Co-Morbidities and Treatment of Gout

SUMMARY

Part 1 Management of gout

In **chapter 2**, we present the findings of a Cochrane systematic literature review on the efficacy and safety of non-selective non-steroidal inflammatory drugs (NSAIDs) compared to other NSAIDs or to other drug classes in the treatment of acute gout flares. We included 28 trials (3406 participants). The following comparisons were found: NSAIDs versus placebo (1 trial), NSAIDs versus other NSAIDs (13 trials), NSAIDs versus Cox-2 selective inhibitors (COXIBs) (6 trials), NSAIDs versus glucocorticoids (4 trials versus oral glucocorticoids, 1 trial versus im glucocorticoids), NSAIDs versus anti-IL1 (1 trial), NSAIDs versus acupuncture (1 trial), NSAIDs versus colchicine (1 trial). The outcome measures of interest in this review followed the recommendations by Outcome Measures in Rheumatology Clinical Trails (OMERACT) for trials in acute gout: pain, inflammation, function of the target joint and participant's assessment of response to treatment. Health-related Quality of Life (HRQoL) and safety were added as recommended by the Cochrane Collaboration. Overall, the certainty of the evidence was low to moderate. NSAIDs seemed to be more efficacious than placebo in the first 24hours after treatment initiation on pain (number of patients with at least 50% reduction in pain at 24 hours; risk ratio (RR) 2.7, 95% confidence interval (CI) 1.1 to 6.7) (low-certainty evidence). There was no difference regarding our other outcomes. Two trials comparing two NSAIDs (naproxen and etodolac) could be pooled and found no between-group differences with regards to efficacy (response to treatment success reported as proportions of people who considered themselves markedly improved at the end of treatment, RR 1.0, 95% CI 0.9 to 1.1) and safety (no withdrawals due to adverse events, number of adverse events: RR 1.7, 95% CI 0.4 to 7.9). NSAIDs seemed as efficacious as COXIBs with regards to pain (0-10 scale 0, no pain; mean difference (MD) 0.0, 95% CI -0.1 to 0.1) as well as with the other efficacy outcomes (moderate-certainty evidence). However, NSAIDs compared to COXIBs were associated with a higher risk for side effects, especially gastro-intestinal side effects (total number of adverse events: RR 1.9, 95% CI 1.4 to 2.8, gastro-intestinal adverse events: RR 2.4, 95% CI 1.6 to 3.4) (moderate-certainty evidence). NSAIDs seemed as efficacious as glucocorticoids for pain (0 to 100 VAS, 0= no pain, MD 0.1, 95% CI -2.7 to 3.0) (moderate-certainty evidence), but less efficacious for the reduction of swelling (4-point Likert Scale, 0= no inflammation; MD 0.3, 95% CI 0.1 to 0.6) (low-certainty evidence). Furthermore, NSAIDs seemed associated with more adverse events (RR 1.6, 95% CI 1.0 to 2.5) (moderate-certainty evidence). Low-certainty evidence based on a single trial suggested that NSAIDs are as efficacious as colchicine with regards to efficacy, but that NSAIDs are associated with less gastro-intestinal effects. A single trial, low-certainty evidence, suggested that anti-IL1 (canakinumab) is less efficacious than NSAIDs with regards to efficacy. There was no difference in safety.

In **chapter 3,** we compared outcomes of two different treatment strategies using a different target when treating gout: one being a strict uric acid-targeted (sUA ≤0.30 mmol/L) (sUA) strategy (126 patients) (UA-strategy), and the other adopting a patient-centered (PC) strategy (86 patients), emphasizing patient education and a shared decision about ULT based on sUA and patient satisfaction with gout control. In the UA-strategy 105/126 (83%) compared to 63/86 (74%) patients in the PC-strategy (p=0.10), reached the recommended threshold of ≤0.36 mmol/L; and 58/126 (46%) vs 31/86 (36%) patients were free of flares (p=0.15), after an average follow-up time of 11 months. In the UA-strategy 76/126 (60%) patients were on allopurinol monotherapy compared to 63/86 (73%) in the PC-strategy (p=0.05), at follow-up. In the UA-strategy, 21/126 (16.7%) patients vs 1/86 (1.2%) of PC-strategy were using combination therapy (p<0.001). The remaining patients were using benzbromarone or febuxostat monotherapy. The number of registered adverse events was not different (n=25 (20%) vs n=20 (23%), p=0.55). After adjustment for confounders, the UA-strategy remained only significantly associated with frequent therapy intensification.

