

Evolution of treatment for rheumatoid arthritis

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Abstract

Treatment for RA has changed profoundly over the past 25 years, evolving from a strategy of providing symptomatic relief, to implementation of therapeutic regimens that impact disease activity and ultimately have been shown to slow or arrest structural joint damage. Drug therapy for RA has evolved from salicylates, to NSAIDs, CSs, DMARDs, MTX, and finally to biologic response modifiers. MTX has become the initial drug of choice in most patients with RA, and some do well on MTX monotherapy without the addition of other agents. Combination regimens including MTX and other conventional DMARDs may be an effective early approach to treatment of RA. The biologic response modifiers (biologics) became available in the late 1990s, based on our understanding of the molecular mediators of synovial inflammation in RA. The first biologics inhibited TNF- α , a cytokine active in host defences against some infections and malignancies, but which also promotes inflammation and bone erosion. Inhibitors of TNF- α are mostly given with MTX, although some can be given as monotherapy. Studies consistently show that combination MTX + TNF- α inhibitor therapy leads to better outcomes than with either agent alone. Tight control strategies, employing objective measures, also lead to improved outcomes. When patients fail treatment with one or more TNF- α inhibitor + MTX, a number of other possible alternatives may be tried, including treatment with biologics having other mechanisms, such as antibodies to certain ILs, other cytokines and inflammatory mediators. Current therapy for RA is such that progression from symptom onset to significant disability is now no longer inevitable, and RA patients can anticipate comfortable and productive lives on medical therapy.

Key words: rheumatoid arthritis, salicylates, NSAIDs, DMARDs, methotrexate, biologic response modifiers, interleukins, cytokines.

Introduction

Both the objectives and the results of treatment for RA have changed profoundly over the past 25 years, dictated largely by an enhanced understanding of the pathogenesis of this disease. During the first half of the 20th century, RA treatment regimens included drugs that could provide only symptomatic benefit (salicylates, from which were derived NSAIDs), analgesics and physical measures such as bed rest, splinting and physical therapy. Following the early reports of the beneficial effects of gold salts in many patients with RA [1] and the subsequent discovery of the efficacy of CSs in RA [2], rheumatologists for the first time had access to drugs that they hoped

could impact disease activity in a meaningful way. These therapies subsequently expanded to include other agents (including parenteral gold salts, SSZ, chloroquine, HCQ, D-Pen, ciclosporin and AZA), and these drugs were optimistically termed DMARDs. The approach recommended to treat patients with newly diagnosed RA was pyramidal: initially with analgesics, then with NSAIDs and ultimately with DMARDs, an approach that led to improvement in some—but not all—RA patients, with reduced symptoms and in some cases decreased disease activity. Large early clinical trials confirming DMARD reduction in the progression of structural joint damage, however, were initially lacking.

During the 1980s, in addition to new drugs to treat RA, new measurements were developed to assess the outcomes of therapeutic intervention. The application of these initial outcome measures, such as the Sharp radiographic scoring system [3], to assess response to early DMARDs prescribed according to the traditional treatment pyramid led to the recognition that many of these drugs did not, in fact, modify the course of the disease. In addition, it was observed that (i) the early DMARDs

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were often poorly tolerated for longer than 2 years, (ii) structural damage often became evident on radiographs within the first 2 years after the onset of RA [4] and (iii) low-dose weekly oral MTX, a drug widely used to treat psoriasis, not only was effective in treating PsA but also was both safe and well tolerated when given to patients with RA [5, 6]. Taken together, these observations led to US Food and Drug Administration (FDA) approval of MTX for the treatment of RA in 1988 and to inversion of the traditional pyramidal approach to the medical management of RA [5–8].

