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COLCHICINE AND DMARDs FOR CHRONIC CALCIUM PYROPHOSPHATE CRYSTAL ARTHRITIS

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ABSTRACT

Background: There is limited data on the treatment of chronic calcium pyrophosphate (CPP) crystal arthritis, and no previous reports have focused on the potential role of combining anti-rheumatic agents.

Objectives: To compare treatment outcomes between combination therapy and monotherapies in chronic CPP crystal arthritis management in clinical practice, along with assessing the impact of sex and advanced age.

Methods: A retrospective cohort study was conducted by seven European centers. Patients diagnosed with chronic CPP arthritis (either persistent or recurrent forms) were selected and monitored at months 3, 6, 12, and 24 to evaluate treatment response and safety. This subanalysis evaluates differences in effectiveness, safety, and drug retention between monotherapy with colchicine, with disease-modifying antirheumatic drugs (DMARDs), and combination of colchicine with DMARDs. Results will also be stratified by sex and age (≤65 vs. >65 years). Linear mixed models were built for comparisons.

Results: A total of 102 treatment lines were analyzed: 71 (69.6%) for colchicine monotherapy, 20 (19.6%) for DMARD monotherapy, and 11 (10.8%) for combination therapy of colchicine plus DMARD. Combination therapy led to a higher chance of obtaining a response > 2/4 (β=+6.22, 95%CI +0.98 to +39.6, p=0.053) than individual agents, although this tendency was observed only in the physician's assessment. Combination therapy was significantly associated with deeper pain reduction, compared to colchicine alone (β=-0.83, 95%CI -1.56 to -0.09, p=0.029). By the end of the study, combined therapy reached 100% response (>2/4), followed by monotherapy with colchicine (95%) and with DMARD

(72%). Adverse events were similar, but the colchicine-only group reported more gastrointestinal disorders. Discontinuation rates were similar between groups.

Superior outcomes were noted in men, with no notable variations by age.

Conclusions: Combination therapy showed superior results in pain reduction and physician-assessed effectiveness. By the end of the follow-up, combination therapy achieved complete response in all patients, colchicine monotherapy was nearly as effective, while DMARD monotherapy showed the lowest response rate. No significant differences were found in discontinuation and safety.

Keywords: Crystal Arthropathies, Calcium Pyrophosphate, Colchicine, Methotrexate**.**

RESUMEN

Introducción: Existe evidencia limitada respecto al tratamiento de la artritis crónica por cristales de pirofosfato cálcico (CPP), y no hay estudios previos centrados en el posible papel de la combinación de agentes antirreumáticos.

Objetivos: Comparar la respuesta entre terapia combinada y monoterapias para el tratamiento de la artritis crónica por CPP, así como analizar las diferencias según sexo y edad.

Métodos: Se llevó a cabo un estudio de cohortes retrospectivo en siete centros europeos. Se seleccionaron pacientes con artritis por CPP persistente o aguda recurrente y se les monitorizó al inicio y a los meses 3, 6, 12 y 24 para analizar la respuesta al tratamiento y la seguridad. Este subanálisis evaluará las diferencias de efectividad, seguridad y continuidad entre la monoterapia con colchicina, la monoterapia con fármacos antirreumáticos modificadores de la enfermedad (FAME) y la terapia combinada con colchicina y FAME. Asimismo, se estratificarán los resultados por sexo y edad (≤65 y >65 años). Se desarrollarán modelos lineales mixtos para las comparaciones estadísticas.

Resultados: Se analizaron un total de 102 líneas de tratamiento: 71 (69.6%) correspondieron a monoterapia con colchicina, 20 (19.6%) a monoterapia con FAME, y 11 (10.8%) a terapia combinada de colchicina con FAME. La terapia combinada mostró una mayor probabilidad de obtener una respuesta > 2/4 (β=+6.22, IC95% +0.98 a +39.6, p=0.053) en comparación con la monoterapia, aunque esta tendencia se observó solo en la evaluación del médico. La terapia combinada también se asoció significativamente con una mayor reducción del dolor en comparación con la colchicina en monoterapia (β=-0.83, IC95% -1.56 a -0.09, p=0.029). Al final del estudio, la terapia combinada alcanzó un 100% de respuesta (>2/4), seguida por la monoterapia con colchicina (95%) y con FAME (72%). Los efectos adversos fueron similares, pero la monoterapia con colchicina produjo más alteraciones gastrointestinales. Las tasas de discontinuación fueron similares entre grupos. Los hombres obtuvieron mejores resultados que las mujeres, mientras que no hubo variaciones por edad.

Conclusiones: La terapia combinada mostró resultados superiores en la reducción del dolor y en la efectividad evaluada por el médico. Al final del estudio, la terapia combinada alcanzó una respuesta completa en todos los pacientes, la monoterapia con colchicina fue ligeramente menos efectiva y la monoterapia con DMARD mostró la menor eficacia. No se encontraron diferencias significativas en discontinuación y seguridad.

Palabras clave: artritis por cristales, pirofosfato cálcico, colchicina, metotrexato.

1. INTRODUCTION AND JUSTIFICATION

Calcium pyrophosphate deposition disease (CPPD) is a prevalent crystal-induced arthropathy that affects joints and soft tissues, leading to inflammation and articular damage.[1–3] CPPD is more frequent in the elderly, intimately associated with osteoarthritis, and sometimes considered part of the normal joint aging process. While no sex predominance seems to occur in clinical CPPD [2,4], asymptomatic crystal deposition in the form of chondrocalcinosis is more prevalent in women[5,6].

CPPD can be asymptomatic or range from the typical acute monoarthritis to persistent or recurrent polyarthritis.[3] Together with poor disease recognition, this often results in diagnostic delay or misclassification as other arthropathies, especially in chronic presentations.[7] Additionally, chronic forms are associated with longer-lasting limitations that affect daily routine, physical and social activities, or sleep, thus reducing quality of life and psychological well-being.[7] This highlights the importance of accurate diagnosis and effective treatment to reduce pain and disability.

Despite its impact, there is still limited data for the management of chronic CPPD, as few randomized controlled clinical trials (RCT) are available, showing modest results. [8,9] Accordingly, management recommendations are usually based on expert opinions [9] or gout evidence due to similar pathogenesis (particularly in the acute flares), and no standardized treatment algorithm exists. Unlike gout, no current treatment modifies CPP crystal formation or favors its dissolution, so treatment focuses on reducing inflammation and structural progression, controlling symptoms and preventing flares. [9,10]

EULAR recommendations propose non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine as first-line options[9,11]. Low-dose corticosteroids, methotrexate and hydroxychloroquine are suggested as second-line options. IL-1 and IL-6 inhibitors are usually reserved for refractory cases. [3,8,9] Among these treatments, colchicine,

methotrexate and hydroxychloroquine have a widespread use [3], despite their limited evidence in chronic CPPD.

Low-dose *colchicine* (0.5–1 mg/day) is commonly favored over NSAIDs for chronic CPPD due to its safety profile[8,12]. Small uncontrolled studies suggest a reduction in flare recurrence and persistent inflammation[11,13]. A double-blind RCT evaluating low-dose colchicine in knee osteoarthritis with inflammatory signs (presumably CPPD, n=39) showed a NNT of 2 for pain reduction at 4 months, with minor, non-significant side effects[14].

