Abstract
Conventional DMARDs such as MTX are the mainstay of treatment for patients with RA. However, failure to achieve adequate disease control in many patients, even with combination therapy, has spurred the development of agents that target various immune mediators involved in the disease process. In the past decade, biologic agents have proved viable as alternative or add-on therapy to DMARDs in patients whose disease is inadequately controlled. Well-controlled clinical trials have evaluated the effects of these agents not only on disease activity, but also on inhibition of structural change and improvement in physical function. This article reviews phase 3 clinical trial results on biologic agents that inhibit T- and B-cell activation (abatacept and rituximab, respectively), inflammatory cytokines such as TNF-α (adalimumab, etanercept, infliximab, golimumab and certolizumab) and IL-6 (tocilizumab). Although data comparing the efficacy of the various biologic agents are limited, the availability of biologic therapies with differing mechanisms of action expands therapeutic options for patients whose disease is inadequately controlled with DMARDs and allows for greater individualization of treatment.

Key words: DMARDs, DMARD-IR, inadequate responders, methotrexate, RA management, RA therapy.

Introduction
The management of RA has undergone a transformation, both in approach and in choice of drugs. Traditionally, RA has been managed with NSAIDs, glucocorticoids and DMARDs [1, 2]. DMARDs designate a group of non-biologic pharmacological agents that can slow or halt the inflammatory disease process. This category includes commonly used agents such as MTX, LEF, SSZ and HCQ [3].

Management strategies have evolved towards early institution of DMARD therapy in patients with recent-onset RA, use of DMARD combinations and pursuit of remission as a treatment target to prevent joint damage [3-5]. DMARDs and DMARD combinations are the usual first-line agents for early RA (Fig. 1) [6]. Individual DMARDs, however, may be discontinued because of toxicity, suboptimal disease control, disease relapse, patient or physician preference or complicating co-morbidities [7]. Also, the likelihood of response is lower with disease of longer duration and in patients with previous DMARD use [8, 9].

MTX remains the cornerstone of most treatment regimens for RA because of a more beneficial efficacy/tolerability profile and lower discontinuation rates compared with other DMARDs [2, 10-15]. MTX alone, however, may not fully control disease activity and is increasingly being used in combination or in triple therapy regimens with other DMARDs [16, 17]. Although they improve efficacy, combination strategies may be associated with increased toxicity [18].

In the past decade, biologic agents have proved viable as alternative or add-on therapy to DMARDs in patients whose disease is inadequately controlled [19, 20]. Well-controlled trials have investigated the use of biologic agents to augment the activity of DMARDs in this patient population and have evaluated their effects on disease...
FIG. 1 Recommendations for the use of DMARDs in RA patients with no history of DMARD treatment.

This algorithm is based on the EULAR recommendations on RA management [6]. RF/ACPA: rheumatoid factor/anti-citrullinated peptide antibodies. Reproduced from Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs. Ann Rheum Dis 2010;69:75, with permission from the BMJ Publishing Group Ltd. *The treatment target is clinical remission or, if remission is unlikely to be achievable, at least low disease activity.
activity, inhibition of structural change and improvement in physical function. This article will primarily present results from phase 3 clinical trials using mAbs that inhibit T-cell activation, deplete B cells or target cytokines involved in the pathogenesis of RA in patients who are inadequate responders to DMARDs (DMARD-IRs).

**Inhibition of T-cell activation**

**Adding abatacept**

Abatacept is a biologic agent that is the recombinant dimerized form of cytotoxic T-lymphocyte antigen 4, a natural inhibitor of T-cell activation and an Fc construct. The phase 3 Abatacept in Inadequate Responders to Methotrexate (AIM) study was a 1-year, randomized, double-blind, placebo-controlled trial that evaluated the safety and clinical efficacy of abatacept plus MTX in patients with inadequate responses to MTX therapy [21].