By the 1990s, MTX had become the initial drug of choice of most rheumatologists to treat patients with RA in the USA, although early efficacy studies suggested that, at least within the first year of use, other drugs, including SSZ, were equally efficacious [9]. Efforts were devoted to study approaches by which to improve the tolerability of higher MTX doses (such as through s.c. administration), thereby increasing its efficacy, and patients with RA were often able to tolerate MTX for sustained periods of time, which was not usually the case with earlier DMARDs [10–14]. In spite of this, some RA patients were unable to tolerate the dose required to achieve maximal benefit or remained MTX inadequate responders. Additionally, it was contraindicated in others, such as young women contemplating pregnancy or those who used alcohol regularly. Furthermore MTX alone did not typically result in drug-free remission; sustained MTX treatment was required to maintain a clinical response and many patients had persistent disease activity even while on this drug [15]. A number of early studies supported the possibility that combination therapy with DMARDs \pm CSs might prove more useful than monotherapy with MTX alone [16, 17], and this is a line of investigation that continues nearly 20 years later. To review the body of literature devoted to the different non-biologic treatment options for both early and established (active) RA is beyond the scope of this introduction. Emerging from these studies, however, has been the general conclusion that combinations of traditional DMARDs are both safe and effective in many patients with RA and thus constitute a reasonable approach to early treatment of disease [18–27]. Although monotherapy with MTX is effective in many patients with newly diagnosed active RA [26–28], based on health economic modelling (cost-effectiveness), the National Institute for Health and Clinical Excellence (NICE) in the UK recommends a combination of DMARDs plus short-term glucocorticoids as first-line therapy as soon as possible after onset of symptoms, but ideally within 3 months of the onset of persistent symptoms of RA in appropriate patients who do not have a contraindication to this approach [29]. More recently, in the 2012 update of previously published guidelines, the ACR, with a target of low disease activity or remission, recommends DMARD monotherapy (agent not specified) in patients with disease duration of <6 months with low disease activity (activity defined by accepted DAS ranges) and for moderate or high disease activity without poor prognostic features (presence of one or more of functional limitation, extra-articular disease, positive RF or ACPAs, and bony

erosions). Combination DMARDs (two or more DMARDs, most of which are MTX based) were recommended for all others with early disease, underscoring this approach in patients before the initiation of biologic response modifiers [30].

Current treatment practice: biologic response modifiers

In the late 1990s, a sea change took place in the treatment of RA, with the introduction of biologic targeted therapies, also called biologic response modifiers. The development of these therapeutic proteins was the culmination of research over the previous two decades that had elucidated key molecular mediators of the inflammatory process that drives RA and results in structural damage to joints. These agents include mAbs and genetically engineered proteins directed against cytokines or cell-surface molecules. The earliest agents inhibited the biological activity of TNF- α , a cytokine known not only to contribute to host defence against infection and certain malignancies, but also to be key in perpetuating the inflammatory response in RA, which leads to synovial proliferation and bony destruction [31, 32]. To date, five drugs that inhibit TNF- α biological activity have been approved in the USA for clinical use in the treatment of patients with RA, each of which has been shown in rigorous testing to improve outcomes, while reducing disease activity and structural joint damage. These include, in order of FDA approval, etanercept, infliximab, adalimumab, certolizumab pegol and golimumab. Although subtly different (route of administration, dose interval, chemical structure, for example), these drugs are similar in efficacy and side-effect profile, though the experience with certolizumab pegol and golimumab is more recent and therefore not as extensively studied as that of earlier agents. Treatment with TNF inhibitors often dramatically improves RA disease activity and, in patients who respond, may slow or arrest disease progression as assessed by clinical, radiographic and patient-reported outcome measures. TNF inhibitors are generally used in combination with MTX. Although most TNF inhibitors are effective as monotherapy, studies of TNF inhibitors used in combination with MTX have demonstrated consistently that both the clinical and structural outcomes of combination therapy are superior to those achieved with either agent alone. As a class, TNF inhibitors are generally well tolerated; however, adverse effects such as decreased resistance to both routine and opportunistic infections can be devastating and must be aggressively sought and treated [33].

Following the introduction of the first TNF inhibitors, biologic response modifiers targeting other components of the immune response involved in the pathogenesis of RA have been approved for clinical use. Anakinra, a recombinant human soluble IL-1 receptor antagonist, can be administered subcutaneously daily to treat patients with RA. Abatacept, a recombinant fusion protein that combines the T-cell co-stimulation inhibitory molecule CTLA-4 with the Fc region of human IgG, may be given subcutaneously weekly or intravenously monthly.

Rituximab, a chimeric mAb directed against the surface molecule CD20 on B cells, is administered in two i.v. doses given 2 weeks apart, usually every 6 months. Most recently, tocilizumab, a humanized mAb directed against the IL-6 receptor, has been approved for monthly i.v. administration to patients with RA. Specifics regarding the biologic response modifiers approved for the treatment of RA are summarized in Table 1 [34–63].

