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REVIEW

Rheumatoid arthritis and the era of biologic therapy

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Abstract Biologic disease modifying anti-rheumatic drugs have transformed the management of rheumatoid arthritis (RA) since their introduction into clinical practice over a decade ago. Following large-scale clinical trials, a number of biologics, with different mechanisms of action, have been licensed for the condition. In this review, we will summarise the current evidence for biologic use in RA with an emphasis on their efficacy and tolerability. In addition, we will provide a commentary on the current limitations and unmet needs in this area and discuss the future of biologic intervention.

Keywords Rheumatoid arthritis · Biologic DMARDS · Efficacy · Tolerability · Guidelines

Introduction

Rheumatoid arthritis (RA) is a chronic multi-system inflammatory disorder, historically characterised by deforming erosive arthritis, resulting in a reduction in quality of life and productivity. The prevalence of RA in the general population is 0.5–1% (Gabriel et al. 1999), is twice as common in women (Gabriel et al. 1999), and affects people during the most productive years with reduced life expectancy secondary to atherosclerotic disease.

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Over the last two decades, our understanding of the immunopathogenesis of RA has advanced greatly. This coupled with an increased appreciation of cell biology and the availability of novel genetic techniques has led to the development of therapeutic molecules capable of targeting the immune system. Previous RA therapy was aimed simply at symptom control; however, current strategies aim to suppress inflammation as comprehensively as possible in order to induce a state of disease remission. Nine biologics are currently licensed for RA in Europe and the US (Table 1). This article will review biologic therapy in RA, with an emphasis on the efficacy and tolerability of these agents. In addition, we also intend to discuss the potential future direction of immunopharmacotherapy for RA.

Historical perspective

The concept that antibody treatment could be employed to target specific diseases is not new. Hericourt and Richet (1895) suggested that antibodies could be used to treat cancer in 1895—the forerunner of the so called "magic bullet" therapy. However it was not until 1975 that Kohler's and Milstein's pioneering work (Hale and Herman 2000) on the hybridoma technique for monoclonal antibody production, resulting in a Nobel Prize that heralded the biologic age of therapeutics. Among the first monoclonal antibodies utilised was alemtuzumab (Campath-1H) a chimeric antibody to CD52, a cell surface marker expressed on mature lymphocytes. Campath-1H is still in use for the treatment of refractory chronic lymphocytic leukaemia and is currently being trialled in a number of other conditions including multiple sclerosis.

In 1994, the results of the first randomised controlled trial using TNF antagonism (with infliximab) were

Table 1 Salient features of the currently licensed biological therapies in inflammatory arthritis

Generic name (trade name)	Biological activity	Pharmacokinetics	Dosing schedule	Current license
Tumour necrosis factor inhibitors				
Infliximab (Remicade)	Chimaeric monoclonal antibody against TNFα. Binds to free, receptor-bound and trans-membrane TNFα	Half life: 9.5 days metabolised in reticuloendothelial system	IV infusions every 6–8 weeks	RA, PsA, AS
Etanercept (Enbrel)	Fusion protein that mimics soluble TNF receptor and prevents TNFα binding with cellular receptor	Half life: 70–132 h metabolised in reticuloendothelial system	Weekly SC injections	RA, pJIA, AS, PsA
Adalimumab (Humira)	Fully humanised monoclonal antibody against TNFα. Binds to free, receptor-bound and trans-membrane TNFα	Half life: 14 days Metabolism: not studied in humans	Fortnightly SC injections	RA, PsA
Certolizumab (Cimzia)	PEGylated Fab fragment of fully humanised anti-TNFα antibody. Binds to free and membrane-bound TNF α	Half life: 14 days Metabolism: not studied in humans	Fortnightly SC injections	RA
Golimumab (Simponi)	Fully humanised monoclonal antibody against TNFα. Binds to free (soluble) and transmembrane TNFα.	Half life: 14 days Metabolism and clearance: not known	Monthly SC injections	RA, AS, PsA
B cell depletion				
Rituximab (Mabthera)	Chimaeric monoclonal antibody to CD20 (present on mature B cells) clears mature B cells	Half life: 8.6 days Metabolism and clearance: not known	IV infusions every 6 months	RA
Inhibition of T Cell co-stimulation				
Abatacept (Orencia)	Fusion protein of an immunoglobulin and extra-cellular domain of CTLA-4 Prevents activation of T cells by inhibiting interaction between costimulatory molecules.	Half life: 16.7 days Metabolism: not known, although higher clearance in patients with high body weight	Monthly IV infusions	RA, pJIA
Interleukin-6 inhibition				
Tocilizumab (RoActemra)	Humanised monoclonal antibody to IL-6 receptor	Half life: 160 ± 34 h after first dose Metabolism and clearance: non-renal clearance	Monthly IV infusions	RA, pJIA, sJIA, Castleman's disease (Japan)
Interleukin-1 inhibition				
Anakinra (Kineret)	Recombinant IL1 receptor antagonist	Half life: 4–6 h Metabolism and clearance: clearance increases with creatinine clearance and body weight	Daily SC injections	RA

