RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Safety and efficacy of colchicine in crystal-induced arthritis flare in 54 patients with severe chronic kidney disease

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To cite: Bausson J, Keller N, Von Hunolstein J-J, *et al*. Safety and efficacy of colchicine in crystal-induced arthritis flare in 54 patients with severe chronic kidney disease. *RMD Open* 2024;**10**:e003872. doi:10.1136/rmdopen-2023-003872

Received 2 November 2023
Accepted 17 January 2024

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ABSTRACT

Introduction Colchicine, commonly used in gout flare, is contraindicated in severe chronic kidney disease (CKD) (estimated glomerular filtration rate <30 mL/min). However, in this context, there are few alternatives, and colchicine use persists. We evaluated the tolerance of colchicine and its efficacy in patients with severe CKD.

Patients and methods All prescriptions of colchicine for managing crystal-induced arthritis flare (gout or calcium pyrophosphate deposition (CPPD) disease) in a hospitalised patient with severe CKD were screened from September 2020 to September 2021. After patient consent and treatment information, clinical and biological safety and efficacy data were prospectively collected from day 1 (D1) to D11.

Results We included 54 patients (median age 75 years (IQR 67–83)) with 62 colchicine prescriptions (cases). Twelve (22%) patients were on dialysis. The main reason for hospitalisation was heart failure (31.5%), acute renal failure (22.2%), infection (18.5%) or an acute joint episode (9.3%). In total, 59.3% of patients had diabetes. The prescriptions concerned 58 cases of gout flares, 1 case of CPPD and 3 cases of both. Initial colchicine dosages were ≤0.5 mg/day in 47/62 (75.8%) cases; no dosage exceeded 1 mg/day (median duration of 6 days (IQR 3–11)). Colchicine was well tolerated in 47/61 (77%) cases. No serious adverse event was reported. Colchicine was considered completely effective by the medical team in 48/58 (83%) of cases.

Conclusion The use of colchicine, at reduced doses, was mostly effective to treat crystal-induced arthritis flare in 54 patients with severe CKD and was well tolerated, without any serious adverse events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Management of gout flare in patients with chronic kidney disease (CKD) is challenging.
⇒ Despite the long experience with colchicine in several conditions, data from patients with severe CKD are limited and are based on scarce literature and case reports.

WHAT THIS STUDY ADDS

⇒ This is the largest prospective real-life study ever published with 54 patients.
⇒ The use of colchicine, at reduced dosage, in patients with crystal-induced arthritis flare and severe CKD was effective (83%) and well tolerated (77%), with no serious adverse events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Colchicine could be used with caution for crystal-induced arthritis flare in patients with severe CKD with dose reduction and close monitoring.

INTRODUCTION

Colchicine has been widely used since its first isolation in 1884. Therapeutic indications are constantly increasing, but its main indication remains the management of crystal-induced arthritis flare. Most of its therapeutic effects would be due to its ability to prevent the assembly of microtubules tubulin, thereby inhibiting their polymerisation and interfering with their cellular functions.[1] In vitro and in vivo studies have suggested that a more important anti-inflammatory mechanism is colchicine's ability to hinder NLRP3 (NOD-like receptor family, pyrin domain containing 3) intracellular transportation and spatial arrangement, thereby inhibiting inflammasome activation within macrophages.[2 3] Colchicine exhibits complex pharmacokinetics with extensive tissue uptake, especially within erythrocytes.[4] Renal clearance accounts for 10% of total elimination,[5] influenced by factors like cyclosporine, which inhibits tubular secretion through P-glycoprotein.[6] Colchicine metabolism is influenced by hepatic enzymes (cytochrome P450 3A4).[7] In patients without comorbidities, the management of gouty arthritis is consensual. According to the 2016 European

Alliance of Associations for Rheumatology (EULAR) recommendations for the management of gout, colchicine, non-steroidal anti-inflammatory drug (NSAIDs) and parenteral/oral glucocorticoids are recommended as first-line treatment options for managing flares.[8] In 2010, the Acute Gout Flare Receiving Colchicine Evaluation trial showed, after 24 hours of early management of gout flare, a better safety profile in the 'low-dose' colchicine group (1.8 mg) similar to that of the placebo group than in the 'high dose' colchicine group (4.8 mg), with no difference in efficacy between the two colchicine arms, superior to placebo.[9] In calcium pyrophosphate crystal deposition disease (CPPD), the efficacy of colchicine was recently evaluated in the COLCHICORT trial, which showed that colchicine and prednisone were equally effective in the short term.[10]

