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Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis

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ABSTRACT

Clinical evidence demonstrates coadministration of tumour necrosis factor inhibitor (TNFi) agents and methotrexate (MTX) is more efficacious than administration of TNFi agents alone in patients with rheumatoid arthritis, leading to the perception that coadministration of MTX with *all* biologic agents or oral disease-modifying antirheumatic drugs is necessary for maximum efficacy. Real-life registry data reveal approximately one-third of patients taking biologic agents use them as monotherapy. Additionally, an analysis of healthcare claims data showed that when MTX was prescribed in conjunction with a biologic agent, as many as 58% of patients did not collect the MTX prescription. Given this discrepancy between perception and real life, we conducted a review of the peer-reviewed literature and rheumatology medical congress abstracts to determine whether data support biologic monotherapy as a treatment option for patients with rheumatoid arthritis. Our analysis suggests only for tocilizumab is there evidence that the efficacy of biologic monotherapy is comparable with combination therapy with MTX.

INTRODUCTION

Methotrexate (MTX), administered alone or with another conventional disease-modifying antirheumatic drug (DMARD), is the recommended first-line treatment for patients with rheumatoid arthritis (RA).^{1,2} MTX plus tumour necrosis factor inhibitor (TNFi) agents is the usual treatment for patients with RA with insufficient response to MTX/DMARDs (MTX-/DMARD-IR).^{1,2} TNFi agents plus MTX reduce disease activity, improve physical function and attenuate radiographic progression in MTX/DMARD-IR patients.^{3–12} When administered with MTX, enhanced efficacy has been observed for TNFi agents infliximab, etanercept, adalimumab and golimumab.^{13–18} The efficacy reported with certolizumab in combination with MTX^{19,20} is higher than that reported in separate studies with certolizumab monotherapy.²¹ The non-TNFi agent rituximab, which targets CD20⁺ B cells, may also be more effective when combined with MTX.²² Despite the efficacy of TNFi agents plus conventional DMARDs and the limited approval of biologics (etanercept, adalimumab, certolizumab, tocilizumab) as monotherapy, biologic monotherapy for managing RA is widespread in clinical practice.^{23–29}

Review of the peer-reviewed published literature (2005–2012) and rheumatology medical congress abstracts (European League Against Rheumatism and American College of Rheumatology (ACR), 2009–2012) was conducted to determine potential

reasons for, and evidence supporting, the use of biologics or oral DMARDs (tofacitinib) as monotherapy (box 1). References in retrieved articles were reviewed to identify trials in which biologics alone were administered. Additional search strategies to identify potential reasons for use of biologics as monotherapy were conducted.

MTX IN COMBINATION THERAPY

The enhanced efficacy of TNFi agents used in combination with MTX compared with TNFi monotherapy is supported by data from randomized controlled trials (RCTs). Patients treated with infliximab plus MTX had longer duration of response than those who received infliximab alone; 20% Paulus criteria were maintained for median 16.5 versus 2.6 weeks ($p=0.006$).¹³ In the PREMIER study, adalimumab in combination with MTX was superior to adalimumab monotherapy; 62% of patients achieved ACR50 response on combination therapy compared with 41% on monotherapy with significantly less radiographic progression ($p<0.001$, both comparisons).¹⁴ In the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study, higher response rates were achieved with etanercept plus MTX than etanercept monotherapy; ACR20, 86% vs 75%; ACR50, 71% vs 54%; ACR70, 49% vs 27% and 28-joint Disease Activity Score (DAS28) remission, 42% vs 22% ($p<0.01$, all comparisons); there was also less radiographic progression ($p<0.05$).¹⁷ In the A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF α Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Rheumatoid Arthritis Despite Methotrexate Therapy (GO-FORWARD) study, ACR20 response was achieved by 56% of patients receiving golimumab in combination with MTX, which was significantly higher than MTX monotherapy (33%, $p<0.001$), and 44% receiving golimumab alone, which was not significantly higher than MTX alone ($p=0.059$).¹⁶ ACR20 responses were reported in 58% of patients treated with certolizumab in combination with MTX in the Rheumatoid Arthritis Prevention of structural Damage 2 (RAPID 2) study¹⁹ and 46% of patients in the Efficacy and Safety of certolizumab pegol – 4 Weekly dosAge in Rheumatoid arthritis (FAST4WARD) study who received certolizumab monotherapy.²¹ Similar results have been reported for rituximab; ACR50 response rates were 41% with rituximab in combination with MTX, which was higher than MTX alone (13%, $p=0.005$), whereas, the response with rituximab monotherapy (33%) was not significantly higher than MTX ($p=0.059$).²²