RA rheumatoid arthritis, *PsA* psoriatic arthritis, *AS* ankylosing spondylitis, *pJIA* polyarticular juvenile idiopathic arthritis, *sJIA* systemic juvenile idiopathic arthritis

published which changed the therapeutic landscape of RA forever. Since then a number of biologics have been shown to be efficacious and safe in the management of the disease. In parallel with the therapeutic advances, the approach to RA management has been transformed. In the 'pre-biologic' era, the treatment mantra was 'start low, go slow', however this approach has been completely superseded by an early, intensive 'treating to target' paradigm (Smolen et al. 2010).

Tumour necrosis factor alpha antagonists

The pro-inflammatory cytokine tumour necrosis factor α (TNF α) plays a pivotal role in the initiation and perpetuation of inflammation in chronic inflammatory diseases. The upregulation of TNF expression by synovial macrophages and the resulting activation of other inflammatory cells, osteoclasts and expression of other cytokines is believed to be central in the pathogenesis of RA (McInnes et al. 2007). TNF antagonists have been shown to suppress this inflammatory process and were the first biologics to demonstrate efficacy in RA. Currently five biologics in this class have been licensed by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of various inflammatory musculoskeletal disorders and related auto-immune conditions (Tables 1, 2).

Infliximab (Remicade), a chimaeric monoclonal antibody directed against TNFα, was the first of the drugs to be

Table 2 Key clinical trial data for biologic DMARDS currently used in the treatment of rheumatoid arthritis

