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Biological agents in monotherapy for the treatment of rheumatoid arthritis

Cem Gabay[a], Paul Hasler[b], Diego Kyburz[c], Alexander So[d], Peter Villiger[e], Johannes von Kempis[f], Ulrich A. Walker[g]

[a] University Hospitals of Geneva, Switzerland
[b] Kantonsspital Aarau, Switzerland
[c] University Hospital Zürich, Switzerland
[d] University of Lausanne, Switzerland
[e] University Hospital Bern, Switzerland
[f] Kantonsspital St. Gallen, Switzerland
[g] Basel University Hospital, Switzerland

Summary

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease, which results in joint destruction and permanent disability. The advent of disease-modifying antirheumatic drugs (DMARDs) has made a profound impact on the outcome and prognosis of RA. Methotrexate (MTX) is a central agent in RA therapy, and is used either alone or in combination with biological DMARDs. However, a large proportion of RA patients (20%–40%) either do not respond to or are unable to tolerate MTX or the alternative agents used in place of MTX (including leflunomide, sulfasalazine, azathioprine, hydroxycholoquine and combination DMARDs). For these patients, monotherapy with biological DMARDs is a key treatment option that balances tolerability with improved clinical outcomes. This article reviews the data for four biological agents approved for use as monotherapy in Switzerland (adalimumab, certolizumab pegol, etanercept and tocilizumab) in order to formulate a consensus statement on their roles in biologic monotherapy of RA.

Abbreviations

ACR:	American College of Rheumatology
CRP:	C-reactive protein
DAS28:	Disease Activity Score using 28 joint counts
DMARD:	disease-modifying antirheumatic drug
EULAR:	European League Against Rheumatism
HAQ-DI:	health assessment questionnaire disability index
Ig:	immunoglobulin
IL:	interleukin
MTX:	methotrexate;
PEG:	polyethylene glycol
RA:	rheumatoid arthritis
sDMARD:	synthetic DMARD
TNF:	tumour necrosis factor.

Key words: *rheumatoid arthritis; TNFα; IL-6; DMARDs; monotherapy; tocilizumab; adalimumab; etanercept; certolizumab pegol; methotrexate*

Introduction and current therapy recommendations

Rheumatoid arthritis (RA) is one of the most frequently occurring autoimmune rheumatic diseases, affecting an estimated 1% of the global population [1, 2]. Deregulation of the pro- and anti-inflammatory homeostasis is the cornerstone of pathogenesis, triggering the induction of autoimmunity [3]. The chronic inflammation that underpins this disease leads to synovial inflammation and effusion, the cardinal signs of which are joint pain, stiffness and swelling, ultimately followed by joint destruction and permanent disability.

The synthetic disease-modifying antirheumatic drug (sDMARD) methotrexate (MTX) is a central agent in the treatment of RA, and can be used either alone or in combination with other sDMARDs or biological DMARDs [4–6]. However, an estimated 20%–40% of patients either fail to achieve remission or are unable to tolerate MTX or standard combination therapy [5, 7, 8]. The use of MTX is associated with significant variability in response, with respect to both efficacy and toxicity [9, 10], and often patients with severe disease exhibit only a partial response to MTX therapy [11]. According to the latest European League Against Rheumatism (EULAR) recommendations, if the treatment goal is not achieved using the first DMARD and there are no poor prognostic factors, then the patient should be switched to another sDMARD (such as leflunomide or sulfasalazine) [12]. If, however, there are poor prognostic factors, the addition of a biological DMARD is recommended [12]. For those patients with insufficient response to MTX or other conventional DMARDs (with or without accompanying glucocorticoids), the EULAR recommends

the inclusion of a biological DMARD, such as tumour necrosis factor (TNF) inhibitors, abatacept or tocilizumab, and, in certain conditions, rituximab [12]. In the case of failure of the biologic therapy, tofacitinib may be considered [12]. Although the efficacy of combination therapy is well documented, it is associated with side effects that may limit its application in certain settings, such as in patients with significant comorbidities [13]. Monotherapy with biological DMARDs is indicated in the case of intolerance to MTX and other sDMARDs alongside persistent active disease [8, 14]. In many cases, however, patients themselves choose to forego the sDMARD (usually MTX) and continue only with the biological agent [15]. The resulting clinical reality is that roughly one-third of RA patients are undergoing treatment with biological DMARD monotherapy [16]. There is thus an urgent need for clear guidance on the application of biological agents in this setting.

Currently, four biological agents are licensed for use as monotherapy in Switzerland: adalimumab, certolizumab pegol, etanercept, and tocilizumab. This review considers the available evidence for these agents, and also provides a brief overview of the nonapproved agents abatacept, golimumab and rituximab in monotherapy. We performed a PubMed literature search for clinical trial data on biologic monotherapy in RA published until May 2013. Included studies were limited to prospective, randomised clinical trials. Owing to the limitations of space, we present the main findings from pivotal trials, and the section on safety will focus on the key issues relevant to therapy with these biological agents. The appendix provides an overview of the main clinical trial data.

