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Advances in the development and application of biological therapies for rheumatoid arthritis: review of the latest clinical evidence

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Since the introduction of the first biological therapies for rheumatoid arthritis – the TNF inhibitors (TNFi) etanercept, infliximab and adalimumab – other biologic agents have been developed and are now approved for use. This article summarizes the evidence for new TNFi (certolizumab and golimumab), B-cell-depleting therapy (rituximab), T-cell co-stimulation modulating therapy (abatacept) and an IL-6 receptor inhibitor (tocilizumab). A proportion of patients may not be suitable for these or may remain resistant to multiple therapies; thus, new biological agents in development will be discussed. Advances in the application of biologic therapies will be explored, including the use of biologics in early rheumatoid arthritis, towards achieving predefined targets, and the emergence of biomarkers introducing the prospect of personalized therapy.

Keywords: abatacept • biologic therapy • biomarker • clinical trial • personalized medicine • remission • rheumatoid arthritis • rituximab • TNF inhibitor • tocilizumab

Rheumatoid arthritis (RA) is associated not only with the traditionally perceived complications of a potentially disabling condition in which uncontrolled synovitis leads to progressive joint destruction, but also the systemic complications of a chronic inflammatory disease, including cardiovascular disease and increased mortality [1]. The potential socioeconomic impact of the disease is readily apparent from observational studies undertaken in the pre-biologic era. A study published in 1987 demonstrated that, 10 years after diagnosis of RA, only 50% of patients were employed in work and 42% of patients considered themselves disabled [2]. Optimal management of RA is therefore paramount. The more aggressive approach to managing RA adopted today, with early diagnosis and immediate intervention, together with the introduction of biologic therapies, has meant a dramatic change in the achievable outcomes, and hence the prognosis of RA.

Advances in the understanding of the pathogenic processes in RA have led to the identification of new therapeutic targets for the development of biologic therapies. Efficacy and safety of a number of therapies have been demonstrated in clinical trials and are now established in clinical use. The first of these, the TNF inhibitors (TNFi) etanercept, infliximab and adalimumab [3–5], have been in use in clinical practice since 1998. For a proportion of patients, however, TNFi therapy is not effective, either from the outset (primary nonresponse), or with a loss of efficacy over time (secondary nonresponse) [6]. The need for alternative treatment options has fuelled the development and subsequent introduction of other biologic agents in RA that are all now available for use in clinical practice: newer TNFi therapies (certolizumab and golimumab), B-cell-depleting therapy (rituximab), a T-cell costimulation inhibitor (abatacept) and an IL-6 receptor monoclonal antibody (tocilizumab). In this

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article we review the principal clinical trials demonstrating their efficacy. Prospective new biologic therapies will also be mentioned. Furthermore, the disproportionate benefits observed with early use of biologic therapy, with the possibility of short-term biologic use at the onset of RA inducing remission that is then sustainable once off biologic therapy, suggests the presence of a therapeutic window of opportunity, which will also be discussed.

Another prospect for the future, with ongoing research in the field of biomarkers, is personalized medicine: with improved ability to predict disease prognosis and response to treatment lies the potential for biologic treatment to be tailored to the individual.

TNFi therapies

The first TNFi to become available was etanercept (approved by the US FDA in 1998), a fusion protein consisting of two TNF-receptor domains and the constant fragment of immunoglobulin. This was shortly followed by the monoclonal antibodies, infliximab and adalimumab (Table 1). Randomized controlled trials demonstrated that all three were effective in patients with RA failing conventional disease-modifying antirheumatic drug (DMARD) therapy, especially when used in combination with methotrexate (MTX) [3–5,7]. Efficacy measures used in these and other trials of RA treatment include achievement of a clinical response as defined by the American College of Rheumatology (ACR); an ACR20, 50 or 70 response pertaining to a 20, 50 or 70% improvement in the number of tender joints, number of swollen joints, and at least three out five further criteria including patient-reported pain, global health or physical function, physician assessment of global health or a laboratory marker of inflammation (C-reactive protein or erythrocyte sedimentation rate) [8]. The ATTRACT study was one of the earliest pivotal Phase III trials assessing efficacy of TNFi: patients were over twice as likely to achieve an ACR20 response at 30 weeks with infliximab and MTX treatment compared with MTX alone (50% achieving ACR20 compared with 20%, respectively) [3]. Observational studies, including those based on large national patient registries, provide evidence of safety and efficacy of these therapies in the wider RA population. In 2004, results from the British Society of Rheumatology Biologics Register were reported: in over 3000 RA patients treated with infliximab or etanercept, approximately two-thirds achieved at least a moderate clinical response at 6 months [9].

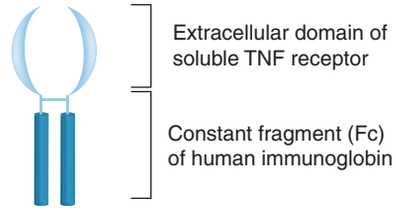
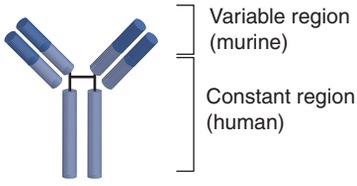
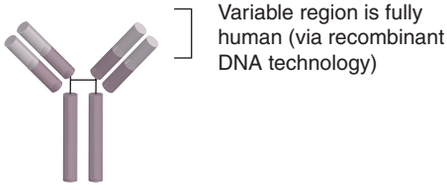
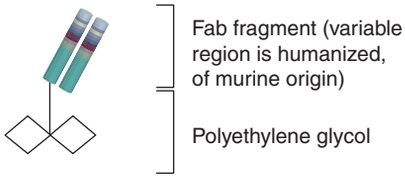
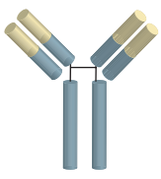
Since the launch of these original TNFi therapies, two new agents, certolizumab and golimumab, have been developed and evaluated in randomized controlled clinical trials. The differences in their structure and administration in comparison with the established TNFi agents are summarized in Table 1. PEGylation of the Fab fragment in certolizumab increases its plasma half-life to approximately 2 weeks allowing fortnightly administration, whilst golimumab offers the advantage of monthly administration.