Methotrexate has shown inconsistent results. Two observational studies[15,16] suggested potential efficacy and safety, while an RCT found no benefit over placebo[17]. Discrepancies may arise from small sample sizes, disease heterogeneity, concurrent therapies, selected tools to assess response, and limited follow-up[18].

Hydroxychloroquine was evaluated in a unique double-blind RCT involving 36 patients, showing a 76% response in the treatment group versus 32% with placebo. 85% of initial placebo responded after crossover[19]. Despite study limitations and no formal replication of results, EULAR supports hydroxychloroquine use in chronic CPPD [9].

A recent retrospective multi-center study described the efficacy, safety, and retention of the drugs used to manage chronic persistent and/or recurrent CPPD in clinical practice. Data concluded that daily colchicine was the first-line therapy, despite proving efficacy in only a third to half of cases. Methotrexate and tocilizumab were employed as second-line. Discontinuations were due to adverse events, insufficient response or loss to follow-up.[3] The study did not provide a focused analysis on combination therapies, which are common in other inflammatory arthritis to enhance anti-inflammatory outcomes and may also benefit chronic CPPD. Schemes have included combinations of different traditional DMARDs or one of them with a biologic[20,21]. This approach for CPPD, and the potential role of colchicine here, needs further research.

This project aims to compare combinations of colchicine plus DMARDs against using colchicine or DMARD as monotherapy in a large chronic CPP crystal arthritis cohort. Additionally, we will assess the potential sex-related variations, as no differences have been reported to date, and whether treatment outcomes may be influenced by age, as often occurs in many other conditions, with the elderly experiencing more adverse events, higher discontinuation rates, and variable efficacy results[22,23]. Our approach will also focus on functional outcomes to improve disability management and clinical care.

2. HYPOTHESES AND OBJECTIVES

2.1 HYPOTHESES

Primary hypothesis

Combination therapy of colchicine plus DMARDs will carry superior outcomes compared to individual agents in the treatment for chronic CPPD.

Secondary hypotheses

1. Combination therapy will demonstrate superior effectiveness to monotherapy, whereas safety will not differ. Retention rates may also be higher in combination therapy.
2. Treatment outcomes in CPPD may differ according to patients' sex.
3. Age may impact on combination therapy outcomes, particularly safety.

2.2 OBJECTIVES

General objective

To compare management outcomes between combination therapy with colchicine and DMARDs and individual treatments in chronic CPPD.

Specific objectives

1. To compare the effectiveness, safety, and retention of combination therapy of colchicine with DMARDs versus monotherapy with either colchicine or DMARDs.
2. To contrast treatment outcomes based on patients' sex.
3. To separate results according to the age of participants (below or above 65 years).

3. METHODS

3.1 STUDY DESIGN AND POPULATION

Post-hoc analysis of a multicenter retrospective series from seven European Rheumatology departments in France, Italy, and Spain interested in crystal-related arthritis. The original study[3], aimed to assess the efficacy, safety, and retention of drugs used to manage chronic CPP crystal arthritis; here we will analyze the data on combination therapy employed in clinical practice.

The study population included patients diagnosed with chronic CPP crystal arthritis with at least two visits to any of the participating centers.[3]

The study collected data from treatments initiated between 1 January 2015 and 1 May 2021.

3.2 SELECTION CRITERIA

3.2.1 INCLUSION CRITERIA

a. Patients aged ≥ 18 years.

b. Diagnosis of chronic CPPD disease (defined as persistent arthritis > 3 months and/or >2 acute episodes per year).

c. At least one long-term conventional treatment for chronic CPPD prescribed since January 1st, 2015, specifically colchicine, methotrexate, and hydroxychloroquine for the present analysis.

3.2.2 EXCLUSION CRITERIA

a. Patient with concomitant inflammatory rheumatic disorder, such as gout, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease-associated arthritis.

b. Use of advanced, targeted therapies (biologics or JAK inhibitors) at the time of colchicine or DMARDs, to avoid their probable influence on outcomes.

3.3 VARIABLES OF INTEREST

3.3.1 DEPENDENT VARIABLES

The dependent variables are **effectiveness**, **safety,** and **retention** of the therapies used for chronic CPPD.

Effectiveness was primarily evaluated as the response to treatment 6 months after the start, using a 5-point scale created for the study (0 = no response, 1 or 2 = intermediate response, 3 or 4 = good response; considering 4 as total response) that was filled out by the investigators using medical reports data. Response to treatment >2/4 was recorded as a positive response.

Additional assessments of effectiveness were performed and collected in months 3, 6, 12 and 24 (M3, M6, M12 and M24 respectively) after the start of treatment: 3-point scale physician assessment of disease activity (low, intermediate, high), 5-point scale patient quality-of-life assessment (translated by the investigator using information of patients'

medical files), patient VAS disease activity, patient VAS pain, number of flares since last visit, number of swollen joints, number of tender joints, and C-reactive protein (CRP) levels.

Safety was studied by collecting data regarding adverse effects attributable to therapies, regarding the total number of episodes, and characteristics. Adverse effects of interest included reactions of site injection, muscular pain, myolysis, hepatic cytolysis, infections, cytopenia, and digestive issues (nausea, vomiting, abdominal pain, diarrhea).

Retention rate was defined as the time until the first definitive treatment interruption (before 24 months of follow-up). The date and cause of treatment interruption were recorded.

3.3.2 INDEPENDENT VARIABLES

The primary independent variable is the type of **treatment scheme**, divided into three groups described below, using colchicine, methotrexate, or hydroxychloroquine.

According to the treatments under study, two monotherapy groups and one combination therapy group were defined. *Monotherapy groups* consisted of uses of colchicine or DMARDs (methotrexate or hydroxychloroquine) as unique agents, while the *combination group* included colchicine with one DMARD. A new drug is classified as a novel treatment, while continuing an existing medication alongside it is considered a combined treatment strategy. All treatments started between 1 January 2015 and 1 May 2021 were studied.

The treatment groups were defined to reflect common clinical practice for managing CPPD. Distinguishing between monotherapy and combination therapy allowed assessment of both individual drug effectiveness and potential synergistic effects. The selected combinations were based on their prevalence in the cohort and therapeutic relevance.

NSAIDs and corticosteroids were not considered in our analysis, as they are frequently used as an add-on anti-inflammatory therapy, often on demand or with tapering doses.

Secondary independent variables are **age** at enrolment (dichotomized as below or equal to or above 65 years old) and **sex** (male or female).

3.4 PROCEDURES AND ETHICS

3.4.1 PROCEDURES

This project obtained data from the primary study [3]. The database included baseline characteristics of patients and information on their follow-up in months 3, 6, 12, and 24, including evaluation of response, safety, and treatment retention.

For this project, we conducted a subanalysis of a retrospective cohort study. The author reviewed the literature, identified the area of interest, and drafted the project, later refined by her supervisor and Prof. Tristan Pascart (PI of the multicenter study). Afterward, access to the primary study database at Lille Catholic Hospital was requested, along with the extraction of the data needed. Once authorization was granted, Dr. Laurène Norberciak, the statistician responsible for data access and processing, managed data. The result interpretation followed.

