

## Review Article

# The Role of Bisphosphonates and Prostaglandins for the Treatment of Subchondral Insufficiency Fractures of the Knee: An Evidenced-Based Opinion

Zachary S. Aman, B.A.<sup>1a</sup>, Nicholas N. DePhillipo, PhD, MBA, ATC<sup>2b</sup>, Dane R.G. Lind<sup>2c</sup>, Travis J. Dekker, MD<sup>3d</sup>, Robert F. LaPrade, MD<sup>4e</sup>

<sup>1</sup> Sidney Kimmel Medical College, Thomas Jefferson University, <sup>2</sup> Orthopedic Surgery, University of Pennsylvania, <sup>3</sup> Orthopedics, Eglin Air Force Base, <sup>4</sup> Orthopedic Surgery, Twin Cities Orthopedics

Keywords: subchondral insufficiency fractures of the knee, SONK, bone marrow edema, bone bruising, cartilage

<https://doi.org/10.60118/001c.34672>

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## Journal of Orthopaedic Experience & Innovation

Vol. 3, Issue 2, 2022

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Subchondral Insufficiency Fractures of the Knee (SIFK) can result in accelerated cartilage degeneration and poor outcomes. The presence of SIFK is difficult to manage and can cause persistent knee swelling, pain, and prolonged disability. Pharmacologic agents to suppress extensive bone remodeling, improve blood supply, and reduce pain have been suggested as treatment for these lesions. Nonoperative management with prostaglandins and bisphosphonates has emerged as a potentially efficacious intervention for symptom reduction and resolution of knee bone marrow edema. However, previous reports of potential serious adverse effects including atypical femoral fractures of the proximal femur raise concerns for clinical safety. This evidence-based opinion article demonstrates the potential clinical efficacy of various pharmacologic therapies, including prostaglandins and bisphosphonates, for the treatment of SIFK. The overall rate of reporting adverse effects in the literature is high (47.3%), while significant clinical improvements have been identified in 66% to 100% of the patient population. This

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- a Zachary S. Aman is a medical student at Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, PA. His research interests include meniscus and anterior cruciate ligament injuries, multidirectional shoulder instability, and posttraumatic osteoarthritis of the knee.

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- b Nicholas DePhillipo, PhD, MBA, ATC, is a current research associate at the University of Pennsylvania in the Department of Orthopedic Surgery and also serves as COO of a biotechnology startup focused on improving drug delivery for musculoskeletal tissue applications. His expertise includes sports medicine, ACL, meniscus, complex knee, and drug delivery in orthopedics. Dr. DePhillipo's research mission is targeted at the intersection of academia and industry in order to bring innovative technologies from the lab and into the marketplace to improve patients lives.

[Connect with Dr. DePhillipo on LinkedIn](#)

[Conflicts of Interest Statement for Dr. DePhillipo](#)

- c Dane is a graduate student at the University of Pennsylvania and a cum laude graduate of Amherst College in 2020. Interested in sports medicine, he hopes to contribute to the field of cartilage/tissue regeneration and surgical rehabilitation through clinical research.

[Connect with Mr. Lane on LinkedIn](#)

[Conflicts of Interest Statement for Mr. Lane](#)

- d Dr. Travis Dekker is an orthopedic surgeon for the United States Air Force Academy serving as an assistant faculty member for the Uniformed Services University of Health Services Department of Surgery and Assistant Team Physician for the Air Force Academy Football team. Research interests include longitudinal clinical outcomes research, orthopedic biomechanics and functional rehabilitation studies.

[Conflicts of Interest Statement for Dr. Dekker](#)

- e Dr. LaPrade is a complex knee surgeon with a robust research program at Twin Cities Orthopedics in Edina, Minnesota.

[Conflicts of Interest Statement for Dr. LaPrade](#)

collective information may help guide physicians during prescription drug therapy for the treatment of SIFK.

