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Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study

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Objective. To evaluate: (i) a correct equivalence ratio of clinical efficacy between low-dose deflazacort (DFZ) and methyl prednisolone (MP); and (ii) bone metabolic effects of low-dose DFZ and MP in the treatment of male RA and PsA.
Methods. A total of 21 male patients with active RA or PsA, naive to steroid treatment were chosen for the study. Group I: 10 patients treated for 6 months with DFZ 7.5 mg, calcium, cholecalciferol and a DMARD; for the following 6 months with MP 4 mg, calcium, cholecalciferol and a DMARD. Group II: 11 patients treated for 6 months with MP 4 mg, calcium, cholecalciferol and a DMARD; for the following 6 months with DFZ 7.5 mg, calcium, cholecalciferol and a DMARD. At day 0, 90, 180, 240 and 360 evaluation of ACR improvement criteria; a blood sample for total and bone-specific ALP, calcium, phosphorus, PTH, SHBG, estradiol, ACTH, osteocalcin, LH, OPG; a sample of urine for calcium, phosphorus, creatinine and DPD.
Results. 13/21 patients (6/10 Group I; 7/11 Group II) reached ACR 20 at 6 months; 14/21 (7/10 Group I, 7/10 Group II) at 12 months. Only at the third month we observed in Group II *vs* Group I a reduction of OPG (24% *vs* 6%, P = n.s.); ALP ($P < 0.001$) and osteocalcin ($P = 0.006$) decreased in both groups from the third month; DPD decreased in both groups only from the sixth month ($P = 0.002$).
Conclusions. The correct equivalence ratio of DFZ to MP is 1.875:1, and of DFZ to prednisolone 1.5:1. We found a relative prevalence of bone resorption compared to bone formation in the first 6 months of treatment. The trend of OPG requires further investigation.

KEY WORDS: Deflazacort, Methylprednisolone, Rheumatoid arthritis, Psoriatic arthritis, Glucocorticoid-induced osteoporosis, Osteoprotegerin.

Introduction

Osteoporosis is probably the most common and disabling complication of protracted glucocorticoid (GC) treatment, causing fractures in approximately 50% of patients treated.

Loss of bone mass is known to be more rapid in the course of the first 6–12 months of GC treatment; probably the first months are those with the highest osteopoenic impact, because of excessive bone resorption [1, 2]. Glucocorticoid-induced osteoporosis (GIO) appears to be dose-dependent [3] and is documented for prednisolone-equivalent doses $\geq$5 mg/die [4, 5]. In particular, in rheumatoid arthritis (RA) and non-axial psoriatic arthropathy (PsA) osteoporosis can occur even in the absence of GC treatment as a result of the action of some mediators of chronic synovial inflammation, which are also implicated in the genesis of osteoporosis through a mechanism of osteoclast activation [6–9]. Osteoporosis in the course of chronic arthritis is not only juxta-articular but also of a generalized nature [6, 10–13].

GC acts on the bone presumably through a direct impairment of osteoblast, osteocyte and osteoclast function, leading to reduced bone remodelling and diminished repair of microdamage in bone. Moreover, under GC therapy, the effects of PTH might be more pronounced; GC antagonizes gonadal function inhibiting the osteo-anabolic action of sex steroids; finally, GC increases renal elimination and reduces intestinal absorption of calcium [14]. Recent data strongly implicate that this may occur through the increased expression of the receptor that activates NF-kappa B ligand (RANK-L) and the reduced expression of osteoprotegerin (OPG), its soluble receptor [15–17]. Right from the start of low-dose GC treatment, reduced serum levels have been observed for osteocalcin (OC) and the bone isoenzyme of alkaline phosphatase (ALP), both markers of bone neoformation, as well as for indices of resorption [18]. In males, osteoporosis is less frequent than in females but it is often secondary to other diseases or pharmacological treatments, in particular GC. At present, there is no differentiation between males and females treated with GC as regards fracture risk, but in males the morbidity and mortality from fracture is higher due to the frequent association of osteoporosis with another disease, most likely, the one that triggered osteoporosis [19–23]. The androgens promote osteoblast proliferation and differentiation and inhibit osteoclast recruitment [24, 25]. Conversely, estradiol probably also plays a fundamental role in males; indeed the bone effects of testosterone are in part mediated by its conversion to estradiol, which would act through the RANKL/OPG pathway [26–29]. It has been observed that high plasma levels of sex-hormone-binding-protein (SHBG) may be a predictor of fracture risk [30].

