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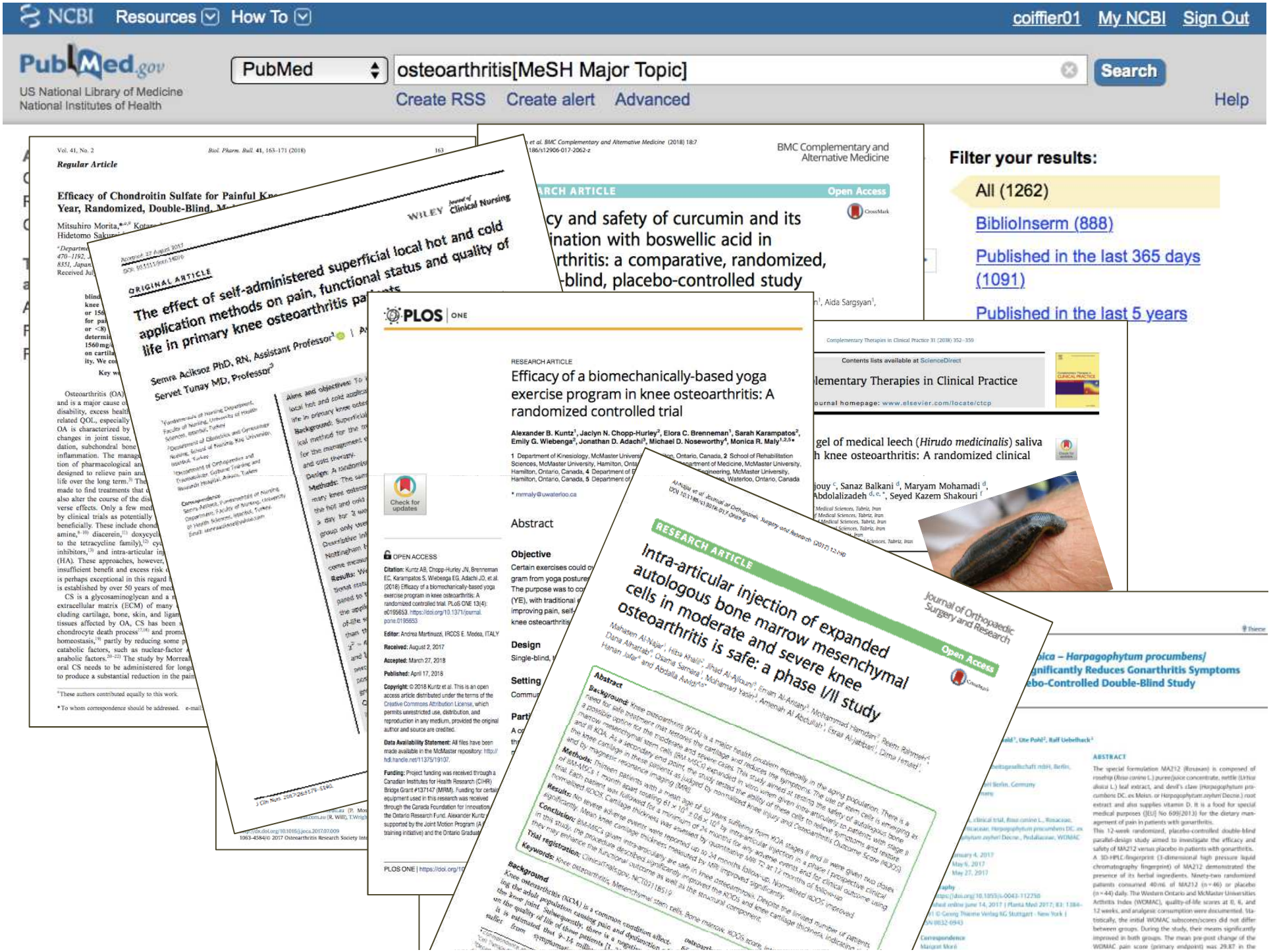
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RESEARCH ARTICLE
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cy and safety of curcumin and its
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rthritis: a comparative, randomized,
-blind, placebo-controlled study
WILEY Journal of Clinical Nursing
ORIGINAL ARTICLE
The effect of self-administered superficial local hot and cold
application methods on pain, functional status and quality of
life in primary knee osteoarthritis pa
Semra Aciksoz PhD, RN, Assistant Professor
Servet Tunay MD, Professor
PLOS ONE
RESEARCH ARTICLE
Efficacy of a biomechanically-based yoga
exercise program in knee osteoarthritis: A
randomized controlled trial
Alexander B. Kuntz, Jaclyn N. Chopp-Hurley, Elora C. Brenneman, Sarah Karampatos, Emily G. Wiebenga, Jonathan D. Adachi, Michael D. Noseworthy, Monica R. Maly
Abstract
Objective
Design
Setting
OPEN ACCESS
Complementary Therapies in Clinical Practice 31 (2018) 352–359
Contents lists available at ScienceDirect
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journal homepage: www.elsevier.com/locate/ctcp
gel of medical leech (Hirudo medicinalis) saliva
h knee osteoarthritis: A randomized clinical
RESEARCH ARTICLE
Intra-articular injection of expanded
autologous bone marrow mesenchymal
cells in moderate and severe knee
osteoarthritis is safe: a phase I/II study
Journal of Orthopaedic Surgery and Research
Open Access
Abstract
Background
Methods
Results
Conclusion
Trial registration
Keywords
Harpagophytum procumbens/
gnificantly Reduces Gonarthritis Symptoms
ebo-Controlled Double-Blind Study
ABSTRACT

MINI-REVIEW

Journal of Cellular Physiology

Systemic and Local Adipose Tissue in Knee Osteoarthritis

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Osteoarthritis is a common chronic joint disorder affecting older people. The knee is the major joint affected. The symptoms of osteoarthritis include limited range of motion, joint swelling, and pain causing disability. There are no disease modifying drugs available, and treatments are mainly focused on pain management. Total knee replacement performed at the end stage of the disease is considered the only cure available. It has been found that obese people have an increased risk to develop not only knee but also hand osteoarthritis. This supports the concept that adipose tissue might be related to osteoarthritis not only through overloading. As matter of fact, obesity induces a low grade systemic inflammatory state characterized by the production and secretion of several adipocytokines that may have a role in osteoarthritis development. Furthermore, hypertension, impaired glucose, and lipid metabolism, which are comorbidities associated with obesity, have been shown to alter the joint tissue homeostasis. Moreover, infrapatellar fat pad in the knee has been demonstrated to be a local source of adipocytokines and potentially contribute to osteoarthritis pathogenesis. Here, we discuss the role of systemic and local adipose tissue in knee osteoarthritis.

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In the past, osteoarthritis (OA) was defined as a degenerative disease mainly related to cartilage degradation. New evidence suggests to consider OA as a whole joint disease (Loeser et al., 2012). According to this, the 2010 EULAR recommendations for diagnosis of knee OA (KOA), defined OA as a common joint disorder showing focal cartilage loss, new bone formation, and involvement of all joint tissues, including menisci and synovial membrane (SM) (Zhang et al., 2010). Actually, only palliative pharmacological treatments are available for this pathology, which is the most common joint disorder causing pain and disability in older adults (Loeser et al., 2012). Since no disease modifying drugs are available, patients still undergo total joint replacement at the end stage disease as the only curative treatment with significant medical costs for the society. The knee is the major joint affected by OA followed by the hip (Cross et al., 2014). OA confirmed by X-ray has been estimated to affect 3.8 % of the people worldwide in 2010 (Cross et al., 2014). The prevalence is higher in females than in males and the peak of onset is at about 50 years of age (Cross et al., 2014). In the United States, OA is the most common joint disorders with a prevalence of 10% in men and 13% in women with 60 years of age or older (Zhang and Jordan, 2010). It is evident that these numbers will increase in the future because of the dramatic increase in average life expectancy associated with population aging and obesity (Zhang and Jordan, 2010). The diagnosis is still based on symptoms (usage-related pain, often worse toward the end of the day and relieved by rest, short-lived stiffness), functional limitation, clinical and radiographic findings, and risk factors (age, gender, body mass index [BMI], occupation, family history of OA, and history of knee injury) (Zhang et al., 2010). Plain radiography is the current "gold standard" for morphological assessment of KOA (Favero et al., 2015a). Classical features are focal joint space narrowing, osteophytes, subchondral bone sclerosis, and subchondral "cysts." The introduction of new imaging techniques such as magnetic resonance imaging (MRI) enables visualization of not only of cartilage defects and subchondral bone changes, but also bone marrow lesions, synovial inflammation (synovitis), and meniscal tears (Favero et al., 2015a).

OA is often associated with low-grade synovitis and increasing evidence supports that synovial inflammation is correlated with joint pain and dysfunction (Sellam and Berenbaum, 2010). Synovitis pathogenesis seems to be related to cartilage degradation: catabolic enzymes and mechanical stress induce the release of cartilage breakdown products from the extracellular matrix in the synovial fluid (SF). Cartilage fragments are phagocytized by synovial cells, the synoviocytes, determining the activation of SM (Sellam and Berenbaum, 2010). As a consequence, SM becomes hyperplasic and hypertrophic and synoviocytes release pro-inflammatory cytokines and matrix hydrolytic enzymes such as

Elisa Belluzzi and Hamza El Hadi contributed equally to the manuscript

Conflict of interest: The authors declare no conflicts of interest related to any aspects of the presented manuscript.

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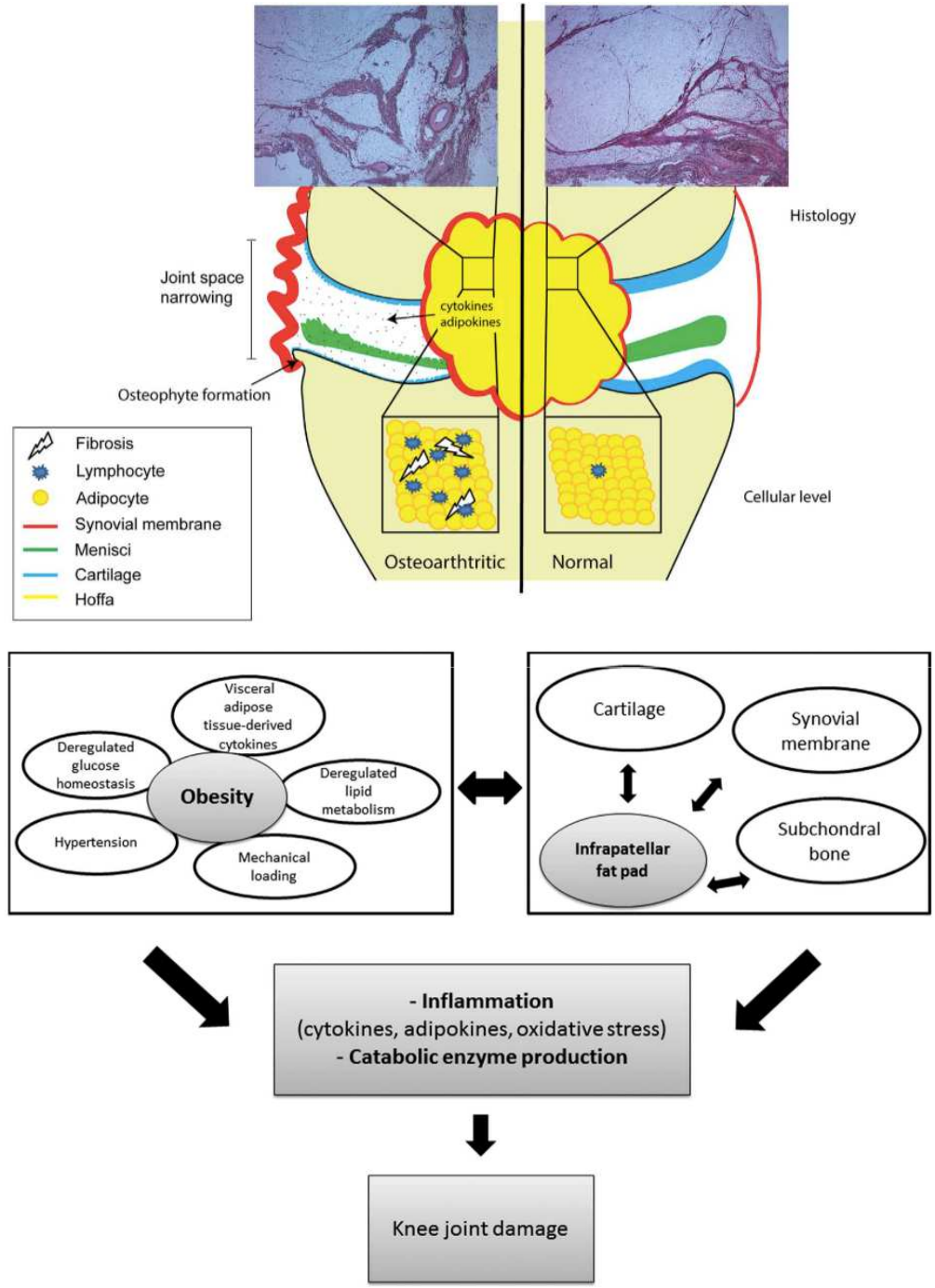

Belluzzi E. J Cell Physiol. 2017;232(8):1971-8.

