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# Efficacy and tolerance of rifampicin–linezolid compared with rifampicin–cotrimoxazole combinations in prolonged oral therapy for bone and joint infections

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## Abstract

Both linezolid and cotrimoxazole are antibiotics that are well suited for oral therapy of bone and joint infections (BJI) caused by otherwise resistant Gram-positive cocci (GPC) (resistance to fluoroquinolones, maccolides, betalactamines). However, in this context, no data are currently available regarding the safety and tolerance of these antibiotics in combination with rifampicin. The objective of this study was to compare the efficacy and safety of a combination of rifampicin and linezolid (RLC) with those of a combination of rifampicin and cotrimoxazole (RCC) in the treatment of BJI. Between February 2002 and December 2006, 56 adult patients (RLC, *n* = 28; RCC, *n* = 28), including 36 with infected orthopaedic devices (RLC, *n* = 18; RCC, *n* = 18) and 20 with chronic osteomyelitis (RLC, *n* = 10; RCC, *n* = 10), were found to be eligible for inclusion in this study. Patients who discontinued antibiotic therapy within 4 weeks of commencing treatment were considered to represent cases of treatment failure and were excluded. Rates of occurrence of adverse effects were similar in the two groups, at 42.9% in the RLC group and 46.4% in the RCC group (p = 1.00), and led to treatment discontinuation in four (14.3%) RLC and six (21.4%) RCC patients. Cure rates were found to be similar in the two groups (RLC, 89.3%, RCC, 78.6%; p = 0.47). Prolonged oral RLC and RCC therapy were found to be equally effective in treating patients with BJI caused by resistant GPC, including patients with infected orthopaedic devices. However, the lower cost of cotrimoxazole compared with linezolid renders RCC an attractive treatment alternative to RLC. Further larger clinical studies are warranted to confirm these preliminary results.

**Keywords:** Chronic osteomyelitis, cotrimoxazole, linezolid, orthopaedic device, rifampicin
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## Introduction

Prolonged therapy with a combination of antimicrobial agents that reach bone concentrations higher than the minimal inhibitory concentration for the pathogens concerned is usually recommended for the treatment of osteomyelitis [1]. In the treatment of bone and joint infections (BJI) caused by Gram-positive cocci (GPC), clinicians are confronted with therapeutic problems arising from the resistance of pathogens, the lack of efficacy of some antibiotics in bone infections and antibiotic toxicity during prolonged therapy. Rifampicin has been shown to be effective in the treatment of staphylococcal osteomyelitis, especially in patients with an infected orthopaedic device, because of its capacity to eradicate slow-growing bacteria that appear at the chronic phase of osteomyelitis and bacteria adherent to prosthetic material in infected joints [2–4]. However, although rifampicin exhibits anti-staphylococcal and anti-streptococcal activity, the emergence of bacterial resistance when it is used alone is of concern [5–7].

There are currently few or no published data on the efficacy and safety of the other available anti-GPC agents, which include fusidic acid, cyclines, pristinamycin, lipopeptides and quinupristin–dalfopristin for treating osteomyelitis [2,8–10]. Moreover, some antibiotics with anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity, such as glycopeptides and lipopeptides, are only available as a parenteral formulation. Linezolid, the first oxazolidinone agent, is an attractive alternative in this setting [11–17]. However, there is concern

regarding the emergence of linezolid-resistant strains [18–24] and the bone marrow and neurological toxicity induced by linezolid therapy [25–27]. *In vitro* studies have recently shown that a combination of linezolid and rifampicin prevents the emergence of rifampicin-resistant mutants [28].

Cotrimoxazole is another antimicrobial agent which has been used for many years and which is active against some *Streptococcus* spp. and most *Staphylococcus* spp., including MRS [29,30]. Recent research has assessed the increasing susceptibility of MRSA strains to cotrimoxazole [7,31–34], which appears to offer an effective and economic alternative for the treatment of MRS-related infections. However, few studies have analysed the impact of this antibiotic in the treatment of BJI [35,36].

The objective of the present retrospective study was to compare the outcomes of prolonged therapy with a rifampicin and linezolid combination (RLC) with those of a rifampicin and cotrimoxazole combination (RCC), in terms of efficacy and safety, in the treatment of patients with chronic osteomyelitis caused by GPC.