Nevertheless, gout is often associated with comorbidities (hypertension, obesity, diabetes, renal lithiasis, heart failure, renal failure, etc), which leads to difficulties in the use of these treatments.[11 12]

Managing gout can be challenging in patients with chronic kidney disease (CKD). This situation is not rare. In a systematic review and meta-analysis of epidemiological studies, the pooled prevalence estimate of CKD stage ≥3 in people with gout was 24% (95% CI 19% to 28%) and 2% (95% CI 0% to 4%) for CKD stage ≥4.[13] Renal failure is a risk factor for incident gout (twofold increased risk with than without CKD at baseline),[14] and the incidence of gout is estimated at 5% in the first year and 15.4% in the first 5 years if on dialysis[15]. NSAIDs are contraindicated in patients with severe CKD (CKD G4-5). Corticosteroids could be a safe option except in an infectious context, particularly in septic arthritis and depending on the clinical context. The use of colchicine is contraindicated in severe CKD (G4-5) because of its narrow therapeutic index and drug–drug interactions.[7 16 17] Thus, data concerning the use of colchicine in CKD are scarce, and its use is largely empirical.[18] A greater knowledge of the safety of treatments used for the management of gout flares has been highlighted by G-CAN (Gout, Hyperuricemia and Crystal-Associated Disease Network) as a research priority.[19]

Indeed, the use of colchicine in this population is debated. On the one hand, the documented toxicity of this molecule in patients with CKD is mainly the result of the use of high doses (intentional or unintentional intoxication), the absence of dosage adjustment or drug–drug interactions.[20–25] On the other hand, the lack of treatment alternatives and data raise questions about its possible use.[26] Despite its contraindication, colchicine is regularly used in daily practice in our hospital.[27]

Therefore, the aim of our study was to prospectively evaluate the prescription of colchicine and its efficacy and safety in managing crystal-induced arthritis flare (gout or CPPD) in patients with severe CKD (estimated glomerular filtration rate, eGFR <30 mL/min) or on dialysis at the University Hospitals of Strasbourg, France.

PATIENTS AND METHODS

Study design

We conducted a monocentric prospective study including hospitalised patients with crystal-induced arthritis flare who received colchicine in the context of severe CKD. Severe CKD was defined according to the CKD-EPIdemiology (CKD-EPI) formula as eGFR <30 mL/min/1.73 m^2. Patients with severe CKD were included after having been prescribed colchicine as part of their routine care (off-label). The screening of colchicine prescriptions in hospitalised patients from our hospital involved using a daily query via our prescription support software. The study was conducted from 21 September 2020 to 21 September 2021. It was approved by the ethics review board of the Strasbourg medical faculty (#CE-2020–116) and patients consented to participate in this study before the first questionnaire was administered and to use of their data. We used hospital files to collect patient demographic features (age, sex, body mass index), gout history (duration of gout, gout arthropathy, flare frequency, previous gout treatments, use of urate-lowering therapy), comedications and CKD history. To investigate colchicine efficacy and safety, we collected prospective medical data, patient-reported outcomes and biological assessments for 10 days, from day 1 (D1) to D11 after colchicine initiation.

Renal function

Patients were included if they had severe CKD corresponding to stage G4 (eGFR 15 mL/min to 30 mL/min) or CKD stage G5 (eGFR <15 mL/min) or if on dialysis. We excluded cases of acute renal failure without severe CKD (G4–5).

Diagnosis

The diagnosis of crystal-induced arthritis flare was made by the patient's medical team. A distinction was made between gout, CPPD or a combination of the 2. Subsequently, at the end of the follow-up, patients with another diagnosis (septic arthritis, erysipelas, etc.) were excluded from the efficacy analysis.