Key messages – biologic monotherapy in rheumatoid arthritis

Efficacy:

- Monotherapy with biological DMARDs provides a critical line of therapy for patients who cannot tolerate MTX and other conventional DMARDs.
- TNF inhibitors show a consistently lower efficacy when used as monotherapy compared with use in combination with MTX, highlighting the preference for concomitant DMARD use with this class of biological agents.
- Tocilizumab monotherapy has been shown to be more efficacious compared with MTX as well as with adalimumab monotherapy.
- The available clinical evidence suggests that tocilizumab monotherapy has comparable efficacy to tocilizumab plus MTX.

Safety:

- The safety issues related to the use of biologic monotherapy are similar to those of combination therapy with biologics.

DMARD = disease-modifying antirheumatic agent; MTX = methotrexate; TNF = tumour necrosis factor

Adalimumab

Adalimumab is a recombinant, fully human monoclonal anti-TNFα antibody that specifically binds to the cytokine and removes it from the circulation. The standard dosage of adalimumab is 40 mg every other week, administered subcutaneously [17]. An initial randomised, double-blind, phase III study showed that adalimumab monotherapy achieved significant improvements in disease activity compared with placebo [18]. Following these findings, the PREMIER trial compared the combination of adalimumab plus MTX versus both agents as monotherapy in MTX-naïve patients with early RA [19]. Results from the PREMIER study demonstrated that combination therapy yielded superior outcomes to either agent alone. After 2 years of treatment, 49% of patients receiving combination therapy achieved a state of clinical remission defined as a Disease Activity Score using 28 joints (DAS28 score) <2.6 and 49% had a major clinical response (defined as American College of Rheumatology [ACR] 70 response for at least 6 consecutive months). These rates were around twice those observed in the patients who received monotherapy with either MTX or adalimumab [19]. Of note, there was significantly less radiographic disease progression with adalimumab monotherapy compared with MTX monotherapy [19].

Recommendations: Adalimumab appears to be most effective when used in combination with MTX, but may be used alone in order to slow radiographic progression.

Certolizumab pegol

Certolizumab pegol is a polyethylene glycol (PEG)-ylated, TNFα monoclonal antibody devoid of the Fc region [20]. Certolizumab pegol monotherapy has been shown to be superior to placebo, as demonstrated by the FAST4WARD study [21]. After 6 months, a significantly higher proportion of the certolizumab pegol group (45.5%) achieved the primary endpoint of ACR20 response, compared with 9.3% of the placebo group. Significant improvements were also seen across the other study endpoints. In the phase IIIb REALISTIC study, certolizumab pegol was compared against placebo plus the patient's current therapy [22]. The study included patients who had inadequate response to at least one DMARD. Treatment with certolizumab pegol resulted in significant improvements in ACR20 across all patient subgroups, irrespective of concomitant DMARD use at baseline. ACR50, health assessment questionnaire disability index (HAQ-DI) and DAS28 also showed significant improvements from baseline with the benefits becoming apparent as early as 2 weeks after treatment initiation [22].

The findings from these two trials demonstrate that certolizumab pegol can yield consistent responses in RA patients with diverse disease characteristics, including those who had failed prior DMARD treatment.

Recommendations: At present, there are no comparative data against MTX for certolizumab pegol monotherapy.

Etanercept

Etanercept is a dimeric fusion protein consisting of the extracellular region of two human p75 TNF receptors plus

the Fc region of human IgG1 [23]. The main data supporting the use of etanercept as monotherapy come from the ERA trial, which compared etanercept with MTX in 632 patients with early RA [24]. At 6 months, the ACR70 response was significantly higher in patients treated with etanercept than in those receiving MTX, though ACR20 or ACR50 response rates were no different in the two treatment arms. Mean increases in bone erosion scores during the first 6 months were significantly lower in the etanercept group than in the MTX group [24].

Results from a more recent randomised, double-blind clinical trial (the TEMPO study), which included MTX-naïve patients, demonstrated that etanercept is more efficacious when used in combination with MTX [25]. As monotherapy, etanercept was not significantly superior to MTX [25, 26]. The COMET study, which also included MTX-naïve patients, compared the etanercept-MTX combination versus MTX monotherapy in the first year, while the second year of the study evaluated etanercept as monotherapy [27]. The findings from the main study as well as from a *post-hoc* analysis demonstrated that the main clinical benefits were derived from the combination of etanercept and MTX [27, 28]. At week 104, the removal of MTX resulted in a worsening of clinical and radiographic responses compared with continuous etanercept-MTX combination therapy. These findings indicate that MTX needs to be administered alongside etanercept in order to achieve optimal clinical and radiographic outcomes for patients with early RA [28].

