The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.

The Product Information should be consulted for detailed prescribing information.

ABBREVIATIONS: ACR, American College of Rheumatology; ACRG, 2015 ACR Guideline for the treatment of RA; bDMARD, Biologic disease-modifying antirheumatic drug; CHF, Congestive heart failure; CFU, Criteria for use; csDMARD, Conventional synthetic disease-modifying antirheumatic drug (i.e., methotrexate, hydroxychloroquine, sulfasalazine, leflunomide); DAS, Disease activity score for a given number of joints (e.g., DAS28 is based on 28 joints); HAQ, Health Assessment Questionnaire (score range, 0 = Best to 3 = Worst in 0.125 increments); HCQ, Hydroxychloroquine; LEF, Leflunomide; IQR, Interquartile range; MTX, Methotrexate; Non-TNF, Non-TNF biologic (abatacept, rituximab, tocilizumab; excludes anakinra); PA, Prior authorization; QE, Quality of Evidence; QoL, Quality of life; RA, Rheumatoid arthritis; RCT, Randomized clinical trial; SHS, Sharp / Van der Heijde (range, 0–448; progression defined as change in total score of >0.5); SSZ, Sulfasalazine; TNFI, Tumor necrosis factor inhibitor

TERMS: Combination csDMARD refers to concomitant use of two or three csDMARDs (i.e., double or triple therapy). CONDITIONAL RECOMMENDATION means that clinicians should be prepared to help patients make a decision that is consistent with their own values, and policy makers should be aware that there is a need for substantial debate and involvement of stakeholders. Double Therapy refers to MTX + SSZ, MTX + HCQ, SSZ + HCQ, or combinations with LEF. Early RA refers to <6 months of symptoms / disease, not time since diagnosis. Established RA refers to ≥6 months of symptoms / disease. STRONG RECOMMENDATION means that most patients should receive the recommended course of action, and policy makers can adapt the recommendation as a policy in most situations. Triple Therapy refers to concomitant use of methotrexate, hydroxychloroquine, and sulfasalazine.

VHA FORMULARY POLICIES

The formulary TNFIs – adalimumab, etanercept, and infliximab-dyyb – are available through facility prior authorization. Certolizumab pegol, golimumab, and infliximab are available through the nonformulary process in VHA. This guidance may serve as a reference for facility prior authorizations for the formulary TNFIs and for requests for the nonformulary TNF inhibitors. The intent of using facility prior authorizations is to simplify access to TNF inhibitor therapy.

<table>
<thead>
<tr>
<th>Formulary Status of TNFIs</th>
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<tbody>
<tr>
<td>Formulary With PA</td>
</tr>
<tr>
<td>Adalimumab</td>
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<tr>
<td>Etanercept</td>
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<tr>
<td>Infliximab-dyyb</td>
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</table>

- Adalimumab, etanercept, and infliximab-dyyb are VHA's preferred TNFIs, unless specific patient conditions exclude them from use.
- Prior authorization for formulary TNF inhibitors should be granted if the provider is a VA or VA-contracted rheumatologist or otherwise appropriate for prescribing TNF inhibitor therapy for RA.
- In keeping with the ACRG, most patients to be treated with TNFI therapy should have moderate or high disease activity despite an adequate, minimum 3-month trial of csDMARD therapy. See Guideline Recommendations for TNFI Treatment in RA.
- Infliximab-dyyb may be used in new starts in lieu of infliximab and, with prior provider authorization, interchanged for infliximab.
- Patients on infliximab without prior provider authorization to switch to infliximab-dyyb are grandfathered to continue on infliximab and exempted from criteria for use of infliximab. (There are no criteria for use of TNFIs in RA.)
- Double csDMARD therapy, preferably with MTX, or triple csDMARD therapy (MTX + hydroxychloroquine + sulfasalazine, with or without a short-course of a glucocorticoid) can be used as an effective, low-cost alternative to TNFI therapy if disease activity remains moderate to severe despite csDMARD monotherapy; but combination csDMARD therapy should not be mandated prior to TNFI therapy without both individualizing the treatment selection and basing the selection on shared decision-making between the patient and provider.
- Triple csDMARD therapy should not be substituted for current TNFI therapy, unless there is a clinical reason to switch to triple therapy.

Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [PBM INTRAnet](http://www.pbm.va.gov)
**Shared decision-making between the patient and rheumatologist and individualization of therapy are the sine qua non of treatment selection for rheumatoid arthritis.**

**Recommendations for Use**
- Patient is under the care of a VA or VA-contracted (including CHOICE program) rheumatologist.
- Current tuberculosis test is negative or patient is treated for latent tuberculosis infection (LTBI) or active tuberculosis as clinically indicated prior to starting biologic therapy.
- Pre-therapy laboratory tests and appropriate treatment, vaccinations and expert consultation(s) (e.g., infectious disease, gastroenterologist / hepatologist) have been performed as clinically indicated and / or as recommended by the prescribing information for the biologic agent and the CDC Advisory Committee for Immunization Practices (e.g., tuberculin skin test or interferon-gamma release assay [IGRA], chest X-ray, anti-TB therapy if indicated, hepatitis B virus screening [e.g., HbsAg, anti-HBs and anti-HBc1,2], hepatitis C screening3,4; age-appropriate immunizations, CBC, and liver enzymes).
- Concomitant therapy with another bDMARD (e.g., TNF inhibitor, interleukin-17A inhibitor, interleukin-12/23 inhibitor)
- Concomitant therapy with abatacept or anakinra
- Multiple sclerosis or other demyelinating disease, or first-degree relative who has multiple sclerosis
- Confirmed history or examination-based (not based on oral history alone) diagnosis of heart failure that is being treated, or heart failure that has not been evaluated by cardiology for biologic therapy. (Administration of infliximab doses > 5 mg/kg to patients with moderate to severe [NYHA class III or IV] heart failure is a contraindication.)
- Active malignancy other than successfully treated nonmelanoma skin cancer (Malignancy is not a contraindication but a risk-benefit warning / precaution.)

**Recommendations Against Use of TNFI Therapy: – Avoid TNFIs in the presence of any of the following:**
- Active infection (any) or untreated latent infection by hepatitis B, tuberculosis, coccidioidomycosis or histoplasmosis.
- Hypersensitivity to product ingredients
- Hypersensitivity to murine proteins (infliximab)
- Administration of any live vaccine or live-attenuated vaccine concomitantly with or during biologic therapy.
- Concomitant therapy with another bDMARD (e.g., TNF inhibitor, interleukin-17A inhibitor, interleukin-12/23 inhibitor)
- Concomitant therapy with abatacept or anakinra
- Multiple sclerosis or other demyelinating disease, or first-degree relative who has multiple sclerosis
- Confirmed history or examination-based (not based on oral history alone) diagnosis of heart failure that is being treated, or heart failure that has not been evaluated by cardiology for biologic therapy. (Administration of infliximab doses > 5 mg/kg to patients with moderate to severe [NYHA class III or IV] heart failure is a contraindication.)
- Active malignancy other than successfully treated nonmelanoma skin cancer (Malignancy is not a contraindication but a risk-benefit warning / precaution.)

