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Newer Biological Agents in the Treatment of Rheumatoid Arthritis

Do the Benefits Outweigh the Risks?

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Abstract

Recently, three new biological agents, rituximab, abatacept and tocilizumab, have become available for the treatment of rheumatoid arthritis (RA) in patients with active disease, who have not responded to at least one disease-modifying antirheumatic drug (DMARD). Rituximab is an anti-CD20 monoclonal antibody, abatacept modulates T-cell activation and tocilizumab is an interleukin-6 receptor antagonist. Clinical studies with these agents have demonstrated that they are effective in RA patients with moderate to active disease, who have not responded to treatment with at least one DMARD and/or tumour necrosis factor (TNF) inhibitor. Thus far, there is no convincing evidence to show that one of these three new drugs has a superior efficacy over the others or that they have other benefits compared with the TNF inhibitors. The use of rituximab, instead of another TNF inhibitor, might be an option in patients who have not responded to TNF blockade. Abatacept could also be considered, but this has not yet been formally tested. A practical advantage of tocilizumab is that it may be administered as a first-line biological agent.

Adverse events, including (usually mild) infusion reactions, are common. There is a small increased risk of serious infections that appears to be similar to that with TNF inhibitors, although each drug may have its own particular risk profile. Thus far, there is no convincing evidence that the new biological agents are associated with an increased risk of malignancies. However, the number of patient-years studied is still rather limited and, hence, continuous postmarketing surveillance is necessary. Adequate studies directly comparing new biological agents with each other and with other biological agents, such as TNF inhibitors, are not available. Hence, no firm conclusions regarding the benefit-risk profile of these agents versus each other can be reached. However, the benefit for a given new biological agent currently appears to outweigh the risk for an individual RA patient with active disease, despite earlier drug treatment.

Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown cause that affects approximately 1% of the population,[1] and which, untreated, may lead to severe disability and a decreased life expectancy. Hence, the treatment goal is to control the underlying inflammatory

process in order to slow or even prevent joint damage. Before the mid 1980s, patients with RA were initially treated with an NSAID, and later on, a disease-modifying antirheumatic drug (DMARD) was added (pyramid approach). More insight into the underlying pathophysiological mechanism, showing destructive synovitis early in the disease, led to early and aggressive DMARD therapy. It was also shown that a combination of DMARDs, aiming at different levels of the underlying processes, provides additive, perhaps synergistic, efficacy without increasing overall adverse effects.

In recent years, cytokine-specific biological therapies ('biologicals'/'biologics') have become available for clinical use. These agents aim to block pivotal cytokines such as tumour necrosis factor (TNF)-α or interleukin (IL)-1, and have shown to be the most effective antirheumatic drugs presently available. The first biological agents to become available were the TNF inhibitors infliximab, etanercept and adalimumab, as well as anakinra, a recombinant human IL-1 receptor antagonist.[2] TNF inhibitors are clinically as effective as methotrexate but have a much faster onset of action, whereas anakinra appears to be significantly less potent than TNF inhibitors.[3] Recently, three other drugs have emerged as treatment options: (i) rituximab, an anti-CD20 monoclonal antibody; (ii) abatacept, a co-stimulation inhibitor; and (iii) tocilizumab, an IL-6 receptor antagonist.[4] This review focuses on these three drugs in the treatment of patients with RA. The relevant literature was retrieved from a search of PubMed to March 2009 for English language articles using the search terms 'rheumatoid arthritis' as one term plus 'abatacept', 'rituximab' and 'tocilizumab' as other terms. Bibliographies of identified articles were scrutinized for additional references and abstract books of recent rheumatology conferences were also scanned (including the 2008 European League Against Rheumatism [EULAR] meeting and the 2008 American College of Rheumatology [ACR] meeting). Finally, the website of the European Medicines Agency (EMEA) was searched, particularly for (additional) safety information.

