



Adalimumab for the treatment of rheumatoid arthritis

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Rheumatoid arthritis is a chronic, inflammatory condition of unknown etiology, affecting about 1% of the general population. Adalimumab was added to our armamentarium against rheumatoid arthritis in December 2002. It can be used either alone or in combination with methotrexate in those patients who continue to have persistent disease activity despite their therapy. Adalimumab has been shown to rapidly improve the clinical status and retard radiographic progression in a substantial number of treated patients. Its clinical efficacy has been shown to be sustained through several years of continued therapy. The rate of adverse events is comparable to that of other tumor necrosis factor inhibitors. As with those agents, while infections are the main adverse event clinicians should be aware of, patients should also be counseled about, and monitored for, rare events such as tuberculosis, opportunistic infections, lymphoma, and demyelinating or autoimmune diseases.

Rheumatoid arthritis (RA) is a chronic, inflammatory condition of unknown etiology, affecting approximately 1% of the general population. Women are affected approximately three times more frequently than men, and the peak incidence of disease is during the fourth and fifth decades of life [1]. Although spontaneous remission can occur, it often progresses to a chronic state associated with significant functional disability. RA is associated with substantial morbidity and economic burden [2]. After 10 years of disease, up to 50% of patients will be disabled; after 20 years of disease, more than 80% will have some disability or deformity [1,3].

The primary goals of therapy for RA are relief of pain, reduction of inflammation, preservation of functional status, prevention of disease complications including joint damage, and, ultimately, resolution of the pathogenic process. Historically, RA had been viewed as a benign disease and managed according to the traditional 'therapeutic pyramid', starting with nonpharmacological agents and nonsteroidal anti-inflammatory drugs (NSAIDs). The more aggressive therapy with disease-modifying antirheumatic drugs (DMARDs) was reserved for those who continued to have persistent disease despite these supportive measures. However, as evidence accumulated suggesting that RA is an aggressive disease that causes erosive joint damage even in the first 2 years of disease, the traditional pyramid has been modified to advocate early, aggressive therapy with DMARDs in attempt to halt disease progression [2,4]. Methotrexate (MTX) is

the most commonly used DMARD, either alone or in combination, for the treatment of both early and established RA due to its long history of documented safety and efficacy [5-8].

Overview of the market

Biological agents, in particular, inhibitors of tumor necrosis factor (TNF)- α and interleukin (IL)-1 have been an important addition to armamentarium against RA. Among its sundry pro-inflammatory and immunoregulatory activities, TNF- α promotes accumulation of inflammatory cells, and synthesis of other pro-inflammatory cytokines (e.g., IL-1, IL-6, GM-CSF) and chemokines [9]. Currently, three TNF inhibitors have been developed and approved: infliximab, a chimeric monoclonal anti-TNF- α antibody; etanercept, a recombinant soluble p75 TNF-receptor-Fc fusion protein; and adalimumab, a human monoclonal anti-TNF- α antibody [10,11]. In addition, there are other biological agents that are being studied for the treatment of RA such as rituximab, and cytotoxic T-lymphocyte associated antigen-4 Ig fusion protein (CTLA-4 Ig), among others.

Introduction to the compound

Adalimumab is a high affinity, recombinant, fully human IgG1 anti-TNF- α monoclonal antibody. It was developed using a phage display technique, and is produced in a Chinese hamster ovary mammalian cell line. It inhibits binding of TNF- α to both Type I and II TNF receptors, (CD120a/p55 and CD120b/p75). It is highly

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specific for TNF- α with $K_d = 6 \times 10^{-10}$ M [12]. Upon binding to TNF- α , it forms a large trimer complex composed of adalimumab and TNF- α [13,14]. It is administered subcutaneously (s.c.) 40 mg every other week with the option to increase the frequency to weekly.

Chemistry

Adalimumab consists of 1330 amino acid with a molecular weight of 148 kDa [Humira[®] (adalimumab). Abbott Corporation, CA, USA (2002), package insert].

