Biologics in rheumatoid arthritis: where are we going?

Biological disease-modifying antirheumatic drugs have significantly improved outcomes for patients with rheumatoid arthritis, but cost limits their use. This article assesses data on patients who have achieved remission or low disease activity with these drugs and the possibility of dose reduction or discontinuation in these patients.

Rheumatoid arthritis is an autoimmune disease which causes irreversible joint damage and functional disability. However, the development of targeted therapeutic biological disease-modifying antirheumatic drugs in the 1990s considerably changed the prognosis of patients with rheumatoid arthritis. Together with earlier treatment and the use of treat-to-target strategies – with regular monitoring and escalating therapy if disease activity remains high – remission has become an achievable goal.

Within the group of biological disease-modifying antirheumatic drugs used in the treatment of rheumatoid arthritis are five drugs targeting the cytokine tumour necrosis factor-α (TNFα) and four targeting other pathways in the disease pathogenesis. Four of the TNF inhibitor agents are monoclonal antibodies (infliximab, adalimumab, golimumab, certolizumab pegol) and one is a receptor fusion protein (etanercept). The others biological disease-modifying antirheumatic drugs include the interleukin (IL)-1 receptor antagonist anakinra, the IL-6 receptor blocking monoclonal antibody tocilizumab, the anti-CD20 B-cell depleting agent rituximab and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) fusion protein, abatacept.

The 12-month randomized placebo controlled double blind trial by Quinn et al (2005) was the first to assess the effect of induction with infliximab in combination with methotrexate in patients with methotrexate-naïve rheumatoid arthritis. One year after discontinuing infliximab, 70% of patients in sustained remission. However, biological agents are expensive and may have potential side effects because of their immunosuppressive mechanism of action (Singh et al, 2011) – factors limiting their more widespread use.

This review addresses strategies of biological disease-modifying antirheumatic drug discontinuation or dose reduction in patients with rheumatoid arthritis who have achieved remission or low disease activity. These are discussed according to different stages of the disease:

1. Established rheumatoid arthritis
2. Early rheumatoid arthritis
3. Early inflammatory arthritis, which includes patients not yet fulfilling rheumatoid arthritis classification criteria.

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Definition of clinical remission

Achieving remission, or at least a state of low disease activity, is the goal of treatment in patients with rheumatoid arthritis, in order to minimize inflammation and limit joint damage and functional disability (Schoels et al, 2010; Smolen et al, 2010). There is evidence that attaining low levels of disease activity early, particularly during the first 3 months of treatment, significantly predicts remission at a later stage (Aletaha et al, 2007). There are many definitions of remission (Felson et al, 2011). Commonly, clinical remission is defined according to a disease activity score of 28 joints (DAS28). This composite score is based on the number of tender and swollen joints, the patient's assessment of global heath and a marker of inflammation, using the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level. Using this measure, the score for remission should be <2.6 and for low disease activity ≤3.2 (Fransen et al, 2004).

Biological disease-modifying antirheumatic drug discontinuation and dose reduction in established rheumatoid arthritis

Biological disease-modifying antirheumatic drug discontinuation

Several studies have reported on the effect of cessation of a biological disease-modifying antirheumatic drug in patients with established rheumatoid arthritis (*Table 1*). The biological disease-modifying antirheumatic drugs studied include adalimumab, infliximab, etanercept, certolizumab pegol, tocilizumab and abatacept. All patients in these studies (mean disease duration from 1.6 to 13.7 years) had failed one or more conventional synthetic disease-modifying antirheumatic drugs – e.g. methotrexate, sulphasalazine or leflunomide – therefore were deemed conventional synthetic disease-modifying antirheumatic drug incomplete responders.

In the multicentre prospective Japanese study, RRR (Remission induction by Remicade in rheumatoid arthritis patients) (Tanaka et al, 2010) 102 patients who had achieved remission with infliximab and methotrexate stopped their treatment with infliximab after 1 or 2 years. The primary end points were the number of patients in low disease activity and the radiographic progression at 1 year. Overall, 55% (*n*=56) of patients maintained low disease activity (DAS28-ESR ≤ 3.2). Yearly progression of total Sharp score was less than 0.5 points (van der Heijde, 2000) in 67% of patients who were in low disease activity compared with 44% of patients who failed to achieve this. Remission (DAS28<2.6) was maintained in 43% of patients who were drug free (Tanaka et al, 2010).