1. Rituximab

Rituximab is a mouse/human chimeric antibody directed against the CD20 antigen expressed on (pre)mature B cells. Rituximab induces depletion of CD20+ B cells, but not plasma cells as these cells are usually CD20– and, consequently, IgG serum levels do not change during rituximab therapy. The exact mode of action of rituximab is unknown and possible mechanisms of the B-cell depletion might be through complement or Fc receptor γ-mediated antibody-dependent cytotoxicity or by induction of apotosis.[5]

Rituximab is a well known agent for the treatment of CD20+ non-Hodgkin's lymphoma. This drug was approved by the US FDA in March 2006 and by the EMEA in July 2006, in combination with methotrexate, for the treatment of moderately to severely active RA in patients who have had an inadequate response to one or more TNF inhibitors. The registered dose for RA is two 1000 mg intravenous infusions, 2 weeks apart. A second course of rituximab can be considered when the disease activity increases after an initial response.

1.1 Efficacy

After initial uncontrolled studies with rituximab suggested that it had a beneficial effect in RA, several clinical trials in patients with active disease, despite methotrexate or TNF inhibitor therapy, were conducted. In the first randomized, double-blind, placebo-controlled trial, 161 patients with active RA,[6] despite treatment with methotrexate ≥10 mg weekly, were randomized to one of four treatment groups: (i) methotrexate; (ii) rituximab; (iii) rituximab plus cyclophosphamide; and (iv) rituximab plus methotrexate. Rituximab 1000 mg was given intravenously on days 1 and 15, and intravenous cyclophosphamide 750 mg was administered on days 3 and 17. All patients received corticosteroids for 17 days. The primary outcome measure was an ACR50 response at week 24 (the ACR response rates are explained in table I).[7] Secondary measures included the ACR20 and ACR70 responses, and the EULAR moderate to good response, based on the Disease

Table I. American College of Rheumatology (ACR) response criteria[a]

Outcome measure
1. Number of swollen joints
2. Number of tender joints
3. Physician's global assessment
4. Patient's global assessment
5. Pain
6. Functional status or physical disability
7. Acute-phase reactant (ESR or CRP)

a The ACR20 response criterion to treatment is a 20% improvement in swollen and tender joints and a 20% improvement in three of the outcome measures 3–7. Similarly, ACR50 and ACR70 responses can be defined as 50% and 70% improvement, respectively.

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate.

Activity Score-28 (DAS28). The DAS28 score is a composite measure of the number of painful and swollen joints (out of 28), the erythrocyte sedimentation rate and the visual analogue scale global disease activity assessed by the patient.[8] This score ranges between 0 and 10, and a DAS28 of >5.1 is considered high disease activity, a DAS28 of >3.2–5.1 moderate disease activity, a DAS28 of 2.6–3.2 low disease activity and a DAS28 of <2.6 is considered remission. The primary endpoint, achieving an ACR50 or better response at 6 months, was noted in a significantly higher proportion of patients receiving rituximab plus methotrexate (43%) than those receiving methotrexate alone (13%). Moreover, the proportions of patients reaching an ACR20 response and a moderate or good EULAR response were significantly higher in the rituximab plus methotrexate group compared with the methotrexate-alone group.

Rituximab was subsequently investigated in a double-blind, placebo-controlled, dose-ranging study (DANCER; Dose-Ranging Assessment International Clinical Evaluation of Rituximab) in 465 RA patients who had active disease despite methotrexate treatment and who had previously not responded to other DMARDs and/or biological agents.[9] Rituximab was studied in both standard (1000 mg, days 1 and 15) and reduced (500 mg, days 1 and 15) doses in combination with methotrexate, in conjunction with high-dose intravenous/oral corticosteroids. Significantly more patients treated with rituximab achieved an ACR20 response at week 24 (54% and 55% for rituximab 1000 mg and 500 mg, respectively) compared with placebo (28%); ACR70 responses were achieved by 20%, 13% and 5% of patients treated with rituximab 1000 mg, 500 mg and placebo, respectively. Corticosteroids did not contribute significantly to the efficacy of rituximab plus methotrexate.

In the placebo-controlled phase III study (REFLEX; Randomized Evaluation of Long-Term Efficacy of Rituximab) 520 RA patients, with active disease despite treatment with methotrexate and a TNF inhibitor, were randomized to either two infusions of rituximab (1000 mg) or placebo.[10] Again, all patients received high-dose intravenous/oral corticosteroids over 2 weeks. At week 24, significantly more rituximab-treated patients than placebo-treated patients demonstrated ACR20 (51% vs 18%), ACR50 (27% vs 5%) and ACR70 (12% vs 1%) responses, and moderate to good EULAR responses (65% vs 22%). The Genant-modified Sharp score was used for assessment of joint damage; this score assesses bone erosion and joint space narrowing, and ranges between 0 and 290. The mean change from baseline in the Genant-modified Sharp score at week 56 was 2.3 in the rituximab group versus 1.0 for patients in the placebo group.[11]