Pharmacodynamics

Adalimumab binds to soluble TNF- α and inhibits TNF binding to cell surface TNF receptors. This prevents the protean downstream pro-inflammatory effects of TNF, such as activation of endothelial adhesion molecules, upregulation of potentially pathogenic cytokines such as IL-6 and IL-1 mRNA, and other effects [14,15]. *In vitro* studies have demonstrated that treatment with adalimumab decreases serum concentrations of acute phase reactants and serum pro-matrix metalloproteinase-1 [14, Humira[®] (adalimumab). Abbott Corporation, CA, USA (2002), package insert]. An immunology substudy from the Phase III DE019 study assessing the efficacy of MTX plus adalimumab demonstrated that adalimumab therapy did not alter the total number of peripheral granulocytes, NK cells, monocytes/macrophages, B-cells, T-cells or T-cell subsets. The ability of lymphocytes to proliferate, demonstrated by *in vitro* proliferation to both mitogen and recall antigen, as well as delayed type hypersensitivity reactivity also appeared to be maintained during therapy with adalimumab. B-cell function, as assessed by total immunoglobulin (Ig) levels, IgG subclass levels and antigen specific antibody response to recall antigen, were also not significantly affected by adalimumab therapy [16].

Pharmacokinetics & metabolism

Pharmacokinetics were assessed in several studies. In a Phase I, randomized, dose-titration study of adalimumab in RA patients receiving concomitant MTX. Patients were given up to two doses of intravenous (i.v.) adalimumab 0.25, 0.5, 1, 3, or 5 mg/kg during the first month of the study. Adalimumab has linear pharmacokinetic properties with the mean plasma concentration and area under the curve (AUC) increasing proportionally with an increase in dose. The mean plasma

concentration ranged from 25 to 284 $\mu\text{g/ml}$ with a volume of distribution of 4.7–5.5l. The mean maximum concentration of $4.7 \pm 1.6 \mu\text{g/ml}$ was reached within $131 \pm 56\text{h}$ (T_{max}) [14, Humira[®] (adalimumab). Abbott Corporation, CA, USA (2002), package insert]. The mean half-life was approximately 14 days [17]. At the recommended dose of 40 mg every other week, with and without MTX, adalimumab had an average steady-state serum concentration of 7.63 and 5.45 $\mu\text{g/mL}$, respectively [14]. Its effective trough level was maintained through 52 weeks of continued therapy [18,19]. In healthy subjects, the average bioavailability after a single dose of adalimumab 40 mg s.c. was 64% [14]. Adalimumab was cleared at a rate of 12ml/l.

Clinical efficacy

Adalimumab monotherapy

Phase I trials

Three randomized, double-blind, placebo-controlled trials (RDBPCT) followed by an open-label period of 1 to 2 years have demonstrated both the efficacy and safety of adalimumab at various doses. In an 8 week placebo-controlled study, 47 patients were randomized to receive placebo or adalimumab 0.5–10 mg/kg intravenously. All patients subsequently entered a 2 year open-label phase where they received adalimumab 1 mg s.c. weekly or 3 mg i.v. every other week. The onset of the clinical response was rapid, with 46% of the patients achieving the European League Against Rheumatism (EULAR) response within the first 2 weeks of therapy. At the 2 year follow-up, adalimumab prevented further radiographic progression in 42% of patients [20]. DE001/DE003 was a randomized, dose-titration, placebo-controlled Phase I study where 120 patients were randomized to receive either placebo or a single dose of 0.5–10 mg/kg adalimumab i.v. followed by a 1 year open-label starting at week 5. Patients on adalimumab had a significant clinical improvement within the first 24 h, reaching its peak effect by 1–2 weeks. There was a dose plateau effect at 1 mg/kg with patients receiving no additional clinical benefit at higher doses. In a subset of patients who underwent radiographic evaluation at 1 year, adalimumab exerted a protective effect against further radiographic progression [21]. DE004, a 3 month RDBPCT with a 2.5 year open-label extension, demonstrated a similar safety and tolerability profile of s.c. adalimumab monotherapy at 0.5–1 mg/kg weekly [19].

Phase III/III trials

Following on the promising results from Phase I trials, multiple Phase II/III trials have been conducted to assess both the efficacy and safety of s.c. adalimumab in patients with established RA. In DE007, 284 patients were randomized to receive placebo or adalimumab at doses of 20, 40, or 80 mg weekly for 12 weeks with an option to enter a 1 year blinded treatment and another year of 40 mg weekly open-label study. A total of 229 patients entered the open-label study with 89.5% remaining on therapy up to 104 weeks suggesting good tolerability of adalimumab. The clinical response and physical function, assessed by American College of Rheumatology (ACR) response and Health Assessment Questionnaire (HAQ), were significantly higher among patients treated with adalimumab throughout the entire study period. The initial clinical efficacy obtained during the first 12 weeks of RDBPCT was sustained throughout the 2 year open-label extension. The ACR 20 was achieved in 54, 79 and 76% at weeks 12, 54 and 104, respectively. A greater percentage of the patients in the open-label extension achieved the ACR 50 and 70 by week 104 (52 and 24%) than observed at the end of the RDBPCT portion (23 and 10%). The clinical efficacy were comparable for 40 and 80 mg weekly doses with the latter dose achieving the ACR responses slightly quicker [12,22].