Another Japanese study, the HONOR study (Hirata et al, 2013) (Humira discontinuation without functional and radiographic damage progression following sustained remission), reported on the discontinuation of adalimumab. The primary end point was the percentage of patients that maintained remission (DAS28-ESR <2.6) at week 24 after discontinuation. Of the 50 patients who stopped treatment, 58% (*n*=29) achieved remission while 42% of patients failed to do so. Of the six patients who restarted adalimumab, 33% achieved remission after 24 weeks. There was no radiographic progression with adalimumab discontinuation (Hirata et al, 2013). The mean dose of methotrexate was 8.96 mg/week which is notably lower than the average dose used in many other countries, based on the assumption that the average body weight of Japanese patients is lower than non-Japanese patients. Results therefore may not be directly comparable to studies of higher dose methotrexate failure.

Brocq et al (2009) reported a discontinuation of 21 French patients treated with infliximab (3 mg/kg/8 weeks), adalimumab (40 mg/2 week or 40 mg/3 weeks) and etanercept (50 mg/week or 25 mg/week). Remission was defined by a DAS28<2.6 without non-steroidal anti-inflammatory drugs and with prednisolone <5 mg/day for at least 6 months. At 1 year, 15 patients (75%) achieved sustained remission. The mean time to relapse after biological disease-modifying antirheumatic drug discontinuation was 14.7 weeks. There was no difference between the low dose of etanercept (*n*=7) *vs* high dose (*n*=7) in terms of time to relapse.

Saleem et al (2010) assessed the clinical and radiographic effect of stopping TNF inhibitor (infliximab, etanercept, adalimumab) in 47 British patients. The TNF inhibitor was introduced after insufficient response to conventional synthetic disease-modifying antirheumatic drugs in 20 patients (delayed treatment group). For oth-

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Table 1. Discontinuation of a biological disease-modifying antirheumatic drug in established rheumatoid arthritis

Study	Biological DMARD	Duration of follow up (months)	No. of patients	Mean duration disease (years)	Mean baseline DAS28 ESR before DMARD initiation	Remission duration (months)	Patients in remission N (%)	Patients in LDA N (%)	Radiographic outcome ΔmTSS<0.5%
Biological DMARD in combination with csDMARDs									
Brocq et al (2009)	Infliximab (3 mg/kg/8 w) Adalimumab (40 mg/2 w or 40 mg/3 w) Etanercept (50 mg/w or 25 mg/w)	12	21	11.29	5.99	19.24	15 (75)*	N/A	N/A
RRR (Tanaka et al, 2010)	Infliximab (3 mg/kg/8 w)	12	102	5.9	5.5	>6	44 (43)†	56 (55)	67
Saleem et al (2010)	Infliximab Etanercept Adalimumab	12	47 27 early 20 delayed	1.6 10	N/A N/A	8 12	16 (59)* 3 (15)*	N/A N/A	N/A N/A
HONOR (Hirata et al, 2013)	Adalimumab (40 mg/2 w)	6	50	7.1	5.06	>6	29 (58)†	N/A	94.9
ADMIRE (Chatzidionysiou et al, 2012)	Adalimumab	12	15	N/A	N/A	≥3	5 (33)*	N/A	N/A
CERTAIN (Smolen et al, 2014a)	Certolizumab pegol (400 mg then 200 mg/4 w)	12	17	3.6	4.5	N/A	3 (17.6)§	N/A	N/A
Aguilar-Lozano et al (2013)	Tocilizumab	3	45	13.7	N/A	N/A	(44)*	N/A	N/A
Biological DMARD monotherapy									
DREAM (Nishimoto et al, 2014)	Tocilizumab (8 mg/kg/4 w or 6 mg/kg/4 w or 4 mg/kg/4 w)	13	187	7.8	6.2	N/A	17 (9.1)†	(13.4)	N/A
ORION (Takeuchi et al, 2013)	Abatacept	3	34	N/A	N/A	N/A	12 (35.3)‡	N/A	N/A

