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Intravenous pegylated liposomal prednisolone outperforms intramuscular methylprednisolone in treating rheumatoid arthritis flares: A randomized controlled clinical trial

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ABSTRACT

Glucocorticoids (GCs) are potent anti-inflammatory drugs but their use is limited by systemic exposure leading to toxicity. Targeted GC delivery to sites of inflammation via encapsulation in long-circulating liposomes may improve the therapeutic index. We performed a randomized, double-blind, active-controlled, multi-center study in which intravenously (i.v.) administered pegylated liposomal prednisolone sodium phosphate (Nanocort) was compared to equipotent intramuscular (i.m.) methylprednisolone acetate (Depo-Medrol®; i.e. a current standards-of-care for treating flares in rheumatoid arthritis patients). We enrolled 172 patients with active arthritis who met all eligibility criteria, eventually resulting in 150 patients randomized in three groups: (1) Nanocort 75 mg i.v. infusion plus i.m. saline injection; (2) Nanocort 150 mg i.v. infusion plus i.m. saline injection; and (3) Depo-Medrol® 120 mg i.m. injection plus i.v. saline infusion. Dosing in each group occurred at baseline and on day 15 (week 2). Study visits occurred at week 1, 2, 3, 4, 6, 8 and 12, to assess both efficacy and safety. The primary endpoint was the "European League Against Rheumatism" (EULAR) responder rate at week 1. Safety was determined by the occurrence of adverse events during treatment and 12 weeks of follow-up. Treatment with Nanocort was found to be superior to Depo-Medrol® in terms of EULAR response at week 1, with *p*-values of 0.007 (good response) and 0.018 (moderate response). Treatments were well tolerated with a comparable pattern of adverse events in the three treatment groups. However, the Nanocort groups had a higher incidence of hypersensitivity reactions during liposome infusion. Our results show that liposomal Nanocort is more effective than Depo-Medrol® in treating patients with rheumatoid arthritis flares and has similar safety. This is the first clinical study in a large patient population showing that i.v. administered targeted drug delivery with a nanomedicine formulation improves the therapeutic index of glucocorticoids.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease leading to disability when insufficiently controlled [1]. Glucocorticoids (GC) can be highly effective in treating joint inflammation, which is confirmed by the 2019 update of the EULAR treatment

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recommendations for RA [2], as Recommendation 6 states: "*Short-term GC should be considered when initiating or changing conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible*". Although the added efficacy of GC when combined with csDMARDs is well established, their systemic application is limited because of the occurrence of adverse effects (AE), including osteoporosis, insulin resistance, easy skin bruising, increased risk of serious infections and cardiovascular events. A recent EULAR task force focused on the risk of harm related to GC treatment, not only on how this depends on drug characteristics (such as dose, duration of exposure and potency of the prescribed drug) but also on patient-specific characteristics [3]. In addition, poor localization in inflamed areas (i.e. the preferred site of action) limits the usefulness of systemic GC in patients, and this requires frequent administration of GC to attain adequate therapeutic benefit and thus the occurrence of side effects [4].

Several lines of investigation have been pursued to improve the therapeutic index of small molecule agents, one of these being targeted delivery of nanoparticles and macromolecules upon intravenous (i.v.) administration, making use of the enhanced permeability and retention (EPR) effect. The EPR effect is a universal phenomenon seen to a variable degree in solid tumors (where it has been studied most extensively), but also in inflammatory lesions enabling drugs bound to nanoparticles and macromolecules to extravasate and preferentially accumulate at these sites, after which the drug is released and can exert its effect [5–7]. Interestingly, Maeda et al. showed in 2012 that the EPR effect in tumor tissues can be enhanced and/or become less heterogenic if inflammatory mediators are involved, indicating that the acute phase of inflammation is a good predictor of target site accessibility [8]. This data meanwhile suggests more effort should be done to capitalize on the EPR in inflammatory diseases with new nanoparticulate drug products [9].