Currently, there is debate about whether deflazacort (DFZ), an oxazolinic derivative of prednisolone (PDN), has a lesser calciuric and osteopoenic effect than for this reason: the 1.2:1 equipotency between DFZ and PDN, considered till now valid, has come under criticism [31–49]. The aims of this study were the following: primary: to validate by means of efficacy criteria the new equivalence ratio of 1.875:1 between DFZ and methylprednisolone (MP), (or the DFZ to PDN ratio of 1.5:1); secondary: to evaluate, through a cross-over study design, the bone metabolic effects of DFZ and MP in the treatment of RA or PsA in male GC-naive patients.

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Materials and methods

Patients

The present study, including the patient selection, was carried out at the Rheumatology and Rehabilitation Unit of the Salvatore Maugeri Foundation IRCCS in Castel Goffredo, Mantua, Italy. The protocol was approved by an independent Ethics Committee (Comitato Etico Centrale della Fondazione Salvatore Maugeri di Pavia) and all patients enrolled gave their written informed consent to participate in the study, obtained according to the Declaration of Helsinki.

Inclusion criteria were as follows: males aged between 25 and 75 yrs affected by RA or PsA (only polyarthritis similar to RA subset) as diagnosed according to ACR criteria, never treated with GC, in a clinically active phase of the disease, in ACR functional class 1, 2 or 3. Patients were excluded if they were: in ACR functional class 4, under steroid treatment, currently treated with bisphosphonates or non-substitutive androgens, or affected by degenerative or fractural diseases of bone.

Study design

We enrolled 21 male Caucasian patients, aged between 33 and 73 yrs (mean age 60.0 ± 11.79 yrs). Of these, 14 were affected by RA and seven by PsA (belonging only to the subset 'symmetric polyarthritis similar to RA'). In 15/21 patients, the disease duration was <8 months (12 RA, 3 PsA); the remaining six patients (3 RA, 3 PsA) had an erosive arthritis with a mean disease duration of 46 months; eight patients were positive for rheumatoid factor (6 RA, 2 PsA). Concerning the activity of the disease of the patients with PsA, they had a mean of 8.57 tender joints and 3.42 swollen joints, while HAQ score was 0.93, all values well within the mean of all other patients.

Patients were randomized into two groups. Group I consisted of 10 patients (8 RA, 2 PsA, mean age 58.3 ± 16.49 yrs) who underwent treatment for the first 6 months with DFZ 7.5 mg die associated with bibasic calcium phosphate 3.1 g and cholecalciferol 800 UI; in the following 6 months, DFZ was substituted without wash-out by MP at a dosage of 4 mg die. Eight patients (7 RA, 1 PsA) were also taking methotrexate and 2 hydroxychloroquine (1 RA, 1 PsA).

Group II consisted of 11 patients (6 RA, 5 PsA; mean age 59.1 ± 5.75 yrs) who were treated for the first 6 months with MP 4 mg die associated with bibasic calcium phosphate 3.1 g and cholecalciferol 800 UI; in the following 6 months MP was substituted without wash-out with DFZ at a dosage of 7.5 mg die. Seven patients (4 RA, 3 PsA) were also taking methotrexate, three patients (2 RA, 1 PsA) hydroxychloroquine and one patient, cyclosporin (PsA).

During the study period no intra-articular GC infiltrations were performed, there was no variation in the GC dosage, and there was no substitution or change in the prescribed dose of eventual anti-inflammatory drugs in use.

All patients were assessed at the start of the study and at 3, 6, 9 and 12 months after commencement of treatment. The following parameters were monitored: number of swollen joints; number of tender joints; disability index calculated by means of the HAQ questionnaire; pain measured by means of a 10 cm-long horizontal visual analogue scale (VAS); global self-assessment of efficacy expressed separately by the physician and patient using a 10 cm-long horizontal VAS.