DE011 was a Phase III, RDBPCT assessing the safety and efficacy of adalimumab over 26 weeks in 544 RA patients. Patients had severe disease, with a mean disease duration of 11 years and previous use of average 3.7 DMARDs. Patients were given placebo, 20 or 40 mg of adalimumab weekly or every other week. The clinical response rates were significantly greater in the adalimumab 40 mg group with 46, 22 and 12% achieving the ACR 20, 50, and 70 respectively. This clinical improvement was seen as early as 2 weeks. Of note, 40 mg weekly dose resulted in a slightly higher ACR response than 40 mg every other week dose [23].

The results from 794 RA patients who have participated in four previous adalimumab monotherapy trials with open-label extensions (DE001/003, DE004, DE007, DE010 and DE011) were combined to assess the long-term efficacy and safety of adalimumab monotherapy in DE018. The clinical responses achieved at year 1 were sustained up to 5 years, with 65, 35 and 14% maintaining the ACR 20, 50 and 70 respectively. A total of 75% of the patients remained in the study up to

5 years, again suggesting high tolerability and compliance to adalimumab therapy [24].

Adalimumab plus MTX*Phase I trials*

Sixty RA patients with 16 years of disease duration and active disease despite MTX participated in a 4 week, dose-titration, RDBPCT with a 26 month, open-label continuation phase. Patients were given MTX plus either placebo, 0.25, 0.5, 1, 3 or 5 mg/kg i.v. adalimumab every other week or monthly. The greatest clinical efficacy was seen in the 0.5 mg/kg group with 64.4 and 24.4% achieving the ACR 20 and 50, respectively. No dose response curve was noted with respect to clinical improvements [17]. DE010 compared the onset and duration of response of i.v. and s.c. adalimumab when combined with MTX. Patients were given two doses of adalimumab 1 mg/kg either i.v. or s.c. during the first month followed by a 2.5 year open-label extension. Both groups (i.v. and s.c.) had a similar magnitude and duration of the EULAR and ACR response rates [19,25]. This study confirmed the equal efficacy of s.c. adalimumab as i.v. and was the basis for the use of s.c. administration for all subsequent open-label and Phase II/III trials.

Phase III/III trials

Most of the patients from the initial DE010 study remained in the open-label study of adalimumab 40 mg s.c. every other week up to 4 to 5 years (66–72%). Throughout the 5 years of therapy, many patients continued to improve clinically with approximately a third of the patients achieving the clinical remission by 26 months. At 5 years, 80, 50 and 27% had achieved the ACR 20, 50 and 70 levels of response, respectively [26,27].

The the Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab in RA (ARMADA) was a Phase III, 24-week, RDBPCT conducted to assess the efficacy and safety of adalimumab with concomitant MTX. A total of 271 patients with a mean 12 years of disease duration and persistent disease activity despite MTX therapy received MTX plus adalimumab s.c. 20, 40 or 80 mg every other week. The clinical improvement in signs and symptoms and functional improvement (e.g., HAQ, fatigue scale score, short form [SF]-36) were evident by week 1 with 67, 55 and 27% achieving the ACR 20, 50 and 70 respectively while taking the currently recommended dose of 40 mg every other week. The clinical efficacy was slightly

lower with 20 mg every other week but comparable for two higher doses (e.g., 40 and 80 mg every other week) [28]. The majority of the patients (262) entered the open-label study with adalimumab 40 mg s.c. every other week plus MTX. In total, 65% completed the 3-year study with only 7% and 9% withdrawing from the study due to a lack of efficacy or adverse events respectively. Similar to other long-term studies, the clinical efficacy observed in the RDBPCT was sustained through 3 years with 78%, 59%, and 33% maintaining the ACR 20, 50, and 70 levels of response, respectively [29].