Colchicine use and dosage

Colchicine was prescribed as part of standard care for the management of flare presumed to be crystal induced. In our pharmacy, colchicine is referenced as a 1 mg scored tablet. Therefore, colchicine doses are in multiples of 0.5 mg. Doses <0.5 mg/day, therefore, correspond to 0.5 mg administered every 2 or 3 days. Colchicine doses were recorded by using our prescribing assistance software. Colchicine doses and duration were not prespecified and left to the discretion of the medical team as part of routine care.

Table 1 Baseline characteristics of patients (n=54)

Demographic and general patient characteristics	
Age, years, mean (IQR)	75 (67–83)
Male, n (%)	36 (66.7%)
Body mass index, median (IQR), kg/m^2	26.8 (24.4–30.1)
Diabetes, n (%)	32 (59.3%)
No dialysis, n (%)	42 (78%)
eGFR according to CKD-EPI (in non-dialysed patients) in mL/min/1.73 m^2, median (IQR)	21.6 (16.8–28.0)
Medical department of hospitalisation	
Nephrology, n (%)	26 (48.1%)
Cardiology, n (%)	15 (27.8%)
Rheumatology, n (%)	4 (7.4%)
Others*, n (%)	9 (16.7%)
Reason for hospitalisation	
Heart failure, n (%)	17 (31.5%)
ARF, n (%)	12 (22.2%)
Non-articular infectious context, n (%)	10 (18.5%)
Acute joint episode, n (%)	5 (9.3%)
Others†, n (%)	10 (18.5%)
Concomitant treatments	
Diuretics (usual treatment), n (%)	11 (20.3%)
Increase in diuretic doses, n (%)	39 (72.2%)
Ciclosporin	9 (14.5%)
Statins	24 (38.7%)
Vitamin K antagonists	22 (35.5%)
Fibrates	1 (1.6%)
Gout characteristics, n (%)	53 (98.1%)
Serum urate, µmol/l, median (IQR)	619 (495–774)
Gout history (previous gout flare), n (%)	39 (73.6%)
Current urate-lowering therapy	
Allopurinol	9
Febuxostat	3

*Pulmonology (2), geriatrics (2), internal medicine (2), neurology (2), urological surgery (1).
†Programmed investigations (2), stroke (2), acute coronary syndrome (1), mechanical fall (1), COVID-19 (1), deterioration of general condition (1), digestive haemorrhage (1), ascites (1).
ARF, acute renal failure; D, day; eGFR, estimated glomerular filtration rate.

Table 2 Colchicine prescriptions and adaptations (n=62)

Treatment plan	
Loading dose 1 mg first day, then 0.5 mg/day, n (%)	9 (14.5%)
In patients on dialysis	3/14 (21.4%)
1 mg/day, n (%)	6 (9.7%)
In patients on dialysis	0
≤ 0.5 mg/day, n (%)	47 (75.8%)
In patients on dialysis	11/14 (78,6%)
Treatment duration in days, median (IQR)	6 (3-11)
< 6 days, n (%)	30 (48.4%)
6–10 days, n (%)	13 (21.0%)
> 10 days, n (%)	19 (30.6%)
Initiation delay from microcrystalline attack in days, median (IQR)	0 (0–1)
Within the first day, n (%)	38 (61.4%)
The following day, n (%)	12 (19.3%)
Other*, n (%)	12 (19.3%)
Median, IQR (days)	2 (2–3.5)
Colchicine dosage adaptation, n (%)	17 (27.4%)
Transient decrease or discontinuation (poor tolerance, expert's intervention or returning home)	14/17 (82%)
Increase (ineffective or expert opinion)†	3/17 (18%)

*Including six reporting the start of the acute attack before hospitalisation or unknown.
†Without exceeding the dose of 1 mg/day.

Efficacy assessment

Treatment efficacy was assessed by patient questionnaires (pain intensity ranging from 0 (no pain) to 10 (very severe pain) on a visual analogue scale; medical data and biological results (C reactive protein (CRP) level) on D1, D3, D6, D8, D11. The efficacy of colchicine treatment was assessed by the medical team as complete efficacy, partial efficacy or no efficacy. We also used a composite criterion including medical effectiveness: reduction in pain ≥50% associated with decrease in CRP level (≥ 50%) as compared with D1.

