ADVERSE EVENTS IN PATIENTS WITH BLOOD LOSS: A POOLED ANALYSIS OF 51 CLINICAL STUDIES FROM THE CELECOXIB CLINICAL TRIAL DATABASE

G. Sands, MD; B. Shell, PhD; R. Zhang, PhD

Pfizer Inc, New York, NY, USA.

INTRODUCTION

- Despite their accepted efficacy, it is well recognized that chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of gastrointestinal (GI) toxicity, including overt bleeding, ulceration, occult blood loss, and the development of clinically significant anemia or blood loss.[1]
- Recent evidence suggests that patients with mildly low or low-normal hemoglobin levels may have an increased risk of frailty, poor functional outcomes, hospitalization, and mortality.[2-5]
- In the recent Celecoxib vs Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis (CONDOR) trial,[1] which compared the risk of GI events across the entire GI tract, clinically significant anemia or blood loss (defined as a decrease in hemoglobin ≥ 2 g/dL and/or hematocrit ≥ 10% points from baseline) was a component of the composite primary end point.
- Although anemia is common in patients taking NSAIDs, few studies have been performed prior to CONDOR[1] to determine the exact burden and clinical impact of this problem in patients taking NSAIDs or aspirin.

OBJECTIVE

- To investigate whether there is a clinically important and relevant difference in the adverse event (AE) profile of patients with clinically significant anemia or blood loss (defined as a decrease in hemoglobin ≥ 2 g/dL and/or hematocrit ≥ 10% points from baseline) vs those without.

METHODOLOGY

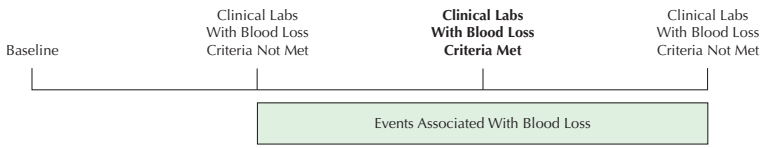
Study design and selection

- This was a retrospective, pooled analysis of 51 blinded, controlled clinical studies ≥ 4 weeks duration comparing celecoxib, a cyclooxygenase-2 selective NSAID, with nonselective NSAIDs or placebo. The median duration of treatment was 6-9 months.
- To be eligible for inclusion all clinical study reports (from Pfizer's Celecoxib Clinical Trial Database) must have been finalized by October 1, 2007.
- All randomized, double-blind, controlled clinical trials with at least 1 celecoxib and 1 comparator (active or placebo) group, and a planned duration of daily treatment ≥ 12 weeks were included.
- All open-label extensions, crossover trials, and healthy volunteer studies were excluded.
- All studies in patients with osteoarthritis and rheumatoid arthritis, ankylosing spondylitis, chronic low back pain, Alzheimer disease, and polyps were eligible for inclusion.

Data collection

- The primary end point was blood loss status (Y/N) defined as "Yes" if a subject had a ≥ 2 g/dL hemoglobin drop and/or ≥ 10% hematocrit drop from baseline.

Figure. AEs associated with blood loss.



- This definition is consistent with the definition of clinically significant anemia or blood loss used (as a component of the composite primary end point) in both the CONDOR and GI-REASONS (Gastrointestinal Randomized Event and Safety Open-label NSAID Study) trials.[1,6]
  - An AE was considered to be associated with blood loss if it occurred at any time during the time window (Figure).

Statistical analysis

- The pooled analysis was performed on the safety population (defined as those patients who were randomized to a Pfizer celecoxib double-blind, placebo- or active-controlled clinical trial, and who had at least 1 dose of the study medication and had at least 1 safety assessment).
- A stepwise logistic regression model was used to explore the association between clinically significant blood loss (Y/N) and AEs (preferred terms based on Medical Dictionary for Regulatory Activities, MedDRA 11.0).
  - Basic demographic variables (ie, age, sex, race) were covariates.
- AEs were collected from the last laboratory day normal hemoglobin/hematocrit values were recorded (prior to the first hemoglobin/hematocrit decrease), to the day hemoglobin/hematocrit values returned to normal ***or*** 30 days after the hemoglobin/hematocrit decrease, whichever occurred first.
- Comparisons were based on the percentage of patients with AEs and not annualized for the duration of the observation period.
- In addition, AEs occurring in < 0.5% of patients in both groups were excluded from any comparisons.
- A 3-fold difference between groups was defined arbitrarily as being markedly higher.