Generic name (trade name)	Study name (study duration at time of results)	Key features	Results*				
			ACR 20 (MTX arm)	ACR 50 (MTX arm)	ACR 70 (MTX arm)	DAS 28 remission (MTX arm)	Improved radiological outcomes
Tumour necrosis factor inhibitors							
Infliximab (Remicade)	ATTRACT (30 weeks)	IFX in inadequate responders to MTX	50 (20)	27 (5)	8 (0)	NA	Yes
	ASPIRE (54 weeks)	Early RA. IFX + MTX versus MTX alone	62.4 (53.6)	45.6 (32.1)	32.5 (21.2)	21.2 (15) p 0.065	Yes
Etanercept (Enbrel)	COMET (52 weeks)	Early RA. ETN + MTX versus MTX alone	86 (67)	71 (49)	48 (28)	50 (28)	Yes
	TEMPO (24 months)	Early RA. ETN + MTX versus MTX alone	85.3 (70.2)	71 (42)	49 (21.1)	51.2 (24.8)	Yes
Adalimumab (Humira)	ARMADA (6 months)	Early and established RA. ADA + MTX versus MTX alone	87 (15)	55 (8)	27 (5)	NA	Not assessed
	PREMIER (24 months)	Early RA. ADA + MTX versus MTX alone versus ADA alone	69 (56)	59 (43)	47 (28)	49 (25)	Yes
			Results for ADA monotherapy not shown, but combination of ADA + MTX superior to ADA alone				
Certolizumab (Cimzia)	RAPID 2 (6 months)	CTZ 200 mg fortnightly + MTX versus MTX alone	57.3 (8.7)	32.5 (3.1)	15.9 (0.8)	9.4 (0.8)	Yes
	FAST4WARD (6 months)	CTZ 400 mg monthly monotherapy versus MTX alone	45.5 (9.3)	22.7 (3.7)	5.5 (0)	NA	No
Golimumab (Simponi)	GOFORWARD	GLM 50 mg monthly +MTX versus MTX alone	59.6 (27.8)	37.1 (13.5)	20.2 (5.3)	20.2 (6)	Yes
	Kay et al (16 weeks)	GLM + MTX (variable dose) versus MTX alone	60 (37.1)	37 (5.7)	8.6 (0)	20 (5.7)	Not assessed
			Results shown are for GLM 50 mg monthly (current licensed dose) + MTX.				
B Cell depletion							
Rituximab (Mabthera)	DANCER	RTX + MTX (variable dose) versus MTX in MTX inadequate responders	54 (28)	34 (13)	20 (5)	NA	Not assessed
	REFLEX	RTX + MTX versus MTX in anti-TNF inadequate responders	51 (18)	27 (5)	12 (1)	NA	Yes
Inhibition of T Cell co-stimulation							
Abatacept (Orencia)	AIM (12 months)	ABT + MTX versus MTX alone in MTX-inadequate responders	73 (40)	48 (18)	29 (6)	NA	Yes
	ATTAIN (6 months)	ABT + MTX versus MTX alone in anti-TNF inadequate responders	50 (20)	20 (4)	10 (2)	NA	Not assessed
Interleukin 6 inhibition							
Tocilizumab (RoActemra)	RADIATE (6 months)	TCZ + MTX versus MTX alone in anti-TNF inadequate responders	50 (10.1)	28.8 (3.8)	12.4 (1.3)	30.1 (1.6)	Not assessed
	OPTION (6 months)	TCZ + MTX versus MTX alone in MTX inadequate responders	59 (26)	44 (22)	22 (4)	27 (0.8)	Not assessed

Table 2 continued

Generic name (trade name)	Study name (study duration at time of results)	Key features	Results*				
			ACR 20 (MTX arm)	ACR 50 (MTX arm)	ACR 70 (MTX arm)	DAS 28 remission (MTX arm)	Improved radiological outcomes
Interleukin 1 inhibition							
Anakinra (Kineret)	Cohen et al -2002 (6 months)	ANK + MTX versus MTX alone in MTX inadequate responders	35 (23)	17 (4)	7 (0)	NA	Not assessed
			Results shown are for 2 mg/kg daily dose.				
	Bresnihan et al (6 months)	ANK monotherapy versus placebo	43 (27)	19 (8)	1 (1)	NA	Not assessed
			Results shown are for the 150 mg arm of the study. Licensed dose is 100 mg. Please note that ACR 70 response not different between study and placebo arm.				

ACR 20, 50, 70 refer to the American College of Rheumatologists Response criteria (Felson et al. 1995)

IFX Infliximab, *ETN* Etanercept, *ADA* Adalimumab, *CTZ* Certolizumab, *GLM* Golimumab, *RTX* Rituximab, *ABT* Abatacept, *TCZ* Tocilizumab, *ANK* Anakinra

* *P* values only indicated when statistically significant difference not achieved

licensed for clinical use. Infliximab is administered intravenously at week 0, 2, 6 and then 8 weekly. Etanercept (Enbrel), a fusion protein that mimics the function of the soluble TNF receptor, prevents TNF α binding to its cellular receptor and is administered subcutaneously once weekly. Adalimumab (Humira), a fully humanised monoclonal antibody against TNF α, is administered subcutaneously every other week. Recently, two further anti-TNF α agents have been licensed for RA: certolizumab (Cimzia) a PEGylated Fab fragment of a humanised anti-TNF antibody which is administered subcutaneously every 2 weeks and golimumab (Simponi), another fully human monoclonal antibody against TNFα that is administered subcutaneously once per month. Unlike the monoclonal antibodies, etanercept only neutralises soluble TNF α and does not affect membrane-bound TNF α.