Efficacy of certolizumab has been demonstrated in three Phase III trials in patients with RA resistant to conventional DMARD therapy: in combination with MTX when administered every 2 weeks in RAPID 1 (in lyophilized form) [10] and RAPID 2 (in liquid form) [11], and as monotherapy when administered every 4 weeks in FAST4WARD [12]. Response rates appear similar to established TNFi in double-blind randomized controlled trials of RA resistant to DMARD therapy (Table 2). Sustained efficacy was demonstrated in RAPID 1, which extended to 52 weeks [10]. At the dose used in clinical practice, 200 mg every 2 weeks, certolizumab in combination with MTX significantly reduced radiographic progression in comparison to MTX alone in RAPID 1 and 2, but this was not assessed in FAST4WARD: the mean change in the modified Total Sharp Score was 0.4 compared with 2.8 ($p < 0.001$) at 52 weeks in RAPID 1 and 0.2 compared with 1.2 ($p \leq 0.01$) at 24 weeks in RAPID 2.

Golimumab has been evaluated in a similar patient population, patients with established RA with active disease despite DMARD therapy, and in both combination with MTX (GO-FORWARD and Tanaka *et al.*) [13,14] and as monotherapy [15]. Rates of response are displayed in Table 3 for the dose used in clinical practice (50 mg every 4 weeks). Although response rates with monotherapy in the trial reported by Takeuchi *et al.* appear low in comparison with other randomized controlled trial results, the study's primary end point was clinical response (ACR20) at week 14, demonstrating efficacy of the TNFi golimumab at an earlier time point than has been employed in other trials in which the primary end point has generally been 24 weeks. In terms of radiographic outcomes, inhibition of radiographic progression of golimumab in combination with MTX was of borderline significance in the study by Tanaka *et al.* (mean change in total van der Heijde Sharp score at 24 weeks was 1.1 compared with 2.5 in controls; $p = 0.04$) [14]. When used as monotherapy, a trend towards less radiographic damage was seen with 50 mg every 4 weeks (mean change was 1.9 compared with 2.6; $p = 0.18$), and in higher doses (golimumab 100 mg every 4 weeks) the difference from placebo reached significance [15].

Efficacy of golimumab in combination with DMARD therapy has also been evaluated in alternative patient cohorts: in MTX-naive patients (GO-BEFORE) [16], and, uniquely amongst TNFi therapies, in patients failing previous TNFi (GO-AFTER) [17]. In GO-BEFORE, a higher number of patients treated with golimumab in combination with MTX achieved the primary end

Table 1. TNF inhibitors approved for use in rheumatoid arthritis by the US FDA and the EMA.

Name and basic structure	FDA approval	EMA approval	Route of administration	Dose and frequency
Etanercept Fusion protein  	1998	2000	Subcutaneous	50 mg weekly or 25 mg twice weekly
Infliximab Chimeric monoclonal antibody  	1999	1999	Intravenous, weekly methotrexate is administered concomitantly to decrease immunogenicity	3–7.5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks
Adalimumab Fully human monoclonal antibody  	2002	2003	Subcutaneous	40 mg every 2 weeks
Certolizumab Pegylated antibody-binding fragment (Fab)  	2009	2009	Subcutaneous	400 mg at 0, 2 and 4 weeks, then every 4 weeks or 200 mg every 2 weeks
Golimumab Fully human monoclonal antibody 	2009	2009	Subcutaneous	50 mg every 4 weeks

point, ACR50 response at 24 weeks, with significance at the 0.05 level (40% of patients compared with 30% treated with MTX alone; p = 0.04). In the GO-AFTER trial, over 50% of patients had received previous TNFi treatment, which was stopped due to lack of efficacy, and approximately one-third of patients had received more than one TNFi in the past [17]. A significant difference in the proportion of patients achieving the primary end point, ACR20 response at 14 weeks, was demonstrated (35 compared with 18%,; p < 0.001). This rate

Table 2. Proportion of rheumatoid arthritis patients achieving the levels of clinical improvement defined by the ACR response criteria with certolizumab in combination with MTX and as monotherapy, in patients with an inadequate response to DMARD therapy.

	RAPID 1 [10]		RAPID 2 [11]		FAST4WARD [12]	
	MTX + placebo (n = 199)	MTX + certolizumab 200 mg every 2 weeks (n = 393)	MTX + placebo (n = 127)	MTX + certolizumab 200 mg every 2 weeks (n = 246)	Placebo (n = 109)	Certolizumab 400 mg every 4 weeks (n = 111)
At 24 weeks (%)						
ACR 20	14	59†	9	57†	9	46†
ACR 50	8	37†	3	33†	4	23†
ACR 70	3	21†	1	16	0	6

†p < 0.001 compared with placebo.

ACR20, ACR50, ACR70: American College of Rheumatology response criteria improvements of 20, 50 and 70%; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate.

of clinical response appears low; however, only two-thirds of patients were taking concomitant MTX and, as mentioned for the study by Takeuchi *et al.* above, the study's primary end point was clinical response at an earlier time point than has been employed in other trials.

Adverse event profiles of certolizumab and golimumab appear similar to that of the established TNFi agents, infliximab, etanercept and adalimumab, with the exception of displaying the advantage of a lower incidence of injection site reactions. Unlike trials of other TNFi therapies, injection site reactions were not increased compared with controls. For example, in the FAST4WARD study, the rate of injection-site reactions was 5% with certolizumab compared with 14% with placebo [12]; in GO-FORWARD the rate was 16 per 11 patient-years (95% CI: 10–24) with golimumab compared with 11 per 100 patient-years (95% CI: 4–24) in controls [18].

As certolizumab and golimumab have only recently been approved, safety data is limited to controlled trial data and does not include registry data as is available for the other TNFi agents. Pooled adverse events in RAPID 1 and 2 revealed that rates of infection were not increased with certolizumab compared with MTX controls; however, the rate of serious infection did differ significantly with a serious infection rate of six per 100 patient-years seen with certolizumab 200 mg in comparison with 1.5 per 100 patient-years in MTX

Table 3. Proportion of rheumatoid arthritis patients achieving the levels of clinical improvement defined by the ACR response criteria with golimumab in combination with MTX and as monotherapy, in patients with an inadequate response to DMARD therapy.

