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Efficacy and safety of diclofenac in osteoarthritis: Results of a network meta-analysis of unpublished legacy studies

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HIGHLIGHTS

- Legacy unpublished randomised controlled trials of diclofenac in osteoarthritis.
- Bayesian NMA model estimated relative treatment effects between pairwise treatments.
- Diclofenac 150 mg/day was more efficacious for pain relief than ibuprofen 1200 mg/day.
- Diclofenac 150 mg/day had likely favourable outcomes for pain relief compared to ibuprofen 2400 mg/day.
- Benefit-risk profile of diclofenac was comparable to that of ibuprofen in osteoarthritis.

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ABSTRACT

Background and aim: Diclofenac is widely prescribed for the treatment of pain. Several network meta-analyses (NMA), largely of published trials have evaluated the efficacy, tolerability, and safety of non-steroidal anti-inflammatory drugs (NSAIDs). The present NMA extends these analyses to unpublished older (legacy) diclofenac trials.

Methods: We identified randomised controlled trials (RCTs) of diclofenac with planned study duration of at least 4 weeks for the treatment of osteoarthritis (OA) from 'legacy' studies conducted by Novartis but not published in a peer reviewed journal or included in any previous pooled analyses. All studies reporting efficacy and/or safety of treatment with diclofenac or other active therapies or placebo were included. We used a Bayesian NMA model, and estimated relative treatment effects between pairwise treatments. Main outcomes included pain relief measured using visual analogue scale at 2, 4 and 12 weeks and patient global assessment (PGA) at 4 and 12 weeks for efficacy, all-cause withdrawals, and adverse events.

Results: A total of 19 RCTs (5030 patients) were included; 18 of which were double-blind and one single-blind. All studies were conducted before cyclooxygenase 2 inhibitors (COXIBs) became commercially available. Data permitted robust efficacy comparison between diclofenac and ibuprofen, but the amount of data for other comparators was limited. Diclofenac 150 mg/day was more efficacious than ibuprofen 1200 mg/day and had likely favourable outcomes for pain relief compared to ibuprofen 2400 mg/day. Diclofenac 100 mg/day had likely favourable outcomes compared to ibuprofen 1200 mg/day in alleviating pain. Based on PGA, diclofenac 150 mg/day was more efficacious and likely to be favourable than ibuprofen 1200 mg/day and 2400 mg/day, respectively. Risk of withdrawal due to all causes with diclofenac and ibuprofen were comparable. Diclofenac 150 mg/day was likely to have favourable efficacy and comparable tolerability with diclofenac 100 mg/day. Results comparing diclofenac and ibuprofen were similar to those from NMAs of published trials.

Abbreviations: AE, adverse event; CFB, change from baseline; CNT, Coxib and tNSAID Trialists'; CrI, credible interval; CSR, clinical study reports; DIC, deviance information criterion; IGA, investigator global assessment; ITT, intention-to-treat; NMA, network meta-analysis; OA, osteoarthritis; PGA, patient global assessment; RCT, randomised controlled trials; SAE, serious adverse event; tNSAID, traditional non-steroidal anti-inflammatory drug; VAS, visual analogue scale.

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Conclusions: Results from these unpublished 'legacy' studies were similar to those from NMAs of published trials. The favourable efficacy results of diclofenac compared to ibuprofen expand the amount of available evidence comparing these two NSAIDs. The overall benefit-risk profile of diclofenac was comparable to that of ibuprofen in OA.
Implications: The present NMA results reassures that the older unpublished blinded trials have similar results compared to more recently published trials and also contributes to increase the transparency of clinical trials performed with diclofenac further back in the past.

1. Background and aims

Osteoarthritis (OA) is a common and progressive joint disorder, mostly affecting the adults and characterised by joint degeneration resulting in extreme pain, disability, and reduced quality of life. The most commonly affected joints include those in the hands, neck, and lower back and weight-bearing joints such as the knees and hip. OA affects over 250 million people worldwide, imposing a substantial burden on society [1]. Currently, no effective disease-modifying treatment options are available to cure OA; the existing symptomatic treatments can only relieve pain and improve joint function [2]. According to reports from a prospective, longitudinal cohort study conducted at 53 centres (1187 patients) in six European countries (United Kingdom [UK], France, Germany, Portugal, The Netherlands, and Italy), 54% of OA patients receiving treatment from general physicians or specialists reported inadequate pain relief [3]. Non-steroidal anti-inflammatory drugs (NSAIDs), both traditional NSAIDs (tNSAIDs) and cyclooxygenase 2 (COX-2) inhibitors (COXIBs), are the most frequently prescribed medicines and considered as cornerstones in the treatment of OA [2] as they intend to provide the desired relief from both pain and inflammation in OA patients.

