Rheumatoid Arthritis: Therapeutic Strategies After Inadequate Response to Initial TNF Inhibitor Therapy

Priyanka Iyer, MD, MPH, Emily Peterson, PharmD, BCACP, and Namrata Singh, MD, MSCI

ABSTRACT

Objective: To discuss the variability in response to tumor necrosis factor inhibitors (TNFis) observed in patients with rheumatoid arthritis (RA) and discuss therapeutic options for patients who do not respond to initial TNFi therapy.

Methods: Review of the literature.

Results: Optimal treatment of RA aims at achieving and then maintaining remission or low disease activity. In a patient with an inadequate response to initial biologic therapy, several therapeutic options exist. Current evidence supports TNFi dose escalation for only infliximab; optimization of concurrent conventional synthetic disease-modifying antirheumatic drug (csDMARD) or switching to a different csDMARD are other options. Cycling (switching to an alternative TNFi) and swapping (switching to a therapy with a different mode of action) strategies are other alternate approaches supported by many observational studies. While no head-to-head trials exist directly comparing the 2 strategies, data suggest superiority of the swapping strategy over the cycling approach. Also, several studies have shown that switching to a drug with a different mechanism of action is associated with higher treatment persistence and lower health care costs than TNFi cycling.

Conclusion: Physicians have a growing list of treatment options to help their patients with RA achieve disease remission. The choice of best treatment for a given patient needs to be individualized, keeping in mind other factors, including comorbidities.

Keywords: biologics; rheumatoid arthritis; swapping strategy; cycling strategy; TNF inhibitors.

Following the discovery of tumor necrosis factor (TNF) as a proinflammatory cytokine 30 years ago, the use of TNF antagonists has revolutionized the treatment of rheumatoid arthritis (RA). Although TNF inhibitors (TNFIs) are frequently used as a first-line biologic disease-modifying antirheumatic drug (bDMARD), they are not uniformly efficacious in achieving remission in all patients with RA. This article highlights the reasons for such variability in observed response and discusses therapeutic options for patients who do not respond to TNFi therapy.

CASE PRESENTATION

A 60-year-old woman is evaluated in the clinic for complaints of pain in her hands, morning stiffness lasting 2 hours, and swelling in her wrists, all of which have been ongoing for 3 months. Physical exam reveals evidence of active inflammation, with synovitis in her second, third, and fourth metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints bilaterally, swelling over both wrists, and a weak grip. Inflammatory markers are elevated, and rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) are both positive at high titer. Radiographs reveal evidence of small erosions at the third and fourth MCPs and PIPs bilaterally and periarticular osteopenia. The patient is diagnosed with seropositive, erosive RA based on history, physical exam, laboratory studies, and imaging. She is started on 20 mg of prednisone for acute treatment of her symptoms along with methotrexate, and, initially, her symptoms are well controlled. A few months after starting treatment, she develops voluminous diarrhea that necessitates cessation of methotrexate.

From the University of Iowa Hospitals and Clinics, Iowa City, IA.

Leflunomide also causes similar symptoms. The combination of sulfasalazine and hydroxychloroquine does not adequately control her symptoms, and ongoing use of low-dose glucocorticoids is required to improve functionality in all joints. Using the treat-to-target (T2T) strategy, adalimumab is initiated. However, she continues to report persistent swelling and pain and still requests oral glucocorticoids to help decrease inflammation. The 28-joint Disease Activity Score (DAS28) is 4.8, suggestive of moderate disease activity.

Why are TNFi agents sometimes ineffective?

The introduction of monoclonal antibodies and fusion proteins to block TNF and other cytokines was a remarkable development in the treatment of RA that revolutionized patient care. Despite the efficacy of TNFis, clinical response to these agents is not universal and only some patients achieve complete remission. In targeting the eventual goal of remission or low disease activity in patients with RA, the concept of "TNF failure" becomes extremely relevant. These inadequate responses to anti-TNF therapy may be due to primary failures, or complete lack of clinical response after initiation of the bDMARD, and secondary failures, or the loss of initially achieved clinical response to therapy. Other reasons for discontinuation of a given TNFi include partial disease control and intolerance to the medication (possible injection-site or infusion reactions). Keystone and Kavanaugh[1] divided causes of failure of TNF agents into 2 broad categories: perceptual (related to natural variations in disease course like hormonal variation and physical and emotional stress) and pathophysiological failures (genetic variations, high body mass index, concomitant cigarette use).