3.4.2 ETHICS

Ethical approval for the study was granted by the hospitals where it was performed: France (Lille Catholic Hospitals IRB RNIPH-2021-01), Italy (Registro Sperimentazioni 2021/ST/234), and Spain (Alicante-ISABIAL IRB ref. 2021-098) [**Supplementary material**]. The present post-hoc analysis was approved by the Responsible Research Office of the Miguel Hernández University of Elche (COIR TFG.GME.MNAC.LJP.250216) [**Supplementary material**].

Due to the retrospective nature of the analyses, the local ethics committee granted a waiver for not requiring informed consent from the participants.

3.5 STATISTICAL ANALYSES

Qualitative variables were described as numbers and frequencies of each response modality; quantitative/discrete variables were described as median [interquartile range].

For the analysis, two monotherapy groups and one combination therapy were defined and compared using chi-square and Kruskal-Wallis tests, based on the variable characteristics. Linear mixed models assessed treatment effect over time, considering its potential effect (likely, the targeted response is finally reached through different approaches, but the speed of achieving it may be relevant for clinical practice) and the baseline status. The colchicine-alone group was used as the reference to calculate the coefficients compared to it. Adjusted β coefficients and 95% confidence intervals (CIs) were calculated. When the linear mixed model was not satisfied, we used the bootstrap method to calculate 95%CIs and p-values.

All statistical analyses were performed using R version 4.3.0. Significance was set at $p<0.050$.

4. RESULTS

The dataset comprised a sample size of 194 lines of treatment in 149 patients. Of them, 129/194 (66.5%) lines were as monotherapy, while 65/194 (33.5%) consisted of combinations: 46/194 (23.7%) involved 2 treatments, 16/194 (8.2%) involved 3 treatments, and 3/194 (1.5%) involved 4 treatments.

Main combination therapies included colchicine, corticosteroids, methotrexate, and NSAIDs as co-treatments (**Table 1**). Colchicine and methotrexate were used either as main therapy or co-treatment. Corticosteroids were present in all 3-drug regimens. The 4-drug combinations involved anakinra as the main therapy combined with corticosteroids, colchicine, and other co-treatments.

Table 1. Observed combination of treatments (n=194) in the 149 enrolled participants.

	Alone	Colchicine	Corticosteroids	MTX	NSAIDs	Distinct lines
Colchicine	71 (36.6%)	71	28	20	3	
Corticosteroids	7 (3.6%)	28	7	15	2	
MTX	16 (8.2%)	20	15	16	0	
NSAIDs	0 (0%)	3	2	0	0	
HCQ	4 (2.1%)	4	1	0	0	8 (4.1%)
Anakinra	15 (7.7%)	9	8	3	1	27 (13.9%)
Canakinumab	2 (1%)	1	0	1	0	3 (1.5%)
Tocilizumab	13 (6.7%)	9	3	2	0	25 (12.9%)
Sarilumab	1 (0.5%)	1	1	0	0	2 (1%)
Distinct lines	129 (66.5%)	124 (63.9%)	46 (23.7%)	43 (22.2%)	3 (1.5%)	

Data in blue does not reflect distinct patients; that is why the subtraction of the cells 194-129 = 65 lines with multiple treatments. MTX: methotrexate. NSAIDs: non-steroidal anti-inflammatory drugs. HCQ: hydroxychloroquine.

We then selected the groups of interest for further analysis, resulting in two monotherapy groups and one combination therapy group, with a total sample size of 102 lines of treatment: 71 lines of colchicine alone, 20 of DMARD alone, and 11 of their combination. **Figure 1** depicts the samples over follow-up. Among lines of treatment, 72 lines (70.6%) involved female patients, and the median age at baseline was 73 years (**Table 2).** Previous colchicine use was reported in 30–36% of patients in the DMARDs-alone and the combination therapy groups; however, all groups were, on average, starting the first line of treatment. NSAIDs, corticosteroids, and biologics were not considered in our analysis.

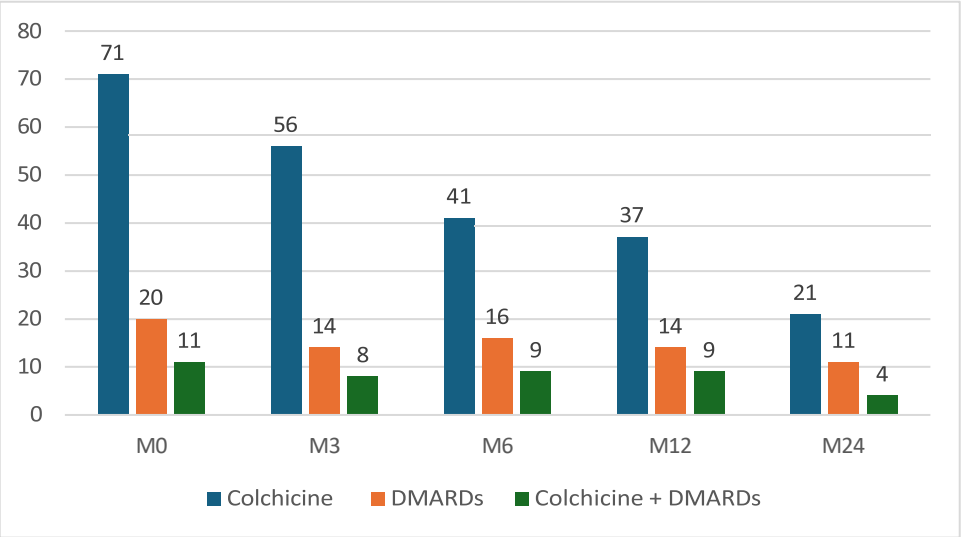

Figure 1. **Sample size at the different months of follow-up (M).** *Bars represent individual treatments. DMARDs = Disease-modifying antirheumatic drugs. DMARD: methotrexate or hydroxychloroquine.*

Table 2. Patients' characteristics at initiation of treatment.

		COLCHICINE + DMARD	COLCHICINE	DMARD
N		11	71	20
Sex	**Females**	7 (63.6%)	52 (73.2%)	13 (65.0%)
	Males	4 (36.4%)	19 (26.8%)	7 (35.0%)
Age in years, median [IQR]		78.0 [71.0;80.0]	73.0 [62.5;80.0]	72.0 [67.2;78.2]
Nr of Treatment line at initiation, median [IQR]		1 [1;2]	1 [1;1]	1 [1;2]
Previous Colchicine use		4 (36.4%)	0 (0%)	6 (30.0%)

4.1 EFFECTIVENESS

Overall, all groups showed a reduction in disease activity, pain, acute flares, joint inflammation, and CRP levels, with the greatest improvements occurring within the first six months. Differences in celerity and magnitude of improvement will be discussed individually.

Primary indicator: Response to treatment >2/4. Clinicians and patients independently assessed treatment response (>2/4), showing consistent results and identical end-of-study outcomes. All groups showed progressive and sustained

improvement, with most achieving a final response rate over 85% (**Figure 2**). Combining colchicine plus DMARDs showed a trend towards a better chance of obtaining a response > 2/4 (β=+6.22, 95%CI +0.98 to +39.6, p=0.053) compared to individual agents, although this tendency was observed only in the physician's assessment. By the end of the study, combined therapy reached 100% response (>2/4), followed by the colchicine-alone group (95%), while the DMARD-alone group showed the poorest outcomes, with 72% response.

