REVIEW

Imrecoxib: Advances in Pharmacology and Therapeutics

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Abstract: Imrecoxib, a cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug (NSAID), was discovered via the balanced inhibition strategy of COX-1/COX-2. It is indicated for the relief of painful symptoms of osteoarthritis. There have been some pharmacological and therapeutic advances since the approval of imrecoxib in 2011. However, an update review in this aspect is not yet available. Relevant literature until January 2024 was identified by search of PubMed, Web of science, Embase and CNKI. From the perspective of efficacy, imrecoxib provides relief of osteoarthritis symptoms, and potential off-label use for treatment of idiopathic pulmonary fibrosis, perioperative pain, hand-foot syndrome, axial spondyloarthritis, COVID-19, cartilage injury, and malignancies such as lung and colon cancer. From a safety point of view, imrecoxib showed adverse effects common to NSAIDs; however, it has lower incidence of new-onset hypertension than other types of selective COX-2 inhibitors, less gastrointestinal toxicities than non-selective NSAIDs, weaker risk of drug interaction than celecoxib, and more suitable for elderly patients due to balanced inhibition of COX-1/COX-2. From a pharmacoeconomic perspective, imrecoxib is more cost-effective than celecoxib and diclofenac for osteoarthritis patients. With the deepening of the disease pathophysiology study of osteoarthritis, new therapeutic schemes and pharmacological mechanisms are constantly discovered. In the field of osteoarthritis treatment, mechanisms other than the analgesic and anti-inflammatory effects of COX-2 inhibitors are also being explored. Taken together, imrecoxib is a moderate selective COX-2 inhibitor with some advantages, and there would be more clinical applications and research opportunities in the future.

Keywords: cyclooxygenase-2, efficacy, imrecoxib, non-steroidal anti-inflammatory drug, older adults, osteoarthritis, safety

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in clinical practice to relieve pain and reduce inflammation. There are two main types of NSAIDs. Non-selective NSAIDs inhibit both cyclooxygenase (COX)-1 and COX-2, and exhibit common gastrointestinal (GI) side effects that may trouble the patients and limit their application. Selective NSAIDs, usually referred to COX-2 inhibitors, selective COX-2 inhibitors, or coxibs, have fewer GI side effects than non-selective NSAIDs, but long-term use of certain coxibs has been associated with cardiac side effects.[1]

Imrecoxib is a selective COX-2 inhibitor launched in China in May 2011.[2] It is indicated for the relief of painful symptoms of osteoarthritis, and the usual dosage for adult patients is 100 mg twice daily. The cumulative duration of imrecoxib medication use was up to 24 weeks. Clinicians may not clearly know the difference between imrecoxib and other oral COX-2 inhibitors that are currently in use (ie, celecoxib, etoricoxib) and have been withdrawn from the market (ie, rofecoxib, lumiracoxib). Also, there have been some pharmacological and therapeutic advances since the approval of imrecoxib. We present an update narrative review, aiming at promoting rational medication use and facilitating related research.

Methods

Search Strategy

Potentially relevant journal papers with title or abstract containing imrecoxib until January 2024 was identified by performing searches in PubMed, Web of science core collection, Embase and CNKI.

Selection Criteria

Two reviewers (WYH and ZLL) independently retrieved the literature and screened the relevant studies. If they have a disagreement over including or excluding an article, the third reviewer (QZ) was consulted. Documents were identified in PubMed (n=32), Web of Science Core Collection (n=38), Embase (n=65) and CNKI (n=124) After excluding duplicated literature, 178 papers underwent further assessment. After reviewing the abstracts, documents were excluded due to reasons [the contents of studies not closely related to therapeutic use of imrecoxib (eg, pharmaceutical analysis, drug quality control, pharmaceutical synthesis, in vivo drug metabolism in rats) (n=19), studies where medication use were in accordance with indications described in the package insert of imrecoxib (n=116), studies where off-label clinical use of imrecoxib were investigated without using randomized control design method (n=1)]. Full-text of forty-two papers were further assessed for eligibility. Ten documents were excluded due to letters and conference abstracts. Thirty-two papers were finally chosen according to the inclusion/exclusion criteria (Figure 1). Valuable information was summarized below.
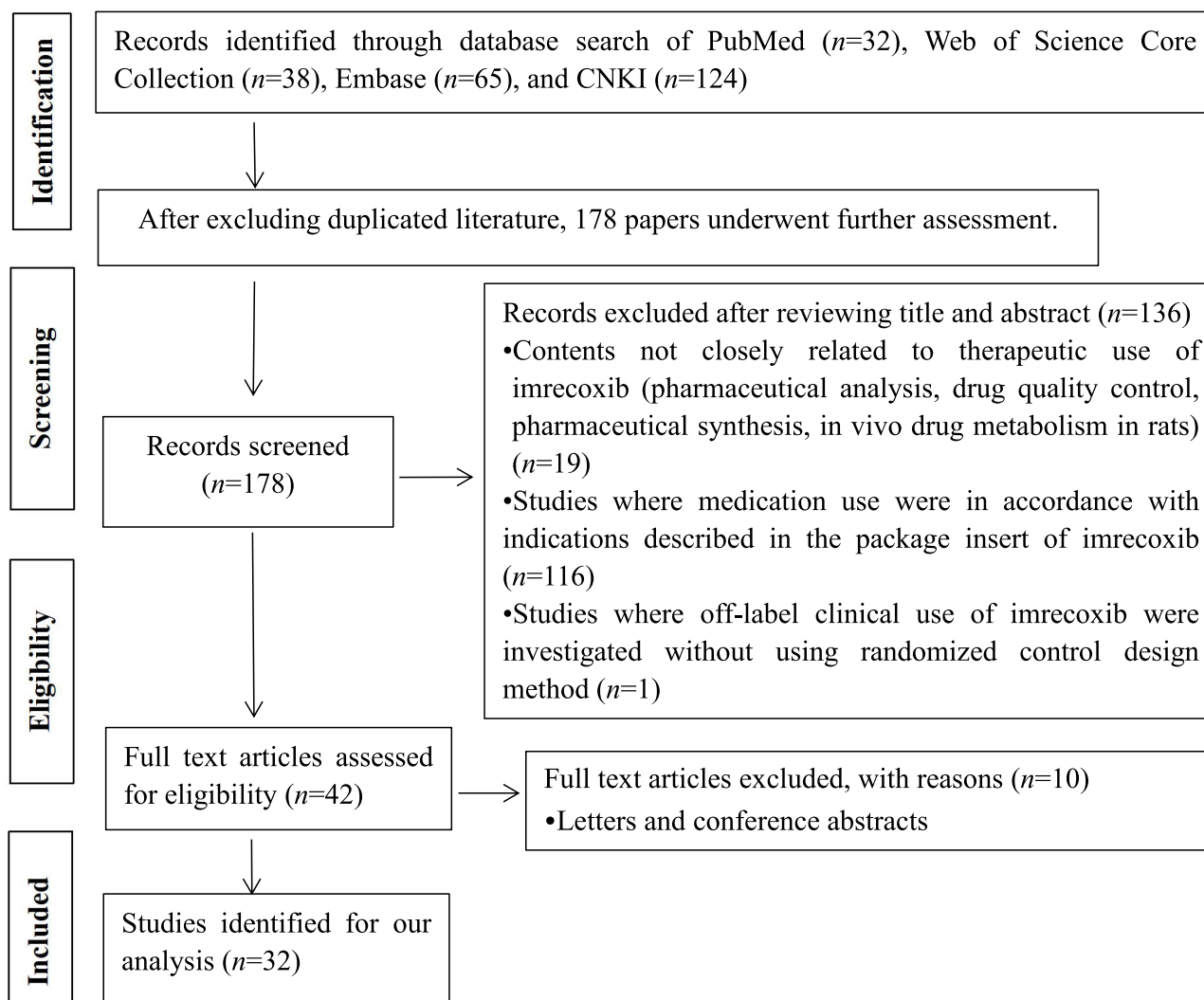

