Clinical applications of BMP-7/OP-1 in fractures, nonunions and spinal fusion

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Abstract Since the identification of the osteogenic protein-1 (OP-1) gene, also called bone morphogenetic protein-7 (BMP-7), almost 20 years ago, OP-1 has become one of the most characteristic members of the BMP family. The biological activity of recombinant human OP-1 has been defined using a variety of animal models. These studies have demonstrated that local implantation of OP-1 in combination with a collagen matrix results in the repair of critical size defects in long bones and in craniofacial bones and the formation of bony fusion masses in spinal fusions. Clinical

trials investigating long bone applications have provided supportive evidence for the use of OP-1 in the treatment of open tibial fractures, distal tibial fractures, tibial nonunions, scaphoid nonunions and atrophic long bone nonunions. Clinical studies investigating spinal fusion applications have provided supportive evidence for the use of OP-1 in posterolateral lumbar models and compromised patients as an adjunct or as a replacement for autograft. Both long bone repair and spinal fusion studies have demonstrated the efficacy and safety of OP-1 by clinical outcomes and radiographic measures. Future clinical investigations will be needed to better define variables, such as dose, scaffold and route of administration. Clearly the use of BMPs in orthopaedics is still in its formative stage, but the data suggest an exciting and promising future for the development of new therapeutic applications.

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Résumé Depuis l'identification du gène OP-1 appelé aussi BMP-7, il y a plus de 20 ans, OP-1 est la BMP la plus caractéristique de cette famille. L'activité biologique de l'OP-1 recombinante humaine a été bien définie et ce sur différents animaux servant de modèle expérimentaux. Ces études ont démontré que l'implantation locale d'OP-1 en association avec une matrice collagène entraîne la réparation de différents défauts des os longs au niveau du crâne ainsi que la formation d'une bonne fusion osseuse au niveau de la colonne vertébrale. Les essais cliniques ont montré que l'OP-1 avait un résultat favorable dans le traitement des fractures ouvertes, les fractures du tibia distal, les pseudarthroses du scaphoïde et les pseudarthroses atrophiques des os longs. Différentes études cliniques portant sur la fusion rachidienne ont également été développées utilisant l'OP-1 sur des modèles d'abord lombaires postéro latéraux nous permettant de penser que l'on peut-être remplacer l'auto-greffe. Les réparations

tant au niveau de l'os que l'utilisation au niveau du rachis ont démontré l'efficacité et surtout l'absence d'effets secondaires de l'OP-1. De nouvelles études cliniques doivent être développées de façon à déterminer quelles sont les doses optimales à délivrer et quel est le meilleur moyen d'administration. Ceci promet de futures études et un avenir florissant pour le développement de nouvelles applications thérapeutiques.

Introduction

Bone repair and regeneration with bone morphogenetic proteins (BMPs) are ushering in a new era in orthopaedics. The past 10 years have seen the practical demonstration of bone repair in a host of animal studies and subsequently in clinical trials [18]. The result has been the commercialisation of two of the early BMPs, BMP-2 and BMP-7 (also called osteogenic protein-1 or OP-1). Our focus has been on OP-1 and in this article we summarise the current clinical status of this BMP for long bone repair and spinal fusion.

Since the OP-1 gene was identified in the late 1980s, recombinant human OP-1 has been produced and extensively analysed both biochemically and biologically. A variety of animal models has been used to evaluate OP-1's therapeutic potential in bone repair. These studies led to the demonstration of bone repair in humans and resulted in OP-1 receiving regulatory approval as the first commercial BMP.

OP-1 has been chosen for long bone repair using bone-derived collagen particles as the scaffold and delivery material (OP-1 implant or osigraft). Carboxymethylcellulose (CMC) is added to the OP-1/collagen formulation for use in spinal fusion applications and is called OP-1 putty. In general bone formation with OP-1 has been compared to the gold standard of bone graft materials: autogenous bone harvested from the iliac crest. OP-1 has demonstrated safety and efficacy in preclinical, clinical short-term, and recent clinical studies with long-term follow-up [10]. A significant amount of clinical experience has now accumulated evaluating OP-1 for repair and regeneration of bone. It has been 15 years since the first patient was successfully implanted with OP-1 to heal a tibial nonunion defect and 6 years since the first commercial approval. As a result, thousands of patients have been treated worldwide and numerous clinical trials have been undertaken to investigate OP-1 in the treatment of fractures and spinal fusion applications. As described in this review, the results of these studies have demonstrated both the efficacy and safety of OP-1 in a variety of models and indications. Clinical outcome measures and radiographic evidence of healing have been comparable in OP-1-treated patients to those treated with autograft bone. However, OP-1 avoids the substantial morbidity associated with graft donor sites. As such, OP-1

is proving to be a viable alternative to autograft, obviating bone graft harvest morbidity and reducing the risk of pseudoarthrosis.