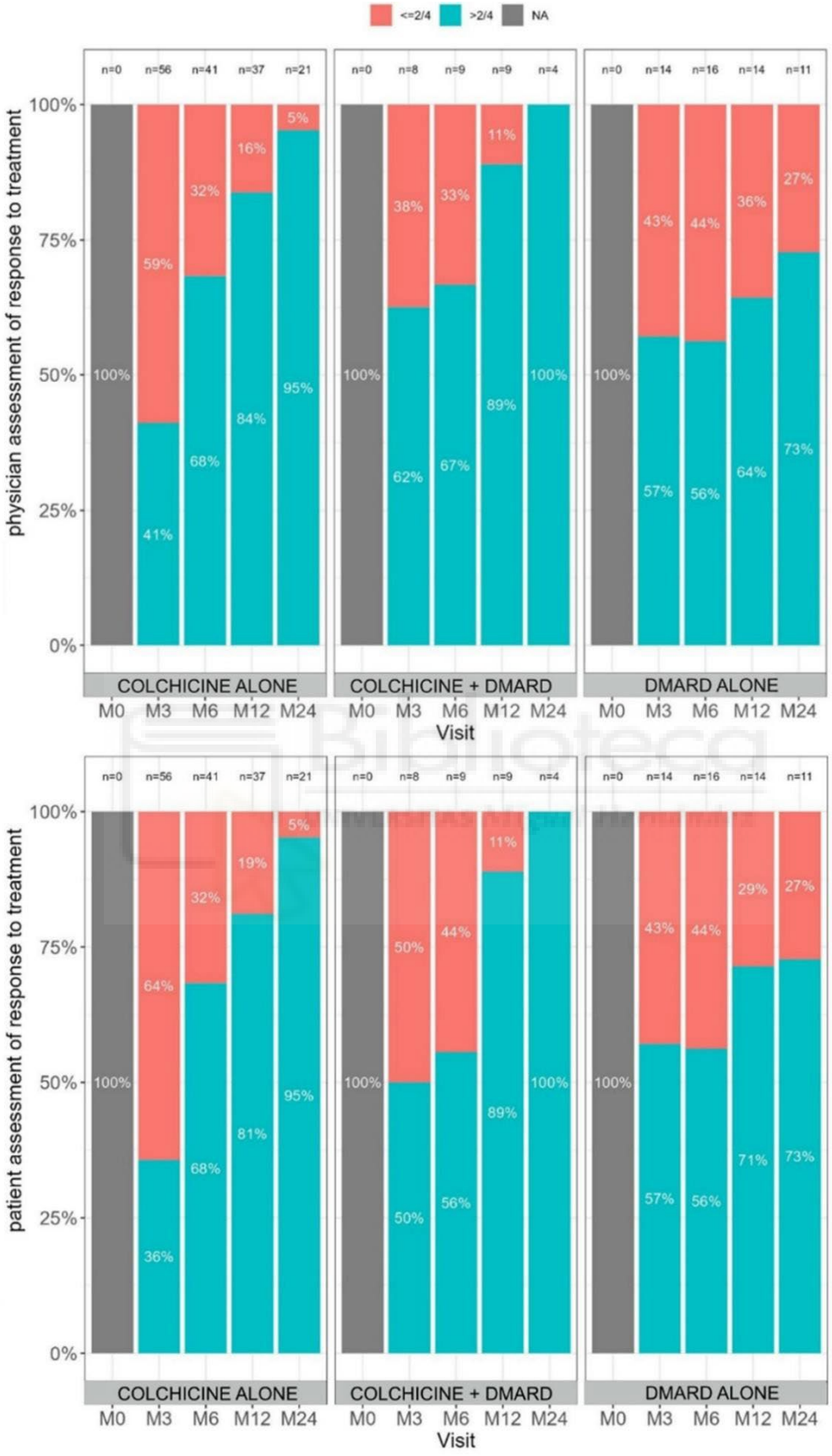

Figure 2. Comparison of physician assessment of response to treatment (left) and patient assessment of response to treatment (right). *M0: month 0; M3: month 3; M6: month 6; M12: month 12; M24: month 24.*

Patient disease activity VAS. A decrease in disease activity was found regardless of the treatment group (**Figure 3**). Colchicine-containing treatments showed a greater long-term reduction (VAS ≤ 2 since month 12), while the DMARDs-alone group showed the poorest response and was the only group to show some deterioration (VAS from 3 to 5 by month 24). Nevertheless, the model found no statistical differences between groups (β=-0.45, p=0.21 for colchicine+DMARDs; β=+0.10, p=0.74 for DMARDs alone).

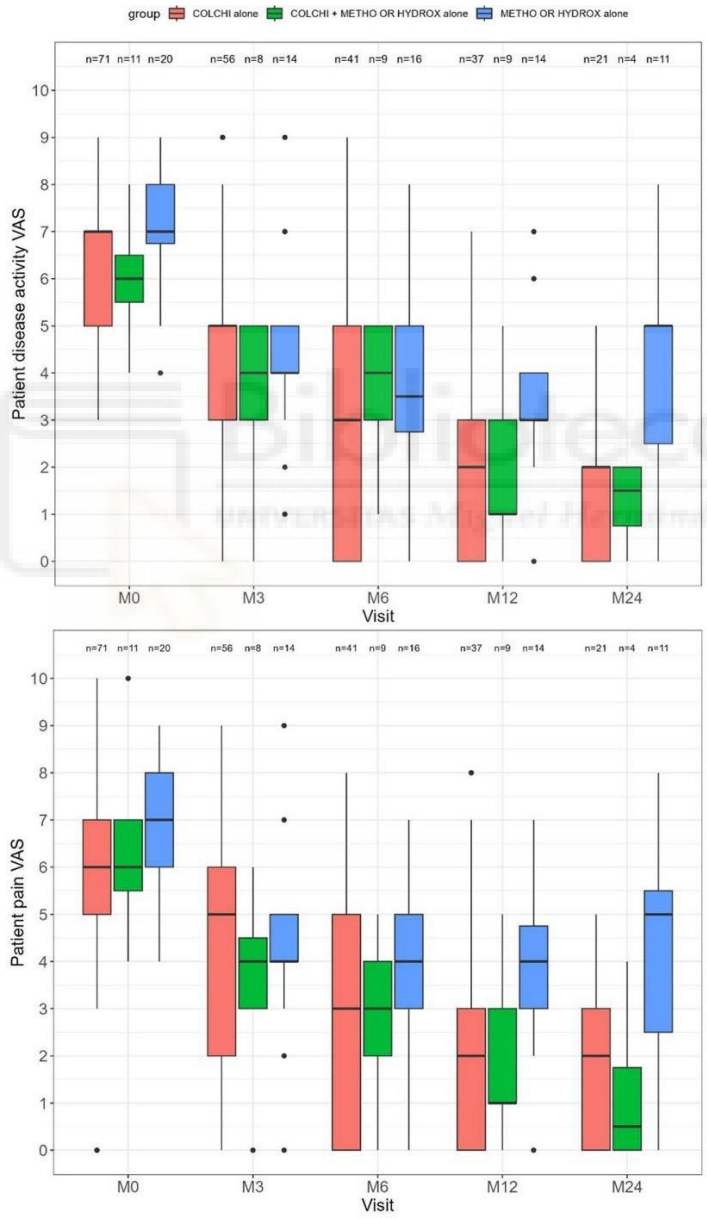

Figure 3. Patients' disease activity and pain assessments by VAS, comparing between therapy groups. *VAS: Visual Analogue Scale; M0: month 0; M3: month 3; M6: month 6; M12: month 12; M24: month 24.*