Another important consideration in patients treated with a TNFi is the consequent formation of anti-drug antibodies (ADAs). TNFi agents are immunogenic and normally elicit an immune response. The appearance of such ADAs may reduce the bioavailability of free drug, resulting in a decreased clinical response,[2] or may lead to serious adverse effects.

How common is discontinuation of the first TNFi?

Several studies have reported that the prevalence of primary failure, secondary failure, and intolerance to TNFis ranges from 30% to 40%.[3-6] Female sex,[7] concurrent prednisone use,[8] high disease activity scores,[6,8,9] and the absence of treatment with low-dose methotrexate[7,8] have all been shown to be negative predictors of bDMARD retention and response.[10]

Are there any factors that predict TNFi failure?

There are no specific parameters to accurately predict responses to TNFI therapy.[11] Several clinical and molecular biomarkers in synovium (initial TNF levels, macrophages, T cells)[12] and peripheral blood (serum myeloid-related protein 8 and 14 complex levels,[13] prealbumin, platelet factor 4, and S100A12)[14] have been described as predictors of clinical response to TNFis, but their utility in clinical practice has not been established and the use of these markers has not yet been incorporated into clinical guidelines.

How is disease activity measured in patients with RA?

In 2010 an international expert consensus panel published treatment recommendations for RA that emphasized a T2T strategy of individualizing and escalating treatment to achieve the lowest disease activity or remission. In clinical practice, numerous tools are available to measure RA disease activity. Herein, we mention several that are most commonly used in clinical practice.

DAS28 combines single activity measures into an overall continuous measure of disease activity and has been endorsed by both the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). It includes a 28-swollen joint count (SJC), 28-tender joint count (TJC), erythrocyte sedimentation rate (ESR; can also be calculated using C-reactive protein [CRP]), and a patient global assessment (PtGA). The cut-offs used for DAS28 interpretation are as follows: remission (< 2.6), low (≥ 2.6 but ≤ 3.2), moderate (> 3.2 but ≤ 5.1), or high (> 5.1).[15] Some of the difficulties in using DAS28 in daily clinical practice include the need for a lab value and the time needed to perform the joint counts. Note also that due to the inclusion of ESR, which is influenced by age and other factors, DAS28 may underestimate remission in the elderly.

Another measure of RA disease activity is the Simplified Disease Activity Index (SDAI), which includes 28

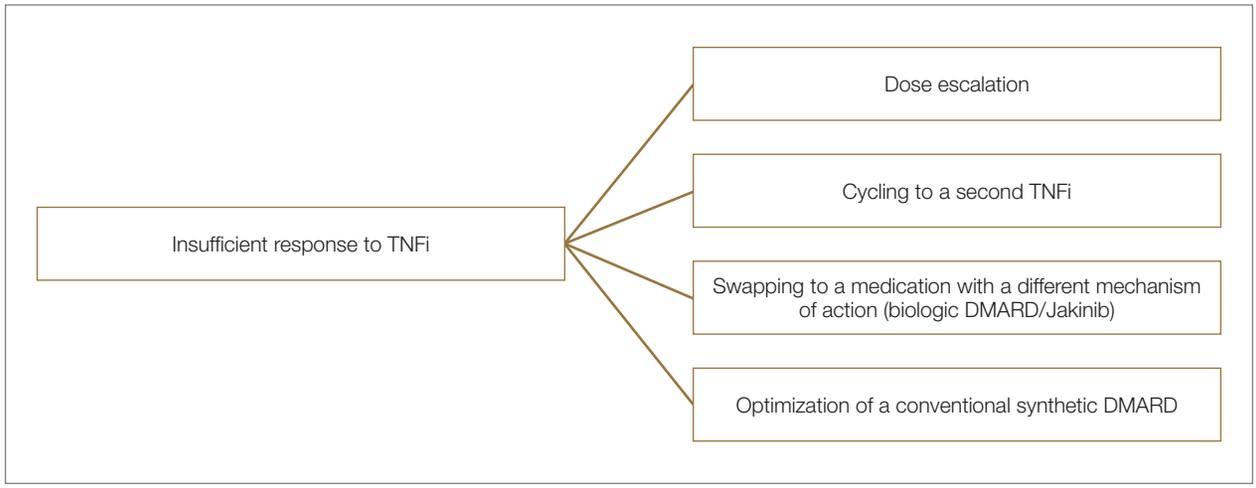

Figure. Treatment options for managing inadequate response to first tumor necrosis factor inhibitor (TNFi). DMARD, disease-modifying antirheumatic drug; Jakinibs; Janus kinase inhibitors; TNF, tumor necrosis factor.

