Ther Adv Musculoskel Dis
2016, Vol. 8(5) 192–202
DOI: 10.1177/1759720X16665330

Combination therapy with biologic agents in rheumatic diseases: current and future prospects

Kentaro Inui and Tatsuya Koike

Abstract: Strategies in rheumatoid arthritis (RA) based on 'treat to target' aim to control disease activity, minimize structural damage, and promote longer life. Several disease-modifying antirheumatic drugs (DMARDs) have been shown to be effective including biological DMARDs (bDMARDs). Treatment guidelines and recommendations for RA have also been published. According to those guidelines, conventional synthetic DMARDs (csDMARDs), as monotherapy or combination therapy, should be used in DMARD-naïve patients, irrespective of the addition of glucocorticoids (GCs). Combination therapies with bDMARDs are also essential for conducting treatment strategies for RA, because in every recommendation or guideline for the management of RA, combination therapies of csDMARDs with bDMARDs are recommended for RA patients with moderate or high disease activity after failure of csDMARD treatment. bDMARDs are more efficacious if used concomitantly with methotrexate (MTX) than with MTX monotherapy or bDMARD monotherapy. Thus, retention has been reported to be longer when combined with MTX. The superior efficacy of combination therapy compared with MTX monotherapy or bDMARD monotherapy could be because: (1) it could help to minimize MTX toxicity by reducing the dose of MTX, thus retention rate of the same therapeutic regimen would become high; (2) anti-bDMARD antibodies are observed at lower concentrations when using MTX concomitantly, so less clearance of bDMARDs *via* less formation of bDMARD and an anti-bDMARD immune complex; (3) of the additive effects of MTX to bDMARD, especially the combination of tumor necrosis factor inhibitors (TNFis) with MTX. Hence, evidence suggests that combination therapy with bDMARDs is more efficacious than monotherapy using a csDMARD or bDMARD, and that MTX is the best drug for this purpose (if MTX is not contraindicated). Finding the most effective drug regimen at the lowest cost will be the aim of RA treatment in the future.

Keywords: biologic agent, biosimilar, combination therapy, disease-modifying antirheumatic drug, methotrexate, rheumatoid arthritis

Correspondence to:
Kentaro Inui, MD, PhD
Department of Rheumatosurgery, Osaka City University Medical School, Abenoku, Asahimachi 1-4-3, Osaka 545-8585, Japan
inuken@med.osaka-cu.ac.jp

Tatsuya Koike, MD, PhD
Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Abenoku, Asahimachi, Osaka, and Search Institute for Bone and Arthritis Disease (SINBAD), Shirahama Foundation for Health and Welfare, Nishimurogun, Shirahamacho, Wakayama, Japan

Introduction

In 'treat-to-target' (T2T) recommendations for rheumatoid arthritis (RA), remission (or at least low disease activity) was the aim [Smolen *et al.* 2016] and has become reality in recent years. T2T strategy is always discussed after taking methotrexate (MTX) and biological disease-modifying antirheumatic drugs (bDMARDs) into consideration. MTX was tested in 1951 in patients with RA and psoriasis, and then used more frequently for RA treatment in the late-1980s [Braun, 2011]. Previously, there was no treatment strategy using powerful drugs supported by solid evidence except for the 'pyramidal plan' [Smyth, 1972]. Thus, no treatment goal could be proposed to RA patients. MTX has been recognized as an 'anchor drug' for RA treatment, and much evidence of MTX efficacy has been accumulated. Another distinct turning point that shifted the paradigm of RA treatment was when bDMARDs were first used in 1998 in the USA. Today, five types of tumor necrosis factor inhibitors (TNFis) along with abatacept (ABT), tocilizumab (TCZ), rituximab (RTX),

and anakinra (ANK) are available for RA treatment. By using these bDMARDs, remission has become a T2T in real practice.

Early diagnosis and a treatment strategy are also important to achieve T2T. The first treatment strategy was proposed in 1989 as a 'step-down bridge' concept [Wilske *et al*. 1989]. Along with the new drugs that have come onto the market, high-quality studies using a prospective cohort design have been published. In 1996, the American College of Rheumatology (ACR) published guidelines for RA management based on definitive evidences [American College of Rheumatology, 1996].

Studies have demonstrated the efficacy of conventional synthetic DMARDs (csDMARDs) and bDMARDs (and their combination) in RA treatment. Patients with early RA started on combined therapy of csDMARDs with bDMARDs showed earlier clinical improvement, less joint damage, with less toxicity at 5 years according to the BeSt study [Klarenbeek *et al*. 2011].

Numerous reports regarding efficacy of bDMARDs have been published in various clinical settings including early and established patient groups, patients with inadequate response for MTX, bio-naïve or use as a second bDMARD, or concomitant use of MTX or not. In this article, we review combination therapies with bDMARDs and discuss their benefits and disadvantages, focusing on RA in line with our clinical questions. A new nomenclature of DMARDs has been proposed in 2014 and we used the newest category in this article [Smolen *et al*. 2014b].

Which combination therapies are available?