In a prospective observational investigation, 116 patients with inadequate responses to at least one TNF inhibitor were treated with either rituximab (n = 50) or a different TNF inhibitor (n = 66).[12] At 6 months, the mean decrease in the DAS28 was −1.61 for patients receiving rituximab versus −0.98 for patients receiving a TNF inhibitor. Altogether, this investigation suggests that rituximab might be more effective than a change of TNF inhibitor in patients who have not responded to a TNF inhibitor, but further randomized comparisons are required before recommendations can be made.

After an open-label extension study demonstrated a sustained clinical response with repeated treatment in RA patients initially responding to rituximab,[13] the efficacy of retreatment with rituximab, at intervals of at least 6 months, in

patients who were initial nonresponders versus responders was addressed in 30 patients with RA.[14] Efficacy could be evaluated in 26 of 30 patients of whom 24 qualified for retreatment. Seventeen patients had similar clinical responses with the second and third courses of rituximab as with the first course, whereas the seven initial nonresponders again did not respond to subsequent courses of rituximab. This suggests that retreatment with rituximab in these patients might not be useful; however, this topic should be addressed in an adequate investigation.

1.2 Adverse Events

The most common adverse events are infusion related, of mild to moderate severity, observed in up to 40% of patients and are particularly associated with the first infusion of rituximab.[15] The most commonly reported infusion-related adverse events are headache, nausea, urticaria, and hyper- and hypotension. Serious events occur in less than 1% of patients, and it appears that these infusion reactions are significantly decreased with premedication with intravenous corticosteroids.[15] Hence, prophylactic treatment with corticosteroids is recommended "in order to prevent severe infusion reactions".[15] Rates of infections and serious infections appear similar to those observed with other biological agents. The rate of opportunistic infections was not increased in clinical trials. However, a few fatal reactivations of viral infections have been reported with the use of rituximab,[16] including one case of progressive multifocal leukoencephalopathy in a patient with RA, leading to a warning from the FDA.[17] It is important to realize that conclusions cannot currently be drawn about the long-term safety of rituximab in RA (i.e. repeated injections) in view of the limited data available. Rituximab may impair responses to vaccines and hence, when indicated, it is recommended that patients are vaccinated before initiation of treatment with rituximab.[18]

In clinical trials, a higher prevalence of human antichimeric antibodies (HACAs) against rituximab has been observed in patients with RA compared with lymphoma; this might be related to a lower dose of the drug being used to treat RA compared with lymphoma. The overall incidence was 5.5% and retreatment with rituximab did not increase the incidence or titre of HACAs. The clinical significance of HACAs is not exactly clear but, similar to infliximab, another antichimeric antibody, they might be related to infusion reactions and decreased efficacy, the latter caused by an increased clearance of rituximab.[15]

2. Abatacept

An important step in the pathogenesis of RA is the presentation of antigens to T-cell receptors by antigen-presenting cells such as macrophages and dendritic cells. However, another (co-stimulatory) signal is required for the complete activation of T cells. This co-stimulation is blocked by cytotoxic T-lymphocyte antigen 4 (CTLA-4) and abatacept is a fusion protein of two covalently linked subunits, extracellular CTLA-4 and human immunoglobulin. Abatacept is given intravenously with the dose adjusted according to bodyweight: 500 mg (<60 kg), 750 mg (60–100kg) and 1000 mg (>100 kg). The dose is repeated at 2 and 4 weeks after the first dose and every 4 weeks thereafter. Abatacept was approved by the FDA in December 2005 for the treatment of RA and may be used as monotherapy or concomitantly with DMARDs but should not be administered concomitantly with TNF inhibitors. The EMEA approved abatacept in May 2007 for the treatment of RA in combination with methotrexate.

