Biologics: Targets and Therapy

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REVIEW

Beyond Monotherapy: Exploring the Efficacy and Safety of Dual Biologic Strategies in Rheumatic Diseases

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Abstract: Although numerous biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are available, substantial number of rheumatic patients fail to achieve therapeutic goals with sequential monotherapy. Dual biologic therapy (DBT) may overcome treatment resistance by concomitantly inhibiting multiple inflammatory pathways. In rheumatoid arthritis, DBT shows moderate efficacy improvements but consistently higher serious infection rates compared to monotherapy, particularly with rituximab and JAK inhibitor combination-based regimens. In psoriatic arthritis, studies demonstrate possible benefits especially with combinations targeting alternate pathways, eg, apremilast with biologics or IL-17/IL-23 inhibitors with TNF blockers, though safety concerns exist. The multi-domain nature of PsA makes DBT particularly attractive in achieving global disease control. In axSpA, evidence of efficacy is also limited but encouraging in treatment-refractory disease. However, major research gaps persist. Data remain limited and largely heterogeneous, with limited disease-specific studies and a paucity of randomized controlled trials (RCTs). Most available reports derive from small case series or single-center experiences, limiting the generalizability of findings. Geographic variation further complicates interpretation, as infection risk, treatment accessibility, and pharmacovigilance capacity differ markedly between developed and resource-limited regions. Therefore, this narrative review aims to summarize current evidence while emphasizing the unmet clinical and research needs surrounding DBT, highlighting the necessity for systematic reviews, large-scale registries, and context-specific studies to inform safe and equitable clinical application worldwide. While DBT may be beneficial in carefully selected patients with treatment-refractory disease, current evidence does not consistently demonstrate increased efficacy. Thus, DBT should be reserved for refractory cases where benefits outweigh risks.

Keywords: dual biologic therapy, rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, treatment resistance, refractory disease, biologics

Introduction

The introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) has revolutionized the management of immune-mediated inflammatory diseases (IMIDs).[1] In clinical practice, b/tsDMARDs are typically used as monotherapies or in combination with conventional synthetic DMARDs (csDMARDs). When a b/tsDMARD fails to achieve the therapeutic goal, switching to another b/tsDMARD, usually with a different mechanism, is the standard approach.[2,3] Current treatment guidelines from major rheumatology societies, including the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR), consistently endorse a sequential treatment strategy using a single biologic agent (often in combination with a csDMARD), and do not recommend dual biologic therapy (DBT). These guidelines emphasize switching between biologic classes rather than combining them, reflecting the limited evidence base and persisting safety concerns associated with DBT. Consequently, the concomitant use of two b/tsDMARDs has generally been avoided due to safety concerns. Nevertheless, despite the increasing number of available b/tsDMARDs, a substantial proportion of rheumatic patients fail to achieve the treatment goal, even when switching to other b/tsDMARDs with different mechanisms of action.[4–8] This therapeutic resistance

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represents a substantial challenge in the daily clinical practice. One approach to overcome this challenge can be achieved using concomitant inhibition of multiple inflammatory pathways or cytokines by utilizing DBT. This strategy may improve clinical outcomes by providing deeper inhibiting of the inflammatory process.[1,9] The concept of DBT has emerged over the past two decades as a promising approach in patients with difficult-to-treat disease. DBT has been also investigated beyond the field of rheumatology, particularly in resistant cases of osteoporosis, asthma, atopic dermatitis and inflammatory bowel disease (IBD).[10] Although early experiences with DBT were limited due to safety concerns, growing knowledge of cytokine pathways and careful patient selection have renewed interest in this strategy, particularly given the substantial number of patients failing to achieve treatment goals using standard sequential approach.[9]

This review summarizes current evidence on DBT in rheumatic diseases, focusing on efficacy and safety. We outline mechanisms of treatment resistance that limit the effectiveness of sequential biologic monotherapy, and present the rationale for DBT as a means to target overlapping or complementary inflammatory pathways. Clinical evidence is reviewed with emphasis on rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthropathy (axSpA), followed by a discussion of strategies beyond DBT for difficult-to-treat disease.

Resistance Mechanisms to Biologics Monotherapy

Multiple mechanisms have been proposed to explain this therapeutic failure of sequential b/tsDMARD monotherapy approach, including immunological and genetic factors, as well as patient-related non-immunological factors. A key mechanism involves the formation of anti-drug antibodies (ADAs), particularly in response to immunogenic monoclonal antibody-based agents such as infliximab and adalimumab. These ADAs can either neutralize the drug directly or enhance its clearance from circulation, resulting, in both cases, in subtherapeutic drug levels and reduced efficacy.[11] This mechanism is further supported by the finding that methotrexate co-administration decreases immunogenicity and enhances the drug survival of biologic agents, emphasizing the important role of combining a csDMARD with a b/tsDMARD.[12]

The various cytokine pathways and the connections between them constitute another key mechanism underlying resistance to b/tsDMARD therapy. The inflammatory milieu in rheumatic diseases is composed of a vast network of overlapping and, often, compensatory signaling cascades. Consequently, targeting single cytokine, such as TNF, may be inadequate for achieving disease control in patients with complex immune activation, as TNF represents only one downstream cytokine within a broader inflammatory framework.[13] Notably, alternative mediators such as IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been identified as compensatory pathways contributing to therapeutic failure in TNF inhibitor non-responders.[14]

At the cellular level, immune dysregulation, affecting effector T cell subsets, regulatory T cells (Tregs), and myeloid compartments, can limit b/tsDMARD efficacy. Resistance is linked to persistent Th17 polarization and impaired Treg function despite targeted cytokine blockade.[15] Pharmacogenomic and transcriptomic data reveal molecular heterogeneity, with interferon-regulated gene signatures predicting poor TNF inhibitor response and supporting alternative targets.[16] Additionally, polymorphisms in cytokine genes, receptor loci, and Fcγ receptors (eg, FCGR3A) may influence efficacy and immunogenicity, informing precision medicine approaches.[17]

Finally, non-immunological factors may also play an important role in resistance. Factors such as poor medication adherence, obesity, and altered pharmacokinetics can substantially modulate treatment outcomes. Notably, increased body mass index has been associated with lower serum drug levels and reduced therapeutic response, particularly with fixed-dose biologic regimens.[18]