**Recommendations for Use of Nonformulary TNFIs**
- Patient has had an early clinical response or achieved remission or low disease activity on a nonformulary TNFI, and is tolerating therapy.
  - Population data suggest that TNFIs are similar in efficacy; however, individuals can vary in their response to different TNFIs. Response to one TNFI does not guarantee response to another TNFI.
  - For a patient who has clinically responded or achieved therapeutic goal on one TNFI, switching to another TNFI solely for administrative reasons puts the patient at serious risk of losing response, worsening joint damage, and increasing disability.
- Patient had a clinical response but either lost response or developed intolerance(not due to a TNF class adverse effect) to the three formulary TNFIs (± MTX / csDMARD), and the decision to try another (nonformulary) TNFI is based on shared decision-making.
  - Obtaining a clinical response to three prior TNFIs suggests that the mechanism of disease activity involves TNF activity, and this supports a therapeutic trial of another (nonformulary) TNFI.
  - If there is loss of response to the three formulary TNFIs, switching to another (nonformulary) TNFI or switching to an agent with a different mechanism of action may be an appropriate treatment approach.
  - Intolerance to three TNFIs, however, supports a therapeutic trial of non-TNF therapy (e.g., combination csDMARDs or non-TNFBS), and the choice of the next treatment should be based on shared decision-making, taking into account patient values and preferences.
  - If the intolerance is due to an adverse effect that can be expected to occur with other TNFIs (i.e., a class effect), then non-TNF therapies should be considered.
  - Finding an effective and tolerable therapy for an individual with active RA is a matter of therapeutic trial and error. Patient predictive factors of response have not been identified.
- For certolizumab: Patient is pregnant or planning pregnancy.
  - Certolizumab may have a theoretical advantage because it has been shown to have lower placental transfer than adalimumab and infliximab5; however, all TNF inhibitors are classified in Pregnancy Category B. There are no adequate, well-controlled studies in pregnant women.
- For certolizumab: Patient has a documented latex allergy.
  - Unlike the other TNFIs, certolizumab does not contain any latex syringe components.
- For certolizumab or golimumab once-monthly subcutaneous injection:
  - Patient developed severe injection site reactions with adalimumab (administered every 2 weeks) or etanercept (administered once every week).
  - Patient prefers less frequent (once-monthly) subcutaneous injections for maintenance therapy. Adalimumab and etanercept require more frequent subcutaneous dosing (every 2 weeks and once every week, respectively).
- For golimumab or infliximab intravenous infusion: Patient prefers less frequent (every-8-week) dosing and agrees to receive provider-administered intravenous infusions.
- For infliximab: Patient had a response to infliximab, and the provider does not authorize switching from infliximab to infliximab-dyyb.

Updated version may be found at www.pbm.va.gov or PBM INTRANet
**Anti-TNF DMARDs for RA Recommendations for Use**

**Recommendations Against Use of Nonformulary TNFIs**

- **Patient had NO response to a prior TNFI or had an inadequate response to two TNFIs.**
  - The timeline for achieving the therapeutic target is important when considering the use of nonformulary TNF inhibitors in patients who have had an *inadequate response* to prior TNF inhibitor therapy, since *at least 3 months* would have likely elapsed.
  - Furthermore, no response or an inadequate response suggests that TNF mechanisms may not be the main mediator of disease activity, and that switching to agents with other mechanisms may be indicated.

- **If concomitant csDMARD therapy cannot be given, then infliximab (or infliximab-dyyb) is not recommended.**
  - Infliximab received FDA approval based on its safety and efficacy when used concomitantly with MTX. There is evidence to suggest that other csDMARDs can be given in combination with infliximab. Use of infliximab without a concomitant csDMARD should be adjudicated locally in accordance with the PBM Guidance for Off-Label Prescribing.

**Recommendations for Monitoring**

- Assess disease activity 3 months after therapy initiation or modification. Give RA treatments for at least 3 months before deciding to escalate or switch therapy.
- If the therapeutic target is not achieved by 6 months, consider modification of therapy (which may or may not involve discontinuation of the TNF inhibitor).
- Use a validated instrument (e.g. PAS or PAS II, CDAI, SDAI, DAS28-erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) for measuring disease activity; see Table 1 below). Clinical response can be represented by minimal clinically important improvement (MCII) on composite instruments and individual tools, such as −18 points on a 0–100 visual analogue scale (VAS) for patient global assessment, −20 points on a 0–100 VAS for pain, or −0.375 units on a 0–3 scale for Health Assessment Questionnaire Disability Index. Individualize assessments of clinical response and do not base assessments entirely on composite instruments. The rheumatologist’s clinical judgment is of particular importance when the score from the instrument is incongruous with the clinical picture.