csDMARDs = conventional synthetic disease-modifying anti-rheumatic drug; DAS28 ESR = disease activity score using 28 joints and based on erythrocyte sedimentation rate; DMARD = disease-modifying antirheumatic drug; ΔmTSS = change from baseline in modified total Sharp score; LDA = low disease activity (DAS28 ESR ≤3.2); N/A = not available; w = weeks. Definition of remission: *DAS28<2.6, †DAS28-ESR<2.6, ‡DAS28-CRP<2.3 § CDAI≤2.8

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ers patients, TNF inhibitors were introduced as first-line therapy (early treatment group). In the delayed treatment group, three patients were able to sustain remission. In the early treatment group, 16 patients maintained remission. No differences in disease activity scores or duration of remission before stopping therapy were seen to explain these results. Patients who had delayed treatment had longer mean symptom duration than patients in the early treatment group. There were no significant differences in ultrasound scan scores between the two groups although the scores were generally low.

In the ADMIRE study, patients were randomized into two arms. The first group (n=15) stopped adalimumab and continued with methotrexate monotherapy. The second group (n=16) continued adalimumab in combination with methotrexate. The primary end point was the proportion of patients in remission (DAS28<2.6) after 28 weeks. Five patients in the methotrexate group sustained remission compared to 15 patients in the adalimumab group (P=0.001)(Chatzidionysiou et al, 2012).

The 52-week, randomized, double-blind CERTAIN study reported data for patients with low-to-moderate rheumatoid arthritis despite conventional synthetic disease-modifying antirheumatic drugs. Ninety-six patients received certolizumab pegol subcutaneously, 400 mg at 0, 2, 4 weeks followed by 200 mg every 2 weeks over 24 weeks. Seventeen patients in remission (Clinical Disease Activity Index ≤2.8)(Aletaha et al, 2005) at weeks 20 and 24 stopped certolizumab pegol and remained on conventional synthetic disease-modifying antirheumatic drugs. Three patients sustained Clinical Disease Activity Index remission at week 52. Ten patients were retreated with certolizumab pegol and attained low disease activity (Smolen et al, 2014a).

Discontinuation of abatacept in patients with a DAS28-CRP <2.3 was studied in a 12-week observational ORION study. The primary end point was the proportion of patients who maintained remission. Clinical remission was maintained in 35.3% of patients at 1 year after abatacept discontinuation (Takeuchi et al, 2013).

A Mexican study reported data after cessation of tocilizumab in combination with methotrexate in active patients with an inadequate response to methotrexate. Forty-five patients stopped tocilizumab but continued methotrexate. Relapse was defined by one or more swollen joints. Forty four per cent of patients maintained remission (DAS28<2.6) and 56% of patients relapsed over the 12-month follow-up period (Aguilar-Lozano et al, 2013).

The DREAM (Drug free Remission/low disease activity after cessation of tocilizumab (Actemra)) study assessed the effect of cessation of tocilizumab in monotherapy in 187 Japanese patients. The primary end point was the proportion in DAS28 remission (DAS28-ESR <2.6) or low disease activity (DAS28-ESR <3.2) at 52 weeks after the cessation of biological disease-modifying antirheumatic drugs. Remission and low disease activity were achieved in 9.1% and 13.4% of patients respectively (Nishimoto et al, 2014).