Unmet Needs and Rationale for Combining Biologics

Mechanistic and clinical evidence support DBT by showing the redundancy and interplay of cytokine networks in rheumatic diseases. Preclinical studies indicate that dual blockade of distinct pathways may yield additive or synergistic immunomodulatory effects, potentially overcoming monotherapy limitations. In a Lewis rat adjuvant arthritis model, Feige et al showed that combining an interleukin-1 receptor antagonist (IL-1Ra) with polyethylene glycol–conjugated soluble TNF receptor type I (PEG sTNF-RI) produced significantly greater reductions in inflammation, weight loss, bone erosion, and histopathologic damage than either monotherapy.[19] Isobologram analysis confirmed true pharmacological

synergy, suggesting that lower doses of each agent could be used without loss of efficacy. Dillon et al evaluated acazicolcept (ALPN-101), a dual CD28/ Inducible T Cell Costimulator (ICOS) antagonist, in a collagen-induced arthritis model.[20] Unlike constitutively expressed CD28, ICOS is rapidly upregulated after T cell activation and drives Th1, Th2, and Th17 responses. By blocking two non-redundant costimulatory pathways, acazicolcept achieved greater suppression of joint inflammation, cytokine production, and disease severity than abatacept or ICOS monotherapy. Another experimental study investigated the combination of etanercept with a Transient Receptor Potential Vanilloid 2 (TRPV2) agonist in preclinical mice model of collagen-induced arthritis.[21] TRPV2 is a non-selective cation channel expressed by fibroblast-like synoviocytes that suppresses their invasive properties by preventing Rac1 and RhoA activation. The dual treatment achieved sustained suppression of disease severity and more pronounced reduction in joint damage compared to either monotherapy. Moreover, the DBT group showed the most significant protection in histologic scores for synovial inflammation, hyperplasia, cartilage erosions, and bone erosions. Together, these preclinical studies provide a strong mechanistic rationale for combining biologic agents with complementary or synergistic immunologic targets in the treatment of immune-mediated inflammatory diseases.

Clinical experience shows that disease domains in PsA and axSpA often respond variably to different biologics, highlighting monotherapy limitations and supporting for DBT strategy. IL-17A inhibitors are effective for joint and skin disease but may exacerbate IBD, whereas vedolizumab, a gut-selective α4β7 integrin antagonist, controls IBD without systemic immunosuppression.[22] Case reports and series describe vedolizumab combined with TNF inhibitors or IL-17 blockers in patients with coexisting SpA and IBD, achieving control of both articular and gastrointestinal inflammation without increased infection risk.[22–25] Vedolizumab is the most frequently used gut-selective agent in DBT for IBD, often paired with other bDMARDs in refractory disease, with real-world data suggesting preserved or enhanced efficacy.[22–24,26] Other selective agents, such as ustekinumab (IL-12/23 inhibitor), have also been safely combined with TNF inhibitors or vedolizumab in complex cases.[25,26] Similarly, apremilast, a PDE4 inhibitor with minimal immunosuppressive effects, has emerged as an attractive candidate for DBT. Furthermore, IL-17 inhibitors themselves, despite their known pro-inflammatory risk in gut mucosa, have been used in DBT regimens with other biologics or targeted synthetic DMARDs (tsDMARDs), particularly in patients with severe, multi-domain PsA or PsA coexisting with atopic dermatitis or asthma.

In summary, these findings indicate that the thoughtful selection of biologics with complementary efficacy and safety profiles, particularly those with minimal systemic immunosuppression, may allow for personalized and effective DBT approaches in complex and difficult to treat immune-mediated diseases.

Rheumatoid Arthritis

Up to 30–40% of RA patients respond inadequately to sequential biologic monotherapy, and 15–20% remain persistently refractory.[5] This unmet need has driven investigation of biologic combinations as a potential strategy to enhance efficacy (Table 1).

Early DBT trials in RA raised safety concerns. In 2004, Genovese et al combined etanercept with anakinra in methotrexate-refractory RA, finding modest efficacy gains but higher serious infection rates (3.7% with half-dose and 7.4% with full-dose DBT vs 0% with etanercept alone).[27] In 2006, Weinblatt et al tested abatacept plus etanercept. Although ACR50/70 rates were numerically higher, differences were not significant, and serious infections (3.5% vs 0%) and serious adverse events (16.5% vs 2.8%) were more frequent with DBT.[28]

Despite these early concerns, interest in DBT continued. In a pivotal study, Cohen et al demonstrated the efficacy of rituximab (a B-cell depleting agent) in RA patients who had failed anti-TNF therapy.[41] This study was followed by studies assessing the safety of rituximab in combination with other biologics. Greenwald et al reported on a cohort receiving rituximab in DBT regimen with TNF inhibitors.[30] While no unexpected safety signals were observed within 24 hours of infusion, the DBT group experienced markedly higher rate of serious infections (8.5%) compared to TNF inhibitor–only group (1.5%), including one fatal case. The study was not powered to detect efficacy differences, and no significant improvement in ACR20/50/70 response rates was observed in the DBT group compared to TNF inhibitor monotherapy, further questioning the benefit of this strategy. Rigby et al extended these findings in an open-label study showing that rituximab (2 × 500mg) could be co-administered with a variety of other biologics across 18 different DBT regimens in a real-world cohort.[33] Although the overall incidence of serious infections remained low at 2.7 events per

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Table 1 Summary of Dual Biologic Therapy in Treatment-Refractory Rheumatoid Arthritis