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ORIGINAL PAPER

Viscosupplementation in patients with severe osteoarthritis of the knee: six month follow-up of a randomized, double-blind clinical trial

André Luiz Siqueira Campos[1,2] · Rodrigo Satamini Pires e Albuquerque[3] · Edmilson Barbosa da Silva[1] · Sami Gobbi Fayad[1] · Lucas Delunardo Acerbi[1] · Felipe Nunes de Almeida[1] · Nelson Hiroyuki Myiabe Ooka[1] · José Sergio Franco[4] · Vinícius Schott Gameiro[3]

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Abstract
Purpose To analyze the early outcomes of viscosupplementation in patients with severe knee osteoarthritis.
Method A randomized, double-blind clinical trial of 143 knees divided into three groups: Group 1 – intra-articular injection of triamcinolone; Group 2 – hylan GF20; and Group 3 – triamcinolone + hylan GF20. Outcomes were evaluated using Lysholm and KSS scores before treatment and after one, three and six months.
Results Within-group comparisons revealed improvements in Lysholm scores in all groups in the one month evaluation relative to pre-treatment levels ($p < 0.01$). This improvement was maintained in the third month after treatment ($p > 0.05$). Scores at six months were significantly lower than those observed in the previous follow-up assessments ($p < 0.05$), but still higher than pre-treatment levels ($p < 0.05$). KSS scores also improved after one month relative to pre-treatment levels ($p < 0.01$). This improvement was still present at three and six months after treatment in the corticosteroid group ($p > 0.05$). Patients treated with hylan GF20 showed lower scores in the last evaluation relative to month one ($p < 0.05$). No significant differences were observed between the treatment groups ($p > 0.05$).
Conclusions Viscosupplementation increased functional scores in patients with severe osteoarthritis of the knee, especially within three months of injection. However, it was not superior to the use of triamcinolone.

Keywords Knee · Osteoarthritis · Treatment · Viscosupplementation

Introduction

Population aging has led to a significant increase in the incidence of degenerative joint disease, and consequently, in joint replacement surgery such as total knee arthroplasty [1–3]. In Brazil, the demand for total knee arthroplasty far exceeds the capacity of the public health system, resulting in long and lengthy waiting lists at reference centres. Since all patients with this condition experience severe pain and functional limitations, palliative care is often required to relieve their suffering as they wait, sometimes years, for surgery.

The administration of corticosteroids by intra-articular injection can provide symptom relief, but only for a limited time [4–6]. Viscosupplementation, on the other hand, has shown positive effects on the medium-term for the treatment of joint pain caused by osteoarthritis of the knee [3, 5–11]. While the results of viscosupplementation only appear after the fourth week of treatment, the addition of corticosteroids to viscosupplementation leads to symptom improvements as early as the first few days after administration [4–6].

To date, few studies have discussed the benefits of viscosupplementation in patients with severe osteoarthritis of

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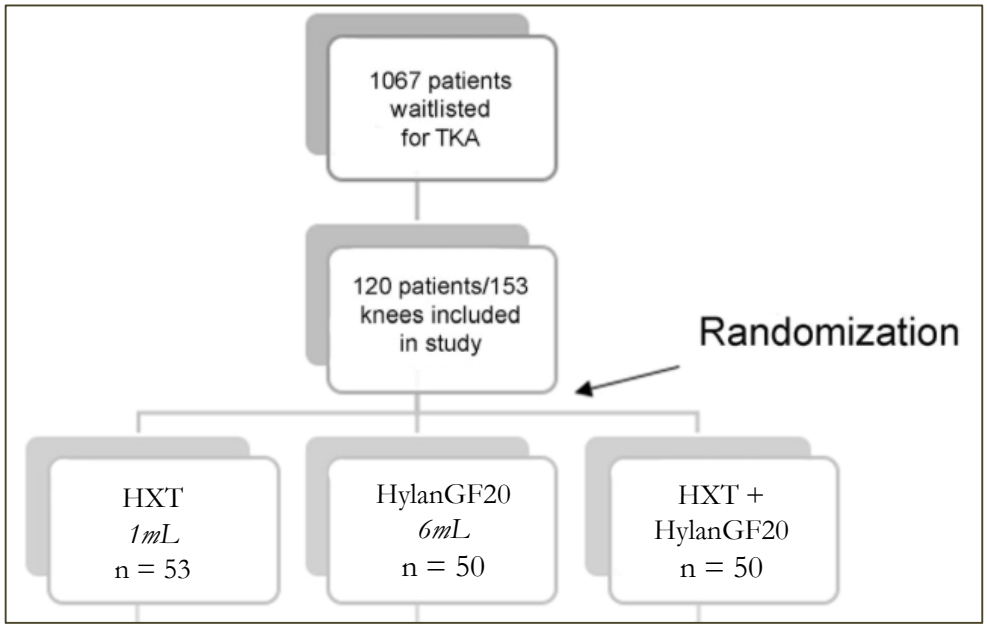
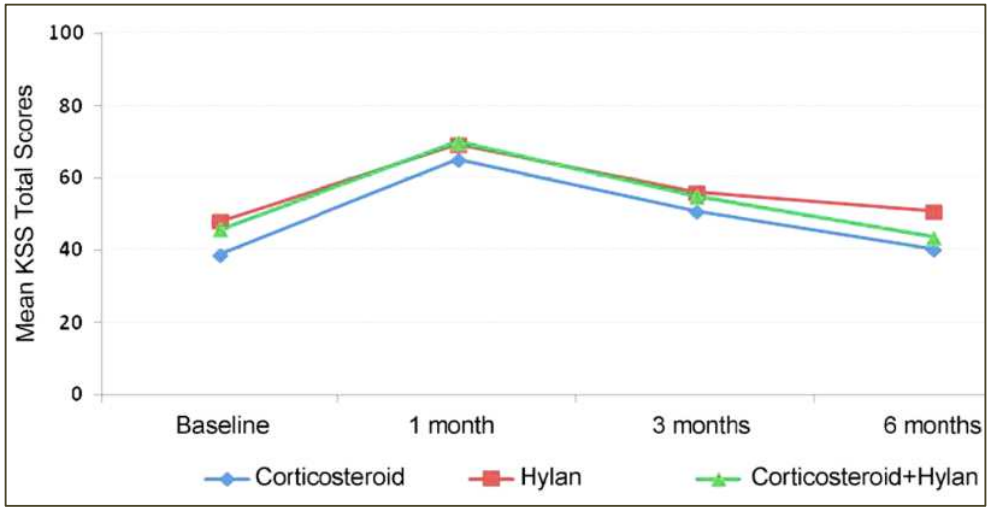
4 Orthopedics Department, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil



88 Femmes, 32 Hommes
Gonarthrose Kellgren-Lawrence IV



Campos ALS. Int Orthop. 2017;41(11):2273-80.

Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(1) 326–334

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SAGE

Efficacy and safety of adalimumab by intra-articular injection for moderate to severe knee osteoarthritis: An open-label randomized controlled trial

Jianping Wang

Abstract

Objective: To evaluate the efficacy and safety of adalimumab (ADA) versus hyaluronic acid (HA) by intra-articular injection for moderate to severe knee osteoarthritis.

Methods: Fifty-six consecutive patients with moderate to severe knee osteoarthritis were randomly allocated to either the ADA group or HA group. On day 0, patients in the ADA group received 10 mg of ADA by intra-articular injection, while those in the HA group received 25 mg of HA. All patients received celecoxib at 200 mg/day for 4 weeks. The pain visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Patient Global Assessment (PGA), and Physician Global Assessment (PhGA) scores were assessed.

Results: At baseline, the pain VAS, WOMAC, PGA, and PhGA scores were similar between the two groups. The decrease in the pain VAS score, WOMAC pain score, WOMAC physical function score, and WOMAC total score from baseline to week 4 were greater in the ADA than HA group. A greater decrease in the PGA and PhGA scores from baseline to week 4 was noted in the ADA than HA group. No difference in adverse events was observed between the two groups.

Conclusion: ADA by intra-articular injection was effective and tolerated for moderate to severe knee osteoarthritis.

Keywords

Efficacy, safety, adalimumab, intra-articular, knee osteoarthritis, hyaluronic acid

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Introduction

Osteoarthritis (OA), a major source of pain, stiffness, and motor disorders, has a remarkable influence on the quality of life of affected patients.[1] As a dominant type of

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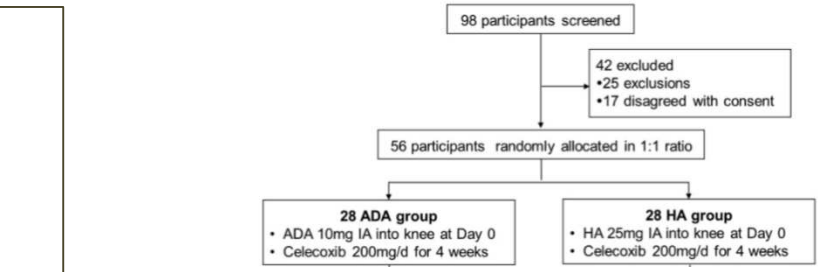
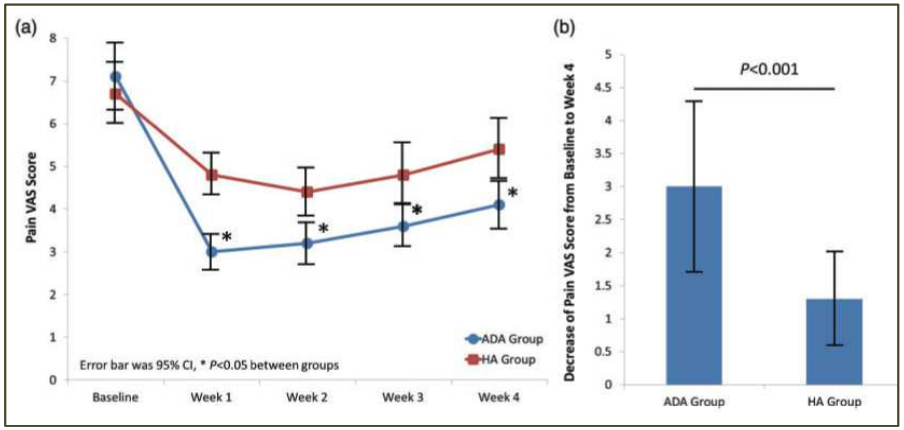
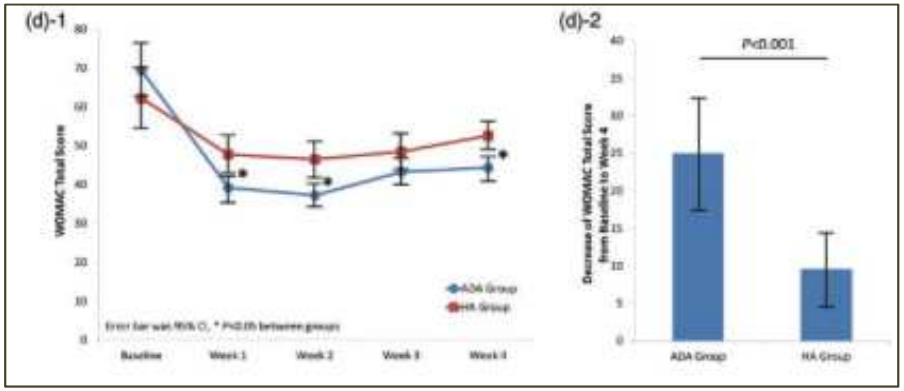


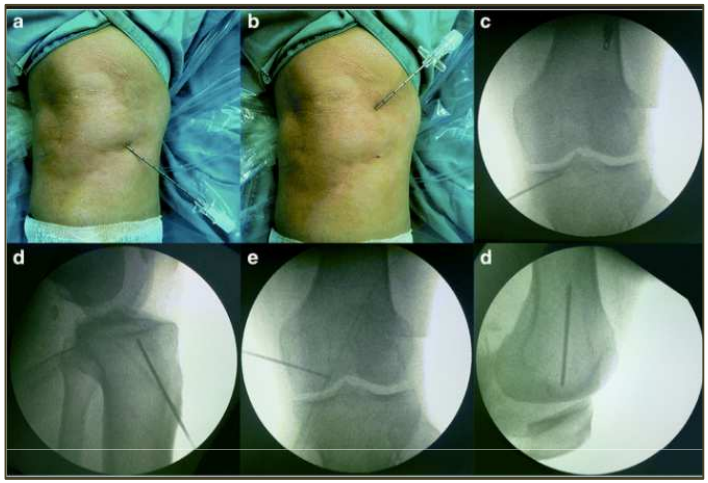


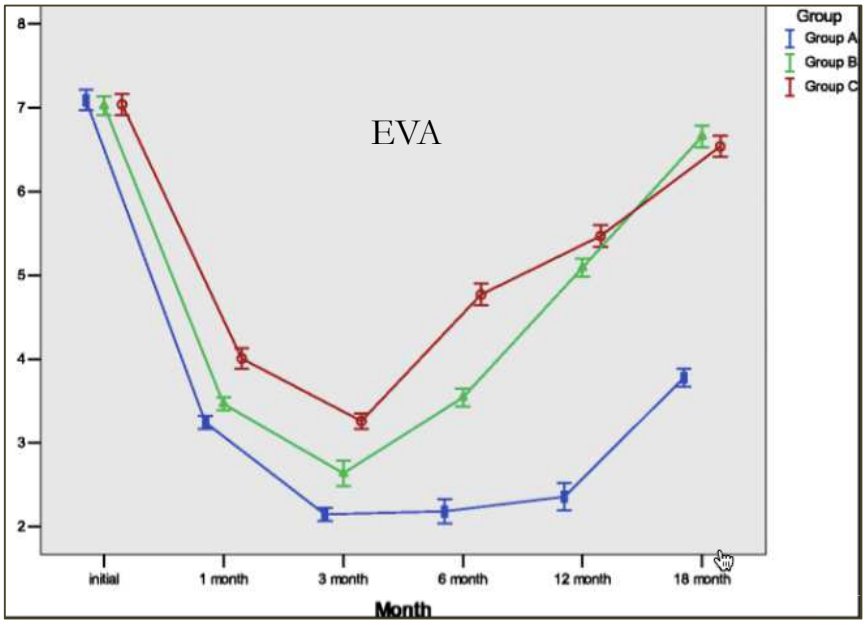


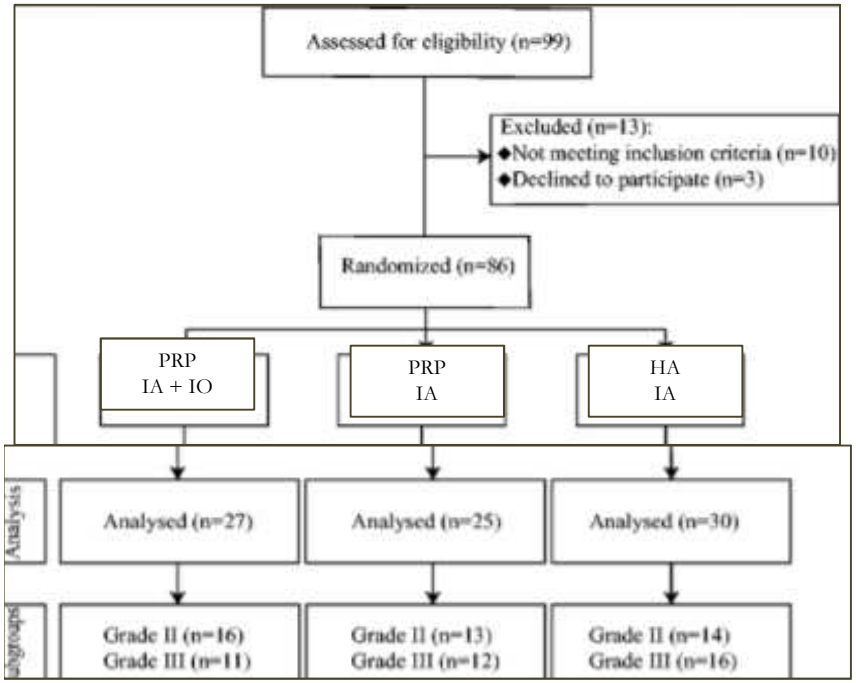
Items	ADA group (n = 28)	HA group (n = 28)	*P*-value
PGA score			
Baseline	7.2 ± 1.6	6.9 ± 1.8	0.513
Week 4	4.7 ± 1.1	5.2 ± 1.4	0.143
Change from baseline to week 4	2.5 ± 1.0	1.7 ± 0.9	0.003
PhGA score			
Baseline	7.5 ± 1.9	7.1 ± 1.9	0.434
Week 4	4.9 ± 1.3	5.4 ± 1.6	0.205
Change from baseline to week 4	2.6 ± 1.1	1.7 ± 1.0	0.002