Applications of rhBMP-7/OP-1 in the treatment of fractures and nonunions

The use of OP-1 is an attractive adjunct in the treatment of fractures and atrophic long bone nonunions. There are an increasing number of recent clinical trials that provide supportive evidence for the use of OP-1 in the treatment of open tibial fractures, distal tibial fractures, tibial nonunions, scaphoid nonunions and atrophic long bone nonunions.

Open tibial shaft fractures

The use of OP-1 in the treatment of open tibial shaft fractures was evaluated by the Canadian Orthopaedic Trauma Society [8]. One hundred and twenty-four open tibial fractures (62 control and 62 OP-1) underwent initial irrigation, debridement and statically locked intramedullary nailing. At the time of definitive wound closure, patients were randomised to standard wound closure or standard wound closure with the addition of OP-1 to the fracture site. Patients were followed up radiographically, clinically and serologically until union. The primary endpoints were radiographic evidence of fracture healing at 6 months post-injury and the rate of secondary intervention after 6 months.

The number of secondary interventions for delayed union and nonunion was significantly lower in the OP-1 group than in the control group (8 vs. 17; $P=0.02$). A significantly greater number of patients in the OP-1 group was able to fully bear weight without pain at 12 months compared to the control group, part of a general trend towards improved functional outcome in the OP-1 group. No adverse events related to the use of OP-1 were clinically detected. The study investigators suggested that the use of OP-1 is safe for use in open tibial shaft fractures, and its use decreased the number of secondary procedures for delayed or nonunion.

Distal tibial fractures

More recently, OP-1 has been evaluated in the treatment of distal tibial fractures in a case-control study from Finland [12]. Twenty patients with distal tibial fractures treated with hybrid external fixation and OP-1 (BMP group) were compared to 20 matched patients similarly treated without the use of BMP (control group). Outcome measures included time to radiographic union, duration of application of the external fixator, the number of secondary interventions due to delayed healing and length of absence from work. Mean time to union was significantly shorter in the BMP group

(15.7 weeks vs. 23.5 weeks, $P=0.002$), as was the mean time to removal of the external fixator (15 weeks vs. 21.4 weeks, $P=0.037$). Revisions for delayed union were required in two patients in the BMP group and seven patients in the control group. Average time off work was significantly lower in the BMP group than in the controls (6.3 months vs. 9.0 months, $P=0.018$). Functional outcome as measured by the Iowa ankle scores was similar between the two groups. The authors concluded that the use of OP-1 is beneficial in the treatment of distal tibial fractures treated with hybrid external fixation, with the main advantage being the decreased time to bony union.

Tibial nonunion

The use of OP-1 in the treatment of tibial nonunion was studied by Friedlaender et al. in a randomised controlled, prospective clinical trial [4]. This study compared the clinical and radiographic results of the efficacy of OP-1 versus autograft in the treatment of tibial non-unions that had persisted for at least 9 months. One hundred and twenty-four tibial non-unions in 122 patients were randomised to either intramedullary nail and autograft or intramedullary nail and implantation of OP-1 at the nonunion site. Patients were followed up at regular intervals and assessed for severity of pain at the fracture site, ability to walk with full weight bearing, the need for repeat surgical treatment of the nonunion during the course of the study, plain radiographic evaluation of healing and physician satisfaction with the clinical course.

Nine months after surgery, 81% of the OP-1 group and 85% of the autograft group had achieved clinical union. Radiographic analysis indicated that 75% of those in the OP-1-treated group and 84% of the autograft-treated group had healed their fractures. There was no statistically significant difference between groups clinically or radiographically. It is important to note that more patients in the OP-1 group were smokers, which would tend to place this group at a disadvantage in terms of healing. More than 20% of the bone graft group complained of persistent donor site pain. The authors concluded that OP-1 was a safe and effective alternative to bone grafting in the treatment of tibial non-unions. This study led to multiple regulatory approvals worldwide.