	GO-FORWARD [13]		Tanaka *et al.* [14]		Takeuchi *et al.* [15]	
	MTX + placebo (n = 133)	MTX + golimumab 50 mg every 4 weeks (n = 89)	MTX + placebo (n = 88)	MTX + golimumab 50 mg every 4 weeks (n = 86)	Placebo (n = 105)	Golimumab 50 mg every 4 weeks (n = 101)
At 14 weeks (%)						
ACR 20					19	51†
ACR 50					6	29†
ACR 70					1	13†
At 24 weeks (%)						
ACR 20	28	60†	33	71†		
ACR 50	14	37†	15	42†		
ACR 70	5	20†	6	27†		

†p < 0.001 compared to placebo.

ACR20, ACR50, ACR70: American College of Rheumatology response criteria improvements of 20, 50 and 70%; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate.

controls [19]. Nevertheless, this appears similar to rates seen with other TNFi agents, with a rate of six-per 100 patient-years calculated from pooled data of patients receiving infliximab, etanercept or adalimumab in the British biologics register (BSRBR) [20]. The rate of serious infection was low with certolizumab monotherapy (1.8% of patients) [12], and amongst trials of golimumab (ranged between 0% with golimumab monotherapy [15] to 3.3% in combination with DMARD therapy in the GO-AFTER trial [17] in the golimumab 50 mg dose groups).

There is an increased risk of tuberculosis with TNFi therapy; either reactivation of latent infection or increased susceptibility to infection. Out of the 10,403 patients receiving TNFi therapy in the BSRBR, there have been 35 cases of tuberculosis, with no cases in the DMARD group [21]. There is a difference in risk within the group of TNFi therapies: adalimumab and infliximab (the monoclonal antibodies) are associated with higher rates compared with the receptor fusion protein etanercept. This observation may be explained by two possible mechanisms: as TNF directly contributes to granuloma formation, binding of cell-surface TNF by the monoclonal antibodies may interrupt this process leading to impaired mycobacterial control [22]. In addition, evidence suggests the monoclonal antibodies may disrupt cell-mediated immunity by inhibiting T-cell activation and the production of IFN-γ, whereas function of IFN-γ is preserved with etanercept treatment [23]. The rate of tuberculosis with certolizumab in pooled data from the RAPID trials was 1.2 per 100 patient-years with no cases seen in the control group [19]. No incidences of tuberculosis were reported in FAST4WARD [12] or the trials of golimumab detailed above.

Rituximab

Rituximab, a human–mouse chimeric monoclonal antibody against the cell-surface protein CD20, selectively depletes CD20-expressing cells (the majority of B-cell subtypes except those in the very early stages of development or plasma cells). It is administered intravenously in two doses of 1 g, 2 weeks apart, with intravenous glucocorticoid, which minimises the frequency and severity of infusion reactions [24]. It has been used to treat non-Hodgkin's lymphoma since 1997, but in the knowledge that B cells play multiple roles in RA (including antigen presentation and cytokine production as well as production of autoantibodies [25]), it was trialled in RA and subsequently licensed to treat RA after failure of TNFi in 2006.

Three initial randomized controlled trials demonstrated its efficacy and safety in RA when used in combination with MTX **(Table 4)** [24,26,27]. Patients in these studies differed in terms of treatment history: Edwards *et al.* included patients with an inadequate response to MTX; the DANCER study included patients with an inadequate response to DMARDs and some who had failed TNFi; in the REFLEX study all patients had failed TNFi treatment. In open-label extension studies of DANCER and REFLEX, patients with active arthritis (swollen or tender joint count of 8 or more) could be retreated with rituximab after at least 16 weeks at the physician's discretion. The duration of response to rituximab was generally between 6 and 18 months, and response to retreatment was similar to initial responses [28].

Since these initial trials, a greater understanding of how to use rituximab effectively and safely has been gained through further studies. Safety and efficacy in combination with alternative DMARDs to MTX, in

Table 4. Proportion of patients with rheumatoid arthritis achieving the levels of clinical improvement defined by the ACR response criteria with rituximab at the dose commonly used in clinical practice (1000 mg on day 1 and day 15).

	Edwards *et al.* [26]				DANCER [24]		REFLEX [27]	
	MTX (n = 40)	Rituximab (n = 40)	CYC + rituximab (n = 41)	MTX + rituximab (n = 40)	MTX + placebo (n = 121)	MTX + rituximab (n = 115)	MTX + placebo (n = 209)	MTX + rituximab (n = 311)
At 24 weeks (%)								
ACR 20	38	65	76	73	28	54†	18	51†
ACR 50	13	33	41	43	13	34†	5	27†
ACR 70	5	15	15	23	5	20†	1	12†
At 48 weeks (%)								
ACR 20	20	33	49	65†				
ACR 50	5	15	27	35				
ACR 70	0	10	10	15				

†p < 0.001 compared with placebo.
ACR20, ACR50, ACR70: American College of Rheumatology response criteria improvements of 20, 50 and 70%; CYC: Cyclophosphamide; MTX: Methotrexate.

particular leflunomide, has been demonstrated [29–31]. Various dose regimens have been compared, with no significant difference in clinical response (or safety outcomes) with either 500 or 1000 mg on days 1 and 15 in SERENE [32], or with three fixed retreatment regimens all with a repeated course of rituximab after 24 weeks (two courses of 2 × 500 mg, 2 × 500 mg followed by 2 × 1000 mg at retreatment, or two courses of 2 × 1000 mg) in MIRROR [33]. In this latter study, response rates at 48 weeks for all levels of clinical response were slightly higher in patients treated with two courses of 2 × 1000 mg,but statistical comparisons did not identify any significant differences between the groups: ACR20, 50 and 70 was achieved in 72, 48 and 23% in this group, compared with 64, 39 and 20% in patients treated with two courses of 2 × 500 mg.

The IMAGE study evaluated rituximab (500 or 1000 mg), with retreatment according to disease activity in MTX-naive patients. The target of treatment was remission: patients were retreated at, or after, 24 weeks if they were not in remission determined by the disease activity score (DAS), a composite measure comprising the number of tender and swollen joints, erythrocyte sedimentation rate and patient self-assessment of their general health, a DAS28 score of less than 2.6 being defined as remission [34]. Clinical benefit was seen with both doses; remission at 1 year was achieved in 30, 25 and 13% of patients treated in the 1000 mg, 500 mg and control groups, respectively ($p < 0.001$ for both rituximab groups compared with controls) [34]. However, the primary end point, inhibition of radiographic damage as measured by change in Genant-modified Sharp score at 1 year, was only met in the higher dose group. After the second year of the study, although the lower dose group had not met the primary end point and therefore formal statistical analysis was not carried out, exploratory analyses suggested both rituximab doses conferred equivalent protection against structural damage over placebo [35].

