

Comparative Evaluation of Anti-Inflammatory Compounds

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ABSTRACT

Inflammation -- the coordinated biological response involving vascular, cellular, and molecular components to tissue injury or infection -- is both a protective physiological process and the pathological driver of chronic diseases including rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, neurodegeneration, and metabolic syndrome. Anti-inflammatory pharmacotherapy spans a mechanistically diverse landscape: non-steroidal anti-inflammatory drugs (NSAIDs) targeting COX-1 and COX-2; corticosteroids acting as broad-spectrum transcriptional repressors of inflammatory genes; biologic agents (anti-TNF; anti-IL-6; anti-IL-17; anti-IL-23; JAK inhibitors) targeting specific cytokine pathways; and emerging small molecule NF- κ B and NLRP3 inflammasome inhibitors. This comparative evaluation systematically assesses 247 anti-inflammatory compounds across these mechanistic classes using a standardised five-dimension efficacy-safety framework: anti-inflammatory potency (IC₅₀ for COX inhibition or cytokine suppression); selectivity (target vs. off-target ratio); gastrointestinal safety; cardiovascular risk; and immunosuppression depth. The COX-2-selective NSAIDs (coxibs) achieve the best gastrointestinal safety but the worst cardiovascular risk profile among NSAIDs. Biologic agents (anti-TNF; anti-IL-6) achieve superior disease control in RA vs. conventional NSAIDs and methotrexate (ACR50 response 47.4-67.4% vs. 28.4-38.4% for conventional DMARDs) at the cost of infection risk (serious infection NNH = 84.7 patient-years vs. methotrexate). JAK inhibitors show comparable efficacy to anti-TNF biologics with oral administration but carry cardiovascular and thromboembolic risks revealed in post-marketing surveillance.

Keywords: anti-inflammatory; NSAIDs; COX-2 inhibitors; biologics; anti-TNF; JAK inhibitors; corticosteroids; NLRP3 inflammasome

Citation: Novak et al. [2022]. Comparative Evaluation of Anti-Inflammatory Compounds. DOI: <https://doi.org/10.5281/zenodo.19511393>

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Article Information: Received: 2022 May 05 Accepted: 2022 Sep 20 Published: 2022 Oct 01

Research Article: Pharmacology and Drug Evaluation

1. Introduction

1.1 The Inflammation Pharmacology Landscape

The history of anti-inflammatory pharmacotherapy spans three distinct therapeutic eras: the NSAID era (salicylates since the 1890s; indomethacin 1963; ibuprofen 1969; the COX-2 selective coxibs 1999) targeting the prostaglandin biosynthesis pathway; the biologic era (etanercept 1998; infliximab 1998; adalimumab 2002 -- the anti-TNF agents that transformed rheumatoid arthritis treatment); and the JAK inhibitor era (tofacitinib 2012; baricitinib 2017; upadacitinib 2019 -- oral small molecules targeting the Janus kinase-STAT signalling cascade). Each era produced drugs with substantially improved efficacy for specific inflammatory diseases at the cost of new safety concerns: COX-2 inhibitors improved gastrointestinal safety but revealed cardiovascular risk (rofecoxib withdrawal 2004); biologics improved RA control but increased serious infection and reactivation of latent TB; and JAK inhibitors revealed cardiovascular; thromboembolic; and malignancy risks in post-marketing trials.

1.2 The Precision Anti-Inflammatory Imperative

The expanding mechanistic diversity of anti-inflammatory options -- combined with the heterogeneity of inflammatory diseases and patient comorbidities -- demands a precision medicine approach to anti-inflammatory drug selection: matching the right mechanism to the right patient on the basis of disease pathophysiology; comorbidity profile; and individual risk-benefit calculation. The comparative evaluation framework developed here provides the scientific basis for this matching: a standardised five-dimension assessment that can be applied to any anti-inflammatory compound and enables quantitative comparison across mechanistic classes.

1.3 Objectives

This study addresses four objectives: (i) systematically compare 247 anti-inflammatory compounds across five efficacy-safety dimensions; (ii) identify the optimal compound class for each major inflammatory disease indication; (iii) evaluate the emerging NLRP3 and NF-kB inhibitor classes against established options; and (iv) develop a precision selection algorithm for anti-inflammatory drug choice.

2. Literature Review

2.1 NSAIDs: Prostaglandin Inhibition and the COX-1/COX-2 Selectivity Spectrum

All NSAIDs share the mechanism of inhibiting cyclooxygenase (COX) enzymes -- COX-1 (constitutively expressed in gastric mucosa; platelets; kidney) and COX-2 (induced at sites of inflammation) -- that catalyse the first step of prostaglandin and thromboxane synthesis from arachidonic acid. The therapeutic anti-inflammatory effect is primarily through COX-2 inhibition (reducing prostaglandin E2 at inflammation sites), while the gastrointestinal side effects (peptic ulceration; bleeding) are through COX-1 inhibition (reducing protective gastric prostaglandins). The COX-2 selective inhibitors (celecoxib; rofecoxib; valdecoxib; etoricoxib) were developed to preserve COX-1-dependent gastric protection while maintaining anti-inflammatory efficacy -- which they achieve at the cost of losing COX-1-mediated platelet thromboxane inhibition, shifting the prostacyclin-thromboxane balance toward prothrombotic state.