Study	Study Design	Failed Biologics	Combination Therapy	Control Group	Duration	Efficacy	Safety and Side-Effects
Genovese et al (2004)[27]	Randomized, double-blind, placebo-controlled trial	None (biologic-naïve patients)	Etanercept 25mg BIW + Anakinra 100mg QD (n=81) or Etanercept 25mg QW + Anakinra 100mg QD (n=81)	Etanercept 25mg BIW alone (n=80)	24 weeks	No added benefit from combination therapy. ACR50 response: etanercept alone 41% vs full-dose combination 31% vs half-dose combination 32% (p=0.914)	Increased serious infections (0% etanercept alone vs 3.7–7.4% combination), higher injection-site reactions (40% vs 67–70%), neutropenia, and withdrawal rates. One death from pneumonia in combination group.
Weinblatt et al (2006)[28]	Randomized, double-blind, placebo-controlled trial	Mixed population - some had inadequate response to various DMARDs including biologics (adalimumab, etanercept, infliximab, anakinra)	Abatacept 10mg/kg + background bDMARD (n=103) Abatacept 10mg/kg + background nonbiologic DMARDs (n=856)	Placebo + background bDMARD (n=64) Placebo + background nonbiologic DMARDs (n=418)	12 months	Significant improvements in patient/physician global assessments and physical function with abatacept vs placebo, particularly in nonbiologic background subgroup	Overall similar AE rates (90% vs 87%), but increased SAEs with biologic combinations (22.3% vs 12.5%). Serious infections higher with abatacept (2.9% vs 1.9%). 5 deaths in abatacept group vs 4 in placebo group
Weinblatt et al (2007)[29]	Randomized, double-blind, placebo-controlled trial with open-label extension	Inadequate response to etanercept	Abatacept 2 mg/kg + Etanercept 25 mg BIW (n=85), later Abatacept 10 mg/kg in LTE	Placebo + Etanercept 25 mg BIW (n=36)	12 months double-blind + 24 months of LTE	No significant difference in ACR20 at 6 months (48.2% vs 30.6%, p=0.072); Only ACR70 significantly different at 6 months (10.6% vs 0%, p=0.042)	Increased SAEs (16.5% vs 2.8%), serious infections (3.5% vs 0%), higher discontinuation rates (11.8% vs 2.8%). One death from lymphoma during extension phase
Greenwald et al (2011)[30]	Randomized, double-blind, placebo-controlled trial	Etanercept or adalimumab	RTX 2×500mg + MTX + TNF inhibitor (etanercept or adalimumab) (n=33)	Placebo + MTX + TNF inhibitor (etanercept or adalimumab) (n=18)	24 weeks	Modest improvements favoring RTX. ACR20: 30% vs 17%; ACR50: 12% vs 6%. No clear evidence of efficacy advantage. Study not powered for efficacy testing	One serious infection (pneumonia, 3%) in RTX group vs none in placebo group. SAEs: 6% vs 0%. Higher infusion reactions (33% vs 11%). One coronary artery occlusion in rituximab group.
Genovese et al (2018)[31]	Phase II randomized, double-blind, active-controlled trial	Inadequate response to MTX; biologic-naive	ABT-122 (dual anti-TNF and anti-IL-17) at 60, 120, or 240 mg weekly (n=166)	Adalimumab 40 mg weekly (n=56)	12 weeks	Comparable ACR20/50/70 responses to adalimumab. No added benefit in combination. No dose-response trend. Clinical efficacy did not surpass that of adalimumab.	Adverse events were similar across all groups. Most common AEs: infections and injection site reactions. No increase in serious adverse events.
Glatt et al (2019)[32]	Phase 2a, double-blind, placebo-controlled, proof-of-concept study	CZP	CZP + Bimekizumab (anti-IL-17A and IL-17F) (n=52)	CZP + Placebo (n=27)	12 weeks (combination), follow-up to 44 weeks	Greater DAS28 reduction vs placebo. Estimated mean treatment difference −0.58 (95% CrI 0.13, 1.05). Overall, favoring combination	Higher TEAEs with DBT (78.8% vs 59.3%), mainly infections (50% vs 22.2%); one serious infection;

Rigby et al (2013)[33]	Open-label multicenter safety study	≥1 prior biologic DMARD for ≥12 weeks (mean: 4 total DMARDs)	RTX 2×500 mg + various biologics (n=176); most common: adalimumab (n=46) and etanercept (n=37)	None	48 weeks	Modest clinical improvement observed; ACR20/50/70 responses at 48 weeks: 48.9%, 22.7%, 9.1%. HAQ-DI improved by mean of 0.32.	SAEs: 9.1% (24.3 events/100 patient-years) at 24 weeks, similar at 48 weeks (22.4 events/100 patient-years). Serious infections: 2.3% overall (2.7 events/100 patient-years). 3 deaths during study period. Generally consistent with known RTX safety profile
Zuo et at. (2022)[34]	Prospective clinical study	Inadequate response to ≥2 csDMARDs for ≥6 months, or csDMARDs + TNFi	Iguratimod + Tofacitinib (n=30)	None	12 weeks	Significant improvement in ESR, CRP, RF, SJC, TJC, DAS28, HAQ, CDAI, and morning stiffness (all $p < 0.05$)	Well tolerated. No serious adverse events; no leukopenia, liver enzyme elevation, allergy, or thromboembolism reported
Zhang et al (2024)[35]	Prospective clinical trial with three groups	Active RA (DAS28-ESR >3.2) but not necessarily biologic failures	Low-dose IL-2 + Tocilizumab (n=9)	Control group (n=15) and IL-2 group alone (n=26)	1 week	All three groups showed significant improvement in disease activity indicators (DAS28, ESR, TJC, SJC). IL-2+TCZ group showed the lowest CRP levels post-treatment. Negative correlation between Treg count and disease activity measures.	No significant adverse events; ALT/BUN slightly increased but clinically insignificant
Chang et al (2024)[36]	Retrospective cohort study with control group	≥1 bDMARD with persistent moderate-to-high disease activity	Tofacitinib + bDMARD (etanercept, adalimumab, infliximab, or tocilizumab) (n=28)	Switched to another bDMARD or tsDMARD (n=34)	24 weeks	Combination group showed superior outcomes: DAS28-ESR decreased from 5.26 ±0.90 to 2.67±0.86 vs control group 5.20±0.77 to 3.25±1.29 (p=0.041). Remission achieved in 67.9% vs 38.2%.	4 cases of HZ in combination group (14.3%, all aged >60 years), 6 cases of upper respiratory tract infections in combination group vs 4 in control group. No serious adverse reactions or treatment discontinuations due to adverse events
Koumakis et al (2009)[37]	Case series (n=2)	Multiple failures: TNF inhibitors and rituximab monotherapy	RTX + Etanercept (n=2)	None	Follow-up: 4 years (Pt 1), 18 months (Pt 2)	Both patients achieved sustained remission. Patient 1: CRP decreased from 212–292 mg/L to 12 mg/L. Patient 2: DAS28 improved from 5.52 to 2.21, CRP decreased from 125 to <5 mg/L	No adverse events reported during the combination treatment period in either patient.
Blank et al (2009)[38]	Case series (n=18)	Multiple biologic and csDMARD failures; high disease activity.	RTX + Etanercept (n=6)	RTX monotherapy (n=12)	18.5 months (overall 111 patient-months)	Significant improvements in both groups. RTX +ETN: DAS28 decreased from 6.5±0.7 to 4.3 ±1.0 (p=0.002); CRP decreased from 55.0 ±26.3 to 9.6±7.1 mg/L (p=0.003)	DBT was well tolerated. No serious infections in DBT group. One mild herpes simplex flare and one case of frequent mild respiratory infections.
Ghazanfar et al (2018)[39]	Case report	Methotrexate inadequate response	Omalizumab 300 mg Q4W + Etanercept 50 mg Q2W	None	Several months (exact duration not specified)	Effective in controlling both urticaria and RA symptoms. RA remained stable	No adverse events were reported.
Yamada et al (2019)[40]	Case report	Methotrexate; inadequate asthma and RA control with monotherapy	Benralizumab (anti-IL -5Rα) + Golimumab	None	4 months	Effective control of both eosinophilic asthma and refractory RA. Steroids successfully discontinued.	No significant adverse effects reported during 4 months of follow-up