2.1 Efficacy

The ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) investigation was the first phase III study to be published.[19] Patients with active disease and an inadequate response to TNF inhibitors were randomized to either abatacept (n = 258) or placebo (n = 133) for 6 months in addition to at least one DMARD. The primary endpoints were the ACR20 response and the proportion of patients with a clinically important improvement (i.e. at least 0.3) in functional disability as reflected by

scores in the Health Assessment Questionnaire (HAQ), at 6 months. Secondary endpoints included ACR50 and ACR70 responses, and changes in DAS28. At 6 months, ACR20 was significantly higher in the abatacept-treated patients compared with the placebo-treated patients (50% vs 20%, abatacept vs placebo), whereas DAS28 remission was achieved in 10% versus 1%. Clinically important HAQ improvements were observed in 47% and 17% of the patients treated with abatacept and placebo, respectively. A total of 317 patients entered the 18-month extension phase of this study, in which all patients were treated with abatacept, and 222 (70%) completed this period of treatment.[20] At 6 months and 2 years, respectively, ACR20 responses in the 222 abatacept-treated patients were 59% and 56%, and the percentage of patients achieving DAS28 remission increased from 11% to 20%.

In the AIM (Abatacept in Inadequate responders to Methotrexate) study, RA patients with active disease were randomized to abatacept or placebo, given in addition to methotrexate, for 1 year.[21] Primary endpoints were the proportion of patients reaching an ACR20 response, the proportion of patients with a HAQ score of 0.3 or more at 1 year and radiographic progression of joint damage at 1 year. A total of 652 patients were randomized to abatacept (10 mg/kg every 4 weeks; n = 433) or placebo (every 4 weeks; n = 219). ACR20 responses at 6 months were 68% for abatacept versus 40% for placebo. HAQ scores improved significantly in 64% versus 39% of patients treated with abatacept versus placebo, and abatacept significantly slowed the progression of joint damage, as assessed with the Genant-modified Sharp score, compared with placebo (i.e. 0.25 vs 0.53 points progression in the total score for abatacept vs placebo, respectively). The open-label extension phase of this study, in patients treated with abatacept for 2 years, revealed a greater reduction in progression of structural damage in the second year than in the first year of treatment.[22]

In ATTEST (Abatacept or infliximab vs placebo, a Trial of Tolerability, Efficacy and Safety in Treating RA),[23] patients with active RA and an inadequate response to methotrexate were either randomized to abatacept (10 mg/kg every 4 weeks; n = 156), infliximab (3 mg/kg every 8 weeks; n = 165) or placebo (every 4 weeks; n = 110) in addition to methotrexate. The primary objective was the mean change from baseline in DAS28 for the abatacept versus placebo groups at day 197. This change was significantly greater for abatacept versus placebo (−2.53 vs −1.48) and also for infliximab versus placebo (−2.25 vs −1.48). At day 365, reductions in the DAS28 were −2.88 versus −2.25 for abatacept and infliximab, respectively. ACR responses and DAS28 remission rates at day 365 tended to be better for abatacept than for infliximab. However, it should be noted that there was no opportunity to increase the dose in the infliximab group.

2.2 Adverse Events

The most commonly reported adverse events associated with abatacept are headache, dizziness, upper respiratory tract infections, pharyngitis and nausea. Approximately 50% of the reports of headache and dizziness were infusion associated: headache 8.2% and 5.1%, and dizziness 4.9% and 3.8% for the abatacept and placebo groups, respectively. Non-infectious respiratory system adverse events occurred mostly in patients with chronic obstructive pulmonary disease (n = 54) and were encountered more frequently in abatacept-treated patients (n = 37) than in placebo-treated patients (n = 17) with frequencies of 43.2% and 23.5%, respectively.[24] Hypertension was reported for 6.6% and 4.6% of the abatacept- and placebo-treated patients, respectively.[24] The trials used for the European registration showed serious adverse events in 14.0% of abatacept-treated patients versus 12.5% of placebo-treated patients.[24] No particular serious adverse event was increased in abatacept-treated patients compared with placebo. However, infections were more frequently observed in the abatacept-treated group than in the placebo group (3.0% and 1.9%, respectively). Herpes simplex infections were increased (1.9% and 1.0% in the abatacept and placebo groups, respectively) and common bacterial infections may also be increased. Abatacept was associated with a

relatively low (2.8%) frequency of antibody development, but there appeared to be no relationship with efficacy and/or safety outcome, albeit the patient numbers are still too low to draw firm conclusions. Presently, the risk of malignancies cannot be addressed adequately.