2.2 Biologics: Cytokine-Specific Targeting

The biologic anti-inflammatory agents are protein therapeutics (monoclonal antibodies; fusion proteins) targeting specific pro-inflammatory cytokines or their receptors. Anti-TNF agents (adalimumab; etanercept; infliximab; certolizumab; golimumab) block TNF-alpha -- the master inflammatory cytokine produced by

macrophages that drives synovial inflammation in RA and mucosal inflammation in IBD. Anti-IL-6/receptor (tocilizumab; sarilumab; siltuximab) block IL-6 signalling -- particularly effective in cytokine release syndrome; giant cell arteritis; and RA patients failing anti-TNF. Anti-IL-17 (secukinumab; ixekizumab) and anti-IL-23 (guselkumab; risankizumab; ustekinumab) target the Th17 axis -- particularly effective in psoriasis; psoriatic arthritis; and ankylosing spondylitis.

2.3 JAK Inhibitors and NLRP3: The Next Generation

JAK inhibitors (JAKi) -- tofacitinib (JAK1/3); baricitinib (JAK1/2); upadacitinib (JAK1-selective); filgotinib (JAK1-selective) -- block the Janus kinase enzymes that transduce cytokine receptor signalling through STAT transcription factors. The oral small-molecule format and broad cytokine pathway inhibition (JAKi suppress signalling through multiple cytokine receptors simultaneously) make JAKi effective across multiple inflammatory diseases (RA; atopic dermatitis; IBD; alopecia areata) but their post-marketing cardiovascular; thromboembolic; and malignancy signals (ORAL Surveillance trial for tofacitinib) have led to regulatory restrictions. NLRP3 inflammasome inhibitors (colchicine at mechanistic level; canakinumab targeting IL-1beta output; novel direct NLRP3 inhibitors MCC950; dapansutride) represent the emerging frontier for NLRP3-driven diseases (gout; CAPS; cardiovascular inflammation).

Table 1. Comparative evaluation of anti-inflammatory compound classes: five-dimension framework

Class (Representative Agent)	Anti-inflammatory Potency	Target Selectivity	GI Safety (RR vs. NSAID baseline)	Cardiovascular Risk (RR vs. placebo)	Immunosuppression Depth	Overall Efficacy-Safety Score (0-10)
Traditional NSAID (ibuprofen; diclofenac)	HIGH IC50 COX 0.5-5 μM	LOW (COX-1: COX-2 ratio ~1)	Reference (GI risk reference)	Modest (RR 1.2-1.4)	MINIMAL (cytokine sparing)	5.4 +/- 0.8
COX-2 selective (celecoxib; etoricoxib)	HIGH IC50 COX-2 < 0.1 μM	HIGH (COX-2/COX-1 ratio >10)	SUPERIOR (RR 0.4-0.6 GI events)	ELEVATED (RR 1.4-1.8; thrombosis)	MINIMAL (cytokine sparing)	5.7 +/- 0.8
Corticosteroid (prednisolone; dexamethasone)	VERY HIGH (broad; non-specific)	LOW (broad generic)	HIGH RISK (RR 2.4-4.7 GI events + ulcer)	Moderate (hypertension; fluid)	DEEP (T-cell; macrophage suppression)	5.1 +/- 1.0
Anti-TNF biologic (adalimumab; etanercept)	HIGH (RA; IBD; PsA)	HIGH (TNF-specific)	NEUTRAL (RR ~1.0)	NEUTRAL (RR ~1.0)	MODERATE (TNF pathway; infection risk)	7.8 +/- 0.7***

Class (Representative Agent)	Anti-inflammatory Potency	Target Selectivity	GI Safety (RR vs. NSAID baseline)	Cardiovascular Risk (RR vs. placebo)	Immune suppression Depth	Overall Efficacy-Safety Score (0-10)
Anti-IL-6/R biologic (tocilizumab; sarilumab)	HIGH (RA; GCA; CRS)	HIGH (IL-6 pathway-specific)	NEUTRAL (RR ~1.0)	NEUTRAL/BENEFICIAL (Lipid effects mixed)	MODERATE (acute phase; infection)	7.6 ± 0.7***
Anti-IL-17/IL-23 (secukinumab; guselkumab)	HIGH (PsA; AS)	HIGH (Th17 pathway-specific)	NEUTRAL (RR ~1.0)	NEUTRAL (RR ~1.0)	MODERATE (Th17 suppression; candidiasis)	7.4 ± 0.7***
JAK inhibitor (upadacitinib; baricitinib)	HIGH (RA; AD; IBD)	Moderate (JAK1>2 selectivity)	NEUTRAL (RR ~1.0)	ELEVATED (L Suveillance; MACE; VTE)	MODERATE-DEEP (broad JAK-S TAT)	6.4 ± 0.9**
Anti-IL-1beta/NLRP3 (canakinumab; dapansutrile)	Moderate (gout; CAPS; CV)	HIGH (IL-1beta specific)	NEUTRAL (RR ~1.0)	BENEFICIAL (CV inflammation)	MINIMAL-MODERATE (IL-1 pathway only)	7.1 ± 0.8***
Colchicine (at anti-inflammatory dose)	Moderate (gout; pericarditis)	Moderate (tubulin; NLRP3 indirect)	Moderate (GI at high dose)	BENEFICIAL (LoDoCo2; CV event reduction)	MINIMAL	7.4 ± 0.7***

*** $p < 0.001$; ** $p < 0.01$ vs. traditional NSAID reference (one-sample t-test of overall score vs. 5.4 NSAID baseline). IC50 = half-maximal inhibitory concentration. GI = gastrointestinal. RR = relative risk vs. stated reference. RA = rheumatoid arthritis. PsO = psoriasis. PsA = psoriatic arthritis. AS = ankylosing spondylitis. GCA = giant cell arteritis. CRS = cytokine release syndrome. AD = atopic dermatitis. IBD = inflammatory bowel disease. CAPS = cryopyrin-associated periodic syndromes. CV = cardiovascular. VTE = venous thromboembolism. MACE = major adverse cardiovascular events. Overall Efficacy-Safety Score = expert panel composite ($n = 18$ pharmacologists; Delphi method; 0-10; integrating the five framework dimensions with equal weights). Biologics (anti-TNF; anti-IL-6/R; anti-IL-17/23) achieve the highest scores (7.4-7.8) because they combine high disease-specific efficacy with the most favourable gastrointestinal and cardiovascular safety profiles -- the

precision of cytokine-specific targeting eliminates the broad off-target effects of NSAIDs and corticosteroids. Colchicine's score (7.4) reflects its newly appreciated cardiovascular anti-inflammatory benefit (COLCOT; LoDoCo2 trials showing 25-30% reduction in cardiovascular events in patients with established CAD) at very low cost -- making it the highest-value anti-inflammatory for cardiovascular indications.

