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Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities

John H Peniston, Morris S Gold, Matthew S Wieman, Lawrence K Alwine

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Background

- Knee Osteoarthritis (OA) occurs commonly in elderly ≥ 65 years who are predisposed to adverse events. Hence, therapy must balance pain relief and potential treatment-related side effects.
- Oral NSAIDs relieve OA pain effectively but possess risks of gastrointestinal, cardiovascular and renal adverse events specially in the elderly and in people with comorbid conditions, such as hypertension (HTN), type 2 diabetes mellitus (T2DM), and cerebrovascular or cardiovascular disease (C/CVD).
- Topical NSAIDs, such as diclofenac sodium 1% gel (DSG), have equivalent efficacy and fewer adverse events compared with oral NSAIDs. Five placebo-controlled studies of 12-week duration showed that DSG was well-tolerated in patients with hand or knee OA who had an elevated risk of gastrointestinal, cardiovascular, or renal adverse events.
- According to the OARSI guidelines, topical NSAIDs like 1% DSG (diclofenac sodium gel) are the recommended first-line therapy for OA patients, considering equivalent efficacy and a lower frequency of adverse events compared with oral NSAIDs.

Study Objective and Methodology

- A multicenter, open-label, post hoc analysis was conducted to determine the long-term (12 months) tolerability of DSG in elderly knee OA patients with an elevated risk of gastrointestinal, cardiovascular, and renal adverse events.

Eligibility Criteria

Inclusion Criteria:

Patients completing either of two primary 12-week studies (continuing patients) (n = 660) and treatment-naïve patients (n= 292)

Treatment-naive patients aged ≥ 35 years, with radiographically confirmed mild to moderate (Kellgren-Lawrence grade 1–3) knee OA (according to ACR criteria), for ≥ 6 months before screening.

Exclusion Criteria: For treatment-naive patients - current evidence or history of secondary OA, history of rheumatoid arthritis, other chronic inflammatory disease, allergy or asthma related to NSAIDs, evidence of peptic ulcer or history of gastrointestinal bleeding, significant injury to the target joint ≤ 30 days before screening, major knee surgery at least one year before screening, significant medical condition that could compromise the patient's medical condition or confound study result.

Study Design

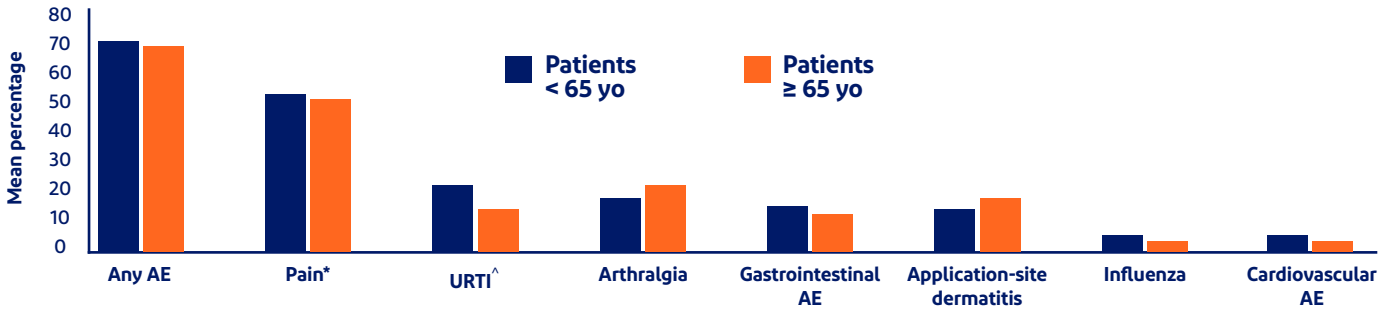
Patient Disposition

- Scheduled visits occurred at baseline, monthly for 6 months, and at month 9. This completed one year of treatment in patients continuing from the active treatment groups in the double-blind studies
- All adverse events and serious adverse events were monitored and recorded. Safety population comprising 947 patients
- Subpopulations were based on:
  - » Age (<65 and ≥65 years of age)
  - » Comorbidities: HTN 46.3%, T2DM 10.6%, AND C/CVD 10.2%
  - » Patients with multiple comorbidities exist in 1.6% of patients in the safety population, which is combined diagnoses of HTN, T2DM and C/CVD in medical history

DSG 1%	Knee OA patients (≥ 35 years) applied 4g DSG to one or both knees for 12 weeks during either of two primary studies followed by an additional 9 months continued treatment: • **Primary study 1:** Treated with DSG until week 12 , n = 144; Treated with placebo until week 12 , n = 147 • **Primary study 2:** Treated with DSG until week 12 , n = 369 • 12 months (for treatment-naive patients) during a long-term extension study
Rescue medication	• Acetaminophen, max 4 g/day allowed

Results

Stratification by age, < 65 years and ≥ 65 years: For both groups, the **percentage of patients who had any adverse event was similar.** Patients aged <65 years were more likely to experience gastrointestinal (GI) adverse events and less likely to experience application site dermatitis (ASD), in comparison to patients aged ≥ 65 years.