The most straightforward strategy to achieve EPR-based targeted delivery for GCs to sites of inflammation is encapsulation in so-called long-circulating liposomes (LCL) [10]. This approach has proven to be highly effective in preclinical studies with experimental animal models of arthritis [11,12] and other inflammatory diseases [13,14]. Clinical studies with identical radiolabeled LCL, but without encapsulated drug, have shown that the approach of selective GC delivery to arthritic joints by employing LCL also applies to humans [15].

We previously performed a Phase 2a study in 22 RA patients showing that a single infusion of GC encapsulated in LCL (referred to as Nanocort) results in a temporary but strong suppressive effect on joint inflammation, with a clear dose-relationship and with a maximum benefit at 150 mg prednisolone phosphate [16]. While Nanocort has been evaluated in small clinical studies in other diseases [17–19], a larger clinical study with a head-to-head comparison to standard-of-care has never been done. We here present the results obtained in 150 patients with active RA, evaluating the efficacy and safety of Nanocort (i.v. administered as two infusions of 75 or 150 mg 2 weeks apart) versus two equipotent doses of 120 mg Depo-Medrol®, which is a current standard-of-care for treating patients with RA flares. Depo-Medrol features methylprednisolone - a 1.25 times more potent glucocorticoid than prednisolone, which is why a dose of 120 mg was chosen as comparator to the 150 mg Nanocort study dose [20].

Our results exemplify the potential of using passively targeted nanomedicine formulations for improving GC delivery and efficacy.

2. Materials and methods

2.1. Design, patients and selection criteria

The study was conducted at 21 sites in the Netherlands and Belgium. The study is registered in ClinicalTrials.gov under number NCT02534896 and complies with the Declaration of Helsinki. The ethical committees of the UMC Utrecht and University Leuven approved the study with subsequent sanctioning of all participating hospitals; all patients signed informed consent before entering the study.

The study population consisted of male and female patients (≥18 years old) with active RA according to the revised 2010 ACR criteria [21], who were experiencing a flare/exacerbation defined as recently switched from a period with well-documented remission or low disease activity to active disease as defined by a Disease Activity Score [22] (DAS 28) ≥ 3.2 This documentation was either based on available detailed DAS28 values (increase in DAS28 > 1.2 or >0.6 if DAS28 ≥ 3.2 compared to last DAS28 measurement; maximum 6 months before), or on a clear description of the previous low disease state by the treating physician (maximum 6 months before). The increase in DAS values had to be related to RA disease activity.

Exclusion criteria included inflammatory joint disease other than RA, a history of multiple thrombotic events, abnormal renal, liver or hematological tests, current pregnancy, breastfeeding, infections or malignancies, clinically severe or unstable medical conditions and endocrine disorders. Oral, rectal or injectable GCs were not permitted within 8 weeks prior to study entry, while defined topical steroids were allowed.

2.2. Study procedures and medication

In total 172 patients were enrolled of which 150 patients were randomized in a 1:1:1 ratio and stratified by site to receive Nanocort 75 mg i.v. plus i.m. saline, Nanocort 150 mg intravenous (i.v.) plus intramuscular (i.m.) saline, or Depo-Medrol (methylprednisolone acetate) 120 mg i.m. (equipotent to the 150 mg dose Nanocort) plus i.v. saline. Initially 330 enrolled patients were planned, however due to slow recruitment the trial was terminated early. The study was performed in a double blind, double dummy fashion. Participants, physicians and outcomes assessors were blinded. Each patient received an infusion and an i.m. injection containing either an active treatment or a dummy treatment. Opaque i.v. lines, sleeved bags and opaque syringes were used to maintain blinding. The preparation of the infusion and i.m. injection was done by an independent unblinded person (pharmacist or designated person) in order to keep the Investigator and other site personnel blinded. The maximum dose level of 150 mg prednisolone in this study was based on the standard dose of 120 mg methylprednisolone frequently used as bridging therapy to treat short-term flares of active RA [23], corrected for the 1.25-fold higher potency of methylprednisolone.