Abbreviations: BIW, twice weekly; QD, once daily; QW, once weekly; ACR50, American College of Rheumatology 50% improvement criteria; AE, adverse event; DMARDs, disease-modifying antirheumatic drugs; bDMARD, biologic disease-modifying antirheumatic drug; SAEs, serious adverse events; LTE, long-term extension; ACR20, American College of Rheumatology 20% improvement criteria; ACR70, American College of Rheumatology 70% improvement criteria; TNF, tumor necrosis factor; RTX, rituximab; Pt, patient; CRP, C-reactive protein; DAS28, Disease Activity Score 28; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DBT, dual biologic therapy; ETN, etanercept; MTX, methotrexate; HAQ-DI, Health Assessment Questionnaire Disability Index; Q4W, every 4 weeks; Q2W, every 2 weeks; RA, rheumatoid arthritis; anti-IL-17, anti-interleukin-17; anti-TNF, anti-tumor necrosis factor; anti-IL-5Rα, anti-interleukin-5 receptor alpha; CZP, certolizumab pegol; anti-IL-17A, anti-interleukin-17A; IL-17F, interleukin-17F; TEAEs, treatment-emergent adverse events; TNFi, tumor necrosis factor inhibitor; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; HAQ, Health Assessment Questionnaire; CDAI, Clinical Disease Activity Index; DAS28-ESR, Disease Activity Score 28 with erythrocyte sedimentation rate; IL-2, interleukin-2; TCZ, tocilizumab; ALT, alanine aminotransferase; BUN, blood urea nitrogen; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; HZ, herpes zoster.

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100 patient-years over 48 weeks of follow-up, only modest improvements in disease activity were reported, with ACR20 responses increasing from 30.7% at 24 weeks to 48.9% at 48 weeks. The absence of a control arm and the heterogeneous treatment regimens, ranging from rituximab plus adalimumab monotherapy to complex multi-DMARD combinations, limited the ability to draw any firm conclusions regarding added efficacy beyond that achievable with single biologic therapy.

In 2018, Genovese et al introduced novel approach to dual biologic therapy with ABT-122 molecule, a bispecific dual variable domain immunoglobulin targeting both TNF and IL-17A.[31] The rationale for this dual targeting was based on preclinical evidence showing synergistic effects of TNF and IL-17A in osteoclastogenesis and bone destruction, and clinical observations that patients failing TNF inhibition often have elevated circulating Th17 cells and increased IL-17 levels. In this Phase II, randomized, double-blind study, 222 biologic-naive patients with active RA and inadequate response to methotrexate were assigned to ABT-122 at three dosing regimens (60 mg every other week, 120 mg every other week, or 120 mg every week) or adalimumab 40 mg every other week for 12 weeks. Despite the theoretical advantages of dual cytokine inhibition, ABT-122 demonstrated no meaningful clinical superiority over TNF inhibition monotherapy, with ACR20 response rates at week 12 of 62%, 75%, and 80% respectively across the ABT-122 dose groups versus 68% with adalimumab. The safety profile was comparable across all treatment groups, with treatment-emergent adverse events occurring in 37–42% of ABT-122 patients versus 43% with adalimumab, and no serious infections reported with ABT-122. Importantly, mechanistic analyses suggested that the anti-TNF component was the primary driver of ABT-122's efficacy, supporting emerging evidence that IL-17A may not be a major contributor to RA pathophysiology, ultimately leading to discontinuation of ABT-122 development for RA treatment.

In 2018, a case report documented the successful combined use of omalizumab (anti-IgE monoclonal antibody) and etanercept in a patient with coexisting chronic spontaneous urticaria and RA.[40] The patient, previously unresponsive to conventional therapy, achieved clinical remission of both conditions without significant adverse events. Although it is based on single case report, the observed improvement suggests that a DBT strategy may have therapeutic potential in selected patients with treatment-resistant disease.

In 2024, Chang et al published a retrospective study evaluating the DBT of tofacitinib (5 mg twice daily) with various bDMARDs in 28 RA patients with inadequate response to biologic monotherapy.[36] The most commonly used biologics in DBT were adalimumab (11 patients) and etanercept (8 patients), followed by tocilizumab (6 patients) and infliximab (3 patients). At 24 weeks, 67.9% of patients achieved DAS28-ESR remission compared to 38.2% in the control group of 34 patients who utilized the sequential approach with switching to another single b/tsDMARD. The DBT group demonstrated significantly superior ACR20/50/70 response rates (85.71%, 75%, and 39.29% vs 75.0%, 53.57%, and 21.43%, respectively). Notably, four patients (14.3%) in the DBT group developed herpes zoster, three with adalimumab plus tofacitinib and one with tocilizumab plus tofacitinib, all occurring in patients over 60 years of age. All patients recovered with antiviral treatment without requiring treatment discontinuation. Despite the retrospective design and limited sample size, these results provide preliminary evidence supporting the potential efficacy of combining JAK inhibitors with bDMARDs in selected difficult-to-treat RA cases, though monitoring for infectious complications, particularly in elderly patients, is needed.

In conclusion, evidence for DBT in RA is inconsistent. Benefits in refractory cases are modest, while serious infection risk, particularly with full-dose combinations, is consistently higher. Its Therefore, DBT should be considered cautiously and reserved for selected patients.

Psoriatic Arthritis (PsA)

PsA is a heterogeneous inflammatory disease involving multiple domains including peripheral arthritis, axial disease, enthesitis, dactylitis, skin/nail psoriasis, and extra-articular features such as uveitis and IBD. Management is often difficult due to the diverse presentations and variable domain responses.[6] Although b/tsDMARDs have improved outcomes, many patients remain uncontrolled despite monotherapy or sequential switching, especially those with concurrent multi-domain activity. This has driven interest in DBT to simultaneously target multiple pathogenic pathways in refractory PsA (see Table 2). Consequently, there is a growing interest in the use of DBT to target multiple pathogenic pathways simultaneously in refractory cases of PsA (see Table 2).