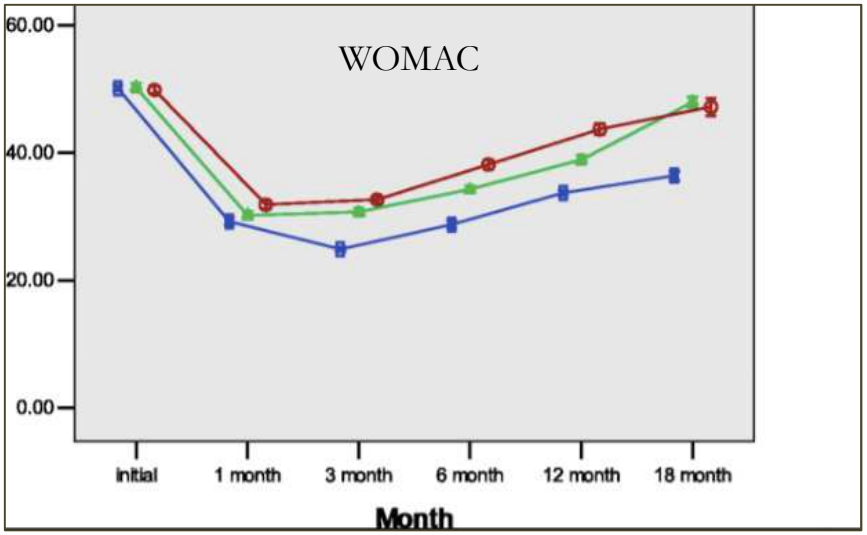
Wang J. J Int Med Res. 2018;46(1):326-34.

Comparison of hyaluronic acid and PRP intra-articular injection with combined intra-articular and intraosseous PRP injections to treat patients with knee osteoarthritis.









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Clinical Interventions in Aging

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ORIGINAL RESEARCH

The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis

This article was published in the following Dove Press journal:
Clinical Interventions in Aging

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Farnad Imani[1]
Seyed Hamid Reza Faiz[2]
Saeed Reza Entezary[3]
Mahnaz Narimani Zamanabadi[4]
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Introduction: Osteoarthritis (OA) is a chronic joint disease that usually occurs in older people and leads to pain and disabilities. OA treatment ranges from drug therapy to surgery. Drug and rehabilitation therapy are preferred over surgery, and, especially, there is a tendency toward compounds causing regenerative changes in the knee joint. In the present study, the effects of platelet-rich plasma (PRP) injection and prolotherapy (PRL) were examined on the level of pain and function of the knee joint in patients with OA.

Methodology: After fulfilling the inclusion criteria and signing the informed consent form, 42 patients with knee OA were scheduled for intra-articular injection in the present randomized, double-blind, clinical trial. Following admission to the operating pain room, the condition of the patient's knee was evaluated first via the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and, then, ultrasound-guided knee injection was done. Accordingly, patients in the PRP therapy group received 7 mL PRP solution and those in the PRL group received 7 mL 25% dextrose. Using the WOMAC, levels of pain and knee function were evaluated and recorded for each patient immediately prior to the first injection as well as at 1 month (immediately prior to the second injection), 2 months (a month after the second injection), and 6 months later. Data collected were analyzed using the SPSS v.20.

Results: During the first and second months, a rapid decrease in the overall WOMAC score was observed in both groups. The overall WOMAC score increased at the sixth month, but was lower than the overall WOMAC score in the first month. Statistical analysis indicated that the overall WOMAC score significantly decreased in both groups of patients over 6 months.

Conclusion: Results of the present study suggested a significant decrease in the overall WOMAC score of patients who undergo either PRP therapy or PRL. This positive change in the overall WOMAC score led to an improvement in the quality of life of patients with knee OA shortly after the first injection. PRP injection is more effective than PRL in the treatment of knee OA.

Keywords: knee osteoarthritis, platelet-rich plasma, prolotherapy, ultrasound

Introduction

Aging affects almost all physiological processes and causes changes in body composition. Recently, a triad encompassing simultaneous destruction of bone, muscle, and adipose tissues has been identified and named the *osteosarcopenic obesity syndrome*.[1–3] Osteopenia is the other problem that affects old people, especially in the neck of the femur or lumbar spine. Almost 80% of the American population over age 65 suffers from osteoarthritis (OA). OA is a chronic age-related joint disease that usually occurs in older people and damages articular cartilage and synovial joints. OA causes

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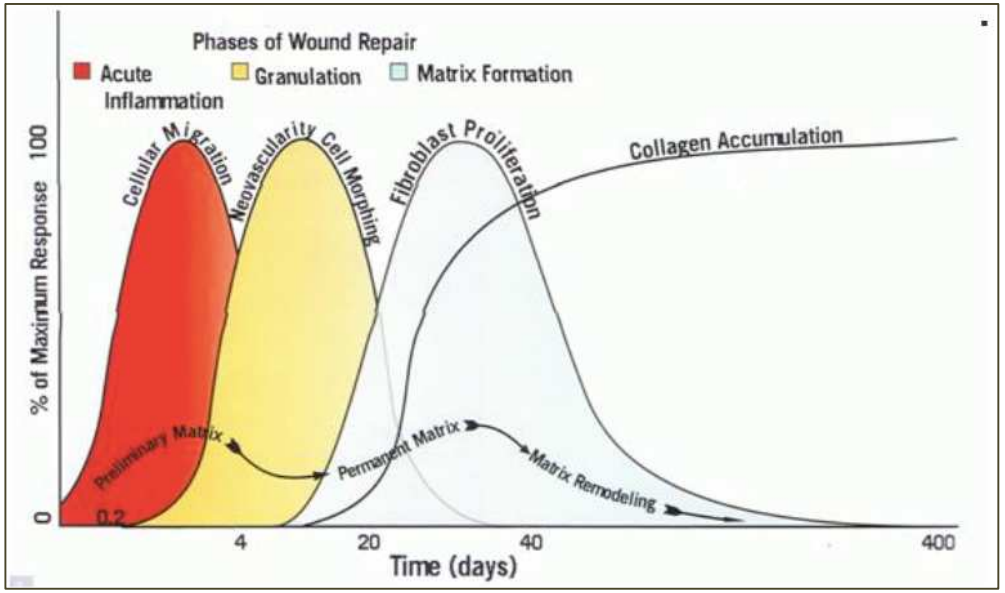

Prolotherapy = Injection Dextrose 25 %

Table 6 Comparison of WOMAC between two groups in successive months

	Pretreatment	First month	Second month	Sixth month	Repeated-measures test All
PRL	67.1±7.9	43.8±8.2	34.8±6.9	38.7±6.6	<0.001
PRP	67.9±7.3	42.9±10.85	27.1±9.1	31.4±10.2	<0.001
P-value of between-group comparison in similar times	0.74	0.77	0.004	0.009	
Mix model ANOVA *P*-values					
Group	0.097				
Time	<0.001				
Time*group	0.001				

Rahimzadeh P. Clin Interv Aging. 2018;13:73-9.

Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Hua-feng Zhang[1]
Chen-guang Wang[1]
Hui Li[1]
Yu-ting Huang[2]
Zhi-jun Li[1]

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Purpose: Platelet-rich plasma (PRP) and hyaluronic acid (HA) have been increasingly used in recent years to treat knee osteoarthritis (OA). However, whether PRP is superior to HA is controversial.

Methods: We conducted an electronic search of PubMed, Embase, ScienceDirect, and Cochrane library. The pooled data were analyzed using RevMan 5.1.

Results: Three prospective and ten randomized trials were identified. PRP injections reduced pain more effectively than HA injections in OA of the knee at 6 months (mean difference [MD]=−14.18; 95% confidence interval [CI]: −26.12 to −2.23; P=0.02; I^2=95%) and 12 months (MD=−15.25; 95% CI: −22.17 to −8.32; P<0.01; I^2=81%) of follow-up evaluated by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, while the VAS showed no significant difference at 3 months (MD=−0.98; 95% CI: −2.55 to 0.59; P=0.22; I^2=90%) and 6 months (MD=−0.82; 95% CI: −1.80 to 0.16; P=0.1; I^2=83%). Additionally, similar results were observed for the function recovery according to the WOMAC function score and EuroQol-visual analog scales.

Conclusion: The intra-articular injection of PRP was not obviously superior to HA in knee OA. Due to the limited quality and data of the evidence currently available, more high-quality randomized controlled trials are required.

Keywords: knee, osteoarthritis, hyaluronic acid, platelet-rich plasma

Introduction

Osteoarthritis (OA) is the most common joint disease with characteristics of progressive loss of joint cartilage, changes in the synovial membrane, and reduced viscosity of the synovial fluid.[1] More than 30% of people over 50 years of age suffer from knee OA based on radiographic imaging.[2] The need for knee arthroplasty has significantly increased, resulting in economic burdens from pain control and work performance loss with an increase in life expectancy[3] and the obesity epidemic.[4,5]

Despite societal and health care advances, there are no medications or surgical interventions yet proven to alter the course of OA development. Topical medications are often used intra-articularly to relieve pain and increase joint functions, but they are not effective in cases of severe OA.[6] Intra-articular hyaluronic acid (HA) injection is widely used for treating knee OA, which provides treatment efficacy due to its visco-induction properties of increasing joint lubrication, as reported in many studies and meta-analysis.[7,8]

The promotion of growth factors in cartilage repair has been studied in vitro and in vivo[9–12] to stimulate cell functions, such as proliferation and differentiation, matrix synthesis, and chondrocyte metabolism.[13] Platelet-rich plasma (PRP) is an autologous

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Reference	Group	Age (years)	Gender (M/F)	OA type (C/E/A)	BMI (kg/m²)	Intervention
Kon et al, 2011[9]	PRP	50.6±13.8	30/20	C22; E20; A8	24.6±3.2	3 times, 5 mL, every 2 weeks
	HWHA	54.9±12.6	25/25	C21; E19; A10	24.8±3.5	30 mg/2 mL, 1,000 to 2,900 kDa
	LWHA	53.2±13.0	27/23	C19; E22; A9	26.2±2.2	20 mg/2 mL, 500 to 730 kDa
Cerza et al,[26] 2012	PRP	66.5±11.3	25/35	E 21/24/15	N	4 times, 5.5 mL, weekly
	HA	66.2±10.6	28/32	E 25/22/13	N	4 times, 20 mg/2 mL
Sanchez et al,[20] 2012	PRP	60.5±7.9	43/46	E 45/32/12	27.9±2.9	3 times, 8 mL, weekly
	HA	58.9±8.2	42/45	E 42/32/11	28.2±2.7	3 times
Spakova et al,[25] 2012	PRP	52.8±12.4	33/27	E 2/39/19	27.9±4.1	3 times, 3 mL, weekly
	HA	53.2±14.5	31/29	E 2/37/21	28.3±4.0	3 times
Say et al,[24] 2013	PRP	55.2±7.8	5/40	E 1/17/27	32.4±4.0	1 time
	LWHA	56.2±5.1	6/39	E 1/15/29	32.3±3.3	3 times, 25 mg/2.5 mL, 730 to 900 kDa, weekly
Vaquerizo et al,[27] 2013	PRP	62.4±6.6	16/32	E 0/14/26; A8	30.7±3.6	3 times, 8 mL, every 2 weeks
	HWHA	64.8±7.7	22/26	E 0/18/21; A9	31.0±4.6	1 time, 60 mg/3 mL
Filardo et al,[28] 2015	PRP	53.3±13.2	60/34	E 2.0±1.1	26.6±4.0	3 times, 5 mL, weekly
	HWHA	57.6±11.8	52/37	E 2.0±1.1	26.9±4.4	3 times, 20 mg/2 mL, >1,500 kDa, weekly
Gormeli et al,[29] 2017	PRP*	53.7±13.1	23/16	E 26; A13	28.7±4.8	3 times, 5 mL, weekly
	PRP#	53.8±13.4	25/19	E 25; A14	28.4±4.4	1 time, 5 mL
	HA	53.5±14	22/17	E 27; A13	29.7±3.7	3 times, 20 mg/2 mL, weekly
Raeissadat et al,[30] 2015	PRP	56.9±9.1	8/69	E6/44/38; A12	28.2±4.6	2 times, 5 mL, monthly
	LWHA	61.1±7.5	15/47	E0/47/37; A16	27.0±4.2	3 times, 20 mg/2 mL, 500 to 730 kDa, monthly
Lana et al,[31] 2016	PRP	60.9±7	7/29	E 9/14/13	27.4±6.9	1 time, 5 mL
	HWHA	60±6.6	3/33	E 9/16/11	28.2±8.8	20 mg/2 mL, 2,400 to 3,600 kDa
	P&A	62±6.1	6/27	E 5/14/14	29.2±7.3	5 mL+2 mL
Duymus et al,[32] 2017	PRP	60.4±5.1	1/32	E 0/22/11	27.6±4.6	2 times, 5 mL per time, every 2 weeks
	HWHA	60.3±9.1	1/33	E 0/24/10	28.4±3.6	40 mg/2 mL, 1,600 kDa
Montanez-Heredia et al,[33] 2016	PRP	66.3±8.3	12/15	E 5/10/12	29.0±5.5	3 times, every 2 weeks
	LWHA	61.5±8.6	9/17	E 2/9/15	30.4±4.9	3 times, 25 mg/2.5 mL, 799 kDa
Cole et al,[21] 2017	PRP	55.9±10.4	28/21	E 3/2620	27.4±3.9	3 times, 4 mL, weekly
	LWHA	56.8±10.5	20/30	E 1/27/22	29.0±6.4	3 times, 16 mg/2 mL, 6,000 kDa

Notes: *Three injections of PRP; #one injection of PRP. OA type (C/E/A): chondropathy, Kellgren grade 0/early, Kellgren grade I to III/advanced, Kellgren grad
Abbreviations: OA, osteoarthritis; BMI, body mass index; PRP, platelet-rich plasma; HA, hyaluronic acid; HWHA, high-molecular weight hyaluronic low-molecular weight hyaluronic acid; P&A, PRP and HA.