Figure 1 Flow chart showing selection of literature.

Brief Summary of Oral Coxibs

Figure 2 illustrates chemical structures of oral coxibs. Table 1 lists brief introduction of coxibs in terms of pharmacokinetics and pharmacodynamics.

Potential off-Label Use

Treatment of Idiopathic Pulmonary Fibrosis (IPF)

IPF is an incurable chronic progressive disease with a poor prognosis and limited effective treatment options.[3] Although nintedanib and pirfenidone were approved for IPF treatment, the clinical demand is far from being met due to high treatment cost, only indications for mild-to-moderate IPF, and adverse drug reactions (eg, GI side effects, nervous system toxicity, liver and kidney function impairment).

Miao et al revealed that imrecoxib could attenuate bleomycin-induced IPF in mice by inhibiting inflammation and the transforming growth factor (TGF)-β1/extracellular signal-regulated kinase (ERK) 1/2 signaling pathway.[4] The model mice were given 100 mg/kg imrecoxib by intragastric administration for 7 or 14 consecutive days, with pirfenidone (200 mg/kg) as positive control. Histopathological examination and hydroxyproline content analysis confirmed that imrecoxib had a similar effect to pirfenidone. Jin et al reported that imrecoxib could inhibit epithelial-mesenchymal transition of paraquat-induced A549 cells and alleviate relevant IPF through the nuclear factor kappa B (NF-κB)/snail signal pathway.[5]

Parra et al examined open lung biopsy specimens from 30 IPF patients, using normal lung tissue as a control. The proportion of alveolar septal cells immunostained for COX-2 was significantly higher in the tissues exhibiting usual interstitial pneumonia than in the control tissue, indicating that strategies aimed at blocking high COX-2 synthesis would have a greater impact on IPF.[6] There is currently no literature on the treatment of IPF with other COX-2 inhibitors, and therefore, imacoxib is the first COX-2 inhibitor with therapeutic potential for IPF.
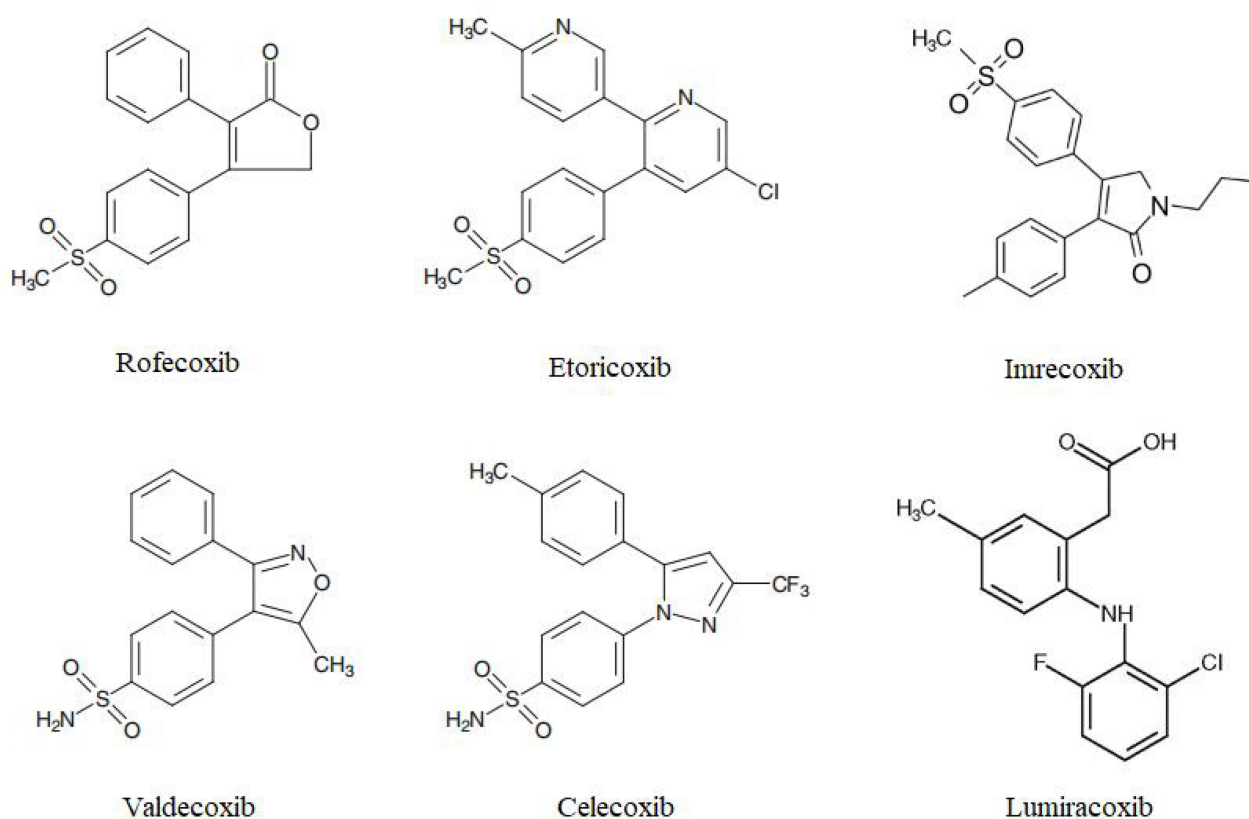