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Box 1 Search terms and strategies for identifying clinical studies that support the use of biologic monotherapy in patients with rheumatoid arthritis

Search strategies:

- ▶ Evidence supporting the use of biologics as monotherapy: [drug name] AND [rheumatoid arthritis] AND [monotherapies OR monotherapy].
- ▶ Reasons for using biologics as monotherapy: [DMARD] OR [methotrexate] AND [intoleran*] AND [management] AND [rheumatoid arthritis].

Drug names: tocilizumab, infliximab, etanercept, adalimumab, anakinra, abatacept, rituximab, certolizumab, golimumab, tofacitinib

Search limits: PubMed, 2005–2012; Congress (EULAR and ACR) abstracts, 2009–2011; phase 3/4 studies and comparator studies only; English language. Monotherapy studies that included background methotrexate were excluded.

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism.

Direct and indirect effects potentially account for the enhanced efficacy of TNFi agents coadministered with MTX. MTX may independently reduce inflammation and radiographic progression.^{4–8} MTX also may increase the bioavailability of TNFi agents (infliximab^{30,31} and adalimumab,³² though no dose adjustments are required). Infliximab can induce formation of anti-infliximab antibodies that may lower circulating infliximab levels³³ and reduce clinical effect. However, MTX coadministration can promote immune tolerance and increase circulating infliximab levels, prolonging therapeutic effect.¹³ A meta-analysis of 17 prospective cohort studies showed that development of antidrug antibodies to adalimumab and infliximab reduced the therapeutic response rates by up to 68%; this was attenuated with concomitant MTX or other immunosuppressive agents (azathioprine, mercaptopurine).³⁴ Compared with MTX, patients receiving no DMARD, leflunomide or sulphasalazine were more likely to discontinue their first TNFi.²⁴

Clinical response to infliximab is related to its trough levels. Pharmacokinetic analysis of RA patients treated with infliximab plus MTX showed good and moderate responders maintained trough serum concentrations $\geq 1 \mu\text{g/mL}$ through 14 weeks of treatment, whereas poor responders had undetectable trough concentrations.³⁵ Increasing MTX or corticosteroid dose improved therapeutic response in poor responders after an initial response, although trough serum concentrations of infliximab remained below the detectable limit.

Autoantibodies, including antinuclear antibodies (28–100%) and antibodies to double-stranded DNA (0–78%), are detected in patients receiving TNFi agents, particularly infliximab.³⁶ Increased autoantibody formation correlates with lack of response to infliximab,³⁷ suggesting immunologic abnormalities influence efficacy. Addition of an immunosuppressant, such as MTX, may reduce the risk of autoantibody development.³⁶ However, concomitant MTX did not suppress autoantibody development in two small studies,^{38,39} and the effect of autoantibody formation on efficacy of TNFis is yet to be confirmed.

Patients taking TNFi agents who discontinue concomitant MTX experience reduced efficacy and shorter responses. A long-term study in Japan comparing the efficacy of continuation

versus discontinuation of MTX when initiating etanercept in MTX-IR patients showed continuation resulted in better clinical and radiographic outcomes at weeks 52 and 104 than discontinuation.^{40,41} Data from a Dutch registry showed discontinuation of DMARDs was not associated with increased disease activity after 6 months.⁴²

Alternatives to initiating DMARD monotherapy include step-up, parallel, or step-down regimens.⁴³ The most effective regimen is unknown and may be different for different patients.

CHARACTERISATION OF RA PATIENTS NOT TAKING MTX

Data from biologic registries^{23–28,44} and US claims databases^{29,45} indicate approximately 30% of patients taking biologics use them as monotherapy. However, this does not capture patients who fill prescriptions but do not take some or all of the medication.