In patients with inadequate response to MTX, the accepted indication for etanercept therapy, published data have been conflicting, with etanercept monotherapy yielding either similar or inferior results to MTX. The ADORE study compared etanercept added to patients' baseline MTX dose versus etanercept monotherapy. Both arms of this study had similar outcomes with respect to ACR and DAS responses [29]. In contrast, the JESMR study showed that patients treated with etanercept plus MTX exhibited significantly better ACR responses than those treated with etanercept alone. Furthermore, the combination regimen resulted in better prevention of structural damage [30]. The CAMEO study examined the effect of MTX withdrawal in patients treated with a combination of etanercept and MTX for 6 months and who were randomised to pursue the combination of MTX plus etanercept or switched to etanercept alone [31]. After 6 months, DAS28 levels remained stable in patients treated with etanercept plus MTX but increased in those treated with etanercept alone. Notably, this difference was observed in patients with DAS28 levels ≥3.2 at the time of randomisation, indicating that the use of MTX is necessary if low disease activity is not achieved [31]. These findings have been supported by registry data, which showed a longer maintenance of drug efficacy when etanercept was combined with MTX, in comparison with etanercept monotherapy [32]. Of note, results from the ETA study indicated that etanercept could also be used in combination with sulfasalazine in patients who had active RA despite ongoing sulfasalazine treatment [33].

Recommendations: The bulk of the data from the above studies supports the use of etanercept in combination with MTX.

Tocilizumab

Tocilizumab is a recombinant, humanised monoclonal antibody directed against the human IL-6 receptor [34].

The first study to demonstrate the safety and efficacy of tocilizumab monotherapy was a Japanese phase I/II study in 162 patients with DMARD-resistant active disease [35]. The patients received treatment with either placebo or tocilizumab. After 3 months, there were significant benefits with respect to ACR20 response in the 8 mg/kg and 4 mg/kg tocilizumab groups (78%, and 57%, respectively). Similar benefits were observed for ACR50 and ACR70 [35].

Both the Japanese SATORI and SAMURAI studies demonstrated the superiority of tocilizumab compared with the control treatment (MTX or other conventional DMARDs) [36, 37]. The primary endpoint of the SATORI study, an ACR20 response at week 24, was achieved in 80.3% of the tocilizumab group compared with 25.0% of the MTX control group [37]. The aim of the SAMURAI study was to assess the ability of tocilizumab monotherapy to reduce progressive structural joint damage in RA patients at risk of disease progression [36]. Results showed that treatment with tocilizumab monotherapy suppressed bone erosion more efficiently than conventional DMARD treatment. Results from both SAMURAI and SATORI underscored the clinical benefits of tocilizumab monotherapy in RA patients who do not respond to treatment with other DMARDs, including MTX. However, the use of low-dose MTX in Japan limits the extrapolation of these data to Western populations.

The AMBITION study also compared tocilizumab monotherapy with MTX, but in patients who were either MTX-naïve or who had not used it in the 6 months prior to the study and were not considered refractory to MTX or TNF inhibitors [38]. Patients were randomised to three treatment arms: tocilizumab, MTX, or placebo for 8 weeks followed by tocilizumab. Significantly more patients on tocilizumab monotherapy (70.6%) achieved an ACR20 response, in contrast to 52.1% of the MTX arm. The benefits of tocilizumab treatment were maintained regardless of whether patients were MTX-naïve or had received prior MTX treatment. Together with the positive results from the SATORI and SAMURAI studies, the findings from AMBITION establish tocilizumab as the first biological agent to show statistically superior clinical efficacy compared with standard MTX monotherapy [38].

The benefits of tocilizumab monotherapy demonstrated in the above trials raised the question of whether tocilizumab can be given in combination with MTX, or whether MTX therapy can be stopped and the patient switched to tocilizumab monotherapy. The ACT-RAY study, although not designed to evaluate tocilizumab monotherapy *per se*, aimed to evaluate the efficacy of switching from MTX to tocilizumab monotherapy in patients with active RA despite MTX treatment [39]. There were no clinically significant benefits of the tocilizumab + MTX combination compared with the switch to tocilizumab monotherapy [39, 40, 41]. The SURPRISE study compared the switch to tocilizumab monotherapy ("switch") versus addition of tocilizumab to an existing MTX regimen ("add-on"), in patients with inadequate response to MTX [42]. Results showed that the

add-on strategy was superior compared with the switch to tocilizumab monotherapy in terms of DAS28 remission. However, results across all other criteria were similar in both groups. Recent data from the FUNCTION study revealed statistically significant improvements in DAS28 remission after 24 weeks of treatment with either the combination of tocilizumab plus MTX, or tocilizumab monotherapy [43]. Taken together, these results support the feasibility of tocilizumab as monotherapy as well as in combination with MTX.