Strategies for retreatment have been compared in open-label studies. Retreatment on demand (at the physician's discretion in patients with at least eight swollen, tender joints) was compared with the treat-to-target approach employed in the IMAGE study [36]. The number of flares of RA with retreatment to target was less than half that associated with retreatment on demand (19 vs 42%); although seemingly more effective, caution with this interpretation must be exercised as patients were from different cohorts. Treatment courses were also more frequent (median frequency every 25 vs every 62 weeks), and although the safety profiles were similar, potential long-term safety and higher costs of this treatment strategy need to be considered. In another much smaller open-label study, fixed retreatment with a single infusion of 1000 mg rituximab at 6 months demonstrated similar efficacy and safety results at 1 year to retreatment on demand [37].

There is conflicting evidence as to whether benefit can be gained from retreatment with rituximab in patients who have not responded to their first cycle of treatment. In the SUNRISE trial, patients were randomized to receive rituximab retreatment or placebo 24 weeks after initial treatment with rituximab [38]. Out of the 257 patients (54%) who did not respond to the first treatment cycle, response with retreatment was no different to placebo. Similarly, no benefit was observed in retreating nonresponders with rituximab at 6 months in an observational study by Thurlings *et al.*; however, the numbers in this study were small (only seven patients were initial nonresponders) [39]. Nonresponse has been shown to be related to the level of B-cell depletion in the blood 2 weeks after the first infusion: at 12 months, 59% of patients with complete depletion of B cells (below 0.0001×10^9/l) had maintained a moderate to good clinical response, compared with only 21% of patients with only partial depletion [40]. Furthermore, nonresponders may be more likely to have higher B-cell concentrations prior to treatment than responders, and hence, fewer may achieve complete depletion after the first infusion [41]. It follows that nonresponders may benefit from retreatment if B-cell depletion can be improved with a second treatment course. Vital *et al.* tested this theory, demonstrating that retreatment at 6 months in nonresponders can lead to a good clinical response: 72% of initial nonresponders went on to achieve a clinical response [41]. Another observational study supports retreatment of nonresponders and suggests there may be additional benefit in retreating nonresponders early [42], although this study was small. Out of 20 nonresponders, 14 were retreated after 6 months and six were retreated earlier (between 4 and 6 months). The mean DAS28 score was significantly improved in both groups 4 months after retreatment; however, in the group retreated early there was a suggestion of superior response with a significant reduction also seen in inflammatory markers.

Safety of B-cell-depleting therapy has been of concern, not least due to the role of B cells in the humoral immune response, and the potential long-lasting effect of rituximab on B-cell depletion. Long-term safety data are now available for patients receiving multiple cycles of rituximab and alternative biologic therapies after rituximab. In pooled data from rituximab clinical trials (including the DANCER, REFLEX, SERENE and MIRROR trials previously mentioned), significant numbers of patients have received repeat cycles of treatment, with over 1000 receiving at least three courses. Infection rates did not increase with repeated

courses [43]; however, low baseline IgG was associated with an increased risk of infection [43]. This was further suggested by an analysis of the French registry (Autoimmunity and Rituximab [AIR]), in which a low baseline IgG at initiation of rituximab was associated with an increased risk of infection with an odds ratio of 4.9 (95% CI: 1.6–15.2) [44]. Caution should therefore be taken when considering initial or repeat cycles of rituximab in the presence of a low serum IgG level, especially in the presence of other risk factors such as co-morbidities or concomitant steroid use.

Safety of other biologic therapy following B-cell depletion with rituximab has also been assessed in an initial report of over 200 patients (178 of whom received a TNFi after rituximab). Peripheral B-cell concentrations were below normal in 86% of these patients at the time they received their next biologic. There was no increase in serious infections: the rate per 100 patient-years was 5.73 prior to subsequent biologic therapy in comparison with 5.36 after commencing another biologic [45].

Abatacept

Abatacept is a recombinant protein consisting of the extracellular domain of cytotoxic T-lymphocyte antigen (CTLA)4 and human immunoglobulin. It inhibits its activation of T cells as CTLA4 interrupts the co-stimulatory signal required for T-cell activation as an antigen-presenting cell binds to a T-cell receptor. It is given intravenously at one of three doses (determined by weight) every 4 weeks following initial loading doses at weeks 0, 2 and 4.

Abatacept has been assessed in combination with DMARD therapy (usually MTX) in randomized controlled trials of patients with RA with an inadequate response to MTX (Kremer *et al.* and the AIM study) [46,47] and following previous TNFi treatment (ATTAIN) [48], the results of which are displayed in Table 5. The AIM study also assessed radiographic change, demonstrating an approximate 50% reduction in the progression of radiographic damage with abatacept: median change in total Genant-modified Sharp score from baseline was 0.25 with abatacept compared with 0.53 in controls (p = 0.012) [47].

Patients completing these trials were eligible to receive abatacept 10 mg/kg with DMARD therapy in open-label extension studies. In all three studies, ACR response rates achieved in the original abatacept groups were maintained at the end of the extension periods in the patients who remained on abatacept. The rate of discontinuation due to lack of efficacy was only 1% over 4 years in the extension study by Kremer *et al.* [49], and 2% over 1 year in the extension study of the AIM trial [50]. However, failure rates were higher in patients who had previously failed TNFi therapy in the extension of the ATTAIN study: 16% over 18 months [51]. In these open-label extension trials, the rate of serious infections was three to five per 100 patient-years across the studies [49–51]. A total of 42 malignancies were seen in the 1167 patients who were exposed to at least one dose of abatacept. The commonest types were non-melanotic skin cancers (21 cases), pulmonary malignancy (six cases) and lymphoma (three cases). This incidence of pulmonary neoplasm and lymphoma is similar to that in the general RA population.

Table 5. Proportion of rheumatoid arthritis patients achieving the levels of clinical improvement defined by the ACR response criteria with combination abatacept and MTX or alternative DMARD.