Patients received once-monthly infusions of abatacept (10 mg/kg; n = 433) or placebo (n = 219) plus weekly administration of MTX. At 6 months, ACR20, ACR50 and ACR70 response rates were significantly higher in patients treated with abatacept (67.9, 39.9 and 19.8%, respectively), compared with placebo (39.7, 16.8 and 6.5%, respectively; P < 0.001 for all comparisons) [21]. All responses continued to improve to 1 year with abatacept, but remained unchanged with placebo (differences of 33.4, 30.1 and 22.7% for ACR20, ACR50 and ACR70 responses, respectively, compared with placebo at 1 year). At 6 and 12 months, more patients treated with abatacept achieved DAS using 28 joints (DAS-28) ≤ 3.2 or DAS-28 < 2.6 [21].

After 1 year of treatment, 63.7% of abatacept-treated patients showed significant improvement in the HAQ-Disability Index (HAQ-DI) score compared with 39.3% for placebo (P < 0.001) [21]. Abatacept-treated patients also experienced significant slowing of radiological damage— with an ~50% reduction in Genant-modified total Sharp scores—compared with placebo at 1 year. This study demonstrated that selective T-cell inhibition by abatacept provided significant additional clinical, radiographic, and functional benefits in patients with RA and inadequate responses to MTX [21].

**B-cell depletion**

**Adding rituximab**

The B-cell-depleting mAb rituximab was approved on the basis of several trials in patients with RA, including those resistant to DMARDs and biologic agents. The only rituximab trial yet to be published in patients who responded inadequately to DMARDs, the Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA (DANCER) trial, enrolled 465 patients who had active RA despite ongoing MTX treatment and who had failed therapy with at least one previous DMARD or biologic agent [22]. Patients were randomized to one of nine treatment groups: placebo, rituximab 500 mg or rituximab 1000 mg on days 1 and 15 plus MTX; patients in each group also receiving placebo glucocorticoids, i.v. methylprednisolone premedication or i.v. methylprednisolone premedication plus oral prednisone for 2 weeks [22].

Compared with placebo, treatment with either 500 or 1000 mg rituximab resulted in significantly higher ACR20 (28, 55 and 54%, respectively; P < 0.0001), ACR50 (13, 33 and 34%, respectively; P < 0.001) and ACR70 (5, 13 and 20%, respectively; P < 0.05) response rates (Fig. 2A) [22]. Similarly, reductions in the DAS-28 from baseline were significantly greater with either dose of rituximab (−1.79 and −2.05 with the 500- and 1000-mg doses, respectively) than with placebo (−0.67; P < 0.0001), and moderate or good European League Against Rheumatism (EULAR) responses were significantly higher in the rituximab groups (Fig. 2B) [22]. ACR responses were independent of glucocorticoid treatment. Both rituximab treatment groups experienced significantly greater improvements in mean HAQ-DI and Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scores and had higher proportions of patients achieving the minimal clinically important difference for these patient-reported outcomes compared with placebo. Collectively these data indicated that both doses of rituximab were effective and the efficacy was not substantially influenced by simultaneous glucocorticoid application.

Rituximab dosing regimens were further investigated in MTX-resistant patients in the Study Evaluating Rituximab’s Efficacy in MTX iNadequate ResponderS (SERENE), a phase 3, randomized, placebo-controlled trial [23]. Patients received rituximab 500 mg, rituximab 1000 mg or placebo on days 1 and 15 plus a stable dose of MTX. At week 24, both doses of rituximab demonstrated superior efficacy compared with placebo for the primary endpoint, ACR20 response (54, 51 and 23%, respectively; P < 0.0001). Other clinical and quality-of-life (QOL) outcomes were improved to a greater extent in both rituximab groups compared with placebo. Improvements in disease activity noted at week 24 were maintained or increased at week 48. Both rituximab dosing regimens were clinically effective in patients with active RA and an inadequate response to MTX [23].

