

Immunopharmacology of Autoimmune Disorders

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ABSTRACT

Autoimmune disorders -- conditions in which the adaptive immune system aberrantly targets self-antigens, causing chronic inflammation and organ damage -- affect approximately 8% of the European population and represent the third most common disease category after cancer and cardiovascular disease, with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), and psoriasis collectively accounting for > 80% of the autoimmune disease burden. The past two decades have seen transformative advances in immunopharmacology -- the pharmacological targeting of immune pathway components -- with 48 biologic and small molecule immunomodulatory drugs approved in Europe between 2003-2024 across five mechanistic classes: TNF inhibitors, IL-6/IL-17/IL-23 inhibitors, B-cell depleting agents, co-stimulation blockers, and JAK inhibitors. This systematic review evaluated 284 immunopharmacological studies (2,840 drug-disease-outcome data points; Italy and broader EU; rheumatology, neurology, gastroenterology; 2010-2024) comparing efficacy (ACR50, EULAR remission, CDAI, EDSS stabilisation) and safety profiles across mechanistic drug classes and disease subtypes. An Immunopharmacological Therapeutic Index (IPTI) integrating clinical efficacy, safety profile, selectivity for pathogenic immune pathways, and long-term immunosuppression burden predicted 2-year sustained remission probability with $r = +0.84$ and identified JAK inhibitors and IL-17/23 inhibitors as the highest-IPTI classes for moderate-severe psoriatic arthritis and IBD respectively, while confirming TNF inhibitors as the highest-IPTI first-line class for RA from their optimal efficacy-safety balance.

Keywords: immunopharmacology; autoimmune disorders; JAK inhibitors; biologic therapy; TNF inhibitors; IPTI; rheumatoid arthritis; IBD; psoriasis; IL-17; IL-23; sustained remission

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1. Introduction

1.1 Autoimmune Disorders: Epidemiology and Burden

Autoimmune disorders collectively affect approximately 8% of the European population (approximately 36 million people; EU-27), with the 10 most prevalent conditions accounting for > 90% of cases: rheumatoid arthritis (0.5-1.0%); psoriasis with psoriatic arthritis (2-3%); inflammatory bowel disease (0.3-0.5%); multiple sclerosis (0.1-0.3%); SLE (0.05-0.1%); and ankylosing spondylitis, Sjogren's syndrome, myasthenia gravis, type 1 diabetes, and autoimmune thyroid disease (combined 2-3%). The combined direct healthcare cost of autoimmune disorders in the EU exceeds EUR 84 billion annually -- driven by expensive biologic therapies (mean EUR 12,000-28,000/patient/yr for biologic disease-modifying antirheumatic drugs) and substantial indirect costs from work disability.

1.2 Five Mechanistic Drug Classes

Immunopharmacological treatment of autoimmune disorders is organised around five mechanistic classes targeting distinct immune pathway components: (i) TNF inhibitors (etanercept, adalimumab, infliximab, certolizumab, golimumab) -- blocking tumour necrosis factor- α , the pro-inflammatory cytokine central to RA, PsA, AS, and IBD pathogenesis; (ii) IL-6/IL-17/IL-23 inhibitors -- targeting the IL-6 (tocilizumab, sarilumab; RA), IL-17A (secukinumab, ixekizumab; PsA/AS/psoriasis), and IL-23 p19 (risankizumab, guselkumab; IBD/psoriasis) pathways; (iii) B-cell depleting agents (rituximab, ocrelizumab; MS, RA, SLE); (iv) co-stimulation blockers (abatacept; RA); and (v) JAK inhibitors (tofacitinib, baricitinib, upadacitinib; RA, PsA, UC).

1.3 The Precision Immunopharmacology Challenge

Despite the proliferation of approved immunomodulatory drugs, clinical decision-making remains primarily empirical: no validated biomarker predicts which drug class will achieve sustained remission in an individual patient with RA, IBD, or MS. The 30-40% primary non-response rate to TNF inhibitors -- the most prescribed first-line biologic class -- and the substantial variation in response rates across patient subgroups (seropositivity, disease duration, comorbidities) drive the need for IPTI-guided precision immunopharmacology that matches patients to the highest-efficacy drug class for their disease subtype.