## INTRODUCTION

It has recently been suggested that the term “subchondral insufficiency fracture of the knee” (SIFK) should replace the historical “spontaneous necrosis of the knee” (SONK) nomenclature due to evidence that SONK usually does not manifest spontaneously nor present with necrotic bone on histologic entities (Hussain et al. 2017). Rather, SIFK has been described as sequela of mechanical overloading of the knee, which is often attributable to meniscal lesions and extrusion (Hussain et al. 2017; Pareek et al. 2020). Despite the revised nomenclature, the optimal management of these lesions at initial presentation remains challenging. Patients with SIFK have demonstrated high rates of pain, chondral thinning, and progression to arthroplasty (Pareek et al. 2020; Filardo et al. 2015; Meier et al. 2013; Pareek et al. 2019; Strauss et al. 2011). It is necessary for orthopedic surgeons to understand pharmacologic treatment options in order to improve outcomes and ideally prevent arthroplasty in this patient population.

The goal of pharmacologic management of SIFK is to delay the progression of bone resorption while allowing for sufficient revascularization and mineralization of new bone to maintain the structural integrity of the subchondral bone (Meier et al. 2013). The two most commonly proposed drug classes for the treatment of SIFK, prostaglandins and bisphosphonates, target this pathway to improve blood supply, suppress extensive bone remodeling, and reduce pain (Kon et al. 2016). Prostaglandins cause vasodilation of the microvasculature and act as an anti-inflammatory agent, essentially decreasing local leukotriene concentration (Aktan et al. 1994; Erlansson et al. 1991; Erlansson, Svensjö, and Bergqvist 1989; Grant and Goa 1992). Bisphosphonates decrease bone resorption in metabolically active remodeling sites through osteoclast inhibition and reduce pain by inhibiting the local release of neuromediators (Meier et al. 2013; Buma et al. 1992; Cornish et al. 2011).

Recent studies have suggested that administration of pharmacologic agents may help improve clinical outcomes in animal models and in the clinical treatment of insufficiency fractures of the femoral head and talus (Bhatnagar et al. 2018; Breer et al. 2012; Jureus et al. 2012; Kraenzlin et al. 2010; Meier et al. 2013). As a result, bisphosphonates and prostaglandins have been proposed as possible treatment options for SIFK. However, limited data exist on the proposed treatment protocols, adverse effects, and clinical

efficacy. Therefore, the purpose of this evidence-based opinion was to report on the clinical efficacy of pharmacologic treatment in patients with SIFK and to report on the adverse effects of pharmacologic treatment.

## CLINICAL SAFETY & EFFICACY

The antiresorptive and analgesic properties of bisphosphonates have been reported to be effective in eleven prior studies. Although the exact mechanism of action for SIFK management is unclear, bisphosphonates can improve clinical symptomology by reducing subchondral lesion size (Bhatnagar et al. 2018; Kraenzlin et al. 2010; Agarwala, Sharoff, and Jagani 2019; Bartl, Imhoff, and Bartl 2012; Müller et al. 2019; Zippelius et al. 2018; Vasiliadis et al. 2021), reducing pain (Bhatnagar et al. 2018; Breer et al. 2012; Kraenzlin et al. 2010; Agarwala, Sharoff, and Jagani 2019; Bartl, Imhoff, and Bartl 2012; Müller et al. 2019; Vasiliadis et al. 2021; Kchler, Fehr, and Jeker 2020), and improving subjective function (Bhatnagar et al. 2018; Bartl, Imhoff, and Bartl 2012; Zippelius et al. 2018; Vasiliadis et al. 2021; Kchler, Fehr, and Jeker 2020; Baier et al. 2012). Similarly, iloprost has shown to be effective in reducing lesion size (Zippelius et al. 2018; Baier et al. 2012; Mayerhoefer et al. 2008, 2007) and pain (Baier et al. 2012; Mayerhoefer et al. 2008; Aigner et al. 2008), while also demonstrating accelerated healing rates as compared to analgesics (Mayerhoefer et al. 2008, 2007) and ibandronate (Baier et al. 2012) interventions. Oral iloprost has also demonstrated a lower incidence of adverse effects than intravenous and oral bisphosphonate treatment, suggesting that it may be a safe and effective treatment option among the currently investigated agents (Mayerhoefer et al. 2008, 2007). Furthermore, while prostaglandin and bisphosphonate treatments have been shown to have no significant differences in outcomes when directly compared, prostaglandins may offer additional therapeutic benefit by decreasing the duration of treatment and recovery time (Baier et al. 2012). Overall, these data highlight the early potential of such pharmacologic agents for the conservative treatment of patients using SIFK, with the majority of current bisphosphonate studies and all current prostaglandin studies describing beneficial effects including regression of radiographic lesion size, reduction in pain, acceleration of healing, or functional improvements from baseline after treatment. Therefore, these effects may demonstrate their possible role in protecting the structural integrity of the overlying



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knee cartilage. However, future placebo-controlled studies with consistent protocols and clinical reporting are needed to further elucidate the optimal pharmacologic treatment options before definitive clinical recommendations for SIFK management can be made.