According to the recommendations set by the ACR [Singh *et al*. 2016] and Japan College of Rheumatology (JCR) [Miyasaka *et al*. 2014], drug treatment starts with csDMARD monotherapy. Then, csDMARD combination therapy, with or without a glucocorticoid (GC), is used if monotherapy fails. Recommendations from the European League Against Rheumatism (EULAR) [Smolen *et al*. 2014a] allow combination therapy of csDMARDs from the beginning of treatment. EULAR recommendations are thought to have a sound therapeutic basis for abiding strictly to the T2T strategy. Indeed, recent studies have reported excellent results of triple DMARD therapy that is equivalent to that seen with bDMARDs [De Jong *et al*. 2014; Karlsson *et al*. 2013; Moreland *et al*. 2012; O'Dell *et al*. 2013; Matsuno *et al*. 2016]. However, evaluation of the results of triple therapy must be cautious because the prevalence of discontinuation of treatment is higher in triple therapy than combination therapy of MTX plus bDMARDs according to Moreland and colleagues (37% *versus* 30%) [Moreland *et al*. 2012] and Karlsson and colleagues (26% *versus* 10%) [Karlsson *et al*. 2013]. If an inadequate response is observed upon csDMARD combination therapy, combination therapy with bDMARDs can be considered.

GCs can also be used in combination therapy. EULAR recommendations state that low-dose GCs should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for $\leqslant$6 months [Smolen *et al*. 2014a]. This recommendation is because of their proven capacity to increase clinical, functional and structural efficacy if combined with csDMARDs [Bakker *et al*. 2012; Svensson *et al*. 2005; Kirwan, 1995]. This combination with low dose of prednisone (PSL) [Goekoop-Ruiterman *et al*. 2005] and with tapered high dose of PSL [Heimans *et al*. 2014] has similar efficacy when compared with TNFis plus MTX. For high risk early RA, MTX associated with a moderate step-down dose of GC was as effective in inducing remission at week 16 as DMARD combination therapies with moderate or high step-down GC doses, and it showed a more favorable short-term safety profile [Verschueren *et al*. 2015]. Of note, an aggressive treatment regimen with tapering PSL was shown to slow radiographic progression even in the patients with little response of clinical disease activity [Boers *et al*. 2013]. According to 2015 ACR guidelines, these state that, in cases of a flare, addition of GC is used at the lowest possible dose and for the shortest possible duration [Singh *et al*. 2016]. In a broad sense, intra-articular injection of triamcinolone with subcutaneous adalimumab (ADA) is also included in combination therapy with bDMARDs [Axelsen *et al*. 2015]. Axelsen and colleagues mentioned that a T2T strategy with oral MTX and an intra-articular injection of a GC, with or without subcutaneous ADA, in patients with early RA reduces synovitis, osteitis and tenosynovitis, and halts progression of structural damage (as judged by magnetic resonance imaging) [Axelsen *et al*. 2015].

Clinical results of combination therapy in comparison with monotherapy

bDMARDs for the treatment of RA patients include infliximab (IFX), etanercept (ETN), ADA, golimumab (GLM), certolizumab pegol (CZP), ABT, RTX, TCZ and ANK. According to EULAR recommendations [Smolen *et al.* 2014a] and ACR guidelines [Singh *et al.* 2016], ANK is not listed for the treatment of RA, so comments regarding ANK have been omitted in this review.

Several randomized clinical trials related to bDMARD therapy in RA patients have been classified into two categories according to disease duration ('early' or 'established'). Then, patients with established RA have been subdivided according to whether they are resistant to csDMARD therapy, including MTX (usually bDMARD-naïve in this group) or to bDMARD therapy. To clarify the efficacy of combination therapies with bDMARDs, only studies in which populations were bDMARD-naïve were selected and are summarized in Table 1.

Among TNFis, use of IFX and GLM was restricted only with MTX. According to the ASPIRE study (early RA) [St Clair *et al.* 2004] and ATTRACT study (established RA) [Lipsky *et al.* 2000], MTX therapy combined with IFX was superior to MTX monotherapy in terms of clinical and radiologic outcomes at 54 weeks. In GO-BEFORE (early RA) [Emery *et al.* 2009] and GO-FORWARD (established RA) [Keystone *et al.* 2009] trials, the study population was allocated randomly into four arms to receive placebo plus MTX (group 1), GLM (100 mg) plus placebo (group 2), GLM (50 mg) plus MTX (group 3), or GLM (100 mg) plus MTX (group 4). At 24 weeks in early RA, combination of GLM plus MTX demonstrated a significantly better response compared with placebo plus MTX in terms of the achievement of at least 50% improvement according to the American College of Rheumatology criteria core set (ACR50), but GLM monotherapy was not inferior to MTX monotherapy. In established RA, identical results were reported in the GO-FORWARD study. That is, the clinical outcomes measured by the achievement of at least 20% improvement according to the American College of Rheumatology criteria core set (ACR20) at 14 weeks were significantly better in the combination therapy group than in the MTX monotherapy group. GLM monotherapy was not inferior to MTX monotherapy. In the GO-BEFORE study and GO-FORWARD study, radiologic examination was not conducted. In Japan, GLM can be used as monotherapy only at 100 mg based on the GO-MONO study [Takeuchi *et al.* 2013]. In the latter, 316 patients with established RA were randomized to receive placebo, GLM (50 mg) and GLM (100 mg) without concomitant MTX in all groups. At week 14, ACR20 response was significantly better in both GLM groups than in the placebo group. GLM monotherapy was also effective in Japanese patients with RA.