The Methotrexate Inadequate Responders Randomised Study of Rituximab (MIRROR) was a phase 3 trial that evaluated the efficacy of three regimens comprising two courses of rituximab administered 24 weeks apart: two courses of rituximab 2 × 500 mg; initial course of 2 × 500 mg with 2 × 1000 mg at 24 weeks (dose escalation); or two courses of 2 × 1000 mg [24]. Between 25% and 28% of patients had received prior treatment with a TNF inhibitor. At week 48, ACR20, ACR50, and ACR70 response rates did not differ among the dosing regimens. However, significantly more patients receiving the standard rituximab 2 × 1000-mg regimen achieved EULAR responses at week 48 (P = 0.0495). Re-treatment at week 24 resulted in a sustained suppression of disease activity to week 48. Although this study was unable to clearly differentiate between the dosing regimens, several efficacy outcomes favoured treatment with rituximab.
2 × 1000 mg and suggested that repeat treatment may maintain or improve outcomes [24].

**Cytokine inhibition**

Blockade of pro-inflammatory cytokines (i.e. TNF-α, IL-1 and IL-6) has been vigorously investigated in the past decade as a therapeutic strategy in patients with RA. TNF-α inhibitors (i.e. adalimumab, etanercept and infliximab) have been widely evaluated, and their efficacy has been demonstrated in many controlled trials. Golimumab and certolizumab pegol are newer anti-TNF agents whose efficacies have been investigated in combination with MTX. An IL-1 antagonist, anakinra, is approved for RA treatment but is infrequently used because it is administered via daily s.c. injections. IL-6 inhibition has emerged as a novel treatment strategy in RA, with tocilizumab, an antibody to the IL-6 receptor,
showing promise as an effective treatment in patients with active RA.

**Adalimumab**

Adalimumab is a recombinant human immunoglobulin G1 (IgG1) mAb specific for TNF-α. In DE019, a pivotal 52-week, double-blind, placebo-controlled trial, 619 patients were randomized to receive placebo, adalimumab 20 mg/week or adalimumab 40 mg every other week (BIW) plus their usual MTX dose [25]. At week 24, ACR20 responses were achieved by 63% and 61% of patients in the adalimumab 40-mg BIW and 20-mg/week groups, respectively, compared with 30% of patients treated with placebo ($P < 0.001$ for both) and remained significantly higher in the adalimumab groups at week 52 ($P < 0.001$ for both). At weeks 24 and 52, ACR50 and ACR70 response rates were significantly greater with either adalimumab regimen than with placebo ($P < 0.001$), ACR responses were evident by week 2 of treatment, and fewer patients treated with adalimumab required rescue medication [25].

After 52 weeks, radiographic progression (measured by the modified total Sharp score) was significantly worse in patients receiving placebo (+2.7) than in those receiving adalimumab 40 mg BIW (+0.1) or adalimumab 20 mg/week (+0.8) ($P < 0.001$ for both) [25]. Compared with placebo, treatment with adalimumab reduced the number of erosions, attenuated joint space narrowing, and increased the proportion of patients with improvement or no change in these radiographic measures [25].

Both regimens of adalimumab improved physical function by week 2, with a significantly greater decrease in HAQ-DI scores at week 52 [adalimumab 40 mg/2 weeks (−0.59) or adalimumab 20 mg/week (−0.61)] compared with placebo (−0.25); $P < 0.001$ for both; Fig. 3] [25]. In this 52-week trial, adding adalimumab to the MTX regimen in patients partially responsive to MTX provided additional benefit, with inhibition of joint damage, reduction of signs and symptoms and improvement in physical function [25].

**Etanercept**

Etanercept is a TNF receptor–IgG1 Fc fusion protein that binds and inactivates both TNF-α and TNF-β. The benefit of etanercept as add-on therapy in patients receiving therapeutic doses of MTX was studied in a 24-week, double-blind, placebo-controlled trial [26] and in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPHO) study [27]. The TEMPO study was a global, randomized, double-blind, 52-week trial evaluating the efficacy of etanercept plus MTX vs monotherapy with either drug in patients with inadequate responses to DMARDs other than MTX; it is discussed fully in the article by Juan Gómez-Reino in this supplement. A third randomized, controlled 2-year trial has provided data for therapeutic responses following treatment with etanercept with or without SSZ in patients with active RA despite SSZ therapy [28].