Table 3 Results of the meta-analysis

Follow-up	Evaluation tools	Studies	Patients (PRP/HA)	MD	95% CI	P<0.05	I^2
3 months	WOMAC total score	3	153/154	−10.82	−19.74 to −1.91	Yes	89%
	WOMAC pain	2	82/84	−0.5	−1.66 to 0.66	No	81%
	VAS	2	78/79	−0.98	−2.55 to 0.59	No	95%
	EQ VAS	2	144/139	5.91	−1.51 to 13.34	No	79%
6 months	WOMAC total score	5	290/289	−14.18	−26.12 to −2.23	Yes	95%
	WOMAC pain	4	219/219	−2.0	−3.60 to −0.39	Yes	90%
	VAS	2	78/79	−0.82	−1.80 to 0.16	No	83%
	WOMAC function	3	170/169	−5.78	−14.73 to 3.16	No	92%
	EQ VAS	4	232/228	2.19	−11.47 to 15.85	No	98%
	IKDC	4	232/228	8.53	4.52 to 12.53	Yes	79%
12 months	WOMAC total score	4	207/194	−15.25	−22.17 to −8.32	Yes	81%
	WOMAC pain	3	158/144	−2.22	−3.65 to −0.79	Yes	92%
	WOMAC function	3	158/144	−11.17	−16.37 to −5.98	Yes	83%
	EQ VAS	2	143/139	−4.64	−21.79 to 12.51	No	98%
	IKDC	2	143/139	6.84	−1.96 to 15.63	No	91%

Abbreviations: CI, confidence interval; EQ VAS, EuroQol-visual analog scales; HA, hyaluronic acid; IKDC, Subjective International Knee Documentation Committee; MD, mean difference; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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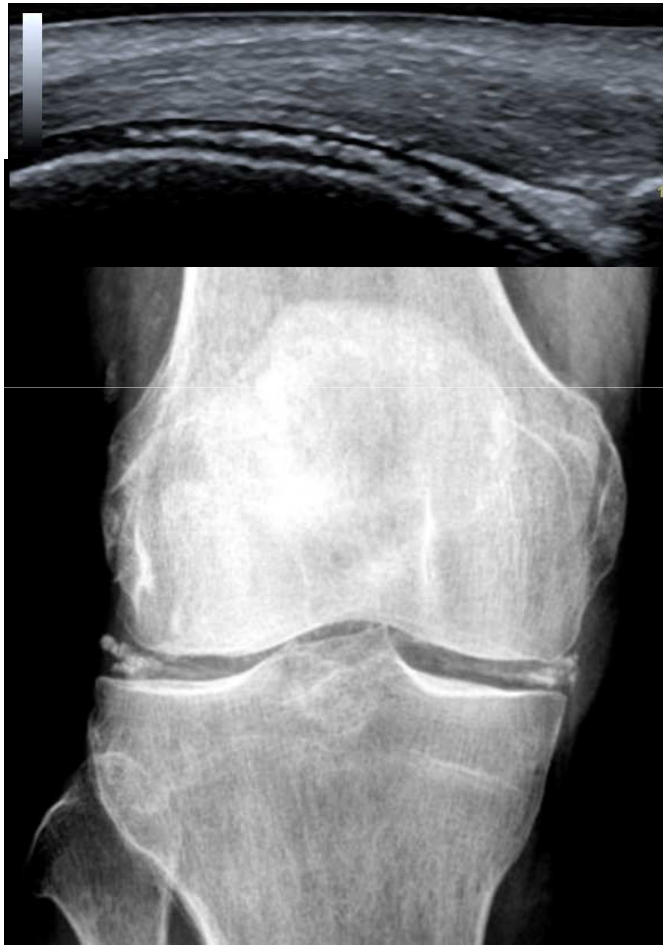
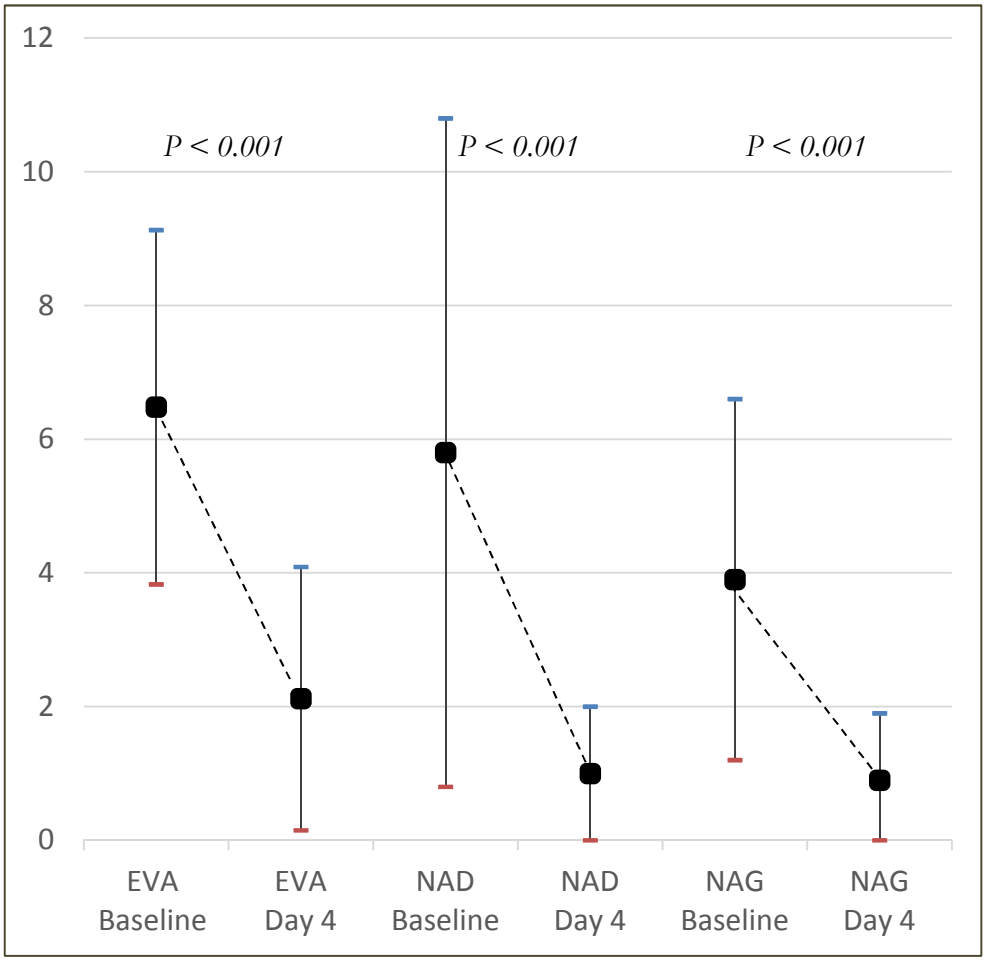
Efficacy and tolerance of anakinra in acute calcium pyrophosphate crystal arthritis: a retrospective study of 33 cases.

33 patients (24 femmes; âge 79.2 ± 12.8 years)





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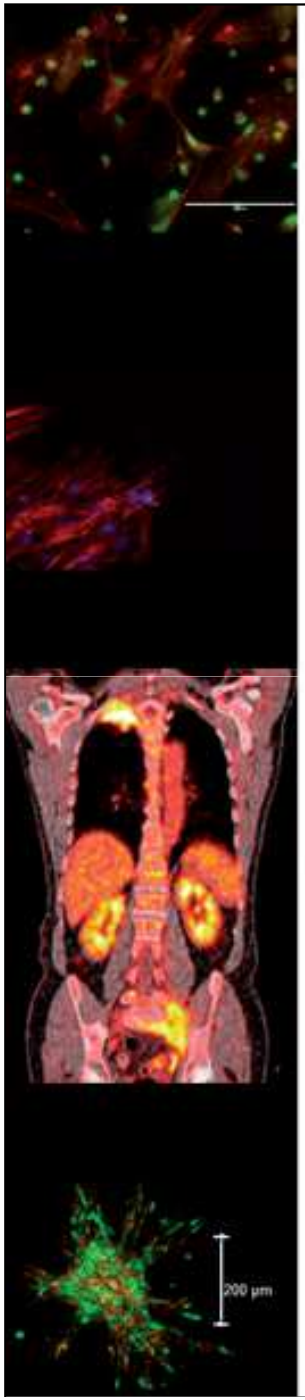

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CURRENT AND EMERGING DRUG OPTIONS IN THE TREATMENT OF GOUT

GUEST EDITOR: PASCAL RICHETTE

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Cardiac and renal protective effects of urate-lowering therapy

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Abstract

Patients with gout often have co-morbidities such as cardiovascular disease, renal failure and metabolic syndrome components. Some studies, but not all, have suggested that hyperuricaemia and gout are associated with increased risk of myocardial infarction, renal failure and death primarily because of increased risk of cardiovascular events. Therefore, knowledge of the effects of urate-lowering therapy (ULT) on co-morbidities, in particular cardiovascular events and chronic kidney disease, is crucial. Randomized controlled trials (RCTs) have suggested that allopurinol, a xanthine oxidase inhibitor, could improve exercise capacity in patients with chronic stable angina and could decrease blood pressure in adolescents. In contrast, a well-designed RCT found no effect of allopurinol in patients with heart failure. The impact of ULT in patients with chronic kidney disease is unclear. Some RCTs found that allopurinol could slow the decline in kidney function, whereas a recent controlled trial found no benefit of febuxostat. Large randomized placebo-controlled trials are warranted to confirm or not the benefit of ULT on co-morbidities.

Key words: urate-lowering therapy, gout, co-morbidities, allopurinol, febuxostat

Rheumatology key messages

- The causality between hyperuricaemia, gout and co-morbidities is controversial.
- Some randomized controlled trials have suggested that urate-lowering therapies might have cardiac and renal benefit.
- Large randomized placebo-controlled trials are warranted to confirm or not the benefit of urate-lowering therapy for cardiorenal co-morbidities.

Introduction

Gout is strongly associated with several co-morbidities, particularly traditional vascular risk factors and chronic kidney disease (CKD) [1–3]. Data from epidemiological studies have suggested that gout and hyperuricaemia are independent risk factors for cardiovascular (CV) diseases and renal dysfunction [4]. In addition, animal studies have uncovered a mechanistic approach to the vascular toxicity of uric acid [5].

However, the causality between hyperuricaemia and these outcomes remains uncertain because confounders, reverse causality or common aetiological factors might explain these epidemiological results. These uncertainties have not been solved by recent studies involving Mendelian randomization. Overall, data from these recent studies are negative: most, but not all [6–8], found no association between hyperuricaemia, CV diseases [9, 10] and CKD [11] or metabolic syndrome components [12, 13]. Causality can also be addressed by investigating the effect of urate-lowering therapy (ULT) on co-morbidities, therefore knowledge of the effects of ULT on CV and renal outcomes is of major interest.