SJC, 28 TJC, PtGA, provider global assessment (PrGA), and CRP in mg/dL. The level of disease activity using the SDAI is interpreted as: remission (SDAI ≤ 3.3), low (≥ 3.4 but ≤ 11), moderate (> 11 but ≤ 26), or high (> 26). The advantage of the SDAI is that a calculator or computer is not required for calculations. Another measure, the Clinical Disease Activity Index (CDAI), includes a 28 SJC, 28 TJC, PtGA, and PrGA. Because a laboratory value is not needed to calculate the CDAI, it is well-suited for use in clinical practice. When using the CDAI, the level of disease activity can be defined as remission (CDAI ≤ 2.8), low (> 2.8 but ≤ 10), moderate (> 10 but ≤ 22), or high (> 22). Again, as with the SDAI, a calculator or computer is not needed for calculations.

What are the alternative treatment options after first biologic failure?

In patients who have failed treatment with an initial biologic, usually a TNFi, the treating rheumatologist has the following options (**Figure**), with the best treatment strategy being driven by individualized patient and disease-related factors (**Table 1** and **Table 2**):

- TNFi dose escalation
- Trial of an alternate TNFi agent (the "cycling" strategy)
- Optimization of therapy conjoined with a conventional synthetic DMARD (csDMARD)
- Use of a non-TNF biologic or targeted synthetic DMARD (the "swapping" strategy)

If all the listed strategies fail, the next step can be the addition of short-term, low-dose glucocorticoid therapy.

TNFi Dose Escalation

The available data have demonstrated the safety, efficacy, and cost-effectiveness of dose escalation in patients with RA receiving infliximab.[16-18] The ATTRACT trial first demonstrated this, with greater clinical and radiographic improvements in those with higher trough serum concentrations, suggesting that doses higher than 3 mg/kg or more frequent than every 8 weeks may be needed for full response in some patients.[19]

There is a lack of studies in RA patients to determine the most effective dose escalation strategy. A study in patients with Crohn disease showed that intensification to 10 mg/kg every 8 weeks (dose doubling) was at least as effective as 5 mg/kg every 4 weeks (halving interval) at 12 months.[16] Due to greater patient and administration convenience of dose-doubling, this strategy may be preferred.[17] A starting dose of 10 mg/kg every 8 weeks is not routinely recommended due to an increased risk of serious infection; these adverse events were not found when the dose was gradually increased, as clinically indicated, starting at 3 mg/kg.[19,20] Further studies are needed to explore this approach in RA patients.

These results, however, have not been replicated with other TNFi agents. No significant clinical improvements were identified with etanercept 50 mg twice weekly,[21]