Therapeutic efficacy according to clinical and radiologic measurements of a combination of MTX with ETN and ADA has been reported to be better than MTX monotherapy in patients with early RA and established RA [Emery *et al.* 2008; Klareskog *et al.* 2004; Breedveld *et al.* 2006; Weinblatt *et al.* 2003]. In patients with early RA, even in those with poor prognostic factors (e.g. high levels of anticyclic citrullinated peptide; positive rheumatoid factor or bone erosion), CZP combined with MTX led to significant inhibition of structural damage and reduction in signs and symptoms at 52 weeks according to the C-OPERA study [Atsumi *et al.* 2016]. The RAPID study [Keystone *et al.* 2008] showed good clinical and radiologic outcomes in patients with established RA.

In a very large double-blind randomized controlled trial (FUNCTION) [Burmester *et al.* 2015b], remission of Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) in combination therapy and TCZ monotherapy were superior to MTX monotherapy. Comparison of the efficacy of adding TCZ to that of switching to TCZ monotherapy was made in inadequate responders to MTX (a situation often encountered in clinical practice) for the ACT-RAY study [Huizinga *et al.* 2015]. Clinically relevant superiority of the TCZ plus MTX regimen over the switch to TCZ monotherapy was not observed. However, Dougados and colleagues drew attention to the fact that structural damage on radiographs became advanced [Dougados *et al.* 2014]. Also, Kojima and colleagues emphasized the importance of MTX therapy concomitant with TCZ treatment in achieving better clinical outcomes and less structural damage for RA patients with high disease activity [Kojima *et al.* 2015].

ABT was also reported to elicit better results at 1 year if used with MTX in a MTX-naïve

Table 1. Summary of biologic disease-modifying antirheumatic drugs.

Biologics (trade name) action/ usage	**Disease indicated**	**Study/ author (year)**	**Study population**	**Study period**
infliximab (Remicade) TNF inhibitor/ with MTX only	RA, AS, PsA, PsO, Crohn, pCrohn, UC, pUC	ASPIRE/ St. Clair (2004)	Early	54 weeks
		ATTRACT/ Lipsky (2000)	Established	54 weeks
etanercept (Enbrel) TNF inhibitor/ MONO	RA, PsA, PsO, AS, pJIA	COMET/ Emery (2008)	Early	52 weeks
		TEMPO/ Klareskog (2004)	Established	52 weeks
adalimumab (Humira) TNF inhibitor/ MONO	RA, AS, pJIA, PsA, PSO, Crohn, pCrohn, UC, HS	PREMIER/ Breedveld (2006)	Early	2 years
		ARAMADA/ Weinblatt (2003)	Established	24 weeks
golimumab (Simponi) TNF inhibitor/ with MTX only	RA, AS, PsA, UC	GO-BEFORE/ Emery (2009)	Early	24 weeks
		GO-FORWARD/ Keystone (2009)	Established	14 weeks (ACR20), 24 weeks (HAQ-DI)
		GO-MONO/ Takeuchi (2013)	Established	14 weeks (ACR-N) 24 weeks (mTSS)
certolizumab (Cimzia) TNF inhibitor/ MONO	RA, Crohn, PsA, AS	C-OPERA/ Atsumi (2016)	Early	52 weeks
		RAPID/ Keystone (2008)	Established	24 weeks (ACR20) 52 weeks (mTSS)
tocilizumab (RoActemra) IL-6 receptor antagonist/ MONO	RA, pJIA, sJIA, Castleman (Jpn)	FUNCTION/ Burmester (2015)	Early	52 weeks
		ACT-RAY/ Huizinga (2015)	Established	2 years
abatacept (Orencia) CTLA 4-Ig/ MONO (with MTX in EU)	RA, pJIA	AGREE/ Westhovens (2009)	Early	1 year
		AIM/ Kremer (2006)	Established	1 year
rituximab (Rituxan) anti-CD 20a/ with MTX only	RA, NHL, CLL, granulomatosis with polyangiitis, microscopic polyangiitis	IMAGE/ TAK (2011)	Early	52 weeks
		SERENE/ Emery (2010)	Established	24 weeks

ACR, American College of Rheumatology; AS, ankylosing spondylitis; bDMARD, biological DMARD; CAPS, cryopyrin-associated periodic syndromes; CD, Crohn disease; CLL, chronic lymphocytic leukemia; COMB, combination therapy of MTX with bDMARD; CTLA, cytotoxic T-lymphocyte-associated protein; DMARD, disease-modifying antirheumatic drug; EU, European Union; HAQ-DI, Health Assessment Questionnaire Disability Index; HS, hidradenitis suppurative; Ig, immunoglobulin; IL-6, interleukin-6; JIA, juvenile idiopathic arthritis; Jpn, Japan; MONO, monotherapy of biologics or with MTX; mTSS, van der Heijde-modified total Sharp score; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; pCrohn, pediatric Crohn's; pJIA, polyarticular onset juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, plaque psoriasis; pUC, pediatric UC; RA, rheumatoid arthritis; REM, remission; sJIA, systemic JIA; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 1. (Continued)