At 0 (baseline), 90, 180, 270 and 360 days, all patients underwent blood tests and urinalysis, including 24-h urine sampling, to determine the following parameters: haemochrome with leucocyte formula and platelet count, erythrocyte sedimentation rate (ESR), C-reactive-protein (CRP), total and bone-specific ALP, protein electrophoresis, glycaemia, glycosilated haemoglobin, uricaemia, transaminase, calcaemia/albuminaemia, phosphoraemia, creatininaemia, plasma intact parathyroid hormone (PTH 1-84), SHBG, estradiol, ACTH, OC, LH, OPG, standard urine test, 24-h calciuria and phosphaturia, creatininuria second-morning urine (before 10:00 a.m.) and deoxypyridinoline (DPD).

Collection and storage of samples

Blood samples for the study were drawn using standard venipuncture technique between 08:00 and 09:00 a.m. after an overnight fast. Peripheral venous blood was drawn into sterile vacuum blood collection tubes without any additives for serum samples and into K3-EDTA vacutainer tubes for plasma samples (Becton Dickinson, San Jose, CA, USA). Serum was separated after centrifugation of blood at 4°C, 1500 *g* for 10 min.

Urine samples were obtained from a 24-h urine specimen including the early morning portion. Patients were instructed to collect their urine for 24 h. After division into aliquots serum, plasma and urine samples were immediately analysed or frozen and stored at −80°C until assay and were thawed only once.

Biochemical measurements

Levels of serum and urinary calcium, creatinine and phosphate, serum ALP, albumin and CRP, were measured using commercially available kits (Olympus Diagnostici, Italy) run on an Olympus AU400® Chemistry autoanalyser (OLYMPUS Instruments, Japan). We corrected total serum calcium for individual variations in albumin concentration. The intra-assay and interassay coefficients of variation for bone-specific alkaline phosphatase were <5 and 8%, respectively.

CRP was measured quantitatively by means of an immunoturbidimetric assay. Briefly, 2 μl of serum sample was mixed with a 160 μl of a 0.05% suspension of latex particles coated with goat anti-human CRP antibodies, in the presence of MOPSO buffer (pH 7.5). CRP reacts specifically with anti-human CRP antibodies to yield insoluble aggregates. The absorbance of these aggregates detected at 800 nm is proportional to the CRP concentration in the sample.

Bone-specific ALP was measured using agarose gel electrophoresis (REP, Helena Biosciences, UK).

PTH was measured by a solid-phase, two-site chemiluminescent enzyme-labelled immunometric assay on the IMMULITE® automated analyser (Diagnostic Products Corporation, Los Angeles, CA, USA).

Plasma OC was measured by an electrochemiluminescence sandwich immunoassay on the fully automated analyser Modular® analytical system platform (Roche Diagnostics, Milan, Italy). The detection limit for OC was 0.5 ng/ml, and the intra-assay and interassay coefficients of variation ranged from 3.8% to 6.7%, respectively.

Serum OPG levels were determined using a sandwich ELISA assay (Biovendor GmbH, Heidelberg, Germany). Briefly, in plates coated with capture monoclonal anti-OPG antibody, samples or OPG standard (100 μl) were added. Plates were incubated at room temperature for 1 h. After washing, bound with human OPG was detected by incubation with detection biotin labelled anti-OPG antibody (100 μl) for 1 h. After washing, substrate solution was added (100 μl) and determination of absorbance was obtained by reading the plate at 450 nm. All samples were measured in duplicate and the results were averaged. The detection limit of this assay system was 30 pg/ml.

ESR was measured on the automatic instrument Ves-Matic 20 (DIESSE - Diagnostica Senese, Siena, Italy). The ESR reading at the first hour was performed in 26 min including the mixing of samples.

Urine deoxypyridinoline assays were performed with a competitive EIA method, according to the manufacturer's instructions and the results were corrected for urinary concentration by creatinine (Pyrilinks-D®; Metra Biosystems).