	Kremer *et al.* [46]		AIM [47]		ATTAIN [48]	
	MTX + placebo (n = 119)	MTX + abatacept (n = 115)	MTX + placebo (n = 219)	MTX + abatacept (n = 433)	DMARD + placebo (n = 133)	DMARD + abatacept (n = 258)
At 6 months (%)						
ACR 20					20	50†
ACR 50					4	20†
ACR 70					2	10†
At 12 months (%)						
ACR 20	36	63†	40	73†		
ACR 50	20	42†	18	48†		
ACR 70	8	21	6	29†		

Abatacept groups received 10 mg/kg every 4 weeks.

†p < 0.001 compared to placebo.

ACR20, ACR50, ACR70: American College of Rheumatology response criteria improvements of 20, 50 and 70%; DMARD: Disease-modifying antirheumatic drug; MTX: Methotrexate.

With the efficacy and safety of intravenous abatacept being established, a subcutaneous form of the drug has been developed. A recent Phase III study compared weekly subcutaneous abatacept to intravenous abatacept every 4 weeks in MTX inadequate responders in a double-blind, double-dummy design, to determine non-inferiority of the two regimens by difference in ACR20 response at 6 months [52]. Non-inferiority was observed with 76.1 and 75.7% of patients achieving ACR20 at 6 months, together with comparable safety profiles, suggesting subcutaneous abatacept may provide an additional treatment option for RA patients in the future.

Abatacept in combination with MTX has also been assessed in MTX-naive patients with early disease (disease duration of less than 2 years) and poor prognostic factors; patients seropositive for rheumatoid factor and/or anticyclic citrullinated protein (anti-CCP), and with at least one radiographic erosion [53]. Remission was achieved in 41% of patients in the abatacept and MTX group compared with 23% receiving MTX alone ($p < 0.001$). Radiographic progression was lower with abatacept: mean change in Genant-modified Sharp score over the first year was 0.6 compared with 1.06 in controls ($p = 0.040$). Furthermore, efficacy of abatacept has been assessed at an even earlier stage in the disease process in patients with undifferentiated arthritis and positivity for anti-CCP (and therefore at high risk of progressing to RA) [54]. In a randomized double-blind design, 6 months of abatacept was compared with placebo. At 6 months after the treatment period, 46% of patients who had received abatacept had developed RA (as defined by the American College of Rheumatology in 1987) compared with 67% of controls (95% CI: for the difference between the groups -47–7%). Abatacept-treated patients also showed significantly less radiographic progression over 1 year: mean change in Genant-modified Sharp score was 0.01 in abatacept-treated patients versus 1.11 in placebo controls (95% CI: for difference between the groups -2.05 to -0.15).

Tocilizumab

IL-6, like TNF, is a pleiotropic cytokine produced by multiple cell types with effects on various biological processes such as inflammatory and immune processes (including stimulation of hepatocytes towards the production of acute-phase reactants), bone metabolism and hematopoiesis. Indeed, amongst the first of its roles to be identified were its roles in the differentiation of B cells into plasma cells and activation of T cells [55,56]. Tocilizumab, administered intravenously every 4 weeks, is a humanized monoclonal antibody against the IL-6 receptor, which inhibits binding of this cytokine.

Double-blind, randomized, controlled trials have demonstrated efficacy of tocilizumab in combination with MTX and other DMARDs (Table 6). In the OPTION [57] and TOWARD [58] studies, patients were those with an inadequate response to at least 8 weeks of DMARD therapy, whereas RADIATE assessed tocilizumab efficacy in patients failing TNFi treatment (~half of patients had failed more than one TNFi) [59].

Tocilizumab is distinct amongst the other available biologic agents in demonstrating significantly greater efficacy versus MTX when used as monotherapy in randomized controlled trials, excepting only etanercept monotherapy in the case of early RA [60]. The AMBITION study demonstrated efficacy of tocilizumab monotherapy over MTX monotherapy in early RA (disease duration <2 years), with 70% of patients achieving the primary end point, ACR20 at 24 weeks, compared with 53% of controls ($p < 0.001$) [61]. One-third of patients achieved remission compared with 12% of patients receiving MTX [61]. In the CHARISMA trial of patients with an inadequate response to MTX, a greater proportion of

Table 6. Proportion of rheumatoid arthritis patients achieving the levels of clinical improvement defined by the ACR response criteria with tocilizumab combination with MTX or alternative DMARD.

	OPTION [57]		TOWARD [58]		RADIATE [59]	
	MTX + placebo (n = 204)	MTX + tocilizumab (n = 205)	DMARD + placebo (n = 415)	DMARD + tocilizumab (n = 805)	MTX+ placebo (n = 160)	MTX + tocilizumab (n = 175)
24 weeks (%)						
ACR 20	26	59†	25	61†	10	50†
ACR 50	11	44†	9	38†	4	29†
ACR 70	2	22†	3	21†	1	12†

Tocilizumab groups received 8 mg/kg every 4 weeks (dose used in clinical practice).

†$p < 0.001$ compared to placebo.

ACR20, ACR50, ACR70: American College of Rheumatology response criteria improvements of 20, 50 and 70%; DMARD: Disease-modifying anti-rheumatic drug; MTX: Methotrexate.

patients achieved the primary end point, ACR20 at 16 weeks, with tocilizumab monotherapy than with MTX monotherapy (63 compared with 41%; $p < 0.05$), however a greater proportion still achieved ACR20 with tocilizumab in combination with MTX (74%) [62]. Since the SAMURAI study, it has also become clear that tocilizumab monotherapy inhibits structural damage. Patients with an inadequate response to DMARD therapy were randomized to tocilizumab monotherapy or to continuing conventional DMARD treatment [63]. At 1 year, the tocilizumab group showed less radiographic progression, with a mean change in total sharp score of 2.3 compared with 6.1 in the DMARD group ($p < 0.01$). Radiographic outcomes with tocilizumab monotherapy have not, however, been directly compared with tocilizumab and MTX combination therapy.