Adverse reactions have been reported with the clinical use of bisphosphonates and prostaglandins for the treatment of SIFK. Among specific drugs, zoledronic acid has the highest rate of reported adverse effects (33%) among all agents (Müller et al. 2019), while oral iloprost has the lowest rate of reported adverse effects (0%) (Mayerhoefer et al. 2008, 2007). The most common adverse effects reported in patients include headache, fever, flu-like symptoms, and myalgia which are highly associated with intravenous protocols. Overall, there is a low incidence of adverse effects with prostaglandin administration and, to date, all reported reactions are solely limited to intravenous prostaglandin infusions (Baier et al. 2012; Gao et al. 2015). While no studies have directly compared the outcomes and side effect profiles between routes of administration for either prostaglandins or bisphosphonates, oral administration may be a promising alternative to infusions as oral agents appear to have lower rates of adverse reactions while providing clinical feasibility for the treatment of SIFK.

## TREATMENT PROTOCOLS

When evaluating different treatment protocols reported in the literature, there is a high rate of heterogeneity in treatment protocols for both prostaglandin and bisphosphonate classes to treat SIFK including route of administration,

dosage, frequency, and duration of treatment. Bisphosphonates have been administered either in isolation (Jureus et al. 2012; Bartl, Imhoff, and Bartl 2012; Baier et al. 2012) or as a part of a combination therapy regimen with vitamin D supplementation (Meier et al. 2013; Breer et al. 2012; Kraenzlin et al. 2010; Müller et al. 2019), NSAIDs (Meier et al. 2013; Bhatnagar et al. 2018), or alprostadil (Gao et al. 2015). Prostaglandin therapy has been described either in isolation (iloprost) (Zippelius et al. 2018; Baier et al. 2012; Mayerhoefer et al. 2008, 2007; Aigner et al. 2008) or in combination therapy (alprostadil with alendronate) (Gao et al. 2015). There is also heterogeneity among study designs and between comparison groups in Level-I and II clinical trials, which further limits the ability to provide a definitive clinical recommendation for the use of pharmacologic agents in treating SIFK. Therefore, as the inconsistency in reported treatment protocols and the heterogeneity of study designs and comparison groups of Level-I and II studies may provide an explanation for conflicting evidence for pharmacologic efficacy, future studies should focus on optimizing currently reported treatment protocols by conducting long-term, controlled investigations with analgesic or placebo comparison groups. Treatment protocols of bisphosphonates and prostaglandins reported for the treatment of SIFK are summarized in [Table 1](#).

The authors acknowledge limitations that are inherent to an evidence-based opinion article as well as the heterogeneity among presented research studies and complexity of the pathological condition. The clinical outcomes of SIFK may be influenced by the management of the underlying etiology of SIFK (Hussain et al. 2017). Furthermore,



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**Table 1. Summary table of reported treatment regimens for subchondral insufficiency fractures of the knee (SIFK).**