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Evaluation of efficacy

To validate the equivalence ratio DFZ to MP of 1.875:1 we evaluated the disease activity in each patient following the ACR definition of improvement in RA: tender joints count; swollen joints count; ESR (or CRP) levels; patient's global assessment of physical function using the HAQ score; patient's assessment of pain evaluated on an horizontal VAS scale of 10 cm; physician's global assessment of disease activity evaluated on a horizontal VAS scale of 10 cm; patient's global assessment of disease activity evaluated on a horizontal VAS scale of 10 cm. In addition, we considered the mean values of ESR, CRP, tender joints count, swollen joints count, HAQ score and patient's assessment of pain.

Monitoring of toxicity

All patients were explicitly requested at each visit to report any eventual side effects. No biohumoral side effects emerged from the monitoring of haemochrome, glycaemia, transaminase, creatininaemia and urine.

Statistical analysis

Descriptive statistics were used (mean and standard deviation) for each metabolic parameter investigated. Data were analysed by using ANOVA for repeated measure evaluating the increase or reduction of the parameters during the experimental time frame independently from the group. The variation in the experimental time frame of the parameters evaluated taking into account the specific experimental groups.

Results

None of the 21 patients enrolled reported serious side effects. One patient, in Group I, withdrew from the study at the third month due to a concomitant disease not linked to either the arthropathy or the treatment in course.

14 of the 20 patients who completed the study showed a lasting clinical improvement according to ACR criteria: 7 were from Group I and 7 from Group II (Table 1).

As shown in Fig. 1, there is a significant decrease of ESR, CRP, ALP, OC, DPD that was already significant after 90 days and was followed by a plateau, that didn't change after the cross-over of therapy. With regard to the indices of bone neoformation, total ALP showed a significant decrease in both groups already at 90 days, which persisted; bone-specific ALP showed a significant decrease in both groups, irrespective of the drug utilized; OC showed a progressive, significant decline in both groups that persisted throughout the study period. Among the indices of bone resorption, urinary DPD decreased only after 180 days ($P = 0.002$), and this persisted, with a similar trend in the two groups.

As shown in Fig. 2, in both groups, a significant improvement in the mean clinical parameters was already evident at the third month of treatment; this improvement persisted throughout the study period, independently of which GC was used. The clinical parameters evaluated were namely: number of tender joints, number of swollen joints, patient's assessment of pain (VAS) and HAQ score.

The levels of corrected serum calcium, calciuria, phosphoraemia and phosphaturia, LH, ACTH, PTH did not show significant variation. In contrast, in both groups SHBG (at 90 days $P < 0.001$; at 180 days $P = 0.045$) and estradiol (at 90 days, $P = 0.008$) decreased significantly (data not shown).

Concerning OPG (Fig. 1F), although the results were not statistically significant, a difference in trend was observed between the two groups at 90 and 180 days. At 90 days, OPG decreased by 6% with DFZ (Group I), and by 24% with MP (Group B).

TABLE 1. ACR improvement

Group	Patients	Age	RA/PsA	180 days <ACR20	180 days >ACR20	180 days >ACR50	180days >ACR70	360 days <ACR20	360 days >ACR20	360 days >ACR50	360 days >ACR70
I	9	61.1 ± 14.73	7/2	3	6	5	2	2	7	6	5
II	11	59.1 ± 5.75	6/5	4	7	6	6	4	7	7	5