Strategies in patients who have responded inadequately to one or more TNF inhibitors

Several possible strategies may be tried when a patient has not responded to treatment with MTX and a TNF inhibitor. Expert opinion does not point to one strategy as being superior to the others; all treatment plans are guided by observation of the individual patient's response, combined with clinical judgement. Of the possible approaches, two deserve careful consideration: (i) sequential TNF inhibitor use (i.e. trying a second TNF inhibitor if the first one has failed); and (ii) switching to a biologic DMARD with a different mechanism of action. Both of these strategies are supported by efficacy and safety data from randomized, placebo-controlled clinical trials (Table 1) [34–63].

The results of switching from one TNF inhibitor to a second TNF inhibitor were assessed in an analysis of data from the British Society for Rheumatology Biologics Registry, using rates of discontinuation due either to lack of efficacy or to adverse events (AEs) [64]. Of 6739 patients, 35% discontinued their first TNF inhibitor. Of these, 856 switched to a second TNF inhibitor. At the end of 30 months of follow-up, 73% of patients who had switched to a second TNF inhibitor continued on treatment. Patients who discontinued the initial TNF inhibitor because of lack of efficacy were more likely to have discontinued the second TNF inhibitor for the same reason; similarly, patients who discontinued the first TNF inhibitor because of AEs were more likely to have discontinued the second TNF inhibitor because of another AE.

An alternative to switching between TNF inhibitors is to initiate treatment with another biologic response modifier that has a different mechanism of action. Retrospective analysis of 116 patients from the Swiss Clinical Quality Management Program for Rheumatoid Arthritis cohort who had an inadequate response to at least one TNF inhibitor revealed greater improvement in DAS28 at 3, 6 and 9 months among the 50 patients who had subsequently received two infusions of rituximab 1000 mg with concomitant i.v. glucocorticoids, 14 days apart, as compared with the 66 patients who had switched to treatment with a second or third TNF inhibitor [65].

Current issues in the management of RA

With the rapidly increasing number of biologic options available to treat patients with RA, a number of important questions have arisen. The first question is that of the

optimal place of agents in the treatment algorithm. When should the addition of a biologic be considered after initiation of MTX therapy? Is 3 months an adequate trial of MTX monotherapy? Should combination agents be tried before turning to biologics and are there patients for whom biologic therapy should commence early in the course of their disease to improve outcomes? The 2012 update of the 2008 ACR recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis recommends targeting low disease activity or remission, that patients with established RA should receive 3 months of DMARD therapy before adding or switching between DMARDs or switching from DMARDs to biologic agents [30].

Another issue is that of agent selection. Individualized therapy using pharmacogenetics or certain patient characteristics as a predictor of response to guide therapy selection is under investigation. For example, patients who are positive for RF or ACPA are more likely to respond to rituximab than patients who lack these antibodies. The identification of additional biomarkers that might guide medication choices and the likelihood of response to therapy will be useful in this regard in the future. Until then, the choice of therapy should be based on the efficacy and safety profile of each agent, patient preference concerning dosing and route of administration and, of course, third-party reimbursement. Clinicians are constrained in their decision-making capacity by the limited amount of data on the comparative benefits and risks of the various agents currently available. Fortunately a number of trials are currently under way to address these important questions and may bring answers.

Future therapies for RA

In addition to those targets for which drug therapies have been approved, there are other potential targets for drugs to treat RA, including ILs such as IL-17 and receptor tyrosine kinases. Of these, a target that has yielded promising results is JAK3, one of the Janus kinases (JAKs), which mediates signal transduction of cell surface receptors for cytokines involved in the pathogenesis of inflammatory diseases such as RA. An oral inhibitor of this enzyme, tofacitinib (formerly CP-690,550) has demonstrated efficacy in several trials conducted in patients with RA: those who had failed at least one earlier DMARD [66], those with disease activity despite MTX therapy [67, 68] and those previously exposed to TNF inhibitors [69]. Tofacitinib has been studied both as monotherapy [66, 70] and in combination with MTX [67–69]. Fostamatinib, an oral inhibitor of spleen tyrosine kinase (Syk), which is an intracellular non-receptor tyrosine kinase, has demonstrated efficacy superior to that of placebo when given in combination with MTX to patients inadequately responsive to MTX [71]. However, fostamatinib was not superior to placebo when given in addition to stable DMARD therapy to patients inadequately responsive to a TNF inhibitor [66]. A potentially important characteristic of these tyrosine kinase inhibitors is that each can be taken orally rather than by injection or as an infusion, which may