Randomization of the patients was performed by an Interactive Web-based Randomization System (IWRS) by an independent party. On Day 1 and Day 15 patients received an i.v. infusion of Nanocort (75 or 150 mg) and an i.m. injection of saline or they received an i.m. injection of Depo-Medrol (3 ml) and 500 ml normal saline (as placebo) as i.v. infusion in the same visit.

The i.v. infusion (either Nanocort/Placebo) was administered over approximately 2.5 h, with an increasing infusion rate over the whole infusion period. In case of an infusion related reaction, the infusion rate could be modified.

2.3. Assessments

After baseline, patients were assessed weekly up to 4 weeks, thereafter biweekly up to 12 weeks. Each visit included clinical evaluation, assessment of the disease activity, vital signs, safety assessments, HAQ, SF-36, FACIT-F and blood sampling. The disease activity was measured by the same assessor using the Disease Activity Score (DAS28 ESR) and Visual Analogue Scale (VAS), and the response to therapy, using the European League Against Rheumatism (EULAR) criteria. The patient VAS pain and RA activity was captured by patient on Day 2, 4, 6 and 16, 18 and 20 in a diary. In case a moderate EULAR response could not be reached, another therapeutic intervention could be started after 2 weeks. In a subset of patients exploratory pharmacokinetic data was collected by measuring liposomal prednisolone phosphate in plasma

besides free (released) prednisolone.

2.4. Statistics

As advised during a meeting with the European Medicines Agency about this study, EULAR response (good and moderate combined) at week 1 (Day 8) was chosen to be the primary outcome. Intention-to-treat analyses included all randomized patients starting treatment; furthermore, a supportive per-protocol analysis of the primary end point was performed. There were three key secondary endpoints were: 1) EULAR response (good) rate at Day 8, 2) EULAR response (good and moderate combined) rate at Day 15, and 3) EULAR response (good) rate at Day 15. The primary and key secondary analyses were completed using Hochberg and gatekeeping methodology [24] and also analyzed using simple chi-square tests. Due to early termination of the study, the sample size was less than planned, however the pre-determined statistical analyses plan was followed. As a result of the lower number of patients, the statistical power could be inadequate for the planned gatekeeping methodology, and therefore standard hypothesis testing methods were also performed.

DAS28 was analyzed at Week 1, 2, 3, 4, 6, 8 and 12. If DAS28 scores were approximately normally distributed by visual inspection, then DAS28 scores were analyzed using analysis of covariance (ANCOVA), including baseline scores and study site as covariates.

Clinical data were expressed as the mean ± SD unless stated otherwise. Several other secondary efficacy measures were analyzed, such as individual components of the DAS, patient assessment for pain, physician assessment for disease activity. Safety and pharmacokinetic analyses were descriptive only. Shift tables and shift plots were used to evaluate changes in clinical laboratory test results at different time points compared to baseline values. Patients whose test values were outside specific ranges and other abnormalities in physical examination, ECG and vital signs were evaluated.

3. Results

3.1. Baseline demographic and clinical characteristics

Fig. 1 provides a summary of patient disposition by treatment group and overall. Of the 172 enrolled patients, 150 were randomized approximately 1:1:1 into the 75 mg Nanocort ($N = 49$), 150 mg Nanocort ($N = 52$) and Depo-Medrol® ($N = 49$) groups. 96% of the patients completed the study; the 75 mg Nanocort group had 4 patients who discontinued the study, compared to single patients who discontinued in the other groups. Adverse events or intercurrent illness were the primary reasons for discontinuation.

Mean duration of disease was comparable across the three groups 9,3 years in the 75 mg Nanocort group, 10,0 years in the 150 mg Nanocort group and 10,5 in the Depo-Medrol arm. Comorbidities at baseline were similar among the treatment groups, though osteoarthritis was more prevalent in the Nanocort groups (15–16% respectively) than in the Depo-Medrol group (4%). Stable hypertension was more prevalent in the Depo-Medrol® group (31%) versus Nanocort groups (15–16% respectively), as was prevalence of gastrointestinal disorders (25% vs 10–19% respectively) and of nervous system disorders (27% vs 13–16% respectively) (see Supplementary Information).