The results of studies addressing biological disease-modifying antirheumatic drug discontinuation in established rheumatoid arthritis are therefore fairly heterogeneous with proportions of patients achieving remission ranging from 15% to 75% (Brocq et al, 2009; Saleem et al, 2010). The relatively high proportion of patients achieving remission in the study by Brocq et al (2009) may be explained by a strategy of dose reduction used in this study. Differences in remission rates between the Japanese studies (Tanaka et al, 2010; Hirata et al, 2013) and the study from the UK on TNF-inhibitor withdrawal (Saleem et al, 2010) may be the result of the difference in disease severity of these patients at study entry. Indeed in Japan, the introduction of biological disease-modifying antirheumatic drugs is recommended after failing methotrexate, defined as DAS28>3.2 (Tanaka et al, 2013), whereas in UK the National Institute for Health and Care Excellence (2009) guidelines recommend their use after failing two conventional synthetic disease-modifying antirheumatic drugs and documenting high disease activity DAS28>5.1 on two separate occasions. For tocilizumab, maintenance of methotrexate may increase the per cent of patients in remission (Aguilar-Lozano et al, 2013; Nishimoto et al, 2014). Overall, however, these data suggest that the majority of patients with established rheumatoid arthritis are unable to maintain clinical remission or at least low disease activity after discontinuation of a biological disease-modifying antirheumatic drug.

Biological disease-modifying antirheumatic drugs reduction

In terms of decreasing treatment, two strategies have been studied: the first, one of dose reduction of the biological disease-modifying antirheumatic drug and the second, spacing of injections (*Table 2*). Three studies have reported on biological disease-modifying antirheumatic drug dose reduction.

The double-blind randomized controlled PRESERVE study assessed the dose reduction of etanercept in patients with an inadequate response to methotrexate and with moderate disease activity. This 36-week open label study included 834 patients treated with etanercept 50 mg/week and methotrexate. Patients who attained low disease activity (DAS28-ESR<3.2) were randomized to receive either etanercept 50 mg/week (full dose), or etanercept 25 mg/week (half dose) or placebo. All patients had methotrexate. In the full-dose group, low disease activity was achieved by 82.6% of patients compared to 79.1% in the half-dose and 42.6% in the placebo group. No difference in radiographic progression was seen between etanercept half-dose and methotrexate monotherapy (P=0.118). Maintenance of low disease activity was greater in the dose-reduction group than in those who

discontinued etanercept and were treated with methotrexate alone. Remission (DAS28-ESR <2.6) was sustained in 60.2% of patients in the half-dose group, 66.7% in the full-dose group and 29.4% in the placebo group (Smolen et al, 2013).

A post-hoc analysis of the DOSERA study compared the effect of discontinuation or dose reduction with etanercept. The study included 73 patients and compared continuing etanercept 50 mg/week plus methotrexate (n=23) to half-dose etanercept 25 mg/week plus methotrexate (n=27) or placebo plus methotrexate (n=23). The primary end point was the proportion of non-failures at week 48, with failure defined by DAS28>3.2 or an increase in DAS28 more than 0.6. The proportion of non-failures was higher for etanercept full dose (52%) and etanercept half dose (44%) than placebo (13%) (P=0.007 and P=0.044 respectively compared to placebo) (Oster-Gaard et al, 2013).

An observational study reported on dose reduction of infliximab in patients with established rheumatoid arthritis who had an incomplete response to conventional synthetic disease-modifying antirheumatic drugs. After 6 months of low disease activity with infliximab 3 mg/kg, the dose was titrated down by 25% of the original dose every 8–12 weeks. A flare was defined by an increase of DAS28≥1.2 and DAS28>3.2. At 1 year, 16% (8/51) stopped infliximab completely and maintained low disease activity. Infliximab could be reduced in 45% of patients. In 39% of patients, the dose of infliximab could not be decreased. The mean dose was reduced from 3 mg/kg to 1.7 mg/kg. The infliximab dose reduction was associated with a median increase in DAS28 from 2.5 to 2.8 after 1 year (P=0.002) (van der Maas et al, 2012).