Safety assessment

Treatment safety was assessed by patient questionnaires (adverse events (AEs) were recorded as diarrhoea, nausea, vomiting, abdominal pain and muscle pain), biological results (leucocyte count, platelet count, serum creatinine level) and by the medical team. Muscle pain was not taken into account in dialysis patients because it is a common condition. If any AE occurred during follow-up, the treatment was classified as non-tolerated. We checked for the absence of symptoms suggesting adverse effects before the initiation of colchicine, so as to not impute this AE to it. If the patient was discharged before D11, follow-up was by phone without any new biological data.

Statistical analysis

Categorical variables are described with number (%) and quantitative variables with median (IQR). Comparisons between paired groups involved Wilcoxon and Mann-Withney tests. P<0.05 was considered statistically significant, and all tests were twosided. Statistical analysis involved using GraphPad Prism 5.0.

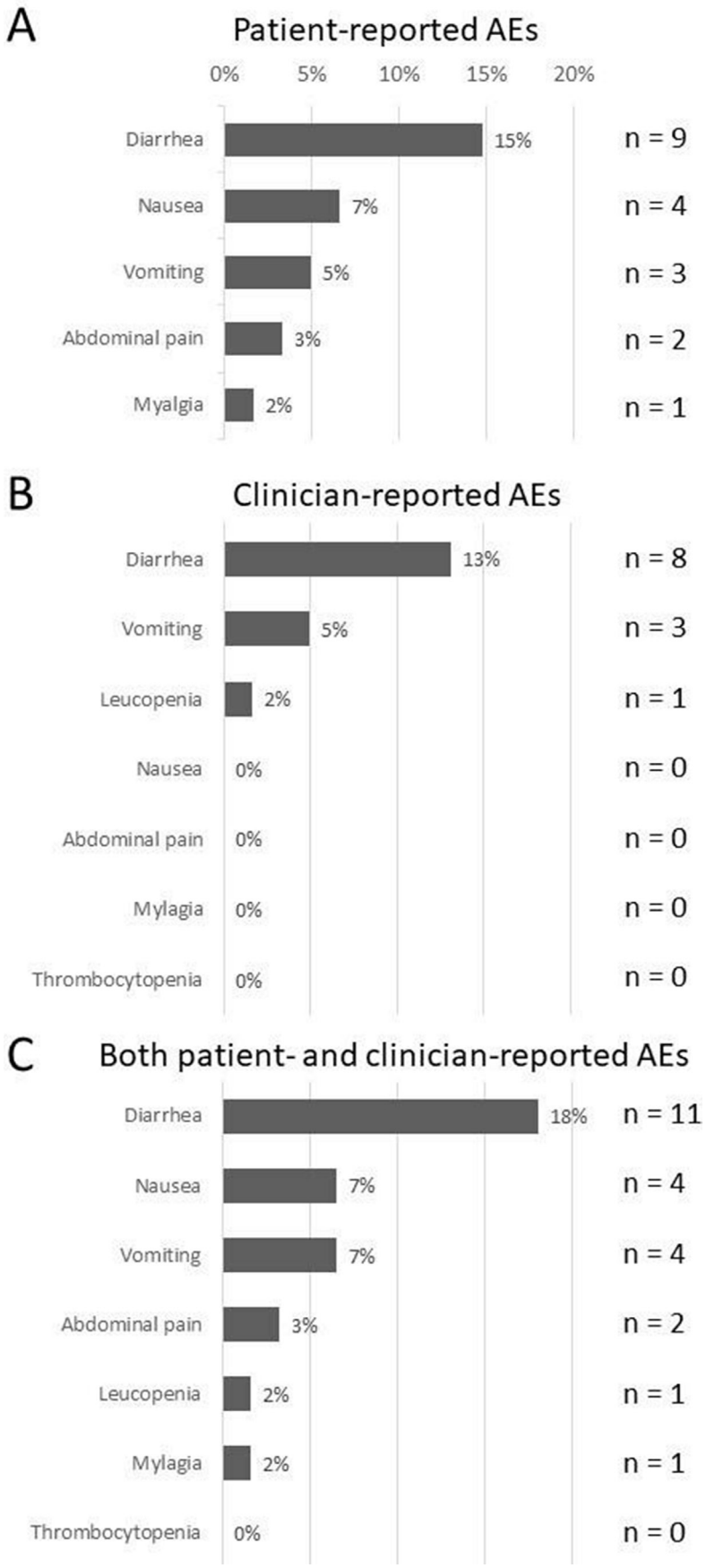

Figure 1 Tolerance of colchicine and occurrence of adverse events (AEs) in patients with chronic kidney disease. (A) Patient-reported cases of AEs. (B) Clinician-reported cases of AEs. (C) Both patient- and clinician-reported number of cases of overall AEs.

RESULTS

We included 54 participants (36 (66.7%) men with median age 75 years (IQR 67–83); there were 62 colchicine prescriptions (cases)). The prescriptions concerned 58 cases of gout flares, 1 case of CPPD and 3 cases of both. Detailed patient characteristics and microcrystalline history are in table 1.

The most frequently used dosage of colchicine was ≤0.5 mg/day: 47/62 (75.8%) cases (table 2). No dosage exceeded 1 mg/day. A loading dose of 1 mg on the first day, decreased to 0.5 mg/day thereafter, was used in 9/62 (14.5%) of cases and 1 mg/day without decrease thereafter in only 6/62 (9.7%). Most treatments were initiated on the same day as the onset of symptoms (38/62 (61.4%)) or the following day (12/62 (19.3%)).

Treatment tolerance