## Materials and methods

### Patients

A retrospective study was carried out examining the chart records of patients with chronic osteomyelitis lasting > 30 days. Patients included in this study had been treated with either RLC or RCC for > 4 weeks in two separate hospitals which work together as a referral centre in northern France: the Dron Hospital, Tourcoing, and the Roger Salengro Hospital, Lille. In these two centres, the choice of antibiotic regimens was based on protocols established 10 years ago: microbiological samples were collected from patients prior to administration of an empirical parenteral antibiotic treatment for 5–7 days consisting of a glycopeptide-associated or not to a third-generation cephalosporin.

In light of the microbiological results, patients with GPC infections were subsequently given our standard treatment of a combination of rifampicin and levofloxacin unless they were known to be intolerant to fluoroquinolones, were infected by fluoroquinolone-resistant GPC strains or had a mixed infection of GPC and Gram-negative strains. This second group, which constitutes the subjects of this paper, were treated either with RLC (28 patients treated during the period February 2002 to December 2004) or with RCC (28 patients treated during January 2005 to December 2006). This change of drug regime represented a response to increasing reports of linezolid-induced toxicity. The RLC patients were also part of a cohort of 66 patients included in a previous study investigating the efficacy of prolonged linezolid treatment in chronic osteomyelitis [25].

The drug regime was as follows. Patients in the RLC group were given linezolid (600 mg twice daily) and rifampicin (10 mg/kg twice daily, maximum 900 mg twice daily), administered i.v. for the first week and subsequently orally, and were subject to weekly haematological monitoring. Patients in the RCC group were given cotrimoxazole (sulfamethoxazole 40 mg/kg/day, trimethoprim 8 mg/kg/day) and rifampicin (10 mg/kg/12 h, maximum 900 mg/12 h) according to the same protocol, except for three patients who refused to be hospitalized and whose treatment was initiated orally.

There were no changes in surgical protocols during the two treatment periods. Patients with chronic prosthetic joint infection underwent revision of the implants with one- or two-stage exchange with the use of a spacer according to the extent of infection, determined perioperatively. Implant retention or permanent removal of the implant was decided in cases of poor clinical condition, contraindicating any invasive surgery or further re-implantation. In cases of osteosynthesis infection, prosthetic material was removed unless the patient was inoperable. Patients were followed up for ≥ 12 months after the end of treatment (EOT).

Only patients with documented bacteriological osteomyelitis based on intraoperative samples and/or joint aspiration cultures were enrolled in the study. Osteomyelitis was diagnosed according to the presence of: fever > 38 °C; inflammation or purulent discharge in the area of osteosynthesis devices; biological inflammatory syndrome (erythrocyte sedimentation rate > 50 mm/h and C-reactive protein > 10 mg/L); radiological evidence of loose osteosynthesis devices or prostheses (luxation or pseudoarthrosis); evidence of bone infection on plain radiography; leukocytes on direct examination of intraoperative samples, and/or positive Gram-stained smear.

The following demographic parameters were analysed: age; sex; diabetes mellitus status; type of osteomyelitis; presence of an infected orthopaedic device; presence of a fistula, and type of surgical intervention.

Patients gave their consent for chart review performed during follow-up consultations. No ethical approval for chart review studies is currently required by our local institutional ethical review board.

### Outcome

In patients with an orthopaedic device, remission of infection was defined by a functional pain-free implant associated with C-reactive protein values of < 10 mg/L and an absence of radiological signs of either loosening or pseudoarthrosis. In patients with chronic osteomyelitis, remission of infection was defined by the absence of local signs of infection, puru-

lent discharge or radiological signs of active osteomyelitis (e.g. bone destruction, new intramedullar or skin and soft-tissue abscesses, fracture) and C-reactive protein values of < 10 mg/L. In both cases these factors were determined after a post-treatment period of ≥ 12 months. Failure was defined by any other outcome, lack of data on follow-up or early discontinuation of antibiotic regimen (< 4 weeks) because of toxicity.

### Follow-up

Biological tolerance to therapy was evaluated focusing specifically on haematological, hepatic and renal parameters during treatment. Anaemia was defined as a haemoglobin value of < 9.0 g/dL, leukopenia as total leukocyte count of $< 4 \times 10^9$/L, and thrombocytopenia as a platelet count of $< 100 \times 10^9$/L. Clinical tolerance of therapy was evaluated based on neurological signs, skin allergy and gastrointestinal disturbances.