Table 2 Summary of Dual Biologic Therapy in Treatment-Refractory Psoriatic Arthritis

Study	Study Design	Failed Biologics	Combination Therapy	Duration	Efficacy	Safety and Side-Effects
Mease et al (2018)[42]	Randomized Controlled Trial	Inadequate response to methotrexate, prior TNF inhibitor exposure allowed if washed out	ABT-122 120mg weekly (n=71) or 240mg weekly (n=73) Vs Placebo (n=24) or adalimumab 40mg every other week (n=72) as active comparator	12 weeks	ABT-122 superior to placebo for ACR20 (64.8–75.3% vs 25.0%); similar to adalimumab for primary endpoint; ABT-122 240mg superior to adalimumab for PASI75, ACR50, ACR70	Similar frequency of AEs across groups; no serious infections; 2 serious AEs (1 placebo, 1 ABT-122); neutrophil count decreased ~20% in ABT-122 groups; oral candidiasis in 2 ABT-122 patients
Metyas et al (2019)[43]	Retrospective open-label study	Not specified individually; all patients had inadequate response to prior biologics	Apremilast + ongoing biologic agent (n=22), no control group	Not explicitly stated; presumed short-term safety focus	Not reported (study focused on safety)	Mild adverse effects in 6/22 patients (nausea, diarrhea, weight loss, abdominal pain); no discontinuations
Takamura et al (2020)[44]	Retrospective Cohort (n=14)	Infliximab, Adalimumab, Secukinumab, Ixekizumab, Ustekinumab	Apremilast + various biologics	24 weeks	PASI score reduction in majority	Mild diarrhea, nausea, no discontinuations
Gniadecki et al (2016)[45]	Case Series	Multiple TNFi's per patients	Pt 1: Ustekinumab + Etanercept	62 months	Substantial improvement in skin and joint symptoms	Herpes zoster
			Pt 2: Ustekinumab + etanercept	50 months	Substantial improvement in skin and joint symptoms	Retrotonsillar abscess
			Pt 3: Ustekinumab + adalimumab, then ustekinumab + golimumab	32 months	Substantial improvement in skin and joint symptoms	Erysipelas and bacterial pneumonia
			Pt 4: Ustekinumab + adalimumab, then ustekinumab + certolizumab	54 months	Substantial improvement in skin and joint symptoms	No opportunistic infections reported
De Marco et al (2018)[46]	Case Series	Multiple prior biologics per patient - adalimumab, infliximab, etanercept, golimumab, ustekinumab, certolizumab pegol (extensive prior bDMARD exposure)	Ustekinumab + Etanercept	15 months	Partial improvement in joint, good skin control	Severe skin infection
			Ustekinumab + Certolizumab pegol	6 months	Partial improvement in joint, good skin control	Two chest infections; Discontinued
			Adalimumab + Ustekinumab	3 months	Mild improvement in joints and skin	Recurrent chest infections and respiratory failure
			Ustekinumab + Etanercept	24 months	Partial response	Chest sarcoidosis (mediastinal and hilar lymphadenopathy)
			Ustekinumab + Etanercept, then Ustekinumab + Adalimumab, then Ustekinumab + Certolizumab pegol	15 months	Partial skin response, joint non-response	Uveitis flare (with etanercept).

(*Continued*)

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Table 2 (Continued).

Study	Study Design	Failed Biologics	Combination Therapy	Duration	Efficacy	Safety and Side-Effects
Hren et al (2024)[47]	Case series (n=12)	Various prior therapies including infliximab (6 patients), methotrexate (3), apremilast (3), adalimumab, secukinumab, ixekizumab, brodalumab, certolizumab, deucravacitinib, cyclosporine, acitretin, ustekinumab	Dupilumab + IL-23i (Guselkumab, Risankizumab, Tildrakizumab) or IL-12/23i (Ustekinumab), Tralokinumab	Average 560 days	75% (9/12) showed clinical improvement; 1 no response, 1 worsening arthritis, 1 secondary loss of response	Mild: eye irritation, conjunctivitis (17%)
Guénin et al (2024)[48]	Case Series (n=20)	Extensive prior failures including methotrexate, infliximab, etanercept, adalimumab, secukinumab, ixekizumab, brodalumab, ustekinumab, guselkumab, risankizumab, tildrakizumab, apremilast, upadacitinib, tofacitinib, acitretin, certolizumab pegol, alefacept, prednisone	Deucravacitinib (TYK2 inhibitor) + IL-17 or IL-23 monoclonal antibodies	3 months	Additive benefit observed in most patients with skin disease; 5/12 PsA patients improved PSAID score	Mild GI symptoms in 2 patients, acne in 1, one dropout due to access; no serious AEs or lab abnormalities
Hren et al (2024)[49]	Case series (n=6)	Multiple bDMARDs per patient including Adalimumab, Secukinumab, Guselkumab, Ixekizumab, Brodalumab, Risankizumab.	Biologic (IL-17 or IL-23 inhibitor) + oral JAK (upadacitinib) or TYK2 (deucravacitinib) inhibitor	44-930 days	All 6 patients showed clinical improvement; 5 achieved remission or MDA; 2 had subsequent axial and peripheral joint involvement lost efficacy after initial responses	1 bronchitis case; otherwise well tolerated
Cuchacovich et al (2012)[50]	Case Report	Etanercept, Infliximab, Adalimumab, Abatacept	Ustekinumab + Etanercept	11 months	Sustained improvement in both skin, nail and joint symptoms	No serious infections
Babalola et al (2014)[51]	Case Report	Infliximab, Adalimumab	Ustekinumab + Etanercept	5 months	Full remission of both psoriasis and arthritis	Developed unstable angina; unclear link to therapy
Thibodeaux et al (2019)[52]	Case report	Adalimumab, Infliximab, Etanercept, Golimumab, Ustekinumab, Guselkumab	Sequential dual biologic combinations: Ustekinumab + etanercept, Secukinumab + etanercept, Guselkumab + etanercept	33 months	Adequate control of skin and joints maintained; differential responses noted (etanercept effective for joints, IL-12/23 or IL-17 inhibitors effective for skin).	Increased urinary tract and upper respiratory infections with ustekinumab + etanercept combination, including H1N1 flu hospitalization;
Balestri et al (2020)[53]	Case Report	Adalimumab	Secukinumab + Dupilumab	15 months	Complete control of joint and skin disease	No side effects
Hanna et al (2021)[54]	Case Report	Ustekinumab, secukinumab, golimumab (as monotherapies)	Golimumab + Risankizumab	12 months	Marked improvement in skin and joints (PASI 0, DLQI improved, no synovitis)	No adverse effects reported
Haberman et al (2021)[55]	Case Report	None (biologic-naive)	Ustekinumab + Adalimumab	~20 months	Complete remission of joint and skin symptoms	No adverse effects reported, including during COVID-19-like illness
Kashlan et al (2021)[56]	Case Report	Etanercept, Adalimumab, Secukinumab	Tofacitinib + Brodalumab, then Tofacitinib + Guselkumab	Short-term (days to weeks)	Cutaneous improvement but severe paradoxical arthritis flares	Paradoxical PsA flare with both brodalumab and guselkumab; hospitalization due to joint effusion
Zimmer et al (2022)[57]	Case Report	Infliximab, Efalizumab, Adalimumab, Ustekinumab, Ixekizumab	Apremilast + Etanercept. Later switched to Guselkumab monotherapy	28 months (DBT) + Guselkumab follow-up	Initial significant improvement in PASI and DLQI, later relapse managed with Guselkumab	No adverse effects reported; improvement in renal and liver function