The treatment tolerance was evaluated in 61 cases (one patient left the hospital prematurely and could not be contacted). Side effects were reported by 14 (23%) patients: diarrhoea by 9 (15%), nausea by 4 (7%), vomiting by 3 (5%), abdominal discomfort by 2 (3%) and myalgia by 1 (2%). Therefore, the tolerance from the patient's perspective was 47/61 (77%). Of note, the tolerance assessed by clinicians was slightly better (51/61, 84%) (figure 1). Among the AEs reported by clinicians, 8 (13%) were diarrhoea, 3 (5%) vomiting and 1 (2%) an aggravation of a pre-existing leucopenia (2210 leucocytes/µl at D1 and 760 at D8). Altogether, these AEs led to a definite suspension in three cases, a dosage reduction in three and a transitory stop and then reduced dosage without a new event for 1. Table 3 summarises colchicine dosages and the occurrence of AEs according to CKD stage.

Table 3 Colchicine prescriptions and tolerance according to CKD stage (n=62)

CKD stage G4 (eGFR 15–30 mL/min)	39 (62.9%)
Loading dose 1 mg first day, then 0.5 mg/day, n (%)	5/39 (12.8%)
Any side effect	1 (20%)
1 mg/day, n (%)	6/39 (15.4%)
Any side effect	3/6 (50%)
≤ 0.5 mg/day, n (%)	28/39 (71.8%)
Any side effect	8/28 (28.6%)
CKD stage G5 (eGFR<15 mL/min)	9 (14.5%)
Loading dose 1 mg first day, then 0.5 mg/day, n (%)	1/9 (11.1%)
Any side effect	0
1 mg/day, n (%)	0
Any side effect	0
≤ 0.5 mg/day, n (%)	8/9 (88.9%)
Any side effect	1/8 (12.5%)
Patients on dialysis	14 (22.6%)
Loading dose 1 mg first day, then 0.5 mg/day, n (%)	3/14 (21.4%)
Any side effect	0
1 mg/day, n (%)	0
Any side effect	0
≤ 0.5 mg/day, n (%)	11/14 (78,6%)
Any side effect	4/11 (36.4%)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Treatment efficacy

Considering only patients for whom the diagnosis of crystal-induced arthritis flare was finally retained (three patients had a diagnosis of septic arthritis, erysipelas and rheumatoid arthritis flare) and patients without missing data (one patient left the hospital prematurely and could not be contacted), the effectiveness of colchicine treatment was evaluated in 58 cases.

Before treatment initiation, the median (IQR) visual analogue scale score for pain was 8 (6–9). Pain and CRP level decreased significantly over time (figure 2A,B).