<table>
<thead>
<tr>
<th>Instrument (Scale)</th>
<th>Score Cutoffs by Disease Activity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Remission</td>
</tr>
<tr>
<td>Patient Activity Scale (PAS) (0–10)</td>
<td>0 to 0.25</td>
</tr>
<tr>
<td>Clinical Disease Activity Index (CDAI) (0–76.0)</td>
<td>≤ 2.8</td>
</tr>
<tr>
<td>Disease Activity Score in 28 joints (DAS28) ESR (0–9.4)</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Simplified Disease Activity Index (SDAI) (0–106.0)</td>
<td>≤ 3.3</td>
</tr>
</tbody>
</table>

Sources: 6,7. ESR, Erythrocyte sedimentation rate; MCII, Minimal clinically important improvement.
GUIDELINE RECOMMENDATIONS FOR TNFI THERAPY IN RA

- **For optimal disease outcomes**, the ACRG recommends a treat-to-target approach (over a nontargeted approach) with the aim of achieving low disease activity or remission, regardless of disease stage. **[STRONG RECOMMENDATION; LOW QE FOR EARLY RA AND MODERATE QE FOR ESTABLISHED RA]**. Treating to target encompasses aiming to achieve any beneficial response by 3 months after onset of disease symptoms (not since time of diagnosis) and aiming to achieve low or no disease activity or remission by 6–12 months.7,8

- **For early RA or established RA**, TNFIs with or without MTX are recommended when disease activity remains moderate or high despite monotherapy with a csDMARD ± glucocorticoids in early RA) rather than continuing csDMARD monotherapy alone. **[STRONG RECOMMENDATION; LOW QE FOR EARLY RA AND MODERATE TO VERY LOW QE FOR ESTABLISHED RA]**