RESULTS

Patients

- A total of 51 double-blind, randomized clinical trials were included in this retrospective pooled analysis.
- Overall, 932/51,048 (1.83%) patients in the Pfizer's Celecoxib Clinical Trial Database experienced clinically significant anemia or blood loss (as defined by a decrease in hemoglobin ≥ 2 g/dL and/or hematocrit ≥ 10% from baseline).
- Baseline demographics were similar in patients with/without clinically significant blood loss (Table 1).
- The majority of patients were treated for > 6 months.

Table 1. Baseline Demographics and Characteristics

	Patients With Blood Loss (n = 932)	Patients Without Blood Loss (n = 50,116)
Age, y		
Mean	60.9	59.8
Median	61.0	61.0
Range	21-91	17-96
Race, n (%)		
White	746 (80.0)	38,166 (76.2)
Black	54 (5.8)	3218 (6.4)
Asian	102 (10.9)	5518 (11.0)
Other	29 (3.1)	2970 (5.9)
Missing	1 (0.1)	244 (0.5)
Sex, n (%)		
Female	547 (58.7)	32,861 (65.6)
Male	385 (41.3)	17,255 (34.4)
Weight, kg		
Female, n (%)	544 (58.4)	32,778 (65.4)
Mean	72.1	76.4
Median	69.2	73.0
Range	36.0-162.7	31.5-249.2
Male, n (%)	383 (41.1)	17,225 (34.4)
Mean	87.3	87.8
Median	85.7	85.4
Range	47.5-158.1	35.0-232.0

Table 2. AEs in Patients With a Markedly Higher[a] Incidence of Clinically Significant Anemia or Blood Loss vs Those Without (Threshold ≥ 0.5% in Either Group)

AEs n (%)[b]	Patients With Blood Loss (n = 932)	Patients Without Blood Loss (n = 50,116)
Any AE	612 (65.7)	29,222 (58.3)
GI-related AEs		
Gastric ulcer	14 (1.5)	101 (0.2)
GI hemorrhage	7 (0.8)	33 (< 0.1)
Esophageal ulcer	5 (0.5)	24 (< 0.1)
Melena	12 (1.3)	57 (0.1)
Potential GI-related AEs		
Anemia	82 (8.8)	317 (0.6)
Increase in blood creatinine	16 (1.7)	207 (0.4)
Decrease in hemoglobin	83 (8.9)	120 (0.2)
Decrease in hematocrit	97 (10.4)	228 (0.5)
Decrease in red blood cell count	7 (0.8)	23 (< 0.1)
Hematochezia	9 (1.0)	126 (0.3)
Non-GI-related AEs		
Coronary artery disease	11 (1.2)	144 (0.3)
Myocardial infarction	6 (0.6)	99 (0.2)
Pneumonia	16 (1.7)	202 (0.4)

[a]Markedly higher = 3-fold difference between treatment groups in the incidence of AEs; [b]Preferred terms based on MedDRA 11.0.

CONCLUSIONS

- Clinically significant anemia or blood loss, defined as decreases in hemoglobin ≥ 2 g/dL and/or hematocrit by ≥ 10% from baseline, may have clinically important adverse consequences beyond the sequelae previously known to be associated with NSAID-related GI effects.
  - The discovery of gastric and esophageal ulcers in the group of patients with a markedly higher incidence of clinically significant blood loss suggests possible occult GI bleeding from this source.
  - The non-GI AE terms found suggest that clinically significant blood loss may be important to those patients needing all of their oxygen-carrying capacity.
- Further studies are required to better understand the clinical importance of clinically significant anemia or blood loss.