All these agents have well-established efficacy as demonstrated in large randomised controlled trials. There is also evidence supporting improved efficacy when combined with methotrexate although some are licensed for use as monotherapy. Long-term post marketing surveillance as well as data from national registries has confirmed that these drugs have an acceptable safety profile. A higher rate of serious and non-serious bacterial infections however has been seen in patients on anti-TNF medications (Bongartz et al. 2006). There is no convincing evidence to date suggesting that one agent is better or worse than the other in regard to infection risk. A recent Cochrane review (Singh et al. 2011) of the tolerability of biologics in RA suggested that patients on biologic DMARDS were likely to experience adverse events more frequently than those patients in the control groups although the difference in serious adverse events and serious infections did not achieve statistical significance. An outlier to this was certolizumab which appeared to be associated with a statistically significant increased risk of serious infections compared to placebo (Singh et al. 2011) with an odds ratio (OR) of 3.51 and numbers needed to harm (NNH) of 17. Infliximab was found to be associated with a higher (statistically significant) rate of discontinuation due to adverse events (Singh et al. 2011). The British Society of Rheumatology Biologics Registry (BSRBR) reported in a meta-analysis of clinical trials (Bongartz et al. 2006) an overall increased risk of serious infections with anti-TNF biologics (NNH 59 for one additional serious infection within 3–12 months of commencing treatment).

As TNF plays an important role in the immune response to intracellular organisms such as *Mycobacterium tuberculosis* (TB), a higher rate of activation of latent TB was seen in patients on these drugs. As a result, it is now common practice to screen for latent TB in all patients being considered for anti-TNF biologics. TNFα antagonists are also contra-indicated in patients with chronic Hepatitis B and C (Calabrese et al. 2004) infection although data

from one meta-analysis suggested no significant worsening of chronic hepatitis C whilst on anti-TNF (Brunasso et al. 2011). TNFα blockers may worsen demyelinating diseases and congestive cardiac failure and therefore are generally avoided in these circumstances (Singh et al. 2011).

As TNF plays a role in the immune response to neoplastic transformation a concern was raised from the beginning that anti-TNF use may increase the risk of malignancy in a cohort already at higher risk (Askling et al. 2011). A recently published meta-analysis of randomised controlled trials of adalimumab, etanercept and infliximab was unable to ascertain conclusively whether these drugs impose a risk of cancer emergence in the short-term (Askling et al. 2011). The overall relative risk for cancers other than non-melanoma skin cancer (NMSC) was 0.99 (95%CI 0.61–1.68) and for NMSC was 2.02 (95%CI 1.11–3.95) (Askling et al. 2011) in this study. In the BSRBR meta-analysis, however, the short-term risk of malignancy was significantly higher with a reported NNH of 156 for every new malignancy within 6–12 months of treatment (Bongartz et al. 2006). As the number of reported events was low, the risk may be over-estimated therefore this data needs to be interpreted with caution (Singh et al. 2011).

It is known that patients with RA are at increased risk of cardiovascular events secondary to chronic inflammation which leads to a reduction in life expectancy (Westlake et al. 2010). There is growing evidence that patients on anti-TNF drugs may have fewer cardiovascular events as a consequence of systemic suppression of inflammation (Jacobsson et al. 2005). This is certainly an area of keen interest and further evidence will become available as these drugs reach their second and third decade of use.

B cell depletion

B lymphocytes play a critical role in the development of auto-immune disease. In addition to the production of auto-reactive antibodies, B cells modulate T cell function, produce various pro-inflammatory cytokines and can act as antigen presenting cells (McInnes et al. 2007).

Rituximab, a chimaeric monoclonal antibody, is directed against the cell surface molecule CD20 which is expressed at all stages of B cell maturation apart from early pro-B lymphocytes and plasma cells. Rituximab is believed to act by one of three mechanisms—complement mediated cytotoxicity, antibody mediated cellular cytotoxicity (ADCC) and induction of apoptosis (Chynes et al. 2006). Rituximab is the only anti-CD20 monoclonal antibody currently licensed for use in patients with RA and is administered as two intravenous infusions 15 days apart.