The ADACTA study was the first head-to-head comparative trial to explore the efficacy of two monotherapy agents (tocilizumab vs adalimumab) [44]. The mean change in DAS28 score as the primary endpoint was significantly better in the tocilizumab arm than in the adalimumab arm; these findings were similar across all other endpoints. These data corroborate the data from previously published studies on both agents [18, 36–39], further supporting the conclusion that more patients may benefit from tocilizumab monotherapy compared with adalimumab monotherapy.

Recommendations: Tocilizumab is the first biological agent to show statistically superior clinical efficacy compared with standard MTX monotherapy. In addition, clinical data suggest a comparable efficacy when used as monotherapy as in combination with MTX.

Nonapproved biological agents used in monotherapy

An overview of the agents that have not received formal approval in Switzerland for use as monotherapy in RA is given in table 1. As these biologicals have significant off-label use, the reader should be aware of the available evidence for each of these agents as monotherapy in the treatment of RA.

The T-cell inhibitor abatacept is currently approved only in the USA for use as monotherapy. In a phase II study, abatacept yielded numerically superior responses compared with placebo in patients with inadequate response to DMARDs [45]. Data from the open-label ARRIVE study, however, showed that abatacept was more efficacious when used in combination with a DMARD [46]. Recently, the efficacy of abatacept monotherapy was shown to be equivalent to that of abatacept with concomitant MTX in the 4–month open-label ACCOMPANY trial [47].

Golimumab is a human anti-TNFα monoclonal antibody with demonstrated efficacy in combination with MTX. However, results from both the GO-BEFORE and GO-FORWARD studies indicated that golimumab monotherapy was not superior to MTX monotherapy [48, 49]. The use of golimumab in combination with MTX yielded consistently better outcomes compared to MTX alone; however, when used alone golimumab yielded similar results to MTX monotherapy [48].

Data for the anti-CD20 monoclonal antibody rituximab were derived from a phase II study, which included RA patients who had inadequate response to MTX. A higher percentage of patients achieved ACR50 and ACR70 responses when treated with a combination of rituximab plus MTX compared with rituximab monotherapy [50]. However, DAS28 scores and the number of patients achieving good or moderate EULAR responses were not significantly different between the two treatment arms [50]. Similar results were observed in a small study which compared rituximab monotherapy with the combination of rituximab plus MTX [51].

Safety and tolerability

In general, the safety and tolerability issues for biologic monotherapy are similar to those for combination therapy, with the exception of the formation of anti-drug antibodies. Table 2 summarises the recommended safety monitoring procedures for each agent.

Infection

Compared with the general population, RA patients have an increased risk of infection, due to the pathobiology of the disease, the impact of age, chronic comorbidities, and the sequelae of immunosuppressive therapy [52, 53]. An increased risk of serious bacterial infections has been associated with TNF inhibitors [54, 55], although conflicting data have been reported [56–58]. Infection rates in patients treated with tocilizumab monotherapy were reported at 4.5 per 100 patient-years [59]. It has been reported that tocilizumab suppressed fever and the increase in C-reactive protein (CRP) levels after joint surgery [60]. This finding is in line with the role of IL-6 in the regulation of the acute-phase response [61], and suggests that CRP cannot be used as a marker of tissue damage and infection during tocilizumab treatment. In general, safety findings suggest that careful monitoring for infections is important during treatment with all biological agents. Special attention should be given when monitoring patients with a history of chronic infections [62].

Malignancies

Compared with the general population, patients with RA have a higher risk of developing certain malignancies [63]. Despite initial concern with the use of TNF inhibitors, meta-analysis of registry data and observational published

Table 1: Biological agents without monotherapy approval in Switzerland.

Agent	Therapeutic target	Administration	Key clinical trials
Abatacept	T-cell costimulation [83].	10 mg/kg i.v. infusion, at weeks 0, 2 and 4 and thereafter every 4 weeks or subcutaneously at a weekly dosage of 125 mg.	Phase II study [45]; subanalysis of the ARRIVE open-label study [46].
Golimumab	TNFα [84].	50 mg once a month in combination with MTX (100 mg as monotherapy).	Phase III studies GO-BEFORE [48] and GO-FORWARD [49].
Rituximab	B cells [85].	1,000 mg i.v. infusion, followed by a second 1,000 mg infusion 2 weeks later.	Phase II study [50]; open-label study [51].