Patient pain VAS. The DMARDs-alone group was the least effective, with higher VAS scores at month 24 and less improvement throughout the treatment (**Figure 3**), but this group showed a higher VAS score at baseline compared to other groups (Pain VAS of 7 vs. 6). The remaining groups showed progressive score reductions, more evident with the combination therapy. In the mixed model, the use of colchicine+DMARDs was significantly associated with deeper pain reduction, compared to colchicine alone (β=-0.83, 95%CI -1.56 to -0.09, p=0.029). Conversely, no association was found for the DMARD-alone group (β=+0.12, 95%CI -0.48 to +0.72, p=0.696).

Number of acute flares. All groups showed a median reduction from 2-3 to 0 acute attacks, starting from the third month onward. This remained stable in the groups including Colchicine, while the DMARDs-alone group showed a median of one attack at month 24. No significant differences were noted.

Number of swollen and tender joints. All groups showed a reduction in swollen and tender joints from month 3 onward. Concerning swollen joints, the colchicine-alone group achieved a complete and sustained median reduction from 2 to 0. In contrast, the colchicine+DMARD group, despite similar baseline characteristics, did not achieve a complete response until month 12. The DMARDs-alone group did not reach complete reduction, likely due to a higher baseline median of one additional swollen joint. Regarding tender joints, the colchicine-alone group was the only one to achieve a reduction to 0 by the month 12 and maintain it.

CRP levels. All groups showed marked reductions by month 3 (>43% of decrease) (**Figure 4**). The colchicine-alone group remained stable, while the DMARDs-alone group and the colchicine+DMARD group fluctuated and eventually increased at month 24, achieving

net reductions of 37.5% and 21.4%, respectively. The effect was comparable among treatment groups (β=-1.52, 95%CI -7.90 to +4.88, p=0.670 for colchicine+DMARDs; β=+1.08, 95%CI -4.04 to +6.14, p=0.644 for DMARDs alone).

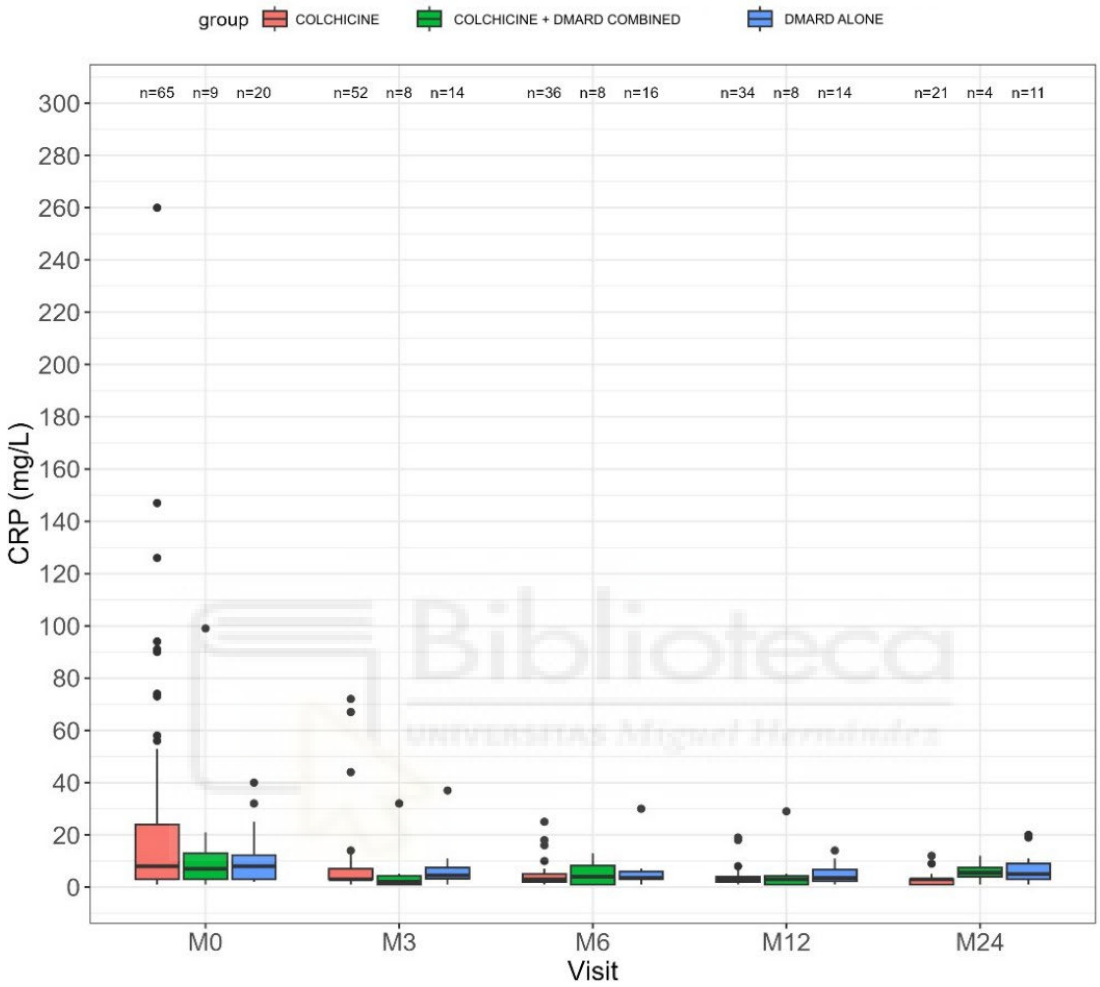

Figure 4. CRP values (mg/dL) comparison between treatment groups over time. *CRP: C-reactive protein; M0: month 0; M3: month 3; M6: month 6; M12: month 12; M24: month 24.*

Patient quality of life assessment. Several life dimensions were assessed, revealing notable differences in domestic limitations, leisure and social activities (**Table 3**).

Combined therapy was superior to monotherapy in reducing domestic activity limitations, reaching full control since month 3, while no monotherapy group obtained full control at any point.

Regarding normal leisure and social life activities, colchicine-alone and colchicine+DMARDs groups got the highest response (75%) with progressive and sustained improvement, while the DMARD-alone group showed the lowest response (<40%).