Table 1. **Biologic Disease-Modifying Antirheumatic Drugs**

Medication	Mechanism of Action/Class	Dose	Baseline Tests	Comments
Abatacept[89,a,b]	Selective T-cell co-stimulation modulator	IV: (< 60 kg) 500 mg, (60-100 kg) 750 mg, (> 100 kg) 1000 mg week 0, 2, and 4 and then every 4 weeks[c] SQ: 125 mg every week (with or without IV loading dose)[c]	TB, hepatitis B, CBC, LFTs, and serum creatinine	Autoantibody development could occur
Adalimumab[90,b]	TNF inhibitor	SQ: 40 mg every 14 days[c]	TB, hepatitis B, CBC, LFTs, serum creatinine	Avoid with anakinra or abatacept Autoantibody development
Anakinra[91,a,b]	IL-1 inhibitor	SQ: 100 mg daily[c]	TB, hepatitis B, CBC with differential, LFTs	Autoantibody development could occur
Baricitinib[92,b]	Jak inhibitor	2 mg once daily[c]	TB, hepatitis B and C, CBC, LFTs, serum creatinine, and lipids	Dose adjustments required if ALC < 500 cells/μL, ANC < 1000 cells/μL, hemoglobin < 8 g/dL
Certolizumab pegol[93,a,b]	TNF inhibitor	SQ: (loading) 400 mg at weeks 0, 2, and 4; (maintenance) 200 mg every 2 weeks or 400 mg every 4 weeks[c]	TB, hepatitis B, CBC, LFTs, serum creatinine	Autoantibody development
Etanercept[94,a,b]	TNF inhibitor	SQ: 50 mg every 7 days or 25 mg twice weekly[c]	TB, hepatitis B, CBC, LFTs, serum creatinine	Autoantibody development
Golimumab[95,b]	TNF inhibitor	SQ: 50 mg every 4 weeks with methotrexate IV: 2 mg/kg at week 0 and 4, and then every 8 weeks with methotrexate	TB, hepatitis B, CBC, LFTs, serum creatinine	Avoid use with abatacept and anakinra Autoantibody development
Infliximab[96,a,b]	TNF inhibitor	IV: 3 mg/kg at 0, 2, and 6 weeks with methotrexate; may be increased to 10 mg/kg every 4 weeks, if clinically indicated	TB, hepatitis B, CBC, LFTs, serum creatinine	Doses > 5 mg/kg should not be used in individuals with heart failure Autoantibody development
Rituximab[97,a,b]	CD20-directed cytolytic antibody	IV: 1000 mg day 0 and 14 with methotrexate every 24 weeks	TB and hepatitis B	Avoid repeat dose sooner than 16 weeks Autoantibody development could occur Premedicate with methylprednisolone 100 mg IV
Sarilumab[98,a,b]	IL-6 inhibitor	SQ: 200 mg every 14 days[c]	TB, hepatitis B, CBC with differential, lipids, LFTs	Autoantibody development could occur Avoid initiation with ANC < 2000 cells/μL, platelets < 150,000 cells/μL, ALT/AST > 1.5 × ULN
Tocilizumab[99,a,b]	IL-6 inhibitor	SQ: (< 100 kg) 162 mg every 14 days; (≥ 100 kg) 162 mg every 7 days[c] IV: 4 mg/kg every 4 weeks[c]; may be increased to 8 mg/kg every 4 weeks, if clinically indicated	TB, hepatitis B, CBC with differential, lipids, LFTs	Autoantibody development could occur Avoid initiation with ANC < 2000 cells/μL, platelets < 100,000 cells/μL, ALT/AST > 1.5 × ULN
Tofacitinib[100,a,b]	Jak inhibitor	5 mg twice daily or 11 mg extended-release daily[c]	TB, hepatitis B, CBC with differential, lipids, LFTs	Avoid initiation with ALC < 500 cells/μL, ANC < 1000 cells/μL, hemoglobin < 9 g/dL

ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CBC, complete blood count; IV, intravenous; Jak, Janus kinase; LFTs, liver function tests; SQ, subcutaneous; TB, tuberculosis test; TNF, tumor necrosis factor; ULN, upper limit of normal.

[a]Avoid concomitant use with other biologic disease-modifying antirheumatic drugs.

[b]Avoid live vaccines.

[c]With or without methotrexate.

