biochemical analysis of the underlying bone tissue has provided important information for treatment of osteoarthritis. In this study, we determined the potential role of formononetin, a phytoestrogen isolated from *Astragalus membranaceus* to alter the expression of metabolic markers and cytokine production of human normal osteoblasts (Obs) and osteoarthritis subchondral osteoblasts (OA Obs).
Methods: Human OA Obs and normal Obs were cultured for 3 days, 7 days or 14 days in presence medium only or were treated with various doses of formononetin. Cells were analyzed for viability by WST-8 assay, alkaline phosphatase (ALP) activity, osteogenic markers (osteocalcin (OCN) and type I collagen (Col I)) and cytokines (interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), bone morphogenic protein-2 (BMP-2)). The level of IL-6, VEGF, BMP-2, OCN and Col I was increased in OA Obs compared with normal Obs.
Results: Formononetin dose-dependently decreased ALP, IL-6, VEGF, BMP-2, OCN and Col I in OA Obs, while markedly increased ALP, VEGF, BMP-2, OCN and Col I in normal Obs. Interestingly, formononetin markedly increased the expression of VEGF and BMP-2 for 3 days of culture and significantly increased OCN and Col I at 14 days in human normal Obs. The remodeling effect of formononetin on osteogenic markers and cytokines of inflammatory mediators was more striking in OA Obs as well.
Conclusions: These results could suggest that formononetin has biphasic positive effects on normal Obs and OA Obs by modifying their biological synthetic capacities.
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OPEN-LABEL, OPEN-ENDED STUDY OF THE SAFETY OF DICLOFENAC TOPICAL SOLUTION FOR MANAGEMENT OF OSTEOARTHRITIS: CHARACTERIZATION OF GASTROINTESTINAL ADVERSE EVENTS

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Purpose: Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for the treatment of osteoarthritis (OA), but their chronic use is associated with serious gastrointestinal (GI), cardiovascular, and potentially other systemic adverse events (AEs). Diclofenac topical solution (TDiclo) has demonstrated efficacy similar to oral diclofenac (ODiclo) in randomized, double-blind, clinical trials in OA of the knee, with fewer GI AEs. The incidence of GI AEs occurring with TDiclo in patients in an office setting was analyzed using safety data from a Canadian compassionate-use treatment program of TDiclo for OA.
Methods: In this multicenter, open-label, open-ended, compassionate-use, Phase 3 study, patients with physician-diagnosed OA were instructed to apply 5 drops (small joint, eg, knuckle), 20 drops (medium joint, eg, wrist), or 40 drops (large joint, eg, knee) of TDiclo to the affected joint 4 times daily in an uncontrolled, real-world setting. Follow-up safety assessments were scheduled at 1, 3, 6, and 12 months, and yearly thereafter. At each visit, patients were asked open-ended questions regarding the onset and nature of any AE that occurred since the last visit. It was at the patient's discretion whether to contact the investigator at the onset of an AE or wait until the next visit.
Results: A total of 4213 patients were evaluated. The duration of exposure to TDiclo extended over 6–12 months in 12.4% and ≥12 months in 19.8%. A GI AE occurred in 35 (0.8%) patients; the most frequently reported were dyspepsia (0.4%), nausea (0.2%), and diarrhea (0.1%). A GI AE was listed as a reason for study discontinuation in 23 patients (0.5%). None of the GI AEs that occurred during the study were deemed by the investigator to be related to TDiclo treatment.
Conclusions: In an uncontrolled office-practice setting, the occurrence of GI AEs in patients receiving TDiclo was low. No individual GI AE was reported in >0.4% of patients, and few patients discontinued therapy because of these events. The results of this open-label study demonstrate that TDiclo is a well-tolerated therapeutic option for those patients who wish to reduce their likelihood of experiencing the GI AEs that are commonly associated with oral NSAIDs.

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OPEN-LABEL, OPEN-ENDED STUDY OF THE SAFETY OF DICLOFENAC TOPICAL SOLUTION FOR MANAGEMENT OF OSTEOARTHRITIS: CHARACTERIZATION OF APPLICATION-SITE ADVERSE EVENTS

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Purpose: Randomized, double-blind trials of diclofenac topical solution (TDiclo) in osteoarthritis (OA) of the knee have demonstrated efficacy similar to oral diclofenac, with fewer systemic adverse events (AEs). The most common AEs occurring with TDiclo were application-site reactions. To characterize these reactions in a clinical setting, safety data were analyzed in patients who received TDiclo in a Canadian compassionate-use treatment program for OA.
Methods: This was a multicenter, open-label, open-ended study conducted in Canada. Patients with physician-diagnosed OA were instructed to apply 5 drops (small joint, eg, knuckle), 20 drops (medium joint, eg, wrist), or 40 drops (large joint, eg, knee) of TDiclo, 4 times daily. Follow-up safety assessments were scheduled at 1, 3, 6, and 12 months, and yearly thereafter. At each visit, the investigator asked the patient open-ended questions about any AE occurring since the last visit, assessed the application site for signs of irritation and scored it (0 = no visible reaction; 0.5 = equivocal response, itching burning sensation, pruritus; 1 = mild erythema; 2 = intense erythema; 3 = intense erythema with edema; and 4 = intense erythema with edema and vesicular eruption).
Results: A total of 4213 patients were enrolled. The duration of exposure to TDiclo extended over 6–12 months in 12.4% and ≥12 months in 19.8%. The most common AEs were application-site reactions in 112 of the 4213 patients (2.7%), which included rash (1.2%), dry skin (0.6%), and pruritus (0.5%). Data regarding skin irritation score were available for 1923 patients; of these, 1798 (93.5%) had a score of 0 (no visible reaction), 59 (3.1%) had a score of 0.5 (equivocal response, itching, burning sensation); and 48 (2.5%) had a score of 1 (mild erythema). A score of 2 (intense erythema) was recorded in 7 (0.4%) and a score of 3 (intense erythema with edema) in 6 (0.3%) patients; a score of 4 (intense erythema with edema and vesicular eruption) was recorded in only 5 patients (0.3%). A total of 40 patients (0.9%) reported discontinuing treatment because of an application-site reaction. No data were collected on potential patient interventions such as emollients or creams.
Conclusions: Consistent with published controlled, clinical trials, the most common AEs in individuals with OA treated with TDiclo in clinical practice were skin-related. Their occurrence was low, and few patients discontinued treatment because of these reactions. Given the risk of systemic AEs associated with oral diclofenac, TDiclo has obvious potential for the reduction of adverse effects.

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SCREENING OF ESSENTIAL OILS AS POTENTIAL SOURCES OF NATURAL INHIBITORS OF iNOS EXPRESSION AND NO PRODUCTION IN HUMAN CHONDROCYTES

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Purpose: Nitric oxide (NO), namely resulting from the activity of the inducible nitric oxide synthase (iNOS) whose expression is increased in osteoarthritic chondrocytes, is an important component of the mechanisms that lead to cartilage degradation and inflammation, the hallmarks of OA. Overexpression of iNOS and the subsequent increased production of NO mediates, at least in part, the inhibition of matrix synthesis and promotion of its degradation induced by pro-inflammatory and catabolic cytokines, like interleukin-1β (IL-1), in articular chondrocytes. Thus, inhibition of NO production and iNOS expression are considered important targets for the development of anti-osteoarthritic therapies. Essential oils are composed of a wide diversity of hydrophobic low molecular weight compounds with favorable pharmacokinetic properties that make them especially suited collections for drug screening. Here we report results on a screening of the ability of five essential oils to inhibit IL-1-induced iNOS expression and NO production in human chondrocytes.