Conclusion

Patients using MTX+HCQ combination therapy are more likely to experience an ADR during the first time drug use compared to MTX and HCQ monotherapies. MTX+HCQ combination therapy also leads to experiencing an ADR sooner compared to both monotherapies. Drug survival of patients treated with HCQ monotherapy as well as MTX+HCQ combination therapy is shorter compared to MTX monotherapy.

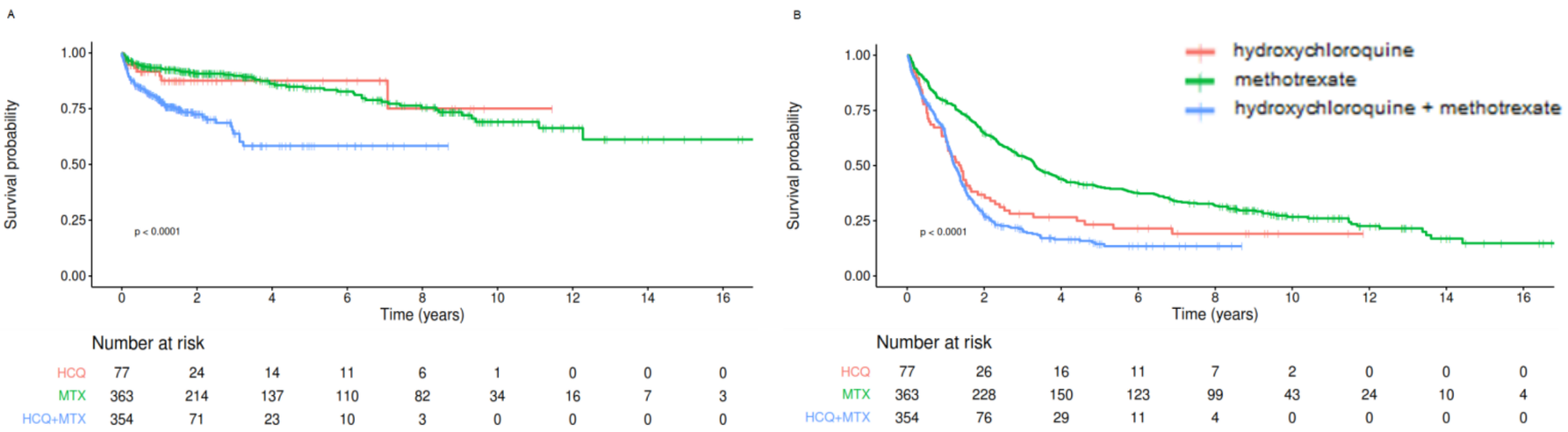

Figure 1: Kaplan-Meier curves of MTX and HCQ monotherapies and MTX+HCQ combination therapy, with (A) survival to first ADR and (B) drug survival

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