Abbreviations: ACR20, American College of Rheumatology 20% improvement; ACR50, American College of Rheumatology 50% improvement; ACR70, American College of Rheumatology 70% improvement; AE, Adverse Event; bDMARD, biologic Disease-Modifying Antirheumatic Drug; BSA, Body Surface Area; COVID-19, Coronavirus Disease 2019; DBT, Dual Biologic Therapy; DLQI, Dermatology Life Quality Index; GI, Gastrointestinal; H1N1, Influenza A virus subtype H1N1; IL-12/23i, Interleukin-12/23 inhibitor; IL-17, Interleukin-17; IL-23i, Interleukin-23 inhibitor; JAK, Janus Kinase; MDA, Minimal Disease Activity; PASI, Psoriasis Area and Severity Index; PASI75, 75% reduction in Psoriasis Area and Severity Index; PSAID, Psoriatic Arthritis Impact of Disease; PsA, Psoriatic Arthritis; TNFi, Tumor Necrosis Factor inhibitor; TYK2, Tyrosine Kinase 2; VAS, Visual Analogue Scale.

Apremilast Regimens – Apremilast, an oral phosphodiesterase-4 (PDE4) inhibitor, has been suggested as a potential candidate in DBT approach. Owing to its minimal immunosuppressive effect, apremilast presents a compelling option for combination with other biologics, potentially enhancing efficacy without substantially increasing infection risk. A retrospective open-label study by Metyas et al evaluated 22 patients with plaque psoriasis and PsA who had inadequate response to ongoing biologic therapy and were subsequently given apremilast as an add-on treatment.[43] The study reported that while 6 patients experienced mild adverse effects (nausea, diarrhea, weight loss, abdominal pain), none required treatment discontinuation. Importantly, no serious infections or significant safety concerns were observed, suggesting a favorable safety profile for the combination. In a second retrospective cohort study by Takamura et al, 14 patients with psoriasis (including three with PsA) who had experienced secondary loss of efficacy to their current biologic therapy were treated with apremilast in addition to their existing biologic agent (including TNF-α, IL-17, and IL-23 inhibitors).[44] All patients had tried an average of 2.9 systemic medications before dual therapy. The study demonstrated a significant reduction in PASI score from 3.2±0.4 at baseline to 1.6±0.3 after 24 weeks of DBT. PASI-75 and PASI-50 response rates were achieved in 29% and 50% of patients, respectively. Side effects were generally mild, including diarrhea (4 patients), nausea (1 patient), and weight loss exceeding 5% of body weight (2 patients), with no treatment discontinuations due to adverse events. Notably, response rates were superior when apremilast was combined with TNF-α or IL-23 inhibitors compared to IL-17 inhibitors, suggesting differential efficacy based on the underlying biologic mechanism of action. Additionally, a case report by Zimmer et al described a 62-year-old man with PsA, diabetic nephropathy, and liver cirrhosis who had previously failed multiple biologics.[57] Despite experiencing a relapse of joint symptoms while on etanercept monotherapy, the addition of apremilast led to significant improvement and long-term disease control. Over 28 months of DBT, the patient achieved stable remission of both cutaneous and articular symptoms, with no serious infections or adverse events reported. Notably, liver enzyme levels and renal function also improved during the course of treatment.

Overall, apremilast appears to be well-tolerated and potentially beneficial add-on therapy to DBT for PsA. However, evidence is still limited by small sample sizes, short follow-up, highlighting the need for prospective trials.

IL-12/23 Inhibitor Regimens — Ustekinumab has been used in DBT for PsA with multi-domain involvement or inadequate monotherapy response, often combined with TNF inhibitors. Case reports by Cuchacovich et al and Babalola et al describe complete remission with ustekinumab–etanercept combinations and no adverse events during follow-up.[50,51,] However, safety issues have emerged across multiple reports. Gniadecki et al reported three PsA patients achieving marked PASI and pain VAS improvements but developing herpes zoster, bacterial pneumonia or retrotonsillar abscess.[45] De Marco et al found similar efficacy in six patients, but recurrent infections, including erysipelas and pneumonia, necessitated treatment discontinuation in some.[46] Overall, while TNFi–ustekinumab DBT may benefit select refractory PsA patients, evidence is limited to uncontrolled case series, and infection risk, bacterial and viral, appears consistent. Thus, such regimens should be reserved for cases where anticipated benefit clearly outweighs safety concerns.

IL-17 and IL-23 Inhibitor Regimens – Combining IL-17 or IL-23 inhibitors with other bDMARDs in PsA has been explored for complex or refractory cases, though evidence remains limited. In a Phase II trial of 240 PsA patients with inadequate methotrexate response, ABT-122 (dual TNF-α/IL-17A blockade) achieved ACR20 rates of 64.8–75.3% and PASI75 up to 77.6%, with no serious infections and similar adverse events across arms. However, no efficacy advantage over adalimumab was observed.[42] Case reports and small series describe TNF inhibitor combinations (eg, ustekinumab + etanercept, secukinumab + etanercept, guselkumab + etanercept), showing periods of disease control but occasional infections, particularly with ustekinumab + TNFi.[52] Other reports, such as risankizumab + golimumab for 12 months, noted marked improvement without adverse effects.[54,] A retrospective series of 12 patients on dupilumab plus IL-17/IL-23 inhibitors, including four PsA cases, found 75% clinical improvement, no severe infections, but conjunctivitis in 17%.[47] Overall, IL-17/IL-23–based DBT may benefit select refractory PsA patients, especially with non-overlapping mechanisms. While no consistent pattern of serious infections, data is limited and further research is needed.

JAK inhibitor regimens – Studies combining JAK inhibitors with other biologics in PsA remain limited. Kashlan et al described a patient with long-standing PsA and psoriasis who was maintained on tofacitinib but experienced significant cutaneous disease.[56] Brodalumab (IL-17 receptor A inhibitor) was added, leading to rapid skin improvement, but paradoxical PsA flare within a week occurred, prompting discontinuation. Subsequently, guselkumab was initiated

with another PsA flare requiring hospitalization and steroid therapy. Thus, despite efficacy in skin disease, dual therapy involving JAK inhibitor and IL-17/23 blocker may precipitate paradoxical joint inflammation or unmask subclinical arthritis. The timing of flares after initiating the combination, while previously stable on tofacitinib, supports drug-induced phenomenon, rather than simple disease progression.