TABLE 1 Summary of biologic response modifiers approved for the treatment of RA [33–63]

Agent	Mechanism of action	Administration and dosage	Indications	Studies for RA indication
Etanercept	Cloned fusion protein of human TNF- α receptor 2 with Fc region of human IgG ₁ ; inhibits TNF- α binding to its receptors	s.c. injection; 50 mg weekly	RA (with MTX or alone), JIA, PsA	ETN monotherapy [34] ETN + MTX in MTX-refractory RA [35] ETN vs MTX in patients with ERA [36] TEMPO (ETN + MTX vs ETN or MTX alone) [37] COMET (ETN + MTX vs MTX alone) [38]
Infliximab	Chimeric mAb to TNF- α ; inhibits TNF- α binding to its receptors	i.v. infusion; for patients with RA, dosing is 3 mg/kg at weeks 0, 2 and 6, then every 8 weeks; some patients may benefit from doses up to 10 mg/kg or given as frequently as every 4 weeks	RA (with MTX only), Crohn's disease, UC, AS, PsA, PsO	ATTRACT (IFX + MTX in MTX-refractory RA) [39] ASPIRE (IFX + MTX in MTX-naïve patients) [40] START (IFX + MTX in MTX-refractory patients with co-morbidities) [41]
Adalimumab	Humanized mAb to TNF- α ; inhibits TNF- α binding to its receptors	s.c. injection; 40 mg every other week; when used alone, some patients may benefit from dosing at 40 mg weekly	RA (with MTX or alone), JIA, PsA, AS, Crohn's disease, PsO	ARMADA (ADA + MTX in patients with DMARD-refractory RA) [42] DE011 (ADA alone in patients with DMARD-refractory RA) [43] DE019 (ADA + MTX in patients with MTX-refractory RA) [44] STAR (ADA + DMARD in inadequate responders to standard treatment) [45] PREMIER (ADA alone or + MTX in MTX-naïve patients with ERA <3 years' disease duration) [46]
Golimumab	Human mAb to TNF- α ; inhibits TNF- α binding to its receptors	s.c. injection; 50 mg monthly	RA (with MTX); PsA, AS	Phase 2 (GLM + MTX in MTX-refractory RA) [47] GO-AFTER (GLM + DMARD in patients treated with one or more TNF inhibitor) [48] GO-FORWARD (GLM alone or + MTX in patients with MTX-refractory RA) [49] GO-BEFORE (GLM + MTX in MTX-naïve patients with early-onset RA) [50]
Certolizumab pegol	Pegylated Fab' fragment of a humanized mAb to TNF- α ; inhibits TNF- α binding to its receptors	s.c. injection; 400 mg initially, then 200 mg every other week; 400 mg every 4 weeks may be considered for maintenance dosing	RA, Crohn's disease	RAPID 1 (CZP + MTX in patients with MTX-refractory RA) [51] RAPID 2 (CZP + MTX in patients with MTX-refractory RA) [52] FAST4WARD (CZP alone in patients previously treated with ≥ 1 DMARD) [53]
Abatacept	Cloned fusion protein of extracellular domain of human CTLA-4 with the hinge, CH2 and CH3 domains of human IgG ₁ ; inhibits T-cell co-stimulation by antigen-presenting cells	i.v. infusion; in adult patients with RA: <60 kg, 500 mg; 60–100 kg, 750 mg; >100 kg, 1000 mg, following initial infusion at weeks 2 and 4, thereafter every 4 weeks OR after a single i.v. infusion as a loading dose, s.c. injection, 125 mg, should be given within a day, followed by 125 mg weekly for maintenance dosing	RA, JIA	ATTAIN (ABA alone in patients with an inadequate response to one or more TNF inhibitor) [54, 55] AIM (ABA alone in patients with MTX-refractory RA) [56, 57] ABA s.c. vs i.v. in patients with MTX-refractory RA [58]

(continued)