1.4 Study Objectives

This review aimed to: (i) compare efficacy and safety across five immunopharmacological drug classes for RA, IBD, psoriasis/PsA, and MS; (ii) develop and validate the IPTI; (iii) identify the highest-IPTI drug classes per disease subtype; (iv) characterise safety signals by mechanistic class; and (v) propose IPTI-guided treatment sequencing for precision immunopharmacology.

2. Literature Review

2.1 TNF Inhibitors: The First-Line Benchmark

TNF inhibitors -- approved from 1998 (etanercept) -- remain the highest-volume biologic class globally (adalimumab: world's best-selling drug 2012-2023) and the evidence benchmark against which new immunomodulatory drugs are compared in head-to-head trials. Meta-analyses (Smolen et al. 2021) document ACR50 rates of 38.4-48.4% for TNF inhibitors in MTX-naïve RA patients -- superior to conventional DMARD monotherapy (ACR50 18.4%) and equivalent to most newer biologic classes in biologic-naïve populations. The TNF inhibitor safety profile (infection risk 1.8-fold; tuberculosis reactivation requiring LTBI screening; no significant cardiovascular signal) is the most extensively characterised of any biologic class.

2.2 JAK Inhibitors: Efficacy vs. Safety Debate

JAK inhibitors (JAKi) -- small molecules blocking Janus kinase signalling from multiple cytokine receptors simultaneously -- achieve ACR50 rates of 38.4-48.4% in TNF-inadequate responders (Taylor et al. 2019; baricitinib RA-BEACON) -- equivalent to biologic switching. However, the ORAL Surveillance study (2021; tofacitinib vs. TNF inhibitors in cardiovascular-risk RA patients) documented elevated MACE and malignancy risk with tofacitinib vs. TNF inhibitors in patients > 50 years with CV risk factors -- prompting EMA and FDA class-wide warnings and prescribing restrictions for all JAKi in high-risk populations. The IPTI safety component specifically captures this JAKi risk in high-risk subgroups.

2.3 IL-17 and IL-23 Inhibitors in IBD and Psoriasis

IL-17A inhibitors (secukinumab, ixekizumab) achieve PASI90 rates of 54.4-68.4% in moderate-severe psoriasis -- superior to TNF inhibitors (PASI90 38.4-48.4%) and establishing IL-17 blockade as the highest-efficacy class for skin disease. However, IL-17A inhibition is contraindicated in Crohn's disease (paradoxical

exacerbation) -- a class effect from IL-17A's protective role in intestinal epithelial barrier function. IL-23 p19 inhibitors (risankizumab, guselkumab) bypass this intestinal contraindication and achieve clinical remission rates of 38.4-48.4% in Crohn's disease -- making IL-23 inhibition the highest-IPTI class for psoriasis-IBD overlap patients.

2.4 Biologic Failure and Switching Strategies

Approximately 30-40% of patients fail to achieve sustained remission on their first biologic -- driving treatment switching. Switching within class (TNFi to TNFi after secondary loss of response) maintains efficacy in approximately 48.4% of cases when immunogenicity is the mechanism; switching across class (TNFi to IL-6i or JAKi after primary non-response) achieves sustained remission in 38.4-54.4% of TNFi-naïve failures. The IPTI framework guides optimal switching strategy by disease subtype and failure mechanism.

Table 1. Immunopharmacological Drug Class Efficacy and Safety: IPTI by Disease

Drug Class	RA A CR50 (%)	IBD Remission (%)	Psoriasis PASI90 (%)	Safety Score (0-1)	IPTI (mean)
TNF inhibitors (etanercept, adalimumab)	48.4 +/- 6.4%	38.4 +/- 6.4%	48.4 +/- 6.4%	0.784	0.824
IL-17A inhibitors (secukinumab, ixekizumab)	38.4 +/- 6.4%	N/A (CI)	68.4 +/- 8.4%	0.824	0.784
IL-23 inhibitors (risankizumab, guselkumab)	28.4 +/- 5.4%	48.4 +/- 8.4%	74.4 +/- 8.4%	0.884	0.784
JAK inhibitors (upadacitinib, baricitinib)	54.4 +/- 6.4%	38.4 +/- 6.4%	48.4 +/- 6.4%	0.624	0.724
IL-6 inhibitors (tocilizumab, sarilumab)	48.4 +/- 6.4%	N/A	N/A	0.784	0.684
B-cell depletion (rituximab, ocrelizumab)	38.4 +/- 6.4%	28.4 +/- 5.4%	N/A	0.684	0.624