3.2. Primary endpoint

The primary analysis involved two comparisons: 1) Nanocort 150 mg vs. Depo-Medrol®, and 2) Nanocort 75 mg vs. Depo-Medrol®. Nanocort was considered more effective since both primary endpoint comparisons resulted in $\alpha_p \leq 0.045$, as per Hochberg methodology (Table 1). These results demonstrated superiority of 150 mg and 75 mg Nanocort over Depo-Medrol® with respect to EULAR Response (Good/Moderate) at Week 1 (Day 8). The primary analysis was designed based on the limited previous clinical trial data on Nanocort 150 mg versus Depo-Medrol®. With the intended 100 subjects per treatment arm and assuming an EULAR responder rate at Day 8 in the Depo-Medrol® arm of 25%, the power for this study to show a statistically significant difference of at least 23% was 92% and 87% for the two primary hypotheses with a two-

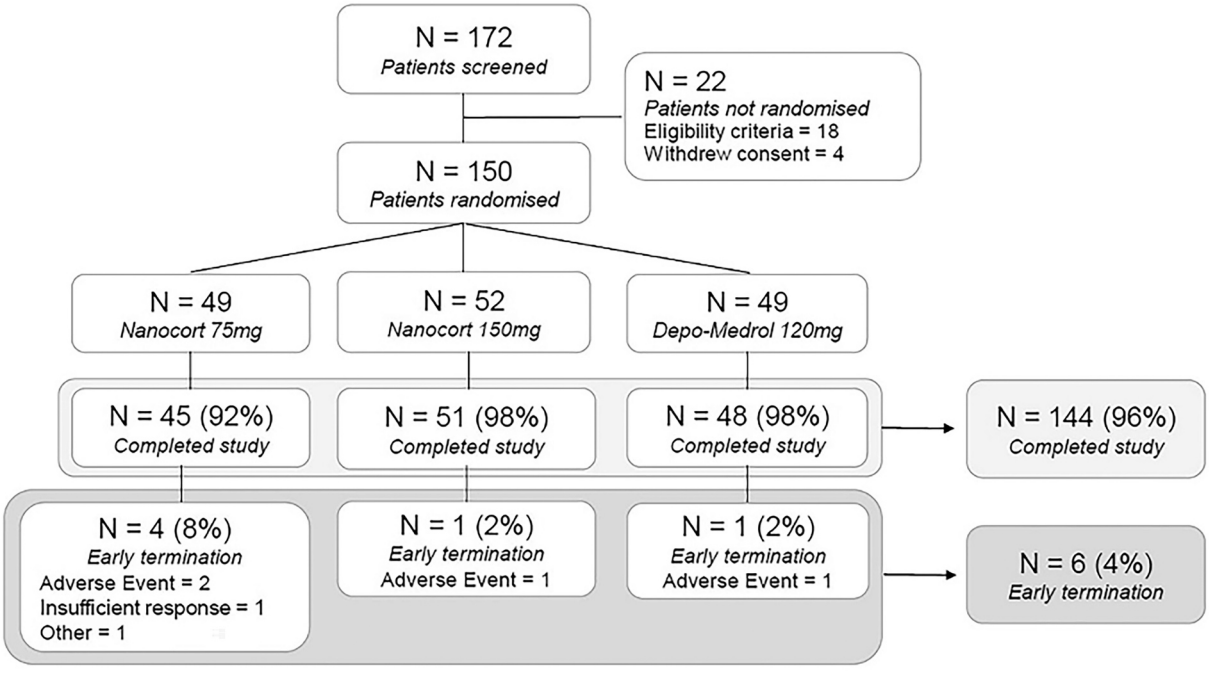

Fig. 1. Patient disposition.
This figure displays the patient flow in the study, the number of patients screened and randomized, and the reasons for the patients to drop out the study.

Table 1
Primary Endpoint and key secondary Endpoints (EULAR responders).