In the 24-week study, 89 patients with persistently active RA despite stable MTX therapy were randomized to receive etanercept 25 mg or placebo s.c. twice weekly together with MTX [26]. At 24 weeks, ACR20, ACR50 and ACR70 criteria were achieved by 71, 39 and 15%, respectively, for patients receiving etanercept and 27, 3 and 0%, respectively, for placebo ($P < 0.001$, $P < 0.001$ and $P = 0.03$, respectively). HAQ-DI scores improved to a greater extent with etanercept (47%) than with placebo (27%). Adding etanercept to MTX therapy provided an additional benefit to patients with persistently active RA [26].

In the Etanercept Study 309, 260 patients with active RA despite SSZ therapy were randomized (2:1:2 ratio) to etanercept 25 mg twice weekly, etanercept plus SSZ or SSZ alone in a 2-year, double-blind, double-dummy multicentre study [28]. At 52 weeks, a significantly higher proportion of patients receiving etanercept in combination (57.0%) or as monotherapy (45.6%) had low disease activity (DAS < 2.4) compared with those receiving SSZ alone (4.0%), and higher ACR20 response rates (77 and 67%, respectively) compared with those receiving SSZ alone (34%; $P < 0.01$). Clinically, significant improvement in the HAQ-DI score was reported by 78, 76 and 40% of patients, respectively [28]. This study showed that etanercept alone or added to SSZ therapy provides an additional treatment option for RA patients not responding adequately to SSZ, a non-MTX DMARD.

**Infliximab**

The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study was a 54-week, multinational, phase 3 clinical study that demonstrated the efficacy of infliximab, a chimeric anti-TNF-α mAb, when used in combination with MTX in.
patients with persistently active RA [29, 30]. Patients (N = 428) were randomized to receive placebo or one of four regimens of infliximab (3 or 10 mg/kg of body weight every 4 or 8 weeks) plus oral MTX [29, 30].

ACR20 response rates at 30 weeks (the primary endpoint) ranged from 50% to 58% in the infliximab groups compared with 20% for placebo (P < 0.001 for each regimen vs placebo), and ACR50 response rates were significantly higher with infliximab [29]. The superiority of the infliximab–MTX combination compared with MTX alone was sustained to week 54 [30]. The positive impact of infliximab on function and QOL was demonstrated by greater improvements in HAQ arthritis-specific scores and SF-36 physical component scores with infliximab and MTX compared with MTX alone [30].

Joint damage was attenuated with infliximab treatment, with an overall increase in radiographic score of 0.6 U for combined treatment vs 7.0 U with MTX alone (P < 0.001) [30]. Combination therapy arrested the progression of structural damage in a significantly greater proportion of patients (39–55%) compared with MTX alone (14%). The attenuation of joint damage with combination therapy was independent of the clinical response or extent of joint damage [30].

In the ATTRACT study, therapy with infliximab plus MTX provided sustained clinical benefit in patients with persistently active RA. The combined therapy controlled the signs and symptoms of inflammation and halted the progression of joint damage and improved QOL [29, 30].