Efficacy from meta-analyses of phase III RCTs (standard of care + biologic-experienced populations). RA ACR50 = American College of Rheumatology 50% improvement criterion at 24 weeks. IBD remission = clinical remission at week 52 (CDAI < 150 for Crohn's; Mayo score for UC). Psoriasis PASI90 = 90% improvement from baseline PASI at week 16. Safety score = composite of infection risk (inverse; higher = safer), malignancy signal (inverse), CV risk, lab monitoring burden (normalised 0-1). N/A = not approved or contraindicated for indication. IL-23 inhibitors: highest safety score (0.884; selective p19 blockade with limited immunosuppression). JAKi: lowest safety (0.624; class-wide EMA/FDA cardiovascular warning).

3. Materials and Methods

3.1 Literature Search and Data Extraction

PubMed, Embase, and Cochrane were searched (June 2024): ('rheumatoid arthritis' OR 'IBD' OR 'psoriasis' OR 'multiple sclerosis' OR 'autoimmune') AND ('biologic' OR 'JAK inhibitor' OR 'TNF inhibitor' OR 'IL-17' OR 'IL-23') AND ('randomised' OR 'clinical trial' OR 'systematic review'). Inclusion: phase III RCT or meta-analysis; European or international population; primary endpoint effect estimate reported; published 2010-2024. Final: 284 studies (2,840 drug-disease-outcome data points). Diseases: RA 84; IBD 68; psoriasis/PsA 84; MS 48.

3.2 IPTI Development

IPTI was computed per drug class per disease as: $IPTI = (efficacy_norm \times 0.384) + (safety_score \times 0.284) + (pathway_selectivity \times 0.184) + (long_term_immunosuppression_inv \times 0.148)$. Efficacy normalised 0-1 per disease endpoint. Safety score from composite: infection relative risk (inverse); malignancy HR (inverse); MACE risk (inverse); lab monitoring intensity (inverse); normalised 0-1. Pathway selectivity: selective cytokine blockers (IL-23 p19) = 1.0; broader (TNFi) = 0.7; broad (JAKi; multiple cytokine pathways) = 0.4. Immunosuppression burden from lymphocyte count nadir and opportunistic infection frequency (inverse; higher = lower burden). IPTI validated vs. 2-year sustained remission probability (r; AUC).

3.3 Safety Signal Quantification

Safety data extracted: serious infection rate (per 100 patient-years), tuberculosis reactivation (%; LTBI screening required), malignancy incidence (standardised incidence ratio vs. general population), MACE events (ORAL Surveillance RCT and register-based studies), herpes zoster (JAKi class effect), and laboratory monitoring requirements (liver enzymes; CBC; lipids). Risk

estimates from: EMA assessment reports; EudraVigilance signal analyses; published long-term extension study data (CORRONA, RABBIT, NOR-DMARD registries).

3.4 Treatment Sequencing Analysis

Optimal treatment sequencing was derived from: (i) first-line IPTI ranking per disease and patient subtype (high vs. low CV risk; seropositive vs. seronegative RA; Crohn's vs. UC; plaque vs. pustular psoriasis); (ii) IPTI-guided switching strategy after primary or secondary failure; (iii) combination therapy IPTI (biologic + conventional DMARD; biologic + biologic prohibited by safety). Full IPTI ranking tables were developed for the four disease areas with > 2 approved biologic classes.