Table 2. **Adverse Effects of Biologic Disease-Modifying Antirheumatic Drugs**

Medication	Adverse Effects
Abatacept[89]	Headache, nausea, infections (nasopharyngitis, sinusitis, UTI), COPD exacerbations, and increased cancer risk (lung, lymphoma)
Adalimumab[90]	Infections (URT, sinusitis), injection-site reactions, headache, rash, demyelinating disease, new or worsening heart failure, drug-induced lupus, hepatitis B and TB reactivation Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections) and malignancy (non-melanoma skin cancer, lymphoma, and leukemia)
Anakinra[91]	Injection-site reactions, worsening rheumatoid arthritis, infections (URI, sinusitis), headache, and nausea
Baricitinib[92]	Infections (URT, herpes simplex, herpes zoster), nausea, thrombosis, gastrointestinal perforations, and laboratory changes (neutrophils, lymphocytes, hemoglobin, LFTs, lipids) Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections), malignancy (lymphoma), and thrombosis
Certolizumab pegol[93]	Infections (URI, UTI), rash, demyelinating disease, new or worsening heart failure, drug-induced lupus, hepatitis B and TB reactivation Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections) and malignancy (lymphoma)
Etanercept[94]	Infections (URI, rhinitis), injection-site reactions, rash, headache, diarrhea, demyelinating disease, new or worsening heart failure, drug-induced lupus, hepatitis B and TB reactivation Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections), malignancy (lymphoma, melanoma and non-melanoma skin cancer, leukemia)
Golimumab[95]	Infections (URI, bronchitis, sinusitis), hypertension, injection-site reactions, dizziness, demyelinating disease, new or worsening heart failure, drug-induced lupus, hepatitis B and TB reactivation Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections) and malignancy (lymphoma)
Infliximab[96]	Infections (URI, sinusitis, pharyngitis), infusion reactions, headache, abdominal pain, hepatotoxicity, cardiovascular reactions before and after infusions, demyelinating disease, new or worsening heart failure, drug-induced lupus, hepatitis B and TB reactivation Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections) and malignancy (lymphoma, hepatosplenic T-cell lymphoma, and cervical cancer)
Rituximab[97]	Infections (URI, nasopharyngitis, UTI, bronchitis), cardiac adverse reactions (arrhythmias), renal toxicity, bowel obstructions, and mucocutaneous reactions Black box warning: fatal infusion reactions, hepatitis B reactivation, progressive multifocal leukoencephalopathy
Sarilumab[98]	Infections (URT, UTI, herpes zoster), gastrointestinal perforations, injection-site erythema, and laboratory abnormalities (neutropenia, thrombocytopenia, elevated LFTs, lipid abnormalities) Black box warning: serious infections (TB, bacterial sepsis, invasive fungal infections)
Tocilizumab[99]	Infections (URT, nasopharyngitis), injection-site reactions, headache, hypertension, lab abnormalities (lipids, neutrophils, LFTs), gastrointestinal perforations, and hypersensitivity reactions Black box warning: serious infections (tuberculosis, bacterial sepsis, invasive fungal infections)
Tofacitinib[100]	Infections (URT, nasopharyngitis), diarrhea, headache, gastrointestinal perforations, and laboratory abnormalities (lymphocytes, neutrophils, hemoglobin, LFTs, and lipids) Black box warning: serious infections (TB; bacterial, invasive fungal, viral, and opportunistic infections) and malignancy (lymphoma)

COPD, chronic obstructive pulmonary disease; LFTs, liver function tests; TB, tuberculosis; URT, upper respiratory tract; UTI, urinary tract infection.

adalimumab 40 mg every week in the PREMIER trial,[18] or certolizumab 400 mg every other week in an open-label extension phase of the RAPID 1 study.[22] A Japanese study found significantly worse clinical outcomes with dose escalation of golimumab.[23] Conversely, 2 studies found clinical benefits after escalating the tocilizumab dose, the first a real-world review from the Consortium of Rheumatology Researchers of North America (CORRONA) registry using the intravenous formulation,[24] and the other the BREVACTA study utilizing subcutaneous tocilizumab.[25] No studies to date have been published on dose escalation of abatacept in patients with RA who respond poorly. Overall, previous studies support dose escalation in individuals being treated with infliximab to improve clinical outcomes, but additional studies are needed for other bDMARDs.

Trial of an Alternate TNF Agent: The "Cycling" Strategy

Per the ACR/EULAR[26,27] guidelines, all approved bDMARDs may be used without hierarchical positioning. However, after the failure of a TNFi agent, these guidelines do not provide specific advice about a preference between the "cycling" strategy (switching to an alternative TNFi) and "swapping" strategy (switching to a therapy with a different mode of action). Cycling might work for several reasons, including differences in the agents' molecular structure, immunological mechanism of action, immunogenicity, and pharmacokinetics.[28-30] The cycling strategy is a well-established approach adopted by more than 94% of practicing rheumatologists, according to a national survey,[31] and its efficacy is supported by trials and additional observational studies.[32-35]

The greater clinical effectiveness of switching to infliximab compared with continuing with etanercept in patients with inadequate response to etanercept (n = 28) was suggested in the open-label OPPOSITE trial.[36] Data from the GO-AFTER trial[37] suggests that a greater proportion of patients with RA refractory to adalimumab, etanercept, or infliximab who were treated with golimumab achieved an ACR20 and ACR50 response compared with patients who received placebo, and this response persisted through 5 years.[38] More recently, certolizumab pegol and adalimumab were compared head-to-head in the EXXELERATE trial.[39] The results of this trial revealed the adequate efficacy of cycling to another TNFi after primary insufficient response to the first.

In studies from Finland and Sweden,[35,40] it has been observed that a better response is achieved in patients in whom TNF failure was initially due to secondary failure or intolerance rather than primary failure. A post-hoc analysis of the results of the GO-AFTER trial[41] and from a few observational studies[35,40,42] revealed that switching from one TNFi to another, especially from a monoclonal antibody to a soluble receptor, was often more beneficial for RA patients than switching from a soluble receptor to a monoclonal antibody.