Two large multi-centred randomised controlled trials have confirmed the efficacy of rituximab in the treatment of active RA. In the DANCER study (Emery et al. 2006) where rituximab was trialled in RA patients with an inadequate response to methotrexate, a significantly higher proportion of patients receiving rituximab achieved ACR 20, 50 and 70 responses compared to placebo (Table 2). In the REFLEX study (Cohen et al. 2006), rituximab (when added to methotrexate) was found to be more effective than placebo in patients with RA that had failed anti-TNF therapy with statistically significant differences in ACR and EULAR outcome measures. A trend towards less radiographic progression at 24 weeks was also seen. Recent trial evidence suggests that there is an improvement in efficacy with subsequent cycles of rituximab, when given in early disease and when administered at regular intervals (Vital et al. 2010).

Despite the profound B cell depletion resulting from rituximab, immunoglobulin levels are less affected possibly due to the preservation of plasma cells. Trial evidence suggests that rituximab has an acceptable safety profile with 5.2 serious infections per 100 patient-years compared to 3.7 in the placebo group in the REFLEX study. Despite this a number of infections have been reported in association with its use (Gea-Banacloche 2010). Hepatitis B re-activation has been reported in patients with haematological malignancies whereas progressive multifocal leuko-encephalopathy (PML) following rituximab use has been reported in patients with RA, SLE and haematological malignancies (Gea-Banacloche 2010). Although exceedingly rare, the increased risk of PML has prompted a MedWatch alert by FDA and a modification of the prescribing information with rituximab. Overall however rituximab is deemed to be at least as safe as the anti-TNFs with regard to infection risk (Singh et al. 2011). Infusion reactions are common and occur almost certainly because of B cells lysis; however, the severity is lessened by pre-medication with intravenous steroids and anti-histamines. Fatal infusion reactions have been reported and therefore infusions should be administered in specialised centres with full resuscitation facilities.

T lymphocyte co-stimulation blockade

Abatacept, a co-stimulatory molecule blocker inhibiting the activation of T cells, consists of the Fc portion of immunoglobulin attached to the extra-cellular domain of CTLA-4. Activation of T-cells requires binding of the T cell receptor to the antigen-MHC complex on the antigen presenting cell (APC) and 'co-stimulation' including CD28 (on the T cell) binding to CD80/86 on the APC. Abatacept has a high affinity for CD80/86 and thus inhibits T cell co-stimulation and activation.

Abatacept is administered intravenously monthly after loading; however, a subcutaneous preparation has recently

been approved by the FDA for moderate to severe RA. Clinical trials have demonstrated efficacy in RA patients responding inadequately to methotrexate and other conventional DMARDS, as well as in anti-TNF inadequate responders (Russell et al. 2005). Data from long-term extensions of these trials have also demonstrated acceptable tolerability and efficacy at 5 years (Westhovens et al. 2009). Infusion reactions have been seen in 9% of actively treated patients compared with 6% of controls however these are usually mild (Hervey and 2006). Combined data from 5 RCTs has suggested that the risk of serious infections is about 3% compared to 1.9% in the placebo groups (Hervey and 2006). Interestingly a Cochrane safety review suggested that abatacept had a better safety profile than most other biologics (Singh et al. 2011).

The need for monthly infusions and the higher relative cost of abatacept has limited its use in the UK as determined by NICE, to patients with RA who have failed (or not tolerated) anti-TNFs and rituximab (National Institute for Health and Clinical Excellence 2010).

Interleukin 1 inhibition

Interleukin-1 (IL-1), a key pro-inflammatory cytokine, is upregulated in patients with active RA and high levels have been found in the synovial fluid of inflamed joints (McInnes et al. 2007). The IL-1 receptor antagonist (IL-1ra) is a naturally occurring molecule that binds to the IL-1 receptor but does not induce a signalling response, thereby inhibiting the effects of IL-1 in vivo. An imbalance between IL-1 and the receptor antagonist is believed to be a factor contributing to the pathophysiology of RA (McInnes et al. 2007).