Figure 2 Chemical structures of COX-2 inhibitors.

Table 1 List of Coxibs in Terms of Pharmacokinetics and Pharmacodynamics

Items	Celecoxib	Etoricoxib	Rofecoxib	Imrecoxib	Valdecoxib	Lumiracoxib
Chemical structure	Sulfonamides	Methylsulphones	Methylsulphones	Methylsulphones	Sulfonamides	Phenylacetic acid derivative
COX-1/COX-2 IC50 ratio	7.6	106	35	6.39	30	515
Market status	Available	Available (not approved by the FDA)	Withdrawn in September 2004	Available	Withdrawn in April 2005	Withdrawn from the Canadian, Australian and EMEA market due to concerns that it may cause liver failure
Drug metabolism	Eliminated by hepatic metabolism involving mainly CYP2C9.	Eliminated by hepatic metabolism involving mainly CYP3A4.	Eliminated predominantly by hepatic metabolism primarily through reduction by cytosolic enzymes.	Eliminated by hepatic metabolism involving CYP2C9 (62.5%), CYP2D6 (21.1%), and CYP3A4 (16.4%).	Eliminated by extensive hepatic metabolism involving CYP3A4, CYP2C9, and glucuronidation.	Eliminated by hepatic metabolism involving mainly CYP2C9.
Drug interaction potential	Celecoxib is a CYP2D6 inhibitor.	No inhibitory effects on CYP2C9, 2C19, 2D6, 2E1 or 3A4 are expected to occur with etoricoxib.	Rofecoxib is a potent, metabolism-dependent inhibitor of CYP1A2	Imrecoxib is a weak inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.	Valdecoxib is not a significant inhibitor of CYP1A2, 3A4, 2D6 and CYP2C9 and a weak to moderate inhibitor of CYP 2C19.	Lumiracoxib does not exhibit any clinically meaningful interactions with commonly used medications.
Elimination half-life	11 ~ 16 h	19~32 h	17 h	20 h (M1: 26.0 h; M2: 15.7 h)	8~11 h	5~ 8 h
Genetic polymorphism in drug metabolism	*CYP2C9* genotype affects the clearance of celecoxib, and personalized dosing based on CYP2C9 phenotype is necessary.	CYP2C9 plays a relatively minor role in the overall clearance.	CYP2C9 plays a relatively minor role in the overall clearance.	It has not been reported yet, but *CYP2C9* genotype appears to have limited influence on the pharmacokinetics of imrecoxib.	*CYP2C9* genotype is expected to affect the clearance.	The pharmacokinetics of lumiracoxib is not significantly impacted by CYP2C9 genetic variants in vivo.

Abbreviations: CYP, cytochrome P450; COX, cyclooxygenase; EMEA, The European Medicines Agency; IC50, the concentration at which an non-steroidal anti-inflammatory drug produces 50% inhibition of COX-1 and/or COX-2.

Perioperative Pain Management

Preemptive Analgesia with Imrecoxib

A randomized controlled study investigated the efficacy of imrecoxib for preemptive analgesia in patients undergoing anterior cruciate ligament reconstruction. The study was divided into four groups: group A and group B started imrecoxib (100mg twice daily) 3 and 1 day before surgery, respectively.; group C received imrecoxib (200 mg) 2 h before surgery, and group D did not take any analgesics before surgery. Lower opioid consumption was observed in groups (A, B, C) than in group D ($P<0.05$). The resting visual analog scores (VAS) of groups (A, B, C) were lower than those of group D at 6 and 24 h after surgery and the scores of group A at 6 h after surgery were lower than those of group C ($P<0.05$). One month after surgery, groups (A, B, C) had lower knee flexion VAS scores, higher knee injury and osteoarthritis outcome score (KOOS) pain scores, and superior KOOS quality-of-life (QOL) scores than group D ($P<0.05$), while the walking VAS scores of groups A and B were lower than those of groups C and D ($P<0.05$). Compared to traditional analgesia, preemptive analgesia with imrecoxib can effectively alleviate early postoperative pain, reduce opioid consumption, and enhance early recovery of limb function.[7] In another randomized controlled study, a total of 91 patients undergoing total hip arthroplasty (THA) were randomly divided into two groups. Group A received imrecoxib 100 mg the night before the operation and on the morning of the operation, respectively, while group B was given no analgesics. All patients received imericoxib regularly (100 mg twice daily starting 6 h after surgery for 1–7 days). Preemptive analgesia with imrecoxib could significantly reduce early postoperative pain, promote early rehabilitation, and did not increase the incidence of adverse events.[8] Jia et al demonstrated that 100 mg of irecoxib administered 30 min before surgery achieved good postoperative analgesia compared with placebo in patients undergoing spinal surgery. Additionally, preemptive analgesia significantly reduced the consumption of fentanyl, total number of compressions of patient-controlled analgesia pump and overall incidence of adverse reactions.[9]

The efficacy of preemptive analgesia with imrecoxib (1 h before surgery) compared with placebo have also been confirmed in both laparoscopic cholecystectomy and laparoscopic choledochoscopy combined with gallbladder-preserving lithotomy.[10,11]

Peripheral inflammation leads to increased COX-2 activity and prostaglandin concentrations in the central nervous system (CNS). Central sensitization may explain long-term pain-related phenomena, and COX-2 inhibitors can achieve significant cerebrospinal fluid (CSF) concentrations and cause analgesia via CNS action. Celecoxib, rofecoxib and valdecoxib can reach the human CNS, with rapid penetration and attainment of concentrations significantly sufficient to inhibit COX-2 activity.[12] In the future, it is worthwhile to conduct quantitative studies on intracranial distribution and concentration of imrexib in cerebrospinal fluid.