bDMARD study	Number of patients				Clinical outcome	Radiological outcome
	All	COMB	MTX	Bio- mono		
IFX ASPIRE	1049	359 (3 mg/kg)	282		ACR-N (COMB *versus* MTX; $p < 0.001$)	mTSS (COMB *versus* MTX; $p < 0.001$)
IFX ATTRACT	428	86 (3 mg/kg/8 w)	88		ACR 20/50 (COMB *versus* MTX; $p < 0.001$, 0.027)	mTSS (COMB *versus* MTX; $p < 0.001$)
ETN COMET	542	274	268		DAS28 REM at 52 w (COMB *versus* MTX; $p < 0{\cdot}0001$)	mTSS from baseline at 52 w (COMB *versus* MTX; $p < 0{\cdot}0001$)
ETN TEMPO	682	231	228	223 (50 mg)	ACR-N at 24 w (COMB *versus* ETN mono & MTX; $p < 0{\cdot}0001$ and $p < 0{\cdot}0001$)	mTSS at 52 w (COMB *versus* ETN mono & MTX; $p < 0{\cdot}0001$, and $p = 0{\cdot}0006$)
ADA REMIER	799	268	257	274	ACR50 (COMB *versus* ADA mono & MTX; $p < 0.001$ & $p < 0.001$)	mTSS (COMB *versus* ADA mono & MTX; $p \leqslant 0.002$ & $p \leqslant 0.002$)
ADA ARAMADA	271	67 (40 mg/eow)	62		ACR50 (COMB *versus* MTX; $p < 0.001$)	
GLM GO-BEFORE	637	159 (100 mg) 159 (50 mg)	160	159 (100 mg)	ACR50 ($p = 0.049$ COMB *versus* MTX; $p = 0.049$, MTX & GLM mono; not inferior)	
GLM GO-FORWARD	444	89 (100 mg) 89 (50 mg)	133	133 (100 mg)	ACR20 (GLM mono *versus* MTX; $p = 0.059$, COMB *versus* MTX; $p < 0.001$), HAQ-DI (GLM mono *versus* MTX; $p = 0.024$, COMB *versus* MTX; $p < 0.001$)	
GLM GO-MONO	316			0 mg (110) 50 mg (102) 100 mg (104)	ACR20 (50 mg & 100 mg *versus* PBO; $p < 0.0001$ for both)	No significant differences in mean changes from baseline
CZP C-OPERA	316	159	157		SDAI REM (COMB *versus* MTX; $p < 0.001$)	mTSS (COMB *versus* MTX; $p < 0.001$)
CZP RAPID	982	393 (200 mg) 390 (400 mg)	199		ACR20 (COMB *versus* MTX; $p < 0.001$)	mTSS (COMB *versus* MTX: $p < 0.001$)
TCZ FUNCTION	1116	290 (4 mg/kg)291 (8 mg/kg)	289	292 (8 mg/kg)	DAS28-ESR REM (TCZ 4 mg + MTX (p <0.0001), TCZ 8 mg + MTX (p <0.0001), TCZ 8 mg (p <0.0001); *versus* MTX)	mTSS (8 mg/kg TCZ + MTX *versus* MTX; $p = 0.0001$)
TCZ ACT-RAY	556	277		276	DAS28-ESR REM rate (COMB *versus* TCZ mono; $p = 0.19$)	Genant–Sharp score progression ⩽ smallest detectable change (COMB *versus* TCZ mono was not different)
ABT AGREE	511	256	253		DAS28 REM (COMB *versus* MTX; $p < 0.001$)	mTSS (COMB *versus* MTX; $p = 0.040$)
ABT AIM	547	385	162		ACR 20, ACR 50, and ACR 70 responses (COMB *versus* MTX; $p < 0.001$ for all)	**Structural damage progression by Genant-modified TSS (COMB** *versus* **MTX;** $p = 0.012$**)**
RTX IMAGE/ TAK (2011)	755	252 (500 mg) 251 (1000 mg)	252		**ACR50 (COMB*** *versus* **MTX;** $p < 0.0001$**)** *RTX 1000 mg group	**mTSS (COMB*** *versus* **MTX;** $p = 0.0004$**)** *RTX 1000 mg group
RTX SERENE	509	167 (500 mg)170 (1000 mg)	172		ACR20 (COMB *versus* MTX: $p < 0.0001$)	

ABT, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological DMARD; COMB, combination therapy of MTX with bDMARD; CZP, certolizumab pegol; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ETN, etanercept; GLM, golimumab, HAQ-DI, Health Assessment Questionnaire Disability Index; IFX, infliximab; MONO, monotherapy of biologics or with MTX; mTSS, van der Heijde-modified total Sharp score; MTX, methotrexate; PBO, placebo; REM, remission; RTX, rituximab; SDAI, Simple Disease Activity Index; TCZ, tocilizumab.

population with early RA and poor prognostic factors in the AGREE trial [Westhovens *et al.* 2009]. This study was assessed over 2 years after a double-blind period of 1 year [Bathon *et al.* 2011]. During the second year, the original ABT plus MTX group continued treatment, whereas ABT was initiated in the MTX-monotherapy group. Clinical outcomes in the original MTX-monotherapy group caught up with those of the ABT plus MTX group, but structural damage was significantly greater in the original MTX-monotherapy group than in the ABT plus MTX group. These results implied that early intervention using more aggressive treatment is important to lower structural damage. In established RA, better clinical and radiographic results were reported at 1 year using ABT plus MTX in the AIM trial [Kremer *et al.* 2006].