DE019, a pivotal trial, was a 52 week RDBPCT conducted to assess the ability of adalimumab to inhibit radiographic progression and reduce disease activity in RA patients with active disease despite concomitant therapy with MTX. Patients were given MTX plus either placebo or adalimumab 20 mg weekly or 40 mg every other week. At week 52, the ACR 20, 50, 70, as well as the Sharp score were significantly better among patients treated with adalimumab plus MTX. The ACR responses were similar and sustained throughout the study in both dosing groups with 59%, 42%, and 23% achieving the ACR 20, 50, 70 versus only 24, 10 and 5% in the placebo group. The functional status and quality of life (QOL) assessed by the HAQ and SF-36, also improved significantly in the treatment group. Perhaps most notably, a greater number of patients on adalimumab halted their radiographic progression with 62% having no new erosions at week 52 compared with only 46% in the placebo group [30]. A subgroup analysis of radiographic progression by demographics and disease severity revealed that African-Americans and those with early disease, defined as disease duration of 2 years or less, tended to have a more rapid radiographic progression than their counterparts on the same therapy [30,31]. After one year of therapy, 457 patients entered the open-label study where they all received adalimumab 40 mg s.c. every other week plus MTX. The clinical responses observed during the DBPCT were sustained with 62, 44 and 28% maintaining their ACR 20, 50, 70 responses at week 104, respectively [32]. The functional improvement and the inhibition of radiographic damage were also sustained throughout the entire open-label study [32,33]. Of note, RA patients with a lesser duration of disease responded more favorably, clinically and radiographically, than those with established RA, suggesting that

earlier therapy with adalimumab may achieve a greater extent of response [34,35].

The results from the DE019 and ARMADA trials were combined to compare health-related (HR) QOL in patients who were treated with MTX plus either adalimumab 40 mg every other week or placebo. HRQOL was measured using a validated health utility index 3 (HUI3) which consists of eight attributes of health status (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain). The treatment group improved rapidly and sustained their improvement (24% in DE019 and 38% in ARMADA) to an extent greater than their placebo-controlled counterparts [36].

Adalimumab plus standard DMARDs (Phase III trials)

The Safety Trial of Adalimumab in RA (STAR) was a Phase III study conducted to assess the safety and efficacy of adalimumab in a heterogeneous group of RA patients with persistent disease activity despite concomitant DMARDs. In this 24-week RDBPCT, 636 RA patients who were on 1–3 DMARDs (e.g., MTX, antimalarials, leflunomide and sulfasalazine) received either adalimumab 40 mg s.c. every other week or placebo while continuing their baseline DMARDs. There was a high compliance rate with approximately 91% of the patients completing the study in both groups. The addition of adalimumab significantly improved their clinical status with 53, 29 and 15% versus 35, 11 and 3.5% of the placebo group achieving the ACR 20, 50 and 70, respectively. The rates of adverse events and withdrawal were similar in both groups, indicating the safety of adalimumab in patients on standard DMARDs [37].

To further confirm the clinical efficacy of adalimumab observed in clinical trials in real life situations, the open-label Research in Active RA (ReAct) trial was conducted. In this study, the safety and efficacy of adalimumab 40 mg s.c. every other week added to standard DMARDs in RA patients with active disease were assessed. The 12 week clinical efficacy data from 2008 patients from more than 400 participating European sites revealed that the addition of adalimumab led to rapid and significant improvement with 67, 39 and 17% achieving the ACR 20, 50 and 70 respectively. These results mirrored closely to those results obtained from previous RDBPCT's, suggesting the generalizability of the results to more heterogeneous patients [38,39]. Interestingly, as has been seen with the other TNF inhibitors,

some patients who have previously failed therapy with other TNF inhibitors responded favorably to adalimumab [38,40,41]. The treatment with adalimumab 40 mg s.c. every other week, given either alone or in combination with other DMARDs, consistently improved patients' functional status as assessed by HAQ, SF-36, and functional assessment of chronic illness therapy-fatigue scale. This improvement was most evident and dramatic in patients with early RA [42–44].

Postmarketing surveillance

Most of the safety issues were identified through pharmacovigilance and postmarketing surveillance and discussed in detail below.

Safety & tolerability

In general, adalimumab was well-tolerated with less than 10% of the patients discontinuing the treatment due to adverse events (AEs) during clinical trials [12,17,30,34,37]. When compared with other TNF inhibitors used in clinical practice, adalimumab was comparable, with a high adherence rate (82%) at 12 month follow-up [45]. AEs associated with adalimumab may be classified as target related or agent related. Target related AEs include those potentially attributable to generalized immunosuppression or specific inhibition of TNF- α . Agent related AEs include allergic and idiosyncratic reactions.