Another strategy to reduce biological disease-modifying antirheumatic drug therapy is spacing of the biological disease-modifying antirheumatic drug injections. The first data on spacing came from the 18-month randomized controlled STRASS study, which reported on the effect of spacing adalimumab and etanercept injections. Patients included (n=137) had established rheumatoid arthritis and were in DAS28 remission. Sixty-four patients were randomized to space their injection and 73 patients continued their treatment. Thirty-three patients were treated with monotherapy, either adalimumab (n=11) or etanercept (n=22), and 104 patients were treated with etanercept or adalimumab (52 in each group) in combination with methotrexate or leflunomide. The spacing strategy was determined by the DAS28 score. The inter-injection interval was increased every 3 months to complete interruption at fourth step. For adalimumab the interval was increased by 7 days for the two first steps and by 14 days for the third step. For etanercept, the interval was increased by 3 days for the first step, by 4 days for the second step and by 7 days for the third step. Relapse was defined by a DAS28>2.6 and ΔDAS28>0.6. Forty-six patients (71.9%) were able to space injections. Seventeen patients (14.1%) stopped their biological disease-modifying antirheumatic drugs. Relapse was more frequent in the spacing group than in the continuation group (81% *vs* 56%). In a subgroup analysis, the risk of relapse was higher with adalimumab than etanercept (Fautrel et al, 2013; Pham et al, 2013).

In summary, the two randomized studies (PRESERVE and STRASS (Fautrel et al, 2013; Smolen et al, 2013) reported clinical remission in 60% and 71% of patients respectively. These data suggest that the two strategies involve a small risk of disease flare. On the other hand compared to results on discontinuation, treatment reduction appeared more consistently successful and may be a strategy to reduce biological disease-modifying antirheumatic drug therapy in patients with established rheumatoid arthritis.

Table 2. Dose reduction or spacing of a biological disease-modifying antirheumatic drug in established rheumatoid arthritis

Study	Biological DMARD	Duration of follow up (months)	No. of patients	Mean disease duration (years)	Mean baseline DAS28 ESR before DMARD initiation	Remission or low disease activity duration (months)	Patients in remission N (%)	Patients in LDA N (%)	Radiographic outcome ΔmTSS<0.5%	Non-failures %
Dose reduction strategy: biological DMARD in combination with csDMARDs										
PRESERVE (Smolen et al, 2013)	Etanercept 25 mg/w	22	201	6.4	4.4	N/A	121 (60.2)*	159 (79.1)	89	N/A
DOSERA (Oster-Gaard et al, 2013)	Etanercept 25 mg/w	12	27	16.6	5.21	LDA ≥11	N/A	N/A	N/A	44
van der Maas et al (2012)	Infliximab 3 mg/kg: down-titrated 25% every 8–12 w	12	51	12	5.9	N/A	N/A	N/A (45)	N/A	N/A
Spacing strategy: biological DMARD in combination with csDMARDs or as monotherapy										
STRASS (Fautrel et al, 2013; Pham et al, 2013)	Adalimumab Etanercept	18	64	9.5	N/A	>6	46 (71.9)†	N/A	N/A	N/A

csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DAS28 ESR = disease activity on 28 joints based on erythrocyte sedimentation rate; DMARD = disease-modifying antirheumatic drugs. ΔmTSS = change from baseline modified total Sharp score; LDA = low disease activity, DAS28<3.2; N/A = not available; w = weeks. Definition of remission: * DAS28-ESR <2.6, †DAS28<2.6.

Biological disease-modifying antirheumatic drug discontinuation in early rheumatoid arthritis

The 'window of opportunity' concept suggests that there is a phase early in the disease during which therapy may potentially alter, possibly even reverse the disease course with complete return to normality (Quinn and Emery, 2003). To achieve this, one method may be to start with the most effective therapies including biological disease-modifying antirheumatic drugs and to withdraw them when the disease is controlled (Smolen et al, 2010; van Vollenhoven et al, 2014). In the long-term follow up of the study by Quinn et al (2005), four patients who received infliximab and methotrexate as induction therapy were in remission after 7 years of infliximab discontinuation compared to no patients in the methotrexate group (Bejarano et al, 2010). Several others have also addressed the possibility of biological disease-modifying antirheumatic drug discontinuation in early rheumatoid arthritis.