Patients not taking MTX are those who never initiate MTX—MTX is contraindicated or declined—and those who initiate MTX but subsequently discontinue (figure 1). Among patients who never initiate treatment with MTX are those with contraindications to MTX such as patients who are pregnant or breastfeeding, are heavy alcohol users, have alcohol-induced or other chronic liver diseases or have immunodeficiency or pre-existing blood dyscrasias, known hypersensitivity to MTX or lung disease.⁴⁶ The ACR recommends MTX not be used in the presence of clinically important RA-associated pneumonitis or interstitial lung disease of unknown cause, or in patients with active bacterial, active tuberculosis or life-threatening fungal or active herpes zoster infection.² Additionally, some patients may decline MTX because of the advice to abstain from alcohol consumption; the combination is associated with increased risk for hepatotoxicity.⁴⁶

Patients or physicians may discontinue treatment for a number of reasons. Gastrointestinal, hepatic, dermatologic and neurologic adverse events (AE), as well as cytopenia and MTX-induced pneumonitis, have been reported with MTX^{46–52} and sometimes cause discontinuation. Even in tightly controlled clinical studies, 5–15% of patients taking MTX discontinued treatment because of AEs.^{3,5,7,8,14,17,22} Despite the well-established benefits of MTX for the treatment of RA, including favourable drug survival rates⁵³ and cost-effectiveness,⁵⁴ data from observational studies representing real-life clinical practice indicate MTX discontinuation rates attributed to AEs range from 10% to 77% after 3–12.7 years' treatment.^{51,55–60} Risk factors for MTX-associated AEs include renal dysfunction, liver disease, active infectious disease and excessive alcohol consumption.^{48,52,61} Renal insufficiency is a major risk factor, because

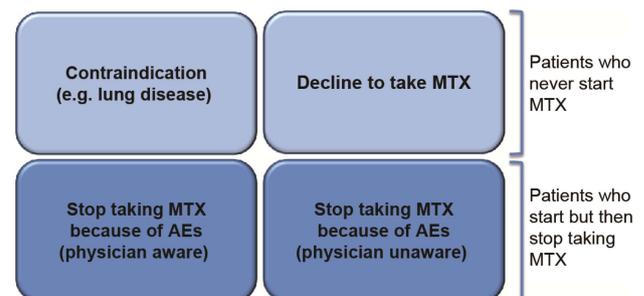


Figure 1 Characterisation of rheumatoid arthritis (RA) patient subpopulations for whom biologic monotherapy may be considered. AE, adverse event; MTX, methotrexate.

lower creatinine clearance rate is associated with reduced MTX clearance, increasing the risk for MTX-related AEs.⁵²

Patients who initiate and subsequently discontinue MTX include those who do not inform their rheumatologists. In an online survey of 1500 patients, 45% admitted to being less than forthcoming with their rheumatologists.⁶² Some patients might be reluctant to admit discontinuation because of minor AEs or unwillingness to abstain from alcohol, but it appears this subgroup exists. Analysis of 6744 patient records from Canadian private and public drug plans showed that, among patients on their first biologic for >6 months, 45% did not purchase a DMARD and 58% did not purchase MTX; 41% of patients taking a biologic for >24 months did not purchase a DMARD (54% for MTX). Independent patient and physician surveys indicated half the patients did not take MTX but continued their prescribed biologic regularly. By contrast, physician surveys indicated a DMARD was prescribed with a biologic for 80–90% of patients.⁶³

Another analysis of 1652 patient records from Canadian private and public drug plans (2009–2010) demonstrated a biologic monotherapy prescribing rate of 12%; however, 29% of patients (43% of those prescribed MTX) did not obtain their DMARD within 6 months after starting biologic therapy.⁶⁴

Collectively, these results demonstrate a substantial gap between prescriptions written and prescriptions dispensed, and between rheumatologists' perceptions and reality of the medications patients are taking.

Therapeutic strategies in patients discontinuing or not initiating MTX

Patients without a contraindication for MTX who decline its use, and those considering discontinuation, may benefit from counselling and education. Patients can be encouraged to use MTX if the potential for progressive joint damage and loss of efficacy with discontinuation or non-compliance is explained.