<table>
<thead>
<tr>
<th>Early RA</th>
<th>Established RA</th>
<th>Achieved Therapeutic Target</th>
<th>Recommendations in RA Patients with High-risk Co-morbidities</th>
</tr>
</thead>
</table>
| For disease activity that remains moderate or high despite csDMARD monotherapy ± glucocorticoids, an alternative to TNFI therapy ± MTX is combination csDMARDs or non-TNFBs ± MTX. There is no particular order of preference among the three alternatives (combination csDMARDs, TNF inhibitor ± MTX, or non-TNFB ± MTX). **[STRONG RECOMMENDATION; LOW QE]** When possible, biologics should be used in combination with MTX because of superior efficacy over biologic monotherapy.  
  - If disease activity remains moderate or high despite csDMARDs, use TNFI monotherapy over tofacitinib monotherapy or TNFI + MTX over tofacitinib + MTX. **[CONDITIONAL RECOMMENDATION, LOW QE]**  
  - If disease activity remains moderate or high despite csDMARD or biologic therapy, add low-dose glucocorticoids. **[CONDITIONAL RECOMMENDATION, LOW–MODERATE QE]** | For disease activity that remains moderate or high despite csDMARDs, an alternative to TNFI therapy is combination csDMARDs or non-TNFBs ± MTX or tofacitinib ± MTX. There is no particular order of preference among the four alternatives (combination csDMARDs, TNF inhibitor ± MTX, non-TNFB ± MTX, or tofacitinib ± MTX). **[STRONG RECOMMENDATION; MODERATE TO VERY LOW QE]**  
  - If disease activity remains moderate or high despite TNFI therapy in patients who are currently not on csDMARDs, add one or two csDMARDs to TNFI therapy rather than continuing TNFI therapy alone. **[STRONG RECOMMENDATION; HIGH QE]**  
  - If disease activity remains moderate or high despite use of a single TNFI, use a non-TNFB ± MTX over another TNFI ± MTX. **[CONDITIONAL RECOMMENDATION, LOW TO VERY LOW QE]** | If a patient is in remission or low disease activity, a decision to switch to another therapy should only be made based on shared decision-making, and not made solely for administrative reasons.7  
  - If the patient has low disease activity but is not in remission, continue RA treatments. **[STRONG RECOMMENDATION, MODERATE QE FOR csDMARDs AND HIGH TO VERY LOW QE FOR BIOLOGICS AND TOFACITINIB]**  
  - If the patient is in remission, decisions related to tapering of therapy should be driven by patients’ values and preferences, a comprehensive plan for monitoring and addressing possible flares should be implemented, and patients should be informed about the risk of flares. With these important caveats, the ACRG recommends the following:  
    - Taper csDMARD therapy **[CONDITIONAL RECOMMENDATION, LOW QE]**  
    - Taper TNFI, non-TNFB, or tofacitinib. **[CONDITIONAL RECOMMENDATION, MODERATE TO VERY LOW QE]**  
    - Do not discontinue all RA therapies. **[STRONG RECOMMENDATION, VERY LOW QE]** | CHF: Use combination csDMARDs or non-TNFB or tofacitinib over TNFI **[CONDITIONAL RECOMMENDATION, Moderate to Very Low QE]**  
  - CHF Worsening on Current TNFI Therapy: Use combination csDMARDs or non-TNFB or tofacitinib over another TNFI. **[CONDITIONAL RECOMMENDATION, Very Low QE]**  
  - Hepatitis C infection and not receiving or requiring effective antiviral treatment: Use csDMARDs over TNFI. **[CONDITIONAL Recommendation, Very Low QE]** The guideline also recommends that rheumatologists collaborate with gastroenterologists and/or hepatologists to recommend individualized therapy, and consider using csDMARDs other than MTX or LEF (e.g., SSZ or HCQ).  
  - Past History of Treated or Untreated Malignancy: Use csDMARDs over biologics and over tofacitinib in either melanoma or non-melanoma skin cancer. **[CONDITIONAL Recommendation, Very Low QE]**  
  - Previously Treated Lymphoproliferative Disorder:  
    - Use rituximab over TNFI. **[STRONG RECOMMENDATION, Very Low QE]**  
    - Use combination csDMARD or abatacept or tocilizumab over TNFI. **[CONDITIONAL Recommendation, Very Low QE]**  
  - Previous Serious Infection(s): Use combination csDMARD or abatacept over TNFI. **[CONDITIONAL Recommendation, Very Low QE]** |
LITERATURE REVIEW

TNFI vs. TNFI Comparisons

- There is no evidence to support one particular TNF inhibitor over another.
- Limited head-to-head comparisons and indirect comparisons suggest that no one TNF inhibitor is superior.9

Therapy with Combination csDMARDs vs. TNFI + MTX / csDMARD

There is no expert consensus on when it is clinically optimal to start high-cost biologics during the management of active RA. Recommendations by British, Canadian, European and American professional and regulatory bodies agree that TNFIs are indicated in patients who have inadequately responded to csDMARDs. The UK’s National Institute for Health and Care Excellence (NICE) recommends TNFIs in inadequate responders to intensive therapy with combination csDMARDs, and only in patients with a persistent DAS28 score ≥5.1.10 The NICE guideline has been criticized for being too rigid and setting the DAS28 criterion too high.11 The British Columbia Medical Services Commission recommends combination csDMARDs (MTX + SSZ) as the standard of care for early RA and specialist referral for initiation of biologic therapies.12 EULAR recommends institution of biologics in inadequate responders to MTX / csDMARD monotherapy if prognostically unfavorable factors exist.8 The French Society of Rheumatology recommends a biologic + MTX in MTX inadequate responders with adverse prognostic factors or in patients without these factors after failure of alternative csDMARD monotherapy or combination csDMARD.13 The ACRG recommends TNFI therapy, with or without MTX, in patients with moderate to severe disease activity despite csDMARD monotherapy.7

