Osteoarthritis and Cartilage 19 (2011) 493–499

Osteoarthritis and Cartilage

Safety issues in the development of treatments for osteoarthritis: recommendations of the Safety Considerations Working Group

V. Strand †*, D.A. Bloch ‡, R. Leff §, P.M. Peloso ||, L.S. Simon ¶

† Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA
‡ Department of Biostatistics, Stanford University School of Medicine, Palo Alto, CA, USA
§ AstraZeneca, Wilmington, DE, USA
|| Clinical Research – Analgesia and Inflammation, Merck Research Laboratories, Rahway, NJ, USA
¶ SDG, LLC, Boston, MA, USA

ARTICLE INFO

Article history:
Received 26 November 2010
Accepted 8 February 2011

Keywords:
Safety assessments
Serious adverse events
Cardiovascular risks
NSAIDs
COX-2

SUMMARY

Objective: The symptomatic treatment of osteoarthritis (OA) remains to be improved, as many patients do not respond well to current palliative therapies and/or suffer unacceptable adverse events. Given the unmet need for innovative, effective and well-tolerated therapies, it is important to develop the means to estimate the ongoing safety profile of novel therapeutic agents over short- and longer term use.
Design: Methods are presented to estimate the number of serious adverse events (SAEs) of interest considered as "acceptable" per 1000 patient-years exposure and to estimate the numbers of patient-years needed in a randomized controlled trial (RCT) to meet objectives. As exposure is increased, more evidence is accrued that the overall risk is within study limits. It is equally important that requirements for delineating the safety of promising new therapies not create barriers that would preclude their development. Therefore, ongoing surveillance of occurrence of SAEs of interest during clinical development is proposed, for example after every incremental 500 patient-years exposure are accrued.
Results: This paper and others in this special issue focus on identification of safety signals for symptomatic treatments of OA. Much less information is available for agents aimed at slowing/preventing structural progression but it is expected that a higher risk profile might be considered acceptable in the context of more promising benefit.
Conclusion: This paper provides a proposal and supporting data for a comprehensive approach for assessing ongoing safety during clinical development of both palliative and disease-modifying therapies for OA.

Introduction

Osteoarthritis (OA) is a common and heterogeneous disease that occurs worldwide, predominantly in older individuals[60,37,52]. The pain, impairment in physical function, and disability associated with OA vary greatly from mild and intermittent to severe and continuous[51,50,53], prompting patients to seek a wide variety of treatments, ranging from intermittent use of analgesics to total joint arthroplasties, with greatly varying associated risks[61,34,32].

As cyclooxygenase-2 selective (COX-2) agents were developed that decreased the risk of gastrointestinal (GI) bleeding[1,45], it became apparent that both non-selective nonsteroidal anti-inflammatory drugs (nsNSAIDs) and selective COX-2s were associated with increased risks for cardiovascular (CV) events[43,47,49,25]. Results to date have led to the conclusion that treatment-associated increases in CV risk vary according to patient characteristics, underlying risk factors, specific NSAID/COX-2 administered, and dose and duration of treatment[13,2,56,55,31,25,26]. Recognizing that absolute rates of risk are small and the large number of factors influencing NSAID/COX-2-associated increases in CV risk[12,31] means that the incidence of treatment-associated CV events require evaluation, not only in multinational randomized control trials (RCTs), but also in large post-approval, randomized pragmatic trials and longitudinal observational studies (LOS)[4,28,56]. RCTs, cohort studies and case control series contribute information to the evolving safety profile of a novel therapeutic, once approved, and

* Address correspondence and reprint requests to: Vibeke Strand, Division of Immunology/Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA
E-mail addresses: vstrand@stanford.edu (V. Strand), dbloch@stanford.edu (D.A. Bloch), Richard.leff@astrazeneca.com (R. Leff), Paul_peloso@merck.com (P.M. Peloso).
URL: http://www.sdgltd.com

1063-4584/$ – see front matter © 2011 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.joca.2011.02.019

each offer different types of information[29,7,4,28]. To the extent that assessment of uncommon serious adverse events (SAEs) relies upon voluntarily reported events in LOS, this may underestimate adverse event (AE) frequency and/or be confounded by channeling bias, other unidentified comorbidities and risk factors[17,40]. In the case of liver toxicity associated with NSAIDs and in particular with a recent COX-2 selective inhibitor, lumiracoxib, large numbers of patients needed be studied to characterize this rare risk.

Uncommon and/or less easily predicted complications of OA treatment (e.g., idiosyncratic skin rashes, including Stevens - Johnson syndrome and/or Toxic Epidermal Necrolysis)[48], those reflective of comorbidities (e.g., hypertension (HTN), diabetes)[6], and/or polypharmacy frequently present in subjects with OA[5,44] should also be considered. Recent data and RCTs indicate as many as 40–50% of OA subjects have HTN; they are twice as likely to develop a myocardial infarction (MI) and 70% more likely to suffer a cerebrovascular accident (CVA). In addition there is an associated increased risk of type II diabetes, with its own attendant CV risks. Other common comorbidities in the OA population include chronic obstructive pulmonary disease (COPD), peptic ulcer and other GI diseases, increased risk of obesity and metabolic syndrome and increased incidence of CV disease with increasing age, impairment in renal function and osteoporosis[11,58,59]. Thus, it is important that novel therapies under development include drug–drug interaction studies in this patient population as well as information regarding instability in blood pressure, blood glucose, and/or renal function during RCTs – and that CV events be carefully surveilled.