The medical team considered the treatment completely effective in 48 (83%) cases and partially effective in 6 (10%) (figure 2C,D). The notion of partial efficacy was explained by the need to add corticosteroids (n=2) or anti-interleukin 1 treatment (n=1), a recurrence requiring a transient increase in dosage (n=1) or an efficacy judged sufficient but not complete at the end of the treatment or at D11 (n=2).

Of note, early management (same or next day after symptom onset; n=47) was significantly more effective than later management (n=11; median 2 days (IQR 2–3.5)) (98% complete efficacy in early management vs 72% in later management; p=0.019).

Drug–drug interactions

Among the 62 prescriptions of colchicine, none had a contraindicated association, only nine had an inadvisable association with ciclosporin. Of these cases, three patients experienced AEs; only one experienced an adverse reaction imputed to colchicine (diarrhoea). In two patients, one experienced nausea and one vomiting (D2), without recurrence during follow-up despite colchicine continuation for one. Note that, in this context, the dosage was always ≤0.5 mg/day. Precautionary use is recommended with vitamin K antagonists, fibrates and statins, which concerned 39 patients (24 on statins, 22 vitamin K antagonists, 1 fibrate). These combinations did not cause any particular adverse effects.

DISCUSSION

Our prospective study, including 54 patients (62 prescriptions) who received colchicine for crystal-induced arthritis flare in the context of severe CKD, showed good efficacy and tolerance of colchicine when used in reduced doses.