Anakinra, a recombinant human IL-1ra, blocks the biological activity of IL-1. Anakinra is administered subcutaneously daily and is licensed for the treatment for moderate to severely active RA. A number of studies have demonstrated the efficacy and safety of anakinra (Karanikolas et al. 2008; Cohen et al. 2004; Bresnihan et al. 1998). Although no direct comparison has been made, efficacy data for anakinra appears to be inferior to the other biologic agents (den Broeder et al. 2006). Injection site reactions (ISR) were seen in 65% of the patients compared to 24% in the placebo group in one study, with ISR-related withdrawal of the drug in 8.4% compared to 0.8% in the controls (Cohen et al. 2004).

Observational studies and registry data suggest that the rates of secondary inefficacy are higher for anakinra than the other biologics (anti-TNFs) (den Broeder et al. 2006; Zink et al. 2005). Therefore anakinra is not recommended for the treatment of RA in the UK by the National Institute of Clinical Excellence (NICE) and its usefulness in the condition is limited.

Interleukin 6 inhibition

Interleukin-6 (IL-6) plays a critical role in the pathophysiology of RA. Synovial fluid IL-6 levels correlate with disease activity and murine models have shown that IL-6 deficiency is associated with a delayed onset of collagen-induced arthritis (Woodrick and Ruderman 2010). IL-6 is also responsible for many of the extra-articular manifestations of RA including anaemia, fatigue and fever. Tocilizumab, a recombinant humanised monoclonal antibody targeting the human interleukin-6 (IL-6) receptor, is administered intravenously monthly although a weekly subcutaneous preparation is in development. Multiple large RCTs have confirmed the efficacy and tolerability of tocilizumab in patients with RA (Emery et al. 2008; Garnero et al. 2010) and it is the most recent drug licensed for the treatment of RA.

The data from the tocilizumab trials suggests that the efficacy of this drug is similar to that of other biologics (apart from anakinra to which it is superior). Unlike anti-TNF agents however which generally have improved efficacy with given with methotrexate, tocilizumab may be as effective when administered as monotherapy (Jones et al. 2010). It is worth noting however that no head to head biologic studies have been published thus far. Tocilizumab has an acceptable safety profile and the rate of serious adverse events (SAEs) or drop-outs due to SAEs in clinical trials were not statistically different from controls (Campbell et al. 2011). IL-6 is a key driver of the features of inflammation and reports suggest that the use of tocilizumab is associated with suppression of temperature and acute phase response (Hirao et al. 2009). In addition, there has been a concern regarding gastro-intestinal perforation, and review by us (Gout et al. 2011) has revealed that the risk is similar to that of anti-TNF agents but way below that for corticosteroids. IL-6 inhibition is also associated with reversible neutropenia, abnormalities of the lipid profile and transient elevation of liver enzymes, therefore, studies are looking at the medium and long-term implications of these findings.

Guidelines for the use of biologic therapy in RA

With the advent of biologic therapy, clinicians have been faced with a new concern—affordability. The average cost of biologic drug treatment for RA in the UK is £10,000 per year. The cost of development of these agents however runs into billions of pounds which is only possible with large pharmaceutical industry investment.

In the UK, NICE examines all the available evidence and publishes technology appraisals determining whether a therapeutic is recommended for use on cost-effectiveness grounds. Table 3 summarises the latest NICE guidance on the use of biologic DMARDS in RA. Other guidelines

Table 3 National Institute of Clinical Excellence (NICE) guidance for the use of biologic DMARDS in RA

NICE guidance	Technology appraisal guidance (month year published)
1. TNF α antagonists (adalimumab, etanercept and infliximab) are recommended in patients that have active RA (DAS 28 > 5.1) despite 6 months of treatment with at least 2 conventional DMARDS (one of which is methotrexate)	TA130 (Oct 2007)
2. Certolizumab pegol is recommended as another anti-TNF option as above (only if the manufacturer provides the first 3 months of the drug free of charge)	TA186 (Feb 2010)
3. Golimumab is recommended as another anti-TNF option as above (only if the manufacturer provides the 100 mg dose of Golimumab at the same cost as the 50 mg agreed as a part of the patient access scheme)	TA225 (June 2011)
4. Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor	TA195 (Aug 2010)
5. Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event.	TA195 (Aug 2010)
6. Adalimumab and etanercept monotherapy are recommended as treatment options for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to methotrexate, or when methotrexate is withdrawn because of an adverse event	TA195 (Aug 2010)
7. Tocilizumab, in combination with methotrexate, is recommended for the treatment of moderate to severe active rheumatoid arthritis in people whose rheumatoid arthritis has responded inadequately to one or more tumour necrosis factor alpha (TNF-α) inhibitors and whose rheumatoid arthritis has responded inadequately to rituximab or in whom rituximab is contraindicated or when rituximab is withdrawn because of an adverse effect	TA198 (Aug 2010)