Evidence for the efficacy of tocilizumab is accruing, with results of three further Phase IIIb studies presented at the ACR annual conference in November 2010: the ACT-RAY substudy [64], and the TAMARA [65] and ACT-SURE [66] studies. ACT-RAY evaluated tocilizumab in combination with MTX in MTX inadequate responders; in the substudy, early effects of tocilizumab on synovitis, osteitis and bone erosions were assessed using MRI [64]. Tocilizumab reduced synovitis in only 2 weeks: over this time, 44% of patients had improved synovitis scores, and by week 12 this had increased to 65%. Over 12 weeks, median erosion score did not change: however, 12% of patients had improved erosion scores (greater than or equal to the smallest detectable change), and 28% showed improvement in pre-erosive osteitis. The German, multicenter, open-label TAMARA study included 239 adults with moderate-to-severe RA despite treatment with conventional DMARDs and/or biologics that were treated with tocilizumab for 24 weeks, after which 48% of had achieved DAS28 remission and 75% had achieved a 'good' or 'moderate' response as defined by the European League Against Rheumatism (EULAR) [65]. ACT-SURE evaluated over 1600 patients treated with tocilizumab monotherapy or in combination with DMARDs in patients who had failed either DMARD or TNFi therapy [66]. Tocilizumab was safe and effective with or without DMARDs, and in both patient groups (DMARD or TNFi inadequate responders). Moreover, 24% of patients in this study had recently received TNFi (within 2 months of receiving tocilizumab) without any differences in the safety profile of tocilizumab seen in comparison with patients who had undergone a longer TNFi washout period (greater than 2 months).

Long-term safety data of tocilizumab has been evaluated using pooled data from patients receiving at least one dose in several randomized, controlled trials (including the 24-week OPTION, AMBITION, TOWARD and RADIATE studies; the 2-year Phase III LITHE study and the ongoing open-label extension studies, GROWTH95 and GROWTH96) [67]. These data reveal a stable safety profile with continued improvement of ACR responses over time and only a 3% withdrawal rate due to lack of efficacy.

Prospective new biologic therapies

New biologic therapies are under continued development in an effort to obtain increased effectiveness, improved safety, a more favorable method of administration and reduced manufacturing costs. With the success of current biologics, more refined drug therapies aimed at already existing targets of action are emerging. Agents directed against CD20 have been trialled in Phase II studies: ocrelizumab (a humanized monoclonal anti-CD20 antibody) [68], ofatumumab (a fully human anti-CD20 antibody) [69] and SBI-087 (a small modular immunopharmaceutical) [70]. Phase III trials of ofatumumab are ongoing; however, a further trial of ocrelizumab in RA was suspended in March 2010 due to an increased incidence of opportunistic infections. Monoclonal antibodies against IL-6 have been developed and used in RA in early clinical trials. Results for ALD518, a humanized monoclonal antibody, administered subcutaneously in a recent Phase I trial [71] or intravenously in a previous Phase II trial [72] have been promising allowing Phase III trials to go ahead, whilst results of a Phase II trial of CNTO 136 (fully human monoclonal antibody administered subcutaneously) are not yet reported.

Prospective new biologics with novel targets of action are also of interest. Monoclonal antibodies against another key cytokine in the pathogenesis of RA, IL-17, have shown efficacy in early (Phase I and II) clinical trials in RA: LY2439821 (humanized antibody) [73] and AIN457 (fully human antibody) [74]. Recent advances in identifying and defining the role of regulatory T cells in the suppression of the immune response against self-antigens, with reduced numbers or functional impairment of these cells being observed in autoimmune diseases including RA, have provided another avenue for biologic therapy. Initial Phase II data for a humanized agonistic monoclonal antibody, BT-061, which selectively activates T-regulatory cell, demonstrates achievement of meaningful clinical responses [75].

In addition to new biologic therapies, small molecules that target intracellular proteins involved in autoimmune pathways are also being investigated. One clear advantage they provide over monoclonal antibodies is the potential option of oral administration. Tasocitinib is a new oral inhibitor of janus kinase (JAK)3, an intracellular enzyme involved in intracellular signaling pathways. Phase II studies have been reported and

Phase III trials are underway [76]. Significant clinical improvements with an inhibitor of spleen tyrosine kinase (Syk) – fostamatinib – were demonstrated in a Phase II trial of patients with active RA [77]; however, in a recent randomised Phase II trial in patients who had failed previous biologic therapy, ACR responses were no different from placebo at 3 months [78].

Application of biologic therapy

Rationale for the management of RA & current guidelines

The fundamental message from an ever-increasing evidence-base is the necessity for early and tight control of inflammatory disease activity to achieve remission, or at least a low-disease activity state. Joint damage occurs early in the disease process, and indeed is most rapid within the first year of diagnosis: annual assessment of hand and feet radiographs in the first 3 years revealed the rate of progression of joint damage to be significantly greater in the first year compared with the second and third years [79]. A comparison of DMARD initiation in early RA (median disease duration 3 months) to late RA (median disease duration 12 months) reported significantly lower radiographic damage at baseline in the early RA group, but also a significant retardation in radiographic progression over the following 3 years [80]. This long-term benefit of early treatment in reducing joint damage has been confirmed in a meta-analysis [81].

Superior outcomes have been achieved with aggressive treatment strategies in early disease [82–84]. In the TICORA study, for example, tight control of disease in the intensive treatment arm proved advantageous over routine treatment; intensive management involved monthly assessment and step-up to combination DMARD therapy according to a target of low-disease activity, in comparison to 3-monthly monitoring without use of a formal measure of disease activity [84]. At 18 months, clinical remission (as defined by EULAR) was achieved in 65% of the intensive therapy group, compared with 16% of the routine treatment group (although the intensive group also received greater steroid doses). Remission has been associated with improved outcomes compared with even low disease activity, including improved physical function, work productivity and quality of life. A cross-sectional study found a statistically significant difference in these measures ($p < 0.01$) between 89 patients in remission and 152 patients with low disease activity. Longitudinal analysis of 100 patients confirmed differences in these outcomes over 1 year [85].

This evidence-base has led to the formalization of the concept of 'treat-to-target' in early RA. In 2010, guidelines were published recommending treatment to target: monthly assessment of disease activity and optimization of treatment to achieve a predefined target, ideally remission [86]. These guidelines resemble recommendations that have proved successful for other chronic conditions such as blood pressure targets in hypertension or glycosylated hemoglobin (HbA1c) levels in Type II diabetes.

TICORA and other pragmatic studies demonstrate that remission is a realistic goal, but it is not always achievable with conventional DMARD therapy alone; in these patients biologic therapy may be indicated (TNFi therapies, and more recently abatacept and tocilizumab, have been licensed for use in these patients). However, in the knowledge that early, rapid control of disease is critical in optimizing patient outcomes, biologics have been evaluated outside of this indication, prior to the failure of conventional DMARDs, with impressive results. Such studies pertaining to the new TNFi therapies and other recently available biologics are described above under the relevant section headings. Studies of the use of TNFi in very early RA suggest a window of opportunity when the disease may be more amenable to modification with TNFi therapies than when disease is established, and research is ongoing to ascertain how biologic therapy may best used in clinical practice.