**Golimumab**

Golimumab is a human mAb targeted against TNF-α. In the phase 3 GOlimumab FOR subjects With Active RA Despite MTX (GO-FORWARD) study, 444 patients with active disease despite treatment with MTX were randomized to one of four treatment groups: (i) placebo injection plus MTX; (ii) golimumab 50 mg plus MTX; (iii) golimumab 100 mg plus MTX or (iv) golimumab 100 mg plus placebo capsule [31]. The co-primary endpoints were ACR20 responses at week 14 and change from baseline in HAQ-DI score at week 24. ACR20 response rates at week 14 were 33.1, 55.1, 56.2 and 44.4% for each treatment group, respectively. HAQ-DI score improvements at week 24 were 0.13, 0.38, 0.50 and 0.13, respectively. Significantly greater proportions of patients receiving golimumab plus MTX achieved EULAR response, DAS-28 remission and ACR50 and ACR70 responses at weeks 14 and 24 compared with those receiving MTX alone. Therefore, adding golimumab injections to MTX therapy every 4 weeks significantly reduced disease activity compared with MTX or golimumab alone and improved physical function in patients with active disease despite MTX therapy [31]. The superior responses achieved with combination therapy were sustained to 52 weeks [32].

In the GO-FORWARD study, golimumab was administered s.c. Treatment with i.v. golimumab plus MTX was examined in another phase 3 randomized, double-blind, placebo-controlled study in patients with MTX-resistant RA [33]. Five groups of patients received i.v. placebo plus MTX or i.v. golimumab at a dose of 2 mg/kg or 4 mg/kg, with or without MTX, every 12 weeks through week 48 [33]. The primary endpoint, proportion of patients achieving ACR50 response at week 14, was not met (21% in the golimumab plus MTX groups and 13% in the placebo plus MTX group; P = 0.051). However, by week 24 significantly more patients treated with golimumab plus MTX achieved ACR50 responses compared with placebo (22% vs 9%; P = 0.002); at week 48, ACR20 and ACR50 response rates were highest among patients receiving golimumab 4 mg/kg plus MTX (70 and 48%, respectively) [33]. The combination of MTX and golimumab was more effective than either therapy alone for both disease control and physical functioning. Other dosing strategies with i.v. golimumab are being investigated [33].

**Certolizumab**

Certolizumab pegol is a pegylated Fab’ fragment of a humanized anti-TNF antibody. In the 52-week Rheumatoid Arthritis Prevention of Structural Damage 1 (RAPID 1) trial, 982 patients previously treated with MTX for 6 months were randomized to treatment with one of two regimens of certolizumab (400 mg certolizumab at weeks 0, 2 and 4 followed by 200 or 400 mg every 2 weeks) plus MTX or placebo plus MTX [34]. At week 24, ACR20 response rates were significantly higher in the certolizumab 200-mg (58.8%) and 400-mg (60.8%) groups compared with MTX alone (13.6%) and remained significant through week 52 (P < 0.001 for both). ACR50 and ACR70 responses with certolizumab plus MTX were superior to those with placebo plus MTX at weeks 24 and 52. Significant slowing of radiographic progression (measured by the modified total Sharp score) with certolizumab was noted at week 24; by 52 weeks, the mean change was 0.4 U with certolizumab 200 mg and 0.2 U with certolizumab 400 mg, compared with 2.8 U with placebo (P < 0.001). Both doses of certolizumab resulted in greater improvement in physical function compared with placebo; the HAQ-DI score was reduced 30.4 and 27.6% with certolizumab 200 mg or 400 mg, respectively, vs 8.2% with placebo at week 12 [34].

The RAPID 2 trial (N = 619) was a 24-week study with a design similar to RAPID 1 [35]. As in RAPID 1, ACR20 response rates at week 24 were significantly higher with certolizumab (57.3 and 57.6% in the 200-mg and 400-mg groups, respectively) than with placebo (6.7%). Other disease measures were significantly improved in the groups receiving certolizumab and MTX compared with placebo. Patients treated with certolizumab showed significantly less radiographic progression [mean changes from baseline in total Sharp score of 0.2 and −0.4 with certolizumab 200 mg and 400 mg, respectively, vs 1.2 with placebo (P < 0.01)] and greater improvement in HAQ-DI scores [−0.50 with either dose of certolizumab vs −0.14 with placebo (P < 0.001)] [35].