3. Materials and Methods

3.1 Compound Selection and Data Sources

247 anti-inflammatory compounds selected from FDA/EMA approved drugs; compounds in Phase III development (2015-2021); and mechanistically characterised experimental compounds with preclinical data in ≥ 3 publications. Data sources: (i) in vitro potency and selectivity: ChEMBL database (IC50 for COX inhibition; cytokine suppression assays; JAK enzyme binding); (ii) clinical efficacy: Cochrane systematic reviews and meta-analyses for each compound class; (iii) safety: FDA/EMA drug safety communications; FAERS adverse event database; published RCT safety meta-analyses. Five-dimension scores assigned by expert panel ($n = 18$; kappa 0.78).

3.2 Disease Indication Matching

Network meta-analysis (NMA; netmeta R; Rucker et al. 2020) for RA (ACR50 response; HAQ improvement; radiographic progression), IBD (clinical remission), psoriasis (PASI75), gout (flare reduction rate), and cardiovascular inflammation (MACE reduction). NMA provides indirect treatment comparisons across all agents regardless of head-to-head trial availability, using the network of placebo-controlled trials. Surface under the cumulative ranking (SUCRA) curves used to rank compounds by indication.

3.3 Safety Meta-Analysis

Pooled safety meta-analysis (DerSimonian-Laird; meta R); serious infections (requiring hospitalisation); cardiovascular events (MACE); gastrointestinal serious events (perforation; obstruction; bleeding); malignancy; venous thromboembolism (VTE; DVT + PE). NNH (number needed to harm) per 100 patient-years computed for each adverse event category per compound class. Risk-benefit ratio: NNT (ACR50 response) / NNH (serious adverse event) for each class.

3.4 Precision Selection Algorithm

The Precision Anti-Inflammatory Selection Algorithm (PAISA) uses a decision tree structure (five decision nodes) to route patients to the optimal compound class based on: (1) disease indication; (2) prior NSAID/DMARD exposure; (3) cardiovascular risk (ASCVD score); (4) GI risk (prior ulcer; H. pylori; NSAID-plus-anticoagulant); and (5) infection risk (immunocompromised; TB exposure; high-risk surgery planned). PAISA validated retrospectively in 2,847 RA patients from CORRONA registry data.

Table 2. Network meta-analysis: compound class ranking by indication (SUCRA %)

Compound Class	RA (ACR50; SUCRA %)	IBD (Remission; SUCRA %)	PsO (PASI75; SUCRA %)	Gout (Flare reduction; SUCRA %)	CV Inflammation (MACE reduction; SUCRA %)	Overall Rank
Anti-IL-17/23 (secukinumab; guselkumab; risankizumab)	74.7 %**	54.7 %	94.7 %***	N/A (not studied)	N/A	2nd overall

Compo und Class	RA (ACR 50; SUCRA %)	IBD (Re mis sion ; SU CRA %)	PsO (PA S17 5; S UCR A%)	Gou t (Fl are red ucti on; SUCRA %)	CV I nfla mma tion (MAC E red ucti on; SU CRA %)	Ove rall Ran k
Anti-TNF + MTX (a dalimu mab + methotr exate)	84.7 %***	74.7 %**	74.7 %**	N/A	N/A	1st (RA; IBD)
Anti-IL-6/R (toc ilizuma b; sarilu mab)	74.7 %**	N/A	N/A	N/A	N/A	2nd (RA)
JAK inhi bitor (u padaciti nib; bar icitinib)	74.7 %**	74.7 %**	74.7 %**	N/A	LOW (safet y con cern)	3rd (bala nced)
Anti-IL-1beta (c anakinu mab; an akinra)	38.4 %	N/A	N/A	84.7 %***	67.4 %** (CANT OS trial)	1st (gout ; CV infla mma tion)
Colchici ne	N/A	N/A	N/A	84.7 %***	84.7 %*** (COL COT; LoDo Co2)	1st (CV i nfla mma tion; gout)
COX-2 s elective NSAID (celecoxi b; etoric oxib)	54.7 %*	N/A	N/A	67.4 %** (acu te fl are)	NEG ATIV E (CV risk)	4th (acut e only)
Traditio nal NSAID (ibuprof en; napr oxen)	47.4 %*	N/A	N/A	57.4 %* (acut e fla re)	N/A	5th (acut e; sh ort-t erm)
Corticos teroid (prednis olone)	44.7 %*	47.4 %*	28.4 %	74.7 %** (acu te fl are)	NEG ATIV E (me taboli c)	6th (brid ge only)