Patient clinical and biological parameters were followed for 4 weeks after discharge from hospital, then at the EOT, and at 6 and 12 months thereafter. Further contacts were made via consultations or telephone. Because linezolid is not approved in France for the treatment of osteomyelitis and cannot be prescribed for > 28 consecutive days, each patient gave consent after information about the potential toxicity of linezolid had been provided by a senior physician.

### Statistical analysis

Comparisons between the RLC and RCC groups were made using Fisher's exact test for categorical values and Student's *t*-test for mean values; the significance level was set at $p < 0.05$. A Kaplan–Meier analysis with log-rank test was performed to compare relapse-free survival rates at 2 years between the RLC and RCC groups.

## Results

### Clinical characteristics

All patients had chronic infections of > 30 days duration and all infections involving prosthetic material had occurred > 2 months after surgical intervention. Two patients who received RCC were considered as failures and rejected from the study: one patient had to discontinue RCC treatment after 6 days because of a skin rash and the other died of co-morbidities during antibiotic therapy.

The clinical characteristics of the two groups were similar and are detailed in Table 1. Median hospital stay was 15 days (mean 18.0 ± 9.8 days, range 6–42 days) in the RLC group and 14 days (mean 15.4 ± 10.05 days, range 0–43 days) in the RCC group. Mean duration of therapy was 17.8 ± 7.5 weeks (range 8–36 weeks) in the RLC group and 15.4 ± 10.1 weeks (range 1–53 weeks) in the RCC group (Table 2). In both the RLC and RCC treatment groups, durations of treatment were similar in patients with prosthetic infections and patients with osteomyelitis.

**TABLE 1. Comparison of patients with chronic osteomyelitis treated with rifampicin–linezolid combination (RLC) or rifampicin–cotrimoxazole combination (RCC)**

| Characteristics | RLC patients (*n* = 28) | RCC patients (*n* = 28) | p-value |
|---|---|---|---|
| Mean age, years (range) | 57 (22–83) | 60 (22–83) | 1.00 |
| Sex, male/female | 15/13 | 16/12 | 1.00 |
| Prosthetic joints, *n* (%) | 11 (39.3) | 11 (39.3) | 1.00 |
| One-stage exchange | 3 (10.7) | 0 | 0.24 |
| Two-stage exchange | 3 (10.7) | 5 (17.9) | 0.70 |
| Debridement with retention | 4 (14.3) | 6 (21.4) | 0.73 |
| Permanent removal | 1 (3.6) | 0 | 1.00 |
| Osteosynthesis, *n* (%) | 6 (21.4) | 7 (25.0) | 1.00 |
| Removal before antibiotherapy | 6 (21.4) | 5 (17.9) | 1.00 |
| Removal during antibiotherapy | 0 | 0 | 1.00 |
| No removal | 0 | 2 (7.2) | 0.49 |
| No prosthetic material, *n* (%) | 11 (39.3) | 10 (35.7) | 1.00 |
| Long bone osteomyelitis | 5 (17.9) | 6 (21.4) | 1.00 |
| Diabetic foot osteomyelitis | 4 (14.3) | 2 (7.1) | 0.67 |
| Spondylodiscitis | 2 (7.1) | 0 | 0.49 |
| Sternitis | 0 | 2 (7.1) | 0.49 |
| Fistula, *n* (%) | 10 (35.7) | 9 (32.1) | 1.00 |
| Risk factors, *n* (%) | | | |
| Malignancy | 0 | 3 (10.7) | 0.24 |
| Steroid therapy | 1 (3.6) | 1 (3.6) | 1.00 |
| Diabetes mellitus | 8 (28.6) | 6 (21.4) | 0.76 |
| Chronic renal failure | 1 (3.6) | 1 (3.6) | 1.00 |