MTX = methotrexate; TNF = tumour necrosis factor

reports did not identify any increase in malignancies [62]. The exception is the incidence of nonmelanoma skin cancer, which has been shown to increase with infliximab, etanercept and adalimumab treatment [64]. In addition, recent data from the Swedish registry showed that the incidence of melanoma is increased with TNF antagonists [65]. There are only limited data on the risk of malignancy with tocilizumab use. Safety data from the STREAM study indicated that the rates of malignancy with tocilizumab treatment were not significantly elevated from those seen in the general population [66], although these results are limited by the relatively short timeframe of the follow-up. Similarly, no increase in rates of malignancies have been detected with rituximab or abatacept [64].

Antibody development

The development of anti-drug antibodies is the most important issue that affects drug efficacy, and is associated with the use of biological agents as monotherapy. However, the long-term clinical relevance of these antibodies is not clear. A prospective cohort study in RA outpatients showed that the presence of anti-adalimumab antibodies was associated with lower circulating drug concentrations and decreased likelihood of minimal disease activity or clinical remission [67]. Interestingly, the concomitant use of MTX has been shown to have a favourable effect on the development of anti-adalimumab antibodies, an effect that was dose dependent [68]. Anti-drug antibodies against certolizumab pegol have been reported in approximately 12% of patients, but the clinical significance of this is unknown [69]. The development of anti-tocilizumab antibodies is relatively rare; a meta-analysis of four clinical trials showed that treatment efficacy was maintained even in the few (18 out of 1,747 patients) who developed neutralising antibodies against the drug [6]. Furthermore, the levels of anti-tocilizumab antibodies were not affected by concomitant MTX treatment [40]. Use of etanercept is not associated with the formation of neutralising antibodies [70].

Injection-site reactions

Meta-analysis of clinical trial data for adalimumab and etanercept indicated that injection-site reactions occurred more frequently compared with placebo [71]. A similar meta-analysis for certolizumab pegol, however, reported rates of injection-site reactions that were similar to placebo controls [64]. Product information sheets report rates of infusion reactions of 8% with tocilizumab (vs 5% in control groups) when used at the approved dose [72]. Treatment with TNF inhibitors and tocilizumab has been associated with allergic skin reactions [73, 74]. Although rare, anaphylactic hypersensitivity reactions have been associated with tocilizumab, adalimumab and etanercept, indicating the need for careful monitoring for this side effect [6, 75–78].

Other adverse events

Minor elevations in the levels of transaminases have been observed in patients treated with tocilizumab. Clinical trial data revealed that these occurred at a similar rate seen with MTX monotherapy, with a higher incidence associ-

Table 2: Recommended clinical monitoring procedures for adalimumab, certolizumab pegol, etanercept and tocilizumab (adapted from http://www.rheuma-net.ch).

TNF inhibitors (adalimumab, certolizumab pegol and etanercept), and tocilizumab				
Administration Adalimumab: 40 mg subcutaneously, every 2 weeks Certolizumab pegol: 400 mg subcutaneously at weeks 0, 2 and 4, thereafter 200 mg subcutaneously every 2 weeks (or 400 mg subcutaneously every 4 weeks) Etanercept: 2 x 25 mg or 1 x 50 mg, per week Tocilizumab: 8 mg/kg body weight (up to a maximum of 800 mg) intravenously once every 4 weeks Preliminary examinations / medical history Infections, particularly respiratory tract infections and tuberculosis Allergic reactions Cardiac insufficiency (in the case of TNF inhibitors) Suspicion of multiple sclerosis (in the case of TNF inhibitors) Lupus or related symptoms (in the case of TNF inhibitors) Presence of malignant tumours				
TNF inhibitors				
Examination	**Before treatment**	**Monitor according to patient's clinical status, comorbidities and comedications**		
Complete blood count	+			
ESR, CRP	+			
AST, ALT	+			
Hepatitis B & C, HIV	+			
Mantoux or IGRA test	+			
Chest X-ray	+			
Tocilizumab				
Examination	**Before treatment**	**1–4 months**	**4–6 months**	**7 months and beyond**
Complete blood cell count	+	Once a month	Every 2 months	Every 3 months
ESR, CRP	+	Once a month	Every 2 months	Every 3 months
AST, ALT	+	Once a month		Every 6 or 12 months
Cholesterol (HDL, LDL), triglycerides	+	From 3 months		
Hepatitis B & C, HIV	+			
Mantoux or IGRA test	+			
Chest X-ray	+			

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; IGRA = interferon-gamma release assay; LDL = low-density lipoprotein; TNF = tumour necrosis factor

ated with the combination of tocilizumab plus DMARD therapy [64, 79]. Other liver function parameters, however, were not affected, and there have been no reports of severe liver injury or liver failure thus far.