Target-related reactions: consequences of generalized immunosuppression

In clinical trials, the most frequent reported infections were upper respiratory tract infections (URIs), rhinitis, bronchitis, and urinary tract infections [17,24,25,27,35, Humira® (adalimumab). Abbott Corporation, CA, USA (2002), package insert]. A retrospective analysis of ARMDA, DE011, DE019 and STAR trials revealed a similar rate of infections for adalimumab and placebo at approximately 1.0 per patient year [14, Humira® (adalimumab). Abbott Corporation, CA, USA (2002), package insert]. However, the rate of serious infections was generally not significantly different from the placebo group with the frequency and types of AEs during open-label extensions remaining similar to those observed during the randomized phase [23–25,27,35]. No dose response or dose-limiting effects on AEs were noted [12,23]. In addition to common infections, various opportunistic infections such as *Pneumocystis carinii*, Listeriosis, Legionella, atypical Mycobacteria, Coccidioidomycosis, Histoplasmosis,

and Aspergillosis have been reported as they have from patients receiving other TNF- α inhibitors (infliximab and etanercept) [45–48]. Therefore, close observation for any signs or symptoms suggestive of infections is required during therapy with adalimumab or other TNF inhibitors.

Similar to other TNF inhibitors, adalimumab therapy has also been associated with lymphoproliferative malignancies – ten cases – especially non-Hodgkin's lymphoma, with a standardized incidence ratio (SIR) of approximately 5, compared with an age and sex matched population. However, studies have shown that RA patients, especially those with more severe disease, are at a higher risk for developing lymphoma compared with the general population, independent of drug treatment. Complicating this analysis is the finding that those with more severe, refractory disease have been the cohort of patients who most often receive biological therapies [50,51, Humira® (adalimumab). Abbott Corporation, CA, USA (2002), package insert].

Target-related reactions: specific consequences of TNF inhibition

Data from numerous animal studies has shown that TNF- α plays a critical role in defense against mycobacterium tuberculosis (TB) infection. Through early 2004, postmarketing surveillance has noted 13 cases of TB among the 4900 patient-years of adalimumab exposure. These TB cases appear to be mostly reactivation of latent TB, with the majority occurring within the first few months of therapy. In contrast to the typical presentation of TB where 80% or more present with pneumonia, nearly half of the cases with adalimumab were more likely to be extrapulmonary or disseminated TB [52]. This is similar to the data from the other TNF inhibitors. Patients should be screened for latent TB prior to starting therapy with adalimumab or other TNF inhibitors.

A report representing 4870 patients' years of exposure through December 2003 has identified four cases of demyelinating conditions similar to multiple sclerosis among patients treated with adalimumab [53]. Given the natural incidence of four to six cases per population of 100,000 per years, the true impact of TNF inhibitors on the development of MS still remains to be defined.

Development of autoantibodies and potentially autoimmune disease has also been a concern with TNF- α inhibitors. Approximately 3 to 12% of the patients treated with

Highlights

Mechanism of action

- Adalimumab inhibits binding of soluble tumor necrosis factor (TNF)- α to cell surface Type I and II TNF receptors.
- Adalimumab inhibits downstream pro-inflammatory effects of TNF such as endothelial adhesion molecule and other inflammatory cytokine activation.

Pharmacokinetic properties

- Pharmacokinetics properties are linear with the area under the curve (AUC) increasing with an increase in dose.
- The volume of distribution is 4.7 to 5.5 l with the majority staying within the intravascular space.
- Mean maximum plasma level is reached within 5.5 days.
- Adalimumab is slowly cleared with an elimination half-life of approximately 14 days.
- The recommended dose is 40 mg subcutaneously every other week with the option to increase the frequency to weekly.
- Adalimumab therapy does not appear to alter the composition or the functions of components of the immune system, including peripheral granulocytes, T- and B-cells.

Clinical efficacy

- Adalimumab, both as monotherapy or combination therapy with other DMARDs, results in rapid clinical improvement with effects by 2 weeks.
- Adalimumab therapy rapidly and significantly improves patients' functional status.
- The clinical response is sustained throughout the treatment period, up to 5 years to date.
- Adalimumab treatment is able to prevent the progression of radiographic damage.