Optimization of Therapy Conjoined with csDMARDs

Methotrexate is one of the oldest and most effective csDMARDs available for the treatment of RA.[43] The 2016 EULAR guidelines recommend the addition of methotrexate and/or other csDMARDs to potentiate the effect of bDMARDs.[26] In the case of TNFi therapy, the observed synergistic effect between the monoclonal antibody and methotrexate may be explained by sustained suppression of ADA formation.[44] In the TEMPO,[45] PREMIER,[18] and GO-BEFORE[46] trials, the addition of methotrexate led to improved clinical and radiological outcomes in patients treated with etanercept, adalimumab, and golimumab,[47] respectively. These findings were also demonstrated in several registries, where significant improvement in clinical response and retention rate of the TNFi agents was noted. Results have been replicated with non-TNFi bDMARDs, including abatacept[48,49] and rituximab.[50] Patients treated with interleukin (IL)-6 inhibitors in combination with methotrexate have shown significantly less radiographic progression compared to those treated with tocilizumab alone and those treated with monotherapy tocilizumab versus monotherapy methotrexate.[51,52] Results possibly favor the use of IL-6 inhibitors alone in those who cannot tolerate or have contraindications to methotrexate.

An open prospective study by Cohen et al added methotrexate to the treatment regimens of individuals on bDMARD monotherapy with a primary failure and found favorable changes in ACR20 and DAS28 scores at 3 and 12 months and therapeutic biological response (ESR, CRP) at

3 months.[53] Unlike monotherapy, in these situations methotrexate is known to be efficacious even at a lower dose, possibly at 7.5 mg to 10 mg per week. Some studies have shown that methotrexate administered parenterally may be more efficacious than when given orally.[54-58]

In clinical trials and observational studies, leflunomide, sulfasalazine, and hydroxychloroquine have been used as alternate csDMARDs added to the treatment regimen.[59-62] There are, however, only 2 trials comparing the efficacy of methotrexate with that of other csDMARDs as concomitant treatment in patients with inadequate response to TNFi therapy. The RABBIT trial found a slight decrease in effectiveness with concomitant TNFi and leflunomide compared to TNFi/methotrexate, but overall each group had similar EULAR responses at 24 months.[63] A study by De Stefano et al found comparable ACR20 and DAS28 responses among individuals receiving TNFis with methotrexate or leflunomide.[61]

The "Swapping" Strategy

The efficacy of the swapping strategy has been shown in 3 randomized clinical trials demonstrating the superiority of abatacept, tocilizumab, and rituximab in the treatment of individuals with RA refractory to TNFis. Tocilizumab was studied in the RADIATE[64] trial, which involved 499 patients with inadequate response to 1 or more TNFi agents. The primary endpoint (24-week ACR20) was achieved by 50.0%, 30.4%, and 10.1% of patients in the 8 mg/kg, 4 mg/kg, and control groups, respectively ($P < 0.001$ for both tocilizumab groups versus placebo). The utility of abatacept as second-line therapy after initial TNF failure was evaluated in the ATTAIN[65] study. Participants with an inadequate response to etanercept or infliximab were randomly assigned to receive either abatacept or placebo. ACR50 response rates after 6 months of treatment were 20.3% with abatacept and 3.8% with placebo ($P < 0.001$). The SWITCH-RA study,[66] an observational study, compared rituximab to TNFis in 1112 participants with inadequate response to initial anti-TNF therapy. At 6 months, mean change in DAS28 was small but significantly greater for the rituximab group (–1.5 vs –1.1; $P = 0.007$). The difference in response rates was greatest among seropositive patients. These data suggest that rituximab has efficacy following TNFi failure, particularly for seropositive patients. Additionally, REFLEX[67] is the sole randomized controlled trial in patients with insufficient response to TNFis that showed significant prevention of radiographic progression at week 56 in patients on rituximab compared to placebo (mean change from baseline in total Genant-modified Sharp score, 1.00 vs 2.31, respectively; $P = 0.005$).