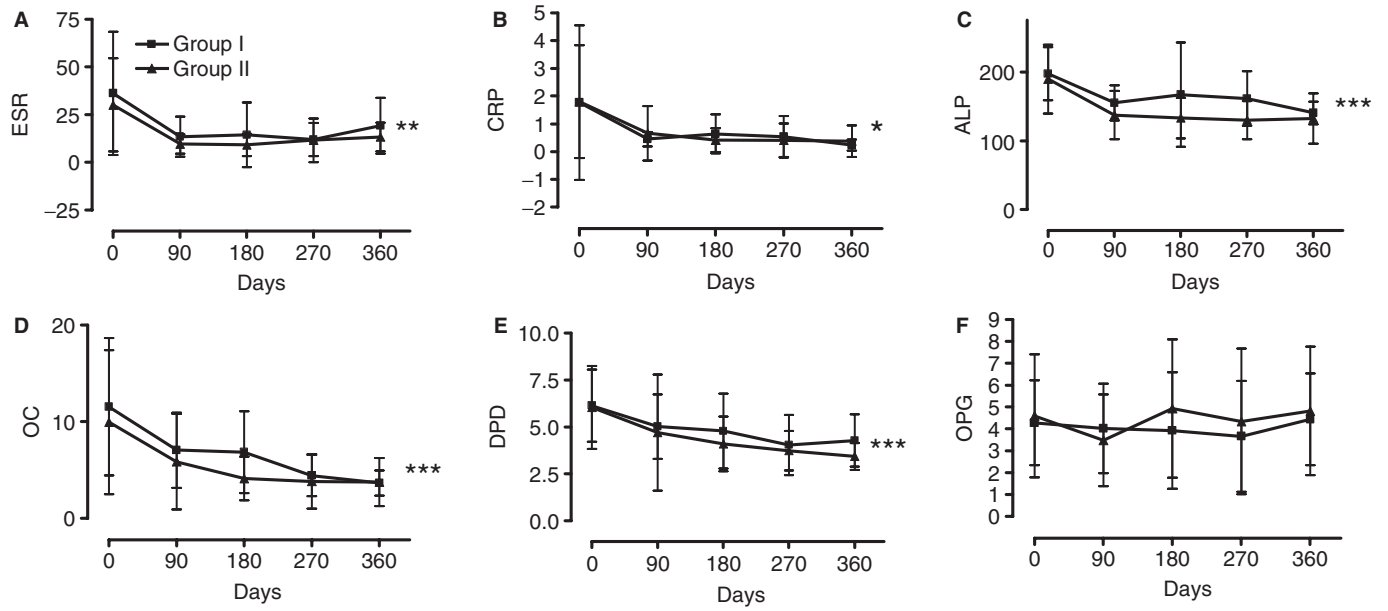

FIG. 1. Effect of the two different treatments, e.g. Groups I and II on the following biochemical parameters: ESR (A), CRP (B), ALP (C), OC (D), DPD (E) and OPG (F). The data are expressed as mean ± S.E.M. *$P < 0.05$; **$P < 0.01$, ***$P < 0.01$ as determined by ANOVA for repeated measures.

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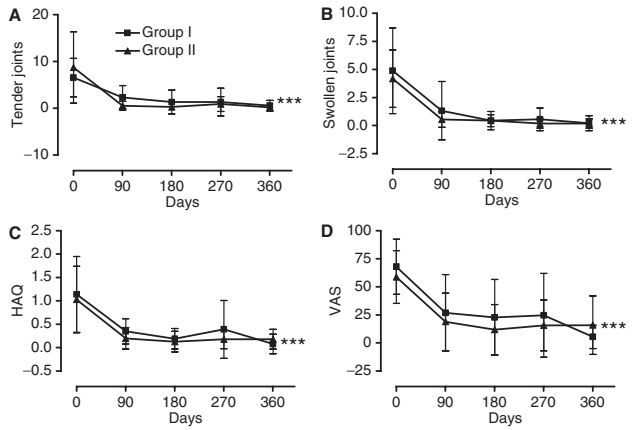

FIG. 2. Effect of the two different treatments, e.g. Group I and Group II on the following clinical parameters: number of tender joints (A), swollen joints (B), HAQ score (C) and VAS score (D). The data are expressed as mean ± S.E.M. ***$P < 0.01$ as determined by ANOVA for repeated measures.

At 180 days, the curve of Group I remained linear while in Group II there was a sharp inversion, at the borderline of significance ($P = 0.06$).

Discussion

The clinical efficacy of low-dose GC in combination with DMARDs—if used appropriately already in the early phase of the arthropathy—has recently been documented [50–52]. According to ACR criteria, here we have demonstrated the equivalence of clinical efficacy between DFZ 7.5 mg die and MP 4 mg die. Indeed, a significant improvement has been found in 14 of the 20 patients that completed the study. This improvement was independent of the GC used, was already evident at 90 days and persisted through to the end of the study, confirming that the equivalence ratio of DFZ to MP is 1.875:1, corresponding to 1.5:1 for that of DFZ to PDN.