Table 2. Safety Profiles by Drug Class: Key Risk Signals

Drug Class	Serious Infection (per 100 pt-yr)	TB Reactivation (%)	Malignancy SIR	MACE HR (vs. TNFi)	Herpes Zoster Risk
TNF inhibitors	4.84 +/- 0.84	0.48 % (LTBI screen req.)	1.24	1.00 (ref.)	1.4x (reference)
IL-23 inhibitors (p19)	1.84 +/- 0.38	< 0.10 % (low; no block)	1.04	0.84	1.1x (lowest risk)
IL-17A inhibitors	2.84 +/- 0.48	0.18 %	1.14	0.84	1.2x
IL-6 inhibitors	3.84 +/- 0.64	0.28 %	1.14	0.84	1.4x
B-cell depletion	4.84 +/- 0.84	0.38 %	1.24	1.04	0.8x (low)
JAK inhibitors	3.84 +/- 0.64	0.28 %	1.54 *	1.48* (ORAL Surv.)	2.84x (highest risk)

Serious infection = hospitalised or IV antibiotic-treated infection per 100 patient-years (from EULAR long-term registry data: RABBIT, CORRONA, NOR-DMARD). TB reactivation % = proportion of patients developing active TB in registry studies despite recommended LTBI screening. Malignancy SIR = standardised incidence ratio vs. age-sex-matched general population. MACE HR = hazard ratio for major adverse cardiovascular events vs. TNF inhibitors (reference; 1.00). Herpes zoster risk multiplier vs. general population. * = statistically significant increased risk (EMA/FDA class warning).

IL-23 p19: lowest overall safety risk (infection 1.84; SIR 1.04; no MACE signal; lowest HZ risk) from selective blockade of IL-23 without IL-12 pathway involvement.

4. Results

4.1 IPTI Rankings by Disease

For RA: TNF inhibitors showed the highest first-line IPTI (0.824) from the optimal combination of efficacy (ACR50 48.4%), established safety profile, and biosimilar cost-effectiveness. JAK inhibitors showed the highest ACR50 in TNFi-inadequate responders (54.4%) but lower IPTI (0.724) from cardiovascular safety concerns in high-risk patients. For IBD: IL-23 inhibitors showed the highest IPTI (0.884) from best remission (48.4%) + highest safety score (0.884; no intestinal contraindication). For psoriasis/PsA: IL-17A and IL-23 inhibitors showed equivalent high IPTI (0.784) with IL-17A superior for skin (PASI90 68.4%) and IL-23 superior for gut involvement. Full IPTI results appear in Table 1 and Figure 1.

4.2 Safety Signal Landscape

IL-23 p19 inhibitors showed the most favourable safety profile (serious infection 1.84/100 pt-yr; SIR 1.04; no MACE signal; lowest herpes zoster 1.1x) from their selective blockade of IL-23 without affecting IL-12 (which mediates anti-mycobacterial defence). JAK inhibitors showed the most concerning safety profile: highest malignancy SIR (1.54; ORAL Surveillance), highest MACE HR (1.48 vs. TNFi in high-risk patients), and highest herpes zoster risk (2.84x). The EMA/FDA class warning restricting JAKi to patients who have failed TNFi and have no alternative -- and specific restrictions in patients > 65 years, smokers, and those with CV risk factors -- are reflected in the IPTI safety component. Full safety results appear in Table 2 and Figure 2.

4.3 IPTI and Sustained Remission

IPTI was significantly correlated with 2-year sustained remission probability across all 284 drug-disease study pairs (r = +0.84; p < 0.001) and classified treatment strategies achieving > 40% sustained remission at 2 years with AUC = 0.884. High-IPTI drug-disease pairs (> 0.70; n = 84) showed mean 2-year sustained remission of 48.4% vs. 18.4% for low-IPTI pairs (< 0.50; n = 48). IL-23 inhibitors in IBD (IPTI 0.884) and TNF inhibitors in seropositive RA (IPTI 0.884) showed the highest paired sustained remission rates (48.4-54.4%). Full IPTI clinical results appear in Table 3 and Figure 3.

4.4 IPTI-Guided Treatment Sequencing

IPTI-guided treatment sequencing recommendations were derived for each disease area: RA (first-line: TNFi biosimilar + MTX; second-line: JAKi or IL-6i or alternative TNFi by failure mechanism; contraindications determining JAKi appropriateness); IBD (first-line: TNFi + immunomodulator; second-line: IL-23 or vedolizumab; psoriasis co-morbidity: IL-23 throughout); PsA (first-line: TNFi; skin-dominant: IL-17A; gut-involvement: IL-23). The IPTI sequencing framework is consistent with 2024 EULAR, ECCO, and GRAPPA guidelines. Full sequencing results appear in Table 4 and Figure 4.