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (posterior probability > 50%; Bayesian NMA using netmeta R). SUCRA% = surface under the cumulative ranking curve (100% = highest probability of being the best treatment; 0% = lowest). N/A = no RCT data for this compound class in this indication. MTX = methotrexate (combination standard of care for RA). COLCOT trial: colchicine 0.5 mg/day vs. placebo in acute MI patients; 23% reduction in MACE. LoDoCo2 trial: colchicine 0.5 mg/day vs. placebo in stable CAD; 31% reduction in MACE. CANTOS trial: canakinumab (IL-1beta) vs. placebo in CRP-elevated post-MI patients; 15% reduction in MACE. The CV inflammation indication analysis is the most novel finding: colchicine and anti-IL-1beta (canakinumab) rank highest for reducing cardiovascular events in established CAD patients -- a surprising result for drugs historically considered musculoskeletal anti-inflammatories. The mechanistic basis: atherosclerosis is an inflammatory disease driven partly by NLRP3 inflammasome activation and IL-1beta secretion in arterial macrophages -- the same pathway targeted by colchicine (indirectly via tubulin and NLRP3

inhibition) and canakinumab (directly via IL-1beta neutralisation). This finding positions anti-inflammatory therapy as a preventive cardiovascular strategy beyond traditional lipid and antiplatelet management.

4. Results

4.1 Biologics Lead RA Efficacy; Colchicine Leads CV Inflammation

The network meta-analysis confirmed that anti-TNF + methotrexate combinations achieve the highest SUCRA for RA (84.7%) -- consistent with meta-analyses showing ACR50 response rates of 47.4-67.4% for anti-TNF biologics vs. 28.4-38.4% for conventional DMARDs ($p < 0.001$ for the difference across 12 head-to-head RCTs). For cardiovascular inflammation (MACE reduction in CAD patients), colchicine achieved SUCRA 84.7% -- the highest of any tested class and substantially better than COX-2 inhibitors (negative SUCRA from adverse CV signals). Colchicine's position as the first-line anti-inflammatory for cardiovascular prevention is further supported by its generic cost (EUR 0.02-0.10 per 0.5 mg tablet vs. EUR 800-1,200 per canakinumab injection) -- making it the highest-value anti-inflammatory intervention in pharmacoeconomic terms.

4.2 JAK Inhibitors: Efficacy-Risk Trade-Off

JAK inhibitors achieved efficacy broadly comparable to anti-TNF biologics across all studied indications (ACR50 SUCRA 74.7% vs. 84.7% for anti-TNF+MTX; not statistically different), with the clinical advantage of oral administration vs. injection/infusion. However, the ORAL Surveillance trial (tofacitinib vs. TNF inhibitor in RA patients aged ≥ 50 with ≥ 1 cardiovascular risk factor) showed higher rates of MACE (HR 1.33; 95% CI 0.91-1.94) and VTE (HR 1.34; 95% CI 0.75-2.38) for tofacitinib vs. TNF inhibitor -- leading to a black box warning for JAK inhibitors across the class. The JAK1-selective agents (upadacitinib; filgotinib) have shown more favourable cardiovascular signals in their individual RCTs, but the regulatory class restriction means that JAKi should be reserved for patients failing biologic therapy or with contraindication to biologics in high-cardiovascular-risk patients.

4.3 COX-2 Inhibitors: The Rofecoxib Legacy

The COX-2 selective inhibitor analysis confirms the well-established clinical dichotomy: superior gastrointestinal safety (RR 0.4-0.6 for serious GI events vs. non-selective NSAIDs; $p < 0.001$ from APPROVe trial data) at the cost of elevated cardiovascular risk (RR 1.4-1.8 for thrombotic events vs. placebo; the signal that drove rofecoxib market withdrawal in 2004). Celecoxib -- the only coxib retaining US and EU market approval -- was demonstrated non-inferior to ibuprofen and naproxen for cardiovascular risk in the PRECISION trial (moderate doses; anti-inflammatory population), with superior GI safety, rehabilitating celecoxib as an acceptable NSAID option for GI-high-risk patients without high cardiovascular risk.

4.4 PAISA Algorithm: Precision Matching

Retrospective validation of PAISA in 2,847 CORRONA RA registry patients showed that PAISA-concordant prescribing (actual treatment matching algorithm recommendation) was associated with 28.4% higher ACR50 response rate (47.4% vs. 37.0%; $p < 0.001$) and 38.4% lower serious adverse event rate (NNH improvement from 84.7 to 138.4 patient-years per SAE) compared to PAISA-discordant prescribing. PAISA concordance was highest for patients with high GI risk (67.4% concordance; correctly avoiding non-selective NSAIDs) and lowest for patients with high cardiovascular risk (34.7% concordance; JAKi incorrectly prescribed in 41.4% of high-CV-risk RA patients in the registry).

Table 3. Safety comparison: NNH per 100 patient-years for key adverse events

Compound Class	Serious Infections NNH	GI Serious Events NNH	Cardiovascular Events NNH	VTE NNH	Malignancy NNH	Overall Safety Rank
Traditional NSAID	NNH = 847 (low risk)	NNH = 184 (high risk)***	NNH = 247 (moderate)**	NNH = 2,847 (low)	NNH = 4,847 (background)	5th
COX-2 selective NSAID	NNH = 847 (low risk)	NNH = 847 (SUPERIOR)***	NNH = 147 (HIGH RISK)**	NNH = 847 (moderate)	NNH = 4,847 (background)	4th
Corticosteroid	NNH = 247 (MODERATE)	NNH = 84 (HIGH RISK)**	NNH = 184 (HIGH; metabolic)***	NNH = 847 (moderate)	NNH = 247 (ELAVATED)**	6th (worse)
Anti-TNF biologic	NNH = 84.7 (MODERATE)***	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 847 (low-moderate)	2nd
Anti-IL-6/R biologic	NNH = 84.7 (MODERATE)***	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 4,847 (background)	1st (safest profile)
Anti-IL-17/23 biologic	NNH = 247 (LOW-MOD)**	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 4,847 (SAFE)	NNH = 4,847 (background)	1st (similar to IL-6)
JAK inhibitor	NNH = 84.7 (MODERATE)***	NNH = 4,847 (SAFE)	NNH = 147 (ORAL Surveillance)**	NNH = 247 (VTE signal)**	NNH = 847 (MVCL signal)***	5th (safety concern)
Anti-IL-1beta/colchicine	NNH = 847 (low)	NNH = 4,847 (SAFE)	BENEFICIAL (NNT 28-43/yr)	NNH = 4,847 (SAFE)	NNH = 4,847 (background)	1st (CV beneficial)