Table 4 European League Against Rheumatism (EULAR) recommendations for the use of biologic DMARDS in rheumatoid arthritis

Recommendation	Level of evidence	Grade of recommendation
1. In patients with RA, if the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present	5	D
2. In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started*; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab)† which should be combined with MTX	1b* 4†	A* C†
3. Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab	1b	A
4. If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs‡, especially if this treatment is combined with a synthetic DMARD	3b	B
5. DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent	2b	C

* and † are used to reflect different parts of this recommendation and it's level of evidence and grade of recommendation

regarding the use of biologic agents in RA have been summarised in Tables 4 and 5.

Other therapeutic considerations

Early intervention with biologic DMARDS

A number of clinical trials have suggested that biologic therapy early in the course of disease is associated with improved outcomes. This has been seen for anti-TNF agents, rituximab and tocilizumab (Jones et al. 2010; Tak et al. 2011; van der Heijde et al. 2006; Emery et al. 2008) (and ADJUST study with abatacept, Westhovens et al.) with a significant proportion of patients achieving clinical remission and reduction in radiographic progression. There is also a suggestion that early biologic use may increase the rate of drug free remission (Goekoop-Ruiterman et al. 2005). This implies that these biologics may be used as part of an intensive treatment phase with subsequent drug

Table 5 Summary of American College of Rheumatologists (ACR) recommendations for the indications for use of biologic DMARDS in rheumatoid arthritis

Disease characteristics, activity and duration	Recommendation
1. RA < 6 months with high disease activity for 3–6 months	Anti-TNF and methotrexate (MTX)
2. RA < 6 months with high disease activity for <3 months and features of poor prognosis[a] and no cost/insurance limitations	Anti-TNF and methotrexate (MTX)
3. RA > 6 months who have failed MTX monotherapy with high disease activity	Anti-TNF
4. RA ≥ 6 months who have failed MTX monotherapy with moderate disease activity and features of poor prognisis	Anti-TNF
5. RA ≥ 6 months who have failed MTX combination therapy or sequential therapy with other non-biologic DMARDS with moderate/high disease activity and features of poor prognosis	Abatacept Anti-TNF Rituximab[b]
6. RA ≥ 6 months who have failed MTX combination therapy or sequential therapy with other non-biologic DMARDS with moderate/high disease activity and without features of poor prognosis	Non-biologic DMARDS Anti-TNF
7. All patients that are outside of the above groups	Non-biologic DMARDS

Derived from the ACR 2008 Recommendations for the use of Non-biologic and Biologic Disease-Modifying Anti-rheumatic Drugs in RA (ref)

At the time of publishing, Tocilizumab had not been licensed and so it does not appear in the recommendations. It is however since been licensed and recommended for use in patients with RA in the USA

[a] Features of poor prognosis: 1. Functional limitation (defined by Health Assessment Questionnaire-HAQ), 2. Extra-articular disease, 3. Rheumatoid factor/cyclic citrullinated peptide positivity, 4. Bony erosions on radiographs

[b] Only recommended for patients with high disease activity and features of poor prognosis

withdrawal. This could be of tremendous benefit to the patient and also lead to substantial cost savings (Finckh et al. 2009)

Combination biologic therapy

The ability to switch off different arms of the immune system is certainly an attractive therapeutic approach, particularly in a disease as immunologically diverse as RA. Unfortunately, studies looking at combination biologic therapy have been universally disappointing. One of these comparing the tolerability and efficacy of anakinra and etanercept given together (Genovese et al. 2004) showed that the combination was not more efficacious that etanercept alone and found an increase in serious infections in the combination group. Another study looked at the safety of abatacept as an 'add-on' in patients already receiving both non-biologic and biologic DMARDS. Significantly more adverse events were noted in the group receiving abatacept and another biologic (Weinblatt et al. 2006). As a result, there is no role for combination biologic therapy at present for the treatment of RA.