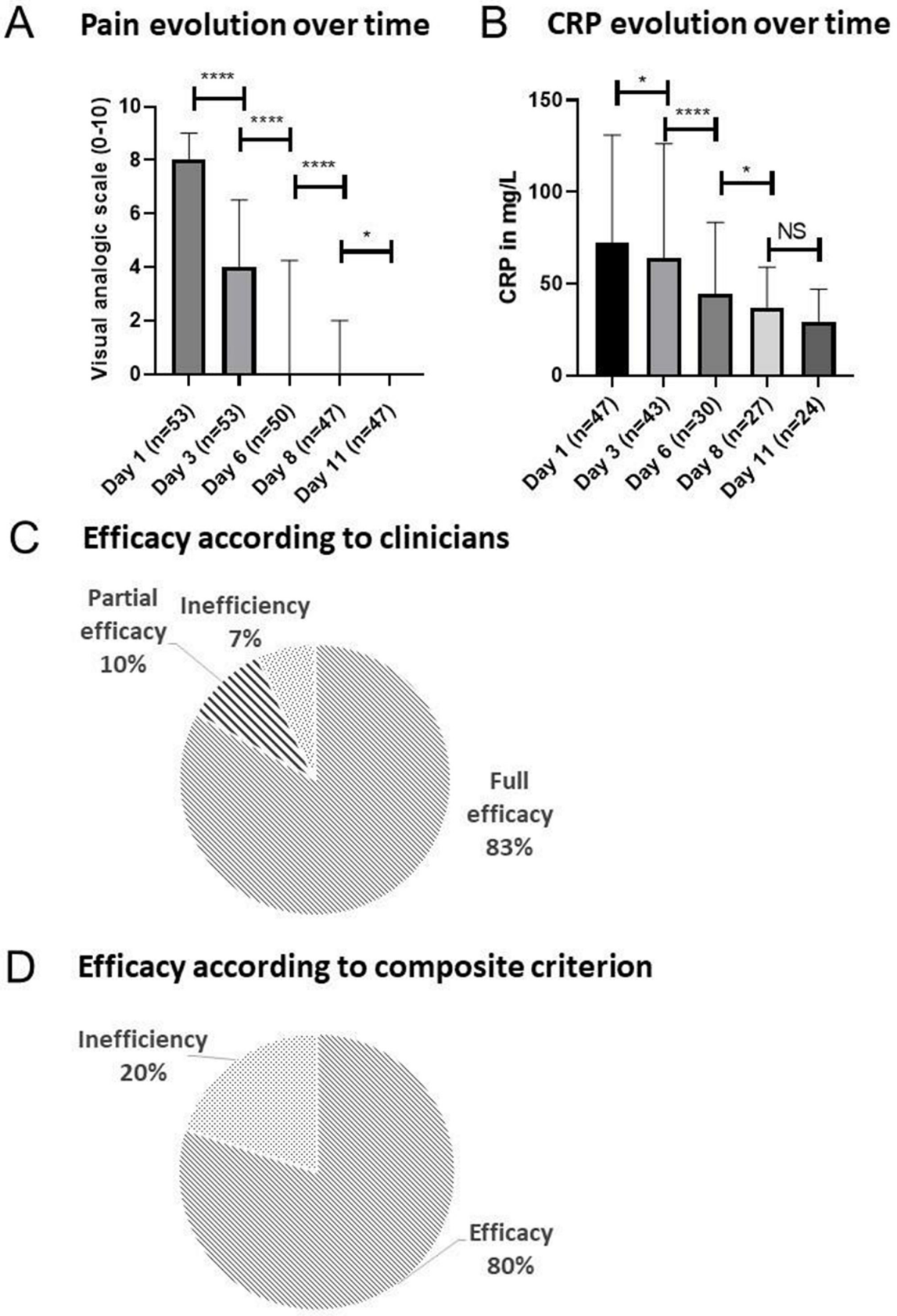

Figure 2 Efficacy of colchicine. (A) Evolution of pain over time. (B) Evolution of C reactive protein (CRP) level over time. Data are median (horizontal lines), interquartile range (box edges) and range (whiskers). *p<0.05; ****p<0.0001. NS: not significant. (C) Colchicine effectiveness according to clinicians (n=58). (D) Colchicine effectiveness according to composite criteria: treatment was considered effective if the clinicians considered it effective and if the patient described a reduction in pain≥50% associated with a decrease in CRP level (≥ 50%) as compared with day 1 (n=30).

Management of gout flare is challenging in patients with CKD because NSAIDs are contraindicated and corticosteroids can exacerbate comorbidities (diabetes) and favour infections (septic arthritis must absolutely be eliminated). However, treatment must be started as soon as possible to obtain good efficacy. For use of colchicine, the EULAR considers two distinct cases. First, for gout-flare, the group considered that it should be avoided in patients with severe CKD (G4–5), because a reduced dosage might be a source of therapeutic misuse. Second, for prophylaxis during the first 6 months of urate lowering therapy, a reduction in dose is recommended without further precision.[8] The American College of Rheumatology mentions the consideration of comorbidities, without further details.[28] In general, in patients with eGFR<30 mL/min, low doses have been proposed, from 0.3 mg daily to 0.3 mg two times weekly for patients on dialysis.[29] The French Society of Rheumatology recommends avoiding the use of colchicine because of its contraindication and the risk of ineffectiveness at reduced doses.[30] This contraindication is based on a lack of data (patients with CKD excluded from clinical studies) and a few case reports relating to drug interactions, which strongly inhibited cytochrome P450 3A4 or P-glycoprotein 1 or the use of inappropriate doses.[23 24 31 32] However, the prescription of colchicine in CKD patients is not uncommon in daily practice.[27] A pharmacokinetic study, established in the context of COVID-19, indicated that in the presence of impaired clearance >70%, the appropriate dosage might be 0.25 mg two times per day for the first 2 days, followed by 0.25 mg/day.[33] Our study is the first to assess the safety and efficacy profiles of low-dose colchicine regimens for treating crystal-induced arthritis flare in patients with severe CKD (G4–5). The results of our study provide practical evidence for using colchicine at reduced doses to treat crystal-induced arthritis flare in patients with severe CKD (G4–5) and differs from case reports.