ULT and CV outcomes

The mechanisms that may link hyperuricaemia and gout with CV events are unclear but may include oxidative stress generated by xanthine oxidase (XO), the enzyme that catalyzes the formation of urate [4, 14]. Other explanations are a direct contribution to endothelial dysfunction [5] and low-grade inflammation associated with increased urate levels and tophi [15]. Recently a cross-sectional

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Association Goutte
et
Syndrome Métabolique
Obésité androide avec hyperinsulinisme
HTA avec hyperuricémie
Dyslipidémie (↗TG et ↘HDLc)
=
Haut risque cardio-vasculaire
(*MAjor Cardiovascular Events*)

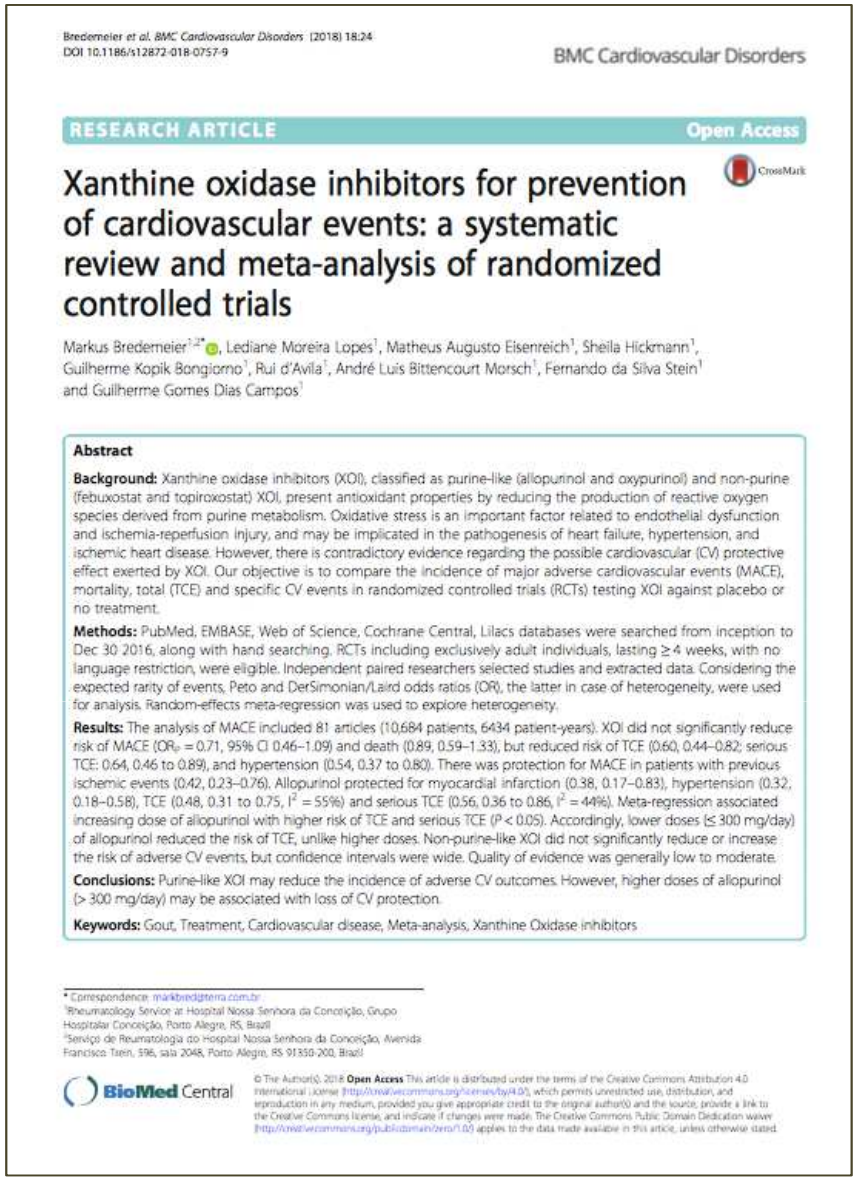
Effet des hypouricémiants (IXO) ?
↘ stress oxidatif ↘ dysfonction endothéliale

Hyperuricémie associée à HTA et vasoconstriction

Association Goutte
et
Insuffisance rénale

↘ fonction rénale ↘ excrétion U d'acide urique

Richette P. Rheumatology (Oxford). 2018;57(suppl_1):i47-i50.



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BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Xanthine oxidase inhibitors (XOI), classified as purine-like (allopurinol and oxypurinol) and non-purine (febuxostat and topiroxostat) XOI, present antioxidant properties by reducing the production of reactive oxygen species derived from purine metabolism. Oxidative stress is an important factor related to endothelial dysfunction and ischemia-reperfusion injury, and may be implicated in the pathogenesis of heart failure, hypertension, and ischemic heart disease. However, there is contradictory evidence regarding the possible cardiovascular (CV) protective effect exerted by XOI. Our objective is to compare the incidence of major adverse cardiovascular events (MACE), mortality, total (TCE) and specific CV events in randomized controlled trials (RCTs) testing XOI against placebo or no treatment.

Methods: PubMed, EMBASE, Web of Science, Cochrane Central, Lilacs databases were searched from inception to Dec 30 2016, along with hand searching. RCTs including exclusively adult individuals, lasting ≥ 4 weeks, with no language restriction, were eligible. Independent paired researchers selected studies and extracted data. Considering the expected rarity of events, Peto and DerSimonian/Laird odds ratios (OR), the latter in case of heterogeneity, were used for analysis. Random-effects meta-regression was used to explore heterogeneity.

Results: The analysis of MACE included 81 articles (10,684 patients, 6434 patient-years). XOI did not significantly reduce risk of MACE (OR_P = 0.71, 95% CI 0.46–1.09) and death (0.89, 0.59–1.33), but reduced risk of TCE (0.60, 0.44–0.82; serious TCE: 0.64, 0.46 to 0.89), and hypertension (0.54, 0.37 to 0.80). There was protection for MACE in patients with previous ischemic events (0.42, 0.23–0.76). Allopurinol protected for myocardial infarction (0.38, 0.17–0.83), hypertension (0.32, 0.18–0.58), TCE (0.48, 0.31 to 0.75, I^2 = 55%) and serious TCE (0.56, 0.36 to 0.86, I^2 = 44%). Meta-regression associated increasing dose of allopurinol with higher risk of TCE and serious TCE ($P < 0.05$). Accordingly, lower doses (≤ 300 mg/day) of allopurinol reduced the risk of TCE, unlike higher doses. Non-purine-like XOI did not significantly reduce or increase the risk of adverse CV events, but confidence intervals were wide. Quality of evidence was generally low to moderate.

Conclusions: Purine-like XOI may reduce the incidence of adverse CV outcomes. However, higher doses of allopurinol (> 300 mg/day) may be associated with loss of CV protection.

Keywords: Gout, Treatment, Cardiovascular disease, Meta-analysis, Xanthine Oxidase inhibitors

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Allopurinol

MACE (65 études)

OR = 0.65 (0.41-1.05), $p = 0.076$, $I^2 = 9\%$

Décès (74 études)

OR = 0.94 (0.62-1.44), $p = 0.785$, $I^2 = 0\%$

Febuxosat

MACE (19 études)

OR = 1.13 (0.40-3.19), $p = 0.824$, $I^2 = 18\%$

Décès (19 études)

OR = 0.71 (0.15-3.40), $p = 0.671$, $I^2 = 0\%$

Bredemeier M. BMC Cardiovasc Disord. 2018;18(1):24.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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From the University of Connecticut School of Medicine, Farmington (W.B.W.); the University of Alabama, Birmingham (K.G.S.); University of Chicago Medicine, Chicago (M.A.B.), and Takeda Development Center Americas, Deerfield (B.H., M.C., L.G.) — both in Illinois; the State University of New York, Downstate Medical Center, Brooklyn (J.S.B.); Michigan State University College of Human Medicine, Grand Rapids (P.B.G.); and Johns Hopkins University School of Medicine, Baltimore (A.W.). Address reprint requests to Dr. White at the Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Ave., Farmington, CT 06032, or at wwhite@uchc.edu.

*A complete list of the CARES investigators is provided in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND

Cardiovascular risk is increased in patients with gout. We compared cardiovascular outcomes associated with febuxostat, a nonpurine xanthine oxidase inhibitor, with those associated with allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients with gout and cardiovascular disease.

METHODS

We conducted a multicenter, double-blind, noninferiority trial involving patients with gout and cardiovascular disease; patients were randomly assigned to receive febuxostat or allopurinol and were stratified according to kidney function. The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization).

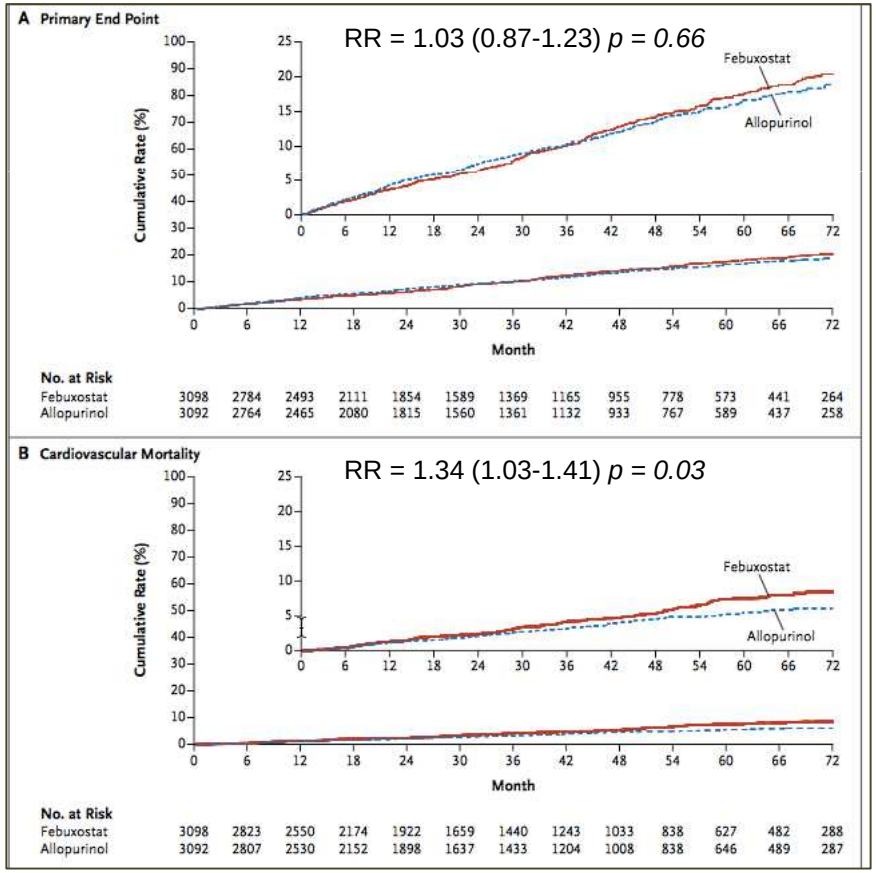
RESULTS

In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up. In the modified intention-to-treat analysis, a primary end-point event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority). All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]). The results with regard to the primary end point and all-cause and cardiovascular mortality in the analysis of events that occurred while patients were being treated were similar to the results in the modified intention-to-treat analysis.

CONCLUSIONS

In patients with gout and major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events. All-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. (Funded by Takeda Development Center Americas; CARES ClinicalTrials.gov number, NCT01101035.)

Cardiovascular risk factors and history — no. (%)		
Diabetes mellitus with small-vessel disease	1193 (38.5)	1213 (39.2)
Hypertension	2864 (92.4)	2851 (92.2)
Hyperlipidemia	2678 (86.4)	2702 (87.4)
Myocardial infarction	1197 (38.6)	1231 (39.8)
Hospitalization for unstable angina	855 (27.6)	869 (28.1)
Coronary revascularization	1129 (36.4)	1182 (38.2)
Cerebral revascularization	69 (2.2)	54 (1.7)
Congestive heart failure	622 (20.1)	631 (20.4)
Stroke	460 (14.8)	410 (13.3)
Peripheral vascular disease	412 (13.3)	375 (12.1)
Median estimated creatinine clearance — ml/min§		
Stage 1 or 2 chronic kidney disease	75.0	73.0
Stage 3 chronic kidney disease	46.0	46.0
Stage of chronic kidney disease — no./total no. (%)		
Stage 1 or 2	1456/3092 (47.1)	1459/3090 (47.2)
Stage 3	1636/3092 (52.9)	1631/3090 (52.8)



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Original article

Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: A retrospective study of 10 centers

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ABSTRACT

Objectives: The allopurinol dose is limited in chronic kidney disease, particularly stage 4/5 chronic kidney disease. Febuxostat has a hepatic metabolism and has been approved without dose adaptation in gouty patients with stage 1–3 chronic kidney disease. We aimed to study the safety and efficacy of febuxostat for stage 4/5 chronic kidney disease.

Methods: In this retrospective study, we included patients with (1) a diagnosis of gout, (2) febuxostat treatment, (3) estimated glomerular filtration rate ≤ 30 ml/min/1.73 m² (Modification of Diet in Renal Disease formula) at febuxostat initiation and (4) follow-up for at least 3 months after febuxostat initiation. Efficacy, safety and variation in estimated glomerular filtration rate were analyzed.

Results: We included 73 patients (mean age 70.2 ± 11.8, 61 men, 31 with vascular chronic kidney disease and 18 renal transplantation) with gout (baseline serum uric acid level = 9.86 ± 2.85 mg/dL, mean gout duration 6.2 ± 7.0 years) from 10 academic centers. Comorbidities included cardiac failure (17.8%), hypertension (98.6%), diabetes mellitus (30.1%), dyslipidemia (64.8%) and history of cardiovascular events (38.4%). At the last visit (mean follow-up 68.5 ± 64.8 weeks), the daily dose of febuxostat was 40 mg for 7 patients (10.5%), 80 mg for 50 (74.6%) and 120 mg for 10 (14.9%). Serum uric acid level was < 6 mg/dL for 49 patients (67%). Renal function improved for 18 patients, was unchanged for 24 and worsened for 31; 19 patients experienced flares and 1 patient, limb edema.

Conclusion: Febuxostat seemed efficient in gouty patients with stage 4/5 chronic kidney disease. However, safety data were not clear regarding renal function. Larger studies are needed to assess safety.

1. Introduction

Gout is one of the most common forms of inflammatory arthritis. It is caused by the deposition of monosodium urate crystals, secondary to chronically elevated serum uric acid (sUA) level [1]. Chronic kidney disease (CKD) is responsible for hyperuricemia and

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1297-319X/

73 patients de 70,2 ± 11,8 ans
Insuffisance rénale de stade 4 (82%) et 5 (18%)
98,6% HTA, 30,1% Diabète, 65% Dyslipidémie
38,4% MACE
43,5% tophus 38,4% arthropathies uratiques

Uricémie
98,6 mg/L (± 28,5) ➞ 50,6 mg/L (± 23,2)
< 60 mg/L ➞ 65,1 %

DFG
21,6 (±6,2) ➞ 20,5 (±9,2) mL/min/1,73 m2

Juge PA. Joint Bone Spine. 2017;84(5):595-8.

RHEUMATOLOGY

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Novel uricosurics

Thomas Bardin[1,2] and Pascal Richette[1,2]

Abstract

Objective. According to recent guidelines, the mainstay of urate-lowering therapies remains xanthine oxidase inhibition. However, some patients with gout show failure to achieve the predefined target of 5–6 mg/dl with xanthine oxidase inhibitors alone, so alternative drugs are needed. The aim of this study was to review studies of novel drugs targeting uric acid transporter 1 (URAT1) and/or other urate transporters for the management of gout.