**TABLE 2. Duration of treatment (weeks, mean ± standard deviation) according to antibiotic regimen (rifampicin–cotrimoxazole, RCC, vs. rifampicin–linezolid combination, RLC), presence of a device[a] and surgical management**

| | RLC patients | | RCC patients | | p-value |
|---|---|---|---|---|---|
| | Mean duration | No | Mean duration | No | Mean duration |
| No device | 16.4 ± 7.9 | 11 | 15.0 ± 8.8 | 10 | 0.5971 |
| Removed/exchanged device | 18.1 ± 8.0 | 13 | 18.3 ± 16.0 | 10 | 0.5765 |
| One-stage exchange | 20.7 ± 5.8 | 3 | – | 0 | – |
| Two-stage exchange | 14.7 ± 8.3 | 3 | 14.6 ± 13.8 | 5 | 0.7857 |
| Permanent removal | 18.4 ± 9.2 | 7 | 22.0 ± 18.6 | 5 | 0.8763 |
| Retained device | 20.2 ± 10.7 | 4 | 13.2 ± 4.6 | 8 | 0.1091 |
| Total patients in group | 17.8 ± 7.5 | 28 | 15.4 ± 10.1 | 28 | |

[a]Prosthesis or osteosynthesis.
No: number of patients

### Microbiological characteristics

The most frequent pathogens were found to be methicillin-resistant staphylococci, which represented 20 of 32 (62.5%) pathogens in the RLC group and 19 of 45 (42.2%) in the RCC group. Methicillin-susceptible staphylococci were less frequent and represented four of 32 (12.5%) pathogens in

**TABLE 3. Distribution of pathogens isolated from patients treated with the rifampicin–linezolid combination (RLC) or the rifampicin–cotrimoxazole combination (RCC)**

| Pathogens | RLC group, *n* (% of total number of strains) | RCC group, *n* (% of total number of strains) |
|---|---|---|
| MRSA | 11 (34.4) | 10 (22.2) |
| MSSA | 4 (12.5) | 7 (15.6) |
| MRCNS | 9 (28.1) | 9 (20.0) |
| MSCNS | 0 (0) | 3 (6.7) |
| *Enterococcus* spp. | 5 (15.6) | 0 (0) |
| *Streptococcus* spp. | 2 (6.2) | 5 (11.1) |
| Other | 1 (3.1) | 11 (24.4) |
| Total | 32 | 45 |

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRCNS, methicillin-resistant coagulase-negative staphylococci; MSCNS, methicillin-susceptible coagulase-negative staphylococci.

the RLC group and 10 of 45 (22.2%) in the RCC group. This is detailed in Table 3. Neither community-acquired MRSA nor vancomycin-resistant *Enterococcus* spp. were detected. In both the RLC and RCC groups, all strains were susceptible to rifampicin, as well as to linezolid and cotrimoxazole, respectively. No case of acquired bacterial resistance to the antibiotic treatment was observed.

Mixed infections (GPC associated with Gram-negative bacilli or anaerobes) were noted in one patient (3.1% of pathogens) in the RLC group and in seven patients (21.7%) in the RCC group.

### Clinical outcome

Cure rates were similar in the RLC and RCC groups (89.3% and 78.6%, respectively; p = 0.47). Table 4 summarizes cure rates according to the antibiotic regimen, the presence of a device (osteosynthesis or prosthesis) and mode of surgical management.

**TABLE 4. Comparison of cure rates (no. of patients cured/no. of patients treated), according to antibiotic regimen (rifampicin–cotrimoxazole combination, RCC, vs. rifampicin–linezolid combination, RLC), presence of a device[a] and surgical management**

| | RLC patients, *n* (%) (*n* = 28) | RCC patients, *n* (%) (*n* = 28) | p-value |
|---|---|---|---|
| No device | 9/11 (82) | 9/10 (90) | 1.00 |
| Removed/exchanged device | 12/13 (92) | 7/10 (70) | 0.28 |
| One-stage exchange | 2/3 (67) | 0 | – |
| Two-stage exchange | 3/3 (100) | 4/5[b] (80) | 1.00 |
| Permanent removal | 7/7 (100) | 3/5 (60) | 0.15 |
| Retained device | 4/4 (100) | 6/8[c] (75) | 0.52 |

[a]Prosthesis or osteosynthesis.
[b]One failure concerned a patient who had to interrupt RCC 6 days after initiation for skin rash.
[c]One failure concerned a patient who died because of co-morbidities during antibiotherapy.