A recent systematic review from 1 January 1959 to 31 January 2018 on gout flare prophylaxis and therapy in patients with CKD (GFR <60 mL/min)[18] found 33 studies that allowed for an analysis of the effectiveness and/or safety according to the renal function. However, only 20 studies concerned colchicine. Only 42 patients with severe CKD (G4–5) were included in this systematic review. Only five studies provided efficacy results, but no conclusions could be drawn because of heterogeneity and lack of details. Regarding tolerance, 15 studies reported the development of neuromyopathy and associated rhabdomyolysis, but the link between these AEs and the use of colchicine was not clearly established. In 2014, Wason *et al* conducted an open-label, non-randomised, single-dose study to determine the pharmacokinetics of a single dose of colchicine (0.6 mg; but haemodialysis patients received 0.6 mg before and after haemodialysis) in patients with various degrees of renal failure (CKD G1–G5).[34] Eight patients were included for each degree of renal function. No accumulation of colchicine was demonstrated, except a doubling of exposure in patients with moderate and severe CKD (G3–G4). These findings cannot be extrapolated to current practice because the study was a single-dose pharmacokinetic study. However, it is a reminder of carefulness.[34] Another study investigated colchicine toxicity in patients receiving chronic colchicine delivery for various conditions, in a context of hemodialysis.[35] It included 22 patients on maintenance haemodialysis who were taking colchicine for >6 months and 20 control patients on haemodialysis not taking colchicine. The two groups did not differ in myoneuropathic signs and symptoms or blood counts except for white blood cell count, which was significantly higher in patients taking colchicine.

In our study, colchicine was mostly used in cardiology and nephrology departments because of the use of diuretics. Colchicine was mostly started at a reduced dosage (≤0.5 mg/day) or at D2 after a loading dose of 1 mg/day. There was no prescription >1 mg/day. Doses were reduced during treatment in response to AEs, which raises concerns about overdosing (diarrhoea, vomiting). These prescriptions led to a global good tolerance of colchicine in our study with 47/61 (77%) patients who did not experience any AE during follow-up. We found no serious AEs. The digestive tolerance described by Robinson *et al* suggested 20% AEs at a dosage of 1 mg or more/day and about 10% at a dosage of 0.5 mg/day, which is comparable with our study.[36] The number of patients did not allow a detailed analysis of the impact of colchicine dosage on AEs (table 3).

Concerning drug–drug interactions, no contraindications were identified. However, we noted concomitant treatment with ciclosporin, which is not recommended. The literature contains a large panel of colchicine–ciclosporin case reports. Only one patient experienced diarrhoea because of this combination. Discontinuation of colchicine after 2 days of treatment resulted in symptom improvement. No muscular AEs were identified in combination with statins or fibrates.

With colchicine, pain significantly decreased over time and efficacy significantly decreased between early and late initiation. These observations confirm the need to start the treatment as soon as possible to increase the chances of a rapid resolution. Among the treatments considered ineffective by clinicians, only one had been started on the same day as the onset of symptoms.

Our study has some limitations. First, it is a real-life study without any predefined intervention, leading to data heterogeneity regarding colchicine dosages. Even if our cohort is the largest in the literature, its limited sample size does not allow for making strong conclusions or for subgroup analyses. In some cases, when the patient was discharged before D11, the follow-up was by phone, without new biological data or clinical examination. Pain assessment could be considered a subjective parameter. Nevertheless, efficacy assessment involved using a composite parameter, including patient and clinical evaluation associated with biological assessments.

Our results suggest that colchicine could be used with caution to treat crystal-induced arthritis flare in patients with severe CKD (G4–5), with dose reduction and close monitoring. Longer term data exploring the efficacy and safety of colchicine use as a prophylactic treatment would be interesting. Clinical trials in this population could be of interest, to evaluate the use of colchicine in prophylaxis for long-term gout flares and thus avoid the recurrence of flare when urate-lowering therapies are initiated.

CONCLUSION

The use of colchicine, at reduced dosage, in 54 patients with crystal-induced arthritis flare and severe CKD (G4–5) was effective (83%) and well tolerated (77%), with no serious AEs. Its use requires monitoring and patient therapeutic education in the case of occurrence of an AE.

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Acknowledgements We sincerely thank the clinicians (especially in nephrology, cardiology and rheumatology departments), and the patients for their participation.

Contributors The authors confirm contribution to the paper as follows: • study conception and design: JB, NK, JJVH, BM, BG, MF and RF• data collection: JB, MS, MF and RF.• interpretation of results: JB, MF and RF• preparation of manuscript: JB, MF and RF. All authors reviewed the results and approved the final version of the manuscript • guarantor: RF.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval Approval of the Ethics Committee of the Strasbourg Faculties of Medicine, Dentistry, Nursing and Maieutics #CE-2020-116. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request.

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