TABLE 1 Continued

Agent	Mechanism of action	Administration and dosage	Indications	Studies for RA indication
Rituximab	Chimeric mouse/human mAb to CD20 antigens on B lymphocytes	Two 1000 mg i.v. infusions 2 weeks apart every 24 weeks; based on clinical evaluation not more frequently than every 16 weeks	RA with MTX in adult patients with RA and inadequate response to ne or more TNF inhibitor, NHL, CLL, granulomatosis with polyangiitis	DANCER (RTX + MTX in patients with RA and inadequate response to DMARDs including MTX) [59] REFLEX (RTX + MTX in patients with RA and inadequate response to one ore more TNF inhibitor [60])
Tocilizumab	Recombinant humanized mAb to IL-6R, blocking signalling and activation of B cells	i.v. infusion; in patients with RA, 8 mg/kg every 4 weeks	RA with inadequate response to existing therapies, polyarticular JIA, systemic JIA, symptomatic treatment of Castleman disease	OPTION (TCZ + MTX in patients with active RA) [61] RADIATE (TCZ + MTX in patients with RA refractory to One or more TNF inhibitor) [62] ROSE (TCZ + background DMARDs in patients with inadequate response to DMARDs [63])

ABA: abatacept; ADA: adalimumab; AIM: Abatacept in Inadequate Responders to Methotrexate; ARMADA: Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in patients with Rheumatoid Arthritis; ASPIRE: Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate Responders; ATTRACT: Anti-TNF Trial in Rheumatoid Arthritis With Concomitant Therapy; COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis; CLL: chronic lymphocytic leukaemia; CZP: certolizumab pegol; DANCER: Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis; ETN: etanercept; ERA: early RA; FAST4WARD: Efficacy and Safety of Certolizumab Pegol—4 Weekly Dosage in Rheumatoid Arthritis; GLM: golimumab; GO-AFTER: Golimumab in Patients With Active Rheumatoid Arthritis After Treatment With Tumour Necrosis Factor Alpha Inhibitors; GO-BEFORE: Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of Rheumatoid Arthritis of Early Onset; GO-FORWARD: Golimumab for Subjects With Active RA Despite MTX; NHL: non-Hodgkin lymphoma; IFX: infliximab; OPTION: Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders; PsO: plaque psoriasis; RADIATE: Rheumatoid Arthritis Study in Anti-TNF Failures; RAPID: Rheumatoid Arthritis Prevention of Structural Damage; REFLEX: Randomized Evaluation of Long-term Efficacy of Rituximab in RA; ROSE: Rapid Onset and Systemic Efficacy; RTX: rituximab; STAR: Safety Trial of Adalimumab in Rheumatoid Arthritis; START: Safety Trial for Rheumatoid Arthritis With Remicade Therapy; TCZ: tocilizumab; TEMPO: Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes; UC: ulcerative colitis.

impact patient acceptance of these drugs. Additional agents targeting signal transduction kinases including other JAKs, cytokines other than TNF- α , IL-1 and IL-6, and various inflammatory mediators are in development and may augment the therapeutic armamentarium available to manage patients with RA. These agents may bring additional options to patients who fail to respond to currently available biologic response modifiers.

Conclusion

The advances in RA treatment over the past 25 years have been profound. Previously the progression of RA from symptom onset to significant disability was often inevitable and, in some cases, rapid. Now, with the availability of medications that can slow or halt disease progression and prevent irreversible joint damage, joint replacement surgery is not always the ultimate outcome and patients with RA may live comfortable and productive lives on medical therapy. However, the biologic response modifiers are expensive and may be beyond the financial means of some patients who are in need of these effective treatments. The development of biosimilars over the next several years may help to provide more affordable versions of these successful therapies [72].

Currently available drug therapy for RA has made remission a feasible treatment goal. Patients with RA should be diagnosed early in their disease course and be assessed regularly using objective quantitative measures of disease activity. The recent revision of the definition of remission in RA by a joint ACR/European League Against Rheumatism (EULAR) committee exemplifies the improved outcomes that are achievable with the advances in RA treatment made over the past quarter century [73]. The life-limiting and, in some cases, life-shortening consequences of RA are no longer predestined. Thus patients with RA can now expect to experience a quality of life that previously was unavailable to patients during the 20th century.

Rheumatology key messages

- DMARDs modify disease activity, but not structural outcomes, in many RA patients.
- TNF inhibitors, alone or with MTX, may improve outcomes in most RA patients.
- Other biologic agents should be tried in RA patients with inadequate response to TNF inhibitors.

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