Safety & tolerability

- Adalimumab is well-tolerated with less than 10% of the patients discontinuing the medication due to AEs.
- The most common AEs were ISRs, headache, rash, pruritus, hypertension and back pain.
- The rate of overall adverse events was comparable between the adalimumab and placebo groups.
- Similar to other TNF inhibitors, adalimumab has been associated with reactivation of TB and hence, all patients should be screened for TB prior to the initiation of adalimumab therapy.

adalimumab developed autoantibody to anti-nuclear antigen and double stranded DNA. However, the clinical implications of these antibodies remain to be defined, as progression to a lupus-like illness appears to be uncommon [12,23,30,34,37]. The mechanisms of increased autoantibody production are also unknown.

Several clinical trials assessing the efficacy of TNF inhibitors (infliximab and etanercept) in patients with congestive heart failure (CHF) have failed to show any benefit and in some, have resulted in increased morbidity and mortality. Adalimumab has not been studied in CHF. The incidence of new onset CHF among RA patients treated with adalimumab was 0.1% and was comparable to placebo [54]. It remains unclear if a true association exists

between the development or worsening of CHF and TNF inhibitors, but caution should be exercised, especially when treating patients with significant CHF.

Agent-related reactions

In clinical trials of adalimumab, the most common AEs among patients treated with adalimumab were injection site reactions (ISRs), headache, rash, pruritus, hypertension and back pain. Most of these AEs were mild to moderate [12,17,21,23,25]. A rare case of an erythema multiforme-like skin reaction has been noted but most cases of ISRs are mild, leading to discontinuation of therapy in only 0.3%. A retrospective analysis of 2070 patients from 4 large Phase II/III trials (ARMADA, DE011, DE019 and STAR) found the incidence of ISRs with adalimumab to be 20.3% [55,56]. Approximately 5% of patients treated with adalimumab developed low titers of antibodies to adalimumab but no correlation with efficacy or development of AEs has been noted [14,17,23,25,34]. As is true with all biologic agents, issues of immunogenicity are complex, as they depend upon novel assays for detection of antibodies to the treating agents. Hyperlipidemia with increases in both cholesterol and triglycerides has been noted among patients treated with adalimumab but its clinical implication remains unknown [12,37, Humira[®] (adalimumab). Abbott Corporation, CA, USA (2002), package insert].

There is no published data on children, pregnant or lactating women as these subjects were excluded from all clinical trials.

Regulatory affairs

Adalimumab was approved in December 2002 for the treatment of moderate and severe RA that has been refractory to or partially responsive to currently available DMARDs. Adalimumab can be used alone or in combination therapy with other DMARDs. Adalimumab is currently under investigation for the treatment of psoriatic arthritis, ankylosing spondylitis, psoriasis, juvenile rheumatoid arthritis, Crohn's disease and other conditions.

Expert opinion

The introduction of TNF inhibitors has dramatically improved the clinical status of many RA patients. Adalimumab has been shown to be an effective therapy for RA with the clinical improvement occurring rapidly and sustained throughout longer term treatment. Adalimumab is well-tolerated with few patients discontinuing

the medication due to side effects. Although the safety profile of adalimumab has been comparable to placebo in trials, clinical trials are an incomplete source of safety information and until more long term data on larger numbers of heterogeneous patients is available, physicians must remain vigilant and closely monitor for the development of opportunistic infections, TB, demyelinating conditions, autoimmune diseases and CHF in patients on adalimumab.

Outlook

Despite significant improvement with the introduction of TNF inhibitors, some patients continue to suffer from progressive and disabling RA and in the majority of treated patients, remission is not achieved. With significant success with TNF inhibitors, research on other key

signaling molecules involved in modulating TNF (e.g., p38 mitogen-activated protein kinase, nuclear factor- κ B, c-Jun N-terminal kinase) are in progress. There is also a large body of evidence suggesting that both T- and B-cells serve a key role orchestrating the immune driven inflammatory response in RA. Initial studies on CTLA-4 Ig, an inhibitor of T-cell costimulation, have been promising. Rituximab, a chimeric monoclonal antibody against CD 20 present only on B-cells, has been shown to be efficacious in refractory RA. In addition, clinical trials assessing the use of agents that modulate the function of adhesion molecules, chemokines and other cytokines are underway. Many trials are currently ongoing to validate these earlier findings and to define the optimal and potentially curative therapies for RA.

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