Methods. MeSH terms were used to identify phase 2/3 trials assessing the efficacy of novel uricosurics. A narrative review of novel drugs targeting URAT1 and/or other urate transporters for the management of gout is provided.

Results. Lesinurad is a recently approved uricosuric that inhibits URAT1 and the organic ion transporter organic anion transporter 4 (OAT4). Phase 3 trials showed that lesinurad, combined with allopurinol or febuxostat, is a potent urate-lowering therapeutic with an acceptable safety profile. Arhalofenate, another emerging uricosuric, also interacts with URAT1 and organic anion transporter 4. Phase 2 trials suggested that it can both lower serum UA levels and reduce the risk of flares.

Conclusions. New drugs inhibiting URAT1 should cover the unmet need for patients with failure to respond or with contraindications to xanthine oxidase inhibitors.

Key words: uricosuric, urate-lowering therapy, lesinurad, arhalofenate, URAT1

REVIEW

Rheumatology key messages

- Uricosurics are conceptually attractive drugs to lower urate levels.
- Lesinurad, in combination with a xanthine oxidase inhibitor, is a potent urate-lowering drug.
- Arhalofenate could prevent flares as well as reduce urate levels.

Introduction

Renal mechanisms are responsible for hyperuricaemia in ~90% of patients with gout since impaired renal excretion is the main mechanism explaining the increase in the urate pool. Approximately 90% of the daily load of urate filtered by the kidneys is reabsorbed through the sequential activities of various transporters located in the renal proximal tubule and move uric acid across the apical and basolateral membranes [1]. These specific urate transporters are uric acid transporter 1 (URAT1), glucose transporter 9 and organic anion transporter 1, 3 and 4 (OAT1, OAT3, OAT4) [2–4]. They are the target of old and new uricosurics (Fig. 1) and are therefore of great interest because they open new therapeutic perspectives for a disease whose prevalence is increasing in developed countries [5].

According to the EULAR [6] and ACR [7] recommendations for treating hyperuricaemia, uricosurics are recommended for patients with failure to respond or with contraindications to xanthine oxidase inhibitors (XOIs). Failure to respond to allopurinol is common because of the high prevalence of chronic kidney disease in patients with gout [8]. Indeed, in this case, and according to the EULAR but not the ACR, the dosage of allopurinol should be adjusted to creatinine clearance and often fails to achieve the predefined target. For these patients, uricosurics alone or in combination, depending on the drug, with an XOI is a therapeutic alternative [6].

Benzbromarone and probenicid act predominantly on URAT1 to prevent reuptake of uric acid (UA) at the proximal renal tubule and thus increase renal excretion of UA.

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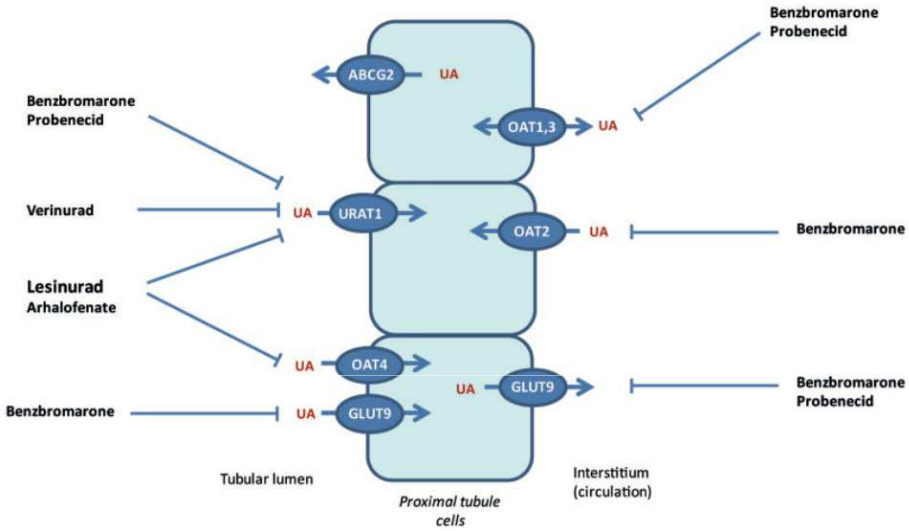
Rationel Physiopathologique

Probénécide
Benzbromarone

Urate transporters at the proximal renal tubule



Nouvel Uricosurique

Lesinurad (ZURAMPIC)
Inh URAT-1 OAT-4

Bardin T. Rheumatology (Oxford). 2018;57(suppl_1):i42-i46.

OPEN ACCESS

EXTENDED REPORT

Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study)

Thomas Bardin,[1] Robert T Keenan,[2] Puja P Khanna,[3] Jeff Kopicko,[4] Maple Fung,[5] Nihar Bhakta,[5] Scott Adler,[6] Chris Storgard,[5] Scott Baumgartner,[7] Alexander So[8]

Handling editor Tore K Kvien

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JK and CS are former employees.

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ABSTRACT

Objectives Determine the efficacy and safety of daily lesinurad (200 or 400 mg orally) added to allopurinol in patients with serum uric acid (sUA) above target in a 12-month, randomised, phase III trial.

Methods Patients on allopurinol ≥300 mg (≥200 mg in moderate renal impairment) had sUA level of ≥6.5 mg/dL (≥387 µmol/L) at screening and two or more gout flares in the prior year. Primary end point was the proportion of patients achieving sUA level of <6.0 mg/dL (<357 µmol/L) (month 6). Key secondary end points were mean gout flare rate requiring treatment (months 7 through 12) and proportions of patients with complete resolution of one or more target tophi (month 12). Safety assessments included adverse events and laboratory data.

Results Patients (n=610) were predominantly male, with mean (±SD) age 51.2±10.90 years, gout duration 11.5±9.26 years and baseline sUA of 6.9±1.2 mg/dL (410±71 µmol/L). Lesinurad at 200 and 400 mg doses, added to allopurinol, significantly increased proportions of patients achieving sUA target versus allopurinol-alone therapy by month 6 (55.4%, 66.5% and 23.3%, respectively, p<0.0001 both lesinurad+allopurinol groups). In key secondary end points, there were no statistically significant treatment-group differences favouring lesinurad. Lesinurad was generally well tolerated; the 200 mg dose had a safety profile comparable with allopurinol-alone therapy. Renal-related adverse events occurred in 5.9% of lesinurad 200 mg +allopurinol, 15.0% of lesinurad 400 mg+allopurinol and 4.9% of allopurinol-alone groups, with serum creatinine elevation of ≥1.5× baseline in 5.9%, 15.0% and 3.4%, respectively. Serious treatment-emergent adverse events occurred in 4.4% of lesinurad 200 mg +allopurinol, in 9.5% of lesinurad 400 mg+allopurinol and in 3.9% of allopurinol-alone groups, respectively.

Conclusion Lesinurad added to allopurinol demonstrated superior sUA lowering versus allopurinol-alone therapy and lesinurad 200 mg was generally well tolerated in patients with gout warranting additional therapy.

Trial registration number NCT01493531.

Linked

► http://dx.doi.org/10.1136/annrheumdis-2016-210519

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INTRODUCTION

Gout is an inflammatory arthritis characterised by the deposition of monosodium urate (MSU) crystals in the joints, tendons and other connective tissues. Crystal deposition secondary to long-standing hyperuricemia can be reversed by lowering the concentration of serum uric acid (sUA) below the MSU saturation point—leading, in the long term, to the potential disappearance of signs and symptoms of gout. As a result, current management guidelines recommend maintenance of sUA to <6.0 mg/dL (<357 µmol/L) in patients with gout.[1–3]

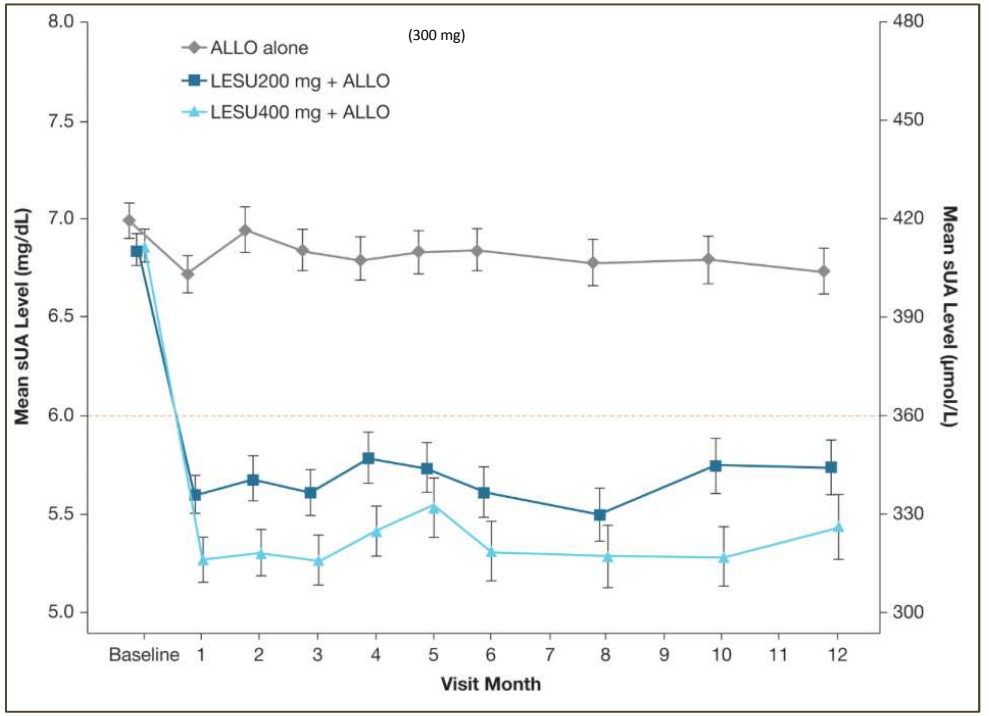
Allopurinol is recommended as a first-line urate-lowering therapy (ULT).[2 4] However, clinical trials have demonstrated that >50% of patients do not achieve sustained reductions in sUA at the most commonly used allopurinol dose of 300 mg.[5–8] Lesinurad (RDEA594) is a novel, selective uric acid reabsorption inhibitor (SURI) for treatment of gout in combination with xanthine oxidase inhibitors. Lesinurad inhibits URAT1, a uric acid transporter responsible for the reabsorption of uric acid from the renal tubular lumen.[9–11] Lesinurad in combination with allopurinol therefore provides a dual mechanism for sUA lowering—an increase in excretion of uric acid and a reduction in urate production.

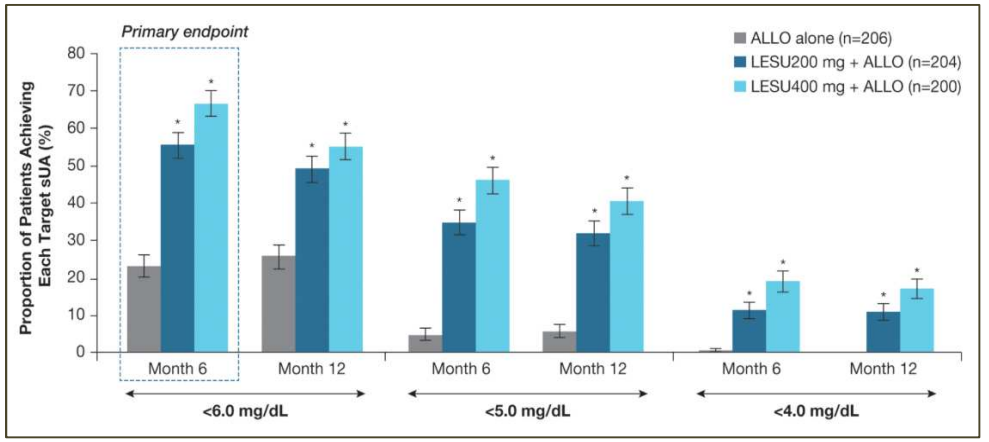
Clinical studies have demonstrated that lesinurad in combination with allopurinol reduces mean sUA concentrations and increases proportions of patients who achieve sUA targets.[12–14] The current phase III study—Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders (CLEAR 2)—is one of two replicate, randomised, double-blind, placebo-controlled, multicentre studies to investigate lesinurad in combination with allopurinol in patients with gout. CLEAR 1 was performed within the USA, included 603 patients with gout and provided outcomes similar to the CLEAR 2 study.[15]