3. Tocilizumab

There is mounting evidence that IL-6 has a pivotal role in the pathogenesis of RA. IL-6 has various pro-inflammatory properties such as antibody production, activation of T cells and macrophages. Moreover, this cytokine is important for the hepatic acute-phase response. These insights have led to the development of tocilizumab, an anti-IL-6 receptor antibody that binds to soluble as well as cell-bound IL-6 receptors. Tocilizumab, in combination with methotrexate, has been approved for the treatment of moderate to severe active RA in patients who have not responded to one or more DMARDS or TNF inhibitors in several countries including Europe (January 2009) and Japan (April 2008). It is not yet approved in the US. The FDA has requested additional preclinical studies to confirm that tocilizumab does not affect peri- and postnatal development. Tocilizumab is administered intravenously in a dose of 8 mg/kg every 4 weeks.

3.1 Efficacy

There is a large investigational (multinational) phase III programme underway for tocilizumab, of which the first findings have recently been published. In OPTION (Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders), 622 patients with moderate to active disease activity and receiving stable doses of methotrexate, were randomized to tocilizumab 4 mg/kg or 8 mg/kg or placebo administered for 24 weeks.[25] ACR20 responses were observed in significantly more patients in the tocilizumab group than in the placebo group (59% in the 8 mg/kg group, 48% in the 4 mg/kg group and 26% in the placebo group). Comparable results were observed for the ACR50 and ACR70 responses and DAS28. A smaller Japanese study where tocilizumab was compared with placebo, in a comparable patient group, revealed similar results.[26]

In the TOWARD (Tocilizumab in Combination with Traditional DMARD Therapy) trial patients with moderate to severe disease activity despite DMARD therapy were randomized to either tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks, while continuing to receive stable doses of DMARDs.[27] A total of 1216 patients were investigated, and at week 24 the ACR20 response was significantly higher in the tocilizumab group than in the placebo group (61% vs 25%, respectively). Similar results were achieved with respect to the secondary endpoints, including ACR50/70 responses and DAS28.

In the RADIATE (Research on Actemra Determining Efficacy after Anti-TNF Failures) study, 499 patients with inadequate response to one or more TNF inhibitors were randomly assigned to either tocilizumab 8 mg/kg or 4 mg/kg or placebo every 4 weeks for 24 weeks.[28] In addition, all patients received methotrexate, and an ACR20 response at week 24 was reached by 50%, 30% and 10% in the three treatment groups, respectively. This response was independent of the previously administered TNF inhibitor. DAS28 remission responses were clearly dose-related and were reached by 30%, 8% and 2% of patients, in the three treatment groups, respectively.

Thus far, only one relatively small long-term follow-up study with tocilizumab has been published. The STREAM (Long-Term Safety and Efficacy of Tocilizumab, an Anti-Interleukin-6 Receptor Monoclonal Antibody, in Monotherapy) study was an open-label 5-year extension of a phase II study in which patients received tocilizumab 8 mg/kg every 4 weeks; thereafter, dose reduction and treatment interval changes were permitted.[29] At 5 years, 79/94 (84%), 65/94 (69%) and 41/94 (44%) of the patients achieved ACR20, ACR50 and ACR70 responses, respectively. A DAS28 of <2.6 (i.e. remission) was achieved in 52/94 (55.3%) of the patients. Altogether, this extension study suggests that tocilizumab has a sustained long-term efficacy.

Radiological outcome was the primary outcome in the SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis)

investigation conducted in 302 Japanese patients, with active RA, who had not responded to at least one DMARD or biological agent.[30] Patients were randomized to either 52 weeks of treatment with tocilizumab 8 mg/kg or conventional DMARD therapy. The Sharp-van de Heijde radiological score was used to assess joint damage; this score assesses bone erosion and joint space narrowing, and ranges between 0 and 398. At baseline, the mean disease duration was 2.3 years, the DAS28 was 6.5 and the radiological score was 29.4. At week 52, the tocilizumab group showed significantly less radiographic progression than the conventional DMARD group (mean total modified Sharp score 2.3 vs 6.1, respectively). To what extent these different progression rates ultimately translate into disability, needs to be addressed in long-term follow-up studies.