The BeSt study reported on the withdrawal of infliximab after achieving sustained low disease activity with infliximab and methotrexate combination therapy in early rheumatoid arthritis. In a sub-analysis of this study, 104 patients who sustained DAS44≤2.4 over 6 months stopped infliximab. Seventy-seven patients received infliximab and methotrexate as first-line treatment and 27 patients had delayed treatment. At 2 years, 67 (88%) patients treated first line with infliximab sustained remission (DAS44<1.6). At 5 years, minimal joint progression was reported in discontinuation groups. After 7.2 years of median follow up, 56% of patients in the early infliximab treatment group (first-line) and 41% in the delayed treatment group sustained low disease activity (DAS 44≤ 2.4). Methotrexate was then successfully tapered (by 2.5 mg every 4 weeks) to a maintenance dose (≤10 mg/week) in 34 patients (62%) without differences between the early and delayed treatment groups (P=0.58) (Goekoop-Ruiterman et al, 2005; van der Bijl et al, 2007; van der Kooij et al, 2009; Klarenbeek et al, 2011; van den Broek et al, 2011).

The double blind randomized placebo-controlled OPTIMA study assessed the effect of withdrawing adalimumab in patients with early rheumatoid arthritis. Patients received adalimumab plus methotrexate or methotrexate alone for 26 weeks. Those in the adalimumab group who achieved the low disease activity target (DAS28<3.2) at weeks 22 and 23 were randomized to continue or withdraw adalimumab for an additional 52 weeks. At week 78, high proportions of patients in both the adalimumab-withdrawal patients and the adalimumab-continuation groups achieved low disease activity (81% *vs* 91% respectively; P=0.0361). More patients in the adalimumab-continuation group sustained DAS28 remission than in the discontinuation group (P<0.0014). Eighty one per cent of patients who stopped adalimumab had no radiographic progression. Loss of response after adalimumab withdrawal appeared minimal, and most patients were maintained with low disease activity without significant radiographical consequence for 1 year (Smolen et al, 2014b).

In the HIT HARD study, 87 disease-modifying antirheumatic drug-naïve patients were treated with adalimumab plus methotrexate. All patients stopped adalimumab at week 24, at which point 47.9% of patients in the biological disease-modifying antirheumatic drug group achieved DAS28 remission. At week 48, 42.4% of the original 87 patients remained in remission (Detert et al, 2013).

Initial data from the PRIZE study reported results of dose reduction of etanercept *vs* discontinuation. In this prospective study, 306 methotrexate-naive patients were treated with etanercept 50 mg/week plus methotrexate over 52 weeks. Seventy per cent of patients achieved DAS28 remission at week 52. In total, 194/306 patients were randomized to receive etanercept 25 mg/week (dose-reduction group) plus methotrexate, methotrexate monotherapy (biological disease-modifying antirheumatic drug-free group) or placebo (drug-free group). After 39 weeks, 63.5% of patients in the dose-reduction group sustained a clinical remission compared to 38.5% in the biological disease-modifying antirheumatic drug-free group and 23% in the drug-free group. There was no significant radiographical progression in any of the treatment groups (Emery et al, 2013).

Data from the AVERT study assessed the withdrawal of abatacept in early rheumatoid arthritis (mean symptom duration 0.56 years). Patients included had active clinical synovitis of two or more joints for more than 8 weeks and less than 2 years and a DAS28-CRP ≥3.2. They were randomized to receive abatacept 125 mg plus methotrexate or abatacept 125 mg or methotrexate over 12 months. Those who achieved low disease activity (DAS28-CRP <3.2) stopped all rheumatoid arthritis treatment. The effect of discontinuation was reported at 18 months. Primary end points were the proportion of patients in sustained clinical remission (DAS28-CRP<2.6) at month 12 and both months 12 and 18. At month 18, 24.7% (18/73) of patients who stopped combination therapy remained in remission, compared to 28% (14/50) in the abatacept-free group and 16.9% (9/53) in those who stopped methotrexate (Emery et al, 2014).

The 78-week IDEA study compared the efficacy of treatment with a biological disease-modifying antirheumatic drug and methotrexate (n=55) and intravenous methylprednisolone and methotrexate (n=57) in disease-modifying antirheumatic drug-naïve rheumatoid arthritis. Fourteen patients achieved sustained clinical remission (DAS44<1.6 for 6 months or more) with infliximab and methotrexate and discontinued infliximab. By week 78, remission was maintained in 78.6% (11/14) of patients (Nam et al, 2014a).