RTX has been approved for RA treatment if given in combination with MTX, but is not approved in Japan. If administered for early RA, the IMAGE trial showed the clinical and radiographic efficacy of RTX at the usual dose [Tak *et al.* 2011]. The SERENE trial [Emery *et al.* 2010] was conducted to determine the efficacy and safety of treatment with RTX plus MTX in patients with active RA who had an inadequate response to MTX and who were naïve to prior treatment with bDMARDs. The SERENE trial showed that RTX plus MTX significantly improved clinical outcomes at week 24, which were improved further by week 48, compared with MTX monotherapy.

In general, bDMARDs are more efficacious if used concomitantly with MTX than in bDMARD monotherapy, and retention has been reported to be longer if they are used with MTX [Zhang *et al.* 2015; Blum *et al.* 2011]. The strongest association between use of concomitant MTX and bDMARD persistence was observed for IFX [hazard ratio (HR) 1.8, 95% confidence interval (CI) 1.7–2.0], but not observed for ABT (HR 1.1, 95% CI 1.0–1.2), or TCZ (HR 1.1, 95% CI 0.9–1.3) [Zhang *et al.* 2015]. However, when considering the use of a bDMARD, MTX cannot always be used concomitantly because of patient factors (e.g. comorbidities, history of adverse reactions to MTX). In fact, up to one-third of RA patients are treated with a bDMARD as monotherapy [Gabay *et al.* 2015; Emery *et al.* 2013]. In this regard, TCZ is useful because TCZ monotherapy has been reported to be comparable with combination therapy with MTX [Emery *et al.* 2013].

Other conventional synthetic disease-modifying antirheumatic drugs that can be combined with biological disease-modifying antirheumatic drugs

csDMARDs other than MTX include sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide (LEF). These agents are listed in ACR guidelines [Singh *et al.* 2016] and EULAR recommendations [Smolen *et al.* 2014a]. csDMARDs such as azathioprine, cyclosporine, minocycline and gold are not included in ACR guidelines or EULAR recommendations. In Japan, tacrolimus and bucillamine are often used. Most of the evidences on combination therapy with bDMARDs is related to MTX only. This situation arises because the protocols of most clinical studies on bDMARDs were planned with MTX (or for patients with an inadequate response to MTX), and recommendations or guidelines on clinical treatment have stated that MTX should be part of the first treatment strategy in patients with active RA. Combination of LEF with biologic agents has been reported to be efficacious, and responses may be even higher than those obtained with LEF plus MTX combinations [Kalden *et al.* 2005]. Singer and colleagues suggested that LEF in combination with a TNFi has comparable efficacy to that of MTX plus a TNFi [Singer *et al.* 2011]. No reports regarding combination therapy of LEF with ABT or TCZ were found in the literature searched with 'leflunomide and abatacept or tocilizumab' as keywords in the title through PubMed. However, little information has been obtained for other csDMARDs compared with MTX because most instances involve addition of a biologic agent to existing DMARD therapy. Hence, studies investigating the efficacy of other csDMARDs for combination with a bDMARD are lacking.

Combination of a bDMARD with another bDMARD is not well documented. Safety of RTX in combination with other bDMARDs (ADA, ETN, AVT or IFX) in RA was reported as an open-label study [Rigby *et al.* 2013]. Rigby and colleagues showed that no serious adverse events occurred within 24 h of any RTX infusion, and that efficacy improved at week 48 compared with that at week 24. Bispecific antibodies against TNFis and interleukin (IL)-17 have been reported to be more effective than single blockade in a model of arthritis in mice [Fischer *et al.* 2015]. Combination therapy using ETN plus ANK was reported to provide no additional benefit as well as an increased risk compared with ETN

monotherapy, so was not recommended for RA treatment [Genovese *et al.* 2004]. Therefore, combination of two bDMARDs should be avoided because of the low benefit–risk ratio.

Why is concomitant use of methotrexate in biological disease-modifying antirheumatic drug therapy more efficacious than monotherapy?

In general, if 'drug A' is combined with 'drug B', intensification of the favorable effects of drug B or reduction of the adverse effects of drug B is expected, which increases the retention of drug B.