Comparison of Postoperative Analgesia Between Imrecoxib and Celecoxib

A multicenter randomized controlled trial demonstrated non-inferiority of imrecoxib to celecoxib for postoperative analgesia in hip osteoarthritis patients who underwent THA and received patient-controlled analgesia for 2 days.[13] Two other studies showed that imrecoxib was non-inferior compared to celecoxib in terms of postoperative analgesia and tolerance in patients receiving arthroscopic knee surgery or oral surgery.[14,15]

Cancer Treatment

COX-2 is frequently expressed in many types of cancers and exerts a pleiotropic and multifaceted role in genesis or promotion of carcinogenesis and cancer cell resistance to chemo- and radiotherapy. COX-2 not only induces cancer stem cell (CSC)-like activity, but also promotes apoptotic resistance, proliferation, angiogenesis, inflammation, invasion, and metastasis of cancer cells.[16] Therefore, COX-2 inhibition offers great possibilities for cancer treatment.

Lung Cancer

Inhibition of invasion and metastasis by imrecoxib was confirmed in xenograft tumor of lung adenocarcinoma A549 cell in male BALB/c nude mice. Compared with the control group, the imrecoxib group (40 mg/kg per day by gavage) and imrecoxib plus lobaplatin group (imrecoxib 40 mg/kg per day by gavage in addition to lobaplatin 7.5 mg/kg per week by injection) had significantly higher expression of phosphatase, tensin homolog (PTEN) protein and mRNA, with

significantly lower expression of cortactin protein and mRNA. Furthermore, compared with imrecoxib alone and lobaplatin alone group, the combined treatment group had more remarkable inhibitory effects on the invasion and metastasis of lung cancer.[17] Wang et al also confirmed the synergistic effects of imrecoxib and lobaplatin on the tumor growth and lymph node metastasis in human lung cancer xenografts in nude mice via down-regulated Ezrin and up-regulated E-cadherin.[18] Imrecoxib seems to enhance the action of lobaplatin. Further studies are needed to investigate whether imrecoxib can be combined with chemotherapy in clinical treatment of lung cancer.

Colon Cancer

COX-2 inhibitors have a potential application prospect in the prevention of colon cancer due to COX-2 overexpression in adenomatous polyps and colon cancer relative to the healthy colonic mucosa and the efficacy of these drugs in animal models of colon cancer.[19] Wang et al reported that imrecoxib (100 mg/kg once daily by gavage) combined with oxaliplatin (30 mg/kg once weekly by injection) for 21 days could inhibit the apoptosis of human colon cancer LOVO cells transplanted into nude mice by modulating the expression of Survivin and Caspase-3, and thus enhance the anti-tumor effect of oxaliplatin.[20] Lu et al demonstrated that imrecoxib combined with oxaliplatin synergistically inhibited tumor angiogenesis in human colon cancer xenografts and enhanced the anti-tumor effect of oxaliplatin. The mechanism may be related to the down-regulation of VEGF and MMP-2 expression.[21] Sun et al observed that imrecoxib (100 mg/kg intragastrically once daily) combined with fluorouracil (20 mg/kg once every 3 days by intraperitoneal injection) for 14 days could synergistically block the invasion and metastasis of human colon cancer xenografts in nude mice, and thus enhance the anti-tumor effect of fluorouracil. The underlying mechanism is down-regulation of COX-2, vascular endothelial growth factor (VEGF)-C and matrix metalloproteinase (MMP)-9 expression by imrecoxib.[22]

A Phase III randomized clinical trial (CALGB/SWOG 80702) showed that the addition of celecoxib 400 mg orally daily for 3 years to standard adjuvant chemotherapy did not significantly improve disease-free survival in patients with stage III colon cancer compared with placebo.[23] Clinical studies of imrecoxib for colon cancer prevention can also be carried out in the future.

Cecil et al demonstrated that COX-2 inhibitors significantly decreased programmed cell death ligand 1 (PD-L1) in colonic lesions and favorably affected the phenotype of tumor-infiltrating lymphocytes to control tumor growth.[24] This finding highlights an important immunologic mechanism of action for NSAIDs in colon cancer prevention. It is interesting to investigate whether imrecoxib is a chemopreventive for patients with PD-L1-positive colonic polyp.

Cartilage Injury Prevention

Li et al investigated the effect and mechanism of imrecoxib on cultured human knee osteoarthritis chondrocytes in vitro. The study was divided into three groups: the control group did not receive any intervention, the model group was treated with 5 μg/L interleukin (IL)-1β complete medium, and the experimental group was exposed to 10 μmol/L imrecoxib in addition to the treatment in the model group. Results showed that imrecoxib could improve the viability of cultured chondrocytes, increase the synthesis of type II collagen, and inhibit cell apoptosis through the inhibition of COX-2 signaling pathway.[25] However, there are currently no in vivo and clinical studies of the chondroprotective effects of imericoxib on cartilage.

Results from an in vitro study on human osteoarthritic chondrocytes showed that a combination of celecoxib and glucosamine sulfate exert synergistic anti-inflammatory and chondroprotective effects on osteoarthritic chondrocyte metabolism, apoptosis, and oxidative stress through the modulation of the NF-κB pathway.[26] So it is necessary to investigate whether imrecoxib has similar synergistic effects in vitro and in patients with osteoarthritis.