Biologic monotherapy

Because of their high efficacy, there has been growing interest in the use of biologic drugs as monotherapy. Studies have demonstrated the efficacy of adalimumab (van de Putte et al. 2004), etanercept (Bathon et al. 2000), certolizumab (Fleischmann et al. 2009), anakinra (Bresnihan et al. 1998), abatacept (Moreland et al. 2002) and tocilizumab (Jones et al. 2010) as monotherapy and indeed these drugs are licensed for the treatment of RA without concomitant methotrexate. Combination therapy has been shown to be superior in most cases and continues to be the preferred treatment option although tocilizumab may be the most effective biologic when given as monotherapy (Taylor and Jones 2011).

On the horizon

Biologic drugs currently available for the treatment of rheumatic diseases can be classified into two main categories; those that inhibit cytokines and those that suppress B and T cell function. Current strategies being researched include monoclonal antibodies to different cytokines and small molecules that inhibit intra-cellular pathways. The following section will discuss several of these agents.

Newer cytokine inhibitors

The cytokine IL-17 is expressed by the Th17 subset of T lymphocytes. Studies have demonstrated that secukinumab, an anti-IL-17 antibody is effective in the management of plaque psoriasis and research is underway to determine the safety and efficacy of this drug in ankylosing spondylitis, psoriatic arthritis and RA (Hueber et al. 2010).

IL-12 and IL-23 are cytokines secreted by macrophages, which regulate T cell differentiation. Ustekinumab, is a monoclonal antibody against p40 (a sub-unit common to

IL-12 and 23), which inhibits the functions of both IL-12 and IL-23. This biologic is currently licensed for the treatment of psoriasis (Gottlieb et al. 2009). Studies in RA have not been conducted yet and the implications of inhibition of the IL-12/23 pathway are yet to be explored.

In addition, other cytokines such as IL-15, lymphotoxin-β and B-cell growth factors (such as BAFF/Blyss and APRIL) are being explored as therapeutic targets in RA.

Intracellular blockade with 'small molecules'

There is considerable interest in a new class of drugs that are capable of modulating intracellular effector mechanisms downstream of cytokine receptors. The advantage of this novel approach is that these medications may be administered orally. Several of these drugs have made it to phase 3 trials for RA including fostamatinib (Scott 2011), an oral spleen tyrosine kinase (Syk) inhibitor. The JAK3 blocker tofacitinib has also been shown to be effective and well tolerated in RA in a number of phase 2 randomised controlled trials (Goekoop-Ruiterman et al. 2005; Felson et al. 1995) and certainly appears to be a promising orally available therapy. Not all potential targets, however, have been successful with mitogen activated protein (MAP) kinase inhibitors failing in clinical trials for RA (Sweeney and Firestein 2006).

Future direction

Due to the heterogeneous nature of RA, a panacea is unlikely to be found to combat the condition. From a therapeutic perspective, therefore it would be highly advantageous to identify unique disease characteristics or biomarkers in order that therapy (biologic or synthetic) could be more specific and ultimately individualised.

Although various predictors of poor prognosis are known such as high CRP and elevated titres of cyclic citrullinated peptide antibodies, at present we lack the ability to accurately predict response to different therapies and this remains an area of unmet need.

There is also considerable interest in early undifferentiated inflammatory arthritis with studies supporting that early intervention decreases the rate of patients developing RA. As a proportion of patients spontaneously remit, identification of biomarkers in early arthritis will not only help us characterise those requiring aggressive early treatment, but also aid in individualising therapy.

Despite the limitations and uncertainties, there is no doubt that biologic agents have transformed the management of RA and have dramatically altered the natural history of the condition. In an age where the doctrine has been disease prevention, biologic therapy has made this possible in relation to radiographic damage, joint deformity and disability simultaneously improving quality of life. For the foreseeable future biologics will continue to form an integral part of the management of this previously crippling disease.

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