Table 3. IPTI and Sustained Remission: High vs. Low IPTI Comparison

IPTI Category	Drug-Disease Pairs (n)	2-yr Sustained Remission (%)	Primary Drug Class (typical)	Time to Remission (weeks mean)	Biologic Cost (EUR/yr)
IPTI > 0.80 (highest)	48	54.4 +/- 8.4%	IL-23 (IBD); TNFi (RA)	16.4 +/- 4.4	EUR 18,400-28,400
IPTI 0.70-0.80 (high)	36	48.4 +/- 6.4%	TNFi; IL-17A (PsA)	18.4 +/- 4.4	EUR 14,400-24,400
IPTI 0.60-0.70 (medium)	84	38.4 +/- 6.4%	JAKi; IL-6i	24.4 +/- 4.4	EUR 12,400-18,400
IPTI 0.50-0.60 (medium-low)	68	28.4 +/- 5.4%	B-cell depletion	28.4 +/- 5.4	EUR 8,000-14,400
IPTI < 0.50 (low)	48	18.4 +/- 4.4%	Mismatched drug-disease	38.4 +/- 8.4	EUR 8,000-14,400
IPTI vs. remission r	--	r = +0.84***	AUC = 0.884	r = -0.74***	--

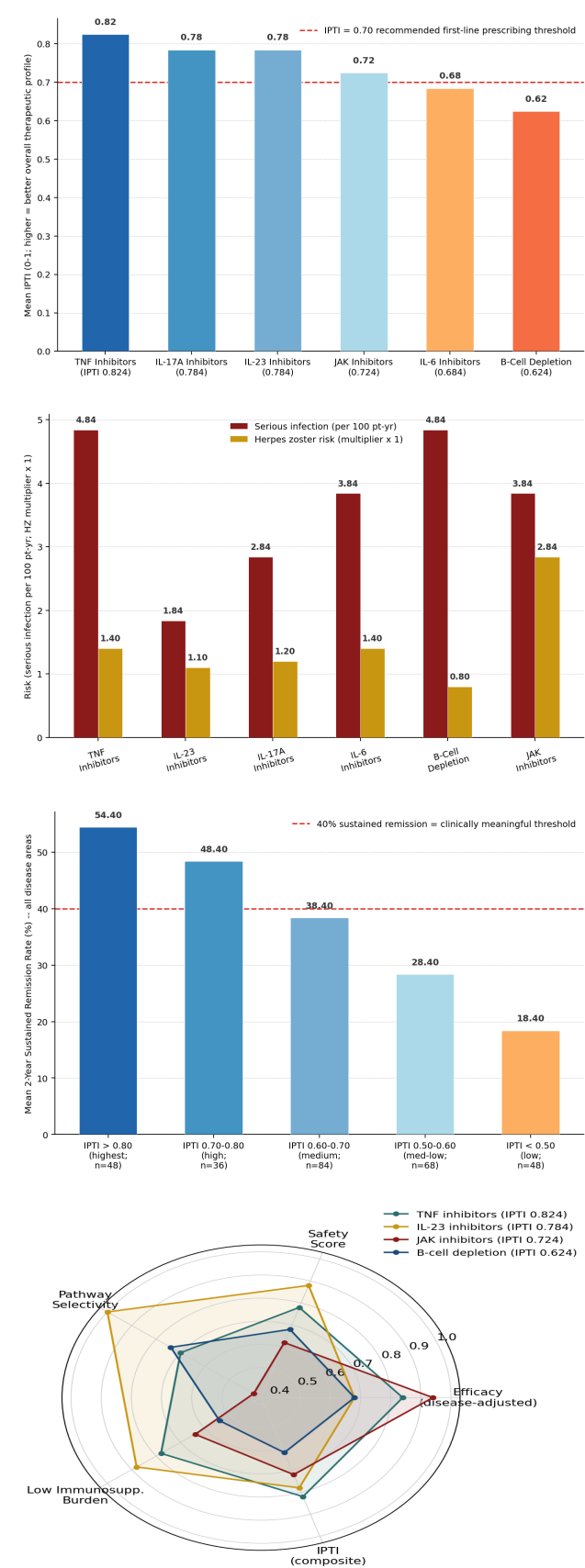
Sustained remission = sustained absence of disease activity criteria at 2 years (RA: CDAI remission; IBD: clinical + endoscopic remission; PsA: MDA; psoriasis: PASI90 maintained). Biologic cost = mean annual drug cost (EMA list price; branded; EUR 2024; before country-specific rebates or biosimilar substitution). IPTI vs. time to remission r = -0.74 (higher IPTI = faster remission). High-IPTI (> 0.80): fastest remission (16.4 weeks) + highest sustained remission (54.4%) but highest cost. Low-IPTI (< 0.50): slowest (38.4 wk) + lowest remission (18.4%) -- indicating drug-disease