Treatment of Hand-Foot Syndrome (HFS)

HFS is a distinctive adverse drug reaction frequently induced by some chemotherapeutic agents (eg, capecitabine, pegylated liposomal doxorubicin, sorafenib and other tyrosine-kinase inhibitors) and can seriously affect the QOL of patients. The pathogenesis of HFS is not entirely clear but is usually considered as a type of inflammation evoked by COX-2.[27] A systematic review and meta-analysis evaluated the efficacy of preventive strategies for HFS, and confirmed that celecoxib could exhibit statistically significant outcomes.[28]

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Liang et al investigated whether imrecoxib could be an additional treatment option for the prevention and treatment of capecitabine-associated HFS. The incidence and severity of capecitabine-associated HFS were significantly lower in the treatment group taking imrecoxib (100 mg twice daily) and placebo (vitamin B6 100 mg twice daily) compared to the control group taking placebo.[29] Further studies are warranted on the potential prophylactic effect of imrecoxib against HFS induced by other chemotherapeutic agents and the comparison of prophylactic effects of HFS between imrecoxib and celecoxib.

Treatment of Axial Spondyloarthritis

Axial spondyloarthritis is a chronic inflammatory rheumatic disease of the axial skeleton associated with significant pain and disability. NSAIDs have generally been viewed as first-line therapy for axial spondyloarthritis. However, this disease is not currently included in the indications for imrecoxib.

A randomized controlled trial showed that patients with axial spondyloarthritis who received either imrecoxib or celecoxib 200 mg twice daily for 12 weeks showed significant improvements in disease activity, functional parameters, and inflammatory markers, and that imrecoxib was noninferior to celecoxib.[30] A randomized, double-blind, parallel-controlled study demonstrated that both imrecoxib and celecoxib equally affected sacroiliac joint inflammation in axial spondyloarthritis by regulating bone metabolism and angiogenesis.[31] A real-world study also showed that imrecoxib was as effective as celecoxib in axial spondyloarthritis treatment in terms of in disease activity, physical function, inflammation markers, and clinical remission rates. In addition, the efficacy of tumor necrosis factor inhibitors (TNFi) combined with imrecoxib in the treatment of axial spondyloarthritis was comparable to that of TNFi plus celecoxib.[32]

Pharmacoeconomics
Imrecoxib versus Celecoxib

Sun et al compared the long-term cost-utility of imrecoxib and celecoxib for osteoarthritis patients based on real-world data from the hospital information systems of 170 hospitals. In the base case analysis (6-month treatment duration, 55 years old and above), imrecoxib was the more cost-effective option compared to celecoxib, with an incremental cost-effectiveness ratio (ICER) of $3,041.14. Probability sensitivity analysis showed that there was a 59.02% probability of imrecoxib as the more cost-effective option, with a threshold of $30,000.[33]

Imrecoxib versus Diclofenac

The cost-utility of imrecoxib versus diclofenac for osteoarthritis patients was also compared from a Chinese healthcare perspective. Imrecoxib was highly cost-effective than diclofenac. The ICER was $401.58 and $492.77 in patients at low and high GI and cardiovascular (CV) risk, respectively. Furthermore, the addition of a proton pump inhibitor (PPI) was more cost-effective compared with single drug. With a threshold of $30,000, the probability for imrecoxib plus PPI to be the most cost-effective option was 59.04% and 57.16% in the low and high GI and CV risk group, respectively.[33] Over a 6-month treatment duration, imrecoxib was a cost-effective option with the ICER of $4309 and $2489 versus celecoxib and diclofenac, respectively. Similar results were seen over a 12-month and 24-month treatment duration. Imrecoxib appears to be an economical option for different courses of treatment in Chinese osteoarthritis patients.[33,34]

Drug Utilization Study

Drug utilization studies are essential to facilitate rational drug use in the society by evaluating the utilization of drugs in terms of safety, efficacy, convenience and economic aspects.

The prescription patterns and safety profiles of oral NSAIDs were evaluated using 8-year prescription databases of three Chinese hospitals involving 50,732 patients. The prescribing patterns of oral NSAIDs were not standardized among high-risk patients (ie, those with related disease, such as GI complications, CV events or other risks).[35] Comparison of adverse drug reactions caused by different NSAIDs were as follows:

Coxibs versus Non-Selective NSAIDs

Patients treated with coxibs experienced significantly lower incidences of GI complications, CV events, and new-onset hypertension compared to those receiving non-selective NSAIDs and combination products of NSAIDS ($P<0.05$). Compared with traditional NSAIDs, coxibs did not increase the risk of CV events ($P=0.0084$). In addition, the proportion of new-onset hypertension caused by coxibs was less than that triggered by traditional NSAIDs and combination products of NSAIDS (2.59% versus 3.41%, 13.04%, $P<0.0001$).[35]

Imrecoxib versus Other Coxibs

Interestingly, the occurrence of GI complications caused by imrecoxib was lower than that caused by etoricoxib (P=0.0177), and incidences of new-onset hypertension were lower in patients taking imrecoxib than those taking other types of coxibs ($P<0.05$). CV events were similar in high-risk patients when receiving different coxibs. However, among the non-risk patients, imrecoxib was safer than celecoxib (0.95% versus 1.80%, $P<0.01$), and triggered less new hypertension than celecoxib (2.32% versus 3.14%, $P<0.05$).[35]

Biomarkers for Evaluating Early Efficacy of Imrecoxib

Because the efficacy of NSAIDs varies greatly among patients, and some patients do not respond to NSAIDs treatment. Therefore, it is necessary to discover biomarkers that can accurately detect the early efficacy of NSAIDs in osteoarthritis treatment, so that patients can get a more personalized treatment plan, thereby improving disease management and efficacy evaluation. Xie et al evaluated the clinical response to imrecoxib in the early treatment of knee osteoarthritis using four-dimensional data-independent acquisition (DIA)-based proteomics. By contrasting the differentially expressed proteins in the plasma of responders and non-responders before and after 4-week drug treatment, galectin-1, galectin-3, and cluster of differentiation 44 (CD44) were identified as potential markers for assessing clinical response to imrecoxib in osteoarthritis patients. Non-responders had higher plasma levels of galectin-1, galectin-3, and CD44 than responders after imrecoxib treatment.[36]

In a prospective clinical trial including knee osteoarthritis patients on imrecoxib therapy for 4 weeks, Wu et al analyzed the plasma steady-state trough concentrations of imrecoxib and its two metabolites with anti-inflammatory activities similar to their parent drug[4'-hydroxyimrecoxib (M1), and 4'-carboxyimrecoxib (M2)]. The mean plasma steady-state trough concentrations of imrecoxib, M1 and M2 were 7.10, 9.49, and 50.91 μg/L, respectively. This study indicated that the plasma concentration of M2 may be more suitable than parent drug or M1 to predict the clinical efficacy of imrecoxib for knee osteoarthritis treatment.[37] It is worthwhile to conduct pharmacokinetic-pharmacodynamic modeling studies of imrecoxib in clinical patients.