EULAR responder		Nanocort 75 mg $N = 49$	Nanocort 150 mg $N = 52$	Depo-Medrol 120 mg $N = 49$	*P*-value 75 mg vs Depo	*P*-value 150 mg vs Depo
Good/Moderate	**Yes**	**42 (85.7%)**	**45 (90.0%)**	**32 (66.7%)**	**0.018**	**0.007**
At Week 1 (Day 8)	**No**	**7 (14.3%)**	**5 (10.0%)**	**16 (33.3%)**		
Good/Moderate	Yes	42 (95.5%)	43 (93.5%)	42 (95.5%)	0.960	0.339
At Week 2 (Day 15)	No	2 (4.5%)	3 (6.5%)	2 (4.5%)		
Good	Yes	21 (42.9%)	26 (52.0%)	10 (20.8%)	0.028	0.003
At Week 1 (Day 8)	No	28 (57.1%)	24 (48.0%)	38 (79.2%)		
Good)	Yes	24 (54.5%)	33 (71.7%)	21 (47.7%)	0.573	0.374
At Week 2 (Day 15)	No	20 (45.5%)	13 (28.3%)	23 (52.3%)		

In bold the number and percentage of Good and Moderate responders according to the EULAR criteria are displayed for each of the three treatment groups 1 week after the first drug administration (primary endpoint).

sided confidence level of 0.045 and 0.0225 (Hochberg's correction), respectively. Even though the study enrollment was terminated prematurely, the primary endpoint was still achieved, indicating a stronger drug effect than initially estimated.

3.3. Key secondary endpoints

At Week 1 the EULAR good responder rate at Week 1 (Day 8) on Nanocort was also significantly higher as both endpoint comparisons resulted in p-value ≤ 0.045. The differences in EULAR both good/moderate and good responder rates at Week 2 (Day 15, before the second infusion), however, did not reach statistical significance (see Table 1).

3.4. Other secondary endpoints

Other secondary endpoints supported the primary endpoint results, showing significant differences in tender joint counts through Week 6; Pain through Week 3 and HAQ through Week 4. Significant or clinically meaningful improvements were also found in other EULAR response evaluations, such as VAS, ACR20/50/70, SF-36 and FACIT-F assessments (see Supplement). In Fig. 2, "good" EULAR response is depicted. Fig. 4 shows the VAS Pain score, showing the rapid therapeutic response to Nanocort.

3.5. Safety results

Table 2 shows that the numbers of patients reporting at least one adverse event (AE) in each of the treatment groups was generally comparable: 42 (86%), 46 (89%) and 39 (80%), respectively, for the 75 mg Nanocort, 150 mg Nanocort and Depo-Medrol groups. The 150 mg Nanocort group had the fewest number of patients reporting a serious or severe AE (10%). The number of patients reporting an adverse event during the i.v. infusion was higher in the Nanocort groups (25%) versus the Depo-Medrol group (8%), all events resolved without sequelae.

Table 2
Summary of adverse events.

Patients with at least 1 AE	Nanocort 75 mg $N = 49$	Nanocort 150 mg $N = 52$	Depo-Medrol 120 mg $N = 49$
Any Adverse Event (AE)	42 (85.7%)	46 (88.5%)	39 (79.6%)
Serious AE (SAE)	4 (8.2%)	1 (1.9%)	2 (4.1%)
Severe AE	5 (10.2%)	4 (7.7%)	7 (14.3%)
AE Related to i.v. Infusion	3 (6.1%)	5 (9.6%)	3 (6.1%)
SAE Related to i.v. Infusion	1 (2.0%)	1 (1.9%)	0 (0.0%)
i.v. Infusion Related AE Leading to Drug Withdrawal	1 (2.0%)	2 (3.8%)	0 (0.0%)
AE Starting During i.v. Infusion	12 (24.5%)	13 (25.0%)	4 (8.2%)
AE Starting within 24 h of End of i.v. Infusion	18 (36.7%)	17 (32.7%)	18 (36.7%)
AE Related to i.m. Injection	0 (0.0%)	3 (5.8%)	2 (4.1%)
SAE Related to i.m. Injection	0 (0.0%)	1 (1.9%)	0 (0.0%)
i.m. Injection Related AE Leading to Drug Withdrawal	0 (0.0%)	1 (1.9%)	0 (0.0%)
AE Leading to Concomitant Medication	15 (30.6%)	24 (46.2%)	16 (32.7%)
AE Requiring Treatment	21 (42.9%)	25 (48.1%)	16 (32.7%)

In Table 2 all adverse events per treatment group are displayed. The relation to the i.v. infusion or i.m. injection is also listed.