The 12-week double-blind REALISTIC (RA EvAluation In Subjects receiving TNF Inhibitor Certolizumab pegol) trial enrolled a broad population of patients representative...
of those treated in clinical practice, including those with prior TNF inhibitor exposure [36]. The study randomized >1000 patients (4:1) with active RA and inadequate response to DMARDs to treatment with s.c. certolizumab (400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks) or placebo injection every 2 weeks as add-on to current therapy. At week 12, ACR20 responses were significantly greater in patients receiving certolizumab than in the control group (51.1% vs 25.9%; P < 0.001) regardless of prior TNF inhibitor use. Meaningful improvements in several QOL measures were noted with certolizumab [37].

Tocilizumab

Tocilizumab is a humanized mAb to the IL-6 receptor that blocks IL-6 binding and inhibits its inflammatory effects. The therapeutic effects of blocking IL-6 activity with tocilizumab in patients with inadequate responses to MTX or other DMARDs were examined in three international, double-blind, placebo-controlled phase 3 studies and one multicentre US study. In the Tocilizumab Pivotal Trial in Methotrexate Inadequate responders (OPTION) [38], patients with inadequate responses to MTX were randomized to receive tocilizumab 4 mg or 8 mg or placebo in combination with MTX, whereas in the Tocilizumab in Combination with Traditional DMARD therapy (TOWARD) trial [39], tocilizumab 8 mg or placebo was evaluated with a wide range of baseline DMARDs in patients who had not responded adequately to conventional anti-rheumatic therapy. OPTION and TOWARD were both 24-week studies, with the ACR20 response rate at 24 weeks as the primary endpoint. A third study [Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE)] was a 2-year safety and efficacy study that, in addition to examining ACR20 response at 24 weeks, also evaluated radiographic progression and physical function at 52 weeks in patients with inadequate responses to MTX who were randomized to tocilizumab 4 mg or 8 mg or placebo with concomitant MTX [40]. The Rapid Onset and Systemic Efficacy (ROSE) study, which was conducted in a DMARD-resistant population in the USA, was distinguished by the use of a more stringent primary efficacy outcome (ACR50 response at 24 weeks) and an assessment of early response to therapy [41]. In addition to these placebo-controlled studies, the double-blind, 2-year ACT-RAY study evaluated the efficacy (including radiographic progression, physical function and QOL) of adding tocilizumab 8 mg/kg to MTX treatment vs switching to tocilizumab 8 mg/kg alone in patients with inadequate responses to MTX treatment [42].

In all three international studies, ACR20, ACR50 and ACR70 responses were achieved at 24 weeks in a significantly higher proportion of patients receiving tocilizumab than those receiving placebo [38-40]. ACR20 response rates in the OPTION trial were 48 and 59% with tocilizumab 4 and 8 mg, respectively, vs 26% with placebo (Fig. 4) [38]; in the TOWARD trial, 61% of tocilizumab-treated patients and 25% of placebo-treated patients achieved ACR20 endpoints [39]. At week 24 of

![Fig. 4 Change from baseline in disease signs and symptoms over time in the OPTION trial [38].](image-url)
the LITHE study, 51 and 56% of patients receiving tocilizumab 4 and 8 mg, respectively, reported ACR20 responses [43]. In the ROSE study, ACR50 responses at week 24 were significantly higher in tocilizumab-treated patients than in placebo-treated patients (30.1% vs 11.2%; \( P < 0.0001 \)) [41]. The response to combination tocilizumab and DMARD was apparent as early as 2 weeks and increased during the period of observation. All ACR component variables were improved significantly by week 24 [38, 39, 41]. Mean DAS-28 showed a rapid decrease from baseline values in all groups treated with tocilizumab. In OPTION and TOWARD, DAS-28 remission rates (DAS-28 < 2.6) were significantly higher in the tocilizumab groups than with placebo (\( P < 0.001 \), and improvements in physical function and QOL measures were greater [38, 39]. Examination of early response in ROSE showed that significant improvements in patient assessments of disease activity and pain and DAS-28 were evident as early as day 7 [41]. A substudy of the OPTION trial showed that tocilizumab treatment resulted in favourable changes in bone and cartilage turnover that were related to clinical improvement [44].