Table 3. Patient quality of life assessment

	M0	M3	M6	M12	M24
Number of patients with limitations in domestic activities					
COLCHICINE	23 (32.4%)	10 (17.9%)	4 (9.8%)	4 (10.8%)	1 (4.8%)
DMARD	11 (55%)	5 (35.7%)	4 (25%)	2 (14.3%)	2 (18.2%)
COLCHICINE + DMARD	5 (45.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of patients with partial loss of autonomy for activities of daily living					
COLCHICINE	2 (2.8%)	0 (0%)	1 (2.4%)	1 (2.7%)	0 (0%)
DMARD	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COLCHICINE + DMARD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of patients with restrictions in social life activities					
COLCHICINE	39 (54.9%)	31 (55.4%)	16 (39%)	12 (32.4%)	4 (19%)
DMARD	8 (40%)	6 (42.9%)	9 (56.2%)	7 (50%)	5 (45.5%)
COLCHICINE + DMARD	6 (54.5%)	5 (62.5%)	5 (55.6%)	4 (44.4%)	1 (25%)
Number of patients with normal leisure and social life activities					
COLCHICINE	7 (9.9%)	15 (26.8%)	20 (48.8%)	20 (54.1%)	16 (76.2%)
DMARD	0 (0%)	3 (21.4%)	3 (18.8%)	5 (35.7%)	4 (36.4%)
COLCHICINE + DMARD	0 (0%)	3 (37.5%)	4 (44.4%)	5 (55.6%)	3 (75%)

M0: month 0; M3: month 3; M6: month 6; M12: month 12; M24: month 24.

Physician assessment of disease activity

Disease activity decreased from the first follow-up in all groups, with over half of the patients reaching low activity levels (**Figure 5**). The combination therapy achieved faster, sustained control, eliminating high activity by month 3. Monotherapy groups showed persistent high activity, though decreasing over time.

By the end of the study, combined therapy reached 100% control and the colchicine-alone group 95%. DMARDS-alone group had the poorest outcomes, with 72% achieving low activity and 9% remaining high, but with a greater baseline of high disease activity (50% vs. 27% and 37%, respectively).

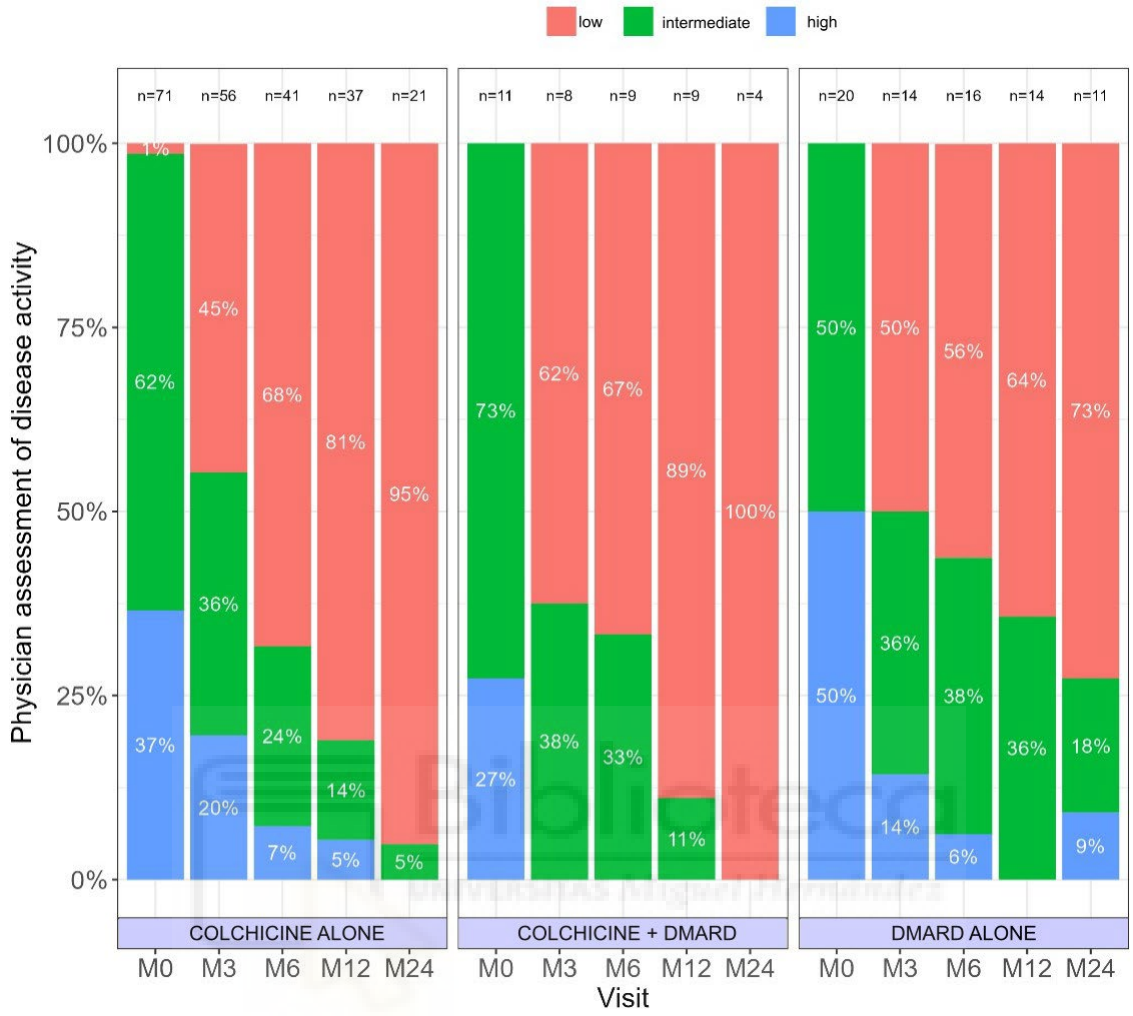

Figure 5. Physician assessment of disease activity. *M0: month 0; M3: month 3; M6: month 6; M12: month 12; M24: month 24*

4.1.2 Effectiveness By Sex

Men presented with more unfavorable baseline characteristics, including higher flare frequency, elevated CRP levels (13 vs. 6.5), and a greater proportion of patients exhibiting high disease activity. However, they achieved superior outcomes across most variables: lower disease activity at study end (VAS 2 vs. 3), greater and faster pain reduction (VAS 1.5 vs. 3 at month 24, with a consistently steeper decrease from baseline), and complete resolution of tender joints by month 12 (vs. 1 joint remaining at month 24 in women). Disease activity was faster controlled in men, with 85% reaching low activity by month 12

(vs. month 24 in women), and no remaining high activity at study end (unlike women). Functional improvements were also faster and more pronounced, particularly in restoring normal leisure and social life activities. Treatment response was achieved earlier in men (85% by month 12), whereas women reached 83% only by month 24.

Women showed faster control of joint inflammation (complete by M3 vs. M6 in men) and achieved slightly lower final CRP levels (2 vs. 3), though differences were modest. No differences were observed in flare resolution, with full control reached by M3 in both groups.

4.1.3 Effectiveness By Age

No clear pattern of superiority was observed between age groups, and differences were generally modest. Older patients experienced less social restriction throughout treatment and showed greater improvement in the ability to lead a normal life. Younger patients had a more pronounced reduction in CRP by the end (CRP = 1 vs 3, both starting at 7) and achieved full resolution of daily limitations earlier (month 6 vs month 24). Both groups achieved full flare control by month 3.

4.2 SAFETY

A total of 26 adverse events (AE) were recorded, with no significant differences in the incidence among groups (**Table 4**). Moreover, discontinuations due to safety issues were also similar (see section 4.3).