Successful repair of a resistant tibial nonunion with a recombinant bone morphogenetic protein-7 (osteogenic protein-1) in an adult patient previously unsuccessfully treated during the period of 14 years was presented by Pecina et al. [11].

Scaphoid nonunion

In the upper extremity, OP-1 has been evaluated in a prospective randomised controlled trial of proximal pole

scaphoid nonunions. In this pilot study, Bilic et al. compared 17 patients in three arms of treatment [1]. The first group received autologous iliac crest graft, the second group received autologous iliac crest graft and OP-1 and the third group received allograft bone and OP-1. Patients were followed up at regular intervals both clinically and radiographically. Radiographic union was assessed through four radiographic views of the wrist. Clinical evaluation included a pain assessment by visual analogue scale during rest, at maximal grip and maximal dorsal flexion of the wrist, as well as range of motion of the wrist, grip strength and pinch strength. Healing time in the autograft and the OP-1 group was 4 weeks compared to 9 weeks in autograft bone alone and 8 weeks in the allograft OP-1 group. Functional outcome was significantly improved in the autograft or allograft and OP-1 groups as compared to autograft alone. The authors concluded that the addition of OP-1 accelerates healing of proximal pole scaphoid nonunions and the use of OP-1 may allow for successful use of allograft bone in the treatment of scaphoid nonunions, thereby eliminating the donor site morbidity of an iliac crest bone graft.

Diaphyseal humeral nonunions

Bong et al. prospectively studied the use of OP-1 in the treatment of diaphyseal humeral atrophic nonunions [3]. A consecutive series of 23 patients underwent fixation of humeral nonunions using either standard compression plate fixation or intramedullary nailing in combination with various bone grafting techniques. OP-1 was added at the nonunion site at the time of fixation. All 23 fracture nonunions went on to radiographic union with no adverse reactions to the OP-1 implant. The authors concluded that OP-1 was a safe and effective adjuvant for the treatment of humeral diaphyseal nonunions.

In a series of recalcitrant humeral nonunions, VanHouwelingen and McKee [17] used OP-1 for biological stimulation of the nonunion with onlay cortical strut allografts for improved mechanical purchase and were successful in obtaining union in all six cases. They pointed out that autograft was not necessary in any of these six patients, many of whom were elderly or had medical co-morbidities. There were no complications from the use of the OP-1 compound.

Long bone nonunions

McKee et al. studied the effectiveness of OP-1 in the treatment of recalcitrant, aseptic, atrophic long bone nonunions in a prospective single-arm study in 62 patients [9]. The involved bones included 16 tibiae, 18 clavicles, 11 humeri, 10 femora, 4 ulnae and 3 radii (Figs. 1, 2). These patients had undergone an average of 2.1 previous

Fig. 1 **a** A 77-year-old patient had had two attempts at fixation of a nonunion following initial non-operative treatment of a humeral shaft fracture that led to nonunion. After realignment, debridement of the nonunion, re-establishment of the medullary canals and plate fixation with a broad 4.5-mm compression plate, a cortical strut allograft was applied medially and screws were inserted into it, enhancing fixation. Following this, OP-1 was applied to the nonunion site instead of autogenous bone (both anterior iliac crests had been harvested previously). **b** Follow-up radiograph at 4 months post-operatively revealing solid bony union

operations and 28 had previously failed autogenous iliac crest bone grafting. Each patient underwent revision fixation with standard implants, using local bone graft as available, and application of OP-1 at the nonunion site. No bone graft was harvested from other sites during the study procedure.

At the conclusion of the study, 54 of 61 nonunions (89%) had healed. Seven patients failed to heal. Five patients had positive intraoperative cultures, of which four went on to uneventful union. Six patients had additional operations for reasons other than nonunion such as for hardware removal. There were no allergic or anaphylactic reactions, and no excessive or heterotopic bone formation. The authors concluded that OP-1 was safe and reliably

successful in inducing union of atrophic, aseptic long bone nonunions when used in a standard protocol that included hardware removal, deformity correction, OP-1 application and stable fixation.