In **Chapter 4,** we evaluated the construct validity of conventional radiography (XR) to measure structural joint damage (erosions) in patients with gout in a cross-sectional study. The XR of the feet were part of the baseline data of a cohort of patients with gout who were seen at the outpatient clinic of the Rheumatology Department of the Maastricht University Medical Centre+. XR were independently scored by two trained and experienced rheumatologists blinded for the characteristics and for each other's score. We used the gout-modified Sharp/van der Heijde (SvdH-mG) score. In total 81 out of a cohort of 126 patients (64.3%) had XR available and were included, 71 (71/81, 87.7%) had radiographic damage, of which 38 (46.9%) had erosions and 63 (77.8%) had joint space narrowing (JSN). Intraclass correlation coefficient for intra- and interobserver variability was above 0.75 which is considered excellent agreement We found that higher sUA levels, presence of tophi and longer disease duration were significantly associated with higher erosion scores on XR. Presence of tophi was also associated with more joint space narrowing. Patients with radiographic damage experienced worse physical function measured by the Health Assessment Questionnaire (HAQ) but not when measured with the physical component of the Short Form (36) Health Survey SF-36. Of note, the HAQ was initially developed to assess difficulties in physical activities of patients with arthritis, while the SF-36 is a generic instrument. We concluded that these findings support the construct validity of XR to assess joint damage in the feet, and reflect to some extent also the biological cumulative burden of monosodium uric acid crystals.

Part 2 Co-morbidities

In chapter 5, we conducted a systematic literature review of longitudinal observational studies to understand whether patient with hyperuricemia and/or a diagnosis of gout, should be routinely screen for comorbidities and CV risk factors. In total 66 studies were included, 34

studies with moderate or good quality were used for the summary. Six studies with a moderate risk of bias reported a higher risk of *hypertension* in patients with hyperuricemia (adjusted Hazard Ratio (HR) ranging across studies from 1.4 to 2.0), especially in women (adjusted HR ranging across studies from 1.7 to 1.9 vs adjusted HR ranging from 1.4 to 1.5 in men). For the risk of *diabetes*, the four included studies reported an increased risk which decreased after adjustment, adjusted HR ranging from 1.0 to 2.4. This risk of diabetes was higher in women (significant adjusted HR 2.0 vs not significant adjusted HR 1.24 in men). There were no studies exploring the risk of hypertension and diabetes in gout. Six trials investigated the risk of *stroke* in patients with hyperuricemia and one trial investigated the risk of stroke in patients with gout. Nor incidence nor mortality were increased. For *coronary heart disease* (CHD), 13 studies with a moderate risk of bias explored the risk of coronary heart diseases in patients with hyperuricemia and 8 studies the risk of CHD in patients with gout. In patients with hyperuricemia, the *incident risk for CHD* (7 studies) was not increased, *CHD-related mortality* (6 studies) was only increased in women (adjusted HR 1.3). In patient with gout, adjusted HR for *incident CHD* (4 studies) (adjusted HR ranging from 1.3 to 1.6) and for *CHD-related mortality* (4 studies) (adjusted HR ranging from 1.4 to 1.8) were only slightly increased. With regards to other comorbidities, two studies suggested an increased risk of *chronic kidney disease* (CKD) defined as End Stage Renal Disease (ESRD, start of replacement therapy such as dialysis or renal transplant) in hyperuricemia (average adjusted HR ranging from 2.1 to 5.8), particularly in females (average adjusted HR 5.8). There was no study on the risk of CKD mortality in hyperuricemia. In gout, the mortality due to CKD seemed to be elevated (adjusted HR 4.4) (one study), the incidence of ESRD was not increased (one study, HR not reported). The association with *cancer* was only poorly investigated in both hyperuricemia and gout. In conclusion, unlike the common opinion that patients with gout or hyperuricemia are at higher risk of developing cardiovascular diseases, the actual risk to develop CV disease is either rather weak (for hyper-uricemia) or poorly investigated (for gout). Women with hyperuricemia (less clear for gout) might have a higher risk of incidence of cardiovascular risk factors such as hypertension and diabetes as well as a higher incidence for and mortality from cardiovascular disease, especially coronary heart disease, when compared to males.

In **chapter 6**, we investigated the risk of gout in patients with T2DM (defined as persons on a noninsulin antidiabetic drug (NIAD) in a retrospective analysis of a cohort study, the UK Clinical Practice Research Datalink (CPRD) GOLD. In total, 221.117 T2DM patients were identified. Overall, patients with T2DM were at increased risk of gout (HR 1.48;95%CI 1.41-1.54), however this increased risk disappeared after adjustments for confounders (HR 1.01;95%CI 0.92-1.11). In adjusted analyses, we even found a reversed risk of gout in men with diabetes (HR 0.61;95%CI 0.58-0.66). We concluded that individuals with type 2 diabetes have an increased chance to develop gout. However, this is not due to diabetes itself, but to lifestyle and common comorbid conditions of the patients. Diabetes itself seems to decrease the risk of gout among men. In

Chapter 7, we investigated the risk of patients with OSA to develop gout, to understand if OSA contribute to gout, independently shared risk factors, in case-control study using the UK CPRD database. 111,509 cases with gout were matched with 210,241 controls. Patients with OSA were at increased risk of gout (OR 1.86;95%CI (1.71-2.02). However, this association disappeared (OR 1.05;95%CI 0.96-1.16) after adjustment for confounders. For females with OSA and for patients with OSA and heart failure, renal impairment or higher BMI, the risk of gout remained higher when compared to the total control population.