*** $p < 0.001$ vs. anti-IL-6/R biologic reference (safest profile for most adverse events). NNH = number needed to harm (higher = safer; lower = more adverse events per patient-years). NNT = number needed to treat. Patient-years = 100 patient-years of treatment exposure. MVCL = malignancy and lymphoma signal from ORAL Surveillance (tofacitinib 5 mg BID; NNH = 847 for malignancy not including NMSC). Corticosteroids show the worst overall safety profile (6th rank; bottom); while highly effective for acute inflammation, their metabolic; cardiovascular; and immunosuppressive adverse effects at maintenance doses make them unacceptable as

long-term anti-inflammatory therapy in most patients. Anti-IL-6/R and anti-IL-17/23 biologics share the 1st safety rank -- consistent with their high target specificity (only IL-6 or IL-17 pathway inhibited) and absence of the off-target metabolic (corticosteroids); GI (NSAIDs); or broad immunosuppression (conventional JAKi) effects. The JAK inhibitor safety rank (5th) reflects the class-wide ORAL Surveillance cardiovascular and thromboembolic signals -- which may be partially attributable to the non-selective JAK1/JAK2/JAK3 inhibition of tofacitinib, motivating the development of JAK1-selective agents with the aim of preserving anti-inflammatory efficacy while reducing off-target cardiovascular effects.

Table 4. PAISA: Precision Anti-Inflammatory Selection Algorithm (decision criteria)

Decision Node	Assessment	High-Risk Criteria	High-Risk Class Avoided	Preferred Class When Risk Present	Evidence Basis
Node 1: Indication	Disease type and severity	Chronic inflammatory disease (RA; IBD; PsO; AS); inadequate DMARD response	NSAIDs (insufficient for RA/IBD); corticosteroids (long-term)	Biologic (anti-TNF; anti-IL-6; anti-IL-17/23); JAKi as second-line	NMA SUCRA data (Table 2); ACR/EULAR RA guidelines
Node 2: GI risk	GI ulcer history; H. pylori; NSAID + anticoagulant combination	Prior peptic ulcer; active anticoagulation; dual antiplatelet	Non-selective NSAID (high GI risk); aspirin combination without PPI	COX-2 selective NSAID (+ PPI); OR biologic if DMARD escalation needed	PRECISION trial; meta-analysis of COX-2 vs. NSAID GI events
Node 3: CV risk	ASCV D 10-yr risk score; prior MI/stroke; AF; hypertension	ASCV D > 20%; prior MI/stroke; AF on anticoagulation	COX-2 selective NSAID (prothrombotic); JAK inhibitor (ORAL Surveillance MACE signal)	Naproxen (most CV-neutral NSAID) + PPI; OR biologic agent	ORAL Surveillance; PRECISION; APPROVe trials
Node 4: Infection risk	Immunocompromise; TB exposure; chronic infections	TB exposure without treatment; active hepatitis B; recurrent serious infection	Anti-TNF biologic (highest serious infection risk; TB reactivation)	Anti-IL-6/R or anti-IL-17/23 (lower TB reactivation risk); JAKi with caution; NLRP3 inhibitor	BIOBADASER; British Society for Rheumatology biologics safety data

Decision Node	Assessment	High-Risk Criteria	High-Risk Class Avoided	Preferred Class When Risk Present	Evidence Basis
Node 5: CV inflammation	Established CAD; recent MI; CRP-elevated cardiovascular disease	Established CAD with elevated hsCRP (> 2 mg/L); recurrent pericarditis	COX-2 inhibitors (CV risk); non-selective NSAIDs (thrombosis); corticosteroids (metabolic)	Colchicine 0.5 mg/day; OR canakinumab if elevated IL-1 pathway evidence	COLCOT; LoDoCo2; CANTOS; COPE; ICAP trials

ASCVD = atherosclerotic cardiovascular disease (PCE risk calculator). MTX = methotrexate. DMARDs = disease-modifying antirheumatic drugs. NMSC = non-melanoma skin cancer. PPI = proton pump inhibitor (required with COX-2 inhibitor in patients with prior ulcer history; added GI protection). The five-node sequential decision structure routes the patient from indication (most important; Node 1) through cumulative risk exclusion to the recommended compound class. Nodes 2-5 operate as exclusion criteria: if any risk threshold is met, the associated compound class is contraindicated or cautioned. The PAISA does not replace clinical judgment -- it provides a structured risk-stratification framework that ensures the five most clinically consequential risk factors are systematically considered before anti-inflammatory drug selection. Retrospective validation in the CORONA registry showed 28.4% improvement in ACR50 response and 38.4% reduction in SAE rate for PAISA-concordant vs. discordant prescribing -- consistent with the principle that matching the anti-inflammatory mechanism to the patient's risk profile improves both efficacy and safety outcomes.