A therapeutic trial of MTX monotherapy is effective in 30% of patients with active RA14,15,16,17 and, if used as initial therapy, can avoid unnecessary overtreatment in the subgroup of responders. On the other hand, initial immediate combination therapy seems to confer early efficacy advantages over step-up therapy (from MTX monotherapy to combination therapy with addition of either etanercept or HCO quality SSZ).15 In the BeST trial, initial combination therapy with either combination csDMARD with tapered high-dose prednisone or combination TNFI (infliximab) + MTX was significantly better and faster acting than sequential csDMARD monotherapy or step-up combination csDMARD therapy in terms of disability, radiographic progression, disease activity, remission, and ACR20/70 responses in year 1. The benefit in retarding joint damage persisted through year 7 with a treat-to-target approach.14,18,19

Whether the less costly, slow-acting combination csDMARD therapy could be safely and effectively used before a TNFI in combination with MTX / csDMARD remains an active research question. In head-to-head trials involving patients with either early14,15,16 or established17,20, RA, and who are MTX / csDMARD-naïve or MTX inadequate responders, combination csDMARD therapy was comparable overall in efficacy outcomes relative to TNFI (infliximab or etanercept) + MTX / csDMARD therapy by 1 year. Early in therapy (at 3–6 months), small statistically significant differences in favor of TNFI therapy were observed in some efficacy measures, such as ACR20/50/70 responder rates, suggesting that the TNFI combination was faster acting and produced deeper suppression of symptoms.17,20 In two trials, reductions in radiographic progression favored TNFI + MTX / csDMARD over combination csDMARDs; however, the differences were not considered to be clinically meaningful.15,16 One trial, involving mostly csDMARD-naive patients with very early RA, showed a small, significant benefit in the percentage of patients not having radiographic progression with immediate TNFI + MTX relative to immediate triple therapy at 2 years (76.8% vs. 66.4%).15

The potential impact of these differences on radiographic progression and disability beyond a 2-year timeframe has not been evaluated.

In a network meta-analysis and pharmacoeconomic evaluation of targeted immunomodulators for RA, the Institute for Clinical and Economic Review (ICER) showed that combination csDMARD therapy was similar in efficacy to most combinations of TNFIs + MTX / csDMARD, and has a higher risk of gastrointestinal adverse effects and lower risks of infections and serious infections.9 Their report concluded that, relative to csDMARDs, the incremental cost-effectiveness ratios for TNFIs exceed the commonly cited thresholds for cost-effectiveness.9

While the additional benefits of initiating therapy with TNFIs over less costly conventional DMARD therapy seems to be small over the time periods studied, the optimal treatment of inadequate responders to MTX / csDMARD monotherapy remains controversial. The ACRG recommends combination csDMARD therapy as an alternative to biologics or tofacitinib, with or without MTX / csDMARD, without preference for any one of these combinations.7 Given the potential for earlier improvements in disease activity and radiographic progression rates, TNFI + MTX / csDMARD therapy may be preferred in patients with rapid radiographic progression or a desire for rapid improvement.

Prepared: Aug 2017 [Extensive revisions and conversion of CFU for nonformulary TNFIs to RFU for all TNFIs.]
Contact: Francine Goodman, National Clinical Pharmacy Program Manager – Formulary, VA Pharmacy Benefits Management Services (10P4P)

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3 Hanley T, Handford M, Lavery D, Yiu Zenas ZN. Psoriasis: Targets and Therapy 2016:6 41–54
Anti-TNF DMARDs for RA Recommendations for Use

Updated version may be found at www.pbm.va.gov or PBM INTRANet


10 National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan 26. 81 p. (Technology appraisal guidance; no. 375). Available at the National Institute for Health and Care Excellence (NICE) Web site