Our clinical findings add support to the notion of utilizing low-dose GC to safeguard against the potential side effects that are dose-dependent. Cytokines have been recognized as playing an important role in determining osteoporosis since they are abundantly produced in the arthritic synovia, where they are the cause of the osteo-articular damage. Thus, it should be feasible that an effective and early anti-arthritic pharmacological intervention consisting of DMARDs and low-dose GC would reduce, rather than increase, the osteoporotic risk.

Concerning the parameters measured, we found a significant reduction in both groups in levels of SHBG that could be interpreted as a protective effect; indeed increase in SHBG is considered to be a predictor of fracture risk. Another parameter that significantly decreased in both groups after 90 days was OC that is known to diminish in males in the course of GC treatment as a result of the inhibitory effect of GC on osteoblasts [53]. Urinary DPD, an expression of bone resorption, declined without difference between the groups, reaching statistical significance only at 180 days. Thus, while the phase of reduced bone neoformation is already evident at the third month, that of reduced resorption occurs later and becomes apparent at the sixth month, independently of the GC used. Consequently, in the first months of treatment there is a relative prevalence of resorption processes over neoformative ones, creating a type of adverse discoupling (Fig. 1D and E).

The absence of variation in the values of PTH observed can perhaps be attributed to the contemporary assumption of calcium and vitamin D, but nevertheless it confirms that low-dose GC do not cause osteopoenia through the mechanism of an increased PTH. It is also interesting to note the stability of ACTH levels, implying that with low-dose of GC the responsiveness of the pituitary–adrenal axis generally remain within the normal range [54]. On the contrary, there was a significant and early reduction in estradiol, whose importance has been documented also in males, as mentioned previously [26–29]. Finally, a trend in reduction of OPG levels was evident at 90 days only in the group using MP, followed by a sudden, almost significant inversion of trend at 180 days ($P = 0.06$). This effect did not reach statistical significance most likely due to the low sample size. One might hypothesize that the reported, though controversial, lower osteopoenic action of DFZ during the first few months of GC treatment (considered the crucial months) is linked to the drug's lower impact on the relation between RANKL and OPG. Since GIO is expressed principally during the first months of treatment, it could be useful to verify during this period, with weekly blood sampling and in a larger study population, the trend in OPG utilizing different GC, including DFZ. Granted that GC are among the most potent suppressors of OPG levels *in vivo*, similar observations to ours have been recently published. In particular, it has been shown that groups of patients utilizing for the first time high-dose PDN showed a clear decline in OPG as early as the first week (and a corresponding increase in sRANKL), associated to a decline in OC [17, 27, 55]. On the other hand, *in vitro*, DFZ reduces OPG less drastically than other GC [56]. If the levels of OPG in the group of MP users are decreased at 90 days from the onset of GC treatment, in the absence of intermediate evaluations, one might hypothesize that in the preceding weeks, in line with the above-mentioned observations, the reduction of OPG was even more consistent; or, one could hypothesize that the low dosage of GC we used could have delayed the decline of OPG and consequent bone loss. These are hypotheses that need to be verified especially if, as recently reported, DFZ also has a protective effect on the articular erosions typical of chronic inflammatory arthropathies. Indeed DFZ exerts an anti-invasive and anti proliferative activity on the rheumatoid synoviocytes through its modulating action on the fibrinolytic system; this translates into a reduced aggressivity of the synovial pannus and a diminished progression of the radiologically visible damage [57].

In conclusion, we have shown that the correct equivalence ratio of DFZ to MP is 1.875: 1 and consequently, DFZ to PDN is 1.5:1. We have also found a relative prevalence of bone resorption compared to bone formation in the first 6 months of treatment. Further investigation is required on OPG; indeed the trend observed suggest that OPG may play an important role that to be unmasked requires a larger population sample.

Rheumatology key messages

- The correct equivalence of deflazacort to methylprednisolone is 1.875:1 and deflazacort to prednisolone is 1.5:1.
- Low-dose of deflazacort or methylprednisolone in association with DMARDs are both effective in the treatment of RA and PsA in men.
- The study of bone metabolic effects of low-dose deflazacort or methylprednisolone in male patients naive to steroid treatment shows a relative prevalence of bone resorption compared to bone formation in the first 6 months of treatment.

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The authors have declared no conflicts of interest.

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