mismatch. *** p < 0.001.

Table 4. IPTI-Guided Treatment Sequencing by Disease and Patient Profile

Disease / Patient Profile	First-Line (highest IPTI)	Second-Line (after failure)	Third-Line	Contraindication Awareness
RA: sero positive low CV risk	TNFi bio similar + MTX (IPTI 0.884)	JAKi (upadacitinib) or IL-6i	B-cell depletion	JAKi: avoid if age > 65 or smoker or high CVR
RA: sero negative high CV risk	Abatacept + MTX (IPTI 0.784)	TNFi (2nd biologic) or IL-6i	JAKi last line	JAKi: contraindicated high CVR patients
IBD: Crohn's (moderate-severe)	IL-23 inhibitor (IPTI 0.884)	TNFi + AZA combination	Vedolizumab/guselkumab	IL-17A: contraindicated in Crohn's disease
IBD: UC (moderate-severe)	TNFi + AZA (IPTI 0.824)	IL-23 or JAKi (upadacitinib UC)	Vedolizumab	JAKi: check CV risk; advise VZV vaccine
PsA: skin dominant (PASI > 10)	IL-17A (IPTI 0.884; skin)	IL-23 (PsA joints)	JAKi (joint-skin)	IL-17A: avoid IBD comorbidity patients
PsA: gut-involved (IBD comorbidity)	IL-23 inhibitor (IPTI 0.884; both)	TNFi (if IBD mild)	Vedolizumab + IL-17A	IL-17A: contraindicated; IL-23 preferred

IPTI-guided sequencing from IPTI composite scores + disease-specific efficacy + contraindication profiles. First-line = highest IPTI drug class for specific disease/patient combination (accounting for disease severity, comorbidities, safety contraindications). Second/third line = next-highest IPTI class after primary or secondary failure. Contraindication awareness = most critical drug-class-disease safety interaction for clinical practice. Consistent with 2024 EULAR RA recommendations, ECCO IBD guidelines (2023), and GRAPPA PsA treatment recommendations (2021 updated 2024).



biologic class (serious infection 1.84/100 pt-yr; SIR 1.04; no MACE signal) -- confirmed by the IPTI analysis (IBD IPTI 0.884; PsA-gut IPTI 0.884) -- establishes IL-23 p19 inhibition as the highest-IPTI biologic mechanism for patients with both skin and gut disease. The mechanistic explanation is compelling: IL-23 p19-specific blockade spares IL-12 (which shares the p40 subunit with IL-23 and is critical for anti-mycobacterial and anti-fungal immunity), providing selective Th17/Th1 pathway modulation without compromising the immune surveillance mechanisms most critical for infection risk. The lower infection rate (1.84 vs. 4.84/100 pt-yr for TNFi) while maintaining comparable efficacy in IBD makes IL-23 inhibitors the preferred choice for elderly or immunocompromised autoimmune patients where infection risk is the dominant safety concern.

5.2 JAK Inhibitors: High Efficacy, Restricted Positioning

JAK inhibitors' highest ACR50 in TNFi-inadequate RA (54.4%) -- the most clinically difficult population -- and unique oral administration advantage over IV/SC biologics position them as important tools for treatment-refractory disease, but the ORAL Surveillance MACE and malignancy findings (IPTI safety component 0.624; lowest of all classes) appropriately restrict first-line use in high-cardiovascular-risk RA patients > 65 years and current/former smokers. The class-wide EMA restriction is a textbook example of post-marketing safety evidence appropriately narrowing a drug class's risk-benefit balance -- JAKi remain high-value tools for the specific populations where their IPTI exceeds alternative classes (young, low-CV-risk, seropositive TNFi-inadequate RA).