Use of TNFi in early rheumatoid arthritis

Several strands of research suggest the presence of a window of opportunity whereby TNFi confers seemingly qualitatively and quantitatively superior response effects compared with those seen with its use in established disease. The COMET study, of particular interest as it was the first trial to use clinical remission as a primary end point, compared etanercept and MTX versus MTX alone in MTX-naive, early RA patients (disease duration less than 2 years). Over 90% of patients in the etanercept group achieved a EULAR response and the remission rate at 1 year was significantly greater with etanercept and MTX than with MTX alone (50% compared with 28%; $p < 0.0001$) [87]. Further subanalysis of patients in the etanercept group revealed that in those with 'very early RA' (disease duration less than 4 months) 70% achieved remission in comparison with 48% of those with 'early RA' (disease duration of between 4 months and 2 years; $p = 0.0035$) [88].

Other outcomes pertinent to the use of TNFi in early RA include the inhibition of radiographic damage and prevention of work impairment. In the PREMIER study evaluating adalimumab and MTX in comparison with MTX alone in a MTX-naive, early RA cohort, structural data revealed that even despite a good clinical response (ACR70 response) to MTX, radiographic non-progression was observed in only 43% of cases, in comparison with 72% of ACR70 responders treated with adalimumab and MTX [89]. The PROWD study evaluated work impairment as an end point in patients with early RA: a

trend for greater job loss of any cause and/or imminent job loss after week 16 with MTX monotherapy (27% of patients) compared with the adalimumab and MTX group (16%; p = 0.092) was seen [90].

Moreover, there is increasing evidence illustrating the ability of early TNFi therapy to induce disease remission that, in a proportion of patients, can be sustained without relapse of disease even after drug withdrawal. This concept was initially explored in a study by Quinn *et al.*: patients with early, untreated RA, with poor prognostic factors such as positive rheumatoid factor, were randomly allocated to MTX or infliximab and MTX for 1 year [91]. At 2 years (one year after stopping infliximab), there was a significant difference in physical function assessed by the Health Assessment Questionnaire and in quality of life assessed by the RA Quality of Life questionnaire ($p < 0.05$). Additional follow-up data have shown that at 8 years, 40% of patients initially treated with infliximab were still in remission, in comparison with none of the controls [92]. An observational study of patients achieving sustained remission with 1 year of initial therapy with TNFi and MTX demonstrated that 60% remained in remission 2 years after stopping their TNFi [93]. Symptom duration of less than 6 months at time of commencement of TNFi predicted sustained remission with an odds ratio of 13 (95% CI: 1.0–825; p = 0.050) [93]. The BeSt study, a randomized, single-blind trial, compared four treatment strategies in early RA: sequential DMARD monotherapy; initial MTX with step-up to combination DMARD therapy; initial combination DMARD therapy with high-dose corticosteroid; and initial biologic therapy with infliximab and MTX [94]. Drug withdrawal was most successful in patients initially treated with infliximab combination therapy: 53% of patients were on just one non-biologic drug for disease control at the end of the 2-year study (compared with 31–36% in other groups).

Several studies, including BeSt, have attempted to compare treatment strategies in early RA, comparing optimal escalation of DMARD therapy versus initial TNFi [94–97]. The randomized double-blind trial TEAR suggested immediate combination DMARD therapy is at least as effective as initial etanercept and MTX therapy in MTX-naive patients, with no significant differences observed in levels of ACR response at 6 months or DAS28 scores at 102 weeks [97]. However, when a combination of DMARDs or MTX with infliximab was used as first-line therapy in the BeSt study, clinical improvement was more rapid with less progression of joint damage seen on radiographs [94]. In patients with early RA, the SWEFOT study compared addition of a TNFi (infliximab) to addition of conventional DMARDs (sulfasalazine and hydroxychloroquine) in patients failing to achieve low disease activity after 3 months of initial MTX monotherapy [98]. The primary end point, a good response (as defined by EULAR) at 1 year, was achieved in significantly more patients randomized to receive infliximab than in those receiving conventional DMARDs (39 vs 25%; p = 0.016). Evidence supporting the early use of TNFi, potentially before the failure of conventional DMARDs, is increasing such that expert consensus on the use of biologic therapies suggests the use of TNFi therapy in combination with MTX as first-line therapy in patients with poor prognostic signs for rapidly progressive disease, such as early radiographic damage or very high disease activity in the case of the EULAR 2010 recommendations [99], and in patients with high disease activity and a poor prognostic feature such as seropositivity for rheumatoid factor in the case of the ACR 2008 recommendations [100]. This remains in the context of potential barriers to early biologic therapy, including treatment cost, medical insurance constraints and national restrictions in state-funded healthcare systems. For example, in the UK, TNFi drugs are only available following failure of at least 2 conventional DMARDs in patients with high disease activity (defined by DAS28).

Optimal order of biologic therapy

Current licensed indications in Europe place TNFi, abatacept or tocilizumab as possible first-line biologic agents after the failure of conventional DMARDs, with rituximab positioned for following TNFi failure. Presently, in the USA, tocilizumab remains licensed in these latter patients only. It should be borne in mind that these remain under review, with it likely that licensing for TNFi use prior to MTX failure will also be approved, and probable that rituximab will receive approval as a first-line biologic with clinical trial data recently available in MTX-naive patients [35]. With a lack of head-to-head trials of biologic therapies, the longer term data and experience with TNFi will perhaps for now maintain its position as a first-line choice unless contraindicated [99]; clearly, however, the availability of other targeted agents enables better tailoring of treatments for individual patients, according to safety risks and preferences of method of administration. For example, in patients with a history of malignancy within the previous 5 years TNFi therapies are avoided, rituximab is usually considered in these cases [101].