Several approaches may improve MTX tolerability. Regular monitoring for signs of hepatic, renal or haematological AEs is advised.⁵⁰ Dose adjustment or interruption with reinstatement at a lower dose may be considered if hepatotoxicity is evident.⁵⁰

Switching from oral to intramuscular or subcutaneous (SC) MTX may benefit patients with poor adherence or gastrointestinal AEs.^{65–70} A retrospective study of 191 patients in the UK who switched from oral to SC MTX (2003–2011) showed among 53 patients who switched because of intolerance, 40 (75.5%) subsequently tolerated parenteral therapy.⁷⁰ Another RCT comparing oral and SC MTX found no difference in tolerability, though SC administration demonstrated better clinical

efficacy at the same dosage.⁷¹ An alternative strategy for improving MTX tolerability is twice-weekly dosing, which increases the bioavailability of MTX above once-weekly dosing⁷²; a preliminary study, however, did not demonstrate an efficacy advantage over once-weekly dosing.^{69–73} Potential adjunctive therapies to mitigate AEs include folate supplementation, which reduces MTX-associated hepatic AEs,^{50–74} and antiemetics, which suppress MTX-induced nausea and vomiting.⁷⁵

Switching to another conventional DMARD may be an option in MTX-intolerant patients receiving combination therapy. Registry data and case series indicate rituximab plus leflunomide is a viable alternative to rituximab plus MTX, with potentially better tolerability.^{76–77} By contrast, a high incidence of AEs has been reported with infliximab plus leflunomide.⁷⁸ Tocilizumab and abatacept, in combination with some non-MTX DMARDs, demonstrated good tolerability.^{79–80}

Several TNFi agents are effective as monotherapy, and biologic monotherapy is currently prescribed in patients who are, for one reason or another, not going to use MTX. However, the efficacy of these agents is generally enhanced by concurrent MTX administration.^{13–17}

Biologic and oral DMARD monotherapy

A summary of biologic and oral DMARDs approved for RA is shown in table 1. The TNFi agents etanercept, adalimumab and certolizumab pegol are approved as monotherapy for patients with RA in the USA and Europe,^{81–86} whereas, infliximab and golimumab are approved only with MTX.^{87–90} Among non-TNFi agents, only tocilizumab is licenced for use as monotherapy in the USA and Europe.^{91–92} Tofacitinib anakinra and abatacept are approved as monotherapy only in the USA.^{93–96} Rituximab is approved only with MTX in the USA and Europe.^{97–98} Two recent analyses of the CORRONA registry showed the likelihood of starting biologic monotherapy was consistently increased if it was approved for use as monotherapy.^{44–99} Other factors that increased the likelihood of a biologic monotherapy prescription included the patient's previous biologic experience and the rheumatologist's prescribing patterns.

For use as monotherapy, a biologic or oral DMARD should be superior to placebo; be at least comparable to MTX/DMARDs and the agent plus MTX/DMARDs in reducing clinical signs, symptoms and radiographic progression; and have an acceptable safety and tolerability profile. Further, duration of efficacy, which is a major concern among rheumatologists familiar with the TNFi combination paradigm, should not be compromised. Trials of biologic and oral DMARD monotherapy that meet these criteria are summarised in table 2.

Table 1 Biologic and oral DMARDs approved for the treatment of patients with rheumatoid arthritis

Agent	Mechanism of action	Location	Regimen
Etanercept	TNFi	USA and Europe	Monotherapy
Adalimumab	TNFi	USA and Europe	Monotherapy
Infliximab	TNFi	USA and Europe	In combination with MTX only
Certolizumab pegol	TNFi	USA and Europe	Monotherapy
Golimumab	TNFi	USA and Europe	In combination with MTX only
Tocilizumab	IL-6 receptor inhibitor	USA and Europe	Monotherapy
Anakinra	IL-1 receptor inhibitor	USA	Monotherapy
Abatacept	Inhibitor of T-cell activation (costimulation modulator)	USA	Monotherapy
Rituximab	Anti-CD20	USA and Europe	In combination with a DMARD only
Tofacitinib	JAK inhibitor	USA	Monotherapy

DMARD, disease-modifying antirheumatic drug; IL, interleukin; JAK, janus kinase; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.