In the case of prosthetic joint infections, all patients would normally have had undergone one- or two-stage exchange, but in 12 patients (eight in the RCC group, four in the RLC group) co-morbidity or severe joint damage was too great to support invasive surgery and thus it was decided to retain the implant in these patients. The 2-year follow-up time-point was achieved for 26 patients in the RCC group (two patients were lost from follow-up) and 25 patients in the RLC group (two patients were lost from follow-up and a third was cured but died because of co-morbidities 18 months after the EOT).

At the 2-year follow-up point, treatment was considered to have been successful in 20 of 26 patients (76.9%) in the RCC group, and in 21 of 25 patients (84.0%) in the RLC group (p = 0.7265). There was no difference in outcome according to the microorganism isolated, the presence of infected prosthetic material, or the type of surgical management (retained vs. removed device, or, in cases of device removal, one-stage vs. two-stage exchange or permanent removal). Relapse-free survival at 2 years after EOT was similar for the RLC and RCC groups (p = 0.1831) (Fig. 1).

### Adverse events

The occurrence of adverse effects was similar in the two groups: 42.9% of RLC-treated patients and 46.4% of RCC-treated patients showed adverse reactions (Table 5). In the RLC group, median time from drug initiation and anaemia onset was 9 weeks (range 8–14 weeks), by contrast with the RCC group, in which no patients suffered from anaemia. Reversible peripheral neuropathy was recorded in one (3.6%) patient, who had to interrupt the RLC regimen after 36 weeks of treatment. In the RCC group, skin rash, elevated hepatic enzymes and gastrointestinal disturbance were reported in three, three and seven patients, respectively,

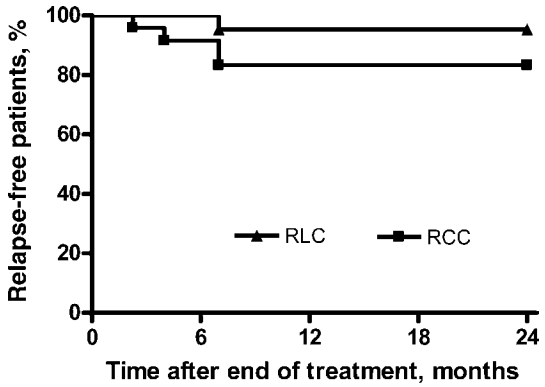


**FIG. 1.** Relapse-free survival at 2 years after end-of-treatment in the rifampicin–linezolid combination (RLC) and rifampicin–cotrimoxazole combination (RCC) groups.

**TABLE 5. Adverse events reported in patients treated with the rifampicin–linezolid combination (RLC) or the rifampicin–cotrimoxazole combination (RCC)**

| | RLC (*n* = 28) | | RCC (*n* = 28) | | |
|---|---|---|---|---|---|
| | Patients, *n* (%) | Discontinuations, *n* (%) | Patients, *n* (%) | Discontinuations, *n* (%) | p-value |
| Reversible anaemia | 4 (14.3)[a] | 3 (10.7) | 0 | 0 | 0.05 |
| Leukopenia | 0 | 0 | 2 (7.7) | 0 | 0.49 |
| Thrombocytopenia | 0 | 0 | 0 | 0 | – |
| Peripheral neuropathy | 1 (3.6) | 1 (3.6) | 0 | 0 | 1.00 |
| Headache | 2 (7.2) | 0 | 0 | 0 | 0.49 |
| Elevated hepatic enzymes | 2 (7.2) | 0 | 3 (10.7) | 1 (3.6) | 1.00 |
| Gastrointestinal disturbance | 4 (14.3) | 0 | 7 (25.0) | 3 (11.5) | 0.50 |
| Renal failure | 0 | 0 | 0 | 0 | – |
| Skin rash or pruritus | 0 | 0 | 3 (10.7) | 3 (10.7) | 0.23 |
| Total | 12[b] (42.9) | 4 (14.3) | 13[c] (46.4) | 6[c] (21.4) | 1.00 |

[a]All patients required blood transfusion.
[b]One patient experienced headache and elevated hepatic enzyme levels.
[c]Two patients experienced elevated hepatic enzyme levels in association with another adverse event (skin rash leading to drug discontinuation, or neutropenia).

with mean times from drug initiation to onset of the adverse effect of 3.2 (range 1–6), 3.3 (range 1–6) and 4.6 (range 0.3–12) weeks, respectively. Equivalent effects were experienced by no, two and four patients, respectively, in the RLC-treated group.