Nevertheless, both benefits and risks associated with various treatments should be analysed to inform clinical decision making. Numerous clinical studies that included this treatment were performed in an era when publication of clinical studies was not as systematic as it is today. Today, there are more formalised good publication practice guidelines that are supported by researchers [4] and many research companies (including Novartis) have publically committed to publish sponsored clinical research [5]. The present review and NMA was conducted to gain insights on the data available from unpublished legacy studies with diclofenac conducted by Novartis in patients with OA. Its value lies in the fact that is presenting to the scientific community a wealth of data from 29 previously unpublished studies in osteoarthritis. The NMA is used as the appropriate quantitative method to synthesise these unpublished data and the authors consider this effort as complementary to a number of (network) meta-analyses and literature reviews that have been published over the last years. Since the legacy studies included in this meta-analysis were conducted before COXIBs became commercially available, comparators are limited to other tNSAIDs. Data from these legacy studies were systematically reviewed, and outcomes were synthesised by means of a Bayesian NMA. Based on these findings, the comparative efficacy and safety of diclofenac (100 and 150 mg/day) versus other NSAIDs in the management of OA were evaluated.

2. Methods

2.1. Study identification and data collection

A list of all legacy clinical trials conducted by Novartis was reviewed to identify randomised controlled trials (RCTs) of diclofenac with planned treatment duration of at least 4 weeks for the treatment of OA, so that their results have some relevance to the clinical treatment of a long-term condition. Blinded RCTs with diclofenac in OA, which were conducted by Novartis or its subsidiaries or predecessors and identified as not being included in a previous systematic review of published studies, were retrieved from the Novartis archives. Only 3 of the 19 studies had previously been published. The relevance of each identified clinical study report (CSR) was assessed according to pre-defined selection criteria (see Appendix 1A) by two independent reviewers in parallel (Anneloes van Walsem and Patricia Guyot), and any disagreement was resolved by consensus. All RCTs in OA that compared diclofenac versus placebo or other analgesic comparators with data on efficacy and/or safety were included. The most common comparators were ibuprofen (1200/2400 mg/day) and naproxen (500/750/1000 mg/day). Other less common comparators, such as piroxicam (20 mg/day), indomethacin (75 mg/day) and paracetamol (1950 mg/day) in combination with dextropropoxyphene (195 mg/day) were also included in a few RCTs.

Visual analogue scale (VAS) and Likert pain scale scores, VAS and Likert scale patients' global assessments (PGA), and VAS and Likert scale investigators' global assessments (IGA) were considered for analysing efficacy outcomes. Efficacy endpoints were assessed at 2, 4, and 12 weeks for VAS pain, at 4 and 12 weeks for PGA VAS, and at 4 weeks for IGA VAS. In addition safety (any adverse events [AEs] and serious adverse events [SAEs]) and tolerability (withdrawals due to all causes, lack of efficacy, and AEs) parameters were included in the analysis.

Study and patient characteristics, as well as efficacy, safety, and tolerability outcomes from the selected studies were recorded on a pre-designed data extraction form. Details on study characteristics such as study design, inclusion and exclusion criteria, comparator interventions, study duration, number of intention-to-treat (ITT) patients, and rescue medication use were extracted. In addition, baseline patient characteristics including age, gender, disease duration, and type of OA were extracted.

For each continuous outcome of interest, an estimate of the change from baseline (CFB) and the standard error of the estimate were extracted (see Appendix 2). For dichotomous outcomes, the number of patients experiencing an event was estimated based on reported percentages and size of the ITT population. Subsequently, the total person-years at-risk follow-up periods were estimated using the dropout rate. Data presented in graphs were extracted using the DigitizeIT software (version 1.5; DigitizeIT, Braunschweig, Germany).

The methodological and reporting quality of the included studies were assessed by using the Oxford quality scoring system for RCTs [6]. The risk of bias was assessed based on the following aspects: randomisation according to an appropriate method, allocation concealment of patients and investigators, and complete and non-selective reporting of study withdrawals and dropouts.

The SLR was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Appendix 3).