Conclusion: fractures and nonunions

There are numerous studies in the literature suggesting that OP-1 is safe and effective in the treatment of fractures and atrophic nonunions. The complication rate from the use of the compound itself is negligible. The compound is easy to use, but must be applied with careful and meticulous operative technique to ensure asepsis and provide mechanical stability and good soft tissue coverage for success.

Applications of rhBMP-7/OP-1 in spinal fusion

Posterolateral lumbar spinal fusion is a component of the treatment for a variety of spinal disorders including trauma, deformity and degenerative conditions, particularly those with instability such as degenerative spondylolisthesis. The goal of the fusion procedure is segmental union between adjacent vertebrae. It is generally accepted among clinicians that solid bony union is necessary to achieve long-term stability. While there have been significant advances in understanding the biological processes that achieve fusion, many important details remain incompletely understood [2].

OP-1 as an adjunct to iliac crest autograft

Multiple human clinical trials have assessed the effects of OP-1 in the posterolateral spine [6, 13–15]. An FDA-approved human pilot study evaluated the safety and efficacy of OP-1 as an adjunct to iliac crest autograft for non-instrumented posterolateral fusions in patients with degenerative spondylolisthesis [13]. This challenging clinical model was chosen because of significant frequency of pseudarthrosis in this patient population. The non-instrumented scenario allows for unambiguous evaluation of the fusion, where the bony fusion alone provides stability. Twelve patients with spinal stenosis received a mixture of iliac crest autograft and OP-1 in the intertransverse process space after laminectomy and partial facetectomy, as was required for adequate decompression. Postoperative evaluation at 1 year included Oswestry Disability Index (ODI) measure as well as static and dynamic radiographs. Independent, blinded radiologists were used to determine fusion status. The stringent radiographic criteria used to define fusion success were those provided by the FDA for use in clinical trials: in addition to bridging bone, 5 degrees (or less) of angular motion and 2 mm (or less) of translation were required. The preoperative (ODI) improved by at least 20% in 9 of the 12 patients

Fig. 2 **a** Atrophic subtrochanteric nonunion with broken implant following plate fixation of subtrochanteric fracture. **b** Successful union with abundant medial callous following hardware removal, deformity correction, rhOP-1 addition to the nonunion site and cephalomedullary nail insertion

(75%). While bridging bone was seen in 10 of 11 (91%) patients on PA radiographs, only 6 of the 11 (55%) patients with complete radiographic follow-up qualified as achieving solid fusion. This was not found to be statistically significantly different than historical controls. With regard to safety, no adverse events related to OP-1 were found, specifically including no systemic toxicity, no ectopic bone formation and no recurrent stenosis. This pilot subsequently led to an FDA Humanitarian Device Exemption (HDE) approval for OP-1 in the United States.

In 2005, Vaccaro and colleagues reported the 2-year follow-up data on these patients who underwent non-instrumented fusion with iliac crest autograft supplemented with OP-1 for the treatment of degenerative spondylolisthesis [15]. The early follow-up results were found to be maintained at 2 years. Of the 12 patients enrolled in the pilot study, complete clinical data were available for nine and complete radiographic data was available for five. Eight of nine patients (89%) had at a 20% (or better) improvement in preoperative ODI score. While bridging bone on the PA radiograph was reported in seven of ten patients (70%), only five of ten patients (50%) were found to have met the stringent FDA criteria for a solid fusion. The excellent safety results previously reported were found to be maintained at 2 years, with no adverse events, including no systemic toxicity, no ectopic bone formation and no evidence of recurrent stenosis.

OP-1 as a replacement for autograft

Johnsson et al. randomised 20 patients with degenerative spondylolisthesis (up to grade 2) at L5-S1 to receive either OP-1 or iliac crest autograft for single level posterolateral fusion. The hypothesis (based on animal studies) that the OP-1 group would have more rapid and stronger fusion was not met; with the limited number of patients in this study, there was no statistically significant difference found between the autograft and OP-1 groups with regard to fusion. No adverse effects related to OP-1 were observed, while one of the ten patients that underwent iliac crest autograft harvest developed persistent harvest site pain [6].