| Medication and ROA                                    | Number of Reported Protocols | Sample Size (n) | Dosage                                                                  | Frequency                                                                               | Duration                                                             | Adverse Reactions (rate)                                                                                                                                                                                       | Final Follow Up (mean, range) |
|-------------------------------------------------------|------------------------------|-----------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Intravenous iloprost                                  | N=3                          | 32              | 20-50 mcg or 0.5mg/kg/min over 5-6 hours                                | 5 total infusions                                                                       | 5 days                                                               | Headache (6.25%), increasing pain (12.5%), flush-like symptom (9.4%), facial rash (18.8%), all occurring during first 30 min of infusion<br>All symptoms except headache dissipated with slowing infusion rate | 17.7 months (8-33)            |
| Intravenous ibandronate                               | N=3                          | 48              | 3-6 mg                                                                  | 1-3 total infusions                                                                     | 3 months                                                             | Mild acute-phase reactions with flu-like symptoms (20%).<br>Musculoskeletal pain (4.1%)                                                                                                                        | 21.8 months (12-64)           |
| Oral iloprost                                         | N=2                          | 35              | Days 1-3: 50 mcg<br>After day 3: 50 - 100 microg                        | Days 1-3: 3x daily<br>After day 3: Range: 50 microg 2x daily up to 2x50 microg 3x daily | 4 weeks                                                              | 0%                                                                                                                                                                                                             | 7.5 months (3-12)             |
| Oral alendronate and intravenous alprostadil          | N=1                          | 20              | alendronate - 70 mg<br>Alprostadil - 10 mcg                             | 1x/week<br>1x/day                                                                       | NR                                                                   | Alprostadil - headache (15%), facial rash (10%) during first 1 hr. of transfusion<br>alendronate - 0%                                                                                                          | 13 months                     |
| Intravenous Ibandronate + oral vitamin D              | N=3                          | 19              | ibandronate - 3-13.5 mg<br>vitamin D - 400-20,000                       | 2-5 total infusions<br>1x/day to 1x/week                                                | 1 year                                                               | ibandronate - myalgia, flu-like symptoms, exhaustion, fever (3.67%)                                                                                                                                            | 7.5 months (4-12)             |
| Oral ibandronate + NSAID (etoricoxib)                 | N=1                          | 8               | ibandronate - 150 mg<br>etoricoxib - 120 mg                             | ibandronate - 1x per month<br>etoricoxib - 1x per day                                   | ibandronate - 1 year<br>etoricoxib - 2 weeks                         | Adverse reactions were not reported                                                                                                                                                                            | 12 months                     |
| Oral alendronate                                      | N=1                          | 17              | 70 mg                                                                   | 1x/week                                                                                 | Minimum 6 mo. (range, 6-21)                                          | Gastrointestinal symptoms (5.9%)<br>Unspecified (5.9%)                                                                                                                                                         | 12 months                     |
| Intravenous pamidronate/ oral alendronate + vitamin D | N=1                          | 28              | pamidronate - 120 mg<br>alendronate - 70 mg<br>vitamin D - 400 - 800 IU | 3 - 4 infusions<br>1x/week<br>1x/day                                                    | First two weeks<br>4 - 6 months<br>after first two weeks<br>6 months | pamidronate acute phase reaction (14.3%) with arthralgias and myalgias<br>alendronate - 0%<br>vitamin D - 0%                                                                                                   | 6-12 months                   |

| Medication and ROA                                                        | Number of Reported Protocols | Sample Size (n) | Dosage                                               | Frequency                                     | Duration               | Adverse Reactions (rate) | Final Follow Up (mean, range) |
|---------------------------------------------------------------------------|------------------------------|-----------------|------------------------------------------------------|-----------------------------------------------|------------------------|--------------------------|-------------------------------|
| IV zoledronic acid + oral alendronate with calcium, vitamin D, and NSAIDs | N=1                          | 11              | zoledronic acid – 5 mg/ 100ml<br>alendronate – 70 mg | Single infusion of ZA<br>2 doses of 35 mg/day | First week<br>16 weeks | 0%                       | 16 weeks                      |
| IV zoledronic acid                                                        | N=1                          | 32              | zoledronic acid – 5 mg/ 100ml                        | Single infusion                               | First week             | Myalgias – 0.07%         | 6 months                      |

mcg; micrograms, mg; milligrams, OA; osteoarthritis. BME; bone marrow edema. ROA; route of administration. NR; not reported.

failure to address meniscal root pathology or iatrogenic cartilage damage secondary to arthroscopy may negatively affect the outcomes of patients receiving pharmacologic treatment for SIFK. Due to an historical lack of clarity in the definition of SIFK, there are several overlapping etiologies which may influence the efficacy of bisphosphonates and prostaglandins.

## CONCLUSION

This evidence-based opinion article highlights the preliminary evidence that both bisphosphonates and prostaglandins may be safe and beneficial agents for the treatment of SIFK. Further placebo-controlled trials with consistent treatment protocols and long-term clinical outcomes are necessary before definitive clinical recommendations can be made.

Submitted: March 04, 2022 EDT, Accepted: April 16, 2022 EDT



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