METHODS

Study design

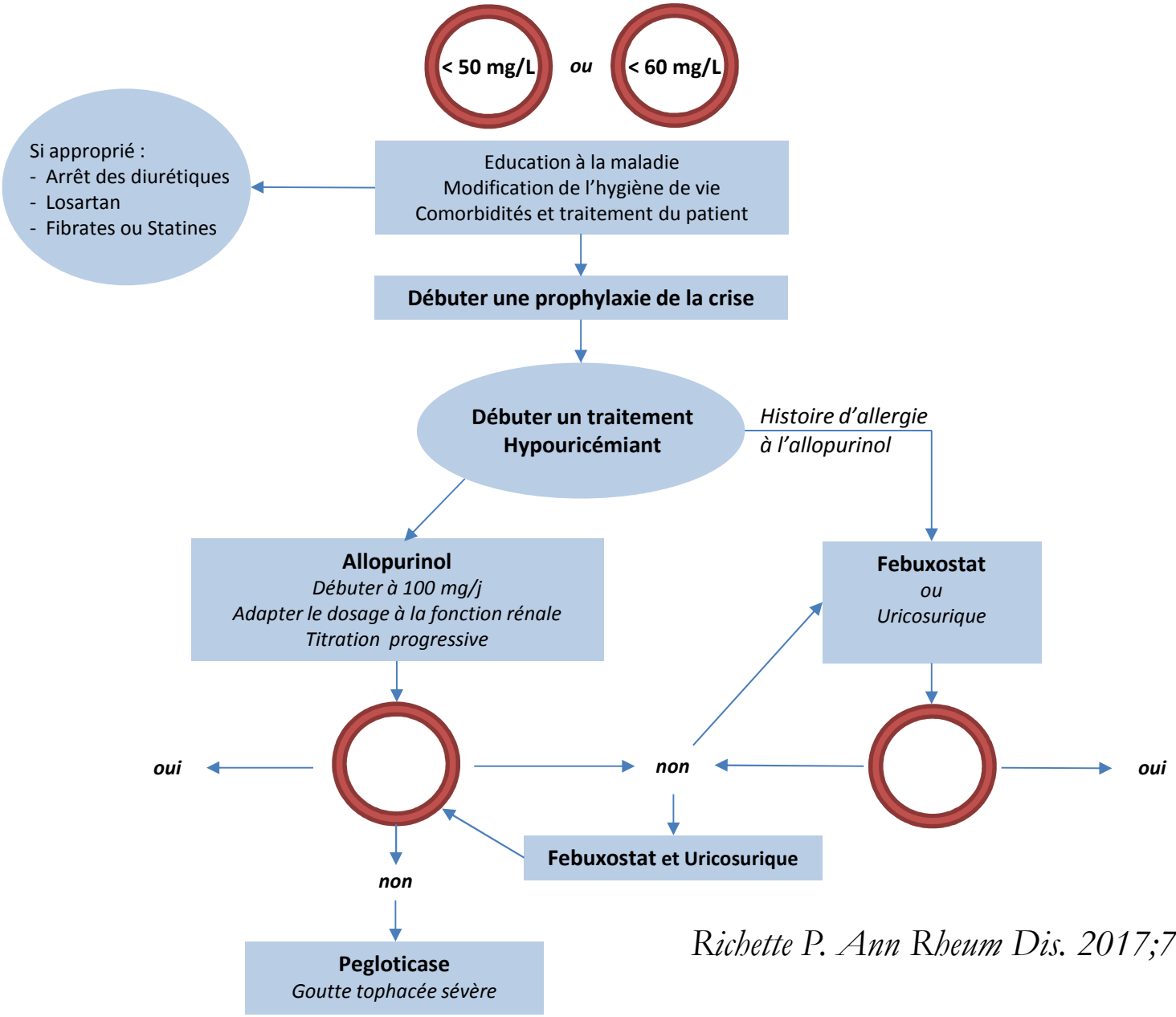
CLEAR 2 was an international, phase III trial to investigate the efficacy and safety of two lesinurad doses (200 or 400 mg oral, once daily) in combination with allopurinol, versus allopurinol combined with placebo (the control arm), in patients demonstrating inadequate response to standard-of-care allopurinol (ClinicalTrials.gov Identifier: NCT01493531). The study was conducted in 12 countries in Europe, North America, South Africa, Australia and New Zealand between December 2011 and July 2014.





Bardin T. Ann Rheum Dis. 2017;76:811-20.

Recommendation EULAR 2016
Traitement de l'hyperuricémie au cours de la Goutte



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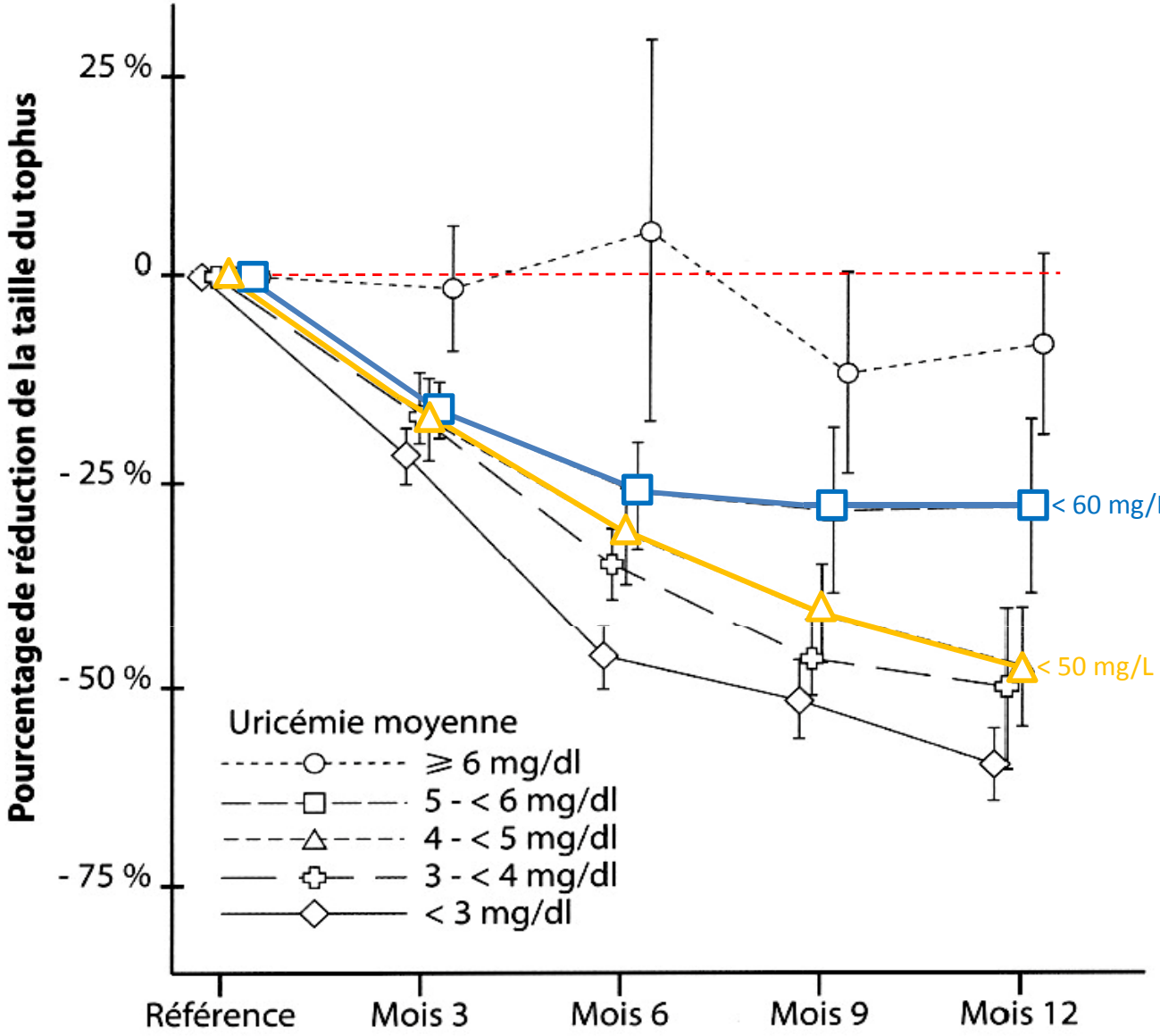
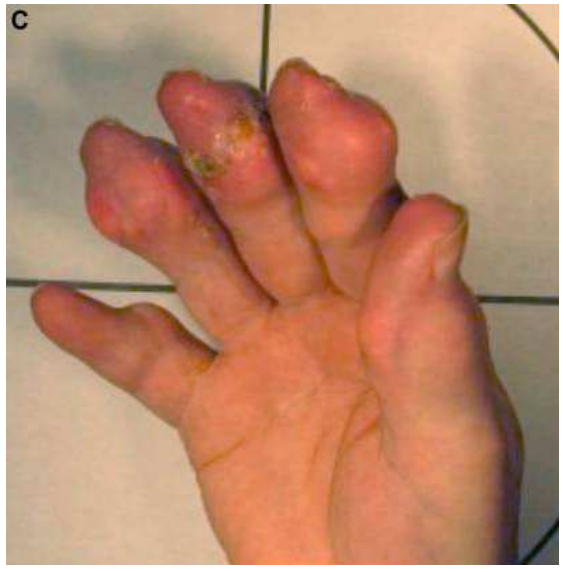
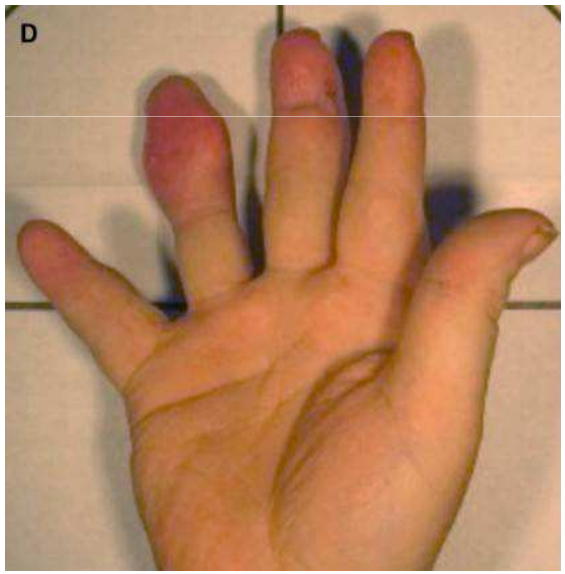


Groupe N	Référence	Mois 3	Mois 6	Mois 9	Mois 12
⩾ 6	118	105	101	97	93
5 - < 6	76	66	64	61	59
4 - < 5	85	76	76	73	70
3 - < 4	75	73	73	65	62
< 3	97	93	89	85	84





< 50 mg/L

ARTHRITIS & RHEUMATOLOGY
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DOI 10.1002/art.40159

Lesinurad, a Selective Uric Acid Reabsorption Inhibitor, in Combination With Febuxostat in Patients With Tophaceous Gout

Findings of a Phase III Clinical Trial

Nicola Dalbeth,[1] Graeme Jones,[2] Robert Terkeltaub,[3] Dinesh Khanna,[4] Jeff Kopicko,[5] Nihar Bhakta,[5] Scott Adler,[6] Maple Fung,[5] Chris Storgard,[5] Scott Baumgartner,[5] and Fernando Perez-Ruiz[7]

Objective. **To investigate the efficacy and safety of lesinurad in combination with febuxostat in a 12-month phase III trial in patients with tophaceous gout.**

Methods. **Patients with serum urate (UA) ≥8.0 mg/dl (≥6.0 mg/dl with urate-lowering therapy) and ≥1 measurable target tophus were given febuxostat 80 mg/day for 3 weeks before randomization to receive lesinurad (200 or 400 mg daily) or placebo in addition to the febuxostat. The primary end point was the proportion of patients achieving a serum UA level of <5.0 mg/dl (month 6). The key secondary end point was the proportion of patients with complete resolution of ≥1 target tophus (month 12). Other end points included the percentage change in total target tophi area. Safety assessments included adverse events and laboratory data.**

Results. **Patients (n = 324) were predominantly male, with a mean age of 54.1 years. Significantly more patients achieved the serum UA target by month 6 with the addition of lesinurad 400 mg (76.1%; $P < 0.0001$), but not 200 mg (56.6%; $P = 0.13$), to the febuxostat therapy as compared with febuxostat alone (46.8%). At all other time points, significantly more patients in the lesinurad 200 mg group achieved the serum UA target. The number of patients with complete tophus resolution was not different between groups. Treatment with lesinurad (200 mg and 400 mg) plus febuxostat reduced the total target tophi area as compared with febuxostat alone (50.1% and 52.9% versus 28.3%, respectively; $P < 0.05$). Safety was generally comparable with that of febuxostat alone, except for higher rates of predominantly reversible elevations in the serum creatinine level, particularly with lesinurad 400 mg.**

Conclusion. **Treatment with lesinurad in combination with febuxostat demonstrated superior lowering**

ClinicalTrials.gov identifier: NCT01510769.
Supported by Ardea Biosciences (a member of the AstraZeneca group).
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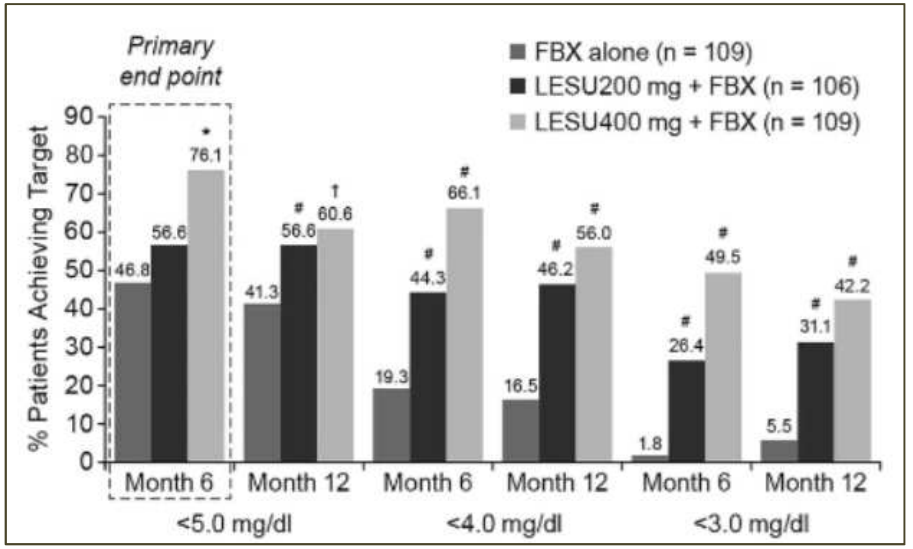

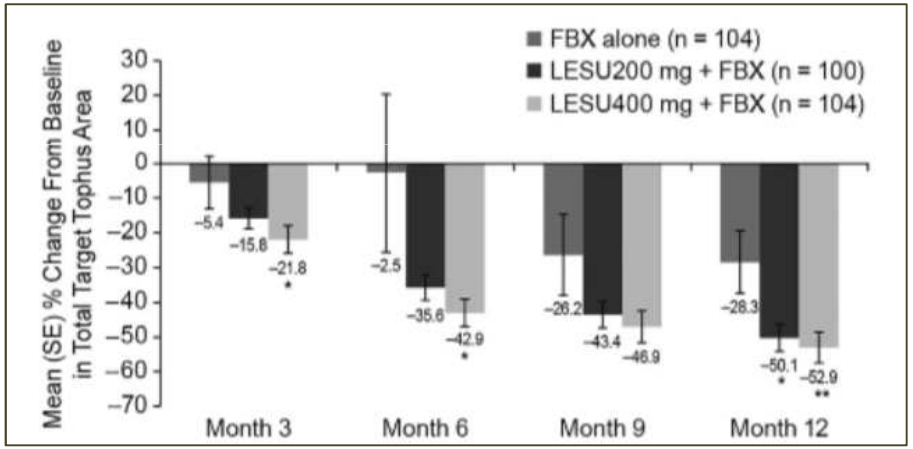

Serum creatinine elevation			
≥1.5 times baseline†	3 (2.8)	5 (4.7)	11 (10.1)
Cases unresolved at last study visit†‡	0	1	1
≥2.0 times baseline	0 (0)	3 (2.8)	6 (5.5)
Cases unresolved at last study visit‡	0	1	1

* Values are the number (%). TEAE = treatment-emergent adverse event; RCTC = Rheumatology Common Toxicity Crite
† All ≥2.0 times baseline elevations were captured in the ≥1.5 times baseline elevations group.
‡ Serum creatinine resolution was defined as return of an elevated serum creatinine level to ≤1.2 times baseline.