Use of MTX combined with bDMARDs could help to reduce the weekly dose of MTX, thereby minimizing MTX toxicity. Conversely, a high dose of MTX has been reported to be required to make combination therapy with bDMARDs most efficacious, but a maximal dose is not always necessary for this purpose. In 2015, the CONCERTO trial [Burmester *et al.* 2015a] revealed that in patients with early RA who were starting ADA combination therapy, administration of 10 and 20 mg/week MTX appeared to have an equivalent effect on treatment efficacy. This phenomenon could be because the percentage of patients with at least an anti-ADA antibody was lower in the high-dose group (6% and 6%; 10 and 20 mg/week of MTX, respectively) than in the low-dose group (21% and 13%; 2.5 mg and 5 mg/week of MTX, respectively). Therefore, if the efficacy of combination therapy of MTX with a bDMARD is not adequate and MTX dose is relatively low, the drug that should be increased in dose is MTX, but it would not have to be the maximum dose approved by the government. However, in the MUSICA study [Kaeley *et al.* 2014], the small differences in clinical, functional, and ultrasound outcomes between 7.5 mg/week of MTX with ADA and 20 mg/week of MTX with ADA in patients with moderate-to-severe RA, unresponsive to previous MTX at >15 mg/week, suggest that reduction in MTX dose should be considered when initiating ADA therapy in some patients with an inadequate response to MTX. Therefore, combination therapy with bDMARDs should enable dose reduction of MTX, thereby lowering the negative effects of MTX. Another reason for the superior outcomes of combination therapy is that MTX provides immunologic tolerance to bDMARDs [Maini *et al.* 1998; Bartelds *et al.* 2007]. Concomitant therapy with low-dose MTX was reported to diminish the appearance of anti-IFX antibody. This would consequently reduce clearance of bDMARDs *via* less formation of bDMARD and anti-bDMARD immune complex [Bartelds *et al.* 2007]. Thirdly, MTX would possibly potentiate the effects of bDMARDs in an additive fashion. MTX appeared to have a greater effect in terms of suppressing circulating IL-6 than on suppressing circulating TNF-α [Nishina *et al.* 2013]. In this regard, it makes sense that TNFis have a greater effect when used in combination with MTX than when used as monotherapy.

Future prospects

As shown above, several types of DMARDs are available for RA treatment, and more drugs are under development. There are three groups of patients for whom more evidence is required for RA treatment. The first group comprises individuals with comorbidities (e.g. renal dysfunction, diabetes mellitus, pulmonary disorders, liver dysfunction). Future treatment for this group must focus on minimal structural damages, by setting the treatment target to an alternative one in order not to aggravate the comorbidities, as the highest priority. For RA patients with comorbidities use of drugs should be limited, for example, tacrolimus and GC in diabetes, MTX in interstitial pneumonia or renal dysfunction. In clinical practice, we need deal with such patients individually, however, it is very helpful if there is guidance how to treat RA patients with comorbidity separately, like hepatitis B virus (HBV), tuberculosis in order to minimize structural damages. So we need evidence obtained by large-scale study to lead a better way to deal with such patients. Secondly, there are the patients who cannot afford the high cost of bDMARDs or targeted synthetic DMARDs (tsDMARDs). For such patients, four options are possible: (1) set the treatment target to an alternative target by accepting some degree of structural damage; (2) make full use of cheaper csDMARDs; (3) use bDMARDs or tsDMARDs at a reduced dose or for longer intervals; (4) use cheaper bDMARDs or tsDMARDs [i.e. biosimilar DMARDs (bsDMARDs)]. For option (2), triple therapy with MTX plus SSZ and HCQ is a good choice with clear evidence. Also one single intramuscular GC injection and a low-dose oral GC tapering scheme were suggested as sufficient bridging therapy [De Jong *et al.* 2014]. For option (3) several reports have focused on tapering studies for DMARDs. For option (4),

combination therapy of MTX with bsDMARDs must be investigated. Thirdly, for patients sufficiently fit to undergo aggressive treatment, abiding strictly to the T2T strategy will result in immunologic remission beyond functional remission, which means that the patients are thought to be 'cured' of RA. Immunologic status of these patients would become double negative again in rheumatoid factor and anticyclic citrullinated peptide antibody, like the status as several years before the development of symptoms [Nielen *et al*. 2004]. It is unclear whether such patients need continue aggressive treatment, although Chan and colleagues warn about the possibility of dangers in dose reduction or cessation of bDMARD approaches especially for established disease [Chan *et al*. 2016].

Conclusion

Combination therapy with bDMARDs is more efficacious than monotherapy using a csDMARD or bDMARD. Evidence suggests that MTX is the best drug for this purpose (provided that MTX is not contraindicated). MTX can be expected to intensify the favorable effects of bDMARDs or reduce their adverse effects, thereby increasing retention of both drugs. In this regard, MTX should be used as an anchor drug. However, MTX can be contraindicated owing to comorbidities, but bDMARD monotherapy could have a role in such cases. Also, the cost of RA treatment for individual patients and governments is a limiting issue. Hence, finding the most effective drug regimen at the lowest cost will be the aim of RA treatment in the future.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

American College of Rheumatology (1996) Guidelines for the management of rheumatoid arthritis. American College of Rheumatology *Ad Hoc* Committee on Clinical Guidelines. *Arthritis Rheum* 39: 713–722.

Atsumi, T., Yamamoto, K., Takeuchi, T., Yamanaka, H., Ishiguro, N., Tanaka, Y. *et al.* (2016) The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. *Ann Rheum Dis* 75: 75–83.

Axelsen, M., Eshed, I., Horslev-Petersen, K., Stengaard-Pedersen, K., Hetland, M., Moller, J. *et al.* (2015) A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. *Ann Rheum Dis* 74: 867–875.

Bakker, M., Jacobs, J., Welsing, P., Verstappen, S., Tekstra, J., Ton, E. *et al.* (2012) Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 156: 329–339.

Bartelds, G., Wijbrandts, C., Nurmohamed, M., Stapel, S., Lems, W., Aarden, L. *et al.* (2007) Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 66: 921–926.

Bathon, J., Robles, M., Ximenes, A., Nayiager, S., Wollenhaupt, J., Durez, P. *et al.* (2011) Sustained disease remission and inhibition of radiographic progression in methotrexate-naive patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. *Ann Rheum Dis* 70: 1949–1956.