These data suggest that a proportion of patients with early rheumatoid arthritis are able to achieve biologic-free

Table 3. Discontinuation or dose reduction in early and very early rheumatoid arthritis

Study	Biological DMARD	Duration of follow up (months)	Patient group	No. of patients	Mean duration disease (weeks)	Mean baseline DAS28 ESR before DMARD initiation	Definition of remission	Patient in remission N (%)	Patient in LDA N (%)	Radiographic outcome ΔmTSS<0.5 %
Quinn et al (2005)	Infliximab	12	Methotrexate-naive	10	30	N/A	DAS 28<2.6	7 (70)	N/A	N/A
Bejarano et al (2010)		96		9				4 (44)		
BeSt (Goekoop-Ruiterman et al, 2005; van der Bijl et al, 2007; van der Kooij et al, 2009; Klarenbeek et al, 2011)	Infliximab	24	Methotrexate-naive				DAS<1.6	67 (88)		
			Early treatment	77	3	4.3*			N/A	N/A
		86	1) Early treatment	77	3				43 (56)	
			2) Delayed treatment	27	2				11 (41)	
OPTIMA (Smolen et al, 2014b)	Adalimumab	19	Methotrexate-naive	101	16	5.9†	DAS 28<2.6	67 (66)	82 (81)	81
HIT HARD (Detert et al, 2013)	Adalimumab	12	DMARD-naive	87	7	6.2	DAS28<2.6	(42.4)	N/A	N/A
PRIZE‡ (Emery et al, 2013)	Etanercept	22	Methotrexate-naive	194	26	6.0	DAS28<2.6		N/A	N/A
			1) Dose-reduced					(63.5)		
			2) bDMARDs-free					(38.5)		
			3) Drug-free					(23)		
AVERT (Emery et al, 2014)	Abatacept + methotrexate	18	Early rheumatoid	73	N/A	4.5†	DAS28CRP<2.6	18 (24.7)	N/A	N/A
	Abatacept alone		arthritis	50	N/A	4.3†		14 (28)	N/A	N/A
IDEA (Nam et al, 2014a)	Infliximab	19	DMARD-naive	14	5	4.05*	DAS44<1.6	11 (78.6)	N/A	N/A
ADJUST (Emery et al, 2010)	Adalimumab	12	DMARD-naive	28	N/A	N/A	DAS28CRP<2.6	(47.4)	N/A	N/A
Empire§ (Nam et al, 2014b)	Etanercept	19	DMARD-naive	55	24	4.10†	ACR/EULAR Boolean remission	(20.9)	N/A	N/A
IMPROVED (Heimans et al, 2013)	Adalimumab	12	DMARD-naive	26	21	3.6	DAS<1.6	17 (65)	N/A	N/A

ACR = American College of Rheumatology; bDMARDs = biologic disease-modifying antirheumatic drugs; DAS = disease activity score; DAS28 ESR = disease activity on 28 joints based on erythrocyte sedimentation rate; DMARD = disease-modifying antirheumatic drugs; EULAR = European League Against Rheumatism; LDA = low disease activity; DAS28≤3.2; ΔmTSS = change from baseline modified total Sharp score; N/A =not available. *DAS44 = disease activity on 44 joints; †DAS28 CRP = disease activity on 28 joints based on C-reactive protein; ‡dose reduction and discontinuation; §very early rheumatoid arthritis

remission. Maintain of clinical remission without functional or radiographic progression, however, is greater with biological disease-modifying antirheumatic drug dose reduction discontinuation (*Table 3*). This 'induction-maintenance' approach may therefore be a reasonable strategy for patients with early rheumatoid arthritis (van Vollenhoven et al, 2014).

Biological disease-modifying antirheumatic drug discontinuation in early inflammatory arthritis

Several studies have also addressed the possibility of biological disease-modifying antirheumatic drug discontinuation at an earlier phase of the disease (*Table 3*). All patients in these studies had inflammatory arthritis with some fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis classification criteria (Aletaha et al, 2010). Not all, however, fulfilled 1987 ACR classification criteria (Arnett et al, 1988) and in the ADJUST study (Emery et al, 2010) this was an exclusion criterion.