Table 2 Studies investigating monotherapy of TNFi and non TNFi agents for the treatment of rheumatoid arthritis

	Monotherapy superior to placebo	Monotherapy at least comparable to MTX/DMARDs	Monotherapy at least comparable to the agent plus MTX/DMARDs
TNFi agents			
Adalimumab	✓ ¹⁰⁰	✓ ¹⁴	χ ^{14 15 101}
Etanercept	NR	✓ ^{3 17 102 103 104}	✓ ^{102 107} χ ^{3 17 40 41 105}
Golimumab	✓ ^{128 129}	✓ ^{16 108 109}	χ ¹⁶
Certolizumab	✓ ^{21 110}	NR	NR
Non-TNFi agents			
Abatacept	✓ ¹¹¹	NR	✓ ¹¹²
Rituximab	NR	✓ ²²	NR
Anakinra	✓ ¹¹³	NR	NR
Tocilizumab	✓ ¹¹⁷	✓ ^{114 115 117 125 130}	✓ ^{79 119 120 122 131}
Tofacitinib	NR	✓ ¹³²	NR

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NR, not reported; TNFi, tumour necrosis factor inhibitor.

Monotherapy with different adalimumab regimens was better than placebo in DMARD-IR patients.¹⁰⁰ Adalimumab monotherapy was associated with similar clinical but more favourable radiological outcomes than MTX alone. Patients with low disease activity at the end of the randomised phase of the study maintained low disease activity and had minimal radiographic progression after 6 years of adalimumab monotherapy.¹⁰¹

Etanercept monotherapy results have been inconsistent. Compared with sulphasalazine monotherapy, etanercept alone, or with sulphasalazine, resulted in significant improvements in disease activity.¹⁰² In the ERA trial, etanercept monotherapy had clinical and radiological advantages over MTX sustained for 24 months in MTX-naïve patients.^{103 104} In the TEMPO study, which included patients with disease durations averaging 6 years, some indices of disease activity and radiographic progression showed greater improvement with etanercept than with MTX. However, the combination was more effective than either agent alone.^{3 17} Etanercept plus MTX was also more effective than etanercept monotherapy in the Japanese Efficacy and Safety of Etanercept on Active Rheumatoid Arthritis (RA) Despite Methotrexate (MTX) Therapy in Japan (JESMR) study.^{40 41 105 106} By contrast, in the open-label ADORE study, clinical improvements (at 16 weeks) were similar with etanercept monotherapy or etanercept plus MTX.¹⁰⁷

Golimumab is not approved for monotherapy. However, studies suggest the efficacy of intravenous golimumab monotherapy is comparable to that of MTX; golimumab plus MTX, however, was more effective than MTX alone.^{16 108 109}

Certolizumab pegol monotherapy demonstrated superiority to placebo in the FAST4WARD study²¹ and was similar to concomitant DMARD treatment in the REALISTIC study, regardless of previous TNFi use.¹¹⁰

Monotherapy with non-TNFi biologics, except for tocilizumab, has not been investigated extensively. In a study involving 214 patients, abatacept monotherapy resulted in a dose-dependent increase in ACR20 response compared with placebo after approximately 3 months of treatment.¹¹¹ In the ARRIVE study, TNFi-IR patients taking abatacept monotherapy experienced similar efficacy to patients taking abatacept plus DMARDs.¹¹² Rituximab monotherapy yielded an ACR50 response rate higher than, but not statistically significantly

different from, MTX.²² Anakinra monotherapy demonstrated increased efficacy compared with placebo, but response rates were modest.¹¹³

Tocilizumab has the largest database on monotherapy and has demonstrated greater efficacy than MTX or other DMARDs, including salazosulphapyridine, bucillamine, mizoribine and D-penicillamine, in lowering disease activity and reducing radiographic progression. Results from Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy (AMBITION) and Study of Active controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with Inadequate response to methotrexate (SATORI) demonstrated higher ACR20, ACR50 and ACR70 response rates with tocilizumab than MTX.^{114 115} Furthermore, patients from AMBITION maintained DAS28 and clinical disease activity index low-disease activity and remission thresholds during long-term tocilizumab monotherapy.¹¹⁶ Tocilizumab monotherapy was more efficacious than non-biologic DMARDs at slowing joint damage in the Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor (SAMURAI) study, even in patients at high risk for structural damage.^{117 118} Contrary to findings with TNFi agents, add-on (tocilizumab plus MTX) therapy was not superior to tocilizumab monotherapy in MTX-IR patients in the ACT-RAY study; ACR responses, swollen and tender joint counts, DAS28 change from baseline, DAS28 ≤ 3.2 and Genant-modified Total Sharp Score were not significantly different between tocilizumab plus MTX and tocilizumab monotherapy ($p > 0.05$), though proportions of patients achieving DAS28 < 2.6 and patients without radiographic progression were significantly higher with tocilizumab plus MTX ($p < 0.05$).^{119 120} These differences in efficacy are unlikely due to immunogenicity because the proportions of patients with neutralising antidrug antibodies were similar between monotherapy (4.4%) and combination therapy (3.7%).¹²¹