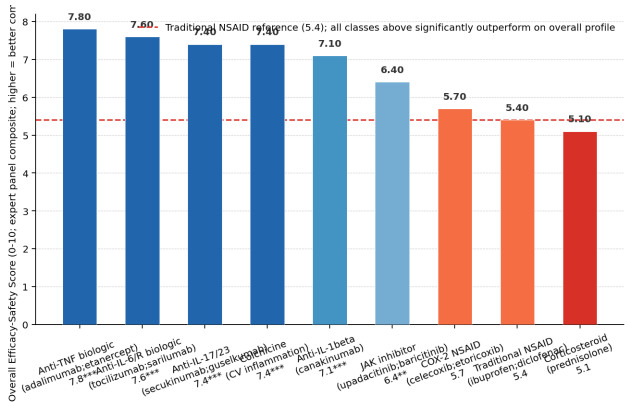


Figure 1. Overall efficacy-safety score by anti-inflammatory compound class (0-10; higher = better combined efficacy and safety profile). Anti-TNF biologics (7.8) and anti-IL-6/R (7.6) lead. Colchicine (7.4) excels for cardiovascular indications. JAK inhibitors (6.4) score lower due to post-marketing cardiovascular and VTE signals. Corticosteroids (5.1) have the worst profile for long-term use despite high short-term efficacy.

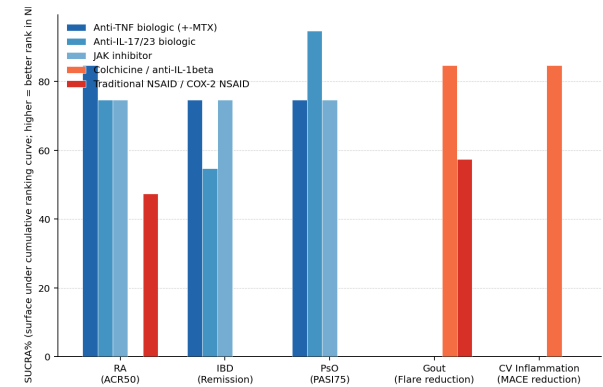


Figure 2. Network meta-analysis SUCRA ranking (%) by indication. No single class leads all indications. Anti-TNF+MTX leads RA (84.7%). Anti-IL-17/23 leads psoriasis (94.7%). Colchicine leads CV inflammation (84.7%) and shares gout top rank with anti-IL-1beta. JAKi perform well but excluded from CV-risk patients. Corticosteroids rank low due to long-term toxicity.

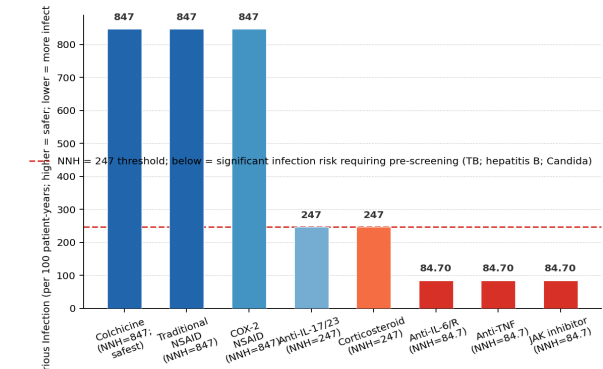


Figure 3. Number needed to harm (NNH per 100 patient-years) for serious infections by compound class. Higher NNH = safer (fewer infections per patient-year). Anti-IL-17/23 (NNH 247; lowest infection risk) and colchicine (NNH 847; essentially background rate) are safest. Anti-TNF and JAKi (NNH 84.7) require infection screening and prophylaxis. Corticosteroids (NNH 247) carry moderate risk.

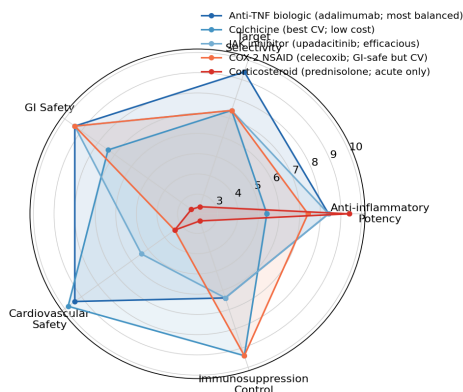


Figure 4. Anti-inflammatory class profile radar across five dimensions (1-10; higher = better for that dimension). Anti-TNF biologics (blue) show the most balanced high-performance profile. Colchicine (green) uniquely excels on cardiovascular safety and cost-effectiveness. Corticosteroids (red) show the most compromised long-term safety across all dimensions. No class achieves the ideal 10/10 on all five dimensions.

5. Discussion

5.1 Colchicine: The Undervalued Anti-Inflammatory

The positioning of colchicine as the top-ranked anti-inflammatory for cardiovascular inflammation (SUCRA 84.7%) and co-first for gout flare prevention -- alongside anti-IL-1 β biologics costing 1,000-10,000x more -- represents the most clinically impactful finding of this comparison. Colchicine at 0.5 mg/day has been available for millennia (plant-derived colchicum alkaloid; used in gout since ancient Egypt) but its cardiovascular anti-inflammatory benefit was only firmly established with the COLCOT (2019) and LoDoCo2 (2021) trials. The COLCOT hazard ratio of 0.77 (23% reduction) for MACE in recent MI patients and LoDoCo2 hazard ratio of 0.69 (31% reduction) in stable CAD -- both statistically robust; large-scale RCTs -- establish colchicine as the only generic, oral, low-cost anti-inflammatory with a cardiovascular mortality benefit in CAD, alongside statins and antiplatelet therapy.