## Discussion

The aim of the present retrospective study was to compare the efficacy and safety of prolonged RLC and RCC therapy in patients with GPC bone and joint infections. The success rates were similar in the two groups, at 89.3% and 78.6% in the RLC and RCC groups, respectively (p = 0.47). The success rate in the RLC group is comparable with rates in previous clinical studies in which linezolid was administered alone [14–17].

The success rate in our RCC group was higher than that reported by Stein *et al.* [35], who analysed the impact of cotrimoxazole as monotherapy in the treatment of infected orthopaedic implants and found an overall success rate of 66.7%. The higher success rate in our analysis may be explained by the positive impact of rifampicin administered in addition to cotrimoxazole, or possibly by better consistency between antibiotherapy and microbiology in our study: indeed 56% of the *Staphylococcus* species in the study by Stein *et al.* [35] were isolated from fistulae, which may not reflect the microbiology of the infected bone sites. Three failures in Stein *et al.* [35] were related to the isolation of cotrimoxazole-resistant *Staphylococcus* spp. strains, but no detailed data about risk factors were given. In our study, there was no selection of resistance to antibiotic treatment within the initial bacterial population during RCC, but new cotrimaxozole-resistant bacterial species were isolated 8–38 weeks after completion of this regimen in three patients who had clinical failure. These patients, however, had risk factors for relapsing infections, namely, the presence of sequestra, retention of an infected orthopaedic device, and concurrent urinary tract infection, which were probably responsible for the re-infection. The clinical success rate in our study was lower than that reported in the study by Sanchez *et al.* [36], in which 20 of 21 (95.2%) patients treated with RCC for staphylococcal osteoarticular infections were cured. However, the true impact of the RCC regimen was difficult to assess in this study because, prior to RCC treatment, the patients had received prolonged parenteral therapy with other antimicrobials for a mean duration of 18 days (range 2–40 days) [36].

In the present study, rates of adverse events were similar in the RLC and RCC groups. In the RLC group, 12 patients (42.9%) had drug-related adverse effects. These results differed significantly from those established in previous studies, especially regarding the frequency of anaemia episodes, which was < 5% in previous studies [14–17,37]. This higher rate of anaemia observed in this study may be explained by longer treatment duration and a greater mean patient age [38]. It is of note that no episode of thrombocytopenia was observed in the RLC group, in contradiction to some previous studies [14–16,37]. Our results are nevertheless consistent with those of Soriano *et al.* [39], suggesting a protective effect of rifampicin on linezolid-induced thrombocytopenia.

Prolonged peripheral neuropathy occurred in one of the 28 RLC patients, despite pyridoxine supplementation. This serious adverse event related to linezolid has been reported earlier, but no data on risk factors are currently available [26,27]. Clinicians should be aware of this when prescribing linezolid and should warn patients to stop linezolid promptly if abnormal effects occur.

In the RCC group, 13 patients (46.4%) experienced adverse effects, reflecting a higher rate than that reported in

the study of Sanchez *et al.* [36]. This discrepancy may be explained by the longer treatment duration in our study (15.4 vs. 4.9 weeks). Skin allergy and gastrointestinal side-effects led to RCC discontinuation in six patients. However, close monitoring of these patients enabled rapid recovery with no sequelae.

The present study had several limitations. Firstly, its population was small as a result of narrow inclusion criteria and type of infection. Secondly, this open, uncontrolled, retrospective study included a heterogeneous group of patients with BJI. Thirdly, as late relapses may occur, especially when an implant is infected, a follow-up period of > 1 year would have provided additional data on the outcome of our patients.

The results of the present retrospective study suggest that both RLC and RCC prolonged oral therapy are equally effective in treating patients with BJI caused by GPC, including infected orthopaedic devices. However, the lower daily cost of cotrimoxazole (US$1) vs. linezolid (> US$100) renders RCC an attractive alternative to RLC. Further wide-scale clinical studies are warranted to confirm these preliminary results.

## Transparency Declaration

The authors have no financial or commercial conflicts of interest to disclose.

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