One study randomly assigned 399 patients with active RA who had inadequate response to prior TNFi therapy to tofacitinib[68] (5 mg twice daily or 10 mg twice daily) or placebo, both with methotrexate.[6] After 3 months of treatment, ACR20 response rates (41.7% for 5 mg, 28.1% for 10 mg, 24.4% for placebo) and DAS28 remission rates (6.7% for 5 mg, 8.8% for 10 mg, 1.7% for placebo) were significantly greater among patients treated with tofacitinib compared to those treated with placebo. More recently, the RA-BEACON trial[69] demonstrated a consistent, beneficial treatment effect of baricitinib in patients with insufficient response to 1 or more TNFis. In this trial, 527 patients with an inadequate response to bDMARDs were randomly assigned to receive baricitinib 2 mg or 4 mg daily or placebo for 24 weeks. A higher proportion of patients receiving baricitinib 4 mg had an ACR20 response at week 12 compared with those treated with placebo (55% vs 27%, $P < 0.001$), and patients receiving the 4-mg dose had significant improvements from baseline in DAS28 and Health Assessment Questionnaire–Disability Index scores ($P < 0.001$ for both comparisons).

In a patient with inadequate response to initial biologic therapy, several therapeutic options exist. The choice of the best treatment for a given patient needs to be individualized, keeping in mind any comorbidities.

To Cycle or to Swap?

Several observational studies (SCQM-RA,[70] STURE,[71] BSRBR,[72] Favalli,[43] MIRAR,[73] SWITCH-RA,[74] ROC[72]) have clearly demonstrated that the swapping strategy is favored over the cycling strategy. In the ROC study,[72] patients were randomly assigned (based on physician discretion)

to receive a non-TNF biologic or a TNFi. More patients in the non-TNF group than in the TNFi group showed low disease activity at week 24 (45% vs 28%; odds ratio [OR], 2.09; 95% confidence interval [CI], 1.27-3.43; $P=0.004$) and at week 52 (41% vs 23%; OR, 2.26; 95% CI, 1.33-3.86; $P=0.003$). The authors concluded that in patients having an insufficient response to TNFi therapy, a non-TNF biologic agent may be more effective than a second TNFi drug. Only a few studies[75-77] have demonstrated similar results between the 2 strategies. Overall, the available evidence seems to suggest the superiority of the swapping over the cycling strategy.

An important clinical pearl to keep in mind is that both swapping and cycling strategies might theoretically increase the risk of infection; however, limited evidence is reported in the literature. In a large retrospective analysis[78] of data on 4332 RA patients from a large US claims database, patients who had cycled between TNFi agents had a 30% to 40% increased risk of infection compared to patients treated with rituximab. Patients on infliximab had a 62% higher hazard of severe infections, and this has also been reported in an observational study.[79] In another study,[70] 41% of 201 patients with RA followed between 1999 and 2013 who swapped to abatacept/rituximab or tocilizumab developed adverse events, as compared to 59% of those who switched to a second TNFi.

What are recent trends in the use of bDMARDs?

Currently, there are no specific guidelines or biomarkers available to facilitate selection of specific treatment from among the classes of biologics. With the development of several new drugs and regulatory approval of baricitinib, physicians now have several biologic options to treat patients. A recent large time-trend study[80] deriving data from more than 200,000 patients with RA showed that etanercept remains the most frequently used agent for the treatment of RA; it also showed that the use of adalimumab and infliximab is decreasing, and that the use of newer agents, especially abatacept, golimumab, and certolizumab, has considerably risen in recent years. In this study, abatacept, rituximab, certolizumab, golimumab, tocilizumab, and tofacitinib accounted for 13.2%, 13.8%, 6.9%, 11.9%, and 7.5% switches from first TNFi therapy.

Jin et al[81] studied factors associated with the choice of bDMARD for initial and subsequent use. They found that patients with commercial insurance had an 87% higher likelihood of initiating a bDMARD. In the Medicaid subgroup, African Americans had lower odds of initiating and switching bDMARDs than non-Hispanic whites. Prior use of steroids and nonbiologic DMARDs predicted both bDMARD initiation and subsequent switching. Etanercept, adalimumab, and infliximab were the most commonly used first- and second-line bDMARDS; patients on anakinra and golimumab were most likely to be switched to other bDMARDs.

Which treatment strategy is the most cost-effective?

Several studies have reported better treatment persistence rates among patients who are treated with the swapping strategy compared to the cycling strategy. In a retrospective analysis of claims data,[82] the authors examined treatment persistence and health care costs in patients switching to biologics with a different mechanism of action or cycling to another TNFi. The mean cost was significantly lower among patients treated using the swapping strategy than among the TNFi cyclers, both for the total cost of care for RA and for the total cost of the targeted DMARDs in the first year after the change in therapy. The authors concluded that switching to a drug with a different mechanism of action is associated with higher treatment persistence and lower health care costs than TNFi cycling.