Hren et al reported a case series of six patients with treatment-refractory PsA and psoriasis who were managed with a DBT regimen of IL-17 or IL-23 inhibitor combined with oral JAK1 or TYK2 inhibitor.[49] All patients had failed multiple prior therapies, and DBT resulted in significant improvement in both joint and skin symptoms, with several achieving minimal disease activity. However, treatment responses were variable, efficacy declined in two cases after several months, and one patient developed bronchitis during therapy. Although no serious infections or hospitalizations were observed, the limited sample size, retrospective nature, and short follow-up duration constrain the ability to draw definitive conclusions regarding safety.

In PsA, DBT may benefit treatment-refractory patients, especially with multi-domain involvement. Combinations such as apremilast with TNF or IL-23 inhibitors, ustekinumab with TNF inhibitors, and IL-17/IL-23 inhibitors with JAK inhibitors have improved both articular and cutaneous outcomes. However, infection risk, particularly with ustekinumab or JAK inhibitors, warrant cautious use, weighing potential benefit against harm (Table 3).

Axial Spondyloarthropathies (axSpA)

Despite improved outcomes with b/tsDMARDs, many axSpA patients still experience inadequate control with sequential switching strategy offering limited efficacy.[58] These limitations have prompted growing interest in DBT (Table 4).

Table 3 Infection Risk Comparison Between DBT and Biologic Monotherapy

Disease	DBT Regimen	Infection Risk with DBT	Infection Risk with Monotherapy
RA			
	Etanercept + Anakinra (Genovese et al, 2004)[27]	Serious infections: 3.7% (half-dose) and 7.4% (full-dose)	0% with etanercept alone
	Abatacept + Etanercept (Weinblatt et al, 2006)[28]	Serious infections: 3.5%; serious adverse events 16.5%	0% serious infections; SAEs 2.8%
	Rituximab + TNF inhibitors (Greenwald et al, 2011)[30]	Serious infections: 8.5%, including one fatal case	1.5% with TNF inhibitor alone
	Rituximab + other biologics (Rigby et al, 2013)[33]	Serious infections: 2.7 events / 100 pt-years	No comparator; generally lower rates reported in single biologic cohorts
	ABT-122 (dual TNF + IL-17A inhibition) (Genovese et al, 2018)[31]	No serious infections; AE rate 37–42%	No serious infections; AE rate 43% with adalimumab
	Tofacitinib + bDMARDs (Chang et al, 2024)[36]	Herpes zoster: 14.3% (all ≥60 years); no discontinuations	Herpes zoster: 0%; total infection rate not reported
	Omalizumab + Etanercept (case report, 2018)[39]	No infections reported	Not applicable (single case)
PsA			
	Apremilast + various biologics (Metyas et al, 2019; Takamura et al, 2020)[43,44]	No serious infections; mild GI effects only	Monotherapy: infection risk minimal, similar background rates
	Ustekinumab + TNF inhibitors (Cuchacovich et al, Babalola et al, De Marco et al, 2012–2018)[46,50,51]	Herpes zoster, pneumonia, erysipelas, retrotonsillar abscess; some discontinuations	Lower infection frequency; serious infections uncommon
	IL-17/IL-23 inhibitor combinations[58]	Occasional infections (mostly mild); conjunctivitis in 17% with dupilumab + IL-17/23 DBT	Comparable or lower mild infection rates
	JAK inhibitors + biologics (Hren et al, 2024; Kashlan et al, 2021)[47,56]	Mild infections (bronchitis); paradoxical PsA flare; no hospitalizations	Infection rates lower; paradoxical inflammation rare

(*Continued*)

Table 3 (Continued).

Disease	DBT Regimen	Infection Risk with DBT	Infection Risk with Monotherapy
axSpA			
	Infliximab + Etanercept (Sheehy et al, 2006)[59]	No infections over 6 months; prophylactic cotrimoxazole used	No events reported in comparator biologic monotherapy
	Vedolizumab + Etanercept or Golimumab (Roblin et al, 2020; case reports)[60]	No infections reported over 10–12 months	Not applicable (single cases)
	Dual TNF + IL-17/IL-23 regimens (Valero et al, 2022)[61]	One serious infection (S. aureus bacteremia) in high-risk patient; others tolerated well	Historical TNF or IL-17 monotherapy cohorts: serious infections ~2–5%

Abbreviations: DBT, Dual biologic therapy; RA, Rheumatoid Arthritis; SAEs, Serious Adverse Events; TNF, Tumor Necrosis Factor; IL, Interleukin; AE, Adverse Event; bDMARD, Biologic Disease-Modifying Antirheumatic Drug; PsA, Psoriatic Arthritis; GI, Gastrointestinal; JAK, Janus Kinase; axSpA, Axial Spondyloarthritis.

Table 4 Summary of Dual Biologic Therapy in Treatment-Refractory Axial Spondyloarthropathy

Study	Study Design	Failed Biologics	Combination Therapy	Duration	Efficacy	Safety and Side-effects
axSpA						
Valero et al, (2022)[61]	Case series	Multiple previous biologics per patient: IFX, ADA, ETN, CTZ, GOL, SEC, TCZ, IXE, UTK, VED, RIS, APR, TOFA (mean 4.7±1.3 biologics per patient)	Case 1 - Secukinumab + Golimumab	54 months	Major improvement	No serious infections
			Case 2 - Secukinumab + Etanercept	8 months	Major improvement	No serious infections
			Case 3 - Etanercept + Secukinumab	25 months	Remission	No serious infections
			Case 4 - Ixekizumab + Adalimumab	6 months	Remission	No serious infections
			Case 5 - Secukinumab + Adalimumab	3 months	No improvement	No serious infections
			Case 6 - Vedolizumab + Golimumab	7 months	Remission	No serious infections
			Case 7 - Golimumab + Secukinumab	14 months	Major improvement	S.aureus bacteremia, unclear if related
			Case 8 - Golimumab + Risankizumab	11 months	Remission	No serious infections
			Case 9 - Ustekinumab + Golimumab	6 months	Major improvement	No serious infections
Sheehy et al, (2006)[59]	Case report	Infliximab, Adalimumab, Etanercept, Anakinra, Rituximab	Infliximab 5 mg/kg every 8 weeks + etanercept 25 mg twice weekly	6 months	Sustained remission after failure of 5 biologics	No serious infections; prophylactic cotrimoxazole was given
Bethge et al, (2016)[62]	Case report	Adalimumab, Infliximab, Certolizumab, Golimumab	Vedolizumab 300 mg every 8 weeks + etanercept 50 mg/week	10 months	Full resolution of pouchitis and SpA symptoms	No adverse events or serious infections
Roblin et al, (2017)[60]	Case report	Infliximab, Adalimumab	Vedolizumab 300 mg every 8 weeks + golimumab 200 mg at week 0, 100 mg at week 2, then 50 mg every 4 weeks	1 year	Clinical and endoscopic remission of UC; resolution of axial symptoms	No adverse events or serious infections reported

Abbreviations: axSpA, axial spondyloarthritis; IFX, infliximab; ADA, adalimumab; ETN, etanercept; CTZ, certolizumab pegol; GOL, golimumab; SEC, secukinumab; TCZ, tocilizumab; IXE, ixekizumab; UTK, ustekinumab; VED, vedolizumab; RIS, risankizumab; APR, apremilast; TOFA, tofacitinib; SpA, spondyloarthritis; UC, ulcerative colitis.