Blum, M., Koo, D. and Doshi, J. (2011) Measurement and rates of persistence with and adherence to biologics for rheumatoid arthritis: a systematic review. *Clin Ther* 33: 901–913.

Boers, M., van Tuyl, L., van den Broek, M., Kostense, P. and Allaart, C. (2013) Meta-analysis suggests that intensive non-biological combination therapy with step-down prednisolone (COBRA strategy) may also 'disconnect' disease activity and damage in rheumatoid arthritis. *Ann Rheum Dis* 72: 406–409.

Braun, J. (2011) Methotrexate: optimizing the efficacy in rheumatoid arthritis. *Ther Adv Musculoskelet Dis* 3: 151–158.

Breedveld, F., Weisman, M., Kavanaugh, A., Cohen, S., Pavelka, K., van Vollenhoven, R. *et al.* (2006) The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 54: 26–37.

Burmester, G., Kivitz, A., Kupper, H., Arulmani, U., Florentinus, S., Goss, S. *et al.* (2015a) Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis* 74: 1037–1044.

Burmester, G., Rigby, W., van Vollenhoven, R., Kay, J., Rubbert-Roth, A., Kelman, A. *et al.* (2015b) Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis* 75: 1081–1091.

Chan, C., Holroyd, C., Mason, A., Zarroug, J. and Edwards, C. (2016) Are there dangers in biologic dose reduction strategies? *Autoimmun Rev* 15: 742–746.

De Jong, P., Hazes, J., Han, H., Huisman, M., van Zeben, D., van der Lubbe, P. *et al.* (2014) Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 73: 1331–1339.

Dougados, M., Kissel, K., Conaghan, P., Mola, E., Schett, G., Gerli, R. *et al.* (2014) Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis* 73: 803–809.

Emery, P., Breedveld, F., Hall, S., Durez, P., Chang, D., Robertson, D. *et al.* (2008) Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 372: 375–382.

Emery, P., Deodhar, A., Rigby, W., Isaacs, J., Combe, B., Racewicz, A. *et al.* (2010) Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis* 69: 1629–1635.

Emery, P., Fleischmann, R., Moreland, L., Hsia, E., Strusberg, I., Durez, P. *et al.* (2009) Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 60: 2272–2283.

Emery, P., Sebba, A. and Huizinga, T. (2013) Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. *Ann Rheum Dis* 72: 1897–1904.

Fischer, J., Hueber, A., Wilson, S., Galm, M., Baum, W., Kitson, C. *et al.* (2015) Combined inhibition of tumor necrosis factor α and IL-17 as a therapeutic opportunity in rheumatoid arthritis: development and characterization of a novel bispecific antibody. *Arthritis Rheumatol* 67: 51–62.

Gabay, C., Riek, M., Scherer, A. and Finckh, A. (2015) Effectiveness of biologic DMARDs in monotherapy versus in combination with synthetic DMARDs in rheumatoid arthritis: data from the Swiss Clinical Quality Management Registry. *Rheumatology (Oxford)* 54: 1664–1672.

Genovese, M., Cohen, S., Moreland, L., Lium, D., Robbins, S., Newmark, R. *et al.* (2004) Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 50: 1412–1419.

Goekoop-Ruiterman, Y., De Vries-Bouwstra, J., Allaart, C., van Zeben, D., Kerstens, P., Hazes, J. *et al.* (2005) Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the best study): a randomized, controlled trial. *Arthritis Rheum* 52: 3381–3390.

Heimans, L., Wevers-De Boer, K., Visser, K., Goekoop, R., van Oosterhout, M., Harbers, J. *et al.* (2014) A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. *Ann Rheum Dis* 73: 1356–1361.

Huizinga, T., Conaghan, P., Martin-Mola, E., Schett, G., Amital, H., Xavier, R. *et al.* (2015) Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. *Ann Rheum Dis* 74: 35–43.

Kaeley, G., Evangelisto, A., Nishio, M., Liu, S. and Kupper, H. (2014) Impact of methotrexate dose reduction upon initiation of adalimumab on clinical and ultrasonographic parameters in patients with moderate to severe rheumatoid arthritis. *Ann Rheum Dis* 73: 238.

Kalden, J., Antoni, C., Alvaro-Gracia, J., Combe, B., Emery, P., Kremer, J. *et al.* (2005) Use of combination of leflunomide with biological agents in treatment of rheumatoid arthritis. *J Rheumatol* 32: 1620–1631.

Karlsson, J., Neovius, M., Nilsson, J., Petersson, I., Bratt, J., van Vollenhoven, R. *et al.* (2013) Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results

of the randomised, controlled, SWEFOT trial. *Ann Rheum Dis* 72: 1927–1933.

Keystone, E., Genovese, M., Klareskog, L., Hsia, E., Hall, S., Miranda, P. *et al.* (2009) Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD study. *Ann Rheum Dis* 68: 789–796.

Keystone, E., Heijde, D., Mason, D., Jr., Landewe, R., Vollenhoven, R., Combe, B. *et al.* (2008) Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 58: 3319–3329.

Kirwan, J. (1995) The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *N Engl J Med* 333: 142–146.

Klarenbeek, N., Guler-Yuksel, M., van der Kooij, S., Han, K., Ronday, H., Kerstens, P. *et al.* (2011) The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the best study. *Ann Rheum Dis* 70: 1039–1046.

