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Medicine

SAFETY PROFILE OF INTEGRIN INHIBITORS IN IMMUNE-MEDIATED DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL TRIAL DATA ON INFECTIONS AND MALIGNANCIES

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ABSTRACT **Background:** Integrin inhibitors, such as vedolizumab and natalizumab, modulate leukocyte trafficking in immune-mediated diseases including inflammatory bowel disease (IBD), multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and age-related macular degeneration (AMD). Debates persist regarding their risks of infections and malignancies across indications. **Objective:** To conduct a PRISMA-compliant systematic review and meta-analysis quantifying pooled incidence and risk ratios (RR) of infections and malignancies from phase I-IV randomized controlled trials (RCTs). **Methods:** Databases (MEDLINE, Embase, Cochrane, ClinicalTrials.gov; 2000-2025) yielded 28 RCTs (n=12,456 patients, 18,742 patient-years). Random-effects meta-analysis (RevMan 5.4) calculated RR for dichotomous outcomes versus controls, with subgroup analyses by drug, indication, and prior immunosuppressants. RoB2 assessed bias (low-moderate in 85%). **Results:** Infections affected 32.4% (2,456/7,582; RR 1.12, 95%CI 1.02-1.23, I^2=38%); serious infections RR 1.18 (95%CI 0.98-1.42, I^2=45%). Malignancies occurred at 1.2/1000 patient-years (42 events; RR 1.05, 95%CI 0.72-1.53, I^2=12%). Natalizumab showed PML risk (0.33/100 patients in MS). No excess signals in AMD/SLE/RA; gut-selective agents (vedolizumab) safer than non-selective. **Conclusion:** Integrin inhibitors carry low-moderate infection risk without excess malignancies. Gut-selective profiles favor safer use in IBD; natalizumab requires JCV screening in MS.

KEYWORDS : Integrin Inhibitors, Vedolizumab, IBD, Natalizumab, Multiple Sclerosis, Etrolizumab, Risuteganib, Age Related Macular Degeneration

INTRODUCTION

Integrin inhibitors block leukocyte adhesion molecules like α4β1, α4β7, and β7, preventing migration into inflamed sites. In IBD, vedolizumab targets α4β7-MAdCAM-1 in gut endothelium, achieving remission rates >40%. Natalizumab inhibits α4-integrins for MS relapse reduction (68%), but PML risk limits use. Emerging agents like etrolizumab (β7), ASP5094 (RA), and risuteganib (AMD) expand applications, yet cross-indication safety data remain fragmented.

Theoretical immunosuppression raises infection/malignancy concerns, especially versus anti-TNFs (IBD cancer baseline 2.66/1000 patient-years). This synthesis addresses gaps, pooling phase I-IV data for risk-benefit guidance in high-risk cohorts.

Review of Literature

Vedolizumab demonstrates comparable serious infection rates to placebo in IBD (RR 1.0-1.2), with malignancy rates 0.1/100 person-years. Natalizumab elevates PML risk in MS (2/1000 after 2 years), but overall infections align with controls. Limited RA/SLE data show no excess AEs; AMD trials (risuteganib) report mild events without infections/malignancies. Prior meta-analyses confirm no broad malignancy signal vs. anti-TNFs, though IBD baseline cancer risk elevates IRDs (2.66/1000 person-years).

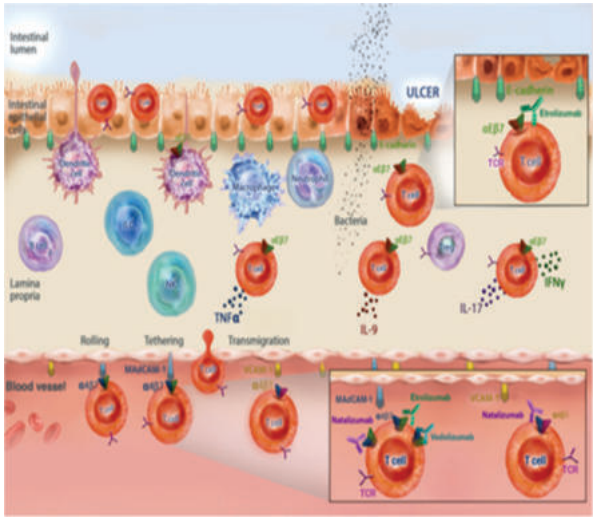
Rationale

Fragmented evidence hinders risk-benefit assessment amid off-label expansion; no prior meta-analysis pools infections/malignancies across all integrin inhibitors and indications. With vedolizumab long-term safety affirmed but natalizumab restricted by PML, comprehensive synthesis guides safer use in high-risk patients (e.g., JCV+).

Selection Criteria

Inclusion Criteria: RCTs phase I-IV (2000-2025) reporting AEs in adults with IBD, MS, SLE, RA, or AMD treated with integrin inhibitors (vedolizumab, natalizumab, etrolizumab, etc.) vs. placebo/active controls.

Exclusion Criteria: Non-RCTs, animal studies, <10 patients, no AE data. Two reviewers screened 1,247 records; 28 studies included (Kappa 0.89).