In the ACT-SURE¹²² and ACT-STAR⁷⁹ studies, which were real-world-type safety studies in patients with active RA despite receiving biologics or DMARDs, comparable improvements in clinical signs and symptoms were observed in patients receiving tocilizumab monotherapy or tocilizumab plus DMARDs, although precise reasons for not receiving DMARDs are unknown. Long-term data from the Safety and Efficacy of Tocilizumab, an anti-IL-6 receptor monoclonal antibody, in Monotherapy, in Patients With Rheumatoid Arthritis (STREAM) study showed tocilizumab monotherapy is not associated with clinically relevant decline in efficacy over time; ACR response rates and improvements in DAS28 were sustained over 5 years of tocilizumab monotherapy.¹²³

In the ADalimumab ACTemra (ADACTA) trial, which directly compared tocilizumab and adalimumab monotherapy in patients who were MTX-intolerant or unable to continue MTX therapy, tocilizumab was superior to adalimumab in reducing signs and symptoms of RA. The AE profile of tocilizumab was consistent with previous findings and comparable with that of adalimumab.¹²⁴

Several additional reports support the efficacy of tocilizumab monotherapy. A systematic review of 10 clinical trials demonstrated tocilizumab monotherapy yielded significantly higher ACR20, ACR50 and ACR70 response rates than MTX.¹²⁵ Additionally, a meta-analysis of six Japanese clinical studies and their five uncontrolled long-term extensions confirmed high rates of ACR20 (91.3%), ACR50 (73.0%) and ACR70 (51.3%) responses and DAS remission (59.7%) were maintained with tocilizumab monotherapy for 5 years.¹²⁶ Finally, a network meta-analysis involving indirect comparison of clinical trials

showed tocilizumab plus MTX had ACR responses comparable to other biologics plus MTX. When used as monotherapy, tocilizumab was likely to show better efficacy than TNFi monotherapy and comparable efficacy to tocilizumab plus MTX.¹⁸

SUMMARY: PHYSICIAN'S PERSPECTIVE

Concurrent use of MTX and a biologic is generally the standard-of-care in patients with RA who continue with disease activity despite MTX. Many patients, however, do not take MTX concomitantly as prescribed. Strategies exist to mitigate MTX-associated AEs; however, a substantial proportion of patients should not or do not take MTX.

Rheumatologists may recognise biologic monotherapy is sometimes necessary when treating patients with RA and comorbidities or patients who consume alcohol. Although consensus is lacking on biologics as monotherapy, accumulating data can inform rheumatologist decision making to treat such patients optimally.

Although we use the generic term 'biologics', these medications have different mechanisms of action that might affect the need for combination with MTX for improved efficacy. It is, therefore, not surprising that biologics appear to differ substantially with respect to the degree of benefit when administered as monotherapy.

Tocilizumab monotherapy has greater efficacy than MTX or other conventional DMARDs in lowering disease activity and reducing radiographic progression and has stable safety and tolerability profiles.^{114 115 117 119 127} Tocilizumab monotherapy also demonstrated superiority over adalimumab monotherapy in reducing signs and symptoms of RA in patients who were MTX-intolerant, or in whom MTX was considered ineffective or inappropriate.¹²⁴

That monotherapy with any biologic is absolutely equivalent to a biologic coadministered with MTX is not a proven notion. Data shed light on how to deal with this treatment issue; treating without MTX appears to be safe and effective when necessary. However, in the subpopulation of patients not taking, or unable or unwilling to take, MTX, but in whom treatment is required, TNFi agents might not be the first choice of monotherapy given the evidence they are less effective as monotherapy than as combination therapy with MTX.

Correction notice This article has been corrected since it was published Online First. The names of the studies AMBITION, SATORI, SAMURAI and STREAM have been amended, Table 1 has been updated and the following sentence amended to read: When used as monotherapy, tocilizumab was likely to show better efficacy than TNFi monotherapy and comparable efficacy to tocilizumab plus MTX.¹⁸

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