Klareskog, L., van der Heijde, D., De Jager, J., Gough, A., Kalden, J., Malaise, M. *et al.* (2004) Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 363: 675–681.

Kojima, T., Yabe, Y., Kaneko, A., Takahashi, N., Funahashi, K., Kato, D. *et al.* (2015) Importance of methotrexate therapy concomitant with tocilizumab treatment in achieving better clinical outcomes for rheumatoid arthritis patients with high disease activity: an observational cohort study. *Rheumatology (Oxford)* 54: 113–120.

Kremer, J., Genant, H., Moreland, L., Russell, A., Emery, P., Abud-Mendoza, C. *et al.* (2006) Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 144: 865–876.

Lipsky, P., van der Heijde, D., St Clair, E., Furst, D., Breedveld, F., Kalden, J. *et al.* (2000) Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 343: 1594–1602.

Maini, R., Breedveld, F., Kalden, J., Smolen, J., Davis, D., Macfarlane, J. *et al.* (1998) Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 41: 1552–1563.

Matsuno, H., Okada, M., Sakai, Y., Abe, C., Katayama, K., Sagawa, A. *et al.* (2016) The usefulness of a new triple combination treatment utilizing methotrexate, salazosulfapyridine, and bucillamine in rheumatoid arthritis. *Mod Rheumatol* 26: 51–56.

Miyasaka, N., Yamanaka, H., Ito, H., Endo, H., Kaneko, Y., Kamatani, N. *et al.* (2014) *Guidelines for the Treatment of Rheumatoid Arthritis, Japan College of Rheumatology*, Vol. 1, 1st ed. Tokyo: Medical Review.

Moreland, L., O'Dell, J., Paulus, H., Curtis, J., Bathon, J., St Clair, E. *et al.* (2012) A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 64: 2824–2835.

Nielen, M., van Schaardenburg, D., Reesink, H., van de Stadt, R., van der Horst-Bruinsma, I., De Koning, M. *et al.* (2004) Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 50: 380–386.

Nishina, N., Kaneko, Y., Kameda, H., Kuwana, M. and Takeuchi, T. (2013) Reduction of plasma IL-6 but not TNF-α by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression. *Clin Rheumatol* 32: 1661–1666.

O'Dell, J., Mikuls, T., Taylor, T., Ahluwalia, V., Brophy, M., Warren, S. *et al.* (2013) Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 369: 307–318.

Rigby, W., Mease, P., Olech, E., Ashby, M. and Tole, S. (2013) Safety of rituximab in combination with other biologic disease-modifying antirheumatic drugs in rheumatoid arthritis: an open-label study. *J Rheumatol* 40: 599–604.

Singer, O. and Gibofsky, A. (2011) Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? *Curr Opin Rheumatol* 23: 288–292.

Singh, J., Saag, K., Bridges, S., Jr., Akl, E., Bannuru, R., Sullivan, M. *et al.* (2016) 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 68: 1–25.

Smolen, J., Breedveld, F., Burmester, G., Bykerk, V., Dougados, M., Emery, P. *et al.* (2016) Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 75: 3–15.

Smolen, J., Landewe, R., Breedveld, F., Buch, M., Burmester, G., Dougados, M. *et al.* (2014a) EULAR

recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 73: 492–509.

Smolen, J., van der Heijde, D., Machold, K., Aletaha, D. and Landewe, R. (2014b) Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 73: 3–5.

Smyth, C. (1972) Therapy of rheumatoid arthritis. A pyramidal plan. *Postgrad Med* 51: 31–39.

St Clair, E., van der Heijde, D., Smolen, J., Maini, R., Bathon, J., Emery, P. *et al.* (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 50: 3432–3443.

Svensson, B., Boonen, A., Albertsson, K., van der Heijde, D., Keller, C. and Hafstrom, I. (2005) Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 52: 3360–3370.

Tak, P., Rigby, W., Rubbert-Roth, A., Peterfy, C., van Vollenhoven, R., Stohl, W. *et al.* (2011) Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. *Ann Rheum Dis* 70: 39–46.

Takeuchi, T., Harigai, M., Tanaka, Y., Yamanaka, H., Ishiguro, N., Yamamoto, K. *et al.* (2013) Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks. *Ann Rheum Dis* 72: 1488–1495.

Verschueren, P., De Cock, D., Corluy, L., Joos, R., Langenaken, C., Taelman, V. *et al.* (2015) Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the careRA trial. *Ann Rheum Dis* 74: 27–34.

Weinblatt, M., Keystone, E., Furst, D., Moreland, L., Weisman, M., Birbara, C. *et al.* (2003) Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 48: 35–45.

Westhovens, R., Robles, M., Ximenes, A., Nayiager, S., Wollenhaupt, J., Durez, P. *et al.* (2009) Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis* 68: 1870–1877.

Wilske, K. and Healey, L. (1989) Remodeling the pyramid: a concept whose time has come. *J Rheumatol* 16: 565–567.

Zhang, J., Xie, F., Delzell, E., Yun, H., Lewis, J., Haynes, K. *et al.* (2015) Impact of biologic agents with and without concomitant methotrexate and at reduced doses in older rheumatoid arthritis patients. *Arthritis Care Res (Hoboken)* 67: 624–632.