Patients treated with tocilizumab often exhibit abnormal lipid profiles, including elevations in cholesterol levels, which increase during the first 6 weeks of treatment and remain relatively stable thereafter [59]. Although RA in itself is known to alter the lipid profile [80], the long-term cardiovascular effects of the cholesterol elevations observed with tocilizumab are unknown [64] and coadministration of a cholesterol-lowering agent must be considered. Demyelinating conditions are rare events that appear to be specific to TNF inhibitors [81]. Cases of multiple sclerosis have been observed in TNF inhibitor trials as well as in surveillance reports; therefore, previous history of multiple sclerosis or optic neuritis is a contraindication for treatment with inhibitors of TNF [63].

Pregnancy

In general, the administration of all biological agents is not recommended during pregnancy and lactation [82].

Conclusions

This review summarises the key clinical data for the four biological DMARDs licensed for use in Switzerland as monotherapy, namely adalimumab, certolizumab pegol, etanercept and tocilizumab. For various reasons, such as intolerance to MTX or patient compliance issues, biologic monotherapy is used in roughly one-third of RA patients [16]. Data from the Swiss Clinical Quality Management registry for RA patients show that biological agents are prescribed as monotherapy in up to 39% of treatment courses, and that 27% of treatment courses with biological agents are begun as monotherapy (Gabay et al., unpublished observations).

For patients who are nonresponders or intolerant to maximal doses of MTX, the choice consists of either introducing DMARD combination therapy or initiating treatment with a biological agent. The available data indicate that TNF antagonists show less efficacy as monotherapy than when used in combination with MTX, whereas tocilizumab is the only biological agent that has demonstrated greater efficacy than MTX and other conventional DMARDs when used as monotherapy. Taken together, the bulk of clinical data supports tocilizumab as a good choice of monotherapy for the subpopulation of RA patients who are not eligible for biological agent combination therapy due to their inability to tolerate MTX or its alternatives.

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Correspondence: *Professor Cem Gabay, MD, Division of Rheumatology, University Hospitals of Geneva, 26 Avenue Beau-Séjour, CH-1211 Geneva 14, Switzerland,* *cem.gabay[at]hcuge.ch*

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Appendix

Summary of the clinical trials using adalimumab, certolizumab pegol, etanercept and tocilizumab as monotherapy in rheumatoid arthritis.

Agent	Study	Number of patients	Patient characteristics	Study design, treatment	Summary of outcomes
Adalimumab	PREMIER [19]	799	MTX-naïve, around one-third had received treatment with other DMARDs, mean disease duration <1 year.	2-year, randomised, double-blind study. Treatment: adalimumab (40 mg s.c. every 2 weeks) + MTX (20 mg/week) versus adalimumab monotherapy or MTX monotherapy. Primary endpoints: Percentage of patients with an ACR50 response, and the mean change from baseline in modified total Sharp score.	The adalimumab + MTX combination yielded the best outcomes. ACR50 response after 1 year: 62% with combination therapy, 46% with MTX monotherapy, and 41% with adalimumab monotherapy (p <0.001). Radiographic progression: Was significantly less (p <0.002) in the combination treatment arm, after year 1 and year 2. Similar results were seen for ACR20, ACR70 and ACR90, after 1 year and 2 years of treatment.
Certolizumab pegol	FAST4WARD [21]	220	Mean of 2 prior DMARDs used, mean disease duration ~9–10 years.	24-week, randomised, double-blind study. Treatment: Certolizumab pegol (400 mg s.c.) every 4 weeks, or placebo Primary endpoint: 20% improvement in ACR20 at week 24	ACR20 response rates were 45.5% for certolizumab pegol versus 9.3% for placebo (p <0.001).
	REALISTIC [22]	1,063	Inadequate response to ≥1 DMARD (37.6% had previously used TNF inhibitors).	12-week, double-blind study. Treatment: Certolizumab pegol (400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks) or placebo (every 2 weeks) plus current therapy stratified by previous TNF inhibitor use, concomitant MTX use and disease duration (<2 vs ≥2 years) Primary endpoint: ACR20 response rate at week 12.	The primary endpoint was significantly better in the certolizumab pegol group (week 12 ACR20 compared with placebo: 51.1 vs 25.9%; p <0.001). Week 12 ACR20 responses were similar across all certolizumab pegol patient subgroups regardless of concomitant DMARD use at baseline.
Etanercept	ERA [24]	632	MTX-naïve, 39%–46% previously treated with other DMARDs, disease duration ~12 months.	12-month randomised, double-blind, placebo-controlled study. Treatment: (1.) 10 mg etanercept s.c. twice a week, (2.) 25 mg etanercept s.c. twice a week, (3.) 3 x 2.5 mg oral MTX weekly Primary endpoints: ACR response; bone erosion and joint space narrowing according to the Sharp scale.	During the first 6 months of assessment, the 25 mg etanercept group showed 20%, 50% and 70% improvement in disease activity compared with MTX (p <0.05). After 6 months, the differences between the etanercept and MTX groups were apparent only for ACR70 scores (p <0.05). Mean increases in bone erosion scores at 6 months were 0.30 in the 25 mg etanercept group versus 0.68 in the MTX group (p = 0.001), and 0.47 and 1.03, respectively (p = 0.002) after 12 months.
	TEMPO [26, 25]	682	~43% previously treated with MTX, mean number of prior DMARDs 2–3, disease duration ~6–7 years.	52-week randomised, double-blind, parallel-group study. Treatment: (1.) 25 mg etanercept s.c. twice a week (2.) Oral MTX (up to 20 mg weekly) (3.) Combination etanercept + MTX Primary endpoints: ACR-N AUC; joint damage according to modified total Sharp score	Combination therapy yielded the best outcomes across all endpoints. ACR-N AUC at 24 weeks was best for the combination group (18.3%-years [95% CI 17.1–19.6]) compared with etanercept alone (14.7%-years [13.5–16.0]) or MTX alone (12.2%-years [11.0–13.4]. Combination therapy was significantly more effective at slowing joint damage.