Drug Interactions

According to the prescribing information of imrecoxib tablet, the results of enzyme inhibition tests in vitro showed that imrecoxib had a weak inhibitory effect on cytochrome P450 1A2 (CYP1A2), CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Meanwhile, clinical studies have also shown a low risk of pharmacokinetic drug interactions with imrecoxib.

Warfarin-Coxibs

Multiple doses of imrecoxib (5 continuous doses of 100 mg twice daily after a loading dose of 200 mg) did not impact the pharmacodynamics and pharmacokinetics of single-dose warfarin 5 mg, and thus adjusting dosage is not necessary when to administer imrecoxib with warfarin.[38] Battistella et al examined the association between the concomitant use of warfarin and non-selective NSAIDs or coxibs in older adults hospitalized for upper GI hemorrhage. Compared with controls, patients receiving warfarin but admitted for GI hemorrhage were significantly more likely to be also taking non-selective NSAIDs [odd ratio (OR)=1.9], celecoxib (OR=1.7), or rofecoxib (OR=2.4) prior to admission.[39] Clinicians who care for elderly patients receiving warfarin should know the potential risks of concomitant use of NSAIDs or coxibs. The

relatively lower contribution of CYP2C9 to drug metabolism of imrecoxib versus celecoxib (62.5% versus 72–92%) may partially explain the minimal risk of imrecoxib-warfarin interaction.

The effects of etoricoxib on pharmacodynamic and pharmacokinetic parameters of warfarin were examined. Coadministration of etoricoxib 120 mg once daily with warfarin resulted in a small (~10%) increase in plasma concentration of $R(+)$-warfarin, but did not affect the pharmacokinetics of the more potent $S(-)$-warfarin enantiomer. The international normalized ratio (INR) increased by about 13% on average, which is unlikely to be clinically relevant in most patients.[40]

CYP2D6 Substrates-Coxibs

The effects of celecoxib and rofecoxib on the pharmacokinetics of metoprolol a CYP2D6 substrate, were studied in a randomized, three-period crossover design. Celecoxib inhibited metoprolol metabolism while rofecoxib did not.[41] Clinically relevant drug interaction may occur between celecoxib and CYP2D6 substrates, particularly those with narrow therapeutic window or those exerting pharmacological action after metabolic activation via CYP2D6 (eg, tamoxifen, codeine, dihydrocodeine, tramadol).

Considering celecoxib is usually combined with CYP2D6 substrates in general clinical practice, it is necessary to monitor the subsequent clinical response of object drug, or choose an alternative NSAID without inhibitory effect on CYP2D6. When there is a clinical need to combine a COX-2 inhibitor with CYP2D6 substrates, imrecoxib may be an alternative to celecoxib.

Fluconazole-Coxibs

Compared with imrecoxib alone, combined fluconazole increased the maximum plasma concentration (C_{max}) of imrecoxib and area under the plasma concentration time curve from time zero to the last measured concentration (AUC_{0-t}) by 88% and 72%, respectively. However, fluconazole caused minimal change in the pharmacokinetic parameters of two active metabolites (M1, M2). Totally, concurrent administration of fluconazole did not seem to alter the safety of imrecoxib.[42]

There is no literature on pharmacokinetic interaction between etoricoxib and fluconazole; however, there is a significant pharmacokinetic interaction between celecoxib and fluconazole. When combined with fluconazole 200mg once daily, the plasma concentration of celecoxib increased by two-fold. The mechanism is that fluconazole can inhibit celecoxib metabolism via CYP2C9. Therefore, celecoxib should be initiated at the lowest recommended dose in patients receiving fluconazole while monitoring closely for celecoxib toxicity.[43]

Discussion
CV Safety

Selective COX-2 inhibitors can reduce the incidence of GI side effects but some are associated with excessive CV risk.[44] COX-1 affects the synthesis of thromboxane A2 (TXA2) in platelets, which is associated with pro-platelet aggregation action and arterial vasoconstriction. The synthesis of prostacyclin (PGI2) in endothelial cells may be affected by COX-1 and COX-2. Because PGI2 has anti-aggregation and vasodilating properties, COX-2 inhibition may reduce the synthesis of PGI2 by the endothelium without directly affecting the synthesis of TXA2 by platelets, and thus may shift the balance of prostaglandin production to TXA2 and promote thrombosis and arterial vasoconstriction.[45]

Discontinuation of rofecoxib and safety concerns about other COX-2 selective inhibitors raise important questions about CV toxicity of these agents. Actually, all NSAIDs carry some level of CV risk, whether non-selective NSAIDs or COX-2 selective agents. There is also some evidence of heterogeneity of adverse CV effects with NSAIDs, with no clear line of demarcation for CV safety based on the degree of COX-2 selectivity.[46] The selectivity ratios for the inhibition of COX-2 (COX-1/COX-2 IC_{50} ratio) in the human whole blood assay were 106, 35, 30, 7.6, 7.3, 2.4, and 2.0 for etoricoxib, rofecoxib, valdecoxib, celecoxib, nimesulide, etodolac, and meloxicam, respectively.[47] Imrecoxib can inhibit COX-1 and COX-2 with IC_{50} value of 115±28 nmol/L and 18±4 nmol/L, respectively, with the COX-1/COX-2 IC_{50} ratio of 6.39.[48] Both GI safety and CV safety would be achieved by applying the concept of balanced inhibition strategy of

COX-1/COX-2 proposed by Guo Zongru (ie, developing selective COX-2 inhibitors by moderately inhibiting COX-2 to avoid breaking the balance between PGI2 and TXA2).[2,49] From this perspective, imrecoxib seems to be a balanced COX-1 and COX-2 inhibiting drug.