The type of AE differed significantly according to the treatment received. The colchicine-alone group was associated with a higher incidence of gastrointestinal disorders compared to the other groups , mainly led by cases of diarrhea and, less often, abdominal pain and others.

In contrast, hepatic cytolysis was observed in the DMARD-alone and the combination therapy groups (75% and 33%, respectively), while non in the colchicine-alone group. No other safety events were noted in the treatment groups.

Table 4. Adverse events among treatment groups

	COLCHICINE + DMARD	COLCHICINE	DMARD	p
N	11	71	20	/
Occurrence of adverse events	4 (36.4%)	19 (26.8%)	3 (15%)	0.39
In patients with at least one adverse event, type of adverse event				
Infectious episode	0 (0%)	0 (0%)	0 (0%)	/
If infectious episode: number	/	/	/	/
Injection site reaction	0 (0%)	0 (0%)	0 (0%)	/
Digestive disorders	1 (25%)	19 (100%)	3 (100%)	**0.002**
If Digestive disorders: Diarrhea	0 (0%)	18 (94.7%)	0 (0%)	**0.0006**
If Digestive disorders: Abdominal pain	0 (0%)	3 (15.8%)	3 (100%)	**0.011**
If Digestive disorders: Other	1 (100%)	0 (0%)	3 (100%)	**0.0001**
Muscle pain	0 (0%)	0 (0%)	0 (0%)	/
Cytopenia	0 (0%)	0 (0%)	0 (0%)	/
Hepatic cytolysis	3 (75%)	0 (0%)	1 (33.3%)	**0.0011**
Myolysis	0 (0%)	0 (0%)	0 (0%)	/
Other adverse event	0 (0%)	1 (5.3%)	0 (0%)	1

4.3 DISCONTINUATION

4.3.1 Discontinuation – Comparison By Treatment

Data is shown in **Table 5**. A high proportion of treatments were discontinued – 18% of treatment discontinuations in the combination therapy group and 40% in the monotherapy groups. Considering loss to follow-up, the discontinuation rates rose to 55% in the DMARDs-alone group and 73% in the rest, respectively.

Lack of effectiveness was the main clinical reason for discontinuation (72%). When including loss to follow-up, this became the primary reason for colchicine-alone and colchicine+DMARDs groups (42% and 75%, respectively). DMARDs-alone group had the highest discontinuation rate due to ineffectiveness (87%, p=0.31), showing a 34% difference from the next highest group. Colchicine+DMARD group had the highest

proportion of loss to follow-up (75% of its discontinuations), notably higher than all other groups (<43%). Remission-related discontinuations were rare, mainly in colchicine-alone group (16%).

Despite the figures described, statistical analyses demonstrated no significant differences between groups.

Table 5. Treatment discontinuation – comparison among treatment groups.

		COLCHICINE + DMARD	COLCHICINE	DMARD	p
N		11	71	20	/
Without integration of those lost to follow-up before month 24					
Treatment discontinuation		2 (18.2%)	30 (42.3%)	8 (40%)	0.31
If affirmative, reason for discontinuation	Ineffectiveness	1 (50%)	16 (53.3%)	7 (87.5%)	0.43
	Intolerance	1 (50%)	4 (13.3%)	0 (0%)	
	Remission	0 (0%)	5 (16.7%)	1 (12.5%)	
	Ineffectiveness + intolerance	0 (0%)	5 (16.7%)	0 (0%)	
	Other	0 (0%)	0 (0%)	0 (0%)	
With integration of those lost to follow-up before month 24					
Treatment discontinuation		8 (72.7%)	52 (73.2%)	11 (55%)	0.29
If affirmative, reason for discontinuation	Ineffectiveness	1 (12.5%)	16 (30.8%)	7 (63.6%)	0.31
	Intolerance	1 (12.5%)	4 (7.7%)	0 (0%)	
	Remission	0 (0%)	5 (9.6%)	1 (9.1%)	
	Ineffectiveness + intolerance	0 (0%)	5 (9.6%)	0 (0%)	
	Other	0 (0%)	0 (0%)	0 (0%)	
	lost to follow-up	6 (75%)	22 (42.3%)	3 (27.3%)	

4.3.2 Discontinuation By Sex

The study included a higher proportion of women (72/102, 71%). Loss to follow-up was the leading cause of discontinuation, followed by ineffectiveness in both genders. Women had a higher rate of discontinuations due to adverse effects (30% vs. 17%), while men had a higher rate of discontinuations due to remission (21.7% vs. 5.9%).

4.3.3 Discontinuation By Age

The study included a higher proportion of elderly people (2/3). No notable differences were observed in discontinuation rates or cause, except for ineffectiveness, which was higher in the younger group (80% vs. 61%) and remained the primary reason for discontinuation when excluding losses to follow-up.

5. DISCUSSION

This project reports the first study comparing combination therapy to monotherapy for CPPD. Our analysis identified two significant findings regarding effectiveness: combination therapy led to a higher likelihood of better responses and a greater pain reduction than monotherapy, supporting our hypothesis of superiority. Despite the results, the first outcome relied mainly on physicians' assessments, which may be biased, and the VAS pain difference was modest (0.83 points), so their clinical relevance remains uncertain. Although not significant, combination therapy also showed superior quality-of-life and disease activity outcomes, while colchicine alone stood out in inflammatory results (CRP levels and swollen and tender joints). Notably, the DMARD-alone group consistently exhibited poorer outcomes, although it presented some poorer baseline values (eg, Pain VAS of 7 compared to 6 in the other groups; greater proportion of high disease activity). Most improvements occurred within the first 3-6 months, suggesting that treatment changes could be considered if no response occurs by then.

Otherwise, discontinuation analysis was hampered by significant loss to follow-up, so the hypothesis of superior retention rate with combination therapy cannot be confirmed or rejected. Discontinuation also limits longitudinal analysis, so end-of-treatment results should be interpreted cautiously.

Regarding treatment safety, no significant differences were found in the incidence of AEs, but their nature notably differed across groups. Gastrointestinal disorders were significantly associated colchicine alone, while hepatic cytolysis occurred only in DMARD-containing groups, consistent with known safety profiles[24,25]. Therefore, liver test monitoring is recommended in patients receiving methotrexate, as in other inflammatory rheumatic diseases, and treatment choice should consider both patient comorbidities and drug safety. Despite that, AEs did not appear to impact treatment retention, which was mainly due to ineffectiveness and loss to follow-up.

Concerning sex and age-based comparisons, men, despite more unfavorable baseline characteristics, achieved faster and more pronounced treatment responses, with higher rates of discontinuation due to remission, suggesting greater sensitivity to the therapy administered. In contrast, women had more discontinuations due to adverse events, reflecting lower tolerability. No consistent age-related difference was observed, although younger patients showed a trend toward higher discontinuation due to ineffectiveness, contrary to previous reports[23]. However, the true impact of sex and age remains uncertain, as limited data access prevented both statistical analysis and safety assessment by these variables. These limitations highlight the need for further research in this area.

This post-hoc analysis, despite its design limitations, provides early insights suggesting combination therapy may have a synergistic benefit over monotherapy for CPPD, similar to rheumatoid arthritis [21]. Further interventional studies are needed to confirm this theory and support the potential inclusion of combination therapy in treatment guidelines[11,13].