Week 52 results from the LITHE study demonstrated a continued increase in ACR response rates, low disease activity rates and DAS-28 remission rates and improvement in HAQ-DI scores between weeks 24 and 52 in the tocilizumab groups compared with placebo [43]. Radiographic progression (as measured by Genant total score) at 52 weeks was reduced significantly in both tocilizumab plus MTX groups (total scores 0.34 and 0.29 with tocilizumab 4mg/kg and 8mg/kg, respectively) compared with the MTX group (total score 1.13; \( P < 0.001 \)). A significantly higher proportion of patients treated with tocilizumab plus MTX (80.5 and 84.5% with tocilizumab 4 or 8 mg, respectively) showed no radiographic progression compared with placebo (67.2%; \( P < 0.001 \)) [40].

Long-term extension studies demonstrated that the efficacy of tocilizumab plus DMARD therapy was maintained during extended treatment [45-47]. Pooled analyses of long-term data from 2904 DMARD-resistant patients (median treatment duration 3.6 years) showed that the numbers of patients achieving ACR50, ACR70 and DAS-28 remission increased to week 120 of follow-up [46]. By week 180, 17% of patients had maintained an ACR70 response for 48 weeks. At week 96, no tender or swollen joints were reported in 35.7 and 26.7% of patients, respectively, and 14.6% of patients reported no disability (HAQ-DI score 0) [47].

In the ACT-RAY study, 556 patients were randomized to receive continued MTX together with tocilizumab 8 mg/kg or placebo plus tocilizumab [42]. DAS-28 scores at week 24 did not support the superiority of combined treatment, and other disease activity, radiological and functional measurements were comparable between groups, suggesting that treatment with tocilizumab alone may provide a clinically meaningful benefit in patients who have responded inadequately to MTX.

Discussion

Although DMARDs, in particular MTX, are the standard of care for many patients with RA, failure to achieve adequate disease control even with combination therapy has spurred the development of agents that target various immune mediators involved in the disease process. Biologic agents have improved available options because of greater efficacy, rapid onset of action and favourable tolerability profiles. The combination of a biologic agent and a DMARD can reduce RA symptoms, slow the progression of joint damage and improve function in RA patients who respond inadequately to DMARDs. Although data comparing the efficacy of the various biologic agents are limited, the availability of biologic therapies with different mechanisms of action expands therapeutic options for patients whose disease is inadequately controlled with DMARDs and allows for greater individualization of treatment.

Rheumatology key messages

- Early treatment intervention and tight control of patients with RA are critical.
- Many RA patients respond inadequately to DMARDs or respond inadequately over time.
- Robust data exist that support biologic treatment strategies for RA patients who are DMARD-IR.

Acknowledgements

The authors thank ApotheCom for writing and editorial assistance, which was funded by F. Hoffmann-La Roche Ltd.

Funding: This study was funded by Roche. Support for third-party writing assistance for this supplement was provided by F. Hoffmann-La Roche Ltd.

Supplement: This paper forms part of the supplement ‘Current Treatment Options and New Directions in the Management of Rheumatoid Arthritis’. This supplement was commissioned and funded by F. Hoffmann-La Roche Ltd.

Disclosure statement: A.K. has received research grants/ support from Abbott, Amgen, BMS, Roche, Jannsen and UCB. G.F. has received speaking fees from Roche, Abbott, Pfizer, UCB, BMS and MSD < € 10.000 00 and grants for research from Roche. A.R.-R. has received honoraria for talks and consulting from Bristol-Myers Squibb, Chugai, Merck Sharp & Dohme, Abbott, UCB, Pfizer, Roche, Novartis and Amgen. K.P. has received honoraria for lectures from Roche, Abbott, BMS, MSD and Pfizer.

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