	COMET [27]	411	MTX-naïve, disease duration 3–24 months.	2-year randomised, double-blind study. Four treatment groups: (1.) Etanercept + MTX in year 1 followed by continued combination treatment in year 2 (EM/EM), (2.) Combination treatment in year 1 followed by etanercept alone in year 2 (EM/E), (3.) MTX monotherapy in year 1 followed by combination treatment in year 2 (M/EM), or (4.) MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2 (M/M). Primary objectives: To evaluate how continuation of and alterations to initial year 1 combination etanercept + MTX therapy and MTX monotherapy regimens affect long-term remission and radiographic progression in early, active RA.	Early sustained combination therapy with etanercept + MTX was superior to MTX monotherapy. Combination therapy resulted in important clinical and radiographic benefits over 2 years. At year 2, DAS28 remission was achieved by 62/108, 54/108, 1/88, and 33/94 subjects in the EM/EM, EM/E, M/EM and M/M groups, respectively (p <0.01 for the EM/EM and M/EM groups versus the M/M group).
	ADORE [29]	315	Patients with active RA taking MTX >12.5 mg/week for >3 months (mean time since primary diagnosis ~10 years), and were MTX inadequate responders.	16-week randomised, open-label study Treatment: Etanercept (25 mg twice weekly) added to the baseline dose of MTX, versus etanercept monotherapy. Primary endpoint: DAS28 (4) improvement of >1.2 units.	The primary endpoint was achieved by 72.8% and 75.2% of patients treated with etanercept and those treated with etanercept + MTX, respectively (nonsignificant difference; p = 0.658).
	JESMR [86, 30]	151	Mean MTX dose ~7 mg/week, disease duration 8–10 years.	52-week randomised, double-blind study. Treatment: Etanercept 25 mg twice a week with 6–8 mg/week MTX (E+M group), or etanercept alone (E group). Primary endpoint: Radiographic progression assessed by van der Heijde-modified Sharp score at week 52.	MTX should be continued when starting etanercept in patients with active RA. No significant differences between the treatment groups in primary endpoint (Sharp score 0.8 vs 3.6, respectively; p = 0.06). However, there was a significant difference in radiographic progression between weeks 24 and 52 (0.3 vs 2.5; p = 0.03), and mean progression of the erosion score was negative in the E+M group, which was significantly better than the E group at week 52 (–0.2 vs 1.8; p = 0.02).
	ETA [33]	254	Patients with active rheumatoid arthritis despite stable sulfasalazine (2–3 g/day) treatment	24-week randomised, double-blind, parallel-group study. Treatment: Group 1: etanercept 25 mg twice a week plus placebo Group 2: sulfasalazine tablets (2.0, 2.5 or 3.0 g daily plus placebo) Group 3: etanercept and sulfasalazine Primary endpoint: ACR20 response at 24 weeks.	Etanercept alone or in combination with sulfasalazine resulted in improvement in disease activity from baseline to week 24: 74% of patients in Group 1 (etanercept alone) and Group 3 (etanercept plus sulfasalazine) achieved the primary endpoint, compared to 28% of Group 2 (sulfasalazine alone) (p <0.01).
Tocilizumab	SATORI [37]	125	MTX inadequate responders, mean disease duration 8.6 years.	24-week, randomised, double-blind, placebo-controlled study. Treatment: Tocilizumab 8 mg/kg every 4 weeks plus MTX placebo (tocilizumab group) or tocilizumab placebo plus MTX 8 mg/week (control group) Primary endpoint: ACR20 response at week 24.	Tocilizumab monotherapy yielded better results compared with MTX. At week 24, 25.0% of the control group and 80.3% of the tocilizumab group achieved ACR20 response (p <0.001). The tocilizumab group also showed superior ACR50 and ACR70 response rates at all timepoints from week 4 onwards.
	SAMURAI [36]	306	Mean number of failed DMARDs ~2.7, baseline DAS28 score of 6.5, mean disease duration 2.3 years.	52-week, randomised, double-blind study. Treatment: Tocilizumab monotherapy at 8 mg/kg every 4 weeks or conventional DMARDs for 52 weeks Primary endpoint: Radiographic outcomes, scored using the van der Heijde-modified Sharp method.	Tocilizumab monotherapy resulted in significantly less radiographic change in total Sharp score (mean 2.3; 95% CI 1.5–3.2) versus DMARDs (mean 6.1; 95% CI 4.2–8.0; p <0.01). Tocilizumab monotherapy also improved signs and symptoms of RA.