A multicenter randomized controlled trial showed that celecoxib at moderate doses was noninferior to ibuprofen or naproxen in terms of CV safety.[50] A systematic review confirmed the CV risk with rofecoxib, but supported that celecoxib at usual doses may not increase the risk.[51]

Walter et al demonstrated that methylsulphones COX-2 inhibitors (rofecoxib, etoricoxib) could increase susceptibility of human low-density lipoprotein (LDL) and plasma to oxidative modification compared to sulfonamides COX-2 inhibitors (celecoxib, valdecoxib) and non-selective NSAIDs (meloxicam, ibuprofen, naproxen, diclofenac).[52] There have been no in vitro experiments to show whether methylsulphone COX-2 inhibitor imrecoxib has the same defect as rofecoxib and etoricoxib. On the contrary, imrecoxib had a lower incidence of new-onset hypertension than other types of COX-2 inhibitors.[35] Thus, further high-quality randomized clinical trials are needed to evaluate the CV safety of imrecoxib.

Genetic Polymorphism

CYP2C9 has a relatively small effect on total clearance of sulindac, naproxen, ketoprofen, diclofenac, rofecoxib and etoricoxib (<or=20% of the dose), so the *CYP2C9* genotype has no clinical significance for the pharmacokinetics of these drugs. In contrast, *CYP2C9* genotype is expected to affect the clearance of ibuprofen, indomethacin, flurbiprofen, celecoxib, valdecoxib, lornoxicam, tenoxicam, meloxicam, and piroxicam.[53] According to Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline,[54] therapeutic recommendations for celecoxib, flurbiprofen, lornoxicam, and ibuprofen based on CYP2C9 phenotype are as follows: (1) For normal metabolizers of CYP2C9, treatment is initiated at the recommended starting dose; (2) For poor metabolizers of CYP2C9, initiate therapy at 25–50% of the lowest recommended starting dose and titrate dose upward to clinical effect, or 25–50% of the maximum recommended dose was used with caution. Upward dose titration should not be performed until a steady-state is reached (ie, at least 8 days for celecoxib and 5 days for ibuprofen, flurbiprofen, and lornoxicam after first dose in poor metabolizers). Blood pressure and kidney function are carefully monitored during treatment. Alternatively, consider an alternate NSAID that is not metabolized by CYP2C9 or not remarkably affected by *CYP2C9* genetic variants.

Imrecoxib is extensively eliminated in the form of metabolites in the human body, and the main metabolic pathway is 4'-hydroxylation through the liver which is catalyzed by CYP2C9 (62.5%), CYP2D6 (21.1%), and CYP3A4 (16.4%), respectively.[55] Theoretically, the *CYP2C9* genotype appears to have limited influence on the pharmacokinetics of imrecoxib, given that CYP2C9 contributes a relatively lower proportion to the metabolism of imrecoxib than celecoxib.

Lee et al reported that inhibitory effects of celecoxib on COX-2 induction were different according to COX-2 genetic polymorphism. In terms of inhibiting COX-2, subjects with the *GG* genotype of *rs689466* would be more responsive to celecoxib than those with *AA* or *AG* genotypes.[56] This study is very interesting and has implications for further research on the response to treatment with imrecoxib.

COVID-19 Treatment

Severe acute respiratory coronavirus 2 (SARS-CoV-2) causes a prostaglandin E2 (PGE2) storm in a substantial proportion of patients via up-regulating COX-2 and down-regulating PGE2-degrading enzymes within the host cell. COX2 inhibition might be a valuable adjunct to treatment strategies for people with initial mild to moderate COVID-19 symptoms.[57] Ghaznavi et al demonstrated that short-term treatment with celecoxib significantly affected blood oxygen saturation and hematological markers in COVID-19 cases. Mean lymphocyte levels were markedly higher in patients who received high doses of celecoxib (400 mg/day) than in patients treated with celecoxib 200 mg/day for one week or the untreated subjects (P=0.004).[58] In a prospective clinical study, celecoxib adjuvant treatment (full dose: 200 mg twice daily; half dose: 200 mg once daily) for 7–14 days promoted recovery of all types of COVID-19 and further reduced mortality in older adults and patients with comorbidities compared to the control group receiving standard care.[59] In a retrospective study of patients older than 50 years with COVID-19 pneumonia, treatment with the COX-2 inhibitor

etoricoxib resulted in beneficial reductions in IL-6 levels.[60] The potential efficacy of imericoxib in patients with COVID-19 warrants further evaluation.

Older Adults

Non-selective NSAIDs are strongly not recommended for geriatric patients according to American Geriatrics Society (AGS) 2023 updated Beers Criteria®. To avoid GI adverse responses, COX-2 inhibitors, or non-selective NSAIDs in combination with PPIs (or histamine H2 receptor antagonists) may be safer choices.[61] Elderly patients are at high GI risk, accompanied by multiple cardiovascular risk factors and polypharmacy. Therefore, as a balance inhibitor of COX-1 and COX-2, imrecoxib may be more suitable for elderly patients.