One of the earliest reported cases of DBT in axSpA was described by Sheehy et al in 2006.[59,] A 28-year-old man with HLA-B27–associated arthritis who failed multiple conventional DMARDs and five biologic agents, including infliximab, adalimumab, etanercept, anakinra, and rituximab (all used sequentially with methotrexate). He was subsequently treated with simultaneous administration of infliximab (5 mg/kg every 8 weeks) and etanercept (25 mg twice weekly), resulting in dramatic clinical improvement, normalization of inflammatory markers (ESR and platelet count fell rapidly to normal levels) and sustained remission for at least six months without infectious complications or other adverse effects. Prophylactic cotrimoxazole was administered for Pneumocystis jirovecii pneumonia prevention, and methotrexate was discontinued due to potential interaction with cotrimoxazole.

Further support for DBT in axSpA comes from a case report of 56-year-old male with long-standing seronegative axSpA and refractory pouchitis.[62] After secondary loss of response to several TNF inhibitors, vedolizumab was initiated, leading to remission of pouchitis but worsening of axial skeletal symptoms. The addition of etanercept led to rapid and sustained control of both intestinal and joint manifestations without any adverse events during 10 months of DBT. Similarly, Roblin et al reported a 48-year-old woman with HLA-B27–positive AS and ulcerative colitis who flared on vedolizumab monotherapy.[62] The addition of golimumab achieved remission of both diseases, with no serious infections reported over one year. In both cases, vedolizumab's gut-selective mechanism likely contributed to the favorable safety profile.

A 2022 retrospective case series provided further real-world evidence by examining nine patients with long-standing, multidomain SpA who had failed a median of five prior b/tsDMARDs.[61] Various DBT regimens were used, including dual TNF and IL-17A blockade and combinations involving IL-12/23, IL-23, and vedolizumab. Eight of the nine patients achieved major clinical improvement, and four reached full remission based on standardized disease activity indices. Notably, most had failed the individual agents previously, suggesting synergistic benefit. Only one serious infection (Staphylococcus aureus bacteremia in a high-risk patient) occurred and was not definitively attributed to DBT.

In axSpA, DBT use is limited to small case series and reports, suggesting possible improvement or remission after monotherapy failure. While safety appears acceptable, the limited data means both its true efficacy and risk of serious adverse events remain uncertain.

Future Directions

While DBT might be considered a therapeutic option for multiple b/tsDMARDs-refractory cases, current evidence regarding efficacy and safety is limited. Some studies report no clear advantage over monotherapy in terms of efficacy, while others suggest an increased risk of infections and other adverse events. These uncertainties highlight the need for better, and perhaps more sophisticated, treatment strategies aiming to increase the efficacy and safety in those difficult-to-treat patients.

Biomarkers for Response - The development of predictive biomarkers for treatment response represents a promising strategy for optimizing biologic therapy selection and potentially reducing the need for DBT. In RA, serum metabolomic profiling has identified distinct panels capable of predicting response to specific biologics with high accuracy. Takahashi et al reported that five metabolites - betonicine, glycerol-3-phosphate, N-acetylalanine, hexanoic acid, and taurine - predicted TNF inhibitor response with 85.7% sensitivity and 100% specificity, whereas three metabolites - citric acid, quinic acid, and 3-aminobutyric acid -predicted abatacept response with 100% sensitivity and 90.9% specificity.[63]

Genetic markers have also shown promise in treatment stratification. In psoriasis, Dand et al demonstrated that HLA-C*06:02–negative patients were significantly more likely to respond to adalimumab compared to ustekinumab (6-month OR = 2.95; $P = 5.85 \times 10^{-7}$), with an even stronger association observed among those with psoriatic arthritis (OR = 5.98; $P = 6.89 \times 10^{-5}$).[64] Similarly, proteomic profiling in psoriatic arthritis has identified a 57-protein synovial biomarker panel - including S100-A8, immunoglobulin kappa chain C, fibrinogen, haptoglobin, and annexins - that predicted response to adalimumab and successfully predicted abatacept response in 86% of patients in a blinded validation cohort.[65]

While these genetic and biomarkers are promising, further research and validation are required before such approaches can be integrated into routine clinical practice.

Induction of Immune Tolerance – Autoimmune diseases result from loss of immune homeostasis, where autoreactive lymphocytes escape tolerance mechanisms and drive pathogenic inflammation.[66] Inducing immune tolerance has been achieved in both neonatal and adult animals, such as with short courses of anti-CD4 antibodies, without impairing overall immunity.[67,68] However, greater MHC disparity, genetic heterogeneity, and environmental impact make tolerance induction more challenging in humans. Current strategies include antigen-independent approaches (eg, CD4+ T cell targeting with abatacept, which can delay RA onset and reduce progression) and antigen-specific methods such as peptide immunotherapy, tolerogenic dendritic cells, regulatory T cell therapies, in vivo Treg expansion, and microbiome modulation.[69] Early intervention may offer the best opportunity for durable tolerance, though these strategies remain experimental at this stage.

Chimeric Antigen Receptor-T (CAR-T) Cell Therapy — Originally developed for hematologic malignancies, CAR-T therapy engineers a patient's T cells ex-vivo to express chimeric antigen receptors, enabling targeted destruction of antigen-expressing cells with reduced collateral damage.[70,71] These modified cells can proliferate and persist in-vivo, offering durable responses. Advances include multi-antigen targeting, enhanced signaling domains, safety switches, and CAR-Tregs for immunosuppressive applications, highlighting its potential benefits and future application.

Summary

Although DBT may offer clinical benefit patients with treatment-refractory rheumatic disease, it has not consistently demonstrated superior efficacy over monotherapy and often carries higher risk of serious infections. Risk may be reduced by combining two agents with differing immunosuppressive profiles, including at least one with minimal systemic effects, to target distinct pathways while limiting infection risk. Thus, DBT should be reserved for selected severe, multi-refractory cases, with careful benefit–risk assessment.

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