	AMBITION [38]	673	Mean number of previous DMARDS / anti-TNF agents ~1.2, 66% of patients were MTX-naïve, mean disease duration ~6.4 years.	24-week, randomised, double-blind, double-dummy, parallel-group study. Treatment: Tocilizumab 8 mg/kg every 4 weeks, or MTX starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. Primary endpoint: ACR20 response rate at week 24.	Tocilizumab monotherapy yielded better results than MTX monotherapy (at week 24, the ACR20 response was 69.9 vs 52.5%, p <0.001; DAS28 <2.6 was 33.6 vs 12.1%, in favour of tocilizumab).
	ACT-RAY [39]	556	Mean MTX dose 16 mg/week, mean number of previous DMARDs (including MTX) 1.9, mean disease duration 8.2 years.	2 year randomized double blind study. Treatment: Continue MTX treatment with addition of tocilizumab (8 mg/kg every 4 weeks), or switch to tocilizumab + placebo. Primary endpoint: DAS28–ESR remission rate at week 24.	The tocilizumab+MTX add-on strategy was clinically equivalent to the direct switch to tocilizumab monotherapy. DAS28–ESR remission rates were 40.4% for tocilizumab+MTX and 34.8% for tocilizumab+placebo (p = 0.19).
	ACT-STAR [87]	886	Around 25% of patients had used ≥3 DMARDs or ≥3 biological agents. Patients in the tocilizumab monotherapy arm had the longest disease duration and greatest number of prior treatments. Mean disease duration 10.5–13.5 years.	24-week, open-label study. Treatment: Patients on biologic monotherapy were assigned to tocilizumab monotherapy (8 mg/kg). All others randomised to tocilizumab 4 mg/kg + DMARDs or tocilizumab 8 mg/kg + DMARDs. Primary endpoint: Number (%) patients with SAEs.	Overall, 69 (7.8%) patients reported ≥1 SAE(s). The rate (95% CI) of SAEs per 100–person years (PYs) was 28.3 (23.1–34.4) overall and was similar across treatment groups: 29.1 (21.0–39.2), 30.3 (22.2–40.2), and 20.6 (10.3–36.9) in TCZ 4/8 mg/kg + DMARDs, TCZ 8 mg/kg + DMARDs, and TCZ 8 mg/kg monotherapy, respectively. ACR response rates and reduction in mean DAS scores were similar across all groups.
	ACT-SURE [88]	1,681	Mean number of previous DMARDs 1.3, mean disease duration 9.6 years.	24-week open-label, single-arm study. Treatment: Tocilizumab (8 mg/kg) every 4 weeks ± DMARDs Efficacy endpoints: ACR response, DAS28 scores, EULAR response.	In patients who were inadequate responders to DMARDs or TNF inhibitors, tocilizumab ± DMARDs yielded rapid and sustained efficacy. At week 24, 66.9%, 46.6%, 26.4% and 56.8% achieved ACR20/ ACR50/ ACR70 responses and DAS28 remission, respectively.
	ADACTA [44]	452	Mean number of previous DMARDs 2.0; mean disease duration 6.3 years (adalimumab group) and 7.3 years (tocilizumab group);	24-week randomised, double-blind, parallel-group superiority study. Treatment: Tocilizumab 8 mg/kg every 4 weeks plus placebo, or adalimumab 40 mg/kg subcutaneously every 2 weeks plus placebo. Primary endpoint: Change in DAS28 score from baseline to week 24.	Tocilizumab monotherapy was superior to adalimumab monotherapy in patients for whom MTX was deemed inappropriate. Week 24 mean change from baseline in DAS28 was significantly greater in the tocilizumab group (–3.3) than in the adalimumab group (–1.8) (difference –1.5, 95% CI: 1.8 to –1.1; p <0.0001).

ACR = American College of Rheumatology; AUC = area under curve; CI = confidence interval; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; MTX = methotrexate; RA = rheumatoid arthritis; SAE = serious adverse event; s.c. = subcutaneously; TCZ = tocilizumab; TNF = tumour necrosis factor