3.2 Adverse Events

The most common clinical adverse events seen with tocilizumab include infections, gastrointestinal disorders, headache and infusion reactions (hypertension, pruritus and skin rash). The registration trials revealed that serious infections, mostly respiratory, skin and gastrointestinal infections, were more common in patients treated with tocilizumab than placebo (2.1% vs 1.5%, respectively).[31] Systemic and opportunistic infections were seldom encountered. Gastrointestinal perforations during tocilizumab treatment occur at a rate of 0.18/100 patient-years, which is slightly elevated in comparison to historical RA patients; liver enzyme abnormalities, neutropenia, thrombocytopenia and increased lipid levels occurred more frequently during the use of tocilizumab compared with placebo.[31] ALT levels increased dose dependently and peaked within 2 weeks after the infusion. The increase in ALT levels was more pronounced when tocilizumab was given in combination with methotrexate, and mostly returned to near baseline values during follow-up. Neutropenia was observed more frequently in the tocilizumab groups and this persisted during the dosing interval. An obvious relationship with infections was not seen. Severe decreases in neutrophils (i.e. counts $<0.5\times10^9$/L) were infrequent and in these patients, neutrophil counts returned to normal after tocilizumab was stopped.

In clinical studies, only a few cases of thrombocytopenia were observed albeit this was mostly as a result of a decrease in the previously slightly elevated platelet count to the normal range. Increases of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol and triglycerides levels were common during tocilizumab treatment, and coincided with decreased inflammatory parameters such as C-reactive protein. However, the atherogenic index (i.e. total cholesterol/HDL cholesterol ratio), an important prognostic indicator for future cardiovascular disease, mostly remained constant. Importantly, there was no direct association between elevated lipid levels and the incidence of cardiovascular disease, but clearly this topic should be further evaluated by long-term prospective studies with cardiovascular endpoints before definite conclusions can be reached.

In view of the above-mentioned adverse events, during treatment follow-up of liver enzymes, whole blood count and lipid profile is necessary according to a risk minimisation activities plan of the manufacturer.[31]

Almost 2900 patients were tested for antibodies against tocilizumab and these occurred in 1.6% (n = 46). An association with allergic reactions was observed in five patients and in ten patients there was a correlation with clinical response.[31]

4. Discussion and Conclusions

At first glance, the efficacy and safety profiles of the three new biological agents discussed in this review do not seem to differ significantly from each other or from the TNF inhibitors, although there might be differences in some drug-specific adverse events, for example hypertension for abatacept, lipid and ALT changes for tocilizumab. However, as unexpected serious adverse events have not been encountered in clinical trials, the benefits outweigh the risks of these new agents. Thus far, there is no convincing evidence for an increased risk of malignancies,

but continuous postmarketing surveillance is necessary to further address this topic. As adequate comparative studies between the individual agents are lacking, final conclusions about the efficacy and safety of the agents versus each other cannot be reached. This problem may partly be solved by meta-analyses. One such analysis by Venkateshan et al.,[32] encompassing 25 investigations with etanercept, adalimumab, infliximab, anakinra and abatacept, demonstrated that these biologicals as a whole group are effective for the treatment of active RA both in methotrexate-naive patients and patients with methotrexate-resistant disease. However, this meta-analysis was still too small to reach conclusions about the individual biologicals. Safety was the focus of a second meta-analysis, which included placebo-controlled trials with rituximab, abatacept and anakinra; this meta-analysis suggested no enhanced risk of serious infections.[33] However, this investigation was inadequately powered to reach conclusions about the safety of rituximab or abatacept. Moreover, a recent systematic review suggested that the risk for serious infections with rituximab and abatacept may be similar to that with TNF inhibitors.[34] Another meta-analysis involving rituximab and tocilizumab is currently underway.

There is at present no convincing evidence that one biological agent should be preferred over another in RA patients who have active disease despite DMARD treatment. However, rituximab and abatacept can only be given when a patient has not responded to at least one TNF inhibitor, whereas tocilizumab does not have this restriction. The choice of tocilizumab over a TNF inhibitor or vice versa will then depend on considerations about the different methods of administration, as well as cost considerations (e.g. reimbursement policies), which may differ from situation to situation. After a lack of response to one anti-TNF agent, the choices are another TNF inhibitor or one of the newer biological agents. In such a case, one could consider the determination of anti-drug antibodies to guide the choice of the next agent. Altogether, these three new biological agents appear to be a significant contribution to the therapeutic armamentarium of the rheumatologist.

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