Incidence of AEs

- In general, patients with clinically significant blood loss had a higher incidence of AEs than those who did not have clinically significant blood loss (Table 2).
- As might be expected following NSAID treatment, the majority of these differences were for the GI disorder AEs (65.7% vs 58.3%) or their likely sequelae; the specific GI disorder AEs showing at least a 3-fold difference are shown in Table 2.
- The incidence of the following non-GI related AEs was also markedly higher in patients with defined clinically significant blood loss compared with patients without such blood loss: coronary artery disease (1.2% vs 0.3% respectively), myocardial infarction (0.6% vs 0.2%), and pneumonia (1.7% vs 0.4%).
- Withdrawals due to AEs were more common among patients who experienced clinically significant blood loss (16.7%) than those who did not (10.4%).

DISCUSSION

- The findings of this post hoc pooled analysis support the clinical relevance of the ≥ 2 g/dL decrease in hemoglobin and/or ≥ 10% hematocrit.
- Overall, the majority of patients with clinically significant blood loss were ≈1-year older than those without blood loss.
- While it appears obvious why many of the GI AEs have a higher incidence in the clinically significant blood loss group, for other AEs it is less so. These include the terms gastric ulcer and esophageal ulcer. The inclusion of these terms among those with at least a 3-fold greater incidence in the clinically significant blood loss group suggests the ulcers could bleed without producing symptoms observable to either the patient or the physician to cause the ≥ 2 g/dL decrease in hemoglobin.
- While the findings of the CONDOR trial[1] and the previous Celecoxib Long-term Arthritis Safety Study (CLASS)[7] suggest clinically significant anemia or blood loss is a GI sequela associated with NSAID use, it is unclear if the clinically significant anemia, and the decreases in hemoglobin/hematocrit found in this analysis are a result of GI blood loss.
- There are likely patients with limited reserves with a ≥ 3-fold increased incidence for coronary artery disease, myocardial infarction, and pneumonia who can ill afford to lose the oxygen-carrying capacity associated with the loss of ≥ 2 g/dL hemoglobin.
- The goal of this analysis was to better understand the clinical implications of a loss of ≥ 2 g/dL hemoglobin and/or ≥ 10% hematocrit drop from baseline over time. The CONDOR[1] and GI-REASONS[6] trials included clinically significant anemia or blood loss, as defined in this analysis, as a component of the composite predefined primary end point for "clinically significant upper and lower GI events." The majority of the primary end point events in CONDOR were from clinically significant blood loss.

LIMITATIONS/STRENGTHS

- This was a post hoc analysis of the celecoxib database pooling data from 51 randomized clinical trials, using post hoc criteria for clinical relevance. While many of the RCTs included have similar study structure, they are not identical, possibly adding bias to this analysis. A number of the AEs examined occurred in too few patients to provide the most robust data.
- One of the strengths of this analysis was the use of the prespecified definition of clinically significant anemia or blood loss (decreases in hemoglobin ≥ 2 g/dL and/or hematocrit by ≥ 10% from baseline) used in both the CONDOR and GI-REASONS trials. Furthermore, more than 51,000 patients with active disease, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis were included in the database, giving a more robust sample size.

REFERENCES

1. Chan FK, et al. *Lancet.* 2010;376:173-9.
2. Eisenstaedt R, et al. *Blood Rev.* 2006;20:213-26.
3. Penninx BW, et al. *J Am Geriatr Soc.* 2005;53:2106-11.
4. Penninx BW, et al. *J Gerontol Med Sci.* 2006;61A:474-9.
5. Chaves PH, et al. *J Am Geriatr Soc.* 2004;52:1811-6.
6. Chan FK, et al. *J Rheumatol.* 2010;37:167-74.
7. Silverstein FE, et al. *JAMA.* 2000;284:1247-55.

ACKNOWLEDGMENTS

The study was sponsored by Pfizer Inc. Editorial support was provided by L. Prevost, of PAREXEL, and was funded by Pfizer Inc.

DISCLOSURE OF INTEREST

G. Sands, B. Shell, and R. Zhang are all employees and shareholders of Pfizer Inc.