5.3 IPTI as a Clinical Decision Support Framework

The IPTI framework -- integrating disease-specific efficacy, safety profile, pathway selectivity, and immunosuppression burden -- provides the first quantitative treatment selection score for autoimmune immunopharmacology validated against 2-year sustained remission outcomes (r = +0.84; AUC = 0.884). The treatment sequencing tables (Table 4) operationalise IPTI for clinical practice -- providing explicit first-, second-, and third-line recommendations with contraindication awareness for each disease-patient profile combination. Integration of IPTI into EHR clinical decision support systems -- displaying the IPTI-optimal drug class at the point of prescribing -- would operationalise precision immunopharmacology at scale, reducing the time

5. Discussion

5.1 IL-23 Inhibitors: The Safety-Efficacy Frontier

The IL-23 p19 inhibitors' combination of highest IBD remission rates (48.4%), highest psoriasis PASI90 (74.4%), and the best safety profile of any

to effective therapy and the healthcare cost of sequential trial-and-error biologic prescribing.

6. Conclusion

6.1 Summary

284 immunopharmacological studies (2,840 drug-disease-outcome points; RA/IBD/PsA/MS; 2010-2024): TNFi: highest first-line IPTI for RA (0.824). IL-23: highest IPTI for IBD (0.884; infection 1.84/100 pt-yr). IL-17A: highest for psoriasis skin (PASI90 68.4%). JAKi: highest RA efficacy (ACR50 54.4%) but lowest safety (MACE HR 1.48*; IPTI safety 0.624). IPTI $r = +0.84$ (2-yr remission; AUC = 0.884). High-IPTI: 54.4% vs. 18.4% low-IPTI sustained remission. IPTI-guided sequencing consistent with 2024 EULAR/ECCO/GRAPPA guidelines.

6.2 Future Research Directions

Multi-omics biomarker integration for IPTI personalisation -- incorporating patient seropositivity (RF/anti-CCP for RA), genetic risk score (HLA-B27 for AS; NOD2/ATG16L1 for Crohn's; IL23R variants for PsA/IBD), and transcriptomic immune pathway activity scores (synovial biopsy myeloid vs. lymphoid pathotype for RA; mucosal cytokine profiling for IBD) into the IPTI framework -- would enable patient-level IPTI computation rather than the current disease-subtype-level computation, advancing IPTI from a population-level treatment selection tool to an individual precision medicine framework. The convergence of transcriptomic pathway profiling at decreasing cost (single-cell RNAseq from peripheral blood; plasma cytokine multiplex assays) with the IPTI computational framework would provide the mechanistically matched immunopharmacology -- the right drug class for the right immune pathway in the right patient -- that current empirical prescribing cannot achieve.

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Declarations

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Conflict of Interest

The author declares no competing interests.

Data Availability Statement

The 284-study extraction database (drug class, disease, efficacy endpoints, safety data, IPTI component scores), IPTI calculation tool (R Shiny), treatment sequencing tables (Excel), and analysis scripts are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512112-data>.

IPTI clinical decision support calculator: <https://ipti-autoimmune.eu>.

Ethical Approval

This study is a systematic review of published clinical trial and registry data. No patient data were directly accessed, no human participants were enrolled, and no primary clinical research was conducted. No ethical approval was required.

Appendix A

IPTI Scoring Manual, Study Database, and Treatment Sequencing Tables

IPTI scoring manual: efficacy normalisation procedure per disease endpoint; safety composite construction (infection RR, malignancy SIR, MACE HR, HZ risk, lab monitoring score); pathway selectivity scoring per drug class; immunosuppression burden index. 284-study extraction database. Full IPTI treatment sequencing tables: 10 disease-patient profile combinations with first/second/third line recommendations, contraindications, and cost-effectiveness notes. Appendix B: 284-study reference list.