What about biosimilars?

Biosimilars are copies of already licensed biologics that are very similar to the biologics, but are made by different sponsors using independently derived cell lines and separately developed manufacturing processes.[83] Regarding biosimilar use, EULAR[26] states that biosimilar bDMARDs approved by the European Medicines Agency or US Food and Drug Administration have similar efficacy and safety as the originator bDMARDs, and recommends them as preferred agents if they are indeed appreciably cheaper than originator or other bDMARDs.

What are the novel treatment targets in RA?

New therapeutics for RA continue to be developed. One of the new agents is peficitinib (ASP015K), an oral, once-

daily Janus kinase (Jak) inhibitor targeting Jak-1, Jak-2, and tyrosine kinase-2, with moderate selectivity for Jak-3. In a phase 2b trial, 100-mg and 150-mg doses of peficitinib achieved a statistically significant ACR20 response (48.3% and 56.3%) compared to placebo (29.4%) at 12 weeks.[84]

Given the benefit of targeting TNF-α and IL-17 in RA, a novel molecule (ABT-122) that targets both human TNF and IL-17 has been developed. Two phase 1 studies[85] showed that dual neutralization of TNF and IL-17 with ABT-122 has characteristics acceptable for further exploration of therapeutic potential of this agent in TNF- and IL-17A–driven immune-mediated inflammatory diseases. Another novel drug is mavrilimumab, a human monoclonal antibody that targets granulocyte–macrophage colony-stimulating factor receptor α. A recent study showed that long-term treatment with mavrilimumab maintained response and was well-tolerated, with no increased incidence of treatment-emergent adverse events.[86]

Namilumab (AMG203) is an immunoglobulin G1 monoclonal antibody that binds with high affinity to the GM-CSF ligand. In a phase 1b, randomized, double-blind study (PRIORA)[87] to assess namilumab in treating active, mild-to-moderate RA, significant improvement was seen in the DAS28-CRP score with namilumab (150 and 300 mg groups combined) compared with placebo at day 43 (P = 0.0117) and also 8 weeks after last dosing at day 99 (P = 0.0154). Adverse events were similar across different doses of namilumab and placebo, and included nasopharyngitis and exacerbation/worsening of RA. Another drug showing promise in RA is fosdagrocorat (PF-04171327), a potential dissociated agonist of the glucocorticoid receptor. A multicenter, double-blind, parallel-group, active- and placebo-controlled phase 2 study randomly assigned 86 patients to receive fosdagrocorat 10 mg, fosdagrocorat 25 mg, prednisone 5 mg, or placebo, all with stable background methotrexate therapy.[88] Both fosdagrocorat doses demonstrated efficacy in improving signs and symptoms in RA patients, with manageable adverse events.

CASE CONCLUSION

There are several available treatment options for the case patient. Based on the PREMIER trial, solely increasing the dose of adalimumab is unlikely to provide a therapeutic benefit. Adding low-dose methotrexate (possibly via a parenteral route because of patient-reported gastrointestinal discomfort) might provide some synergistic and therapeutic effect. However, because of primary failure with TNFi therapy, she may benefit from the initiation of a biologic with a different mechanism of action (ie, swapping strategy). Therapeutic options include tocilizumab, abatacept, rituximab, and the Jak inhibitors (tofacitinib and baricitinib).

Summary

The optimal treatment of RA aims at achieving, and then maintaining, remission or a low disease activity. The choice of best treatment must be individualized to the patient, keeping in mind other factors, including comorbidities like fibromyalgia, history of diverticulitis (prior to use of tocilizumab), history of chronic obstructive pulmonary disease (prior to the use of abatacept), malignancy, and the presence of risk factors for infections (age, diabetes, chronic bronchitis). In a patient with inadequate response to initial biologic therapy, several options exist for the rheumatologist. Current evidence supports TNFi dose escalation for only infliximab; optimization of concurrent csDMARD or switching to a different csDMARD are other options. Cycling and swapping are other alternate approaches supported by many observational studies. While no head-to-head trials exist comparing the 2 strategies, data suggest superiority of the swapping strategy over the cycling approach. With the continuing development of novel therapeutics in RA, physicians have a growing list of treatment options to help their patients achieve disease remission.

Corresponding author: Namrata Singh, MD, 200 Hawkins Drive, Iowa City, IA 52242.

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