Despite the significant benefits of TNFi, it is clear that response is not universal, with lack of efficacy to these drugs either initially or with a loss of response over time being observed in trials and clinical experience [6,102]. All the available biologic agents have demonstrated efficacy following TNFi failure in randomized controlled trials [18,28,49,60], including alternative TNFi therapy (golimumab) [18]. A recent meta-analysis of these trials illustrated no notable differences between these

agents [103]; however, to date there have been no randomized trials comparing one biologic to another in the event of TNFi failure. Several observational studies have reported comparisons between rituximab and alternative TNFi therapy [104–106]; all illustrate benefits of switching to either therapy. Some suggest greater benefit can be gained with switching to rituximab in specific groups, however studies are contradictory: Finckh *et al.* demonstrated better results with rituximab in patients switching therapy due to inefficacy of TNFi [104], whereas data from the Stockholm registry suggests better results are seen with rituximab following intolerance to TNFi [106]. This inconsistency and the lack of controlled data argue for some caution in forming any definitive conclusion. Indeed, EULAR recommendations state all are appropriate options with the evidence to date unable to support use of one agent over another [99]. There is evidence that rituximab is less effective in rheumatoid factor and anti-CCP negative patients, in whom the use of alternate biologic agents such as alternative TNFi may be more appropriate, but other biomarkers to aid physicians' decisions of which second-line biologic to prescribe are not yet available (discussed in further detail below).

National restrictions apply to various countries, such as the UK where the National Institute of Health and Clinical Excellence (NICE) currently permits TNFi as first-line biologic agents, followed by rituximab in the event of TNFi failure. Switching to alternative TNFi, abatacept or tocilizumab is permitted after failure of TNFi and rituximab or in the presence of a contraindication to rituximab.

Biomarkers

It is generally accepted that our management of RA is likely to further refine over the coming years, not only with the increasing availability of therapies, but with a better understanding of how best to apply such therapies in a more tailored fashion: the identification of biomarkers should ensure more efficient use of therapeutic agents. Poor prognostic factors are recognized in current clinical practice, such as raised inflammatory markers (C-reactive protein or erythrocyte sedimentation rate), presence of radiographic erosions, seropositivity for rheumatoid factor and/or anti-CCP, level of functional disability at disease onset (measured by the Health Assessment Questionnaire), and presence of human-leukocyte antigen shared epitope. Nevertheless, ongoing research to ascertain more sensitive and specific biomarkers is needed in order to predict, with greater reliability, individuals with severe disease prognoses in whom early biologic therapy may be more beneficial and cost effective.

Investigation for potential biomarkers of response to the available biologic agents has provided some insights. Data from the British Society for Rheumatology Biologic Register demonstrated patients currently smoking or with high levels of disability at baseline (defined by the Health Assessment Questionnaire) were less likely to achieve a good EULAR response with infliximab or etanercept. Concomitant MTX and non-steroidal anti-inflammatory agents were associated with a superior rates of response, however, this may reflect a lower prevalence of co-morbidities in these patients [10]. No genetic marker has been found to predict primary response to TNFi therapy with consistency across a number of cohorts, although research in this field is ongoing [107]. Scientific research into potential non-genetic biomarkers is also being undertaken, including gene expression profiling and proteomic studies [108,109].

Data from clinical trials as well as registries illustrate superior rates of response to B-cell depletion therapy with rituximab in patients that are seropositive for rheumatoid factor and/or anti-CCP [25,35,39,110–113]. In addition to confirming that seropositivity confers greater efficacy, the SMART study also identified raised serum immunoglobulin G as an independent positive predictor of response [114]. A specific genotype (VV-genotype) encoding for the low-affinity immunoglobulin gamma Fc region receptor III-A (FcγRIIIa) has been suggested to be associated with increased clinical response in patients with non-Hodgkin's lymphoma and systemic lupus erythematosus. This is yet to be similarly evaluated in RA excepting preliminary data from a small number of RA patients [115].

Future perspective

Over the past decade, the management of RA and prospects for patients has advanced dramatically. Early, effective therapy with tight monitoring towards a predefined target (clinical remission or at least low disease activity) is of key importance; recent recommendations have endorsed this approach [86,99,100]. With a range of biologic therapies now available, remission and prevention of joint damage in particular has become a realistic target for treatment. The identification of biomarkers should lead to more efficient use of such therapies.

Applying biologic therapy early, especially in poor prognosis patients, is encouraged [99], although the optimal application of such therapies remains an area of continued research. There are increasing data suggesting the presence of a window of opportunity when significantly greater benefits can be attained with early biologic intervention [88,91,93]. The ability of TNFi to induce sustained remission, with biologic-free and even drug-free remission achievable in a proportion of patients, portrays an emerging treatment goal. How best to introduce TNFi with the aim of achieving optimal biologic-free remission, with the potential for this treatment approach to prove more cost-effective, remains to be clarified.

Refractory disease, as well as a desire for more refined therapies, continues to drive drug development, with increasing availability of less immunogenic molecules and new targeted treatments. Finally, the identification of biomarkers of disease and treatment response will hopefully permit the management of RA to enter the arena of personalized medicine.

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Executive summary

- Rheumatoid arthritis (RA) is a chronic, systemic inflammatory condition. If not adequately controlled it can cause significant joint deformity, extra-articular complications such as pulmonary disease or vasculitis, and is associated with accelerated atherosclerosis with cardiovascular morbidity and mortality.
- Recent evidence and management guidelines emphasise the need for early, aggressive treatment and suggest a treatment-to-target approach for the treatment of RA, with the aim of achieving clinical remission (or at least low disease activity).
- Advances in understanding of the pathogenesis of RA have led to the development of several biologic therapies, which are now approved for use: several TNF inhibitors (etanercept, infliximab, adalimumab, certolizumab and golimumab), B-cell-depleting therapy (rituximab), a T-cell co-stimulation inhibitor (abatacept) and an IL-6 receptor monoclonal antibody (tocilizumab).
- At present, use of biologic therapy (with a TNF inhibitor generally used first-line) is mainly directed to patients with severe disease activity, who have failed conventional treatment with methotrexate (MTX) and/or other disease-modifying antirheumatic drugs (DMARDs).
- However, a proportion of patients do not respond to initial biologic therapy (~40%), and the remission rate achieved is in the region of 30%.
- Early use of biologic therapy, prior to the failure of DMARDs, achieves higher remission rates and prevents joint damage compared with MTX or DMARD monotherapy.
- Short-term use of TNF inhibitors in the early stages of the disease may induce remission that is sustainable after biologic therapy is withdrawn (demonstrated in the BeSt study and by Quinn *et al.* in very early RA). Biologic and even drug-free remission is emerging as a future treatment goal.
- With a wide range of biologic treatments now available and with variable response to treatment (particularly in late disease), continued efforts to identify biomarkers will hopefully enable more effective tailoring of therapy.

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