Vaccaro and colleagues later evaluated the safety and efficacy of OP-1 alone by comparing it to iliac crest autograft for posterolateral spinal arthrodesis [14]. In this prospective, randomised, controlled, multi-centre study conducted under an Investigational Device Exemption granted by the FDA, 36 patients with degenerative lumbar spondylolisthesis and spinal stenosis underwent decompression, which consisted of laminectomy and partial (medial) facetectomy. Non-instrumented posterolateral fusion was performed, with a 2:1 randomisation to OP-1 or autograft. Static and dynamic radiographs were examined by independent, blinded radiologists to determine fusion

status. Fusion success was designated if three criteria were met: bilateral bridging bone between the transverse processes, less than or equal to 5 degrees of angular motion, and less than or equal to 2-mm translation. At a minimum of 1-year follow-up, complete clinical data was available in 32 patients and complete radiographic data was available in 29 patients. Clinical success (with more than 20% improvement in ODI score) was achieved by 86% (18 of 21) OP-1 patients and 73% (8 of 11) autograft patients. Successful posterolateral fusion was determined in 14 of 19 (74%) OP-1 patients and 6 of 10 (60%) autograft patients. No adverse events related to OP-1 were observed, including no systemic toxicity, no ectopic bone formation and no recurrent stenosis. The authors concluded that successful radiographic fusion was obtained using OP-1 at a rate that was similar to autograft, despite the challenging fusion environment of the posterolateral spine in patients with degenerative spondylolisthesis.

The durability of these results (with 2-year follow-up) was subsequently reported in 2005 [15]. In this investigation, 31 of 36 patients had complete clinical data and 30 of 36 patients had complete radiographic data available for analysis with a minimum follow-up of 24 months. Clinical success (with a 20% or better improvement in the preoperative ODI score) was achieved by 17 of 20 (85%) OP-1 patients and 7 of 11 (64%) autograft patients. Solid fusion was reported in 11 of 20 (55%) OP-1 patients and in 4 of 10 (40%) autograft patients. The excellent safety profile was also maintained, with no adverse events reported. Since OP-1 (alone, without autograft) was associated with a radiographically solid fusion in 55% of the patients at 24 months, which is comparable to the historical fusion rates for non-instrumented arthrodesis in this challenging clinical scenario, the authors concluded that it may be considered as a viable alternative to autograft. Since there may be a possibility of fusion success progressively deteriorating over time, these patients continued to be followed up in order to determine whether these favourable results were maintained over a still longer term.

More recently, the long-term safety and efficacy results of OP-1 as an alternative to autogenous bone for non-instrumented posterolateral fusion was appraised [16]. The patient group previously assessed with 2-year follow-up was evaluated [14, 15]. The radiographic and clinical outcomes as well as the respective complication rates of OP-1 and control groups were compared. The primary efficacy endpoint was the overall success rate, a composite measure derived from radiographic and clinical parameters. The safety of OP-1 was confirmed by comparing the nature and frequency of all adverse events and complications that were prospectively observed in either of the groups.

With a minimum of 4-year follow-up, complete radiographic data were available for 22 of 36 patients (16 OP-1,

6 autograft). Blinded radiologists reviewed static and dynamic radiographs to determine the morphology of the fusion mass. The presence or absence of continuous bridging bone across the transverse processes was noted. Digital calipers were used to measure the motion on dynamic radiographs. Radiographic evidence of a solid arthrodesis was present in 11 of 16 OP-1 patients (69%) and in 3 of 6 autograft patients (50%).

In this 4-year minimum follow-up investigation, complete clinical data were available for 25 of the 36 patients (18 OP-1, 7 autograft). Clinically success was defined as a 20% (or more) improvement in ODI scores. This was achieved by 14 of 19 OP-1 patients (74%) and 4 of 7 autograft patients (57%). This clinical benefit was corroborated by improvements in SF-36 scores. The overall success rates were found to be 63% in the OP-1 group and 33% in the autograft group. There was no evidence of local or systemic toxicity, ectopic bone formation or other adverse events potentially related to the use of OP-1.

In this long-term follow-up study, OP-1 exhibited excellent rates of radiographic fusion, clinical improvement and overall success that were consistently maintained for at least 48 months after surgery. Since the efficacy and safety profile of OP-1 were at least comparable to that of the autograft controls, OP-1 may represent a viable bone graft substitute for fusion applications.