A question posed by the U.S. Food and Drug Administration (FDA) in 2007 regarding the Draft 1999 Guidance Document for development of novel agents for treatment of OA was "What should the size and duration of exposure of the safety database be for agents offering symptomatic relief?"[18]. This paper outlines recommendations for ongoing evaluation of the safety of novel agents for symptomatic treatment of OA. Other therapies, including topical or intra-articular agents that do not result in significant systemic drug exposure are not considered. In addition, pure analgesics without anti-inflammatory effects are not addressed. Simple analgesics, over-the-counter (OTC) acetaminophen and oral opioid drugs, have significant well-recognized safety risks, and are not included in this discussion[46,42,41,10].

Recommendations provided address studies of novel agents and it is acknowledged that the known safety profile for any new therapy will almost certainly evolve after approval and subsequent administration to thousands and millions of patients rather than the limited numbers typically involved in a clinical development program, also including those with comorbidities that would otherwise preclude their participation in pre-approval RCTs. The following discussion is also undertaken with the assumption that any new molecular entity in development for symptomatic relief of OA should have no evidence of risks beyond those identified with currently approved therapies since these agents are palliative in nature and do not alter the natural history of the disease. An acceptable safety profile for a disease-modifying agent may also be very different than that for a symptomatic therapy and a certain degree of greater risk may be acceptable for achievement of this benefit[57]. The magnitude of benefit with a novel palliative therapy for OA should be an important determinant of the number of patients required to demonstrate an acceptable understanding of its associated risk.

Current guidances

Safety databases vary according to size and populations studied, whether pre- or post-approval, by recognized risks, and class of therapeutic agent (Table I). Depending upon an *a priori* concern regarding SAEs based upon nonclinical information or results from early trials, larger studies may be required to better characterize the safety profile of a new therapy. As it is difficult to predict the safety profile of a novel agent and accurately determine the 95% confidence intervals (CIs) around the incidence of uncommon to rare SAEs, it is recommended that ongoing estimates of risks during clinical development be performed to inform decisions regarding the size of the database required for approval.

The previous 1999 FDA OA Draft Guidance Document did not specifically address safety recommendations[19] and International Conference on Harmonization (ICH) recommendations published in 1994[33] were generally applied for development of novel agents that would be used both intermittently and regularly on a chronic basis. The ICH guidelines recommend 1500 patients as the minimum number of subjects to have received a new therapeutic at any dose for any time period; 300–600 patients be treated for 6 months and a minimum of 100 patients for at least one year at the proposed dose.

With identification of relatively rare SAEs of variable incidence, the evaluation of risk based upon exposure (e.g., number of events per 100 patient-years) has become important. For example, clinical development programs with 3-month RCTs in OA aimed at assessing symptomatic relief typically have resulted in databases with approximately 1000 patient-years of exposure. As noted above, these limited databases may not permit identification of rare but likely important SAEs. For example, early biologic inhibitors of tumor necrosis factor (TNFα) for treatment of rheumatoid arthritis (RA) were approved with limited databases, and post-marketing surveillance was required to identify uncommon SAEs such as opportunistic infections, lymphomas and malignances[38,27]. Post-approval recognition of these SAEs motivated the requirement for 2500 patient-years of exposure for approval of subsequent new disease-modifying anti-rheumatic drugs (DMARDs) for treatment of RA[22–24].

Similarly, FDA has recently issued two guidances for evaluation of new agents for treatment of diabetes mellitus (DM), recommending a minimum of 3000 patient-years of exposure[20] and based on recognition of increased CV risk in subjects with Type 2 DM, 5000 patient-years of exposure[21].

Requirements for safety assessments are based upon point estimates of relative risk and the 95% CIs estimated around that risk. In the past relatively rare risks were better defined and 95% CIs narrowed by performance of large post-marketing safety trials conducted with the goal of increasing exposure by ~5000 patient-years and/or by studies which included subjects with more

Table I
Size of safety databases

	Patient-years exposure (approximate)
Osteoarthritis efficacy studies and ICH guidelines (estimated summation)	1000
DMARD approvals in RA (disease-modifying anti-rheumatic drugs: synthetics: 1998–; biologic agents: 2002–)	2500
DM CV risk guidance for approval (based upon RR 95% upper CI <1.8)	3000
DM CV risk guidance safety study (based upon RR 95% upper CI <1.3)	5000
OA CV outcome studies (TARGET, MEDAL, PRECISION studies)	10,000–30,000