Adverse events

*Pain included Headache, Back pain, pain in extremity, Pain, Toothache, Myalgia, Neck pain
^URTI included Upper respiratory tract infection, Nasopharyngitis, Sinusitis, Sinus congestion

Stratification by comorbidity

- The percentage of patients who experienced any adverse event was similar between patients with and without hypertension (65.5% versus 69.7%), type 2 diabetes mellitus (64.0% versus 68.2%), or cerebrovascular or cardiovascular disease (61.9% versus 68.5%), respectively.
- Among the 15 patients with all three comorbidities, the percentage of patients with any adverse event (53.3%) was less than that of patients who did not have all three comorbidities (68%).

Total adverse events stratified by comorbidity

	Gastrointestinal AE (%)	Cardiovascular AE (%)	Application-site dermatitis (%)	Any AE (%)
With HTN (n=438)	8.9	5.0	8.2	65.5
Without HTN (n=509)	7.9	1.8	12.4	69.7
With T2DM (n=100)	7.0	8.0	10.0	64.0
Without T2DM (n=847)	8.5	2.7	10.5	68.2
With C/CVD (n=97)	12.4	6.2	8.2	61.9
Without C/CVD (n=850)	7.9	2.9	10.7	68.5
With MultiCom (n=15)	0	13.3	0	53.3
Without MultiCom (n=932)	8.5	3.1	10.6	68.0

- Treatment-emergent adverse events were reported in ≥3% of any comorbidity group (with or without HTN, T2DM, C/CVD and MultiCom).
- Pain is the key treatment emergent adverse event, and this includes headache, arthralgia, back pain, pain in extremity, neck pain, myalgia etc., and was higher in "without comorbidity group" (T2DM, C/CVD and MultiCom) as compared to "with comorbidity group"

Treatment-emergent adverse event

	With HTN (%)	Without HTN (%)	With T2DM (%)	Without T2DM (%)	With C/CVD (%)	Without C/CVD (%)	With Multicom (%)	Without Multicom (%)
Pain	58.4	53.5	45.0	54.3	39.2	57.5	33.4	45.9
Upper respiratory tract infection	14.8	17.9	11.0	17.1	16.5	16.5	20.0	11.9
Infuenza	1.8	5.1	0	4.0	4.1	3.5	NA	NA
Myalgia and muscle spasms	0.9	4.3	1.0	3.0	NA	NA	13.4	3.5
Diabetes mellitus	NA	NA	3.0	0	NA	NA	6.7	0.2

Strengths

- The subgroup analyses indicated that diclofenac sodium gel was well tolerated in patients aged 65 years or older, as well as in patients with comorbid conditions of HTN, T2DM, or C/CVD and even in patients with all three comorbidities combined.
- The frequency of any adverse event was not increased in these subpopulations compared with < 65 years of age or patients without these comorbid conditions.
- DSG provides local pain relief as effectively as oral NSAIDs, with limited systemic exposure, thus reducing the risk of adverse events.
- DSG may be safely used over a longer period (almost 12 months) to treat knee osteoarthritis in patients at higher risk of experiencing adverse events.

Limitations

- This analysis was limited by the small sample size of a number of the subgroups, particularly patients with T2DM or C/CVD and those in the multiple comorbidity group, thus precluding statistical testing of differences in tolerability between subgroups.
- Absence of comparator groups treated with placebo or an oral NSAID.

Conclusion

- Long-term treatment (12 months) with diclofenac sodium gel is safe in patient subpopulations with an elevated risk of NSAID-related adverse events.
- DSG may be safely administered as long-term therapy in elderly patients with knee osteoarthritis and in patients with comorbid conditions that predispose them to NSAID-related adverse events.

References
Peniston, J.H, Gold, M.S., Wieman, M.S., Alwine, L.K. (2012). Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. Clinical interventions in aging, 2012:7:517-23.