When comparing the number of AEs within 24 h after i.v. infusion, these were comparable in all groups (see Table 2). There was a low incidence of AEs related to the i.m. injection: no patients in the 75 mg Nanocort group, 3 in the 150 mg Nanocort and 2 in the Depo-Medrol group. No clinically significant changes in any laboratory parameter were observed in any group. Also the vital signs, physical exam and 12-lead ECG evaluations did not show clinically significant changes.

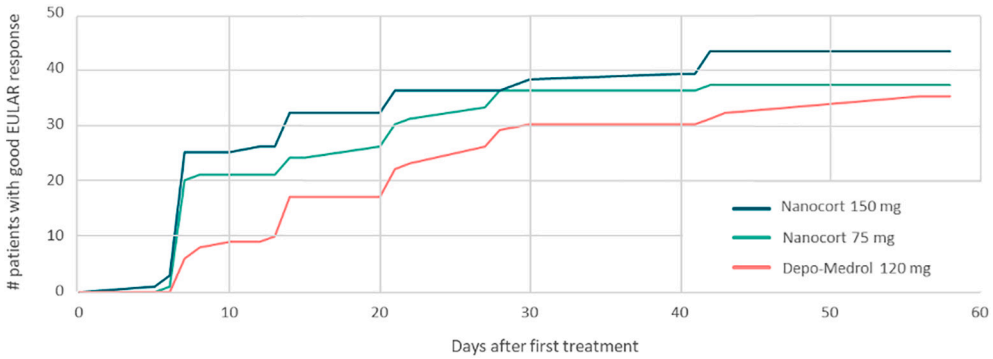

Fig. 2. Cumulative therapeutic response. For each treatment group, the cumulative number of patients is shown that achieve a good EULAR response during treatment and follow up. After the first treatment half of the patients receiving the high dose of Nanocort show a good EULAR response. Even the Nanocort low dose group performs twice better than the control group. While this difference in outcome gradually becomes less pronounced after the second treatment and in further follow up, both Nanocort treatments continue to show a better result.

3.6. Pharmacokinetics

In contrast to the well-known PK behaviour of free corticosteroids, encapsulation in LCL results in very high plasma levels and a long half-life. The extremely high plasma concentration of 50 microgram/mL prednisolone phosphate after 150 mg points to a very small volume of distribution, which is not much larger than the plasma volume itself. Also, the half-life is long (almost three days), as opposed to only a few hours widely reported for free prednisolone. This data is in line with what is observed for other LCL-based drug products [25]. The corresponding curves are shown in Fig. 5, which also shows that some free prednisolone enters the circulation upon LCLP administration, presumably as a result of liposomal clearance by liver macrophages and lymphoid organs [12]. However, compared to the encapsulated prednisolone phosphate concentrations, the systemic exposure to free prednisolone is proportionally very low, and most marked only in the first week after LCLP administration.

4. Discussion

The current study was designed as a phase 3 trial in which a novel and innovative PEG-liposomal GC product (Nanocort) is compared with one of the GC standard-of-care options for active RA with the aim to achieve an improved efficacy to safety ratio. The comparator standard-of-care chosen here was 120 mg of a systemic (i.m.) methylprednisolone depot formulation (Depo-Medrol), and this treatment was compared with an equipotent 150 mg i.v. dose Nanocort, both administered twice with a 2-week interval to achieve a long-term effect. Nanocort was also dosed at a lower level of twice 75 mg to assess a possible dose-effect relationship.