Dalbeth N. Arthritis Rheumatol.2017;69(12):2386-95.

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Stepwise dose increase of febuxostat is comparable with colchicine prophylaxis for the prevention of gout flares during the initial phase of urate-lowering therapy: results from FORTUNE-1, a prospective, multicentre randomised study

Hisashi Yamanaka,[1] Shigenori Tamaki,[2] Yumiko Ide,[3] Hyeteko Kim,[4] Kouichi Inoue,[5] Masayuki Sugimoto,[6] Yuji Hidaka,[7] Atsuo Taniguchi,[1] Shin Fujimori,[8] Tetsuya Yamamoto[9]

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ABSTRACT

Objectives To determine whether febuxostat with stepwise dose increase is as useful as colchicine prophylaxis in reducing gout flares during the initial introduction of urate-lowering therapy in patients with gout in comparison with febuxostat with no dose titration.

Methods In this prospective, multicentre, randomised open-label comparative study, patients were randomised to group A (stepwise dose increase of febuxostat from 10 to 40 mg/day), group B (fixed-dose febuxostat 40 mg/day plus colchicine 0.5 mg/day) or group C (fixed-dose febuxostat 40 mg/day) and observed for 12 weeks. Gout flare was defined as non-steroidal anti-inflammatory drug use for gout symptoms.

Results A total of 255 patients were randomised, and 241 patients were treated. Among the treated patients, gout flares were experienced by 20/96 (20.8%) in group A, 18/95 (18.9%) in group B and 18/50 (36.0%) in group C. The incidence of flare was significantly lower in groups A and B than that in group C (P=0.047 and P=0.024, respectively), although the differences were not significant after correction for multiple comparisons. No significant difference was noted between the incidence of gout flare in groups A and B.

Conclusions Our data suggested that stepwise dose increase of febuxostat and low-dose colchicine prophylaxis effectively reduced gout flares in comparison with fixed-dose febuxostat alone. Stepwise dose increase of febuxostat may be an effective alternative to low-dose colchicine prophylaxis during the introduction of urate-lowering therapy.

Trial registration number UMIN 000008414.

INTRODUCTION

The number of patients with gout is increasing,[1–3] and the debilitating pain of gout flare can severely impact quality of life. In addition, gout and hyperuricaemia are closely associated with diseases related to metabolic syndrome and renal impairment and may be causally related to cardiovascular disease.[4–6] Gouty arthritis and gouty tophus, clinical presentations of monosodium urate (MSU) crystal deposition, result from persistent hyperuricaemia and can be treated by reducing the body urate pool. This can decrease the long-term incidence of gout flares and urate tophi.[7–11]

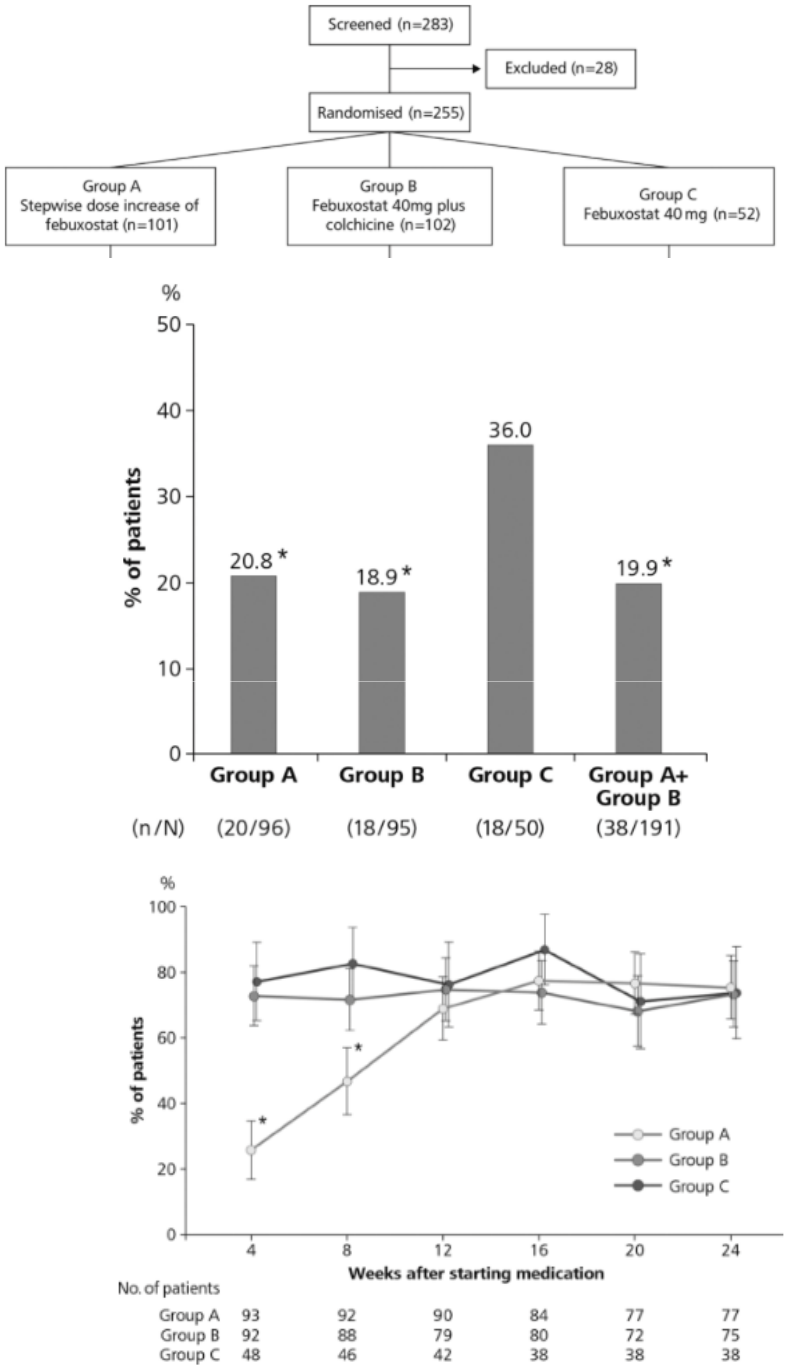
However, gout flares frequently develop during the first several months of urate-lowering therapy (ULT).[10–12] The initial serum urate level, the presence of tophus and the dose of urate-lowering drugs can affect the risk of gout flares during ULT. Unfortunately, medication adherence is poor,[13–16] partly because gout flares decrease the motivation of patients to continue treatment.[17 18] The prevention of gout flares is thus of key importance when initiating ULT.

Concomitant colchicine can help[1 19]; recent publications from the European League Against Rheumatism and the American College of Rheumatology recommend colchicine for at least the first 6 months.[1 20] However, although widely used for both therapeutic and prophylactic purposes, colchicine is potentially toxic and caution is advised.[21–23]

ULT induces the shedding of deposited MSU crystals in the joints. Such crystal shedding may be facilitated by the dissolution of urate crystals, and also by decreased urate levels in the joint fluid.[24] Thus, a rapid decrease in serum urate could contribute to gout flares, whereas a gradual decrease should favour flare prevention.[10–12]

In Japan, clinical trials using a stepwise increase in febuxostat dose at the initiation of treatment have shown a lower incidence of gout flares than trials using fixed-dose febuxostat.[25 26] Thus, there are at least two potential strategies to reduce early treatment-related gout flares: stepwise dose increase and colchicine prophylaxis. However, no prospective clinical trials have been conducted to compare the efficacy of these two strategies.

The present study was designed to investigate the incidence of gout flares during early-stage febuxostat treatment, comparing fixed-dose monotherapy both to stepwise dose increase and to low-dose colchicine prophylaxis.



Yamanaka H. Ann Rheum Dis. 2018;77(2):270-6.

Jiang et al. BMC Ophthalmology (2018) 18:11
DOI 10.1186/s12886-018-0669-6

BMC Ophthalmology

CASE REPORT Open Access

Retinal complications of gout: a case report and review of the literature

Ying Jiang[1], Jason E. Brenner[1] and William J. Foster[1,2*]

Abstract

Background: There have been few reported findings of posterior segment complications of gout. While exudative lesions, an increased risk of macular degeneration, and vascular occlusions have been previously reported, to our knowledge, refractile macular lesions have not been reported in a patient with chronic uncontrolled gout.

Case Presentation: Highly refractile, crystal-like lesions were found in the macula of a 62 year old male patient with chronically uncontrolled gout. The lesions appeared at the termination of retinal arterioles and were located at the level of the retinal pigment epithelium. The lesions did not stain with fluorescein and were associated with larger areas geographic atrophy. Review of the patient's blood tests revealed well-controlled vasculopathic risk factors. Fundus appearance and best-corrected visual acuity remained stable over 12 months of follow-up during which the uric acid levels were well controlled.

Conclusion: Retinopathy may be associated with chronically uncontrolled gout and patients with visual complaints should undergo a dilated examination in addition to the typical anterior segment slit-lamp exam.

Keywords: Crystalline retinopathy, Gout, Hyperuricemia, Retina, Retinopathy, Uric acid, Case report

Background

Gout is a systemic condition in which uric acid is deposited in tissues as monosodium urate, leading to an inflammatory reaction. The classic clinical finding is an inflammatory arthritis. However, the systemic nature of the condition has led to the involvement of various other organs, including the eye. Previous case reports and publications have demonstrated ocular involvement in the anterior segment. Several studies have noted associations with inflammatory reactions such as conjunctivitis and anterior uveitis [1–4]. There have also been reports of gouty crystal deposits in the cornea, sclera, and iris [5, 6]. A recent study by Lin et al. [7] investigated 380 patients with gout and reported two cases of corneal and one case of scleral uric crystal deposits. Additionally, these authors noted an association between gout and the presence of transparent conjunctival vesicles with metal-like reflection in the subconjunctival space, suggesting any similar findings warrant a suspicion of gout. Other associations between gout and elevated intraocular pressure, blurred disc margins, and possibly posterior uveitis have also been published in a case report [8].

To date, there have been few reported findings of posterior segment complications of gout. A case report [9] described an association between allopurinol use and exudative lesions in the macula. An older study in the French literature by Bourde [10] found that of 46 patients who presented with retinal vascular disorders without diabetes or hypertension, 76% had elevated uric acid levels. No retinal crystals were noted and the vascular findings were primarily venous occlusions and retinal hemorrhage. A more recent study [11] found an additional association between gout and Age-Related Macular Degeneration, which was hypothesized to be related to a systemic inflammatory reaction. However, there have not been any reports of direct urate crystal deposits in the retina. We describe here a patient with macular crystals and advanced systemic gout.

Case report

A 62 year old African American male with a long-standing history of uncontrolled gout, demonstrated by chronic joint

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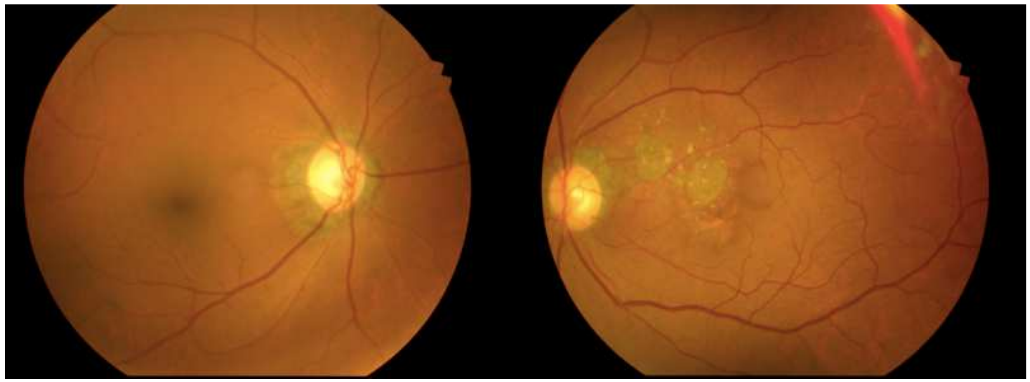

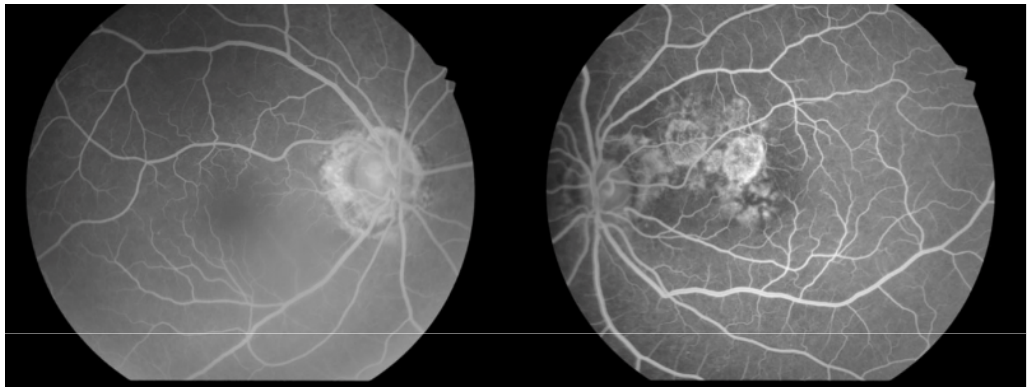

Jiang Y. BMC Ophthalmol. 2018;18(1):11.