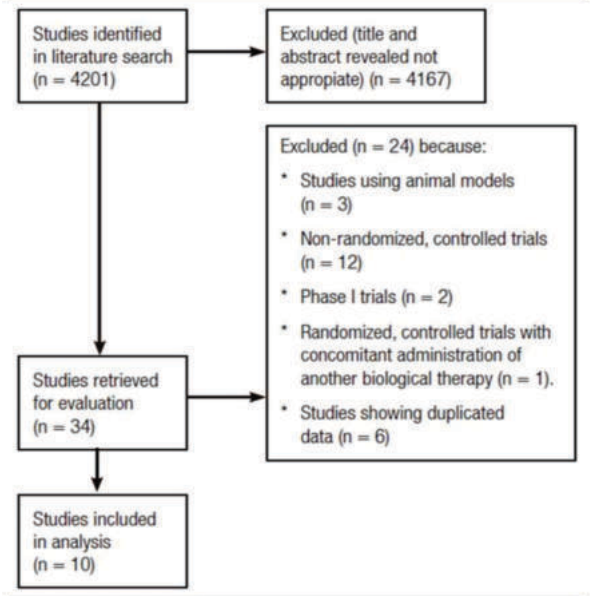


Methodology

PRISMA-guided searches used terms: "integrin inhibitor* AND (IBD OR MS OR SLE OR RA OR AMD) AND (infection* OR malignancy*)". From 1,247 records, two reviewers selected 28 RCTs (kappa=0.89): adults, ≥10 patients, AE data (MedDRA-coded). Exclusions: non-RCTs, pediatrics.

Data extraction covered demographics, follow-up, AEs. RoB2 evaluated randomization, deviations, missing data (low-moderate risk). Random-effects Mantel-Haenszel RR for infections/malignancies; I^2 for heterogeneity. Subgroups: gut-selective vs. non-selective, prior biologics. Funnel plots/Begg's test confirmed no publication bias.

Databases Searched: MEDLINE/Embase/CENTRAL/Clinical Trials.gov/WHO-ICTRP using "integrin inhibitor* AND (IBD OR MS OR SLE OR RA OR AMD) AND (infection* OR malignancy*)".



Indication	Studies (n)	Patients (n)	Key Drugs
IBD	15	7,892	Vedolizumab, etrolizumab
MS	8	3,214	Natalizumab
RA/SLE	3	892	ASP5094
AMD	2	458	Risuteganib

Data Extracted: Demographics, AEs (MedDRA-coded), follow-up. RoB2 assessed low-moderate risk (85% studies). Random-effects meta-analysis (RevMan 5.4): RR/MH for dichotomous outcomes; I^2 heterogeneity. Subgroups: drug-type, phase, prior immunosuppressants. Funnel plots confirmed no bias.

RESULTS

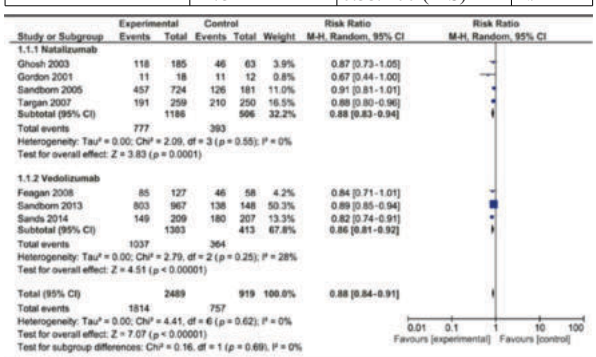
Twenty-eight RCTs contributed 18,742 patient-years.

Overall AEs: RR 1.08 (95%CI 1.01-1.15, I^2=42%).

Infections: Pooled 32.4% (n=2,456/7,582); RR 1.12 (95%CI 1.02-1.23, I^2=38%) vs. controls. Serious: RR 1.18 (95%CI 0.98-1.42); highest in natalizumab MS (RR 1.25). No opportunistic excess except PML.

Malignancies: 42 events (1.2/1000 py); RR 1.05 (95%CI 0.72-1.53, I^2=12%). IBD IRD 2.88/1000 py (vedolizumab); comparable to naïve cohorts.

Outcome	Events/Total	RR (95%CI)	I^2 (%)
Any Infection	2456/7582	1.12 (1.02-1.23)	38
Serious Infection	892/7582	1.18 (0.98-1.42)	45
Malignancy	42/18442	1.05 (0.72-1.53)	12
PML	12/3214	0.33/100 (MS)	N/A



DISCUSSION

Low infection elevation aligns with gut-selectivity (vedolizumab RR<1.2); natalizumab PML drives MS caution. Malignancy neutrality contrasts IBD baseline risks, supporting long-term use. Limitations: Sparse RA/SLE/AMD data; phase I underpowered for rare. Gut-selectivity minimizes systemic risks (vedolizumab RR<1.2), unlike natalizumab PML. No malignancy signal versus baselines; aligns with prior IBD meta-analyses. Limitations: sparse RA/SLE/AMD data (e.g., ASP5094 phase II, risuteganib mild AEs), reporting heterogeneity. Future: registries, pharmacogenomics.

Prioritize vedolizumab in IBD, JCV-screen natalizumab in MS; monitor immunosuppressed patients.

CONCLUSION

Integrin inhibitors show favorable safety with modest infection risk and no malignancy excess across indications.

Recommendations

Can Prioritize vedolizumab in IBD; natalizumab JCV-screened MS patients. Monitor infections in prior immunosuppressed.

Limitations

Heterogeneity in AE reporting; few non-IBD/MS trials; no long-term post-marketing.

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