It was hypothesized that EPR-mediated targeted delivery GC into arthritic joints would result in a much higher tissue concentration, leading to stronger efficacy [5–8]. While this unique property of inflamed target site delivery of GC by LCL has been shown in several studies and in several manifestations of inflammatory disease, thus far these studies were mostly preclinical or performed in small patient populations [11,12,16–18]. The current study is the first to show that this therapeutic approach can provide a clinical benefit in a large cohort of patients.

Nanocort appears to provide the strongest benefit in the early phase of the intervention leading to more good responders in the first weeks after treatment (Fig. 2). Nanocort showed a pronounced and early beneficial treatment effect (Figs. 2 and 3), with the higher dose having the largest effect. Patient perceived pain, one of the most important symptoms for the patient, improved faster and better for both Nanocort doses compared to Depo-Medrol® (Fig. 4). After 6–8 weeks, efficacy results became comparable among treatment arms. A second injection seems to be needed for sustained response.

With regard to safety, the frequency of AEs reported is comparable across treatment arms, with most AEs being mild and with nausea, headache and common cold among the most frequently reported. While generally more deleterious GC-related adverse effects at the level of metabolism, endocrinology and immunology were infrequently seen, these effects are not typically expected within the short term (i.e. below 12 weeks) and in view of the relatively low systemic GC exposure resulting from both Depo-Medrol® and Nanocort (see Supplementary Information). Likewise, Nanocort is well-tolerated, with improved efficacy, especially in the early phase of the intervention.

Special attention needs to be paid to the potential occurrence of hypersensitivity reactions upon Nanocort infusion, as liposomes are particulates from an immunological point of view [26]. In this study we did not opt for pretreatment with antihistamines and antipyretics, but for future studies pretreatment could be considered to minimize frequency and severity of these reactions.

A limitation of the study was that direct measurement of delivered drug in inflamed joints could not be done. It may, however, be postulated that the ability of LCL to keep the full dose of GC circulating in blood for a very long period of time strongly drives inflamed target lesion accumulation given that EPR is present at these sites. Indeed, the very rapid onset of the therapeutic effect points to a quick release on the target site, most likely induced by a significant population of locally present macrophages and other inflammatory key cells [11]. At the same time it must be pointed out that the glucocorticoid quantity in the Depo-Medrol control medication is intended to be an intramuscular depot from which free drug is slowly released with only low, but persistent drug concentrations as a consequence.

It is tempting to speculate that high concentrations of prednisolone delivered by LCL to the inflamed target sites may allow for beneficial nongenomic GC actions besides their well-know effects at the level of steroid-responsive genes. These nongenomic effects are typically seen with high local GC tissue concentrations, which cannot be achieved by the current low-dose standard-of-care and for which local treatment or targeted joint delivery is instrumental [20].

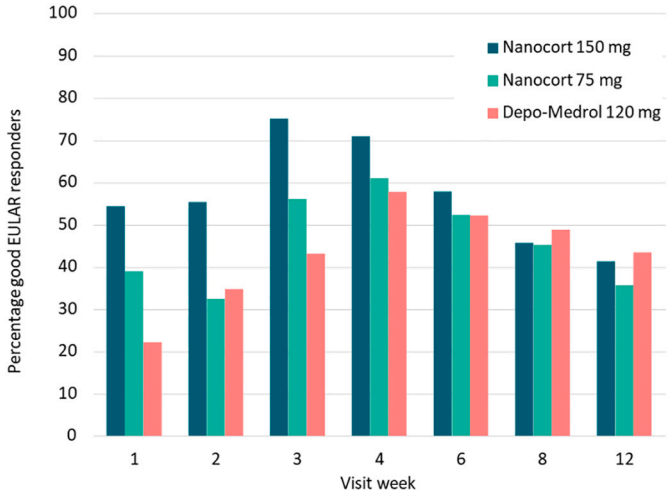

Fig. 3. Individual therapeutic response.
Percentage good EULAR responders at each visit during treatment follow up. The most pronounced difference in efficacy between Nanocort treatments and the control is observed in the first three weeks.