The ADJUST study reported on the effect of adalimumab in undifferentiated arthritis. Patients were treated with abatacept (n=28) or placebo (n=28) for 6 months. At year 1, the proportion of patients in DAS28 remission (DAS28-CRP<2.6) was 47.4% in the abatacept-induction group *vs* 38.5% in the placebo group (Emery et al, 2010). In this group with very early disease, biological disease-modifying antirheumatic drugs were able to induce clinical remission in some patients, although others developed established rheumatoid arthritis.

The randomized controlled EMPIRE study aimed to investigate the induction of remission in patients with disease-modifying

antirheumatic drug-naive early inflammatory arthritis (one or more tender and swollen joints and within 3 months of diagnosis) with etanercept and methotrexate *vs* methotrexate monotherapy. At week 52, all patients in the etanercept and methotrexate arm stopped the etanercept and remained on methotrexate. After 26 weeks of discontinuation, remission according to the 2010 ACR/EULAR (Boolean) criteria (Felson et al, 2011) was achieved in 20.5% of patients treated with methotrexate and in 20.9% for the etanercept-discontinuation group (Nam et al, 2014b).

In the IMPROVED study, which included patients with undifferentiated arthritis and early rheumatoid arthritis, those who did not achieve early remission at 4 months with prednisone and methotrexate were randomized to receive either a combination of conventional synthetic disease-modifying antirheumatic drugs and prednisone or adalimumab and methotrexate. After achieving sustained remission for 8 months, patients stopped their treatment and remained on methotrexate. At 1 year, 17/26 patients in the adalimumab-free group were in remission (DAS44<1.6) compared with 11/30 patients in the conventional synthetic disease-modifying antirheumatic drug-free group (P=0.02) (Heimans et al, 2013).

Conclusions

There is good evidence for the efficacy of biological disease-modifying antirheumatic drugs in rheumatoid arthritis, but their use remains limited, largely by cost. Increasingly, studies have been undertaken aiming to address different treatment approaches using these agents. These include remission induction with a biological disease-modifying antirheumatic drug then stopping the drug, or where this may not be feasible to consider dose reduction or increasing the intervals between drug administration.

There are data across the rheumatoid arthritis disease spectrum addressing the possibility of biological disease-modifying antirheumatic drug dose reduction or stopping in patients who have achieved good disease control. Study designs have varied and several definitions have been used to define clinical remission, preventing direct between-study comparisons. Nevertheless, the evidence suggests that in established rheumatoid arthritis relatively small proportions of patients are able to stop their biological disease-modifying antirheumatic drugs and maintain biologic-free remission. However, dose reduction or injection spacing may be an option. In patients with early rheumatoid arthritis, remission induction with a biological disease-modifying antirheumatic drug and maintenance of remission after biological disease-modifying antirheumatic drug withdrawal may be achieved in a greater proportion of patients. In patients diagnosed and treated in the very early stages of the disease, halting disease progression and achieving drug-free remission may even be possible in some.

Areas for further research and questions which remain include how long patients should be in remission before discontinuing or reducing a biological disease-modifying antirheumatic drug and which patients are able to stop treatment altogether. **BJHM**

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KEY POINTS

- Early diagnosis and treatment are important to achieve good outcomes in patients with rheumatoid arthritis.
- Biological disease-modifying antirheumatic drugs have improved the prognosis of patients with rheumatoid arthritis, but they are expensive and their side-effect profile needed to be considered when used.
- In patients with established rheumatoid arthritis on biological disease-modifying antirheumatic drugs, many are not able to maintain disease control when the biological disease-modifying antirheumatic drug is stopped. However, biological disease-modifying antirheumatic drug dose reduction may be possible in those patients who have achieved good disease control.
- In early rheumatoid arthritis, an 'induction-maintenance' approach may be possible – using a biological disease-modifying antirheumatic drug to achieve remission then maintaining biological disease-modifying antirheumatic drug-free and potentially drug-free disease control.

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