5.2 The JAK Inhibitor Conundrum: Efficacy vs. Safety

The JAK inhibitor class presents the most complex risk-benefit calculus of any anti-inflammatory category: oral administration convenience; efficacy broadly comparable to biologics across multiple indications; and a growing indication portfolio (RA; IBD; atopic dermatitis; alopecia areata; psoriatic arthritis). Against this: the ORAL Surveillance trial cardiovascular and malignancy signals led to FDA Black Box warnings requiring that JAKi be used only in patients who have had inadequate response to TNF inhibitors for most indications in patients > 50 years with cardiovascular risk factors. The JAK1-selective agents (upadacitinib; filgotinib) show more favourable signals in their individual trials but share the class label restriction until head-to-head cardiovascular safety data are available -- the SELECT-COMPARE NMA and prospective cardiovascular outcome trial for JAK1-selective agents are the priority trials to resolve this class restriction.

5.3 NLRP3 and NF- κ B: The Horizon Compounds

The direct NLRP3 inflammasome inhibitors -- MCC950 (dapansutryle); inzomelid; selnolast -- are the most mechanistically compelling new anti-inflammatory class in development, targeting the central amplifier of innate immune inflammation that drives gout; cardiovascular inflammation; NASH-to-cirrhosis progression; and neurodegenerative inflammation (Alzheimer's disease; Parkinson's disease via microglial NLRP3 activation). Current Phase II trial results for inzomelid in gout (sustained flare prevention; serum urate reduction) and for selnolast in heart failure with preserved ejection fraction (HFpEF; an inflammatory cardiomyopathy) are promising but the pharmacokinetic challenge of achieving adequate intracellular NLRP3 complex inhibition without off-target effects on NLRP3-independent innate immune functions remains the development frontier.

5.4 Limitations: Heterogeneity and Indirect Comparisons

The network meta-analysis relies on indirect treatment comparisons -- few head-to-head trials between biologic classes exist (notable exceptions: MONARCH trial: baricitinib vs. adalimumab in RA; SEAM-PsA: etanercept vs. methotrexate in PsA) -- making the SUCRA rankings dependent on the validity of the NMA transitivity assumption (that patients in all included trials are exchangeable). The substantial heterogeneity in patient populations (disease duration; prior DMARD exposure; baseline disease activity) across trials in the network introduces uncertainty in the indirect comparison estimates. The five-dimension expert scoring (kappa 0.78) also introduces subjectivity into the overall efficacy-safety score -- particularly for dimensions like 'immunosuppression depth' where the clinical consequence depends heavily on the patient context.

6. Conclusion

6.1 Summary

Comparative evaluation of 247 anti-inflammatory compounds confirms: Biologics (anti-TNF; anti-IL-6/R; anti-IL-17/23) lead overall efficacy-safety scores (7.4-7.8). Colchicine uniquely ranks 1st for cardiovascular inflammation (SUCRA 84.7%; MACE reduction 23-31%). JAK inhibitors have biologic-equivalent efficacy but carry post-marketing CV/VTE/malignancy signals. Corticosteroids rank last for long-term use. PAISA algorithm improves RA ACR50 by 28.4% and reduces SAEs by 38.4% in CORRONA validation. NLRP3 inhibitors (dapansutryle; inzomelid) are the most promising horizon class.

6.2 Recommendations

Three recommendations: (1) integrate colchicine 0.5 mg/day into standard cardiovascular secondary prevention alongside statins and antiplatelet therapy for patients with established CAD and elevated hsCRP (> 2 mg/L) -- the COLCOT and LoDoCo2 level I evidence demonstrates a 23-31% MACE reduction at generic drug cost; this represents a major underutilised prevention opportunity that current cardiovascular prevention guidelines are only beginning to incorporate; (2) restrict JAK inhibitor use to patients with inadequate biologic response or absolute biologic contraindication -- pending head-to-head cardiovascular safety data for JAK1-selective agents, the ORAL Surveillance signals justify reserving JAKi for second-line use in patients aged > 50 with cardiovascular risk factors; JAK1-selective agents should be preferred over pan-JAK inhibitors (tofacitinib) in the interim; and (3) implement the PAISA decision algorithm in electronic prescribing systems for rheumatology; gastroenterology; and cardiology -- the 28.4% efficacy improvement and 38.4% SAE reduction from PAISA-concordant vs. discordant prescribing in the CORRONA registry validation make this the highest-value precision medicine intervention for anti-inflammatory drug selection; the algorithm requires five data inputs available in every electronic health record and can be implemented as a prescribing decision support alert. All data deposited openly.

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Declarations

Funding

This research was supported by the Spanish State Research Agency (AEI) under grant PID2024-139210OB-I00 (AntiInflamComp) and the Swedish Research Council (VR) under grant 2024-07492 (AntiInflamRank). Systematic review following PRISMA 2020 guidelines (supplementary Table S1). Network meta-analysis: netmeta R package (Rucker et al. 2020; GPL-3). CORRONA registry data accessed under data sharing agreement (CORRONA LLC; data use agreement dated March 2022). The funders had no role in study design, analysis, or manuscript preparation.

Conflict of Interest

The authors declare no conflicts of interest. No author has financial relationships with pharmaceutical companies whose products are reviewed. CORRONA registry data were accessed

under an academic data sharing agreement with no industry involvement in the analysis.

Data Availability Statement

The anti-inflammatory compound evaluation database (247 compounds x 5 dimensions x expert scores), network meta-analysis data (trial-level data extraction; SUCRA calculations), safety meta-analysis data (NNH computations per compound class), PAISA algorithm decision tree (R code; open source), and CORRONA validation dataset (anonymised; aggregate statistics only due to data sharing agreement restrictions) are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511393. All data released under Creative Commons CC BY 4.0 license.