Pharmacokinetic and safety profiles of imrecoxib in elderly healthy subjects indicated that no dose adjustment should be required for elderly population.[62] In osteoarthritis patients with renal insufficiency, the exposure to imrecoxib decreased compared with that in healthy subjects, whereas the M2 exposure increased markedly and the clearance reduced noticeably, which means that the dose of imrecoxib should be appropriately reduced in these populations.[63] Renal function decline is common in older adults. By the age of 70, renal function may have declined by 40%. Therefore, the dose of imrecoxib in older adults can be adjusted based on glomerular filtration rate. For celecoxib and etoricoxib, dose adjustment in older adults is not generally necessary. However, for patients weighing less than 50 kg, celecoxib should be initiated at the lowest recommended dose.[43]

Management of Osteoarthritis
Disease Pathophysiology

In recent years, the research of the disease pathophysiology of osteoarthritis have been reported in the literature. Osteoarthritis is a degenerative joint disease typically characterized by decreased cartilage and bone quality at the synovial joint interface, resulting in pain, stiffness, and reduced mobility.[64] During the development of osteoarthritis, disrupted cartilage homeostasis, activated chondrocytes, and upregulated extracellular matrix (ECM)-degrading enzymes (eg, MMPs and aggrecan) can be observed, thereby increasing the degradation of native collagen and aggrecan, ultimately leading to cartilage damage. Also, inflammatory mediators are involved in the destruction of cartilage ECM. Overexpression of cytokines such as IL-1, IL-4, IL-6 and TNF-alpha can be seen in chondrocytes of early osteoarthritis cartilage, and enhanced secretion of these cytokines can lead to abnormal chondrocyte phenotypes and impair ECM collagen and proteoglycan synthesis.[65]

At the onset of osteoarthritis, abnormal mechanical loading can cause excessive osteoclast generation and resorption of subchondral bone, resulting in rapid transformation of subchondral bone, cyst formation, sclerosis, and ultimately articular cartilage degeneration. Additionally, osteoclast-mediated angiogenesis and sensory innervation of subchondral bone can cause abnormal vascularization and osteoarthritis pain.[66]

Chang et al revealed that COX-2 could play a pathophysiological role by preventing terminal differentiation of articular chondrocytes by upregulating parathyroid hormone-related protein (PTHrP) expression at the early stage of osteoarthritis progression.[67] COX-2 levels were significantly higher in osteoarthritic cartilage than in normal cartilage, and thus inhibition of COX-2 activity by coxibs may influence downstream targets in human articular chondrocytes.

Treatment Strategy
Natural Products

Diterbutyl phthalate, an active constituent in traditional Chinese medicine *Panax notoginseng*, could prevent osteoarthritis progression by suppressing abnormal osteoclast generation and related angiogenesis and neurogenesis in subchondral bone.[66] Also, betaine, an ingredient isolated from the Lycii Radicis Cortex, could attenuate osteoarthritis by blunting osteoclastogenesis via inhibiting reactive oxygen species (ROS) production and subsequent mitogen-activated protein kinase (MAPK) signaling, and angiogenesis in subchondral bone.[68] Yabas et al reported that a novel formulation of curcumin could ameliorate experimentally induced osteoarthritis in rats by reducing levels of inflammatory mediators [eg, TNF-alpha, IL-1β, IL-6, cartilage oligomeric matrix protein (COMP), and C-reactive protein (CRP)], and protein expressions of MMP-3, 5-lipoxygenase (5-LOX), COX-2, and NF-κB in synovial tissue.[69]

NSAIDs

Most guidelines recommend the use of NSAIDs and opioids for the non-operative treatment of osteoarthritis. Short-term NSAID therapy has been shown to improve patients' disease-specific QOL, and reduce the levels of proinflammatory cytokines (IL-6, VEGF, and TNF-alpha) in the synovial fluid in patients with knee osteoarthritis. MAPK signal transduction pathway may be involved in regulating the anti-inflammatory effects of NSAIDs.[70] It has been shown that celecoxib can downregulate the expression of PTHrP in osteoarthritis cartilage while inhibiting COX-2 activity.[67] Compared to postoperative use of placebo, postoperative imrecoxib medication more effectively improved joint function, reduced the levels of synovial fluid MMP-2 and MMP-13, and improved QOL in patients with knee osteoarthritis after arthroscopic debridement (all $P<0.05$).[71] It is of great significance to combine the latest pathological mechanisms of osteoarthritis to further explore and compare the pharmacological and therapeutic differences of different NSAIDs for osteoarthritis.

Extracellular Vesicles (EVs)

A narrative review by Zeng et al has shown that mesenchymal stem cell-derived EVs (MSC-EVs) may provide a possible therapeutic strategy for osteoarthritis by blocking macrophage activation, reducing inflammation by suppressing inducible nitric oxide synthase (iNOS), inhibiting chondrocyte apoptosis, and promoting cell proliferation and migration through various pathways.[72] The engineering of IL-6 signal transducer (IL6ST)-bearing decoy EVs could offer a potential therapeutic strategy for the treatment of inflammatory arthritis by inhibiting phenotype remodeling of tissue-resident cells in articular joint including chondrocytes, osteoclasts, and synovial fibroblasts.[73] Curcumin primed small EVs derived from adipose tissue-derived MSCs (ADMSCs) exert enhanced protective effects on osteoarthritis by down-regulating oxidative stress and chondrocyte apoptosis.[74] It is worthwhile to investigate whether COX-2 inhibitor reinforces MSC-derived exosomes in attenuating osteoarthritis.

In summary, from the perspective of efficacy, imrecoxib provides relief of osteoarthritis symptoms, and potential off-label use for treatment of idiopathic pulmonary fibrosis, perioperative pain, hand-foot syndrome, axial spondyloarthritis, COVID-19, cartilage injury, and malignancies such as lung and colon cancer. From a safety point of view, imrecoxib showed adverse effects common to NSAIDs; however, it has lower incidence of new-onset hypertension than other types of selective COX-2 inhibitors, less gastrointestinal toxicities than non-selective NSAIDs, weaker risk of drug interaction than celecoxib, and more suitable for elderly patients due to balanced inhibition of COX-1/COX-2. From a pharmacoeconomic perspective, imrecoxib is more cost-effective than celecoxib and diclofenac for osteoarthritis patients. With the deepening of the disease pathophysiology study of osteoarthritis, new therapeutic schemes and pharmacological mechanisms are constantly discovered. In the field of osteoarthritis treatment, mechanisms other than the analgesic and anti-inflammatory effects of COX-2 inhibitors are also being explored.

Conclusion

Imrecoxib is a moderate selective COX-2 inhibitor with some advantages. There would be more clinical applications and research opportunities related with imrecoxib.

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Disclosure

The authors report no conflicts of interest in this work.

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