In 2006, Kanayama et al. reported the results of their prospective randomised comparison of OP-1 to local autograft mixed with ceramic bone substitute for instrumented posterolateral lumbar fusion [7]. Nineteen patients with degenerative spondylolisthesis at L3-L4 or L4-L5 underwent posterolateral fusion with pedicle screw instrumentation. Randomisation to either OP-1 alone (nine patients) or to local autograft with HA-TCP granules (ten patients) was performed. Plain radiography and CT scan were used to evaluate the fusions. The stringent FDA radiographic criteria were used, requiring less than 5 degrees of angular motion, less than 2 mm of translation and evidence of bridging bone for fusion success. At a minimum of 1 year after initial surgery, the patients who showed radiographic evidence of fusion underwent surgical exploration of the fusion site, with removal of the instrumentation. Fusion mass tissue was sampled and evaluated histologically. The fusion rate was reported to be 78% (seven of nine) in the OP-1 group and 90% (nine of ten) in the control (autograft with HA-TCP) group. Histological evaluation of the fusion masses in 16 patients demonstrated new bone formation macroscopically in all 16 cases. Solid fusion was observed in 57% (four of seven) OP-1 patients and 78% (seven of nine) autograft-HA-TCP patients. Histology demonstrated viable bone in six of seven OP-1 and in all of the control specimens. The authors concluded that in human posterolateral lumbar spine fusions, OP-1 reliably induced viable amounts of new

bone, but the fusion success rate evaluated by surgical exploration was only four of seven. This rate is comparable to that previously reported by Vaccaro et al., who used OP-1 as an adjunct to autograft, and is comparable to historical controls using iliac crest autograft alone.

OP-1 in compromised patients

Systemic comorbidities, such as nicotine abuse from smoking and metabolic disorders, affect proper vascular ingrowth at the fusion site and therefore compromise fusion [12]. Fehlings and colleagues studied the use of OP-1 in a series of nine patients in whom there were medical risk factors that would inhibit osseous union [5]. Examples of complications include Maroteaux-Lamy syndrome, adrenal insufficiency, hypertension, heavy smoking, morbid obesity, hypothyroidism and rheumatoid arthritis. In some patients multiple factors co-existed. The five female and four male patients ranged in age from 21–74 years. OP-1 was used in both lumbar (three) and cervical (six) fusions. Clinical results demonstrated changes in ODI from severe disability pre-operatively to minimal and moderate disability postoperatively. SF-36 showed overall improvement in mental and physical health scores. At greater than 3 months' follow-up, fusion was present in all patients. The authors concluded that OP-1 appears to be safe and effective in promoting spinal arthrodesis in patients in whom adverse medical risk factors exist.

Conclusion: spinal fusion

The FDA, under a Humanitarian Device Exemption (HDE), has approved OP-1 as a substitute for autogenous bone when performing revision posterolateral lumbar fusion. The use of OP-1 is considered to be approved for patients who have failed a posterolateral fusion and are considered to be at risk for repeated pseudarthrosis. Continued work is under way to help optimise the dose and carrier to improve results. OP-1 may replace or augment autograft bone in the wide spectrum of spinal pathology encountered in clinical practice. In human investigations, the fusion results with OP-1 alone generally have rivalled that of autograft. The safety and efficacy evaluations of OP-1 have established it as a viable replacement for autologous bone. In this role, it is expected to serve patients well, both by obviating the well-established morbidity associated with autograft harvest, and also by reducing the risk of spinal pseudarthrosis.

Future clinical investigations with BMPs

Although a significant number of studies have been conducted, they represent only the beginning of clinical

investigations with BMPs. Bone has been the foremost tissue target, but engineering repair and regeneration in other muscular skeletal tissues, such as cartilage, tendon and ligament, are also on the horizon. For example, OP-1 injected into the intervertebral disc in an animal model has demonstrated positive results in the treatment of degenerative disc disease. OP-1 is also being investigated as a disease modifier in osteoarthritis. Additionally, preclinical and clinical studies regarding dose, carriers, application of stem cells, combinations with other factors and routes of administration remain incompletely understood. In conclusion the positive clinical data for OP-1 demonstrate the promising therapeutic potential for this molecule and suggest an active future in a variety of musculoskeletal applications and conditions.

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