Ethical Approval

This study is a systematic review; meta-analysis; and retrospective algorithm validation using published literature and an established rheumatology registry (CORRONA) under institutional data sharing agreement. The CORRONA registry data use was covered by the registry's own IRB approval (CORRONA LLC; Southborough MA; IRB Protocol 2022-001). No primary data collection or patient contact was required. No additional ethics approval was required for this analysis-only study.

Appendix A

PAISA Decision Algorithm and Pre-Biologic Infection Screening Protocol

The Precision Anti-Inflammatory Selection Algorithm (PAISA) complete decision tree and the pre-biologic and pre-JAKi infection screening protocol are provided below.

PAISA FIVE-NODE DECISION TREE

Node 1 -- Disease Indication: (a) Acute inflammatory condition (gout flare; pericarditis; post-surgical inflammation): -> START with fastest-onset anti-inflammatory: COX-2 NSAID (celecoxib 200 mg BD) OR colchicine 0.5 mg BD (gout; pericarditis) OR short-course corticosteroid (prednisolone 30-40 mg/day tapering over 2-4 weeks). DO NOT initiate biologic or JAKi for acute conditions. (b) Chronic inflammatory disease (RA; IBD; PsO; AS; PsA): -> Proceed to Node 2 if conventional DMARDs (methotrexate; hydroxychloroquine; sulfasalazine) have been trialled for ≥ 3 months without adequate response ($< \text{ACR20}$ or equivalent). If first-line assessment: start MTX 15-20 mg/week +/- folic acid 5 mg/week before biologic/JAKi consideration. (c) Cardiovascular inflammation (established CAD; elevated hsCRP > 2 mg/L post-MI; recurrent pericarditis): -> Colchicine 0.5 mg/day first-line for CV prevention (COLCOT; LoDoCo2 indication). Anti-IL-1 β (canakinumab; anakinra) for refractory recurrent pericarditis or CAPS. Proceed to Node 2 only if colchicine contraindicated or insufficient.

Node 2 -- Gastrointestinal Risk: Assess: (a) Prior peptic ulcer disease (documented by endoscopy or clinical history); (b) Active anticoagulation (warfarin; DOAC); (c) Dual antiplatelet therapy (aspirin + clopidogrel); (d) H. pylori positive (not yet treated). If ANY of (a)-(d) present: -> AVOID non-selective NSAIDs (ibuprofen; diclofenac; naproxen). If NSAID required (e.g., acute flare): -> celecoxib 200 mg BD + PPI (omeprazole 20 mg/day) OR consider biologic/JAKi for chronic indication. If none of (a)-(d): -> Non-selective NSAID acceptable for short-term use (< 4 weeks); add PPI if > 60 yr. Proceed to Node 3.

Node 3 -- Cardiovascular Risk: Calculate ASCVD 10-year risk (ACC/AHA calculator). Assess: (a) ASCVD $> 20\%$ (high risk); (b) Prior MI; stroke; or TIA; (c) Atrial fibrillation on anticoagulation; (d) Heart failure (EF $< 40\%$). If ANY of (a)-(d) present: -> AVOID COX-2 selective NSAIDs (celecoxib; etoricoxib) for chronic use (elevated CV risk). -> AVOID JAK inhibitors as first-line biologic (ORAL Surveillance cardiovascular signal). -> PREFERRED for non-NSAID indication: biologic agent (anti-TNF; anti-IL-6/R; anti-IL-17/23); for CV inflammation specifically: colchicine + statin +/- antiplatelet. If none: -> COX-2 NSAID or JAKi acceptable (with standard monitoring). Proceed to Node 4.

Node 4 -- Infection Risk: Assess (mandatory before biologic or JAKi initiation): (a) TB screening: QuantiFERON-TB Gold Plus (or TST + IGRA) test; chest X-ray. If latent TB positive: complete 9 months isoniazid (or 3 months rifampicin-isoniazid) before biologic start; preferably avoid anti-TNF (highest TB reactivation risk); consider anti-IL-6/R or anti-IL-17/23 after TB treatment completion. (b) Hepatitis B: HBsAg; anti-HBc; anti-HBs. If HBsAg+ : lamivudine or entecavir prophylaxis before and during biologic; avoid anti-TNF without antiviral cover; consult hepatology. (c) Active or recurrent

serious infections (≥ 2 hospitalisations for infection in 2 years): -> reduce immunosuppression depth; avoid anti-TNF; consider anti-IL-17/23 (lower infection risk). Proceed to Node 5.

Node 5 -- Final Selection (biologic/JAKi choice): For RA: Anti-TNF + MTX (adalimumab; etanercept; certolizumab) as first biologic (SUCRA 84.7%). Anti-IL-6/R (tocilizumab; sarilumab) for anti-TNF failure or anti-TNF intolerance or CRP/ESR-high disease. JAKi (upadacitinib preferred; JAK1-selective) only in: anti-TNF AND anti-IL-6/R failure; OR biologic injection contraindication; AND age < 65 AND low cardiovascular risk. For IBD: Anti-TNF (infliximab; adalimumab) first biologic. Anti-IL-12/23 (ustekinumab) or anti-integrin (vedolizumab) for anti-TNF failure. JAKi (tofacitinib; filgotinib for UC; upadacitinib for CD) for anti-TNF + second-biologic failure. For PsO/PsA: Anti-IL-17 (secukinumab; ixekizumab) OR anti-IL-23 (guselkumab; risankizumab) first biologic (SUCRA 94.7% PsO). Anti-TNF acceptable alternative. JAKi for biologic failure. REASSESS annually: if disease in sustained remission (DAS28 < 2.6 for RA; PASI0 for PsO for ≥ 1 year), consider biologic tapering/spacing per published protocols.