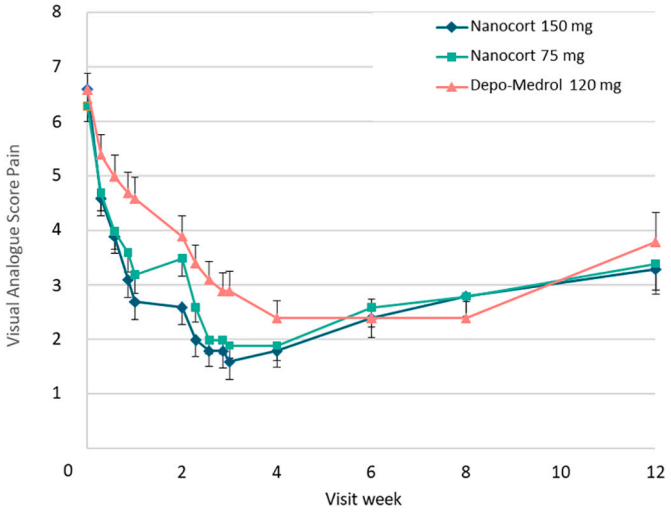

Fig. 4. Pain reduction.
Patient pain scores obtained during visits and reported in between, showing how rapid pain reduction was achieved in patients treated with Nanocort. Within one week pain scores dropped more than twofold as compared to baseline both with the high and the low dose of Nanocort.

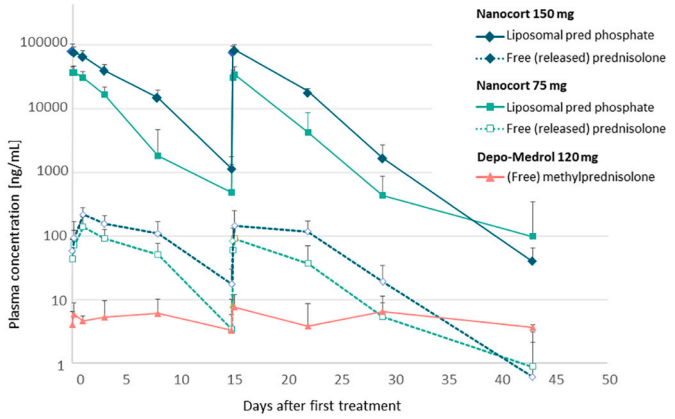

Fig. 5. Pharmacokinetic analysis.
Plasma concentration – time curves for all three treatment groups obtained in a subpopulation of patients. The upper solid green curves are showing the concentrations of liposomal encapsulated prednisolone phosphate. While these very high liposomal AUCs can be assumed to drive target localization and activity upon release from the liposomes there, in the circulation the drug remains encapsulated and is not available for activity at these high concentrations. The fraction of free, active drug that is apparently released back in the circulation is shown as the dashed green curves and these concentrations are roughly 500-fold lower in the ng/mL range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In conclusion, the results of this larger clinical study point to the therapeutic potential of intravenous GC targeting to inflamed joints using LCL. The treatment seems to result in a favorable benefit-risk ratio as compared to current GC standard-of-care therapy with fast, pronounced and sustained efficacy observed in a substantial number of patients. I.v.-targeted delivery of GC using Nanocort may lead to the first LCL-based drug product specially developed for human use capitalizing on the EPR effect in inflammatory disease.

Declaration of Competing Interest

J.M. Metselaar, C.H. Wortel are affiliated to Enceladus Pharmaceuticals.

Consultant: J.W.J. Bijlsma to SUN, L.M. Middelink to Accelovance and Enceladus.

Employee: C.H. Wortel employee of Accelovance, S.Yao, M. Kothekar, A. Raut employees of Sun.

R. Westhovens: Advisory Board and Speakers Bureau Celltrion and Galapagos/Gilead.

H.E. Vonkeman, R. Bos, T. Lammers: none relevant to this work.

J.M. van Laar: honoraria from Arxx Tx, Boehringer Ingelheim, Gesyntha, Eli Lilly, Sanofi Genzyme, Leadiant, grants and honoraria from Roche, grants from Astra Zeneca, grants from MSD, grants from Thermofisher.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jconrel.2021.12.007.

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