Consistent with previous studies[11,13], colchicine monotherapy effectively reduced recurrent flares, persistent inflammation, and pain. DMARD monotherapy showed the poorest results, but whether this is due to patient profile, study limitations, or drug weakness for CPPD requires further investigation. As some effect was observed, we align

with previous research[15,16,19] in suggesting it may be effective. Additionally, since methotrexate and hydroxychloroquine were analyzed together, their individual effects remain unknown.

5.1 STRENGTHS AND LIMITATIONS

This study provides the largest chronic CPPD sample to date, assessing several effectiveness, safety, and drug retention endpoints. Unfortunately, small sample sizes and a high discontinuation rate, largely influenced by loss to follow-up, limited statistical power. Potential explanations include adverse effects, lack of effectiveness, remission, logistical issues, or adherence challenges. The high discontinuation rate may introduce bias, leading to over- or underestimating treatment effectiveness and safety. Future studies should investigate loss to follow-up causes and explore strategies to improve retention.

Lack of randomization may bias treatment assignments and outcomes. In this study, previous colchicine use –possibly indicating refractory patients– was reported in 30–36% of patients in the DMARDs-alone and combination groups, respectively. This could potentially underestimate treatment effectiveness compared to colchicine-alone.

Study data were retrospectively extracted from patients' records. Some outcome variables, such as levels of pain or function, lacked VAS scales in many patients and should be interpreted by the local investigators according to other annotations.

CPPD predominantly affects older adults, limiting the sample size of younger patients for reliable subgroup analyses.

Sex and age-based comparisons were descriptive only due to incomplete availability of statistical analyses, and safety data for these groups was entirely unavailable, requiring further research to confirm these findings.

Moreover, this study involves post hoc subgroup analyses, which carry inherent bias. While the findings may generate new hypotheses, additional studies are needed to verify these outcomes.

6. CONCLUSION

Combination therapy of colchicine and DMARDs shows promising outcomes compared to individual agents, particularly in pain reduction and physician-reported effectiveness for chronic CPPD. By the study's end, combined therapy achieved full disease control, followed by colchicine alone, which stood out in inflammatory outcomes. DMARD monotherapy appeared to be the least effective.

Adverse event rates were similar across groups, but their characteristics differed, which could impact drug selection by considering both comorbidities and drug's safety profile.

No significant differences in treatment discontinuations were noted, although limited by a global high discontinuation rate and loss to follow-up.

Sex and age-based comparison lacked statistical analyses but suggested a trend toward a superior response in men and no clear age-related differences.

In conclusion, combination therapy is a potential treatment option for chronic CPPD and may be considered in further CPPD treatment guidelines. However, additional studies are needed to confirm our findings and improve the limited evidence for CPPD management.

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8. SUPPLEMENTARY MATERIAL

8.1 APPROVAL FROM THE ETHICS COMMITTEE OF DR. BALMIS GENERAL UNIVERSITY HOSPITAL OF ALICANTE

COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE
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Ref. CEIm: 2021-098 - Ref. ISABIAL: 2021-0233

DICTAMEN DE ESTUDIO EOm NO Prospectivo

Dr. Luis Manuel Hernández Blasco, Secretario del Comité Ético de Investigación con Medicamentos del Hospital General Universitario de Alicante.

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor **Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL)** para el investigador principal **Mariano Andrés Collado** del Servicio de Reumatología del Hospital General Universitario de Alicante para que se realice el estudio:

TÍTULO	Treatment of chronic pyrophosphate deposition disease: a European experience
PROMOTOR	Groupement des Hôpitaux de l'Institut Catholique de Lille (GHICL)
CÓDIGO DEL PROTOCOLO	CHRONIC-CPPD
VERSIÓN DEL PROTOCOLO	1
FECHA DEL PROTOCOLO	19-01-2021
HOJA DE INFORMACIÓN AL PACIENTE (Versión y fecha)	V.1 12-03-2021

Y tomando en consideración las siguientes cuestiones:

-La pertinencia del estudio, teniendo en cuenta el conocimiento disponible, así como los requisitos del Real Decreto 957/2020, de 3 de Noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano y el Real Decreto 1344/2007, de 11 de octubre, por el que se regula la farmacovigilancia de medicamentos de uso humano.

-Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.

-El seguro o la garantía financiera previstos son adecuados.

-El procedimiento para obtener el consentimiento informado, incluyendo la hoja de información para los sujetos versión de (día/mes/año), modificación nº ... versión (día/mes/año), y el plan de reclutamiento de sujetos previstos son adecuados, así como las compensaciones previstas para los sujetos por daños que pudieran derivarse de su participación en el ensayo.

-La capacidad del investigador y sus colaboradores son apropiados para llevar a cabo el estudio.

COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE
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-Las instalaciones y medios disponibles son apropiados para llevar a cabo el estudio.

-El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.

Por tanto, este Comité habiendo tenido en cuenta los informes recibidos de los CEIm implicados (seleccionar el texto u opción que proceda),

Emite un DICTAMEN FAVORABLE para la realización de dicho estudio en España en aquellos centros que hayan emitido un informe favorable sobre los aspectos locales.

Que el Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, de 4 de diciembre, y su composición actual es la siguiente:

- **Presidenta:** Dra. Caridad Tapia Collados, Jefe de Sección de Pediatría en el Hospital General Universitario de Alicante
- **Vicepresidenta:** Dra. Sofía Lorenzo García. Facultativo Especialista en Análisis Clínicos en el Hospital General Universitario de Alicante.
- **Secretario:** Dr. Luis Hernández Blasco. Facultativo Especialista en Neumología en el Hospital General Universitario de Alicante.
- y **Vocales:**
  - Dra. Cristina Alenda González, Jefe de Sección de Anatomía Patológica y Directora Científica de Bíobanco en el Hospital General Universitario de Alicante y miembro de la Comisión de Investigación.
  - Dra. Amparo Burgos San José, Facultativo Especialista en Farmacia Hospitalaria del Hospital General Universitario de Alicante.
  - Dr. Mariano Esteban Fontecha, Facultativo Especialista y Jefe de Sección de UCI del Hospital General Universitario de Alicante.
  - Dña. Sonia Balboa Esteve, Enfermera en el Servicio de Medicina Preventiva en el Hospital General Universitario de Alicante.
  - Dr. José Antonio Monge Argiles, Facultativo Especialista en Neurología en el Hospital General Universitario de Alicante.
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- Dra. Paloma Vela Casasempere, Jefa del Sección de Reumatologla en el Hospital General Universitario de Alicante.
- Dra. Ana María Palacios Marqués, Jefa de Sección de Obstetricia y Ginecología en el Hospital General Universitario de Alicante.
- Dr. Eduardo Muñoz de Bustillo, Facultativo Especialista de Nefrología en el Hospital General Universitario de Alicante.

- y **Miembro Lego:**

- D. José Diego Espadas Ruiz, Miembro de la Asociación AFA {Asociación de Alzheimer de Alicante) Alicante.

Lo que firmo en Alicante, a 30 de junio de 2021.

Firmado por Luis Manuel Hernandez Blasco - 21424371D **el** 01/07/2021 14:28:43

Fdo : O_ Luis Hemández Blasco